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Current concepts in epidemiology, diagnosis, associated co-morbidities, and therapeutics of non-melanoma skin cancers: beyond basal cell and squamous cell carcinomas

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Current concepts in epidemiology, diagnosis, associated co-morbidities, and therapeutics of non-melanoma skin cancers: beyond basal cell and squamous cell carcinomas

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Case report: Abrikossoff's tumor of the facial skin

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Abrikossoff tumors, also known as granular cell tumors (GCT), originate from Schwann cells. The most common location is in the oral cavity, followed by the skin, but they can also be found in the breast, digestive tract, tracheobronchial tree, or central nervous system. They can affect both sexes at any age, with a higher incidence between 30 and 50 years and a slight predisposition for female sex. They are usually solitary tumors but may also be multifocal. Most of the time, they are benign, with malignancy being exceptional in <2% of cases. Clinically, they appear as solid, well-defined, painless tumors, located subcutaneously with dimensions that can reach up to 10 cm. The definitive diagnosis is based on the immunohistochemical examination, and the treatment for benign tumors consists of surgical excision. Chemotherapy or radiotherapy may be required for malignant lesions, but the treatment regimens and their benefits remain unclear. This manuscript presents the case of a 12-year-old girl with a benign GCT, located in the skin on the mandibular line.

KEYWORDS

tumor, skin cancer, Abrikossoff, granular cell tumor, facial skin, Schwann cells, oral tumors

1. Introduction

Abrikossoff tumors, also known as granular cell tumors, are rare and often benign soft tissue tumors of Schwann cell origin (1). Although a granular cell tumor (GCT) usually develops in the skin or oral mucosa, it has been described as seen in many other organs (2). GCT typically presents as a solitary tumor, although it may sometimes be multiple, and in recent years, there have been reports of cases associated with Noonan syndrome and neurofibromatosis (3). It has also been described in association with other diseases. The vast majority of cases are reported in the skin and subcutaneous tissue. However, 2% of Abrikossoff tumors can be malignant (4). There is no predisposition for a certain sex although they can be found at all ages, and they predominate between the fourth and sixth decades of life (1, 5).

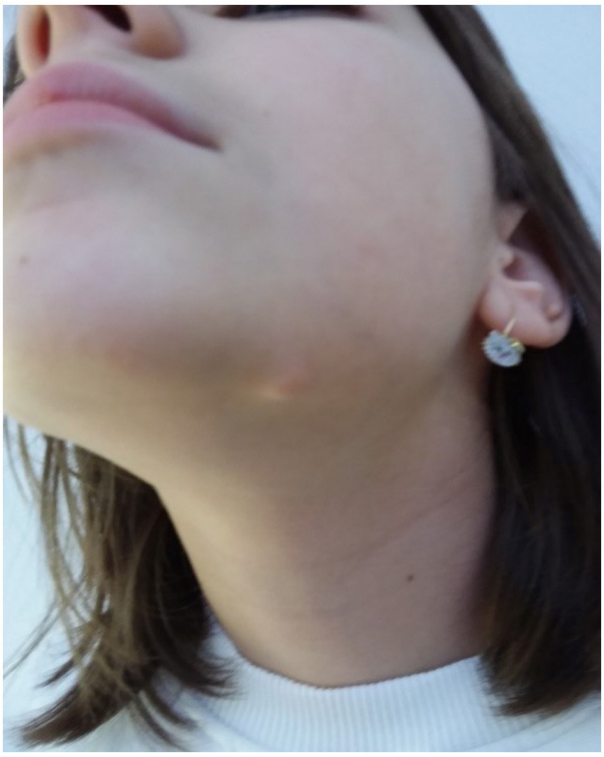

FIGURE 1
Well-defined, skin-colored, nodular lesion beneath the left mandible.

2. Case report

A 12-year-old female patient presented with a 12 mm mass in the area of the left mandible. Examination showed a 15 mm round, well-defined, non-tender, skin-colored nodular lesion, with a slightly depressed center (Figure 1).

An excision biopsy under local anesthesia was carried out and atypical-appearing, partially fatty tissue was removed, which was sent for histopathology. An Abrikossoff tumor was diagnosed, and a wider excision was carried out. Immunohistochemistry of the first piece of the tissue showed a tumor containing residual granular Abrikossoff cells surrounding the dermal fibrous scar tissue. The tumor appeared to have been completely excised, with the exception of a tumor fascicle extending perineurally, involving the deep margins of the resected area. Immediately adjacent to and beneath, this is an area of tumor proliferation comprised of cubes, sheets, and arches of large cells with small, round nuclei, central nuclei with an abundant eosinophillic, granular cytoplasm (Figures 2, 3).

S100 protein was diffusely expressed by the entire tumor and was not expressed at the level of the resection limit, demonstrating the complete excision of the tumor mass, with the exception of an area of tumor cells extending around a nerve strand that reaches to the deeper margins of the resected lesion (Figures 2–4 correspond to the microscopic aspect of the tumor).

The cytoplasms of the tumor cells stain positively for CD68 in a granular manner.

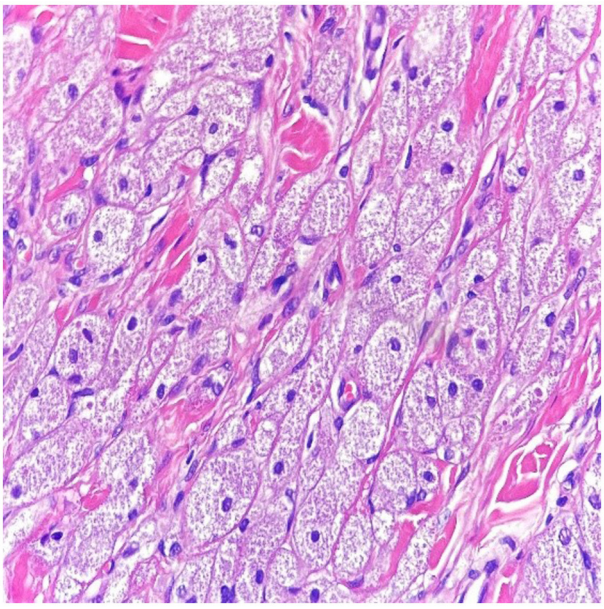

FIGURE 2
In high power magnification (10 x magnification-H & E stain), the cells have abundant eosinophilic granular cytoplasm with a small nucleus within a collagenous stroma.

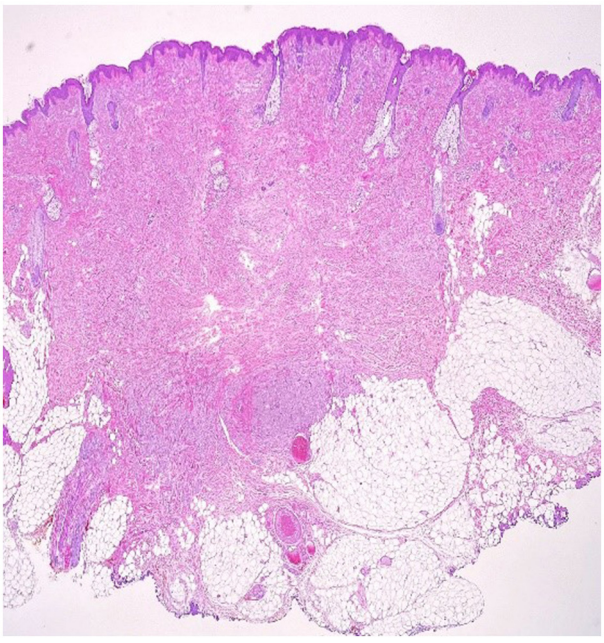

FIGURE 3
Cutaneous fragment with central fibrosis in the dermis, aside from this fibrous tissue, there is a non-encapsulated tumor proliferation with irregular borders and perineural extension (10 × magnification–H & E stain).

Staining for tyrosinase was negative in the tumor but positive in the melanocytes, which were of normal number at the dermoepidermal junction. PRAME (Preferentially Expressed

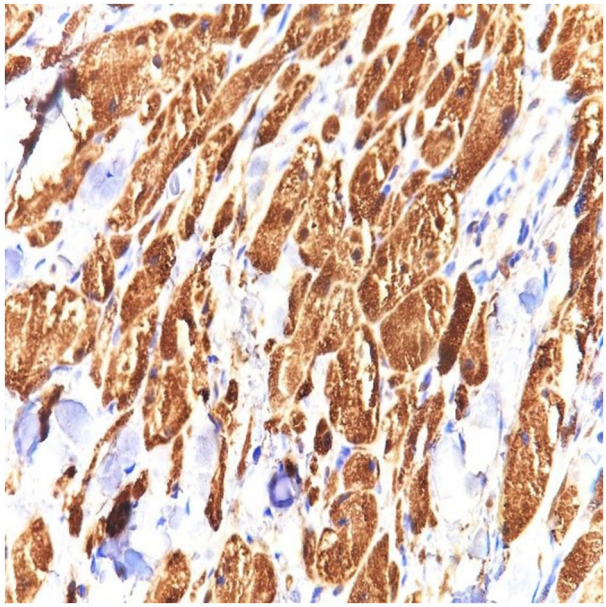

FIGURE 4
S100 stain in granular cell tumor strongly stains the cytoplasm and the nuclei of the granular cells. Strong and diffuse S100 expression is characteristic of this tumor (40 × magnification).

Antigen in Melanoma) was not expressed by tumor cells. The postoperative course was without complications.

3. Discussion

The etiology of these tumors is not known; initially, they were thought to be derived from myoblasts, and this fact is supported by the usual infiltration in the muscle fibers and by the damage of the tongue, a muscular organ (6). They were subsequently considered as developmental cells, histiocytes, neuroendocrine cells, fibroblasts, or undifferentiated mesenchymal cells (1). Fisher and Wechsler first showed by electron microscopy that these tumors are derived from nerve cells (7). In 1990, Mozur, Schultz, and Myers, using specific antibodies, also confirmed that GCT was derived from nerve cells (8), and with the advent of immunohistochemistry, it was established that GCT was derived from Schwann cells (9). GCTs are not common in children, they appear more between 30 and 50 years of age, and the distribution by sex is not clear in some studies predominates in women (9, 10), and in other studies, it predominates in men (11–13).

In terms of location, in order of frequency, they can be found at the level of the tongue (the most common) followed by the torso and limbs (5). Most of the time the tumor is solitary, but there can be multiple foci, including in the internal organs, with the percentage of multiple localizations reaching, according to some studies, up to 30% of cases (4). Multiple localizations in adults have been associated with some diseases such as neurofibromatosis and Hodgkin's lymphoma (4), and in children, they have been associated with cryptorchidism, pulmonary stenosis, congenital heart disease, or Noonan syndrome (14). Noonan syndrome is part of a group of diseases called *RASopathies*, characterized by genetic mutations in *RAS* proteins, that play an important role in cell differentiation and development, comprising Noonan syndrome and neurofibromatosis, Legius syndrome, and Costello syndrome and Leopard (PTPN1 gene mutation) (5, 15). Extracutaneous localization may affect the mammary gland, mediastinum, thyroid, larynx and trachea, lungs, ovary, testicle, heart, digestive tract, urinary tract, and rarely the central nervous system, but the central nervous system has the most severe clinical manifestations (1). At the breast level, GCT represents <0.1% of all tumors and <6% of all GCT tumors, and the preferred location being the superior-internal quadrant (16).

Clinically, it manifests as a round, painless, skin-colored tumor, located subcutaneously, with slow growth, with somewhat unclear margins, measuring between 5 mm and 10 cm in diameter, sometimes with a warty appearance due to epidermal hyperplasia (5, 6, 17). As the tumor affects the innervation of the skin, sometimes skin contractions occur. Malignancy is very rare, <2% of cases, and is considered clinically as malignant only when they metastasize and when the size of the tumor exceeds 4 cm (18, 19). Malignant tumors have an accelerated growth rate and can cause metastasis to the lungs, bones, and brain, and metastases can be detected by positron emission tomography and F-18 fluorodeoxyglucose (16, 18). The differential diagnosis comprises lipoma, dermatofibroma, fibro-histiocytoma, pilar cyst, basal cell carcinoma, squamous cell carcinoma, pilomatrixoma, and other types of lesions (20). When they appear on the breast, they may look like breast cancer, but the therapeutic behavior and prognosis are completely different, and sometimes they can be concomitant with invasive ductal carcinoma either in the same breast or in the opposite breast (14, 21).

What is important to follow is the potential conversion from benign to malignant, which is a necessary clinical and histopathological correlation because some very precise criteria of malignancy are missing only on a histological basis. Other diagnostic methods, which may permit a more accurate assessment of the degree of malignancy as well as prognosis in such cases may exist (22).

Histologically, GCT is an unencapsulated tumor consisting of large polyhedral cells with small hyperchromatic central nuclei and a cytoplasm with abundant eosinophilic granules due to the accumulation of secondary lysosomes in the cytoplasm, often extending to the superficial hypodermis. Tumor cells often look like large eosinophilic granules surrounded by a transparent halo known as Milian's pustulo-ovoid bodies, the number of which increases with the age of the tumor (11). Occasionally, binuclear cells, stripped nuclei, dirty nuclei, and intranuclear inclusions may also be observed. The overlying epithelium is often characterized by prominent pseudoepitheliomatous hyperplasia that can be confused with squamous cell carcinoma if the biopsy is taken superficially. Pseudoepitheliomatous hyperplasia can be considered not as a tumor extension but rather as a reaction-type change in the underlying tumor (21).

Immunohistochemistry is positive for S100 protein, CD68 antigen (KP-1), and (neuron-specific enolase) (NSE). Some tumors may be S100-negative and are known as non-neural GCTs; these tumors have recently been reported to overexpress ALK and cyclin D1 and are probably different entities (22).

Fanburg and Smith proposed a classification to evaluate the malignancy of these tumors. Thus, he proposed the following parameters of analysis (23):

- Necrosis
- Spindling
- Vesicular nuclei with large nucleoli
- >2 mitoses/10 high-power fields at ×200 magnification
- High nuclear-to-cytoplasmic ratio
- Pleomorphism

Tumors that did not meet any of these criteria were considered benign, and those that met one or two criteria were considered atypical, and those with three or more were classified as malignant.

Since we are discussing about a pediatric case, the first differential diagnosis would be a spitzoid melanocytic tumor; therefore, tyrosinase and PRAME were performed. In our case, we used tyrosinase, which is positive in melanocytic proliferations and negative in Abrikossoff tumor.

From a histopathologic point of view, we can consider also other differential diagnoses, such as congenital granular cell epulis, cutaneous non-neural granular cell tumor, hibernoma, malignant melanoma, and granular cell dermatofibroma.

Other innovative imaging techniques can be used for diagnosis, such as optical coherence tomography (OCT). Optical coherence tomography (OCT) is an emerging imaging technique that is capable of acquiring high-resolution cross-sectional images of a tissue, being similar to ultrasound; however, infrared waves are used instead of sound waves (24).

The OCT images of the GCT reveal verrucous epidermal hyperplasia, seen as hyperreflective, uneven surface of the tissue. The dermo-epidermal junction is obscured in the OCT images of GCT, while it is discernible in the adjacent healthy skin. Blood vessels are visible in the dermis of the healthy skin but not in the images of GCT (25). Other emerging imaging techniques, such as reflective confocal microscopy, photoacoustic imaging, may also be combined with OCT to improve the diagnosis of GCT (26).

The simple excision of the tumor is the treatment of choice, followed by histopathological examination and possibly immunohistochemical examination. Only if the resection edges are positive is secondary recovery recommended. In malignant tumors, surgical treatment can be supplemented with chemotherapy or radiation therapy, the benefits of which remain unclear (27). The recommended monitoring is done for 10 years as the data from the literature show a local recurrence rate of up to 8% for situations with surgical negative margins and nearly 20% for those with positive surgical margins (28).

Abrikossoff tumor is a rare entity; thus, our case will contribute to growing the body of evidence on its presentation and potential therapy, as well as pave the way for further research. We did not report possible correlations with the COVID "era" nor did we find associations with SARS-CoV 2 infection, as in other cases (29).

4. Conclusion

GCT are a rare entity. They are usually benign, occasionally malignant. The diagnosis is based on the S100 immunohistochemical examination. The treatment of choice was simple surgical excision. In the case of benign tumors, the evolution and prognosis are favorable. Clinicians should be aware of its existence and bear it in mind as a possible differential diagnosis.

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 authors.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and it was conducted in a private clinic of plastic and aesthetics surgery procedures. It was approved by the Institutional Review Board of the Arestetic Clinic from Galaţi, Romania (63/04.07.2022). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual's next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

VA, RJ, and AT: conceptualization. TT, FB, and RT: software. VA, FB, and AT: validation. VA: methodology, formal analysis, data curation, and writing—original draft preparation. VA, LM, and MM: resources. LN, LM, and MM: writing—review and editing. FB, LM, and MM: visualization. TT: supervision. All authors have read and agreed to the final version of the manuscript.

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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.

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Treatment of metastatic squamous cell carcinoma arising in sacrococcygeal pilonidal sinus: a case report series

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Background: Squamous cell carcinoma (SCC) arising in a sacrococcygeal pilonidal sinus is rare, with cases of metastatic disease being even rarer. Among published cases, almost none have reported on systemic treatment.

Objective: This disease has a poorer prognosis than other forms of cutaneous SCC; therefore, our objective is to shed some light on the treatment of metastatic disease.

Methods: We present a series of nine cases treated at a single center, four of whom received systemic treatment. Additionally, other previously reported cases of metastatic disease are included in an attempt to draw stronger conclusions.

Results: Four patients were treated under several treatment regimens, with a median progression-free survival of only 2 months and two instances of partial response (18%). The best result was achieved with cemiplimab. Across all the cases, there was a trend toward a benefit of the use of systemic treatment (HR 0.41, 95% CI 0.15–1.12, $p = 0.083$; median overall survival 13 vs. 8 months).

Limitations: Limitations include the significant lack of information on previously published cases and the extremely heterogeneous nature of the existing information.

Conclusion: The initial systemic treatment should be an anti-PD-1, as with other SCCs. After progression on anti-PD-1, there is no strong evidence to support the recommendation of a specific treatment or sequence: options include cetuximab and/or chemotherapy (platinum, paclitaxel, 5-fluorouracyl).

KEYWORDS

pilonidal sinus, squamous cell carcinoma, metastatic, chemotherapy, anti-PD-1, case report

Introduction

Pilonidal sinus (PS) is a common and well-recognized condition that is often complicated by infection. The condition was described by Herbert Mayo in 1833 as a cyst in the sacrococcygeal area with hair inside it (1). Fifty years later, Hodge suggested the term "pilonidal" from two words in Latin: "pilus" (hair) and "nidus" (nest) (2).

The condition mainly affects young men (3). Treatment usually consists of surgical excision, and the rate of recurrence is high.

Malignant degeneration is a rare complication (occurring in 0.1% of cases) (4–9) and is observed mainly in cases of chronic, recurrent, and neglected primary pilonidal sinus infection. Squamous cell carcinoma (SCC) is the most frequent form of lesion. Metastatic disease is even rarer, with very few cases published to date.

This article presents a series of cases consisting of nine patients treated at our center, five of whom had metastatic or unresectable disease and received systemic treatment. Our intention is to share our experiences with the aim of establishing better therapeutic strategies.

Clinical cases

Case 1

Case 1 was that of a 63-year-old white man with a history of PS diagnosed in the last 30 years, with recurrent episodes of suppuration. The patient was a smoker, but had no other comorbidities. In March 2003, a lesion began to grow (measuring up to 20 cm in diameter), so a computed tomography (CT) scan was performed. Extensive local involvement was observed with sacral invasion, inguinal lymph nodes (LNs), and multiple lung nodes (measuring <1 cm). The LNs were punctured and tested negative for neoplasia (the lung nodes were too small to perform a puncture, but were stable for a year).

Due to extension of the condition and symptomatology, an abdominoperineal resection (APR) with sacral resection was performed in February 2004. The patient was diagnosed with well-differentiated SCC with bone and anal sphincter invasion. The LNs were not affected by the tumor. No complementary treatment was administered.

A local relapse was observed in February 2006. Palliative radiotherapy was proposed, but the patient declined and died on 19 January 2007.

Case 2

Case 2 was that of a 40-year-old white man with a history of PS, diagnosed in 2003. The patient was a smoker, was obese, and had a history of hepatitis B virus (HBV), hepatitis C virus (HCV), asthma, and chronic obstructive pulmonary disease (COPD). The PS was resected in October 2014, and the patient was diagnosed with well-differentiated SCC with affected margins. The patient was reoperated for wider resection (including the presacral fascia) and intraoperative radiotherapy (16 Gy). No additional treatment was proposed. There was no evidence of relapse at least until March 2022, when the patient was lost to follow-up.

Case 3

Case 3 was that of a 53-year-old white man with a history of PS, diagnosed ∼20 years ago and involving chronic suppuration, without prior surgical treatment. The patient was a smoker without other comorbidities. Due to hyporexia and weight loss of 10 kg in the last year, a biopsy was performed in May 2017. The patient was diagnosed with well-differentiated SCC with local bone involvement based on magnetic resonance imaging (MRI). Due to the extension of the lesion, neoadjuvant radiotherapy was performed between 13 July 2017 and 9 August 2017 (50 Gy). APR with in-bloc resection of the sacrum was performed in October 2017. After surgery, the patient required multiple reinterventions due to ischemia of the flaps, with associated necrosis and extensive debridement. After preparation of a dorsal flap, the patient presented with thrombosis of the basilic vein and the brachial and radial arteries, with associated yeast fungemia. Despite treatment with antifungals, the patient died of septic shock on 15 March 2018.

Case 4

Case 4 was that of a 69-year-old white man with hypertension and a history of PS, resected in 2007. In March 2018, a lesion began to grow in the sacral area, and a biopsy was performed. The patient was diagnosed with well-differentiated verrucous SCC. At the time of diagnosis, he presented with involvement of the sacrum and the anal sphincter. The patient required intravenous antibiotics due to local infection. Subsequently, APR with in-bloc resection of the sacrum was performed on 21 June 2018, with a dorsal flap and intraoperative radiotherapy (12 Gy).

The patient required reoperation for debridement of necrotic margins. During the postoperative period, he presented with progressive anemia, which progressed to hematemesis. Gastroscopy revealed esophageal and duodenal ulcerations. Upon sudden respiratory deterioration, the patient was intubated and presented massive hemoptysis of unknown origin. He died on 20 July 2018.

Case 5

Case 5 was that of a 70-year-old white man with a history of PS for an unspecified number of years with recurrent infections, who presented for consultation in May 2021 due to bleeding and worsening of pain. The patient was a smoker with a history of hypertension, COPD, hypercholesterolemia, and grade 1 chronic kidney disease. A biopsy was performed in June 2021, and the patient was diagnosed with well-differentiated verrucous SCC. At the time of diagnosis, he presented with iliofemoral adenopathies and coccygeal bone involvement, observed in a PET scan. As the

Abbreviations: APR, abdominoperineal resection; CI, confidence interval; CR, complete response; CT, computed tomography; DCR, disease control rate; HR, hazard ratio; HS, hidradenitis suppurativa; LN, lymph node; mg/m2, milligrams per square meter; mOS, median overall survival; mPFS, median progression-free survival; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PD-1, programed death 1; PD-L1, programed death ligand 1; PET, positron emission tomography; PFS, progression-free survival; PS, pilonidal sinus; psSCC, squamous cell carcinoma arising in pilonidal sinus; SCC, squamous cell carcinoma.

lesion was considered unresectable, chemo-radiation treatment was administered, consisting of 5-fluorouracyl (1,000 mg/m^2/day for 4 consecutive days) and cisplatin (40 mg/m^2; two cycles, every 28 days), plus 58.8 Gy between 19 October 2021 and 21 November 2021. The patient exhibited a partial response, so surgery was proposed. APR with in-bloc resection of the sacrum was performed on 24 May 2022, revealing free margins and no bone or LN involvement. Currently (as of June 2023), there is no evidence of recurrence of the disease.

Case 6

Case 6 was that of a 57-year-old white man with a history of PS, operated on several times in 1992. The patient was a smoker and had diabetes. Due to bleeding and new local infection, a biopsy was performed, and he was diagnosed in March 2004 with well-differentiated SCC. At the time of diagnosis, the presence of bone involvement meant that the lesion was considered unresectable, so neoadjuvant radiotherapy was administered (50 Gy) in July 2004. Local progression was observed, with invasion of the anal canal in September 2004. The patient received first-line chemotherapy treatment with cisplatin (80 mg/m2) and 5-fluorouracyl (800 mg/m^2/day, 5 consecutive days) from 10 November 2004 to 2 December 2004. The patient had a prolonged admission due to infection, and local and LN progression were evident in June 2005. A second line of treatment was decided upon, with weekly methotrexate (25 mg/m^2) from 2 June 2005 to 8 September 2005, but the patient exhibited new local progression. He died in February 2006.

Case 7

Case 7 was that of a 68-year-old white man with a history of PS since he was 17 years old, operated on several times. The patient was a smoker with a history of hypertension. In February 2011, he presented with sepsis of presacral origin; upon fistulectomy, the patient was diagnosed with well-differentiated SCC. No additional treatment was administered. The patient presented with a local relapse in August 2011, with bone involvement. The lesion was considered unresectable; radiotherapy (66 Gy) was administered, along with weekly cisplatin (40 mg/m^2) from 1 September 2011 to 25 October 2011. New local progression occurred in January 2012. The patient received weekly cetuximab (250 mg/m^2) from 24 April 2012 to 4 June 2012, but did not respond to this treatment and died on 14 June 2012.

Case 8

Case 8 was that of a 54-year-old white man with a history of PS since he was 18 years old, operated on several times. He was a smoker and occasional drinker. The patient presented for consultation in September 2016 due to suppuration and was diagnosed with well-differentiated SCC. At the time of diagnosis, he had unresectable locoregional LN involvement. He received first-line chemotherapy with carboplatin AUC 6 every 21 days plus weekly cetuximab (250 mg/m^2) from 23 November 2016 to 31 January 2017. The patient exhibited skin response, but bone progression occurred, so second-line radiotherapy treatment (37.5 Gy) was administered, along with a single cycle of mitomycin-C (10 mg/m^2) and 5-fluorouracyl (1,000 mg/m^2/day for 4 consecutive days) in March 2017. The patient then presented with LN, skin, and lung progression in April 2017.

He received a third line of treatment with Tegafur (1,000 mg/m^2/day in three doses) from 1 June 2017 to 4 July 2017, with clinical progression. He was therefore switched to a fourth line of treatment with weekly paclitaxel (80 mg/m^2) from 20 July 2017 to 29 August 2017. The patient presented further local progression and died on 15 September 2017.

Case 9

Case 9 was that of a 64-year-old white man with a history of PS, resected when he was 45 years old. The patient presented for consultation in July 2010 due to a mass in the presacral area and was diagnosed with well-differentiated SCC. LN involvement was ruled out by fine-needle aspiration. The lesion was considered unresectable, so treatment with radiotherapy (70 Gy), together with weekly cisplatin (40 mg/m^2), was administered between 23 August 2010 and 8 August 2010.

In terms of relevant history, the patient was a smoker, was hypertensive, and underwent surgery for bladder carcinoma in January 2017 (with neoadjuvant chemotherapy).

The patient presented with a local relapse of the SCC in the right buttock. Salvage surgery was performed on 31 January 2018, which included fragments of the sacrum (free of disease upon histological inspection). A new local recurrence in May 2018 affected the other buttock, and a new resection was performed. LN involvement was suspected in a PET scan performed in August 2018, and this was confirmed by fine-needle aspiration. The lesion was again considered unresectable, so the patient received first-line treatment with cisplatin 100 mg/m^2 every 3 weeks between 11 September 2018 and 23 October 2018 (three cycles), resulting in a partial LN response, but with local progression.

A second line of treatment with biweekly cetuximab (500 mg/m^2) from 13 November 2018 to 21 February 2019 was decided upon. The patient presented local and nodal progression, so a decision was made to re-irradiate the sacral and LN area with 30 Gy. Upon new progression of the disease, also involving the peritoneum and lungs (Figure 1A), a third line of treatment with cemiplimab was initiated on 3 May 2019, achieving a partial response (Figure 1B). Progression was observed in October 2019, so a fourth line of treatment with weekly paclitaxel plus cetuximab (80 mg/m^2; 250 mg/m^2) was initiated on 5 November 2019. A partial response was achieved. This treatment was administered until March 2020, with progression occurring in April 2020, and the patient died on 27 May 2020.

Our cases are summarized in Table 1.

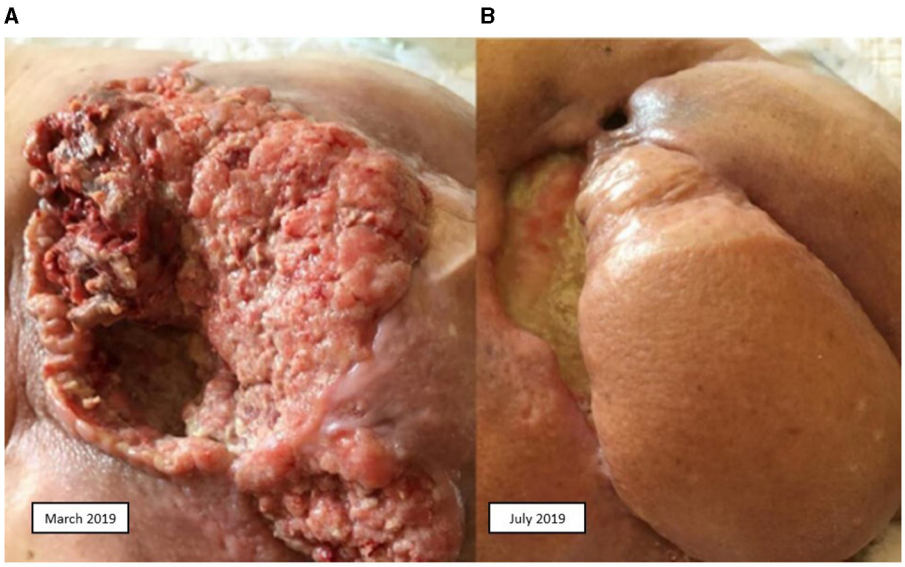

FIGURE 1
Squamous cell carcinoma. **(A)** Before treatment with cemiplimab. **(B)** After treatment with cemiplimab.

Discussion

Localized disease

Malignant degeneration of PS probably has similar causes to those of other chronic wounds or ulcers [as reported by Marjolin (10)], but the exact mechanism is unknown. In chronic inflammation, normal DNA repair mechanisms are impaired. The process probably begins with the release of free oxygen radicals by activated inflammatory cells, which causes genetic damage and subsequently leads to neoplasia transformation (11). Multiple theories have been proposed to explain this carcinogenic process, and although it is difficult to distinguish primary malignant ulcers from secondary ones, the time course of evolution may help in differentiating them (12).

The most affected patients are men (80%), with a median age of 52 years and a median duration of symptom complaints of 20 years. The most frequent histology is SCC (92%) (13). Other histologies have also been described (14–17).

Before any procedure, it is recommended to perform an exhaustive extension study: computed tomography of the chest, abdomen, and pelvis to rule out distant metastasis (7, 13, 16, 18), and magnetic resonance to determine the local extension. An endoscopic study could be considered to rule out rectal involvement (13, 15, 18). Locoregional LNs may be affected at diagnosis; when this is suspected, a puncture and/or a positron emission tomography (PET) scan should be performed (19).

Treatment approach

The prevailing treatment approach remains wide excision with margins, including the presacral fascia (6–8, 13, 15, 18), subcutaneous tissue, gluteal muscle, and, if LNs are affected, lymphadenectomy. Prophylactic lymphadenectomy has not been shown to increase survival, although the number of reported cases is too low to draw firm conclusions (11, 20).

In cases of local bone involvement, this can be resected in bloc together with the primary lesion (6–8, 13, 16, 18). APR can also be performed if the rectum is involved (8, 13, 15, 16, 18). Closure of the defect can be achieved with flaps or grafts, or it can be allowed to heal by secondary intention (5, 7, 8, 13, 15, 16, 21).

There is controversy as to whether adjuvant radiotherapy improves prognosis in cases of SCC (22–24). For SCC originating in PS (psSCC), many researchers recommend it, as it has been linked to a reduction in local recurrences from 44 to 30% (8, 13, 15, 18, 21, 25).

Whether the addition of chemotherapy is beneficial remains an unanswered question. In the few published cases (7, 11, 26–28), the drugs used have been 5-fluorouracyl, cisplatin, Adriamycin, and mitomycin-C, in addition to a rare combination without radiotherapy (28).

Unresectable disease

If upfront surgery is not feasible, treatment with radiotherapy can be considered in conjunction with chemotherapy (13, 25, 27, 29–33). This approach sometimes makes the tumor operable (25).

Cetuximab could also be considered instead of chemotherapy. There are some retrospective studies with other forms of SCC, involving very few patients (median $n = 8$), in which radiotherapy (median dose 60–70 Gy) was administered with weekly cetuximab (34–38). This approach has been found to produce an overall response rate (ORR) of 57–80%, a complete response (CR) rate of 36–75%, and a disease control rate (DCR) of 91–100%. At 2 years, the progression-free survival (PFS) rate has been found to be 50–83% [median PFS (mPFS): 1.6–6.4 months], and the overall survival

TABLE 1 Clinical cases.

ID	Year (age)^	Time of PS*	Local invasion	Surgery	RT	Relapse (months)	Metastatic sites	Systemic treatment	OS**	Died
1	2003 (63)	33	No	APR	No	Local (24)	No	-	35	Yes
2	2014 (40)	11	No	WR	Yes[a] (16 Gy)	No	No	-	89	No
3	2017 (53)	20	Bone	APR	Yes[b] (50 Gy)	No	No	-	10	Yes
4	2018 (69)	11	Bone, rectal	APR	Yes[a] (12 Gy)	No	No	-	1	Yes
5	2021 (70)	-	Bone	APR	Yes[c] (58.5 Gy)	No	No	Yes[c]	24	No
6	2004 (57)	12	Bone	No	Yes[b] (50 Gy)	Yes, local (2)	No, local LN	Yes[e]	23	Yes
7	2011 (68)	51	No	Simple excision	Yes[d] (66 Gy)	Yes, local (6)	No, only local	Yes[d,e]	16	Yes
8	2016 (54)	36	LN	No	Yes[d] (37.5 Gy)	-	Lung, bone, skin	Yes[d,e]	12	Yes
9	2010 (64)	19	No	No	Yes[c] (70 Gy)	Yes, local (93)^^	Lung, LN, skin	Yes[c,e]	121	Yes

ID, case identification number; PS, pilonidal sinus; RT, radiotherapy; LN, lymph nodes; APR, abdominoperineal resection; WR, wide resection with presacral fascia; QRT, chemo-radiotherapy.
^All cases of well-differentiated squamous cell carcinoma.
*In years.
**In months.
^^At this point, two salvage surgeries were performed before administering systemic treatment.
[a]Intraoperative radiotherapy.
[b]Neoadjuvant radiotherapy.
[c]Neoadjuvant chemo-radiotherapy.
[d]Palliative chemo-radiotherapy.
[e]Palliative chemotherapy.

(OS) rate to be 51–87.5% [median OS (mOS): 3–35 months]. Cetuximab monotherapy could also be considered, as one study has shown that 55.9% of tumors became resectable upon this treatment. Unfortunately, the follow-up duration and the number of patients were excessively low (39).

Another alternative is cryosurgery, based on a series of seven cases with a recurrence rate of 29% and a survival rate of 86%, with at least 7 years of follow-up (40).

The most promising strategy may be neoadjuvant cemiplimab, based on recent data in patients with resectable stage II-IV(M0) SCC, since 51% of such patients achieved CR. However, it was also the case in this study that the median follow-up duration was too short to draw firm conclusions (41).

Relapses and outcomes

In the case of locoregional relapse, a new resection should be considered, if feasible (6–8). This approach prolongs survival and can even cure the disease (7, 15, 42, 43). Radiotherapy may be considered if it has not been previously administered (9, 44). If surgery is not possible, alternatives include cryosurgery (40), radiotherapy alone (45, 46), and/or systemic treatment, either as a definitive or as a preoperative approach (13, 25).

A 5-year survival rate of 55–61% has been reported (6, 18, 26, 47), representing poorer prognosis compared with other localized SCCs (48, 49).

Metastatic disease

Metastatic disease is even rarer, with only 22 reported cases (9, 16, 27, 29, 30, 32, 40, 45, 50–56). To these, we add two instances of metastatic cases and two instances of unresectable disease (Table 2).

In most cases, the OS cannot be inferred, and only two reports have published their chemotherapeutic schedules: one consisting of cisplatin plus 5-fluorouracyl (16) and another consisting of various chemotherapeutic agents (mitomycin-C, vincristine, epirubicin, carboplatin, and 5-fluorouracyl), without mentioning the sequence or whether some drugs were combined (52). No details of either PFS or ORR have been published. At our center, four patients have undergone various treatment regimens. If we group all of the treatments, the mPFS was only 2 months, with two partial responses (18%) (Supplementary Table 1). Again, if we group all the cases in the literature, a trend can be observed toward a benefit of chemotherapy (HR 0.41, 95% CI 0.15–1.12, $p = 0.083$; mOS 13 vs. 8 months; Figure 2).

Treatment choice for SCC has always been a challenge, and regimens have been based on cetuximab and several other chemotherapeutical agents, with platinum, paclitaxel, and fluoropyrimidines being the predominant choices (57–64).

Regarding cetuximab, a phase II study showed a 69% DCR at 6 weeks, ORR of 28% (6% CR), mPFS of 4.1 months, and mOS of 8.1 months (57). Another retrospective study, examining regimens with or without carboplatin, showed similar results: 70% DCR, ORR of 20%, mPFS of 2.65 months, and mOS of 10.35 months. The

TABLE 2 Characteristics of metastatic patients.

Characteristics	Value*
Age: median (range), years	55 (36–68)
Sex: male, *n* (%)	26 (100%)
Median time of PD (range), years	25 (1.5–51)
Differentiation, *n* (%)	
Well-differentiated	10 (63%)
Moderately differentiated	5 (31%)
Poorly differentiated	1 (6%)
Timing of metastasis	
Unresectable	2 (8%)
In relapse	18 (69%)
At diagnosis	6 (23%)
Affected at diagnosis, *n* (%)^	
Local nodes	9 (36%)
Bone	8 (40%)
Rectum	2 (10%)
Treatment at diagnosis, *n* (%)	
No treatment	4 (15%)
Surgery	9 (35%)
Surgery + RT	7 (27%)
QT + RT	4 (15%)
RT	1 (4%)
Other	1 (4%)
Metastatic sites, *n* (%)^	
Lung	9 (53%)
Liver	3 (18%)
Bone	6 (35%)
Lymph nodes	8 (47%)
Skin	2 (12%)
Systemic treatment"	7 (27%)

PD, pilonidal disease; RT, radiotherapy; QT, chemotherapy.
*Numbers do not always sum to 26 due to missing data on some patients.
^The sum is not 100% because options are not mutually exclusive.
"Including systemic QT for metastatic patients and QT + RT for unresectable disease or relapses.

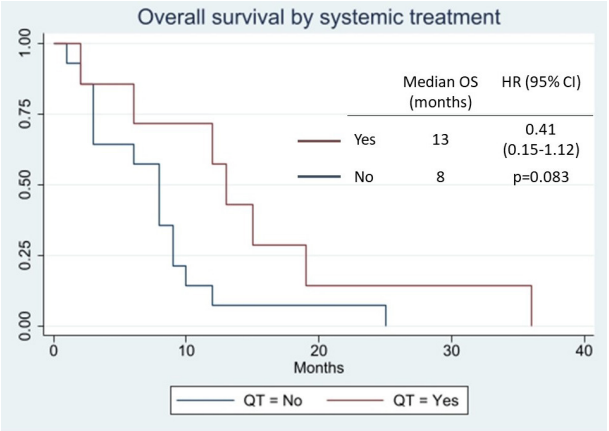

FIGURE 2
Overall survival by systemic treatment.

addition of carboplatin could not be adequately evaluated, but it was not found to be superior (58).

Platinum, in contrast, has produced controversial results when compared with cetuximab. One systematic review showed better results for platinum (mPFS 3.5 vs. 1.9 months; mOS 15.1 vs. 9.8 months) (59), while in another, cetuximab was superior (mPFS 25 vs. 14.6 months; ORR 78 vs. 45%) (60).

Polychemotherapy regimens are less well-tolerated and have not been shown to be better than monotherapy. The largest retrospective study (82 patients) showed an ORR of 18.3% and mOS of 15.3 months. Carboplatin and paclitaxel was the most used combination (61). Cisplatin and 5-fluorouracyl may produce higher response rates, but this regimen is also tolerated less well (62). The addition of bleomycin (63) or anthracyclines (64) has not been shown to achieve better results than cisplatin alone.

It seems that survival is greater in patients who achieve any kind of response than in those who only achieve stabilization. Intralesional methotrexate may be considered for patients with skin lesions that worsen their QoL and who are not suitable for or have exhausted other regimens (65).

However, a revolution in the treatment of SCCs has occurred in the realm of immunotherapy, with findings being reported on cemiplimab in 2018 and on pembrolizumab in 2020 in two phase II studies. Cemiplimab showed an ORR of 47% (CR 7%), estimated progression rate of 53% after 12 months (mPFS not reached), and estimated probability of OS of 81% at 12 months (66). In another study where cemiplimab improved QoL, the results were similar (ORR 46.1% and CR 16.1%), with an incidence of grade 3–5 adverse events of 7.3% (67). Pembrolizumab demonstrated an ORR of 34.3% (CR 3.8%), mPFS of 6.9 months without reaching mOS, and a rate of grade 3–5 adverse events of 5.7% (68).

Hidradenitis suppurativa

Another entity on which a cutaneous SCC can develop is hidradenitis suppurativa (HS), as this is a chronic inflammation. A recent review summarizes 95 cases (69). As in psSCC, the majority of cases are observed in men (77.9%); furthermore, most patients have a long mean time to malignancy (25.5 years) and present mostly well-differentiated histology (62.7%). The most frequently affected areas are the buttocks and the perianal region (47.5 and 18.9%, respectively), and treatment modalities are very heterogeneous. Similarly, this condition also shares the same diagnostic difficulties, usually requiring several biopsies to reach it. The main causes of death are metastases (34.1%) and sepsis (13.6%). Extensive information on systemic treatment is also not available, with a total of 12 patients having received such treatment in different modalities (12.7%). A recent case report has highlighted

successful treatment with cemiplimab (70), showing that anti-PD-1 drugs are a credible treatment option for cSCC, regardless of origin.

Conclusions

Initial management should include computed tomography of the chest, abdomen, and pelvis, as well as an MRI scan. An endoscopic study could be considered to rule out rectal involvement. In the case of suspected involvement of regional LNs, a puncture should be performed. The treatment of choice is surgery with wide margins, including the presacral fascia, with or without resection of the sacrum in bloc. If necessary, APR can be performed. Adjuvant radiotherapy is recommended.

However, due to the high rate of postoperative complications occurring in these cases (three deaths out of six cases of surgery), it might be interesting to consider neoadjuvant treatment (radiotherapy ± chemotherapy; immunotherapy) in the case of large tumors, even if they are resectable.

In cases of unresectable disease, radiotherapy can be administered in combination with chemotherapy (cisplatin with or without 5-fluorouracyl) or cetuximab, although it is possible that the best option may be to assess the use of cemiplimab. If the disease responds to the treatment, resection can be considered. Cryosurgery or intralesional methotrexate are alternatives for frail patients. If local relapse occurs, new surgery should be considered.

In cases of metastatic disease, the absence of studies, the lack of information, and the high levels of heterogeneity among the published cases (including on our part) further complicate decision-making. The most frequently used drugs have been platinum, 5-fluorouracyl, and cetuximab, in a clear attempt to reproduce the results of SCC studies, with little success. However, since this condition is a cSCC, albeit in a different location, we believe that the systemic treatment should be the same as for other forms of cSCC. The proof of this is that the first reported response to systemic treatment in psSCC occurred in one of our patients who received cemiplimab. It should be noted that this response was maintained for 5 months and was observed after the patient had received two other lines of treatment. Subsequently, the same patient presented with a new response to the combination of paclitaxel and cetuximab for another 5 months.

This evidence reinforces the idea that the initial systemic treatment of psSCC should be an anti-PD-1, as in the case of other cSCCs, as established in several clinical guidelines, namely EADO (71), EORTC (71), and NCCN (72). Direct comparisons are lacking, but there exist retrospective studies that have demonstrated an advantage over other systemic therapies (73). After progression to anti-PD-1, there is no strong evidence to recommend a specific treatment or sequence. Options include cetuximab and/or chemotherapy (platinum, paclitaxel, and 5-fluorouracyl).

The lack of information remains a challenge in this condition.

Patients' perspective

At the time of article submission to the journal, all patients gave consent for publication, with the understanding that this information may be publicly available.

Data availability statement

The datasets presented in this article are not readily available because of ethical/privacy restrictions. Requests to access the datasets should 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

AS, SB-A, EV, ÓM-A, LC-M, AM-M, FL-C, SC, IP-M, FG, and MS provided the clinical cases from their own experience. AS and JS contributed to conception of the manuscript. JS wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1248894/full#supplementary-material

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Embolia cutis Medicamentosa (Nicolau syndrome): case series

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Introduction: Embolia cutis medicamentosa or Nicolau syndrome is a rare drug reaction associated with the administration of various injectable medications. The pathogenesis of the disease is unknown, though intra and periarterial injection of the drug is a possible cause. The aim of this study was to describe and analyze the clinical characteristics of Nicolau syndrome in patients examined in daily dermatological practice.

Methods: We performed a retrospective chart review, between January 2011 and December 2020, in patients diagnosed with Nicolau syndrome, from the cases of a private dermatology medical office in Târgu Mureș, Romania.

Results: During the 10-year period, 7 patients were diagnosed with Nicolau syndrome. Of these, 4 (57%) patients were males and 3 (43%) were females, The male to female ratio was 1.33. The median age was 64 (interquartile range, IQR, 62–71), with the youngest patient being diagnosed at age 61 and the oldest at age 74. Regarding the drugs classes that caused Nicolau syndrome, these were intravenous antibiotics in 57%, and non-steroidal anti-inflammatory drugs in 43% of cases.

Conclusion: All patients healed in a period of 6 to 8 weeks. No complications occurred. In conclusion, Nicolau syndrome is a rare side effect of injectable drug administration.

KEYWORDS

adverse drug reaction, Nicolau syndrome, embolia cutis, cutaneous gangrene, rare drug reaction

1. Introduction

Nicolau syndrome was first described in the early 1920s by Nicolau as an adverse effect of using intramuscular injections of bismuth salts in the treatment of syphilis (1). Since then, several case reports of this disease occurring after intramuscular, intra-articular, intravenous, and subcutaneous injections, especially in an oily or suspension form, have appeared in the literature associated with a large variety of drugs (2). The pathogenesis of the disease is unknown, though intra and periarterial injection of the drug is a possible cause (3). Stimulation of the sympathetic nerve due to periarterial injection causes spasms and consequent ischemia. Inadvertent intra-arterial injections may cause artery and branch embolization and occlusion,

associated with artery wall irritation. Lipophilic drugs can produce fat embolization and cytotoxic drugs may produce inflammation with tissue necrosis. An acute ischemia syndrome of the segmental skin area can occur. The extent and severity of the lesions are closely related to the size of the affected artery. Necrosis ensues in this stage, with possible ulceration (4, 5).

The purpose of this retrospective review was to investigate and chronicle the clinical and disease progression of Nicolau syndrome in patients encountered during routine practice in order to uncover shared characteristics that might foster the medical understanding of the disease.

2. Materials and methods

We performed a retrospective chart review between January 2011 and December 2020, in patients diagnosed with Nicolau syndrome, from the cases of a private dermatology medical office in Târgu Mureș, Romania. All patients were Caucasian. Written informed consent of the patients was obtained at the moment of consultation. When making the decision to write this paper, some of the patients were personally invited to the office, and others were contacted by phone to have the study explained and reconfirm the informed consent on the processing of patient personal data. The diagnosis was established by dermatological clinical examination. One investigator evaluated patients and collected data (general data, disease onset, clinical aspect, and evolution, relevant personal history, and present comorbidities). Patients were followed-up during treatment until healing by clinical examination and /or telephone interview. Other investigators, who were blinded to the clinical cases, performed data analysis and interpreted the results.

3. Results

Table 1 presents the history and clinical findings. During the 10-year period, 7 patients were diagnosed with Nicolau syndrome. From these, 4 (57%) patients were males and 3 (43%) were females. The male to female ratio was 1.33. The median age was 64 (IQR 62–71) years, with the youngest patient being diagnosed at age 61 and the oldest at age 74.

The disease manifested at a median of 24 (IQR 24–36) hours after injection. In 4 out of 7 cases, the lesions appeared within 24 h, while in 3 cases they appeared 36 h after injection. In 4 cases, the lesions were situated on the anterior area of the forearm, the rest on the dorsal area of the fist. Regarding the clinical appearance of the lesions, all of them were red-purple plaques, between 5 and 8 cm in diameter, with a livedoid aspect, centrally necrotic, very painful, with well-defined edges and geographic contours. The lesions were round-oval, apart from one case in which they were rectangular, after using an intravenous branula (Figure 1).

For the verification of outliers, we have applied the Grubbs test (6, 7), which did not detect any outlier.

For all patients the treatment was topical, and consisted of the use of antibiotics and epithelializing ointments, with good results. In some cases, however, surgical debridement was necessary. All patients recovered within a period of 6 to 8 weeks. No complications occurred. All patients suffered from multiple morbid conditions, which was the reason for prescribing injectable, intravenous treatments. Regarding the drugs that caused Nicolau syndrome, in 4 cases it was intravenous antibiotics, and in 3 cases non-steroidal anti-inflammatory drugs. In the group of antibiotics, we found 3 cases of Cefuroxim 1 g as a causative agent 2x1g /day, used intravenously, and in one case Ciprofloxacin 400 mg, 2×400 mg/ day intravenously. Regarding the group of non-steroidal anti-inflammatory drugs in all the 3 cases, the drug was Diclofenac 75 mg, used intravenously (Table 1).

Table 2, row labeled "time to resolution," presents a descriptive statistic of the healing time. For the verification of outliers, we used the Grubbs test, which did not detect any outlier.

4. Discussions and conclusion

Embolia cutis medicamentosa or Nicolau syndrome is a rare drug reaction associated with the administration of various injectable medications. It is a rare disease, and the true incidence is unknown. The disease can occur at any age, depending on the need to administer intravenous, muscular, or intra-arterial drugs, being linked to the presence of severe comorbidity. The patient's data analyzed in this study was carefully collected and recorded in a database during the

TABLE 1 Anamnestic and clinical findings.

Case	Age	Gender	Onset of disease	Clinical aspect/ Localization/ Size	Healing	Comorbidities	Incriminated drug
1	74	Female	24 h	Round-oval, anterior forearm right/ 8 cm	8 weeks	Multiple, cardiac and metabolic	Ciprifloxacin 400 mg, iv.
2	71	Female	36 h	Round-oval, anterior forearm right/ 6 cm	6 weeks	Chronic leg ulcer, Diabetes	Cefuroxim 1 g, iv.
3	69	Female	24 h	Dorsal area fist/ 6 cm	6 weeks	Discopathia, Lumbago	Diclofenac 75 mg, iv.
4	62	Male	36 h	Rectangular anterior forearm right/2×6 cm	6 weeks	Chronic leg ulcer, Diabetes	Cefuroxim 1 g, iv.
5	64	Male	36 h	Dorsal area fist/ 5 cm	8 weeks	Chronic leg ulcer, Coxartrozis	Diclofenac 75 mg, iv.
6	61	Male	24 h	Round-oval, anterior forearm right/ 6 cm	6 weeks	Osteolistezis, Leg ulcer, Diabetes	Diclofenac 75 mg, iv.
7	62	Male	24 h	Dorsal area fist/ 5 cm	8 weeks	Chronic leg ulcer, Diabetes	Cefuroxim 1 g, iv

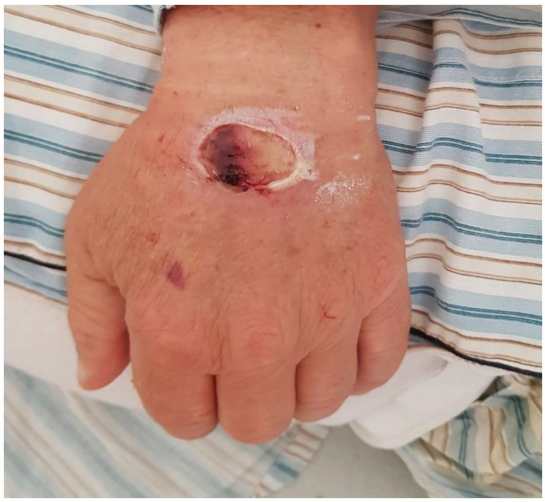

FIGURE 1
A case of Nicolau syndrome showing a well-defined, oval ulcer with necrotic base on the dorsum of the left hand.

TABLE 2 Descriptive statistic of the onset of the disease.

Characteristics	Time
Latency [h]	24 (24–36)
Time to resolution [d]	42 (42–56)

Continuous data is reported as median and interquartile range.

10-year period. Over this time, we detected 7 patients, 4 males and 3 females, median age 64 years, having suffered from Nicolau syndrome.

Mojjarad et al., analyzing 135 cases from multiple databases on Nicolau syndrome and concluded that the disease can occur mainly in females of any age group, but mainly in children and the age group 31–40 years (8). Regarding the onset of the disease due to the appearance of pain at the level of injection, in our cases, the latency was between 24 and 36 h, which corresponds to the data from meta-analytical studies (8). The clinical appearance of the skin lesions is identical in each case, regardless of the cause, the site of injection being a single round oval lesion with a diameter between 5 and 8 cm, well delimited, with ulceration and necrosis on the surface. In our retrospective case series, the healing period was between 6 and 8 weeks, regardless of the causative agent or location. The prescribed treatments were similar in these cases and the disease course was favorable. Local treatments included antibiotics, epithelisants, magistral prescriptions with Silver nitrate, and Peru Balsam used in difficult-to-heal ulcers (9). In our cases, previously reported complications such as fasciitis, superinfections, amputations, or deaths did not occur (10–13). A multitude of drugs can cause this disease, among which the most important groups of drugs are non-steroidal anti-inflammatory drugs and antibiotics. In a review assessing 145 articles, Mojjarad et al. found that the most common causes of the syndrome are diclofenac (35 articles, 24%) and penicillins (32 articles, 22%) (8). In our cases, the cause of the injection was Diclofenac in 3 patients; Cefuroxime in 3 patients and Ciprofloxacin in 1 patient. According to previously published literature, Gentamicin (14) and Penicillins (15, 16) are among the most frequently reported antibiotics causing Nicolau syndrome. Among the non-steroidal anti-inflammatory drugs, Diclofenac is the most frequently reported drug, followed by other drugs such as Naltroxene, Etofenamate, and Ketofrofenid (17–20). Cases of Nicolau syndrome caused by dermatocosmetic procedures such as hyaluronic acid injections (21), meso, and sclerotherapy (22, 23) have been described. Other drug classes have been mentioned as causative factors such as: triamcinolone (24), glatiramer acetate (25), terlipressin (26), bortezomib (27), hydroxyzine (28), interferon alfa (29), etc. At the same time, it may occur as a local reaction after the administration of vaccines such as the hexavalent vaccine (30), or the DTP vaccine (31). In conclusion, Nicolau syndrome is a rare side effect of injectable drugs which can be severe.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Dermamed private office ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant/patient(s) for the publication of this article.

Author contributions

GF, LF, and JF: conceptualization, methodology, validation, formal analysis, investigation, and writing—review and editing. LI: software, data curation, and writing—original draft preparation. GF and LF: resources. GF, LF, JF, and LI: visualization. GF: supervision, project administration and funding acquisition. 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.

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Clinical and histopathological characteristics, diagnosis and treatment, and comorbidities of Bowen's disease: a retrospective study

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Background: Bowen's disease (BD) is a slow-growing precancerous skin condition, often concurrent with other diseases, with a high misdiagnosis rate. Previous studies show that patients with BD in different populations have differentiated characteristics.

Materials and methods: A retrospective study was conducted in a tertiary hospital in Shenzhen, China. Data about demographic information, diagnosis and treatment, clinical and pathological characteristics, and comorbidities of 50 patients with BD were collected and analyzed.

Results: Clinical data of onset age and disease course of 43 patients with BD were available, the average onset age of male and female patients are 55.1 (standard deviation (SD) = 15.29) and 58.2 (SD = 15.59) years old, respectively; the average disease course of male and female patients are 25.3 (SD = 28.63) and 33.9 (SD = 49.65) months, respectively. The onset age ($p = 0.52$) and disease course ($p = 0.49$) between male and female patients are not significantly different. Interestingly, there is a negative correlation between onset age and disease course ($r = -0.245$, $p = 0.11$). The correct rate of clinical diagnosis is relatively low (54.00%); Some patients with BD are misdiagnosed as Bowenoid papulosis (10.00%), actinic keratosis (8.00%), basal cell carcinoma (8.00%), seborrheic keratosis (6.00%), and pigmented naevus (4.00%). Trunk and limbs are the most common distribution sites of BD lesions, and 94.00% patients with BD are treated with surgical resection; 66.00% patients with BD had comorbidities, including skin diseases (48.48%), cardiovascular diseases (39.39%), gastrointestinal diseases (30.30%), respiratory diseases (27.27%), and tumors (18.18%). The most commonly observed histopathological characteristics of BD are squamous-cell hyperplasia (86.00%), disordered maturation with atypical keratinocytes (74.00%), atypical mitoses (60.00%), hyperkeratosis with hypokeratosis (48.00%), dermal inflammatory cell infiltration (36.00%), and koilocytosis (22.00%).

Conclusion: BD often occurs in middle-aged and elderly people and is easily misdiagnosed. The onset age and disease course of patients with BD are not significantly different between males and females, whereas there is a negative correlation between the onset age and disease course. BD is more likely to occur

in trunk and limbs in the Chinese population, and most patients with BD are concurrent with comorbidities.

KEYWORDS

Bowen's disease, characteristic, diagnosis, treatment, comorbidity, retrospective study

1 Introduction

Bowen's disease (BD), also known as squamous cell carcinoma (SCC) *in situ*, is a slow-growing precancerous skin condition, and 3%–5% BD may progress to invasive tumors (1). The incidence of BD varies due to the difference in sun exposure in different latitudes and climates (2, 3). The etiology of BD is not entirely clear; it may be related to irradiation, carcinogens, human papillomavirus (HPV), and others (such as chronic injury, dermatoses, and heredity) (4–6). BD presents as a well-demarcated, asymptomatic, erythematous hyperkeratotic plaque with irregular margins that is more likely to occur on the exposed site in light-skinned people (5), which is difficult to differentiate from Bowenoid papulosis, actinic keratosis, and seborrheic keratosis. Clinically, patients with BD are concurrent with other diseases, but few studies have focused on the comorbidities of BD. In addition, there are differences in the characteristics of patients with BD in different populations. In order to improve the understanding of BD, we conducted a retrospective study in a tertiary hospital in China, the data about demographic information, clinical and pathological characteristics, diagnosis and treatment, and comorbidities of 50 patients with BD were collected and analyzed.

2 Materials and methods

2.1 Study design and participants

A retrospective study was conducted in a tertiary hospital (Peking University Shenzhen Hospital) in Shenzhen, China. In total, 50 patients with BD from outpatient or inpatient department were confirmed by histopathological examination from January 2016 to August 2023, including 26 males and 24 females. Demographic information, distribution of lesions, clinical diagnosis, onset age, disease course, treatment methods, histopathological characteristics, and comorbidities of BD were collected. The chronological age at the visit or admission time and the disease course were available in the majority of patients with BD; here, we obtained the onset age by chronological age minus the disease course. All patients with BD were called to recall whether there were some predisposing factors present at that time, including sun exposure, radiation, carcinogens, HPV infection, chronic injury, and genetic history. Meanwhile, all patients were called to inquire information about the recurrence of BD.

2.2 Division of the body sites and definition of comorbidities

In this study, the lesion distribution of BD in different parts of the body was studied. According to the conventional division method of the body, we divided the body into five parts: head and neck, upper limbs, trunk (including armpit and groin), lower limbs (including buttocks), and genital parts. The sun-exposed parts include ears, cheek, nose, forehead, opisthenar, and fingers. In addition, the comorbidities of patients with BD were collected for further analysis. Here, we defined "comorbidities" as those diseases that occurred before or during the course of BD; the diseases that occurred after the treatment time were not included.

2.3 Statistical analysis

Quantitative data were described by mean and standard deviation (SD), while qualitative data were described by number (N) and percentage (%). SPSS V22.0 (IBM Corp., Armonk, NY) and GraphPad Prism V9.0 (San Diego, CA) were used for statistical analysis. Q-Q plot was used to test whether the dataset followed a normal distribution or not. Continuous variables were evaluated by *t*-test or *t*-test with Welch's correction according to the distribution of the dataset. The relationship between the onset age and disease course of patients with BD was calculated using Pearson's correlation analysis. p-value <0.05 was considered statistically significant.

3 Results

3.1 Onset age, disease course, and skin lesion distribution of Bowen's disease

Clinical data of 50 BD patients were collected. The patients' chronological age ranged from 22 to 86 years old, with a mean age of 59.9 (SD = 14.66) years old. The onset age and disease course of 43 patients with BD were available for further analysis (Figure 1). The average onset age of 43 patients with BD is 56.7 (SD = 15.35) years old and that of male and female patients with BD are 55.1 (SD = 15.29) and 58.2 (SD = 15.59) years old, respectively. The disease course of 43 patients with BD ranges from 1 to 240 months, and the disease course of most patients is distributed in 12 to 24 months. The average disease course of 43 patients with BD is 29.9 (SD = 40.99) months and that of male and female patients are 25.3 (SD = 28.63) and 33.9 (SD = 49.65) months, respectively. The distribution of onset age is in accordance with normal distribution, and the distribution of disease course is approximately normal (Figure 1). The onset age of male and female patients is not significantly different by unpaired *t*-test ($F = 1.04$, $p = 0.94$; $t = 0.65$, $p = 0.52$). The difference in disease course between male and female patients is not significant by unpaired *t*-test with Welch's correction ($F = 3.01$, $p = 0.02$; $t = 0.70$, $p = 0.49$). The correlation between onset age and disease course of patients with BD is negative (Pearson's $r = -0.245$, $p = 0.11$). For the lesion distribution of BD

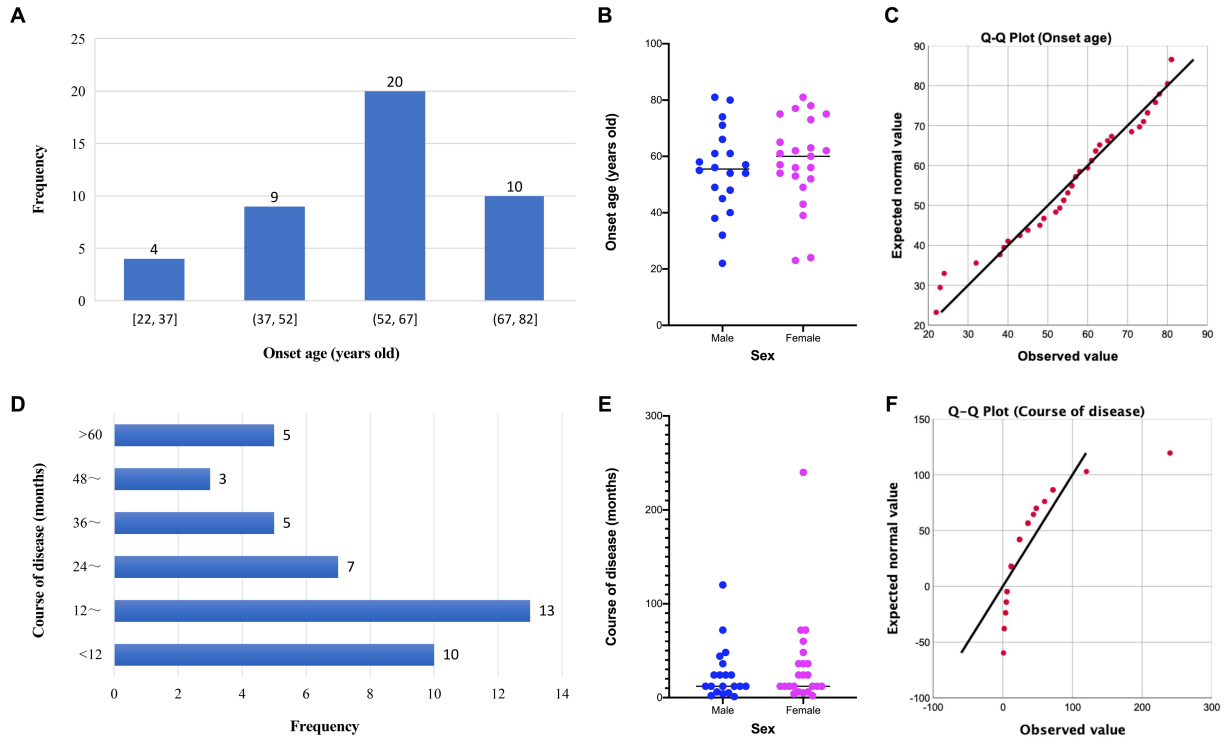

FIGURE 1
Distribution and comparison of onset age and disease course of patients with Bowen's disease. **(A)** Distribution of onset age of patients with Bowen's disease; **(B)** comparison of onset age of patients with Bowen's disease between males and females; **(C)** Q-Q plot of onset age; **(D)** distribution of disease course of patients with Bowen's disease; **(E)** comparison of disease course of patients with Bowen's disease between males and females; **(F)** Q-Q plot of disease course.

(Table 1), trunk and limbs are the most commonly observed distribution sites; there are 26.00% patients with lesions in sun-exposed parts. In particular, 5 patients developed lesions on their fingers and 1 patient developed lesion on her feet.

3.2 Clinical diagnosis and treatment methods of Bowen's disease

The correct rate of clinical diagnosis is 54.00%. Some patients with BD are misdiagnosed as Bowenoid papulosis (10.00%), actinic keratosis (8.00%), basal cell carcinoma (8.00%), seborrheic keratosis (6.00%), and pigmented naevus (4.00%). One case each was diagnosed as verruca vulgaris, infectious granuloma, eczema, Paget's disease, fibrous rash, glomus tumor, and SCC. For the treatment, 94.00% patients with BD received surgical treatment, and imiquimod cream was applied in 1 patient. 2 patients were treated with combined therapy, including surgery combined with photodynamic therapy (PDT) or liquid nitrogen cryotherapy. There were 30 patients with BD who gave feedback on information about recurrence, and 3 patients had a recurrence in the treatment area.

3.3 Predisposing factors and comorbidities of Bowen's disease

In total, 30 patients with BD gave feedback on predisposing factors, and 5 patients with BD had trauma at the lesion locations. For the comorbidities of 50 patients with BD, 33 patients had comorbidities: 48.48% (16 of 33) patients were comorbid with skin diseases, including allergic dermatosis ($n = 7$), infectious dermatosis ($n = 4$), keloid ($n = 2$), hemangioma ($n = 2$), actinic keratosis ($n = 2$), and other skin diseases; 39.39% (10 of 33) patients were comorbid with cardiovascular diseases, of which hypertension was the most common comorbidity ($n = 9$); 30.30% (10 of 33) patients were comorbid with gastrointestinal disease, mainly chronic gastritis or proctitis ($n = 7$); 27.27% (9 of 33) patients were comorbid with respiratory diseases, including allergic rhinitis ($n = 4$), pharyngitis ($n = 3$), and bronchitis ($n = 3$); 18.18% (6 of 33) patients were comorbid with tumors. In addition, patients with BD were also comorbid with some other diseases, such as lumbar disk herniation, diabetes mellitus, benign prostatic hyperplasia or prostatitis, and hyperlipidemia; 21.21% patients with BD had 1 kind comorbidity, followed by 3 and 4 kinds of concomitant diseases with the same proportion (18.18%). It is worth noting that more than three-quarters of patients with BD had more than 2 kinds of comorbidities.

3.4 Histopathological characteristics of Bowen's disease

The histopathological characteristics of 50 patients with BD were summarized, including squamous cell hyperplasia (86.00%), disordered maturation with atypical keratinocytes (74.00%), atypical mitoses (60.00%), hyperkeratosis with hypokeratosis (48.00%), dermal inflammatory cell infiltration (36.00%), and koilocytosis (22.00%). In

TABLE 1 Lesion distribution of Bowen's diseases.

Body parts	Subsites	Frequency	Frequency—total	Percentage	Cumulative frequency	Cumulative percentage
Head and neck	Ears*	3	6	12.00%	6	12.00%
	Cheek*	1				
	Nose*	1				
	Forehead*	1				
Upper limbs	Opisthenar*	2	10	20.00%	16	32.00%
	Upper arms	2				
	Forearm	1				
	Fingers*	5				
Trunk	Waist	6	16	32.00%	32	64.00%
	Back	6				
	Breast	2				
	Chest	1				
	Abdomen	1				
Genitals	Vulva	4	7	14.00%	39	78.00%
	Penis	2				
	Foreskin	1				
Lower limbs	Lower legs	4	11	22.00%	50	100.00%
	Thigh	4				
	Pygal	1				
	Perianal region	1				
	Foot	1				

*Sun-exposed areas.

addition, it also includes some other pathological characteristics, such as dyskeratosis, elastic fiber degeneration, pigment deposition, and scattered pigment incontinence.

4 Discussion

BD often occurs in middle-aged and elderly people; it is slightly more common in women (5). The sex ratio of male and female patients with BD was approximately 1:1 in our study. Of 50 patients with BD, the clinical data of onset age and disease course were available in 43 patients. The average onset age and average disease course of female patients with BD are higher than male patients, but the differences are not significant. We explored the correlation between onset age and disease course of patients with BD, result showing that these two with negative correlation, it means the elderly patients with BD had shorter disease course, it is possible that elderly people are more concerned about their own physical health.

BD is mostly involved in sun-exposed areas of the body and lesions often appear on the head, face, and limbs (7); more recent studies suggest BD has a predilection for the head and neck (8, 9). Trunk and limbs were the most common distribution, while lesions in the head and neck with the lowest proportion in our study, which is slightly different from previous findings (7–9). Interestingly, the lesions of 46.00% patients with BD located on non-sun-exposed sites, such as the trunk and genitals, suggest that we should pay more attention to rashes in non-sun-exposed sites. In particular, skin lesions of BD occurred on the fingers in 5 patients and on the feet in 1 patient. Previous studies indicated that HPV infection may be a potential risk factor for BD (10), multiple BD on the finger associated with HPV-34 (11) and HPV-16 (12), and BD on the dorsum of the foot associated with HPV-16 (13). Therefore, it is necessary to test HPV for BD occurring in the fingers and feet.

In clinical practice, the diagnosis of BD is usually made on the basis of clinical manifestations. Dermoscopy, as a non-invasive tool, is increasingly used in the clinical auxiliary diagnosis of BD (14). Ultrasound biomicroscopy (UBM) and high-frequency ultrasound (HFUS) also have potential as diagnostic tools for BD (15). Skin biopsy is often necessary to arrive at an accurate diagnosis of BD; all patients in our study underwent pathological examination. The correct rate of clinical diagnosis of BD before pathological examination is relatively low; BD is most easily misdiagnosed as Bowenoid papulosis, followed by actinic keratosis, basal cell carcinoma keratosis, seborrheic keratosis, and pigmented naevus. Interestingly, BD and seborrheic keratosis could be correctly identified by the deep learning model (area under the curve score > 0.97), the results of which should be confirmed by qualified histopathologists (16). Hopefully, more diagnostic methods with high accuracy will be developed in future.

The treatment methods for BD include topical therapies (5-fluorouracil (5-FU), imiquimod), cryotherapy (cryosurgery), curettage with cautery, PDT, standard surgical excision, Mohs micrographic surgery, laser (CO_2 laser, non-ablative neodymium:

YAG), radiotherapy, systemic treatments, and combination therapy (5). Some novel treatment approaches, such as pembrolizumab (a humanized monoclonal anti-PD-1 antibody for the treatment of melanoma and other malignancies) (17, 18) and thermotherapy (19), have also been tried for the treatment of BD. Previous studies reported that the complete clearance rate can reach 94.40% when the surgical margin is 5 mm (20). In this study, more than 90.00% patients with BD received surgical treatment, and two patients were treated with combined therapy, including surgery combined with PDT or cryotherapy. A previous study showed that PDT is a relatively effective treatment modality for BD, the overall clearance rate was 63.40% (21). An observational study compared different therapies: cryotherapy with the longest average treatment period, followed by imiquimod, PDT, and excision; surgical excision with the highest and PDT with the lowest therapeutic efficacy; imiquimod with recurrence rate was the highest (22). The efficacy of PDT in the treatment of BD varies among different studies, a meta-analysis shows that PDT treats BD with better efficacy, less recurrence, and better cosmetic outcomes than cryotherapy and 5-FU (23). Although a variety of methods have been applied to the treatment of BD, more therapeutic targets and methods need to be explored to enrich the treatment of BD in future.

More and more attention is being paid to the coexistence of diseases, but few studies focus on the comorbidity of BD. Previous studies reported that Merkel cell carcinoma (24, 25), cutaneous pseudolymphoma (26), breast cancer (27), and extramammary Paget's disease (28), were concurrent with BD. In this study, 66.00% BD patients had comorbidities, mainly including skin diseases (48.48%), cardiovascular diseases (39.39%), gastrointestinal diseases (30.30%), respiratory diseases (27.27%), and tumors (18.18%). It is noticed that more than three-quarters of patients with BD had more than 2 kinds of comorbidities, and 1 patient had 14 kinds of comorbidities. Patients with so many kinds of comorbidities, which may be related to that most of the patients with BD are elderly people who have more underlying diseases. Therefore, it is necessary to pay attention to the comorbidities of patients with BD in diagnosis and treatment.

BD exhibits the histopathological features of full-thickness cell atypia, intact stratum basale, widened and elongated epidermal processes, and lymphocyte inflammatory cell infiltration around the superficial dermis vessels. In our study, the most common histopathological characteristic of BD is squamous cell hyperplasia, followed by disordered maturation with atypical keratinocytes, atypical mitoses, hyperkeratosis with hypokeratosis, dermal inflammatory cell infiltration, and koilocytosis. The summarization of these pathological characteristics is helpful for the diagnosis of BD in the Chinese population. Although there are some auxiliary diagnostic methods for the diagnosis of BD, histopathological examination is still necessary for the diagnosis of BD. The combination of fluorescence lifetime imaging microscopy (FLIM) and phasor approach (phasor-FLIM) is a screening tool for the differential diagnosis of BD, actinic keratosis, and basal cell carcinoma based on histopathological analysis (29). More diagnostic pathological characteristics need to be found in future.

5 Conclusions

BD often occurs in middle-aged and elderly people and is easily misdiagnosed clinically. The onset age and disease course of BD are not significantly different between males and females, whereas there is a negative correlation between the onset age and disease course of BD. BD is more likely to occur in the trunk and limbs in the Chinese population, and most BD patients are diagnosed with comorbidities. The associations between BD and its comorbidities should be further studied.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Peking University Shenzhen Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CZ: Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. BJ: Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. KZ: Data curation, Writing – original draft, Writing – review & editing. JW: Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. CH: Data curation, Writing – original draft, Writing – review & editing. NX: Data curation, Writing - review & editing. TY: Resources, Writing – review & editing. BC: Resources, Supervision, Writing – review & editing. BY: Resources, Supervision, Writing – review & editing. YZ: Conceptualization, Resources, Supervision, Writing – review & editing. CS: Conceptualization, Data curation, Resources, Supervision, Writing – original draft, Writing - review & editing.

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Conflict of interest

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Multiple verrucous squamous cell carcinomas developing on chronic hidradenitis suppurativa lesions—a rare case report from Romania

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Hidradenitis suppurativa (HS) is an uncommon, recurrent, inflammatory skin illness of the apocrine glands, with a questionable etiology. The disease is associated with a multitude of comorbidities, of which the appearance of malignancy is the most important. Squamous cell carcinoma is considered the most frequent malignancy that can appear in HS. A case report of a 72 years-old male is presented, who suffered over 40 years from persistent, extensive hidradenitis suppurativa in stage Hurley III, on the buttocks and perianal region, who recently presented two verrucous semi-consistent, skin-colored tumors on the right buttock. The biopsy and histopathological exam confirmed a verrucous type of squamous cell carcinoma. There are about 100 reported clinical cases of squamous cell carcinoma complicating hidradenitis suppurativa in the literature, but only a few describe a verrucous carcinoma as a clinical form. The particularity of the case is the rare appearance of multiple verrucous types of squamous cell carcinomas in a male patient, in Hurley Stage III, with a long HS disease duration, appearing on the perianal/gluteal region, being the first case report in our country. We suggest that a tumor screening should be done for all the patients with HS who have these risks.

KEYWORDS

hidradenitis suppurativa, squamous cell carcinoma, verrucous carcinoma, inflammatory lesions, comorbidities

1 Introduction

Hidradenitis suppurativa is a chronic inflammatory disease, with the appearance of follicular obstructions, abscesses, fistulas, foul mucopurulent secretions, and vicious, often debilitating scarring of the apocrine gland areas of the skin (1). The average prevalence in Europe of the disease is about 1% (2). The first case was published in 1839 by Valpeau (3). The disease was described by Verneuil (3), mentioning that the chronic inflammatory lesions

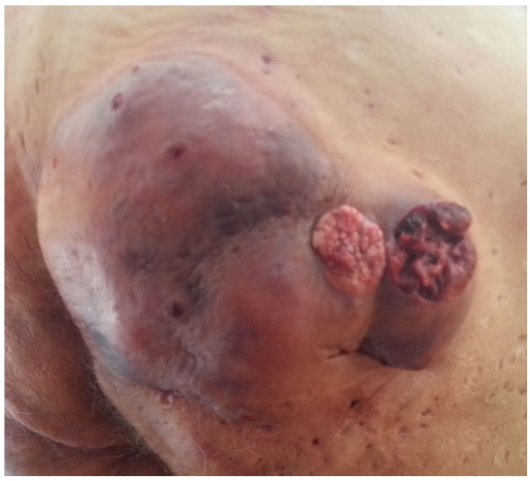

FIGURE 1
Clinical aspect of the tumors on the right buttock.

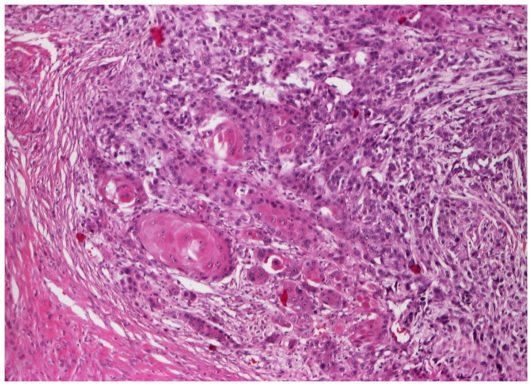

FIGURE 2
Biopsy, buttocks (H&E 10×): poorly differentiated verrucous squamous cell carcinoma with marked cytonuclear pleomorphism and atypical mitoses infiltrating into the dermis.

typically involve the folds and the buttock. The appearance of the clinical features can develop symptoms like pain, pruritus, and debilitating scars, with implications for the quality of life (4). The disease is at the border of different specialties like dermatology, general surgery, or plastic surgery and for this reason, a precise diagnosis is generally delayed (5). In the evolution of HS, a large number of associated diseases can occur. From these, the appearance of malignancies is the most important. In a recent review, Gierek et al. (6) highlighted that in the evolution of HS, the appearance of nonmelanoma skin cancer (NMSC), hematologic malignancies, and metastatic cancers are possible. From these, the most frequent complication is the development of squamous cell carcinoma (SCC). Also from this review, the authors analyzed 74 cases of SCC that appeared on HS, and they concluded that the majority of the primary squamous cell carcinomas were an ulcerated or nodule-type form (6). There are about 100 reported cases of squamous cell carcinoma complicating hidradenitis suppurativa in the literature, but only a few describe a verrucous carcinoma type as a clinical form (6). We present a clinical case of verrucous squamous cell carcinoma developing on chronic HS.

2 Case report

We present a clinical case of a 72 years-old, non-smoking, immune-competent normoponderal patient, who suffered over 40 years from persistent, extensive hidradenitis suppurativa on the buttocks and perianal region. He was treated for over 40 years with oral antibiotics and retinoids, local topical antibiotics, steroids, and a multitude of antiseptics without success. He had periods of remission and exacerbation. During the dermatological consultation, we found an active area of HS in stage Hurley III on the buttocks and perianal region and two verrucous semi-consistent, skin-colored tumors on the right buttock, having a base diameter of 2.5 and 3 cm, presenting spontaneous bleeding (Figure 1). These tumors developed relatively quickly in approximately 3 months. The patient is suffering from several chronic diseases, like chronic obstructive pulmonary disease, essential hypertonia, arthrosis, and osteoporosis, which were under medical control and are not related to HS. He is not suffering from diabetes. His family medical history was unremarkable. The results of routine laboratory testing like hematology and biochemistry were within the normal limits. The treatment decision was the surgical removal of the tumors. The histopathological examination of the two excised tumors confirmed the verrucous type of squamous cell carcinoma (Figure 2). Based on the clinical and histological examination, the patient was transferred to an oncology service for further examination and treatment options. Unfortunately, due to the advanced stage of the carcinoma, the evolution was fatal for the patient.

3 Discussion

Hidradenitis suppurativa (HS) is a chronic and exhausting dermatologic disease of the apocrine glands, characterized by the formation of multiple inflammatory lesions, abscesses, fistulas, and scars, especially arising on folds and buttocks. The exact prevalence of HS is unknown, it has been estimated to be as high as 4.1%, and it is three times more frequent in women than in men (7). The etiology is still unclear, but the illness is frequently associated with smoking, poor hygiene, immunocompromised status, and diseases like metabolic, cardiovascular, endocrine, gastrointestinal, rheumatologic, and psychiatric ones, and also with reduced cutaneous levels of calprotectin, zinc, or ascorbate, which all together compromise the life quality of these patients (4). The clinical aspect of HS is multiform, from inflammatory lesions to nodules, abscesses, fistulas, and scars that can be present, as is well defined by the Hurley staging. The differential diagnoses can include bacterial, especially Staphylococcal skin infections, with or without elementary lesions like abscesses, carbuncles, and furuncles, and cutaneous Crohn's disease. Also, different types of cysts, like Bartholin or epidermoid cysts can resemble HS (8). Squamous cell carcinoma (SCC) is the second most common skin cancer, accounting for 20% of skin cancers (9). Squamous cell carcinomas comprise different types of cancers that are

formed on the surface of the skin and mucous membranes (10). The most important general risk factors for the development of SCC on the skin, are sun exposure, age, and phototype of the skin, especially in cases of phototype I–III was described the mutation in the suppressor protein (TP53) (11). Squamous cell carcinomas may arise in a multitude of chronic inflammatory dermatoses, wounds, and scars such as thermal burn scars, discoid lupus erythematosus, chronic ulcerations, chronic radiodermatitis, precancers, etc. (12–19). In the literature, we have found published cases of SCC as a severe complication of chronic HS lesions. The relationship between HS lesions and SCC is poorly understood and must be further explored (20). The development of SCC in cases of HS, is multifactorial. HS is more prevalent in women, but the appearance of SCC on the disease is more frequent in men (6). Immunosuppression due to chronic disease is one of the risk factors. Also, the location of HS lesions is important, because most of the published cases of SCC on HS lesions are located in the gluteal and perianal region (21–26). Gierek et al. (6), found that 94.59% of the cases of SCC were developed in the perianal/gluteal region of HS. Most of the reported cases were in Hurley stage III of the disease and were males, like in our presented case (25, 27–29). Also, Gierek et al. (6), concluded that the average age of the patient with SCC in HS lesions was 52.6 years, and the mean time from onset SCC was 25.79 years (range 8 years to 53 years), and most of the patients were in Hurley Stage III (97.2%). In two articles the authors suggest the presence of the HPV virus as a causative factor for the appearance of SCC in HS (30, 31). We cannot prove this hypothesis in our case. The studied references present mostly ulcerated, nodular, and metastatic clinical forms of SCC developed from HS. Cosman et al. (32), present a paper about a verrucous form, mentioning that their case is the second published with this clinical form, like in our case presentation. Also, we did not find any references about the presence of two SCC tumors at the same time in a patient with HS. New ultrasound techniques are used to diagnose the possible transformation of HS into squamous cell carcinoma. Wortsman (33) describes the ultrasound diagnostic criteria for HS and suggests new scores for the severity of the disease. Zussino et al. (34) describe the usefulness of color Doppler in the staging and the follow-up of the evolution of HS. Nazzaro et al. (35) comparing the clinical forms and sonographic scores in hidradenitis suppurativa, propose a new ultrasound scoring system for the follow-up on the evolution of HS, including malignant transformation. Treatment of HS is difficult due to a lack of effective medical therapies. Modern possibilities, like biological therapies, open a new era in the treatment of this disease (36). The treatment of this complication is surgical and depending on the staging of the tumor, is oncologic. Considering the high mortality rate in these cases, we suggest screening for an early diagnosis for the possibility of the appearance of SCC lesions in all HS patients (37).

4 Conclusion

The particularity of the case is the rare appearance of multiple verrucous types of squamous cell carcinomas on a chronic, recurrent, inflammatory dermatologic disease like HS, which is the first case published in our country. The potential risk factors such as sex, advanced stage, chronic evolution, and specific localization as perianal/gluteal and buttock region should be considered in the malignant transformation of HS. We recommend a dermatological cancer screening to all patients with HS who have these risks.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Dermamed Private Office Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. 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

GF: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, Project administration. LF: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. LI: Visualization, Writing – review & editing, Data curation, Software. JF: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. IB: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing.

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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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A randomized trial of a wearable UV dosimeter for skin cancer prevention

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Background: Non-melanoma skin cancer (NMSC) is the most prevalent cancer in the United States. Despite guidelines on ultraviolet (UV) avoidance, it remains difficult for people to assess their exposure, as UV is invisible and the onset of UV-induced symptoms is delayed.

Methods: In a prospective randomized trial, 97 elderly patients with a history of actinic keratoses (AK) were followed over 6 months. Fifty patients received UV counseling from a dermatologist and a wearable UV dosimeter that provided real-time and cumulative UV exposure. Forty-seven patients received only UV counseling from a dermatologist.

Results: Over 75% of participants recorded UV exposure at least once a week during the summer. After 6 months of intervention, when comparing the device group to the control group, we observed a non-significant 20% lower ratio of incidence rates of AKs (95% CI = [−41, 55%], p-value = 0.44) and a significant 95% lower ratio of incidence rates of NMSCs (95% CI = [33, 99.6%], p-value = 0.024). Surveys demonstrated that the control group's score in self-perceived ability to participate in social activities significantly increased by 1.2 (p-value = 0.04), while in the device group, this score non-significantly decreased by 0.9 (p-value = 0.1). We did not observe changes, or between-group differences, in anxiety and depression surveys.

Conclusion: This pilot clinical trial has a short duration and a small sample size. However, device adherence and quality of life questionnaires suggest a smartphone-connected wearable UV dosimeter is well accepted by an elderly population. This trial also indicates that a wearable UV dosimeter may be an effective behavioral change tool to reduce NMSC incidence in an elderly population with a prior history of AKs.

Clinical trial registration: clinicaltrials.gov, identifier NCT03315286.

KEYWORDS

skin cancer, basal cell carcinoma, squamous cell carcinoma, photoprotection, ultraviolet exposure

Background

Skin cancer is the most common cancer in the United States, affecting more than 3 million Americans per year (1), and its incidence is still on the rise worldwide (2). Genetic, phenotypic, and environmental factors, specifically ultraviolet (UV) radiation, are considered the largest contributing factors to the development of skin cancer (3). Over the past three decades, there has been a push towards protecting the skin from the dangers of UV through educational campaigns about the harmful effects of UV (4), topical application of physical and chemical blockers in sunscreens (5), UV protective clothing (6), and vitamin supplementation such as niacinamide (7). More recent controversies on the effectiveness (8) and safety (9) of sunscreens have created a critical need for safer strategies to help reduce the overall UV exposure to our skin. Public health agencies, like the EPA, have published guidelines using the forecasted UV index (UVI) per zip code. This information is easily accessible but it provides an estimate of the sun's strength in one's zipcode, so it does not take into account one's location-driven UVI variations (e.g., cloud cover, shade of a building) and one's duration of exposure to UV. On the other hand, the International Commission on Non-Ionizing Radiation Protection recommends a daily cumulative UV exposure limit of 30 erythemaly-weighted Joules per square meter (equivalent to 30% of one Standard Erythema Dose (10–13), or "SED") for direct exposure to eyes or the skin (14). However, this limit of cumulative UV exposure cannot be easily measured without a wearable UV dosimeter. Among this new class of wearables, the Shade UV sensor accurately records erythemaly-weighted UV exposure and has reached standard benchmarks making it superior to other wearable dosimeters (15, 16). However, wearable UV dosimeters possess inherent limitations, as their measurements may not accurately reflect the UV exposure of various sun-exposed body parts or capture the variations in cumulative exposure across different locations. In this prospective, randomized clinical trial, we assessed the clinical efficacy of the Shade UV sensor and its companion mobile application on pre- and cancerous lesions against the standard of care over six months overlapping a summer in an elderly patient population disposed to developing skin cancer.

Methods

Study design

This prospective, randomized, observer-blinded, controlled clinical trial enrolled elderly patients with a history of actinic keratoses at a single site in New York City, NY. The trial was conducted under the oversight of the Institutional Review Board (IRB) of Weill Cornell Medicine and the National Cancer Institute (NCI). It adhered to applicable governmental regulations. The IRB and the NCI approved the protocol and the consent forms. As a requirement of contract HHSN261201700005c with NCI, the protocol and all amendments were submitted and approved by the program officer. All participants provided written informed consent before enrollment. The sponsor, YouV Labs, Inc., and the trial's principal investigator (GV) were responsible for the overall trial design, site selection, monitoring, and data analysis. Investigators were responsible for data collection, recruitment, and treatment. The authors vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol. The trial was registered on clinicaltrials.gov under the identification NCT03315286 on October 20, 2017.

Participants, randomization, and data blinding

Eligible participants were individuals aged 18 years or older who had a history of actinic keratosis (AKs), with at least one AK diagnosed clinically in the 12 months before enrollment, or a minimum of five clinically diagnosed AKs in the 5 years before enrollment. Patients having received UV therapy in the past 6 months or field therapy for the treatment of actinic keratosis in the past 3 months were excluded. Participants were assigned using randomly-generated blocks of four, stratified by skin type, to receive a wearable UV dosimeter and standard-of-care UV education or solely standard-of-care UV education (avoid going outside between 10 am and 4 pm, apply sunscreen with SPF 30–50 and re-apply every 2 hours including when coming out of the water, wear sun protective clothing, such as a hat). The UV education was provided in person by the study dermatologist at the end of all three clinical visits. Patient adherence to these guidelines was not measured as primary endpoints in our clinical trial. We used randomization in blocks of four to balance seasonal trends in UV exposure. All participants received $50 per visit (up to $150 across the study) to cover for their visit co-pays and transportation, and participants receiving a dosimeter were encouraged to wear it every day and received a compliance payment of $20 per visit if their dosimeter recorded UV at least 2 days per week (up to $40 across the study). The compliance payments were designed to encourage participants to wear the dosimeter at least during the weekend. Participants were enrolled from April to July 2018 and had two follow-up visits at 3 months intervals. The final visits ran from November to January 2019. All participants from both groups were examined by the same dermatologist who was blinded to their group assignment.

Wearable UV dosimeters

The sponsor provided the Shade UV dosimeters (16) and a companion smartphone application. The dosimeters measured the erythemaly-weighted UV exposure every second and aggregated the cumulative dose every 6 min. They were designed to be worn on the chest using a magnetic attachment (Figure 1). The sponsor developed an application for both Apple and Android smartphones connected to the UV dosimeter via Bluetooth. The smartphone application displayed a real-time UV index, real-time cumulative UV exposure, and historical data of daily UV exposure. At enrollment, the device participants were trained to use the dosimeter and select a daily UV dose threshold on the application. This threshold was customizable through the application and could be changed by the participant. Participants' daily UV exposure would reset to zero at midnight and, as it increases throughout the day, would be compared to the threshold they had set. With every further attainment of 20% of the daily UV dose threshold, the app pushes a smartphone notification (e.g., "You have reached [20%, 40%, 60%] of your daily UV dose"). Participants could also inform the smartphone app if they were using sunscreen by

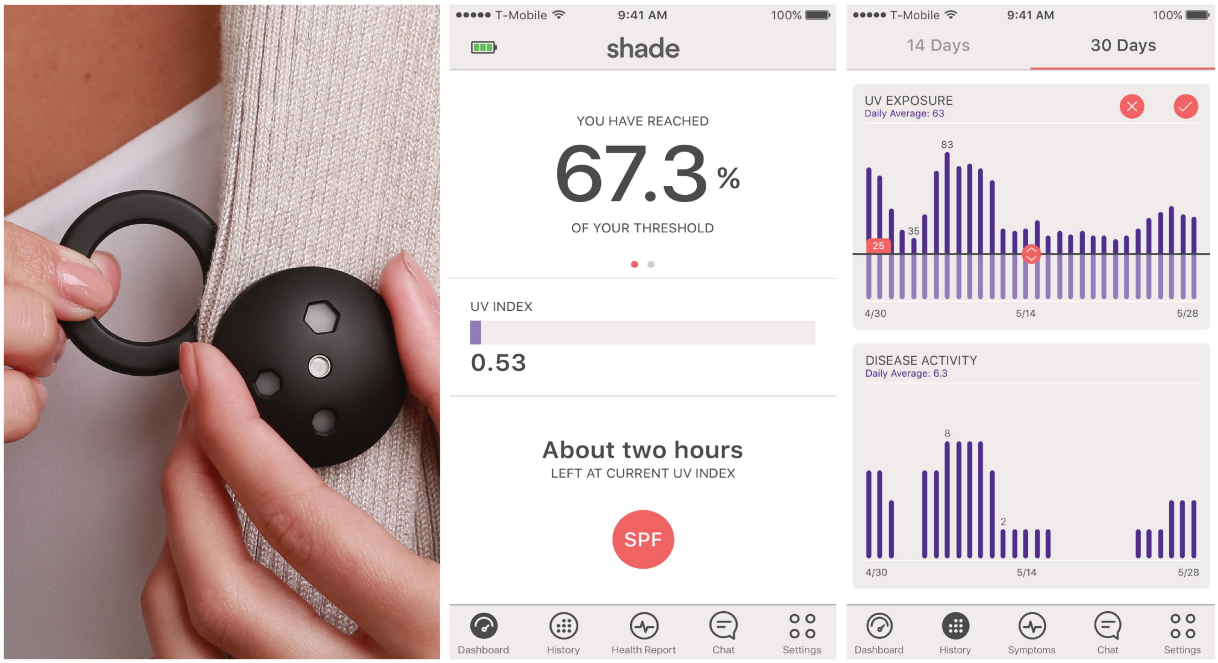

FIGURE 1
Wearable ultraviolet dosimeter, its magnet, and its companion smartphone application. The erythemaly-weighted UV measurements by the dosimeter were referred to as "UV index" for simplicity in the mobile application.

indicating the overall SPF but not the body location of the application. The cumulative UV exposure would be divided by the sun protection factor (SPF) during the two hours following sunscreen application before being added to the daily UV exposure (17).

Safety assessments

Safety assessments included monitoring of adverse events related or possibly related to the device or sun exposure experienced within the study period.

Efficacy assessments

A single, blinded dermatologist counted AKs and NMSCs on sun-exposed areas (scalp, face, hands) at enrollment and at each subsequent visit (3 months after enrollment and 6 months after enrollment). Pictures of every lesion and its locations were recorded. AKs may manifest clinically as keratotic macule(s) or papule(s) on an erythematous base. To ensure that only new AKs or NMSCs after enrollment were counted, each lesion's location and picture were compared to prior lesions (AK or NMSC). The primary endpoint was the incidence rate of AKs at disenrollment compared to the intermediary visit. Secondary clinical endpoints included the incidence rate of NMSC at disenrollment compared to the intermediary visit. All AKs were treated and eliminated at the time of each visit with cryotherapy, ensuring an accurate calculation of the longitudinal AK incidence. All lesions suspected of being cancerous were biopsied, and a blinded pathologist confirmed the diagnoses. The dermatologist would surgically remove a cancerous lesion if a patient were diagnosed with it. Other secondary endpoints included scores on three NIH PROMIS 8-question surveys on anxiety, depression, and the ability to participate in social activities.

Data entry

Case Report Forms (CRFs) were filled out by participants, the study coordinator, and the dermatologist on paper. CRFs were monitored by the sponsor for completeness, consistency, and agreement with underlying medical records periodically during the study. During monitoring, the sponsor, however, did not know if a CRF belonged to an intervention or a control participant, minimizing the risk of influencing the outcome of the trial if it were to modify the CRFs.

Statistical analysis

We first compared all collected clinico-demographic features to identify imbalances between the control and intervention groups. All feature showing a difference between groups (p-value <0.2) was selected for the subsequent multivariate analyses, regardless of their potential association with AK or cancer (Table 1). These features were age ($p = 0.0001$) and gender ($p = 0.119$).

Incidence rates (IR) of AK and NMSC within 3 months intervals at the intermediary visit and disenrollment were calculated using a multivariate Poisson model controlled for age and gender. The incidence rate ratio (IRR) between groups was calculated using a longitudinal approach, comparing the changes in IRs between the intermediary visit and disenrollment in each group, and controlled

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TABLE 1 Demographic and clinical characteristics.

Characteristics	Control (*N* = 43)	Device (*N* = 49)	Total (*N* = 92)	*p*-value
Gender – no. of participants (%)				0.119
Male	24 (56%)	35 (71%)	59 (64%)	
Female	19 (44%)	14 (29%)	33 (36%)	
Mean age (SD) – yr	69 (7.0)	64 (10)	66 (9)	0.0001 (*)
Race – no. of participants (%)				n/a
White	43 (100%)	49 (100%)	92 (100%)	
Non White	0 (0%)	0 (0%)	0 (0%)	
Ethnicity – no. of participants (%)				0.494
Hispanic or Latino	0 (0%)	2 (4%)	2 (2%)	
Not Hispanic or Latino	38 (88%)	39 (80%)	77 (84%)	
Unknown	5 (12%)	8 (16%)	13 (14%)	
Fitzpatrick type – no. of participants (%)				0.429
Type 1	11 (26%)	19 (39%)	30 (33%)	
Type 2	27 (63%)	26 (53%)	53 (58%)	
Type 3	5 (12%)	4 (8%)	9 (8%)	
Education – no. of participants (%)				0.931
Did not complete college	5 (12%)	6 (12%)	11 (12%)	
Completed college	37 (86%)	42 (86%)	79 (86%)	
Unknown	1 (2%)	1 (2%)	2 (2%)	
Risk factor for skin cancer – no. of participants (%)				
Being diagnosed with a cancer at enrollment	4 (9%)	8 (16%)	12 (13%)	0.49
Current smoker	1 (2%)	1 (2%)	2 (2%)	1.000
Regular user of a tanning bed	1 (2%)	0 (0%)	1 (1%)	0.467

SD, standard deviation; no., number. All demographic characteristics were reported by the participant except for the Fitzpatrick skin type, reported by the clinical principal investigator. For categorical covariates, *p*-values were calculated using Chi-square tests (gender, education, and being diagnosed with skin cancer at enrollment) and Fisher's exact tests when the Chi-squared test requirement was not met (ethnicity, smoking status, skin type, use of a tanning bed). We used a Spearman *t*-test for the age.

for age and gender. The trial was designed for the null hypothesis that the efficacy of the UV dosimeter is less than 25% in reducing the rate of newly-formed AKs over 3 months in a population of 102 participants. Analyzing over 7,000 patient visits from January 31, 2013 to January 31, 2018 at the department of dermatology at Weill Cornell Medicine, we applied Monte Carlo simulations to determine that a 25% decrease in the number of AKs would be significantly observed (Student's *t*-test, $p < 0.05$; power ≥80%) across a population of 102 participants.

Results

Trial population

Between April 1, 2018, and July 31, 2018, 97 patients underwent randomization. 50 were assigned to the device group and received a Shade UV sensor and UV protection counseling. 47 were assigned to the control group and received UV protection counseling only (Figure 2). Skin type, defined by the Fitzpatrick scale (from 1 to 6) (18), was balanced between the device and the control group (Table 1). Gender, skin type, ethnicity, race, education, and known skin cancer risk factors were balanced in the two groups. The mean age of the participants was 66 years. Despite randomization, the participants in the device group were significantly younger than the participants in the control group by 5 years on average.

Safety

No adverse events were reported during the trial.

Efficacy

In Figure 3, we present the incidence rates for AK and NMSC at the intermediary visit (3 months after enrollment) and disenrollment (after summer, 6 months after enrollment). Six months into the intervention, when comparing the device group to the control group, we measured a non-significant 20% lower ratio of IRs of AKs (95% CI = [−41, 55%], *p*-value = 0.44) and a significant 95% lower ratio of incidence rates of NMSCs (95% CI = [33, 99.6%], *p*-value = 0.024).

Each PROMIS form has 8 questions rated from 1 to 5, for a combined score between 8 and 40. We found a significant relative decrease of 2.1 points (*p*-value = 0.010, 95% CI: −3.69, −0.50) in self-reported ability to participate in social events in the device group compared to the control group. We did not measure any difference in anxiety or depression.

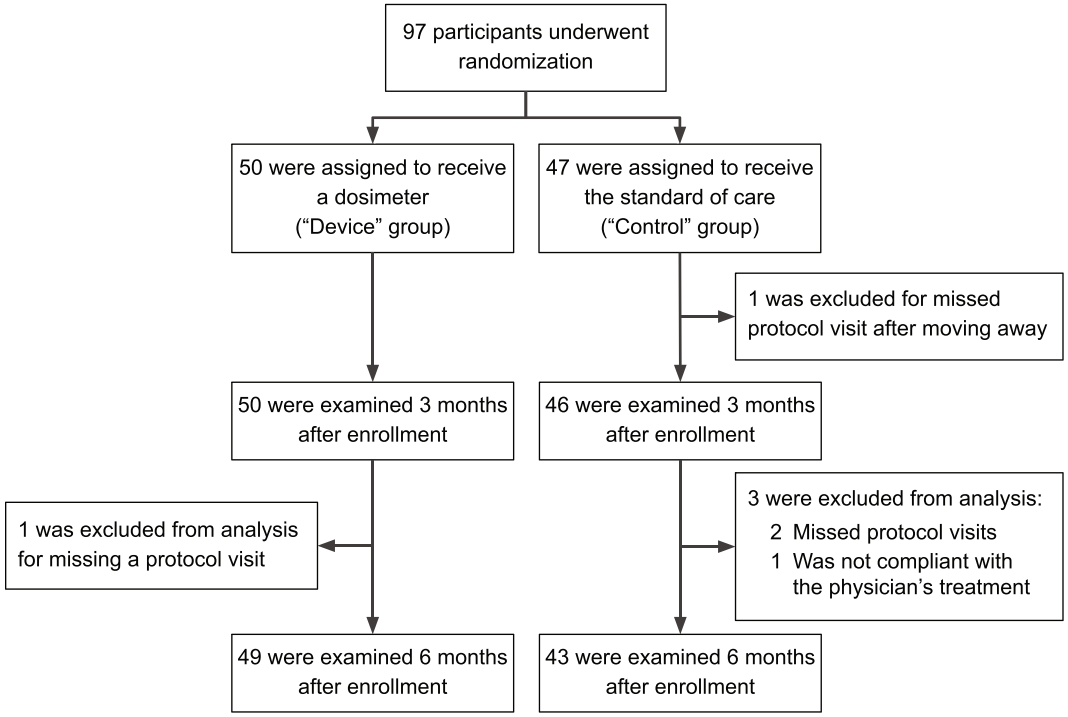

FIGURE 2
Randomization and analysis populations.

Subgroup	3 months Incidence Rate	6 months Incidence Rate	Incidence Rate Ratio (6 vs 3 months)	Relative Difference, % (95% CI)	p-value
Control group (n=43)					
AK	4.5	4.0	0.9		
NMSC	0.02	0.19	10		
Device group (n=49)					
AK	5.4	4.2	0.7	20.1 (-41.5 to 55.0)	0.44
NMSC	0.09	0.05	0.5	95.0 (33.0 to 99.6)	0.024 (*)

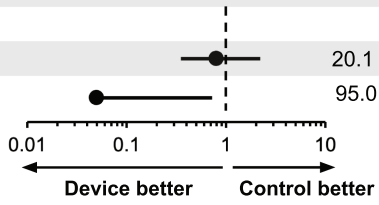

FIGURE 3
The incidence rate of new actinic keratosis (AK) and non-melanoma skin cancer (NMSC) at 3 and 6 months in the intervention group. The incidence rate ratio (the ratio of the changes in incidence rates in the two groups, IRR), relative differences (1 – IRR, multiplied by 100), and *p*-values are estimated from a Poisson model that includes all variables whose *p*-value is below 0.2 as covariates (gender and age). When the covariates gender and age were omitted from the model, the conclusions remained unchanged. The ratio of incidence rates of NMSCs at 6 months was significantly lower in the device group than in the control group (relative difference: 95.0%, *p*-value = 0.024). This benefit with the device was also observed for AKs but not significantly (relative difference: 20.1%, *p*-value = 0.44). In the supplementary information, a detailed analysis of Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC) is included. Given the higher prevalence of BCC compared to SCC, the findings might predominantly apply to BCC cases.

UV behavior

Figure 4A displays weekly device compliance and sunscreen use over time. As explained above, sunscreen-related data recorded in this study were self-reported. Therefore, we only report them as descriptive data. Weekly device compliance is approximated by registering UV once a week. Sunscreen usage was measured by the number of self-reported sunscreen applications through the mobile application. The device compliance remained above 75% for most of the summer and dropped below 50% after November, which is unsurprising given the low levels of UV in New York at that time. On average, participants reported applying sunscreen once or twice per week over the summer, a frequency markedly lower than dermatological recommendations. This deficiency in proper sunscreen application is likely to escalate the risk of developing skin cancer.

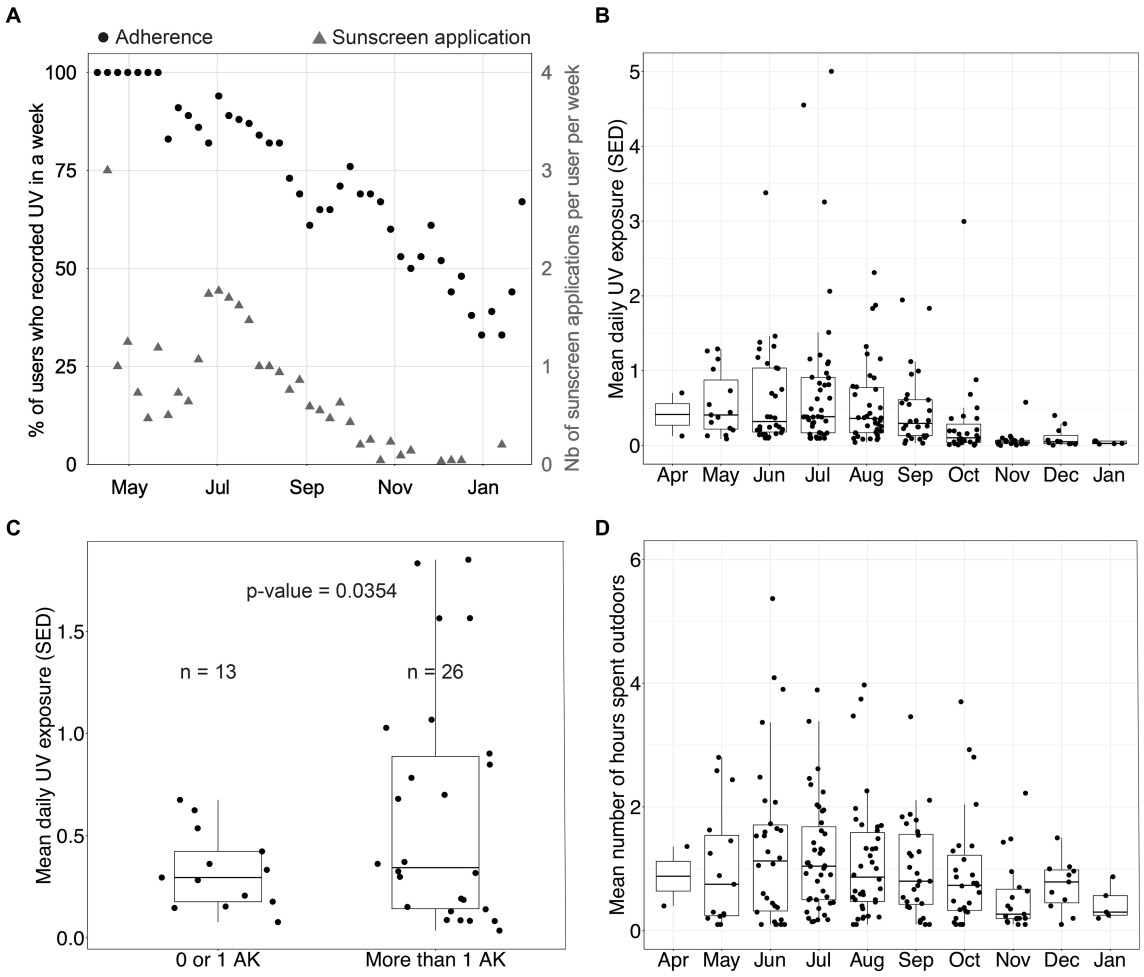

FIGURE 4
UV exposure data in the device group. **(A)** Percentage of participants who recorded ultraviolet (UV) exposure in a week and number of sunscreen applications per user per week. **(B)** Distribution of the mean daily UV exposure per month (one data point per participant per month). **(C)** Distribution of the mean daily UV exposure over August and September as a function of the number of actinic keratoses (AKs) measured at disenrollment among participants. Using Welch's 2-sample *t*-test, we found that the group with a low number of AKs had a mean UV exposure of 0.33 standard erythema dose (SED), and the group with a high number of AKs had a mean UV exposure of 0.60 SED (p-value = 0.0354). **(D)** Distribution of the mean daily time spent outdoors per month (one data point per participant per month).

Figures 4B,D show the mean daily UV exposure and the mean number of hours spent outdoors per month per participant. These were approximated by using the number of hours the sensor was recording UV exposure. Figure 4C clusters participants by the number of AKs diagnosed at disenrollment into two groups and displays the average daily UV exposure over August and September. Device group participants with more than one AK at disenrollment experienced a daily average of 0.60 SED across August and September. In contrast, participants with 0 or 1 lesion experienced a daily average of 0.33 SED across August and September ($p = 0.0354$, Welch's *t*-test). This data suggests that sub-erythemal chronic exposure beyond 0.34 SED, as measured on the trunk, may contribute to the appearance of lesions on sun-exposed skin. This observation gains additional significance when considering that the International Commission on Non-Ionizing Radiation Protection posits a daily exposure threshold of 0.3 SED to mitigate the enduring impact of UV radiation on the skin and eyes (14). Our analysis, however, does not control for potential confounding factors as this was not the primary endpoint studied. Therefore, additional evaluation is needed.

Discussion

This randomized clinical trial was designed to evaluate a novel sun protection strategy over 6 months overlapping one summer where real-time, accurate UV information with personalized alerts is provided to participants against the standard of care in UV education. It was powered to detect a 25% reduction in the incidence rate ratio of newly-formed AKs. Our trial was underpowered (92 completed the study vs. 102 participants to reach power), which explains why the 20% lower ratio of IRs of AKs in the device group compared to the control group is not significant. However, Figure 4C shows that, in the device group, participants with more than two AKs at disenrollment had a significantly higher average daily UV exposure than participants with less than one AK diagnosed at disenrollment ($p = 0.035$). The

non-significant decrease in the incidence of AK in the device group compared to the control group suggests that real-time measurement of UV exposure using a wearable UV dosimeter could help patients manage their UV exposure and complement standard prevention recommendations.

Additionally, we measured a statistically significant 95% lower ratio of incidence rates of NMSCs (p-value = 0.024, 95% CI: [33, 99.6%]) after controlling for all variables whose p-value was below 0.2 (age and gender). While these findings suggest that managing UV exposure using real-time and personalized UV information might be useful to prevent UV-related NMSCs, the strong reduction of NMSC incidence rate over only six months is surprising at first. Although we cannot rule out that the observed incidence rate ratio of NMSCs might occur by chance through random sampling, it is unlikely as the p-value of 0.024 indicates that there is only one chance in forty that our observation is a false positive. Also, given the low number of NMSC measured during the trial, the 95% confidence interval of the incidence rate ratio ranges from 33 to 99%, so we believe a larger trial would show an impact of the dosimeter on the NMSC incidence rate ratio closer to the effect size measured for AKs (20%). Finally, our observations are consistent with the current cancer biology and epidemiology knowledge which we detail below.

From an epidemiology standpoint, carcinogenesis arises from the accumulation of driver mutations over years or decades (19). However, the risk of NMSC, like several other cancer (20), increases exponentially with age (21). Therefore, as people age, the amount of cumulative UV exposure required to induce NMSC reduces exponentially to the point where only a few weeks of summer UV exposure may be necessary to induce NMSC. This exponentially increasing risk of cancer has been well explained by the percolation theory, which models human tissue as a network of elements whose probability of transitioning from non-cancer to cancer follows a sudden and dramatic increase as driver mutations accumulate (22). For these reasons, a drastic reduction in exposure to one of the most important driver mutations for skin cancer, UV exposure, could lead to an improvement in NMSC incidence over a few months when UV is at its highest (summer). Notably, our trial is not the first to measure an intervention's impact on skin carcinogenesis over a short period. In 2015, Chen et al. demonstrated through a randomized clinical trial that nicotinamide significantly reduces the incidence rate of NMSC over just 12 months in an elderly population (7). Finally, the two NMSCs reported at disenrollment in the intervention group occurred in participants who had ceased using the device just days after enrollment. This provides additional evidence of the impact of the wearable UV dosimeter on NMSC incidence.

From a molecular biology standpoint, our result is consistent with two established molecular mechanisms. The first one is related to p53 immunopositive epidermal keratinocytes, also called p53 "patches." These p53 patches follow UV exposure (23) and are associated with skin carcinoma, with 50% of all skin cancers expressing these mutations (24, 25). The prevalence of p53 patches increases with age until saturation when people reach the age of 60 years old (26). Using a murine model, Rebel et al. showed that squamous cell carcinomas (SCC) start appearing after p53 patch saturation, and that the SCC count grows exponentially with time when mice continue to be exposed to daily UV (27). Together, these data indicate that the percolation critical transition for skin cancer would occur when the skin is saturated with p53 patches. Once saturated with p53 patches, additional UV-induced driver mutations are exponentially more likely to lead to skin cancer. In addition, UV radiation induces immunosuppression, which in turn triggers a rapid development of NMSC (28). UV radiation can induce immunosuppression via various mechanisms, including direct immune cell activation and the activation of suppressor immune cells (29). Both UVA and UVB have distinct effects on immune cell function, and it is possible that seasonal reduction in UV exposure in our device group may have allowed for increased immune surveillance and NMSC clearance. Together, these biological mechanisms provide a possible rationale for the deceleration of NMSC development in an elderly population following UV avoidance, even after a few months.

Finally, we found a significant relative decrease of 2.1 points (p-value = 0.010, 95% CI: −3.69, −0.50) in self-reported ability to participate in social events in the device group compared to the control group. We did not measure any difference in anxiety or depression. This result suggests that real-time UV data and feedback increase participants' awareness of UV, while UV counseling leads participants to become overconfident.

There are several limitations to this study. First, all patients were at high risk of skin cancer, as they had been previously diagnosed with AKs, making them perhaps more sensitive to an intervention. Second, the number of NMSCs is low, so we could not perform stratified analyses by squamous cell carcinoma and basal cell carcinoma, as such analyses would have been underpowered. The breakdown of NMSC by type and body location is available in the supplementary information. Given the higher prevalence of BCC compared to SCC, our findings might predominantly apply to BCC cases. Also, the study population came from a single recruiting site in New York City, where the highest UVI ranges from 6 and 9 during the summer. It is likely that the impact of the device would vary depending on the UV of the recruiting sites, with a lower impact in low UV versus high UV regions. While this hypothesis needs to be confirmed in a multicentric study, our study provides a baseline estimate of the efficiency of a wearable dosimeter as a preventive tool in regions with similar UV exposure. In addition, over 85% of our participants completed college, twice the national average; although this could limit the generalization of our findings to the US population, we did not observe any significant impact of education on the impact of the device as the unadjusted incidence rates of NMSC at disenrollment in the device and control groups stratified by education. Besides, the population was followed for one summer only, leaving the possibility that the device's impact would be short-lived. UV dosimeters, like sunscreen, are seasonal tools mostly used when UV is at the highest, as shown in Figure 4A. Another limitation of our trial is that we do not know the UV exposure behavior in the control group, so we cannot establish that the device participants have lower UV exposure than the control participants. We chose not to survey control participants' UV exposure based on their recollection because these surveys are unreliable (30, 31). We also wanted a clean comparison to standard-of-care, and we were concerned that simply wearing the device could influence patients' UV behavior in the control group (32). Further, wearable UV dosimeters used in this trial measure UV exposure from a single location (the trunk), which is not necessarily representative of sun-exposed body locations (e.g., hands, face, or scalp). Selecting the trunk was a compromise between the forehead and the wrist. The first one would be stigmatizing and could hinder enrollment and observance. The second one is subject to higher within-subject variability and higher variability between subjects than

the trunk. Even though a dosimeter on the trunk underestimates UV exposure on the face (33), this underestimation is true for all participants, and the measurement is stable across participants, thus unlikely to bias our results.

Conclusion

Over the past few years, consumers have learned about their health by using sensors in wearable devices such as smartwatches. This clinical trial is the first to quantify the impact of an accurate wearable UV dosimeter on skin cancer prevention for an elderly population. Because of the small size of our trial, our findings need to be further validated through a larger prospective trial. However, the clinical advantages observed in this pilot study indicate that using wearable UV sensors could enhance traditional UV-prevention strategies. This approach can assist patients in managing and adjusting their UV exposure habits and could also be beneficial for younger individuals who may be more receptive to innovative wearable sensor technology. Wearable UV sensors may therefore offer significant potential in substantially lowering cumulative UV exposure throughout the lives of younger patients, thereby reducing their risk of developing skin cancer in later years.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Institutional Review Board of Weill-Cornell Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ED: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. PK: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. CD: Conceptualization, Formal analysis, Funding acquisition, Methodology, Writing – review & editing. SB: Funding acquisition, Writing – review & editing. MB: Data curation, Project administration, Writing – review & editing. KE: Formal analysis, Methodology, Supervision, Writing – review & editing. JZ: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. GV: Data curation, Investigation, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

ED, PK, JZ, and SB are shareholders of Shade, a startup manufacturing wearable UV sensors and the sponsor of this clinical trial.

The remaining 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.2024.1259050/full#supplementary-material

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Basal cell carcinoma—a clinical indicator of immunosuppression

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Background: Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are skin-derived carcinomas. The literature strongly connects SCC with acquired immunosuppression. Current data regarding BCC's association with immunosuppressive comorbidities are vague. The primary objective of this study was to establish the correlations between BCC and immunosuppressive comorbidities of patients. Materials and methods: We conducted a retrospective cohort study on 275 patients with a histopathological proven diagnosis of BCC from October 2019 to October 2023. Demographic data, BCC characteristics, and patients' comorbidities were analyzed. Comorbidities were classified as non-immunosuppressant and immunosuppressant (primary and secondary immunodeficiencies).

Results: We recorded 292 BCCs from 275 patients (142 females, 133 males), with equally distributed skin phototypes. 66.44% of the BCCs were detected in patients with various comorbidities ($p < 0.001$), of which 81.44% had immunosuppressive comorbidities ($p < 0.001$). All the immunosuppressive comorbidities were secondary and included diabetes mellitus (47.55%), history of solid or hematogenous cancer in the last 5 years (26.57%), chronic kidney disease (8.39%), chronic infections (9.09%), and antirheumatic immunosuppressive therapies (8.39%) ($p < 0.001$). BCC patients with immunosuppressive comorbidities did not develop larger BCCs ($p = 0.2577$) or more aggressive subtypes ($p = 0.4269$) and BCC did not arise earlier in their life ($p < 0.001$). BCC on the nasal pyramid was frequent in cancer history patients ($p = 0.008$). The ulcerated form of BCC is more confined to patients with chronic kidney disease ($p = 0.006$). Multiple BCCs are more frequent in patients with secondary immunodeficiencies ($p = 0.027$).

Conclusion: BCC represents a clinical indicator of secondary immunodeficiency. Further research should establish if cancer screening campaigns may be beneficial in BCC patients.

KEYWORDS

basal cell carcinoma, immunosuppression, skin cancer, diabetes mellitus, cancer, carcinoma

1 Introduction

Basal cell carcinoma (BCC) is a non-melanoma skin cancer (NMSC) and represents the most common neoplasm in humans. The lifetime risk of developing a BCC is 20–30% and the incidence rates are predicted to continue to grow at least for the following 15 years. Due to its indolent behavior, the cancer registries do not collect data regarding BCC (1, 2). Age is an independent risk factor for BCC, even if some BCCs may arise early in life. The incidence of BCC doubles from 40 to 70 years of age. Men have higher BCC rates (1.5:1), but distribution does not vary among genders in young patients (2). Most of the BCCs arise secondary to UVB exposure, with more than 75% of cases with DNA mutations-cyclobutane dimer formation (UV signature mutation) and C>T transitions at pyrimidines sites. Hedgehog signaling pathway constitutive activation is displayed in most BCCs. This pathway regulates cell type differentiation and proliferation and regulates the cell cycle (3–5).

Based on the recurrence risk, basal cell carcinoma is classified into low-risk (superficial, nodular, pigmented) and high-risk (morpheiform/ infiltrative, basosquamous, micronodular, and ulcerated) subtypes (6, 7). Chronic sun exposure is a well-established environmental risk factor for developing BCC, alongside intermittent sun exposure (2). Other acknowledged risk factors are fair skin phototypes, artificial tanning, arsenic exposure, ionizing radiation, ultraviolet A light phototherapy, and immunosuppression in organ transplant recipients (OTRs) (2). Surgical excision represents the gold-standard treatment for BCC. Other therapies include destructive treatments and the new emerging therapies for advanced BCC: the Hedgehog pathway inhibitors (vismodegib, patidegib, taladegib, sonidegib) and cemiplimab. Vismodegib and sonidegib are currently approved for patients with locally advanced BCC ineligible for radiation therapy or surgery (8, 9).

OTRs have an increased risk of developing keratinocyte cancer: BCC incidence is 10 times higher, and cutaneous squamous cell carcinoma (cSCC) incidence is 250 times higher than the general population. BCC does not display aggressive behavior in OTRs, unlike cSCC. OTRs develop cSCC at a younger age than the general population (10, 11). The relationship of cSCC to immunosuppression is generally understood (11), and that of BCC is still being elucidated among researchers.

In the last few decades, BCC has been highly studied in OTRs. However, organ-transplant-associated immunosuppression does not stand as the most frequent cause of impaired immunocompetence. While primary immunodeficiencies consist of rare, inherited conditions, secondary immunodeficiencies are more prevalent in daily practice and generally include chronic viral infections, solid and hematogenous malignancies, chronic kidney disease (CKD), diabetes mellitus (DM), asplenia, end-stage heart failure and treatment with immunosuppressive drugs (including biologics and long-term systemic steroids) (12, 13).

The main objective of this study is to establish the correlations between BCC and immunosuppressive comorbidities of patients. An additional purpose is to characterize patients' demographic data and BCC characteristics (size, localization, histopathological subtypes) in a southeastern European population.

2 Methods

2.1 Study design

This research represents a cross-sectional, retrospective study conducted at two academic centers from "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania. The study was conducted on patients with confirmed BCC diagnosis over 4 years (from October 2019 through October 2023). STROBE guidelines for cross-sectional studies were followed.

2.2 Study population and data collection

Electronic medical records were reviewed for patients with a biopsy-proven BCC diagnosis and included the following variables: sex, age at diagnosis, living environment, skin phototype, patient detailed history, tumor size, localization, and histopathological subtypes. Patients with Gorlin-Goltz syndrome, albinism, *Xeroderma pigmentosum,* and incomplete electronic medical records were not included in the analysis. Skin phototype was evaluated according to the Fitzpatrick scale (14).

Subjects were divided into immunosuppressed patients (IPs) and non-immunosuppressed patients (NIPs) upon their second diagnosis (comorbidity), if any. Solid and hematogenous malignancy history in the last 5 years, chronic viral infections, chronic kidney disease (CKD), diabetes mellitus (DM) (type I and II), asplenia, end-stage heart failure, and treatment with antirheumatic immunosuppressive drugs (including biologics and long-term systemic steroids) were considered immunosuppressive comorbidities.

The anatomical BCC sites were classified as follows: nose, forehead, cheeks, neck, ears, scalp, trunk, and extremities. The neck and face were highlighted as photo-exposed areas and the trunk and extremities as regions with intermittent sun exposure. BCC size was divided into three subgroups: small (<10 mm), medium (10–30 mm) and large (>30 mm). The BCC specimens were analyzed by an expert in dermatopathology and the classification was made upon the 2018 World Health Organization (WHO) guidelines (15). BCCs were divided into low-risk and high-risk recurrence subtypes based on their pathology features.

2.3 Statistical analysis

All investigative data were collected into a central database (Microsoft Excel). The statistical analysis was completed using the R software. Descriptive and graphical analysis was used to check assumptions of normality and linearity for all study variables. Clinical and demographic characteristics were compared between patients with BCC who had immunosuppressed comorbidities and those who did not.

The normality of the distributions was tested rigorously by the Shapiro–Wilk Test and the symmetry of the non-normal distributions was analyzed by looking at the skewness and kurtosis indicators. Regarding the age of the patients from both groups, the p-value is greater than 0.05, therefore, the distribution of the given data is not different from the normal distribution significantly. Moreover, by testing the normality of the data concerning the size of the carcinoma, it results that our data is not distributed normally ($p < <0.001$).

TABLE 1 Demographic characteristics of patients.

Total ($N = 275$)			NIPs	IPs	p-value
			132 (48%)	143 (52%)	0.5465[a]
Age, mean (SD)		65.24 (0.70)	62.38 (1.12)	67.88 (0.80)	<0.001[b]
Age group, n (%)	31–54	42 (15.27%)	32 (24.24%)	10 (6.99%)	<0.001[c]
	55–74	171 (62.18%)	79 (59.85%)	92 (64.34%)	
	>75	62 (22.55%)	21 (15.91%)	41 (28.67%)	
Gender, n (%)	M	133 (48.36%)	65 (49.24%)	68 (47.55%)	0.8733[c]
	F	142 (51.64%)	67 (50.76%)	75 (52.45%)	
Skin type, n (%)	2	142 (51.64%)	66 (46.48%)	76 (53.52%)	0.6885[c]
	3	133 (48.36%)	66 (49.62%)	67 (50.38%)	
Living environment, n (%)	Rural	138 (50.18%)	65 (49.24%)	73 (51.05%)	0.8582[c]
	Urban	137 (49.82%)	67 (50.76%)	70 (48.95%)	

IP, immunosuppressed patient; NIP, non-immunosuppressed patient.
[a]Proportion test.
[b]t-test.
[c]Chi-square test.

TABLE 2 Comorbidities, living environment, and gender distributions among IPs.

Comorbidity	Living environment		Gender		Total, n (%)
	Rural, n (%)	Urban, n (%)	F, n (%)	M, n (%)	
Cancer history	16 (42.11%)	22 (57.89%)	25 (65.79%)	13 (34.21%)	38 (26.57%)
Immunosuppressants	6 (50.00%)	6 (50.00%)	12 (100%)	—	12 (8.39%)
DM	37 (54.41%)	31 (45.59%)	32 (47.06%)	36 (52.94%)	68 (47.55%)
CKD	9 (75.00%)	3 (25.00%)	4 (33.33%)	8 (66.67%)	12 (8.39%)
Chronic infections	5 (38.46%)	8 (61.54%)	2 (15.38%)	11 (84.62%)	13 (9.09%)
	$p = 0.2799$[a]		$p < 0.001$[a]		$p < 0.001$[b]

CKD, chronic kidney disease; DM, diabetes mellitus.
[a]Fisher exact test.
[b]Chi-square-goodness-fit.

Differences between various subgroups were analyzed using an unpaired two-tailed t-test or Mann–Whitney U test for all continuous scale data between subgroups, where appropriate. Chi-square test (χ^2) with/ without Yates' continuity correction, Fisher's exact Test, or Fisher's exact test with simulated p-value (based on 1×10^8 replicates) were used, where applicable. They were also used in the subgroup analysis, where we assessed whether there were statistical differences between IPs and NIPs concerning sex, skin type, site of lesion, tumor size (<10 mm, 10–30 mm, ≥30 mm), and age groups (30–54, 55–74, >75). The Chi-Square Goodness fit Test was used to study if the distribution of comorbidities among IPs is uniform while proportions tests were used to examine the prevalence of a particular group/ feature. Linear relations with a p-value (two-sided) ≤0.05 were considered significant.

3 Results

This study included 275 patients with 292 BCCs, as follows: 262 patients had one BCC, 11 patients had two BCCs and 2 patients had four BCCs. The patients were divided by sex into 142 female and 133 male patients, with a F/M ratio equal to 1.067. Most of the patients (64.73%) had various secondary health conditions ($p < 0.001$) and among them, IPs represented 80.34% ($p < 0.001$). Gender distribution, living environment, and skin phototypes did not vary between IPs and NIPs. The average age of IPs (67.88) is higher than the average age of NIPs (62.38). IPs were more likely to present multiple BCCs ($p = 0.02706$, Fisher's Exact Test). Table 1 displays the demographic characteristics of patients.

The distribution of comorbidities among IPs (Table 2) reveals a non-uniform distribution ($p < 0.001$), DM (type II) being the most frequent comorbidity and representing almost 50% of the IPs. Patients undergoing immunosuppressive therapies were treated for arthritis (62.5%) and lupus erythematosus (38.5%) with oral steroids and immunosuppressant regimens. Patients with chronic infections had a history of hepatitis viruses (62.5%) and pulmonary tuberculosis (37.5%).

Patients with a cancer history represented almost 30% of IPs. Among these, breast cancer was the most prevalent (29.27%), followed by thyroid cancer (10.64%), lung cancer (9.76%) and prostate cancer (9.76%) (Figure 1). None of the patients had an HIV infection, asplenia, end-stage heart failure, or primary immunodeficiencies, nor did they undergo organ transplantation. All patients with CKD had a pre-dialysis stage. IPs comorbidities did not vary with respect to the

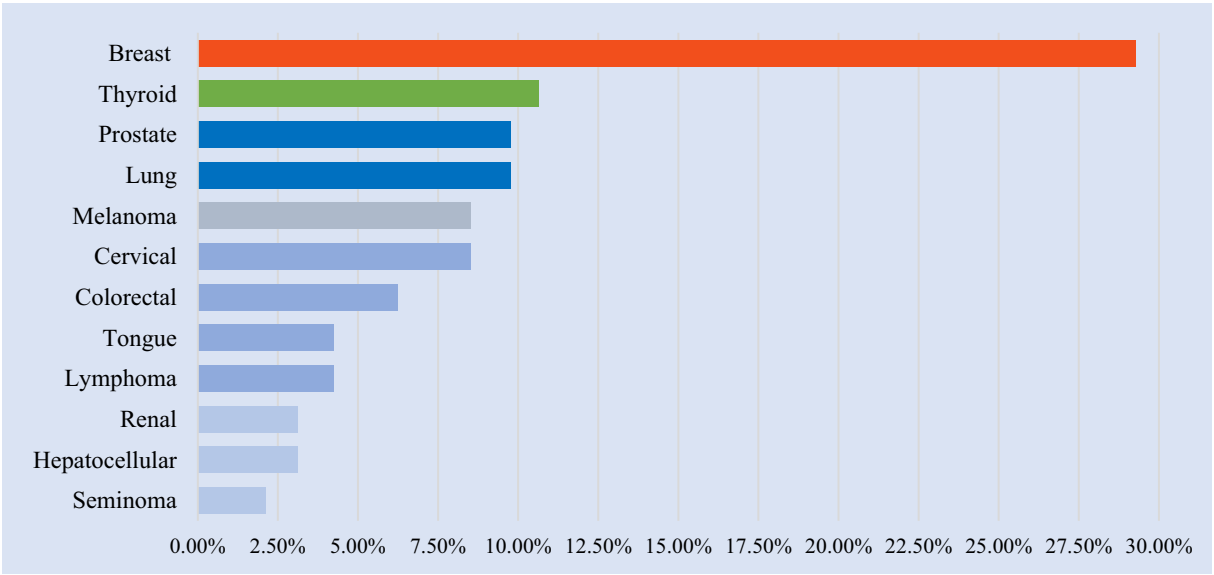

FIGURE 1
Distribution of cancer history among BCC patients. Breast, thyroid, prostate, and lung cancer represented the most encountered malignancies.

TABLE 3 Specimen characteristics in IPs and NIPs.

		Total (*N* = 292)	BCCs in NIPs (*N* = 134)	BCCs in IPs (*N* = 158)	*p*-value
Size (mm), mean (SD)		14.55 (11.15)	14.44 (10.90)	14.65 (11.39)	0.2577[a]
Size group (mm)	<10	92 (31.51%)	49 (36.57%)	43 (27.22%)	0.0806[b]
	10–30	175 (59.93%)	71 (52.98%)	104 (65.82%)	
	>30	25 (8.56%)	14 (10.45%)	11 (6.96%)	
Subtypes	Superficial	124 (42.46%)	59 (44.03%)	65 (41.14%)	0.1727[c]
	Nodular	58 (19.86%)	23 (17.16%)	35 (22.15%)	
	Ulcerated	47 (16.10%)	19 (14.18%)	28 (17.72%)	
	Pigmented	7 (2.40%)	1 (0.75%)	6 (3.80%)	
	Infiltrative	27 (9.25%)	14 (10.45%)	13 (8.23%)	
	Others	29 (9.93%)	18 (13.43%)	11 (6.96%)	
Localization area	Intermittently/not sun-exposed areas	119 (40.75%)	57 (42.54%)	62 (39.24%)	0.6514[b]
	Photo-exposed areas	173 (59.25%)	77 (57.46%)	96 (60.76%)	
Localization	Trunk	105 (35.96%)	47 (35.07%)	58 (36.71%)	0.3328[d]
	Limbs	14 (4.79%)	10 (7.46%)	4 (2.53%)	
	Nose	66 (22.61%)	31 (23.14%)	35 (22.15%)	
	Cheeks	54 (18.49%)	20 (14.93%)	34 (21.52%)	
	Frontotemporal	28 (9.59%)	15 (11.19%)	13 (8.23%)	
	Ears	7 (2.40%)	3 (2.24%)	4 (2.53%)	
	Scalp	10 (3.42%)	3 (2.24%)	7 (4.43%)	
	Neck	8 (2.74%)	5 (3.73%)	3 (1.90%)	

IP, immunosuppressed patient; NIP, non-immunosuppressed patient.
[a]Mann–Whitney test.
[b]Chi-square test.
[c]Fisher exact test.
[d]Fisher exact test with simulated *p*-value.

TABLE 4 BCC subtypes distribution.

BCC subtype	*n* (%)				
	Cancer history	Immunosuppressants	DM	CKD	Chronic infections
Infiltrative	—	1 (6.25%)	10 (14.71%)	1 (7.69%)	1 (7.14%)
Nodular	16 (34.04%)	1 (6.25%)	16 (23.53%)	2 (15.38%)	—
Pigmented	1 (2.13%)	—	5 (7.35%)	—	—
Superficial	17 (36.17%)	10 (62.5%)	22 (32.35%)	5 (38.46%)	11 (78.57%)
Ulcerated	10 (21.28%)	1 (6.25%)	11 (16.18%)	5 (38.46%)	1 (7.14%)
Other	3 (6.38%)	3 (18.75%)	4 (5.88%)	—	1 (7.14%)

CKD, chronic kidney disease; DM, diabetes mellitus.

TABLE 5 BCC localizations distributions among subgroups, *n* (%).

Localization	Cancer history	Immunosuppressants	DM	CKD	Chronic infections
Nose	14 (29.79%)	—	15 (22.06%)	1 (7.69%)	5 (35.71%)
Forehead	7 (14.89%)	2 (12.5%)	2 (2.94%)	2 (15.38%)	—
Cheeks	10 (21.28%)	4 (25%)	15 (22.06%)	4 (30.77%)	1 (7.14%)
Neck	—	1 (6.25%)	1 (1.47%)	—	1 (7.14%)
Ears	2 (4.26%)	1 (6.25%)	1 (1.47%)	—	—
Scalp	—	—	7 (10.29%)	—	—
Trunk	11 (23.40%)	8 (50%)	27 (39.71%)	5 (38.46%)	7 (50%)
Limbs	3 (6.38%)	—	—	1 (7.69%)	—

CKD, chronic kidney disease; DM, diabetes mellitus. p-value = 0.008063, Fisher exact test with a simulated p-value.

living environments. In regards to the gender of the patients, we found that female patients with BCCs more frequently presented a cancer history or underwent immunosuppressive therapies than men (Table 2).

Sample sizes did not vary among IPs ($p = 0.0958$, Fisher exact test) (see Table 3). BCC subtypes were evaluated among IPs ($p = 0.0064$, Fisher Exact Test with simulated p-value) as shown in Table 4. Nodular and superficial subtypes were the most frequent subtypes in patients with a history of cancer and DM patients. Patients with CKD presented superficial and ulcerated BCCs in equally high proportions. The superficial subtype remained the most prevalent for each group.

BCC subtypes also vary between patients with a history of cancer and the other IPs ($p = 0.0308$), as nodular and superficial subtypes are most relevant to this subset of patients (34.04 and 36.17%, respectively). Low-risk and high-risk histopathological subtypes did not vary between IPs and NIPs ($p = 0.4269$) nor among IPs ($p = 0.5819$).

A significant difference was found between BCC localizations in IPs, as shown in Table 5. Patients with chronic infections and DM most often had trunk BCCs and nose BCCs, while patients with CKD and following immunosuppressants most frequently presented truncal BCCs and cheeks BCCs. The nose was the most prevalent localization for cancer history patients, followed by the trunk.

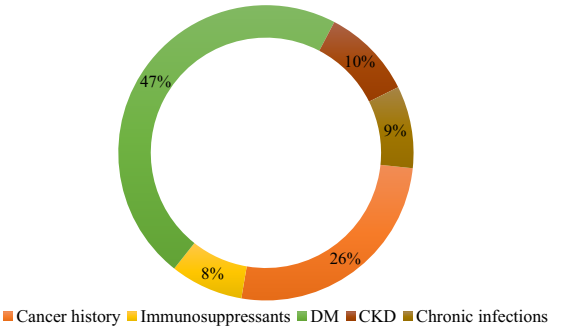

FIGURE 2
Comorbidities distribution among IPs. Diabetes mellitus type II was found in almost half of the IPs, a history of cancer in a quarter of the IPs, and each of the other three categories in approximately a tenth of the IPs. DM, diabetes mellitus; CKD, chronic kidney disease.

4 Discussion

Basal cell carcinoma is a skin cancer that arises from the basal keratinocytes. Its incidence rate increases with age (16). Most of the patients were between 55–74 years old, in line with the literature (17). More than 66% of BCC patients presented a secondary diagnosis (comorbidity). This finding can be explained by the majority of patients older than 55 years.

Interestingly, more than 80% of the BCC patients' comorbidities represented an immune-impairing disorder and were regarded as immunosuppressive comorbidities (Figure 2). Multiple BCCs (epitheliomatosis) were more frequent in IPs. This last finding was previously attributed to SCC (11), but not to BCC.

The medium BCC size (1.5 cm) did not vary significantly between IPs and NIPs, and BCCs between 10 and 30 mm were the most common in both groups. A study that compared clinicopathologic characteristics of BCC (including size) in 69 immunosuppressed renal transplant recipients (RTCs) did not find any differences from non-RTCs (18). Among IPs and NIPs, the superficial BCC was the

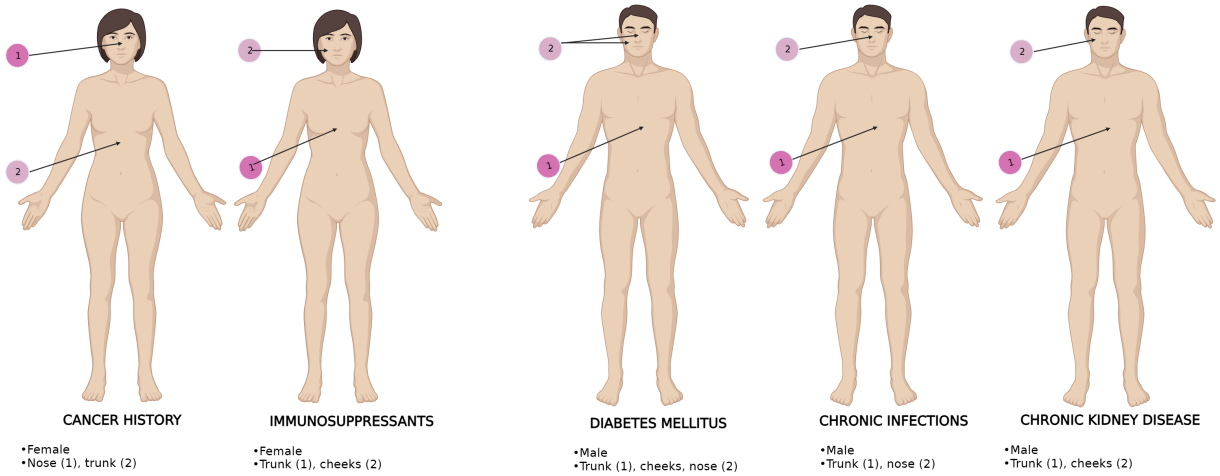

FIGURE 3
BCC anatomical distribution upon gender and comorbidities in IPs. The most frequent (1) and second most frequent (2) localizations are displayed. BCC localizations are represented for each comorbidity. The most representative gender is shown for each comorbidity.

most frequent, followed by nodular and ulcerated BCC. Additionally, as BCC usually arises in photo-exposed areas (2, 16), almost 60% of all specimens were distributed in these areas.

Diabetes mellitus represents a public health problem worldwide, with an incidence of 11.6% in Eastern Europe (19). It was the most frequent comorbidity among IPs (Figure 2). This observation is consistent with a study that revealed a high association between DM and BCC. Hyperglycemia and hyperinsulinemia were proposed as possible carcinogenesis factors, via reactive oxygen species (ROS) (20).

Nearly a quarter of IPs had a history of cancer. Likely, the neoplastic microenvironment may promote BCC carcinogenesis by inducing immune tolerance, recruitment of regulatory T cells, and suppression of NK cells (21, 22).

As regards BCC dimensions, they did not vary significantly among IPs, but the gender distributions, histopathological subtypes, and anatomical localizations (Figure 3) were different among IPs. Although the superficial subtype remained the most prevalent, the ulcerated subtype was equally high in patients with CKD. Patients with pre-dialysis CKD have a high risk of developing BCC (18). We presume high ulceration rates may be secondary to increased oxidative stress in CKD patients, who present high levels of chlorinated, nitrosative, and carbonyl stress, alongside the usual ROS (23). Additionally, the same particular neoplastic microenvironment (21) may be responsible for different pathology specimens in this subset of patients compared to all the other IPs.

5 Strengths and limitations

The large number of participants is a strength of this study. Unlike most studies, OTRs were not encountered in this BCC population and novel results regarding BCC characteristics in non-OTRs were obtained. Additionally, the correlations between BCC localizations and secondary immunodeficiencies represent a potential clinical innovation and may be particularly useful in daily practice. Finally, this study has its limitations as well. Since data were not collected in a predefined proforma, the precise interval between BCC appearance in healthy skin and comorbidities diagnoses was not available. The retrospective, observational analysis represents a limitation of the study.

6 Conclusion

Patients with BCC predominantly have immunosuppressive comorbidities. Immunosuppressed patients do not develop aggressive BCC subtypes and BCC does not arise earlier in their life, unlike patients with cSCC. BCC on the nasal pyramid is frequent in patients with a history of cancer. The ulcerated form of BCC is more confined to patients with chronic kidney disease. BCCs in patients with secondary immunodeficiencies contrasted with immunocompetent patients regarding gender, histopathological subtype, and localizations. Multiple BCCs were more frequent in patients with secondary immunodeficiencies. Hence, we consider BCC a clinical indicator of immunodeficiency.

Prospective studies regarding the spectrum of BCC in cohorts with neoplastic history and chronic kidney disease are necessary. Understanding the relationships between basal cell carcinoma and solid or hematogenous cancers may be the promoter of early cancer screening campaigns in BCC patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Colentina Clinical Hospital Board. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or

the participants' legal guardians/next of kin because the study was retrospective and non-interventional. Data were collected from an electronic database.

Author contributions

LS: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. MPe: Formal analysis, Methodology, Software, Writing – original draft. FS: Data curation, Formal analysis, Writing – original draft. AS: Data curation, Formal analysis, Writing – original draft. MPo: Visualization, Writing – original draft, Data curation. OS: Conceptualization, Methodology, Supervision, Validation, Visualization, Writing – review & editing.

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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.

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An overview of cutaneous squamous cell carcinoma imaging diagnosis methods

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Cutaneous squamous cell carcinoma, a type of non-melanoma skin cancer, is a form of keratinocyte carcinoma that stands as one of the most prevalent cancers, exhibiting a rising frequency. This review provides an overview of the latest literature on imaging methods for diagnosing squamous cell carcinoma (SCC) and actinic keratosis (AK). It discusses the diagnostic criteria, advantages, and disadvantages of various techniques such as dermatoscopy, skin ultrasound (US), *in vivo* and *ex-vivo* reflectance confocal microscopy (RCM), and line-field confocal optical coherence tomography (LC-OCT). These methods offer benefits including non-invasiveness, rapidity, comprehensive lesion imaging, and enhanced sensitivity, but face challenges like high costs and the need for specialized expertise. Despite obstacles, the use of these innovative techniques is expected to increase with ongoing technological advancements, improving diagnosis and treatment planning for keratinocyte carcinomas. Standardizing LC-OCT imaging algorithms for AK, Bowen's disease, and SCC remains an area for further research.

KEYWORDS

cutaneous squamous cell carcinoma, Dermoscopy, skin ultrasound, confocal microscopy, line-field confocal optical coherence tomography

1 Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most frequent form of cutaneous cancer with a high global growing incidence due to age (1). The clinical aspect of SCC is multiform and it varies according to histological subtype and tumor location (2). Usually an erythematous squamous plaque appears on photo-exposed areas on face, neck and forearms. Recurrence and metastasis are most commonly associated with a tumor diameter of more than 2 cm, thickness of more than 2 mm, perineural extensive invasion and poor differentiation in histology examinations (3). Most cases of cSCCs respond well to treatments such as surgical removal, photodynamic therapy, laser therapy, cryosurgery, and radiation. However, a small fraction, about 5% of patients, may have cSCCs that cannot be removed surgically, known as locally advanced (lacSCC) or metastatic (mcSCC) disease. Current research is focused on targeting the PD-L1/PD-1 axis to address lacSCC and mcSCC. Recently, Cemiplimab and Pembrolizumab received FDA approval for treating locally advanced and metastatic cSCCs, while ongoing studies are assessing the effectiveness and safety of Nivolumab and Ipilimumab for these conditions (4).

cSCC accounts for 20% of keratinocyte carcinoma (KC), with ratios of basal cell carcinoma (BCC) to cSCC ranging from 2 to 4:1. The European data on metastatic risk reveal a 2.1% cumulative incidence after a median follow-up of 15.2 months, with higher risk in males, older individuals, and certain anatomical locations (5).

Although comprehensive documentation of mortality rates is lacking, research findings indicate 5-year relative survival rates for localized cSCC, with percentages of 88% for women and 82% for men, and for advanced cSCC, with percentages of 64% for women and 51% for men (6).

Currently, biopsy and histopathologic examination serve as the gold standard for diagnosing skin cancer, but this approach has its drawbacks. Actinic keratoses (AK) often occur in multiple sites, making multiple biopsies impractical due to time, cost, and aesthetic concerns. Noninvasive imaging can guide biopsies effectively. Many dermatologists utilize dermoscopy as a rapid and low-cost way to assess lesions that look suspicious to the unaided eye. However, relying solely on clinical and dermoscopic data can be challenging, particularly for distinguishing AK from SCC. Large studies assessing diagnostic accuracy, especially in this context, are scarce. Dermoscopy also misses subclinical AK (7).

Recent advancements like reflectance confocal microscopy (RCM), optical coherence tomography (OCT), and high-frequency ultrasound (US) enhance skin cancer diagnosis accuracy.

The purpose of this review is to provide an update on the literature regarding the main methods of imaging diagnosis for squamous cell carcinoma and actinic keratosis, to highlight the diagnostic criteria, and to present the advantages and disadvantages of these methods. An electronic search of the literature was conducted using PUBMED and SCOPUS databases, encompassing articles published between inception and February 2024. The following search terms were used: "cutaneous squamous cell carcinoma" and cutaneous squamous carcinoma and imaging diagnosis." Following the electronic search, bibliographies of included articles were reviewed and original articles and review articles were included.

1.1 Dermoscopy

Dermoscopy is a rapid and cost-effective method widely used by dermatologists to evaluate suspicious lesions and there is a growing evidence suggesting that dermoscopy improves early detection of skin cancer compared to naked-eye examination (7). Integration of dermoscopy into the diagnostic process also reduces the necessity for biopsies. However, dermoscopy is a subjective procedure requiring extensive training, posing a risk of misidentification of lesions.

Specific dermoscopic criteria for SCC, including keratin, scale, blood spots, white circles, white structureless zones, and perivascular white halos, have been established. For SCC, keratin and white circles exhibit diagnostic sensitivity and specificity rates of 79 and 87%, respectively (8).

Lallas et al. identified significant differences in the dermoscopic pattern of poorly differentiated SCC compared to well- and moderately differentiated tumors. White-colored criteria, including keratin, white circles, white halos, and structureless whitish areas, were associated with well- or moderately differentiated variants. Conversely, poorly differentiated SCC exhibited a predominantly red color due to dense vascularity, without keratin or other white-colored criteria.

The quantity and caliber of vessels were correlated with the differentiation grade. Tumors with vessels covering more than 50% of the lesion surface had a 30- to 120-fold increased likelihood of poor differentiation. The size of vessels emerged as a notable predictor of differentiation grade, with smaller sizes linked to a threefold higher probability of poor differentiation, whereas tumors with larger vessel sizes had an 83% lower likelihood of being poorly differentiated. Similar to a previous study, a central distribution of keratin proved to be a strong predictor of well-differentiated tumors (9).

In 2012 Zalaudek et al. proposed a progression model of AK into SCC *in situ* and invasive (10). The grading system for AK categorizes lesions based on their clinical and dermoscopic characteristics. Grade 1 lesions are clinically discernible but slightly palpable, displaying a red pseudonetwork pattern and discrete white scales under dermoscopy. Grade 2 lesions are thicker and easily visible and felt, featuring an erythematous background with white to yellow, keratotic follicular openings resembling a 'strawberry pattern'. Grade 3 lesions are extremely thick and hyperkeratotic, clinically evident, and may exhibit enlarged follicular openings filled with keratotic plugs or marked hyperkeratosis presenting as white to yellow, structureless areas. Dermoscopy shows high diagnostic sensitivity and specificity for classical AK (98 and 95%, respectively) (11). Pigmented AK often displays a superficial brown network surrounding keratotic follicles, occasionally with red pseudonetwork and scales, while lichenoid AK may resemble lentigo maligna with grey dots, grey-brown lines, and asymmetrical pigmented follicular openings (12).

Non-Pigmented Intraepidermal Carcinoma (Bowens' Disease, BD) is characterized by opaque, yellow to white scales, in addition to dotted and glomerular capillaries grouped in lines or clusters near the periphery (13). The diagnostic has a 98% sensitivity (14).

In Pigmented BD dermoscopic examination may reveal various structures, including thick, pigmented lines, brown spots, and/or structureless brown to grey regions (15). Alongside pigmented areas, pink, skin-colored, or white structureless regions, as well as coiled or dotted vessels, are commonly observed. An important diagnostic indicator for pigmented BD is the presence of radially oriented lines or dots arranged linearly at the periphery. Yang et al. identified two new dermoscopic signs: the double-edge sign, characterized by parallel pigmented edges at the lesion's periphery (seen in 30.1% of lesions) and clusters of brown structureless areas, typically found around the lesion's periphery (observed in 38.4% of lesions) (16).

In invasive SCC, vascular patterns are observed (linear-irregular and/or hairpin vessels) associated with indicators of keratinization (amorphous, structureless white to yellow areas or follicular openings with a targetoid appearance, characterized by an opaque, yellow center encircled by a white halo, named white circles) (10).

The various histological subtypes of SCC exhibit varying types and frequencies of vascular patterns and keratin clues.

Well-Differentiated SCC (Keratoacanthoma-type) is characterized by a central mass of keratin, appearing as an amorphous, structureless, white to yellow keratotic area, surrounded by elongated telangiectasias, described as linear, dull, red vessels with a large caliber and few branches. A polymorphous pattern including hairpin and dotted vessels may be also seen.

In a prospective study conducted by Phyne et al., 100 cases of keratoacanthoma (KA) and 410 cases of invasive SCC were analyzed. The study found that branching vessels were more common in KA compared to invasive SCC. However, the presence of pink within the

tumor and the distribution of central versus peripheral tumor vessels were not identified as useful diagnostic features for distinguishing KA from SCC using dermoscopy (17).

Moderately differentiated SSC typically presents with peripheral hairpin vessels and diffuse, structureless, yellow to light brown, or white amorphous areas (keratin) that are often accompanied by extensive, variable areas of ulceration. Additional significant criteria include targetoid-appearing hair follicles (white circles), white, diffuse, structureless areas, masses of keratin interspersed with blood spots, and ulceration. The diagnostic sensitivity for keratin (structureless, white to yellow areas) has been reported to reach 78.7%, and the diagnostic specificity of the white circles is 86.9% (8).

Poorly differentiated subtypes frequently show no keratinization at all. Rather, they are identified by a variety of polymorphous vascular patterns, which include small-caliber linear vessels, hairpin vessels, or glomerular vessels against a reddish background. Occasionally, structureless white areas may be visible at the periphery, and these can be a crucial diagnostic indicator (12).

The occurrence of pigmented SCC (PSCC) varies significantly, with reported rates ranging from 0.01 to 7% of all SCCs in English literature. In his study, Corneli et al. highlight the specific features of PSCC, such as blue areas and linear polymorphous vessels around a hyperkeratotic region, also bluish diffuse pigmentation with central ulceration. Additionally, PSCC may exhibit dermoscopic features resembling those of melanocytic lesions, such as radial brown streaks and globules (18).

Dermoscopy reaches 79% sensitivity and 87% specificity in the diagnosis of SCC (19).

1.2 US

Skin ultrasound (US) is proven to be of assistance in evaluating size, thickness, tumor vascularization, relation with neighboring vascular structures and invasion. This information is essential before surgery for choosing the type of incision and evaluate conservative treatment options. Based on US characteristics (size, thickness, hyperechoic spots, posterior amplification and Doppler pattern) Chen Zt et al. demonstrated the value of HFUS in differentiating high risk basal cell carcinoma (BCC) and SCC (20). Another US difference between BCC and SCC is the disposition of the neovascularization. In SCC, the vascular pattern is increased diffusely throughout the mass, unlike BCC where the vascularization is less prominent and often located in the lower part of the lesion (21).

A study conducted by Bergón-Sendín M et al. on a group of 40 patients with SCC following a treatment with Methotrexate found positive correlation between ultrasound and histological diameter thickness evaluation (22). US utility in differential diagnosis between SCC, actinic keratoses and Bowen disease was evaluated by Zhu AQ et al. in a retrospective study of 160 patients. US characteristics for actinic keratoses were regular surface and irregular base. For Bowen disease, the US characteristics were crumpled surface and layer involvement confined by epidermis. For *in situ* SCC the US characteristics described were concave surface stratum corneum detachment, irregular based border and convex surface (23).

Keratoacanthoma are tumors that can be distinctly described through clinical examination and histopathology. Differentiating to SCC remains a controversial subject (24). The most common variant of keratoacanthoma is the solitary type with irregular shape, variable dimension and a characteristic evolution that can be divided in a proliferative, stationary and regressive phase (24–26). On US imaging keratoacanthoma is a hypoechoic lesion with relatively good definition, homogenous pattern, with hypoechoic stroma and a hyperechoic keratin crater (26).

1.3 Confocal microscopy

In vivo reflectance confocal microscopy (RCM) is a non-invasive diagnostic technique that makes several high-resolution two-dimensional images at various skin depths (from the stratum corneum to the papillary dermis). In order to increase diagnostic precision for both melanocytic and non-melanocytic cutaneous lesions as well as certain non-neoplastic disorders, RCM is being used more and more in clinical practice (27).

RCM has proven its usefulness in differentiating between invasive and *in situ* SCC. Manfredini M et al. propose the following criteria for invasive SCC: presence of erosion/ulceration, architectural disarrangement, speckled nucleated cells in the dermis, and absence of hyperkeratosis (28). The most described RCM aspects found in SCC are: scale, hyperkeratosis, parakeratosis, architectural disarray in stratum granulosum, atypical honeycomb pattern in stratum granulosum, atypical honeycomb pattern or architectural disarray in stratum spinosum, round nucleated cells, dilated blood vessels, increased number of blood vessels, nest-like structures in superficial dermis, pleomorphic nucleated cells in superficial dermis (29).

The RCM of *in-situ* SCC resembles an unusual honeycomb pattern, with non-confluent spindle-shaped cells and delicate dendritic branches penetrating the suprabasal epidermis, which is consistent with Langerhans cells. Furthermore, numerous bright dermo-epidermal junction (DEJ) -edged papillae are present, primarily along the margin of the lesion. These papillae are tiny, spherical, and have enlarged interpapillary gaps (30).

According to Peppelman et al. the diameter of blood vessels and the number of blood vessels visualized with RCM is increased in the case of AK and SCC compared to healthy skin, being higher in the case of SCC (31).

RCM has proven useful in differentiating actinic cheilitis (AC) from SCC. Lupu M et al. propose the following characteristics for AC: atypical honeycomb pattern and the presence of target cells in the epidermis (32). By preventing needless biopsies, particularly in lesions with persistent residual postinflammatory erythema, RCM may be a useful tool in the diagnosis of *in situ* SCC and in tracking the effectiveness of nonsurgical treatment (33).

Ex-vivo confocal microscopy was created to help Mohs surgery by providing a quick perioperative evaluation of the surgical margins in addition to enabling prompt identification of recently removed tissues. As *ex-vivo* confocal microscopy determines residual tumour tissue more quickly than histopathologic evaluation of frozen sections, it may be a useful and expedient substitute for traditional Mohs surgery. Additionally, it prevents material waste that could result in sections that run the risk of significant degradation for the future examination using conventional pathology and enables digital sectioning of the specimens without causing injury to the tissue (34).

A relatively new technique is *ex vivo* fluorescence confocal microscopy (FCM). This allows the evaluation of the tumor and the

resection margins directly in freshly excised tissue, with a resolution comparable to histology, but in a shorter time. Characteristics such as fluorescence, tumor silhouette, keratin pearls (ie, concentric laminated low fluorescent whorls of keratinized squames), nuclear pleomorphism (ie, variation in size, shape, and fluorescence of the keratinocytes), and keratin formation can categorize SCC as being well, moderately, or poorly differentiated (35).

1.4 Line-field confocal optical coherence tomography

Line-field confocal optical coherence tomography (LC-OCT) is a novel noninvasive technique for skin imaging that combines the advantages of optical coherence tomography (OCT) and reflectance confocal microscopy (RCM) in terms of spatial resolution, penetration depth, and image orientation. LC-OCT achieves superior resolution (~1 µm) compared to OCT and greater penetration depth (~500 µm) than RCM. Additionally, LC-OCT enables the simultaneous generation of vertical and horizontal images in real time (36).

Using LC-OCT, Ruini et al. visualized AKs and their main histopathological features. The sample size of AK subtypes was limited, but they observed the flattened rete in hypertrophic AKs, thinned epidermis in atrophic AKs, and full-thickness keratinocyte dysplasia with rounded contours in bowenoid AKs. In early AKs, dermoscopic structureless red areas interrupted by follicular openings corresponded to dilated and tortuous hyporeflective vessels in the superficial dermis and hyperreflective follicular hyperkeratosis.

Within BD, the thickened epidermis is characterized by enlarged, atypical keratinocytes forming round contours throughout all layers, termed the bowenoid pattern.

In both BD and AK, the dermoepidermal junction (DEJ) appeared well-preserved, presenting as a distinct darker band separating the basal keratinocytes from the bright dermal collagen.

SCC presented disorganized clusters of large polygonal cells with irregular shapes, accompanied by round, bright, homogeneous structures indicative of horn pearls. When tumor strands and masses were apparent, the dermis showed signs of elastosis and collagen changes along with increased and irregular vascularization (including dilated arteries and neoangiogenesis). LC-OCT aids in accurate classification of keratinocyte carcinoma subtypes, achieving a 100% correct classification rate (37).

While LC-OCT offers benefits in direct navigation and cellular resolution imaging, it may miss deeper layers in hyperkeratotic lesions.

Ruini et al. demonstrated that based on the histological PRO classification of AK, LC-OCT can reliably assess the basal keratinocyte development pattern *in vivo* (38). PRO classification delineates different stages of downward extension of basal keratinocytes into the papillary dermis. Specifically, PRO I involves the "crowding" of atypical keratinocytes in the basal layer, PRO II entails their "budding" in round nests into the upper papillary dermis, and PRO III is characterized by "papillary sprouting," where spikes of atypical keratinocytes protrude into the dermis, thicker than the overlying epidermis (39).

Donelli et al. showed in their study that LC-OCT exhibited higher specificity and a slightly increased sensitivity compared to dermoscopy in diagnosis of skin carcinomas. LC-OCT showed superior capability in ruling out malignancy rather than providing a precise diagnosis (40).

In a study conducted by Cinotti et al., evaluations of AK and SCC by RCM and LC-OCT were compared. Both techniques showed a significant level of agreement, the majority of the tumors had an irregular epidermis, but LC-OCT provided a clearer picture of parakeratosis, dyskeratotic keratinocytes, and both linear and glomerular vasculature than RCM did ($p < 0.001$). In more than half of the cases, erosion or ulceration was seen using both techniques, and there was a significant level of agreement (41).

2 Discussion

By employing specific dermatoscopic patterns, it becomes feasible to differentiate SCC from other nonmelanocytic tumors. Moreover, the invasive progression of precursor lesions can be identified earlier and with increased certainty within the framework of a "progression model." Skin US has demonstrated its utility in assessing dimensions, thickness, tumor vascularity, proximity to adjacent vascular structures, and invasion. *In vivo* RCM is a non-invasive diagnostic method that captures high-resolution skin images at various depths, effectively distinguishing between invasive and *in situ* SCC. *Ex-vivo* RCM can rapidly identify residual tumor tissue, offering an efficient alternative to traditional Mohs surgery. LC-OCT enables simultaneous real-time imaging in both vertical and horizontal orientations, aiding in precise keratinocyte carcinoma subtype classification and offering greater penetration depth than RCM.

A summary of the main imagistic aspects identified in actinic keratosis, Bowen's Disease and invasive Squamous Cell Carcinoma are presented in Table 1 and some of the imagistic features of a well differentiated squamous cell carcinoma are illustrated in Figure 1. The patient's informed consent was obtained.

These novel approaches offer advantages including rapidity, non-invasiveness, comprehensive lesion imaging, remote diagnostic capabilities, and enhanced sensitivity. Nevertheless, their widespread adoption is hindered by factors such as high expenses, requisite expertise of operators and interpreters, anatomical constraints, and limited specificity. The utilization of these innovative techniques for diagnosing skin cancer is anticipated to rise as ongoing research refines their technology and diagnostic precision. The incorporation of clinical, dermoscopic, and imaging data improves the diagnosis and treatment planning for keratinocyte carcinomas. Further research is necessary to standardize line-field confocal optical coherence tomography (LC-OCT) imaging algorithms for actinic keratoses, Bowen's disease, and squamous cell carcinomas.

There are few review articles in the literature providing an overview of imaging diagnostic techniques in squamous cell carcinoma. In recent years, numerous imaging diagnostic techniques have emerged, increasing the specificity and sensitivity of diagnosis. In many cases, clinical and dermoscopic diagnosis are sufficient for a probable diagnosis, but additional techniques are needed to improve diagnostic accuracy. Moreover, to assess the size and depth of the lesion, supplementary techniques are required for surgical intervention planning. In the future, more diagnostic techniques with increased sensitivity and specificity, easy to use and cost-accessible, will certainly emerge, and an artificial intelligence program will be developed to integrate and analyze data from these techniques. The main strengths of the manuscript are: it

TABLE 1 Summary of the main imagistic aspects in actinic keratosis, Bowen's disease and invasive squamous cell carcinoma, advantages and disadvantages of each technique.

	Actinic keratosis	Bowen's disease	Invasive squamous cell carcinoma	Advantages	Disadvantages
Dermatoscopy features	Erythema-reticular vessels surrounding follicular openings, strawberry pattern, rosettes [11]	opaque, yellow to white scales, dotted and glomerular capillaries grouped in lines or clusters near the periphery [14]	amorphous, structureless white to yellow areas or follicular openings with a targetoid appearance, linear-irregular and/or hairpin vessels [11]	rapid and cost-effective; widely used by dermatologists; sensitivity and specificity rates of 79 and 87% for SCC [20]	subjective procedure; requiring extensive training
Ultrasound features	regular surface and irregular base [24]	crumpled surface and layer involvement confined by epidermis.[24]	concave surface, stratum corneum detachment, Irregular based border, the vascular pattern is increased diffusely throughout the mass[24]	essential before surgery for choosing the type of incision; evaluating the size and depth of tumors [21]	depends on the operator; subjective technique, time-consuming, requires a lot of experience, difficult in assessing concave areas, internal angle of the orbit, requires high-frequency probes especially for lesions under 1 mm.
Reflectance confocal microscopy features	atypical honeycomb pattern and the presence of target cells in the epidermis [33]	honeycomb pattern, with non-confluent spindle-shaped cells and delicate dendritic branches penetrating the suprabasal epidermis, numerous bright dermo-epidermal junction edged papillae [31]	hyperkeratosis, parakeratosis, atypical honeycomb pattern in stratum granulosum, atypical honeycomb pattern in stratum spinosum, round nucleated cells, dilated and increased number of blood vessels, nest-like structures in superficial dermis [30]	differentiating between invasive and *in situ* SCC; offers horizontal sections; evaluation of therapeutic effects [34]	time consuming, expensive method, offers an imaging depth less than 250 mm; requires a lot of experience, difficult in assessing concave areas
Line-field confocal optical coherence tomography features	flattened rete in hypertrophic AKs, thinned epidermis in atrophic AKs, full-thickness keratinocyte dysplasia with rounded contours in bowenoid AKs [38]	enlarged, atypical keratinocytes forming round contours throughout all layers [38]	disorganized clusters of large polygonal cells with irregular shapes, round, bright, homogeneous structures indicative of horn pearls, increased and irregular vascularization [38]	greater penetration depth (~500 µm) than RCM; aids in accurate classification of keratinocyte carcinoma subtypes, generation of vertical and horizontal images in real time [37]	may miss deeper layers in hyperkeratotic lesions, expensive technique, novel technique, that requires experience.

provides the main features of the each diagnostic technique, based on the most important references published in the literature, the advantages and disadvantages of each technique. The limitations of the manuscript: there is a limited depth on standardization. While the manuscript acknowledges the importance of standardizing LC-OCT imaging algorithms for AK, Bowen's disease, and SCC, it could provide more detailed insights into the specific challenges and potential strategies for achieving standardization. Another limitation could be the potential bias: depending on the selection and interpretation of the literature reviewed, there may be a risk of bias towards certain imaging techniques or approaches.

After an exhaustive study of the literature, we found relatively few studies on cutaneous ultrasound in squamous cell carcinoma. In this review, we included all the research we found and did not notice the presentation of the US diagnostic criteria for CSC, as well as the sensitivity and specificity of this imaging technique. If criteria were found for BCC (relatively well-defined tumors, with variable vascularization and with presence of hyperechoic spots) additional studies are needed among CSC. US patterns could be identified depending on the histological type and specific anatomical location of CSC. Also, we did not find studies that show the correlation between the histological thickness and US thickness, considering that the treatment is guided according to the tumor thickness. Being an invasive tumor both locally and at a distance, future perspectives could show the role of US in the loco-regional evaluation of the disease. In the case of superficial carcinomas, the response to topical therapy could be evaluated by measuring the tumor thickness before and after treatment.

In conclusion, among the diagnostic methods discussed in this article, we believe that significant progress has been made by confocal microscopy, both in diagnosing skin cancers and non-tumor pathology. However, the greatest potential to revolutionize

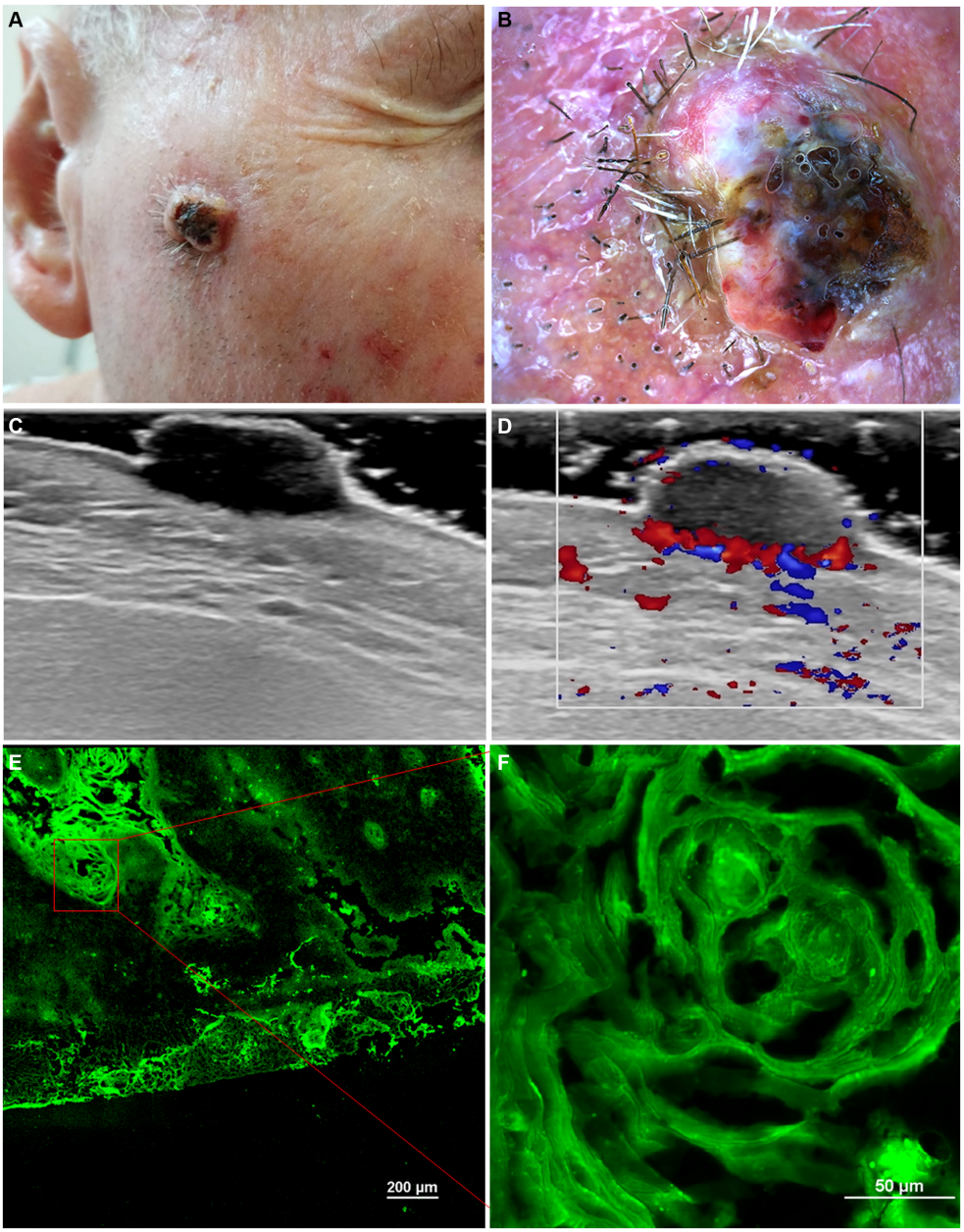

FIGURE 1
Clinical picture of well-differentiated keratinizing squamous cell carcinoma **(A)**. Dermoscopy shows white structureless areas, surface keratin, ulceration and looped vessels **(B)**. Ultrasonography (US) shows a hypoechoic lesion, imprecisely delimited, located at the level of the epidermis and dermis **(C)**. Doppler mode shows an increase in tumor and peripheral vascularity **(D)**. *Ex vivo* confocal microscopy with fluorescence (FCM) shows a highly fluorescent area with keratin pearls **(E, F)**.

dermatology and skin cancer lies with LC-OCT, both in terms of precise diagnosis and evaluating tumor margins for Mohs surgery. Nevertheless, there is a need for improvement in skin penetrability, cost accessibility, and easier-to-handle equipment.

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Conflict of interest

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Case report: Variability in clinical manifestations within a family with incontinentia pigmenti

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Diagnosing skin diseases in children can be a complex interdisciplinary problem. Incontinentia pigmenti (IP), also known as Bloch-Sulzberger syndrome, is a rare hereditary genodermatosis related to a mutation in the *IKBKG* gene. We present a family case of IP described from the perspective of various specialists, including dermatologists, oncologists, geneticists, dentists, and trichologists. The peculiarity of this case is the development of squamous cell carcinoma (SCC) on the shin of a 10-year-old female patient with IP. The patient had a positive family history: her mother and two sisters also displayed clinical manifestations of IP with involvement of skin, teeth and hair. The presence of exons 4–10 deletion in the *IKBKG* gene in all affected females was confirmed by detailed genetic evaluation using long-range PCR, and also high degree of X-chromosome inactivation skewing was demonstrated. The family underwent a comprehensive examination and was followed up for 2 years with successful symptomatic treatment of dermatologic manifestations. Recommendations were also made regarding dental and hair problems. By the end of the follow-up period, patients had stabilized, with the exception of a 36-year-old mother who developed generalized morphea. The study demonstrates the varying expressiveness of clinical symptoms among family members and emphasizes the importance of timely diagnosis for effective management of patients with IP.

KEYWORDS

incontinentia pigmenti, squamous cell carcinoma, dental abnormalities, hair, IKBKG/NEMO deletion, X-chromosome inactivation, family case report

1 Introduction

Incontinentia pigmenti (IP) is a very rare dominant disease, with an incidence of 1.2 per 100,000 births, affecting skin and its derivatives (teeth, hair, nails, sweat and sebaceous glands), as well as other ectodermal tissues (central nervous system) (1). IP is caused by mutations in the *IKBKG* gene located on the X chromosome at locus Xq28. The encoded NEMO/IKKγ protein plays an important role in the activation of the NF-κB signaling pathway involved in immunity, inflammation, cell proliferation, and apoptosis (2). Hemizygous variants with loss of IKBKG/NEMO function are lethal in males, while IKBKG/NEMO variants with partial suppression of protein function are observed in heterozygous females with IP (3), as well as in males with the mosaic form of the disease or XXY genotype (Klinefelter syndrome) (4).

The disease usually starts in a few days after birth and looks like a neonatal skin infection (1, 5). The acute inflammatory process tends to subside and the initial vesiculobullous rash is replaced by a verrucous stage in postneonatal period, then progresses to a hyperpigmented stage that lasts until adolescence, and finally, to a hypopigmented or atrophic stage in adulthood (1, 6). Teeth and hair are also most often affected from infancy and childhood. Dental abnormalities include hypodentia or oligodentia, tooth shape disturbance (conical dystrophy) (6, 7). Manifestation in the scalp region presents as scarring alopecia and is seen in 28% (8) to 70% of cases (9). Eye abnormalities occur in every third patient and often manifest as microphthalmia, optic atrophy, retinopathy, cataract, pseudoglioma, and retrolental fibroplasia. In 33% of cases neurological manifestations, such as convulsive syndrome, spastic paraplegia are observed; in 16% of cases developmental disability is detected (1, 8).

A rather rare event in IP is painful subungual tumors, which usually manifest after puberty (10). Single cases of multiple aggressive subungual SCC or SCC arising on the skin of patients with IP have also been described, mainly in adult patients (11–13). In this report, we presented a family with four cases of IP (mother and her three daughters) with very rare manifestation of the disease, SCC developing on the shin of the eldest daughter at the age of 10 years. The diversity of clinical features within this familial case and implications for management of the patients with IP is discussed.

2 Case presentation

A 13-year-old girl (P) was referred to a dermatologist due to skin lesions on the front of her right leg. It was known from the medical history the presence of erythematous areas and pustules on her skin at birth. By the 8th day of life, rashes arose on her limbs, back, scalp, then vesicles began to disappear with the formation of erosions. The geneticist suspected IP, and hormonal therapy (prednisone) and topical treatment (salicylic zinc) were prescribed. Papules were observed on the skin up to 1.5 years of age, and then only areas of depigmentation persisted.

At the age of 10 years, a rapidly growing hyperkeratotic nodular skin tumor appeared on the right shin. The firm nodule up to 2.5 cm in diameter with central hyperkeratotic masses, partially with hemorrhagic crust, fused with surrounding tissues and accompanied by periodic moderate itching. Six months later, wide excision of the nodule was performed with local tissue replacement of the defect. Histological examination revealed invasive well-differentiated keratinizing SCC (Figures 1A–D). A comprehensive analysis was performed to exclude tumor dissemination and the presence of metastatic lesions.

Two years after excision, the same area presented a linear rash distributed along Blaschko's lines, with grayish macules in the upper third, interrupted by star-shaped red-brown lichenoid plaques in the operated area. *In vivo* confocal laser scanning microscopy confirmed lichen planus with partial disruption of the epidermis, dyskeratosis and hyperkeratosis, irregular acanthosis, inflammatory infiltration, hypergranulosis, dilated vessels, and fibrosis (Figures 1E,F). Detailed phenotypic characteristics of P are presented on Figures 1G–P. The family history revealed the presence of characteristic skin defects, dental and hair abnormalities in other female relatives: mother and two sisters. Detailed examination was done for all affected family members.

A 34-year-old mother (M) presented in infancy with erythematous patches and pustules on the skin, later replaced by papules and vesicles. During the first year of life, she was periodically admitted to hospital with the following diagnoses: herpetic infection, erythema multiforme, and lichen planus. Our examination revealed rounded pigmented atrophic patches on the skin of the right shoulder, chest, and back, as well as linear areas of hypopigmentation with mild skin atrophy on the lower extremities. Moderate thinning of hair in the parietal region, and dental malocclusion were observed (Figures 2A–F). Obstetric history revealed five pregnancies: three ended in delivery, one in miscarriage at 12 weeks, and the fifth pregnancy was medically terminated.

A 7-year-old girl (S1) is the second child in the family. At birth, a widespread vesicular, erythematous rash was observed on the skin. Local therapy with antiseptic solutions was performed. By the age of 1 year, the rash had resolved, and only areas of hyperpigmentation persisted. At present, the parietal zone with sparse hair growth and mild dental malformations were observed (Figures 2G–J).

A 3-year-old girl (S2) is the third child in the family. At birth, she had a widespread vesicular, erythematous rash on the skin. Topical therapy was successful, but by 9 months of life, after remission, the vesicular skin rash reappeared. The whole process was wavy and the most severe compared to other affected members. On examination, "star-like" pigment spots were observed on the skin in the axillary region, trunk, groin area, shins and back. The hair loss on the vertex of scalp was obvious. The most pronounced dental malformations compared to other family members were identified. The absence of temporary teeth resulted in a change in facial configuration by reducing the height of the lower third of the face. Compensatory contraction of facial muscles led to functional remodeling, which could be observed when smiling or talking, and the habit of placing the tongue over the area of the dental defect was developed. Orthopantomogram reveled the absence of several deciduous teeth (lactodentia; Figures 3A–G).

Detailed examination of scalp and hair conditions of the family members demonstrated the loss of follicular orifices. White peripilar dots were identified in S1 and S2, but not in M and P, indicating stabilization of the scarring process with age. Both S1 and S2 exhibited lamellar microshealing characteristic of the subacute stage of squamous lichen planus, and the proximal portions of the hair shafts had a boomerang-like bend. Discoloration, honeycomb pigmentation,

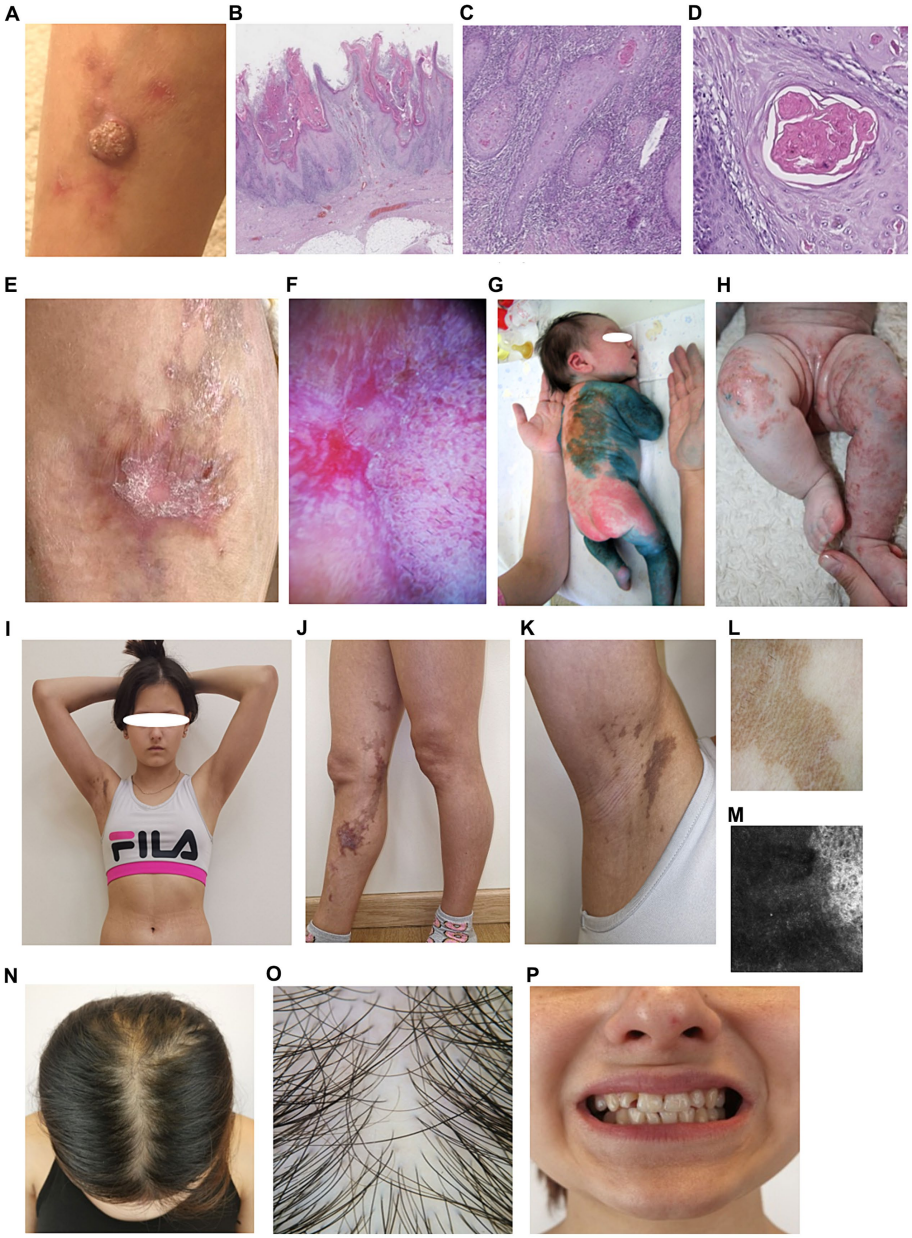

FIGURE 1
Phenotypic characteristics of the proband P. **(A)** Hyperkeratotic nodule on the skin of right shin. **(B)** Skin area with growth of an exophytic mass, epidermis with marked hyperkeratosis, verrucous papillomatosis and acanthosis, linear lichenoid lymphocytic infiltration (hematoxylin and eosin), x80. **(C)** Invasive complexes of neoplastic epithelium in the dermis, with dense lymphocytic infiltration, x200. **(D)** Concentric aggregations of the neoplastic epithelium with central keratinization, impaired maturation, moderate cytologic atypia, x350. **(E)** Current state of the area of operation. **(F)** Dermatoscopy reveals Wickham streae (left) and pseudo follicular openings surrounded by violaceous halo (right), typical for hypertrophic lichen ruber planus. **(G,H)** First days of life. **(G)** Erythematous rush. **(H)** Vesicles and erosions on the patient skin. **(I–K)** Present state. **(I)** Overview. **(J,K)** Areas of hyperpigmentation involving inner leg and armpit. **(L)** Homogenous brown pigmentation is visible under dermoscopy (Dermlite 4, polarized mode). **(M)** Confocal microscopy reveals uneven melanin accumulation in hyperpigmented spots. **(N)** Parietal hair thinning, brownish discoloration of the scalp in previously affected areas. **(O)** Areas of scarring alopecia, single hairs predominate (Dermlite x 10, polarized mode). **(P)** Dental malformations.

and single hair growth were characteristic for all females; M had an increased number of vellus hairs on the vertex, indicating miniaturization of hair follicles, possibly due to their own sensitivity to androgens (Figures 3H–K).

Genomic DNA isolated from peripheral blood was used in genetic studies. A long-range PCR was performed with primer pairs specific for the *IKBKG* gene and the *IKBKGP* pseudogene, as previously described (14). The deletion of exon 4–10 of *IKBKG* gene was present in mother and three daughters, while absent in father and healthy control (Figures 4A,B). To examine the skewing of X-chromosome inactivation (XCI), the methylation pattern of the repeat region $(CAG)_n$ in exon 1 of the *AR* gene was investigated in the affected females using a HUMARA assay (15). All females had unbalanced inactivation of the X chromosome (> 90%) in peripheral blood leukocytes with the following values: P and M had 98%, S1 had 96%, and S2 had 99% of skewing (Figure 4C).

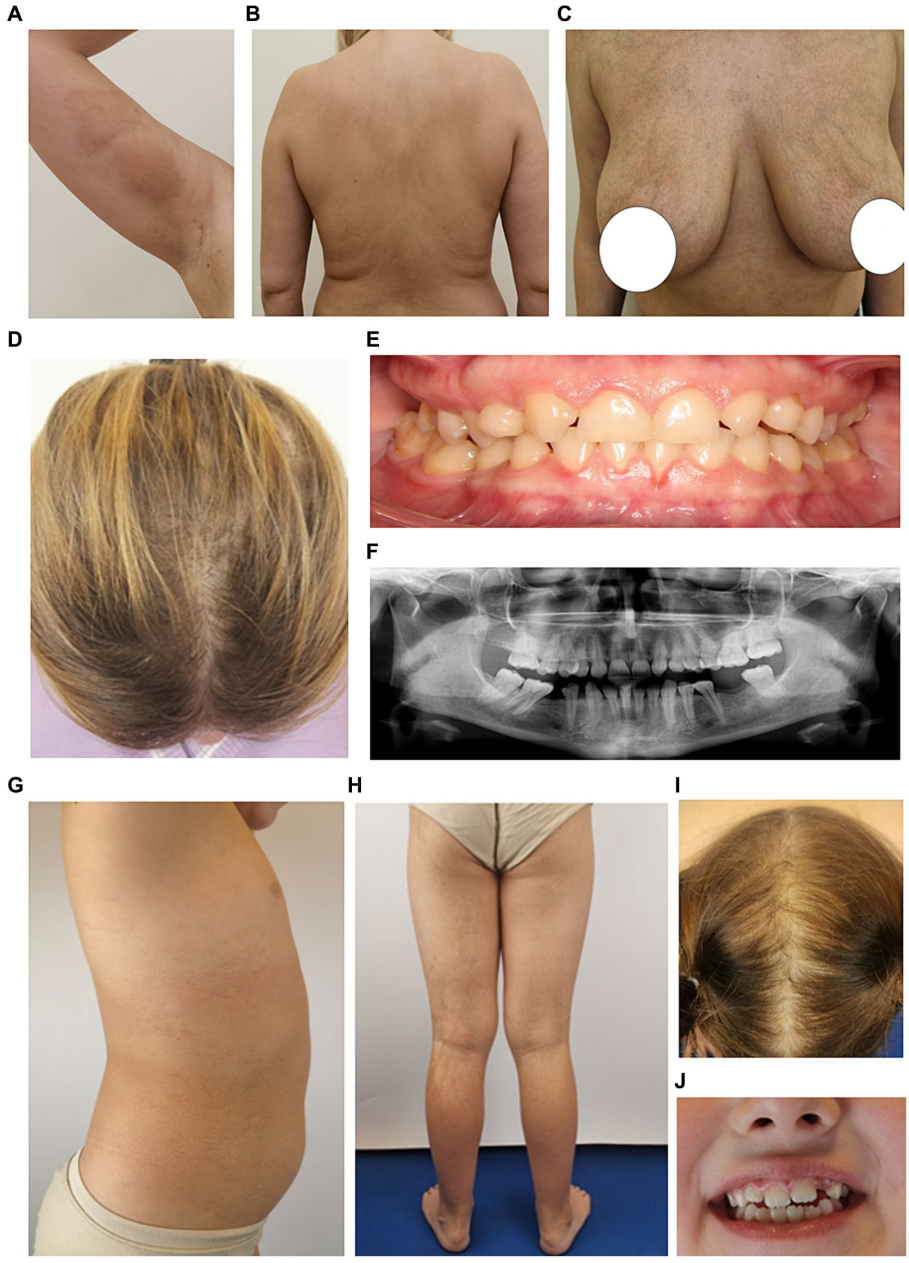

FIGURE 2
Phenotypic characteristics of the proband's mother M **(A–F)** and sister S1 **(G–J)**. **(A–C)** Areas of irregular pigmentation in M. **(D)** Parietal zone with hair thinning. **(E)** Dental malocclusion (adentia of both upper lateral insicors and also two molars on the lower jaw are missing). **(F)** Orthopantomogram shows anomalies in the positioning of individual teeth, adentia of both maxillary lateral insicors and two molars on the lower jaw. **(G,H)** Areas of hyperpigmentation on the trunk and legs in S1. **(I)** Parietal zone with sparse hair growth. **(J)** Mild dental malformations.

The family was consulted and then followed-up by multidisciplinary team for the last 2 years. Recommendations on symptomatic and compensatory treatment aimed at stabilization of pathological processes were given. To solve skin problems of P, topical treatment of lichen planus with clobetasol propionate for 2 weeks with further tapering was prescribed. Soon, the rashes smoothed and faded, but did not disappear completely, so emollients were recommended as supportive therapy. Further, the flattening of the lichen planus lesions and partial regression of hyperpigmented papules was noted. For M, S1 and S2 having minor skin lesions, supportive care with sun protection and emollients was recommended, as well as avoiding trauma and keeping the skin cool and dry. The status of S1 and S2 remained stable throughout the follow-up period. In a year and a half, M noted the appearance of multiple asymptomatic skin lesions that rapidly spread to the skin of the abdomen, upper and lower extremities, and the gluteal region. A diagnosis of generalized morphea was established. Systemic treatment with penicillin, pentoxifylline, bovhyaluronidaze azoximer was used to stabilize the disease.

To alleviate dental problems, M. was recommended prosthetics in the area of missing teeth, periodontal treatment and rehabilitation. The treatment of children with several congenitally missing teeth is

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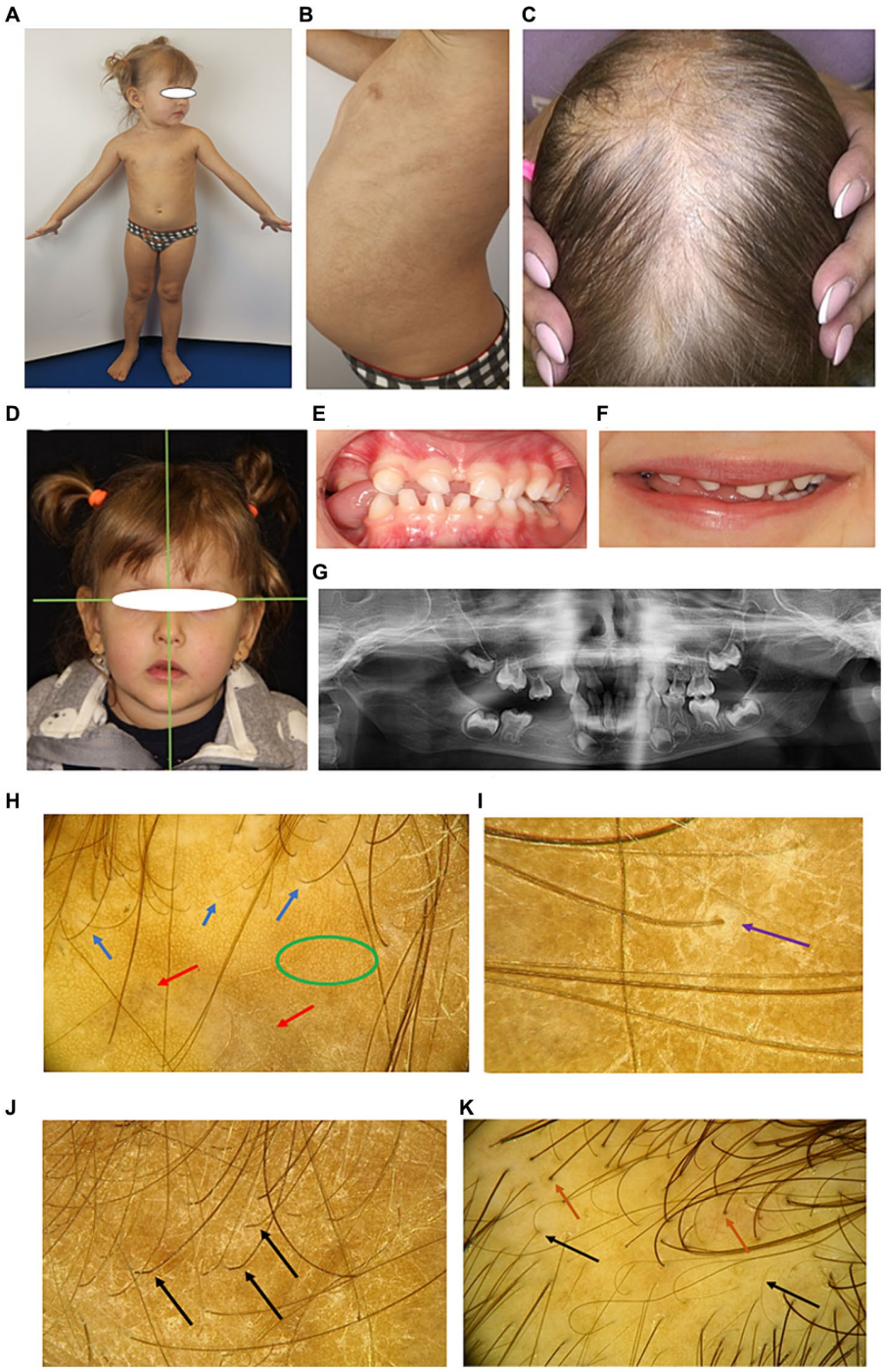

FIGURE 3
Phenotypic characteristics of proband's sister S2 **(A–G)** and trichoscopic hair evaluation of family members **(H–K)**. **(A)** Overall view. **(B)** Light brown linear, curved and "star-like" macules are preserved on the trunk. **(C)** Severe alopecia in parietal zone. **(D)** Compensatory tilt of the head to the left, corners of the mouth downwards, lips are not closed in the resting position. **(E)** Laying of the tongue between the teeth on the right side in the area of missing teeth. **(F)** The smile is asymmetrical, the tongue is inserted between the teeth on the right side. **(G)** Orthopantomogram reveals multiple tooth adentia. **(H)** Trichoscopy of the scalp of S1 and S2 demonstrates growth of mostly single hair, white peripilar dots (blue arrows), honeycomb-shaped pigmentation (green oval), and scalp discoloration (red arrows). **(I)** Keratinous perifollicular desquamation (purple arrow). **(J)** Boomerang-type hair bending in the proximal zone of growing single hair (shown by arrows). **(K)** A large number of single growing hair (brown arrows) and the presence of vellus hair (black arrows) on the scalp of M.

challenging, especially when combined with malocclusion, because growth and development of the oral structure must be considered at the same time. Individualized treatment plans for P, S1, and S2 with missing teeth were made based on a comprehensive assessment of age and the need to restore occlusal and chewing function, as well as esthetic requirements for tooth shape and alignment.

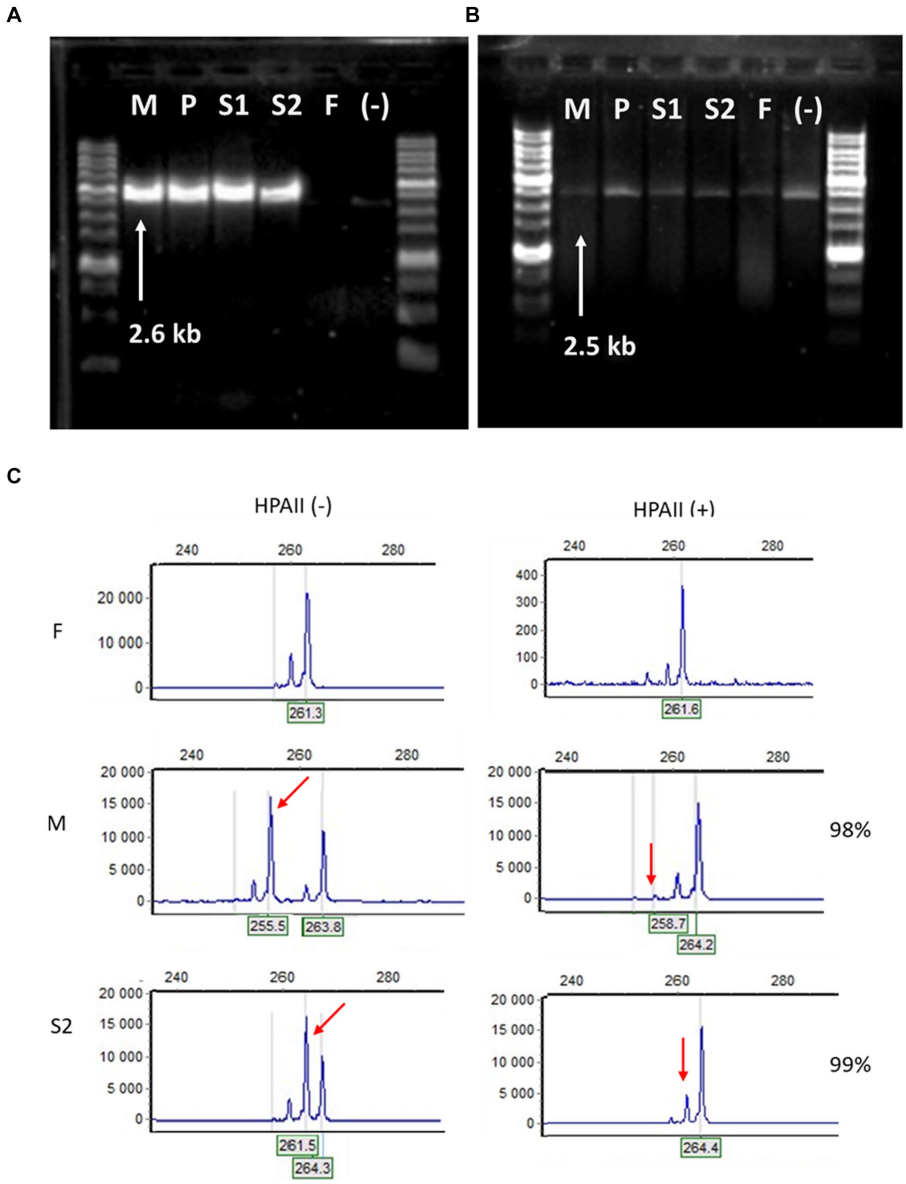

FIGURE 4
Molecular-genetic analysis. **(A)** Long-range PCR with *IKBKG* primer pair In2/JF3R revealed IP-specific 2.6-kb band in patient samples (M – mother, P – proband, S1 – sister 1, S2 -sister 2) and the absence of PCR-product in healthy people (F – father of the family and (–) – negative control). **(B)** In contrast, bands amplified with primers specific for *IKBKGP* (JF3R/Rev2) showed no appreciable specificity between patients and controls. **(C)** Fragment analysis of PCR products amplified from undigested HPAII (–) and digested HPA (+) DNA of F, M and S2. In the F DNA, one major peak decreases significantly after HpaII digestion. In the undigested M DNA, the two major peaks represent two alleles with different numbers of short tandem repeats at the *AR* locus, after digestion the short allele is practically disappeared (red arrow). The S2 DNA displays the preferential loss of the active father's (F) allele (red arrow), while the inactivated M allele is preserved.

To stabilize secondary scarring alopecia, betamethasone treatment was offered to younger daughters S1 and S2, as the scalp trichoscopy revealed mild perifollicular hyperkeratosis. This sign indicates the persistence of an active pathological process in the lesions. In the older family members, M and P, no signs of active hair loss were revealed, so they were offered hair transplantation or trichopigmentation to camouflage baldness.

3 Discussion

The penetrance of IP is 100%, but the expressiveness of clinical manifestations can vary widely between patients, even within the same family (8). When analyzing the clinical data of 381 patients from the IP Genetic Biobank, it was shown that erythematous-vesicular rash in the neonatal period is the most characteristic feature and occurs in 90% of patients. Transition to the verrucous stage within first year of life was observed only in 46% of patients, while the third stage with hyperpigmentation again was described in the majority of patients (85%). The fourth hypopigmentation stage is observed in 20% of patients, with the age of manifestation ranging from childhood to adults (1, 16, 17). In our case, characteristic skin lesions at the first erythematous stage were observed in all family members, but the second stage was absent, at least in S1. In M, areas of hypopigmentation and linear skin atrophy were noted in adulthood; in the daughters, hypopigmented areas were observed from 1.5 years of age. Thus,

omission or superimposition of different stages of skin lesions is quite common and can lead to blurring of the clinical picture and underdiagnosis of the disease.

In most cases, skin lesions disappear completely with age. Nevertheless, benign (subungual tumors) and malignant skin neoplasms may develop in individual cases (10–13). In our case, P was diagnosed with SCC on the skin of the right leg at the age of 10 years. Extremely rare cases of SCC have been described previously in adult patients (11), but only one case of SSC on the skin of the leg in a 16-year-old female patient (12). Also, basal cell carcinoma (BCC) was described in a 22-year-old female with IP (18).

SCC and BCC are non-melanoma skin cancer (NMSC) with similar pathogenesis: SCC develops through malignant proliferation of epidermal keratinocytes, while BCC arises from basal cells (19–22). Moreover, basosquamous carcinoma is described, which is characterized by a combination of clinical, dermoscopic, and histologic features from both BCC and SCC, as well as the presence of a transition zone (23). The malignization of keratinocytes may be associated with ultraviolet radiation, HPV infection, RAS/RAF/MEK/ERK and PI3K/AKT pathways (24). The development of malignant neoplasms in IP cases may be explained by inactivation of the NF-kB pathway due to *NEMO* gene mutation, which may promote uncontrolled cell proliferation (25, 26).

Treatment options of NMSC include surgery, Mohs micrographic surgery, curettage and electrodessication, radiation, photodynamic therapy, immunotherapy, topical (5-fluorouracil, imiquimod) and systemic therapy (chemotherapy, epidermal growth factor receptor inhibitors, hedgehog pathway inhibitors) (21, 27). Surgical excision alone leads to successful treatment of most NMSCs, and the cure rate is over 90% (28). In our case, only radical surgery was performed, and there was no recurrence of SCC during 5-year follow-up, but persistent inflammation at the surgical site requires continuous monitoring (19).

The frequency of dental anomalies in patients with IP ranges from 50 to 80% in different studies (9, 29, 30). Conical teeth, hypodentia (absence of one or more teeth) and oligodentia (absence of 6 or more teeth), and delayed tooth eruption are the most common manifestations. The population incidence of hypodontia of permanent teeth ranges from 2.7 to 12.2% in different ethnic groups (31), while the prevalence of dental hypo-and oligodentia in patients with IP is significantly higher, 31.2% (30). At the same time, adentia is a genetically heterogeneous phenomenon: both nonsyndromal hereditary forms caused by mutations in the genes *MSX1*, *PAX9*, *LTBP3*, *EDA*, and those associated with various hereditary syndromes have been identified (31).

In our study, hypodentia and anomalies of tooth arrangement were detected in M; also, serious abnormalities were found in P (delayed eruption of teeth, absence of a number of primary teeth, absence of 12 permanent teeth, conical teeth) and in S2 (prominent lactodentia). It should be noted that characteristic and pronounced dental anomalies are considered as an independent diagnostic criterion for the diagnosis of IP (6), nevertheless, this criterion is still more correctly applied in groups of patients with sick first-line relatives. The absence of temporary teeth in early childhood leads to the development of various functional disorders, which negatively affects the physical and psycho-emotional development of the child. Orthopedic and orthodontic care is provided to such children from 2.5–3 years of age in order to normalize the function of mastication, swallowing, speech, position of the mandible and tongue, and continues until the age of 18 years, when planning and carrying out permanent prosthetics is possible. The priority of complex early dental treatment of patients with missing teeth is restoration of masticatory function with removable plate prosthesis, and later with implantation (32).

In about 38% of patients with IP, alopecia on the vertex of the head is mild and goes unnoticed; this is probably why scarring alopecia retains its place in the minor criteria of the IP (5, 6). Agenesis or hypoplasia of the eyebrows and eyelashes is even rarer (8). On the other hand, scarring alopecia could be used as a marker to identify adult women affected with IP as older patients may have minimal cutaneous manifestations (33). In our family case, trichoscopic imaging showed the hallmarks of scarring alopecia on the skin and hair of the scalp. Discoloration, honeycomb pigmentation and absence of follicular orifices were found in both the mother and her daughters. White dots around follicles, characteristic of the period of destruction foci formation, as well as peripilar keratin desquamation were determined in S1 and S2, in which the period of scarring alopecia formation was shorter. A boomerang-type hair bend was detected in the proximal zone of growing single hairs. In general, hair auto transplantation can be considered to cover the most pronounced areas of alopecia when the pathological process on the scalp stabilizes with age.

The most common genetic mutation in IP is a deletion of exons 4 to10 in the *IKBKG* gene, which occurs in 65–80% of patients in different ethnic groups worldwide (2, 14, 34). Other types of mutations in the *IKBKG* gene have also been identified (point mutations, small insertions/deletions, and splice site mutations) (35). In our case, the disease is caused by the deletion of exon 4–10 of *IKBKG* gene, which results in the loss of large part of nucleotide sequence and, consequently, protein function. At the same time, clinical features among family members vary markedly in severity of manifestation. The phenomenon of X-chromosome inactivation has been shown to contribute significantly to the variability of clinical features (36). In our case, all affected members have unbalanced X-chromosome inactivation with XCI scores ranging from 96 to 99%, so the differences observed between patients are likely to be explained by other molecular mechanisms. The limitation of our study is that the follow-up is confined to short period and we could not follow the clinical presentation from birth to present for all family members.

In the neonatal period, the differential diagnosis of IP and skin infection can be made according to a number of clinical features: female gender, location of the rash along Blaschko's lines, staging of skin manifestations, extensiveness of the lesion, persistent eosinophilia, lack of effect from antibacterial therapy, and absence of infectious history. In older age, special attention should be paid to patients with congenital adentia, abnormalities of the shape and location of teeth, and with hair problems. In our case, the mother had all characteristic skin lesions during first year of the life, but no proper diagnosis was established. Only after the birth of the first affected child, the family suspected and then confirmed the presence of IP. Despite this, the mother was not counseled by a geneticist about carrying the mutation and the possibility of passing this defect to her children, resulting in the birth of two more sick girls and one miscarriage. Accurate diagnosis of IP requires molecular genetic testing. But also, medical and genetic counseling in the family is very important both for pregnancy planning and for further treatment and dispensary observation of the mother carrying the mutation.

4 Conclusion

From a clinical standpoint, it is imperative to distinguish IP from other dermatologic conditions, because cells containing the mutated gene remain in the body after the lesions have repaired and further progression of the disease may occur. In the family described, one daughter developed SCC, so oncologic awareness should be ensured in patients with IP. In adulthood, the mother developed generalized morphea, which may be another clinical manifestation of the IP. Proper diagnosis and management of patients with IP requires a multidisciplinary approach involving physicians from different specialties.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Local Ethics Committee of the N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

TB: Conceptualization, Funding acquisition, Project administration, Writing – original draft. TN: Conceptualization, Supervision, Writing – original draft. IK: Data curation, Investigation, Writing – original draft. DV: Data curation, Methodology, Visualization, Writing – original draft. IB: Investigation, Methodology, Visualization, Writing – original draft. VS: Investigation, Methodology, Writing – original draft. AG: Data curation, Investigation, Visualization, Writing – original draft. EZ: Investigation, Validation, Writing – original draft. TV: Formal analysis, Writing – original draft. ES: Data curation, Validation, Writing – original draft. AM: Data curation, Investigation, Methodology, Visualization, Writing – original draft. AA: Data curation, Investigation, Validation, Writing – original draft. DP: Data curation, Formal analysis, Project administration, Validation, Writing – original draft.

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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.

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Advanced lung cancer inflammation index is associated with prognosis in skin cancer patients: a retrospective cohort study

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Background: Skin cancer ranks as one of the most prevalent malignant tumors affecting humans. This study was designed to explore the correlation between the advanced lung cancer inflammation index (ALI), a metric that gauged both nutrition and inflammation statuses, in skin cancer patients and their subsequent prognosis.

Methods: Data from the National Health and Nutrition Examination Survey (NHANES) spanning 1999-2018 were scrutinized, along with mortality tracking extending to December 31, 2019. Kaplan-Meier survival curves and COX regression analysis, utilizing NHANES-recommended weights, delineated the association between ALI levels and skin cancer prognosis. To decipher the potential non-linear relationship, a restricted cubic spline analysis was applied. Additionally, stratified analysis was conducted to affirm the robustness of our findings.

Results: The 1,149 patients participating in NHANES 1999-2018 were enrolled. We observed a reverse J-shaped non-linear relationship between ALI and both skin cancer all-cause mortality and cancer mortality, with inflection points at 81.13 and 77.50, respectively.

Conclusions: The ALI served as a comprehensive indicator of a patient's nutrition and inflammation status and was demonstrably linked to the prognosis in skin cancer cases. The meticulous evaluation and continuous monitoring of these parameters in skin cancer patients bear clinical importance.

KEYWORDS

skin cancer, all-cause mortality, cancer mortality, advanced lung cancer inflammation index, NHANES

Introduction

Skin cancer remains the most prevalent form of cancer, comprising approximately 8% of all cancers (1). Reports from the U.S. National Cancer Institute, utilizing data from the Surveillance, Epidemiology, and End Results (SEER) program, suggested that in 2022, an estimated 100,000 individuals in the U.S. were diagnosed with a form of skin cancer, with an anticipated 7,650 fatalities (2). There were three primary skin cancer types: basal cell carcinoma, squamous cell carcinoma, and melanoma. Basal cell and squamous cell carcinomas represented the majority of cases, whereas malignant melanomas were less common yet still significant in number. Malignant melanoma, known for its invasiveness, frequently metastasizes. Without early intervention, it could prove lethal. Despite advancements in skin cancer treatment over the last decade, outcomes for certain patients, particularly those with melanoma, remained suboptimal. To decrease mortality further, effective biomarkers were essential for clinicians to refine preventive and therapeutic strategies.

The concept of chronic inflammation as a critical component of the tumor microenvironment dated to 1828 and has been increasingly underscored by research (3, 4). The link between inflammation and cancer has become well-recognized. Studies indicated that an inflammatory milieu could accelerate tumor progression and foster an immune-suppressive environment. This was characterized by the recruitment of suppressive cells like CD4+, CD25+, FOXp3+ Treg (regulatory T cells) and included elements such as bone marrow-derived suppressor cells, tumor-associated macrophages, and regulatory dendritic cells. This recruitment was redundant and could be streamlined for clarity. Immunosuppression, mediated by factors like TGF-beta and IL-10, might facilitate immune evasion by tumor cells (5). Evidence consistently pointed to inflammation as a factor in skin cancer development (6, 7). Cancer-associated malnutrition, influenced by both the malignancy and its treatments (8), profoundly impacted patient prognoses. Notably, inflammation could diminish albumin levels and cause weight loss (9, 10), necessitating a more effective prognostic indicator that encapsulated the interplay between inflammation and nutrition. Cachexia in cancer patients was often the result of the chronic systemic inflammatory response and frequently indicated a poor outcome for cancer patients (11). Moreover, Sarcopenia, which has been reported to correlate with body mass index (BMI), was an important nutritional component of cancer cachexia syndrome (12).

The advanced lung cancer inflammation index (ALI) prognosticated outcomes across several cancer types, combining body weight, albumin, and neutrophil to lymphocyte ratio (NLR) to evaluate systemic inflammation (13). Studies corroborated ALI's prognostic relevance in cancers like lung (14) and colorectal (15). ALI's unique composition, which included both inflammatory and nutritional markers, could make it a superior systemic inflammation indicator. Yet, the scarcity of studies focusing on ALI's relation to skin cancer prognosis remained.

This pioneering large-scale study investigated the ALI's correlation with skin cancer, aiming to inform the condition's diagnostic and therapeutic frameworks.

Materials and methods

Study population

National Health and Nutrition Examination Survey (NHANES) (16) was a nationally representative cross-sectional survey periodically conducted in the United States by the National Center for Health Statistics, employing a stratified multistage random sampling design. Our retrospective analysis utilized publicly accessible NHANES data spanning from 1999 to 2018.

Within the 1999–2018 NHANES dataset, our scrutiny was confined to 96,811 participants. From this pool, exclusions were made as follows: 41,790 individuals with incomplete cancer information, 49,894 without a cancer diagnosis, 3,693 diagnosed with cancers other than melanoma or non-melanoma skin cancers, 75 with missing follow-up data, 116 lacking essential values such as albumin, BMI, neutrophils, and lymphocytes. Furthermore, an additional 94 were excluded due to missing covariate data. Consequently, the study cohort was consolidated to encompass 1,149 participants (Figure 1).

Calculation of ALI

The ALI was calculated using the formula: BMI (kg/m^2) × serum albumin (g/dL)/NLR. Patients were stratified into quartiles based on their ALI scores, forming four distinct groups: Q1 group (ALI ≤ 37.87), Q2 group (ALI > 37.87 and ≤ 52.84), Q3 group (ALI > 52.84 and ≤ 73.20), and Q4 group (ALI > 73.20).

Primary outcome

The primary outcomes of interest were all-cause mortality and cancer mortality. The cause of death was determined using the International Classification of Diseases, 10th Edition (ICD-10) codes. All-cause and cancer mortalities were identified using ICD-10 codes ranging from I00 to I078. For participants included in the NHANES cohort from 1999 to 2018, mortality follow-up data was available up to December 31, 2019.

Definitions of variables of interest

Demographic variables such as age, gender, and race were self-reported by participants. Laboratory measurements, including alanine aminotransferase (ALT), lactic dehydrogenase (LDH), creatinine (Cr), albumin, neutrophil, and lymphocyte counts, were obtained using standardized automated hematological analysis equipment. The National Center for Health Statistics provided detailed methodologies for these measurements on its website. The BMI was determined by the standard calculation of weight (kg)/[height (m)]^2. Smoking status was categorized based on participant responses; they were identified as never smokers, former smokers, or current smokers according to their smoking

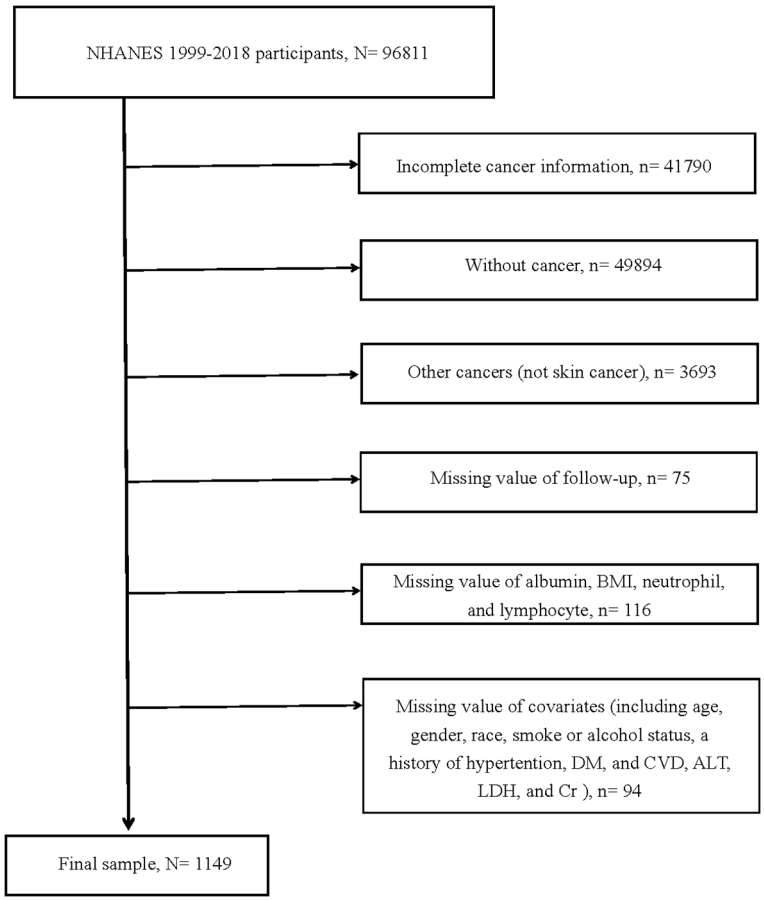

FIGURE 1
Flow chart of study participants. BMI, body mass index; DM, diabetes mellitus; CVD, cardiovascular disease; ALT, alanine aminotransferase; LDH, lactic dehydrogenase; Cr, creatinine N, The number of patients being included. n, The number of patients being excluded.

history and current smoking habits. Alcohol consumption was assessed and participants were grouped as non-drinkers, former drinkers, mild drinkers, moderate drinkers, or heavy drinkers based on their self-reported alcohol intake. The criteria for hypertension included either taking anti-hypertensive medication or having a mean systolic blood pressure (SBP) ≥ 140 mmHg or a mean diastolic blood pressure (DBP) ≥ 90 mmHg at the time of measurement or a self-reported diagnosis. Diabetes mellitus was defined by the use of hypoglycemic agents or insulin, hemoglobin A1c levels ≥ 6.5%, fasting glucose ≥ 7.0 mmol/L, a random blood glucose ≥ 11.1 mmol/L, a 2-hour oral glucose tolerance test ≥ 11.1 mmol/L, or a self-reported diagnosis. Prediabetes was characterized by fasting blood glucose levels between 6.0-7.0 mmol/L or 2-hour postprandial glucose levels between 7.8-11.1 mmol/L. A history of cardiovascular disease (CVD) was determined by self-reported history of conditions such as congestive heart failure, heart attack, coronary heart disease, angina, or stroke.

Statistical analyses

We used the NHANES-recommended weights to calculate the appropriate weights for specific groups. Continuous variables were presented as mean ± standard deviation, and for those not following a normal distribution, we represented them by the median (25th percentile, 75th percentile). Categorical variables were reported as counts (percentages). To compared baseline characteristics among the four groups, we applied variance analysis (ANOVA) for continuous variables and the $\chi 2$ test for categorical variables.

In analyzing the association between ALI and skin cancer all-cause mortality and cancer mortality, our analysis included Kaplan-Meier and Cox regression analyses, utilizing the NHANES-recommended weights. Model 1 adjusted for demographic factors: age (years), gender (male or female), and race (White, Black, Mexican American, or other). Enhancing Model 1, Model 2 incorporated adjustmented for smoke status (never, former, or current), alcohol consumption (never, former, mild, moderate, or heavy), and disease status (presence or absence, including history of hypertension, diabetes mellitus (DM), and CVD). Further refining our analysis, Model 3 added ALT (U/L), LDH (mmol/L), and Cr (umol/L) to the adjustments made in Model 2. To identify potential non-linear relationships between ALI and all-cause mortality and cancer mortality, we employed restricted cubic splines (RCS). An inflection point was determined from the RCS analysis, and its impact was assessed using segmented Cox analysis. To quantify the ALI's impact, we divided the ALI levels of each participant by 10, assessing the effect of every 10-unit

change in ALI on all-cause mortality and cancer mortality in skin cancer patients. Subsequent COX regression analysis was performed on the variables required for ALI calculation. We also undertooked a stratified analysis to explore the ALI and skin cancer all-cause and cancer mortality relationship across different subgroups, including age, gender, smoke status, hypertension, DM, ALT, and Cr, enhancing the robustness of our findings.

All analyses were conducted using R software (version 4.3.1), with a two-sided P-value of <0.05 designated as the threshold for statistical significance in all analyses.

Results

Patient characteristics

Among all 1149 participants who met the study criteria, the average age was 63.13 (62.14, 64.13). The proportion of males was higher (n = 653, 56.83%), with the majority being White (n = 1075, 93.56%). Based on ALI quartiles, patients were divided into four groups: Q1 (n = 288), Q2 (n = 286), Q3 (n = 287), and Q4 (n = 288). The ALI median values for Q4 (105.64), Q3 (45.11), and Q2 (61.61) were higher than for Q1 (29.39).

Participants in the higher ALI groups were younger (Q1: 68.04 vs. Q2: 63.80 vs. Q3: 61.89 vs. Q4: 59.93) and had higher BMI (Q1: 25.64 vs. Q2: 27.13 vs. Q3: 28.78 vs. Q4: 30.88). In the higher ALI groups, participants had lower neutrophil levels (Q1: 5.34 vs. Q2: 4.49 vs. Q3: 4.00 vs. Q4: 3.40) but higher lymphocyte levels (Q1: 1.44 vs. Q2: 1.77 vs. Q3: 1.99 vs. Q4: 2.91). Statistical differences in albumin, ALT, and Cr were also observed across the groups. However, other indicators, including the number of gender, race, LDH, smoking status, alcohol consumption, disease status, and the proportion of skin cancer among the groups, showed no statistically significant difference. More data on the baseline characteristics of the study population can be found in Table 1.

ALI and skin cancer mortality

Among the 1,149 skin cancer patients included, there were 234 (20.37%) with melanoma, 615 (53.52%) with non-melanoma, and 300 (26.11%) with Skin (unknown). These were divided into Q1, Q2, Q3, and Q4 groups using quartile methods for Kaplan-Meier survival analysis curves. From the graph, we could see that ALI was correlated with both all-cause mortality and cancer mortality in skin cancer patients (all *P*-values <0.05, Figure 2).

The univariate Cox proportional hazard results (Table 2) showed that, compared to the Q1 group, the all-cause mortality risk in skin cancer patients in the Q2 group (HR: 0.54, 95% CI: 0.38–0.77), Q3 group (HR: 0.30, 95% CI: 0.21–0.43), and Q4 group (HR: 0.31, 95% CI: 0.22–0.44) decreased by 46%, 70%, and 69%, respectively. This difference was statistically significant (*P* for trend <0.001).

After adjusting for potential confounding factors such as age, gender, race, smoking status, alcohol consumption, hypertension, DM, CVD, ALT, LDH, and Cr, compared to the Q1 group, the all-cause mortality risk in skin cancer patients in the Q2 group (HR:

TABLE 1 Baseline demographic and medical characteristics of patients with skin cancer in the NHANES 1999–2018 cohort.

Characteristics	ALI					
	Total	Quantile 1 29.74 [4.14,37.87]	Quantile 2 44.73 (37.87,52.84]	Quantile 3 60.98 (52.84,73.20]	Quantile 4 89.14 (73.20,977.87]	*P*
Participants, n	1149	288	286	287	288	
ALI, mean	62.93 (58.87,67.00)	29.39 (28.56, 30.21)	45.11 (44.50, 45.72)	61.61 (60.79, 62.44)	105.64 (94.80,116.49)	< 0.0001
Age, year	63.13 (62.14,64.13)	68.04 (66.16,69.92)	63.80 (61.81,65.79)	61.89 (60.16,63.62)	59.93 (58.20,61.66)	< 0.0001
Gender, n (%)						0.57
Female	496(43.17)	104(44.26)	126(48.56)	120(43.48)	146(49.43)	
Male	653(56.83)	184(55.74)	160(51.44)	167(56.52)	142(50.57)	
Race, n (%)						0.77
White	1075(93.56)	278(97.46)	271(97.69)	265(97.25)	261(96.41)	
Black	15(1.31)	2(0.32)	3(0.39)	3(0.29)	7(0.92)	
Mexican American	25(2.18)	2(0.17)	7(0.59)	8(0.76)	8(0.42)	
Other	34(2.96)	6(2.05)	5(1.33)	11(1.69)	12(2.25)	
BMI, Kg/m2	28.29 (27.87,28.71)	25.64 (24.88,26.40)	27.13 (26.43,27.84)	28.78 (28.01,29.55)	30.88 (30.05,31.72)	< 0.0001

(Continued)

TABLE 1 Continued

Characteristics	ALI					
	Total	Quantile 1 29.74 [4.14,37.87]	Quantile 2 44.73 (37.87,52.84]	Quantile 3 60.98 (52.84,73.20]	Quantile 4 89.14 (73.20,977.87]	*P*
Albumin, g/dL	4.26 (4.24,4.28)	4.18 (4.13,4.23)	4.26 (4.22,4.30)	4.30 (4.27,4.34)	4.30 (4.26,4.33)	< 0.001
Neutrophil, K/uL	4.24 (4.13,4.35)	5.34 (5.03,5.65)	4.49 (4.31,4.67)	4.00 (3.84,4.15)	3.40 (3.25,3.55)	< 0.0001
Lymphocyte, K/uL	2.07 (1.86,2.29)	1.44 (1.36,1.51)	1.77 (1.71,1.83)	1.99 (1.92,2.05)	2.91 (2.20,3.61)	< 0.0001
ALT, U/L	24.36 (23.19,25.53)	22.01 (19.15,24.87)	22.62 (21.10,24.15)	26.55 (23.81,29.29)	25.63 (24.07,27.19)	0.03
LDH, mmol/L	136.94 (134.74,139.13)	142.13 (137.54,146.73)	135.30 (131.33,139.27)	134.71 (131.77,137.66)	136.44 (132.50,140.38)	0.05
Cr, umol/L	83.44 (81.50,85.38)	91.14 (84.48,97.80)	81.81 (78.26,85.36)	82.41 (80.15,84.67)	79.88 (77.13,82.64)	0.03
Smoke status, n (%)						0.86
Never	508(44.21)	132(48.93)	116(43.49)	123(46.10)	137(47.59)	
Former	508(44.21)	126(36.65)	133(43.55)	128(40.53)	121(40.99)	
Now	133(11.58)	30(14.42)	37(12.96)	36(13.37)	30(11.42)	
Alcohol, n (%)						0.11
Never	129(11.23)	43(11.96)	25(7.26)	29(7.55)	32(9.68)	
Former	264(22.98)	76(20.61)	68(19.82)	63(16.95)	57(14.72)	
Mild	532(46.3)	134(50.33)	137(49.75)	128(47.32)	133(46.98)	
Moderate	139(12.1)	17(6.71)	32(13.39)	44(19.56)	46(19.20)	
Heavy	85(7.4)	18(10.40)	24(9.78)	23(8.63)	20(9.43)	
Hypertension, n (%)						0.1
No	435(37.86)	83(34.61)	118(47.10)	113(41.35)	121(45.45)	
Yes	714(62.14)	205(65.39)	168(52.90)	174(58.65)	167(54.55)	
DM, n (%)						0.1
No	763(66.41)	190(71.56)	207(77.41)	185(66.85)	181(68.56)	
preDM	119(10.36)	34(9.28)	19(6.01)	29(9.23)	37(12.93)	
DM	267(23.24)	64(19.16)	60(16.58)	73(23.91)	70(18.51)	
CVD, n (%)						0.1
No	875(76.15)	199(77.60)	217(81.25)	227(86.10)	232(83.53)	
Yes	274(23.85)	89(22.40)	69(18.75)	60(13.90)	56(16.47)	
Skin cancer, n (%)						0.68
Melanoma	234(20.37)	49(18.03)	64(24.15)	61(19.80)	60(19.83)	
Non-melanoma	615(53.52)	148(54.25)	153(54.70)	159(57.20)	155(56.41)	
Skin (unknown)	300(26.11)	91(27.71)	69(21.15)	67(23.01)	73(23.76)	

ALI, advanced lung cancer inflammation index; BMI, body mass index; ALT, alanine aminotransferase; LDH, lactic dehydrogenase; Cr, creatinine; DM, diabetes mellitus; CVD, cardiovascular disease.

Values are weighted mean (IQR) for continuous variables or numbers (weighted %) for categorical variables. Wilcoxon rank-sum test was used for continuous variables, and chi-squared test with Rao & Scott's second-order correction was used for categorical variables.

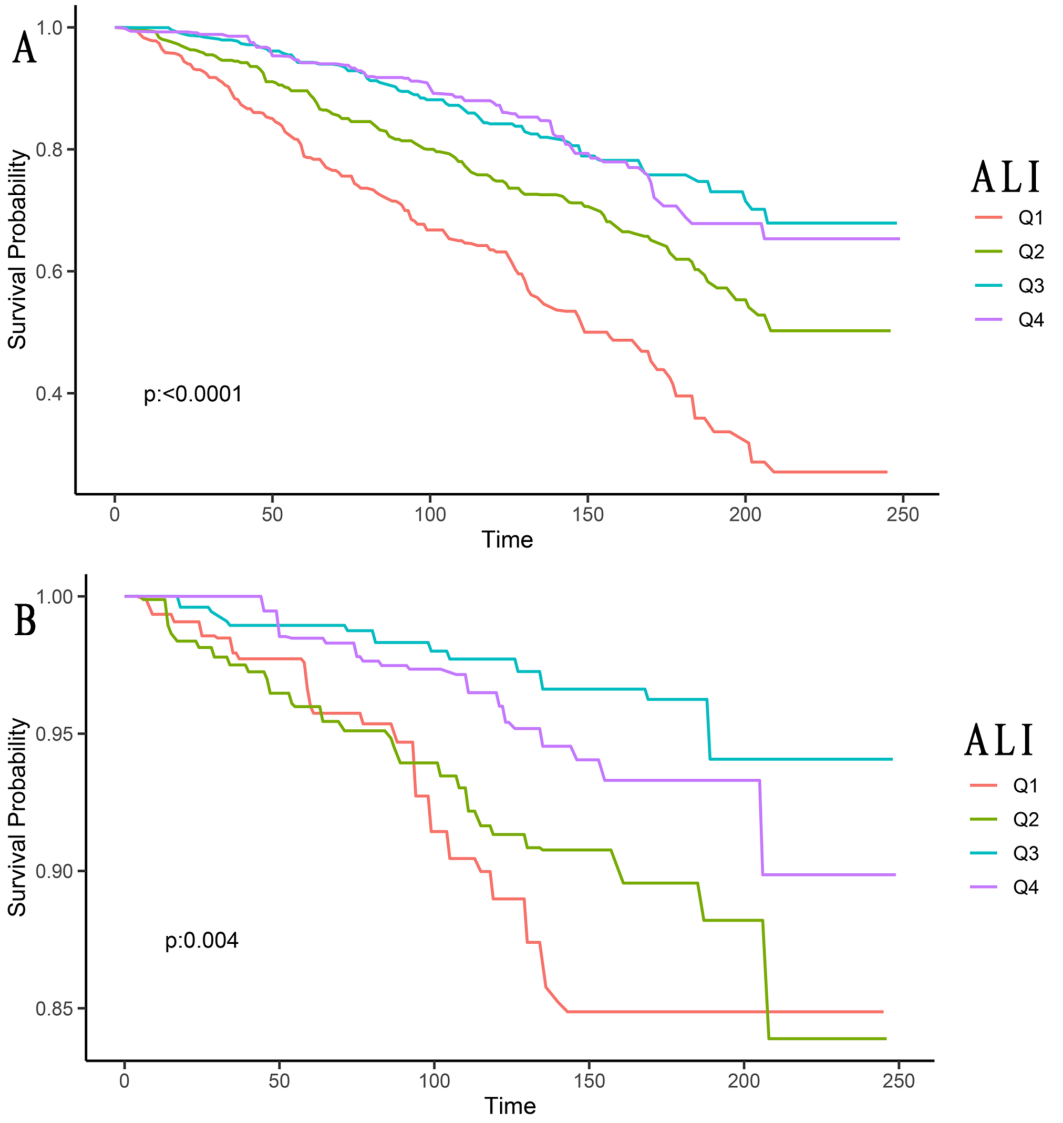

FIGURE 2
Kaplan-Meier survival curves of ALI impact on long-term all-cause mortality **(A)**, and cancer mortality **(B)** in patients with skin cancer (weighted). ALI, advanced lung cancer inflammation index; Q1, Quantile 1; Q2, Quantile 2; Q3, Quantile 3; Q4, Quantile 4.

0.77, 95% CI: 0.57–1.05), Q3 group (HR: 0.50, 95% CI: 0.36–0.69), and Q4 group (HR: 0.54, 95% CI: 0.38–0.77) still showed varying degrees of reduction. This difference was statistically significant (*P* for trend <0.001).

Similarly, both the unadjusted and adjusted Cox proportional hazard results showed that, compared to the Q1 group, the cancer mortality risk in skin cancer patients in the Q2, Q3, and Q4 groups all decreased to varying degrees. This difference was statistically significant (*P* for trend = 0.005 and *P* for trend = 0.049).

The detection of the non-linear relationship

Through restricted cubic splines analysis combined with the Cox proportional hazards model, we found a reverse J-shaped non-linear relationship between ALI and all-cause mortality and cancer mortality in skin cancer, as shown in Figure 3. Our results indicated that the inflection point for all-cause mortality in skin cancer was 81.13, and for cancer mortality, it was 77.50.

When the ALI was above the inflection point, an increase of 10U in ALI resulted in a 2% and 6% increased in the multivariate-adjusted HR for all-cause mortality and cancer mortality, respectively (HR 1.02, 95% CI: from 1.00 to 1.04 and HR 1.06, 95% CI: from 1.05 to 1.07). On the other hand, when the ALI was below the inflection point, an increase of 10U in ALI resulted in a 20% and 21% decrease in the multivariate-adjusted HR for all-cause mortality and cancer mortality, respectively (HR 0.80, 95% CI: from 0.74 to 0.86 and HR 0.79, 95% CI: from 0.66 to 0.95), as shown in Table 3.

The stratified and sensitivity analyses

When participants were stratified by age (*P* for interaction = 0.12), gender (*P* for interaction = 0.22), smoking status (*P* for interaction = 0.63), hypertension (*P* for interaction = 0.43), DM (*P*

TABLE 2 Relationships of ALI with all-cause and cancer mortality in patients with skin cancer from the NHANES 1999–2018 cohort.

ALI	All -cause mortality			
	Crude	Model 1	Model 2	Model 3
Skin cancer*	HR, 95%CI	HR, 95%CI	HR, 95%CI	HR, 95%CI
Quantile 1	ref	ref	ref	ref
Quantile 2	0.54(0.38,0.77)	0.80(0.59,1.08)	0.75(0.56,1.01)	0.77(0.57,1.05)
Quantile 3	0.30(0.21,0.43)	0.51(0.37,0.70)	0.48(0.35,0.66)	0.50(0.36,0.69)
Quantile 4	0.31(0.22,0.44)	0.60(0.42,0.84)	0.53(0.37,0.74)	0.54(0.38,0.77)
***P* for trend**	<0.001	<0.001	<0.001	<0.001
	Cancer mortality			
	Crude	Model 1	Model 2	Model 3
Skin cancer*	HR, 95%CI	HR, 95%CI	HR, 95%CI	HR, 95%CI
Quantile 1	ref	ref	ref	ref
Quantile 2	0.84(0.46,1.54)	1.16(0.65,2.08)	1.18(0.65, 2.16)	1.20(0.66, 2.18)
Quantile 3	0.28(0.12,0.63)	0.40(0.17,0.94)	0.38(0.16, 0.89)	0.38(0.16, 0.89)
Quantile 4	0.42(0.20,0.91)	0.67(0.31,1.47)	0.64(0.30, 1.38)	0.64(0.30, 1.35)
***P* for trend**	0.005	0.090	0.060	0.049

ALI, advanced lung cancer inflammation index; ref, reference; HR, hazard ratios; CI, confidence interval; CVD, cardiovascular disease; ALT, alanine aminotransferase; LDH, lactic dehydrogenase; Cr, creatinine.
Values are n or weighted HR (95% CI). Model 1: adjusted for age (years), gender (male or female), and race or ethnicity (White, Black, Mexican American, or other). Model 2: model 1+ adjusted for smoke status (never, former, or now), alcohol (never, former, mild, moderate, or heavy), and disease status (yes or no, including a history of hypertension, diabetes mellitus, and CVD). Model 3: model 2+ adjusted for ALT (U/L), LDH(mmol/L), and Cr(umol/L).
* Skin cancer, including melanoma, non-melanoma, and skin (unknown type).

for interaction = 0.67), ALT (*P* for interaction = 0.67), and Cr (*P* for interaction = 0.15), the association between ALI and all-cause mortality did not change. Sensitivity analysis showed that among individuals with Cr levels ≥106 umol/L, those with ALI greater than 81.37 had a 68% reduced risk of all-cause mortality in skin cancer patients (HR 0.32, 95% CI: from 0.14 to 0.87, *P* for trend = 0.01). No other indicators had significant associations. Similarly, when participants were stratified by age (*P* for interaction = 0.27), gender (*P* for interaction = 0.71), smoking status (*P* for interaction = 0.39), hypertension (*P* for interaction = 0.65), DM (*P* for interaction = 0.63), and Cr (*P* for interaction = 0.59), the association between ALI and cancer mortality did not change. Sensitivity analysis showed that the results for ALI and cancer mortality in skin cancer were consistent with the main effects (Additional file 1).

Discussion

To our knowledge, this was the first large-scale study of ALI and skin tumors to investigate the relationship between ALI and long-term health outcomes in patients with skin cancer. We observed an inverse J-shaped non-linear relationship between ALI and both all-cause and cancer mortality. Specifically, when the ALI was above the inflection point, an increase of 10U in ALI resulted in a 2% and 6% increased in the multivariate-adjusted HR for all-cause mortality and cancer mortality, respectively. Conversely, when the ALI was below the inflection point, an increase of 10U in ALI led to a 20% and 21% decreased in the multivariate-adjusted HR for all-cause mortality and tumor mortality, respectively.

Skin cancer is one of the most common malignant tumors, primarily caused by prolonged exposure to ultraviolet radiation. It is also influenced by the patient's susceptibility related to their skin type (17). Basal cell carcinoma is a low-grade malignant epithelial tumor that originates in the basal cells of the epidermis or the outer root sheath of hair follicles. It typically progresses slowly and has a lower incidence of distant metastasis compared to other malignant skin tumors. However, its incidence has been steadily increasing in recent years. Squamous cell carcinoma is another type of malignant skin tumor that arises from epidermal keratinocytes. Although its incidence is lower than that of basal cell carcinoma, it has a higher rate of distant metastasis and mortality. In contrast, melanoma, while having the lowest incidence among skin cancers, carries a very high risk of metastasis and significantly higher mortality compared to the previous two types. Recent research indicated that early detection of skin cancer was crucial, as it led to the highest relative survival rates. Therefore, the early diagnosis and detection of skin cancer hold significant research significance and practical value (18).

Inflammation and malnutrition associated with cancer played crucial roles in tumor progression, and the prognosis of cancer largely depended on the baseline inflammation and nutritional status of the patient. Recent years have seen a growing body of evidence highlighting the connection between inflammation and the onset and progression of cancer (19, 20); Systemic inflammation

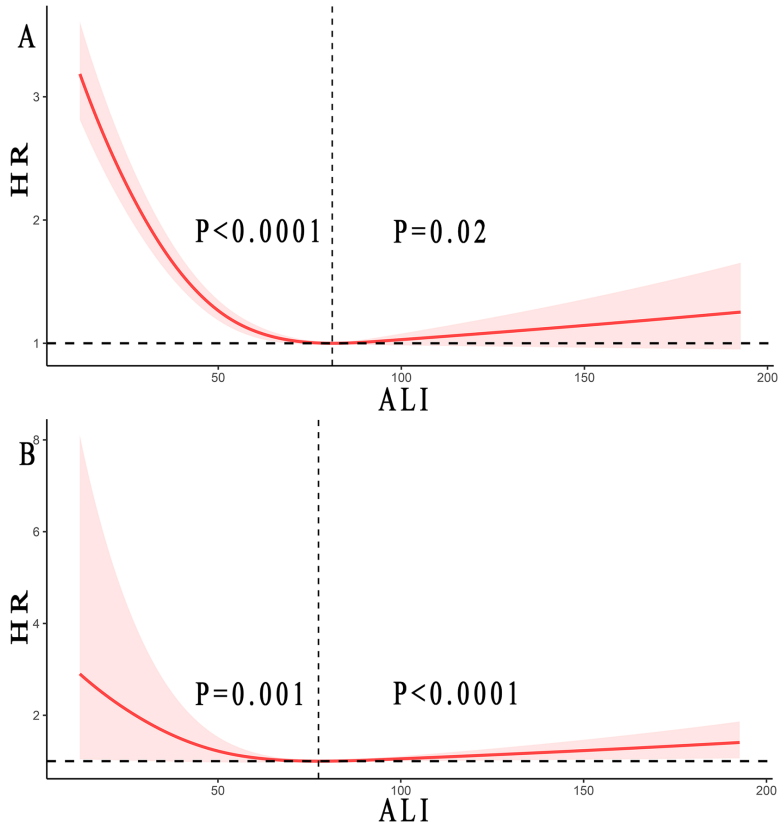

FIGURE 3
Relationship between ALI and all-cause mortality **(A)** and cancer mortality **(B)** in patients with skin cancer. Adjusted for age, gender, race, smoke status, alcohol, a history of hypertension, diabetes mellitus, and CVD, ALT, LDH (mmol/L), and Cr (umol/L). The solid and red shadow represent the estimated values and their 95% CIs, respectively. ALI, advanced lung cancer inflammation index; CVD, cardiovascular disease; ALT, alanine aminotransferase; LDH, lactic dehydrogenase; Cr, creatinine. Regarding all-cause mortality, when ALI was below 81.13, the P <0.0001, while when ALI exceeded 81.13, the P =0.02. For cancer mortality, when ALI was less than 77.50, the P =0.001, whereas when ALI was greater than 77.50, the P <0.0001.

TABLE 3 Threshold effect analysis of ALI on all-cause, and cancer mortality in patients with skin cancer.

	All -cause mortality	
	Per 10U increment	*P*
Skin cancer*		
<81.13	0.80 (0.74,0.86)	<0.0001
>81.13	1.02 (1.00, 1.04)	0.02
	Cancer mortality	
	Per 10U increment	*P*
Skin cancer*		
<77.50	0.79 (0.66,0.95)	0.001
>77.50	1.06 (1.05,1.07)	<0.0001

ALI, advanced lung cancer inflammation index; CVD, cardiovascular disease; ALT, alanine aminotransferase; LDH, lactic dehydrogenase; Cr, creatinine.
Values are n or weighted HR (95% CI). Model is adjusted for age (years), gender (male or female), race or ethnicity (White, Black, Mexican American, or other), smoke status (never, former, or now), alcohol (never, former, mild, moderate, or heavy), disease status (yes or no, including a history of hypertension, diabetes mellitus, and CVD), ALT (U/L), LDH(mmol/L), and Cr(umol/L).
*Skin cancer, including melanoma, non-melanoma, and skin (unknown type).

could manifest in changes in peripheral blood leukocytes, which could be quantified using the NLR (21). Recent studies have suggested that melanoma patients with a high NLR tend to have a poorer prognosis (22, 23).

Malnutrition and cachexia were significant concerns in cancer patients, as they involved various mechanisms related to tumor development, the host's response to the tumor, and anti-tumor treatments (20). Several methods existed to assess the nutritional status of cancer patients, along with numerous indicators for evaluating nutritional status, such as hematocrit, hemoglobin, albumin, transferrin, heme, serum creatinine, urine creatinine, and BMI, among others (24). In clinical practice, the most commonly used nutritional indicators are albumin and BMI. The impact of albumin on the prognosis of skin cancer was evident. Cancer patients often experience cachexia due to inadequate nutrient intake and tumor-related consumption. Serum albumin could promptly reflect changes in the patient's nutritional status, and hypoalbuminemia often occurred as cancer progresses (25). Many scholars have found that BMI was closely related to the prognosis of skin cancer (26, 27). However, research results on the relationship between BMI and skin cancer were inconsistent (28–30).

ALI incorporated multiple values, including BMI, serum albumin, absolute neutrophil count in peripheral blood, and absolute

lymphocyte count. These values effectively reflected the patient's nutritional, immunological, and overall inflammatory status. Initially used to assess systemic inflammation in patients diagnosed with metastatic non-small cell lung cancer (14). ALI was now increasingly employed in the study of various clinical tumors (31–33).

Our research results demonstrated a correlation between ALI levels and the prognosis of skin cancer. This finding aligned with the previous discoveries by Xi Cheng and colleagues (34), indicating that ALI could function as an independent predictive biomarker for the prognosis of metastatic melanoma with immunotherapy. What distinguishes our study was that, for the first time on a large sample scale, we explored the relationship between ALI and skin cancer, revealing an inverse J-shaped non-linear relationship between ALI and both all-cause and cancer mortality. Below the inflection point, all-cause and cancer mortality decreased as ALI increased, while above the inflection point, both all-cause and cancer mortality increased with higher ALI levels. The complex non-linear relationship between ALI and skin cancer might be attributed to the composition of the ALI index.

However, this study has some limitations. Firstly, it was an observational study, and despite the large sample size, it could not definitively establish a causal relationship between ALI and mortality in skin cancer patients. The causality between ALI and mortality should be confirmed through future interventional studies with large samples. Secondly, despited our efforts to eliminate biases, there might still be unknown confounding factors.

In summary, as a comprehensive assessment of patients' nutritional and inflammatory status, ALI revealed an inverse J-shaped non-linear relationship with all-cause and cancer mortality. This suggested that maintaining the appropriate level of ALI might have a certain effect on improving the prognosis of patients, thereby providing some new ideas for clinical research.

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 authors.

Ethics statement

The studies involving humans were approved by The Institutional Review Board of the National Center for Health Statistics. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WL: Methodology, Validation, Writing – original draft, Writing – review & editing. WZ: Conceptualization, Data curation, Investigation, Software, Writing – review & editing. RW: Methodology, Validation, Formal analysis, Visualization, Writing – review & editing. XW: Data curation, Formal analysis, Methodology, Project administration, Supervision, Writing – original draft. ZL: Data curation, Formal analysis, Project administration, Validation, Writing – original draft. LF: Formal analysis, Supervision, Validation, Writing – review & editing. YZ: Formal analysis, Funding acquisition, Project administration, Writing – review & editing. YW: Funding acquisition, Project administration, Resources, Visualization, Writing – original draft.

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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/fonc.2024.1365702/full#supplementary-material

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Angiomatoid fibrous histiocytoma with EWSR1-CREB1 gene fusion occurs in lungs and ribs with systemic multiple metastases: a case report and review of the literature

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Angiomatoid fibrous histiocytoma (AFH) is a rare soft tissue tumor with intermediate malignant potential, and it rarely metastasizes. We encountered a unique AFH case where, the tumor was discovered initially in unusual locations—the left lung and the left 4th rib. Combined histological features with FISH and NGS analysis, the diagnosis of AFH was supported, however, it is difficult to determine which of these two is the primary lesion. Eight months after the initial surgery, multiple systemic metastases were detected, eventually leading to the patient's death 18 months later due to widespread metastasis. Our case signifies the first reported occurrence of systemic metastasis in either bone-originating or pulmonary-originating AFH, and it is the initial instance of mortality resulting from multifocal metastasis originating from an atypical site.

KEYWORDS

angiomatoid fibrous histiocytoma, bone, EWSR1-CREB1, lung, metastasis

1 Introduction

Angiomatoid fibrous histiocytoma (AFH), initially described by Enzinger in 1979, was classified by the World Health Organization in 2020 as a "differentiation uncertain tumor" with moderate biological potential and unclear differentiation, accounting for 0.3% of soft tissue tumors (1). While the prognosis for most AFH patients is favorable, approximately 15% experience local recurrence, and 1-5% develop distant metastases (2). AFH predominantly occurs in the superficial extremities of children and young adults, with rare cases reported in non-trunk soft tissue locations such as the lungs, mediastinum, bones, reproductive system, oral cavity, adrenal glands, skull, breasts, and spinal canal.

Clinical symptoms are related to the site of onset (3). We present a rare case of AFH, initially occurring in uncommon sites—the lungs and ribs—followed by widespread metastasis, ultimately leading to the patient's death due to disease progression.

2 Case report

A 34-year-old male presented with intermittent left chest pain, accompanied by cough and sputum on July 10, 2022. Chest Computed tomography (CT) scan revealed a nodular high-density shadow of 2.5cm×1.9cm in the lingual segment of the left upper lobe, exhibiting clear borders and surrounded by ground-glass opacities. Localized bone expansion and cortical interruption with soft tissue density filling in the left 4th rib were observed, which were mistakenly considered by the radiologist to be caused by inflammation. The patient was readmitted to the hospital on August 7, 2022, for no improvement. A subsequent CT scan showed an enlargement of the pulmonary lesion to 2.8cm×2.1cm, with no significant changes in the left 4th rib lesion, raising suspicions of a tumorous condition (Figures 1A, B). Preoperative biopsies of the pulmonary lingual segment nodule and the left 4th rib lesion revealed consistent histological features, sparking suspicion of malignancy. However, a specific diagnosis could not be confirmed based on the histopathological findings and immunohistochemical analysis of the biopsy specimen.

The patient underwent video-assisted thoracoscopic surgery (VATS) on September 6, 2022. The procedure included wedge resection of the left upper lung lobe and excision of the lesion in the left 4th rib. VATS revealed the lung tumor located in the posterior segment of the left upper lung apex, measuring 2.0×2.0×1.5cm, with no observed pleural depression. The lesion in the left 4th rib exhibited unclear boundaries, a firm texture, and measured 2.0×2.0×1.0cm. No residual tumor was observed at the margins of the lung and rib lesions. However, the pathological examination still failed to yield a specific diagnosis.

Eight months post-surgery, the patient sought medical attention at another hospital due to left iliac region pain. The Magnetic resonance imaging (MRI) on May 21, 2023, revealed bone destruction in the left iliac bone, accompanied by a surrounding mixed solid and cystic mass measuring approximately 9.0cm × 6.4cm, exhibiting a fluid-fluid level (Figure 1D). Additionally, a subcutaneous nodule measuring 1.1cm×1.0cm was identified in the right buttock, raising concerns about metastases from lung or rib tumors (Figure 1E). A 18-fluorodeoxyglucose (FDG) positron emission tomography with CT (PET/CT) revealed increased metabolic activity in multiple regional lymph nodes in the chest, localized regions of the left 4th-7th ribs and adjacent chest wall, and increased metabolism associated with localized bone destruction in the right 11th posterior rib. Soft tissue mass formation and invasion into the left gluteus medius and lateral fascia of the upper thigh were noted in the left iliac bone region, suggesting metastasis. A subcutaneous nodule in the right buttock showed increased metabolic activity, again indicating potential metastasis from lung or rib tumors (Figure 1C). To obtain a definitive diagnosis, the patient underwent another surgical procedure to remove the left iliac bone and surrounding lesions. External specialist consultation revealed a diagnosis of AFH. In October 2023, the patient experienced symptoms such as dizziness and headaches, leading to another hospitalization for treatment. A CT examination revealed the presence of metastatic lesions in the brain and pleura (Figures 1F, G). In March 2024, the patient died from the progression of AFH, 18 months following the initial surgery.

Histologically, the left upper lobe tumor exhibited consistent tissue morphology with the rib lesion and left iliac bone lesion. The tumor had clear boundaries, and the surrounding area showed chronic inflammatory cell infiltration, predominantly lymphocytes and plasma cells, forming a sleeve-like structure and enveloped by a thick fibrous pseudo-capsule. The tumor mainly consisted of spindle-shaped, plump spindle-shaped, and oval-shaped cells, arranged in bundles or irregular patterns, exhibiting mild atypia without nuclear pleomorphism or deep staining. Clearly visible nucleoli and 0-2 mitotic figures/10 HPF were observed, with no necrosis. Focal or scattered plasma cell infiltration and hemosiderin deposition were seen in the tumor stroma. Multiple bleeding areas were observed within the tumor cell nests, presenting as pseudo-vascular cystic or cleft-like structures without endothelial cell lining (Figure 2A). Immunohistochemistry revealed positive staining for Vimentin, CD68, CD99, EMA, and Desmin (Figures 2B A2-D2), weak positive staining (10%) for P53, negative staining for CD21, CD34, S-100 (Figures 2B E2), Myoglobin, CK-P, P63, SMA, calponin, and CD21. Fluorescence *in situ* hybridization (FISH) analysis showed rearrangement of the EWSR1 gene with CREB1, confirming the presence of the EWSR1-CREB1 fusion gene (Figures 2B F2). RNA level next-generation sequencing (NGS) directly confirmed the fusion of the 7th exon of the EWSR1 gene with the 7th exon of the CREB1 gene. These findings supported the definitive diagnosis of angiomatoid fibrous histiocytoma in the lungs, ribs, and left iliac bone.

3 Discussion

The etiology of AFH remains enigmatic. Multipotent mesenchymal stem cells are considered a potential source, while there are viewpoints suggesting that AFH may emerge as a secondary malignancy in various cancer patients, including those with HIV (4).

AFH presents with extensive morphological characteristics, comprising four primary histological features (5). Firstly, the tumor consists of irregularly distributed polygonal, spindle, oval, and round cells with histiocytic or myoid features. Secondly, the tumor nests exhibit multifocal hemorrhagic cystic spaces devoid of endothelial cell lining, resembling pseudo-vascular cavities or slit-like clefts. The third hallmark is the presence of a thick and incomplete fibrous pseudo-capsule. Lastly, the tumor is densely infiltrated by lymphoplasmacytic cells or cystic envelopes, potentially including the formation of germinal centers (5).

While many reported cases lack all four major histological features simultaneously, the first feature remains consistently

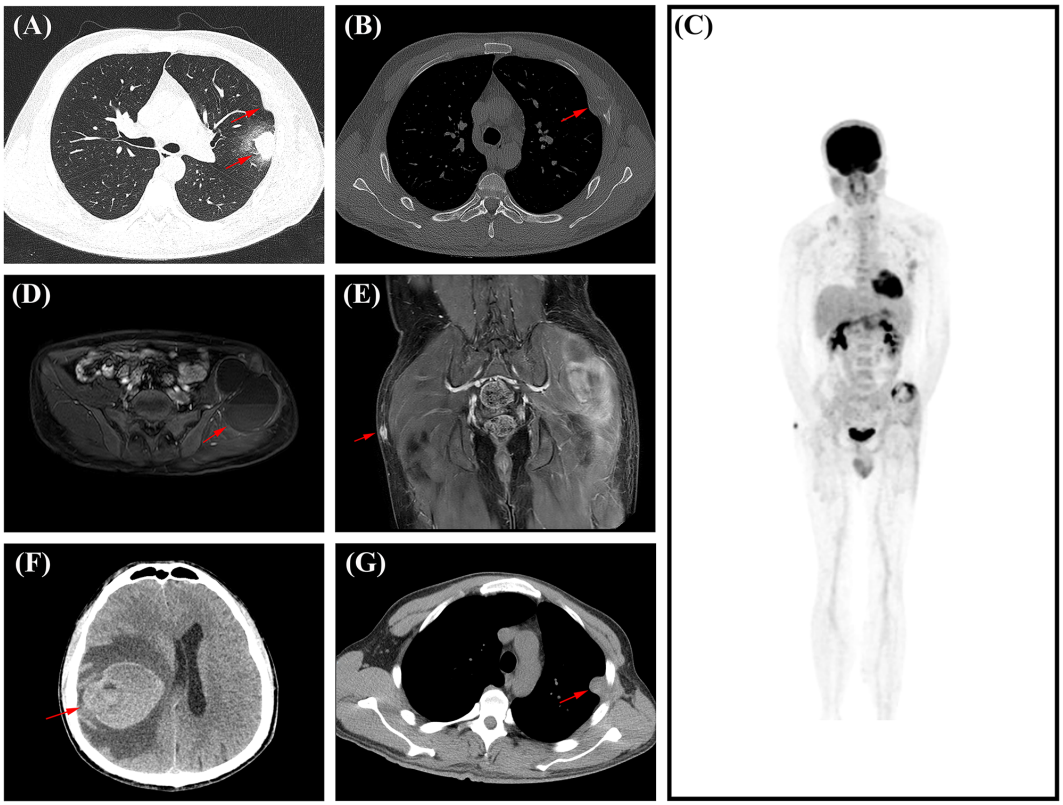

FIGURE 1
The imaging data of this patient's disease progression. **(A)** In August 2022, chest CT showed a 2.8cm×2.1cm mass in the upper lobe of the left lung. **(B)** In August 2022, on chest CT, the red arrow refers to the left fourth rib lesion. **(C)** In May 2023, PET/CT showed multiple metastases throughout the body. **(D)** In May 2023, Axial T1 MRI contrast of the pelvis shows metastases in and around the left iliac bone, measuring 9.6 cm×6.4 cm, with a visible fluid-fluid level within it (arrow). **(E)** In May 2023, coronal T1 MRI enhancement showed a subcutaneous nodule on the right buttock, approximately 1.1 cm×1.0cm in size (arrow). **(F)** In October 2023, brain CT showed large patches of hyperdense opacities in the right basal ganglia and frontoparial lobe, with the maximum level ranging from about 6.2cm×5.0cm (arrow). **(G)** In October 2023, chest CT showed a soft tissue nodular opacity at the base of the left pleura, about 1.6 cm×2.6cm in size (arrow).

invariant (6). Our case encompasses all four primary histological features. Although immunohistochemical staining may provide some support for AFH diagnosis, specific markers are lacking. Approximately half of the cases express desmin, while the expression of epithelial membrane antigen, CD99, and CD68 varies, reported in approximately 40% to 50% of cases (6).

Due to its rarity, extensive histomorphological characteristics, and lack of a specific immunological spectrum, diagnosing AFH becomes extremely challenging when the lesion occurs in unusual locations and exhibits rare biological behaviors. However, molecular studies are particularly helpful for diagnosing AFH with unusual locations and rare biological behaviors such as metastasis. The majority of AFH cases display unique chromosomal translocations, with three common translocations: EWSR1/CREB1 (most frequent), EWSR1/ATF1, and FUS/ATF1 gene fusions (7). In our case, Fluorescence *in situ* hybridization (FISH) testing revealed the EWSR1/CREB1 gene fusion. RNA level next-generation sequencing (NGS) confirmed the fusion of exon 7 of the EWSR1 gene with exon 7 of the CREB1 gene, supporting the main histological features of AFH, along with immunohistochemical support for vimentin, CD99, and CD68.

In our case, the lesion in the left iliac bone and surrounding areas exhibited fluid-fluid levels (FFL) on imaging. Histologically, these lesions were characterized by blood-filled cystic spaces lined with tumor cells rather than endothelial cells, a characteristic feature of AFH. This histological feature was observed in all surgically excised lesions in the patient. The pathophysiological mechanism underlying the formation of FFL is not yet fully understood (8). Besides AFH, other cystic lesions with liquefactive necrosis, hemorrhagic tumors, abscesses, chronic hematomas, epidermal cysts, and complex cysts can also present with FFL (8, 9). FFL are not specific to any particular lesion and can occur in benign tumors, malignant tumors, and non-neoplastic entities (8). In soft tissue and bone tumors, FFL are commonly seen in synovial sarcoma(SS), aneurysmal bone cyst (ABC), telangiectatic osteosarcoma(TO), and Ewing sarcoma(ES), all of which need to be differentiated from each other (8). SS primarily affects individuals aged 15 to 40 and is most common in the extremities, especially the lower limbs (10). SS often presents as a multilocular mass with internal septations or cyst formation, exhibiting FFL on MR imaging. Histologically, there are various subtypes, with cyst formation frequently observed in the monophasic variant. The cysts have smooth walls and contain mucoid fluid or blood (10, 11). ABC is most common in patients with immature skeletons, particularly within the first 20 years of life (12). It widely affects the skeleton, with the cranial bones, vertebrae, and metaphysis

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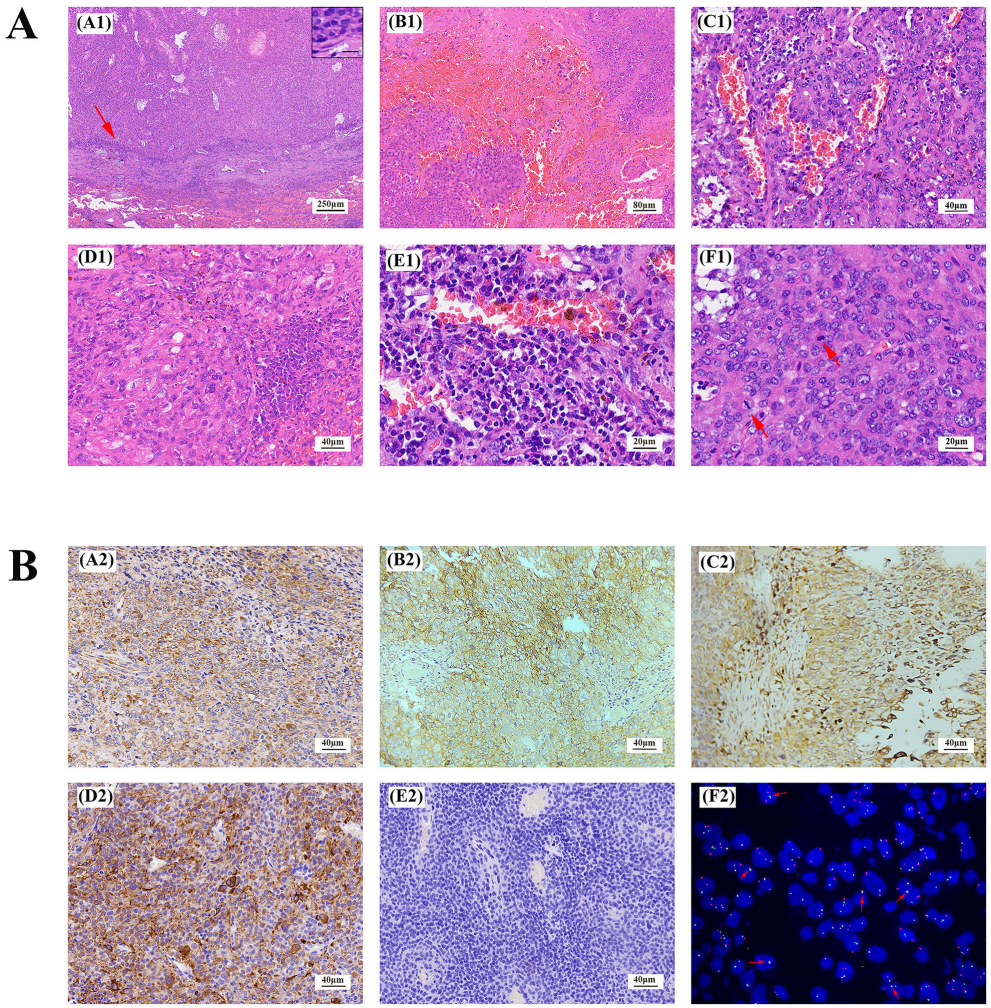

FIGURE 2
Lung AFH stained with hematoxylin and eosin **(A)**. (A1) There is a distinct fibrous pseudocapsule and pericapsular sleeve of lymphoplasma cells around the tumor nodule (×40). Inset: Lymphoplasma cells densely distributed around the fibrosham capsule (×400), the scale represents 20μm. (B1) A pseudohematous hemorrhagic sac cavity may be seen within the tumor (×100). Slit hemorrhagic areas with hemosiderin deposition and lymphocyte plasmacytic infiltration may be seen within the tumor (×200). (D1) Tumors are mainly composed of fat spindle cells and ovoid cells (×200). (E1) There is more plasma cell infiltration within the tumor (×400). (F1) A mitotic image is visible within the tumor, indicated by arrows (×400). **(B)** Immunohistochemical staining and fluorescence *in situ* hybridization of AFH. Tumor cells were positive for Vimentin, CD99, CD68, Desmin (A2-D2), and negative for S-100 (E2). (F2) Fluorescence *in situ* hybridization analysis revealed fusion of EWSR1 and CREB1. The red fluorescence signal is the CREB1 (2q33) probe, and the green fluorescence signal is the EWSR1 (22q12) probe. The arrow indicates the yellow fluorescence signal, which indicates fusion of EWSR1 and CREB1. (magnification, ×200 for all, tumor cells with brownish–yellow staining are immunohistochemically positive).

of long tubular bones being more commonly involved (12). Histologically, ABC presents as multiloculated cystic lesions with cyst walls collapsing against a background of hemorrhage (12). The cysts typically lack any lining, but flattened endothelial-like cells may be seen (12). TO typically affects individuals aged 15 to 20 and most commonly occurs in the metaphyses of long bones such as the distal femur, proximal tibia, and proximal humerus (13). Histologically similar to ABC, TO lesions are primarily composed of hemorrhage and necrotic debris, with blood pools lacking an endothelial layer (13, 14). Septa containing atypical stromal cells of varying sizes can be found within these blood lakes (13, 14). ES predominantly affects individuals aged 10 to 19, with most cases arising in the skeleton (15). Skeletal ES most commonly affects the diaphyses or metaphyses of long bones (15). Pathologically, areas of hemorrhage and necrosis are commonly observed, leading to soft or partially liquefied regions resembling purulent exudate (15). Although these tumors exhibit FFL on imaging, their corresponding histological features do not necessarily include blood-filled pseudovascular cystic spaces.

Due to the diverse histological characteristics of AFH, its differential diagnosis encompasses a wide range of conditions. The first differential diagnosis to consider is aneurysmal fibrous histiocytoma, which retains the typical structural characteristics of dermatofibroma, such as epidermal hyperplasia and peripheral collagen bundles (16). Blood-filled pseudocysts, lacking an endothelial lining and surrounded by storiform-arranged spindle cells, can be observed (17). This tumor does not exhibit the genetic

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alterations seen in AFH (17). The second differential diagnosis is inflammatory myofibroblastic tumor (IMT). IMT and AFH exhibit spindle tumor cells with lymphocyte and plasma cell infiltration (7). However, IMT lacks other characteristic morphological features and molecular genetic alterations that are characteristic of AFH (7). In our case, one of the two lesions identified during the patient's initial presentation was located in the lung. Although it was unclear if it was a primary site, differentiation from primary pulmonary myxoid sarcoma (PPMS) was necessary. Primary pulmonary AFH (PPAFH) and PPMS show significant overlap in clinical, pathological, and molecular characteristics (7). PPMS is predominantly a myxoid tumor with a myxoid stroma comprising up to 30% of the tumor, whereas in PPAFH, it is only focal (7). PPAFH's distinctive histological features, such as a fibrous pseudocapsule, lymphoplasmacytic infiltrate, and fibrosclerosis, are more common compared to PPMS, which lacks a peritumoral lymphoplasmacytic cuff. EWSR1 rearrangement is found in 100% of PPAFH cases and in 79% of PPMS cases, with EWSR1-ATF1 fusion present in 37.5% of PPAFH but rarely in PPMS (7). Finally, metastasis of a fibrohistiocytic tumor to a lymph node should be considered in the differential diagnosis. AFH's typical histological features include a fibrous pseudocapsule and dense lymphoplasmacytic infiltration or pericystic arrangement around the tumor, sometimes forming germinal centers (18). These features can lead to confusion when fibrohistiocytic tumors metastasize to lymph nodes (18). Imaging studies or a detailed patient history may help identify the primary site, and histological examination for the presence or absence of subcapsular and medullary sinuses, along with further molecular testing, can aid in differentiating between AFH and metastasis of a fibrohistiocytic tumor to the lymph node (6).

Primary pulmonary AFH is exceedingly rare, first reported in 2009 (19). According to current English literature records, only 16 cases are documented (Table 1) (4, 7, 19–27). Among these cases, only one had localized lymph node metastasis. The case reported by G. Bermudo et al. did not specify whether the subcutaneous lesion was a metastasis (26). Documented cases of AFH originating in bones are only 10, with one case showing inguinal lymph node metastasis (Table 1) (20, 28–34). No cases of AFH originating in the ribs have been reported. Our case is the first instance of widespread systemic metastasis, regardless of whether originating in bone or lungs. It is also the first reported case of mortality resulting from multifocal metastasis originating from an atypical site.

The primary treatment for AFH is extensive surgical excision. The local recurrence rate is approximately 15%, associated with incomplete initial excision (35). The metastasis rate of AFH is less than 5%, most commonly involving regional lymph nodes and sometimes affecting the lungs, liver, and brain (6). Ossama M. Maher et al. conducted a retrospective analysis of reported cases of AFH with metastasis from 1979 to 2015, encompassing a total of 17 cases, including their own documented case (36). None of these metastatic AFH cases originated in the lungs, and only one case originated in the bones, involving inguinal lymph node metastasis from a primary lesion in the tibia has been counted in Table 1 (36). These cases exhibited significant variation in the timing of metastasis, ranging from 5 months to 16 years after the primary

TABLE 1 Literature describing the clinical and pathology features of AFH in the primary lungs and bones.

	Sex/Age (years)	Location	Treatment	Size	Fibrous capsule	Lymphoplasmatic infiltrate	Pseudoh-emangiomatous lumen	Molecular genetics	Outcome	References
1	M/46	RLL	Lobectomy	25 mm	Partially surrounded	Present	No	EWSR1-ATF1	Well at 24ms after excision	Ren et al. (19)
2	F/60	LUL	Excision	15 mm	Partially surrounded	Present	NA	EWSR1-CREB1	Well at 24ms after excision	Chen et al. (20)
3	M/43	Lung	Excision	24 mm	Partially surrounded	Present	NA	NA	NA	Chen et al. (20)
4	M/64	Endotracheal (LLL)	Lobectomy	15 mm	Partially surrounded	Present	No	EWSR1-CREB1	NA	Thway et al. (21)
5	M/61	Endotracheal (RMB)	Sleeve resection	15 mm	Partially surrounded	No	No	EWSR1-ATF1	NA	Thway et al. (21)
6	M/27	Endotracheal	Sleeve resection	31 mm	NA	No	Present	EWSR1 rearranged	NA	Chen et al. (22)

(*Continued*)

TABLE 1 Continued

	Sex/ Age (years)	Location	Treatment	Size	Fibrous capsule	Lymphopl-asmatic infiltrate	Pseudoh-emangio-matous lumen	Molecular genetics	Outcome	References
7	F/70	RUL	Wedge resection+ excision of the lymph node	13 mm	Partially surrounded	Present	No	EWSR1 rearranged	NA	Tay et al. (23)
8	NA/NA	NA	NA	NA	NA	NA	NA	EWSR1 rearranged	NA	Cheah et al. (24)
9	F/22	Endotracheal	HBSR	15 mm	Present	Present	Present	EWSR1-CREB1	Well at 36ms after excision	Bouma et al. (25)
10	M/50	LLL	Wedge resection	20 mm	Present	Present	No	EWSR1-CREB1	Well at 22ms after excision	Wang et al. (7)
11	F/33	RML	Lobectomy	80 mm	Present	Present	Present	EWSR1-CREB1	Well at 17ms after excision	Wang et al. (7)
12	F/55	LUL	Lobectomy	15 mm	Present	Present	No	EWSR1-CREB1	Well at 13ms after excision	Wang et al. (7)
13	M/35	RLL	Lobectomy	15 mm	Present	Present	No	EWSR1-CREB1	Well at 30ms after excision	Wang et al. (7)
14	M/29	Endotracheal (LLL)	Lobectomy+ excision of the lymph node	35 mm	Present	Present	Present	EWSR1 rearranged	NA	Çetin et al. (4)
15	M/25	Upper lobes of both lungs	Excision	NA	NA	NA	Present	NA	NA	Bermudo et al. (26)
16	F/40	LLL	Excision	NA	NA	NA	NA	EWSR1-CREB1	NA	Vargas et al. (27)
17	34/F	Left tibia	Excision	N/A	N/A	N/A	N/A	N/A	Well at 60ms after excision [a]	Enzinger et al. (28)
18	M/11	Right proximal humerus	Excision	50 mm	NA	NA	Present	EWSR1-ATF1	Well at 16ms after excision	Mangham et al. (29)
19	M/5	Left ischium	Treated by curettage and Excision	NA	Present	Present	Present	EWSR1 rearranged	Recurrence at 12ms	Petrey et al. (30)
20	F/7	Right mandible	NA	NA	NA	NA	NA	NA	NA	Chen et al. (20)
21	M/8	Right proximal humerus	Treated by curettage and Excision	NA	NA	NA	NA	NA	Recurrence at 3ms and 9ms	Chen et al. (20)

(Continued)

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TABLE 1 Continued

	Sex/ Age (years)	Location	Treatment	Size	Fibrous capsule	Lymphoplasmatic infiltrate	Pseudoangiomatous lumen	Molecular genetics	Outcome	References
22	M/47	Right proximal ulnar shaft	Treated by curettage and Excision	NA	NA	NA	NA	NA	Recurrence at 84ms	Chen et al. (20)
23	M/10	Left parietal bone	Excision	30 mm	Present	Present	Present	NA	Well at 12ms after excision	Zheng et al. (31)
24	M/54	Right shoulder blade	Excision	45 mm	NA	Present	Present	EWSR1-CREB1	Well at 60ms after excision	Kobayashi et al. (32)
25	F/17	Right temporal bone	Excision	18 mm	Present	Present	No	EWSR1-ATF1	Well at 6ms after excision	Gillon et al. (33)
26	M/42	Right mandible	Excision	39 mm	Present	No	Present	EWSR1-ATF1	Well at 17ms after excision	Hu et al. (34)

F, female; HBSR, hybrid bronchoscopic and surgical resection; LLL & LUL & RMB & RML & RUL (L, left; R, right; LL, lower lobe; MB, main bronchus; ML, middle lobe; UL, upper lobe); M, male; NA, not available data; No, no present.
[a]The tumor in the left tibial region recurred 3 months after resection and metastasized to the inguinal lymph node one year later. The patient did not recur or metastasize 5 years after surgical resection of recurrent and metastatic lesions.

tumor excision, resulting in extremely rare deaths due to distant metastasis. Overall, the prognosis of AFH is not poor, but due to the potential for recurrence and metastasis, long-term follow-up is recommended.

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

The studies involving humans were approved by Ethics Committee of the First Affiliated Hospital of Dali University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. 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

DF: Writing – original draft. YL: Writing – review & editing, Investigation, Resources. ZL: Investigation, Writing – review & editing. YP: Investigation, Resources, Writing – review & editing. YG: Investigation, Writing – review & editing. JC: Investigation, Writing – review & editing. CZ: Supervision, Writing – review & editing, Funding acquisition, Resources.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1420597/full#supplementary-material

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Pattern of dermatoses in Wolaita zone prison setting: a call for improved dermatology services

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Background: Skin diseases are not uncommon among prisoners, primarily due to confined living conditions, limited access to proper hygiene facilities, and higher rates of skin-to-skin contact. The study aims to describe the skin disease spectrum among prison inmates Wolaita zone, southern Ethiopia.

Methods: A cross-sectional study was conducted at the Wolaita zone prison to determine the spectrum of skin diseases among the prison inmates from January 1 to February 30, 2020. Every inmate with skin complaints underwent a comprehensive skin examination, and a detailed history of their skin-compliant was documented. The diagnosis primarily relied on clinical assessment by dermatologists. The data collected from paper-based abstraction sheets was entered into EpiData entry forms twice to ensure accuracy. A descriptive analysis was performed such as frequencies, mean, standard deviation and median. The statistical significance was set at 0.05.

Result: Out of the 418 prison inmates who took part in the study, 223 (53.3%) were found to have skin disorders. The vast majority of the participants, specifically 381 (91.1%), were male. The age range of the participants varied from 17 to 60 years old, with an average age of 29.29 years ± 9.08 years. Skin infections were identified as the most prevalent type of skin disease, with 113 patients (50.67%) affected. Among the skin infections, fungal infections and scabies infestations were the most common, accounting for 41 cases (18.4%) and 37 cases (8.85%) respectively. In terms of inflammatory skin problems, 50 cases (11.9%) of Eczematous skin diseases were diagnosed. Within this category, Atopic Eczema and Nummular eczema accounted for 19 (4.5%) and 8 (1.9%) cases, respectively. Notably, a case of Leprosy was also diagnosed and linked to treatment within this prison.

Conclusion: In this study, infectious skin diseases and manageable inflammatory skin diseases are commonly diagnosed as dermatoses among prison inmates at Wolaita zone Prison. The inmates have the right to the best of health, including skin health, so health professionals posted to prison services must be trained to diagnose and manage skin disorders in prisons.

KEYWORDS

skin diseases, prevalence, dermatology service, prison, Ethiopia

Background

Skin diseases among prison inmates have been documented in both developed and developing countries, highlighting significant health challenges, particularly related to skin conditions (1, 2). Prisons have long been a feature of society, serving correctional centres for lawbreakers (3). In developing countries, the infrastructure of prisons is usually in poor condition; as a result, skin diseases are quite common among prisoners due to inadequate housing conditions, overcrowding, hot and humid environments, lack of ventilation, poor nutrition, poor personal hygiene and close living quarters, exacerbate the prevalence and severity of skin diseases (4–6). This has a significant public health impact because the vast majority of people in prison will return to the community, further burdening the existing healthcare facilities. The length of imprisonment has also been demonstrated to have a substantial association with skin infections (5). All of these contribute to further stress and psychosocial damage, which leads to neglect of one's health (1). Studies conducted in different countries have shown varied patterns of skin diseases among prison inmates in Cameron (7), prison inmates in India (8), and Nigeria (4), female prison inmates in Turkey (9), and prison inmates in Southern Lazio, Italy (10). However, it is difficult to compare the morbidity of skin diseases in different countries because the diagnostic methods are inconsistent. Some of the cases are diagnosed based on disease history and clinical findings (7), histopathological examination (4), and diagnosis by skin disease specialists without sufficient details (9, 10).

Due to heredity, environmental factors, hygiene standards, and social conventions, skin illness patterns differ from country to country and even region to region within the same country (11, 12). In Ethiopia, there is a limited dermatology service at prison clinics and getting through a referral system. There is a scarcity of studies on the profile of skin diseases among prison inmates. Also, there is no data regarding patterns of skin diseases among prison inmates in the Wolaita zone, southern Ethiopia. The World Health Organization has suggested reducing any "avoidable or unfair" health differences, stating that prisoners are entitled to have equal access to health services (13). Therefore, this study helps to document the spectrum of skin diseases among prison inmates of Wolaita zone seen at the prison clinic in Wolaita Sodo for the study period availing a service within the prison.

Aim

To describe the spectrum of skin diseases among prison inmates of Wolaita zone, southern Ethiopia, between January 1st to February 30th, 2020.

Methods

Study setting

The study was conducted in Wolaita zone prison in South Ethiopia. It is located 330 km away from the capital city, Addis Ababa. The prison consisted of a total of 1,656 inmates. A prison clinic provides outpatient and emergency services for prison inmates. The service is offered by two health officers, three BSc nurses, and two diploma nurses, and it offers 24-h service. There is no medical check-up before entering the prison. Skin diseases are managed by the health officer or BSc nurses in routine practice. When dermatology consultation is needed, the prisoners are referred to the Wolaita Sodo University comprehensive specialized Hospital dermatological clinic. The waiting period to get a dermatologist is 15–30 days because outpatient visits require prison staff to arrange a secure transfer to the hospital.

Study design, study population, and sampling

This cross-sectional study design was performed from January 1st to February 30, 2020, in a Wolaita zone prison in Wolaita Sodo, southern Ethiopia. Prison inmates aged ≥18 years and who visited the prison clinic during the study period were the study population.

During the study, all inmates who visited the clinic were examined for skin diseases and dermatological conditions at work. All the inmates with dermatological compliant were subjected to a detailed cutaneous examination. A brief history of the skin complaints was elicited, further laboratory investigations were sent to Wolaita Sodo Comprehensive Specialized Hospital. Patients were counseled correctly and prescribed appropriate treatment.

Data collection and quality control

Diagnosis and management of skin diseases

All prison inmates who present with skin conditions are managed by three Tropical dermatology professional specialists at the prison clinic. Diagnosis is made on clinical grounds as well as by laboratory support. Relevant laboratory tests include KOH tests, skin smear tests, and gram stain or histopathology, and other investigations as necessary.

A structured interview questionnaire was used in the local language once translated from the English version to Amharic and then back to English by different professional translators to ensure the consistency of the information.

Additional data was reviewed from the clinical examination cards of the prison inmates. The interview was conducted among the prison inmates at the prison clinic visit during the study period.

Analysis and statistic

Data was double-entered from the paper-based abstraction sheets into EpiData software *(v4.2.0.0 for entry Epi-Data Association, Odense, Denmark)*. A descriptive analysis of frequencies, mean, standard deviation and median were perform. Categorical variables about skin diseases, age, sex, and residence were compared using the Chi-square test. Continuous variables like age were compared and presented using the appropriate means. Levels of significance were set at 5%.

Ethics considerations

Ethics approval was obtained from the Ethical Review Committee College of Health Science and Medicine, Wolaita Sodo University (CARD 865/869/12). Accordingly, Permission for the study was secured from the Wolaita zone prison administrator and Zonal health department before data collection. Prison inmate Patient identification variables were not used in the study. The studies do not inflict harm on or expose prisoners to unnecessary risk because of examining prisoners and interviewing them. Written Informed consent was obtained during the interview. When interviews and physical examinations were completed, those inmates who had the problem were treated accordingly.

Results

Of the total of 422 prison inmates chosen for the study, 418 participated, resulting in a response rate of 99%. Of the sampled inmates, only 223 (53.3%) presented with skin problem complaints, while 381 (91.1%) being male and 37 (8.9%) being female. The age of the participants ranged from 17 to 60 years, with an average age of 29.29 ± 9.08 years. More than half of the inmates (83.7%) stayed in rural environments while less than a fifth (16.3%) lived in urban areas before getting in the prison. Additionally, 343 (82.1%) were literate. Sociodemographic characteristics are shown in Table 1.

Among 223 new cases, skin infections were the most common skin disease 113 (50.67%). Of these fungal infections were the most common type of skin infection, followed by infestation, bacterial infection and viral infections. Scabies was the most common contagious skin disease observed from ecto parasitic diseases or infestations. From non-infectious disorder, Eczema was identified as the most common disorder among prisoners, followed by Pilosebaceous, pigmentary disorders, and other miscellaneous skin diseases. A new confirmed case of lepromatous leprosy case was diagnosed among chronic bacterial skin diseases (Table 2).

Age of participant, educational status, and residence before imprisonment were significantly associated with skin diseases [chi-square (x^2) = 0.029, x^2 = 0.001 and x^2 = 0.02 respectively].

Discussion

This is the first observational study that identified the spectrum of skin diseases among prison inmates in southern Ethiopia. Prisons are a suitable environment for many skin diseases. Inmates live in a dynamic equilibrium between prison and community. Hence, timely case detection and treatment of skin diseases is important to decrease the community's spread, recurrences, complications, and disease burden (14).

In this study, the prevalence of infectious skin diseases was higher compared to the study conducted countries, such as Cameroun (7), India (8), Nigeria (5) and Turkey. Our research has shown that infectious skin diseases are the most frequent type, accounting for more than half of all cases (50.67%). This high prevalence suggests a combination of factors, including overcrowding, poor hygiene facilities, and compromised immune systems due to stress or pre-existing health conditions. These differences could be due to variations in environmental conditions, healthcare accessibility, cultural practices, and demographics across different regions. Additionally, socioeconomic factors, such as prison infrastructure and healthcare provisions, may affect the prevalence and management of skin diseases within correctional facilities.

The spectrum of skin diseases observed in this study differs from those reported in other studies study conducted in Taiwan by Jiesisibieke et al. (15), has reported eczematous skin diseases was higher followed by infectious diseases (15). However, in the current study cutaneous infectious diseases like, parasitic

TABLE 1 Socio-demographic characteristics of prisoner inmates (*N* = 418) Wolaita zone prison, southern Ethiopia, 2020.

Variables		Frequency	Percent (%)
Sex	Male	381	91.1
	Female	37	8.9
Residence before imprisonment	Rural	350	83.7
	Urban	68	16.3
Able to read and write	Yes	343	82.1
	No	75	17.9
Highest grade completed	Primary (1 to 8)	193	46.2
	Secondary (9 to 12)	124	29.7
	Tertiary	2	0.5
	Diploma	10	2.4
	Degree and above	14	3.3
Age category	18–27 yrs	199	47.6
	28–37 yrs	149	35.6
	38–47 yrs	44	10.5
	≥48 yrs	26	6.2

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TABLE 2 Spectrum of skin diseases among prison inmates (*N* = 418) Wolaita zone prison, southern Ethiopia, 2020.

Sr.N	Diseases category	Frequency (N)	Percentages (%)
1	**Fungal infections**	**41**	**9.8**
	Tinea corporis	9	2.2
	Tinea manu	3	0.7
	Onychomycosis	1	0.2
	Tinea pedis	4	1
	Pityriasis versicolor	24	5.7
2	**Bacterial infections**	**29**	**6.8**
	Impetigo	**6**	**1.4**
	Folliculitis	**10**	**2.4**
	Ecthyma	**5**	**1.2**
	Carbuncle	**5**	**1.2**
	Furuncle	**2**	**0.4**
	Leprosy	**1**	**0.2**
3	**Viral infections**	**6**	**1.4**
	Cutaneous wart	4	1
	Mulloscum contagisum	2	0.4
4	**Infestations**	**37**	**8.85**
	Scabies	37	8.85
5	**Eczema**	**50**	**11.9**
	Atopic dermatitis	19	4.5
	Nummular eczema	8	1.9
	Seborrehic dermatitis	3	0.7
	Allergic contact dermatitis	5	1.2
	Lichen Simplex chronicus	15	3.6
6	**Papulosquamous disorders**	**6**	**1.4**
	Psoriasis	3	0.7
	Lichen planus	3	0.7
	Pityriasis rosea	1	0.2
7	**Pilosebaceous disorders**	**13**	**3.1**
	Acne vulgaris	12	2.9
	Rosacea	1	0.2
8	**Drug Eruptions**	9	2
	Urticaria	9	2
9	**Pigmentary disorders**	**13**	3.1
	Vitiligo	8	1.9
	Melasma	5	1.2
10	**Miscellaneous diseases**	**19**	4.2
	Keloid	7	1.7
	Lichen sclerosus	2	0.4
	Alopecia areata	6	1.4
	Nevus	4	1

Bold values: indicate the sum in the category of the disease.

infestations and fungal and bacterial infections were prevalent. These disparities may be attributed to variations in geographic locations, sample size, study duration, study design, differences in the prison environment or, variations in the setup of prison clinics, and differences in the socioeconomic status of the populations studied.

The burden of infectious skin diseases and other chronic diseases, mental diseases, and cognitive disability is higher among prison inmates (16). This is associated with poor environment and hygiene safety considerations, and it might not be convenient for prison inmates to receive timely treatment.

The results of our study are consistent with findings from various other countries, where infectious skin diseases were identified as the most prevalent cases, accounting for 50.7% of all cases. Among these, 36.3% were attributed to fungal infections, 32.7% to scabies infestation, 25.7% to bacterial infections, and 5.3% to viral infections. This underscores the significant impact of infectious skin diseases on public health and emphasizes the need for effective prevention and treatment strategies.

In this study, scabies 8.85% is the most common ecto-parasitic contagious skin disease observed among prisoners. Our finding shows that the prevalence of scabies is low compared to studies conducted in Cameroon 32% (17) and Nigeria 12% (18). However, this study differs from others in that the prevalence of scabies was found to be higher study conducted in Italy and Poland prison (0.72 and 2.24% respectively) (10, 19). This could be attributed to the regular administration of ivermectin in this particular prison to prevent onchocerciasis, which may have contributed to the reduced prevalence. This may emphasize the need for integrated case management of skin neglected tropical diseases (Skin-NTDs) and adhering to appropriate managmentto combat the spread of diseases within prison environments.

The prevalence of pitriasis versicolor infections is the most common among fungal infections disorders. This is supported by studies conducted in Jimmu, India (20). In fact, in tropical countries, the prevalence of pityriasis versicolor is in between 30 and 40% (21). This can be attributed to factors such as overpopulation, misuse of topical steroids, humidity, hot weather, and also in developing countries, immunosuppression (HIV); all of which create favorable conditions for the growth and transmission of fungal infections.

In this study, there was a significant relationship between the participant's age, educational status, and residence before imprisonment with the likelihood of developing skin diseases ($x^2 = 0.029$, $x^2 = 0.001$ and $x^2 = 0.02$ respectively). This implies that age substantially influences the prevalence and type of skin conditions observed within prison populations; from our study observed most of the prisoners identified with skin diseases were aged between 18 and 27 years, and the study is in line with a study conducted in Nigeria (22). In our study, most of prisoners have lower educational attainment before incarceration, which can affect their health literacy and understanding of skin care. Rural residence before enrollment in correction centers showed a significant number of skin disease this could be due to the lack of dermatological service at peripheral units for rural communities in the study area (23). Furthermore, in this study, we identified and connected with a patient suffering from Leprosy. This disease is often overlooked and can affect the peripheral nerves, leading to various complications. This discovery highlighted the importance of providing dermatological services at the prison level, benefiting the prisoners and contributing to the prevention and control of such neglected tropical skin diseases within the broader community.

According to Italian research, around 40% of patients with skin illnesses altered or discontinued treatment without consulting physicians due to a lack of understanding about COVID-19 (24). The findings suggested that the COVID-19 pandemic had a detrimental impact on skin health-related treatment. Furthermore, COVID-19 prevention challenges may lead to patients with chronic diseases being overlooked, especially in low- and middle-income countries (25). In prisons, healthcare professionals should maintain health services for prisoners with chronic diseases such as skin diseases through teledermatology since it is possible to use in the prison environment for multiple reasons like security and unnecessary mobilization of prison inmates (26).

The study was limited to prison inmates seeking treatment for skin diseases at a single prison in Wolaita Sodo, southern Ethiopia. This limitation should be considered as a potential drawback of our study.

Conclusion

The prison environment is overcrowded and is suitable for contagious skin problems and other inflammatory skin diseases compared to the general population. However, there was no dermatology service for proper prevention and management in the prison where the study was conducted.

In this study, infectious skin diseases and manageable inflammatory skin diseases are commonly diagnosed as dermatoses among prison inmates at Wolaita zone prison. So, it is important to give due attention to the periodic screening of prison inmates by dermatologists for early prevention, management of infectious skin diseases and other skin diseases.

The inmates have the right to the best of health, including skin health, so health professionals posted to prison services must be trained in the diagnosis and management of skin disorders in prison settings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethical Review Committee College of Health Science and Medicine, Wolaita Sodo University (CARD 865/869/12). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. EB: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. AM: Data curation, Validation, Writing – review & editing.

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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.

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