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# Cutaneous vasculitis and vasculopathy

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# Cutaneous vasculitis and vasculopathy

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# Editorial: Cutaneous vasculitis and vasculopathy

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KEYWORDS

**vasculitis, small vessel vasculitis (SVV), cutaneous vasculitis, vasculopathia, IgA vasculitis**

Editorial on the Research Topic
Cutaneous vasculitis and vasculopathy

Vasculitis is a disorder group with inflammation and necrosis of blood vessel walls, causing hemorrhagic and ischemic features. It can appear in any organ of the body, and can influence blood vessels of any size. The severity of vasculitis can range from mild and temporary to life-threatening. The skin is commonly affected by vasculitis, with small-vessel vasculitis being the most prevalent form. Cutaneous vasculitis can occur as part of systemic vasculitis, either as a skin-limited or skin-dominant expression, or as a variant of the systemic condition. Eventually, it may be an isolated-vessel inflammation of the skin. The term (occluding) vasculopathy is used to describe the blockage of blood flow in a vessel due to occludung events such as emboli, thrombi, cryoproteins, high blood visosity or proliferative processes of the vessel wall (while livedoid vasculopathy is a term for a special entity withing this group). Vasculopathy is sometimes also used as a broad term to encompass any disorder affecting the blood vessels.

Dermatologists have an advantage in recognizing and diagnosing cutaneous vasculitis early. This is because vasculitis often involves the skin, which is visible and easily accessible for examination and biopsy. Additionally, the presence and/or spectrum of skin lesions can indicate severe systemic vasculitis. This special "Dermatology" Research Topic is dedicated to focusing on the dermatological aspect of the disease. Taking into account the multisystemic nature of the disease, we also tried to deal with cutaneous vasculitis and vasculopathy in all respects. Therefore, this title is expected to be of interest to a wide range of disciplines. Our focus is on the current knowledge of epidemiology, etiopathogenesis, clinical features, diagnosis, differential diagnosis and therapeutic approaches for the treatment of cutaneous vasculitis and vasculopathy.

Cutaneous vasculitis includes various conditions, ranging from limited skin involvement to severe systemic forms. In the last years interdiscplinary agreement has been reached on the terminology for cutaneous vasculitides. In this special supplement, we analyze the latest advancements and open questions in the terminology of cutaneous vasculitis. Although the skin is frequently affected by vasculitides, it was not until 2018 that a specific set of terms, based on the Chapel Hill Consensus Conference (CHCC) nomenclature, was introduced to identify the distinct features of cutaneous vasculitides. Caproni et al.'s article emphasizes the importance of the Dermatologic Addendum to CHCC2012 (D-CHCC) and its impact on the scientific community, as discussed in "The impact on the scientific community of the 2018 addendum to the CHCC (Chapel Hill Consensus Conference)."

Immune complex vasculitides present with inflammation of the vessel walls associated with perivascular deposition of immunoglobulins, particularly immune complexes. This group includes systemic and skin-restricted IgA vasculitis variants, cryoglobulinemic vasculitis, rheumatoid, lupus and hypocomplementaemic vasculitides, serum sickness as well as cutaneous IgM/IgG-vasculitis or recurrent macular vasculitis (such as hypergammglobulinemic or exercise-induced). Sunderkötter et al. provide a comprehensive overview of the pathophysiology and clinical manifestations of immune complex vasculitides, revealing that some pathomechanisms, e.g. in IgA vasculitis, may differ considerably from the mere concept of serum sickness or the Arthus reaction.

In the "*Recent topics related to etiology and clinical manifestations of cutaneous arteritis*" title, Ikeda underlines that adenosine deaminase 2 deficiency cases are included among the cases diagnosed with cutaneous arteritis. Due to clinical similarities with cutaneous arteritis but differences in treatment approaches, if cutaneous arteritis is diagnosed or developed, especially in early childhood, it should prompt consideration of ADA 2 deficiency as a possible cause.

In two separate reviews, we tried to analyze the most recent literature on the clinical and immunohistopathological features of cutaneous vasculitis caused by systemic SARS-CoV-2 infection and cutaneous vasculitis secondary to SARS-CoV-2 vaccine. While Corrà et al. specifically focus on possible underlying pathogenetic mechanisms, Maronese et al. perform a detailed clinicopathological evaluation.

Livedoid vasculopathy is a chronic, relapsing, thrombo-embolic disease characterized by occlusion of the dermal vessels of the lower extremities. Burg et al. provide an overview of the current literature on livedoid vasculopathy, provide a diagnostic and therapeutic approach, and review diseases that fall under the differential diagnosis of livedoid vasculopathy. In their comprehensive review, Seguí and Llamas-Velasco also provide a detailed analysis of the pathogenesis, associations, clinical features, and treatment strategies associated with livedoid vasculopathy.

Kim et al. focus on the pathogenesis of vasculitis in Behçet's disease, which is classified as variable vessel vasculitis. The authors provide updated clinical information and therapeutic recommendations for mucocutaneous Behçet's disease, with a special emphasis on idiopathic immune-mediated vasculitis.

In the review titled "Cutaneous vasculitis; An algorithmic approach to diagnosis," Alpsoy presents a systematic diagnostic approach. The approach combines current literature knowledge and the author's expertise in the field to offer a rational framework for selecting the most suitable diagnostic methods.

Micheletti discusses the treatment of cutaneous vasculitis, emphasizing that the choice of treatment depends on the type, severity, and patient comorbidities. Well-planned treatment can achieve disease remission with minimal drug toxicity. The treatment of systemic vasculitis is evolving toward more targeted therapies based on improved understanding of the disease.

In conclusion, we have endeavored to elucidate the multifaceted aspects of cutaneous vasculitis and vasculopathy in a comprehensive manner, utilizing the expertise of renowned figures in this field. In this Research Topic, the aim has been to write each title in an up-to-date and concise manner. Furthermore, evidence-based algorithmic approaches have been proposed in appropriate topics. It is our hope that this Research Topic will prove a valuable resource for physicians engaged in the clinical management of cutaneous vasculitis and vasculopathy.

## Author contributions

EA: Writing – original draft, Writing – review & editing. CS: Writing – original draft, Writing – review & editing. WP: Writing – original draft, Writing – review & editing.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

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CASE REPORT
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# Case Report: Idiopathic Subcutaneous Thrombotic Vasculopathy

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Lower extremity ulcers have significant morbidity, with treatment determined by the underlying disorder. Reported is a 32-year-old female presenting with small skin nodules and bruises across her legs 4 weeks following her second COVID vaccination. These lesions progressed into large, necrotic ulcers over several months. Initial work-up showed widespread pannicular thrombotic vasculopathy with ischemic skin necrosis. The tissue was negative for calcification on Von Kossa histochemistry, and a working diagnosis of subcutaneous thrombotic vasculopathy was suggested. The ulcers progressed despite treatments with corticosteroids, therapeutic anticoagulation, intravenous immunoglobulin, plasmapheresis, sodium thiosulfate, wound care, and repeat debridement. Later debridement specimens demonstrated rare vascular and pannicular calcifications. This finding supports the hypothesis that subcutaneous thrombotic vasculopathy is a precursor to calciphylaxis, the patient's current working diagnosis. However, based on the patient's entire clinical picture, a definitive diagnosis has yet to be found. This report highlights the challenges of working with rare diseases and the importance of multidisciplinary cooperation.

**Keywords: vasculopathy, calciphylaxis, ulcers, COVID, polyarteritis nodosa, thrombophilia**

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## INTRODUCTION

Chronic lower extremity ulcers affect over 7 million patients in the United States per year (1). Common causes of lower extremity ulcers include venous insufficiency, arterial insufficiency (ischemia), and neuropathy. Less frequent causes of ulcers include infection, neoplasms, hypercoagulable states, pyoderma gangrenosum, and hematologic disease. Ulcers with a presentation of retiform purpura or livedo racemosa are rare and suggest either systemic vasculitis or occlusive vasculopathy (1). Calciphylaxis, a rare yet highly morbid type of occlusive vasculopathy, is characterized by extensively necrotic and painful ulcers on fatty areas such as the abdomen, buttocks, and thighs (1, 2).

Thrombosis secondary to SARS-CoV2 (COVID-19) infection is well recognized. Thrombosis following vaccination against COVID-19 is very rare (3, 4). To our knowledge, this is the first case of post-COVID vaccination thrombotic vasculopathy resulting in progressive necrotic ulcers. Here, we describe a case of calciphylaxis-like occlusive thrombotic vasculopathy which commenced

four weeks after the second dose of mRNA COVID-19 vaccination. We discuss the differential with other ulcerating skin diseases with vascular pathology, including vasculitis, subcutaneous thrombotic vasculopathy, and non-uremic calciphylaxis.

## CASE DESCRIPTION

A 32-year-old female presented to her primary care physician with tender erythematous nodules on her bilateral lower extremities four weeks following her second Moderna COVID vaccination (**Figure 1**). She had a past medical history of Ehlers-Danlos syndrome, psoriasis, 3 possible first-trimester pregnancy losses, and chronic diarrhea. There were no other family members with similar conditions. Serologic testing for SS-A, SS-B, JO-1, RF, CCP, ANA, DNAse B, TG2, PR3/MPO with reflex to ANCA, protein electrophoresis with immunofixation, complement C3c and C4c, tuberculosis, and hepatitis B and C was negative. A punch biopsy was reported by a community pathologist to be consistent with leukocytoclastic vasculitis. Additional testing for HIV antigen/antibody and Lyme disease was negative. Vascular studies revealed no abnormalities. As her clinical presentation did not match a small vessel vasculitis, a provisional diagnosis of cutaneous polyarteritis nodosa (PAN) was made by a community rheumatologist in the setting of ulcerating retiform purpura consistent with a medium vessel process.

Treatment with 50 mg oral prednisone daily, 0.6 mg colchicine twice daily, and daily wound care with Medihoney for suspected cutaneous PAN was ineffective. Her dose of prednisone was decreased to 40 mg. One week later, the patient reported "a feeling of gravel" on her legs. At this time, her legs contained many necrotic ulcers and nodules, requiring debridement under anesthesia at an outside institution. Cultures showed extended spectrum beta-lactamase (ESBL)-producing *E. coli* and she was started on intravenous (IV) vancomycin and fluconazole, with collagenase and xeroform wound care.

In early September, the patient was admitted to our institution for pain control and wound management, with her prior antibiotic regimen stopping 3 days prior. Estrogen based hormones were stopped at this time, and she was started on ertapenem 1 g IV and fluconazole 400 mg daily with wounds dressed in sulfamylon cream. Alternative diagnoses were discussed at this time due to lack of response to treatment of medium vessel vasculitis, including pyoderma gangrenosum. Repeat autoimmune and infectious testing was negative. A colonoscopy showed no evidence of inflammatory bowel disease. Magnetic resonance imaging (MRI) of her chest, abdomen, and pelvis was negative for vasculitis. The initial outside punch biopsy was reviewed, and the pathology findings were reclassified as thrombotic vasculopathy instead of vasculitis. Repeat punch biopsy revealed subcuticular necrosis with fibrin thrombi within blood vessels. No significant immunoglobulin (Ig) G, IgA, IgM, or C3 deposits were identified *via* direct immunofluorescence. Testing for coagulopathies was positive for prothrombin variant G20210A. The remainder of her thrombophilia evaluation, including testing for cold agglutinins, JAK2 with reflex, paroxysmal nocturnal hemoglobinuria, antithrombin III deficiency, factor V Leiden, platelet factor 4 antibodies, antiphospholipid labs, platelet count, and protein C and S levels were normal. The patient started taking warfarin due to concern of vasculopathy and was transitioned to apixaban once negative antiphospholipid antibodies were confirmed. Her antibiotic regimen was altered to 3 g IV ampicillin-sulbactam and 100 mg micafungin daily after a wound swab grew *Klebsiella*.

In October, a diagnosis of cutaneous PAN was no longer favored due to evidence of ulcers eroding further into adipose tissue despite patient's steroid treatment (**Figure 2**). The patient's steroid treatment was tapered. After being on prolonged antibiotic treatments, the patient developed diarrhea secondary to clostridium difficile infection. Oral vancomycin was added, and she underwent two surgical debridements to lessen the load of necrotic tissue. Her anticoagulant regimen was switched to a heparin drip prior to the first procedure. By the end of October, it was discovered the patient was resistant to heparin. At the end of this month, the patient was transferred to the intensive care unit for sedation due to uncontrollable pain.

By the beginning of November, the patient received her third debridement. The most likely cause of the patient's progressive necrotic ulcers at this time was thought to be a thrombotic vasculopathy. A review of the literature found a case series on subcutaneous thrombotic vasculopathy similar to the patient's presentation. The possibility of an autoimmune reaction following COVID vaccination was discussed by the hematology and immunology teams at this time. A larger incisional biopsy at the edge of a developing lesion on her flank was performed. She was started on therapeutic enoxaparin, 81 mg aspirin daily, dipyridamole 75 mg four times daily, and pentoxifylline 400 three times a day in addition to treatments with IV immunoglobulins. Despite appropriate 1 mg/kg twice daily dosing of enoxaparin, the patient's anti-factor X activity level was subtherapeutic requiring escalation to 1.5 mg/kg twice a day. In addition, the patient was given 1 g IV solumedrol and transitioned to prednisone. The biopsy results came back as diffuse small vessel thrombosis with rare small vessel calcification, suggesting a thrombotic vasculopathy (**Figure 3**). Despite the less conspicuous tissue calcification present in the patient's biopsy, calciphylaxis was considered as a diagnosis. The low risk of IV sodium thiosulfate was weighed with the potential benefits, and it was started twice weekly. Over the next 2 weeks, the patient experienced improvement in pain – however during this time she started oral ketamine and received a hydromorphone PCA.

In mid-November, the patient had a spontaneous retroperitoneal bleed resulting in discontinuation of therapeutic anticoagulation. By the end of November, pentoxifylline was restarted with prophylactic enoxaparin. Wounds continued to progress (**Figure 4**), most notably on patient's bilateral flanks. The decision was made to stop intravenous immunoglobulin and initiate plasmapheresis in attempt to reverse any unknown immune-mediated processes. Her bilateral legs were debrided again early December 2021 to decrease necrotic tissue burden. She is now on argatroban due to difficulty with enoxaparin dosing, has received 7 treatments of plasmapheresis, and is

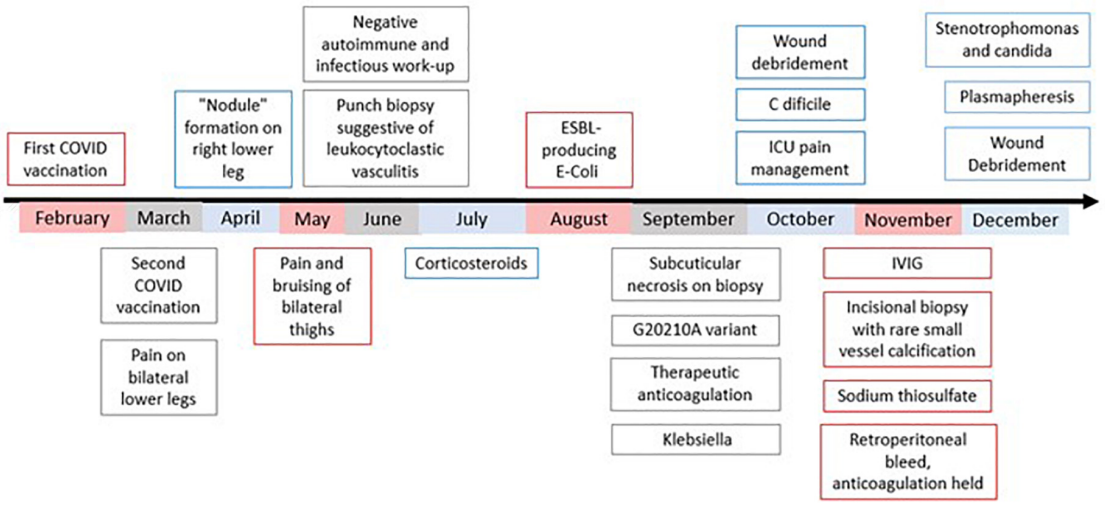


**FIGURE 1 |** Chronological depiction from patient's initial presentation to current working diagnosis. Work-up prior to September was performed at outside institutions. In September, the patient was admitted to our institution for treatment. At no point during this course have lesions stopped progressing. In early February, the patient unfortunately passed away.

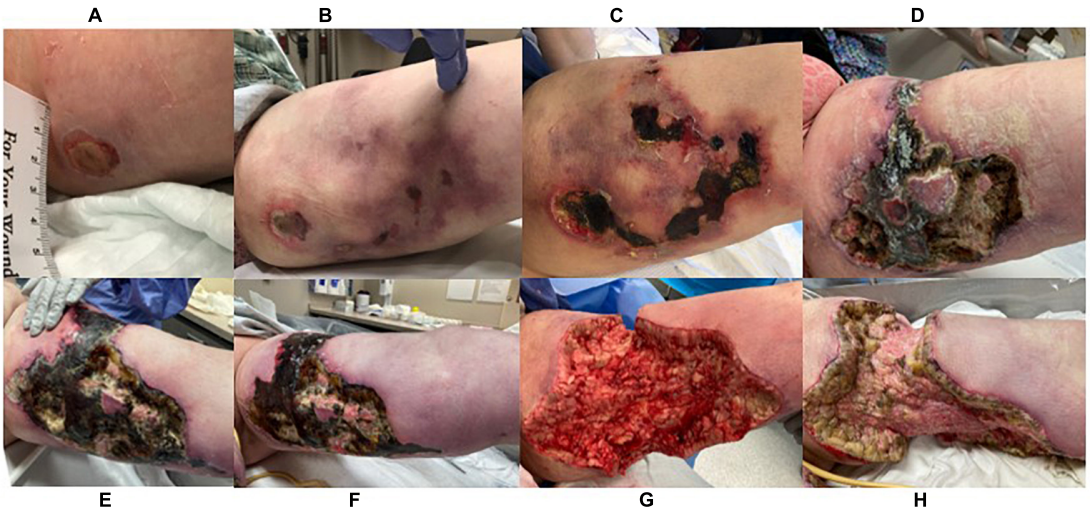


**FIGURE 2 |** Lesion progression of left medial thigh over 3.5 months. **(A)** 8/27/21**, (B)** 9/11/21, **(C)** 9/27/21, **(D)** 10/26/21, **(E)** 11/16/21, **(F)** 11/30/21, **(G)** 12/1/21, taken immediately post debridement in operating room **(H)** 12/7/21.

receiving IV sodium thiosulfate 25 g five times weekly. A recent tissue culture was positive for *Stenotrophomonas maltophilia*, *Mucor*, and *Candida parapsilosis*, and her antibiotic regimen consists of 100 mg minocycline twice daily, 1 g imipenem/cilastin intravenous every 8 h, 5 mg/kg IV amphotericin B every 24 h as tolerated, and oral 125 mg vancomycin four times daily.

Her prognosis remained guarded, with differential diagnoses including idiopathic subcutaneous thrombotic vasculopathy, non-uremic calciphylaxis sin calcifications, or an autoimmune response to her COVID vaccination. She reported depression,and high levels of pain despite a rigorous pain control regimen. She chose not to see the lesions on her bilateral lowerextremities since November as she believed it would worsen her mental health. Although it was difficult at times to havehope, she and her family continued to search for answers and have aggressive treatment goals. She wanted to share her story with the medical field in hope other providers would be able to provide insight to help her, and future patients with similar afflictions. In early February, the patient was transitioned to comfort care and passed away surrounded by her family.

## DISCUSSION

We report a case of idiopathic subcutaneous thrombotic vasculopathy four weeks following the second dose of

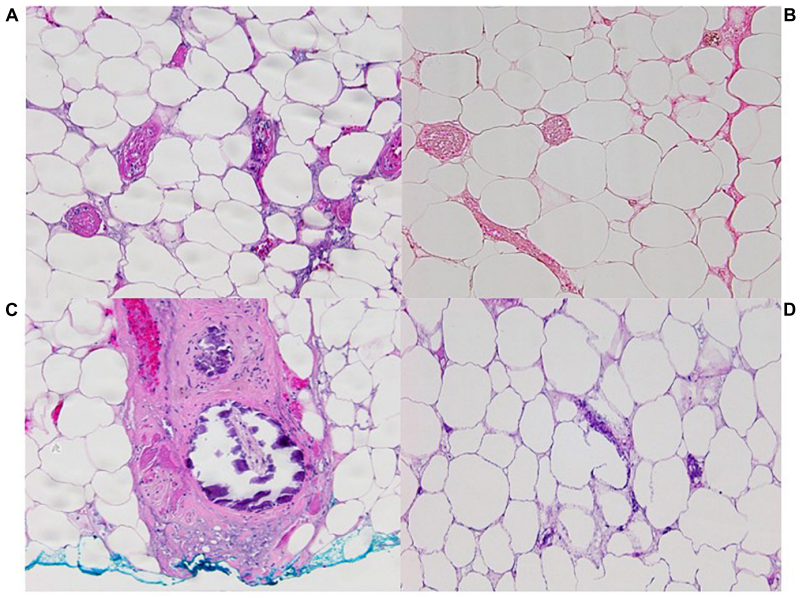


**FIGURE 3 |** Pathology images from incisional biopsy on left flank on 11/12/21 at 100x OM with **(A)**. Widespread pannicular thrombotic vasculopathy with ischemic pannicular necrosis (H&E) **(B)**. Negative for calcification on Von Kossa histochemistry with **(C)**. A single subcutaneous arteriole with mural calcification at the biopsy base (H&E). **(D)** Pathology image from incisional biopsy 12/1/21 at 100x OM with H&E showing adipocyte calcification.

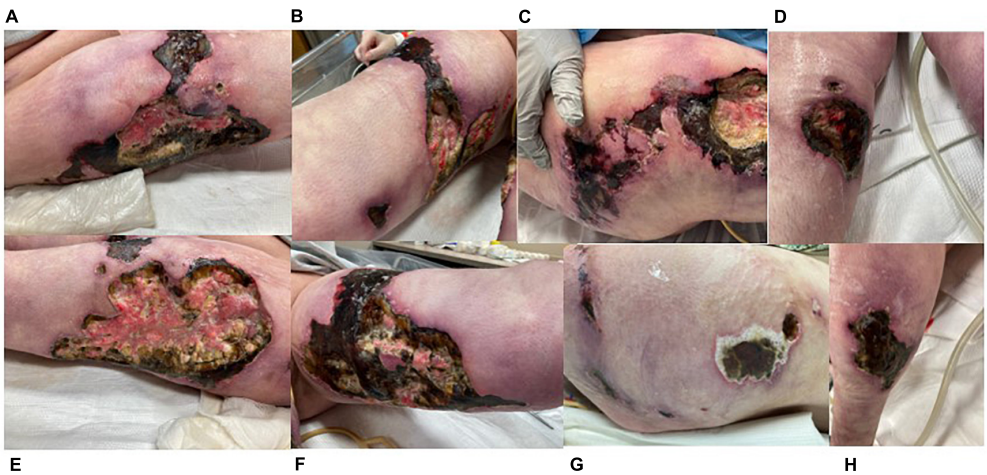


**FIGURE 4 |** Images of progressive necrotic ulcers taken 11/30/21 (other than C). **(A)** Right lateral thigh. **(B)** Right medial thigh. **(C)** Right flank (11/23/21). **(D)** Right anterior lower leg. **(E)** Left lateral thigh. **(F)** Left medial thigh. **(G)** Left flank. **(H)** Left posterior lower leg. Lesions not shown: right posterior lower leg, left anterior lower leg.

mRNA COVID vaccination in a patient with Ehlers Danlos syndrome. It is unknown whether subcutaneous thrombotic vasculopathy is a unique disease, a manifestation of calciphylaxis, or other thrombophilia. For this patient, other possible causes of thrombophilia include an inherited thrombophilia or novel form of vaccine induced thrombophilia.

Zembowicz and co-workers coined the term subcutaneous thrombotic vasculopathy syndrome to describe three patients with diffuse subcutaneous capillary and arteriolar thrombosis associated with ischemic skin necrosis. The findings were similar to those seen in calciphylaxis, but devoid of tissue calcifications (5). The histopathology is identical to that in our patient's initial biopsies. Unlike our case, the patients described by Zembowicz et al. were older with serious underlying medical conditions. Zembowicz et al. also found that 73% of cases of conventional calciphylaxis had foci of subcutaneous thrombi without calcifications and raised the possibility that subcutaneous thrombotic vasculopathy may represent calciphylaxis *sine* calcifications (5).

Calciphylaxis is a highly morbid and often fatal vasculopathy usually associated with end stage renal disease (ESRD). Early clinical findings of this disease include erythema, induration, and severe pain out of proportion to the physical exam (6). With time, papules and plaques coalesce into retiform purpura, which will progress to eschar and ulcer formation (6). These exam findings are thought to be secondary to medial layer calcification of the vessels in the subcuticular adipose layer, followed by subintimal fibrosis and thrombus formation (2). There are rare reports of non-uremic calciphylaxis in patients without prior renal impairment. Risk factors in patients without ESRD include female sex, obesity, hypercoagulability, autoimmune disorders, other connective tissue disorders, and medications such as Warfarin and corticosteroids (5, 7, 8). All such risk factors are present in this patient. For patients with end stage renal disease matching the clinical presentation of calciphylaxis, a biopsy is not necessary to make the diagnosis (6). In the absence of ESRD, biopsy is recommended.

McMullen et al. found a sensitivity of 0.85 and specificity of 0.88 for von Kossa histochemistry for diagnosis of calciphylaxis (9). Von Kossa staining was negative for tissue calcifications in our patient's initial punch biopsy specimens. However, the clinical efficacy of punch biopsies can be low if the quantity or depth of tissue obtained is not enough for diagnosis, a limitation of this patient's initial testing (10). Deep incisional cutaneous biopsy however provides adequate tissue for histologic study (11) as shown whensubsequent larger tissue samples revealed focal sparse subcutaneous vascular and adipocyte calcifications visible on routine hematoxylin-eosin- stained histologic sections. While the calcification is not as diffuse as classical calciphylaxis, these later biopsy specimens support the hypothesis that subcutaneous thrombotic vasculopathy syndrome is a precursor to calciphylaxis. However, this patient still does not have the traditional risk factors for calciphylaxis, did not manifest calcium, phosphorus, or parathyroid hormone elevation, and failed to respond to therapeutic anticoagulation and sodium thiosulfate.

Physicians should be aware of atypical presentations of calciphylaxis as treatments for common differentials, such as vasculitis and vasculopathies, can worsen the disease. The patient described was originally treated with corticosteroids for suspected cutaneous PAN, in addition to Warfarin for suspected vasculopathy. These treatment regimens were decided based on the current literature and are not unique to this patient alone. Notably, 60–80% of patients with non-uremic calciphylaxis were treated with corticosteroids prior to the development of calciphylaxis and 25–60% of patients had a history of warfarin administration (12, 13).

There are elements in this patient's history suspicious for inherited thrombophilia. She reported three pregnancy losses in the first trimester. Pregnancy loss in the first trimester is more consistent with antiphospholipid syndrome, but testing was negative for antiphospholipid antibodies (14). Late fetal losses and family and personal history of thromboemboli are suggestive of inherited thrombophilia (14). This patient has a prothrombin mutation, but not the classic disease history. Her resistance to heparin is notable. Heparin resistance could be due to non-specific binding, antithrombin deficiency, platelet interactions, elevated coagulation factors, adexanet alfa administration, or infection with COVID-19 (15). This patient's thrombophilia work-up, and lack of adexanet alfa administration rule out all causes except non-specific binding, which can cause a wide variability in patient response and dose requirement (15). This variability could explain the increased heparin requirements followed by retroperitoneal bleed. Ultimately, there is some level of inherited thrombophilia indicating need for indefinite anticoagulation in the future which could be contributing, if not causing, her disease process.

One last important feature of this case is the timing of the patient's COVID-19 vaccination prior to disease onset. Multiple reports have discussed concerns regarding thromboembolic events, macro and microvascular, related to the COVID disease and vaccine (3, 16, 17). Magro et al. examined skin, lung, and various other tissues in patients with mild to fatal COVID-19. In their Weill Cornell and Regional Medical Laboratory review from March of 2020 to June of 2021, 14 cases of patients with moderate to severe COVID were found to have cutaneous lesions attributable to complement-mediated microvascular injury due to spike glycoprotein activation of the complement pathway and a procoagulant state (17–19). This same group also identified 13 cases of cutaneous reactions developing 1 day to 7 weeks following COVID-19 vaccination (9 Moderna, 2 Pfizer, remainder vaccine type unknown). The most common cutaneous skin manifestation was noted to be eczematous dermatitis, but other cutaneous findings of patients included urticarial vasculitis, Grover disease, Herpes Zoster, and perniosis (17). Most of these cases were determined to be a self limited type IV delayed hypersensitivity reaction. The cases of post vaccine vasculitis were believed to be humorally mediated however, consisting of a type III immune complex reaction of the spike glycoprotein bound to antibody (17). Upon tissue sample analysis of the post-vaccination patients, microvascular localization of spike glycoproteins was observed *via* viral spike glycoprotein immunohistochemistry (IHC). Interestingly, this finding is similar to the findings of patients with severe/critical COVID19 with thrombotic retiform purpura (17).

This information is interesting in the context of this case as the patient discussed presented with cutaneous symptoms following her COVID19 vaccination. Although similar cutaneous symptoms have been identified in severe cases of patients with COVID19, they have not been observed following vaccination despite the similarity of microvascular localization of the spike protein. In contrast to the post vaccination patients in the review by Magro et al. the patient in this case did not have spike glycoprotein IHC performed, and her skin lesions did not resolve either spontaneously or with systemic steroid treatment. Additionally, her complement levels were within normal limits and she had negative direct immunofluorescence with no significant IgG, IgA, IgM, or C3 deposits identified on pathology specimens. However, given our evolving information about the COVID vaccination, it is possible that this patient's vaccination may have been one of many factors contributing to her unique presentation.

This case report is limited by lack of a definitive diagnosis and effective treatment. This complex case is important to the literature in order to spread awareness of atypical presentations of calciphylaxis and prevent physicians from doing accidental

harm by prescribing regimens that worsen the disorder, such as warfarin and corticosteroids. Without a specific diagnosis or effective method of preventing disease progression, the patient passed away in early February of 2022. It is our hope that further discussion of this patient's case will help similar patients in the future.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

KG wrote the case description, portions of the discussion section, created figures, and cared for the patient. AE wrote portions of the discussion section. GF assisted with pathology interpretation, literature review, and thorough editing of manuscript. PC, CW, PH, MT, DB, and RK assisted with editing the manuscript, in addition to caring for the patient. All authors agreed to be accountable for the content of this work.

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# Cutaneous vasculitis and vasculopathy in the era of COVID-19 pandemic

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Cutaneous vasculitides encompass a heterogeneous group of clinicopathological entities, which may occur as single-organ vasculitis of the skin or present as skin-limited variant of systemic vasculitis (i.e., skin-limited ANCA-associated vasculitis), and are triggered by various factors, including infections, drugs and vaccines. The COVID-19 pandemic has challenged us with a variety of both disease- and vaccine-associated skin manifestations, including vasculitis. Among the latter, cutaneous small-vessel vasculitis, previously known as leukocytoclastic vasculitis, seems to be the most reported in either scenario, i.e., natural infection and vaccination. Vasculopathy without true vasculitic changes on histology develops in but a minority of cases, mostly severe/critical COVID-19 patients, and appears to be the result of endothelial injury due to pauci-immune thromboembolic mechanisms. Herein, we provide an overview of the available literature on COVID-19-associated and anti-SARS-CoV-2-vaccine-associated cutaneous vasculitis. Although evidence is mostly limited to isolated reports, with a proportion of cases lacking histopathological confirmation, ample overlap with pre-pandemic forms is shown.

KEYWORDS

**vasculitis, vasculopathy, COVID-19, COVID vaccines, cutaneous manifestation**

## Introduction

Cutaneous vasculitides are a heterogeneous group of inflammatory disorders affecting skin blood vessels (1). In 2018 the dermatologic addendum to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (D-CHCC) provided a renewed framework and nomenclature for cutaneous vasculitides (CV), devising a classification whereby cutaneous features of systemic vasculitides are discussed and cutaneous single-organ vasculitides that have no systemic counterparts are introduced (2).

Although the D-CHCC substantially furthered our understanding of CV, a wealth of new evidence has become available in the last 5 years. Provisional entities, such

as macular lymphocytic arteritis also known as lymphocytic thrombophilic arteritis (LTA) (3) and recurrent cutaneous necrotizing eosinophilic vasculitis (RCNEV) (4), have been characterized more accurately. For instance, LTA has started being recognized as distinct from cutaneous polyarteritis nodosa (cPAN), presenting with a non-infiltrated, asymptomatic, and more widespread pattern of livedo racemosa (3). RCNEV, on the other hand, typically affects middle-aged Asian females, manifesting erythematous to purpuric papuloplaques, angio-oedema on the extremities and peripheral eosinophilia (4). Another provisional entity introduced in the D-CHCC is the so-called immunoglobulin (Ig) M/IgG vasculitis, a form of leukocytoclastic vasculitis involving dermal small-vessels, particularly post-capillary venules. This definition is meant for those cases of skin-limited vasculitis showing IgM/IgG deposits that are not related to cryoglobulinemia, monoclonal gammopathy and connective tissue diseases (2, 5).

The ongoing pandemic has added to the complexity of this scenario, challenging us with a variety of skin manifestations, including cutaneous vasculitis and vasculopathy, either as a direct result of the Coronavirus Disease 2019 (COVID-19) or following vaccination.

Pathogenic mechanisms are not fully understood, although the roles of a hyperactive immune response, complement activation and microvascular injury have been hypothesized.

Herein, we provide an overview of the available evidence on COVID-19-associated and anti-SARS-CoV-2-vaccine-associated CV.

## COVID-19-associated cutaneous vasculitis/vasculopathy

COVID-19-associated cutaneous manifestations include six main clinical phenotypes: (i) urticarial, (ii) maculopapular, (iii) papulovesicular, (iv) chilblain-like (6), (v) livedo reticularis/racemosa-like and (vi) purpuric vasculitic-like (7). Latency varies (7–9) and their incidence ranges between 1.8 and 20.4% of COVID-19-patients (9)—though these estimates mainly reflect data from the beginning of the pandemic.

In an Italian multicenter study investigating the clinical spectrum of COVID-19 associated cutaneous manifestations, only 13/200 adult patients presented a purpuric vasculitic pattern, with the latter being a significative risk factor for dyspnea (10)—although no clear relationship was shown with severity. Presentation may vary with livedoid features, retiform purpura and/or acro-ischemic phenomena (Table 1) (10). Systemic corticosteroids (CS) have shown some benefit, but a clear treatment protocol is lacking due to the rarity and incomplete characterization of these forms, as well as their presentation in critically ill patients (11).

### Cutaneous small-vessel vasculitis

Cutaneous small-vessel vasculitis, also known as leukocytoclastic vasculitis (LCV), is one of the most common CV reported in COVID-19 patients (Supplementary Table 1) (8, 12–24). Nevertheless, it is rare compared to other COVID-19-related dermatological manifestations. Indeed, according to a case-control study on 198 severe COVID-19 patients, LCV accounts for only 1.8% of all cutaneous findings (25). Clinical appearance spans from classic, bilateral symmetric palpable purpura favoring dependent body sites (Supplementary Figures 1a,b) to vesicobullous, hemorrhagic or targetoid eruptions. Oral or intravenous CS, with or without topical CS, were the mainstay of treatment, whereas intravenous immunoglobulin (IVIg) was employed only in a minority of cases (19, 20, 23). As for the prognosis, most patients experienced complete recovery, except for a few who developed vasculitis-associated gangrene or died due to COVID-19-related complications (12, 19, 20, 24).

### IgA vasculitis

IgA vasculitis is a form of small vessel vasculitis characterized by perivascular deposition of hypogalactosylated IgA1 and neutrophil activation, being the most common vasculitis in the pediatric age. Palpable non-thrombocytopenic purpura of lower extremities and buttocks is a characteristic sign of skin-limited IgA vasculitis (IgAV) and Henoch–Schonlein purpura (HSP) (26, 27). Hemorrhagic blisters, as well as targetoid lesions, have been suggested to occur more frequently in skin-limited IgA vasculitis (Supplementary Figure 1c) than cutaneous small vessel vasculitis with IgM/IgG deposits, i.e., LCV (5). Fifteen COVID-19-associated cases (12 males, 3 females), half of which were children, have been reported so far. Palpable purpura (13/15) as well as renal (8/15), gastrointestinal (8/15) and articular (3/15) involvement were documented. In 8 subjects, onset of vasculitis was simultaneous with the infection. All these patients received systemic CS. Biologics and immunosuppressants were administered only in 4 individuals due to concomitant renal impairment (1 rituximab, 2 mycophenolate mofetil, 1 cyclophosphamide), with a favorable response across published reports (28).

### Urticarial vasculitis

Urticarial vasculitis (UV) is a rare clinicopathological entity manifesting with indurated wheal-like lesions lasting more than 24 h (Supplementary Figure 1d) and usually leaving post-inflammatory hyperpigmented *sequelae* upon resolution (29). Although the cause of UV often remains unclear, trigger factors such as drugs, infections, autoimmune diseases, and

TABLE 1 Clinical and histopathological features of the main cutaneous vasculitides associated with COVID-19 and/or anti-SARS-CoV-2 vaccination.

| | Clinical features | Histopathological features |
|---|---|---|
| Cutaneous small-vessel vasculitis* | Palpable purpura, petechiae and/or hemorrhagic macules or (rarely) blisters. Occasionally, ulcerations can be observed. Lower extremities are commonly affected. Extracutaneous involvement is uncommon and usually mild. | Postcapillary venules are primarily affected, with endothelial swelling, a neutrophilic infiltrate with leukocytoclasia, red blood cell extravasation, and fibrinoid necrosis of blood vessel walls. Variable numbers of mononuclear cells and eosinophils may be detected. Intravascular thrombi and ischemic necrosis of the overlying epidermis may sometimes be observed. Evidence on direct immunofluorescence findings in both COVID-19- and vaccine-associated cases is inconclusive. |
| Skin-limited IgA vasculitis | Erythematous macules or papules evolving into palpable purpura predominantly on the lower limbs, thighs, and buttocks. Hemorrhagic bullae and targetoid lesions can also be observed. | A picture of leukocytoclastic vasculitis of small dermal blood vessels is usually seen (see above). Direct immunofluorescence demonstrates IgA deposition in vessel walls. Fibrinogen and C3 are usually present as well. |
| Urticarial vasculitis** | Erythematous, oedematous wheal-like lesions persisting more than 24 h, associated with non-blanchable purpura and resolving with hyperpigmented *sequelae*, most commonly on the trunk and proximal extremities. Burning, rather than itching is typically reported. | A picture of leukocytoclastic vasculitis of small dermal blood vessels is usually seen (see above). Lymphocytic perivascular cuffing without leukocytoclasia has also been reported in a proportion of patients. |
| Lymphocytic vasculitis | Maculo-papular erythemato-violaceous lesions with purpuric aspects located on lower and upper limbs. Chilblain-like appearance (i.e., "COVID toes"). | Lymphocytic perivascular cuffing of superficial and deep dermal small vessels, along with endothelial cell swelling. Dermal microthrombi may also be seen. |
| Pauci-immune thromboembolic vasculopathy*** | Necrotic lesions, retiform purpura, finger or toe cyanosis, gangrene, blisters or livedoid rash. | Epidermal necrosis. Thrombotic vasculopathy of small and medium vessels in superficial and deep dermis, with sweat gland necrosis, little-to-absent inflammatory infiltrate but complement deposition in vessel walls. |

IgA, immunoglobulin A; C3, complement component 3.
*Most common form in both COVID-19- and vaccine-associated settings.
**Mostly normocomplementemic.
***Associated with severe COVID-19 exclusively.

malignancy have been described (30, 31). Though rare, UV has been described in either symptomatic or asymptomatic COVID-19 patients (32–34). Interestingly, its onset has also been reported a few weeks following recovery from COVID-19 (35). Antihistamines alone or in combination with oral CS were administered in all the subjects (32–35).

## Other vasculitides associated with COVID-19

Anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) can sometimes mimic COVID-19 in terms of pulmonary involvement and COVID-19 may occur simultaneously with AAV. (36). Six patients, 4 of whom were males, were diagnosed with AAV simultaneously or shortly after COVID-19. Three had serum antibodies directed against myeloperoxidase (anti-MPO), while the others had anti-proteinase 3 (anti-PR3) antibody positivity. Fever, respiratory and gastrointestinal symptoms were reported. All patients survived after adequate treatment with immunosuppressive medications (37).

## COVID-19-associated cutaneous vasculitides in the pediatric age

According to a recent systematic review by Batu et al., which gathered 36 pediatric patients, the median age of onset of vasculitis was 13 years, with a male predominance (M/F: 2.3). The median time from infection to onset of vasculitis was 17.5 days (range: 2–150). Among those with potential skin involvement, the most frequently reported in that pediatric age included IgAV/HSP (25%) chilblains (19.4%), UV (5.5%), cutaneous leukocytoclastic vasculitis (2.7%), and acute hemorrhagic edema of infancy (AHEI, 2.7%) (38).

Kawasaki disease (KD) is an acute systemic vasculitic syndrome primarily affecting children below the age of 5, that involves small and medium-sized vessels with a predilection for coronary arteries (39). As SARS-CoV-2 infection can lead to

endothelial inflammation and dysfunction, it can also trigger the development of KD in certain individuals (40). Moreover, older children (median age of 8 years) can be affected by a similarly severe inflammatory disorder with multisystem involvement (MIS-C), also known as Pediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV-2 (PIMS-TS) (41). MIS-C is mainly characterized by systemic vasculitis, mucocutaneous inflammatory signs (rash), multisystem involvement, and hypercoagulation, although thrombotic or embolic events were rare, when compared with adult COVID-19 (42). Although it may present a clinical overlap with KD or toxic shock syndrome, it is regarded as a separate entity (43).

## Pathophysiology of COVID-19-associated vasculopathy and vasculitis

Distinct pathomechanisms have been implicated in the genesis of the above-mentioned COVID-19-associated cutaneous findings, depending on the presence/absence of a robust type I interferon signature: (i) transient, true vasculitis in mild cases (e.g., COVID-toes) and (ii) small vessel thromboembolic disease, without true vasculitis (i.e., vasculopathy) in patients with severe disease. A number of other forms may be placed between the two ends of this spectrum (44).

In greater detail, vasculitic changes with lymphocytic perivascular cuffing and infiltration, possibly leading to secondary luminal thrombosis, result from type I interferon responses, akin to familial chilblain lupus or STING-associated vasculopathy with onset in infancy (45, 46).

In contrast, dysfunction of vascular endothelium due to the SARS-CoV-2 infection has been suggested in the pathogenesis of the COVID-19 vasculopathy (47). Initially, it was speculated that endothelial injury was due to direct viral infection (48), but recent evidence demonstrated that endothelial cells present low Angiotensin Converting Enzyme 2 (ACE2) expression and are resistant to SARS-CoV-2 infection, supporting the involvement of an indirect mechanism of endothelial injury in the pathogenesis of COVID-19 vasculopathy (47, 48). This is best exemplified by patient with severe COVID-19 pneumonia. In the lungs, when respiratory and alveolar epithelial cells get infected by SARS-CoV-2 in the setting of defective antiviral interferon signaling, an exacerbated innate inflammatory loop is induced with elevation of Interleukin (IL)-1β, IL-6 and Tumor Necrosis Factor (TNF)α. The subsequent release of several proinflammatory cytokines/chemokines at a systemic level, together with secondary complement activation due to ischemia, leads to indirect endothelial cell injury through loss of their antithrombogenic properties and barrier function (49). This process, known as pulmonary immunothrombosis, possibly followed by pulmonary venous microembolism, may account for the clinico-pathological picture observed in severe COVID-19 cases, with pauci-immune thrombogenic vasculopathy and terminal complement activation in vessel walls (50), but only sporadic SARS-CoV-2 spike protein deposition (44).

Increased levels of galactose deficient IgA1 (gd-IgA1) are necessary for the development of IgA nephritis, with a multi-hit model involving IgA1 and anti-endothelial cell antibodies currently accepted to explain its vasculitic, extrarenal manifestations. Mucosal infections, such as COVID-19, are believed to enhance IL-6 production thereby stimulating poor glycosylation/galactosylation of IgA1 in predisposed subjects. The subsequent formation gd-IgA1 may contribute toward the disease process of IgA vasculitis in a proportion of COVID-19 patients (51).

A humoral response against SARS-CoV-2 antigens, leading to immune-complex formation, could underscore cases of COVID-19-associated urticarial vasculitis and leukocytoclastic vasculitis (52). Indeed, SARS-CoV-2 antigens have been detected in skin biopsies from two UV patients with COVID-19, supporting the existence of a causal link (33). Consistent with a type III hypersensitivity response, circulating immune complexes could act as triggers for classic complement pathway activation, thus promoting neutrophil recruitment, vascular leakage and subsequent vessel wall injury and inflammation (52).

It is noteworthy that anti-phosphatidylserine/prothrombin complex antibodies have been implicated in models of cutaneous vasculitis (53) and that anti-prothrombin antibodies increase after infection with SARS-CoV-2 (54).

Concerning ANCA-associated vasculitides, NETs overproduction has been described during COVID-19. Prolonged exposure of NETs to proteins as well as their reduced clearance may be key in explaining the onset of ANCA autoimmunity in predisposed subjects infected by SARS-CoV-2 (36).

Main proposed pathomechanisms are summarized in Figure 1.

# Anti-SARS-CoV-2 vaccination-induced cutaneous vasculitis

Vasculitides and other vascular affections have also been reported following anti-SARS-CoV-2 vaccination (55).

## Cutaneous small-vessel vasculitis

Skin-limited small vessel vasculitis or LCV (56) represents the most common CV reported after anti-SARS-CoV-2 vaccination. It has been observed after the Pfizer-BioNTech mRNA vaccine (BNT16B2b2) (57–65). Moderna mRNA

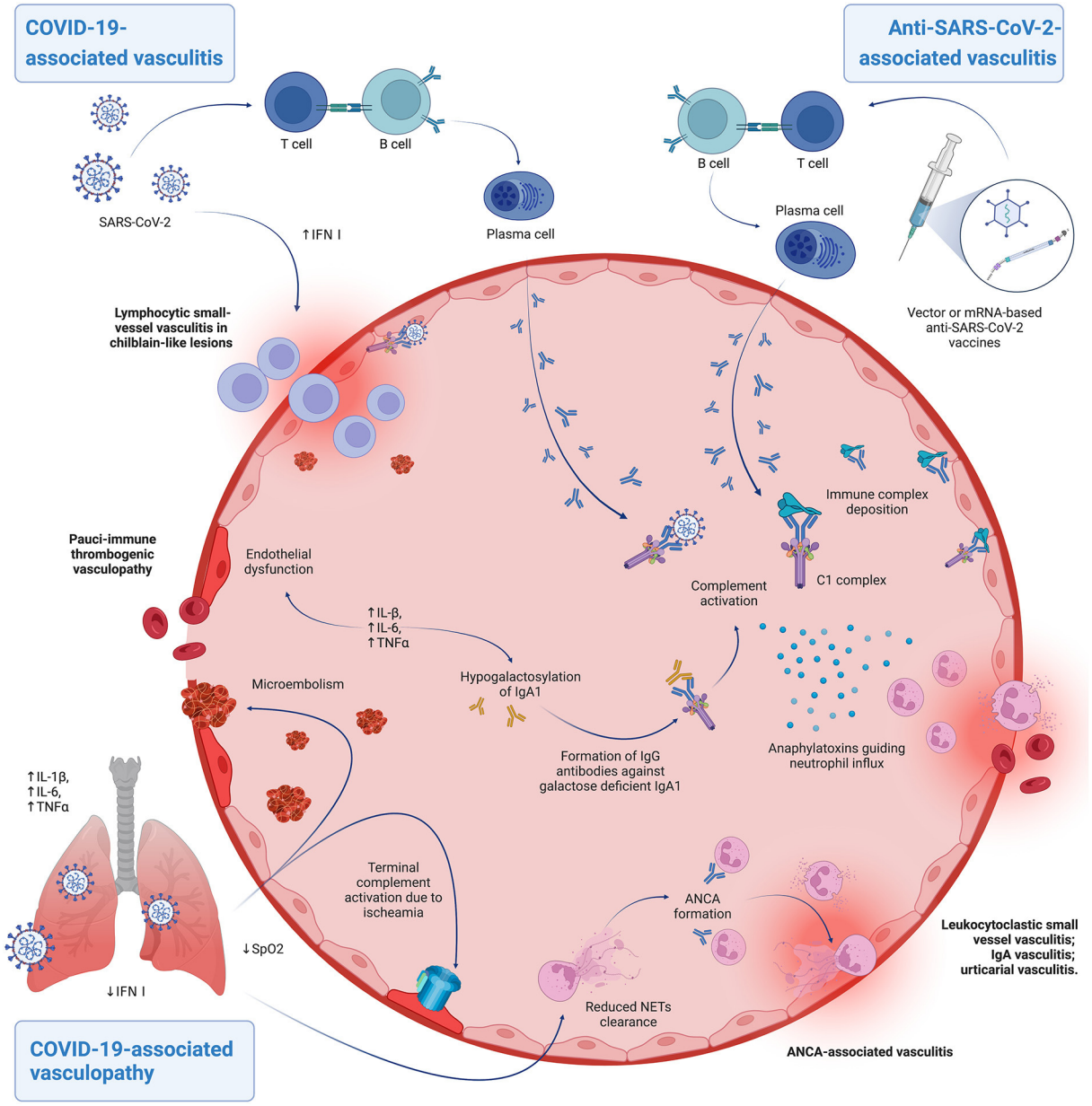


FIGURE 1
Hypothesized pathomechanisms of COVID-19-associated vasculitis/vasculopathy and anti-SARS-CoV-2-vaccine associated vasculitis. Patients able to mount a robust type I interferon response can develop lymphocytic perivascular cuffing during infection, leading to chilblain-like lesions. The virus can also cause immune complex deposition, with subsequent complement activation and neutrophil recruitment, determining the clinicopathological picture of leukocytoclastic vasculitis. A similar process, possibly with anaphylatoxins inducing exaggerated mastocyte activation, is thought to underscore cases of urticarial vasculitis. Both these forms can occur also in vaccine-related cases. Patients that develop severe COVID-19 due to a defective antiviral response may experience indirect endothelial injury, due to elevated proinflammatory cytokines at a systemic level and ischaemia-induced complement activation. This process is known as pulmonary immunothrombosis and may be complicated by pulmonary venous embolism. Speculatively, the inflammatory *milieu* brought about by the infection can lead to other forms of cutaneous vasculitides. Elevated IL-6 levels may contribute to hypogalactosylation of IgA1 in predisposed individuals triggering an IgG-mediated response that may result in IgA vasculis. Prolonged exposure and reduced clearance of Neutrophil Extracellular Traps (NETs) in the context of COVID-19 dysregulated inflammatory responses may set the basis for ANCA-associated autoimmunity and vasculitis. Created with BioRender.com.

vaccine (mRNA-1273) (66–68). Oxford-AstraZeneca adenoviral vaccine (ChAdOx1 nCoV-19 AZD1222) (69–79). Johnson & Johnson adenoviral vaccine (Ad26.COV2.S) (80–82), and inactivated vaccines [Sinovac CoronaVac (83), Bharat

Biotech Covaxin (84), Sinopharm BBiBP-CorV] (85, 86) (Supplementary Table 2).

Almost every case was biopsy-confirmed. Notably, some of these cases were reported as "immunocomplex vasculitides" (65–68). Some patients experienced systemic symptoms such as joint pain (64, 70, 73, 80, 84), and microhematuria (79, 80). In one patient, gastrointestinal involvement with melena and diarrhea was reported (65). In some cases, cryoglobulins were detected on serological analysis (82, 87); notably, the case by Nastro et al. also featured a concomitant atypical herpes zoster of the right leg (59). Among reviewed cases, one had history of SARS-CoV-2 infection (78) and one had a previous diagnosis of leukocytoclastic vasculitis (58).

Treatment was generally represented by oral CS and antihistamines (local corticosteroids, non-steroid anti-inflammatory drugs (NSAIDs), colchicine, antibiotics, analgesics, pentoxifylline, dapsone were also prescribed in a minority of cases). Spontaneous remission was occasionally reported. All patient recovered in 1–8 weeks, except for one individual who developed COVID-19 20 days after vaccination with Oxford-Astrazeneca ChAdOx1 nCoV-19 vaccine (78). This patient presented with cough, myalgia, and fatigue, and developed progressive skin manifestations, including urticarial and purpuric lesions over her upper and lower extremities and abdomen. After 9 days, she developed multiorgan failure and died. In this case it is likely that the SARS-CoV-2 infection rather than the vaccination could have acted as trigger of the vasculitis (78).

## IgA vasculitis

IgA vasculitis (88) has been observed after vaccination with Pfizer-BioNTech mRNA vaccine (BNT16B2b2) (57, 89–93), Moderna mRNA vaccine (mRNA-1273) (94, 95), Oxford-AstraZeneca adenoviral vaccine (ChAdOx1 nCoV-19 AZD1222) (96–98), and Sinovac inactivated vaccine (CoronaVac) (99) (Supplementary Table 3). Of note, histology was not available in all cases. Some patients also experienced systemic symptoms such as joint (93, 96–98) or abdominal pain (94), hematuria or renal impairment (90, 94, 96). Treatment of choice was generally represented by oral CS, but spontaneous remission was also occasionally reported. All patients recovered in several weeks. Interestingly, of the reviewed cases, two had history of SARS-CoV-2 infection (97, 99); three had history of previous IgA vasculitis (90, 94) or Henoch-Schönlein purpura (92).

## Lymphocytic vasculitis

Lymphocytic vasculitis is a histologic reaction pattern with a dominant lymphocytic inflammatory infiltrate (100). Reported cases of lymphocytic vasculitis followed the inoculation of Pfizer-BioNTech mRNA vaccine (BNT16B2b2) (101), Oxford-AstraZeneca adenoviral vaccine (ChAdOx1 nCoV-19 AZD1222) (102), inactivated vaccine Bharat Biotech Covaxin (103) and mRNA-1273 Moderna vaccine (104) (Supplementary Table 4).

Treatment of choice was generally represented by oral antihistamines or local CS (one case was managed with follow up only). All patients fully recovered in 2 weeks. Notably, one of the patients had SARS-CoV-2 infection before vaccination (101).

## Urticarial vasculitis

Cases of UV were reported after Moderna mRNA vaccine (mRNA-1273) (99, 105), Oxford-AstraZeneca adenoviral vaccine (ChAdOx1 nCoV-19 AZD1222) (106), and inactivated vaccine Sinovac CoronaVac (107) (Supplementary Table 5). Treatment of choice was generally represented by oral corticosteroids, but oral antihistamines, dapsone and indomethacin were also used. All patient fully recovered in 1–8 weeks, this being in line with the expected course of drug-induced UV (31).

## Other vasculitides: ANCA-associated vasculitis and other forms

Only one case of AAV presenting with cutaneous involvement has been reported following anti-SARS-CoV-2 vaccination (Pfizer-BioNTech mRNA vaccine) (BNT16B2b2) (108). Interestingly, the patient had been taking propylthiouracil for Graves' disease and therefore her condition was identified as a propylthiouracil-induced ANCA-associated vasculitis. In this case, the treatment of choice was represented by oral corticosteroids and the patient recovered after 3 weeks. Of note, there are case reports of AAV with systemic involvement and absence of cutaneous features, triggered by anti-SARS-CoV2 vaccination (80, 109).

Among the unclassifiable forms, we also describe the peculiar vasculitis reported by Nasr et al. The 64-year-old female patient had history of Raynaud's disease, hand arthritis, photosensitivity, Sjogren's syndrome and leukocytoclastic vasculitis; 3 days after receiving the first dose of Pfizer–BioNTech mRNA vaccine she developed fingertip necrosis (caused by a type II cryoglobulinemia) and a new episode of purpuric rash on the lower extremities (likely leukocytoclastic vasculitis). The workup revealed cryoglobulinemia, hypocomplementemia, elevated antinuclear antibodies and IgM antiphospholipid autoantibodies, suggesting a diagnosis of systemic lupus erythematosus and antiphospholipid syndrome (110).

Lastly, multisystem inflammatory syndrome (MIS) after vaccination deserves a brief mention. MIS has been associated with SARS-CoV-2 infection, has a latency of 4–6 weeks, and can

be ultimately described as a vasculopathy clinically resembling Kawasaki disease and potentially leading to acute cardiac dysfunction and multiorgan failure (111, 112). It usually occurs in children (MIS-C), but adult forms are also reported (MIS-A) (112). Interestingly, very rare cases of MIS are reported in absence of viral infection, after anti-SARS-CoV-2 vaccination (MIS-V) (113). In children, MIS-V had a frequency of 1.5 cases per million of injected doses, with patients aged 12–20 years, presenting with fever, coagulopathy, mucocutaneous, cardiac, gastrointestinal, and renal involvement. They were treated with systemic CS and/or IGIV and had a favorable outcome (111, 114). Similarly, adult MIS-V forms are also reported, with comparable course, treatment, and outcome (112, 115–118) (Supplementary Table 6).

### Pathophysiology of anti-SARS-CoV-2-vaccine-associated vasculopathy and vasculitis

Immune-complex deposition with ensuing complement activation is currently regarded as the plausible pathophysiology for most anti-SARS-CoV-2-vaccination-associated cutaneous vasculitides (119). SARS-CoV-2 vaccine components sharing structural similarities to host proteins may promote a pro-inflammatory state followed by the activation of autoreactive B/T cells, antibody formation, and subsequent immune complex deposition in the small vessels of the skin with potential involvement of internal organs as well (120). Molecular mimicry phenomena may also have a role. An unrelated antigen or an underlying genetic predisposition unmasked, due to the vaccine's immune enhancing properties, should be considered as well.

## Conclusions

In conclusion, we reviewed available evidence on COVID-19-associated and anti-SARS-CoV-2-vaccine-associated CV, showing superimposable findings with pre-pandemic cases.

Although IgA immune deposits were prevalent, lack of reporting of immunofluorescence findings in most papers hinders a thorough analysis of above-mentioned cases and calls for further studies, as the very nature of immune deposits in the non-COVID-19/COVID-19-vaccine-associated setting is still debated (5).

Patients referred for purpuric lesions often pose a challenge to dermatologists and many algorithms have been proposed to simplify their differential diagnosis and thereby stratify their prognosis (121). Signs of retiform (i.e., branched) purpura at acral sites or generalized, particularly, have been suggested to portend poor prognosis in patients with complex purpura (121) and, though they may be lacking validation in this specific scenario, they could pose as a useful clue also in COVID-19 patients, to promptly recognize those at a higher risk of immunothrombotic vasculopathy.

Adequately assessing the causal link on an individual case basis along with thorough patient counseling should aim to minimize vaccine hesitancy, as seen in other vaccine-associated dermatological conditions (122).

Despite the wealth of clinical evidence available concerning COVID-19-associated and anti-SARS-CoV-2-vaccine-associated cutaneous vasculitis and vasculopathy, there is a paucity of studies addressing the pathophysiology of these manifestations. Further research is therefore needed to inform pathogenesis-driven treatment.

## Author contributions

EZ, GA, CM, MR, and CAM reviewed the pertaining literature and wrote the manuscript. AM, SR, and PQ supervised the draft. CAM and AM edited and approved the final draft. All authors have made substantial contribution to the work and have approved the final version of this article.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.996288/full#supplementary-material

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# Cutaneous vasculitis; An algorithmic approach to diagnosis

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Vasculitides, characterized by inflammation and damage of blood vessels, encompass a broad spectrum of diseases. They can occur with different pathophysiological mechanisms and have a rich clinical heterogeneity depending on the vessel diameters they affect. Vasculitides may also present with a broad spectrum of severity, ranging from a mild self-limiting to a potentially life-threatening disease. The high prevalence of skin involvement in vasculitis, visible character and, finally, the easy accessibility of the skin for both physical examination and biopsy offers important advantages for prompt disease recognition and diagnosis. Thus, dermatologists are privileged to diagnose the disease earlier and more effectively than any other discipline. As a consequence, a detailed clinical and histopathological evaluation of the skin is one of the most critical steps in diagnosing vasculitis. Besides obtaining a good medical history, laboratory and radiological evaluation methods are used in the diagnosis. In this review, a practical and algorithmic approach is aimed to assist in the diagnosis of vasculitis. However, this approach should not be seen as strict rules. This stepwise algorithmic diagnostic approach for vasculitis was developed by combining the current literature knowledge and the author's experience in this field to provide a rational framework for selecting the most appropriate among various diagnostic approaches.

KEYWORDS

**vasculitis, leukocytoclastic, cutaneous, algorithms, IgA vasculitis**

## Introduction

Vasculitis refers to a broad and heterogeneous disease spectrum characterized by inflammation and damage of the blood vessel. It may occur in any organ of the body. When skin vessels are affected, the term cutaneous vasculitis is used. In systemic vasculitis, blood vessels of at least one organ are affected in addition to the skin. Of note, besides being a component of systemic vasculitis, including the skin, cutaneous vasculitis can be a skin-limited or skin-dominant expression or variant of systemic vasculitis. Finally, it may be a single-organ vasculitis of the skin (1). The skin is one of the most frequently affected organs in vasculitis, and small-vessel vasculitis of the skin is the most common vasculitis dermatologists encounter in their clinical practice (2). While the disease affects both genders equally, its frequency increases with age at diagnosis.

Cutaneous vasculitis may present at any age, but it is more common in adults than children. The clinical course of the disease is usually self-limiting in children, and IgA vasculitis is the most common vasculitis in this age group. Idiopathic etiology is more prominent in adults and infectious etiology in children. Compared with children, underlying systemic vasculitis, connective tissue disease, or malignancy are more common in adult patients (3, 4).

The skin is a visible and easily accessible organ for physical examination and biopsy, providing significant advantages over other organs' vasculitides in diagnosing vasculitis. Accurate identification of cutaneous lesions and a good histopathological examination with biopsy that can be easily and safely taken from the skin can provide precious information for the recognition and diagnosis (5). This review overviews the current literature knowledge regarding the diagnosis of vasculitis by combining the author's experience in this field and proposes a stepwise algorithmic diagnostic approach to enable clinicians to rationalize the selection of the most appropriate diagnostic approach.

## Clinical presentation

Vasculitis may occur with different pathophysiological mechanisms and may cause different clinics depending on the vessel's diameter (1, 2, 5). In addition, some vasculitis patients with initially non-severe mild symptoms and limited organ involvement may progress in severity over several days to weeks, affecting multiple organs. In summary, patients with vasculitis may present with a broad spectrum of severity ranging from a mild self-limiting disease to a potentially life-threatening one (6).

Physicians should carefully consider some critical steps in clinical practice when diagnosing vasculitis. First, skin manifestations should be morphologically and histologically compatible with vasculitis. Then, the underlying etiological cause/s should be investigated. For this purpose, a good medical history, possible triggering factors, especially recently introduced drugs and recent infections, should be questioned in detail, and finally, extracutaneous involvement should be evaluated (2, 5).

How does vasculitis suspicion begin in the clinic? The first question to be answered in the clinical examination is whether the lesions are compatible with vasculitis. Palpable purpura is the main dermatological finding of small-vessel vasculitis. The suspicion of vasculitis increases if the palpable purpura is symmetrically located on the lower extremities. Purpura often develops in groups and may be accompanied by pain, burning, and itching (2, 6). Although palpable purpura is the most critical elementary lesion in the vasculitis spectrum, a wide range of elementary lesions can be obtained. Other skin findings of vasculitis include urticarial papules, plaques, nodules, vesicles, bullae, pustules, ulcers, and target-like lesions (5, 7). There is almost no disease-specific primary lesion or organ involvement (7).

The clinical appearance in patients with vasculitis is closely related to the diameter of the involved vessel. For this reason, vasculitis is classified according to the vessel diameter. Ulcers, nodules, pitted scars, white atrophy and livedo racemosa indicate the deep plexus, and medium-sized vessel involvement at the dermohypodermal junction. On the other hand, edematous papule, plaque, and palpable or non-palpable purpura occur due to the involvement of small vessels within the superficial or subpapillary plexus (5, 7). It should be kept in mind that a proper clinical examination may help limit the diagnosis to a specific area by eliminating many diseases within the vasculitis spectrum.

## Skin biopsy: Number, timing, depth, and location

When the suspicion of vasculitis occurs, the first step should be to confirm the diagnosis by skin biopsy. Histopathology is the "gold standard" for the diagnosis of cutaneous vasculitis. An appropriate sampling of skin biopsy is crucial to increase its diagnostic value. In this sense, **one** of the first questions to be considered is the number of skin samples biopsied. Two separate skin biopsies are recommended. In addition to the skin biopsy for routine evaluation with a light microscope, taking a second skin biopsy for direct immunofluorescence (DIF) is also recommended. Vasculitis is a dynamic process, and the inflammatory infiltrates change over time. Therefore, the timing of the skin biopsy is also critical. Typical histopathological changes for vasculitis develop 24–48 h after the appearance of lesions. Biopsy should be performed at the appropriate depth. Deep punch biopsy or excisional biopsy reaching the subcutis is recommended. As a result, small- and medium-sized vessel vasculitides of the skin can only be evaluated with an appropriate biopsy (2, 6).

Identifying the most appropriate area for the skin biopsy is another critical step in diagnosing vasculitis. Lesional skin should be preferred. Biopsy should be performed from purpuric papules for a light microscope and from a blanchable macule for DIF to detect immunoglobulin deposition in the vascular wall. Diascopy helps select the appropriate lesion for biopsy. Blanchable areas by diascopy show inflammation (erythema), while non-blanchable areas correspond to purpura (erythrocyte extravasation). It should be kept in mind that negative DIF results may be obtained in lesions older than 48 hours due to the rapid destruction of immune accumulations. Therefore, the diagnosis of vasculitis should not be based solely on positive or negative DIF findings. Instead, it should be interpreted together with history, clinical, histopathological, and other laboratory findings (2, 5, 7).

When histopathology is consistent with vasculitis, leukocytoclastic vasculitis is the most commonly observed histopathological appearance. It is distinguished by neutrophilic infiltration of the vessel walls, nuclear dust, fibrinoid degeneration, endothelial edema, and erythrocyte extravasation around postcapillary venules. In older lesions, neutrophils decrease, and mononuclear cells, particularly lymphocytes, predominate. Notably, granulomatous vasculitis was reported more frequently with systemic vasculitis, especially in lymphoproliferative diseases (8). On the other hand, lymphocytic vasculitis is more common in connective tissue diseases, viral infections and drug eruptions (2).

## Etiological examination

The following step after the diagnosis of vasculitis should be the investigation of etiological causes. According to the current literature, the etiologic factor cannot be detected in approximately half of the vasculitis cases (idiopathic etiology; 45–55%). Infection, especially streptococcus pyogenes, Hepatitis B and C virus, and HIV can be detected in 15–20% of cases (2, 9, 10). Although mostly limited to isolated reports, COVID-19-associated and anti-SARS-CoV-2-vaccine-associated cutaneous vasculitis has been reported during the pandemic (11, 12). Inflammatory diseases (inflammatory bowel diseases, cryoglobulinemia type 2 and 3, antineutrophilic cytoplasmic antibody (ANCA)-related vasculitis and Behçet's disease) and connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis, sjögren syndrome) are the etiologic factors in 15–20% of the cases. Drugs (β-lactam antibiotics, sulfa preparations, minocycline, non-steroidal anti-inflammatory drugs, granulocyte-macrophage colony-stimulating factor, propylthiouracil, tumor necrosis factor (TNF)-alpha inhibitors, levamisole loaded cocaine, etc.) in ∼10–15% of cases, and malignancy in 5% of cases (hematologic malignancies, solid organ cancers, etc.,) play a role in the development of vasculitis (2, 9, 10).

All patients with vasculitis are evaluated as a laboratory to detect the underlying cause and possible systemic involvement. There is no agreement on a standard screening protocol yet. Nevertheless, the primary goal should be to identify the underlying cause and severity of organ/s involvement based on clinical signs and symptoms. All patients with suspected vasculitis should be evaluated for complete blood count, creatinine, sedimentation rate, liver function tests, urinalysis, and chest X-ray. If the patient has symptoms such as fever, weight loss, fatigue, arthralgia, myalgia, hematuria, abdominal pain, blood in the stool, numbness, paresthesia, neuralgia, dyspnea, chest pain, cough, hemoptysis, sinusitis, more detailed examinations are required. A detailed etiological investigation is also conducted in patients with chronic and recurrent vasculitis whose etiology cannot be determined in previous episodes of vasculitis. In addition to the above, more extensive tests including ASO, throat culture, CRP, HBV, HCV, ANA, Anti-ds DNA, Anti Ro, Anti-La antibodies, RF, CCP, HIV, C3, C4, ANCA, cryoglobulin, immune electrophoresis, peripheral smear, chest X-ray, fecal occult blood, etc. should be performed (2, 7).

## Stepwise algorithmic approach in the diagnosis of cutaneous vasculitis

Medical history, clinical, histopathological, radiological, and other laboratory evaluations are used to diagnose vasculitis. It is challenging to develop a stepwise algorithmic diagnostic approach for all vasculitis. The algorithmic approach given here is intended to aid in the diagnosis. However, this approach should not be considered as strict rules to be followed. The following algorithmic diagnostic approach was developed by combining the current literature knowledge and the author's experience in this field. It should be kept in mind that vasculitis, which initially seems limited to the skin, may also develop systemic involvement over time. Stepwise, algorithmic diagnosis of vasculitis is summarized in Figure 1.

In ANCA negative cases, if cryoglobulin 2 or 3 are positive in DIF and clinically palpable purpura, Raynaud's phenomenon, and acrocyanosis are present, cryoglobulinemic vasculitis should be considered in the first place. Types 2 and 3 cryoglobulins are called mixed cryoglobulinemia and may be associated with B-cell lymphoproliferative diseases, autoimmune diseases, and infection. It can affect the peripheral nerves and kidneys as well as the skin. Type 1 causes Reynaud's phenomenon with vascular occlusion, ulcers, pain and oedema in the extremities, or hyperviscosity syndrome (1).

With hypergammaglobulinemia, if there are recurrent and short-term hemorrhagic macules occurring mainly on the lower extremities and dorsum of the feet, recurrent macular vasculitis should be the diagnosis. Polyclonal hypergammaglobulinemia, primarily composed of IgG, is the hallmark of the disease. It usually has a good prognosis; however, sometimes, it can be a sign of underlying connective tissue disease or hematological malignancy (13).

In the presence of IgA deposition in DIF and clinically round or oval and retiform palpable purpura, sometimes accompanied by hemorrhagic vesicle/bulla, on the lower extremities, especially in a school-age child, IgA vasculitis should be considered. The other main clinical symptoms are arthritis, gastrointestinal bleeding or pain, and glomerulonephritis with mesangial IgA deposits (14). IgA vasculitis is more severe in adults. While joint and gastrointestinal involvement is more common in younger patients, severe purpura and glomerulonephritis are more common in older patients (15). IgA vasculitis is the most common vasculitis of childhood. It constitutes approximately 10% of cutaneous vasculitides (16, 17).

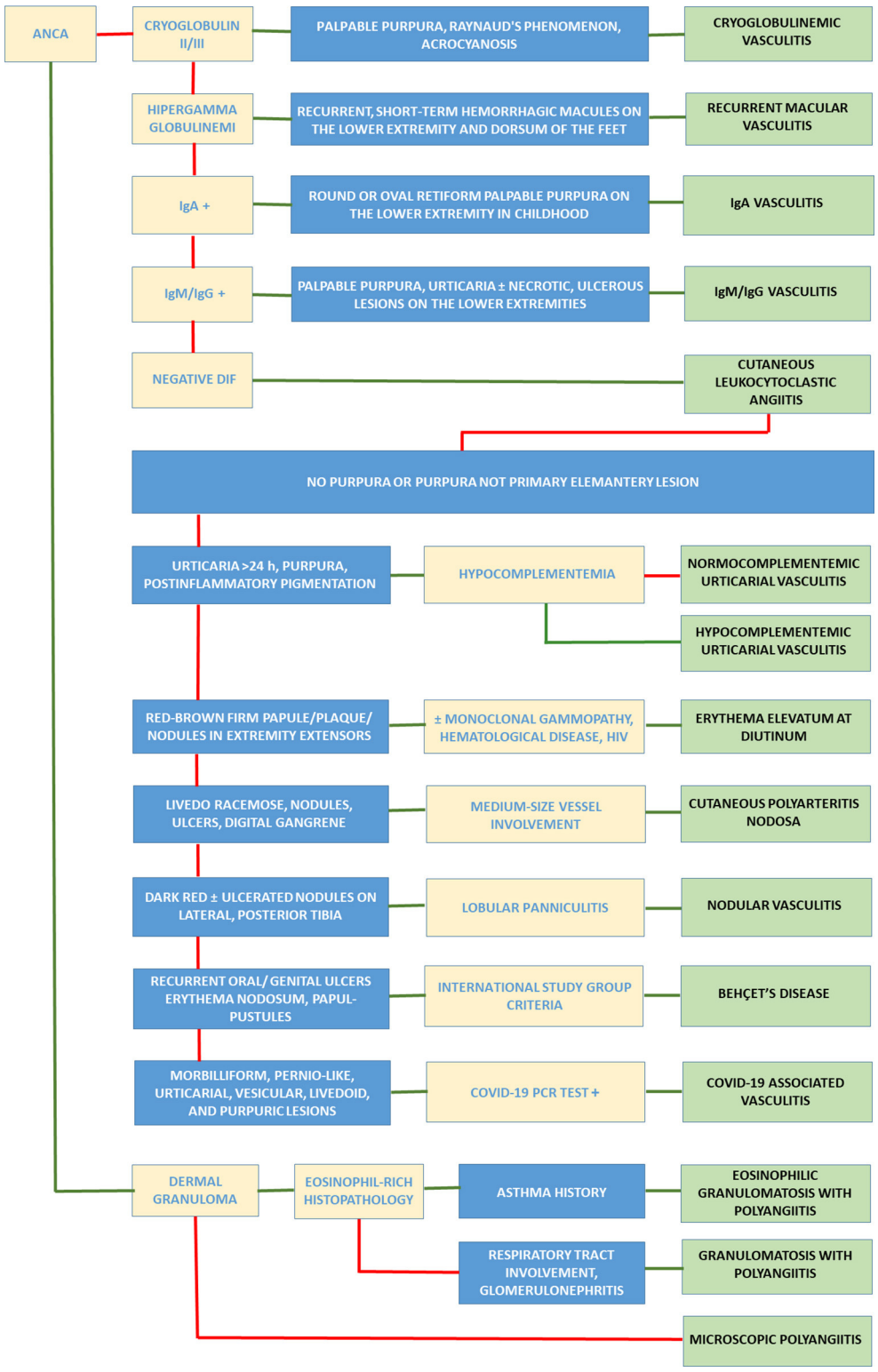


FIGURE 1
Stepwise, algorithmic diagnosis of vasculitis. In the flowchart, all disease diagnoses are placed one under the other in the far right column. Algorithms start from the boxes in the upper left corner. The green arrow means "yes", and the red arrow means "no". ANCA, antineutrophilic cytoplasmic antibody; Ig, Immunoglobulin; DIF, direct immunofluorescence.

Similarly, the diagnosis of IgM/G vasculitis is achieved in patients who show IgM/G deposition instead of IgA deposition in DIF with a similar clinical presentation with palpable purpura, urticaria and sometimes necrotic/ulcerous lesions symmetrically located on the lower extremities (18).

If there is no immunoreacting in the vessel wall, and there are clinical and light microscopic findings similar to IgA vasculitis, the diagnosis of cutaneous leukocytoclastic angiitis is achieved. It is an isolated cutaneous vasculitis characterized by the involvement of post-capillary venules without systemic involvement. Thus, cutaneous leukocytoclastic angiitis is a diagnosis of exclusion. However, some systemic vasculitides (IgA vasculitis, granulomatosis with polyangiitis**,** microscopic polyangiitis) may initially present as cutaneous leukocytoclastic angiitis (17).

If the primary lesion is not purpura or the patient does not have purpura, the diseases summarized below should be considered first.

When urticarial papules and plaques persisting for more than 24–48 h are accompanied by purpura and postinflammatory hyperpigmentation, urticarial vasculitis should be considered. In these patients, when the complement level is within the normal range, the diagnosis is normocomplementemic vasculitis, and when the complement level is low, the diagnosis is hypocomplementemic vasculitis. While normocomplementemic urticarial vasculitis is often idiopathic, hypocomplementemic urticarial vasculitis represents systemic vasculitis, with various manifestations, mainly musculoskeletal (e.g., SLE, primary Sjögren's syndrome) and ocular involvement associated with anti-C1q antibodies (5, 19).

In the presence of red-brown firm papules, plaques and nodules on the extensor surfaces of the fingers, hands, elbows, ankles, and knees, erythema elevatum at diutinum are considered. It should be kept in mind that monoclonal gammopathy, hematological disease, and HIV may accompany these conditions (6, 20).

If the primary clinical lesions are livedo, especially livedo racemose, nodules, ulcers, digital gangrene in the absence of systemic involvement, and histopathologically medium-sized vessels in addition to small-sized vessels are involved, cutaneous polyarteritis nodosa should be considered. The lower extremities are frequently involved. Atrophy Blanche, Raynaud's phenomenon, plaques surrounded by inflammatory papulonodules may accompany (1, 6). Deficiency of Adenosine deaminase 2 (DADA2) is the first molecularly described monogenic vasculitis syndrome, caused by mutations in ADA2 gene, which encodes an extracellular enzyme acting as a monocyte differentiation factor. DADA2 has been defined as a clinical picture resembling polyarteritis nodosa, including livedo racemose, recurrent fever, and musculoskeletal complaints (21). Therefore, it can be considered in the differential diagnosis of cutaneous polyarteritis nodosa in selected cases.

If there are recurrent, dark red-violet, sometimes ulcerated nodules on the lateral and posterior surfaces of the tibia and lobular panniculitis are seen in light microscope examination, nodular vasculitis should be considered first. Nodular vasculitis may develop as an id reaction due to hypersensitivity to M. Tuberculosis, especially in endemic areas. In this case, it is called "erythema induratum bazin" (1).

Behçet's disease should be considered first in patients presenting with recurrent oral and genital ulcerations, erythema nodosum-like lesions and papulopustular lesions. Pustular lesions with a purpuric rim (pustular vasculitis) and superficial thrombophlebitis can be seen in the course of the disease (22). International Study Group criteria are the most widely used diagnostic criteria in diagnosis (23).

The cutaneous manifestations of Coronavirus disease 2019 (COVID-19) are significantly varied and include morbilliform, pernio-like, urticarial, vesicular, livedoid, and purpuric lesions. COVID-19-associated vasculitis most commonly presents as cutaneous small vessel vasculitis. However, its prevalence is lower (1.8%) than other dermatological manifestations. The clinical presentation ranges from classic, bilaterally symmetrical palpable purpura preferring the lower extremities to vesiculobullous, hemorrhagic, urticarial, or targetoid eruptions (24, 25). Therefore, in the presence of morbilliform, pernio-like, urticarial, vesicular, livedoid, and purpuric lesions together with COVID-19 PCR test positivity, COVID-19-associated vasculitis should be considered.

In ANCA-positive vasculitis, histopathology can be in the form of leukocytoclastic vasculitis, vasculitis of small arteries and arterioles, or granulomatous inflammation without vasculitis. Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss Syndrome) should be considered first if there is a history of asthma with eosinophil-rich histopathology in addition to granulomatous inflammation. Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) should be considered in the presence of granulomatous inflammation without vasculitis in histopathology and upper and lower respiratory tract involvement and rapidly progressing glomerulonephritis. When these two diseases are excluded, the diagnosis should be microscopic polyangiitis (MPA) (17)**.** In a large cohort including 1,184 patients with ANCA-associated vasculitides, cutaneous involvement were found more frequently in those with EGPA (47%) compared to GPA (34%) and MPA (28%). Petechiae/purpura (15%) in all types of ANCA-associated vasculitides was the most frequently reported skin manifestation, followed by painful skin lesions (8%) and maculopapular rash (8%). Allergic and nonspecific manifestations such as pruritus, urticaria, and maculopapular rash were significantly more common in EGPA patients than in GPA and MPA patients. Livedo reticularis and livedo racemosa were reported more frequently in MPA patients. Systemic involvement was more pronounced in patients with skin lesions,

especially those with GPA and EGPA, than those without skin manifestations (26).

## Limitations and strengths

The presented algorithmic diagnostic approach reflects a standardized diagnostic approach limited to the author's knowledge and experience in this field and is not consensus-based. Moreover, evidence that the use of the diagnostic algorithm presented here improves patient outcomes is lacking. On the contrary, this diagnostic algorithm can be beneficial by highlighting the diagnostic steps and diseases not being immediately considered in clinical practice.

## Conclusions

Dermatologists are in a privileged position in the recognition and early diagnosis of cutaneous vasculitis because of the high prevalence of cutaneous involvement in vasculitis and the easy accessibility of the skin. In addition, the presence and/or spectrum of skin lesions can also be a predictive sign for diseases associated with severe systemic manifestations. Any type of skin lesions resembling vasculitis, including palpable or non-palpable purpura, edematous papule, plaque, ulcers, nodules, pitted scars, white atrophy, livedo racemosa, requires a skin biopsy which is the gold standard for the diagnosis of cutaneous vasculitis.

## Author contributions

Writing, acquisition of clinical data, conception, and design: EA. The author contributed to the article and approved the submitted version.

## Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Livedoid vasculopathy – A diagnostic and therapeutic challenge

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Livedoid vasculopathy is a rare, chronic-recurrent occlusive disorder in the microcirculation of dermal vessels. The clinical appearance is characterized by *Livedo racemosa*, painful ulceration, located in the distal parts of the lower extremities, followed by healing as porcelain-white, atrophic scars, the so-called *Atrophie blanche*. Different conditions that can promote a hypercoagulable state, such as inherited and acquired thrombophilias, autoimmune connective-tissue diseases and neoplasms, can be associated with livedoid vasculopathy. Therefore, livedoid vasculopathy is currently considered to be a coagulation disorder, clearly distinguished from inflammatory vasculitis. Although there are hints to hypercoaguability and secondary inflammation, pathophysiology is not completely understood. Diagnosis is made by synopsis of history, clinical and histopathological findings. Early and adequate therapy is essential to maintain life quality and avoid irreversible complications. Better understanding of molecular mechanisms is required to establish appropriate therapy regimens. This article presents the current state of knowledge about livedoid vasculopathy and proposes an algorithmic approach for diagnosis and therapy.

KEYWORDS

**livedo, *Livedo racemosa*, *Livedo reticularis*, vasculopathy, livedoid vasculitis, vasculitis, thrombosis**

Abbreviations: ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; Apo(a), apolipoprotein(a); C3, complement factor C3; COVID-19, corona virus disease 2019; DOAC, direct oral anticoagulant; HIT, heparin-induced thrombocytopenia; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IVIG, intravenous immunoglobulins; LDL, low density lipoprotein; LMWH, low molecular weight heparin; LV, livedoid vasculopathy; MTHFR, methylentetrahydrofolat; NSAID, non-steroidal anti-inflammatory drugs; ox-Lp(a), oxidative form of Lp(a); PAI-1, plasminogen-activator-inhibitor-1; PAN, Panarteriitis nodosa; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; PUVA, psoralen plus UVA; RILIVA, rivaroxaban for livedoid vasculopathy; SARS-CoV-2, Severe acute respiratory syndrome coronavirus type 2; TF, tissue factor; TFPI, tissue factor pathway inhibitor; tPA, tissue-type plasminogen-activator; TRALI, transfusion-related acute lung insufficiency.

# Introduction

Livedoid vasculopathy (LV) is a rare, chronic-recurrent, thrombo-embolic disease with occlusions in dermal vessels, especially on the lower extremities (1).

In the literature, different names for this disease were introduced. First described as *atrophy blanche* by Milian et al. (2), Feldaker et al. used the term *Livedo reticularis with summer ulceration* 1956 (3). Milstone et al. focussed on the clinical appearance with *Painful Purpuric Ulcers With Reticular Patterning on the Lower Extremities (PURPLE)* (4). Bard and Winkelmann (5) established the term *Livedo vasculitis* and suggested that LV was a segmental hyalinizing form of vasculitis (5). Also findings in direct immunofluorescence with deposition of fibrin, immunoglobulins, and complement components localized to the hyalinized vessel walls were initially misinterpreted as a consequence of primary vasculitis (6).

However, normal serum-complement levels, a diffuse homogenous instead of granular deposition pattern, a slight perivascular infiltration of leukocytes and the absence of nuclear dust (so called leukocytoclasia) argue against an immunocomplex-mediated disease like inflammatory vasculitis (7, 8). The characteristic intraluminal thrombi as well as the response to anticoagulation therapy support the theory that thrombotic or microcirculatory mechanisms might be acting in the pathogenesis of LV, not vasculitis, so that McCalmont, Jorizzo and colleagues first proposed the term *livedoid vasculopathy* in 1992 (3, 7).

Although LV is an orphan disease, it can be very limiting for the affected patient's quality of life (9). Occluding vasculopathy in the dermal vessels lead to ischemia and so massive pain (9, 10). Early and correct diagnosis as well as adequate therapy is important to prevent acute ischemia and so long-term consequences such as a chronic pain syndrome and dysaesthesia.

In this review, we give an overview of the current state of literature about LV, provide a diagnostical and therapeutical approach and distinguish LV from other differential diagnoses, especially inflammatory vasculitis.

# Methods

## Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (11).

From March of 2022 until July of 2022 a structured literature search was performed on PubMed and Cochrane. The final literature search was performed on 31 July 2022. Inclusion criteria comprise the key words "livedoid vasculopathy" AND/OR "livedoid vasculitis" English or German full text and content appropriate to the investigated topic. No other filters or tools were used. Studies without a definite diagnosis of LV were excluded. All abstracts and included full texts were reviewed by the first author.

## Study selection

The first search process showed 527 articles from the PubMed and Cochrane online electronic databases, removing 224 duplicated records. Another 11 articles were noticed from references of the screened articles. The first author screened the abstracts of the identified articles and selected records for full-text view. The PRISMA flow diagram represents the process of literature search and study selection (**Figure 1**).

Inclusion criteria comprise (1) articles about LV or LV mentioned in the text; (2) article types including research articles, reviews, case series, case reports and correspondences; and (3) articles in english or german language. Exclusion criteria were as follows: (1) Articles containing information that is not matching to LV; (2) articles written in languages other than English or German. (3) No further information available. Therefore, 84 records were excluded because of the following reasons: (1) not published in english or german language ($n$ = 25); irrelevant subjects ($n$ = 39); and (3) lack of further details ($n$ = 20).

The risk of bias is assessed to the Cochrane handbook of systematic reviews of interventions. We did not only enroll research articles, but also reviews, case series and case reports. Although this could lead to overreporting and overestimation of particular results, we did not want to renounce this information due to the rareness of the disease and the limited evidence.

# Results

## Epidemiology

LV is an orphan disease with an estimated incidence of 1:100,000, often affecting young to middle-aged women with a median age of 32 years up to 53 years in other study populations (1, 12, 13). The female-to-male ratio is described between 2.1:1 (12, 13) to 3:1 (14). In greater patient populations few pediatric patients were mentioned (15, 16).

Criado and colleagues recently reported in the context of a study on 75 patients with LV in Brasil, that the most affected age group was between 20 and 48 years with a median age of 34.7 years (17). Interestingly, 14 out of 75 patients (18.7%) were under 18 years old at the beginning of the disease (17). Similarly, Feng et al. described a very young patient population from china with 24 patients with LV with a median age of 17.0 years at beginning of the disease (18).

Although incidence is often indicated as 1:100,000 in the literature, as LV maybe unfamiliar to many physicians and

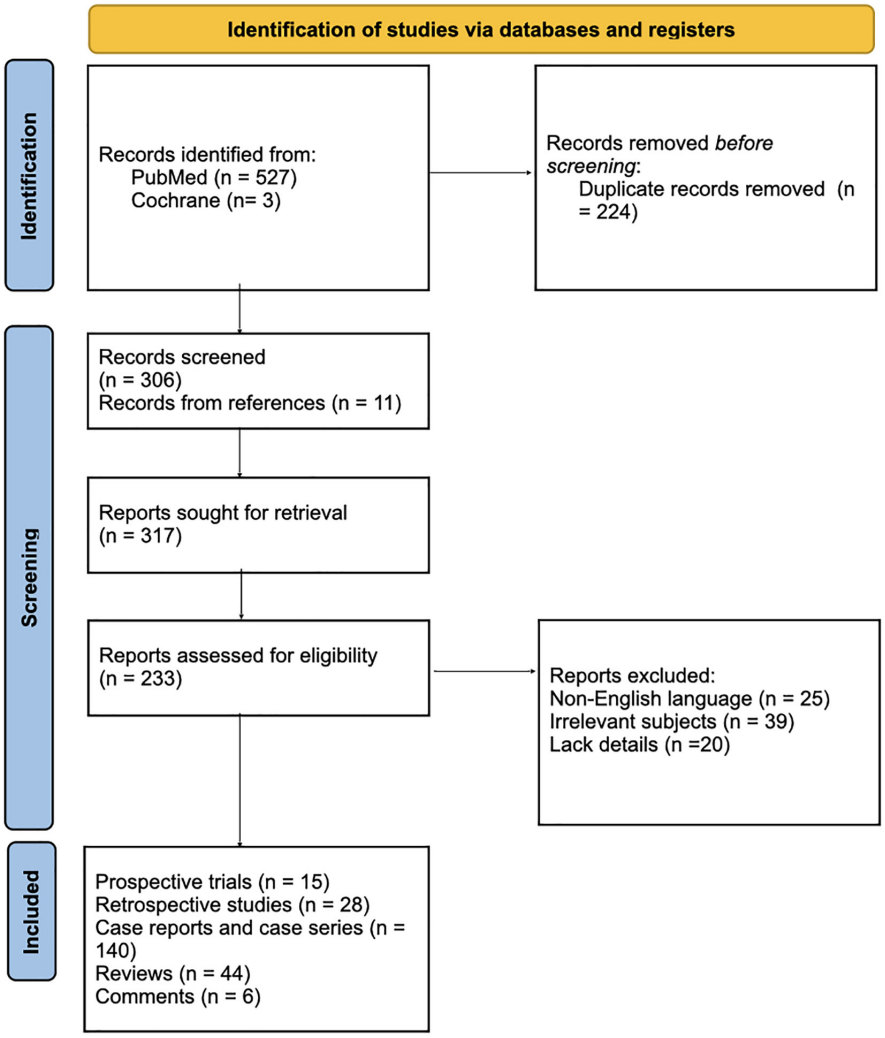



FIGURE 1
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only. From Page et al. (72).

in regard to our own experience, we assume a much higher incidence. Some studies report a delay from first symptoms to diagnosis of median 6.65 years, ranging from 1 to 20 years (17).

## Pathophysiology

The pathomechanism of LV is not completely understood at the current state. Initially LV was considered as vasculitis (19). Up to date LV is seen as a vascular disease with a domination of procoagulatory factors leading to a status of hypercoagulability (14). The thrombotic effect possibly results from defects in endothelial dysfunction such as impaired plasminogen activation, dysfunction of platelets or increased or restricted fibrin formation or lysis, respectively. Fibrin deposition and thrombus formation act as a diffusion barrier and lead to a decreased oxygen supply with subsequent necrosis (=skin infarction) (14, 20). Moreover, slight tissue perfusion leads to poor wound healing – a vicious circle develops (21). Hypercoagulability, stasis and endothelial damage, the so-called Virchow trias, also act as risk factors for microvascular thrombosis in LV (20, 22). Lower concentration of thrombolytic factors as well as differences in perfusion pressure and in temperature are supposed to be reasons for the manifestation of LV on the lower extremities (22, 23).

Associations to various diseases linked to hypercoagulability in patients were described in LV, including hereditary and acquired thrombophilias (e.g., Faktor V Leiden-mutation, protein C- and protein S-deficiency, antithrombin-III-deficiency, prothrombin G20210A-mutation, plasminogen-activator-inhibitor-1(PAI-1)-promoter-mutation,

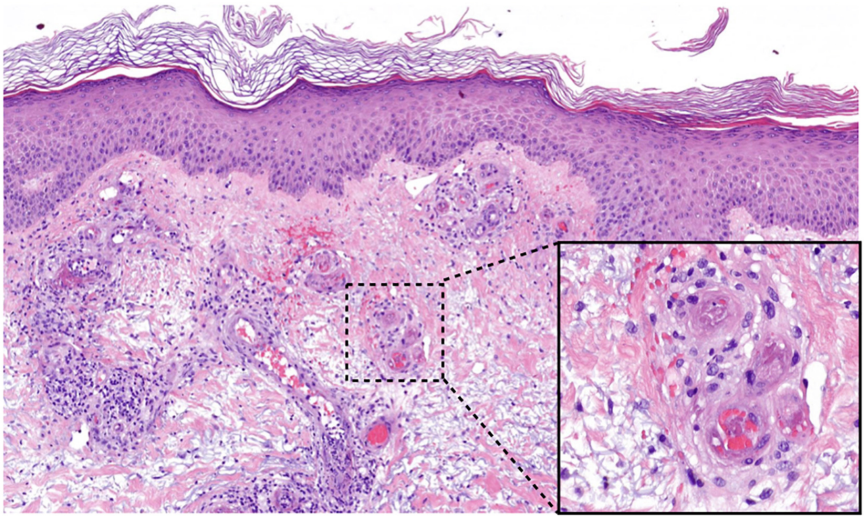


FIGURE 2
Histology of LV lesions. Fibrinoid thrombi and erythrocyte sludge in small vessels of the upper dermis with perivascular lymphocytes and extravasated erythrocytes (HE, magnification 50×, detail 400×).

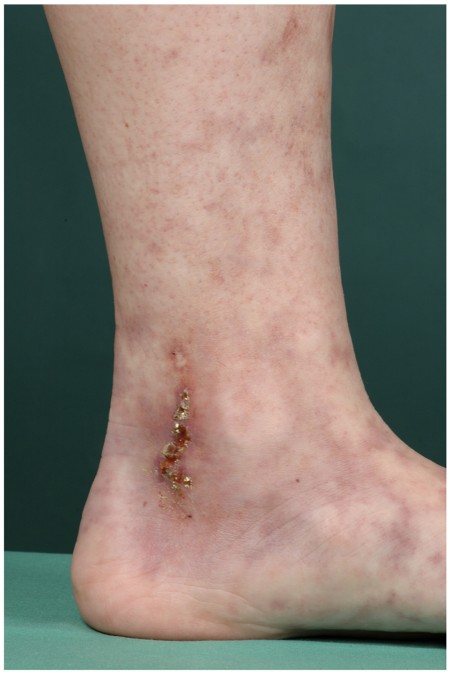


FIGURE 3
Typical presentation of LV. 33-year old female patient with typical presentation of LV: *Livedo racemosa*, ulcers and *Atrophie blanche*.

lipoprotein(a) (Lp(a)), methylentetrahydrofolat(MTHFR)-gene-mutation, homocysteinemia, antiphospholipid-antibodies), autoimmune diseases (e.g., systemic lupus erythematodes) and malignancies (14, 24).

Recently, a systematic review about genetic variants in LV by Gao et al. showed, that *PAI-1* -675 4G/5G was the most common genetic variant, accounting for 85% of 95 LV (81/95) patients analyzed. Further genetic variants comprise PAI-1 A844G (56% of 18 LV patients), MTHFR C677T and MTHFR A1298C variants (55% of 129 LV patients and 44% of 82 LV patients, respectively) (24). Less frequent findings were Factor V G1691A and Prothrombin G20210A polymorphism in 14% out of 135 and 11% out of 85 LV patients, respectively. Genetic variants differed depending on geographical and ethnical factors (24).

Among the mentioned thromophilic factors identified in LV patients, attention should be paid to Lp(a).

Lp(a) represents an independent, genetically determined and not life-style-driven risk factor for cardiovascular diseases and was frequently detected to be increased in patients with LV (25). It has a lipid core of Low Density Lipoprotein (LDL)-cholesterol bound to an apoB-100 particle, connected to the glycoprotein apolipoprotein(a) (Apo(a)) by a disulphide bridge. Apo(a) has structural similarity with plasminogen (25). It is presumed that Lp(a) has pro-thrombotic and anti-fibrinolytic properties due to (1) competition with plasminogen and consecutive impairment of plasminogen activation and/or formation of active plasmin, (2) enhancement of PAI-1 by the oxidative form of Lp(a) (ox-Lp(a)), (3) elevation of tissue factor (TF)-expression and (4) blocking of tissue factor pathway inhibitor (TFPI) (26, 27).

Criado et al. presented a greater patient cohort of 75 in Brazilian patients with LV (17). Among the 72 patients, who received a complete exam, 66% (48/72)

showed associated thrombophilia factors and most of all, elevated Lp(a)-levels in 42% (30/72). The same team also reported about increased Lp(a) expression in lesional skin compared to control skin (27). Weishaupt et al. reported increased Lp(a) (42%, 5/12) and homocysteine (83%, 10/12) levels as the most frequently observed thrombophilia factors in their cohort of 25 patients (13). It must be noted that Lp(a) was only screened in a few studies.

Although a plethora of pro-thrombotic factors were identified as potential triggers of LV, most studies showed that in less than half of patients a known procoagulatory factors could be identified (Hairston et al.: 41%/12/29), Di Giacomo et al.: 52% (18/34), Weishaupt et al.: 44%/11/25), Lee et al.: 42.5% (17/40) (13, 15, 28, 29).

Only few studies showed a higher percentage of thrombophilia factors of LV patients, such as Gardette et al. with 77% (20/26) of patients with at least one positive thrombophilia factor (16) and Gao et al. with 73% (8/11) of patients (30). Gao et al. did not declare further specifications, whereas Gardette et al. again reported about hyperhomocysteinemia as most common thrombophilia factor in 50% of patients. However, prospective, well designed clinical studies involving higher patient numbers are lacking.

Because of the heterogeneity of procoagulatory factors and aetiology, LV can be divided in a primary form (idiopathic) and a secondary form on the basis of underlying other diseases (1, 31).

Besides direct participation by a hypercoagulability condition in affected vessels, there is evidence that inflammation plays a role in pathogenesis of LV. Examples are molecules like interleukins (such as interleukin-2 and soluble interleukin-2-receptor) that are released by the endothelium in the progression of the disease followed by the recruitment of leukocytes promoting inflammation (19). Even if LV is no vasculitis, the potential association to autoimmune diseases as well as the potential therapeutic respond to immunosuppressive and immunomodulatory agents, such as prednisolone, azathioprine and colchicine or intravenous immunoglobulins, suggest at least a secondary inflammatory component (14).

Furthermore, some mechanisms involved in inflammation and coagulation in patients with corona virus disease 2019 (COVID-19) show similarities with the microthrombosis detected in LV patients (32). Kyriakoudi et al. recently presented a critically ill, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2)-positive patient with respiratory failure and livedoid skin lesions (33). Histology showed an occlusive, pauci-inflammatory vasculopathy of the cutaneous small vessels (33). Similar findings were described by Llamas-Velasco et al. (34). Perry et al. reported about a patient with secondary cryofibrinogenemia-induced LV associated with COVID-19 (35). Moreover, an exacerbation and a relapse of LV were reported after an infection with COVID-19 (36, 37).

## Histology

Histology of skin biopsies shows fibrin deposition in the vessel walls (often difficult to recognize), endothelial proliferation and frequently intraluminal hyaline thrombi in blood vessels, especially of the upper and middle dermis, in the acute phase (**Figure 2**). A spare perivascular inflammatory infiltrate and leukocytoclasia maybe detected in the acute phase, but these findings are not decisive for the diagnosis (13).

If the biopsy is taken at a later stage, for example in the stage of *Atrophie blanche*, histology shows scar tissue with few vessels and an atrophic epidermis (38). In addition, a reorganization of the thrombi with subintimal proliferation and segmental hyalinization of the vessel walls and the dermis can occur (31, 39). It should be paid attention to the fact, that histological findings differ according to the stage of the disease (13).

Interestingly, in LV multiple immunoreactants, especially complement factor C3 (C3), fibrinogen and Immunoglobulin M (IgM), less Immunoglobulin A (IgA) and Immunoglobulin G (IgG), can be found in direct immunofluorescence stainings, although these findings are rated as non-specific and non-diagnostic (8, 15, 40, 41). The most reported pattern is granular deposition in the walls of blood vessels combined with or without depositions at the dermoepidermal junction (42). Positive results in the direct immunofluorescence were statistically significant more frequent in older patients and more recent lesions (<6 months) (8).

## Clinical findings

LV is characterized by the clinical trias of (i) *Livedo racemosa*, (ii) very painful ulcers followed by healing as (iii) porcelain-white scars, the so-called *Atrophie blanche* (**Figure 3**) (13).

*Livedo racemosa* describes a net-like red to livid coloration of the skin with discontinuous circles and reflects a pathological reduced blood flow followed by a local tissue hypoxia and ischemia. *Livedo racemosa* is not only localized on the lower extremities, but can also involve body parts above the waistline including arms, hands and back (13).

The physiological reaction of reduced blood flow following exposure to the cold presenting as closed livid ring structures is called *Livedo reticularis* in the german-speaking community of dermatologists. Thus, *Livedo racemosa* clearly differs from *Livedo reticularis* and is characterized by irregular and open ischemic rings indicating an occlusive vascular disease such as LV (**Figure 4**).

Although *Livedo racemosa* can often be found in patients with LV, it is not pathognomonic and can be seen in other diseases (**Table 1**) (43). The in **Table 1** presented disorders are mainly responsible for Livedo racemosa, but far not complete.

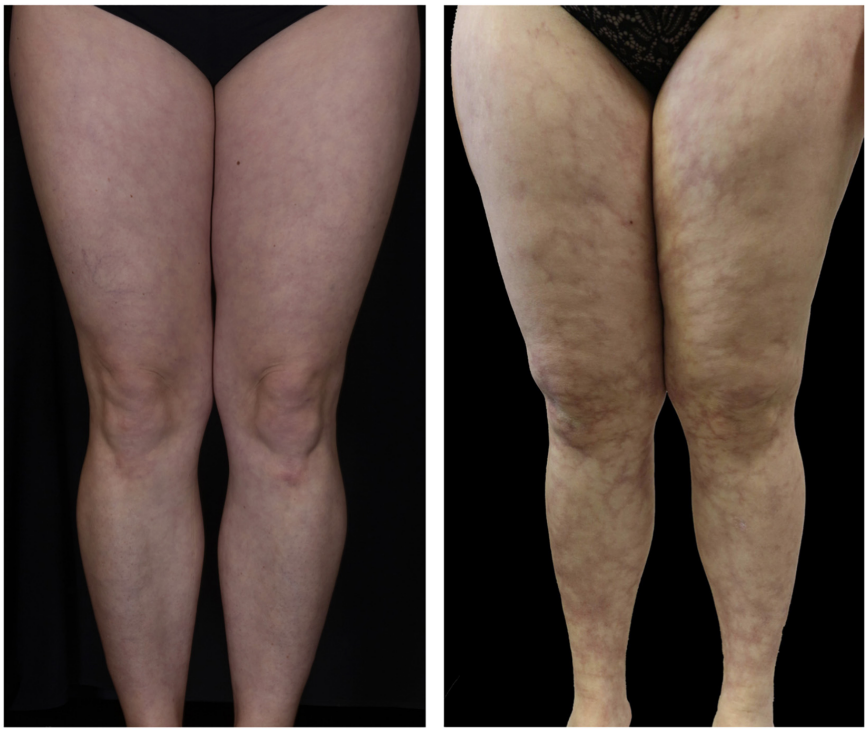


FIGURE 4
*Livedo reticularis* vs. *Livedo racemosa*.

TABLE 1 Diseases associated with *Livedo reticularis* and *Livedo racemosa* (selection).

| *Livedo reticularis* | *Livedo racemosa* | |
|---|---|---|
| **Vasoconstriction** | **Obstacle in in-/outflow** | **Enhancement in viscosity** |
| Cutis marmorata | Livedoid vasculopathy | Cryoglobulinemia |
| Amantadine-induced | Panarteriitis nodosa | Hematological causes (e.g., thrombocythemia) |
| | Antiphospholipid syndrome | Intravasal coagulation or agglutination |
| | Sneddon's syndrome | |
| | Calciphylaxis/Martorell's hypertensive ulcer | |
| | Systemic lupus erythematodes | |
| | Thrombangitis obliterans | |
| | Cholesterol embolization syndrome | |
| | Infectious diseases (e.g., tuberculosis, syphilis, borreliosis) | |

For more details see the reviews by Georgesen et al. and Llamas-Velasco et al. (34, 44).

Initial lesions of LV can be flat to elevated purpuric lesions, which can ulcerate in the further course (**Figure 5**) (14). These ulcerations are typically sharply but bizarre defined, superficial and small (4–6 mm in diameter) and are localized on the malleolar region, dorsal feet and lower legs, but not above the knees (**Figure 6**; 13–15).

After healing the skin remains atrophic, stellate, scar-like, porcellain-white plaques with teleangiectasia and peripheral hyperpigmentation – the so-called *Atrophie blanche* (**Figure 7A**; 15). Dermatoscopy shows shallow crusted ulcers and ivory white scar-like areas in the center of the lesions and hyperpigmentation in form of reticular pigmentation and increased vascular structures in the periphery of the lesions (**Figure 7B**; 45, 46). Histopathological correlation reveals dermal fibrosis at the center of lesions with ivory white areas in the dermatoscopic picture following the healing of the ulcers. The reticular pattern at the periphery is related to hyperpigmentation of the basal layer of the epidermis or melanin within melanophages in the dermal papillae. The vascular structures is correlated with dilatation and proliferation

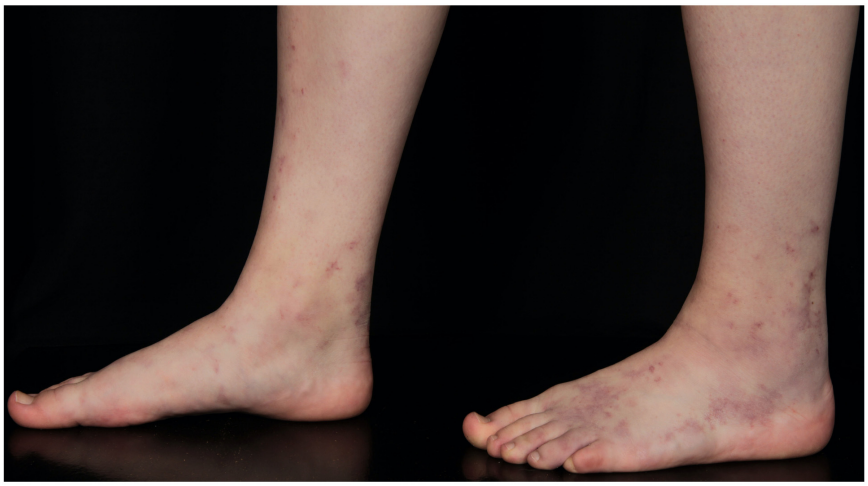
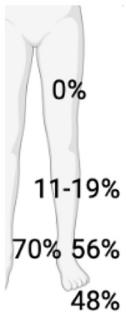


FIGURE 5
16-year old female patient with initial lesions of LV.

| Erythematous macules / ulcerations (=active lesions) Atrophie blanche (=residue of active lesions) in 100% of patients (= disease defining symptoms) | |
|---|---|
| **Localization** | **Frequency** |
| Medial ankle area | 70 % |
| Lateral ankle area | 56 % |
| Dorsal foot | 48 % |
| Ventral distal lower leg | 11–19% |
| Cranial of the knee | 0 % |
| No side preference | |




| Livedo racemosa in 85% of patients (=indicatory symptom) | |
|---|---|
| **Localization** | **Frequency** |
| Foot | 100 % |
| Upper leg | 74 % |
| Lower leg | 26 % |
| Lower arm | 17 % |
| Upper arm | 13 % |
| Trunk | 9 % |
| Hand | 0 % |
| No side preference | |

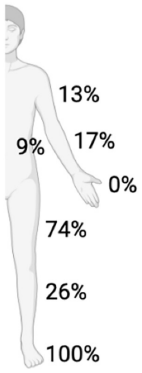



FIGURE 6
Clinical presentation of LV. Distribution of clinical symptoms of LV – adapted from Weishaupt et al. (13).

of capillaries in the upper dermis (45). Lesions of LV are mainly located at the malleolar region or dorsal feet with a bilateral appearance (**Figure 5**; 13). Although LV was first described as *Livedo reticularis with summer ulcerations* by Feldaker et al. (47), LV occurs perennial, not seasonal, even if the course of disease is often recurrent and some authors describe exacerbation during warm weather seasons (17, 38).

Some authors reported a mentionable delay from first symptoms to diagnosis from 1 to 20 years (median 6.65 years), possibly due to lack of knowledge about LV, confusion with other

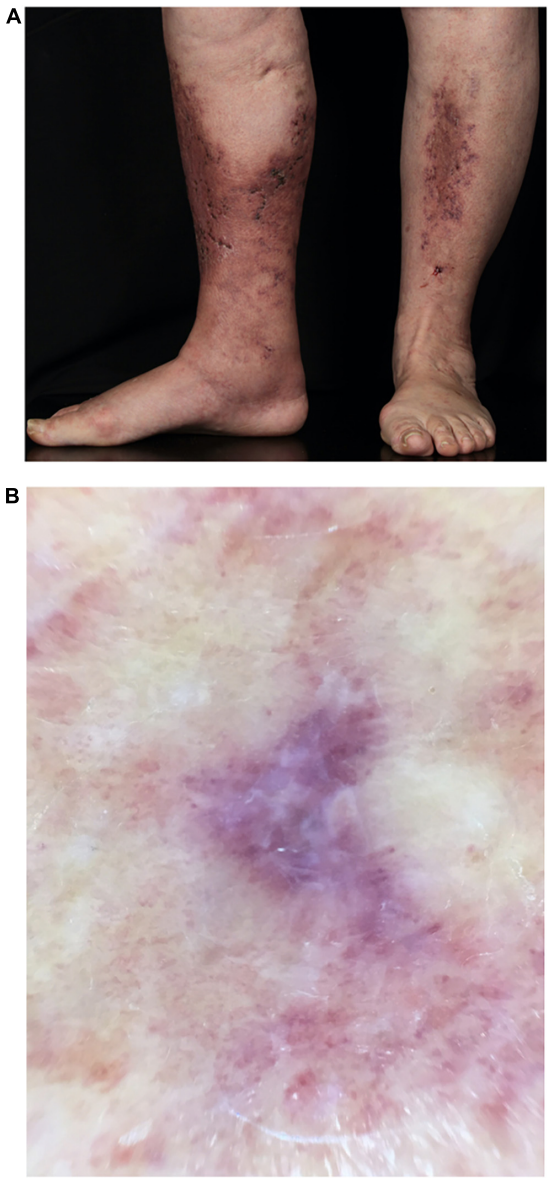



FIGURE 7
**(A)** *Atrophie blanche*. 78-year old female patient with multiple small ulcerations below the knees leaving porcellain-white, atrophic scars after healing (*Atrophie blanche*). **(B)** Dermatoscopy of LV. Ivory white scar-like areas in the center and hyperpigmentation in the periphery of the lesions.

diseases or delayed consultation of medical centers familiar with this disease (17). Other authors described a period of 10 months from first symptoms to diagnosis and 22.5 months to beginning of treatment (13, 48). LV is characterized by intensive pain (median pain on the visual analogue scale 65·0) triggerd by skin ischemia due to the occlusion of dermal vessels (10). Studies show that the intermittent tormenting pain leads to a dramatical impairment of life quality (9, 10).

In a very severe form of LV patients also describe symptoms of a polyneuropathy, like dys- and hypoesthesia. Patients report of abnormal skin sensations sometimes associated with pain or hypoesthesia mainly located at the outside part of lower legs and back of the foot. These symptoms can often be associated to Mononeuritis multiplex, a peripheral neuropathy with possible associations to diabetes, neoplasms and infections. In contrast to other diseases associated with mononeuritis multiplex, where vasculitis can be seen in the vasa nervorum, in LV thrombus formation can be seen in the vasa nervorum comparable to thrombus formation in the dermal vessels (49, 50).

The most reported comorbidities in LV are systemic hypertension, obesity, type II diabetes mellitus and venous insufficiency (13, 17).

## Diagnosis

Even if the clinical appearance of LV is very typical (51), the diagnosis of LV should only be made in synopsis of clinical and histological findings for exclusion of differential diagnoses (**Figure 8**; 34, 52).

At present, there is no validated score for diagnosis of LV.

LV often affects the superficial and middle dermis, less often also the deep dermis. A deep excision in the acute stage of the disease is especially acquired to exclude other differential diagnoses affecting deeper lying areas of the skin, e.g., panarteriitis nodosa (PAN) as a vasculitis of middle-sized arteries (53). A superficial punch biopsy could probably not reach these areas and is not adequate (1, 31).

Moreover, taking tissue directly out of an ulcer should be avoided. Histology of ulcerated areas only show granulation tissue and a secondary inflammatory reaction as part of wound healing (15).

Frequently, more than one biopsy (we suggest at least two biopsies at once) is necessary to find the vascular changes typical for LV as the histopathological characteristics are segmental and not ubiquitous (15).

Detection of different laboratory parameters is especially important for distinction of differential diagnoses but has only modest therapeutical consequences for the affected patients, e.g., with regard to genetic consultation or vitamin substitution in case of hyperhomocysteinemia (31). In most cases detection of a thrombophilic factor has no therapeutical consequences and therefore a general detection of any with coagulopathies associated laboratory parameters is not recommended (54). Exceptions are antithrombin-III-deficiency and antiphospholipid antibodies (Lupus anticoagulant, Anticardiolipin antibodies IgG or IgM, Anti-beta-2-glycoprotein-I antibodies IgG or IgM) due to their therapeutical consequences during pregnancy or in case of immobilization. Moreover, we recommend analyzing

| Clinical findings indicative for LV | |
|---|---|
| main findings | specific aspects |
| Livedo racemosa + | bilateral, disseminated |
| Ulcers +/- Atrophie blanche + | below the knees |
| Pain | |
| | + therapeutical response to anticoagulation (especially low molecular weight heparin) |

| Histology consistent with LV | | |
|---|---|---|
| | main findings | attention to |
| Acute phase | intraluminal hyaline thrombi | at least two deep excisions |
| | endothelial proliferation | biopsy at acute phase of disease |
| | fibrin deposition in the vessel walls | not directly out of an ulcer |
| Later phase | subintimal proliferation | exclude other, e.g. Panarteriitis nodosa |
| | segmental hyalinization of the vessel walls and the dermis | no typical signs of vasculitis |

| Supported by laboratory | | |
|---|---|---|
| **Aim** | **Parameter** | **Important for** |
| **Exclusion of differential diagnoses** | Antinuclear antibodies | Connective tissue diseases |
| | Differential blood count, protein electrophoresis, immunoglobulins, hepatitis serology, inflammatory markers | Neoplastic / infectious diseases |
| **Therapeutical consequences** | Antithrombin-III-deficiency, antiphospholipid antibodies | Pregnancy, immobilization |
| | Homocystein, vitamin B6, vitamin B12, folic acid | Substitution |
| | Lipoprotein(a) | Risk factor for cardiovascular diseases |
| **Supplementary** | Factor-V-Leiden-mutation, prothrombin G20210A-mutation, methylen-tetrahydrofolat-reductase C677T-mutation, plasminogen-activator-inhibitor, cryoglobulinemia, cryofibrinogenemia, von Willebrand Factor, ADAMTS-13, factor VIII | Individual aspects, clinical studies or academic reasons |
| | D-dimers | Marker for thrombotic events, follow-up |

FIGURE 8
Diagnostical approach.

homocystein, vitamins B6, B12 and folic acid as substitution can be easily performed. Finally, Lp(a) as a risk factor for cardiovascular diseases should be measured as well as antinuclear antibodies to exclude connective tissue diseases. The german guidelines further suggest the measurements of protein C and S (38). In order to be comprehensive following thrombophilic factors or genetic analysis can be performed (i.e., due to individual aspects, clinical studies or academic reasons):

Factor-V-Leiden-mutation, prothrombin G20210A-mutation, methylen-tetrahydrofolat-reductase C677T-mutation, plasminogen-activator-inhibitor, cryoglobulinemia, cryofibrinogenemia, von Willebrand Factor, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13), factor VIII and factor IX.

To exclude a neoplastic or infectious disease a regular blood test including protein electrophoresis, immunoglobulins, hepatitis and HIV serology and inflammatory markers should be performed (31).

Please note that coagulation tests could be influenced by a thromboembolic event or under anticoagulatory therapy. Furthermore, secondary reasons for a status of hypercoagulability should be considered, like immobilization due to hospitalization, trauma or surgery, consuming diseases (e.g., malignancies), pregnancy, medicaments (e.g., anticoagulation or oral contraceptives), adipositas or advanced age (20, 54). D-dimers are indeed unspecific for a distinct disease, but represent also in LV a rapid test for thrombotic events and is increasingly seen as follow-up marker (55).

## Differential diagnoses

Differential diagnoses contain cutaneous PAN, cutaneous immune-complex vasculitis, antiphospholipid-syndrome, pyoderma gangraenosum, cryoglobulinemia type I, Sneddon's syndrome, and warfarin-induced cutaneous necrosis (**Figures 9A,B**; 31).

*Livedo racemosa* represents a good indication of LV. However, *Livedo racemosa* can not only be seen in LV, but in various other diseases, including PAN, Sneddon's syndrome, antiphospholipid-syndrome, calciphylaxis, autoimmune diseases like systemic lupus erythematodes, malignancies or secondary after certain medicaments (e.g., warfarin) (43). The presence of livedo racemosa often leads to patient referrals to dermatology for exclusion of Sneddon's syndrome. Thus far, there is no evidence that LV affects any other organ than the

A

| Main differential diagnoses | LV | cPAN | Sneddon's syndrome | APS | Calciphylaxis / Martorell's hypertensive ulcer | Cryoglobulinemia type I |
|---|---|---|---|---|---|---|
| Clinical findings | • Livedo racemosa<br>• small ulcers<br>• Atrophie blanche<br>• pain | • Livedo racemosa<br>• ulcers<br>• painful papules and nodules | • generalized Livedo racemosa<br>• no ulcers | • Livedo racemosa (20%)<br>• ulcers (5%) | • Livedo racemosa<br>• ulcers<br>• necroses | • Livedo racemosa<br>• ulcers<br>• necroses<br>• acrocyanosis |
| Histology | • intraluminal hyaline thrombi<br>• endothelial proliferation<br>• fibrin deposition<br>• little inflammatory signs | • necrotising vasculitis with nodules (mid-size and small arteries)<br>• secondary thromboses | • focal proliferation of subendothelial muscle cells | • thromboses<br>• little inflammation (eventually secondary) | • calcifications (of cutaneous arterioles, neurilemma, fat tissue) | • deposition of monoclonal IgM / IgG |
| Laboratory | • <50% thrombophilic factors detected | - | • APL antibodies in 50% | • APL antibodies | - | • monoclonal cryoglobulins |
| Special aspects | • distal lower extremities<br>• recurrent | • inflammatory constellation<br>• often nerval involvement<br>• myalgia | • neurological symptoms (cerebrovascular insults) | • vascular obliterations (thromboses, thromboembolism)<br>• gestational complications<br>• laboratory criteria | • +/- terminal renal failure | • hyperviscosity syndrome + vascular obliterations |
| Therapy | • AC<br>• IVIG | • GCS | - | • AC | • sodium thiosulfate | • like multiple myeloma |

| Less important | ANCA-positive vasculitis | Venous ulcer | Arterial ulcer | Pyoderma gangraenosum |
|---|---|---|---|---|
| Special aspects | • palpable purpura<br>• MPO, PR3 | • chronic venous insufficiency | • peripheral arterial obstructive disease | • different morphology |

B

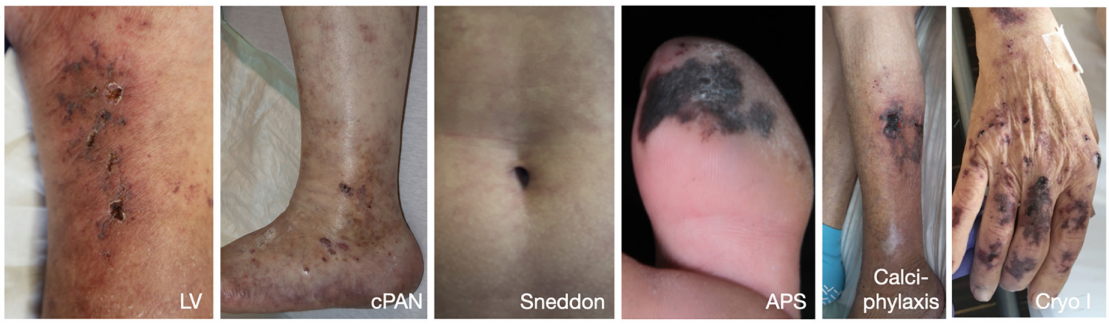



FIGURE 9
**(A)** Differential diagnoses. AC, anticoagulation; ANCA, anti-neutrophil cytoplasmatic antibodies; APL, antiphospholipid; APS, antiphospholipid syndrome; cPAN, cutaneous Panarteriitis nodosa; GCS, glucocorticosteroids; IgG, immunoglobulin G; IgM, immunoglobulin M; IVIG, intravenous immunoglobulins. **(B)** Differential diagnoses – clinical examples. LV, livedoid vasculopathy; cPAN, cutaneous Panarteriitis nodosa; APS, antiphospholipid syndrome; Cryo I, cryoglobulinemia type I.

skin and patients with neurologic findings and LV need to be referred to neurologists for further examination.

The most important differential diagnosis is cutaneous PAN, a small- to medium necrotizing vessel vasculitis of the deep dermis and/or hypodermis. The symptoms are comparable with LV including *Livedo racemosa* and painful ulcers. However, PAN almost always shows subcutaneous nodes and signs of Mononeuritis multiplex (31). Finally, histopathological examination will distinct both entities.

Although the term *Atrophie blanche* is sometimes used as a synonym for LV, atrophie-blanche-like scars can also be seen in other diseases, e.g., chronic venous insufficiency, antiphospholipid-syndrome, cutaneous immune complex-vasculitis, systemic lupus erythematodes and sclerodermia, and is not pathognomonic for LV (1, 52, 56).

## Therapy

There are many different treatment approaches in LV, however no standardized and evidence-based therapeutic strategies are published. The aim of treatment in LV is an improvement of skin lesions, prevention of relapses and especially a reduction of pain (57). A single therapy approach is not equally effective for all patients, so that several treatment options have to be considered or combined (**Figure 10**) (21).

Because of the pathophysiological concept of the formation of microthrombi, an anticoagulatory therapy, e.g., with low molecular weight heparins (LMWHs) or direct oral anticoagulants (DOACs) is widely accepted as first line treatment and recommended by the german S1 guidelines (28, 38, 57).

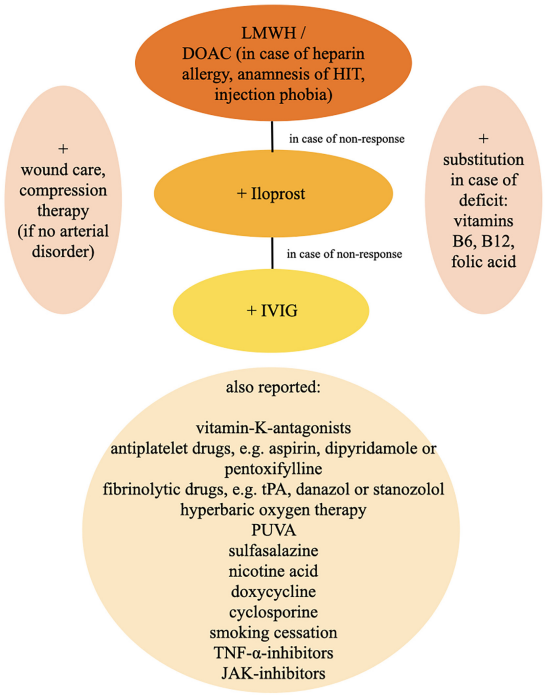



FIGURE 10
Therapy algorithm. DOAC, direct oral anticoagulants; HIT, heparin-induced thrombocytopenia; IVIG, intravenous immunoglobulins; JAK-inhibitors, januskinase-inhibitors; LMWH, low-molecular-weight heparin; PUVA, psoralen plus UVA; TNF-α-inhibitors, tumor necrosis factor-alpha-inhibitors; tPA, tissue-type plasminogen-activator.

In our clinics we start with a LMWH (i.e., tinzaparin or enoxaparin). LMWHs are most effective, safe and relatively favourable in contrast to other therapy options (13). We recommend a therapeutic dose first (i.e., tinzaparin 175 I.E./kg BW 1x/d, enoxaparin 1 mg/kg BW 2x/d) and a semi-therapeutic dose for maintenance therapy at a stable stage of the disease or after healing of the ulcers. LMWHs are usually well-tolerated and show no drug interaction. Increased risk of bleeding, hematoma, menorrhagia, anemia or local reactions at the injection site can be reported as side effects. Attention should be paid to severe adverse effects like allergic reactions and heparin-induced thrombocytopenia (HIT). In case of impaired renal function dosage must be decreased or treatment is even contraindicated. Regular monitoring under treatment is not necessary. In LV, a successful and prompt response to LMWH was not only reported for adolescents (58), but also for pediatric patients (17, 59).

DOACs are assumed to show a similar effect as LMWHs in the treatment of LV. The so far only registered multi-centre, single-arm, prospective study about rivaroxaban for LV (RILIVA) was recently published (10). 25 patients with LV and a minimum pain score of 40 on the visual analogue scale received oral rivaroxaban for 12 weeks. The initial dosage was 10 mg 2x/d, which was reduced to 10 mg 1x/d, if pain was decreased by 50% on the visual analogue scale. As a backup treatment, subcutaneous enoxaparin 1 mg/kg 1–2x/d could be administered in case of insufficient therapeutical response or exacerbation of pain. During the trial, 5 of 25 patients dropped out of the study. The study showed a significant reduction of median pain. 30% of the patients needed an additional treatment with enoxaparin. 8 treatment-related adverse events were reported in 24% of patients. Weishaupt and coworkers showed with this trial, that rivaroxaban seems to be an effective and safe treatment option for patients with LV.

According to the RILIVA study, we suggest a dosage of 10 mg 2x/d rivaroxaban for initial treatment and a dosage of 10 mg 1x/d in the maintenance phase. Most frequent reported side effects are bleeding, hematoma, menorrhagia, anemia, dizziness, gastrointestinal symptoms, hypotension, skin rash and pruritus. So far, other DOACs such as apixaban were not analyzed in the treatment of LV, but because of equivalent mode of action as direct factor-Xa-inhibitors the effect in treatment of LV is supposed to be similar. We suggest a dosage of 2 × 5 mg daily in the initial therapy with a reduction to 2 × 2, 5 mg daily for maintenance therapy.

The oral instead of subcutaneous application and the absent need of a monitoring of blood values increase the compliance of the patient to DOACs in comparison to LMWHs, although possible side effects, especially increased bleeding tendency, drug interaction, renal and liver impairment have to be elucidated (10, 60). Especially in case of heparin allergy, anamnesis of heparin-induced thrombocytopenia (HIT) or injection phobia DOACs represent an alternative to LMWHs.

Interestingly, therapeutic response to anticoagulation therapy can be accessed rapidly as the patient notices a pain relief within a few days (10, 59). For the initial treatment of LV or in case of exacerbation we recommend a therapeutic dosage of LMWHs or DOACs and continue with this dosage in great risk of progression (**Figure 11**). After pain relief and healed ulcers and in case of stable disease, a reduction to semi-therapeutic dosages up to an escape attempt is suggested.

In case of an insufficient therapeutical response, we add prostacycline-analoga such as iloprost as an intravenous therapy in a maximum dosage of 20 µg per day over 3–5 days every 4 weeks (61). Dosage is adapted to individual tolerance. Frequently reported side effects under therapy with iloprost contain headache, flush, nausea, emesis and hypotension. Thus, cardiovascular function should be monitored carefully and advanced heart insufficiency must be excluded. In therapy resistant cases we finally add intravenous immunoglobulins (IVIG) in a dosage of 2 g/kg over 2–5 days every 4 weeks. Overall, IVIG is a well-tolerated treatment option in most patients. Possible side effects comprise shivering, headache, fever, dizziness, nausea, vomiting, allergic reactions, arthralgia, hypotension and back pain. In order to detect even very rare adverse effects such as sudden hypotension, anaphylactic

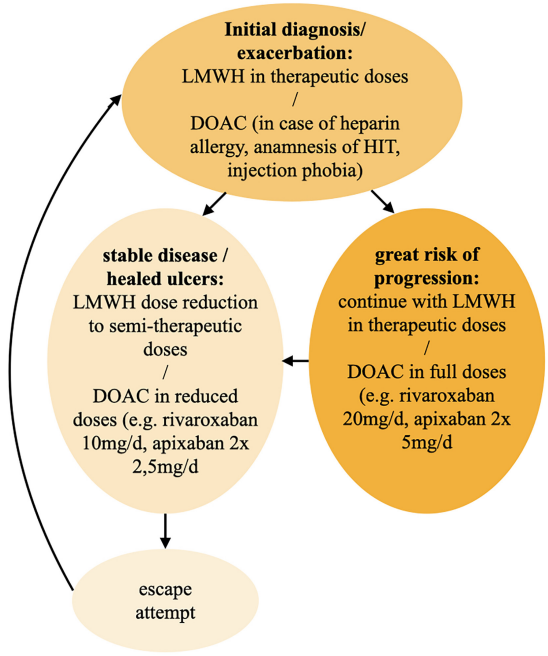



FIGURE 11
Therapy algorithm for 1st line anticoagulation. DOAC, direct oral anticoagulant; HIT, heparin-induced thrombocytopenia; LMWH, low molecular weight heparin.

shock and transfusion-related acute lung insufficiency (TRALI), infusion rate should be reduced in the initial 30 min of application and can be increased, if well tolerated. Vital signs as well as renal function and blood count must be controlled. IVIG is very effective in the treatment of LV and shows in almost all patients a prompt and sufficient response. Almost all studies report a prompt benefit in >90% of LV patients treated with IVIG (62, 63). However, application should be well considered due to high costs (57, 63–66).

Further therapy options include vitamin-K-antagonists, antiplatelet drugs, e.g., aspirin, dipyridamole or pentoxifylline, fibrinolytic drugs, e.g., tissue-type plasminogen-activator (tPA), danazol or stanozolol (31, 57). Furthermore, there are case reports about a beneficial application of hyperbaric oxygen therapy as well as psoralen plus UVA (PUVA), sulfasalazine, nicotine acid, doxycycline and cyclosporine (31, 57). Moreover, it is presumed, that smoking cessation could have a positive effect for the disease (61). Some authors reported about patients who responded well to therapies with tumor necrosis factor (TNF)-alpha-inhibitors adalimumab and etanercept (67, 68). Recently, positive outcomes upon treatment with januskinase-inhibitors, like Tofacitinib (69) and Baricitinib (70), were reported. Because of often co-existent venous insufficiency a compression therapy for reduction of edema and stimulation of fibrinolysis seems to be effective after exclusion of an arterial disorder (31, 39). An adequate therapy of pain is crucial for impairment of quality of life (9), whereas a pain reduction is often achieved by usage of anticoagulants (71) as well as an appropriate wound care (31). Although an anti-inflammatory therapy with non-steroidal anti-inflammatory drugs (NSAID) is often applied, this therapy failed to show a significant success rate (13).

## Discussion

The present article highlightens the recent findings of current research on LV. The understanding of this still somewhat enigmatic disease has evolved over time and important works have helped to understand, that LV needs to be classified as a thrombotic disease of the cutaneous microcirculation rather than a primary inflammatory vasculitis (1, 3, 15, 17). What remains unexplained up to now is the precise description of the exact molecular mechanism underlying this disease. We have learnt from patient register studies and trials, that pro-coagulatory factors can be identified in about 50% of LV-patients – however, these are heterogenous and thus in the overall description not specific enough (13, 17, 38). What is the specific trigger that tips the physiological balance of continuous fibrin formation and thrombolysis toward thrombotic vessel occlusion? As we observe, that LV is a coagulation disorder strictly limited to the cutaneous microcirculation we need further explanations in how far the cutaneous capillary bed differs from that found in the e.g., renal, hepatic, pulmonary or cerebral microcirculation? What role can be attributed to the altered levels of blood pressure and perfusion velocity that prevail in the lower extremity, with an observed prevelance of LV-ulcerations that are mostly located on the foot and never exceed the knee level (13). This observation clearly points to specific regional conditions leading to reduced blood flow – but what are they exactly?

In terms of differential diagnoses that need to be separated from LV the authors in their treatment centers follow the strategy, that in case of doubt, a hard-facted diagnosis of e.g., antiphospholipid syndrome outweighs the clinical diagnosis of LV rather than diagnosing a LV "secondary" to an antiphospholipid syndrome as other authors suggest (1, 28). Indeed, we observe that there is either a clear diagnosis of a "primary" LV that also responds immediately to treatment or a clinical condition presenting aspects of LV that do not respond adequately to treatment (10) and would thus need additional efforts for finding the right alternative diagnosis. As mentioned above, the fact that LV is strictly limited to the skin helps to separate the impact of *Livedo racemosa* in patients with systemic neurologic disease suffering from Sneddon's syndrome from those with the same skin lesions affected by LV.

The fact, that there is accumulating evidence and understanding, that LV is a coagulatory disease has significantly influenced the way it is treated over the years. Treatment

options that are primarily anti-inflammatory have been used in the past, whereas antithrombotic strategies have evolved over time (58).

Although the exact molecular mechanism that leads to thrombosis is still ignored most authors and guidelines (38) agree, that low-molecular weight heparin is capable of reducing LV-activity (10, 22). Antithrombotic strategies that include fibrinolysis through recombinant t-PA have limitations in their accessibility and might present unwanted side effects hard to manage in an ambulatory setting. With the introduction of novel oral anticoagulants it has been effectively shown in a clinical trial that rivaroxaban is a successful agent in treating LV (10) and was confirmed in subsequent studies (60). The future will show, if the introduction of anticoagulatory drugs might help to further understand LV, if these selectively would not succeed in preventing cutaneous vessel occlusion.

This review is limited by the quality and amount of studies published. There are no randomized, controlled trials on this topic available. Only few prospective studies could be identified. Hence, evidence for diagnosis and treatment of LV is rare. So, even more expert advice is necessary for adequate handling of LV patients.

We conclude that the efforts of all groups in understanding LV have helped to reveal important aspects of the disease, however, we must admit as of now, that there are still huge gaps in the complete understanding of this skin-specific coagulation disorder.

## Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

## Author contributions

All authors wrote the main manuscript text, contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Recent topics related to etiology and clinical manifestations of cutaneous arteritis

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Cutaneous polyarteritis nodosa (cPAN) was first reported by Lindberg in 1931. It has been recognized as a skin-limited vasculitis whose cutaneous histopathological features are indistinguishable from those of PAN. Cutaneous arteritis (CA) was defined as a form of single-organ vasculitis in the revised Chapel Hill Classification and was recognized as the same disease as cPAN. It became known that deficiency of adenosine deaminase 2 (DADA2) cases were included in cases that had been diagnosed with CA. Because of their similarity and differences in the treatment methods, DADA2 should be considered in CA cases, especially if they are diagnosed or developed in early childhood. Cutaneous arteritis may be classified as an immune complex-mediated vasculitis. It was reported that the pathogenesis of anti-lysosomal-associated membrane protein-2 (LAMP-2) antibodies and anti-phosphatidylserine-prothrombin complex (PS/PT) antibodies as good parameters in CA. The main skin manifestations include livedo racemosa, subcutaneous nodules, and ulcers. Although CA is recognized to have a benign clinical course, it has become known that it is easy to relapse. The existence of skin ulcers upon diagnosis or sensory neuropathies was suggested to be a predictor of poor prognosis. Cutaneous arteritis with them may need to be treated with more intensive therapies.

KEYWORDS

**anti-lysosomal-associated membrane protein-2 antibody, anti-phosphatidylserine-prothrombin complex antibody, cutaneous arteritis, deficiency of adenosine deaminase 2, livedo racemosa, polyarteritis nodosa**

## Introduction

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that involves medium-sized muscular arteries as well as small-sized muscular arteries without glomerulonephritis. It can form segmental lesions in the damaged vessels and can affect multiple organs, such as the skin, nerves, and kidneys.

Kussmaul and Maier (1) have reported inflammatory arterial nodules as periarteritis nodosa. It was then revealed that the distribution of inflammation was observed in the whole arterial wall rather than the periarterial area, which was then renamed as PAN. Anti-neutrophil cytoplasmic antibodies (ANCA) were identified in cases with glomerulonephritis in 1982 (2) and in cases with microscopic polyangiitis in 1985 (3), and their pathogenicity was proven. Moreover, a group of small vessel

vasculitides, such as microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis in which ANCA was involved in the pathogenesis, were classified as separate diseases from PAN. According to the revised Chapel Hill Classification (4) published by the Chapel Hill Consensus Conference in 2012, PAN is defined as a necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in the arterioles, capillaries, or venules, that is not associated with ANCA. It is also considered as a rare disease.

Cutaneous polyarteritis nodosa (cPAN) was first reported as a skin variant of periarteritis nodosa by Lindberg in 1931 (5). It has been recognized as a skin-limited vasculitis without any other organ manifestations whose cutaneous histopathological features are indistinguishable from those of PAN. It affects medium-sized arteries at the dermal-subcutis junction and subcutis and small-sized arteries, and often shows subcutaneous nodules and livedo racemosa. The revised Chapel Hill Classification (4) classified the category of single-organ vasculitis, which affects arteries or veins of any size in a single organ and is not a limited expression of another systemic vasculitis. Cutaneous arteritis (CA) was described as a form of single-organ vasculitis and was recognized as the same disease as cPAN.

As mentioned in the classification, it was reported that cases with CA progressed into PAN (6, 7). This phenomenon is thought to be very rare, but cases with CA occasionally show general symptoms, such as musculoskeletal and peripheral neurologic manifestations within the distribution of skin lesions. As such cases can be diagnosed with PAN, Nakamura et al. proposed a diagnostic criteria for cPAN (8).

Cutaneous arteritis usually has a chronic and favorable clinical course, but occasionally relapses and needs to be treated with more intensive therapies.

## Epidemiology

Polyarteritis nodosa has been considered a rare disease due to the changes in the disease concept of PAN and the reduced onset of hepatitis B virus infection attributed to hepatitis B virus vaccination, with an estimated prevalence of 30.7 per million (9). On the contrary, CA is a rarer disease, and its prevalence has not been determined yet. Although it is known that the peak of the onset of PAN is in the sixth decade of life and that PAN predominantly affects females, CA develops commonly in the fourth and fifth decades of life and predominantly affects males. Recent cohort studies reported a female-to-male ratio of 1.22–3.53 and that the mean or median age of onset was around the fourth decade of life (Table 1) (7, 10–15). Like PAN, CA also affects children.

## Etiology

Classic PAN and CA are diseases with unknown etiology. Although the hepatitis B virus has already been considered pathogenetic, hepatitis B virus-associated PAN is still considered rare in Japan. Other reported pathogenetic factors for CA included infections, such as *Mycobacterium* infection, Group A *Streptococcus* infection, hepatitis C virus infection etc.; autoimmune diseases; and medications, such as minocycline.

It became known that cases of deficiency of adenosine deaminase 2 (DADA2) were included in cases that had been diagnosed with PAN or CA.

Adenosine deaminase 2 (ADA2) is an extracellular protein that is secreted by monocytes, macrophages, etc. It deaminates and converts adenosine into inosine and regulates the extracellular adenosine concentration.

Deficiency of adenosine deaminase 2 is a recessively inherited autoinflammatory disease caused by the biallelic pathogenic variants in the ADA2 gene on chromosome 22q11, wherein many mutations have been reported. Family history is also often negative. Although most DADA2 cases develop during infancy or early childhood, adult-onset cases have also been reported. The genotype–phenotype correlations were known (16), but differences in the phenotypes, such as the age of onset, severity, and symptoms, can be observed between and within families even if the mutation is common within the families (17, 18).

Deficiency of adenosine deaminase 2 has a broad clinical spectrum and is characterized by vasculitis, which causes strokes and cutaneous manifestations, such as livedo racemosa and livedo reticularis; hematologic abnormalities, such as pancytopenia and bone marrow failure; and immunological manifestations. Vasculitis, which is observed in DADA2, affects medium- and small-sized vessels with histopathologic features that are indistinguishable from those of PAN.

Deficiency of adenosine deaminase 2 was first described in 2014. It was found that PAN cases, most of whom were pediatric and familial cases, have been associated with recessive loss-of-function mutations of ADA2. They were characterized by livedo reticularis and early-onset cerebral infarcts (17). Simultaneously, another study group reported nine cases, including two siblings with PAN characterized by livedo racemosa, early-onset lacunar strokes, and other neurovascular manifestations, carried recessively inherited loss-of-function mutations of ADA2 (18). Moreover, Gibson et al. showed that 9 of 60 primary chronic pediatric vasculitis cases that had been registered in the Pediatric Vasculitis Initiative international study had DADA2 and that 5 of 16 cases that had been diagnosed with PAN were proven to be variants (19). Schnappauf et al. showed that 9 of 118 cases with PAN carried variants in ADA2, while 4 cases had biallelic variants that were pathogenic or likely pathogenic (20).

TABLE 1 Summary of previous reports on clinical manifestation.

| | Daoud 1997 USA | Kawakami 2013 Japan | Criado 2016 Brazil | Alibaz-Oner 2017 USA | Ikeda 2020 Japan | Munera-Campos 2020 Spain | Bettuzzi 2022 French |
|---|---|---|---|---|---|---|---|
| Number of cases | 79 | 101 | 22 | 41 | 84 | 31 | 68 |
| Females/males | 1.72 | 2.37 | 3.40 | 1.92 | 2.36 | 1.82 | 3.53 |
| Mean age | — | 45.4 ± 17.9 | 39.4 ± 15.2 | 49.1 ± 18.8 | 45.7 ± 15.3 | 47.5* | 39* (as the median) |
| (range) | (6–81) | (—) | (9–61) | (—) | (—) | (18–76) | (—) |
| **Distribution of skin lesions** | | | | | | | |
| Lower limbs | Legs 97.5% | Legs 100.0% | 100.0% | — | Lower legs 84.5% Thighs 6.0% | Lower legs 100.0% Thighs 41.9% | 100.0% |
| Upper limbs | Arms 32.9% | — | 27.3% | — | 2.4% | 32.3% | 20.5% |
| Trunk | 7.6% | — | 27.3% | — | 0.0% | 19.4% | 11.8% |
| **Skin symptoms** | | | | | | | |
| Livedo racemosa | — | 83.2% | 54.5% | — | 60.7% | — | 77.9% (as livedo) |
| Livedo reticularis | 55.7% | — | | 39.0% | 3.6% | 45.2% | |
| Subcutaneous nodules | — | — | 50.0% | — | 23.8% | 90.3% | — |
| Nodules | 79.7% | 100.0% | | 61.0% | — | — | 69.1% |
| Ulcers | 49.4% | 48.5% | 63.7% | 14.6% | 30.0% | 35.5% | 16.1% |
| Purpura | — | 66.3% | 27.3% | 31.7% | 40.5% | 3.2% | 17.6% |
| Edema | — | 31.6% (as leg edema) | | 12.8% (as peripheral extremity edema) | 30.0% | — | — |
| Erythema | — | — | | — | 73.8% | — | — |
| **Constitutional symptoms** | | | | | | | |
| Fever | — | — | 9.1% | 19.5% | 14.3% | 9.7% | 11.8% |
| Asthenia | — | — | — | — | — | 67.7% | 33.8% |
| Weight loss | — | — | 4.5% | 5.0% | 0% | 6.5% | 11.8% |
| **Extra-cutaneous symptoms** | | | | | | | |
| Arthralgia | — | 66.3% | 9.1% | 41.5% | — | 19.4% | 36.8% |
| Arthritis | — | — | — | — | 36.9% | — | 2.9% |
| Myalgia | — | 44.6% | — | — | 21.4% | 58.1% | — |
| Paresthesia | — | — | 36.3% | — | — | 45.2% | — |
| Peripheral neuropathy | — | — | — | 2.4% | 33.3% | — | — |
| Neurological sensory involvement | — | — | — | — | — | — | 32.4% |
| Mono-neuritis multiplex | — | 56.4% | 22.7% | 0% | — | 29.0% | — |

—, Not described.
*Cases older than 18 years of age were studied.

In a cohort study of 58 cases of DADA2, cutaneous involvement was the most prevalent symptom. Of the cases, 90% had a history of skin involvement, 74% had livedo racemosa, and 57% had nodules (21). The initial symptoms in infancy or early childhood may include livedo racemosa, and severe systemic vasculitis and strokes may occur during in childhood as the patients grow. Other manifestations, such as subcutaneous nodules, purpura, livedo, Raynaud's phenomenon, and skin ulcerations, can also be observed (22).

Zavialov et al. have reported that ADA2 promoted macrophage differentiation from monocytes and its proliferation (23). Zhou et al. also reported the reduction of the serum levels of ADA2 and ADA2-specific enzyme activity in cases with recessively inherited mutations in ADA2 and monocytes from these cases differentiation into proinflammatory M1 macrophages rather than into anti-inflammatory M2 macrophages (18). This can result in a hyper-inflammatory environment that damages the blood vessels (24). Carmona-Rivera et al. have reported that neutrophil extracellular trap (NET) formation mediated by extracellular adenosine was enhanced and macrophages that were stimulated by NETs produced tumor necrosis factor (TNF)-α as well as determined the pathological roles of neutrophils in DADA2 (24).

Tumor necrosis factor-α inhibitors are common treatments for the vasculitis phenotype of DADA2. They improve the symptoms due to inflammation and vasculitis and significantly prevent strokes (25). However, they have an insignificant effect on the symptoms of bone marrow failure or immunodeficiency (26). The 2021 American College of Rheumatology/Vasculitis Foundation guidelines for managing PAN strongly recommended the treatment with TNF-α inhibitors over corticosteroids alone in cases with the clinical manifestations of DADA2 (27). Because of the similarity between DADA2 and PAN or CA and the differences in the treatment methods, DADA2 should be considered in PAN or CA cases, especially if they are diagnosed or developed in early childhood.

Although vascular damage during viral replication in hepatitis B virus related PAN or ADA2 mutation in DADA2 indistinguishable from PAN has been suggested to involve the onset, the pathogenesis of classic PAN or CA remains unclear.

However, Diaz-Perez et al. have shown that a direct immunofluorescence study using the skin samples obtained by excision biopsies indicated the C3 deposition in the vessel walls in 4 of 10 cPAN cases that were not associated with hepatitis B virus and IgM in 6 of 10 cases (28). Kawakami et al. showed a direct immunofluorescence study indicating the deposition of C3 in 22 (66.7%) of 33 cPAN cases that were not associated with hepatitis B virus and IgM in 19 (57.6%) of 33 cases (29). Overall, these results suggest a complement activation in the vessel walls and CA may be classified as an immune complex-mediated vasculitis. It was also reported that some antibodies might be pathogenetic in PAN or CA.

Lysosomal-associated membrane protein-2 (LAMP-2) is a glycoprotein in membranes of lysosomes and intracellular vesicles within neutrophils and endothelial cells and is an antigen for minor ANCAs. Kawakami et al. showed that the serum levels of anti-LAMP-2 antibodies in cases with cPAN were significantly higher than those in cases with microscopic polyangiitis (30). Takeuchi et al. observed that the intraveneous injection of anti-LAMP-2 antibodies to premorbid env-pX rats, which were the model mice of PAN-like necrotizing vasculitis, induced the neutrophilic infiltration to cutaneous small vessels and allowed the detection of anti-LAMP-2 antibody-binding neutrophils (31). Li et al. also found that the serum LAMP-2 levels in PAN cases were significantly higher than those in ANCA-associated vasculitis cases and were correlated with the Birmingham Vasculitis Activity Score and hypersensitive C-reactive protein (32). These results confirmed the pathogenesis of anti-LAMP-2 antibodies in cutaneous vasculitis.

Anti-phosphatidylserine-prothrombin complex (PS/PT) antibodies have been found to be associated with the clinical manifestations of antiphospholipid syndrome. It was reported that serum anti-PS/PT IgM antibodies were detected in 81.3% of cPAN cases although they were not detected in healthy individuals, and their levels in cPAN cases were significantly higher than those in systemic lupus erythematosus or microscopic polyangiitis cases (33). The levels of anti-PS/PT IgM antibodies were significantly higher in cPAN cases with livedo racemosa than in those without it (29). It was also reported that the levels of anti-PS/PT antibodies in PAN cases with active skin manifestations showing necrotizing vasculitis decreased significantly after treatment (34). Moreover, Sánchez-Cubías et al. described that the levels of anti-PS/PT IgM antibodies in all cases with inactive PAN and those of anti-PS/PT IgG antibodies in all cases except one case with inactive PAN were negative (35). These results suggest that anti-PS/PT antibodies may be good parameters of PAN and CA.

Furthermore, Kawakami et al. reported that the serum anti-PS/PT IgM antibodies levels were higher in the group of cases of systemic vasculitis with skin involvements (three cases of IgA vasculitis, two cases of eosinophilic granulomatosis with polyangiitis, one case of microscopic polyangiitis, and one case of granulomatosis with polyangiitis) and one case of CA than those in the group of cases of systemic vasculitis without skin involvements (two cases of eosinophilic granulomatosis with polyangiitis, two cases of microscopic polyangiitis, one case of granulomatosis with polyangiitis, one case of rheumatoid vasculitis, and one case of PAN), but no significant difference was observed in the serum anti-PS/PT IgG antibody levels (36). These results suggest that serum anti-PS/PT IgM antibodies might be involved in the pathogenesis of cutaneous vasculitis. Okano et al. reported the overexpression of moesin in affected skin vessels and that the titer of serum anti-moesin antibodies in PAN cases with skin involvements due to necrotizing vasculitis is positively correlated with the Birmingham Vasculitis Activity Score results and the Vasculitis Damage Index (34).

## Clinical features

Table 1 summarizes the clinical features that were reported in previous articles (7, 10–15). Constitutional symptoms such as fever, fatigue, asthenia, and weight loss are shown in only a few CA cases, but their incidence is lower than those in PAN cases. In the cohort study by Alibaz-Oner et al. the incidence of weight loss or fatigue in PAN cases was significantly higher than that in CA cases (7). The cause of constitutional symptoms in CA cases is unknown but it was explained that they resulted not from systemic vasculitis but from inflammatory reactions or the distribution of local inflammatory mediators (7, 14).

The main skin manifestations include livedo, subcutaneous nodules, and ulcers. Previous studies have shown that their prevalence was as follows: livedo racemose, 60.7–83.2%; livedo reticularis, 3.6–55.7%; nodules or subcutaneous nodules, 23.8–100%; skin ulcers, 14.6–19.4%. In the cohort study of Alibaz-Oner et al. the incidence of nodules in PAN cases was significantly lower than that in CA cases (7). The cutaneous symptoms usually concentrate in the lower extremities, and

occasionally in the upper extremities, and to a lesser extent may involve the trunk.

Livedo racemosa is a morphologic incomplete network or net-like pattern composed of interrupted rings and is recognized as the consequence of the persistent disruption of blood flow secondary to organic rather than functional disorders (14, 37). On the other hand, livedo reticularis presents a complete lace pattern with regular rings and can be secondary to either organic or functional disorders (14, 15). Munera-Campos et al. have observed atrophie blanche in 25.8% of the study participants (14), while Criado et al. in 45.4% (12). These manifestations are characteristic but not specific for CA, requiring differentiation from systemic vasculopathy or thrombosis due to antiphospholipid syndrome, systemic lupus erythematosus, livedo vasculopathy, etc.

Musculoskeletal and peripheral neurologic manifestations of CA are occasionally observed. These incidences still remain lower than those in PAN. Previous studies have reported an incidence of arthralgia of 9.1–66.3%; myalgia, 21.4–58.1%; paresthesia, 36.3–45.2%; and mononeuritis multiplex, 0–56.4%. In the cohort study of Alibaz-Oner et al. the incidence of peripheral neuropathy in PAN cases was significantly higher than that in CA cases (7). It was suggested that these were secondary to the deep and intense focal skin damages (12) and appear within the distribution of skin lesions. When extracutaneous symptoms are observed outside the range of skin symptoms, systemic vasculitis such as PAN should be considered.

Although CA is recognized to have a benign clinical course, it has become known that CA is easy to relapse. Munera-Campos et al. have observed that 54.8% of CA cases experienced relapses (14), while Alibaz-Oner et al. found that the 5-year cumulative relapse rate was 45.2% in CA cases and 9.6% in PAN cases (7). Bettuzzi et al. showed that 31% of CA cases achieved complete response after first-line therapies, but 63% of CA cases had relapsing/refractory course and received second-line treatments (15). Cases that received a second-line treatment presented fever, nodules, or sensory neuropathy more frequently than those that received no treatment or a single treatment. On the other hand, Munera-Campos et al. showed that CA cases with relapse had ulceration upon diagnosis significantly more frequently than those without relapse (14). Shirai et al. showed that the relapse rate of CA cases with skin ulcers or necrosis was significantly higher than that of CA cases without ulcer or necrosis or that of PAN cases (38). Colchicine, dapsone, or corticosteroids alone is often administered for the treatment of CA, probably because CA damages a single organ and is recognized as having a favorable prognosis. It was suggested that the high relapse rate of CA might be due to the trend that immunosuppressive therapies had not been used frequently (7). Cutaneous arteritis with ulceration or peripheral neuropathy may require an early add-on intensive therapy.

## Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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## Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Treatment of cutaneous vasculitis

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Cutaneous vasculitis encompasses a spectrum of disease states, with varied morphology, severity, and potential for systemic involvement. Even vasculitis which is skin-limited can have a significant quality-of-life impact, necessitating treatment. This manuscript summarizes the available evidence for management of various types of skin-limited vasculitis and provides a proposed therapeutic ladder based on published studies and expert opinion.

KEYWORDS

**vasculitis, cutaneous vasculitis, treatment, management, skin**

## Principles of therapy

Vasculitis of the skin (cutaneous vasculitis) encompasses a spectrum of disease states, ranging from cutaneous manifestations of systemic vasculitis (e.g., purpura in a patient with granulomatosis with polyangiitis), to skin-limited variants of systemic vasculitis (e.g., cutaneous polyarteritis nodosa), to various types of single-organ vasculitis found only in the skin (e.g., erythema elevatum diutinum) (1, 2). Whether systemic or skin-limited, the severity of symptoms also varies. That severity—and the presence or absence of internal organ involvement—guides therapy.

In cases of systemic disease where the skin is involved, appropriate systemic treatment will often, though not always, effectively manage the skin. In cases where the skin is primarily affected, specific therapies with activity in the skin and a favorable risk-benefit profile are preferred. Finally, in many cases of skin-limited vasculitis, no treatment at all may be necessary, provided the process is minimally symptomatic and self-limited.

Ultimately, the types of vasculitis affecting the skin are varied, and the data guiding their management are poor, based primarily on case series and expert opinion (Table 1). Yet, the importance of effective management of cutaneous vasculitis is clear: A survey of patients with cutaneous manifestations of vasculitis (all major types) demonstrated that cutaneous vasculitis is associated with diminished health-related quality-of-life across multiple domains, showing a significant impact on patient symptoms, wellbeing, and self-perception of health (3). For this reason, effective management of cutaneous vasculitis, in all its forms, is vital.

## Cutaneous IgM/IgG immune complex vasculitis

Cutaneous IgM/IgG immune complex vasculitis, as defined in the dermatologic addendum to the Chapel Hill Consensus Conference nomenclature, is a type of immune complex-mediated small vessel vasculitis which is limited to the skin (2). This entity is the most common subgroup of patients presenting with palpable purpura on the lower extremities, referred to elsewhere (and less precisely) in the literature as "cutaneous leukocytoclastic angiitis," "cutaneous small vessel vasculitis," "hypersensitivity vasculitis," or "leukocytoclastic vasculitis."

At the time of initial presentation, it generally is not yet clear whether small vessel vasculitis of the skin is associated with systemic vasculitis, secondary to some underlying trigger, or possibly consistent with cutaneous IgM/IgG immune complex vasculitis instead. A systematic approach to evaluation is needed to differentiate these possibilities (4). Biopsies for routine processing and direct immunofluorescence studies help confirm the diagnosis and rule out other conditions, like IgA vasculitis (which carries an increased risk of systemic involvement), while thorough examination, review of systems, and stepwise laboratory testing help identify those patients with internal organ involvement or important underlying disease states.

The need for treatment depends on the presence of underlying disease states, if any, as well as the chronicity and severity of the vasculitis. Because most initial episodes of small vessel vasculitis presenting in the skin are skin-limited and self-limited, resolving within 3–4 weeks (5), systemic therapy is not needed acutely in most cases. Identifiable triggers should be treated or removed. Simple measures, like rest, elevation, or compression, and topical steroids for itch relief, may be all that is required. More than half of patients require no systemic treatment at all (6).

However, those with severe, chronic (lasting longer than 4 weeks), or recurrent disease should receive treatment, even if the lesions are relatively asymptomatic, because of the quality-of-life impact (3). Unfortunately, no robust literature is available to guide management; treatment recommendations are based on case reports, case series, and expert opinion (Table 2). For those with painful, ulcerative, or otherwise highly symptomatic disease, oral glucocorticoids (e.g., 0.5–1 mg/kg/day prednisone equivalent) may be appropriate. In most cases, systemic glucocorticoids help speed resolution and can be tapered successfully over 3–6 weeks (6, 7). However, not all patients respond adequately to systemic glucocorticoids, or they experience flares with attempted taper. Given the many associated side effects, systemic glucocorticoids are not an appropriate long-term option for treatment of cutaneous vasculitis (8–11). Therefore, those with chronic/recurring vasculitis, and those with vasculitis which flares with attempted taper, should initiate an appropriate steroid-sparing agent.

Lacking high-quality data, there is considerable practice variation regarding the choice of steroid-sparing agents. Based on available studies and expert opinion, colchicine, dapsone, and azathioprine are reasonable initial options (12). These drugs are relatively safe and well-tolerated and are commonly used for cutaneous vasculitis. However, often more than one drug must be tried in order to find that which is most effective and best tolerated.

Colchicine (0.6 mg twice daily) has been reported effective for skin and joint symptoms in open-label series (13, 14). However, it showed no benefit compared to placebo in a small, 1 month long randomized controlled trial (15). Gastrointestinal side effects (abdominal discomfort, loose stools) are limiting in some patients.

Dapsone (typically 100–150 mg/day) is another option, supported by case reports and expert opinion (16). Testing for glucose-6-phosphate dehydrogenase deficiency must be performed prior to initiation, and routine monitoring should be conducted to monitor for anemia. Methemoglobinemia is a rare side effect of dapsone which should be considered in patients reporting low pulse oximetry readings or dyspnea. Dapsone is sometimes combined with colchicine for added benefit in cutaneous vasculitis (12).

Azathioprine (usually 2 mg/kg/day divided twice daily) has been reported to be efficacious for cutaneous vasculitis and is frequently used for treatment of various systemic vasculitides (14, 17). Screening for reduced thiopurine S-methyltransferase (TPMT) activity is common practice for identifying and excluding patients with increased risk of leukopenia. Hepatic injury, hypersensitivity, and infectious complications are other risks.

Alternative options can be considered in those who fail to respond to the above therapies. These include methotrexate (15–25 mg/week) (18) and mycophenolate mofetil (2–3 g/day) (19) and, in rare instances, more aggressive therapies, such as cyclosporine (20), cyclophosphamide, rituximab (21), infliximab (22), or intravenous immune globulin (23). Absent high-quality data supporting these agents, disease severity and potential drug toxicities should be carefully weighed in determining appropriate next steps.

## Skin-limited IgA vasculitis

IgA vasculitis (otherwise know as Henoch-Schonlein purpura) is an IgA-mediated systemic vasculitis. While the presentation of IgA vasculitis in the skin may be indistinguishable from that of cutaneous IgM/IgG immune complex vasculitis, patients with IgA vasculitis are much more likely to have gastrointestinal, joint, or renal manifestations. Fortunately, the overall prognosis is favorable, and the condition is frequently skin-limited.

TABLE 1 Proposed therapeutic ladder for patients with various types of skin-limited vasculitis.

| Disorder | First-line treatment | Second-line treatment | Third-line treatment |
|---|---|---|---|
| **Cutaneous IgM/IgG Immune Complex Vasculitis** (primary cutaneous small vessel vasculitis/cutaneous leukocytoclastic angiitis/hypersensitivity vasculitis) | Eliminate/treat potential triggers<br>Supportive care (rest, elevation)<br>NSAIDs<br>Topical steroids | Colchicine (0.6 mg BID) (13–15)<br>Dapsone (50–200 mg/day) (16)<br>AZA (2 mg/kg/day) (14, 17)<br>CS (e.g., prednisone up to 40-60 mg/day tapered over 3-4 weeks) (6, 7) | COL + DAP (12)<br>MTX (18)<br>MYC (19)<br>CSA (20)<br>CYC<br>Rituximab (21)<br>Infliximab (22)<br>IVIg (23) |
| **Skin-limited IgA vasculitis** (Henoch–Schönlein purpura) | Supportive care<br>NSAIDs<br>Topical steroids | Colchicine<br>Dapsone (24)<br>AZA (25)<br>CS | Rituximab (55)<br>MYC (56)<br>CSA (57)<br>CYC (57)<br>PEX (58) |
| **Cutaneous polyarteritis nodosa** | Supportive care (31)<br>NSAIDs (31)<br>Colchicine (31)<br>Dapsone (31)<br>CS (0.5–1 mg/kg/day tapered over months) (28) | AZA (2 mg/kg/day) (31)<br>MTX (15–25 mg/wk) (35) | TNF-αinhibitors (36, 37)<br>MYC<br>CYC (38)<br>HCQ (32)<br>IVIg (39) |
| **Urticarial vasculitis** | Antihistamines (42)<br>NSAIDs (42)<br>Dapsone (100–200 mg/day) (42)<br>CS (42) | Colchicine (0.6 mg BID–TID) (42)<br>HCQ (42)<br>MYC (42)<br>AZA (42)<br>MTX (42)<br>Dapsone + pentoxifylline (42) | Omalizumab (42)<br>Anakinra/Canakinumab (42)<br>Rituximab (42)<br>CYC (42)<br>CSA (42)<br>IVIg (42)<br>Tocilizumab (42) |
| **Cryoglobulinemic vasculitis** (skin-predominate) | Direct-acting antivirals (e.g., sofosbuvir-velpatasvir) if HCV+ (59)<br>Supportive care | Colchicine (43, 44)<br>Dapsone | Rituximab (60)<br>CS (58)<br>IVIg (61)<br>PEX (62) |
| **Erythema elevatum diutinum** | Dapsone (45)<br>Intralesional CS (45)<br>NSAIDs (45) | Colchicine (45)<br>Chloroquine (45)<br>Tetracyclines± niacinamide (45) | MYC (45)<br>MTX (45)<br>CS (45) |
| **Acute hemorrhagic edema of infancy** | Supportive care (63)<br>Antihistamines | CS (46) | |
| **Nodular vasculitis** (erythema induratum) | Eliminate/treat potential triggers (anti-TB therapy, if indicated)<br>Supportive care<br>NSAIDs<br>Potassium iodide (300 mg TID) (47, 48) | Colchicine (49) | CS (49)<br>MYC (49) |

AZA, azathioprine; BID, twice daily; CS, corticosteroids; COL, colchicine; CSA, cyclosporine; CYC, cyclophosphamide; DAP, dapsone; HCQ, hydroxychloroquine; HCV, hepatitis C; Ig, immunoglobulin; IVIg, intravenous immunoglobulin; MTX, methotrexate; MYC, mycophenolate mofetil; NSAIDs, nonsteroidal anti-inflammatory drugs; PEX, plasma exchange; TID, three times a day.

As with other forms of vasculitis, the treatment of IgA vasculitis is dictated by the extent and severity of the condition. Those with IgA vasculitis which is skin-limited should be treated similarly to patients with cutaneous IgM/IgG immune complex vasculitis. Because IgA vasculitis is often self-limited, resolving over weeks to months, nothing more

TABLE 2 Expanded treatment ladder for skin-limited cutaneous small vessel vasculitis.

| Clinical scenario | Treatment |
|---|---|
| Initial episode* | Eliminate underlying cause, e.g., drug, infection (if identified) |
| ~90% of patients | Rest, elevation, compression |
| | NSAIDs for pain; topical steroids for itch |
| | If severe, consider systemic steroids (e.g., prednisone up to 40-60 mg daily tapered over 3-4 weeks) (6, 7) |
| Chronic/recurrent† | First-line: |
| ~10% of patients | Colchicine 0.6 mg twice daily (13–15) |
| | Dapsone 100-150 mg daily (16) |
| | Azathioprine 2 mg/kg daily (14, 17) |
| | Systemic steroids (used sparingly during flares) (6, 7) |
| Severe or refractory | Second-line: |
| | Combination therapies, e.g., dapsone plus colchicine (12) |
| | Mycophenolate mofetil 2-3 g daily (19) |
| | Methotrexate 15-25 mg weekly (18) |
| | Hydroxychloroquine 200-400 mg daily‡ (42) |
| | Pentoxifylline 400 mg three times daily‡ (42) |
| | Severe disease only: |
| | Rituximab 1 g intravenous on days 1 and 15 (21) |
| | Infliximab 5-10 mg/kg every 4-8 weeks (maintenance) (22) |
| | Cyclosporine 2.5-5 mg/kg daily in divided doses (20) |
| | Intravenous immunoglobulin 2 g/kg monthly, divided over 2-4 days (23) |

*Most episodes resolve within 3-4 weeks; †Persisting or recurring over > 4 weeks; ‡Usually in combination with other agents.

than supportive care may be needed for management of a minimally symptomatic initial episode. For symptomatic or chronic/recurring lesions, colchicine and dapsone are reasonable options, as is azathioprine (24, 25). Because of the association of IgA vasculitis with glomerulonephritis, systemic glucocorticoids have been evaluated for prevention of renal complications but have not been shown to be beneficial as prophylaxis (26).

## Cutaneous polyarteritis nodosa

Cutaneous polyarteritis nodosa (cPAN) is a skin-predominate medium-sized vessel vasculitis representing perhaps 4% of polyarteritis nodosa cases (27). Patients typically present with fixed livedo racemosa (so-called "starburst" livedo) and tender subcutaneous nodules involving the lower legs. Less commonly, the arms and trunk are involved. Ulcerations are seen in up to half of patients (28). Mild systemic symptoms are common, including fever, myalgias, arthralgias, and peripheral neuropathy in the territory of current or prior skin lesions (29). However, the presence of more prominent constitutional, visceral, or neurological symptoms suggests a diagnosis of systemic PAN instead. A chronic, relapsing course is typical of cPAN, though available data suggest the risk of evolution to systemic PAN is extremely low (30).

Limited data are available to guide the treatment of cPAN, but like other forms of skin-limited vasculitis, disease severity should guide management. NSAIDs, rest, and elevation may improve mild symptoms (31), but a trial of colchicine (0.6mg twice daily) or dapsone (50–150mg daily) is appropriate for most patients presenting with subcutaneous nodules (31). These agents are commonly used for treatment of skin-limited vasculitis and have a favorable risk profile. Other non-immunosuppressive agents (e.g., sulfapyridine, hydroxychloroquine, pentoxifylline) are supported by case reports and series and are reasonable options unless symptoms are severe (32–34).

Systemic corticosteroids may be indicated during acute flares, especially for management of pain, ulceration, or systemic symptoms, such as arthralgias, paresthesias, and malaise. Prednisone 30mg per day or equivalent is generally sufficient, but higher doses (e.g., 1 mg/kg prednisone daily) should be considered in the setting of more severe symptoms (e.g., digital ischemia), or if lower doses produce an insufficient response (28). Once remission has been achieved, systemic steroids should be tapered slowly. Coadministration of a steroid-sparing agent may facilitate successful taper.

For those with severe or treatment-refractory cPAN, various immunosuppressive agents should be considered. Azathioprine (2mg/kg daily) (31) or methotrexate (15–25mg weekly) (35) are commonly used. Patients with severe, painful, ulcerative disease who fail to respond to these agents may respond to therapy with a TNFa inhibitor (36, 37), cyclophosphamide (38), or intravenous immunoglobulin (39). In cPAN, ulcerative disease correlates with a relapsing course and the need for more aggressive therapy (40).

## Alternative regimens and special situations

Therapeutic options for less common types of skin-limited vasculitis are even less well defined, drawing mostly upon the experience with other types of cutaneous or systemic vasculitis. Nevertheless, based on limited data, certain therapies may be more effective in specific disorders, as noted below and in Table 1.

## Urticarial vasculitis

Urticarial Vasculitis is a condition consisting of hive-like skin lesions with histologic features of leukocytoclastic

vasculitis. Urticarial vasculitis with normal complement levels is best thought of as a variant of skin-limited cutaneous small vessel vasculitis where the lesions just happen to look hive-like. By contrast, those with low complement levels (hypocomplementemic urticarial vasculitis) are much more likely to have systemic manifestations of disease (such as musculoskeletal, gastrointestinal, or pulmonary symptoms) and to meet criteria for systemic lupus (41).

No trials have been performed to evaluate treatment options for urticarial vasculitis. Because diagnosis and classification of this condition can be difficult, existing case series may include a range of patients, including some with chronic idiopathic urticaria and related disorders.

Antihistamines may reduce swelling and pain associated with skin lesions. Oral steroids are often beneficial but are not appropriate long-term therapy. Dapsone with or without pentoxifylline, hydroxychloroquine, colchicine, and mycophenolate mofetil have been reported to be efficacious in some cases. Omalizumab, anakinra, canakinumab, and rituximab are options for management of recalcitrant hypocomplementemic urticarial vasculitis. A systemic review of treatments identifies a range of potential therapies with variable supporting evidence (42) (Table 1).

## Skin-predominant cryoglobulinemic vasculitis

Cryoglobulinemic vasculitis, resulting from the presence of type II or III cryoglobulins, typically affects the skin, joints, peripheral nervous system, and kidneys. Clinical findings reflect a mixed small and medium-sized vessel vasculitis. Characteristic cutaneous manifestations include palpable purpura on the lower extremities, livedo reticularis, retiform purpura, and necrosis/ulceration.

Some patients with cryoglobulinemic vasculitis have only mild manifestations; in fact, a skin-limited subtype is recognized in the dermatologic addendum to the Chapel Hill Consensus Conference Nomenclature (2). Patients with cutaneous manifestations (e.g., palpable purpura) but lacking significant systemic findings may respond well to agents like colchicine or dapsone (43, 44). Such patients should be monitored over time for disease response and progression. Those with underlying hepatitis C should receive appropriate antiviral therapy.

## Erythema elevatum diutinum

Erythema elevatum diutinum (EED) is a rare, chronic type of cutaneous vasculitis characterized by red-brown papules and plaques which favor acral and extensor surfaces, with histologic features showing leukocytoclastic features and fibrosis. Though it is usually skin-limited, underlying joints and the eyes may be involved.

Dapsone is the therapy of choice for EED. Other options include intralesional steroids, NSAIDs, tetracyclines +/− niacinamide, chloroquine, and colchicine. Treatment of any underlying autoimmune, inflammatory, or hematologic disorder is also advised (45).

## Acute hemorrhagic edema of infancy

Acute hemorrhagic edema of infancy (AHEI) is a rare form of small vessel vasculitis affecting children under 24 months of age and characterized by annular or targetoid purpuric plaques favoring the face, ears, and extremities. While the course is benign, with spontaneous resolution typically occurring within 1–3 weeks, fever, arthralgias, abdominal pain, and glomerulonephritis may occur.

Treatment of AHEI is supportive. Antihistamines and systemic steroids may improve acute symptoms (46). Rarely are therapies indicated on a chronic basis.

## Nodular vasculitis (erythema induratum)

Nodular vasculitis is a lobular panniculitis with vasculitis of small and/or medium-sized vessels in the panniculus. When occurring in the setting of tuberculosis, it may be referred to as erythema induratum (of Bazin). The process is skin-limited/skin-predominate but may be associated with peripheral neuropathy and symptoms related to an underlying/associated disorder, if any.

Initial therapy of nodular vasculitis/erythema induratum should include withdrawal or treatment of any underlying trigger. If associated with tuberculosis, it should be treated with standard anti-tuberculous therapy. Additional options for therapy include nonsteroidal anti-inflammatory drugs and supportive care. Case series describe rapid improvement with potassium iodide (300mg three times daily) (47, 48). Other options (e.g., colchicine, systemic steroids, mycophenolate mofetil) may also be beneficial (49).

## Conclusion and future directions in vasculitis therapy

Presently, the data guiding management of cutaneous vasculitis are extremely limited. Because many vasculitis subtypes are quite rare, multi-institutional collaborations will be necessary to pool combined experiences and conduct high-quality studies.

A multicenter, randomized trial is currently underway comparing colchicine, dapsone, and azathioprine for

management of patients with one of the more common subtypes of isolated cutaneous vasculitis (primary cutaneous small vessel vasculitis, skin-limited IgA vasculitis, and cutaneous polyarteritis nodosa; ClinicalTrials.gov Identifier: NCT02939573) (50).

Vasculitis type, severity, and patient comorbidities determine treatment selection, with the goal of inducing and maintaining disease remission while minimizing drug toxicity. Recent trends in the management of systemic vasculitis demonstrate a shift away from broadly immunosuppressive regimens toward more targeted therapies, based on an improved understanding of disease pathogenesis. Terminal complement inhibition for management of ANCA-associated vasculitis with avacopan (51) and blockade of interleukin-5 for treatment of eosinophilic granulomatosis with polyangiitis with mepolizumab illustrate this trend (52).

The Cutaneous Transcriptomics in Systemic Vasculitis (CUTIS) study is another multicenter collaborative effort to evaluate the histopathologic and transcriptomic features of systemic, and skin-limited, vasculitides through analysis of blood and lesional skin biopsies (NCT03004326). Observations of cutaneous vasculitis in the setting of COVID-19 (53) and in the recently described VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome (54), illustrate the evolving nature of the field. Information gained from these and other studies which enhances understanding of disease pathophysiology may lead to new, targeted approaches to disease management.

## Author contributions

RM drafted the manuscript and takes responsibility for its content.

## Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# The impact on the scientific community of the 2018 addendum to the CHCC

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**vasculitides, nomenclature, Chapel Hill Consensus Conference, addendum to Chapel Hill Consensus, provisional definitions of vasculitides**

## Introduction

The term vasculitis encompasses a wide and heterogeneous group of disorders with shared histopathological findings, namely inflammation and necrosis of the blood vessel wall with variable hemorrhagic and ischemic features. Vasculitis may range in severity from a self-limited disorder in one single organ to a life-threatening disease as vessels of any size can be affected (1).

The 1994 Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC1994) managed to provide a consensus on definitions of such conditions instead of a classification system or shared diagnostic criteras. At first, vasculitides were distinguished according to the size of the affected vessels and the involved immunopathogenic process. Because of the scientific advances in the understanding of the underlying mechanisms, the classification was further expanded and updated with the 2012 revised International CHCC (CHCC2012), which resulted in the introduction of new categories namely Variable vessel vasculitis, Vasculitis associated with systemic disease and Vasculitis associated with probable etiology (2).

However, even though vasculitides frequently involves the skin, it was only in 2018 that a standardized specific nomenclature was proposed on the basis of the CHCC nomenclatures to highlight the special features of cutaneous vasculitides (CV). These acquirements were included in the Dermatologic Addendum to CHCC2012 (D-CHCC). Accordingly, CV were divided into three groups: (1) CV as part of a systemic vasculitis; (2) skin-limited or skin-dominant vasculitis as a variant of a systemic vasculitis which is restricted to the skin without clinically visible or manifested systemic vasculitis and (3) single organ vasculitis of the skin (SOV). The SOVs group has no equivalent in

other organs and they differ from the skin-dominant forms since they do not fulfill sufficient clinical, laboratory, and/or pathologic features of a known systemic vasculitis. They encompass Nodular vasculitis (erythema induratum of Bazin), Erythema elevatum et diutinum, Recurrent macular vasculitis in hypergammaglobulinemia (hypergammaglobulinemic purpura of Waldenstrom) and Normocomplementemic urticarial vasculitis (3). However, other forms, e.g., IgM/IgG immune complex vasculitis, may be also included in this group in the future if supported by research. A good example of systemic vs. skin-limited vasculitis would be IgA vasculitis (IgAV), since many patients with vasculitis which present at dermatology offices have skin-limited IgA: the latter is confirmed by leukocytoclastic vasculitis on histopathology and perivascular IgA deposition on immunofluorescence. While these patients do not show pathological urine, i.e., no erythrocytes urine and no abdominal pain as well as absence of signs of nephritis (non-pathological urine analysis, no dysmorphic erythrocytes, no rise in blood pressure), of gastrointestinal vasculitis (no postprandial abdominal pain, negative hemoccult) and of arthritis, though one cannot exclude that they would show microscopic alterations such as IgA deposition in kidneys since one would not subject these patients to renal biopsies. Systemic but also skin limited IgAV present with perivascular deposition of hypogalactosidated IgA (GdIgA), so this modified IgA1 is not the reason for the difference (4), but patients with systemic IgAV appear to have higher serum levels of GdIgA during active disease (5, 6). None of these Consensus conferences was ever meant to provide diagnostic criteria, but rather to standardize an expanding terminology of different nosologic entities. In more recent years the Diagnostic and Classification Criteria in Vasculitis (DCVAS) represented an interdisciplinary attempt to implement the classification criteria of systemic vasculitides by recruiting 6,991 participants from 136 sites in 32 countries starting from January 2011 to December 2017 (7). The extensive data set collected internationally thanks to the DCVAS study has been subsequently analyzed and resulted in the 2022 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification for Microscopic polyangiitis (MPA), Granulomatosis with Polyangiitis (GPA) and Eosinophilic Granulomatosis with Polyangiitis (EGPA) (8, 9) These new formal criteria are based on weighted items, including also ANCA testing and modern imaging techniques. Because of their excellent sensitivity and high specificity, they represent a useful tool for the clinician, in the setting of clinical research, in differentiating cases of MPA/GPA/EGPA from similar types of vasculitides, when a diagnosis of small- or medium-vessel vasculitis has already been made and other conditions that potentially mimic vasculitides have already been excluded. It is important to note once more that even though these criteria are not meant for diagnostic purpose in the everyday clinical practice, they have been validated to replace the European Medicines Agency (EMA) algorithm published in 2007, previously used to harmonize and rationalize the use of the ACR and CHCC classification systems for epidemiologic purposes (10).

Finally, Diagnostic and Classification criteria in VASculitis (DCVAS) also developed diagnostic criteria for ANCA Associated Vasculitis (AAV) in a large study recruiting patients into an international cohort from 2010 until December 2017 with AAV and comparator diseases (11–13).

## The impact of dermatological addendum in scientific community

We performed a review of the literature to evaluate the actual impact that the D-CHCC has had during the last 4 years in the scientific community. From 2018 until September 2018, the Addendum has been cited in 115 publications on Pubmed and the number of citations per year showed an increasing pattern with a maximum peak reached in 2021 ($n = 36$) (Figure 1). Of these publications, 107 (1, 2, 4, 6, 14–115) were written in English and published by Journals specialized in Dermatology ($n = 41$), Rheumatology ($n = 20$) and Immunology ($n = 13$) and their Countries of publication were mainly represented by the United States of America ($n = 37$), Germany ($n = 21$), United Kingdom ($n = 16$).

Limiting the research to the new described CV, we only found one study in the English literature that was aimed to further investigate the clinical and immunopathologic features of cutaneous IgM/IgG immune complex vasculitis (8) Its main goal was to elucidate the clinical differences between IgM/IgG vasculitis and the more common skin-limited IgA vasculitis (sI-IgAV), thus proposing practical advice for the everyday medical practice. Hemorrhagic blisters and targetoid lesions seemed to be more frequent in the sI-IgAV group, suggesting that these two features could represent a valuable clinical tool that may help differentiating the two forms when immunological tests are unavailable or unaffordable. A group of researchers tried to link special clinical characteristics to the "Recurrent macular vasculitis in hypergammaglobulinemia" category in 2019, while this term was hardly used before 2018 and the clinical symptoms or very similar diseases were referred to with many different names (golfer's vasculitis, Waldenström purpura, exercise-induced vasculitis, Saturday night vasculitis). Concerning "Normocomplementemic urticarial vasculitis," a slight increase in its usage was appreciable after the introduction of the D-CHCC. In fact, before 2018, eight articles only reported this term over 27 years (1991–2018), while after 2018, nine cases could be counted until now (Figure 1). The "Erythema elevatum et diutinum" category, although largely adopted throughout the years, reached its peak of use the biennium 2019–2020 (Figure 1).

Extending our search to other forms of vasculitis, such as IgA vasculitis, we found many discrepancies. In fact, the term

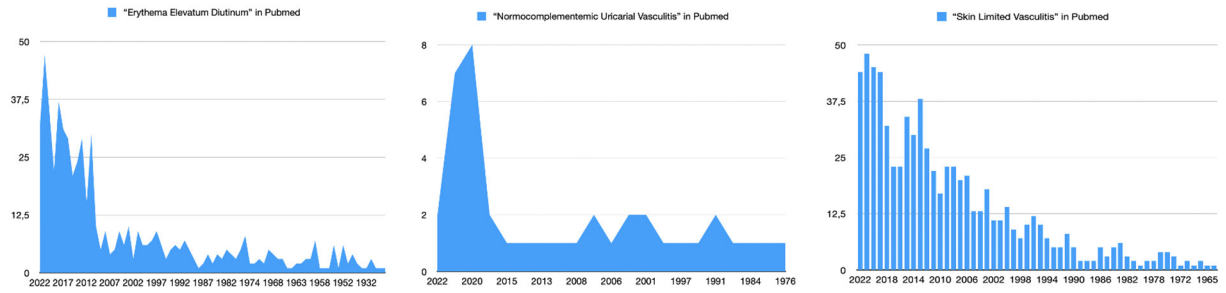


FIGURE 1
Count of the articles that used the terms "Normocomplementemic Urticarial Vasculitis", "Erythema Elevatum Diutinum" and "Skin Limited Vasculitis" over the years in Pubmed.

"Henoch-Schonlein purpura" has been used 962 times, mainly by Pediatrics journals, instead or together with the updated and more accurate terminology of "IgA vasculitis." These data show that there is still confusion in the use of terminology, often based on old classifications and highlight the need for a synergistic work to reach a real widespread consensus on the nomenclature of vasculitis. Moreover, only a few articles (48 in 2021) use the term "skin limited vasculitis" to distinguish these forms from the ones with systemic involvement, although its number has risen since publication of D-CHCC (Figure 1). Thus, although this phenomenon has been known for a long time by dermatologists, it is still not reflected by a punctual use of the specific terms.

## Discussion

The D-CHCC has been adopted internationally by several experts of the field. According to our data, many authors have cited the D-CHCC in their work in the last years as it has been quoted almost 200 times so far, thus recognizing its clarifying role in the nomenclature of CV. Many are becoming more familiar with the new terminology, mainly dermatologists and rheumatologist and especially experts in the field of vasculitis or dermatopathology have explicitly welcome its appearance and supported its use. However, it is not yet mentioned in all articles on CV and several recent publications on vasculitis do not use the terminology as it was consented on. In this regard, it is not of secondary importance the still widespread use of eponymous terminology. This issue is linked to that of the provisional definitions or unsolved problems in the actual nomenclature. For example, while the term IgG/IgM vasculitis will likely continue to be used, further data must be provided for the existence of an isolated form of IgG/IgM vasculitis (no IgA involvement; no other, IgG-IC generating autoimmune disorders associated) (56). The establishment of a standardized and universally accepted nomenclature will also provide a fundamental base for multicentric studies, which would allow us to collect and compare a more significant set of data that is nowadays lacking for a deeper understanding of CV. As modifications to the actual nomenclature are possible, dermatologists and rheumatologists, among others, are invited to contribute with suggestions for improvement. In fact, the D-CHCC represent a basis for interdisciplinary discussion on CV offering written statements which can be either falsified or verified by clinical observation on patients. One of the aims of the D_CHCC group was the chance to test the practicability of the D-CHCC definitions in the clinical setting. In particular it would be useful to know, if each dermatosis with histopathologically proven vasculitis, can be assigned to the various defined forms of vasculitides. Another aim of the D-CHCC was to encourage the acquisition of new data to help clarify e.g., the existence of lymphocytic or eosinophilic vasculitis according to the consented, but provisional definitions.

To conclude, CV encompass a wide and heterogeneous group of rare conditions, probably often underdiagnosed and under investigated by clinicians with no specialized dermatologic competences, especially in the cases where clinical manifestations are minor and self-limiting. Even though some clinical entities are now known to have specific clinical features, much more needs to be done to further implement our knowledge in the underlying pathogenetic mechanisms, which remain partially unknown and is of fundamental importance for a better diagnostic and therapeutic management of patients suffering from CV.

## Author contributions

MC, EA, and CS conceptualized the work. VC and EM wrote the text. AV and CA collected the data. AC, LQ, and WV revised

the drafts. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Mucocutaneous manifestations of Behçet's disease: Pathogenesis and management from perspectives of vasculitis

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Behçet's disease (BD) is a systemic inflammatory disorder characterized by vasculitis affecting blood vessels of any caliber or type. It can present with a wide spectrum of vasculitic lesions, including erythema nodosum-like lesions and retinal vasculitis, and may also lead to larger vessel diseases, such as aortic aneurysm and deep vein thrombosis. The full etiology of BD remains unclear, but it is considered a polygenetic disease with multiple genetic risk factors that promote immune dysregulation and thrombophilia. Inflammation can be triggered by environmental factors, such as bacteria or viruses, and the dysregulation of innate and adaptive immune cell subsets. Neutrophils and lymphocytes are the primary players involved in BD pathogenesis, with specific innate (i.e., neutrophil-derived reactive oxygen species and neutrophil extracellular traps) and adaptive (i.e., anti-endothelial cell antibodies) processes inducing endothelial cell activation and chemotaxis of inflammatory cells, leading to coagulation and vasculitis. These inflammation-induced vasculitic or vasculopathic features are observed in most mucocutaneous BD lesions, although vasculitis *per se* is often pathologically evident only during a brief period of the disease process. Due to the multifactorial nature of BD-associated inflammation, broad-spectrum anti-inflammatory medications, including glucocorticoids and immunosuppressive drugs, have been the mainstay for managing BD. In addition, inhibitors of interleukin (IL)-1, tumor necrosis factor (TNF)-α, and IL-17, which target innate and adaptive immune functions dysregulated in BD, have emerged as promising new therapeutics. In this review, we discuss the muco-cutaneous manifestations of BD by focusing on the underlying vasculitic components in their pathologies, as well as the current array of treatment options.

KEYWORDS

**Behçet's disease, vasculitis, mucocutaneous, pathogenesis, thrombosis**

# Introduction

The term vasculitis generally refers to an inflammation within the blood vessel wall, leading to its destruction. In contrast, conditions involving the formation of a thrombus within the vascular lumen that compromises blood flow, as well as more general blood vessel diseases, are known as vasculopathies. Historically, vasculitides—autoimmune diseases characterized by vasculitis—have been classified by the size of the vessel involved. However, one member of this group, known as Behçet's disease (BD), has been defined as variable vessel vasculitis by the 2012 Revised International Chapel Hill Consensus Conference (1), meaning it can affect vessels of any size (i.e., small, medium, or large) and type (i.e., arteries, veins, or capillaries). For example, many BD patients develop posterior uveitis with severe retinal vasculitis, including typical vascular pathologies with endothelial activation and diffuse capillary leakage. Conversely, in a subset of BD patients, inflammatory vascular damage occurs on larger vessels, and this often presents with life-threatening sequelae, such as an aortic aneurysm or deep vein thrombosis (DVT). Critically, the pathologic cues driving vessel damage in BD remain elusive, and not all clinical manifestations of BD, particularly mucocutaneous lesions, are directly related to vasculitis in their pathology. Herein, we review BD pathogenesis with respect to vasculitis and provide updated clinical information and therapeutic recommendations for mucocutaneous BD, with special emphasis on idiopathic immune-mediated vasculitis.

# Pathogenesis

## General overview of Behçet's disease pathogenesis

Behçet's disease is a systemic inflammatory disease characterized by recurrent oral and genital ulcerations, inflammatory skin lesions, and uveitis. Various systemic manifestations, including arthritis, as well as gastrointestinal, neurological, and vascular involvements, can also occur, and life-threatening complications may be accompanied by severe inflammation of internal organs. The etiological mechanisms underlying BD pathogenesis remain to be elucidated, although it is hypothesized to result, in part, from immune dysregulation in genetically susceptible individuals, which is provoked by environmental factors, such as an infectious agent or trauma. Consequently, genetic predisposition, the role of environmental factors, and innate/adaptive immunological consequences have been widely studied in the context of BD (2, 3).

### Role of genetic factors

Previous studies have found that the HLA-B51 allele of the major histocompatibility complex (MHC) is strongly associated with BD development across all ethnicities. In particular, a meta-analysis that included data from 78 independent studies and 4,800 BD patients reported that the odds ratio (OR) of BD development in those with the HLA-B5/B51 allele vs. those without this allele was 5.78 (95% confidence interval: 5.00–6.67) (4). However, it seems unlikely that one specific HLA allele can fully explain the pathogenesis of BD. Accordingly, genome-wide association studies (GWAS) have further contributed to our understanding of BD pathogenesis by uncovering novel susceptibility genes. A recent GWAS, for example, identified a genetic interaction between HLA-B*51 and the endoplasmic reticulum aminopeptidase 1 (*ERAP1*) gene in BD (5). As its name suggests, the product of this gene is an endoplasmic reticulum-expressed aminopeptidase that trims antigen peptides to an optimal size before loading onto MHC class I molecules. Intriguingly, the observed genetic epistasis in which homozygosity for *ERAP1* p.Arg725Gln mutation strongly increases the OR for BD development in HLA-B51 + vs. HLA-B51- individuals, suggests a role for MHC-I, peptide, and T cell interactions in BD pathogenesis, thereby revealing a possible MHC-I-opathy (6). However, the severe phenotype of BD is not uncommon in patients lacking HLA-B51; thus, the causal role of MHC in BD should not be overrated (7).

In addition to HLA and *ERAP1*, a series of GWAS further identified BD susceptibility loci at multiple genes related to innate and adaptive immune function. In one case, polymorphisms on interleukin (*IL)23R/IL12RB2* and *IL10* loci were found to be closely correlated with dysregulation of inflammatory cytokine profiles in BD patients (8). Levels of both T helper (Th)1- and Th17-related cytokines such as IL-12, interferon (IFN)-γ, IL-17A, IL-17F, IL-22, and IL-23 have also been widely investigated in serum, blood immune cells and tissues of active BD patients (9). These studies suggest genetic variants in the adaptive immune system are directly related with immunophenotype of BD. Notably, the *IL10* variants associated with BD-susceptibility generate a reduced expression of this anti-inflammatory cytokine, which may lead to an imbalance between pro-inflammatory processes and immune regulation (8). In addition, many other susceptibility loci for BD development are also located in genes related to the innate immune system, including C–C motif chemokine receptor (*CCR)1-CCR3,* killer cell lectin-like receptor C4 (*KLRC4*), *IL1B*, interferon regulatory factor (*IRF)8* and interferon gamma receptor 1 (*IFNGR1*) (5, 10, 11). Thus, a genetic predisposition for BD is associated with alterations in both adaptive and innate immune system function, which correspond to the clinical spectrum of BD characteristics, more broadly, to the manifestations of numerous autoimmune diseases and autoinflammatory syndromes.

### Role of environmental factors

Infectious agents have long been proposed as triggering factors for BD development. In particular, many studies suggest

that a cross-reactive immune response against human proteins possessing high homologies with certain antigens from bacteria (i.e., *Streptococcus sanguinis*) or viruses [i.e., herpes simplex virus (HSV)-1] plays a key role in BD pathogenesis (12). Results from one previous study revealed that the product of the Bes-1 gene and heat shock protein (HSP)-65 derived from an uncommon serotype of oral *S. sanguinis* show high degrees of sequence similarity to the retinal protein BRN3b and human HSP60, respectively (13). Clinically, pathergy tests with self-saliva were found to elicit an increased prevalence of positive reaction compared with control saline, suggesting that hypersensitivity to oral streptococci may induce an innate immune response contributing to BD pathology (14). In addition, the observation of distinct Th1 cell responses in peripheral blood mononuclear cells (PBMCs) derived from HLA-B51 + carriers and non-carriers upon challenge with *S. sanguinis* antigens suggests that antibacterial T cell-mediated immune responses may be at least somewhat dependent on genetic predisposition (15).

Studies have also suggested a viral etiology for BD by reporting the detection of greater quantities of HSV-1 DNA in saliva, genital ulcers (GUs), intestinal ulcers, and PBMCs from BD patients (16, 17). Additionally, using an *in vitro* model with cultured human dermal microvascular endothelial cells, HSV-1 was found to increase expression of cell adhesion molecules, such as intracellular adhesion molecule 1 (ICAM1/CD54), vascular adhesion molecule 1 (VCAM1), and E-selectin on endothelial cells, resulting in increased binding of immune cells to the endothelium (18). Moreover, repetitive inoculation of HSV-1 on the scratched earlobe of the Institute of Cancer Research (ICR) mice induces BD-like symptoms, including skin and GUs, eye symptoms, arthritis, and gastrointestinal ulcers (19). Intriguingly, in addition to HSV-1, the housing environment and fecal microbiota were also important factors for eliciting an inflammatory phenotype in this induced mouse model (20). Given the clinical ineffectiveness of anti-viral agents alone for treating active BD patients (21), this suggests that rather than a direct role for HSV-1 infection in BD, HSV-1-induced immune dysregulation may contribute to the induction of BD pathology in conjunction with immune responses to other environmental factors, including bacteria. Recent epidemiological trends showing a decreasing incidence of BD in developed countries further support the importance of infectious agents in triggering BD pathogenesis (22–24).

## Immunological dysregulation

### Innate immune system

Neutrophil hyperreactivity is a key feature of BD pathogenesis, with neutrophils from active BD patients showing a higher migratory capacity (25) and exhausted phagocytic activity (26), relative to those from healthy controls. Neutrophil infiltration and release of reactive oxidative species (ROS) from these cells also contribute to tissue injury, inflammation, and thrombosis (27), and the release of neutrophil extracellular traps (NETs) may further augment these processes (28). Of note, neutrophils from BD patients exhibit spontaneous NETosis compared with those from healthy controls, suggesting that targeting NETosis might represent a promising therapeutic approach for preventing BD-associated thrombosis and vascular events (29).

Various other innate immune cell subsets, including monocytes, natural killer (NK) cells, and γδ-T cells, are also thought to contribute to BD pathogenesis. Notably, inflammatory monocytes are increased in BD, and these cells express higher levels of TLR2 and TLR4, both of which contain genetic susceptibility loci for BD development (30, 31). Another GWAS-identified locus, which is associated with decreased expression of CCR1 and increased expression of CCR3, is also related to monocytes (5), as functionally, this allele corresponds to their polarization into inflammatory M1 macrophages over regulatory M2 macrophages (32). Moreover, the *IFNGR1* gene has been recently identified as a susceptibility locus for BD in a large multi-ethnic GWAS, and functionally, BD-risk variants show increased expression of IFNGR1 on monocytes (10). Taken together, these findings suggest that certain cellular subsets involved in innate immunity, including neutrophils and monocytes, are closely associated with a genetic predisposition for BD development *via* their critical roles in microbial sensing, thrombogenesis, and fine-tuning of the adaptive immune system.

### Adaptive immune system

The adaptive immune system, including both Th1- and Th17-mediated immune responses and related cytokines, also plays an important role in the pathogenesis of BD. Upon IL-12 or IL-23 stimulation, naïve CD4 + T cells can differentiate into two cell types: (1) Th1 cell subsets, which secrete IFN-γ, IL-2, and TNF; and (2) Th17 cells expressing IL-17A/17F and IL-22. Of these, the levels of IL-12 and IFN-γ are significantly increased in the blood of BD patients (33), and IFN-γ is increased in the aqueous humor of patients with BD uveitis (34). Similarly, a higher percentage of Th17 cells are present in blood from individuals with active BD, and serum levels of Th17-related cytokines, including IL-17 and IL-23, are increased in BD patients (35, 36). In contrast, regulatory T cells are suppressed in active BD in a Th17-derived IL-21-mediated manner (37). These data, combined with the identification of disease susceptibility loci in *IL23R-IL12RB2, IL10, STAT4*, and *IFNGR1,* as noted above, further support a direct role for a Th1- and Th17-skewed adaptive immune response in BD pathogenesis (5, 8, 10). As monocytes from BD patients facilitate Th1 and Th17 differentiation of T cells in an allogeneic co-culture model (38), it is likely that innate players, including antigen-presenting cells (APCs), are involved in shaping the dysregulated adaptive immune response present in BD.

## Vasculitis and thrombosis in Behçet's disease

Although the precise mechanisms remain unclear, it is thought that the inflammatory processes outlined above induce activation of the vascular endothelium *via* cytokine signaling, resulting in BD-associated vasculitis. This condition has a number of key features suggesting the close connection between inflammation, endothelial damage, and thrombogenicity. Under normal physiological conditions, activation of the coagulation cascade by inflammation is part of a natural defense mechanism against pathogens. However, aberrant inflammation can induce thrombosis, which in turn, amplifies inflammation, leading to so-called immuno-thrombosis (39). This process may further lead to the recruitment and activation of neutrophils and other immune cells, which are partially modulated by the endothelium.

The early observation of polymorphonuclear neutrophils adhering to endothelial cells and their subsequent migration into inflamed areas supports the importance of enhanced leukocyte chemotaxis and the critical role of vasculopathy in BD pathogenesis (40, 41). It was subsequently shown that excessive levels of ROS produced by neutrophils modify the structure of fibrinogen, generating an altered architecture that is less susceptible to plasmin-induced lysis (27). In addition, as noted above, neutrophil-produced NETs are also associated with thrombophilia in BD (29). Collectively, these data are consistent with early ultrastructural observations suggesting that endothelial cell damage and subsequent necrosis of damaged cells are the initial events leading to thrombosis in BD skin lesions (42, 43). Radiological observation of thickened vessel walls in patients with, or even without, vascular BD, when compared to vessel walls (i.e., femoral vein) in healthy controls, further supports the hypothesis that endothelial activation, not thrombosis, is the primary event in this disease (44, 45).

A different approach for investigating the factors that initiate endothelial damage in BD identified serum anti-endothelial antibodies as a key trigger. Specifically, using endothelial cells from human umbilical veins and adipose tissue, Cervera et al. detected an increased level of serum anti-endothelial antibodies in BD patients, which are correlated with disease severity (46). These anti-endothelial cell antibodies induce increased expression of cell adhesion molecules on endothelial cells (47), a phenotype that is functionally associated with neutrophil recruitment (48). Subsequent proteomics analyses identified target proteins for the different isotypes of anti-endothelial antibodies, including IgM anti-human α-enolase and IgA anti-heterogeneous nuclear ribonucleoprotein (hnRNP) A2/B1 antibodies, which cross-react with streptococcal antigens (49, 50). Subsequently, additional proteins, including prohibitin (51), HSP27 (52), and annexin A2 (53), were identified as targets for anti-endothelial cell antibodies. Given the strong association between levels of anti-hnRNP A1 IgG anti-endothelial antibodies and DVT observed in a large cohort study, it is likely that the autoimmune mechanism of BD is closely linked to vascular involvement and thrombotic tendency (54). However, the specific question regarding precisely how endothelial damage can induce thrombotic tendency in BD remains unanswered. Overall, the data suggest a model whereby increased oxidative stress at sites of inflammation resulting from neutrophil recruitment and activation likely contributes to endothelial cell damage, and the production of anti-endothelial antibodies against various antigens exposed from endothelial cells further stimulates endothelial activation *via* molecular mimicry. In addition, subsequent dysregulation in thrombogenesis and fibrinolysis, subsequently, a multifactorial process related to fibrinolysis including secretion of endothelial-derived proteins [i.e., plasminogen activator inhibitor 1 (PAI1)], tissue factor exposure, and inherent dysregulation in plasma homocysteine levels may contribute together to vascular involvement in BD (**Figure 1**) (55, 56).

Behçet's disease partly shares clinical and pathogenic features with other types of primary vasculitides. Anti-neutrophil cytoplasmic antibody (ANCA)-associated-vasculitis (AAV), a representative vasculitis group involving small sized vessels, also manifests various clinical symptoms and signs related to a systemic inflammatory response, end organ microvascular injury, or the mass effect of granulomas. Despite heterogeneity among subgroups of AAV, both arterial events and venous thrombosis occurs frequently in AAV. Furthermore, genetic risk alleles for the development of AAV include HLA SNPs (i.e., HLA-DP, HLA-DQ), innate (i.e., *TLR9*) or adaptive (i.e., *CTLA4, FCGR3B, IL10, IL2RA*) immune response, and signal transduction (i.e., *PTPN22*) (57). However, characteristic predilections for organ involvement in AAV subgroup exist and the presence of ANCA directed to proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA) can be differentiated from BD. Of note, genes encoding ANCA associated proteins such as proteinase 3, serpin family A member 1 are associated with disease development, and the direct role of ANCA binding to Fcγ receptor on neutrophils in NET formation and endothelial damages is more clearly defined (58–60). In summary, comparison between BD and other type of primary vasculitides highlights both similar features as immune-mediated vasculitis/thrombophilia and disease-specific dissimilarities in genetic and immune pathogenesis between conditions.

# Clinical features

Diagnosis of BD is primarily based on clinical symptoms, as there are no diagnostic laboratory findings. Oral ulcers (OUs), GUs, skin lesions, and uveitis comprise the major Japanese diagnostic criteria (61), whereas the International Study Group

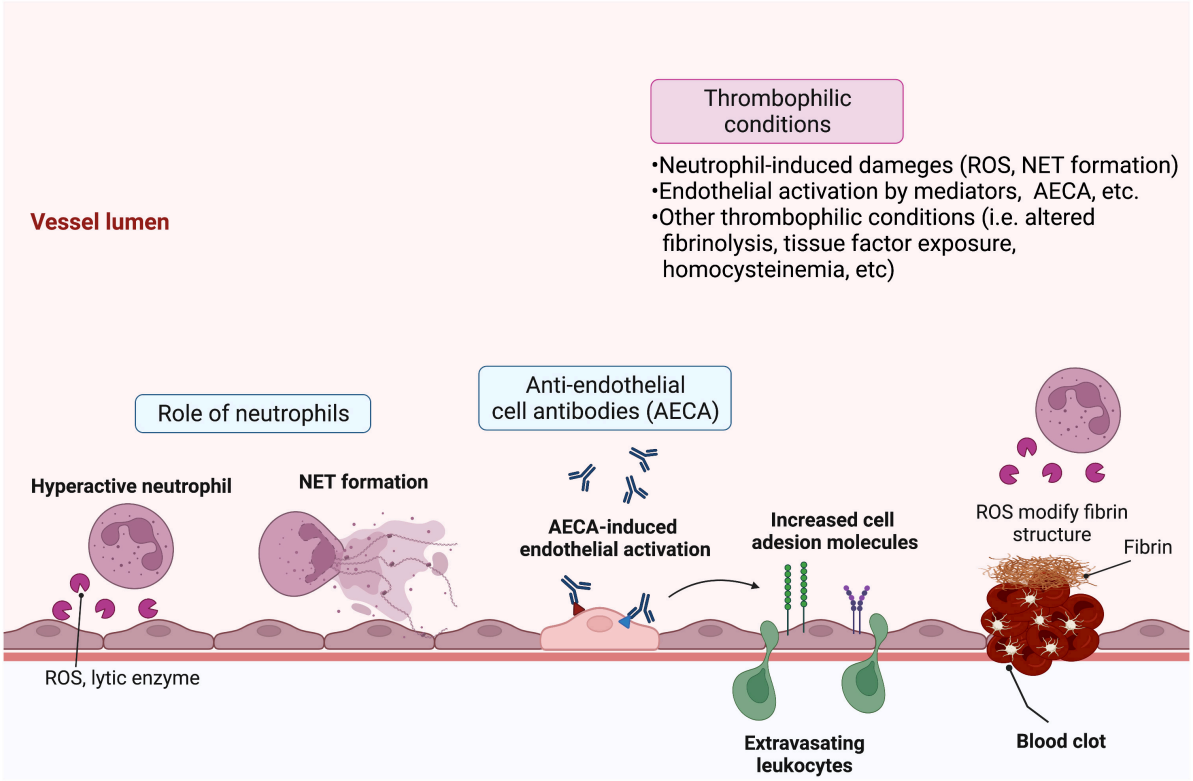


FIGURE 1
Schematic overview of the pathologic features of Behçet's disease (BD) that lead to vasculitis and thrombosis. Various factors contribute to endothelial damage and subsequent vasculitis and thrombosis in BD. Hyperactive infiltrating neutrophils release reactive oxygen species (ROS) and lytic enzymes and may form neutrophil extracellular traps (NETs), which activate or damage endothelial cells. Circulating anti-endothelial cell antibodies specific for various endothelial target proteins can further activate endothelial cells. In turn, they upregulate cell adhesion molecules that stimulate leukocyte migration. Moreover, activated endothelial cells can secrete proteins, including plasminogen activator inhibitor-1 (PAI-1) and tissue factor, which contribute to clotting and thrombosis. Patient characteristics, such as high levels of plasma homocysteine or neutrophil-derived ROS, can further augment thrombophilic activity *via* dysregulation of fibrinolysis. Created with BioRender.com.

(ISG) criteria include OUs, GUs, uveitis, skin lesions, and positive pathergy test (62). The International Criteria for Behçet's Disease (ICBD) criteria also include a positive pathergy test with the four major symptoms noted above, as well as the presence of neurologic and vascular lesions (63).

## Mucocutaneous manifestations

Mucocutaneous lesions, which are included in all the above-mentioned diagnostic criteria, are the most common symptom of BD at onset or at any stage of the disease and persist with recurrent attacks throughout the disease course. These may include erythema nodosum (EN)-like lesions, papulopustular lesions (PPLs), superficial thrombophlebitis, and pathergy reactions. Notably, the appearance of mucocutaneous lesions precedes by several years the onset of internal organ involvement, such as the development of ocular or vascular lesions, suggesting that these represent a key manifestation of early BD pathogenesis (64).

### Oral ulcers

Oral ulcers often appear as the first disease manifestation and are present in most patients with BD. These can develop on the lips, gingiva, buccal mucosa, and tongue and resemble recurrent aphthous stomatitis (RAS). BD-associated OUs can be classified as minor, major, or herpetiform, depending on their size and number. Minor OUs are the most common (80–85% of cases) and are distinguished by small (<1 cm), shallow ulcers that heal within 1–2 weeks without scarring. Major OUs are less commonly seen (10–15% of cases); they are morphologically similar to minor OUs but are larger (>1 cm), deeper, and more painful. Major OUs also last longer than minor OUs and frequently heal with scarring and tissue loss. Herpetiform OUs are the rarest form (5% of cases); these are 1–3 mm in size and 10–100 in number (65). Notably, the presence of major

OUs is a characteristic of BD that allows it to be clinically differentiated from RAS.

The recurrence of OUs in BD is affected by fatigue, stress, food, smoking cessation, and menstruation. In addition, conditions associated with poor oral hygiene, such as periodontitis, chronic tonsilitis, and tooth decay, are often observed in BD patients. Therefore, we have previously proposed that species of oral bacterial flora, particularly *S. sanguinis,* can be triggers for OUs in BD (66). In support of this hypothesis, results from *in vitro* experiments revealed that inflammatory cytokines, including IFN-γ and IL-6, are produced by PBMCs from BD patients in response to stimulation with Streptococcal antigen derived from *S. sanguinis* (67). Titers of serum antibodies against *S. sanguinis* were also found to be elevated in BD patients (68). Further, as noted above, HSP-65 peptides produced by *S. sanguinis* show considerable sequence homology to the human HSP60 protein, and intriguingly, the human HSP60 peptide induced proliferation of T cells in BD patients, but neither in healthy controls nor patients with rheumatoid arthritis (69). Elevated serum levels of HSP60 and VEGF were detected in BD patients, and the serum level of VEGF is correlated with vascular involvement (70). Thus, it is thought to be involved in the generation of vascular inflammation, leading to vascular damage in BD.

### Genital ulcers

Genital ulcers, which occur in more than 60% of BD patients, are the second-most common manifestation at disease onset after OUs and are also a specific clinical finding for BD diagnosis. In male patients, GUs often occur on the scrotum and penis, whereas in women, GUs are commonly found on the major and minor labia. Large ulcers are deep and sometimes leave a scar. For diagnosis of BD, these painful ulcers should be differentiated from herpes infection, which produces grouped, small, shallow ulcers that recur in the same location. The presence of multinucleated acantholytic cells in the Tzanck smear or HSV-PCR test positivity can differentiate HSV infection from the GUs of BD.

### Erythema nodosum-like lesions

Erythema nodosum-like lesions are identified in one-third to half of BD patients and are more common in females. These are painful oval-shaped erythematous subcutaneous nodules that frequently involve the pretibial region and are often associated with fever, malaise, and arthritis. EN-like lesions of BD are relatively small and heal within 1–3 weeks without a scar; however, they typically recur over long periods. EN is not specific to BD, and classic EN is often associated with bacterial and viral infections, as well as with conditions such as pharyngitis, Crohn's disease, ulcerative colitis, and Sweet's syndrome. Therefore, both clinical and histological differential diagnosis is necessary to distinguish EN-like lesions of BD from classic EN.

### Papulopustular lesions and acneiform eruption (pseudofolliculitis)

Papulopustular lesions and acneiform eruption in BD are folliculitis- or acne-like sterile pustules on the face, neck, and extremities that rapidly appear and are present in more than 60% of BD patients. They are usually small, uniformly shaped, non-follicular lesions, which heal quickly without scaring but often recur with pain. PPL can be developed either as non-follicular or follicular based on lesion morphology but non-follicular PPL localized in the lower extremities has been reported to be more specific for BD (71).

### Pathergy

Pathergy, or needle reaction, is a test that measures erythematous papule or pustule formation in response to a prick with a sterile needle, which develop 24–48 h after the test is administered. Positive pathergy is a cutaneous hypersensitivity reaction against trauma and a characteristic feature that occurs more frequently in active BD patients. In the early phase of BD, pathergy is identified at the site of injection and infusion. The positivity rate for needle reaction among BD patients is 50% in the eastern Mediterranean region, such as in Turkey and Iran, but relatively low at less than 30% in Asian countries, such as Korea and Japan. These contrasting results in distinct geographic regions are attributed to differences in pathergy test application methodology and ethnic characteristics (65). It has been suggested that the pathergy reaction might be a response to bacteria residing on the skin surface, although, at present, no clear causation has been confirmed. Notably, we previously showed that needling with autologous oral salivary fluid on it induced a positive pathergy reaction on the forearm of BD patients (14). However, because the patient numbers in this study were small, a definitive conclusion awaits further investigation.

### Superficial thrombophlebitis

Superficial thrombophlebitis is a cord-like painful induration along the vein in the legs, which also sometimes occurs on the forearm after intravenous injection in those with BD. Importantly, when multiple superficial thrombophlebitis lesions are observed in a BD patient, the individual should be carefully examined for vascular lesions involving the deep veins or major vessels in the internal organs (e.g., pulmonary arterial thrombosis).

## Histopathological features of vasculitis in mucocutaneous symptoms of Behçet's disease

Vasculitis is the fundamental pathologic characteristic of the BD skin lesions described above, with thrombophlebitis (i.e.,

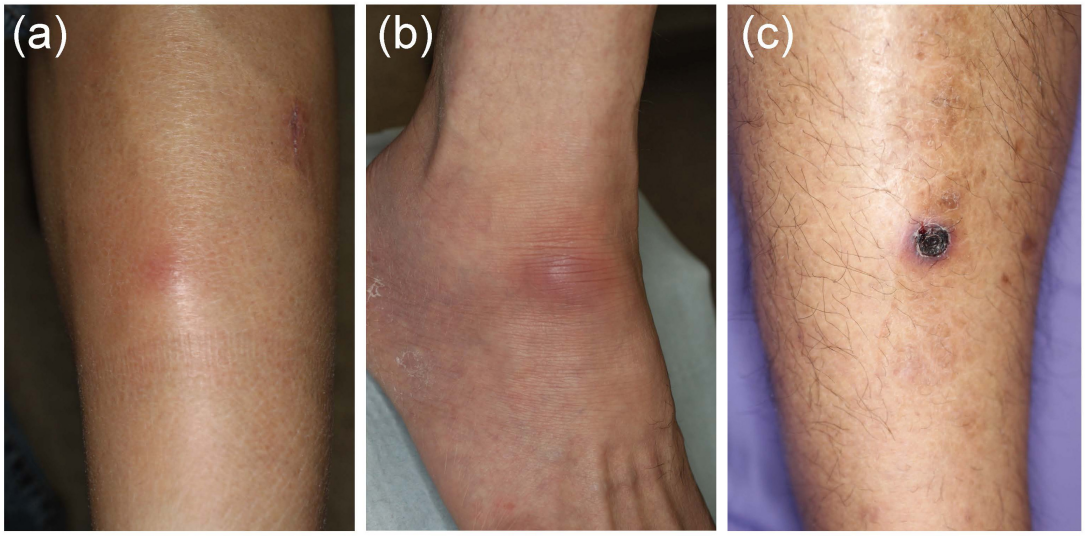


FIGURE 2
Various skin lesions that may be present on the lower legs in Behçet's disease (BD) patients. **(a)** Case 1, erythematous subcutaneous nodule on the leg. **(b)** Case 2, erythematous plaque on the ankle. **(c)** Case 3, crusted ulcer on the leg.

thrombus-associated inflammation) representing the second-most important manifestation in mucocutaneous BD lesions. Critically, both of these characteristic features are also present in the major organs of the intestinal, vascular, and central nervous systems that are affected by BD. Because the onset of major internal organ involvement follows the appearance of mucocutaneous symptoms by several years, the observation that key histological features of mucocutaneous lesions precede and predict the appearance of major internal organs affected by BD is an extremely important finding.

Aphthous OUs in BD patients typically contain neutrophilic perivascular infiltration, and both macrophages and phagocytic apoptotic cells can be identified in the damaged epithelial layers, a feature that is not present in normal oral mucosal tissue (72). We have further shown that the epithelial component at the margin of BD-associated OUs is immunostained by anti-human IgA, IgM, complement, and streptococcal antibodies in BD patients (66).

In EN-like lesions of BD, septal panniculitis can be histologically identified, with a predominantly neutrophilic infiltration in combination with lymphocytes. The blood vessels also often show prominent infiltration of neutrophils and vascular changes (**Figures 2A**, **3A,B**), and venous thrombosis caused by neutrophil infiltration may also be present in the deep dermis. In some cases, vascular damage that is similar to necrotizing vasculitis has further been reported in EN-like BD lesions (**Figures 2B**, **3C–E**). Moreover, as shown in representative ulcerative lesions with crusts on the legs of BD patients, venous thrombosis may be identified in the deep dermis through fat tissue in cutaneous lesions, and this is indicative of vascular BD (**Figures 2C**, **3F,G**). Importantly, because classic EN-like lesions do not ulcerate, when ulcerating EN-like lesions are observed, vascular BD, as well as necrotizing vasculitis and peripheral blood insufficiency should all be considered (73).

Detection of perivascular neutrophil infiltration in the dermis is an important initial histological finding in BD skin lesions. Histochemical analysis showed enhanced expressions of IL-8 and CCL20 (MIP-3α) in pustular skin lesions from BD patients, and the isolated skin-infiltrated T cells produced high amounts of IL-8 (74). Moreover, the serum level of IL-8 correlates with disease activity, and the serum IL-8 level was elevated in active BD patients with vascular involvements (75). These data suggest that the cytokines and other proinflammatory factors, which activate neutrophils, contribute to the induction of both vasculitis and venous thrombosis. After inflammation, a secondary cause of thrombophilia in BD is thought to be myeloperoxidase, which is produced by active neutrophils and may be associated with endothelial cell abnormalities and induction of vascular damage (48). In addition, as noted above, NETs have been reported with thrombophilia in BD (29).

Papulopustular lesion in Behçet's disease presents with papules and pustules that are mainly observed on the trunk, lower extremities, upper extremities, and face (76). Of note, similar to OUs and EN-like lesions in BD, vascular-related histological findings have also been reported in BD-associated PPL (77, 78). One study found that out of 42 BD patients with PPL, seven (16.7%) showed histological features of leukocytoclastic vasculitis, and 27 (64.3%) displayed superficial and deep perivascular inflammation and/or interstitial infiltration; no vasculitis was observed in controls with acne

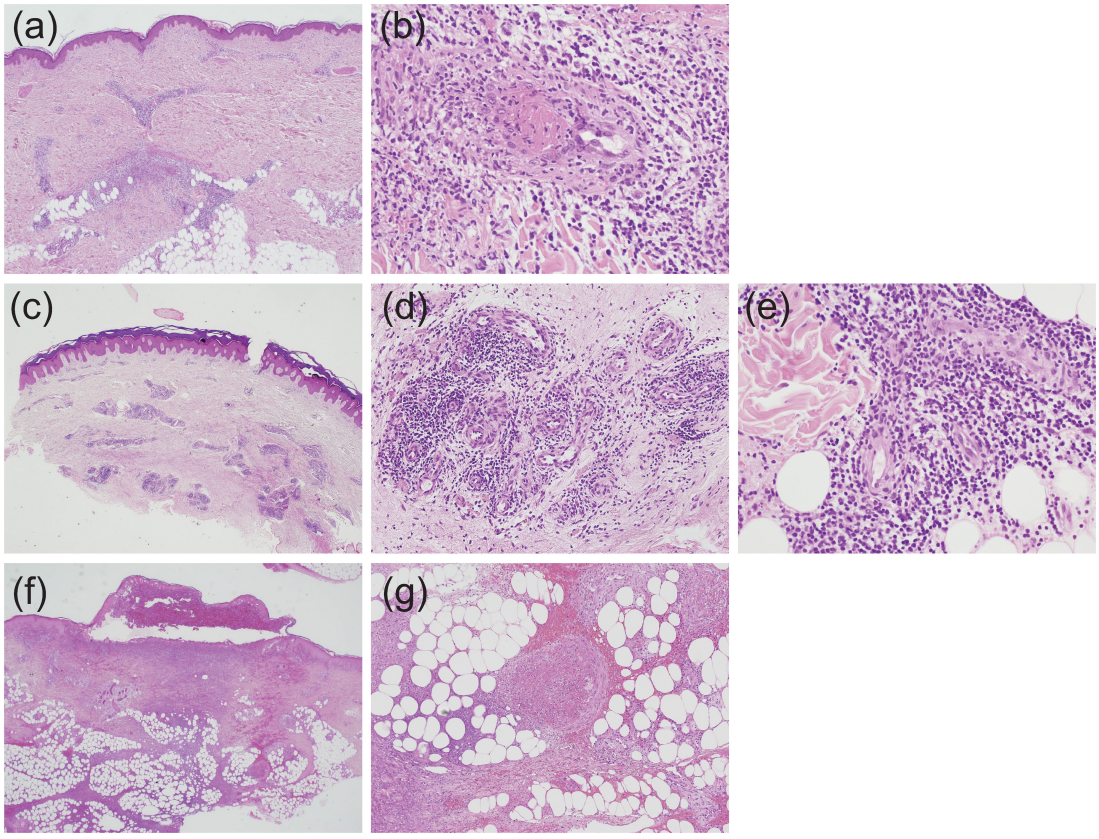


FIGURE 3
Histopathological findings indicative of vasculitis in Behçet's disease (BD) skin lesions; all slides were stained by hematoxylin and eosin, and the magnification is shown in parenthesis. **(a,b)** Case 1, perivascular neutrophilic infiltration in the dermis (**a**, ×20) and subsequent occlusion of the involved blood vessel (**b**, ×400). **(c–e)** Case 2, perivascular dense infiltration in the dermis (**c**, ×20), and prominent accumulation of neutrophils and lymphocytes around blood vessels in the mid (**d**, ×200) and deep (**e**, ×400) dermis. **(f,g)** Case 3, extensive dermal infiltration of neutrophils beneath a crusted lesion (**f**, ×20) and occlusion of venous blood vessels and neutrophilic infiltration in septal regions (**g**, ×100).

vulgaris (77). In a separate study, Chen et al. (79) reported that 20 out of 42 patients (48%) had signs of cutaneous vasculitis, with 17% showing leukocytic vasculitis and 31% displaying lymphocytic vasculitis. Consistent with these observations, on histology, non-follicular PPLs from BD patients were found to contain significantly more leukocytoclastic vasculitis than non-lesional skin, with lesional vessels showing IgM, IgG, C3, and fibrin deposition (71). These features indicate that non-follicular PPLs are characteristic cutaneous manifestations of BD with significant diagnostic value for identifying vasculitis in BD lesions. Interestingly, most BD patients with clinical PPL histologically displaying signs of vasculitis were male (90%), a finding consistent with the natural course of BD, in which severe cases occur more commonly in males than in females.

In superficial thrombophlebitis, occlusion of the lumen within venous blood vessels can be histologically identified in subcutaneous lesions, along with perivascular neutrophilic infiltration. Therefore, this condition shares clinical features with EN-like lesions and vasculitis in the leg, wherein induration is cord-like, and histological examination is necessary in such cases. The ultrastructural examination can identify vascular changes in cutaneous BD lesions (80), and multiple superficial thrombophlebitic lesions are often associated with the existence of DVT. Thus, to examine DVT and differentiate BD from superficial thrombophlebitis, magnetic resonance imaging (MRI), computed tomography (CT), and other imaging techniques are helpful.

## Therapeutic approaches for mucocutaneous Behçet's disease

### Topical treatment

The European Alliance of Associations for Rheumatology (EULAR) task force has stated that treatment decisions for patients with BD may depend on the severity of mucocutaneous lesions, as well as the dominant or codominant lesions present (81, 82). Topical treatment is generally prescribed as an adjunct

to systemic therapy. However, topical measures alone can be administered in cases showing remission for a long period, those without major organ involvement, or elderly patients without severe organ involvement (83). In mild cases of OU, therapeutic approaches may also involve a mild diet and avoiding consumption of spicy, salty, or hard to digest foods, as well as synthetic additives (83).

Topical corticosteroids are efficacious for the treatment of most mucocutaneous lesions. One randomized comparative study showed better efficacy for 0.1% triamcinolone acetonide ointment vs. an active comparator, phenytoin syrup, for the control of OUs in BD (84). Thus, based on the clinical benefit of topical corticosteroids for OUs in RAS, these are recommended as the initial treatment choice for uncomplicated OUs in BD. Further, while the effectiveness of topical corticosteroids for the treatment of GUs and EN-like lesions has not been investigated in randomized clinical trials, they have long been empirically used to treat GUs and are listed as first-line treatment in the EULAR recommendations (82). Topical steroids can also be used to treat EN-like lesions, and the Japanese guideline for mucocutaneous lesions recommends topical steroids for mild-to-moderate cases with EN-like lesions (85). The efficacy of topical steroids for BD-associated PPL is limited. However, PPL is more common in patients with a positive pathergy test, suggesting that topical steroids may hold potential benefits for resolving inflammatory PPL caused by the hypersensitivity reaction in BD (76). In addition to topical corticosteroids, 3 months of topical sucralfate treatment for OUs effectively reduces pain and time to healing (86). Pimecrolimus cream in combination with colchicine also helps to shorten the healing time of GUs in BD (87).

## Systemic treatment

Several systemic treatments may be considered in BD patients with mucocutaneous lesions, depending on the clinical spectrum and severity of the disease (81, 82, 85). They are described in more detail below.

### Colchicine

Colchicine suppresses neutrophil function and cytokine release, and it is therefore an integral component of first-line treatment for BD patients with lesions in various organs (81, 85). Notably, the effectiveness of colchicine for the treatment of OUs, Gus, EN-like lesions, and arthritis in BD has been demonstrated in a placebo-control trial (88). In contrast, another study did not find significant benefits for colchicine in controlling OUs, and it was found to be effective for GUs and EN-like lesions in female patients but not in males (89). However, this study may have been biased due to the fact that topical therapy, acetaminophen, and NSAIDs were not strictly controlled. Thus, despite inconsistent performance across multiple studies, colchicine can be generally recommended for moderate-to-severe mucocutaneous cases, such as those involving OUs, GUs, EN-like lesions, and PPL (85).

Colchicine has also been reported to inhibit platelet aggregation and prevent thrombosis effectively (90), and a combination of anticoagulant and colchicine was shown to be effective in pediatric BD cases involving venous thrombosis (91). Based on results from these studies, we recommend colchicine for the treatment of moderate-to-severe cases of superficial thrombophlebitis, even though, to date, no randomized trial of colchicine for superficial thrombophlebitis has been performed.

### Corticosteroids

Systemic corticosteroids rapidly suppress inflammation and cytokine production, and thus, these have been empirically used to control acute and severe attacks of mucosal ulcerations in BD (92). One randomized trial found that intramuscular injection of methylprednisolone acetate was effective for EN-like lesions, but not for GUs (93). Overall, despite the paucity of well-designed studies, we recommend systemic corticosteroids as a treatment option for mucocutaneous lesions in severe or intractable BD cases (85).

### Apremilast

Apremilast is an oral phosphodiesterase-4 inhibitor that has recently become available for the treatment of inflammatory skin diseases, such as psoriasis. In a randomized trial, apremilast effectively decreased both pain and the total number of OUs after 12 weeks of treatment compared to placebo, and these effects were maintained for up to 64 weeks (94, 95). A recent meta-analysis on eight related trials further verified that apremilast significantly induces symptom-free remission for GUs, EN-like lesions, pseudofolliculitis, and arthritis at 12 weeks (96). However, as the side effects of apremilast include diarrhea, headache, and nausea, the EULAR task force has recommended the use of apremilast only in selected BD cases (81).

### Mucosal protectants and antimicrobial agents

Rebamipide, a mucosal protectant, has been shown to reduce both the number and pain of BD-associated OU lesions (97). Similarly, sucralfate suspension, most commonly used for treating duodenal ulcers, was also found to improve oro-genital BD ulcers. Therefore, both of these agents are recommended for treatment of mucosal ulcerations in BD (86). Antimicrobial drugs have also displayed efficacy for BD treatment. For example, benzathine penicillin significantly improved the frequency and duration of OUs when used with colchicine (98). Similarly, various formulations of topical antimicrobial agents, including chlorhexidine gel, penicillin G potassium troches, amlexanox, tetracycline suspension, and doxycycline powder, are effective for RAS and can be used to treat OUs in BD patients (83). Minocycline has both anti-inflammatory and antibacterial activity and was shown to

be effective for decreasing symptoms associated with EN-like lesions, although the study sample size was small and the trial design was non-randomized (99). In summary, these data suggest that topical and systemic antimicrobial agents can be used as auxiliary therapeutics to reduce mucocutaneous inflammation in BD.

## Anticoagulants

Despite the presence of inflammation-related thrombophilia in BD pathophysiology, the efficacy of anticoagulants for BD treatment remains controversial. In particular, no solid evidence supporting the benefit of warfarin for BD thrombophlebitis has been reported (100). Nonetheless, anticoagulants are often administered along with steroids and immunosuppressive drugs to treat vascular changes in BD. One study by Emmi et al. (101) reported no significant difference in the recurrence rate of venous thrombosis in the group of subjects treated with immunosuppressive drugs alone vs. those treated with both immunosuppressives and anticoagulants. In contrast, another study found that the risk of severe post-thrombotic syndrome, a chronic complication of leg vein thrombosis, was increased in BD patients who did not take anticoagulants in combination with immunosuppressants at the onset of thrombosis (102). This suggests a potential benefit for anticoagulants in patients with chronic lower leg vein thrombosis. In this context, the recently updated Japanese guidelines support the addition of warfarin as an option along with steroids or immunosuppressive agents in clearly indicated situations (85). However, answering the question of whether the addition of anticoagulants to BD therapeutic regimens is effective for treating venous thrombosis will require further investigation in clinical trials, particularly those focused on the use of novel oral anticoagulants (103).

## Immunosuppressants and immunomodulatory agents

Given the role of inflammation in disease pathogenesis, several immunosuppressant agents have been utilized for BD treatment. For example, azathioprine effectively decreased the number of OUs and GUs in BD patients in a randomized controlled trial (104). Therefore, the EULAR task force recommends azathioprine use in selected cases with mucocutaneous lesions. Additionally, in a small cohort study, cyclosporine A showed clinical efficacy for treating GUs, skin lesions, and superficial thrombophlebitis (105). However, given the potential risk for the development of neuro-BD, the use of cyclosporine A should be reserved for selected cases.

Dapsone (diamino-diphenyl sulfone) inhibits the activation of neutrophils and is widely used to treat of inflammatory skin diseases. In a double-blind controlled study, a decreased number of OUs, GUs, EN-like lesions, and PPL was observed in dapsone-treated BD patients (106). Thus, dapsone can be used as an alternative immunomodulatory drug in refractory cases with mucocutaneous symptoms. In addition, thalidomide has been reported to induce long-term remission of OUs, GUs, and PPL in BD patients; however, this agent should be used only in selected cases due to its potentially severe side effects (107).

## Tumor necrosis factor-α inhibitors

Inhibitors of the cytokine TNF-α are used to treat various inflammatory diseases, including BD. In particular, a randomized trial and some case reports have provided convincing evidence favoring the use of TNF-α inhibitors for OU treatment. Similarly, the efficacy of TNF-α inhibitors for treating GUs was demonstrated in multiple case reports, and etanercept was found to be beneficial for EN-like lesions in a randomized clinical trial (108). However, given the potentially severe side effects, TNF-α inhibitors can be considered only in cases of severe and intractable mucocutaneous lesions (109).

Tumor necrosis factor-α inhibitors have also been investigated for the treatment of BD-associated thrombosis. One cohort study on BD patients with DVT and/or superficial vein thrombosis found that the adalimumab-based treatment groups (i.e., adalimumab administered alone or in combination with immunosuppressive agents) showed rapid clinical and ultrasonographic improvement compared with those receiving immunosuppressive agents only during a mean follow-up of 26 months (110). In addition, a steroid-sparing effect was observed in the adalimumab-based groups. Thus, we suggest that TNF-α inhibitors, alone or in combination with immunosuppressive agents, can be an option for severe cases of superficial thrombophlebitis or DVT, although further studies are needed.

## Other biologic therapies

Among the various cytokine therapies available, the efficacy of IFN-α has been widely verified for the treatment of mucocutaneous BD. A placebo-controlled study showed that IFN-α was effective in reducing the healing time and pain of OUs, as well as the frequency of GUs and PPLs (111). In addition, a systematic review examining the use of anti-IL-1 antibodies has shown beneficial effects of anakinra and canakinumab for controlling mucocutaneous lesions of BD (112). Similarly, both ustekinumab, an anti-IL-12 and anti-IL-23 antibody (113), and the anti-IL-17 antibody secukinumab, were found to be effective for treating refractory mucocutaneous BD lesions (114). Thus, these biologics can be tried in patients with intractable cases of mucocutaneous BD.

## Disease specificity in drug selection

As mentioned above, various therapeutic options exist for the management of mucocutaneous BD. However, it is still not clear how essential the vasculitis itself in clinical presentation of mucocutaneous symptoms. Actually, there is a practical difference in the management compared to other primary vasculitides. The treatment options for other types of primary vasculitides, such as AAV, include cyclophosphamide,

mycophenolate mofetil, plasma exchange, and rituximab, which are rarely tried in BD management. On the contrary, apremilast is indicated for the treatment of plaque psoriasis and active psoriatic arthritis but not in primary vasculitis other than BD. Moreover, the favorable efficacy of TNF-α inhibitors as glucocorticoid-sparing agents is shown in managing large vessel vasculitis such as Takayasu's arteritis, not in most small vessel vasculitis (115). The fact that the treatment option for BD only partially overlaps with other vasculitides suggests a disease-specific aspect of BD pathogenesis and not all treatments directly target the core process of vasculitis itself.

## Conclusion

Behçet's disease, a systemic vasculitis affecting blood vessels of any caliber or type, is a polygenetic disease associated with multiple genetic risk factors. Inflammation in BD is thought to be triggered by environmental factors, such as microbes or trauma, in genetically susceptible individuals, and both innate and adaptive immune cell subsets, including neutrophils and T cells, are the primary players involved in BD pathogenesis. Histopathological analysis of BD tissue has shown that neutrophils and lymphocytes infiltrate blood vasculatures. This results in vascular endothelial dysfunction and neutrophil-mediated vascular inflammation, which are the key factors inducing thrombophilic features in patients with BD. However, it has been challenging to accurately assess the initial pathologic changes that occur during mucocutaneous lesion formation due to the short-living properties of acute inflammatory cells, such as neutrophils. Therefore, it is still debatable how pivotal the vascular inflammation plays role in the pathogenesis of BD skin lesions despite all the research efforts so far.

Based on the inflammatory origin of BD, broad-spectrum anti-inflammatory medications, including glucocorticoids and immunosuppressive drugs, are the mainstay for managing BD inflammation. In addition, drugs that target dysregulated innate and adaptive immune responses, such as TNF-α and IL-17 inhibitors, have emerged as promising new therapeutics for this disease. However, we are acutely aware that due to the heterogeneity and complexity of this condition, a magic bullet treatment to cure BD is unlikely to be found. Therefore, accumulating an efficacious armamentarium of treatments for BD patient care through the relentless development and verification of diverse therapeutics will continue to be the mission of BD researchers.

## Author contributions

DK, KN, and DB conceptualized and determined the scope for the review. DK and KN drafted the manuscript. DB, FK, and EA were involved in wrote the manuscript and/or revising it critically for intellectual content. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# A comprehensive review on pathogenesis, associations, clinical findings, and treatment of livedoid vasculopathy

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Livedoid vasculopathy (LV) is a thrombo-occlusive vasculopathy that involves the dermal vessels. Clinically, it is characterized by the presence of painful purpuric ulcers on the lower extremities. Histopathologically, it shows intraluminal fibrin deposition and thrombosis, segmental hyalinization, and endothelial proliferation. It is important to notice that the term "atrophie blanche" is descriptive and it includes not only patients with LV but also patients with a combination of vasculitis and vasculopathy, that is, LV and medium-sized vasculitis such as cutaneous polyarteritis nodosa (PANc). Diagnosis is based on a proper clinicopathological correlation, excluding the main differential diagnosis and considering vasculitis as a mimicker or concomitant diagnosis. Coagulation disorders must also be studied although they are not found in all LV. Its frequency is reviewed as well. Treatment of LV is challenging, and different therapies have been attempted. Among them, pain management, wound care, control of cardiovascular risk factors, and both antiplatelets and anticoagulants, mostly rivaroxaban, are the main therapies used. These different therapies as well as their degree of evidence are reviewed.

KEYWORDS

**livedoid vasculopathy (LV), atrophie blanche, livedo racemosa, retiform purpura, thrombosis, rivaroxaban, anticoagulant, antiplatelet**

## Introduction

Livedoid vasculopathy (LV), first described by Milian (1), is a thrombo-occlusive vasculopathy involving the postcapillary venules of the dermis. It can be considered a syndromic concept, including patients with a locoregional manifestation of a venous thrombus guided by three key factors: (1) flow disruption, (2) endothelial injury, and (3) coagulation disorder (2). Different names, including *atrophie blanche*, segmental hyalinizing vasculitis, Milian white atrophy, livedo reticularis with summer ulceration, livedo vasculitis, segmental hyalinizing vasculitis, or painful purpuric ulcers with a reticular pattern of the lower extremities (PURPLE), have also been used to refer to

patients with LV. Bard and Winkelman were the first authors to use the term LV in 1967 (3).

## Epidemiology

Livedoid vasculopathy is a rare disease, with an estimated incidence rate of 1 in 100,000 (4). This disease predominantly affects women, with a female-to-male ratio of 3:1, and it occurs mainly in young to middle-aged patients. As reported in the literature, the median age ranges from 35 to 53 years (5, 6). It is noteworthy that there is a 5-year delay from the first symptoms until an accurate diagnosis and thus promoting a better knowledge of LV may help decrease the diagnostic delay (7).

## Etiopathogenesis

Livedoid vasculopathy can be classified as primary (idiopathic) and secondary when coagulation disorders are associated (4, 8). Although the pathogenesis of LV remains unclear, it is thought to involve a locally favored alteration in either an increased local or systemic thrombotic activity or a decreased fibrinolytic alteration, that is a coagulation disturbance, that leads to the formation of fibrin thrombi within superficial dermal blood vessels (9). The resulting tissue hypoxia within the involved area of the dermis leads to poor wound healing and an ineffective barrier, thus enhancing the risk of infection (10).

Livedoid vasculopathy may appear to be associated with any conditions related to stasis, autoimmune connective tissue diseases, thrombophilias, or neoplasms (4).

On the one hand, due to the clinical evidence of increased ambient temperature as a trigger, this disease raised the possible existence of "pyroglobulins" analogous to cryoglobulins; however, this was not evidenced and was just a hypothetical way of explaining why we have cases with no clear reason to explain the coagulation alteration (11).

On the other hand, a large number of hypercoagulable states have been associated with LV, including antiphospholipid antibodies, factor V Leiden mutation, protein C and S deficiency, prothrombin mutation, antithrombin III deficiency, hyperhomocysteinemia, and increased levels of lipoprotein(a) (4, 8, 12). The fact that there is a good response to treatment with anticoagulants, fibrinolytics, and antiplatelet drugs supports the suggested underlying prothrombotic pathogenesis (4).

However, the underlying coagulation disorders are diverse and have been found variably in the literature. In a retrospective study of 75 Brazilian patients with LV, about 66% of the cases had thrombophilic factors, with lipoprotein(a) being the most common thrombophilic factor detected in 30 (41.66%) of 72 patients (13). In another recent study, prothrombotic parameters were found in 11 (44%) of 25 patients with LV (14). Increased homocysteine in 10 of 12 patients (83%) and lipoprotein(a) in 5 of 12 patients 42%) were the most frequently observed. Few authors have investigated Lp(a) levels in patients with LV, not being included in the rest of the studies. In a prospective study of 34 patients, 18 of them (52%) presented laboratory abnormalities of procoagulant conditions (15). The most common prothrombotic factors observed were antiphospholipid antibodies (17.64%), factor V Leiden mutation in heterozygosis (17.64%), and protein C and/or S deficiency (8.82%). In another study, 29 patients were tested for abnormalities in coagulation, 12 of them (41.4%) were found positive, with the anticardiolipin antibody being the most frequent (16). **Table 1** provides data about the thrombophilic findings in articles with more than 30 cases reported.

Other genetic disorders associated with the pathogenesis of LV are the presence of polymorphisms in plasminogen activator inhibitor-1 (PAI-1) and methylenetetrahydrofolate reductase (MTHFR). A recent systematic review of genetic variants in LV found that PAI-1 675 4G/5G was the most common, accounting for 85.26% of the patients, followed by PAI-1 A844G, MTHFR C677T, and MTHFR A1298C variants (17). It is suggested that the distribution of variants may be related to geographical location or ethnicity. Prothrombin G20210A and factor V G1691A were mostly seen in patients with LV from Europe, North America, and South America.

Regarding the association of clinical phenotypes and certain thrombophilic factors or genetic variants, as discussed, no genetic or thrombophilic factors have been associated with

TABLE 1 Thrombophilic findings in livedoid vasculopathy case series.

| | Criado et al. (13) | Di Giacomo et al. (15) | Hairston et al. (16) |
|---|---|---|---|
| Thrombophilic factors | 48/72 (66.66%) | 18/34 (52%) | 12/29 (41.4%) |
| Factor V (Leiden) mutation (G1691A) | 3 | 6 | 2 |
| Prothrombin gene mutation (G20210A) | 2 | 1 | 1 |
| Protein C | 2 | 3 | 2 |
| Protein S | 3 | | |
| Antithrombin III | 3 | 1 | – |
| Lipoprotein (a) | 30 | – | – |
| Factor VIII | 9 | – | – |
| Factor IX | 5 | – | – |
| Homocystein | 5 | 2 | 3 |
| Lupus anticoagulant | 7 | 1 | 5 |
| IgM anticardiolipin antibodies | 10 | 4 | 5 |
| IgG anticardiolipin antibodies | 10 | 0 | 1 |
| IgM + IgG anticardiolipin antibodies | 8 | 2 | 2 |

a particular clinical picture. Therefore, we cannot assume that LV is primary or secondary based on the clinical or histopathological findings.

Livedoid vasculopathy is usually limited to the lower legs, thus it is assumed that local factors such as stasis and temperature are important factors related to its pathogenesis. Furthermore, additional unknown individual trigger factors must also play a role since only a small number of patients suffering from different coagulopathies develop LV (18, 19).

## Clinical features

Livedoid vasculopathy is a chronic disease with periodic and recurrent exacerbations. Clinically, it is characterized by three main typical features: livedo racemosa, skin ulcerations, and atrophie blanche (18, 19). The disease is mostly bilateral (4).

Livedo racemosa is defined as a persistent, erythematous to violaceous discoloration of the skin characterized by broken, branched, discontinuous, and irregular pattern (14) (**Figure 1**). Livedo racemosa is frequently and consistently associated with LV, but it is not a specific feature as it can appear also in a wide range of occlusive vasculopathies (9). In a recent study, Weishaupt et al. found that livedo racemosa was present in 85% of patients with LV (14). It usually affects the lower limbs but can also affect the upper limbs or the trunk when associated with LV. Livedo racemosa may be viewed as an early manifestation of LV (9).

Other clinical features of LV include purpuric macules, papules, and retiform purpura, followed by the formation of acute-onset, painful, small crusted ulcers (**Figure 2**). Ulcers represent the active stage of the disease (9). They are usually located beneath the knees, the most compromised location being the ankle area (medial more common than lateral), followed by the dorsal foot and the ventral distal lower leg (14) (**Figure 3**). Some authors have also found lesions on the upper extremities in a small proportion of patients (20). These ulcers are typically small (<1 cm), painful, with a punched-out appearance, frequently bilateral, and recurrent. Edema can also be present. Burning pain, sometimes excruciating, often precedes the ulceration and may be a prodromal clue for this diagnosis (10). A cross-sectional study showed that patients with LV have significantly impaired quality of life, especially during disease activity, having an impact on their psychological, physical, and social aspects of life (21).

The ulcerated lesions slowly tend to heal within 3–4 months resulting in the so-called "*atrophie blanche,*" stellate porcelain white atrophic scars surrounded by hyperpigmentation and telangiectasias (10) (**Figure 4**). *Atrophie blanche* is the residual state of ulcers of LV; therefore, it is located where these appear (14). *Atrophie blanche*, also known as *capillaritis alba*, may also be seen in many other conditions such as chronic venous insufficiency or some autoimmune connective tissue diseases (lupus erythematosus, dermatomyositis), and even associated with medium-sized vessel vasculitis (8, 22, 23).

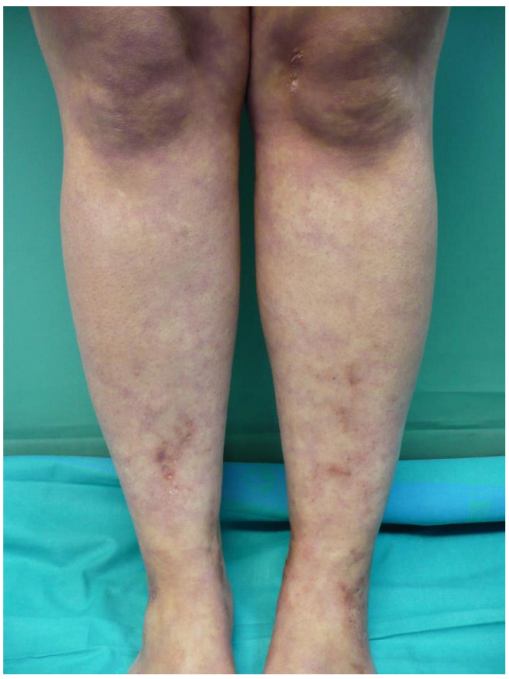

FIGURE 1
Livedo racemosa lesions on the legs with erythematous to violaceous broken network pattern.

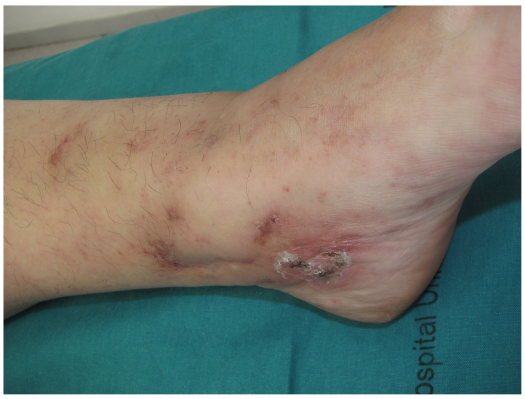

FIGURE 2
Retiform purpura with small crusted ulcers distributed on the ankles.

Peripheral neuropathy is the only known extracutaneous manifestation of LV. Although rarely described in the literature, a recent study has revealed a higher incidence of peripheral neuropathy (50% of patients), including cases of mononeuritis multiplex, sensory polyneuropathy, and small fiber neuropathy (5). The main etiopathogenic explanation is based on the occurrence of thrombotic disease involving vessels of the

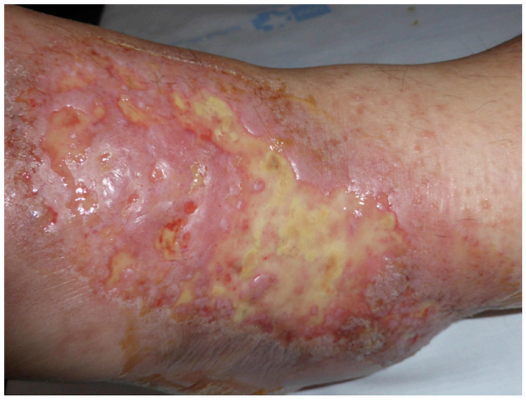

FIGURE 3
Active ulcers on the ventral distal lower leg with associated edema.

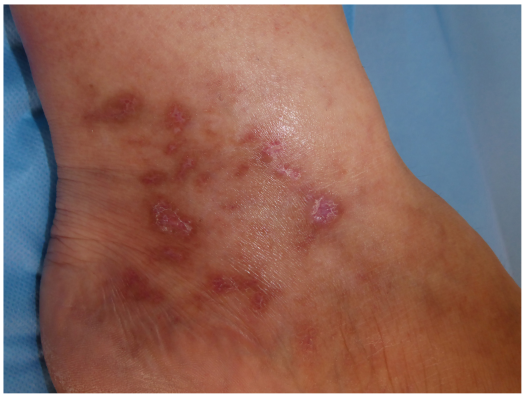

FIGURE 4
Atrophie blanche with small, round scars surrounded by hyperpigmentation and telangiectasias.

nerve and thus causing nerve injury due to hypoxia (24). In a study involving 16 patients with peripheral neuropathy and LV, asymmetric axonal polyneuropathy was found as the most frequent EMG pattern, followed by sensorimotor mononeuropathy in one case. The most frequently affected sensory nerve was the sural nerve, followed by the superficial fibular, median and ulnar nerves [four cases each (24)]. Peripheral neuropathy in LV requires further investigation because the conventional techniques (EMG, nerve biopsy) explore only large nerve fibers, which is in contrast to our study which involved smaller nerves (**Figure 5**). Peripheral neuropathy is probably underestimated and would explain the high percentage of patients with neuropathic pain persisting after the healing of ulcers, despite having a normal EMG (5).

Dermoscopic features of LV consist of pink or white background, irregular linear and glomerular vessels, central crusted ulcers, and ivory-white areas associated with peripheral pigmentation in a reticular pattern (25, 26).

On histopathological examination, the ivory white areas correlate with dermal fibrosis, the reticular pigmentation corresponds to epidermal basal layer hyperpigmentation or melanin within melanophages in the dermal papillae, and the vascular structures correlate with dilated vessels and proliferation of capillaries (25).

## Histopathological features

The histopathological findings of LV are characterized by occlusion of dermal blood vessels due to intraluminal fibrin deposition and thrombosis, segmental hyalinization, and endothelial proliferation (8) (**Figure 6**). No signs of true vasculitis are found as there are no neutrophilic polymorphonuclear leukocytes permeating the vessel wall or surrounding the dermal vessels (27).

Histopathological changes depend on the stage of the lesion. In the early stage, the hyaline thrombus is formed in the lumen of small vessels in the mid and papillary dermis, and it is sometimes associated with the deposition of fibrinoid material on the vessel walls and in the perivascular estroma (4, 8). In addition to these angiocentric findings, most cases present with overlying ulceration (infarction) of the epidermis and adjacent superficial dermis. A sparse perivascular lymphocytic infiltrate may be seen, with no signs of leukocytoclastic vasculitis. Extravasation of red blood cells in the superficial dermis can be found as well. A non-specific papillary dermis increase in small blood vessels is also common (4).

Partially developed lesions show a hyalinization and thickening of the vessel walls in the papillary dermis, followed by secondary endothelial proliferation (8).

Fully developed lesions demonstrate dermal sclerosis and scarring with some dilated lymphatic and epidermal atrophy (4).

Direct immunofluorescence, when done in patients with LV, demonstrates deposition of immunoglobulins, complement, and fibrin (8, 28). Direct immunofluorescence (IFD) study in patients with LV showed positive immunoreactants ranging from 42.9 to 100% (28). C3 and IgM are the most common immunoreactants found, followed by IgA and IgG. The most commonly reported IFD pattern is immunoreactant deposition in blood vessels and at the dermoepidermal junction. Nuttawong et al. reported that older patients and those with more recent lesions (<6 months) have a significantly higher percentage of positive IFD results for LV than younger patients and those with older lesions (≥6 months) (28).

## Diagnosis

The diagnostic criteria of LV are not well-defined (14). This could be due to limited or missing data referred to this entity that will need clarification through clinicopathological studies

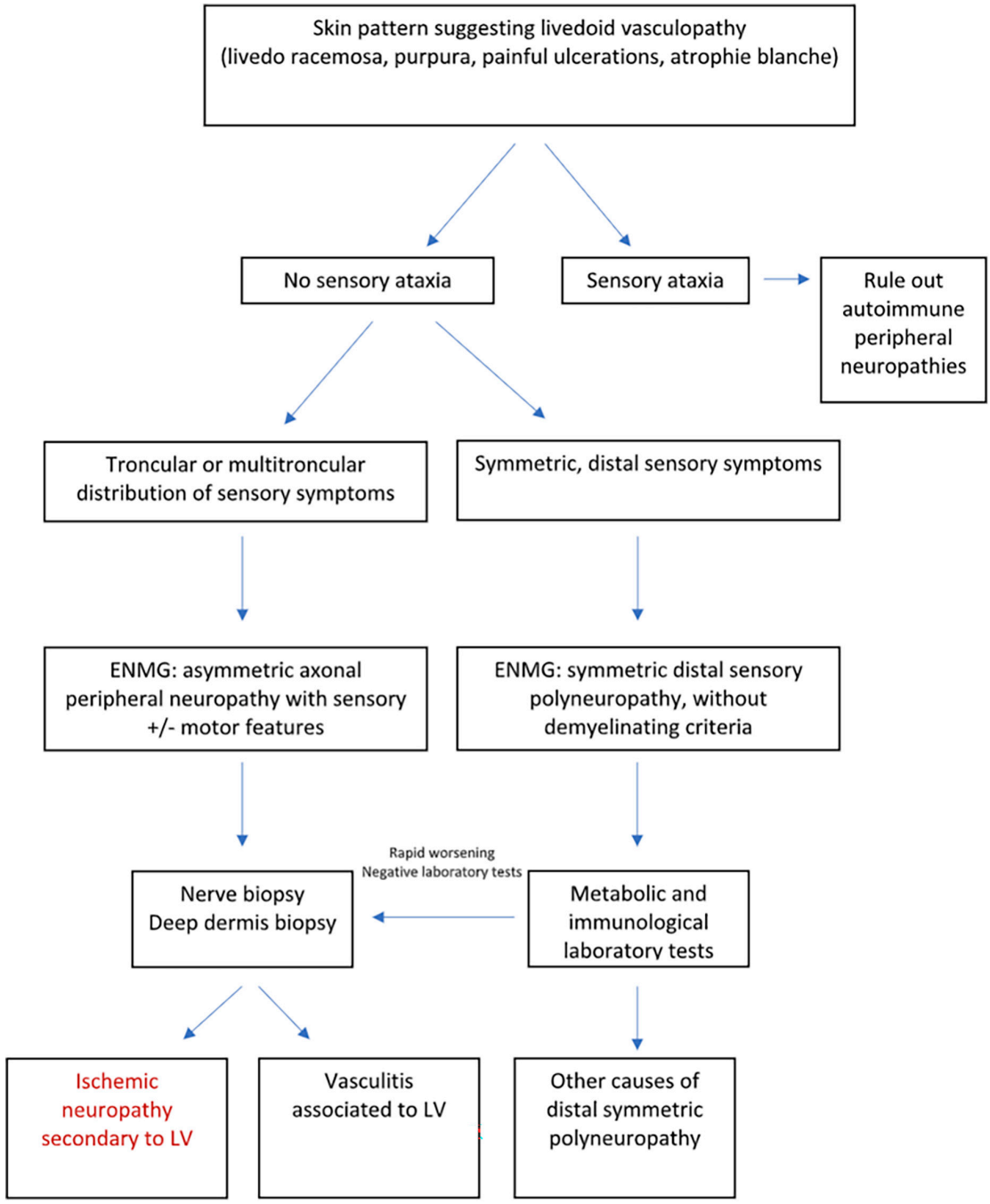


FIGURE 5
Diagnostic approach of peripheral neuropathies associated with LV adapted from Soulages et al. (24).

to encompass that diverse range of laboratory findings. Clinical, histopathological, and laboratory data are necessary to make a correct diagnosis of LV (4).

There is no list of diagnostic criteria, but LV must be suspected in patients with recurrent small painful ulcerations mainly around the ankles when the temperature rises. Edema can be present and irregular lesions of atrophie blanche may be found either in previously ulcerated skin or without ulceration. Livedo racemosa as well as papules or dark irregular purpura that evolve to ulceration can be found along with the previously described features (11).

When a clinical suspicion of LV exists, a skin biopsy is required to confirm and rule out other differential diagnoses. The biopsy specimen should be taken of the immediate borders

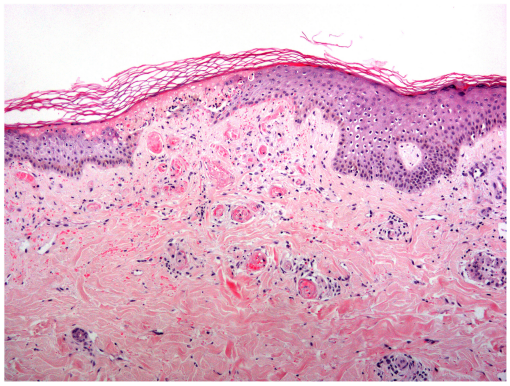

FIGURE 6
Livedoid vasculopathy histology: An acutely necrotic epidermis is observed overlying an area where all the vessels in the papillary dermis are completely occluded by a hyaline thrombi.

of a new ulcer and include both healthy surrounding skin and the eventual ulcer (9). It should ideally be an incisional biopsy containing subcutaneous fat.

Once the presence of LV is confirmed, an accurate laboratory evaluation must be carried out to exclude any possible underlying diseases (**Table 2**). Regarding prothrombotic markers, nowadays, the value of testing them for a particular patient can be discussed as they do not always change the therapeutic approach and no cost-effectiveness studies have been made. Alavi and Kerk also challenged the idea of testing all patients (4, 19). In any case, if we want to analyze in-depth pathogenesis, this type of analysis would be helpful. Detailed laboratory investigations for connective tissue diseases are also recommended. In addition, it should also be ruled out the presence of paraproteinemia and underlying infections (4).

Other appropriate tests for the diagnostic investigation of LV include venous and artery Doppler ultrasound, pulse examination, and ankle-brachial index, to study venous insufficiency and arterial peripheral disease. It is also advisable to rule out a pregnancy.

Although not located in the lower legs, SARS-CoV2 infection is related to the presence of a thrombotic occlusive vasculopathy in the skin (29). With the previous knowledge, as SARS-CoV2 presents endothelial tropism and has the ability to favor microthrombosis in different tissues, it is not unexpected that the viral infection can worsen LV in previously affected patients, even in non-severe cases (30).

Despite performing a deep investigation into the underlying conditions, 20% of all the cases are classified as idiopathic LV (9).

## Differential diagnosis

It includes many diseases where ulcers, white stellate atrophy, or pain involves mostly the legs. Most cases of chronic venous insufficiency can be identified by the presence of stasis dermatitis along with varicose veins and an abnormal venous Doppler.

Regarding peripheral arterial disease, the presence of cardiovascular risk factors, intermittent claudication, and abnormal arterial Doppler along with an altered ankle-brachial index test leads us to rule out this diagnosis.

There are many vasculitis where inflammatory retiform purpura may appear as they involve both small and median-size vessels. ANCA-vasculitis and IgA vasculitis are within this group of diseases. A skin biopsy will show a real vasculitis, while direct IF will show IgA and, to a lesser extent, IgM or IgG. In ANCA-associated vasculitis, p-ANCA or c-ANCA is positive and other organ damage such as renal, pulmonary, or neurological diseases also occur. Antiphospholipid antibody syndrome may produce stellate scarring in the lower limb, but the diagnosis requires clinical and laboratory criteria based on the International Consensus Statement (31).

Regarding cutaneous arteritis, previously named cutaneous polyarteritis nodosa, although livedo, nodules, and mononeuritis multiplex are found, a skin biopsy will show a medium-sized artery involvement rather than the histopathological findings of LV.

TABLE 2 Laboratory testing for livedoid vasculopathy.

| Disease | Investigation |
|---|---|
| Hypercoagulable states | Tests of Haemostasis: PT, aPTT, Fibrinogen, D-dimer<br>Factor V Leiden mutation<br>Prothrombin G20210A mutation<br>Antithrombin III deficiency<br>Protein C and S deficiency<br>Homocystein<br>Folic acid, vitamin B12 and vitamin B6<br>Lipoprotein (a)<br>Methylene-tetrahydrofolate-reductase C677T mutation<br>Plasminogen activator inhibitor<br>Anticardiolipin antibodies (IgM and IgG)<br>Lupus anticoagulant<br>Anti-b2-glioprotein I antibodies<br>Cryoglobulin<br>Cold agglutinins |
| Connective tissue diseases | ANA<br>ANCA<br>ENA<br>Anti-Ro<br>Anti-La<br>Anti-CCP<br>Rheumatoid factor<br>Complement (C3, C4) |
| Paraproteinemias | Cryofibrinogen<br>Immunoglobulin, Kappa and lambda chain<br>Protein electrophoresis, immunofixation |
| Infections | Hepatitis B and C<br>HIV |

Arteritis macular is a lymphocytic arteritis of dermo-hypodermal vessels characterized by a fibrin hyalinized ring and hyperpigmented or pink macules (32). Some authors have considered this entity as a latent form of cutaneous polyarteritis nodosa (33, 34). Typical histopathology and, most commonly, the absence of ulceration and scarring are useful to rule out this entity.

As previously stated, it is noteworthy to highlight the finding of a coexistence of cutaneous panarteritis and LV (35) as well as some cases with other underlying subcutaneous necrotizing vasculitis (36).

Degos disease presents clinically characteristic porcelain white atrophic lesions surrounded by dilated vessels, but any area of the body can be involved and all the lesions are similar in size.

Regarding Sneddon syndrome, livedo racemosa is also found in LV. But this group of patients is characterized by the presence of cerebrovascular stroke and an underlying mutation in CERC1 (37).

## Treatment

As LV is painful and often scarring, it is mandatory to establish a treatment. Pain management, wound care, control of cardiovascular risk factors, and anticoagulants could be the main treatment options (**Figure 7**).

Despite a growing number of therapies, some based on a successful case, LV treatment still represents a challenge as no single therapeutic approach is effective for all patients and there are no standardized guidelines available due to the low incidence of the disease and lack of large studies. There are several recent reviews focusing mostly on rivaroxaban and intravenous immunoglobulin (38–40).

Supportive measures are the basic step to managing patients with LV. Cessation of smoking is a crucial preventive measure as vasoconstriction and hypoxia may increase tissue damage. Despite the negative effects of smoking on wound healing, a significantly higher proportion of smokers with LV was found compared with the control population (16). Therefore, patients should be advised to enter a smoking cessation program. Compression therapy may also be beneficial, especially in patients with venous insufficiency, as it reduces edema and improves ulcer healing (10). Other preventive measures include avoidance of massive temperature changes and the topical application of perfusion-promoting formulations (18).

Although the optimal treatment approach for LV remains controversial, some authors proposed a therapeutic stair in which the first-line step is antiplatelet therapy including agents such as clopidogrel, ticlopidine, abciximab, buflomedil hydrochloride, and beraprost sodium, but most of the cases are treated with aspirin, pentoxifylline, and dipyramidole (9). These agents have been successfully used either as monotherapy or combined (38). The mechanism of action of aspirin is through the inhibition of cyclooxygenase that suppresses thromboxane $A_2$ and prostaglandin $I_2$, resulting in an antithrombotic effect (10). Aspirin has also proved to help ulcer healing in the treatment of chronic venous leg ulceration in previous studies (41). The recommended dose ranges from 75 to 325 mg three times a day. A significant improvement has been reported in patients with LV associated with sickle cell trait when treated with aspirin (42). Dipyramidole inhibits the synthesis of thromboxane $A_2$ and stimulates the release of prostaglandin $I_2$. It is usually given in a dose of 50 mg, three times a day (10). Pentoxifylline, a competitive non-selective phosphodiesterase inhibitor, has a hemorheological effect, and its recommended dose is 400 mg three times a day. The low cost, tolerability, and wide availability are important advantages of antiplatelet agents that make them a good first-line therapy option.

If there is no significant improvement in a short period after the instauration of antiplatelet treatment and in cases with a demonstrated thrombophilia, the next step in the therapeutic approach of LV is the initiation of anticoagulants (9). In this case, warfarin, heparin, low-molecular-weight heparin, other vitamin K antagonists, sulodexide, and mostly rivaroxaban have been used (9). A recent systematic review showed that anticoagulants were the most commonly reported monotherapy, achieving a consistent favorable response in up to 98% of the patients (38). Rivaroxaban was the anticoagulant most frequently used, followed by low-molecular-weight heparin, high-molecular-weight heparin, warfarin, and fluindione. The good response observed in patients with LV to anticoagulants supports the proposed pathogenic mechanism of a locally increased occlusive vasculopathy.

In the past years, rivaroxaban, a direct factor Xa inhibitor, has been widely used for the treatment and prevention of major thromboembolic diseases. Compared with other anticoagulants such as enoxaparin and warfarin, rivaroxaban is often preferred due to the advantage of oral administration and the unnecessity of international normalized ratio monitoring. In 2013, Kerk et al. first reported that patients with LV were successfully treated with rivaroxaban (43). Since then, several case reports and case series have been published treating up to 73 patients in a recent review (39). It is of note that rivaroxaban is the only drug with a clinical trial involving 25 patients with LV (RILIVA), showing statistically significant improvement in pain with a mean score of 65 to 6 on a 0- to 100-point visual analog scale after 12 weeks of treatment (6). Acute pain due to cutaneous infarction is a great challenge in LV. The results of this study showed that pain was reduced by 50% within 11 days. A recent systematic review found that a rivaroxaban dose of 10–20 mg/day was effective in 82.2% of patients with LV with thrombophilic factors as well as in those with idiopathic disease (39). Furthermore, improvement of pain can be observed soon within the first week and remission lasted 4 weeks to 23 months with an initial dose of 20 mg that can be tapered to 10 mg/day

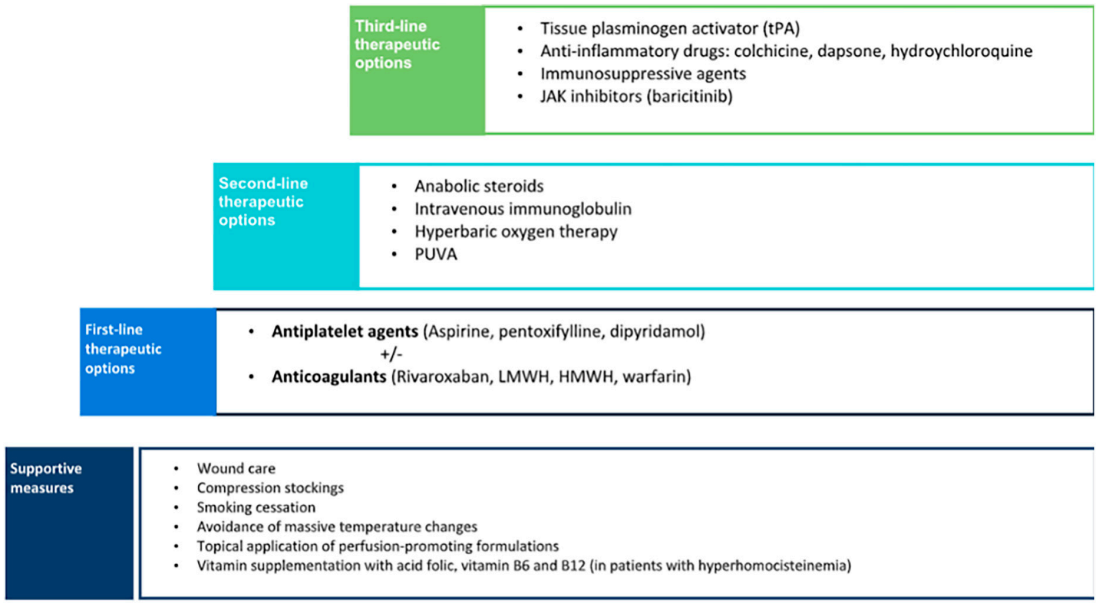


FIGURE 7
Stepped-care treatment of livedoid vasculopathy.

for maintenance (39). Few adverse effects were observed, with menorrhagia being the most commonly reported in the RILIVA clinical trial (6). Therefore, clinical evidence suggests that rivaroxaban is an effective and well-tolerated drug for LV.

Anabolic steroids were the second most frequently reported monotherapy for the treatment of LV (38). Danazol was the most commonly used steroid, given in a dose of 200 mg/day, although stanozolol 4 mg/day can also be used (38, 44). Systemic steroids increase fibrinolysis, inhibit coagulation, and induce hepatic synthesis of protease inhibitors (such as proteins C and S). Steroids have been reported to be an effective option, especially in patients with an associated connective tissue disease (9, 38). Despite being considered the second option, when we performed a survey in our country including dermatologist management of up to 200 patients (unpublished data), if supportive measures and anti-aggregation or hemorheological agents were not enough, the second line was mostly anticoagulants. Our experience is aligned with combination therapy including anti-inflammatory drugs with anticoagulant therapy in a Thai cohort (12).

Treatments such as intravenous immunoglobulin, psoralen and UV-A (PUVA), and hyperbaric oxygen therapy (HBOT), which have reported favorable clinical outcomes, may be more suitable for refractory cases of LV, because of high cost and difficulties in patient compliance (9, 38). Intravenous immunoglobulin was the third most commonly used and effective treatment (38). A recent review has found 3 studies and 14 case reports and series encompassing up to 80 treated patients, mostly females (70%) with 22.2% of them presenting positive thrombophilic factors and refractory to previous treatments, although rivaroxaban was not used in any of these patients (40). Although the mechanism of action is not fully understood, it induces a reduction of cytokine production, neutralization of pathogens, inhibition of complement-mediated damage, and blockage of Fc receptors (4). It is often used as monthly infusions with a recommended dose of 2 g/kg (45). Reported efficacy is high with 95% of the global response, starting between the first and third cycles, decreased up to 80% of values of the visual analog scale, and no differences between patients with thrombophilic factors and idiopathic ones (40). Treatment intervals can be prolonged based on its efficacy and it is noteworthy an improvement in dysesthesia. Remission periods are quite good, ranging from 3 months to 8 years. Although the most common adverse event is headache, intravenous immunoglobulin is an effective and safe therapy for LV, and due to the high cost and relatively complex administration, it is preferred as an alternative therapy for refractory LV cases. PUVA has been used for the treatment of LV in a small number of patients with good outcomes and minimal adverse events (46). HBOT has also been reported to be an effective alternative for LV (47, 48). HBOT releases 100% oxygen at high pressures, increasing tissue oxygenation and improving tissue ischemia. It also promotes fibrinolysis and angiogenesis, resulting in better ulcer healing (38).

There are other treatment alternatives, including fibrinolytics, vasodilators, anti-inflammatory, and immunosuppressive agents, that may be considered when conventional therapies have failed and should be reserved as the third-line option. Fibrinolysis with recombinant tissue plasminogen activator (tPA) has been reported as an effective

treatment for non-healing ulcers in LV (49). It is suggested that tPA lyses microvascular thrombi, restores circulation, and eventually promotes wound healing. The recommended dose is 10 mg administered intravenously, a much smaller dose than the one used to treat other thrombotic diseases; nevertheless, the risk for severe bleeding-related adverse events still exists and the efficacy and safety of tPA should be further studied (38). The use of vasodilators such as nifedipine was found to be useful as adjuvant therapy in anecdotical reports (50). Anti-inflammatory drugs including colchicine, dapsone, and hydroxychloroquine have also shown a favorable response (51). The use of corticosteroids in the treatment of LV is controversial. Prednisolone has principally been used in flares up for rapid disease control with good results (10).

Vitamin supplementation with folic acid, vitamin B6, and vitamin B12, all being the cofactors of homocysteine metabolism, can be considered in cases of demonstrated hyperhomocysteinemia (52).

It has recently been reported the use of baricitinib, a relatively new JAK 1 and JAK 2 inhibitor, to treat 3 cases of LV that were resistant to conventional therapy showed marked improvement and no adverse events (53). Another pilot study included 5 patients refractory to danazol or corticosteroids treated with etanercept 25–50 mg once a week for 12 weeks with a pain reduction of 34.3% (54). Thus, anti-TNF and JAK inhibitors emerge as new targets and potentially effective therapeutic alternatives for LV, although further studies are needed to confirm their efficacy and long-term safety. Currently, the best evidence supporting use favors anticoagulants, especially rivaroxaban, antiplatelets, and intravenous immunoglobulin as well as supportive measures.

## Author contributions

ML-V and MS contributed to conception and design of the study, wrote the first draft of the manuscript, and prepared the graphs to illustrate it. Both authors contributed to manuscript revision, read, and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Cutaneous vasculitis: Lessons from COVID-19 and COVID-19 vaccination

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Cutaneous vasculitis (CV) is an inflammatory skin-limited vascular disease affecting the dermal and/or hypodermal vessel wall. From the pathogenetic point of view, idiopathic forms are described as well as the induction from various triggers, such as drugs, infections, and vaccines. Following SARS-CoV-2 pandemic outbreak, cases of CV induced by both COVID-19 and COVID-19 vaccinations have been reported in literature. The aim of our work was to collect multiple cases available in the literature and analyze the frequency of the different forms of induced vasculitis, as well as their histological and immunopathological features. Although rare, CV induced by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and vaccines may provide interesting insights into the pathogenesis of these inflammatory processes that may in the future be useful to understand the mechanisms underlying cutaneous and systemic vasculitis.

KEYWORDS

**vasculitis, cutaneous vasculitis, COVID-19, leukocytoclastic vasculitis, IgA vasculitis, urticarial vasculitis, COVID-19 vaccines, vaccine-induced vasculitis**

## Introduction

The term vasculitis encompasses a wide and heterogeneous group of disorders with shared histopathological findings. It is a pathological process characterized by an inflammatory process affecting the vessel wall, both arterial and venous, of different sizes and of any body area (1). Inside the vessel wall, there is an infiltrate, which can create discontinuity of the wall itself with red blood cells leaking. One of the most successful attempts at proper classification of such condition has been proposed by the 2012 Chapel Hill consensus cVonference nomenclature of vasculitides (CHCC 2012) (2), which divides them according to the diameter of the affected vessel: Large Vessel Vasculitis and Medium Vessel Vasculitis, which in the skin can cause necrosis and ulceration and livaedo reticularis; Small Vessel Vasculitis, manifesting with purpura and vesiculo-bullous lesions.

Since the skin is one of the most affected organs in vasculitides, in 2018, a Dermatological Addendum has been suggested to further help the clinician in dealing with such conditions, improving the definition of some forms of cutaneous vasculitis (CV) and adding other dermatological relevance (3). Accordingly, CV may be a cutaneous manifestation of systemic vasculitis or a skin-limited or skin-dominant variant of systemic vasculitis, but when affecting only the skin in the absence of any other systemic involvement, the term single-organ vasculitis (SOV) should be used.

CV is mainly a small-vessel vasculitis affecting dermal and/or hypodermal capillaries and venules, which usually show histopathologic findings consistent with leukocytoclastic vasculitis, characterized by fibrinoid necrosis of vessel wall, erythrocyte extravasation, and neutrophilic infiltrate with degeneration known as leukocytoclasis with nuclear dust (karyorrhexis) (4). The immune infiltration may be mainly lymphocytic in lesions that appeared more than 48 h before. Direct immunofluorescence (DIF) of lesional skin is helpful in the diagnosis of CV, with maximum efficacy for the diagnosis of IgA vasculitis and lupus vasculitis. It can aid in the accurate diagnosis even when the histological changes are minimal (5–7). However, DIF positivity is strongly influenced by the timing of the biopsy (8).

Even though in more than half cases of CV it is impossible to assess the disease-inducing or promoting factor, it is well-known that the most common triggering factors are related to immunopathogenic mechanisms secondary to infections or drug intake (9, 10). Therefore, it is not surprising that since the beginning of the COVID-19 pandemic and after the introduction and administration of COVID-19 vaccines on a global scale, cases of COVID-19-associated and vaccine-associated CV have been reported (11–13).

When involving the skin, clinical manifestations of the COVID-19 infection show a great range of signs and symptoms (14). Five major classes of cutaneous manifestations in the setting of COVID-19 infection have been proposed by Tan et al. (15), e.g., pseudo-chilblains lesions, urticarial rash, vesicular (varicella-like) eruption, maculo-papular rash, and vaso-occlusive lesions. Several cases of both new onset and flares of CV have also been linked to COVID-19 and SARS-CoV-2 vaccination. However, they are not included in the aforementioned classification due to their low frequency (12, 16, 17).

Similarly, many heterogeneous cutaneous reactions to COVID-19 vaccination have been reported and classified by Shakoei et al. into the following major categories: local site reactions, type 1 (immediate) hypersensitivity reactions, type 4 (delayed) hypersensitivity reactions, autoimmune-mediated reactions, functional angiopathies, and reactivation of other viral conditions (18). In this classification, CV are classified among the auto immune-mediated reactions. Most of the cases reported occurred after the administration of messenger ribonucleic acid (mRNA)-based vaccines (19). In the literature, vaccine-associated CVs have been more frequently reported than CVs secondary to the COVID-19 infection. The number of persons that received at least one dose of the vaccine worldwide is larger when compared to that of the persons who contracted the infection. However, it is known that the vaccine reproduces only a small degree of adverse effects provoked by the natural infection of the immune system. Therefore, more vaccine-associated CVs are diagnosed and reported due to the greater attention that has been given by patients to all the side effects related to the COVID-19 vaccine.

In this review, we analyze and compare the current and most recent literature on clinical and immunohistopathologic features of CV induced by systemic SARS-CoV-2 infection and CV secondary to the SARS-CoV-2 vaccine, focusing on the possible underlying pathogenetic mechanisms.

## SARS-CoV-2 infection and cutaneous vasculitis

We collected clinicopathological features of a series of CV that occurred in association with the SARS-CoV-2 infection available in the literature (Table 1). Our search was restricted to cases with histological confirmation of leukocytoclastic vasculitis. Totally, 19 cases were included, mostly males (13/19) with variable age distribution ranging from 13 to 93 years with an average of 48.4 years. In three cases, the diagnosis was COVID-19-associated IgA vasculitis, while in five cases the patients had been diagnosed with COVID-19-associated urticarial vasculitis; finally, the other cases may be considered as cutaneous leukocytoclastic vasculitis associated with COVID-19, being not further classified according to the Dermatologic Addendum to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (3). Regarding the clinical presentation, a comparison between the frequency of different types of lesions did not reveal feasible given the heterogeneity of their description. However, it is reasonable to consider palpable purpura as the main clinical manifestation, sometimes with necrotic features and hemorrhagic blistering. The most common sites affected were the lower limbs and trunk, as for the idiopathic forms of CV. The cases diagnosed with urticarial vasculitis showed slight clinical differences, since skin lesions were characterized by wheals or urticarial manifestations, associated with purpuric aspects. The edematous component of cutaneous lesions in COVID-19-associated urticarial vasculitis was appreciable at histological evaluation in 2 out of 5 cases, whose report mentioned dermal or endothelial swelling. The latency time between skin rash occurrence with SARS-CoV-2 infection is highly variable, ranging from concomitant signs appearing at the time of onset to more than 30 days after the first positive nasopharyngeal swab. The totality (3/3) of COVID-19-associated IgA vasculitis cases presented kidney involvement, but it is of interest that in

two out of three cases, the direct immunofluorescence (DIF) performed on lesional skin resulted negative while positivity was seen in all three cases when performed on kidney biopsy. Although based on a few cases, our results are in accordance with Jedlowski *et al.*, which published a case series of 10 subjects with COVID-19-associated systemic IgA vasculitis; in fact, authors found positive skin DIF in less than half of the series (40%) while kidney biopsies showed IgA deposition in all the cases. Moreover, it is of note that COVID-19-associated IgA vasculitis more commonly affects adults when compared to the classical form of IgA vasculitis in which 90% of cases occur in the pediatric population. In our series, one DIF resulted non-specifically positive for C3, while in nine cases, it was negative for all the reactants. No cases of cutaneous IgG/IgM vasculitis were diagnosed and in eight subjects DIF was not performed. Interestingly, three cases assessed the colocalization of SARS-CoV-2 in the vessel wall, finding positivity in 2/3 cases by the PCR technique. This may support the direct role of SARS-CoV-2 in the pathogenesis of cutaneous vasculitis and its tropism for a broad variety of human tissues.

## SARS-CoV-2 vaccination and cutaneous vasculitis

In the mini-series presented (Table 2), only patients with histological confirmation of leukocytoclastic vasculitis were included. Totally, 39 patients developed CV after the COVID-19 vaccine. Women were found to be more involved than men, counting 24 females vs. 15 males developing CV. The weighted average of the patients reported was of 53.2 years (range 22–94).

Clinically, purpuric papules or maculae in the lower extremities were the most commonly reported skin manifestation (Figure 1). DIF was not reported in 21 cases (53.8%) and in 5 cases (12.8%) it was negative. Features were heterogeneous in the remaining 13 cases, with 5 cases (12.8%) of IgA vasculitis and 3 cases (7.7%) of vasculitis with C3 deposition, and some isolated cases of IgM vasculitis with fibrinogen deposit.

Most of the reported cases ($n$ = 19, 48.7%) were associated with mRNA vaccines; particularly, 13 patients underwent BNT162b2 [BioNTech/Pfizer] vaccines and five patients underwent mRNA-1273 [Moderna] vaccines. In one case, the commercial name of the vaccine was not reported. Eleven cases (28.2%) of CV were associated with adenoviral vector-based vaccines, of whom 10 were with ChAdOx1 nCoV-19 [Oxford-AstraZeneca] and one was with Ad26.Cov2.S [Johnson & Johnson].

Among the nine cases (23.1%) associated with inactivated vaccines, only one was not named, three cases were found after the administration of both Covaxin and Sinovac, and two cases after Sinopharm administration.

Nineteen patients (48.7%) developed CV after the first dose of the vaccine, while 16 (41%) after the second dose; only 3 (7.7%) cases were reported to occur after the third dose of the vaccine injection. In one case (2.6%), the dose number was non-specified.

## Discussion

Our review reported the main aspects of both CVs induced by COVID-19 infection and vaccines. Only leukocytoclastic vasculitis was included, and DIF pattern was also analyzed. Unfortunately, in many of the reported cases, DIF was not conducted, while some cases were negative. Its evaluation is extremely important in defining the type of CV and DIF positivity may raise the suspicion of systemic disease, providing useful prognostic information where histology alone cannot. Therefore, DIF should be always performed especially on early lesions because immune deposits may disappear in lesions that occurred more than 48 h before.

To date, the exact pathogenetic mechanisms underlying COVID-19-associated CV have not been fully understood. Since its outbreak in 2019, COVID-19 had spread all over the world causing a global pandemic affecting more than 500 million people and at least 6 million deaths (20). The enveloped RNA virus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the etiologic agent, which primarily affects the respiratory tract leading to general symptoms like fever, fatigue, anosmia, and dysgeusia, while respiratory symptoms are variable in severity ranging from cough and rhinorrhea to dyspnea, pneumonia, or acute respiratory distress syndrome. However, evidence about the involvement of other organs and systems is increasing; in fact, knowledge about the neurological, gastrointestinal, and ocular manifestations of SARS-CoV-2 infection is deepening (21, 22). Similarly, cutaneous signs of COVID-19 are continuously reported and attempts at classifications are already available in the literature, together with the first prevalence estimations in which dermatologic manifestations would place between 1.8 and 20.4% of the COVID-19 patients (23, 24). In particular, several works identified clusters of skin manifestations that are suggestive of skin vascular damage, namely chilblain-like lesions, acral ischemia, acral vasculitis, livedo reticularis, livedo racemosa, purpuric "vasculitic" rash, or petechial eruptions (25–27). While a definitive nomenclature is justifiably actually lacking, considering the novelty of these entities, it is well known that SARS-CoV-2 features a markable tropism for endothelial cells. The first hypothesis of vascular damage provoked by the novel coronavirus was provided from autoptic studies showing platelet-fibrin thrombi in lung blood vessels in patients who died of severe COVID-19 (28), advancing the evidence of coagulopathy as a main pathogenetic mechanism of single- or multiorgan damage induced by SARS-CoV-2. Indeed, the term "immunothrombosis" is now used to refer to the typical pattern of lung damage resulting from massive viral-induced inflammation, which leads to the activation

TABLE 1 Clinical, histological, and immunological findings in patients with COVID-19-associated CV.

| Case no | Age | Sex | Comorbid | Time to infection | Clinical presentation | Histology | DIF | SARS-CoV-2 in dermal vessels | Ref |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 93 | M | CKD<br>PAD<br>Hypertension | 8 days | purpuric macules and papules on legs, hands, and periumbilical area | Fibrin deposition,<br>Obliteration of vessels<br>Extravasated red blood cells | Negative for IgG, IgA, IgM, C3 | N/A | Capoferri et al. (45) |
| 2 | 66 | M | T2DM<br>Hypertension<br>CAD | 15 days | Palpable purpuric papules with necrotic center<br>Maculo-papular lesions on legs and forearms | Fibrin extravasation in vascular structures<br>Inclusion bodies in endothelial cells<br>Perivascular neutrophil, lymphocyte infiltrate<br>Leukocytoclasis in the dermis | Negative for IgG, IgM, IgA, C3 | N/A | Bay et al. (46) |
| 3 | 16 | F | None | N/A | Edematous, maculopapular erythematous rash on extremities, abdomen, back, thighs and face | Neutrophilic vasculitis<br>Karyorrhectic debris<br>Focal degeneration of vessel wall<br>Rare intraluminal fibrin deposits<br>Micro-thrombi | Negative for IgG, IgM, IgA, C3 | N/A | Gosnell et al. (47) |
| 4 | 13 | M | None | 28 days | Petechial and purpuric rash on both feet and ankles | Superficial epidermal necrosis | Negative for IgG, IgM, IgA, C3 | Positive (PCR) | Kumar et al. (48) |

*(Continued)*





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TABLE 1 (Continued)

| Case no | Age | Sex | Comorbid | Time to infection | Clinical presentation | Histology | DIF | SARS-CoV-2 in dermal vessels | Ref |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Small-vessel neutrophilic vasculitis | | | |
| 5 | 32 | F | Crohn disease | 14 days | Erythematous to violaceous macules and papules on lower extremities and dorsum of feet | Perivascular karyorrhectic material<br>Stromal edema and purpura<br>Capillary ectasia<br>Thrombotic vasculopathy | Not performed | N/A | Nassani et al. (49) |
| 6 | 49 | M | None | 14 days | Palpable purpura on inferior limbs and abdomen | Hyperkeratosis<br>Moderate neutrophilic infiltration<br>Extravasated red blood cells<br>Lymphocytes around dermal vessels | Not performed | N/A | Iraji et al. (50) |
| 7 | 70 | M | None | N/A | Palpable petechiae on dorsal feet, thighs, abdomen<br>Purpuric plaques | Leukocytoclastic vasculitis | Positive for IgA | N/A | Jedlowski et al. (51) |
| 8 | 27 | M | None | N/A | Painful purpuric papules<br>Vesicobullous hemorrhagic lesions Necrotic lesions | Leukocytoclastic cutaneous vasculitis<br>Microthrombi | Negative for IgG, IgM, IgA, C3 | N/A | Gouveia et al. (52) |
| 9 | 43 | M | Hypertension | N/A | Painful hemorrhagic bullae | Leukocytoclastic vessel vasculitis | Negative for IgG, IgM, IgA, C3 | N/A | Kösters et al. (53) |

*(Continued)*



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TABLE 1 (Continued)

| Case no | Age | Sex | Comorbid | Time to infection | Clinical presentation | Histology | DIF | SARS-CoV-2 in dermal vessels | Ref |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Necrotic lesions on trunk, arms, legs | Neutrophilic infiltration<br>Eosinophils and histiocytes | | | |
| 10 | 29 | M | None | 28 days | Purple palpable papules<br>Necrotic lesions<br>Serohaematic blisters on abdomen, buttocks, lower legs, feet | Heavy neutrophilic infiltrate in small vessel wall<br>Leucocytoclasis<br>Fibrinoid necrosis<br>Extravasation of red blood cells | Negative for IgG, IgA, IgM, C3 | Positive (PCR) | Camprodon Gómez et al. (54) |
| 11 | 47 | M | Hypertension, impaired glucose tolerance | 18 days | Multiple, raised erythematous wheals, alone or in cluster, some with central purple<br>Hyperpigmentation on head, trunk and upper arms | Orthokeratotic hyperkeratosis<br>Spongiosis<br>Focal lymphocytic exocytosis<br>Perivascular neutrophilic infiltration<br>Vessel wall damage | Not performed | N/A | Skroza et al. (55) |
| 12 | 64 | F | Hypertension, T2DM | Concomitant | Annular and polycyclic urticarial lesions with purpuric component on trunk and limbs | Dermal edema<br>Leukocytoclastic vasculitis | Not performed | N/A | Nasiri et al. (56) |
| 13 | 59 | M | N/A | 35 days | Maculopapular purpuric exanthema on face, trunk, limbs | Perivascular neutrophilic infiltrate | Not performed | N/A | Caputo et al. (57) |

*(Continued)*





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TABLE 1 (Continued)

| Case no | Age | Sex | Comorbid | Time to infection | Clinical presentation | Histology | DIF | SARS-CoV-2 in dermal vessels | Ref |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Leucocytoclasis<br>Red blood cell extravasation<br>Fibrinoid necrosis of vessel walls | | | |
| 14 | N/A | F | N/A | N/A | Painful erythematous patches on trunk, hips | Red blood cell extravasation | Not performed | N/A | de Perosanz-Lobo et al. (58) |
| | | | | | Purpura | Neutrophilic perivascular inflammation<br>Karyorrhexis | | | |
| 15 | N/A | M | N/A | N/A | Erythematous and edematous plaques with a purpuric center | Perivascular neutrophilic inflammation<br>Red blood cell extravasation<br>Endothelial swelling<br>Necrotic lesions<br>Fibrin deposition | Not performed | N/A | de Perosanz-Lobo et al. (58) |
| 16 | 79 | F | N/A | 7 days | Purpuric macules and papules on legs | Fibrinoid necrosis of vessel walls<br>Transmural infiltration by neutrophils<br>Karyorrhexis<br>Leukocytoclasia<br>Red blood cell extravasation | Positive for C3 | Negative (PCR) | Dominguez-Santas et al. (59) |

*(Continued)*





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TABLE 1 (Continued)

| Case no | Age | Sex | Comorbid | Time to infection | Clinical presentation | Histology | DIF | SARS-CoV-2 in dermal vessels | Ref |
|---|---|---|---|---|---|---|---|---|---|
| 17 | 83 | F | Hypertension<br>TIA<br>AF<br>CKD | 30 days | Purpuric palpable papules and serohematic blisters on lower legs, feet, toes | Perivascular neutrophils<br>Fibrins in vessel wall of the dermis<br>Leukocytoclasia | Not performed | Not performed | Mayor-Ibarguren et al. (60) |
| 18 | 30 | M | No | Concomitant | Painful purpuric rash | Leukocytoclastic vasculitis | Negative for IgA, IgG, IgM, C3 | Not performed | Li et al. (61) |
| 19 | 22 | M | None | Concomitant | Palpable purpura with central vesicles on extremities, gluteal region, lower abdomen | Perivascular infiltrate of neutrophils, lymphocytes<br>Red blood cell extravasation<br>Fibrinoid necrosis of vessel wall | Negative for IgG, IgM, IgA, C3 | Not performed | Sandhu et al. (62) |

CKD, chronic kidney disease; PAD, peripheral artery disease; T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; TIA, transient ischaemic attack; AF, atrial fibrillation.



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TABLE 2 Clinical, histological, and immunological findings in patients with COVID-19-vaccine associated CV.

| Case no | Age | Sex | Vaccine type | Vaccine name | Exclusion of SARS-CoV-2 infection | Comorbid | Temporal relation to the vaccine | Clinical characteristics of CV reported | Systemic involvement | DIF | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 30 | M | Adenoviral vector-based | Johnson-Johnson | Negative nasopharyngeal RT-PCR swab | None | 17 days after the first dose | Painful hemorrhagic papules and vesicles on soles, shins, elbows | Mild proteinuria<br>Hypocomplementemia<br>Cryoglobulinemia | Granular deposits of IgM, C3, and fibrin/fibrinogen in the walls of the dermal small vessels | Betetto L et al. (63) |
| 2 | 45 | M | Inactivated vaccine | Sinopharm | Not mentioned | None | 2 days after the first dose | Papular lesions on upper and lower limbs | Pruritus | Not performed | Shakoei et al. (18) |
| 3 | 61 | F | Adenoviral vector-based | Oxford-AstraZeneca | Negative nasopharyngeal RT-PCR swab | Hypertension | 5 days after the first dose | Pruritic erythematous-purpuric macules involving the lower legs, feet, buttocks, axillae, abdomen | Myalgia<br>Fatigue | Not performed | Criado et al. (13) |
| 4 | 52 | M | m-RNA-based | Moderna | Not mentioned | Not mentioned | 11 days after the second dose | Erythematous, non-pruritic petechial rash on lower limbs | Not reported | Not performed | Gázquez Aguilera et al. (11) |

*(Continued)*





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TABLE 2 (Continued)

| Case no | Age | Sex | Vaccine type | Vaccine name | Exclusion of SARS-CoV-2 infection | Comorbid | Temporal relation to the vaccine | Clinical characteristics of CV reported | Systemic involvement | DIF | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | 80 | M | m-RNA-based | BioNTech/Pfizer | Negative serologic investigations | Psoriasis | 4 weeks after the second dose | Targetoid erythematous lesions | Fever | Negative for IgG, IgM, IgA, C3 | Wollina et al. (19) |
| | | | | | | | | | Fatigue<br>General malaise | | |
| | | | | | | | | Necrotic lesions on legs<br>Erythematous lesions on the soft palate | | | |
| | | | | | | Hemochromatosis<br>Nodular goiter | | | | | |
| | | | | | | | | Purpuric macules on fingers and palmar creases<br>Splinter hemorrhages on nails | | | |
| 6 | 57 | F | Adenoviral vector-based | Oxford-AstraZeneca | Not mentioned | Fibrocystic mastopathy | 5 days after the second dose | Purpuric macules and papules on lower legs | Not reported | Linear and granular deposition of IgM within small vessels | Fiorillo et al. (64) |
| | | | | | | Hypertension | | | | | |

*(Continued)*





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TABLE 2 (Continued)

| Case no | Age | Sex | Vaccine type | Vaccine name | Exclusion of SARS-CoV-2 infection | Comorbid | Temporal relation to the vaccine | Clinical characteristics of CV reported | Systemic involvement | DIF | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | 51 | F | m-RNA-based | Moderna | No prior history of SARS-CoV2 infection | Sjögren syndrome Cryoglobulinemic vasculitis | 3 weeks after the second dose | Palpable purpura and ulcers Lower extremities pitting edema | Acute kidney injury<br>Nephrotic syndrome | Not performed | Vornicu et al. (65) |
| 8 | 59 | F | m-RNA-based | BioNTech/ Pfizer | No prior history of SARS-CoV2 infection | Sjögren syndrome Cryoglobulinemic vasculitis | 2 days after the first dose | Palpable purpura<br>Small cutaneous malleolar ulcers | Fatigue<br>Fever<br>Myalgias<br>Acute kidney injury<br>Nephritic syndrome | Not performed | Vornicu et al. (65) |
| 9 | 55 | F | Adenoviral vector-based | Oxford-AstraZeneca | Negative RT-PCR | None | 5 days after the first dose | Palpable purpura on lower limbs | Fever<br>Myalgia<br>Wrist swelling | Negative | Sandhu et al. (66) |
| 10 | 48 | M | Adenoviral vector-based | Oxford-AstraZeneca | Negative RT-PCR | Hypertension | 2 days after the second dose | Palpable purpura on hands, forearms, gluteal region, lower limbs | Fever<br>Myalgia | Negative | Sandhu et al. (66) |

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TABLE 2 (Continued)

| Case no | Age | Sex | Vaccine type | Vaccine name | Exclusion of SARS-CoV-2 infection | Comorbid | Temporal relation to the vaccine | Clinical characteristics of CV reported | Systemic involvement | DIF | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 11 | 46 | F | m-RNA-based | BioNTech/Pfizer | Not mentioned | Psoriasis<br><br>PsA<br>Irritable bowel syndrome<br>Leukocytoclastic vasculitis | 2 days after the first dose (1st flare), 2 days after the second dose (2nd flare) | Exacerbation of palpable purpuric papules lower legs (first flare)<br><br>Palpable purpuric papules on the lower legs, feet, upper extremities, lower back, and abdomen (second flare) | Not reported | Not performed | Cohen et al. (67) |
| 12 | 83 | F | m-RNA-based | BioNTech/Pfizer | Not mentioned | None | 5 days after the second dose | Palpable purpura with erythema and edema on lower extremities | Elevated levels of C-reactive protein, elevated sedimentation rate,<br><br>Rheumatoid factor<br>Hypocomplementemia | Deposition of fibrinogen around superficial blood vessels | Larson et al. (68) |

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TABLE 2 (Continued)

| Case no | Age | Sex | Vaccine type | Vaccine name | Exclusion of SARS-CoV-2 infection | Comorbid | Temporal relation to the vaccine | Clinical characteristics of CV reported | Systemic involvement | DIF | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Cryoglobulinaemia | | |
| 13 | 57 | F | m-RNA-based | Not mentioned | Not mentioned | Epilepsy<br>Bipolar disorder<br>Depression | 7 days after the first dose | Erythematous confluent papules and plaques involving trunk, extremities | Not reported | Not performed | Bostan et al. (69) |
| 14 | 46 | F | Inactivated | Covaxin | Negative oro-nasopharyngeal RT-PCR swab | None | 5 days after the first dose | Palpable purpura on legs<br>Pitting edema on ankles | Arthralgia<br>Ankle swelling | Not performed | Kar et al. (44) |
| 15 | 47 | M | m-RNA-based | BioNTech/Pfizer | Not mentioned | Intermittent abdominal pain | 3 days after the first dose (first episode); 4 days after the second dose (flare) | Reddish spots in his ankles (first episode)<br>Purpuric papules on legs, forearms (second episode) | Elevated C-reactive protein<br>Proteinuria<br>Decreased glomerular filtration rate | C3/C4 deposits | Gambichler et al. (70) |
| 16 | 59 | F | m-RNA-based | Moderna | Not mentioned | Hypertension<br>Hyperlipidemia | 1 day after the second dose | Violaceous petechiae on legs, pelvis, abdomen, upper limbs | Intermittent abdominal pain | Not performed | Ireifej et al. (71) |

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TABLE 2 (Continued)

| Case no | Age | Sex | Vaccine type | Vaccine name | Exclusion of SARS-CoV-2 infection | Comorbid | Temporal relation to the vaccine | Clinical characteristics of CV reported | Systemic involvement | DIF | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Elevated C-reactive protein | | |
| | | | | | | Prediabetes<br>Obesity<br>COVID-19 in April 2020 | | | | | |
| 17 | 57 | F | Inactivated | Sinopharm | Not mentioned | None | 5 days after the second dose | Purpuric papules with central blistering<br>Necrotic lesions<br>Black eschars on legs<br>Palpable purpura on thighs, buttocks, abdomen, back, forearms | Fatigue<br>Arthralgia | Not performed | Azzazi et al. (39) |
| 18 | 94 | M | m-RNA-based | Moderna | Not mentioned | AF | 10 days after the second dose | Palpable purpura | Not reported | IgA immune deposits in the blood vessel walls | Grossman et al. (72) |

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TABLE 2 (Continued)

| Case no | Age | Sex | Vaccine type | Vaccine name | Exclusion of SARS-CoV-2 infection | Comorbid | Temporal relation to the vaccine | Clinical characteristics of CV reported | Systemic involvement | DIF | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Aortic valve replacement<br>Hypothyroidism<br>Anemia | | | | | |
| 19 | 76 | M | m-RNA-based | BioNTech/Pfizer | Not mentioned | Liver cirrhosis<br>Heart failure<br>Previous gastroesophageal junction cancer and prostate cancer | 12 days after the second dose | Pruritic purpuric macules on hands, feet, legs, thighs, abdomen | Bloody diarrhea | Not performed | Mücke et al. (73) |
| 20 | 65 | M | m-RNA-based | BioNTech/Pfizer | Not mentioned | T2DM<br>Hypertension | 2 days after the third dose | Purpuric palpable lesions on legs | Not reported | Not performed | Dicks et al. (74) |
| 21 | 50 | M | m-RNA-based | BioNTech/Pfizer | Not mentioned | None | 2 days after the second dose | Rash on the legs | Not reported | IgA-dominant immune deposits in the blood vessel walls | Mohamed et al. (75) |

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TABLE 2 (Continued)

| Case no | Age | Sex | Vaccine type | Vaccine name | Exclusion of SARS-CoV-2 infection | Comorbid | Temporal relation to the vaccine | Clinical characteristics of CV reported | Systemic involvement | DIF | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 22 | 40 | F | m-RNA-based | BioNTech/Pfizer | Not mentioned | Hashimoto's thyroiditis | 20 days after second dose | Purpuric rash on gluteal region | Headache | Not performed | Hines et al. (76) |
| 23 | 57 | M | Adenoviral vector-based | Oxford-AstraZeneca | Not mentioned | Hypertension | 14 days after the first dose | Purpura on lower limbs, abdomen, trunk, head | Not reported | Not performed | Cavalli G et al. (77) |
| 24 | 57 | F | Adenoviral vector-based | Oxford-AstraZeneca | Not mentioned | Hypertension<br>Hypothyroidism | 5 days after the first dose | Palpable purpura on buttocks, legs, arms | Not reported | Negative for IgG, IgM, IgA, C3 | Guzmán-Pérez et al. (78) |
| 25 | 77 | F | Adenoviral vector-based | Oxford-AstraZeneca | Not mentioned | None | 10 days after the first dose | Palpable indurated purpuric papules Erythematous plaques and bullae on lower limbs, hands. Purpuric lesions on soft palate, tongue | Not reported | Negative for IgG, IgM, IgA, C3 | Shahrigharahkoshan et al. (79) |
| 26 | 68 | F | Adenoviral vector-based | Oxford-AstraZeneca | Not mentioned | None | 7 days after the first dose | Erythematous to purpuric non-blanching macules on lower extremities | Not reported | Not performed | Jin et al. (80) |

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TABLE 2 (Continued)

| Case no | Age | Sex | Vaccine type | Vaccine name | Exclusion of SARS-CoV-2 infection | Comorbid | Temporal relation to the vaccine | Clinical characteristics of CV reported | Systemic involvement | DIF | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 27 | 60 | F | Adenoviral vector-based | Oxford-AstraZeneca | Not mentioned | Chronic liver disease<br>Portal hypertension<br>Polycythemia vera<br>Hypothyroidism<br>T2DM | 11 days after the second dose | Painful purpuric lesions on lower limbs | Not reported | IgA and IgM deposits on the walls of postcapillary vessels | Fritzen et al. (81) |
| 28 | 76 | F | Adenoviral vector-based | Oxford-AstraZeneca | Not mentioned | None | 7 days after the first dose | Maculopapular rash on lower extremities | Hematuria<br>Arthralgia | Not performed | Sirufo MM et al. (43) |
| 29 | 46 | F | Inactivated | Covaxin | Negative oropharyngeal RT-PCR swab | None | 5 days after the first dose | Purpuric papules on legs | Arthralgia<br>Ankle swelling | Not performed | Kar et al. (44) |
| 30 | 31 | F | Inactivated | Covaxin | Negative oropharyngeal RT-PCR swab | None | 4 days after the second dose | Palpable purpura on left leg<br>Pitting edema | Not reported | Not performed | Kharkar et al. (82) |
| 31 | 77 | M | Adenoviral vector-based | Sinovac | Negative nasopharyngeal RT-PCR swab | None | 2 weeks after the third dose | Palpable violaceous patches | Gastrointestinal involvement (abdominal pain, stool tests on occult blood-positive) | Negative for IgG, IgM, IgA, C3 | Oskay et al. (83) |

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TABLE 2 (Continued)

| Case no | Age | Sex | Vaccine type | Vaccine name | Exclusion of SARS-CoV-2 infection | Comorbid | Temporal relation to the vaccine | Clinical characteristics of CV reported | Systemic involvement | DIF | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Bullous hemorrhagic lesions on lower limbs, hands | | | |
| 32 | 33 | M | Adenoviral vector-based | Not mentioned | Mildly symptomatic COVID-19 three months before | None | 3 days after the first dose | Violaceous eruption<br>Erythematous macules<br>Palpable papules on legs, forearms | Not reported | IgA deposition within small vessel walls | Bostan et al. (84) |
| 33 | 91 | F | m-RNA-based | BioNTech/Pfizer | No evidence of acute SARS-CoV-2 infection | Dementia<br>Hypertension<br>T2DM | 4 days after the third dose | Palpable purpuric lesions on lower limbs | Not reported | Not performed | Carrillo-Garcia et al. (37) |
| 34 | 38 | M | m-RNA-based | BioNTech/Pfizer | Not mentioned | None | 4 days before the first dose | Purpuric-erythematous macules, papules, and plaques on lower limbs | Arthralgia | Not performed | Altun et al. (36) |
| 35 | 52 | M | m-RNA-based | Moderna | Not mentioned | Not mentioned | 11 days after the second dose | Erythematous, non-pruritic rash on legs | Not reported | Not performed | Gázquez Aguilera et al. (11) |

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TABLE 2 (Continued)

| Case no | Age | Sex | Vaccine type | Vaccine name | Exclusion of SARS-CoV-2 infection | Comorbid | Temporal relation to the vaccine | Clinical characteristics of CV reported | Systemic involvement | DIF | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Petechiae on lower limbs | | | |
| 36 | 42 | F | m-RNA-based | BioNTech/Pfizer | Not mentioned | Hypertension Obesity | 4 days after injection (dose number non-specified) | Cutaneous eruption on lower limbs, gluteal area | Not reported | Not evaluable | Erler et al. (85) |
| 37 | 22 | F | m-RNA-based | BioNTech/Pfizer | Not mentioned | None | 7 days after the second dose | Small, red, raised, itchy lesions on legs. Purpuric lesions on lower limbs | Not reported | Not performed | Ripalta Colia et al. (38) |
| 38 | 23 | F | Inactivated | Sinovac | Not mentioned | None | 36 h after first dose | Non-blanchable erythematous plaques with purpura on extremities | None | C3 and fibrinogen deposition around blood vessel walls | Bencharattanapet al. (86) |
| 39 | 26 | F | Inactivated | Sinovac | Not mentioned | None | 4 h after first dose | Non-blanchable purpuric purpura on extremities | None | IgM, C3, and IgA deposition | Bencharattanaphakhi et al. (86) |

CKD, chronic kidney disease; PAD, peripheral artery disease; T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; TIA, transient ischaemic attack; AF, atrial fibrillation.



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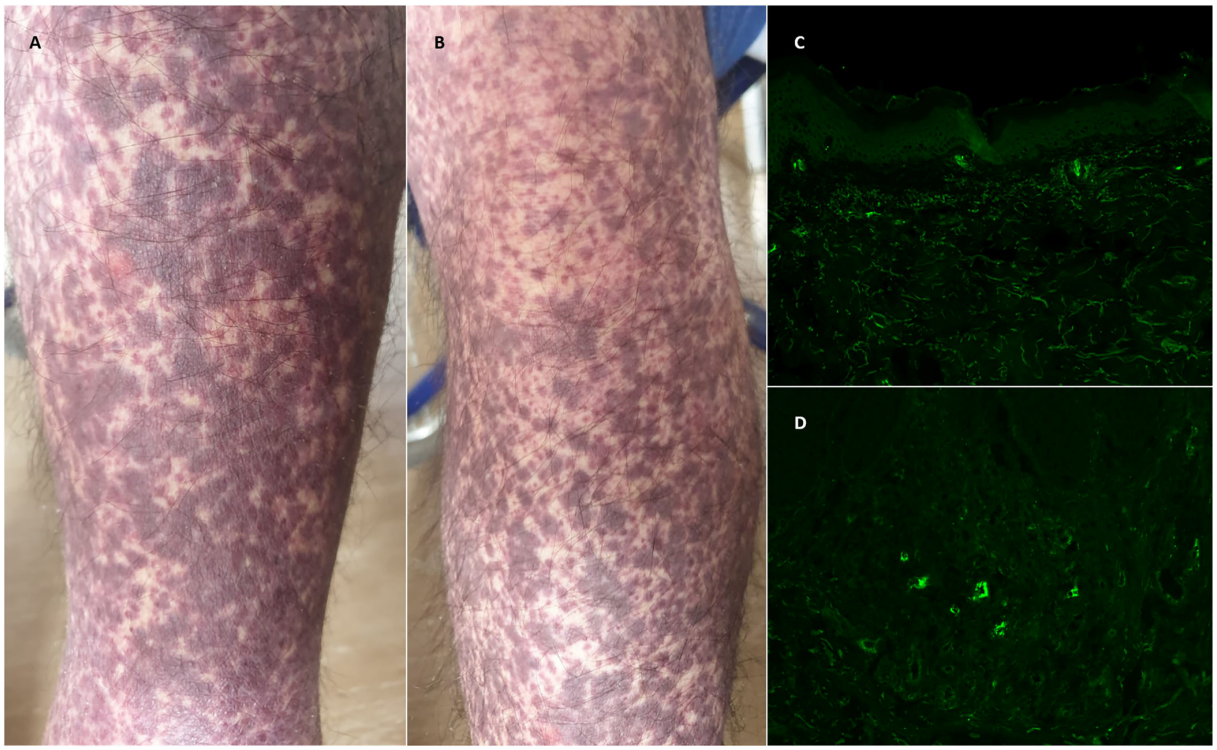


FIGURE 1
**(A,B)** Purpuric maculae and papules in the lower extremities in a patient with a recent anamnesis of COVID-19 vaccination. **(C,D)** Direct immunofluorescence performed on lesional skin, with evidence of perivascular deposition of C3. (c: 10% magnification, d: 20% magnification).

of the endothelium and triggers intravascular coagulation. Similar mechanisms may be responsible for skin manifestations reflecting vascular dysfunction or true vasculitis, since it was demonstrated that ACE2 is expressed in the skin basal cell layer, dermal vessels endothelium, eccrine glands, and subcutaneous fat tissue and act as a receptor for SARS-CoV-2 Spike protein binding (29). Viral uptake precludes the ACE2-dependent protective action of angiotensin 1–7 and results in oxidative stress, inflammatory cytokine production, and vasoconstriction (30, 31). Endotheliitis following virus internalization enhances endothelial injury, thrombogenesis, and immune recruitment, while the cytokine storm typical of severe cases may additionally boost the same mechanism in multiple anatomical districts (32). Moreover, sustained activation of the complement system causes microvascular injury and a procoagulant state triggered by the deposition of complement component C4d and colocalization of SARS-CoV-2 Spike protein in dermal vessels (33). All these mechanisms contribute to the inflammatory dermal microenvironment, which may be the subject of the innate and adaptive immune cell recruitment leading to the extension of inflammatory process toward the vessel wall, causing vasculitis. Another proposed pathogenetic mechanism may involve an autoimmune response targeting vessel wall components following a break of tolerance or molecular mimicry with SARS-CoV-2 proteins (34). Furthermore, CV was described in the context of Kawasaki-like syndrome, a generalized inflammatory disease affecting mainly infants for which the term "multisystem inflammatory syndrome in children (MIS-C) has been coined. However, the specificity of skin vasculitis in the setting of MIS-C still remains unclear, also due to the less frequency of skin biopsies performed in children.

All vaccines authorized for use by the U.S. *Food and Drug Administration* (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) have been thoroughly studied and found to be safe and effective in preventing severe COVID-19 cases (35). However, as globally millions of people have now been vaccinated, with increasing frequency, vaccination-related diseases have been observed (36), including CV.

Almost all the available COVID-19 vaccines have been associated with CV, e.g., mRNA vaccines (Pfizer BioNTech), mRNA-1273 (Moderna), adenoviral vector-based vaccines (ChAdOx1 nCoV-19; Oxford-AstraZeneca), and inactivated vaccines (Covaxin, Sinovac). Correlations between vaccination and the subsequent appearance of several types of vasculitis have been also described in the literature with vaccines against influenza, hepatitis B, serogroup B meningococcus, hepatitis A, Human Papilloma Virus (HPV) and with Bacillus of Calmette-Guérin (BCG) (37).

An important criterion guiding the assessment of causality is the temporal relationship between immunization and the side event: for drug- and vaccine-induced vasculitis it is considered to be in the range of 1–6 weeks (38). Most of the cases were self-limiting skin forms without systemic involvement, solved spontaneously or after systemic treatment.

The link between vasculitis and vaccination from a pathogenetic point of view is not clear but may involve an immune complex and antibodies deposition in the blood vessel walls (39). Recently, cytoplasmatic granular positivity for SARS-CoV-2 Spike protein was found in some skin specimens of infection-related CV (40). The vaccine proteins are structurally analogous to the wild viral antigens and could induce a pro-inflammatory cascade similar to that caused by the viral protein. Thus, vaccine antigens may activate B/T cells and cause antibody formation with subsequent immune complex deposition in small-caliber vessels. Along with this, Baiu et al. demonstrated the role of Th1 response and suggested that interferon-gamma is critically required for the initiation of vascular inflammation (41). Then, the whole-virion inactivated SARS-CoV-2 vaccine induces primarily a Th1-biased response, which could lead to the induction of an inflammatory response in the vessel wall (42). An open issue for patients who developed such adverse events following COVID-19 vaccination is whether the booster dose should be administered or not. In fact, repeating the administration could potentially cause more severe immunologic reactions (43). However, cutaneous small-vessel vasculitis secondary to infections, drugs, and vaccines is reported to have a less protracted course when compared to primary vasculitis. Therefore, this should not be a deterrent to the use of the COVID-19 vaccine, which is the most effective weapon to curb the pandemic (44).

## Conclusion

Although rarely, CV has been reported in both SARS-CoV-2 -infected and SARS-CoV-2-vaccinated patients. In many cases, these were self-limiting skin forms without systemic involvement, solved spontaneously or after systemic treatment. Studies on this topic are however important to better understand the pathogenetic mechanisms underlying their origin.

With the evolution of the infection and with the finding of less aggressive SARS-CoV-2 variants, it will be necessary to follow the patients who will develop a CV, to better define their characteristics, and possibly understand which variants are more associated with the development of CV. Moreover, the epidemiological trend of COVID-19 infection and the need to protect especially the fragile population made it necessary to start a vaccination campaign with a fourth additional dose. Therefore, careful monitoring of these patients is essential to identify the presence of CV and to make a correct diagnosis, based not only on histological examination but also on DIF, essential to better define the characteristics of SARS-CoV-2 and vaccine-related CV.

## Author contributions

AV, CHS, and MC contributed to conception and design of the study. EM organized the database of cases collected. AC, EM, VR, and AV wrote the first draft of the manuscript. LQ and CA wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Pathophysiology and clinical manifestations of immune complex vasculitides

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Immune complex (IC) vasculitides present inflammations of vessel walls associated with perivascular deposition of immunoglobulins (Igs), mostly ICs. They encompass systemic and skin-limited variants of IgA vasculitis (IgAV), cryoglobulinemic vasculitis (CV), rheumatoid, lupus, and hypocomplementemic vasculitides, serum sickness cutaneous IgM/IgG (non-IgA) vasculitis, and recurrent macular (hypergammaglobulinemic or exertion-induced) vasculitis. Serum sickness and CV fulfill the criteria of a type III hypersensitivity immune reaction as large lattices of the IC precipitate at vessel walls and activate polymorphonuclear neutrophils (PMNs). Immunoglobulin-A vasculitis differs with regard to the causes of perivascular deposition of ICs since here many IgA1 molecules are hypoglycosylated (Gd-IgA1), which appears to facilitate their perivascular deposition in skin and mesangium (via e.g. CD71). The reasons for increased generation of immunoglobulins or formation of IC and their perivascular deposition in either skin or systemic organs are different and not fully explored. A common denominator of OC vasculitides is the activation of PMNs near the vessel wall *via* Fcγ or Fcα receptors. Acute episodes of IgAV additionally require PMNs to become preactivated by IgA1 or by IC already in circulation. This intravascular priming results in increased adherence and subsequently vessel-destructive NETosis when they encounter IgA deposited at the vessel walls. Binding of IgA1 to PMNs in blood stream is associated with increased serum levels of hypogalactosidated IgA1. The characteristic clinical picture of IgAV (and also of so-called IgG/IgM vasculitis) comprises palpable or retiform purpura with a clear predilection for lower legs, probably due to stasis-related reduction in blood velocity, while in other IC vasculitides, additional factors influence the sites of vasculitides. Our knowledge of distinct forms and different pathophysiological pathways of IC vasculitides may lead to in efficacious or targeted therapies. Antibodies to complement components or intestinal budesonide for IgAV are promising agents (the latter suppresses the pathophysiologically related IgA nephropathy by reducing the generation of mucosal IgA.

KEYWORDS

**IgA vasculitis, cryoglobulinemic vasculitis, rheumatoid vasculitis, hypocomplementaemic vasculitis, serum sickness, glomerulonephritis IgA1, cutaneous IgM/IgG-vasculitis, immune complex disease**

## 1. Definition and different forms of immune complex vasculitides

Immune complex vasculitides present inflammations of vessel walls associated with and mainly elicited by perivascular deposition of immunoglobulins, mostly in the form of immune complexes (ICs).

There are different forms of immune complex vasculitides (Table 1) (1): systemic and skin-limited variants (1) of IgA vasculitis (IgAV) (Figure 1), cryoglobulinemic vasculitis (CV), rheumatoid vasculitis (RV), lupus vasculitis (LE vasculitis), hypocomplementemic vasculitis (Figure 2), and serum sickness, as well as the provisionally defined forms of cutaneous IgM/IgG immune complex vasculitides and a recurrent macular vasculitis induced by hypergammaglobulinemia (Waldenström) (Figure 3) or by exertion or heat, or a, vasculitis in gammopathy other than cryoglobulinemic vasculitis (2, 3).

According to Coombs and Gell, the so-called type III hypersensitivity reaction has been considered among immunologists as a model for immune complex vasculitis. The prototype would have been that of serum sickness that occurs when a certain antigen in the circulation encounters approximately equimolar concentrations of fitting antibodies (4, 5) so that large lattices of circulating immune complexes form, which subsequently become deposited at the walls of small blood vessels, where they activate the complement system and polymorphonuclear neutrophils (PMNs).

This disease has has long been considered to present the prime example for immune complex vasculitis and corresponding animal models, including the Arthus reaction, and has largely dominated the pathophysiological concept of immune complex disease in general and immune complex vasculitis in particular.

However, the pathophysiology of IgA vasculitis has been revealed to differ at least in its initial stages from serum sickness, because it is primarily the altered galactosidation of the IgA1 molecule which mediates its deposition at certain vasculatures and not the size of the IC (6, 7).

Circulating complexes have also been demonstrated to present a major pathophysiological factor for vasculitis in cryoglobulinemia and in rheumatoid arthritis (RA) (1).

Common denominators for immune complex vascultides are perivascular deposition of altered immunoglobulins or immune complexes, and their subsequent full activation of PMNs close to the vessel wall *via* FcγR or FcαR. Histologically, the resulting picture of small vessel vasculitis is generally that of leukocytoclastic vasculitis of post-capillary venules, which sometimes extends into small veins and may also involve small arterioles. Clinically, the inflammatory infiltrates and ensuing extravasation of blood manifests as hemorrhagic maculae, papules, and plaques, sometimes in a retiform pattern [branched or retiform purpura, a term coined by Warren Piette (8)]. The most characteristic clinical picture as it has engraved in the clinician's eye is that presented by IgA vasculitis, i.e., palpable and macular, round or oval, and sometimes branched or retiform purpura with a predilection for dependent parts, namely the legs (Figure 1). In the other forms of immune complex vasculitis, the lesions are not as numerous and not as accentuated on the lower legs as in IgA vasculitis.

As reflected by the nomenclature of Chapel Hill Consensus Conference (CHCC) 2012 for cutaneous vasculitides, several of the different forms of systemic immune complex vasculitides have a counterpart that seems to occur exclusively on the skin but has the same cutaneous manifestations clinically and histologically as the systemic form. They are referred to as a skin-limited or cutaneous form of the respective systemic vasculitis (e.g., cutaneous IgA vasculitis) (1).

While most cutaneous vasculitides are immune complex-mediated vasculitides of mainly small vessels, there are several other vasculitides of small vessels (ANCA-associated vasculitides), medium (cutaneous periarteritis nodosa), and even large vessels (9) that affect the skin.

## 2. Serum sickness disease

Serum sickness disease is a paradigm of a systemic immune complex disease (type III hypersensitivity reaction). In its complete form, it apparently results when large amounts of heterologous (non-human) proteins as antigens encounter approximately equimolar concentrations of fitting antibodies leading to formation of large lattices of immune complexes. It induces not only IgG but also IgE, so serum sickness causes symptoms due to a varying involvement of the activated complement cascade and IgE, depending on the antigen. Histamine-mediated vascular permeability of vessels and joints facilitates perivascular deposition of ICs. Nowadays, serum sickness disease occurs not only after the administration of antithymocyte globulin (rabbit serum) but also after the administration of other foreign sera (antidotes), rituximab, streptokinase, or other drugs. However, one may speculate that there are attenuated or abortive forms with perhaps only skin-limited perivascular deposition of immune complexes, one of whose clinical manifestations could be cutaneous IgG/IgM vasculitis (refer to the following).

The typical symptoms are persistent fever, arthralgia or arthritis mostly of the large joints, lymphadenopathy, asthma, and a polymorphic picture with urticae, maculopapular exanthema, itchy papules, or palpable purpura. In contrast, IgA or IgG/IgM vasculitis would typically present on the skin with only macular or palpable round, oval, or retiform purpura with a predilection for the legs. Symptoms occur 7–14 days after primary administration (and 2–4 days after repeated administration) of a foreign protein. Accordingly, high levels of circulating immune complexes are detectable after 10–12 days and low levels of C4 and C3 on the 10th day, while C3a anaphylatoxin is elevated, accompanied by leukocytosis and sometimes eosinophilia, hematuria, and proteinuria.

## 3. IgA vasculitis

Immunoglobulins A vasculitis is an inflammation of small vessels related to tissue deposits of immunoglobulins A (IgA), or, more precisely, galactose-deficient or hypogalactosidated IgA1 (Gd IgA1), most likely bound in immune complexes. It may

TABLE 1 Immune complex vasculitides.

| | |
|---|---|
| IgA vasculitis (IgAV)<br><br>(Henoch-Schönlein purpura)<br><br>- systemic IgAV<br>- skin-limited IgAV<br>- provisional: IgA nephropathy (IgAN) (if considered as kidney-limited IgAV) | Vasculitis, with immune deposits of hypogalactosidated IgA (Gd-IgA1), affecting small vessels (predominantly post-capillary venules) |
| IgM/IgG vasculitis (provisional, skin-limited) | Vasculitis, with IgM and/or IgG dominant immune deposits, not containing IgA, and independent of Gd-IgA1, affecting small vessels (predominantly post-capillary venules) in the skin |
| Cryoglobulinemic vasculitis (CV)<br><br>- systemic CV<br>- skin-limited CV | Vasculitis with cryoglobulin immune deposits, mostly IC, affecting small vessels and associated with serum cryoglobulins, usually type II or III |
| Vasculitis associated with systemic, usually collagenous vascular, disease: e.g.,<br><br>- rheumatoid vasculitis (RV)<br>- LE vasculitis<br>- systemic skin-limited forms of vasculitis | Vasculitis that is associated with and maybe secondary to (caused by) a systemic disease (e.g., rheumatoid vasculitis, LE, sarcoid vasculitis, etc.). The name (diagnosis) should have a prefix term specifying the systemic disease (e.g., rheumatoid vasculitis, lupus vasculitis, etc.) |
| Hypo-complementemic urticarial vasculitis (HUV) (anti-C1q vasculitis) | Vasculitis accompanied by urticarial lesions and hypo-complementemia affecting small vessels and associated with anti-C1q antibodies. Glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common. |
| Hypo- or normocomplementemic urticarial vasculitis (non-anti-C1q) (provisional) (skin-limited) | Cutaneous, leukocytoclastic vasculitis, clinically appearing as urticarial lesions or wheals with hemorrhagic macules, affecting small vessels and not associated with anti-C1q antibodies (it is a provisional term); several previously published cases of so-called urticarial vasculitis may today be diagnosed as neutrophilic urticarial dermatosis (NUD) and not as vasculitis |
| Recurrent macular vasculitis in hypergammaglobulinemia (formerly benign hypergammaglobulinemic purpura of Waldenström) or recurrent macular vasculitis mediated by exertion (Golfer's vasculitis, cocktail party vasculitis, heat-induced vasculitis) | Relapsing, short-lasting cutaneous small vessel vasculitis with recurring macules and purpura associated with vascular immunoglobulin deposits and hypergammaglobulinemia or possibly vasodilation induced by exertion, alcohol, long standing, or heat |

present as a variant restricted only to the skin (skin-limited IgAV) or as systemic vasculitis [IgAV–Henoch-Schönlein Purpura (HSP)], which manifests as arthritis, gastrointestinal vasculitis, renal vasculitis, and rarely pulmonary or cerebrovascular vasculitis. The reason why there is a skin-limited or a systemic form is not due to presence or absence of perivascular deposition of Gd-IgA1 because we detected Gd-IgA1 around cutaneous vessels in both systemic as well as skin-limited IgAV (10).

Similar to skin-limited IgAV, IgA nephropathy (IgAN), the most frequent form of nephritis in adults, may also present an organ-limited variant in the spectrum of IgA-related vasculitides, restricted to the kidneys. Histopathologically, IgA-nephritis in the course of systemic IgAV is indistinguishable from IgAN [for review (6, 7, 11, 12)]. There are, however, some differences, as the episode of kidney injury in IgAN is mainly chronic and presents with less crescentic lesions and more sclerotic lesions than in IgAV-nephritis; in addition, IgAV-nephritis shows more glomerular capillaritis with subendothelial IgA deposition and significant elevation of serum inflammatory cytokines (13).

The short-term prognosis of systemic IgAV depends on the severity of potential acute involvement of the gastrointestinal tract, while the long-term prognosis is dependent on the extent of the kidney damage. End-stage renal failure may occur more than 10 years after the onset of IgAV (14, 15).

## 3.1. IgA and Gd-IgA1

Immunoglobulins A presents an important immunoglobulin in mucosal immunity. It is produced by the B cells in the mucosal-associated lymphoid tissue and the bone marrow. The major part of serum IgA (90%) is IgA1. More than 90% of serum IgA1 is monomeric, while IgA1 secreted by mucosal tissues is mainly polymeric (linked by joining chains), a quality that is relevant for IgAV [for review (6)].

Hypoglycolysation occurs only in IgA1 and not in IgA2 because IgA1 has an extended hinge region with the insertion of two octapeptide repeats in its heavy chain. The repeats have three to six common O-glycan sites consisting of serine or threonine residues to which galactose or sialic acid bind. This binding is catalyzed by several transferases such as polypeptide N-acetylgalactosaminyl transferase 2 or core-1 β1,3-galactosyltransferase (which catalyzed the binding of Gal to GalNAc) and acetylgalactosamine-specific α-2,6 sialic acid transferase, respectively. Altered expression and activities of galactosyltransferase would result in altered exposure of terminal GalNac residues or more Gd-IgA [for review, refer to Heineke et al. (6), Barratt et al. (12), and Xu et al. (16)].

Gd-IgA1 is also found in healthy individuals, albeit in low concentrations [Suzuki et al. (17), for review: (12)]. In contrast, adult patients with IgAN and IgAV nephritis appear to have an inherited autosomal dominant or a constitutional disposition for elevated levels of Gd-IgA1 (12, 18, 19). In addition, immortalized B cells from patients with IgAV and IgAV nephritis both produced similarly high amounts of GdIgA1, while cell lines from patients with IgAV without nephritis produced mostly normally galactosidated IgA (17). Formation of Gd-IgA1 at least in IgAN is additionally enhanced by interleukin-6 (IL-6), interleukin-4 (IL-4), and even by some miRNA (miR-148b); their respective actions result in reduced activity of transferases or other reactions in glycosylation [for review, refer to Xu et al. (16)].

Most, but not all, studies have demonstrated elevated serum levels of Gd-IgA1 compared to controls in the majority of patients with IgAN [e.g., 75% of children with IgAN (20)] and also in patients with IgAV-nephritis [e.g., 52% of children with IgAV nephritis (20)]. In other studies [from France or in China (21, 22)], significantly higher serum levels of Gd-IgA1 were not only found

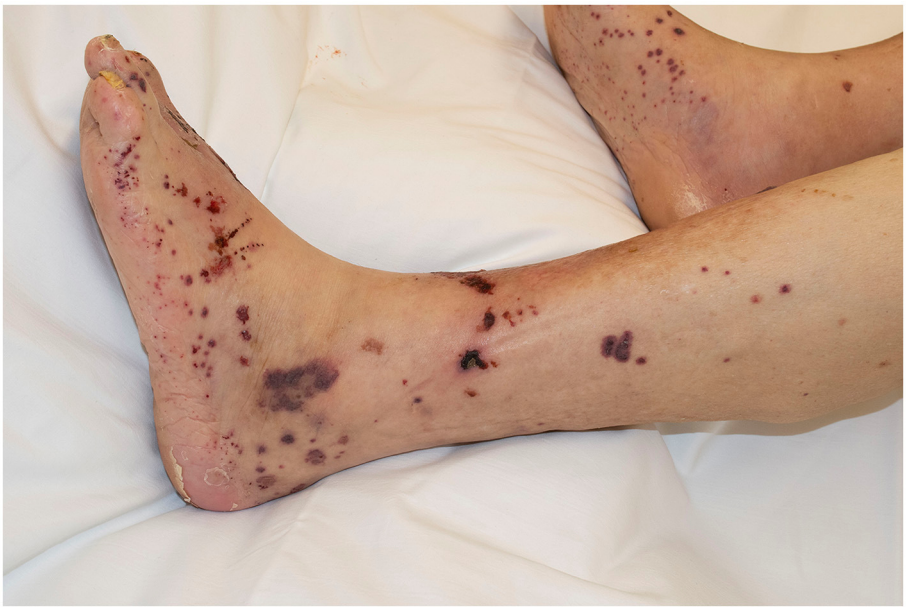

FIGURE 1
Round or oval and retiform (or branched) palpable purpura in IgA vasculitis.

when compared with healthy controls but also when distinguishing children or adults with IgAV nephritis from those with IgAV ***without*** nephritis. In contrast, other studies showed that serum levels did not significantly differ (i) between IgAV ***without*** nephritis (likely what we now call skin-limited IgAV) and healthy controls (12, 23) or (ii) between children with IgAV and children with inactive IgAV-nephritis or with controls (12).

## 3.2. Causes for increased serum levels

A major reason for the overall rise of IgA, IgA1, and Gd-IgA1 is probably the stimulation of B cells and their IgA production by infectious organisms or other agents.

In IgAN, one has several hints that dysregulation of lymphoid organs in the intestine may be the inciting event that leads to stimulation of GdIgA1 production [for review (7)], partially since (i) budesonide, a corticosteroid that acts exclusively in the gastrointestinal tract, has improved IgAN in phase 2 (NEFIGAN) and phase 3 (NEFIGARD) clinical trials (24, 25), (ii) microorganisms induce activation factors for B lymphocytes, (iii) certain compositions of the intestinal microbiota are associated with IgAN, and (iv) pan-genomic association genetic studies (GWAS) show an association between IgAN and genes involved in immunity to intestinal pathogens or in the maintenance of intestinal barrier [for review (7)].

In contrast, one has only circumstantial evidence that in IgAV, other mucosal surfaces and immune systems also are involved in the stimulation of IgA production. As such, IgAV has been observed to be often preceded by an infection of e.g., the upper digestive or respiratory tract (streptococcus, adenovirus, parvovirus, and *Mycoplasma pneumoniae*) or by systemic infection with Parvovirus B19, EBV, CMV, HIV, and COVID-19 [(26), for more literature (7, 12)], as well as by the intake of drugs, certain toxins, or food, especially in children.

Therefore, a situational rise in IgA1 together with a proportional or even disproportional increase in Gd-IgA1 (due to genetic predisposition in response to mostly mucosal infection and IL-6 production) is one incipient step in the pathophysiology of IgAV. The question remains if some of these probably eliciting agents are physically enclosed in immune complexes or facilitate the formation of, in particular, large immune complexes.

One further prerequisite besides elevated Gd-IgA1 levels appears to be indeed their binding in immune complexes. In patients with IgAN, but also in children with IgAV, IgG autoantibodies to Gd-IgA1 were found in IgAN (27) and in those children with IgAV nephritis (17). Patients with active IgAV nephritis showed higher serum levels of Gd-IgA1-specific IgG autoantibodies than patients with inactive IgAV-nephritis or than patients with IgAV ***without*** renal involvement whose levels rather were similar to healthy controls (17).

In the rarely performed serial determination of the levels of IgG autoantibodies, serum levels of IgG autoantibodies appear to correlate with serum levels of Gd-IgA1 in IgAN (28). IgG autoantibodies were found to be enriched in the glomerular immune deposits of kidney biopsies from patients with IgAN, but not those from patients with other forms of nephritis, i.e., lupus nephritis or membranous nephropathy (28).

In IgAV, levels of circulating IgA immune complexes were significantly correlated with the detection of IgA in kidneys (29) and with the presence of signs of clinical and histological activity. These signs were the magnitude of microscopic hematuria, a past history of macroscopic hematuria, and the percentage of glomeruli

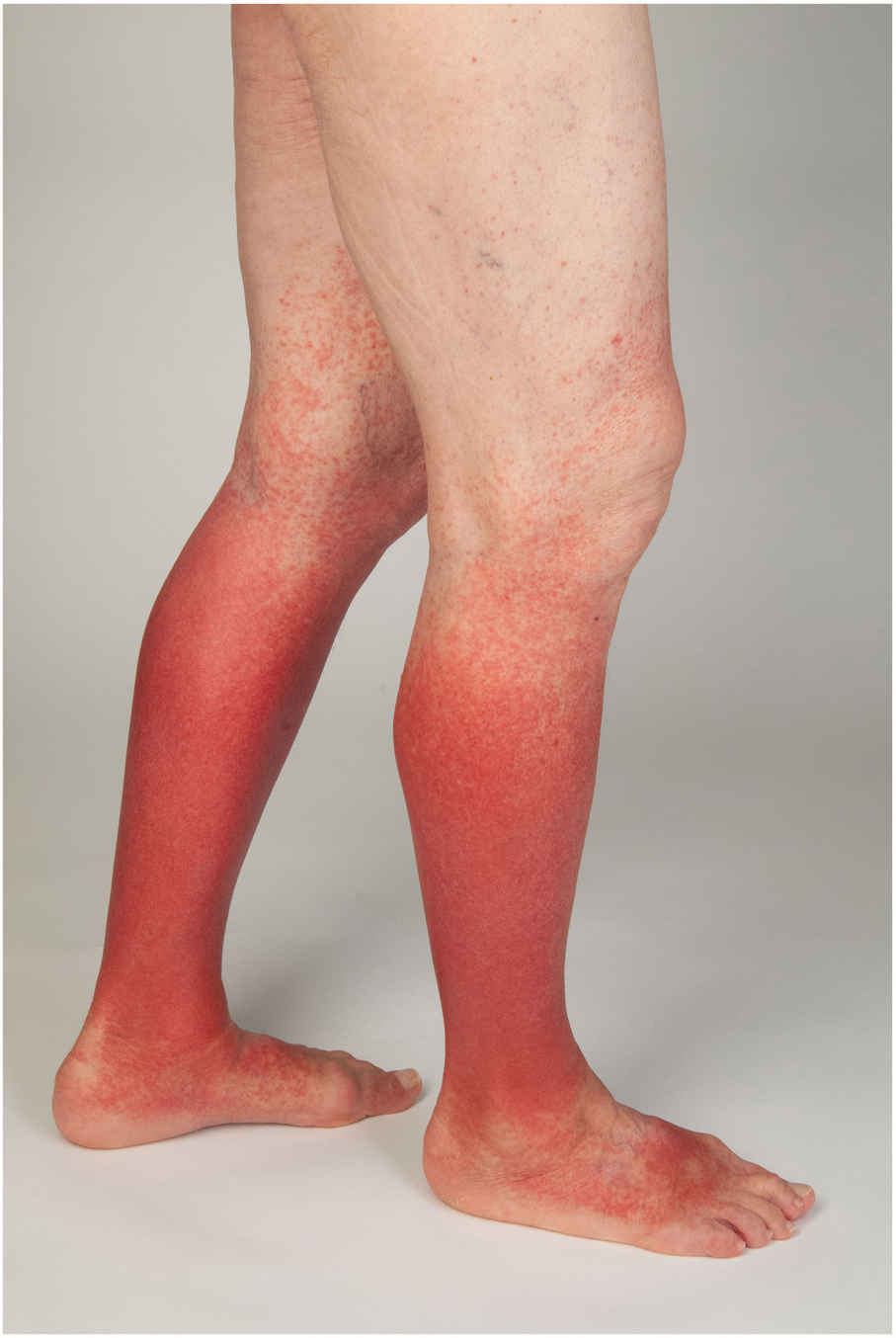

FIGURE 2
Cutaneous hypocomplementemic IgG/IgM-vasculitis.

with florid epithelial crescents [(30), for further literature, refer to (16)].

In addition, the size of immune complexes appears to be decisive for the occurrence of IgAN or IgAV nephritis. While all patients with IgAV had circulating IgA1-containing ICs of a relatively small molecular mass, patients with IgAV nephritis had additional large-molecular mass IgA1–IgG immune complexes. This is in line with our observation that only large ICs or aggregated IgA would deposit on vessel walls and elicit ensuing reactions (31).

## 3.3. Perivascular and mesangial deposition of Gd-IgA1

The reason for the perivascular and mesangial deposition of IgA or GdIgA1 apparently has to do with the reduced glycosylation of IgA1, which modifies the binding affinity to its receptors, (i) the RFcαI (CD89) on circulating monocytes and neutrophils, and (ii) the transferrin receptor (CD71) on mesangial cells. Moreover, the binding of abnormally glycosylated IgA molecules to CD89 induces

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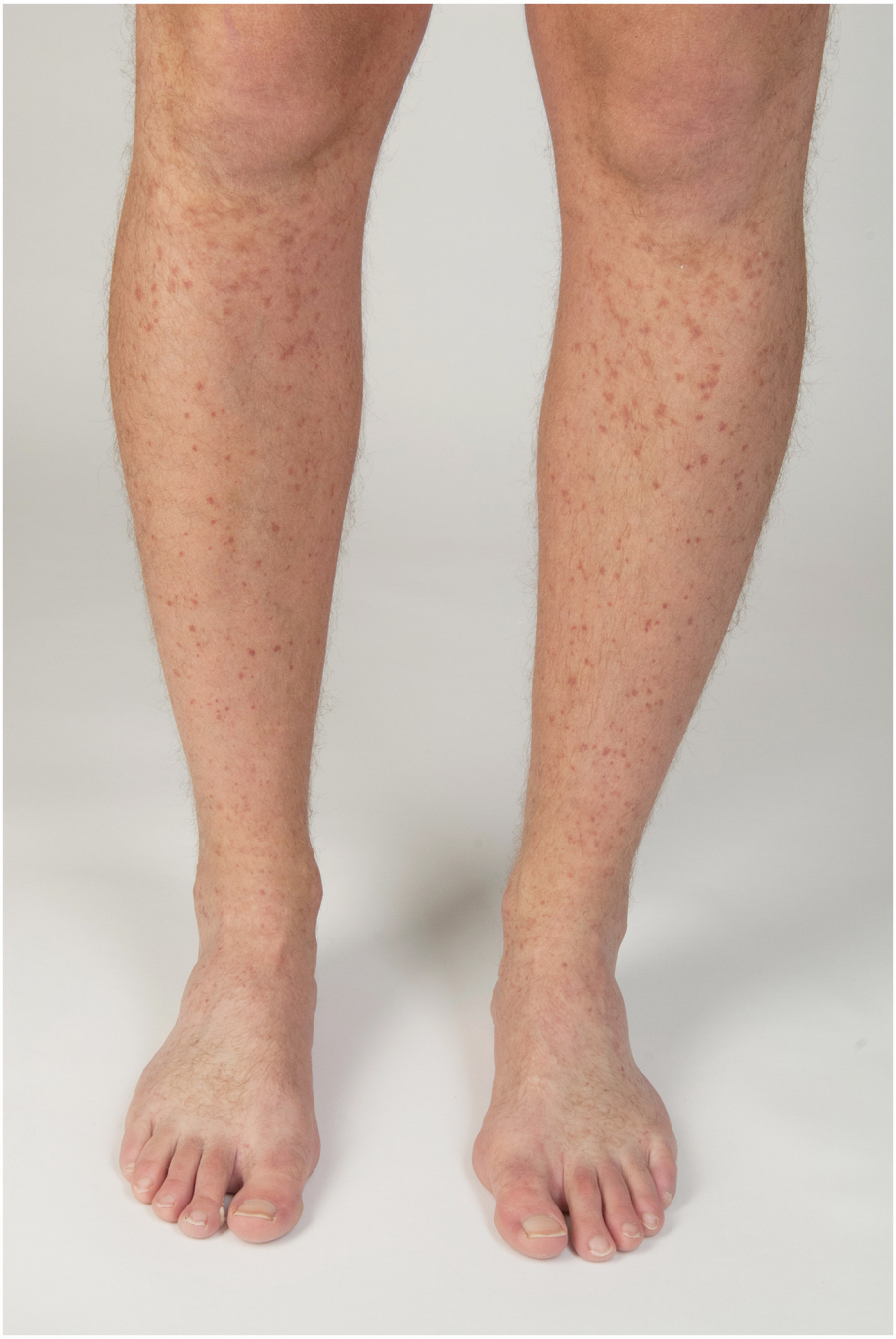

FIGURE 3
Recurrent macular vasculitis associated with hypergammaglobulinemia and induced by exertion.

its release into the circulation, so that blood contains circulating complexes of soluble CD89 and IgA in both IgAV nephritis and IgAN (21, 23).

While the deposition of this complex in the renal mesangium is facilitated by binding to CD71, which is supposed to be even overexpressed by mesangial cells in patients with IgAN, the reason for its deposition in post-capillary venules of the skin is less clear. Endothelial cells (EC) have been shown to express FcγR (32), and while FcRαI (CD89) and CD71 are not explicitly listed as receptors of EC (33), CD71 is known to be expressed by most cells, albeit in low levels, and there are several additional IgA receptors. Thus, one could speculate (i) that IgA is bound by so far unidentified receptors on dermal EC, but perhaps not only when IgA levels in serum are high or (ii) that it may become physically trapped between EC and pericytes, especially when it is part of a larger complex (e.g., IgA sCD89 or IgA–IgG) and when there are vasodilatory gaps between EC. Such larger molecules in the blood may drift to the vascular wall when blood flow slows down considerably

in the vascular beds of post-capillary venules (according to the model of laminar, parabolic flow) or when blood flow becomes partially turbulent (according to newer models on blood flow). This resembles the concept proposed for large complexes and their perivascular deposition in serum sickness (34). The predilection at lower legs where blood flow is supposed to slow down due to (physiological) stasis further supports the relevance of reduced blood velocity for perivascular depositions. An additional factor could be the activation of EC because we observed *in vitro* that IgA complexes adhere more readily to EC (HUVEC) when they are activated (31). The molecular basis for this observation is not known.

It remains noteworthy that in all these studies, not all patients with active disease presented elevated levels of IgA and, in particular, of Gd-IgA1 or sCD89-Gd-IgA1. One can speculate that it has to do with only a transient rise, which was no longer detectable at the time of blood sampling. Yet, the presence of elevated serum Gd-IgA1 levels alone still would not result in IgAV nephritis or IgAN. This is underlined by the fact that high serum levels are inherited in pediatric patients with IgAN and IgAV nephritis, but their first-degree relatives who also had elevated serum Gd-IgA1 levels never had clinical features of IgAN or IgAV (18, 19).

Similarly, glomerular Gd-IgA1 deposition is not specific for IgAN and IgAV nephritis, but may also occur in IgAN with hepatitis B virus antigen or in lupus nephritis [only that their amount is higher in IgAN, and glomerular IgG seems indeed specific for Gd-IgA1 (35)].

## 3.4. Activation of PMNs and destruction of vessel walls

The deposition of immune complexes in the vascular wall is one major igniting factor of the local vasculitic reaction, mainly by activating PMNs (8, 36). *In vitro*, IgG (37–39) and IgA (40), when fixed in the solid phase, activate PMNs to undergo oxidative burst, degranulation, and NETosis. However, deposits are also found in clinically and histologically normal skin between or after flares of vasculitis (10), so perivascular deposition of IgA, IgG, and IgM is mandatory, but not sufficient for eliciting vasculitis in the tissue.

We demonstrated that during episodes of active IgAV, circulating PMNs additionally bind and are primed by circulating IgA complexes. The IgA complexes were elevated in serum during these intervals. This binding of IgA to circulating PMNs greatly amplified two ensuing processes critical for local vessel destruction, i.e., (i) firm and continuous adherence of PMNs to the wall of post-capillary venules with deposited IgA, and (ii) release of high amounts of cytotoxic NETs in proximity to the vessel wall. This priming only occurred after the binding of large polymeric IgA molecules or of IgA-immune complexes, but not in presence of monomeric IgA (which normally is more prevalent in the blood). Priming is mediated by (crosslinking of) FcαRI (CD89) (31). When FcαRI is cross-linked by IgA-immune complexes or by aggregated IgA, it can form complexes with the FcR γ chain, which contains the "Immunoreceptor Tyrosine-based Activation Motifs" (ITAMs). This way it propagates downstream signals and activates neutrophils for pro-inflammatory functions, such as phagocytosis, production of reactive oxygen species (ROS), NETosis, and release of cytokines or chemokines. In contrast, monomeric IgA can bind to, but not cross-link, FcαRI. The binding of only a single FcαRI subsequently induces anti-inflammatory responses, because monovalent targeting of FcαRI results in the formation of "inhibisomes," which impair the signaling of neighboring activated receptors [for review, refer to (6)].

These processes were not encountered in other non-vasculitic inflammations such as psoriasis.

Polymorphonuclear neutrophils can also be primed by IL6, which is one of the cytokines found to be elevated in patients with IgAV.

Immunoglobulins A-binding PMNs from patients with IgAV even show spontaneous NETosis in static *in vitro* assay. Such a lower threshold to undergo spontaneous NETosis has been reported only rarely, such as in ANCA-associated vasculitis (AAV) (41, 42), systemic lupus erythematosus (43), and in the context of SARS-CoV-2 infection (44). Yet, in IgAV, it did not become meaningful *in vivo*, unless PMNs had adhered to EC, explaining why NETosis is not observed in the circulation *in vivo* in IgAV or other systemic diseases (31).

In the skin, IgAV and other IC-mediated vasculitides occur in the post-capillary venules, notably the site of leucocyte transmigration, where damaging events start at the luminal aspect of the vessel (45). One would expect that cytotoxic reagents would rapidly be spilled away by the bloodstream, but (i) blow flow is considered to be very slow at the wall of vessels and (ii) binding of IgA-immune complexes to circulating PMNs promotes and augments PMN adherence to ECs. PMN have been shown to cause damage to ECs by NETosis in static *in vitro* assays (46, 47). We recently demonstrated that under flow conditions in a perfusion system, NETs, instead of floating freely or flowing away, co-localized spatially and temporally with the site of damage in the EC layer. Correspondingly, we were able to visualize *in vivo* in vasculitic lesions that NET proteins were located on the luminal side of post-capillary venules and associated with damaged blood vessels in incipient lesions of IgAV (31).

In summary, for marked NETosis to occur, as well as for oxidative burst and degranulation (37, 48), PMNs require both exposure to IgA-IC in the circulation and adherence to ECs, which, however, then occurs so close to endothelial layers that it results in damage.

With regard to complement, PMN activation in the skin is ***not*** dependent on the activation of complement. This holds true although IgA aggregates can activate complement *in vitro via* alternative pathway and *via* the lectin pathway carbohydrate recognition molecule, MBL (49). In contrast, activation of complement appears to be mandatory in the kidneys for the pathophysiology of IgAN (49) or even IgAV with nephritis (50). Deposits of C3 and other components of complement are seen deposited around some cutaneous vessels in IgAV, but not as regularly as in kidneys, and are not *per se* signs of complement activation [reviewed in Damman et al. (50)].

The tissue-specific microenvironment, the complex glycocalyx of the kidney [which has influence on complement regulation

(51)], combined with genetic differences in complement genes (49), may offer one clue: why in the spectrum of IgA-immune complex diseases we see either isolated IgAN or skin-limited IgAV, or both.

### 3.5. A possible sequence of events

We suggest the following sequence of events for the development of cutaneous, and possibly systemic, IgAV lesions (31): 1 general stimulation of B cells due to, e.g., infection or drug intake in patients with constitutional production of GdIgA; 2 intermittently raised levels of both GdIgA and IgG autoantibodies directed against GdIgA; 3 formation of circulating IgA-immune complexes of GdIgA1 with IgG antibodies or soluble CD89 or of aggregated Gd-IgA whose size surpasses a certain threshold to enable cross binding of IgA receptors on PMNs and deposition at vascular wall; 4 binding of IgA-immune complexes to PMNs in the circulation (to a much larger extent than in healthy individuals or even in other pathological conditions); 5 pre-stimulation of PMNs, lowering the threshold for NETosis, but not eliciting NETosis yet without adhesion of PMNs; 6 additional, albeit minor, PMN prestimulation also occurs through exposure to cytokines which are elevated in IgAV, e.g., IL-6; 7 activation of EC with expression of adhesion molecules, vasodilation, IgA receptor molecules on EC, the higher serum levels, or large size of immune complexes facilitate deposition of immune complexes at vessel walls; 8 IgA-bearing PMNs firmly adhere to EC; resulting in 9 complete PMN activation and marked release of NETs; which 10 anchor to the luminal side of the EC layer without being cleared by the blood stream; and 11 cause destruction of the post-capillary venule walls. This concept still entails some as far unresolved steps but would explain why IgA-immune complexes are found around blood vessels for some time (and likely also in kidneys and other organs) without causing tissue damage.

The sequence of events in the kidney and other organs is similar [reviewed, e.g., by Pillebout and Sunderkotter (7)], but differs in certain respects, e.g., in the steady colocalization of C3 with IgA1 deposits and the necessity for activation of complement.

Animal models, which usually are run with IgG-containing immune complexes, have lead to similar concepts, i.e., that the deposition of ICs in the vascular wall is the major igniting factor of the inflammatory cascade (7), mainly by activating PMNs (8). *In vitro* studies support this proposition, as IgG (9–11), similar to IgA (12), activates PMNs to undergo oxidative burst, degranulation, and NETosis when fixed in the solid phase.

## 4. IgG-/IgM-positive (IgA-negative) immune complex vasculitis

If no IgA, but IgG or IgM, is detected around vessels, this indicates another subtype of immune complex vasculitis, e.g., cryoglobulinemic vasculitis, hypocomplementaemic vasculitis (Figure 2), or systemic disease associated with IC-mediated vasculitis such as rheumatoid arthritis or vasculitis in SLE (Table 1).

Primary or genuine IgG-/IgM-vasculitis (i.e., IgG-/IgM-vasculitis without an underlying systemic disease which is associated with dysregulation of B cells or antibodies), analogous to IgA1-vasculitis, is much rarer than originally assumed. It was mostly meant in the literature and in clinical practice when the terms hypersensitivity vasculitis or leukocytoclastic vasculitis were used. Yet, while many dermatologists are convinced that it exists and that it presents an entity of its own, there are only a few published studies so far which would confirm it (52). Its underlying cause would be the deposition of immune complexes containing IgG or IgM, but no IgA. It may, thus, present a form of a—likely skin-limited—serum sickness reaction. The reason for perivascular deposition of immune complexes in these cases would then be their sheer size (presumably not altered galactosidation). Their larger size might propel them to the edge of vessels where blood flow is much slower (according to the model of laminar, parabolic flow) or also partially turbulent (according to newer models on blood flow). The altered flow or markedly reduced velocity of blood and particles along the vessel wall and the size of the IC may facilitate their entrapment between EC and pericytes (53). Marginating PMNs, which are in the process of adhering to endothelial cells and of transmigration, will also bind to the IgG/IgM complexes *via* their FcyR. Once PMNs are adherent, they become more easily and more vigorously activated after their FcyR are crosslinked by IgG/IgM complexes (36, 37, 48). The ensuing release of cytotoxic products would subsequently occur close to the vessel wall, perhaps during the diapedesis of PMNs, thus damaging the vessel, a scenario long described and ultrastructurally shown in the Arthus reaction in animals (54).

We learned from IgA vasculitis that this scenario may contain some oversimplifications. Clinically, it would feature palpable and retiform purpura as in IgAV.

## 5. Recurrent macular vasculitis in hypergammaglobulinemia (formerly called benign hypergammaglobuline mic purpura of Waldenström) or mediated by exertion (Golfer's vasculitis, cocktail party vasculitis, and heat-induced vasculitis)

Recurrent macular vasculitis in hypergammaglobulinemia is a chronic episodic vasculitis of small blood vessels with vascular deposits of immunoglobulins, often associated with (a) a hypergammglobulinemia (usually polyclonal, but sometimes also monoclonal) and an elevated sedimentation rate and/or (b) induction by vasodilatory or stasis-associated events, such as long-standing and consumption of alcohol (cocktail party), or playing golf, extended hikes in association with warm weather, or other kinds of exertion (thus the different names for it). A characteristic feature is the chronic relapsing sudden occurrence of many (>50) small short-lived hemorrhagic macules on lower legs which hardly leave any traces except occasionally slight macular hyperpigmentation. In contrast to other immune complex-related vasculitides, these lesions are regularly associated with a burning sensation. Since biopsies often, but not regularly, reveal perivascular deposits of IgG or also IgA, the clinical picture may putatively be due to a very transient vascular

deposition of immune complexes. In several, but not all patients, IgG or IgA rheumatoid factor (RF) is detected in serum, which is highly soluble and could therefore resolve rapidly after vascular deposition (55). Therefore, vascular damage may be subtle and quickly reversible, thus leading to leakage of red blood cells but not to full, irreversible destruction of vessel walls.

## 6. Cryoglobulinemic vasculitis (CV)

Cryoglobulinemic vasculitis is a leukocytoclastic immune complex vasculitis seen in type II, less often in type III, hypersensitivity mixed cryoglobulinemia. In rare cases, it has been described with type I monoclonal cryoglobulinemia, which, however, are not immune complexes *per se* (56, 57); it needs to be carefully clarified if it exists independently from gelling of type I cryoglobulins (similarly in vasculitis associated with monoclonal gammopathy) (58).

Cryoglobulins are immunoglobulins that precipitate *in vitro* at temperatures below 37°C (*in vivo* depending on pH, ion concentration, high content of hydrophobic amino acids, low content of tyrosine residues, or galactose and sialic acid). Types II and III are immune complexes because in type II cryoglobulinemia, monoclonal IgM forms a complex with IgG. In many cases, this IgG is directed against the non-enveloped core protein of the hepatitis C virus and can then precipitate *via* a conformational change in the complex at cold temperatures.

In type I cryoglobulinemia, the monoclonal cryoglobulins gel directly in cold and in the presence of one of the above factors, causing hyperviscosity and subsequently vascular occlusion and ischemic necrosis.

Both features may occur simultaneously because the i) slowing of blood flow, cooling, and gelation, as well as ii) the deposition of immune complexes, influence and reinforce each other. Thus, in rare cases, mixed cryoglobulinemia also leads to hyperviscosity (<3%), and slowing down of blood flow with ensuing deposition of immune complexes and cryoglobulinemia type I result in vasculitis (57).

This vasculitis mainly affects small vessels and can also include medium-sized and even large-sized vessels (aorta and branches). Vasculitis usually involves the skin in the systemic form, but there is a skin-limited form without the involvement of visceral organs.

Thus, the involvement of skin in cryoglobulinemia is due to two major mechanisms of tissue damage: (i) leukocytoclastic immune complex vasculitis (with the formation of cryoglobulins being primarily unrelated to cold) and/or (ii) occlusion of cutaneous vessels by gelling or precipitation of mostly monoclonal type I cryoglobulins in cold-exposed skin areas (all small blood vessels of the upper or deep dermis, as well as the capillaries of the fat lobule, may be involved) (vasculopathy) (59).

Clinically, leukocytoclastic immune complex-mediated vasculitis manifests as palpable or retiform purpura lesions that may coalesce. Occlusion of vessels by cryoglobulins manifests clinically as retiform purpura with dominant central necrosis (larger than the surrounding inflammatory erythema) in cold-exposed, acral areas (hands, feet, lips, ears, and nose), sometimes accompanied by livedo due to only partial obstruction of blood flow.

## 7. Rheumatoid vasculitis, lupus vasculitis, and Sjögren's syndrome

Rheumatoid vasculitis (RV) is a severe complication of **rheumatoid arthritis** (RA), characterized by cutaneous and systemic vasculitis affecting small or medium-sized vessels and occurring usually in patients who had high titers of RF over a long period of time. Other factors associated with the development of RV were male gender, joint erosions, subcutaneous nodules, presence of nail fold lesions, and any other extra-articular feature 1 year before the time of diagnosis of RV and intensive treatment with antirheumatic drugs (60).

Rheumatoid factor is an immune complex. Circulating RF contain IgG and IgA (61). Decreased C3 complement levels indicate marked activation of the complement system. Although there is not much recent research on RV, all facts known so far indicate that it is an immune complex vasculitis owed to similar mechanisms as in cryoglobulinemic vasculitis or the Arthus reaction.

Since cutaneous vasculitis in rheumatoid vasculitis ranges from leukocytoclastic vasculitis of post-capillary venules to arteritis located at the dermo-subcutaneous junction or in the panniculus (62), it clinically reveals a spectrum from palpable purpura as in IgAV or IgG/IgM vasculitis to livedo reticularis (racemosa) and ulcerating nodules similar to cutaneous arteritis, or even digital infarcts and gangrene (62).

Cutaneous vasculitis in **Lupus erythematodes** often occurs as small vessel vasculitis with perivascular IgG deposits, or as so-called hypocomplementemic (urticarial) vasculitis with or without C1q antibodies. It likely is the result of several pathomechanisms, but encompassing immune complexes.

Vasculitis in **Sjögren's syndrome** is often either r*ecurrent macular vasculitis in hypergammaglobulinemia* (as mentioned earlier) *or* cryoglobulinemic vasculitis or vasculopathy. In the former high titers of small circulating immune complexes containing IgG or IgA, RF has been detected in some but not all cases as part of the gammaglobulin fraction (55). Cryoglobulinemic vasculitis in Sjögren's syndrome bears a risk for lymphoma (57, 63), whereas recurrent macular vasculitis in hypergammaglobulinemia does not share this risk (63).

## 8. Concluding remarks

Although several steps in the pathophysiology of the different immune complex vasculitides have been elucidated, several remain to be explored; some of them emerging from the fog in the form of already deducted hypotheses that wait to be verified or falsified, while others remain in the dark. Shrouded in the mist are the steps to target efficacious therapies, but in this field, light may be ahead

at least for some small steps because budesonide or antibodies to complement components showed effects in first clinical trials.

## Author contributions

CS contributed to the conception of the work and drafting of the work. LG contributed to the design of the work, drafting of the work, revising it critically for important intellectual content, and provide approval for publication of the content. EP and CM contributed to the conception of the work, drafting of the work, and revising it critically for important intellectual content. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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