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Updates on giant cell arteritis: pathogenesis, diagnosis and treatment, volume II

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Updates on giant cell arteritis: pathogenesis, diagnosis and treatment, volume II

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Editorial: Updates on giant cell arteritis: pathogenesis, diagnosis and treatment, volume II

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Editorial on the Research Topic
Updates on giant cell arteritis: pathogenesis, diagnosis and treatment, volume II

Introduction: the complexity of GCA diagnosis and management

Giant Cell Arteritis (GCA) presents significant diagnostic and treatment challenges, given its systemic nature, primarily targeting large, and medium-sized arteries in patients over 50. Without timely intervention, GCA can cause devastating complications such as sight loss, stroke, and aortic aneurysms. Recent advancements in imaging technologies, classification criteria, and novel therapies have greatly improved our ability to diagnose and manage this complex disease. However, important questions remain regarding relapse monitoring and long-term treatment strategies.

This editorial presents the latest evidence published in this issue regarding diagnostic innovations, phenotypic variability, clinical management of relapses, and emerging steroid-sparing treatments.

Temporal artery biopsy: still relevant despite advancements

The role of temporal artery biopsy (TAB), while debated, remains pivotal in diagnosing cranial GCA. Stamatis et al. underscore its continued importance despite the rise of imaging techniques such as ultrasound (US) and Positron Emission Tomography (PET). TAB has high specificity for cranial GCA, though its sensitivity can vary, particularly in patients with large-vessel GCA (LV-GCA). Specimen length, number of sections, and biopsy timing (preferably within 2 weeks of starting glucocorticoids) influence TAB's diagnostic yield.

Although imaging techniques have improved, Stamatis et al. underscore that TAB is essential for differentiating healed arteritis from age-related atherosclerosis, which can be diagnostically challenging. Thus, TAB continues to play a role in diagnosing cranial GCA, especially when imaging results are unclear.

Imaging advances: expanding diagnostic possibilities

US has emerged as a non-invasive alternative to TAB for diagnosing GCA, mainly through the halo sign, which may indicate temporal artery inflammation. In a landmark study by Haaversen et al., ultrasound was critical for diagnosis and follow-up, though its sensitivity for relapse detection was only 61.2%. To improve monitoring, Haaversen et al. introduced the GCA Activity Score (GCAS), which integrates ultrasound, clinical symptoms, and inflammatory markers like CRP, proving helpful in detecting subclinical relapses. PET and Magnetic Resonance Imaging (MRI) have demonstrated value in identifying LV-GCA, where inflammation extends beyond cranial vessels. Gorlen et al. showed that PET is particularly effective for excluding malignancies in patients with suspected polymyalgia rheumatica (PMR) or GCA.

A retrospective cohort study by Andel et al. using the updated 2022 ACR/EULAR classification criteria found that mixed-GCA (cranial and large-vessel involvement) was the most common phenotype, supporting the use of advanced imaging to identify and classify GCA subtypes more effectively.

Phenotypic diversity and clinical challenges

GCA presents with diverse clinical phenotypes, complicating the diagnostic process. The classic cranial GCA is characterized by headache, jaw claudication, and vision problems, while LV-GCA manifests more subtly, with systemic symptoms like fever and weight loss. Skaug et al. found that patients with non-cranial GCA experienced longer diagnostic delays than those with cranial involvement.

These findings suggest the importance of regularly imaging non-cranial arteries in suspected GCA cases, especially in younger patients, to avoid diagnostic delays. Given that non-cranial GCA patients are often underdiagnosed, prompt imaging can reduce the risk of complications such as aortic aneurysms and stroke, as supported by Ayo-Martin et al., who found that vertebral vasculitis is significantly associated with increased stroke risk.

Relapses: a persistent challenge in GCA management

Relapses in GCA remain a primary clinical concern, with rates as high as 60.6%, as Haaversen et al. noted. Contrary to earlier beliefs, relapses occur at similar rates across cranial, large-vessel, and mixed subtypes, underscoring the need for consistent monitoring. The GCA Activity Score (GCAS), which combines clinical, biochemical, and imaging data, has emerged as an essential tool for identifying subclinical relapses that might otherwise go undetected.

In cases where ultrasound is inconclusive, Monti et al. highlight the complementary value of PET and MRI, particularly for monitoring large-vessel involvement. These imaging techniques are essential in capturing ongoing inflammation in patients who remain asymptomatic yet have active disease.

Complications: preventing high-stakes outcomes

Complications from untreated or inadequately managed GCA can be severe, including sight loss, stroke, and aortic aneurysms. Ayo-Martin et al. introduced a novel method of using vertebral artery diameter measured via ultrasound to indicate vertebral vasculitis, which is associated with an increased risk of stroke.

Brekke et al. also highlighted traditional cardiovascular risk factors such as age, smoking, and hypertension as the strongest predictors of mortality in GCA patients. Interestingly, their long-term study found no significant increase in cancer incidence among GCA patients, suggesting that routine cancer screening may not be necessary.

Mental health in GCA: an overlooked burden

Beyond its physical complications, GCA imposes a significant psychological burden. In a cross-sectional study by Froehlich et al., 40% of GCA patients were found to suffer from major depressive disorder. The study also found a strong correlation between elevated CRP levels and depressive symptoms, suggesting that systemic inflammation may contribute to mental health impairment in GCA patients. These findings underscore the importance of integrating mental health assessments into the routine care of GCA patients, especially considering the potential link between inflammatory markers and psychological distress.

Steroid-sparing therapies

While glucocorticoids remain the cornerstone of GCA treatment, their long-term use is associated with significant side effects, including osteoporosis, diabetes, and increased infection risk. Biologic therapies, such as tocilizumab, offer a targeted approach to reducing inflammation while sparing patients from glucocorticoid-related side effects. Pankow et al. reported promising results using mycophenolate mofetil (MMF) as a steroid-sparing therapy for GCA, significantly reducing CRP levels and disease remission in a small cohort. These findings pave the way for future randomized controlled trials to establish MMF's role in the broader treatment landscape for GCA.

In addition, glucocorticoids reduce the sensitivity of various diagnostic methods. Stamatis et al. emphasize that TAB should

ideally be performed before initiating glucocorticoids to preserve diagnostic accuracy.

Conclusion: a path toward precision medicine

GCA remains a complex condition that requires a dynamic approach to diagnosis and management. The combined use of advanced imaging and the GCAS represents a significant step forward in diagnosing, monitoring, and managing GCA. Haaversen et al. and Monti et al. emphasize the importance of a multimodal approach that includes imaging to track disease progression and detect relapses. The use of steroid-sparing therapies such as mycophenolate mofetil and the focus on personalized care is transforming the landscape of GCA. In the future, treatment will be tailored to each patient's unique disease characteristics, ensuring optimal outcomes while minimizing complications.

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Updates on the diagnosis and monitoring of giant cell arteritis

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This mini-review offers a critical appraisal of the currently employed imaging or histopathological tools to diagnose and monitor giant cell arteritis (GCA). An overview of the most updated evidence and current application of color duplex ultrasonography (US), temporal artery biopsy (TAB), 18-fluorodeoxyglucose [18F] FDG-PET/CT, magnetic resonance imaging, and computed tomography angiography is provided. The main limitations of each tool, and the most relevant research developments are discussed. The review highlights the complementary value of the available modalities to ensure a correct diagnosis of GCA, and to provide valuable prognostic information. Novel evidence is accumulating to support the role of imaging, and particularly US, as a monitoring tool for the disease, opening new perspectives for the future management of large vessel vasculitis.

KEYWORDS

giant cell arteritis, diagnosis, monitoring, imaging, biopsy

1. Introduction

In recent years, the management of giant cell arteritis (GCA) has been going through some paradigmatic changes. Even though the first report of the potential applicability of color duplex ultrasonography (US) for the diagnosis of GCA dates back to 1997 with the first description of the "halo sign" as an indication of inflammatory vessel wall edema (1), it was only in 2018 that formal international consensus was achieved (2) and dedicated recommendations for the use of imaging in large vessel vasculitis (LVV) became available (3). Temporal artery biopsy (TAB) remains the gold standard for the diagnosis of GCA with optimal specificity, however, recent studies have proven a higher diagnostic yield, cost-effectiveness, and prognostic impact of imaging (4, 5). Indeed, the introduction of fast-track clinics for the urgent referral of patients with suspected GCA to be assessed clinically and with US has significantly reduced the rate of permanent visual loss for these patients compared to standard clinical practice (5–7). Moreover, increasing knowledge of the clinical characteristics and outcomes of large-vessel GCA (LV-GCA) have shed new light on the importance of assessing extra-cranial involvement in patients with GCA (8, 9). Moreover, the use of imaging as a monitoring tool for LVV has long been affected by uncertainties regarding the exact meaning of residual subclinical inflammatory findings in patients in remission. Nevertheless, new evidence is accumulating to support a potential role for imaging, and

especially US, as a monitoring tool to assess response to treatment and detect relapses in patients with GCA (10). Finally, the assessment of biologic drugs in randomized controlled trials of GCA has significantly improved the therapeutic options for these patients and has provided new flourishing research in the field (11).

2. Updates on the use of temporal artery biopsy for giant cell arteritis

A definite diagnosis of GCA often requires a TAB (12). TAB is a mini-invasive procedure with low risk of complications, generally performed under local anesthesia on an outpatient basis. Both EULAR and ACR recommend unilateral TAB or temporal arteries imaging in all patients presenting with symptoms compatible with GCA, in particular in those with cranial manifestations (13, 14). US of the temporal arteries has shown good sensitivity and specificity for the diagnosis of GCA when performed by operators with expertise in the technique, and, in these circumstances, it can be considered a diagnostic surrogate for TAB. However, in the centers without long-standing expertise in temporal artery US, and in all cases in which temporal artery US is negative in a clinically suggestive case, TAB remains the recommended diagnostic test for the diagnosis of GCA(13, 14).

The classic histologic picture of GCA is a transmural inflammatory infiltrate consisting of lymphocytes, macrophages, and, in approximately 75% of cases, giant cells. The lesion frequently has a "concentric rings" appearance, with a thicker inflammatory band surrounding the external elastic lamina and a thinner inflammatory band along the internal elastic lamina. A peculiar laminar necrosis, consisting of a band of acellular eosinophilic material sometimes bordered by palisading histiocytes along the internal elastic lamina, is present in approximately 25% of cases. Fibrinoid necrosis is extremely rare, and its presence should prompt consideration for the possibility of an alternative diagnosis (i.e., one of the systemic necrotizing vasculitides). In around 20% of positive TABs, the inflammatory infiltrate (typically lymphocytic) is restricted to the adventitial vasa vasorum or periadventitial small vessels (15). Most of these patients have a final diagnosis of GCA (16), even if the presence of restricted inflammation at TAB has low sensitivity and specificity for GCA diagnosis. To date, the diagnostic and prognostic significance of these restricted forms of inflammation remains unknown and in these cases, GCA diagnosis and treatment should be based on clinical ground (17).

In the absence of a definitive diagnostic test for GCA, it is hard to estimate the diagnostic performance of TAB for the diagnosis of the disease. The specificity of TAB is excellent, approaching 100%, but the most important limitation of TAB remains the lower sensitivity, that ranges from 50 to 95% in most studies (18). A recent systematic literature review and meta-analysis provided a pooled sensitivity of 77.3% (95% CI: 71.8, 81.9%) of TAB for the diagnosis of GCA, showing indirect evidence that TAB is not less sensitive than temporal artery imaging for the diagnosis of GCA (18). Expertise is important also in the pathologist's ability to evaluate TAB and discern which features are compatible with GCA. In a multicenter study in which pathologists were not trained in the evaluation of TABs, the sensitivity of TAB for the diagnosis of GCA was 39%, significantly lower than that reported in previous studies in which a single pathologist expert in GCA reviewed all TABs (4, 18, 19).

The sensitivity of TAB for the diagnosis of GCA may also be affected by:

- *Biopsy length, number of sections evaluated and bilaterality of the procedure:* False-negative biopsies are usually attributed to the patchy involvement of the temporal artery, where areas of inflamed artery may alternate with areas of normal artery (skip lesions). In order to minimize the risk of skip lesions, and thus of a false negative result, it is generally recommended to remove longer segments of temporal artery. However, a post-fixation TAB specimen longer than 5 mm may suffice to reduce the risk of a false negative result according to two recent studies that retrospectively evaluated 1,520 and 694 TABs, respectively. Nevertheless, international recommendations still suggest that a long-segment temporal artery biopsy (>1 cm) should be preferred (14). Since the arterial specimen shrinks after excision, surgeons should remove a temporal artery segment longer than 10 mm to improve the diagnostic yield of TAB (20, 21). Furthermore, inflamed sections are found at deeper levels in 6–12% of TABs in which the first section was uninflamed (21, 22). In all TABs showing a negative first section, at least three additional deeper biopsy sections should be cut and evaluated by the pathologist to reduce the risk of a false negative result. The increased yield of contralateral biopsy for the diagnosis of GCA is in the range of 5% (23). Unilateral biopsy, possibly from the symptomatic side, is recommended. Contralateral biopsy is suggested only in cases of a first negative or inappropriate result and high clinical suspicion of cranial GCA (14).
- *Glucocorticoid treatment:* The inflammatory infiltrate involving the wall of the temporal arteries resolves slowly after starting glucocorticoid treatment, persisting for at least 2–4 weeks (24–26). Recommendations suggest to ideally obtain TAB within 2 weeks as the sensitivity decreases from 78% (within 2 weeks) to 65% (within 2–4 weeks) (14). However, inflammatory changes indicating GCA may still be present after 4 or more weeks of glucocorticoid treatment. A longitudinal histopathologic study reported that GCA may still be demonstrated on repeated TABs in 75% at 6 months, and 44% at 12 months (14). In order to maximize the diagnostic yield of the procedures, TAB should be obtained within 2–4 weeks after starting glucocorticoid therapy. Beyond this time limit, TAB may be considered in selected cases at the discretion of the physician and the patient (27). The role of TAB as a monitoring tool for treatment response has been previously reported in a limited number of patients by gene expression analysis, showing decreased pro-inflammatory activity and increased vascular remodeling (28).
- *Disease phenotype:* Extra-cranial or large vessel GCA indicates the inflammatory involvement of the aorta and its major branches. These patients typically lack cranial manifestations and are often asymptomatic or can present with systemic manifestations and refractory polymyalgic symptoms. When performed in patients with suspected GCA, TABs are positive in 25–35% of cases, mainly in patients with the cranial phenotype of the disease, and inadequate in around 4% (14).

TABLE 1 Diagnostic performance and monitoring utility of the different imaging tools available for the assessment of giant cell arteritis.

	Sensitivity	Specificity	Role in monitoring the disease
TAB (4, 17)	Ranges 39–77.3% (95% CI: 33, 81.9)	100% (95% CI: 97, 100)	Invasive procedure limits repeatability in clinical practice. Vasculitis still demonstrated on repeated biopsies up to 12 months from diagnosis; tissue pro-inflammatory markers change in response to treatment.
Ultrasound (30, 31)	Ranges 54–81% (95% CI: 48, 88) compared with a clinical diagnosis of GCA Ranges 70 (95% CI: 56, 81) compared to TAB	Ranges 95–96% (95% CI: 85, 99) compared with a clinical diagnosis of GCA Ranges 84 (95% CI: 73, 91) compared to TAB	Significant sensitivity to change of halo count and intima-media thickness in response to treatment. US findings of temporal artery correlate with signs of disease activity. Emerging role in detecting relapses.
MRI (30, 57, 64)	Ranges 73–75% (95% CI: 57, 85) compared with a clinical diagnosis of GCA Ranges 91–93% (95% CI: 89, 96) compared to TAB 78.4% for cranial MRI	Ranges 88–89% (95% CI: 81, 92) compared with a clinical diagnosis of GCA Ranges 78–81% (95% CI: 73, 87) compared to TAB 90.4% for cranial MRI	Monitoring role of cranial MRI is being currently investigated. Reduced findings after 5 days of high-dose glucocorticoids. Persistent vessel wall enhancement described in extra-cranial arteries in one third of patients in remission treated with tocilizumab.
PET (30, 43, 65)	Ranges 61–80%; 73.3% for cranial arteries 77% compared with a clinical diagnosis of GCA 67% compared to TAB	Ranges 66–100%; 97.2% for cranial arteries 100% compared with a clinical diagnosis of GCA 66% compared to TAB	Controversy on the significance of a persistent uptake in patients in clinical remission (vascular remodeling? Subclinical activity?). PET vascular activity score (PETVAS) has been used to assess response to treatment.
CTA (30)	73% (95% CI: 45, 92) for a diagnosis of LV-GCA	78% (95% CI: 40, 97)	Useful for the long-term monitoring of structural damage (aneurysms/stenosis).

US-guided TAB does not improve the sensitivity of TAB for diagnosing GCA, but US may be useful for locating the artery before or during the biopsy procedure, reducing the risk of inadequate specimens (9).

In clinical practice, TABs performed for evaluation of patients with suspected GCA are positive in 25–35% of cases, and inadequate in around 4% (21). US-guided TAB does not increase the positive yield of TAB but is useful for locating the artery in preparation for the biopsy procedure, reducing the proportion of inadequate specimens (29).

3. Updates on the use of ultrasound for giant cell arteritis

The current international EULAR recommendations indicate US as the preferred early imaging test in patients with a suspected clinical diagnosis of GCA. Moreover, in patients with a high clinical probability for the diagnosis, and a supportive imaging test, the diagnosis can be confirmed without the need for further testing. US of the temporal and/or axillary arteries should be the primary imaging test in patients with predominantly cranial features provided that adequate expertise and equipment are available (3). The halo sign has been recently defined by an Outcome Measures in Rheumatology (OMERACT) working group as a "homogenous, hypoechoic wall thickening that is well delineated towards the luminal side and is visible both in longitudinal and transverse planes, most commonly concentric in transverse scans" and represents the main US finding in active GCA (2). The compression sign is used to confirm the presence of a halo and is less dependent on the operator's experience (2). Nonetheless, high expertise and adequate equipment, including a high frequency probe (>15 MHz) are essential to ensure reliable temporal artery exploration with good sensitivity. Previous evidence informing EULAR recommendations had provided a pooled sensitivity for the halo sign of 77% (95% CI: 62–87%) and pooled specificity of 96% (95% CI: 85–99%) compared with a clinical diagnosis of GCA (30). The most recent systematic literature review and meta-analysis has confirmed the good sensitivity [67% (95% CI: 51, 80)] and specificity [95% (95% CI: 89, 98%)] of the halo sign in the diagnosis of GCA (**Table 1**) (31). Overall, US has a significantly better sensitivity than TAB while retaining very high specificity, reaching 100% in case of bilateral halo. Moreover, US can easily be implemented as a point-of-care test in dedicated fast-track clinics for the early diagnosis of GCA. Fast-track clinics are currently available in a growing number of specialist referral centers for the care of patients with LVV, leading to a substantial reduction in the rate of permanent blindness (6, 7). Nevertheless, the relapse rate during follow-up did not seem to be reduced since the introduction of fast-track clinics (5), highlighting the unmet need of appropriate risk stratification and tailored treatment based on the clinical characteristics of GCA at diagnosis. The core US assessment of GCA provides the best diagnostic yield balanced with the time needed to perform the procedure and includes scanning of the temporal arteries along the whole length of their common, parietal, and frontal branches bilaterally, and the axillary arteries (32). Several studies, including some recent evidence, have assessed the adjunctive role of extended US protocols including the assessment of other cranial or extra-cranial arteries confirming the generally optimal sensitivity and specificity of the core set (temporal and axillary arteries). In a recent study including 83 patients with GCA, the inclusion of the subclavian artery increased the sensitivity by 1%, and the inclusion of the brachiocephalic and common carotid arteries increased the sensitivity by 3% (33). Nevertheless, the deep anatomical distribution and difficulties in examination make the assessment of the brachiocephalic artery trunk subject to variation and lack of reproducibility. Generally, besides research purposes, the extension to other explorable vessels can be suggested in patients with a high clinical probability of GCA in whom the temporal and axillary arteries do not display signs of active GCA.

While the accepted definition for a diagnostic US in GCA is based on qualitative ultrasonographic findings and halo compressibility, and a definite consensus has not been reached, studies have identified cut-off values for the intima media thickness (IMT) that can distinguish vasculitic from normal arteries (34, 35). A normal temporal artery in a 70 years old patient has an IMT of ∼ 0.2 mm, while an inflamed artery has an IMT of ∼ 0.5–0.6 mm; a normal axillary artery has an IMT of ∼ 0.6 mm, while an inflamed artery in a patient with GCA has an average IMT of ∼ 1.7 mm. The proposed cut-off values range between 0.29 and 0.42 mm for the different branches of the temporal artery, and 1.0 mm for the axillary arteries (35). Similar cut-off values with high levels of diagnostic accuracy (≥0.4 mm for temporal, facial and occipital arteries, ≥0.7 mm for vertebral arteries, and ≥1 mm for carotid, subclavian and axillary arteries have been proposed by other research groups (34).

Ultrasonography has traditionally been considered in a binary fashion (positive/negative according to the presence of a halo in at least one of the assessed vascular territories), however, recent research trends have focused on the role of a quantitative assessment of US findings combining information on the number of sites with halos and the degree of the IMT measurable by US (36). The disease extent and severity as measured by US quantitative scores has been demonstrated to have important diagnostic value, and has been correlated with the probability of having a diagnostic TAB (36). Moreover, quantitative US scores have been associated with the probability of ocular ischemia at diagnosis (37). On the other hand, the prognostic role of a baseline quantitative score over follow-up is still to be defined (36).

The increasing interest in the quantitative US findings in GCA has led to a better understanding of the halo characteristics in response to treatment and has provided important evidence on the monitoring potential of this tool (**Table 1**). IMT size in the temporal arteries (but not in the axillary arteries) has been demonstrated to reduce following the first 7 days of glucocorticoid treatment supporting its role as an early marker of disease activity (38). Moreover, sensitivity to change in response to treatment has been demonstrated for the halo sign (in terms of number of halos and IMT thickness) starting from week 1 throughout week 24 for the temporal artery, and only after week 6 for the axillary halo features. Moreover, the number of temporal artery segments with halo and maximum halo IMT show significant correlation with signs of disease activity (erythrocyte sedimentation rate, c-reactive protein, Birmingham Vasculitis Activity Score) and cumulative glucocorticoid doses. On the other hand, halo at the level of the axillary arteries seems to display a different behavior without significant correlation with other aspects of disease activity (10).

Quantitative US has been employed in a randomized controlled trial to monitor the response to treatment to high-dose glucocorticoids and Tocilizumab, demonstrating the remission-induction effect of Tocilizumab and supporting the important monitoring role of US (39).

The monitoring utility of US has also been demonstrated by the ability to effectively detect relapses. Halo sign has been identified in 94% of first disease relapses in an international cohort of patients with GCA followed with a standardized protocol, but with a lower mean number of segments with halo and sum of halo IMT compared to disease onset (10, 32).

The monitoring assessment of GCA with US has provided valuable information not only on the quantitative changes of the halo over time, but also on the qualitative modification of halo, particularly for chronic changes at the level of the axillary arteries. The OMERACT definition and reliability assessment of chronic US lesions of the axillary artery has been provided for patients with long-standing GCA. The definition is based on measurement and appearance of the intima media complex. The inter- and intra-reader reliability of the new definition among experts was good to excellent (40). Moreover, the IMT of the axillary arteries is known to decline more slowly than the temporal artery, with a reduction persisting in the first 18 months of treatment. An IMT of 0.87 mm has been proposed to be highly specific (specificity 96%, sensitivity 61%) for the diagnosis of chronic axillary involvement in GCA (41).

4. Current use and new aspects regarding other imaging modalities (other than US)

4.1. 18-fluorodeoxyglucose FDG-PET/CT

FDG-PET/CT has proven to be highly accurate in identifying large vessel GCA. Several studies have looked at its diagnostic performance and determined that it has a sensitivity of 61–80% and a specificity of 79–100% (**Table 1**) (42–45). Recently published studies have also shown that 18-fluorodeoxyglucose [18F] FDG-PET/CT may efficiently identify even cranial GCA of the temporal arteries (43, 46–48).

A likely positive 18-FDG uptake is grade III, whereas a probable LVV is grade II.

It is critical to consider pre-analytical conditions that can affect 18-FDG uptake, such as hyperglycemia, tracer dose, and acquisition time between injections. Further, it is difficult to distinguish arteriosclerosis from LVV using 18-FDG uptake, but grade III uptake and involvement of the supra-aortic trunk or homogenous involvement of the entire aorta make it more likely to be due to vasculitis (3, 49–51).

By using the same interpretation modalities, the PETVAS score can help to homogenize interpretations and improve patient follow-up (52, 53).

The main limitations of FDG-PET/CT are linked to its inferior performance in cases of diabetes and its decreased sensitivity after commencing therapy with high doses of glucocorticoids. Three days of high-dose GC therapy can already attenuate FDG uptake of inflamed large vessels; such timeframe is still not defined for the assessment of temporal arteries with PET (54). In a prospective study, Imfeld et al. (55) evaluated the diagnostic performance of US and conventional [18F] FDG-PET/CT and concluded that both tests were complimentary. Indeed, typical [18F] FDG-PET/CT provides for greater exploration of the aorta, whereas ultrasonography allows for a better evaluation of cranial arteries (47, 48). When using PET/CT, one must consider the substantial irradiation of up to 25 mSv, making it not a standard imaging approach for diagnosing and monitoring of patients with GCA. Novel PET radiotracers that target cells (macrophages, T cells, and endothelial cells) implicated in the pathophysiology of GCA are being researched currently (56).

4.2. Magnetic resonance imaging and computed tomography angiography

Contrast MRI angiography (MRA) is used to examine cranial arteries, displaying arterial wall thickness and artery wall gadolinium enhancement. When compared to clinical diagnosis, a recent meta-analysis of ten studies of MRI in cranial-GCA revealed a pooled sensitivity and specificity of 75 and 89%, respectively. Sensitivity and specificity rose to 91 and 78%, respectively, when compared to TAB (**Table 1**) (57). Improved diagnostic performance for assessing wall thickness and mural enhancement in GCA patients was also established using fat-suppressed 3D High-resolution T1-weighted black-blood MRI (CUBE T1) versus 2D contrast-enhanced vessel-wall MRI (58). The benefit of adopting 3D MRI is its multiplanar reconstructions, which are beneficial when analyzing extracranial and intracranial arteries (59). Few studies have compared the accuracy of MRI to US in GCA patients. Yip et al. revealed that US was more sensitive than MRI in identifying changes in supra-aortic large arteries, particularly in individuals with chronic GCA (defined as active disease diagnosed at least 6 months before inclusion in the study). There were no variations in cranial artery evaluation between MRI and US (60). However, in a diagnostic emergency, MRI availability remains the fundamental barrier, while keeping in mind that this should not delay the delivery of glucocorticoids. A common method for diagnosing LVV is computed tomography angiography (CTA), which requires the intravenous administration of iodine-based contrast agents. After intravenous injection of a iodine-based contrast agent, arteritis on CTA manifests as mural thickening and double ring enhancement (61). In a prospective study of 24 patients with suspected GCA, 15 of whom were eventually diagnosed as GCA on an individual basis by experienced clinicians, mural thickening on CTA had a slightly lower specificity (84.6 versus 100%) and a positive predictive value (84.6 versus 100%) than increased FDG uptake on PET scanning, while sensitivity reached 73.3% for CTA and 66.7% for FDG-PET (42). In a study of 28 patients with GCA, de Boysson et al. (62) compared CTA to FDG-PET/CT. In a per-patient analysis, CTA demonstrated excellent sensitivity (95%) and specificity (100%) when compared to FDG-PET/CT. Sensitivity and specificity were 61 and 97.9%, respectively, in a per-segment analysis.

Few studies have found that CTA has high diagnostic accuracy. The authors of one study (42) observed a sensitivity of 73% and a specificity of 78% for the diagnosis of LV-GCA. Berthod et al. published a 2.2 mm aortic wall thickening threshold in favor of GCA (63). The primary limitation of CTA is the use of iodinated contrast material and irradiation, as well as the absence of evaluation of the temporal arteries.

5. Discussion

This mini-review focuses on the most updated evidence supporting the main tools available to diagnose and monitor LVV. The advantages, limitations, and innovative applications for each tool are discussed. The review highlights how the different diagnostic modalities should be used in a complementary way according to local availability and expertise, predominant clinical phenotype (cranial versus LV-GCA), timing from glucocorticoid treatment initiation (with the longest diagnostic yield demonstrated for TAB), patient's preference, and cost considerations. Often, the different diagnostic or monitoring options can be applied in a step-wise fashion guided by pre-test clinical probability and initial findings (i.e., TAB requested in case of negative temporal artery US in a patient with predominantly cranial features, or PET/CT performed in a patient with negative axillary artery US and ongoing high suspicion for LV-GCA). One of the most relevant achievements emerging from the review is the increasing body of evidence supporting the role of imaging for the monitoring of the disease and to assess response to treatment which will considerably improve the management of GCA in the future.

Author contributions

SM, VS, and FM contributed equally in the conception and writing of the manuscript. CS, CM, and RL contributed to the conception and design of the manuscript and critically revised it. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Patient-reported outcomes provide evidence for increased depressive symptoms and increased mental impairment in giant cell arteritis

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Objectives: The spectrum of giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) represents highly inflammatory rheumatic diseases. Patients mostly report severe physical impairment. Possible consequences for mental health have been scarcely studied. The aim of this study was to investigate psychological well-being in the context of GCA and PMR.

Methods: Cross-sectional study with *N*=100 patients with GCA and/or PMR (GCA-PMR). Patient-reported outcomes (PROs) were measured using the Short Form 36 Version 2 (SF-36v2) and visual analog scale (VAS) assessment. Moreover, the Patient Health Questionnaire 9 (PHQ-9) was used in 35 of 100 patients to detect depression. To compare PROs with physician assessment, VAS was also rated from physician perspective. To assess a possible association with inflammation itself, serological parameters of inflammation (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) were included.

Results: In all scales of the SF-36v2 except General Health (GH) and in the physical and mental sum score (PCS, MCS), a significant impairment compared to the German reference collective was evident (MCS: d=0.533, $p<0.001$). In the PHQ-9 categorization, 14 of the 35 (40%) showed evidence of major depression disorder. VAS Patient correlated significantly with PHQ-9 and SF-36 in all categories, while VAS Physician showed only correlations to physical categories and not in the mental dimensions. Regarding inflammatory parameters, linear regression showed CRP to be a complementary significant positive predictor of mental health subscale score, independent of pain.

Conclusion: PRO show a relevant impairment of mental health up to symptoms of major depression disorder. The degree of depressive symptoms is also distinctly associated with the serological inflammatory marker CRP.

KEYWORDS

giant cell arteritis, PRO, depression, mental impairment, SF-36, PHQ-9, VAS, polymyalgia rheumatica

1. Introduction

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are rheumatic diseases of people of older age (1). Both entities belong to a common spectrum of highly inflammatory diseases and are closely related (2, 3). While GCA is primarily a vasculitis of the large vessels, PMR is a mostly symmetrical inflammation of the extracapsular structures, primarily of the shoulders and pelvic girdle (4). Both conditions can occur isolated, overlapping or sequential (2, 5, 6). Patients frequently experience severe pain and also report unspecific symptoms such as disturbed night sleep, weakness, and malaise, lowering quality of life (7, 8). To date, structured data on psychological dimensions of well-being in the context of the GCA-PMR spectrum are scarce, especially how strongly the disease is associated with major depression disorder (9, 10). It is also unclear whether the inflammatory activity itself impacts the mental state and quality of life (summarized from here as "psychological impairment") or whether the impact is due the unspecific variables such as pain and sleep disturbances. Isolated case reports exist on brain organic symptoms in the context of GCA (11–13) that may lead to psychological impairment. Therefore, the aim of the present cross-sectional study was to investigate health related quality of life (HRQoL), the amount of depressive symptoms, and major depression disorder in patients with initial diagnosis or recent relapse of GCA-PMR, using patient reported outcome measures (PRO). As we know from rheumatoid arthritis (RA) (14), disease activity is assessed differently by patients and physicians. The visual analog scale (VAS) is a widely used tool for assessment by patients and physicians in the context of GCA-PMR. Therefore, our aim was to investigate the VAS-based agreement between both, in particular, the value of the VAS for estimating HRQoL. To further investigate a possible association between inflammation and psychological impairment, we created a regression model using C-reactive protein (CRP) as an inflammatory protein.

2. Patients and methods

2.1. Patients

Hundred consecutive patients with initial diagnosis ($n = 88$) or recent relapse ($n = 12$) of a condition of the GCA-PMR spectrum were recruited by the Department of Rheumatology and Immunology of the University Hospital of Wuerzburg between May 2019 and January 2021. Informed consent was obtained from each participant. A total of $n = 120$ patients were studied, of whom $n = 20$ were excluded for further analysis because of incomplete data, i.e., questionnaires were not completely filled out or blood values were missing. The final sample size was $n = 100$. All patients met either the ACR 2022 classification criteria for GCA (15) or the 2012 provisional EULAR classification criteria for PMR (16) and were part of the "Wuerzburg GCA Registry." A defined set of patient-related outcome measures was collected in all patients, namely VAS Patient, SF-36v2 and PHQ-9. Since the PHQ-9 was not originally collected from all participants, a sample size of only $n = 35$ could be collected specifically for the PHQ-9. Patients completed the questionnaires while they were in the hospital or outpatient clinic. They received a short briefing and then completed the questionnaires themselves without any time limit. Physicians evaluated VAS during the visit. Furthermore, serological inflammatory markers were collected (C reactive protein, erythrocyte sedimentation rate [ESR]), the VAS Physician and the Glucocorticoid Toxicity Index (GTI). The present study was designed as a cross-sectional study at new onset/recent relapse of GCA and/or PMR to investigate the impact of the disease on HRQoL and depression.

2.2. Methods

2.2.1. Questionnaires

To assess HRQoL, the second version of the SF-36v2 was used. In addition, to examine depression symptoms, the depression-specific module of the Patient Health Questionnaire (PHQ), the PHQ-9, was added. In all cases, the German version of the questionnaires was used. To obtain an assessment of current GCA activity and disease-related limitations, both the patient and the treating physician were asked to provide an individual score on a visual analog scale: VAS Patient and VAS Physician.

2.2.1.1. SF-36v2

The SF-36v2 (*QualityMetric Inc.*) assesses subjective well-being and health with 8 different scales and 2 summary scales for physical and mental health. The eight scales include general health (GH), physical functioning (PF), role physical (RP), role emotional (RE), social functioning (SF), bodily pain (BP), vitality (VT), and mental health (MH). In addition, summary scores for the mental (MCS) and for the physical components (PCS) can be calculated from these scales. Scores between 0 and 100 are possible for each scale, with a higher score representing greater well-being and better health. Both the SF-36v2 and its predecessor, the SF-36, are reliable and valid (Cronbach's $\alpha = 0.81$–0.94) (17, 18). For comparison with healthy controls, reference collectives exist that consider age, sex, and home country. For our study, the age-matched German reference collective was used.

2.2.1.2. PHQ-9

The PHQ-9 is a well-established and economic questionnaire to assess depression and consists of 9 questions, each of which corresponds to a diagnostic criterion for major depression disorder according to DSM-IV (19). These include perceptions of pleasure in activities, depressed mood, sleep disturbances, feelings of low energy or fatigue, decreased or increased appetite, feeling like a failure, difficulty concentrating, slowed speech and slowed movements or a strong urge to move, and suicidal thoughts and self-harming behavior. The questionnaire assesses the past two weeks (20) and can be scored categorically to obtain a cut-off score that makes a diagnosis of depression likely or as a summative score to determine the severity of depressive symptoms (19). It can be useful for diagnostic purposes, but can also be used to analyze treatment progress (21). Responses are scored in ascending order of 0, 1, 2, or 3 points, resulting in a total score ranging from 0 to 27, with a higher score indicating a higher amount of symptoms (19). A major depression is likely if 5 or more items are answered with at least "more than half of the days" and one of these items is depressed mood or anhedonia (item 1 or 2). A classification as "other depression" can be made if 2–4 items are answered as described above. When the PHQ-9 is used to measure the severity of depressive symptoms, a classification is made into minimal (total score: < 5), mild (total score: 5–9), moderate (total score: 10–14), moderately severe (total score: 15–19), and severe symptoms (total score: ≥ 20). Good validity and reliability values have been demonstrated (Cronbach's $\alpha = 0.89$) (19, 22).

2.2.1.3. VAS

In the context of GCA, the VAS represents a tool to numerically assess disease activity and disease burden, with 0 mm representing the minimum value and 100 mm representing the maximum value. This was rated from the perspective of the patient (VAS Patient) and in a separate VAS also from the perspective of the treating physician (VAS Physician) (23). The VAS was collected as a paper version. VAS scales are commonly used to measure subjective attitudes, pain, or moods because they are easy to implement and can reflect the continuous nature of the measured value (24). Good psychometric properties have been found in various situations (23, 25, 26).

2.2.2. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 27.0 (IBM Corp., 2020) and jamovi 2.2.5 (The jamovi project, 2022). Means and 95% confidence intervals per scale were calculated from the SF-36v2 and compared with a German age- and sex-matched norm sample. This norm study was conducted between 2008 and 2011 by the Robert Koch Institute and the results were published in 2013 (27). For the comparison, one-sample *t*-tests with a significance level of $p < 0.05$ and Cohen's d as a measure of effect size were calculated for each scale, with $d \geq 0.2$ indicating a small effect size, ≥ 0.5 indicating a medium effect size and ≥ 0.8, indicating a large effect size (28). The PHQ-9 was evaluated categorically and using the sum score according to the suggestions of the questionnaire authors described earlier. Again, the mean score was compared with a German age- and sex-matched norm study conducted between 2003 and 2008 (29), using a one-sample t-test with a significance level of $p < 0.05$ and calculating Cohen's d as an effect size measure. Pearson correlations (Pearson's r) were calculated to assess associations between SF-36v2, PHQ-9, VAS scores, and C-reactive protein, with $r \geq 0.1$ indicating a weak correlation, ≥ 0.3 to ≤ 0.5 indicating a moderate correlation and > 0.5, indicating a large effect size (28). Finally, we investigated whether the detectable mental health symptoms are a consequence of bodily pain as a frequent trigger of mental health symptoms or whether they are independently associated with the inflammatory activity of the GCA. For this purpose, we performed a two-step hierarchical linear regression analysis using the bodily pain subscale of the SF-36v2 as a predictor and the SF-36v2 mental health subscale as the dependent variable and C-reactive protein (CRP) as an additional second-step predictor.

3. Results

3.1. SF-36v2

The SF-36v2 questionnaire was collected from $n = 100$ patients of the "Würzburg GCA Registry." The characteristics of the patients are summarized in Table 1. For the evaluation of the SF-36v2 questionnaire, the mean values were compared to the mean values of the German norm sample. With the exception of the GH dimension ($p = 0.14$), all other 7 scales of the SF-36v2 showed a significant decrease in score ($p < 0.001$ for all 7 scales) compared to the control sample, corresponding to a decrease in well-being in both the physical and mental dimensions. In the categories RE, RP the effect size was strong, in the remaining categories the effect size was moderate. The component scores, PCS and MCS, were also significantly reduced with moderate effect size ($p < 0.001$ for both, PCS $d = -0.58$, MCS $d = -0.53$). The results are shown in Figure 1 and Supplementary Table S1.

TABLE 1 Patients' characteristics at time of evaluation.

Variable	Total *N*=100
Clinical parameters	
Female	61 (61%)
Age (years)	71.5 ± 8.5
Giant cell arteritis	66 (66%)
Polymyalgia rheumatica	25 (25%)
Giant cell arteritis/polymyalgia rheumatica	9 (9%)
New diagnosis	88 (88%)
Relapse	12 (12%)
Therapy-naïve patients at time of assessment	28 (28%)
Dose of steroids at time of assessment	40 ± 149 mg
Patients on immunosuppressants	14 (14%)
Markers of inflammation	
C reactive protein (CRP)	2.2 ± 2.94 mg/dl
Erythrocyte sedimentation rate (ESR)	30.67 ± 26.53 mm/1st hour ($N = 92$)

Percentages are given in parentheses. Standard deviations reported for age, dose of steroids at time of assessment, C reactive protein, and erythrocyte sedimentation rate.

3.2. PHQ-9

The PHQ-9 questionnaire was collected in 35 of 100 patients in addition to the SF-36v2. Evaluation of the PHQ-9 yielded a mean score of 8.8 (SE = 0.82), which was significantly above normal (M = 3.3, SE = 0.13), $t(35) = 6.606$, $p < 0.001$, $d = 1.117$. In addition, the PHQ-9 was evaluated according to the severity of symptoms (Figure 2). Minimal symptoms were present in 8 subjects (22.86%), mild symptoms in 11 subjects (31.43%), moderate symptoms in 12 subjects (34.43%), moderately severe symptoms in 3 subjects (8.57%), and severe symptoms in 1 subject (2.86%). Overall, 77.14% of patients had values above the cut-off value of ≥5 (at least mild symptoms) and 45.71% of patients had symptoms above the cut-off value of ≥10 (at least moderate symptoms).

According to the PHQ-9 categorization approach, 8 subjects met the proposed criteria for major depression (22.86%) and 6 subjects met the criteria for other depression (17.14%) (Figure 2). Thus, in total, 14 (40%) of the 35 patients had depressive symptoms that were categorized as clinically relevant or in other words, relevant to consider for depression-specific clinical interventions.

3.3. VAS

The mean value of the VAS Patient was 42.8 ± 28.4 mm, the mean value of the VAS Physician was 32.8 ± 31.5 mm. Thus, the assessment of disease activity differed significantly between patients and physicians ($p = 0.003$). In no VAS Patient and no VAS Physician was

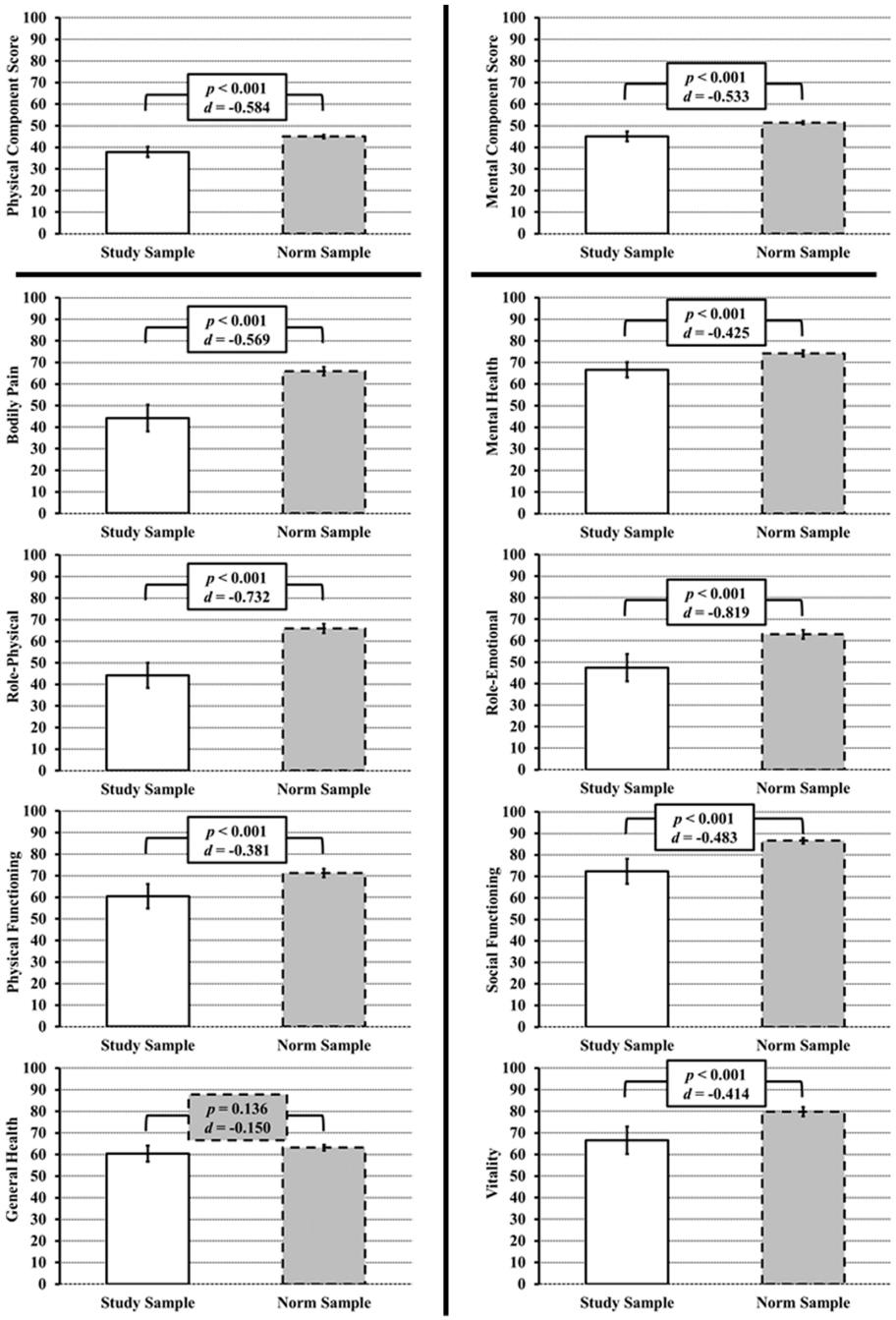

FIGURE 1
SF-36v2 scores at initial diagnosis/relapse of GCA and/or PMR. Left: Physical Component Score and all its subscales (Physical Pain, Physical Role, Physical Functioning) except General Health show a significantly lower score as compared to the SF-36v2 healthy norm sample (gray bars). Right: For the Mental Component Score and all its subscales (Mental Health, Role Emotional, Social Functioning, Vitality), a significantly lower score as compared to the SF-36v2 healthy norm sample is also evident.

activity reported as 0 mm, i.e., according to patient and physician assessment, disease activity was present in all patients at the time of assessment.

3.4. Correlations of SF-36v2, PHQ-9, and VAS

Some of the items of the mental components of the SF-36v2 refer to depressive symptoms, but unlike the PHQ-9 it does not explicitly examine depression. Therefore, a comparison of SF-36v2, PHQ-9 and VAS Patient and VAS Physician was made. The results are shown in Table 2. All individual scales of the SF-36v2 showed significant negative correlations with the sum of the PHQ-9; accordingly, the higher the depression in the PHQ-9, the lower the well-being reported in the SF-36v2. The sum scores (PCS and MCS) also showed a strong negative correlation, although this was more pronounced for the MCS than for the PCS: MCS: $p < 0.001$, $r = -0.79$, PCS: $p < 0.001$, $r = -0.57$.

The VAS Patient showed a significant negative correlation of medium size with the PHQ-9 score and significant negative

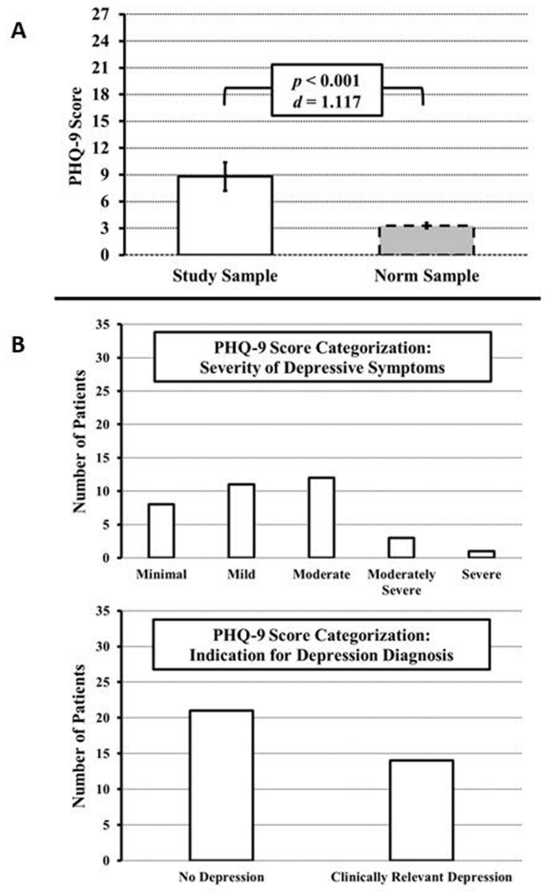

FIGURE 2
PHQ-9 scores at initial diagnosis or at relapse of GCA and/or PMR to detect depressive symptoms. **(A)** Compared to the German PHQ-9 healthy norm sample, the prevalence of depressive symptoms is significantly increased. **(B)** PHQ-9 categorization approach. Top: Distribution by severity of depressive symptoms (minimal to severe). Bottom: Classification into non-clinically relevant and relevant depression according to Kroenke et al. (19).

correlations of small to strong effect sizes with the SF-36v2, both in the individual categories and the sum scores. In contrast, the VAS Physician showed a significant negative correlation of medium size only in the physical categories of the SF-36v2. No correlation was detectable in the mental categories, respectively MCS, of the SF-36v2 as well as the PHQ-9. VAS Patient and VAS Physician showed also a significant positive correlation with moderate effect.

3.5. Prediction of mental health symptoms based on bodily pain and CRP

In the first step, the bodily pain subscale score could be shown to be a significant positive predictor for the mental health subscale score. Adding CRP as an additional predictor in the second step of the hierarchical regression could significantly explain additional unique variance, with CRP as a complimenting significant positive predictor for the mental health subscale score. The results are summarized in Table 3.

4. Discussion

The aim of the study was to shed light on the relationship between GCA-PMR and impairment of mental health, here defined as the degree of depression symptoms and health related quality of life. Our results support the assumption that patients with GCA-PMR have worse HRQoL, higher depression scores and are in general not only physically but also mentally affected. These results are in line with recent studies, whereas the proportion of patients with depressive symptoms is significantly higher in our sample, possibly due to the additional application of the specific depression questionnaire PHQ 9 in a sub-cohort (30). Examination of the 8 scales of the SF-36v2 and the 2 component scores revealed that our collective was significantly below normal in all scales except the GH scale, with moderate to strong effect sizes (Cohen's d). This shows that the disease can affect all areas of HRQoL.

Of note, regression analysis showed also that mental impairment correlates with the inflammatory disease activity as measured by the CRP level. This suggests that inflammatory activity itself has an impact on psychological well-being, especially since several studies have associated higher blood CRP levels with more severe depression symptoms and poorer response to antidepressant treatment (31). This association has also recently been demonstrated in patients with rheumatoid arthritis (RA) and concurrent depression (32, 33).

Our results further demonstrate depressive symptoms as prevalent. PhQ-9 scores of patients in our sample were clearly above the norm ($\geq$ 10) and about 46% presented with moderate to severe symptoms of depression. In the comparative group of the German norm study, this value was found only in about 6% of the participants in all age groups (29). This score is often used as cut-off to decide whether further examinations such as a clinical-psychological interview should be conducted to validate the diagnosis of major depression (34). In a study of the authors of the PHQ-9, a cut-off score of $\geq$10 showed a sensitivity and specificity of 88% for major depression (19). Using the categorical evaluation of the PHQ-9, 40% of the participants in our study met the proposed criteria for major- or other depression.

In line with the previous studies mentioned above, correlations between the PHQ-9 and all scales of the SF-36v2 were also found in the present study, including the MH, VT, and MCS scales, which are relevant for the assessment of depressive symptoms. Consequently, both questionnaires are useful in assessing depressive symptoms.

Physicians' assessment of disease activity using the VAS correlated well with the physical dimensions of the SF-36v2 and with patients' VAS. However, similar to other rheumatologic entities, disease activity was rated significantly lower by the physician than by the patient (14, 35). With respect to the mental categories of the SF-36v2 and the PHQ-9, a significant discrepancy was demonstrated between the VAS physician and the PROs. No correlations were found. This suggests that mental impairment is underestimated by the physicians, especially since the VAS patients showed significant correlations, suggesting that the VAS is an appropriate instrument for assessing mental dimensions. Nevertheless, the direct comparison of VAS Patient and VAS Physician should be evaluated with caution, because the assessment is purely subjective and the respective assessment basis of the VAS is not precisely defined. Patient-reported outcome measures (PROs) give patients the opportunity to evaluate their current health status and the effect of a therapeutic intervention, taking their individual needs into

TABLE 2 Correlations of SF-36v2, PHQ-9, and VAS.

		PHQ-9	VAS Physician	VAS Patient	PCS	MCS
PHQ-9	Pearson's r	—				
	value of *p*	—				
	N	—				
VAS Physician	Pearson's r	0.131	—			
	value of *p*	0.491	—			
	N	30	—			
VAS Patient	Pearson's r	0.414	0.472	—		
	value of *p*	0.017	<0.001	—		
	N	33	97	—		
PCS	Pearson's r	−0.572	−0.455	−0.618	—	
	value of *p*	<0.001	<0.001	<0.001	—	
	N	35	93	97	—	
MCS	Pearson's r	−0.795	−0.032	−0.255	0.296	—
	value of *p*	<0.001	0.762	0.012	0.003	—
	N	35	93	97	100	—

The SF-36v2 sum scores (PCS and MCS) show a significant negative correlation with the PHQ-9 with moderate to strong effect sizes ranging from $r = -0.408$ to $r = -0.802$. The VAS Patient correlates significantly with the VAS Physician.

TABLE 3 Overview of the hierarchical linear regression analysis for the prediction the SF-36v2 subscale mental health, based on the SF-36v2 subscale bodily pain (including 100 patients) and CRP (including 98 patients).

Model 1: $R^2 = 0.178$	
Single predictor	0.237 [0.052]
B (bodily pain) [*SE*]	0.422
Beta (bodily pain)	$p < 0.001$
Model 2: $R^2 = 0.237$	
1st step predictor	0.306 [0.056]
B (bodily pain) [*SE*]	0.545
Beta (bodily pain)	$p < 0.001$
2nd step predictor	1.650 [0.607]
B (CRP) [*SE*]	0.273
Beta (CRP)	$p = 0.008$
Model 1 vs. Model 2: $\Delta R^2 = 0.059$	
$p = 0.008$	

B = unstandardized regression coefficient. SE = standard error. Beta = standardized regression coefficient. R^2 = explained variance.

account (36). The perspective of the treating physicians and nurses is thus supplemented by the patient's view and PROs can therefore offer a deeper insight into the success of the therapy and the patient's current quality of life (37). Furthermore, active involvement of the patients and continuous monitoring can generally improve adherence and communication between patient and physician and has also been associated with fewer reported symptoms of depression during treatment (38–40). Overall, PROs in combination with clinical data (blood count, imaging techniques, etc.) can provide a comprehensive picture of current well-being and the impact of interventions. There is no specific PRO for GCA-PMR yet, but it is currently developed by the Outcome Measurement in Rheumatology (OMERACT) Vasculitis Working Group (41). Patients with GCA were asked about important aspects of their HRQoL and possible items were developed from these: The result is a draft questionnaire, with psychometric testing still pending, that includes questions on topics such as: Fear of potential blindness, fatigue, pain, difficulty in socializing and despondency (42). A GCA-PMR-specific PRO could refine the course of treatment by better understanding patients' concerns. Perhaps we could find out whether there are different subgroups in the spectrum of GCA and PMR in relation to the recognition that both diseases belong to a spectrum of inflammatory diseases with different clinical manifestations (2). Robson and colleagues recently published a first draft for a GCA specific PRO-set, that now has to be further evaluated (42). In the case of GCA-PMR, PROs could be used to screen for depressive symptoms and then, if necessary, provide additional psychological treatment or referral to a psychiatric department.

A limitation of this study is that depressive symptoms were only assessed in a sub-cohort by the PHQ-9 questionnaire. Therefore, to solidify the interpretation of the PHQ-9, scatterplots of its correlations with the VAS and SF-36v2 scales are attached as a Supplementary Figure S1. Supplementary Figure S1 also includes scatterplots for the regression analysis variables as well as for the PCS with its subscales and the MCS with its subscales. Visual analysis of these scatterplots supports the idea that the significant correlations were not caused by outliers. However, the subpopulation that additionally used the PHQ-9 questionnaire did not have any special characteristics that could influence the results. Another limitation is that glucocorticoids may have effects on psychological well-being (43). 28 patients were treatment-naive at the time of the study; all other patients had glucocorticoid treatment. However, we demonstrated that psychological impairment was related to inflammation, although the treatment itself might have an impact on psychological well-being, this should be calculated with, as glucocorticoids are the cornerstone of GCA-PMR therapy. Future work is planned to extend the reported results with a larger sample and to evaluate the course of treatment, as well as to define different subgroups of patients, first, to identify those patients who need special care such as psychological intervention and,

second, to possibly associate specific symptoms or conditions with psychological impairment, e.g., via a network analysis approach [such as for example Schuler et al. (44)], provided for COPD and depression (44) that however, would need a considerably large sample size to reveal valid information [in the example of Schuler et al., (44), $N = 590$].

5. Conclusion

Symptoms of depression up to clinically relevant depression disorders are highly probable in patients with GCA-PMR and are probably linked to inflammation itself. The SF-36v2 is a good instrument to detect physical and mental impairment and correlates highly with the PHQ-9 as a depression-specific questionnaire. On the other hand VAS physician is not suitable to adequately assess depressive symptoms in patients with GCA-PMR. The underestimation of mental symptoms by physicians strengthens the current view that GCA-PMR specific PROs are mandatory to assess comprehensively patients' well-being.

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 human participants were reviewed and approved by Ethics Committee of University of Wuerzburg (Code: 109/19-am, Date: 25.04.2019). The patients/participants provided their written informed consent to participate in this study.

Author contributions

MF and PZ: conceptualization and project administration. MF, AK, and PZ: methodology. MA and AZ: software and formal analysis. MS, MG, and P-PS: validation. MF, AZ, P-PS, SH, JP, and PZ: investigation. MZ and AK: resources. MF, AZ, and PZ: writing—original draft preparation. MS, MG, SE, AK, JH, and MS: writing—review and editing. MF, AZ, and PZ: visualization. MS, AK, and JH: supervision. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

MF received speaker's fees, travel grants or compensation for board memberships from AbbVie, Novartis, Janssen, and Eli Lilly. MS received speaker's fees, travel grants, research funding, or compensation for consultancies or board memberships from AbbVie, Actelion, AstraZeneca, BMS, Boehringer/Ingelheim, Celgene, Chugai/Roche, Eli Lilly, Genzyme, Gilead, Hexal/Sandoz, Janssen-Cilag, MSD, Novartis, Pfizer, Sanofi Pasteur, Takeda (Shire), UCB (less than $ 10,000 each). MG received travel grants, compensation for advisory boards or speaker's fees from AbbVie, Chugai, Eli Lilly, Hexal, Janssen, Novartis, Pfizer, Takeda. P-PS received travel grants from AbbVie and Janssen-Cilag. JP received travel grants from CSL Behring, Galapagos, AbbVie. SE received speaker's fees, travel grants, research funding, or compensation for consultancies or board memberships from Janssen, Eli Lilly, Chugai, Roche, Takeda (Shire), AbbVie, Novartis, Pfizer, Galapagos, Amgen.

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.2023.1146815/full#supplementary-material

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Factors predicting death and cancer in patients with giant cell arteritis in Western Norway 1972–2012: a retrospective observational cohort study

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Objectives: Evidence as to whether or not giant cell arteritis (GCA) confers added risk of cancer or death is conflicting. Our aim was to identify factors predicting death or cancer in a large Norwegian GCA-cohort.

Methods: This is a retrospective observational cohort study including patients diagnosed with GCA in Western Norway during 1972–2012. Patients were identified through computerized hospital records using the International Classification of Diseases coding. Medical records were reviewed and data about registered deaths and cancer occurrences were extracted from the Norwegian Cause of Death Registry and the Cancer Registry of Norway. We investigated predicting factors using Cox proportional hazards regression.

Results: We identified 881 cases with a validated diagnosis of GCA (60% biopsy-verified). 490 patients (56%) died during the study period. Among 767 patients with no registered cancer prior to GCA diagnosis, 120 (16%) were diagnosed with cancer during the study period. Traditional risk factors were the main predictors of death; age at time of GCA-diagnosis [hazard ratio (HR) 2.81], smoking (HR 1.61), hypertension (HR 1.48) and previous cardiovascular disease (HR 1.26). Hemoglobin (Hb) level was also associated with risk of death with increasing Hb-levels at time of GCA-diagnosis indicating decreased risk of death (HR 0.91). Other GCA-related factors were not predictive of death. We did not identify any predictors of cancer risk.

Conclusion: In our cohort of GCA-patients, the risk of death was predominantly predicted by age and traditional risk factors. We found no significant associations with regards to the risk of incident cancer.

KEYWORDS

vasculitis, giant cell arteritis, temporal arteritis, epidemiology, death, cancer

Introduction

Giant cell arteritis (GCA) is the most common systemic vasculitis in adults. It is almost exclusively a disease of persons older than 50 years, with peak onset between 70 and 80 years. The population aging trend is most advanced in Europe and Northern America, where also the highest incidence of GCA has been reported. Further increase in life expectancy will affect both cancer-and GCA-epidemiology. The pathogenesis of GCA is recognized as a widespread inflammatory state affecting large and medium-sized arteries, and irreversible ischemic complications may follow. Furthermore, chronic inflammation is a well-documented risk factor for cancer (1). Nevertheless, evidence as to whether or not GCA confers added risk of cancer or death is conflicting and the understanding of contributing risks is incomplete (2–7). A major challenge for investigators has been lack of or limited ability to adjust for confounders, and limitations due to small sample sizes and/or short periods of follow-up. We report a 41-year follow-up study of 881 patients with validated GCA-diagnoses for whom multiple candidate risk factors were assessable. This study aims to investigate possible individual risk factors for cancer and death within the GCA-population.

Methods

This is a retrospective cohort study including patients diagnosed with GCA in Bergen Health Area (Norway) during 1972–2012. Patients were recruited from three somatic hospitals: Haukeland University Hospital, Haraldsplass Deaconess Hospital and Voss Hospital. The population size in the uptake area of these hospitals is approximately 440,000 inhabitants. Patients were identified through computerized hospital records using the International Classification of Diseases coding system. We collected data by reviewing medical records of all patients registered with a GCA-diagnosis following an outpatient visit or admission to any ward in the study hospitals from January 1st in 1972 until the end of study December 31st in 2012. We use the term "validated diagnosis" to indicate that an expert (rheumatologist), following chart review, agreed that clinical information was consistent with the diagnosis of GCA and not more likely to represent another disease. Clinical features including laboratory findings and histology were registered at the time of diagnosis. The status for traditional risk factors were also, and only, registered at time of diagnosis, i.e., upon entry into the cohort (baseline). Pharmacologic treatment (dose and type) was registered based on hospital documentation with extracted variables limited to the starting-dose and maximal dose of prednisolone prior to first registered remission or end of study. The observation period ended when the patient died or when the study ended. Further details about the inclusion process and characteristics of the GCA-population have been published previously (8). Extensive demographic and clinical data were collected. If vasculitis-related symptoms or clinical findings we sought were not mentioned in the medical records, they were considered absent. If laboratory or imaging parameters were missing they were registered as missing in the data set. To ensure accuracy and completeness of demographic and clinical data not related to the vasculitis (i.e., date/type of cancer and date/cause of death), information on these variables was obtained from national registries. We thus had available data allowing risk estimates for the following variables: age at GCA-onset (years, continuous variable), sex (male/female), centrality (urban/rural), year of diagnosis (categorized into 1972–1982, 1983–1992, 1993–2002, or 2003–2012), smoking status (yes/no/unknown), pre-existing diabetes (yes/no), pre-existing hypertension (yes/no), previous cardiovascular disease (yes/no), temporal artery biopsy (positive/negative), giant cells in biopsy (yes/no), polymyalgia rheumatica (PMR; present/absent), jaw claudication (present/absent), visual disturbance (any type assumed related to arteritis – yes/no), blindness (assumed related to GCA – yes/no), temporal artery tenderness or reduced pulsation (yes/no), C-reactive protein (CRP, mg/L), erythrocyte sedimentation rate (ESR, mm/h), hemoglobin (Hb, g/dL), white cell count ($x10^9$/L), platelets ($x10^9$/L), initial prednisolone-dose (i.e., first dose following GCA-diagnosis, mg/day), maximum prednisolone-dose (i.e., prednisolone-dose before first attempt at tapering, mg/day). Unfortunately, large vessel (LV) involvement was not systematically documented in the time period of our study. Data, based on medical imaging technologies, on LV involvement was available for <1% of the cohort. Hence, this variable could not be included, nor could we attain data on complete duration of steroid treatment or cumulative steroid dose as late follow-up was partly done in general practice and data thus unavailable. Date of deaths were obtained from the Norwegian Cause of Death Registry to which the death of every Norwegian is mandatorily reported. Date and type of incident cancers were obtained from the Cancer Registry of Norway, in which all new cases of cancer in Norway (except basal cell carcinomas) have been registered since 1952. For cancer-analyses, we excluded patients with registered cancer diagnosis prior to GCA-diagnosis. This study was approved by REK sør-øst B regional ethics committee (study reference number 2012/643/REK sør-øst B).

Statistical analysis

We investigated predicting factors for hazard of death or cancer within the GCA-cohort using Cox proportional hazards regression. Selected variables were first analyzed in univariate and block regression models (block 1: clinical features including histology, block 2: laboratory and treatment factors, block 3: demographic and traditional risk factors). Variables included in the final multivariable model were selected on the following basis: value of $p < 0.1$ in univariate or block regression or otherwise deemed clinically relevant. For the analysis concerning hazard of death all parameters included in the final multivariable model were selected based on results (value of $p < 0.1$) in uni- or block analysis. For the analysis concerning hazard of cancer the parameters "age at GCA diagnosis" and "year of diagnosis" were included in the multivariable regression due to presumed clinical relevance despite value of $p > 0.1$ in uni- and block analyses. To minimize the risk of variable structure impacting the findings we kept "unknown," in addition to "yes" and "no," as possible values for the predictor "smoking status." Though presumed to have high clinical relevance, the variable "LV involvement" was omitted from the analyses due to a high degree of missing data. Significance level in the final model was set to 0.05.

Abbreviations: CI, Confidence Interval; CRP, C-reactive Protein; ESR, Erythrocyte Sedimentation Rate; GCA, Giant Cell Arteritis; Hb, Hemoglobin; HR, Hazard Ratio; LV, Large Vessel; PMR, Polymyalgia Rheumatica; SD, Standard Deviation; SPSS, Statistical Package for the Social Sciences.

Computing was done using SPSS version 26 (IBM Corp, Armonk) and R 4.0 (9). Graphics were created using Matlab 9.0 (Mathworks Inc., Natick).

Results

A total of 881 patients (71% female) were included following validation of the GCA-diagnosis. Mean age was 73 years (SD 9). 490 patients (56%) died during the study period. In final multivariable analysis, the traditional risk factors were most strongly associated with hazard of death: age at onset of GCA (HR 2.81, 95% CI 2.41–3.27, $p < 0.01$), smoking (HR 1.61, 95% CI 1.22–2.12, $p < 0.01$), hypertension (HR 1.48, 95% CI 1.18–1.86, $p < 0.01$) and previous cardiovascular disease (HR 1.26, 95% CI 1.00–1.58, $p = 0.05$). Among laboratory parameters only Hemoglobin (Hb) levels were significantly associated with hazard of death with increasing Hb-levels indicating decreased risk (HR 0.91, 95% CI 0.85–0.98, $p = 0.01$). Presenting with visual disturbance (any) was associated with increased hazard of death in univariate analysis (HR 1.40, 95% CI 1.12–1.75, $p < 0.01$). However, this association was not observed in the multivariable analyses. Complete results from univariate and the final multivariable model are presented in Figure 1.

Among the 767 patients (72% female) with no registered cancer prior to GCA diagnosis, 120 (16%) were diagnosed with a first cancer during the observation period. No investigated variable was significantly associated with hazard of cancer in the final multivariable model (Figure 2). The complete uni-, block- and multivariable regression results are attached as supplementary material; Supplementary Table 1 for death analyses and Supplementary Table 2 for cancer analyses.

Discussion

In our large cohort of GCA-patients, the risk of death was predominantly predicted by age at onset of GCA and traditional risk factors (smoking, hypertension and previous cardiovascular disease). These are common risk factors for cardiovascular events, which were the most frequent causes of death in this cohort (3). Cardiovascular disease has also been identified as the most frequent causes of death in other GCA-cohorts (2, 10–13). However, recent publications indicate that GCA-patients may have beneficial risk profiles with regards to some cardiovascular risk factors. A significant inverse relationship between body mass index and GCA was demonstrated in a meta-analysis published in 2015 (14). More recently, Wadström et al. documented that GCA-patients had significantly lower fasting blood glucose, cholesterol and triglycerides compared to controls (15). These apparent contradictions challenge our understanding of what actually causes cardiovascular deaths in GCA-patients. Cardiovascular disease risk is multifactorial and contribution of one risk factor may be difficult to quantify independently of other factors. Furthermore, to our knowledge, robust data on the risk attributable to factors with great complexity, such as diet, physical activity patterns and socio-economic status are hitherto non-existent in the context of GCA. Furthermore, there is an inevitable connection for both carcinogenesis and mortality with increasing age. The exponential increase in death risk with chronological age is often referred to as the rate-of-aging. A recent study exploring whether the onset of severe chronic disease alters the rate-of-aging concluded that the rate-of-aging process in itself is not affected by disease history, but rather an underlying process of aging that causes mortality to increase at a

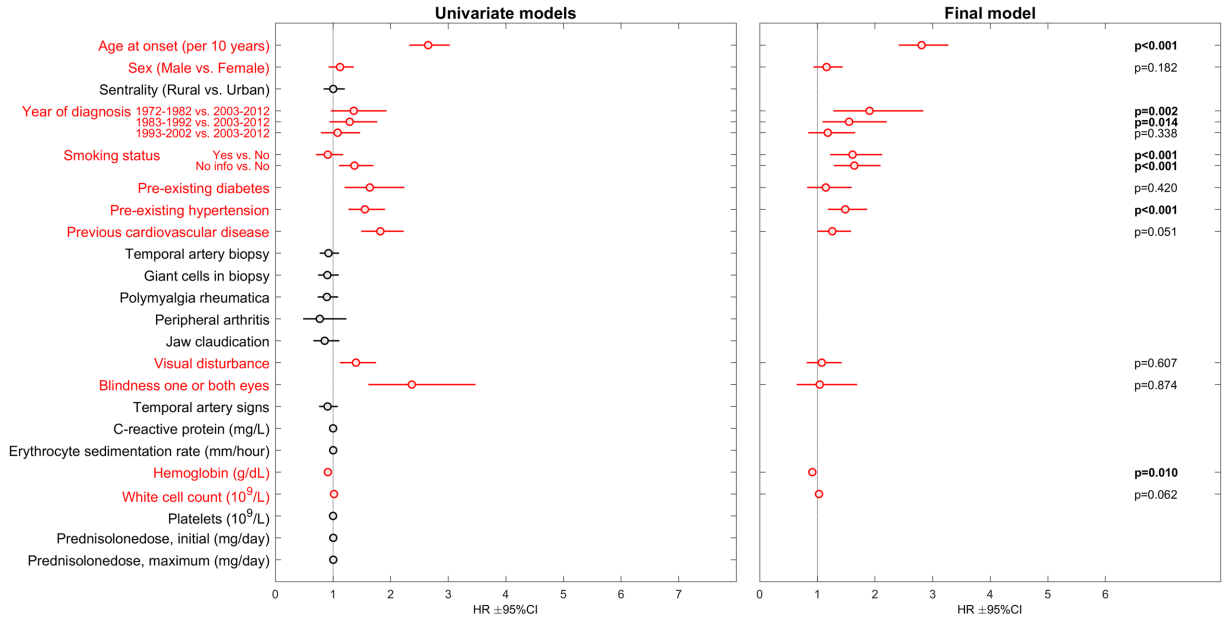

FIGURE 1
Results of Cox proportional hazards regression regarding risk of death in GCA-patients. HR, hazard ratio; CI, confidence interval. Parameters included in the multivariable analysis are presented in red.

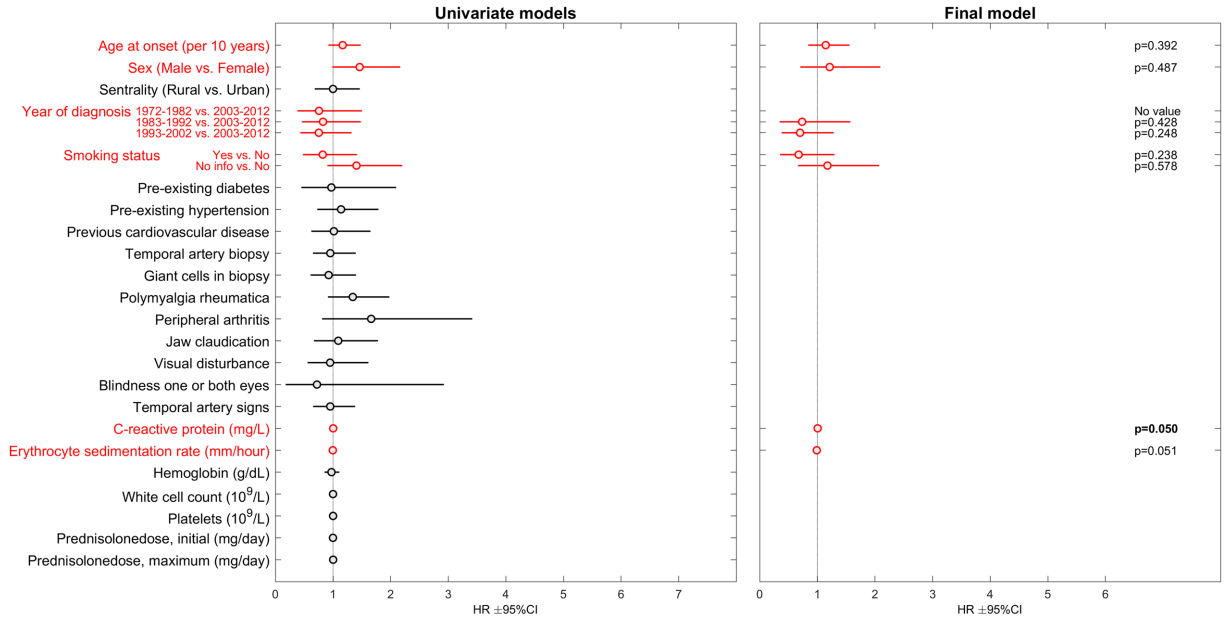

FIGURE 2
Results of Cox proportional hazards regression regarding risk of cancer in GCA-patients. HR, hazard ratio; CI, confidence interval. Parameters included in the multivariable analysis are presented in red.

set pace (16). Our results may be viewed as support to this perception.

The widening clinical spectrum of GCA has been well described in recent years, but there are still no definitions for disease subsets other than rough categorization into pure cranial GCA, mixed cranial and LV GCA and purely non-cranial GCA. Data on the presence or absence of LV involvement was available for <1% of our sample. Hence, this variable could not be included in our analyses. However, more recent studies with improved stratification of disease subsets are limited by shorter follow-up and the possibility of incomplete capture of deaths due to late vascular complications.

Macchioni et al. reported that presenting with PMR was associated with reduced mortality risk (17). We were not able to confirm this finding. In fact, no GCA-specific clinical feature was significantly associated with death in our multivariable model. Visual disturbance (HR 1.40), and visual loss (HR 2.37), were associated with risk of death in univariate analyses. Few events may explain the lack of association in our multivariable analysis. No specific GCA-symptom, finding, laboratory-parameter or treatment factor were found to be predictive of cancer risk in our GCA-cohort. This is in line with our previous finding of similar cancer risk in GCA-patients compared to population controls (7). However, our analyses could not confirm the known association of cancer with advancing age and smoking. This may be due to small numbers of events (120 incident cancers in 41 years).

Limitations

Our data are limited by the retrospective design and lack of information about LV involvement and cumulative steroid burden. A power analysis was not performed and weaker associations, or associations pertaining only to subgroups, may be undetected. Competing risk analysis was not performed in this work despite death being a competing risk when performing Cox analysis with cancer as the outcome of interest. Furthermore, some potential risk factors were not accounted for (e.g., diet, body mass, activity patterns, and sun exposure). However, a major strength of our study is the large cohort of patients with validated GCA-diagnoses resulting from thorough review of clinical data and exclusion of misclassified cases. Furthermore, the long follow-up period is vital when studying potential late outcomes such as death and cancer. Access to national registries with mandatory reporting provided excellent completeness of data on cancer and death.

Conclusion

Deaths in our cohort were predominantly predicted by modifiable cardiovascular risk factors in addition to age and existing co-morbidity. However, contributing risk factors for circulatory death needs to be further explored as this patient group is expected to expand along with the phenomenon of global aging.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: data is not available for privacy reasons. Requests to access these datasets should be directed to lene.kristin.brekke@hsr.as.

Ethics statement

The studies involving humans were approved by REK sør-øst B Regional Ethics Committee. 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 of the long duration of the study and the late onset of the disease.

Author contributions

All authors were involved in drafting the article or revising it critically for intellectual content and approved the final version submitted for publication.

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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

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SUPPLEMENTARY TABLE 1
Complete uni-, block and final multivariable regression results for mortality analysis. N, number of observations; HR, hazard ratio; CI, confidence interval.

SUPPLEMENTARY TABLE 2
Complete uni-, block and final multivariable regression results for cancer analysis. N, number of observations; HR, hazard ratio; CI, confidence interval.

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Increased vertebral canal diameter measured by ultrasonography as a sign of vasculitis in patients with giant cell arteritis

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Introduction: The diagnosis of giant cell arteritis (GCA) by ultrasonography including large vessels, apart from the temporal artery increases the sensibility of the study and informs about the risk of specific complications. However, there is less information about the study of these arteries, whose affection carries higher proportion of severe complications.

Objectives: To describe and analyze the value of the diameter of the cervical vertebral canal of the vertebral artery (VA) as a sign of vertebral vasculitis (VV) related to GCA and estimate the risk of stroke complications.

Materials and methods: Observational study of a population that includes patients with GCA with and without VA vasculitis as well as healthy subjects. We evaluated whether there were differences in VA diameter in the groups and, if so, we estimated the diagnostic capacity of the variable that best defines VA diameter using a ROC curve. Cut-off points with their associated reliability chosen thereafter.

Results: There were 347 subjects included:107 with GCA of whom 37 had vertebral vasculitis, 240 healthy controls. In patients with GCA and VV, the VA diameter was increased (No GCA 3.4 mm, GCA without VV 3.6 mm, GCA with VV 5.2 mm $p < 0.01$). According to the ROC curves, the variable defining vertebral diameter with best diagnostic accuracy is the sum of both sides (area under the curve of 0.98). With a cut-off point of 8.45 mm, the reliability values are: sensitivity 94.1%, specificity 94.5%, PPV 82.1% and NPV 98.4%. With a cut-off point of 9.95 mm, the sensitivity is 52.9% and the specificity is 100%. Likewise, VA diameter is independently associated with the presence of stroke in the vertebrobasilar territory (OR 1.6, range 1.2–2.2).

Conclusion: The VA diameter, measured as the sum of both sides, is an objectively measurable sign with very high reliability for detect vertebral vasculitis in patients with GCA. It is proposed here as a novel echographic sign, which can aid the detection of the involvement of an artery where the complications are especially serious.

KEYWORDS

giant cell arteritis, temporal arteritis, vasculitis, vertebral artery, stroke, neurosonology, ultrasound

Introduction

Giant cell arteritis (GCA) is the most frequent primary systemic vasculitis in adults (1). It is a granulomatous arteritis of large and medium-sized vessels, mainly affecting the supra-aortic trunks and their branches. Superficial temporal artery involvement is characteristic and is responsible for most of the typical symptoms associated with this disease (2, 3).

Depending on the arteries affected, GCA can cause potentially serious complications such as permanent visual loss, aortic aneurysm and dissection, ischemic stroke, and limb arterial ischemia. Even, it is infrequent the presence of vasculitis in large vessels (main branches of supraortic trunks), this subgroup of patients carries more frequently these severe complications (4).

Complications in the nervous system, mainly ischemic stroke, are mostly due to the involvement of the extradural vertebral arteries, rather than carotid and intracranial vasculitis (2, 4–6). In more than half of the cases, strokes are attributable to GCA as a result of vertebrobasilar system involvement (7). Vertebral artery (VA) involvement, which causes neurological deficits in the brainstem and/or cerebellum, results in high mortality if not diagnosed and treated in time (2, 7). In contrast, documented involvement of intracranial vessels in GCA is very rare (7).

In general, GCA is a rare cause of stroke. Stroke occurs in only 3 to 7% of cases but is the leading cause of death in patients with GCA (7, 8). Nevertheless, compared to atherosclerosis, stroke recurrence and mortality is much higher in GCA (9, 10). Although rare, it is important to identify them early on because these patients have a high mortality rate, however, treatment is available that drastically modifies this outcome if commenced promptly (11).

The classic clinical presentation of GCA revolves around cardinal signs and symptoms stemming mainly from systemic involvement and extracranial arteritis: subacute or chronic headache, constitutional syndrome, fever, elevated acute phase reactants, and macroscopic changes in the temporal artery. Indeed, due to the frequency with which they occur, the American College of Rheumatology use these as their clinical diagnostic criteria (12), currently considered the reference diagnostic benchmark for GCA and, in fact, constitute the diagnostic gold standard superseding all available complementary tests. Although these manifestations are frequent, a high percentage of patients exists where the diagnostic criteria are not met, this percentage being 27% according to a systematic review of cases (13). Indeed, the patients affected by vasculitis in large arteries often present with non-specific symptoms (4). Those uncommon symptoms can be the only presenting clinical picture. Thus, there are situations in which patients may present with a clinical picture that in most cases is very clear, allowing the diagnosis by the established diagnostic criteria; but also, others with very nonspecific symptoms in which the initial clinical suspicion may be, in some cases, low (3). According to some case series of GCA patients affecting the vertebral arteries, all patients presenting with stroke. Most of them did not have the classical symptoms of GCA associated with stroke (11). This subgroup of patients with VA involvement resulting from GCA is associated with increased mortality rates (3, 4, 7, 11). In these latter patients, the diagnosis becomes a challenge, since the detection of the disease, its treatment, and the speed of its onset and the swiftness of treatment can influence mark the appearance of complications and therefore the short and long term prognosis. For this reason, complementary tests are warranted in order to achieve rapid diagnosis with multiple diagnostic techniques having been developed to aid diagnosis promptly and in the greatest number of patients. All are based on the demonstration of vessel inflammation. Until a few years ago, the principal technique available was temporal artery biopsy. Indeed, it is still the reference technique in many centers for the diagnosis of GCA and remains as the first diagnostic test in some guidelines (14). However, it does have several disadvantages: delay in performing and obtaining the PA report and false negatives due to inadvertent biopsy of non-inflamed areas. In addition, it can be a crude technique, with potential for complications such as ischemia of the territory supplied by the artery which, importantly, includes facial skin. Due to this, alternative non-invasive techniques have been introduced, such as angioCT, angioMRI, PET, and temporal artery ultrasound (15).

Of these, it is worth noting that, in recent years, color duplex ultrasound has been proposed as a non-invasive diagnostic tool and as a screening test for suspected GCA (16, 17). The demonstration of a concentric-shaped hypoechoic area around the temporal artery (halo sign) is a common feature of GCA and is indicative of vasculitic mural edema (17, 18), which may lead to stenosis or even occlusion (altering the flow profile and changing the velocity of the blood flow in the affected areas of the vessels) (19). Meta-analyses indicate high reliability for this sign in the diagnosis of GCA (15, 17, 20–23). Since ultrasonography is an easy and accessible technique and reproducible with good reliability, it has been postulated in different guidelines as the first diagnostic test for suspected GCA (3, 17).

Furthermore, the halo sign is not exclusive to the temporal artery (19). In recent years, similar findings have been described in other arteries such as the vertebral, occipital, or axillary arteries. This points to the possibility of finding vasculitic signs by means of ultrasonography (11, 23–25).

The study of other vascular beds may allow considerably improved sensitivity of the test, and indeed this extended ultrasound protocol is recommended in multiple guidelines (3, 16, 17, 23, 26). It also allows identification of which arteries are affected and, in turn permits which specific complications the patient may suffer from to be predicted, for example, stroke in patients with vertebral involvement.

Thus, ultrasonography, which is a widely available technique allows fast and reliable diagnosis of GCA in many patients, enabling effective treatment to be started promptly thereby lessening the chances of severe complications. This benefit is not limited solely to patients who are screened for specific suspicion of GCA. There are some diseases, such as ischemic stroke, in which ultrasonography is routinely used in the acute phase of the disease. Thus, even in patients

with stroke as the only manifestation of GCA, without any cardinal symptoms as described in the diagnostic criteria, this disease can be diagnosed early in those centers where the staff are familiar with the typical vasculitic signs of GCA in the vessels usually studied (supra-aortic trunks and Circle of Willis).

In the subgroup of GCA patients suffering from ischemic stroke, the VA is the most frequently artery affected (6, 7), especially in the pars vertebralis, within the vertebral canal. There are several well described ultrasound signs used to detect this vasculitis, primarily consisting of the demonstration of a concentric thickening of the wall (macaroni sign) (11, 27, 28). This is detectable in many affected patients. The physicians in charge of the Neurosonology Laboratory of our center have analyzed a large number of patients allowing us to become familiar not only with the typical halo image in the temporal artery, but also with the vasculitic findings in other arteries. As a result, it has been possible to subjectively confirm that those patients with GCA who present vasculitic involvement of the VA are accompanied by a striking thickening of the diameter of the vertebral canal along the course of the artery between the transverse processes of the vertebrae (pars vertebralis or V2 segment). To our knowledge, this finding demonstrating pathologically increased thickness, has not previously been described as a sign of VA vasculitis. In this article, we present our case series of patients with GCA, with and without VA involvement. The main objective is to analyze whether GCA with vertebral vasculitis (VV) is accompanied by a pathological increase in the diameter of the vertebral canal and whether this diameter is a reliable diagnostic sign for vasculitis in this artery. Since this sign is easy to identify, were it to be included in diagnostic criteria, there would potentially be an increase the ability to diagnose GCA, even in those patients with paucisymptomatic or less frequent but more severe presentations (stroke). In these patients the ultrasonographic study of the acute phase may be the key to reaching the etiological diagnosis early enough for effective treatment and to avoid the poor prognosis that accompanies the subgroup of patients with GCA and vasculitic involvement of the vertebral arteries.

Patients and methods

Study population and ultrasonographic assessment

The design of the study corresponds to a unicentric retrospective observational study carried out in the Neurology Department of the Complejo Hospitalario Universitario de Albacete. A database was created for every patient diagnosed in our center (World Health Organization International Classification of Diseases version 9, code 446.5 and version 10 codes 31.5 and 31.6) between 2012 to 2022. The diagnosis for each case was checked for compliance with the diagnostic criteria of the American College of Rheumatology (12) and confirmed according to follow-up during 6 months. From this initial list, we selected those subjects who had undergone an ultrasonographic study in the Ultrasonography Laboratory of the Neurology Department, as part of the diagnostic process before starting treatment for GCA. The ultrasonographic study was carried out with the same devices (Esaote MyLab models 70 and 9, Modena, Italy) by a neurologist specifically trained for the diagnosis of GCA, following international standards (17).

The ultrasonographic study included in all patients the analysis of the cervical trajectory of the supra-aortic trunks the arteries of the Circle of Willis, and the temporal and occipital arteries. In patients with visual symptoms, a study of orbital blood vessels was added.

For superficial TA we used an 8–24 MHz frequency transducer [B-mode frequency, 18 MHz; depth, 15 mm; focus point below the artery, depending on the depth of the segment; color Doppler frequency, 12.5 MHz, pulse repetition frequency (PRF), 1.5 KHz]. The B gain was bright enough for distinguishing lumen and halo. Colour gain was the maximum possible without covering the halo. A 8–14 frequency transducer was used for extracranial arteries (B-mode frequency, 6 MHz; depth, 3 cm; focus point under the artery studied, depending on the depth of the segment; color Doppler frequency, 3.3 MHz; PRF, 1.0–1.5 kHz). Colour box was at least 15° between artery flow and sound waves.

All retained data from these studies are stored, including an image of any artery, suitable for morphological and hemodynamic measurements.

The presence of cervical VA vasculitis was evaluated in the par vertebralis (V2 segment), which is the only cervical portion where wall alterations can be correctly evaluated. The ultrasonographic criteria consisted of the existence of iso or hypoechoic, concentric, homogeneous wall thickening with homogeneous content. The thickening of the wall stenoses the lumen of the artery and leaves a filiform color mode image in the blood flow with a variable degree of stenosis (Figure 1) (11, 27, 28).

Therefore, patients with GCA were divided into two groups. Patients with ultrasonographic signs of vasculitis in one or both vertebral arteries in the pars vertebralis were considered to have vertebral vasculitis. The rest were identified as patients with GCA without VV. A group of control patients without GCA, who had undergone the same ultrasonographic study, was included.

Finally, a third control group was added consisting of subjects referred to the Neurosonology Laboratory for suspected GCA in whom GCA could be ruled out. The same ultrasonographic study was performed in all cases.

The diameter of the vertebral canal along the pars vertebralis was analyzed in all study subjects from the saved images of the previously performed ultrasonographic study. All measurements were performed by the same investigator. For this purpose, the distance of the canal was calculated defining the limits of the canal by the anterior and posterior borders of the bony surface within the vertebral canal (Figure 1). Although the canal is homogeneous in diameter in most of the subjects, a minimum of 3 measurements were taken and the mean of these was calculated as the final value. Those subjects in whom the image of the VA was not appropriate for such measurement were eliminated.

The value of the VA diameter (VAD) on each side was obtained from each patient. Based on these data, two different variables were used to define the vertebral diameter. In the analytical study, the variable with the best capacity to diagnose VV was calculated. The diameter of the vertebral arteries and the vertebral canal is asymmetric in most healthy individuals. Although in most subjects the difference in diameter is small, in up to 10% of cases, the asymmetry is very marked. In these cases, one artery is hypoplastic and the other is abnormally large in diameter (27). It is considered that there is hypoplasia of a VA when the channel on one side is less than 2.0–2.5 mm or the contralateral diameter equals less than 50% of the

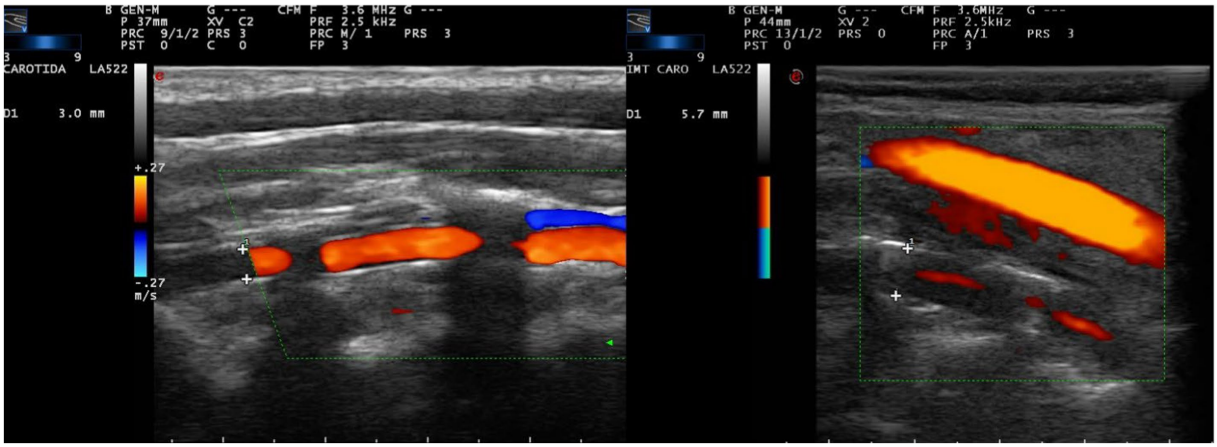

FIGURE 1
Color mode ultrasound at cervical level in paramedial sagittal projection, centered on the pars vertebralis of the vertebral artery, inside the vertebral canal. The diameter of the vertebral canal is measured defining the limits of the canal by the anterior and posterior borders of the bony surface within the vertebral canal (crosses). This value is referred in the left side of each image. **(A)** Vertebral artery of normal morphological characteristics and diameter (3.0 mm). **(B)** Common carotid artery (superficial) of normal characteristics and vertebral (deep) with data of vasculitis, with symmetric concentric wall thickening, with hypo/anechoic content, which leaves a filiform passage of central flow. The diameter of the canal is pathologically increased (5.7 mm).

contralateral (29). Nevertheless, the sum of both diameters remains similar to that of the general population. Therefore, a value of vertebral diameter taken individually could have less diagnostic power in diseases in which there is dilatation of the vertebral diameter. The calculation of the sum of the VA diameter of both sides may allow a better differentiation between pathological dilatations and healthy subjects with hypoplasia of one VA and contralateral compensatory hyperplasia.

Therefore, the two variables used in the analytical study were the vertebral diameter of each artery (Unilateral VAD) and the sum of the VA diameter of both sides (Sum of VAD).

Statistical analysis

Baseline analysis

First, a descriptive study was carried out indicating the baseline characteristics of the sample. Categorical variables were described as percentages. Quantitative variables were indicated as mean and confidence interval (95%). The overall values and those of the three subgroups (No GCA, GCA without VV and GCA with VV) were indicated. We analyzed whether the baseline characteristics were homogeneous among the three subgroups of subjects or whether there were any variables in which the baseline values showed statistically significant differences. Since there were three subgroups, qualitative variables were analyzed using a Chi-square test, while continuous variables were analyzed using ANOVA. The results are shown numerically and graphically.

Analytical study

In the first part of the analytical study, we evaluated whether there was a difference in the mean vertebral diameter between the subjects of the three subgroups using an ANOVA study. The results are shown numerically and graphically. As described in the results, differences were found in one subgroup of patients (GCA with VV) versus the rest of the sample. Therefore, the sample was thereafter divided into two groups of patients: Patients without VV (No VV) and patients with VV due to GCA (GCA with VV). With the sample dichotomized into two subgroups, we analyzed by the t-Student's test whether the mean vertebral diameter in the subjects was different between the two subgroups.

Following this, a multivariate study was performed using logistic regression to demonstrate whether the relationship between the vertebral diameter value and the presence of VV was independent of the presence of other confounding factors.

In all analyses, the vertebral diameter value was measured considering the two selected variables: Unilateral VAD and Sum of VAD.

In the second part of the analytical study, the reliability of the diagnosis of VA vasculitis in patients with GCA was evaluated using VAD values. For this purpose, a ROC curve was performed using the presence of VV (yes or no) as the dependent variable. The two indicators of vertebral diameter were evaluated as independent variables: Unilateral VAD and Sum of VAD. A ROC curve was constructed with each of the two independent variables. The ROC curve with a higher area under the curve value defined the VAD variable with the highest diagnostic capacity for the presence of VV.

From the ROC curve, the cut-off points of greatest reliability and clinical interest were selected, based on the sensitivity and specificity values they provided. The positive and negative predictive values for each VAD variable and each proposed cut-off point were calculated using the Chi-square test.

Finally, a similar analysis was performed to evaluate the association of the vertebral diameter value with the presence of GCA and with ischemic stroke in the vertebrobasilar territory. If a strong association was found, diagnostic capability was evaluated.

Ethical-legal aspects

This study was conducted in compliance with the Declaration of Helsinki principles and received ethics approval by the local Research

Ethics Committee of the Complejo Hospitalario Universitario de Albacete. No written informed consent was needed by the ethics committee because of the retrospective study design, in accordance under the national legislation and the institutional requirements.

Results

Study population

A total of 347 subjects were included in the study over a period from September 2021 to February 2023. Of the total sample, there were 107 (30.8%) subjects with GCA and 240 without (Table 1).

Within the group of GCA patients, 37(34.6%) had vasculitic involvement affecting the cervical segment of some VA (GCA with VV).

The mean age of the sample was 73.1 years. The distribution according to sex was 54.1% female and 45.8% male (Table 2). The ANOVA study showed that the sample was not homogeneous in age (Table 2), indicating that patients with CGA were older. In the case of sex, the Chi-square study showed no statistically significant differences (Table 2).

Stroke in vertebrobasilar territory

Of the 347 patients studied, 17 had a stroke (4.9% of the total sample, 15.9% of patients with GCA) (Table 3). All strokes affected the vertebrobasilar territory.

All the strokes occurred in patients with GCA. Moreover, within patients with GCA, 15 were in patients with VV. The proportion of patients with stroke was significantly higher in the subgroup of patients with signs of vasculitis in the vertebral arteries (88,25) (Table 3).

Analytical study

Diagnosis of vertebral vasculitis associated to GCA

The analysis of the VAD showed differences between the three groups (Table 4). It was demonstrated using the two variables considered (Individual VAD and Sum of VAD) for VAD. Specifically, the subgroup of GCA patients with VV showed obviously higher VAD values compared with the rest of the patients (GCA without VV and No GCA) (Figure 2 and Table 5). In a multivariate analysis, the larger VAD in the subgroup of patients with GCA with VV was independent of the confounding factors studied. With these three variables, the logistic regression model has an R^2 of 0.76. The Sum of VAD reveals a statistical association ($p < 0.01$) and an OR of 8.1 (3.9–16.9). Neither age nor sex have a statistical association with the presence of VV.

In the analysis of the ability to detect VV by measuring VAD, the two variables used (Unilateral VAD and Sum of VAD) show a very high area under the curve on the ROC curve (AUC Unilateral VAD: 0.96, Sum of VAD: 0.98). The variable Sum of VAD showed the highest reliability (Figure 3).

Regarding the selection of the cut-off points with the greatest diagnostic capacity, in both variables there were two values of clinical interest: one with a lower value in which the balance of sensitivity and specificity was very favorable. The other cut-off point, with a higher value, offers a specificity of 100%, so that all measurements above that value correspond to patients with VV.

In the same way as the ROC curve values, the sensitivity, specificity, positive and negative predictive value were better when using the sum of the VAD of both sides as the variable (Table 6).

TABLE 1 Description of the sample (study population): frequency and percentage of patients.

GCA		NO GCA
107 (30.8%)		240 (69.2%)
VV	NO VV	
37 (34.6%)	70 (65.4%)	

GCA, giant cell arteritis; VV, vertebral vasculitis.

TABLE 2 Baseline characteristics of the whole population and subgroups.

	TOTAL	No ACG	GCA without VV	GCA with VV	*p*
Age (Years)	73.1 (11–91)	70.8	76.7	78	<0.01
Sex (Female %)	54.2	54.1	54	48.6	0.83

GCA, giant cell arteritis; VV, vertebral vasculitis.

TABLE 3 Clinical diagnosis of stroke in patients with GCA and patients without GCA.

		Stroke	No stroke	*p*
No GCA		0 (0%)	240 (100%)	<0.01
GCA	No VV	2 (3.2%)	68 (97.1%)	
	VV	15 (38.9%)	22 (61.1%)	

GCA, giant cell arteritis; VAD, vertebral artery diameter; VV, vertebral vasculitis.

TABLE 4 ANOVA test to compare the means of VAD diameter in patients without ACG, ACG without vertebral vasculitis and ACG with vertebral vasculitis.

	No GCA	GCA no VV	GCA with VV	*p*
Unilateral VAD	3.4 (3.3–3.5)	3.6 (3.5–3.7)	5.2 (5.0–5.5)	<0.01
Sum of VAD	6.9 (6.7–7.1)	7.2 (6.8–7.5)	10.4 (9.8–10.9)	<0.01

GCA, giant cell arteritis; VV, vertebral vasculitis; VAD, vertebral artery diameter.

Diagnosis of GCA

The reliability values for the diagnosis of GCA by VAD was poor. In the student *t*-test study, the mean sum value of the vertebral diameter of both arteries was significantly higher in patients with GCA compared to controls without the disease (Table 7). However, the ROC curve had an area under the curve of 0.70, from which no diagnostic cut-off point values could be obtained (Figure 4).

Evaluation of stroke risk

A student *t*-test study showed higher values of VAD in patients suffering an ischemic stroke in the vertebrobasilar area (Table 8).

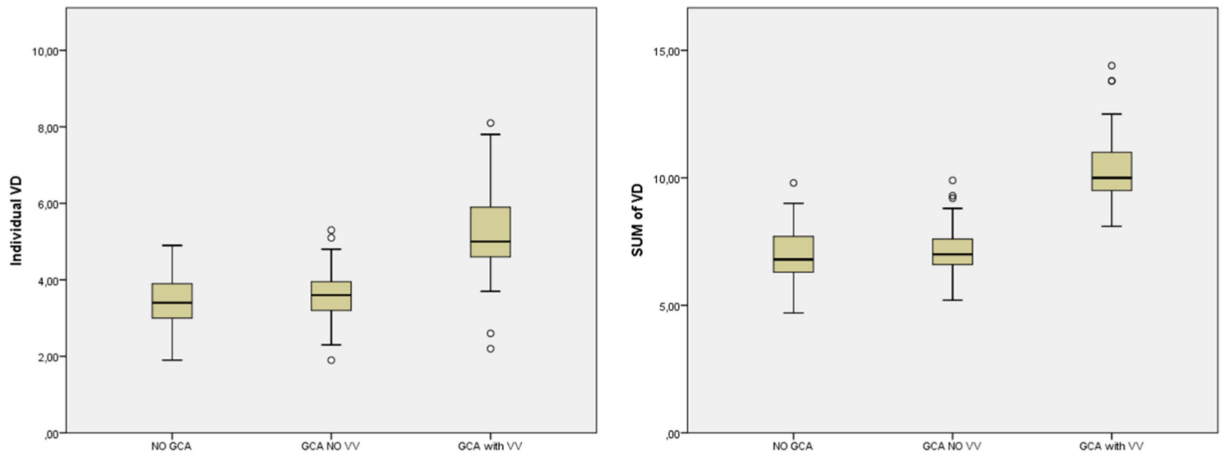

FIGURE 2
Mean VAD in patients without GCA, GCA without VV and GCA with VV. GCA, giant cell arteritis; VAD, vertebral artery diameter; VV, vertebral vasculitis.

TABLE 5 *t*-student test to compare the means of VAD diameter (mm) in patients with and without vertebral vasculitis.

	No VV	VV	*p*
Unilateral VAD (mm)	3.4 (3.3–3.5)	5.2 (5.0–5.5)	<0.01
Sum of VAD (mm)	6.9 (6.7–7.1)	10.4 (9.8–10.9)	<0.01

VV, vertebral vasculitis; VAD, vertebral artery diameter.

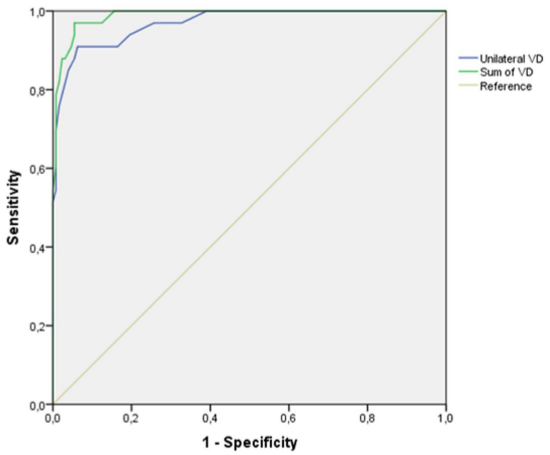

FIGURE 3
ROC curve for the evaluation of the validity of the variables of vertebral artery diameter to diagnose vertebral vasculitis due to GCA.

In a multivariate study using logistic regression, VV was independently associated with the presence of stroke in the vertebrobasilar territory. The Sum of VAD was significantly associated with the presence of stroke. The risk of vertebro-basilar stroke increases 1.62 times in relation to the increase 1 mm in the Sum of VAD (Table 9).

Discussion

In summary, the present study has demonstrated that in patients with GCA involving the cervical portion of the VA there is an increase in the caliber of the VAD detectable by ultrasonography. It has been possible to determine that the thickening is independent of other possible confounding factors.

Likewise, VAD has a high diagnostic reliability for VV in patients with GCA. The ideal way to evaluate the VAD can be defined as the sum of the diameter of the canal on both sides. This parameter shows an area under the curve with a very high value that corroborates the high diagnostic potential of the variable in an objective numerical form. Thus, it has been possible to establish cut-off values (Sum of VAD of 8.45 and 9.95 mm) with very high values of sensitivity, specificity, positive predictive value, and negative predictive value.

Notwithstanding, VAD, in isolation, shows low diagnostic reliability values for GCA.

Finally, the presence of thickening of the vertebral canal such as seen in this study is associated with the presence of an increased risk of ischemic stroke in the territory of the affected artery.

Regarding the main objective of the study, the VAD was clearly increased in those subjects who show vasculitic changes in the VA. To date, in our Laboratory of Neurosonology Laboratory, we only had the subjective impressions accumulated from the experience of physicians examining patients with GCA was evident. Now, all statistical analyses in this study have demonstrated this objectively by numerical analysis.

On the one hand, the results of the multivariate analysis have allowed us to determine that the association between VAD and the presence of vasculitis is independent of the cofactors studied. Given that this is a retrospective analysis, other variables that would have been interesting to include in the linear regression, such as the patient's anthropometric indicators (height, weight, or body mass index), were unfortunately not available. Given the strong association between VAD and the existence of vasculitis, it is to be expected that these other variables were not a confounding factor explaining the association found. However, their inclusion would have given greater quality to the results presented.

The ROC curve analysis confirmed that the VAD variable with the greatest diagnostic value is the Sum of VAD. It is this variable that confer the maximum benefit for the diagnosis of VV.

As explained at the beginning of the results, it is common to find healthy subjects in whom, together with a hypoplastic VA, the

TABLE 6 Cut-off points selected as the value of the variables which measures VAD: unilateral VAD Sum of VAD as discriminating cases of VV.

	Cut-off value (mm)	True/False Positives	True/false negatives	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Unilateral VAD	4.35	46/25	267/6	88.5	91.4	64.8	97.8
	5.35	27/0	292/25	51.9	100	100	92.1
Sum of VAD	8.45	32/7	121/2	94.1	94.5	82.1	98.4
	9.95	18/0	128/16	52.9	100	100	88.9

PPV, positive predictive value; NPV, negative predictive value; GCA, giant cell arteritis; VAD, vertebral artery diameter; VV, vertebral vasculitis.

TABLE 7 *t*-student test to compare the means of VAD diameter in patients with and without GCA.

	No GCA	GCA	*p*
Sum of VAD	6.9 (6.6–7.1)	8.5 (8.0–9.0)	<0.01

GCA, giant cell arteritis; VV, vertebral vasculitis; VAD, vertebral artery diameter.

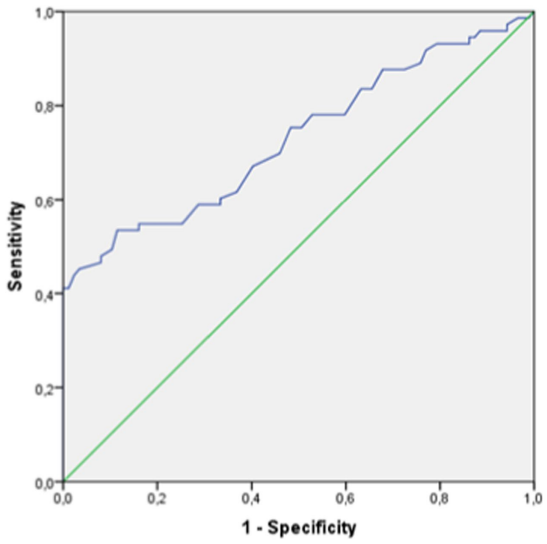

FIGURE 4
ROC curve for the evaluation of the validity of vertebral artery diameter to diagnose GCA.

TABLE 8 *t*-student test to compare the means of VAD diameter in patients with and without an ischemic stroke in the vertebrobasilar area.

	No stroke	Stroke	*p*
Sum of VAD (mm)	7.5 (7.2–7.7)	9.3 (8.3–10.5)	<0.01

GCA, giant cell arteritis; VAD, vertebral artery diameter.

TABLE 9 Multivariate analysis of factors associated to risk of ischemic stroke in the vertebrobasilar area.

	OR	*p*
Age	1.04 (0.96–1.12)	0.37
Sex	0.54 (0.16–1.88)	0.34
Sum of VAD	1.62 (1.19–2.19)	<0.01

GCA, giant cell arteritis; VAD, vertebral artery diameter.

contralateral VA has a somewhat larger diameter than usual. In daily clinical practice, the physician who performs studies of supra-aortic trunks is used to encountering this asymmetry. In the case of finding a VA with a small caliber flow signal, the physician must elucidate whether it is an individual constitutional characteristic or due to acquired pathology. One of the criteria that aid in determining that the small caliber artery is constitutional is to find the contralateral artery with a somewhat increased diameter, through which the flow is similar to that of subjects with symmetrical vertebral arteries (27, 29). Since physiological hyperplasia can reach values similar to those of arteries with vasculitis, the value that best defines such vasculitis is the Sum of VAD, where there is no contralateral hypoplasia in order to reduce the effect of constitutional confounder.

Consequently, when a study of supra-aortic trunks is performed by ultrasonography, it is part of the systematic study to check the caliber of the vertebral canal. Therefore, changes in VAD immediately draw attention. The knowledge of this diagnostic sign can help to have a suspicion of the presence of vasculitis just with the first B-mode image, even before checking other vasculitic changes by including the color mode.

Although vasculitic changes in the VA are usually detectable by sight for a physician accustomed to the study of this pathology, it is interesting to incorporate a new echographic sign that also provides numerical objective criteria, with robust validation. The reliability analysis indicates a very high discriminatory power of the variable, with a very low number of false positives and negatives. Specifically, in the case of the highest cut-off point (9.95 mm) there are no false positives at all, since all those with higher values show vasculitis in the VA. In addition, there are some patients in whom the assessment of the classic diagnostic criteria for VV is complicated (27). These criteria are based on the morphological evaluation of the lumen and the arterial wall, technically defined by the color mode. The VA is located in a deep area, and color mode differentiation may be poor, especially in patients with thick fat pads, somewhat limiting its utility. In the case of the VAD, the diameter data can be obtained in a simple way using only the B mode.

This echographic sign, the thickening of the VAD, is easy to recognize in any patient, even in those patients in whom there is no specific clinical suspicion of GCA when the study is performed. Its detection serves a dual purpose, not only detecting the presence of VV, but also completing the specific ultrasonographic study that leads to the diagnosis of GCA. Specifically, a high percentage of patients with GCA and VA involvement have a clinical presentation of ischemic stroke without the accompanying cardinal symptoms of GCA. In addition, the presence of vasculitis in this location is associated with a very poor clinical prognosis as seen in case of lack

or delay of specific treatment (7, 11). For this reason, it is crucial to maximize efforts to detect this subgroup of patients with subtle symptoms of GCA but a higher risk of severe complications in the absence of proper diagnosis and specific treatment. Protocols for the etiological study of ischemic stroke usually incorporate ultrasonographic study of the supra-aortic trunks within the first few hours of hospital admission. This led to the recommendation of fast-track clinics for detecting GCA which includes extended ultrasound studies in the early phase of the disease (18, 30). This diagnostic approach has been associated with lower rates of complications and better outcome (3, 15). Knowing and detecting the thickening of the vertebral canal within VV due to GCA may be indirectly the key to reaching an etiological diagnosis, early enough to start specific treatment to avoid serious complications.

Despite the evidence of the usefulness of the use of ultrasound for the diagnosis of GCA, not all scientific societies recommend its use as the first diagnostic test (14). The contribution of new evidence on the use of the technique may help this recommendation to become unanimous.

With respect to the internal validity of this study, the methodology and the population studied allowed us to obtain results which constitute evidence for the defense of the initial hypothesis. Regarding external validity, the studied population includes, with a sufficiently large sample number, the three clinical categories studied in daily clinical practice. The proportions of subjects do not reflect the real prevalence of the disease in the general population. Therefore, the basal data provided are not valid for estimate the prevalence of the disease. Nevertheless, this is not part of the objects of the study. Instead, the selected population reinforces the study's ability to evaluate the primary objective: the reliability of the vertebral diameter for the diagnosis of vasculitis in the vertebral artery. Specifically, it is worth emphasizing the size of the series of patients with GCA which was available for the study, including a high number of cases of VV. In general, the location studied, whilst possible, is reported as being infrequently used in many published clinical series (4). In addition, the studies were carried out with the required equipment/instruments in a laboratory as opposed to a clinical setting. Furthermore, the training required for the personnel performing the studies is the same as that required for any conventional supra-aortic trunk study.

There are no similar studies available that have analyzed the VAD as a sign of VV; this study is unprecedented to our knowledge and therefore the results cannot be compared with those of other studies. However, there are data available about the normal values of VAD in the normal population, which is comparable to the values of healthy subjects in this study (31).

In terms of evaluating the ability to diagnose the presence of giant cell arteritis by vertebral diameter, it does not seem to be a useful value, as indicated by the area under the ROC curve. However, we do see that all patients with pathological vertebral diameter values present with GCA. Therefore, although the vertebral diameter by itself is not a useful tool for the diagnosis of GCA, as we have previously stated, it has two advantages. On the one hand, in patients who are not believed to be suffering from GCA, the presence of vertebral vasculitis can facilitate the suspicion of this disease in patients without cardinal symptoms and the same ultrasonographic study can lead to the diagnosis of GCA by means of examination of the temporal artery. On the other hand, in those patients with known GCA, it is of great interest to discern whether the VA is affected, as this indicates a much higher risk of serious complications compared to those patients with unaffected vertebral arteries.

Among the study's weaknesses, there are several issues worth discussing. Firstly, it has already been indicated that the study is retrospective. While this is generally a lower quality criterion for a study, given the results obtained in this study, it does not seem likely that a prospective study would reveal very much more. Secondly, it would have been interesting to have studies carried out by two different observers which would permit calculation of the K index. Since ultrasonography is postulated as a test in which the results may be observer-dependent, this would be valuable information. However, with this in mind, the measurement of the vertebral canal by ultrasonography is very simple and does not require specific equipment or software, nor special training, since it is part of a very basic procedure within ultrasonography. Therefore, significant interobserver variability is not expected.

Finally, it is, of course, worth highlighting the strengths of the study. It is important to emphasize the sample size of the work. It has been possible to collect clinical information and ultrasound studies of a very high number of patients with GCA, with and without VV. This has been the key to being confident in the ng able to defend the results presented as validity of the results.

Conclusion

VAD as a marker of vasculitis in the VA by GCA is a highly sensitive and specific ultrasound sign, sufficiently reliable for use in routine clinical practice as a new diagnostic sign. As noted, it is easy to subjectively note the presence of an enlarged vertebral canal. The Sum of VAD leads the numerical variable with the best reliability to demonstrate VV. Given this, it is easy to locate an artery at risk of complications and even arouse suspicion of GCA in patients in whom there are no characteristic symptoms of this disease. Early diagnosis of GCA and VA involvement allows rapid initiation of pharmacological treatment, which has been shown to prevent complications, which are especially serious in the case of patients with vertebral involvement due to ischemic stroke in the territory of this artery (3, 11).

Scope statement

The present study shows a new ultrasound sign with high reliability for diagnosing the presence of vertebral artery vasculitis in the context of giant cell arteritis. The vertebral diameter is very easy to measure for any person skilled in ultrasonography. In addition, the cut-off points provided clearly differentiate cases of GCA with vertebral vasculitis from the rest of subjects; both from healthy subjects and those with GCA without vertebral artery involvement. This marker improves the diagnostic benefits of ultrasonography for several reasons. Firstly, it facilitates the detection of the subgroup of patients with the highest risk of severe complications (ischemic stroke) and worse functional prognosis. Secondly, it may be the key to reach the diagnose of GCA in paucisymptomatic patients who present with ischemic stroke as the only clinical picture.

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 Comité de Ética de la Investigación con medicamentos (CEIm) by Gerencia de Atención Integrada de Albacete. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because The study was retrospective with an anonymous database.

Author contributions

OA-M: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JG-G: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – review & editing. FH-F: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – review & editing. MPo: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – review & editing. BP-H: Investigation, Writing – review & editing. TB-E: Investigation, Writing – review & editing. AG-R: Investigation, Writing – review & editing. EM-C: Investigation, Writing – review & editing. BS-S: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – review & editing. MPa: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. TS: Conceptualization, Formal analysis, Methodology, Project–administration, Resources, 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1283285/full#supplementary-material

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Mycophenolate mofetil in giant cell arteritis

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Introduction: Giant cell arteritis (GCA) is a systemic granulomatous vasculitis affecting the large arteries. Abnormal lymphocyte function has been noted as a pathogenic factor in GCA. Mycophenolate mofetil (MMF) inhibits inosine monophosphate dehydrogenase and is therefore a highly lymphocyte-specific immunosuppressive therapy. We aimed to assess the efficacy of MMF for inducing remission in GCA.

Methods: Seven patients (5 female, 2 male) with GCA under therapy with MMF and who were treated at the outpatient clinic for rare inflammatory systemic diseases at Hannover Medical School between 2010 and 2023 were retrospectively included in the study. All patients underwent duplex sonography, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), magnetic resonance imaging (MRI), and/or biopsy to confirm the diagnosis. The primary endpoints were the number of recurrences, CRP levels at 3–6 and 6–12 months, and the period of remission.

Results: All patients in this case series showed inflammatory activity of the arterial vessels in at least one of the imaging modalities: duplex sonography ($n = 5$), ^{18}F-FDG PET ($n = 5$), MRI ($n = 6$), and/or biopsy ($n = 5$). CRP levels of all patients decreased at the measurement time points 3–6 months, and 6–9 months after initiation of therapy with MMF compared with CRP levels before MMF therapy. All patients with GCA in this case series achieved disease remission.

Discussion: The results of the present case series indicate that MMF is an effective therapy in controlling disease activity in GCA, which should be investigated in future randomized controlled trials.

KEYWORDS

Mycophenolate mofetil, giant cell arteritis, vasculitis, case series, imaging

Introduction

Giant cell arteritis (GCA) is a systemic granulomatous vasculitis that predominantly affects large-sized arteries. GCA is one of the most common primary form of vasculitis and has a prevalence of 24–280 cases per 100.000 persons older than 50 years (1). GCAs are associated with significant morbidity. The arterial inflammatory process may involve the aorta, coronary arteries, or vessels of the extremities in addition to the extracranial arteries. The most serious consequences are blindness, aortic aneurysm, myocardial infarction and stroke. Clinically, GCA is characterized by cranial symptoms such as headache and scalp pressure tenderness. In most

patients, a systemic inflammatory response is seen with fever, weight loss, night sweats and a rapid response to glucocorticoid therapy (2).

Abnormal lymphocyte function was found as one pathogenic factor in large vessel arteritis (3). Mycophenolate mofetil inhibits the inosinemonophosphate dehydrogenase DNA synthesis pathway, and is therefore a highly lymphocyte-specific immunosuppressive therapy (4). Considering the pathogenesis of GCA, it is apparent that MMF may be a suitable therapeutic approach for the treatment of GCA, nevertheless there is little data on the success of the therapy so as to date.

Despite the lack of randomized clinical trials, the putative crucial role of lymphocytes in the pathogenesis of GCA and the safe, well-tolerated treatment and proven efficacy of MMF in other vasculitis, such as ANCA vasculitis (5), have led to the use of MMF in clinical practice.

Although there are no defined biological markers to assess disease activity, patients with GCA usually have elevated C-reactive protein (CRP) levels. Therefore, normal CRP levels are good indicators of disease remission (6).

The guideline on therapeutic procedures in diagnosed GCA recommends glucocorticoid-sparing therapy with tocilizumab and, if necessary, methotrexate after individual consideration. MMF is not recommended in national guidelines due to lack of randomized trials. To our knowledge, there are currently two published studies on the usefulness of MMF in GCA, however, they were single case studies (7, 8).

Patients and materials

Inclusion of patients

The included patients were treated at the outpatient clinic for rare inflammatory systemic diseases at Hannover Medical School between 2010 and 2023 and retrospectively included in this study. Diagnosis was confirmed by typical clinical symptoms, laboratory, duplex sonography, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), magnetic resonance imaging (MRI), and/or biopsy. Table 1 summarizes the detailed patients characteristics.

Definition of disease activity and remission

According to the GiACTA study (9) active disease was defined as the presence of clinical signs and symptoms attributable to GCA and increased levels of inflammatory markers (CRP $\geq$1 mg/dL).

Remission was defined as the absence of signs and symptoms of GCA and normalization of CRP (<1 mg/dL) for more than 6 months. We extended the definition and included imaging findings, so patients were not allowed to show any activity in an imaging diagnostic.

Data extraction

Age, sex, clinical presentation, time of diagnosis, course of therapy and time since remission were extracted from the patient record. In addition, inflammatory parameters in the blood at 3 time points (therapy start with MMF, 3 months after therapy start with MMF, 6 months after therapy start with MMF) were collected from the laboratory data. Furthermore, various radiological findings (duplex sonography, ^{18}F-FDG PET, MRI) and histopathological findings (biopsies of the temporal artery) were extracted from the electronic patient record.

Results

Seven adult patients (five women and two men) aged between 67 and 83 years (mean age 77 years) with GCA presented with differing clinical symptoms. The most common symptoms were general fatigue, general feeling of sickness and headache ($n = 5$). Two patients described visual disturbances and four patients myalgias. All patients in this case series showed inflammatory activity of the arterial vessels when diagnosed with GCA. Duplex sonography was performed at diagnosis in most of the patients. Three patients showed a classic 'halo sign' in one or both temporal arteries. One patient showed arterial occlusion of the femoral artery on the right and on the left side.

Temporal artery biopsy was taken in five patients to confirm the diagnosis. A classic finding of temporal arteritis was found in all patients. Six patients were examined by MR angiography as part of the diagnostic process. Aortitis was seen in four patients. One patient showed pronounced signs of cerebral microangiopathy while no inflammation was seen in one patient on MR angiography. ^{18}F-FDG PET scans were performed in five patients. Here, large vessel vasculitis was seen in the area of the aorta ($n = 3$), and lower extremity arteries ($n = 1$). In one patient, no activity was seen in the ^{18}F-FDG PET scan. Two patients underwent a baseline ^{18}F-FDG PET scan at time of start of therapy with MMF and a follow-up ^{18}F-FDG PET scan during the course of therapy. Here, a marked reduction in inflammatory activity could be seen, consistent with response to therapy (see also Figure 1) (Detailed description is given in Table 1). The most frequent therapy before starting therapy with MMF apart from glucocorticoids was MTX ($n = 5$). During therapy with MTX 3 patients relapsed.

High dose glucocorticoid therapy (40–60 mg/day prednisone-equivalent) was initiated immediately for induction of remission in active GCA. Once disease was controlled, the GC dose was tapered to a target dose of 15–20 mg/day within 2–3 months and after 1 year to $\leq$5 mg/day. In case of relapse under methotrexate, the glucocorticoid dose was increased to a dose at which CRP had normalized. We recommended adjunctive therapy for all patients, since there was an increased risk of glucocorticoid-related adverse events or complications.

Mycophenolate mofetil was generally administered with a starting dose of 2 × 500 mg a day. After patients had no side effects, the dose was increased up to 3 × 500 mg a day. Two to three years after starting treatment, MMF was tapered to 2 × 500 mg, after 6 months to 2 × 250 mg, and MMF was discontinued individually. Patient 7 was started on MMF about 18 months ago and is still on therapy. In two of the patients (patient 6 and patient 7) MMF had to be switched to Mycophenolic acid (Myfortic) early in the course of therapy due to gastrointestinal symptoms such as diarrhea.

CRP levels (mg/l) of all patients decreased at the measurement time points 3–6 months (median 1.9, min 0.5, max 7), and 6–9 months (median 1.0, min 0.4, max 3.7) after initiation of therapy with MMF compared with CRP levels before MMF therapy (median 12.5, min 3.9, max 36.7). All patients with GCA tolerated MMF without major

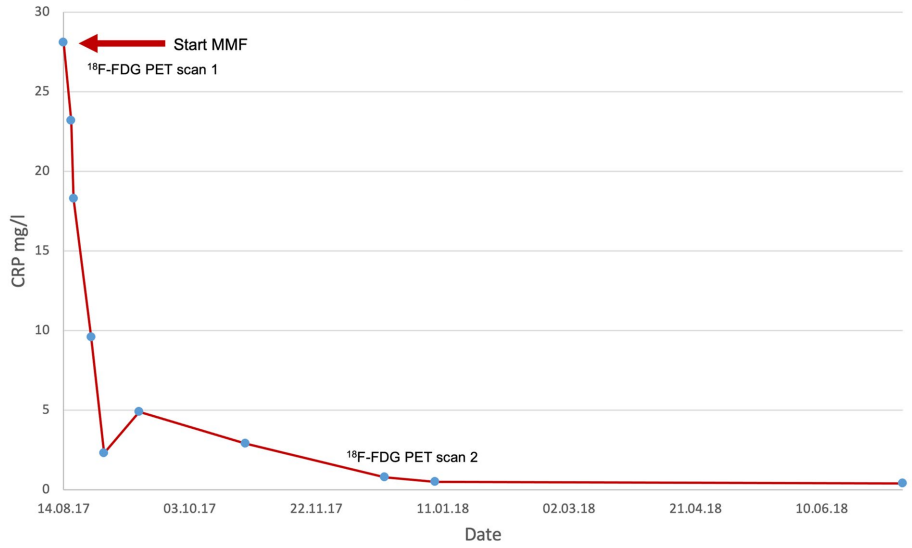

FIGURE 1
CRP values at the beginning of therapy with MMF and in the course of therapy.

side effects. All the patients in this case series achieved disease remission. Among them, 6 patients were able to stop the therapy and are still in remission. On average, patients have been in remission for 25 months (min. 8 months, max. 58 month). One patient is still on MMF therapy today.

Cases

Patient 1

A 82-year-old woman first presented in 2012 with shortened walking distance, exertion-dependent pain in calves and swelling of right thigh since 2010. Furthermore, she described a general state worsening and double vision when looking to the left. Duplex ultrasonography in November 2012 revealed a femoral-type arterial occlusion with moderate-grade stenosis of the distal superficial femoral artery on the right and higher-grade stenosis in the same place on the left. MRI of the head and neck revealed a high-grade suspicion of left vertebral artery dissection with only minimal flow, as well as fresh punctate infarction in the dorsal pons at the level of the superior cerebellar peduncle paramedian on the right. The patient was treated with prednisolone 60 mg and then cyclophosphamide. She subsequently received methotrexate as baseline medication. The patient then relapsed in November with mildly elevated CRP (10 mg/L). After that she received MMF in February 2016 until September 2019. This resulted in a decrease in CRP levels (see Table 1, summerizes all patients, please refer to the table after the last patient). MMF could be stopped in 2019. The patient has been in remission since then.

Patient 2

A 81-year-old woman presented in June 2017 with unilateral left-sided headache, intermittent visual disturbances, reduced general condition and weight loss. She also had claudication of the upper extremities. Attempts to measure blood pressure in the upper extremities failed. A duplex ultrasonography of the cerebral arteries showed a 'halo sign' at the exit side of the left temporal artery, preauricular, and in the more posterior region of the branch of the temporal artery and occlusions of the axillar arteries. Two ^{18}F-FDG PET scans in 2017 revealed large-vessel vasculitis throughout the aorta as well as the supra-aortic branches and popliteal arteries. MRI showed arterial wall contrast enhancement of the descending aorta, the subclavian artery in the proximal part on both sides, and the left common carotid artery. A biopsy of the temporal artery in 2017 showed intramural inflammatory infiltrates plus giant cells consistent with a diagnosis of temporal arteritis. The patient was treated with one cycle of cyclophosphamide followed by MMF from 2017 to 2022. The patient has been in remission for 16 months.

Patient 3

A 72-year-old man first presented in 2017 with worsening general condition, lack of performance, exhaustion and fatigue. ^{18}F-FDG PET at the time of diagnosis showed increased metabolic activity and a markedly thickened wall of the thoracic aorta and proximal abdominal aorta, as well as in the supra-aortic branches, particularly in the brachiocephalic trunk bilaterally. At diagnosis, the patient was receiving glucocorticoids and MMF. CRP levels dropped from 28.1 mg/L at diagnosis to 0.5 mg/L after 3 months of MMF treatment (see Figure 1). ^{18}F-FDG PET 1 year later, after discontinuing MMF, showed a marked signal (see Figure 2). The patient has been in remission for 3.5 years.

Patient 4

A 80-year-old woman first presented in 2014 with headache, polymyalgia rheumatica (myalgias in the shoulders and pelvis), heavy legs, heavy sweating and vertigo when changing position. ^{18}F-FDG

TABLE 1 Demographic data, symptoms, diagnostics and therapy for all patients.

Patient, age (years), sex (♀, ♂)	Clinical presentation	Time of diagnosis of GCA	Ultrasound	Biopsy of arteria temporalis
Patient 1, 82/♀	Shortened walking distance, worsening of general condition, swelling of the right thigh with prolonged walking distance, bilateral pain in the calves due to exertion, double vision when looking to the left, temporary hypesthesia of the legs, claudication in the calf area	11/12	11/12 Arterial occlusion of the femoral type with moderate stenosis of the distal superficial femoral artery on the right and higher-grade stenosis at the same site on the left 07/13 Exclusion of carotid stenosis 10/13 Circulation of legs stable, sonographic changes indicating vasculitis appear regressive	n/a
Patient 2, 81/♀	Unilateral headache on the left, intermittent visual disturbances, reduction in general condition, claudication in the upper extremities, severe feeling of illness, blood pressure measurement in the upper extremities not possible	06/17	06/17 'Halo sign' at the exit of the left temporal artery, preauricularly and in the posterior region of the branch of the temporal artery; occlusions of the axillary artery on both sides. 12/17 Longitudinal homogenous wall thickening of the left common carotid artery up to 2 mm, at the junction with the axillary artery there is considerable wall thickening with sound deletion and monophasic signals in the brachial artery and the forearm, vasculitic involvement of the axillary artery is pronounced on both sides. 06/18 On the left side, continuity of the vessel of the left axillary artery can now be demonstrated and on the right side, an occlusion with strong collateralisation.	6/17 Intramural inflammatory infiltrates consistent with diagnosis of temporal arteritis plus giant cells
Patient 3, 72/♂	Worsening of the general condition, poor performance, fatigue, tiredness	08/17	n/a	n/a
Patient 4, 80/♀	Headache, polymyalgia rheumatica (myalgia of shoulder and pelvis), heavy legs, sweating, dizzy sensations when changing position	04/16	n/a	04/16 Classical for temporal arteritis
Patient 5, 71/♂	Myalgias and muscle weakness in the proximal pelvic muscles and later in the shoulders, headache in both temples, loss of appetite, weight loss, fatigue, tiredness	08/15	08/15 No 'Halo sign' at the temporal artery, but intermittent wall thickening	08/15 Classical for temporal arteritis
Patient 6, 83/♀	Fall and unconsciousness, headache, deterioration of general condition, weight loss, reduced performance, right auricular pain	08/10	08/10 'Halo sign' right auricular	08/10 Classic signs of temporal arteritis in the right superficial temporal artery
Patient 7, 67/♀	12/16 Polymalgia Rheumatica (myalgias in shoulders and pelvis) 6/21 stabbing pain in right lower jaw and headache	06/21	06/21 'Halo sign' at the temporal artery 03/23 No 'Halo sign', no other signs of vasculitis	07/21 Giant cells and lymphohistiocytic inflammation and incipient fibrinoid vessel wall necrosis

(Continued)

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TABLE 1 (Continued)

Patient, age (years), sex (♀, ♂)	PET	MR-angiography
Patient 1, 82/♀	n/a	11/12 High grade suspicion of dissection of the left vertebral artery with only slight flow, fresh punctate infarction in the dorsal pons at the level of the upper paramedian cerebellar peduncle on the right. 4/13 Thoracic and abdominal aorta evidence of aortitis, findings appear to continue into the superior mesenteric artery 07/13 Normal caliber aorta, no suspicious enhancement
Patient 2, 81/♀	06/17 Large vessel vasculitis in the area of the aorta, as well as the supra-aortic branches 10/17: Known large vessel vasculitis in the entire course of the aorta as well as the supra-aortic branches and the popliteal artery on both sides	n/a In the thoracic aorta, contrast medium-receiving vessel wall of the descending aorta and the subclavian artery in the proximal part on both sides as well as the left common carotid artery 11/17 Contrast-enhancement of vessel wall of the descending aorta and the proximal part of the subclavian artery on both sides as well as the left common carotid artery in known giant cell arthritis
Patient 3, 72/♂	08/17 Markedly thickened wall of the thoracic aorta and proximal abdominal aorta, supra-aortic branches, especially brachiocephalic trunk 12/17 Regredient aortitis in the supra-aortic branches, but still detectable residual inflammatory activity	08/17 Signs of severe hilar chronic aortitis of the aortic arch to the proximal abdominal aorta 12/17 Constant pronounced chronic impinging aortitis of the aortic arch to the proximal aorta abdominalis, emphasis at the aortic arch and proximal aorta abdominalis 07/18 Persistent signs of florid aortitis of the thoracic aorta 07/19 No significant wall thickening of the abdominal aorta
Patient 4, 80/♀	07/16 Inflammatory activity of the femoral and popliteal arteries, suspected minor peripheral vasculitis in femoral and popliteal pathways and a typical pattern of findings of polymyalgia rheumatica	07/16 No evidence of florid inflammation in thoracic and abdominal aorta
Patient 5, 71/♂	08/15 Increased vascular metabolic activity, consistent with large-vessel vasculitis (aorta, supra-aortic branches including subclavian arteries as well as arterial vessels of the leg) 02/16 Significant decrease in metabolic activity with evidence of continued moderate activity in the supra-aortic vessels on both sides and the aorta up to kidney level 07/16 Further decrease in inflammatory activity	12/16 Constant thickening of the vessel wall with a slight decrease in contrast medium uptake of the aortic wall, possibly to be interpreted as a response to therapy 04/17 Contrast affinity slightly decreasing 11/17 Continued regredient contrast affinity of the aortic wall
Patient 6, 83/♀	n/a	08/11 Pronounced signs of cerebral microangiopathy 05/16 No indication of active vasculitis 09/22 No indication of active vasculitis
Patient 7, 67/♀	07/21 No evidence of large vasculitis, no evidence of giant cell arteritis	n/a

Patient, age (years), sex (♀, ♂)	CRP in mg/L			Relapse	Course of therapy	Remission
	Therapy start with MMF	3 months after therapy start with MMF	6 months after therapy start with MMF			
Patient 1, 82/♀	10.8	1.2	1.3	02/16 under MTX	12/12 Prednisolone 04/13–08/13 Cyclophosphamide 8/13–01/16 MTX 1/16–03/16 Azathioprine 5/16–09/22 MMF	Since 09/22

(Continued)

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TABLE 1 (Continued)

Patient, age (years), sex (♀, ♂)	CRP in mg/L			Relapse	Course of therapy	Remission
	Therapy start with MMF	3 months after therapy start with MMF	6 months after therapy start with MMF			
Patient 2, 81/♀	3.9	2.7	2.2	no	06/17–02/20 Prednisolone 07/17–10/17 Cyclophosphamide 11/17–02/22 MMF	Since 02/22
Patient 3, 72/♂	28.1	0.5	0.4	no	Since 08/17 Prednisolone 08/17–09/18 MMF	Since 09/18
Patient 4, 80/♀	14.2	7	3.7	08/16 under MTX	12/14 Prednisolone 7/16–08/16 MTX 08/16–08/19 MMF	Since 08/19
Patient 5, 71/♂	36.7	4.7	0.8	no	08/15–2016 Prednisolone 10/15–03/16 MTX 03/16–07/21 MMF	Since 07/21
Patient 6, 83/♀	7.5	0.7	0.5	04/18 under MTX	Since 08/10 Prednisolone 08/10–11/10 Cyclophosphamide 12/10–05/18 MTX 05/18–07/22 MMF/ Mycophenolic acid (Myfortic)	Since 07/22
Patient 7, 67/♀	14.8	7.8	9.3	no	01/17 Prednisolone Since 07/21 Prednisolone 07/21–08/22 MTX Since 08/22 MMF/ Mycophenolic acid (Myfortic)	Since 11/22

n/a, not available; MTX, Methotrexate; MMF, Mycophenolate mofetil.

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PET in 2016 showed marked inflammatory activity in the femoral and popliteal arteries with a suspicion of minor peripheral vasculitis in femoral and popliteal stromal pathways. A biopsy showed classic finding for arteritis temporalis. At time of diagnosis the patient received 75 mg prednisolone, then as a baseline medication of 15 mg methotrexate (MTX). Relapse occurred while trying to reduce prednisolone. Therefore, MTX was stopped and therapy with MMF was started. This resulted in a remission, so that MMF could be discontinued in 2019. Clinical remission has been achieved for 2.5 years.

Patient 5

A 71-year-old man first presented in 2015 with myalgias and muscle weakness in the proximal pelvic muscles and later in the shoulder girdle, headache in both temples, loss of appetite (weight loss of 7 kg within 1 year) fatigue and tiredness. Ultrasound showed no 'halo sign' at the temporal arteries, but intermittent wall thickening. ^{18}F-FDG PET in 2015 showed increased vascular metabolic activity, consistent with large-vessel vasculitis. Vasculitis signs were accentuated in the aorta, the arteria subclavian in both sides and the supra-aortic branches as well as in the in the lower extremities. A biopsy in 2015 showed classic finding for arteritis temporalis.

After diagnosis, the patient received MTX and Prednisolone until 2016 when he showed elevated transaminases. He then was switched to MMF, the therapy could be discontinued in 2021. The patient developed steroid-induced diabetes mellitus type 2 during the course of the disease.

Two follow-up^{18}F-FDG PET scans after treatment start with MMF in 2016 showed significant decrease in metabolic activity of large vessel vasculitis with evidence of continued moderate activity in supra-aortic vessels bilaterally and aorta.

Clinical remission and normalization of the laboratory parameters have been achieved under MMF for 2 years.

Patient 6

A 83-year-old woman first presented in 2010 with a fall with unconsciousness, headache, worsening of general condition, weight loss, reduced performance and right auricular pain. A duplex ultrasonography of the cerebral arteries showed a 'halo sign' right auricular. A biopsy of the right superficial temporal artery showed classic signs of temporal arteritis. In 2011 an MRI was conducted and showed pronounced signs of cerebral microangiopathy. The patient was given MTX in 2010–2018. In 2018, the patient had a relapse with retro auricular pain on the left and mildly elevated CRP levels. The therapy was thus changed, therapy with MMF was initiated. Clinical remission has been achieved for 1 year.

Patient 7

A 67-year-old woman was diagnosed with polymyalgia rheumatica (myalgias in shoulder and pelvis) in 2016 and treated with MTX and Prednisolone. In 2021 the patient had a glucocorticoid-induced complicated urinary tract infection. In 2022, the patient developed achillodynia under MTX. In 2021 she presented with stabbing pain in the right lower jaw and headache. A 'halo sign' was detected at the right temporal artery in an ultra sound. ^{18}F-FDG PET showed no evidence of large vasculitis and no evidence of giant cell arteritis. However, a biopsy revealed giant cells and lymphohistiocytic inflammation as well as incipient fibrinoid vessel wall necrosis. The patient was changed to MMF, which she is still given. CRP has decreased, but is still slightly elevated. This is due to active furunculosis, the patient suffers from as a comorbidity. As far as her vasculitis is concerned, she is still in remission. An overview of demographic data, symptoms, diagnostics and therapy for all patients is provided in Table 1.

Discussion

We observed 7 patients with giant cell arteritis who were treated with MMF, mostly after relapse of the disease under medication with MTX ($n = 3$). Most of the patients tolerated MMF well without any adverse drug reactions, matching safety signals from other studies (7, 8). Two patients developed diarrhea under MMF, so they were switched to Mycophenolic acid (Myfortic). During the treatment with MMF no severe adverse events were observed. Our study presents a very heterogeneous group of patients regarding the constellation of symptoms in giant cell arteritis involving the extracranial vessels with typical arteritis temporalis, but also involving the thoracic and abdominal aorta and the arteries of the upper and lower extremities, which illustrates the difficulty of finding a diagnosis and the existence of subgroups of different phenotype (10).

Untreated large-vessel vasculitis can lead to serious complications such as blindness or stroke (11). Temporal artery biopsy has been the preferred diagnostic method for GCA, but its sensitivity is limited by sample quality and investigator skills (12, 13). Diagnostic imaging, such as ultrasound and MRI, is gaining importance and is part of the EULAR recommendations, with ultrasound being the favored method for cranial GCA, and MRI being equivalent but less accessible. MRI, CT, and ^{18}F-FDG PET can be used for diagnosing extracranial GCA, whereas ^{18}F-FDG PET is particularly useful in differentiating vasculitis from other conditions (14, 15). In our case series, imaging techniques were used in all patients to establish the diagnosis and in most cases a biopsy of the temporal artery was performed. To confirm the diagnosis and to exclude differential diagnoses in case of nonspecific clinical symptoms such as B-symptoms, we predominantly used ^{18}F-FDG PET. Imaging techniques were used to determine the extent of vascular involvement and to objectify the response to therapy with MMF. Furthermore, dangerous events could be averted, such as dissections, through early detection.

In addition to imaging methods, we used laboratory parameters to assess disease activity. Although not a specific marker for the diagnosis of giant cell arteritis, serum CRP is commonly used for disease monitoring during treatment (16). In 2017, the multicenter phase III GiACTA trial showed a benefit of tocilizumab in sustained remission versus placebo with comparatively significant steroid sparing and defined remission by normalization of CRP levels in the absence of clinical symptoms for disease activity. Supportive imaging techniques were not used (17). All patients of our case series had

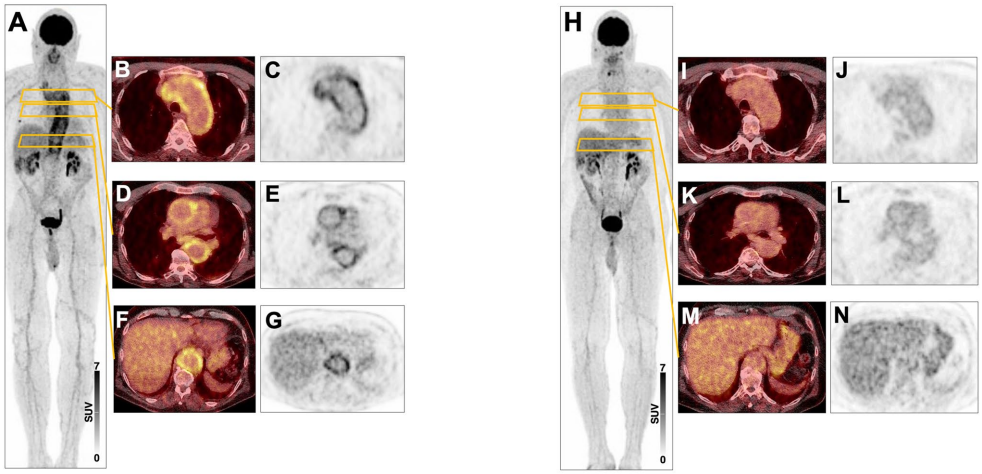

FIGURE 2
(A) 08/17 Maximum-intensity projection (MIP) ^{18}F-FDG PET image showing active large vessel vasculitis in a 3-year-old male patient. **(B–G)** Transversal fused PET/CT and PET images showing high inflammatory arterial wall signal in the aortic arch **(B,C)** and the thoracic **(D,E)** and abdominal aorta **(F,G)**. **(H–N)** 12/2017 Corresponding PET images after treatment showing markedly reduced signal within arterial walls.

elevated CRP levels at the time of diagnosis and CRP levels decreased after starting medication with MMF until normalization. Only in one patient serum CRP did not normalize due to an active furunculosis, which confirms that this biomarker can still be utilized for disease monitoring and detecting severe infections. We also considered normalization of CRP as remission and in most patients the dynamics of the CRP serum level could be correlated with a reduction of disease activity in the imaging used during the course ($n = 6$). This is also how remission was confirmed in the patient with furunculosis.

Steroids are the basic therapy for giant cell arteritis and are used over a long time. Recent studies on ANCA vasculitis visualized the undesirable side effects of steroid toxicity by using the Glucocorticoid Toxicity Index and to show positive effects by steroid sparing (18). Currently, tocilizumab is the only approved and effective therapeutic option for GCA making steroid sparing possible. Tocilizumab acts via interleukin-6 blockade resulting in a reduction of acute phase proteins such as CRP in serum. During therapy with Tocilizumab, CRP can no longer be used reliably as an indication of disease activity or relapse of giant cell arteritis (19), which emphasizes the importance of the additional use of imaging techniques. This also indicates that CRP cannot be utilized as a reliable marker of severe bacterial infection in these patients (20), and in contrast to the GiACTA trial, a multicentre study in patients with GCA given tocilizumab reported far more serious infections (11.9%) (21).

The withdrawal of CRP as a monitoring parameter and the fact that relapses were observed in up to 30% of patients treated with tocilizumab, indicate the need for additional treatment options (9).

Considering the pathogenesis of giant cell arteritis and the already existing experience with MMF in remission induction in ANCA vasculitis (5), the use of MMF in giant cell arteritis seems obvious. To our knowledge, there are two other case series besides ours that investigated MMF in GCA in the past. Sciascia et al. (7) showed in 3 patients that MMF may be considered a steroid-sparing agent in elderly patients with GCA. The second case-series included 37 patients retrospectively suffering from GCA with large vessel involvement who were treated with MMF. After 2 years, most of the patients ($n = 31$) remained on MMF, whereas 6 had switched to MTX or tocilizumab due to relapse (8). In line with the results of these case series, that showed that MMF is effective in controlling disease activity and reduces corticosteroid dosage, all patients in this case series achieved remission on medication with MMF; some patients showed sustained remission even years after end of treatment. Since we did not assess the cumulative steroid dosages, we cannot make any further statement on steroid sparing, even if steroids could be reduced in all patients.

Especially in patients with GCA refractory to treatment with disease modifying antirheumatic drugs (DMARDs), MMF could be an important alternative. Economically, MMF also represents a more cost-effective alternative to tocilizumab. Since MMF potentially exhibits less severe toxic effects than MTX, the effectiveness of MMF in GCA should be investigated in future randomized studies. These results should be considered in future treatment guidelines.

Conclusion

The results of our case series suggest that MMF could be an effective additional therapeutic option for the treatment of GCA considering remission induction and sustained remission. Our cohort presented a very heterogeneous group of patients including the classic pattern of cranial GCA and large-vessel GCA (10). Remission was induced independent of the phenotype of GCA. In addition to serum CRP levels, diagnosis and monitoring of disease activity was accompanied by extensive imaging techniques, leading to more safety in the assessment of disease activity and remission.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the [patients/participants OR patients/participants legal guardian/next of kin] was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

AP: Formal analysis, Visualization, Writing – original draft. SS: Writing – original draft. TD: Methodology, Visualization, Writing – review & editing. MH: Writing – review & editing. AW: Conceptualization, Methodology, Writing – review & editing.

Conflict of interest

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

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Vasculitis distribution and clinical characteristics in giant cell arteritis: a retrospective study using the new 2022 ACR/EULAR classification criteria

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Introduction: Giant cell arteritis (GCA) is the most common vasculitis of the elderly. In recent years, advanced imaging has to a certain extent replaced temporal artery biopsy (TAB) to aid diagnosis in many institutions and helped to identify three major phenotypes of GCA, namely, cranial GCA (c-GCA), large-vessel non-cranial GCA (LV-GCA), and a combination of these two patterns called mixed-GCA, which all show different clinical patterns. Recent 2022 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria respect the changing conception and clinical practice during the last two decades. In this cohort study, we present vasculitis distribution and baseline characteristics using the 2022 ACR/EULAR classification criteria as well as the EULAR core data set.

Methods: In this retrospective study from Southern Norway, we identified all patients diagnosed with GCA between 2006 and 2019 in our single-center fast-track clinic (FTC). We included all patients who were examined using ultrasound (US) of cranial as well as non-cranial large vessels at diagnosis to depict vascular distribution. EULAR core data set, ACR 1990, and 2022 ACR/EULAR classification criteria were used to characterize the cohort.

Results: Seventy-seven patients were diagnosed with GCA at our institution in the aforementioned period. Seventy-one patients (92.2%) were diagnosed with the help of US and included in the further analysis. The 2022 ACR/EULAR classification criteria allocated 69 patients (97.2%), while the ACR 1990 classification criteria allocated 49 patients (69.0%) in our cohort as having GCA. Mixed-GCA was the most common type in 33 patients (46.5%). Weight loss was significantly more common in patients with large-vessel non-cranial vasculitis in LV-GCA and mixed-GCA. Headache, on the other hand, was significantly more common in patients with involvement of cranial vessels.

Conclusion: Mixed GCA was the most common form of GCA in our cohort. In our study, the 2022 ACR/EULAR classification criteria seem to be a more useful tool compared with the old ACR 1990 classification criteria to allocate GCA patients diagnosed and treated at our US-based FTC as having GCA.

KEYWORDS

large-vessel vasculitis (LVV), giant cell arteritis (GCA), ultrasound, classification criteria, imaging

Introduction

Giant cell arteritis (GCA) is the most common form of large-vessel vasculitis in the elderly population (1). If left untreated, it poses a medical emergency due to impending vision loss and stroke risk (2). In certain subpopulations, GCA has also been associated with increased mortality (3, 4). GCA predominates in women and populations of northern European descent (5).

In the last two decades, advanced imaging techniques have changed the understanding of GCA, which seems to be a systemic, rather than a localized vasculitis of cranial arteries (2, 6, 7). Recent studies using positron emission tomography of radioactively labeled glucose (PET) or ultrasound (US) with experienced examiners and extended US protocols identified high rates of large-vessel involvement in GCA (6–9). These findings seem important as they were associated with refractory disease and specific complications such as posterior stroke in vertebral vasculitis or thoracic aortic aneurysm in aortitis (10–14). New classification criteria incorporating these new imaging modalities have recently been published by the American College of Rheumatology (ACR) together with the European Alliance Of Associations For Rheumatology (EULAR) and proved to be applicable to GCA cohorts (15, 16).

The fast-track clinic (FTC) approach incorporating US enables diagnosis and treatment within 48 h and has shown success in reducing vision loss (17, 18). Furthermore, outcome has been improved by new treatment options beyond prednisolone (19–21).

Southern Norway has consistently reported an annual incident rate among the highest in the world, though it shows a declining trend (4). US-based diagnosis was introduced in our rheumatology center on a regular basis in 2010. It has replaced temporal artery biopsy as the first diagnostic modality in diagnosing GCA while US-based FTC algorithms were finally implemented routinely in 2012 (18).

The primary aim of this study was to describe vasculitis distribution in cranial and non-cranial arteries in an FTC using US for diagnosis of GCA. Furthermore, we wanted to characterize our cohort using the 2018 EULAR core data set, the ACR 1990 classification criteria, and the new 2022 ACR/EULAR 2022 classification criteria for GCA (15, 22, 23).

Method

All patients diagnosed with GCA at the central referral FTC in Agder County, Southern Norway, between 2006 and 2019 were retrospectively identified using the International Classification of Disease version 10 (ICD-10) coding system with the codes M31.5 and M31.6 in the central electronic hospital database.

All applicable medical records were thoroughly reviewed manually before the diagnosis was confirmed or rejected based on medical record information. Patients with a sustained diagnosis of GCA on the basis of clinics, imaging results, and temporal artery biopsy (TAB) were identified. Patients without US examinations at diagnosis were excluded for further analysis.

Data were collected in accordance with a structured protocol following the 2018 EULAR recommendations for a core data set to support observational research and clinical care in GCA. However, general disease assessment of patients and examiners was not routinely recorded in most patients prior to 2018 and was therefore not included, while history of cancer was not further stratified (22).

Standard US procedure contained an assessment of both temporal arteries (superficial temporal artery with frontal and parietal branches) in longitudinal and transversal planes with and without color Doppler mode. A positive US test was defined in the presence of hypoechoic vessel wall thickening (halo sign) that was confirmed by the compression sign (24, 25). The axillary and subclavian arteries were assessed in B-mode, and intima–media thickness (IMT) was measured in a longitudinal visualization. A positive test was defined if IMT $>$ 1 mm (2). Other arteries, such as facial-, carotid-, and occipital arteries, were only sporadically assessed and therefore not further analyzed. The US examination was carried out at the FTC, 48 h after referral at the latest. US procedures were conducted by three experienced sonographers (APD, HB, and PMA) using Esaote (Esaote, Genua, Italy) machines up to 2019 and General Electric (General Electric Healthcare, Horten, Norway) Vivid machines in 2018 and 2019. Linear transducers were used with pre-specified settings according to common recommendations (26). Magnetic resonance imaging and PET were not part of a standard assessment and were only used sporadically. TAB was performed by the surgical department at the same hospital, and the specimens were assessed by several local pathologists.

Descriptive statistics were used to characterize the study cohort. Mean and standard deviation were calculated for continuous metric variables and frequencies for nominal and categorical variables.

To compare characteristics between the three major patterns of GCA, the chi-square test was used for categorical variables, and ANOVA and Bonferroni as a *post-hoc* test for continuous variables. Additionally, a multivariate analysis with multiple comparisons was conducted.

The level of significance of all tests was set at a p-value of $\leq$0.05. The Statistical Package for the Social Sciences (SPSS), version 28 (IBM, Chicago, IL, USA), was used for the statistical analysis.

The study was registered and approved by the local patient data safety council.

Results

Seventy-nine patients were identified, and two patients were excluded as their diagnoses were later changed. Six patients were excluded because of missing US examination at baseline. The resulting 71 patients, 50 women (70.4%), with a confirmed diagnosis of GCA were included. The mean age was 69.7 years (SD: 7.2), range of 56–86 years. Apart from two patients (one Latin American and one from Thailand), all were of Caucasian origin (97.2%).

Characteristics of the cohort in accordance with the EULAR core criteria set are shown in Table 1.

The number of patients in our cohort fulfilling the original ACR 1990 classification criteria was 49 (69.0%), while 69 patients (97.2%) fulfilled the 2022 ACR/EULAR classification criteria. Table 2 shows the absolute number of patients fulfilling the

TABLE 1 Characteristics of the GCA cohort of 71 patients in accordance with EULAR core data set.

		All	c-GCA	LV-GCA	Mixed-GCA	*P*-value
Total number of patients (%)		*N* = 71 (100%)	*N* = 22 (28.6%)	*N* = 12 (15.6%)	*N* = 33 (46.5%)	
Demographics	Age	69.7 years (7.2)	69.8 (7.4)	70.3 years (9.2)	69.3 years (6.8)	0.915
	Female sex	50 (70.4%)	13 (61.9%)	9 (75.0%)	24 (72.7%)	0.635
	Weight	70.6 kg (14.3)	68.0 kg (14.6)	68.9 kg (11.5	73.4 kg (15.1)	0.381
	Height	168.2 cm (7.3)	168.2 cm (7.0)	167.3 cm (5.9)	168.9 cm (8.2)	0.826
	Smokers*	19 (26.8%)	9 (42.9%)	2 (16.7%)	7 (21.2%)	0.173
	Diagnostic delay (first symptom until diagnosis)	4.6 months (7.7)	2.6 months (3.5)	7.7 months (14.6)	5.1 months (5.3)	0.391
Cranial GCA-related signs and symptoms	Ocular symptoms	24 (33.8%)	10 (47.6%)	3 (25.0%)	9 (27.3%)	0.241
	Permanent/partial vision loss	2 (2.8%)	2 (9.5%)	0	0	0.110
	Headache	43 (60.6%)	16 (76.2%)	2 (16.7%)	21 (63.6%)	0.003
	Scalp tenderness	19 (26.8%)	6 (28.6%)	2 (16.7%)	8 (24.2%)	0.745
	Jaw claudication	22 (31.0%)	8 (38.1%)	2 (16.7%)	12 (36.4%)	0.396
	Cord-like thickening/ nodularity/ tenderness/ reduced/ pulse and/ or pulselessness	25 (35.2%)	10 (47.6%)	2 (16.7%)	11 (33.3%)	0.193
	Sonographic evidence of arteritis	65 (91.5%)	20 (95.2)	12 (100%)	33 (100%)	0.337
	Histological arteritis/biopsy^	19 (26.8%)	5 (23.8%)	0	14 (42.4)%	
Constitutional	Fever/pyrexia symptoms	17 (23.9%)	4 (19.0%)	3 (25.0%)	10 (30.3%)	0.652
	Weight loss¤	20 (28.2%)	1 (4.8%)	5 (41.7%)	12 (36.4%)	0.018
	Night sweats¤	5 (7.0%)	2 (9.5%)	1 (8.3%)	2 (6.1%)	0.891
	Nausea or other constitutional symptoms¤		3 (14.3%)	0	10 (30.3%)	0.058
Laboratory	ESR	64.4 mm/t (31.6)	53.8 mm/t (22.1)	64.7 mm/t (41.0)	74.0 mm/t (30.9)	0.136
	CRP	76.26 mg/dl (82.4)	86.5 mg/dl (97.4)	71.3 mg/dl (59.2)	77.5 mg/dl (88.0)	0.917
	Hemoglobin	12 g/dl (1.7)	12.6 g/dl (1.7)	11.3 g/dl (1.7)	11.8 g/dl (1.6)	0.091
	Thrombocyte count¤	403.8 ×1000/µl (115.3)	411.7 ×1000/µl (89.6)	407.1 ×1000/µl (134.5)	386.9 ×1000/µl (121.6)	0.840
PMR	PMR	33 (46.5%)	11 (52.4%)	5 (41.7%)	16 (48.5%)	0.839
Arthralgia¤	Arthralgia¤	1 (1.4%)	0	0	1 (3.0%)	0.602
Dry cough¤	Dry cough¤	12 (16.9%)	1 (4.8%)	1 (8.3%)	9 (27.3%)	0.067
Large vessel/extra cranial involvement at diagnosis	Change in peripheral pulses or bruits over peripheral arteries	6 (8.5%)	2 (9.5%)	0	4 (12.1%)	0.456
	Blood pressure	145.5 (18.2)/80.2 (9.8) mmHg	147.6 (15.9)/80.8 (8.8) mmHg	141.4 (15.9)/76.8 (11.0) mmHg	146.9 (21.2)/80.7 (10.6) mmHg	0.672/0.539
	Dilatation/aneurysm	0	0	0	0	
	Inflammatory wall thickening (US, MR, CT)	65 (91.5%)	20 (95.2%)	12 (100.0%)	33 (100.0%)	0.337
	Stenosis	0	0	0	0	
	Carotidynia¤	3 (4.2%)	1 (4.8%)	1 (8.3%)	1 (3.0%)	0.752

(Continued)

TABLE 1 (Continued)

		All	c-GCA	LV-GCA	Mixed-GCA	*P*-value
Death	Death	0	0	0	0	
Cardiovascular events/conditions	Stroke or TIA (history of)	2 (2.8%)	1 (4.8%)	0	1 (3.0%)	0.602
	Myocardial infarction	1 (1.4%)	0	0	0	
	Arterial hypertension	33 (46.5%)	11 (52.4%)	4 (33.3%)	16 (48.5%)	0.556
Endocrine events and conditions	Diabetes	6 (8.5%)	2 (9.5%)	0	3 (9.1%)	0.542
	Osteoporosis	7 (9.9%)	2 (9.5%)	1 (8.3%)	4 (12.1%)	0.918
Infections	Active tuberculosis	0	0	0	0	
Malignancy	History of malignancy	7 (9.9%)	3 (14.3%)	2 (16.7%)	2 (6.1%)	0.476
Treatment	Prednisolone start dose	47.5 mg (12.8)	43.5 mg (13.5)	50.8 mg (17.7)	49.4 mg (10.3)	0.200
	Methylprednisolone	21 (29.6%)	8 (38.1%)	5 (41.7%)	7 (21.2%)	0.269
	Last dose after months of treatment[§]	33.5 months (21.8)	32.0 months (23.8)	26.9 months (7.1)	38.9 months (25.1)	0.319
	MTX	14 (19.7%)	2 (9.5%)	5 (41.7%)	6 (18.2%)	0.079
	Leflunomide	13 (18.3%)	4 (19.0%)	1 (8.3%)	6 (18.2%)	0.691
	Tocilizumab	11 (15.5%)	5 (23.8%)	1 (8.3%)	5 (15.2%)	0.490
	Gevokizumab	3 (4.2%)	0	0	3 (9.1%)	0.208
	Antiplatelet agents (ASA)	16 (22.5%)	4 (19.0%)	4 (33.3%)	6 (18.2%)	0.589
	Phenprocoumon	4 (5.6%)	0	1 (8.3%)	2 (6.1%)	
	Apixaban	3 (4.2%)	2 (9.5%)	0	1 (3.0%)	

Continuous variables are presented as mean with (SD) and categorical variables as frequency with (%). A comparison of groups was calculated between the three major GCA patterns as indicated. SD, standard deviation; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PMR, polymyalgia rheumatic; US, ultrasound; CT, computed tomography; MR, magnetic resonance imaging; TIA, transient ischemic attack; MTX, methotrexate; ASA, acetylsalicylic acid. ¤Items are not part of the EULAR Core data set. *Smoking status was recorded in 61 patients at diagnosis. ^TAB was executed in 33 patients. Valid percent 46.5%. §Ongoing treatment at the timepoint of data collection in 24 patients (33.8%).

separate criteria for the ACR 1990 classification criteria and the 2022 ACR/EULAR classification criteria. US was crucial for the classification of 27 patients (38.0%), while biopsy was crucial in one patient (1.4%).

Detailed results for vasculitis distribution found by US examination are shown in Table 3.

Mixed-GCA was observed in 33 patients (46.5%) patients, c-GCA in 22 (28.6%) patients, and LV-GCA in 12 (15.6%) patients. Nine patients had a positive finding at just one site. Five patients had isolated unilateral subclavian vasculitis, and two patients had isolated unilateral frontal artery and superficial artery involvement each.

In five patients (7.0%), the diagnosis was based on clinical grounds only without evidence of vasculitis in ultrasound (all five patients), biopsy (four patients), or magnetic resonance (one patient). The ACR 1990 classification criteria were fulfilled by 14 patients (66.7%) in the c-GCA group, 3 patients (25%) in the LV-GCA group, and 29 patients (87.9%) in the mixed-GCA group. The 2022 ACR/EULAR classification criteria were fulfilled in all patients with positive ultrasound findings, irrespective of the subtype but only in three of the five patients (60%) without evidence of vasculitis in the US examination.

Three ischemic events in two patients were observed. One patient who already received treatment with aspirin for concomitant diagnosis developed a posterior stroke as well as an anterior ischemic optic neuropathy, and another patient without aspirin or oral anticoagulation treatment developed an anterior optic neuropathy. Of the seven patients on oral anticoagulation treatment, none developed ischemic complications. The paucity of ischemic events precluded a further associative analysis.

Weight loss was significantly more frequent in patients with large-vessel non-cranial involvement ($p = 0.018$), but between mixed-GCA and LV-GCA, no significant difference was found. Headache was significantly more frequent in cranial vasculitis in c-GCA and mixed-GCA compared with LV-GCA ($p = 0.003$). No significant differences between GCA patterns could be demonstrated for other characteristics from the EULAR core data set nor arthralgia, dry cough, carotidynia, night sweats, and other constitutional symptoms. The three events of new vision loss were seen in two c-GCA patients.

TABLE 2 Comparison between the 1990 ACR criteria and the new 2022 EULAR/ACR criteria in our cohort of 77 patients diagnosed with GCA on a clinical basis.

1990 ACR criteria		N (%)	2022 ACR/EULAR criteria		Points	N (%)
Criterion 1	Age ≥ 50 years	71	Absolute requirement	Age ≥ 50 years at the time of diagnosis		71
Criterion 2	New onset of or new type of localized pain in the head	43 (60.6%)	Additional clinical criteria	Morning stiffness in shoulder/neck	+2	33 (46.5%)
				Sudden visual loss	+3	2 (2.8%)
				Jaw and tongue claudication	+2	22 (31.0%)
				New temporal headache	+2	43 (60.6%)
				Scalp tenderness	+2	19 (26.8%)
				Abnormal examination of the temporal artery	+2	25 (35.2%)
Criterion 3	Abnormal temporal artery palpation tenderness, decreased pulse	25 (35.2%)	Laboratory, imaging, and biopsy criteria	Maximum ESR ≥ 50 mm/h or maximum CRP ≥ 10 mg/liter	+3	66 (93.0%)
				Positive temporal artery biopsy or halo sign on temporal artery ultrasound	+5	66 (93.0%)
Criterion 4	ESR > 50 mm/h	56 (78.9%)		Bilateral axial involvement	+2	25 (35.2%)
Criterion 5	Abnormal artery biopsy	19/33 (57.6%)		FDG-PET activity throughout the aorta	+2	2/2
Number of patients fulfilling 1990 ACR criteria (%)		49 (69.0%)	Number of patients fulfilling 2022 ACR/EULAR criteria		69 (97.2%)	

In ACR 1990 criteria, ≥3 points are necessary to classify a patient as having GCA. In 2020 ACR/EULAR criteria, a score ≥6 is necessary to classify a patient as having GCA. ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FDG-PET, 18-F-FDG positron emission tomography with computed tomography localizer.

TABLE 3 Distribution of the reported positive ultrasound vasculitis findings in the 71 patients receiving US at baseline.

	Non-cranial large-vessel arteritis		Cranial arteritis of the temporal artery		
	Subclavian artery *N* = (%)	Axillary artery *N* = (%)	Common truncus *N* = (%)	Parietal branch *N* = (%)	Frontal branch *N* = (%)
Right side	13 (16.8%)	36 (50.7%)	19 (26.8%)	20 (28.2%)	32 (45.1%)
Left side	13 (16.8%)	27 (38.0%)	18 (25.4%)	18 (25.4%)	32 (45.1%)
Total	15 (19.5%)	38 (53.5%)	22 (31.0%)	20 (28.2%)	40 (56.3%)
Total	41 (57.7%)		45 (63.4%)		

Discussion

In this study, we present all patients in Agder County who were diagnosed with GCA in the given period and underwent expert ultrasound to characterize the extent of the vasculitis. However, this study comes with relevant shortcomings. Among others, they encompass, that some parts of the vasculature deemed relevant, such as the vertebral-, occipital-, and facial arteries but also the aorta, were inconsequently or never assessed (2, 6, 27). US follow-up data and IMT were not documented (28). Incomplete data were collected in the follow-up regarding medication dose, steroid tapering, steroid toxicity, and relapse. As no data on patients, in which a GCA diagnosis was rejected in the FTC was collected, no conclusion on the performance of the two criteria sets could be made.

Mixed-GCA was the most common form in our cohort, confirming recent findings (6, 9, 29–32). Mixed-GCA was observed in 33 patients (46.5%), c-GCA in 22 patients (28.6%), and LV-GCA in 12 patients (15.6%). Our data highlight the importance of an extended US examination of cranial and non-cranial large arteries for diagnosing GCA in daily clinical care, comparable to other recent literature (6, 7, 9). The US data demonstrated the widespread nature of arterial inflammation in GCA that rarely involves only one site. However, the relatively lower numbers of large-vessel vasculitis compared with other studies may be a consequence of an often-limited US examination executed in this

cohort, only occasionally encompassing subclavian, carotid, aortic, vertebral, facial, or occipital arteries (6). Furthermore, the training and experience of sonographers varied as well as US machines. This may also explain why five (7.0%) patients showed no objective vasculitis in the US examination and nine patients were identified with just one single involved vascular site. An US was executed after a maximum of three oral doses of prednisolone. Even though some vasculitic changes, especially in the cranial vasculature, may have vanished by then, in our cohort, LV-GCA showed a trend toward a longer diagnostic delay that did not reach significance (14, 33). Six patients were excluded due to a missing ultrasound at baseline. Only two of these patients underwent TAB and PET. Both modalities showed positive findings in these two patients. The remaining four patients were solely diagnosed by TAB without further assessment of possible large-vessel vasculitis.

Headache was significantly associated with cranial vasculitis. However, no significant difference between c-GCA and mixed-GCA could be demonstrated (7, 17, 18, 29). Weight loss was significantly associated with vasculitis in large non-cranial vessels, but no further significant difference between LV-GCA and mixed-GCA could be shown. In contrast to other studies, neither age, sex, treatment length, nor any laboratory markers differed significantly between the three patterns (14, 29, 33).

The 2022 ACR/EULAR classification criteria allocated a much higher proportion of our US-based FTC cohort as having GCA than the 1990 ACR classification criteria. This is in accordance with other recent cohort studies (16, 34, 35). This was especially true for the LV-GCA subgroup where only 25% of the patients would have been classified as having GCA using the 1990 ACR classification criteria, while all patients fulfilled the 2022 ACR/EULAR classification criteria. As previously demonstrated in FTCs, ischemic complications were few as only two patients (2.8%), both with c-GCA, developed three ischemic events (17, 18). However, diagnostic delay based on retrospective first symptom occurrence to the specialist investigation was 4.6 (SD: 7.7) months despite an established FTC that is set up to see patients on the next working day. This potentially mirrors the unspecific nature of symptoms that both the patient and the primary health service are confronted with in GCA patients. Treatment length, indicated by the last corticosteroid dose, reflected on the one hand the relapsing nature of GCA and on the other hand the need for steroid-sparing strategies. In our small cohort, GCA subgroups by US stratification alone were associated with some clinical features. However, this approach was insufficient to predict the duration of the treatment, indicating the need for better risk stratification using improved imaging parameters or scores as well as laboratory markers (36, 37).

Conclusion

Our study confirms that GCA is a multisite vasculitis with distinct clinical features depending on the involved vessels. This should be considered in any workup procedure. 2022 ACR/EULAR classification criteria allocated a much higher percentage of our GCA cohort (97.2%) as having GCA compared with the 1990 ACR classification criteria (69.0%) and reflected the clinical practice in our FTC better.

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 patient data safety council, Sørlandets Sykehus, Kristiansand, Norway. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

PA: Conceptualization, Investigation, Methodology, Project administration, Writing—original draft, Writing—review & editing. AD: Investigation, Supervision, Writing—review & editing. GM: Supervision, Writing—review & editing. GH: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, 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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Giant cell arteritis: incidence and phenotypic distribution in Western Norway 2013–2020

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Objectives: There is an increasing awareness of the spectrum of phenotypes in giant cell arteritis (GCA). However, there is sparse evidence concerning the phenotypic distribution which may be influenced by both genetic background and the environment. We established a cohort of all GCA-patients in the Bergen Health Area (Western Norway), to describe the phenotypic distribution and whether phenotypes differ with regards to incidence and clinical features.

Methods: This is a retrospective cohort study including all GCA-patients in the Bergen Health Area from 2013–2020. Data were collected by reviewing patient records, and patients considered clinically likely GCA were included if they fulfilled at least one set of classification criteria. Temporal artery biopsy (TAB) and imaging results were used to classify the patients according to phenotype. The phenotype "cranial GCA" was used for patients with a positive TAB or halo sign on temporal artery ultrasound. "Non-cranial GCA" was used for patients with positive findings on FDG-PET/CT, MRI-, or CT angiography, or wall thickening indicative of vasculitis on ultrasound of axillary arteries. Patients with features of both these phenotypes were labeled "mixed." Patients that could not be classified due to negative or absent examination results were labeled "unclassifiable".

Results: 257 patients were included. The overall incidence of GCA was 20.7 per 100,000 persons aged 50 years or older. Overall, the cranial phenotype was dominant, although more than half of the patients under 60 years of age had the non-cranial phenotype. The diagnostic delay was twice as long for patients of non-cranial and mixed phenotype compared to those of cranial phenotype. Headache was the most common clinical feature (78% of patients). Characteristic clinic features occurred less frequently in patients of non-cranial phenotype compared to cranial phenotype.

Conclusion: The overall incidence for GCA was comparable to earlier reports from this region. The cranial phenotype dominated although the non-cranial phenotype was more common in patients under 60 years of age. The diagnostic delay was longer in patients with the non-cranial versus cranial phenotype, indicating a need for examination of non-cranial arteries when suspecting GCA.

KEYWORDS

vasculitis, large vessel, giant cell arteritis, temporal arteritis, phenotypes, epidemiology, incidence, clinical features

Introduction

Giant cell arteritis (GCA) is a heterogeneous disease predominantly affecting women and almost exclusively persons over the age of 50 years (1). A pathogenic hallmark of GCA is wall inflammation of large and medium-sized arteries, but the underlying etiology is unclear (2). The triad of headache, jaw claudication, and visual disturbances has historically been viewed as a clinical hallmark (3). However, already in 1932 Horton et al. described an atypical variant with absence of peripheral pulses (4). Temporal artery biopsy (TAB) has long been considered as the gold standard in diagnosing GCA. Still, current recommendations suggest that a diagnosis also can be established based on strong clinical suspicion with positive imaging results (5). New imaging techniques have been developed and shown useful in the diagnostic process of GCA (6–9), and vascular imaging has been widely adopted in GCA (10, 11).

In recent decades there has been a growing interest in non-cranial GCA, also termed extra-cranial or large vessel GCA (LV-GCA). Still, no standardized classification of disease phenotypes exists. Studies on GCA phenotypes have mainly applied a binary division between cranial and non-cranial phenotype though acknowledging that some patients have a combination of the two (12–15), while a few recent studies have incorporated overlapping phenotypes (10, 16). Some authors have proposed that the disease spectrum also encompasses polymyalgia rheumatica (PMR) (1, 17).

This study included all GCA-patients diagnosed in the Bergen Health Area (Western Norway) from 2013 to 2020. Brekke et al. found that the incidence of GCA in the same area increased from 1972–1992 but remained stable from 1993–2012 (18, 19). However, imaging data were unavailable for the vast majority of patients diagnosed from 1972–2012, and < 1% of the GCA-patients had documented involvement of large arteries. The aim of the current study is to describe the phenotypic distribution in GCA and whether phenotypes differ with regards to incidence and clinical features.

Materials and methods

Study design and geographic setting

This is a retrospective cohort study including all GCA-patients diagnosed from 1 January 2013 to 31 December 2020 in the Bergen Health Area (BHA) in Western Norway. BHA serves a population of around 465.000. An overwhelming proportion of the population are Caucasian, and all other ethnicities represent minorities in this region. The only rheumatological department is located at Haukeland University Hospital in Bergen, and patients with suspected vasculitis are referred there, although sometimes via other departments at the hospital, such as the department of ophthalmology.

Patient selection

Patients were identified by the diagnostic coding in the hospital register. All patients receiving in- or out-patient health care in a Norwegian hospital are assigned at least one diagnostic code from the International Classification of Diseases (ICD) on discharge. The ICD version 10 (ICD-10) was used for the entire study period. For the initial patient selection, we used the ICD-10-codes M31.5 "Giant cell arteritis with polymyalgia rheumatica," M31.6 "Other giant cell arteritis," and I77.6 "Arteritis, unspecified." Patient records were reviewed, and data were recorded electronically. Cases were registered as clinically likely GCA if the following criteria were met: (1) the treating physician(s), according to patient records, considered GCA as the most likely diagnosis and chose to treat thereafter, and (2) the reviewing physician agreed that GCA was the most likely diagnosis. Among patients with clinically likely GCA, only those fulfilling at least one of the following sets of classification criteria were included: the American College of Rheumatology 1990 (ACR 1990) (20), the modified ACR 1990 proposed by Dejaco et al. (1), or the 2022 classification criteria from the American College of Rheumatology and the European Alliance of Associations for Rheumatology (ACR/EULAR 2022) (21).

Collected variables and phenotype definitions

Data were collected according to a custom-made Excel template (Supplementary material). Date of symptom onset was registered when the uncertainty was maximum one month, otherwise it was registered as missing. Symptoms and clinical findings at the time of diagnosis were registered as present if they were noted to be present in the patient records, otherwise they were assumed to be absent. Laboratory values were registered if analyses were performed before treatment initiation. Missing laboratory results were registered as missing data. The variables regarding the results of TAB and imaging examinations [vascular ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission tomography (FDG-PET)] were registered as missing if the examinations were not performed or the results were unavailable.

Imaging findings were regarded as positive if the radiologist described a thickening of the arterial wall compatible with vasculitis or, in the case of FDG-PET/CT, if the nuclear radiologist described FDG-uptake in the arterial wall compatible with vasculitis. Evaluated arteries included the thoracic and abdominal aorta, subclavian arteries, brachiocephalic trunk, axillary arteries, carotid arteries, and vertebral arteries, and in some cases common iliac arteries and proximal parts of the internal and external iliac arteries.

We defined three phenotypes of GCA according to the results of TAB and imaging diagnostics. The phenotype "cranial GCA" was used for patients with a positive TAB or halo sign on temporal artery ultrasound. "Non-cranial GCA" was used for patients with positive findings on FDG-PET/CT, MRI-, or CT angiography, or wall thickening indicative of vasculitis on ultrasound of axillary arteries. Patients with features of both these phenotypes were labeled "mixed." Patients that could not be classified due to negative or absent examination results were labeled "unclassifiable".

Statistical analysis

Data registration was performed in Microsoft Excel and all data preparation, analysis, and visualization was done in R (22, 23). Descriptive statistics are presented as counts and proportions for

discrete variables, whereas continuous variables are presented as median with interquartile range (IQR).

Using GCA patients ≥50 years of age and the corresponding background population, we estimated annual cumulative incidence and corresponding 95% confidence intervals by an exact Poisson method. Population data were acquired from Statistics Norway.[1] Cumulative incidence, i.e., number of cases divided by population at risk, was calculated for each year, both in total and stratified by age group (<60 years, 60–69 years, 70–79 years, and 80+ years), sex, and phenotype.

We tested for association between phenotype and the following variables: sex, age group, diagnostic delay, and levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) before treatment. We also tested for association between phenotype and the presence of different clinical characteristics. Depending on sample size, Chi square test or Fisher's exact test was applied for categorical variables, while Kruskal-Wallis rank sum test was applied for continuous variables. Significance level (α) was set to 0.05. Altogether 19 significance-tests were performed, thus requiring the calculation of an adjusted α, corrected for multiple testing. The Bonferroni method, i.e., dividing α by the number of tests, gave an adjusted α of 0.0026. As the Bonferroni method is known to be conservative we also calculated the adjusted α by the less conservative Benjamini-Hochberg procedure (24), which gave an adjusted α of 0.018.

Ethical considerations

The study was approved by the Regional Committee for Medical and Health Research Ethics (REC) (reference number REK-Vest 264,780). REC permitted access to patient records without obtained consent as it was considered that the participants' integrity was sufficiently protected to grant this exemption in accordance with Norwegian law. We evaluated possible impacts of the data handling for the included patients through the preparation of a data protection impact assessment (DPIA).

Results

Patient characteristics and classification

The cohort comprises 257 patients (Figure 1). Table 1 shows characteristics according to GCA phenotype, and the cranial phenotype was dominant. Time from symptom onset to diagnosis was longer for patients with non-cranial and mixed phenotype ($p < 0.001$) and the ESR ($p < 0.001$) was highest for patients with non-cranial phenotype (Table 1). Overall, more than 90% of the patients had undergone TAB. However, the proportion decreased in the last years of the study period. In 2018, 88% of the patients had undergone TAB, compared to 85% in 2019, and 76% in 2020. Similarly we observed an increasing proportion of patients who were examined by temporal artery ultrasound without having performed a TAB. For 2018 this constituted 5% of the patients, in 2019 12%, and in 2020 15%. The proportion of patients having undergone diagnostic imaging of non-cranial vessels increased throughout the study period from 18% in 2013 to 76% in 2020. Among all the patients only three had neither undergone biopsy nor imaging diagnostics.

The majority of patients under 60 years of age had non-cranial phenotype, while in the older age groups this proportion was lower ($p < 0.001$). The opposite was seen for cranial phenotype (Figure 2).

191 (70%) patients fulfilled all three sets of classification criteria (Figure 3). Nearly all patients with cranial phenotype were captured by the classification criteria, and the modified ACR 1990 and ACR/EULAR 2022 captured all patients of mixed phenotype (Table 2). Capture of the non-cranial phenotype ranged from 49% (ACR 1990) to 90% (Modified ACR 1990) (Table 2).

Overall, localized headache was the most common clinical feature (78% of patients) followed by constitutional symptoms (69%). All other clinical features were each present in less than 50% of the complete cohort (Figure 4).

Four features showed a significant association with phenotype after the conservative Bonferroni correction: localized headache, jaw claudication, and tenderness over temporal artery ($p < 0.001$), and limb claudication ($p = 0.001$). Another three features showed significance with the less conservative correction (Benjamini-Hochberg): Constitutional symptoms ($p = 0.01$), vascular bruit ($p = 0.01$), and reduced pulse in temporal artery ($p = 0.018$).

Incidence estimates

The overall annual incidence during the study period was 20.7 (95% CI 18.2–23.5) per 100,000 persons aged 50 years or older. Figure 5 shows the overall as well as age-, sex- and phenotype-specific incidences during the study period. The cranial phenotype was predominating throughout the study period (Figure 5B). Incidence, as well as the variation in incidence, was lowest for patients below 60 years of age (Figure 5C).

Discussion

In this large Norwegian GCA cohort, we found an overall incidence comparable to that shown by Brekke et al. for the predecessing time period in the same area (18). Incidence estimates are also comparable to other studies from Scandinavian countries (11, 25, 26), and the cohort is comparable to other studies regarding age and sex (11–13, 18). A Swedish study found a decreasing incidence of biopsy-confirmed GCA in the period 1997–2019, and the authors proposed that changes in the diagnostic work-up could be an explanation (27). A Danish study on GCA from 1996–2018 showed that the use of TAB declined while the use of diagnostic imaging increased (11). Our findings also reflect a change in the diagnostic work-up of GCA-patients. There is increased use of diagnostic imaging, but TAB remains a dominant diagnostic tool. These changes can be seen in conjunction with the observed changes in incidence, namely the decreasing tendency of the cranial phenotype and the increasing tendency of the non-cranial and mixed phenotypes. While the cranial phenotype was most prevalent overall, the non-cranial phenotype was significantly more common in patients under 60 years of age, in whom this was the most common presentation. Similar findings have been presented before (12, 13, 28).

1 www.ssb.no

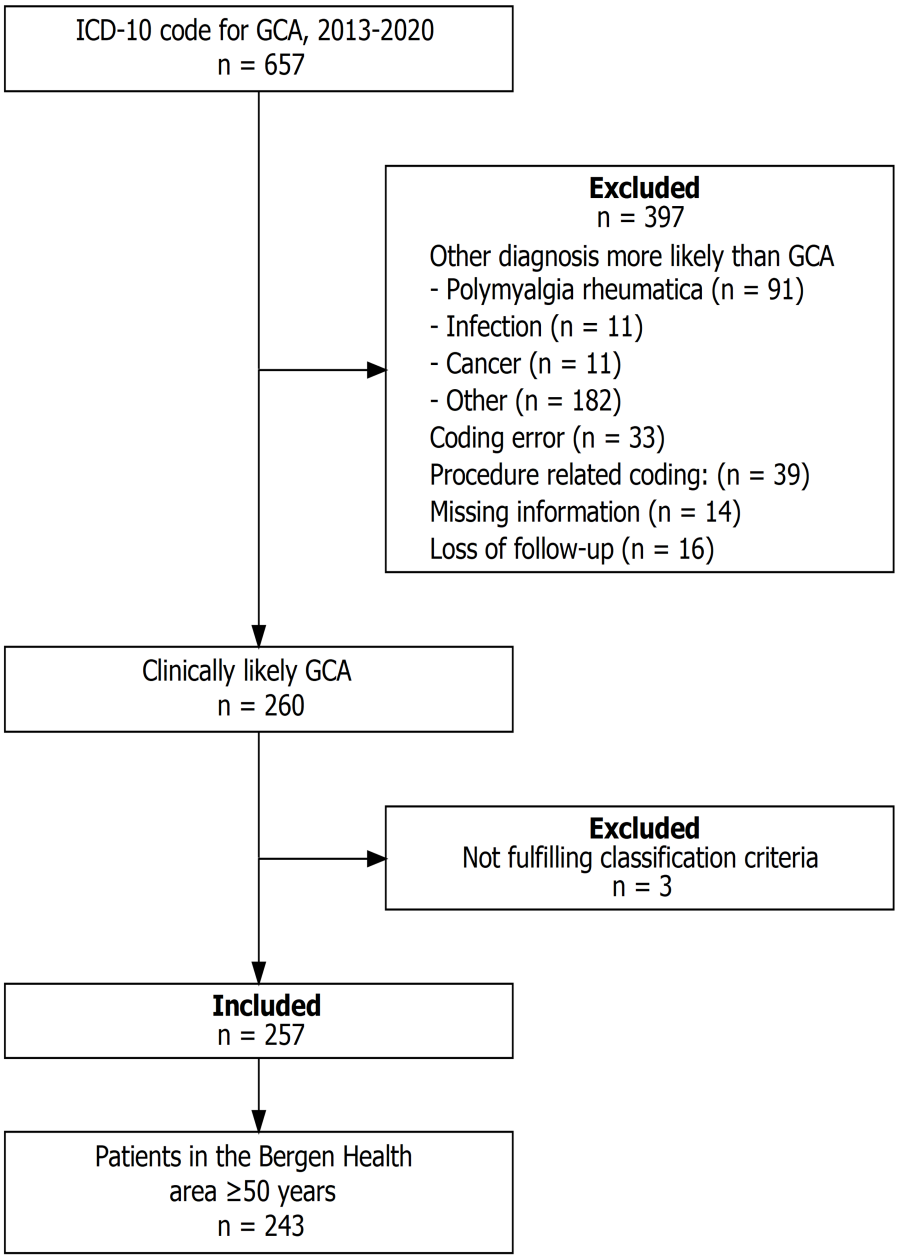

FIGURE 1
Flowchart showing the inclusion and exclusion of patients.

Though headache was significantly more common in patients with cranial and unclassifiable phenotype, more than 50% of patients with non-cranial phenotype also had new localized headache. Some other studies have reported similar findings (10, 29, 30). Constitutional symptoms were more common in non-cranial and mixed phenotype, with borderline significance (depending on method of multiple-testing correction). For the non-cranial phenotype, the occurrence of all other clinical features each were < 25%, underlining the difficulties clinicians may face in the diagnostic process for these patients. The low occurrence of "hallmark" GCA-features could explain why patients of non-cranial phenotype have longer diagnostic delays. This supports the current recommendations regarding examination of non-cranial arteries in the work-up of GCA (5).

The present study is one of the first to systematically analyze the distribution of GCA phenotypes beyond the binary division between cranial and non-cranial phenotypes. A GCA-cohort based on the ACR/EULAR-endorsed study to develop Diagnostic and Classification Criteria for Vasculitis (DCVAS) reported a phenotype distribution comparable to our findings (10). A small study using CT angiography to examine newly diagnosed GCA-patients found that two thirds had involvement of non-cranial arteries, whereas a study based on FDG-PET/CT-results showed involvement of non-cranial arteries in 83% of GCA-patients (31, 32). A Norwegian study using vascular ultrasound showed involvement of non-cranial vessels in 93 of 133 patients (70%) (16). A major difference between these studies and our study is the study design, with the possibility of missing imaging data for some patients in

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TABLE 1 Cohort characteristics and overview of diagnostic procedures.

	Phenotype				
	Cranial *N* = 159	Non-cranial *N* = 41	Mixed *N* = 19	Unclassifiable *N* = 38	Total *N* = 257
Female sex	108 (68%)	30 (73%)	12 (63%)	31 (82%)	181 (70%)
Age at diagnosis[1]	74 (69, 81)	66 (58, 73)	66 (65, 74)	70 (63, 79)	72 (66, 79)
CRP before treatment[1]	71 (40, 115)	86 (62, 117)	61 (42, 108)	54 (33, 84)	70 (41, 114)
ESR before treatment[1]	78 (57, 95)	105 (74, 110)	89 (73, 100)	66 (40, 98)	80 (56, 101)
Days from symptoms to diagnosis[1]	40 (20, 94)	82 (59, 170)	80 (60, 116)	34 (15, 64)	51 (22, 96)
Any imaging performed	66 (42%)	41 (100%)	19 (100%)	18 (47%)	144 (56%)
Temporal artery biopsy					
Performed	155 (97%)	29 (71%)	16 (84%)	35 (92%)	235 (91%)
Positive	152 (96%)	0	14 (74%)	0	166 (65%)
Giant cells in biopsy	118 (74%)	0	8 (42%)	0	126 (49%)
Vascular ultrasound					
Performed[2]	52 (33%)	16 (39%)	11 (58%)	13 (34%)	92 (36%)
Axillary arteries examined	13 (8.2%)	9 (22%)	8 (42%)	2 (5.3%)	32 (12%)
Positive ultrasound[2]	41 (26%)	2 (4.9%)	9 (47%)	1 (2.6%)	53 (21%)
Halo in temporal artery	37 (23%)	0	8 (42%)	0	45 (18%)
Bilateral axillary involvement	0	2 (4.9%)	5 (26%)	0	7 (2.7%)
CT					
Performed[3]	7 (4.4%)	20 (49%)	9 (47%)	1 (2.6%)	37 (14%)
CT angiography	6 (3.8%)	6 (15%)	7 (37%)	0	19 (7.4%)
CT positive	0	13 (32%)	6 (32%)	0	19 (7.4%)
MR angiography					
Performed	6 (3.8%)	13 (32%)	3 (16%)	2 (5.3%)	24 (9.3%)
Positive	0	7 (17%)	3 (16%)	0	10 (3.9%)
Bilateral axillary involvement	0	0	0	0	0
FDG-PET/CT					
Performed	9 (5.7%)	35 (85%)	13 (68%)	3 (7.9%)	60 (23%)
Positive	0	35 (85%)	13 (68%)	0	48 (19%)
Bilateral axillary involvement	0	12 (29%)	4 (21%)	0	16 (6.2%)
Activity throughout aorta	0	33 (80%)	12 (63%)	0	45 (18%)

Statistics are presented as *n* (%) if not otherwise specified. 1 Median (IQR). 2 Includes ultrasound of any artery. 3 Includes both CT angiography and contrast CT, given that the arterial wall was described. CRP C-reactive protein; ESR Erytrhcyte sedimentation rate; CT Computed tomography; MR Magnetic resonance; FDG-PET Fluorodeoxyglucose positron emission tomography; IQR Interquartile range.

our study causing a possible underestimation of non-cranial involvement. A retrospective study from Japan found that 18 out of 36 (50%) patients had involvement of non-cranial arteries (33), while another retrospective study from New Zealand found documented involvement of non-cranial arteries in only 10 out of 142 (7%) patients (29).

Strengths and limitations

Limitations of our study are largely due to the observational retrospective design. There is a risk of missing data and wrongfully recorded data. This is especially relevant for the group of patients excluded based on a diagnosis of polymyalgia rheumatica, alone. It is possible that some of these are misdiagnosed GCA-patients, and this could result in underestimation of the true incidence. However, we did a thorough review of the patient records and included patients only when sufficient information was available.

A major strength of our cohort is its completeness. We screened patient records of all patients who received an ICD-code applicable for GCA and included only validated GCA cases. Another strength is the objectively defined phenotypes based on results of biopsy and imaging diagnostics.

Our high exclusion proportion suggests a discrepancy between medical coding and clinical evaluation. In particular, we noticed a practice of using a disease-related ICD-code for diagnostic procedures, specifically TAB. The validation process for our cohort incorporating the use of classification criteria, however, gives a strong basis for a cohort of correctly identified GCA-patients.

A major problem when comparing studies on non-cranial GCA has been a lack of a standardized classification for GCA phenotypes.

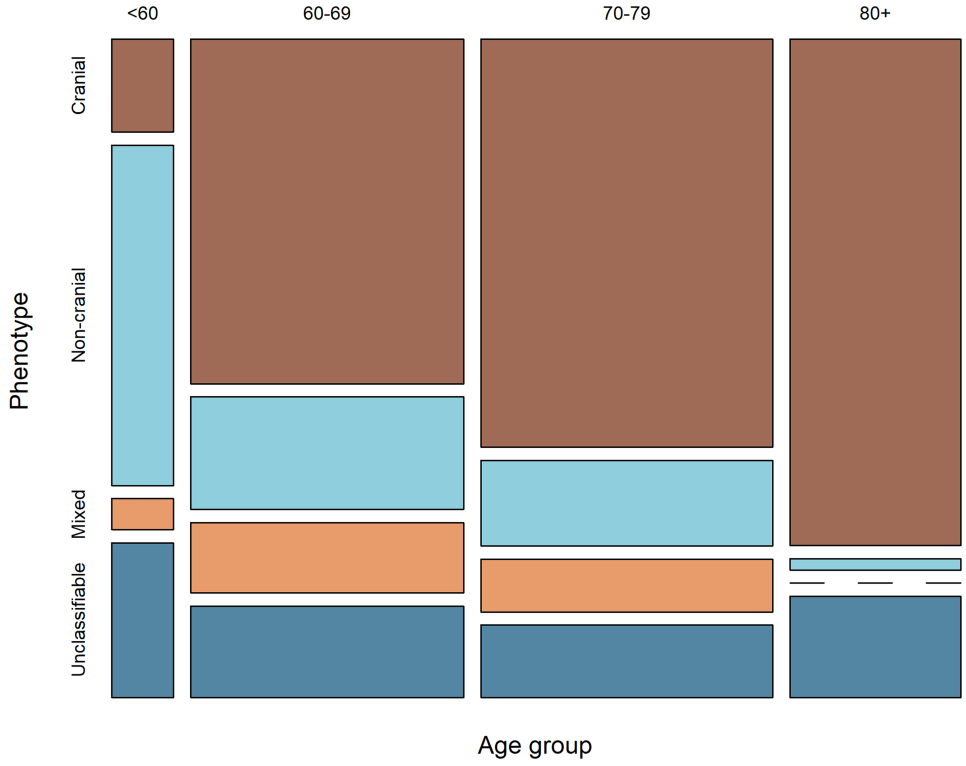

FIGURE 2
Mosaic plot showing the relationship between age-group and phenotype. The width of the columns indicates the proportion of patients within each age-group, while the height of the rectangles indicates the proportion of patients of each phenotype within each age-group.

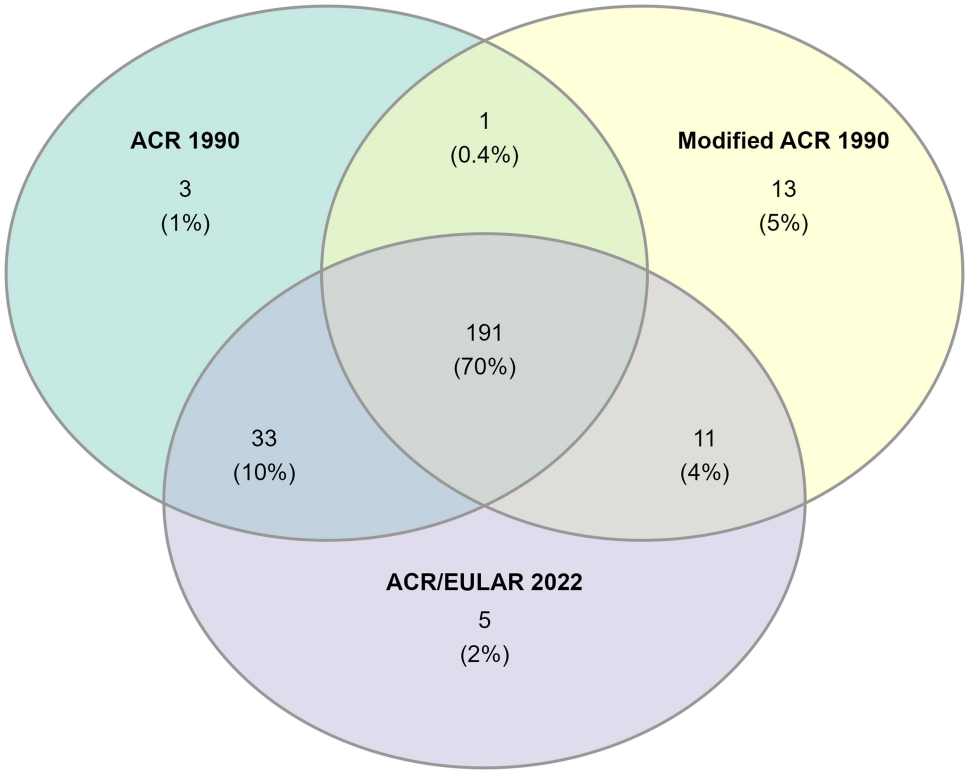

FIGURE 3
Venn-diagram showing the number of patients fulfilling each set of classification criteria.

TABLE 2 Fulfillment of classification criteria by phenotype.

	Phenotype				
	Cranial N = 159[1]	Non-cranial N = 41[1]	Mixed N = 19[1]	Unclassifiable N = 38[1]	Total N = 257[1]
ACR 1990	158 (99%)	20 (49%)	17 (89%)	33 (87%)	228 (89%)
Modified ACR 1990	159 (100%)	37 (90%)	19 (100%)	1 (2.6%)	216 (84%)
ACR/EULAR 2022	159 (100%)	26 (63%)	19 (100%)	36 (95%)	240 (93%)

[1]n (%) (column wise percentage).

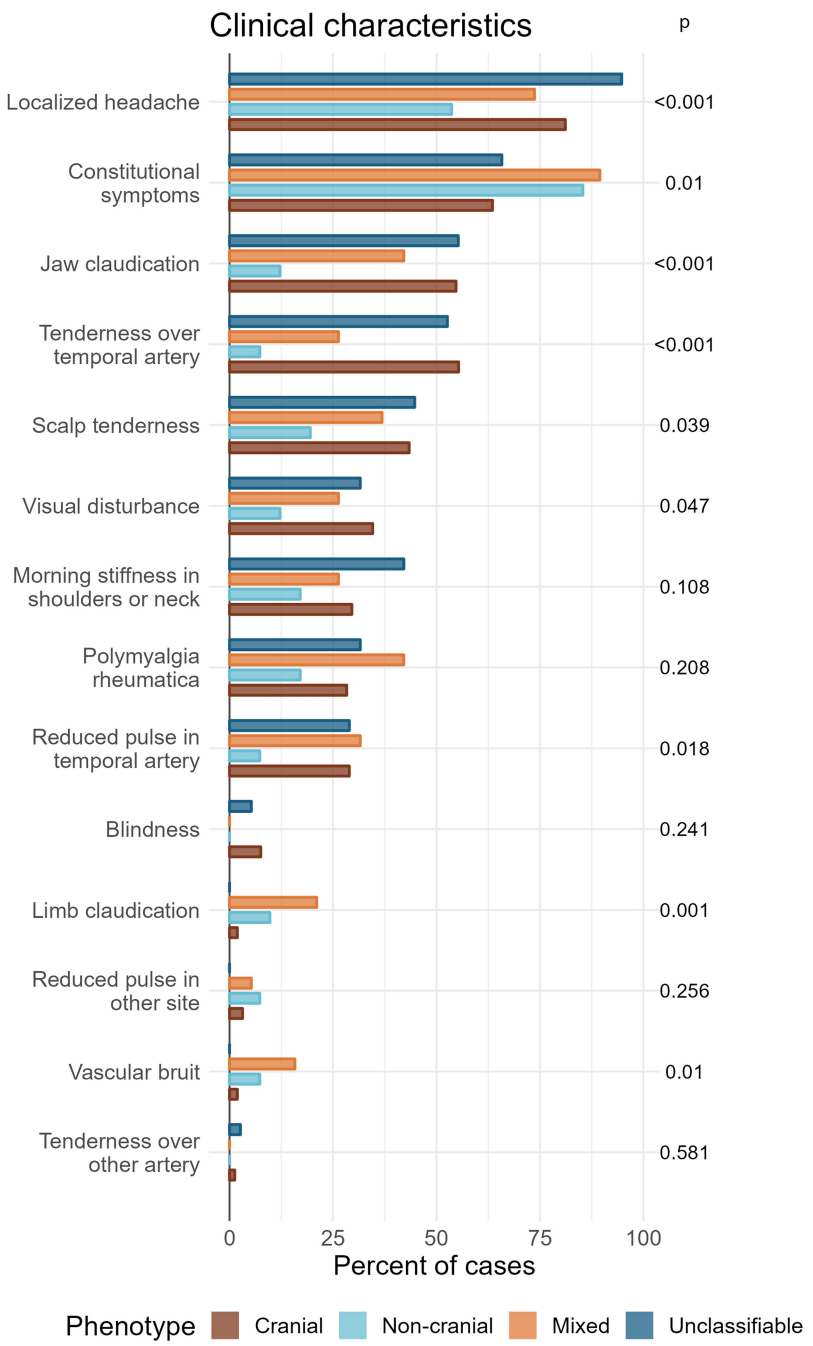

FIGURE 4
Grouped bar plot showing the percentage of patients of each phenotype expressing different clinical characteristics, ordered according to frequency of occurrence in total. p-values (unadjusted) are calculated by Chi-square test or Fisher's test. Corrections for multiple testing gives a significance level of 0.0026 by the most conservative method (Bonferroni) or 0.018 by the less conservative method (Benjamini-Hochberg).

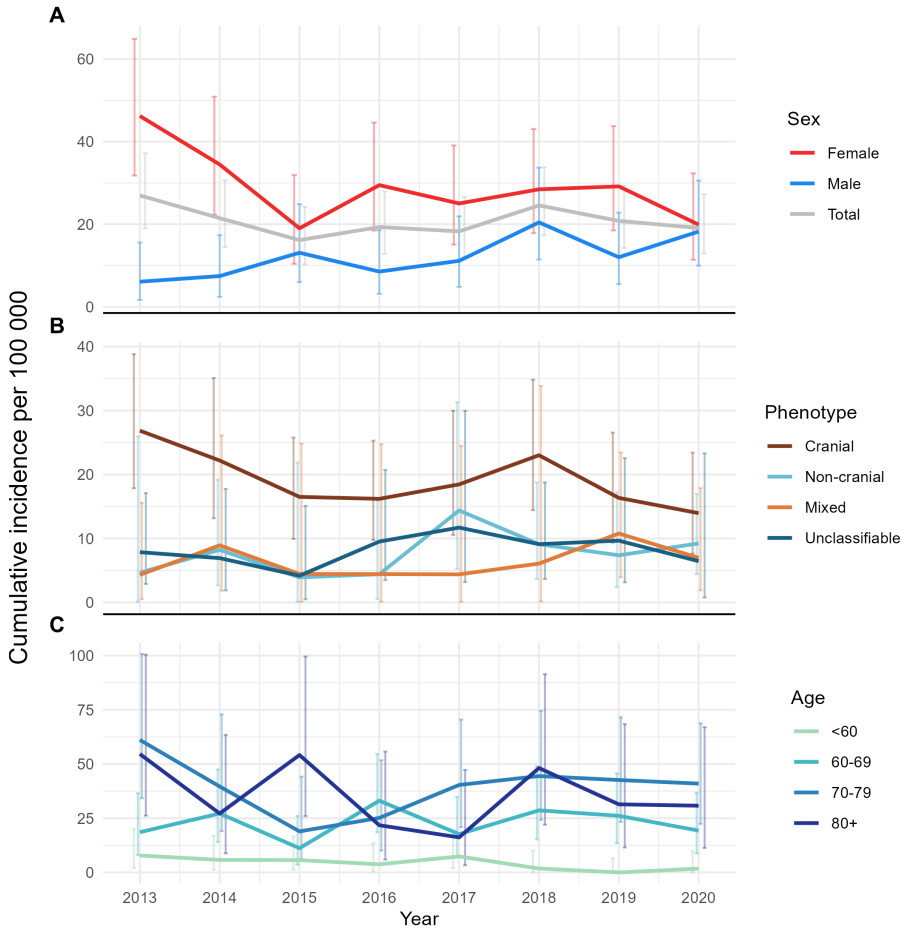

FIGURE 5
Line plots of annual cumulative incidence with error-bars showing the corresponding 95% confidence interval. **(A)** Overall and by sex, **(B)** by phenotype, and **(C)** by age-group.

We believe that our classification can be an example for future studies as it encompasses a broader spectrum better reflecting the GCA patient population.

Conclusion

In conclusion, we found that the overall incidence for GCA in Western Norway remained stable from 2013 to 2020, and was comparable to earlier reports from the same region. The cranial phenotype dominated although the non-cranial phenotype was more common in patients under 60 years of age. The diagnostic delay was longer in patients with the non-cranial versus cranial phenotype, indicating a need for examination of non-cranial arteries when suspecting GCA.

Data availability statement

The datasets presented in this article are not readily available because the data contains identifyable information. Requests to access the datasets should be directed to hans.kristian.skaug@hsr.as.

Ethics statement

The studies involving humans were approved by Regional Committee for Medical and Health Research Ethics (REK Vest). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

HS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. BF: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing. JA: Data curation, Formal analysis, Writing – review & editing. AD: Writing – review & editing. GM: Writing – review & editing. LB: Conceptualization, Funding acquisition, Methodology, Validation, Writing – review & editing, Supervision.

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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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1296393/full#supplementary-material

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Low incidence of malignancy in patients with suspected polymyalgia rheumatica or giant cell arteritis, examined with FDG-PET/CT

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Introduction: The need to systematically examine patients suspected of polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) for malignancy is controversial. The aim of this study was to assess the frequency of malignancy in patients with suspected PMR and/or GCA who have been referred to a 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography with computed tomography (FDG-PET/CT) as part of the diagnostic investigation.

Method: The records of all patients referred to FDG-PET/CT from Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup with the suspicion of PMR and/or GCA during a two-year period, were retrospectively reviewed. Data was analyzed with descriptive statistics, and a standard incidence ratio was calculated based on background cancer incidences extracted from the NORDCAN database.

Results: 220 patients were included in the study. Findings suspicious of malignancy were found in 19 of the examinations, and in seven cases (3.2%), malignancy was confirmed. In three out of the seven cases the patients were diagnosed with PMR concomitantly with malignancy. The estimated standardized incidence ratio (SIR) for cancer compared to the background incidence of cancer in Denmark was 1.58 (95% CI 0.63–2.97), i.e., not statistically significant. There were no statistically significant differences in characteristics of the patients that were diagnosed with malignancy compared with those that were not.

Conclusion: The frequency of malignancy in this cohort of patients with suspected PMR/GCA who underwent PET/CT was low. Our results, though based on a small cohort, do not suggest that all patients with suspected PMR/GCA should systematically be examined with FDG-PET/CT for excluding malignancy.

KEYWORDS

polymyalgia rheumatica (PMR), giant cell arteritis (GCA), FDG (18F-fluorodeoxyglucose)-PET/CT, malignancy, diagnostic examination

Introduction

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are related inflammatory conditions, that may occur concomitantly (1). Classical symptoms of PMR are pain and stiffness of the shoulder girdle, the proximal muscles of the arms, neck, pelvic girdle and the proximal part of the thighs (2, 3), whereas GCA is a vasculitis of medium-sized and/or large arteries, that can affect aorta and its branches and/or the cranial arteries, especially the temporal arteries (2, 4). Both conditions can be accompanied by malaise and constitutional symptoms like fever, weight loss and fatigue, and are usually characterized by elevated inflammatory markers and rapid glucocorticoid response (2–4).

Both conditions can be difficult to diagnose. There is no gold standard available for the diagnosis of PMR, but ultrasound can demonstrate bursitis and synovitis in shoulders and hips (5), and 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography with computed tomography (FDG-PET/CT) can reveal FDG enhancement in bursae, entheses and joints in certain anatomical sites, such as, shoulders and hips, sternoclavicular joints, lumbar spine, and ischial tuberosities (6). Clinical guidelines do however, recommend that a variety of medical conditions, including malignancy, should be considered before making the final diagnosis (7, 8). GCA is a serious condition, and the need for a quick diagnosis is important due to the risk of severe complications such as permanent blindness. GCA can be diagnosed with the use of a temporal artery biopsy, FDG-PET/CT, ultrasound, or Magnetic Resonance Imaging (9, 10). However, the nonspecific symptoms, especially in patients without cranial features can propose a challenge for the clinician (11, 12).

A possible connection between PMR/GCA and malignancy is a subject of controversy, and in a diagnostic context, there are two relevant issues to be considered in relation to this. Firstly, malignancy may mimic PMR/GCA due to unspecific symptoms like malaise, weight loss, widespread pain, and elevated inflammatory markers. Secondly, it has been hypothesized that PMR/GCA may occasionally appear as a paraneoplastic phenomenon, and thus co-occur with malignancy (13). Previous studies have focused on malignancy in patients with already diagnosed PMR or GCA (based on classification criteria, diagnose coding, temporal artery biopsy etc.) (14–17), and have thus not included the issue of malignancy as a differential diagnosis to PMR/GCA. It remains to be established whether it is indicated to systematically examine all patients with PMR/GCA-like symptoms for detecting occult malignancy as routine part of the diagnostic work-up.

One way to investigate malignancy is by use of FDG-PET/CT, which is a hybrid imaging modality that combines the visualization of functional processes (glucose metabolism) with anatomy. Thus, it allows the detection of specific body-sites with a high glucose metabolism, such as sites of inflammation, infection, or cancer (18, 19). In Denmark, access to PET/CT-scans in the investigation of infectious and inflammatory diseases have increasingly been prioritized. Consequently, FDG-PET/CT is widely used among rheumatologists and is readily available for hospital rheumatologists in Denmark for supporting the diagnostic set-up for PMR/GCA. It is, however, a costly procedure with long patient preparation time, a substantial radiation dose, and in many countries with limited availability. Therefore the extent of its use should be carefully considered.

In order to evaluate the relevance of routine use of FDG-PET/CT for all patients with PMR/GCA-like symptoms, the aim of the current study was to assess the frequency of malignancy in patients with suspected PMR and/or GCA, referred to an FDG-PET/CT examination.

Materials and methods

In this retrospective study, we included all those patients with suspected PMR and/or GCA, referred to an FDG-PET/CT as part of their diagnostic process from the Center of Rheumatology and Spine Diseases, Rigshospitalet, in the period 04.21.19–04.21.21. In this period, an estimate of 390 patients were seen in our department suspected of having PMR/GCA.

We included both patients with suspected PMR/GCA who were referred with suspicion of underlying malignancy and patients with suspected PMR/GCA referred for diagnostic reasons, as possible occult cancer could also occur in the latter. To identify these patients, we obtained a list of all patients referred for FDG-PET/CT examinations in the study period from our department to the Department of Clinical Physiology and Nuclear Medicine, Rigshospitalet, Copenhagen. The patient charts including the referral to FDG-PET/CT were screened to identify the examinations that were performed based on suspicion of PMR, GCA or both, with and without a concurrent suspicion of malignancy. Patients referred to an FDG-PET/CT with clinical suspicion of conditions other that PMR/GCA were excluded from the study.

Patient history, clinical signs and symptoms, laboratory results, the suspected diagnosis upon referral to FDG-PET/CT, FDG-PET/CT findings, and the final diagnosis after full diagnostic work-up were registered for each patient based on review of patient records. All solid and hematological malignancies, except for non-melanoma skin cancer, were registered as a malignant outcome. Non-melanoma skin cancers are common, but usually do not metastasize and are not likely to cause B-symptoms. For this reason, non-melanoma skin cancer was not included in our analysis.

The local research ethics committee evaluated the project and did not find ethical approval necessary (J.no. F-23029632). Project approval was obtained by the legal department at Rigshospitalet, Copenhagen.

Statistics

Descriptive statistics were applied to determine frequencies of different characteristics in the study population. To determine differences between the patients with and without malignancy, student's T-test and Mann–Whitney U test were used as appropriate on continuous variables, and Fisher's exact test was used in comparison of binary variables. Statistics were performed using IBM SPSS 28.0.0.0.

Cancer incidences from Denmark across all locations, except for non-melanoma skin cancer, were extracted from the NORDCAN[1]

1 https://nordcan.iarc.fr/en

database. A weighted mean incidence was calculated based on incidences according to the age and sex distribution in the FDG-PET/CT-cohort, in order to determine an estimated standardized incidence ratio (SIR). Confidence intervals were calculated using the Vandenbroucke method.

Results

In total 314 FDG-PET/CT examinations were identified in the inclusion period. All examinations were screened, and 92 of the patients were referred with other provisional diagnoses than PMR or GCA, and thus excluded from this study.

In 222 of the FDG-PET/CT examinations the referral diagnosis was PMR, GCA or both. Two of the patients had undergone two FDG-PET/CT examinations in the study period, and in these two cases, we chose to include the first exam, as the second one did not provide any additional information. Thus, a total of 220 FDG-PET/CT examinations were included. Most of the examinations were performed as FDG-PET combined with a low-dose computed tomography (FDG-PET/ldCT), but 40 (18.2%) of the examinations were performed with a diagnostic computed tomography (dCT), including the use of an intravenous CT contrast agent. All scans were performed as a conventional whole-body PET/CT scan; from vertex to mid-thigh, including arms, which were positioned along the trunk with hands flat on the bed. Findings suspicious of malignancy were reported in 19 (8.6%) of the exams, and a definite malignant diagnosis was confirmed in 7 (3.2%) cases, of which two were priorly known malignancies. Cohort characteristics and descriptive statistics are summarized in Table 1. The cohort consisted of 146 (66.4%) female patients and 74 (33.6%) male patients. The mean age of all patients was 69.8 years. The patients that were not diagnosed with malignancy had a mean age of 69.6 years, and the group of patients in whom malignancy was confirmed had a mean age of 76.6 years. However, this difference did not reach statistical significance ($p = 0.07$). In the group of patients with confirmed malignancy, 71.4% had a symptom duration of more than 3 months at the time of FDG PET/CT, versus only 39.4% of the patients that were not diagnosed with malignancy, though not statistically significant. There were no significant differences in the mean C-reactive protein (CRP) levels or the mean hemoglobin levels between the patients with and without malignancy (Table 1).

Referral diagnoses and symptoms

The clinical suspicion at referral to FDG-PET/CT (Table 1) was solely PMR in 83 (37.7%) patients, solely GCA in 31 (14.1%) patients, and PMR with GCA in 41 (18.6%) patients. Sixty (27.3%) patients were referred with a suspicion of malignancy concomitantly with PMR, GCA or both. In 42.9% of patients with malignancy, there was a suspicion of malignancy upon referral to FDG-PET/CT. Among patients without malignancy, only 26.8% were referred to FDG-PET/CT with a suspicion of malignancy. However, the difference in the

TABLE 1 Patient characteristics at time of FDG-PET/CT.

Characteristic	Total $N = 220$	Patients not diagnosed with malignancy $N = 213$	Patients diagnosed with malignancy $N = 7$	Value of p
Age				
Mean (SD)	69.8 (10.1)	69.6 (10.1)	76.6 (7.7)	0.07
Range	45–93	45–93	63–85	
Sex				
Male, n (%)	74 (33.6)	70 (32.9)	4 (57.1)	0.23
Female, n (%)	146 (66.4)	143 (67.1)	3 (42.8)	
Duration of symptoms[1]				
≥ 3 months	89 (40.5)	84 (39.4)	5 (71.4)	0.21
< 3 months	84 (38.2)	83 (39.0)	1 (14.3)	
Unknown	47 (21.4)	46 (20.9)	1 (14.3)	
Biochemistry				
CRP, mean (SD)	36.6 (46.8)	36.3 (46.9)	44.5 (45.0)	0.75
Hemoglobin, mean (SD)	8.04 (0.9)	8.05 (0.9)	7.87 (1.4)	0.60
Suspected diagnosis upon referral to PET/CT				
PMR, n (%)	83 (37.7)	81 (38.0)	2 (28.6)	0.71
GCA, n (%)	31 (14.1)	29 (13.6)	2 (28.6)	0.26
PMR and GCA, n (%)	41 (18.6)	41 (19.2)	0 (0)	0.35
Malignancy[2], n (%)	60 (27.3)	57 (26.8)	3 (42.9)	0.39
Other[3], n (%)	5 (2.3)	5 (2.3)	0 (0)	1.00

[1]Symptoms: pain and stiffness of shoulder- and/or pelvic girdle, joint pain, headaches, jaw claudication, visual disturbances, weight loss, fatigue, nights sweats and/or fever.
[2]Includes suspected PMR and/or GCA + malignancy.
[3]Includes suspected PMR and/or GCA + infection/arthritis/polymyositis/other pathology.
PMR, Polymyalgia rheumatica; GCA, Giant cell arteritis.

TABLE 2 FDG-PET/CT findings.

Findings	N (scans)	%
Enhanced FDG-uptake in some PMR predilection sites - Fulfills PET-criteria for PMR	120 54	54.5
Vasculitis - Aorta and thoracal branches - Cranial arteries	20 15 11	9.1
Intraarticular inflammation	39	17.7
Suspected malignancy	19	8.6
Suspected infection	8	3.6

PMR, Polymyalgia rheumatica.

TABLE 3 Final diagnosis.

	N	%	Comments
Malignancy	7	3.2	*Includes 3 patients with a diagnose of malignancy + PMR, 1 patient with malignancy + RA.*
PMR	102	46.4	*Includes 4 patients with the diagnosis of PMR + RA, 1 patient with PMR + CPPD and 1 patient with PMR + aplastic anemia.*
GCA	31	14.1	*Includes 8 patients with GCA + PMR.*
Rheumatoid arthritis	15	6.8	*Includes 1 patient with RA + gout*
Other	36	16.4	*Includes diagnoses of different non-inflammatory musculoskeletal conditions, eye diseases, psoriatic arthritis, unspecified polyarthritis, fibromyalgia, crystal arthritis, unresolved tumors, endocarditis, vascular claudication, unspecified infection, pleura-pericarditis, Granulomatosis with polyangiitis and polymyositis.*
Unresolved	29	13.2	

PMR, Polymyalgia rheumatica; GCA, Giant cell arteritis; RA, Rheumatoid arthritis; CPPD, Calcium Pyrophosphate Deposition.

pattern of referral diagnoses between the patients with and without malignancy was not statistically significant.

The symptoms leading to the referral to FDG-PET/CT included pain in shoulder and hip girdles as well as in the proximal muscles, swollen joints, weight loss, fatigue, night sweats, headaches, jaw claudication, fever, and/or visual disturbances. There were no statistically significant differences in symptoms, including the frequency of constitutional symptoms, between the patients with and without malignancy, however data from patient records was incomplete in relation to this issue.

Findings in patients without malignancy

In 120 (54.5%) of the exams there was an enhanced FDG-uptake at PMR predilection sites. In 20 (9.1%) of the scans signs of vasculitis was found. In 19 (8.6%) of the scans there were findings suspicious of malignancy (Table 2).

Table 3 summarizes the final diagnosis after completion of the full diagnostic process. In 102 (46.4%) cases the final diagnosis was PMR, while GCA in 31 (14.1%) cases. Rheumatoid arthritis was diagnosed in 15 (6.8%) patients, and 36 (16.4%) patients received other (rheumatic as well as non-rheumatic) diagnoses. In 29 (13.2%) cases, the diagnosis was unresolved.

Findings suspicious of malignancy

In total 25 findings suspicious of malignancy were reported in 19 scans (Table 4). In seven cases (3.2%), malignancy was confirmed, of which five (2.3%) were newly diagnosed solid cancers (lung cancer, kidney cancer, breast cancer and two cases of colorectal cancer), and two were related to already known malignancies. In four of the cases, the patients received a rheumatological diagnosis concomitantly with the malignant disease (three patients with PMR and malignancy and one patient with rheumatoid arthritis and malignancy).

In two of the suspicious findings, malignancy could not be confirmed or ruled out with certainty. In both cases, the patients were regularly monitored with imaging, and follow-up was ongoing at time of study-end. Two cases of possible intestinal polyps with enhanced FDG-uptake were not subjected to further follow-up based on the decision of the treating physician, and one finding in a costa was not investigated further due to patient wish. One case of non-melanoma skin cancer was found in a patient with solid cancer and was not included in the data analysis.

An estimated SIR for cancer for the total cohort and stratified by sex was calculated as the ratio between the actual and expected number of malignancies in our cohort. The expected number was based on the sex and age-matched incidence of cancer in the background population in Denmark in 2020[2]. The SIR for the total cohort was 1.58 (95% CI 0.63–2.97), while for men 2.19 (95% CI 0.73–4.42) and for women 1.33 (95% CI 0.35–2.94), and thus, the slightly higher incidence of malignancy in our cohort compared to the expected, was not statistically significant.

2 https://nordcan.iarc.fr/en

TABLE 4 Cancer-suspicious findings on FDG-PET/CT.

Site of suspicious finding	Outcome
Parotid gland (2)	1 Malignancy dismissed
	2 Malignancy dismissed
Thyroid gland (3)	1 Malignancy dismissed
	2 Malignancy dismissed
	3 Malignancy dismissed
Mamma (1)	Breast cancer confirmed
Costa (1)	Not examined further
Thoracal vertebrae (1)	Malignancy dismissed
Lung (3)	1 Lung cancer confirmed
	2 Malignancy dismissed
	3 Malignancy dismissed
Kidney (2)	1 Kidney cancer confirmed
	2 Follow-up still ongoing at time of study end
Retroperitoneal process (1)	Follow-up still ongoing at time of study end
Colon (5)	1 Colorectal cancer confirmed
	2 Colorectal cancer confirmed
	3 Malignancy dismissed
	4 Not examined further
	5 Not examined further
Rectum (2)	1 Malignancy dismissed
	2 Malignancy dismissed
Iliac bone (1)	Malignancy dismissed
Gluteal region (1)	Sarcoma confirmed (priorly known)
Spleen and bone marrow (1)	Myelodysplastic syndrome confirmed (priorly known)
Skin (1)	Basal Cell Carcinoma

Discussion

In this retrospective study, we found malignancy on FDG-PET/CT in only 7/220 patients referred for FDG-PET/CT as part of the diagnostic work-up for suspected PMR, GCA or both. In 3/7 cases where malignancy was established, this diagnosis occurred concomitantly with PMR, and the total cancer incidence in the cohort did not statistically significantly differ from a sex and age matched background incidence in Denmark. The patients in our cohort with malignancy were numerically older, as compared to patients without malignancies, and most of them had had symptoms for more than 3 months, though the differences were not statistically significant.

Whereas existing studies have focused on malignancy in patients with *diagnosed* PMR or GCA, the current study investigated the frequency of malignancy in patients with *suspected* PMR and/or GCA, and only approximately 60% of the patients in our cohort were ultimately diagnosed with PMR and/or GCA. Thus, our data reflects a real-life diagnostic setting, in which the clinician might consider malignancy as a differential diagnose to PMR/GCA as well as the aspect of PMR/GCA as possible paraneoplastic conditions.

Several studies have examined the relationship between established PMR/GCA and malignancy. Ji et al. and Muller et al. found an increased risk of cancer within the first 6 to 12 months after the diagnosis of PMR and GCA in large-scale register-based studies (20, 21). Similarly, Dar et al. and Bellan et al. both found an increased risk of cancer in patients with GCA and PMR, respectively, and both studies found that male sex and older age were independent predictors for malignancy (16, 22). Conversely, other studies, such as those from Pfeifer et al. and Hill et al. have not been able to confirm a higher risk of malignancy in patients diagnosed with PMR/GCA (23, 24).

Two recent prospective studies have addressed the issue of systematic examination for malignancy in patients with PMR/GCA. Ramon et al. examined patients who met the 2012 ACR/EULAR classification criteria for PMR with a diagnostic computed tomography of the thorax, abdomen and pelvis (dCT-TAP) and found a frequency of malignancy of 7.6% and an SIR of 4.63 compared to the background population. They did not find differences in age, disease duration, symptoms, or inflammatory marker levels in patients with and without malignancy (17). Emamifar et al. examined patients with PMR/GCA with FDG-PET/CT and found a frequency of solid cancers of 5.2%. They found that patients with solid cancers were older than the patients without cancer (25). These frequencies are higher than in the present study. However, the patients in these studies were already diagnosed with PMR/GCA, and the population is thus different from ours which comprises patients suspected of PMR/GCA. Another potential reason for the higher frequency found by Ramon et al. may be the difference in imaging modality. However, similar results were found in a recent study of patients with large vessel vasculitis, including GCA, on FDG-PET/CT. Tumors were found in 7.2% of the patients, though it is not reported whether these were all malignant or also included benign tumors (26).

As healthy people without symptoms of, e.g., malignancy rarely undergo FDG-PET/CT examinations, the frequency of malignancy as incidental findings on FDG-PET/CT in a normal population is not known. Wan et al. found cancer as an incidental finding on PET/CT in 6/259 (2.31%) otherwise healthy patients with moderate-to-severe psoriasis (27). These results are quite comparable to ours, especially when taking into consideration that the mean age in their cohort was lower (45.3 years).

A strength of this study is that it is based on individual patient chart reviews, as opposed to registry-based studies, in which wrongful categorizations might occur. Limitations of this study include the relatively small sample size, the retrospective design which entails some incomplete data, as well as the lack of an actual control group. A formal control group of healthy patients regarding FDG-PET/CT is ethically very difficult to obtain. Furthermore, there is a risk of selection bias, as not all patients evaluated for PMR/GCA in the study period would have undergone an FDG-PET/CT, and that patients with atypical presentations, would probably be more likely to be referred to an FDG-PET/CT.

In conclusion, this retrospective study found a total frequency of malignancy of 3.2% in PMR/GCA suspected patients referred to an FDG-PET/CT, and almost half of these patients received a concomitant diagnosis of PMR/GCA. Thus, malignancy as the solitary cause of the patients' symptoms was infrequent in the current study, and the observed number of detected malignancies in the cohort did not exceed the expected number in the background population with statistical significance. Our results, though based on a small cohort,

do not suggest that all patients with suspected PMR/GCA should systematically be examined with FDG-PET/CT for excluding malignancy.

Data availability statement

The datasets presented in this article will be made available by the authors upon reasonable request within the scope of the research project's legal approval. Requests to access the datasets should be directed to tanja.fromberg.gorlen@regionh.dk.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

TG: Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Conceptualization. JMB: Writing – review & editing, Conceptualization. MØ: Supervision, Writing – review & editing, Resources. BF: Writing – review & editing. UD: Conceptualization, Methodology, Writing – review & editing. LT: Conceptualization, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

LT has received speaker/consultant fees from UCB, Novartis, Janssen and GE. BF has previously been part of advisory boards for MSD and Immedica. MØ has received research grants from Abbvie, BMS, Merck, Novartis and UCB, and speaker and consultancy fees from Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli Lilly, Galapagos, Gilead, Hospira, Janssen, MEDAC, Merck, Novartis, Novo, Orion, Pfizer, Regeneron, Roche, Sandoz, Sanofi and UCB.

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Vascular ultrasound as a follow-up tool in patients with giant cell arteritis: a prospective observational cohort study

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Objectives: To evaluate relapses in giant cell arteritis (GCA), investigate the utility of vascular ultrasound to detect relapses, and develop and assess a composite score for GCA disease activity (GCAS) based on clinical symptoms, ultrasound imaging activity, and C-reactive protein (CRP).

Methods: Patients with GCA were prospectively followed with scheduled visits, including assessment for clinical relapse, protocol ultrasound examination, and CRP. At each visit, patients were defined as having ultrasound remission or relapse. GCAS was calculated at every visit.

Results: The study included 132 patients, with a median follow-up time of 25months [interquartile range (IR) 21]. The clinical relapse rate was 60.6%. There were no differences in relapse rates between GCA subtypes (cranial-GCA, large vessel (LV)-GCA, and mixed-GCA) (p=0.83). Ultrasound yielded a sensitivity of 61.2% and a specificity of 72.3% for diagnosing GCA- relapse in our cohort. In 7.7% of follow-up visits with clinical relapses, neither high CRP nor findings of ultrasound relapse were registered. In comparison, in 10.3% of follow-up visits without symptoms of clinical relapse, there were both a high CRP and findings of ultrasound relapse.

Conclusion: We found moderate sensitivity and specificity for ultrasound as a monitoring tool for relapse in this prospective cohort of GCA patients. The extent or subtype of vasculitis at the diagnosis did not influence the number of relapses. Based on a combination of clinical symptoms, elevated CRP, and ultrasound findings, a composite score for GCA activity is proposed.

KEYWORDS

giant cell arteritis, ultrasound, relapse, follow-up, large vessel vasculitis

Introduction

Giant cell arteritis (GCA) involves both the cranial and large vessels (LV) (1, 2). The disease presents in three different subtypes: isolated cranial GCA (c-GCA), isolated LV-GCA, and mixed-GCA with involvement of both cranial vessels and LV (1, 3, 4). The relapse rate is known to be as high as 30–60%, depending on the study design and definition

of relapse (5–13). Studies have shown that the relapse rates may be lower in patients with c-GCA (11, 14). However, in many studies, the characterization of c-GCA may be inaccurate, given the absence of systematic examination of the supraaortic tree. The European Alliance of Associations for Rheumatology (EULAR) guidelines for the management of large vessel vasculitis recommends regular follow-up and monitoring of GCA disease activity based on symptoms, clinical findings, and systemic inflammation measured by erythrocyte sedimentation rate (ESR) and CRP levels (15). Imaging may confirm a suspected relapse in cases where laboratory markers of disease activity are unreliable or in the long-term monitoring of structural abnormalities (16, 17). There is no consensus on the optimal imaging modality for follow-up of relapses and/or structural abnormalities. Disease activity assessment in patients with GCA can be challenging as some patients may not have clinical symptoms or elevated acute phase reactants despite active disease (18, 19). Additionally, an isolated increase in inflammation markers is non-specific and should not lead to a modification in the immunosuppressive medication. Furthermore, the increasing use of interleukin-6 inhibitors in GCA treatment renders markers of inflammation unreliable (18–20).

There is no gold standard to evaluate disease activity, which leads to an unmet need for a better understanding and validation of GCA relapses. Given the limitations of blood tests and clinical symptoms as markers of GCA relapse, there is an increasing interest in imaging as a monitoring tool for GCA disease activity. Imaging may be helpful in assessing active disease, yet it is important to emphasize that the lack of a gold standard for disease activity evaluation influences any effort to compare any imaging modality with GCA disease activity. Positron emission tomography (PET), magnetic resonance imaging (MRI), and ultrasound may demonstrate findings that could represent active disease (4). However, imaging may show abnormalities in asymptomatic patients with normal inflammatory markers, and it remains unknown whether this can predict the progression of vascular damage (21). While ultrasound is widely used as a diagnostic tool in patients examined for GCA and is now recommended as a first-line imaging modality by both EULAR and the Norwegian Society of Rheumatology (16, 17, 22), it is not clear if it is useful for disease activity monitoring in clinical practice.

Short-term follow-up studies indicate that ultrasound may be valuable, but studies with longer follow-up times are scarce (12, 23, 24).

In Takayasu arteritis (TAK), which is a rare LV vasculitis primarily afflicting young women, disease activity has since 1994 been evaluated by a composite score including four domains: clinical symptoms, ischemic symptoms, ESR, and LV imaging by angiography (25). While it has been suggested that this composite Takayasu activity score, called the Kerr's or National Institute of Health (NIH) criteria, could be useful in GCA, it has not been validated in any GCA population. In Norway, a modified version of Kerr's criteria is used to evaluate disease activity in patients with GCA (22). There remains an unmet need for tools to assess disease activity in GCA better, and given the different subsets, it is likely that a composite score utilizing multiple different domains will be more sensitive than relying on any one measure alone.

The aims of this prospective cohort study were: (i) To assess the number of relapses in GCA patients, including by disease subtype. (ii) To evaluate the utility of ultrasound as a monitoring tool in patients with GCA. (iii) To develop a composite score for measuring disease activity in patients with GCA.

Methods

The prospective GCA cohort

Patients with new-onset GCA referred to the Department of Rheumatology, Martina Hansens Hospital in Bærum, Norway, from September 2017 and prospectively followed until September 2022 were included. Patients with confirmed GCA were included in this study. The diagnosis was based on clinical manifestations (headache, jaw claudication, visual disturbance/vision loss, scalp tenderness, bilateral aching of the shoulder girdle and stiffness, limb claudication, and/or constitutional symptoms like fever, fatigue, or weight loss) and imaging findings. All the patients were classified using the ACR 1990 criteria modified by Maz et al. (21). The diagnosis was again reassessed and confirmed 12 months later. All the patients were examined at diagnosis using the extended A2-US method. The Extended A2-US method consists of a continuous ultrasound visualization of the large supraaortic vessels (common carotid, vertebral, segment 1–4, the whole subclavian in the right side and the distal part of subclavian in the left side, axillary proximally, and axillary distally including the proximal brachial artery).

Ultrasound examination was performed using high-end equipment, and the sonographers (ACBH, APD) were experienced (APD > 5,000 vascular scannings) and trained (ACBH) according to a standardized program (23). The examination utilized a General Electric S8 ultrasound machine with a 9–12 MHz linear probe for the large vessels, an 8–18 MHz hockey stick probe for the cranial arteries, or a Canon Aplio 800 ultrasound machine with a 3–11 MHz linear probe for the large vessels, and a 8–22 MHz hockey stick probe for the cranial arteries. We used B-mode for all vessels and in addition color Doppler (PRF range 2–3.5 kHz) for the cranial arteries. Colour gain was adjusted according to noise level with a minimum of blooming. Focus was at the level of interest. Frequency for Doppler was the highest possible. The characteristics of this GCA cohort have been described in a previous paper (26). The follow-up included a monthly visit until remission was achieved and then at months 3, 6, 12, and yearly thereafter. Several visits were postponed because of the Covid-restrictions in the period 2020–2022. Patients suspected of having a relapse were evaluated in an unscheduled visit. Data collected at each visit included assessment of clinical relapse (see below), ultrasound examination, serum CRP measurements, Prednisolone dose, and use of other immunosuppressive agents.

Definitions of GCA relapse

At each visit, data on patients' symptoms were collected. The consultant rheumatologist clinically classified the patient as having a relapse or being in remission according to the EULAR definitions of key symptoms and clinical findings suggestive of active disease (15). The definitions are shown in Table 1. Per the EULAR recommendations, we considered a clinical relapse (Table 1), the gold standard definition of GCA relapse, and all other parameters were compared to the clinical relapse.

TABLE 1 Definitions of clinical remission and relapse, and definitions of remission and relapse by ultrasound.

Clinical remission	No clinical signs and symptoms attributable to active vasculitis (morning stiffness of the shoulder or neck, sudden visual loss, jaw claudication, headache, scalp tenderness, constitutional symptoms, limb claudication).
Clinical relapse	Clinical signs and symptoms attributed to vasculitis (morning stiffness of the shoulder or neck, sudden visual loss, jaw claudication, temporal headache, scalp tenderness, constitutional symptoms, limb claudication) after a period of clinical remission.
Ultrasound relapse	Involvement of new arterial segments (cranial, temporal, fascial) and/or LV (carotid, vertebral, subclavian, axillary proximal, axillary distal) or augmentation of the IMT ≥0.2 mm in the already involved arteries (LV) compared to the ultrasound findings at the previous visit.
Ultrasound remission	No involvement of new arterial segments (cranial, temporal, fascial) and/or LV (carotid, vertebral, subclavian, axillary proximal, axillary distal) or augmentation of the IMT ≥0.2 mm in the already involved arteries (LV) compared to the ultrasound findings at the previous visit.

Ultrasound examinations

The patients were examined by extended ultrasound using the extended anteromedial method (A2-US) by the consultant rheumatologist, who was also experienced in vascular ultrasound (26). A halo and compression sign were considered positive findings for the temporal and facial arteries (27). The presence or absence of a halo sign in the cranial and vertebral arteries and the maximum intima-media-thickness (IMT) (thickest area visualized, upper or lower vessel wall) in the supraaortic arteries, assessed by ultrasound, was recorded for all arterial segments at every visit. The patients were classified as having ultrasound findings consistent with ultrasound remission or ultrasound relapse (as defined in Table 1) for every visit during the follow-up period. Settings of ultrasound equipment are presented in previously published papers (4, 26). To compare the ultrasound extent of vasculitis at diagnosis and the number of clinical relapses, we evaluated a combination of halo counts based on the halo score (but not similar) (28): 1. *Simple halo count* (1 point for each temporal, 1 point for each facial and 1 point for every large vessel involved), 2. *Extended halo count* (1 point for every cranial branch involved temporal common, temporal, frontal, temporal parietal, facial) and 1 point for every large vessel involved (carotid, vertebral, subclavian, axillary proximal, axillary distal), and 3. *Modified extended halo count* (1 point for every cranial branch involved temporal common, temporal, frontal, temporal parietal, facial) and 2 points for every large vessel involved (carotid, vertebral, subclavian, axillary proximal, axillary distal).

GCA disease activity score

We assessed GCA disease activity at diagnosis and every visit by a preliminary composite GCA disease activity score (GCAS) based on the LV vasculitis NIH criteria (25) and modified as follows: 1. Clinical symptoms (features of vascular ischemia or inflammation and/or systemic features) not attributable to conditions other than GCA; 2. Elevated CRP (> 5 mg/L, which is the usual upper reference limit in Norway) not attributable to conditions other than GCA; 3. Positive imaging (ultrasound or other imaging modalities) (involvement of new arterial segments or augmentation of the IMT in the already involved arteries). The cut-off for active disease was ≥2 of 3 criteria.

Statistical analysis

The chi-square test was used to measure categorical variables. Phi-test, ANOVA, and ANCOVA regression analysis were used for continuous variables, and the phi-test was used to analyze correlations. Statistical analyses were performed using SPSS, version 21 SPSS Inc., Chicago, IL. $p < 0.05$ were considered to be significant.

Ethical considerations

According to the Declaration of Helsinki, written informed consent was obtained from all participating patients. The Ethics Committee of South-Eastern Norway (Regional Etisk Komite Sør-Øst) approved the study.

Results

The study included 133 patients with GCA, one patient (subtype LV-GCA) dropped out before the first follow-up visit. For the rest 132 patients, 65.9% female, the mean (SD) age was 72.8 (8.8) years at diagnosis. 31.1% were classified as c-GCA, 15.2% as LV-GCA, and 53.8% as mixed-GCA. The total follow-up time was 3,406 patient months. The median follow-up time was 25 months (IR 21 months), and 80 (60.6%) patients suffered at least one clinical relapse during the study period (Table 2). There was no significant difference in duration of follow-up between GCA subtypes; mean follow-up time for c-GCA 24.7 months (CI 95% 21.1–28.3), for LV-GCA 30.1 months (CI 95% 25.3–34.8), and for mixed-GCA 26.3 months (CI 95% 23.2–29.5) ($p = 0.27$).

There were no statistical differences with regards to clinical relapse between the different GCA subtypes (c-GCA 26/41 patients (63.4%), LV-GCA 11/20 patients (55.0%) or mixed- GCA 43/71 patients (60.6%) ($p = 0.82$)), or among cranial isolated (63.4%) versus LV involvement 54/91 patients (59.3%) ($p = 0.83$) or between cranial vessel involvement 69/112 patients (61.6%) or LV isolated (55.0%) ($p = 0.58$) (Figure 1).

Extent of vasculitis by ultrasound at diagnosis and clinical relapse rates

To evaluate whether the extent of vasculitis by ultrasound at diagnosis had any impact on clinical relapse rates during follow-up, we compared the number of vessels having ultrasound findings consistent with vasculitis (defined by halo count-scores at diagnosis) with rates of clinical relapse corrected for time of follow-up. No difference was observed between the extent of vasculitis at diagnosis and the occurrence of a clinical relapse (Table 3), indicating that the extent of vessel involvement is not a predictor for relapse.

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TABLE 2 Characteristics of the GCA cohort.

	Patients with clinical relapse (n = 80)	Patients without clinical relapse (n = 52)	Total	p-value
Gender				0.9
Men, n(%)	27(20.5)	18(13.6)	45(34.1)	
Female, n(%)	53(40.2)	34(25.8)	87(65.9)	
Age at diagnosis, years, mean (SD)	72(9.3)	73(7.8)	72.8(8.8)	0.3
Follow-up time, months, median (IR)	**28.5(21)**	**23(17)**	**25 (21)**	**0.015**
Number of visits, median (IR)	**7(4)**	**4(2)**	**6(4)**	**<0.05**
Subtype GCA, n(%)				0.8
c-GCA	26	15	41(31.1)	
LV-GCA	11	9	20(15.2)	
Mixed-GCA	43	28	71(53.8)	
Use of DMARD, n(%)	**52(65.0)**	**11(21.2)**	**63(47.7)**	**<0.005**
Ultrasound relapse ever, yes/no	**75/6**	**30/21**	**132**	**<0.05**
CRP > 5 mg/L during follow-up, yes/no	**69/12**	**33/18**	**132**	**0.006**
Prednisolone dose initially mg, median (IR)	**40 (20)**	**40 (0)**	**40(19)**	**0.02**

SD, standard deviation; IR, interquartile range; GCA, giant cell arteritis; c-GCA, cranial GCA; LV-GCA, large vessel GCA; DMARD, disease modifying drug; CRP, C-reactive protein.
Bold values are statistically significant.

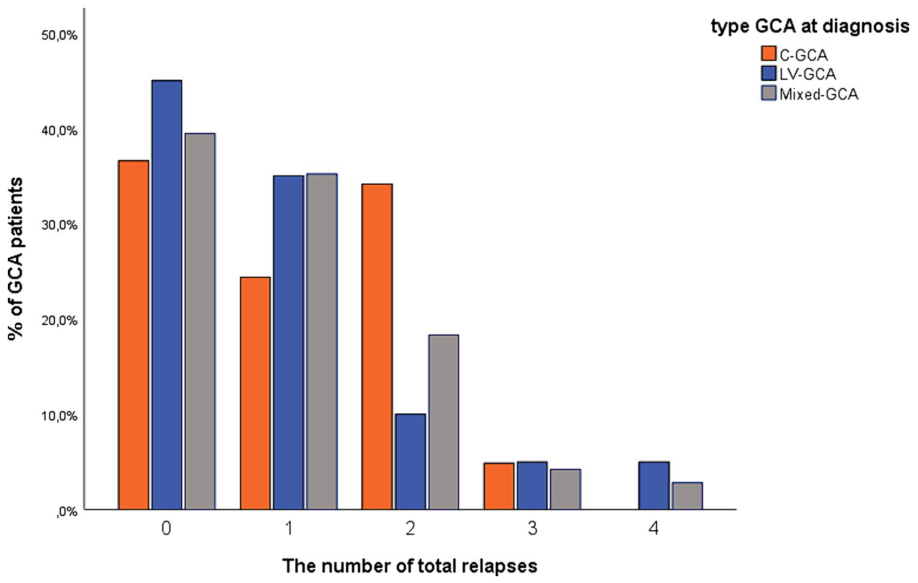

FIGURE 1
Percentage of GCA patients in the three different subtypes with registered clinical relapse in the study period. c-GCA, cranial-GCA; LV-GCA, large vessel-GCA.

TABLE 3 Influence of different halo count-scores of disease extension at diagnosis on clinical relapse during follow-up.

Ultrasound findings at diagnosis	Status during follow-up		p-value
	Clinical relapse (n = 139)	Clinical remission (n = 581)	
Simple halo count, mean (SD)	4.5 (2.6)	4.9 (2.6)	0.35
Extended halo count, mean (SD)	6.2 (3.3)	6.8 (3.2)	0.31
Modified extended halo count, mean (SD)	8.7 (5.4)	9.7 (5.2)	0.22

SD, standard deviation.

TABLE 4 Ultrasound relapse and CRP > 5 mg/L compared to clinical relapse.

GCAS component	Follow-up, clinical remission visits (n = 485)	Follow-up, clinical relapse visits (n = 130)	Sensitivity	Specificity
CRP > 5 mg/L, n = 281(%)	189(67.3)	92(32.7)	70.8	61.0
Ultrasound relapse, n = 246(%)	161(65.4)	85(34.6)	61.2	72.3
CRP > 5 mg/L AND ultrasound relapse, n = 123(%)	66(53.7)	57(46.3)	43.8	86.4
CRP > 5 mg/L OR ultrasound relapse, n = 376(%)	262(69.7)	114(30.3)	82.0	45.9

GCAS, giant cell arteritis activity score; CRP, C-reactive protein.

Use of disease-modifying antirheumatic drugs

Of the 132 patients, 63 (47.7%) used DMARDs during the follow-up period, 34.1% of all patients with c-GCA (p = 0.06), 65% of all patients with LV-GCA (p = 0.03), and 50.7% of all patients with mixed-GCA (p = 0.09). The most used immunosuppressive agents were Methotrexate (48 patients) and Leflunomide (15 patients). Seven patients switched to a 2nd DMARD (4 MTX, 2 Leflunomide, 1 Tocilizumab), while 2 patients switched to a 3rd DMARD (1 Tocilizumab, 1 Azathioprine).

Ultrasound findings at follow-up visits

During the study period, 750 follow-up visits were registered. In 30 follow-up visits (4.0%), ultrasound was not performed, resulting in 720 follow-ups included in the analyses. In 474 (65.8%) visits, ultrasound findings were consistent with our definition of ultrasound remission. In 246 visits, ultrasound findings were consistent with relapse. Ultrasound relapse was isolated to the cranial arteries in 73 visits (29.7%), isolated to LV in 134 visits (54.5%), and involved both cranial and LV in 39 visits (15.9%).

Comparison of clinical relapse and ultrasound relapse

Of the 139 follow-up visits with clinical relapse, 85 visits had ultrasound relapse as well. In 161 of 581 visits in which patients were in clinical remission, there was evidence of ultrasound relapse, yielding a sensitivity of 61.2% and a specificity of 72.3% for ultrasound relapse in GCA patients. A weak to moderate positive correlation of 0.28 was calculated (p < 0.01) among the clinical and ultrasound relapse with a cut-off for LV involvement of 0.2 mm. When the cut-off was raised to 0.3 mm, the correlation increased to 0.3 (p < 0.01) and the specificity was raised to 79.0%, while the sensitivity fell to 54.5%. Raising further the cut-off to 0.4 mm reduced sensitivity to 44.0% and raised specificity to 83.0% with an unchanged correlation of 0.3 (p < 0.001).

Clinical relapse and CRP

A total of 615 follow-up visits included CRP values, with CRP >5 mg/L in 281 visits. Median CRP for visits with clinical relapse was 13 (IR 24) mg/L. The correlation of CRP with clinical relapse was 0.28 (p < 0.01). Ultrasound activity had a weak correlation of 0.15 with CRP (p < 0.01).

TABLE 5 GCAS compared to clinical relapse.

		GCAS ≥ 2		Total
		No	Yes	
Clinical relapse	No	435	50	485
	Yes	10	120	130
Total		445	170	615

GCAS, giant cell arteritis activity score.

Clinical activity and GCA disease activity score

In 105 visits, CRP measurement was missing; hence, GCAS could be calculated for 615 visits. Ultrasound relapse and CRP > 5 mg/L, together with combinations of them, are compared to clinical relapse in Table 4. One hundred and seventy visits were scored with a positive GCAS (≥2), while 445 visits were GCAS negative (<2).

In 10 (7.7%) follow-up visits with clinical relapses, there were neither CRP >5 mg/L nor ultrasound relapses (GCAS<2), and in 50 (10.3%) follow-up visits with clinical remission, there were both CRP>5mg/L and ultrasound relapse (GCAS ≥ 2) (Table 5).

Discussion

The moderate sensitivity and specificity of ultrasound in diagnosing clinical relapse in GCA patients are the main findings of our study. To our knowledge, this is the first study addressing the use of ultrasound as a follow-up tool in a prospective cohort of GCA patients during a long period, which included both the cranial and the majority of the supraaortic large vessels. Prior research on vascular ultrasound's role in monitoring GCA has been limited, and mainly on the correlation between disease activity and the presence of a temporal artery halo for a short period or by monitoring small groups of patients and few supraaortic vessels. One prospective study highlighted the ultrasound halo sign's potential in monitoring GCA. However, it demonstrated sensitivity mainly in temporal arteries without significant findings in the axillary halo regarding disease activity or clinical remission (12). This study included only 6 months of follow-up, and few of the patients in this cohort had axillary involvement (11/49 patients), which poorly reflects the distribution of patients of different

subtypes of GCA (12). In a Danish study, different vascular ultrasound scores were evaluated for sensitivity to change (24). They reported that scores containing TA were sensitive to change, while LV responded poorly (24). However, they evaluated only the distal part of the axillary artery and the carotid artery [rarely involved in GCA (26)]. In addition, the follow-up time for most patients was only 24 weeks. Other smaller studies have demonstrated the persistence of axillary halos compared to TA halos, irrespective of clinical remission (12, 23, 29–31).

CRP levels have previously been identified as a marker of low reliability for GCA disease activity due to its lack of specificity and sensitivity, and this was confirmed in our study as well (8, 32, 33). The relapse rate in our study was in the upper range (60.6%) compared to reported in other studies (5–12). This could be explained by the prospective design, the extended follow-up time, and the high rate of DMARD use (47.7%). Our study is the first in which the patients were classified into three groups (cranial-GCA, LV-GCA, and mixed- GCA) by performing ultrasound at diagnosis and following them by ultrasound of both cranial and LV for an extended period. Conflicting data are published on relapse rates in patients with LV versus cranial involvement, with some studies showing that patients with LV involvement did not relapse more often than patients with c-GCA (34, 35), while other studies found that patients with LV involvement relapse more often and earlier than the patients with cranial- GCA (11, 14, 36–39). One reason could be that the majority of studies lack an extended baseline visualization of supraaortic large vessels, thus missing a significant proportion of patients with LV involvement (14, 35, 38, 39).

In our study, we did not observe any influence in the number of relapses of the extent of vasculitis at diagnosis, by using halo count and modifications and corrected for follow-up time in the different groups. A recently published study prospectively performing PET-CT or MRI at the time of treatment discontinuation found no significant difference in the number of vasculitic vessel segments on imaging on relapse rate (40).

The use of DMARDs was observed in 47.7% of the patients in our cohort. Methotrexate was the most used DMARD. This could be explained by The Norwegian Tender System which requires the use of Methotrexate as the first-line Prednisolone-sparing agent in GCA patients (22). In our cohort, only two patients were treated with Tocilizumab—one as a second DMARD switch and the other as a third DMARD switch, with the second patient initiating Tocilizumab treatment very late during the follow-up period. Consequently, the follow-up duration was limited after the initiation of Tocilizumab. This results in a small sample size and insufficient follow-up time, compromising the accuracy and reliability of any comparisons with the Methotrexate group concerning relapse rates.

A greater proportion of patients with LV disease received additional immunosuppressive therapy compared to those with c-GCA, which aligns with previously published data (14).

Interestingly, we did not observe any significant differences in the number of clinical relapses between patients with isolated cranial arteritis and those LV involvement. This finding is somewhat unexpected given the severity often associated with LV involvement. One possible explanation for this observation is the early introduction of DMARDs in patients exhibiting LV involvement. Previous studies have demonstrated that patients with LV involvement typically require higher doses of corticosteroids and have higher relapse rates compared to those with cranial arteritis alone (11, 14). This evidence likely influenced our clinical practice, leading to the proactive and early administration of DMARDs in the LV group. Specifically, Methotrexate was more frequently employed in patients with LV involvement as an adjunct to corticosteroid therapy. Despite these proactive measures, it is important to note that the absence of a significant difference in relapse rates between the two groups may also reflect the heterogeneity of the disease and the complexity of managing GCA. The similar initial corticosteroid doses observed in both groups (44 mg in the LV group vs. 44.13 mg in the cranial group, $p = 0.9$) further support that the baseline treatment approach was comparable, thereby underscoring the potential impact of early DMARD intervention in achieving comparable relapse rates. Thus, our findings suggest that early and aggressive management with DMARDs in patients with LV involvement may mitigate the expected higher relapse rates typically associated with this subgroup. This hypothesis warrants further investigation in larger, prospective studies to confirm the benefits of early DMARD introduction and to refine treatment protocols for GCA patients with varying patterns of vascular involvement.

Several quantitative scores have been developed for using ultrasound in GCA patients (23, 41, 42). Our study employs a method focusing on the development of vasculitic changes in new vascular beds or increased IMT in previously involved vessels. This approach aims for efficiency in clinical practice, contrasting with the time-consuming quantitative scores designed for research purposes. The provisional OMERACT ultrasonography score (OGUS) was shown to have a high sensitivity to change between baseline and follow-up for 24 weeks. Still, the only LV assessed was the axillary artery (6 of 8 arterial segments included were cranial) (42). Most importantly, the calculation of this score is meant for use in clinical trials and not for daily clinical practice. The same applies to the score used in the GUSTO trial, which was also time-consuming/complicated to calculate (23).

There are no well-defined and clinically used outcome measures regarding disease activity in patients with GCA. In the present study, the combination of ultrasound and CRP to judge disease activity yielded high sensitivity and low specificity (ultrasound relapse OR CRP >5 mg/L positive) and low sensitivity and high specificity (ultrasound relapse AND CRP >5 mg/L positive). Interestingly, in TAK, the combination of inflammatory markers, imaging, claudication, and clinical symptoms has been used as an outcome measure for the disease activity (active disease >2 positive components) (43–46). Based on the findings in the present study and the experience with a similar disease (TAK), we propose the combination of clinical symptoms, CRP, and ultrasound findings of activity into a composite score (GCAS) in which two positives of three components indicate active disease. Coath and Mukhtyar used modified NIH criteria (constitutional symptoms, claudication symptoms, CRP >10 mg/L, ultrasonographic changes of GCA) as an aid to diagnose relapse in GCA (31). The Norwegian Society of Rheumatology recommends using NIH criteria to register disease activity (22).

Major strengths of this study are the prospective design, the long-term follow-up with a systematic ultrasonographic protocol, the standardized collection of the follow-up data, the high total number of follow-up visits, and the real-life setting of an outpatient clinic. The ultrasound examination followed a predefined protocol for visualizing blood vessels, and all scans were performed by experienced ultrasonographers using high-end ultrasound equipment. The use of the extended anteromedial ultrasound examination with visualization of all supraaortic vessels (both upper and lower wall) ensured that all vasculitic changes in the vessel wall were visualized and measured (26). Another strength is that our cohort also includes patients

diagnosed with LV disease and that the patients were classified into three different subgroups for the very first visit, in contrast to many other studies, which mainly included patients with cranial involvement based mainly on biopsy.

A main limitation is that temporal and facial artery halo were assessed only as present/absent instead of assessment of ultrasound-specific halo features, like the number of segments with halo sign involved and the halo IMT. Another significant limitation is the absence of a universally accepted gold standard for defining relapse in GCA. Our study utilized the EULAR relapse definition, which is based exclusively on clinical criteria. This approach lacks a comprehensive perspective that includes imaging modalities such as PET, MRI, and ultrasound, which are increasingly used to identify relapses. However, as our study suggests, interpreting results from these imaging techniques can be challenging, and many patients may exhibit changes without showing clear signs of active disease. Ultrasonographic changes may persist in some cases in patients thought to be in clinical remission (47, 48). The ultrasonographers were not blinded to the clinical data and CRP level and thus could have been influenced by this information.

In conclusion, ultrasound demonstrates moderate sensitivity and specificity as a monitoring tool in the follow-up of GCA patients. The extent of vasculitis at the diagnosis did not influence the number of relapses in GCA patients, and no difference was seen in relapse rates regarding different GCA subtypes. A composite GCA activity score, combining clinical observations, CRP levels, and ultrasound findings, may be useful to guide the management of this complex condition.

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 Ethics Committee of Southeastern Norway (REK SørØst). 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

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Temporal artery biopsy in giant cell arteritis: clinical perspectives and histological patterns

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Although its role has been debated, temporal artery biopsy (TAB) remains the gold standard for the diagnosis of cranial giant cell arteritis (GCA). The specificity of TAB is excellent and the sensitivity, albeit lower, is comparable with other diagnostic modalities used for the diagnosis of GCA. This outpatient procedure has a low rate of complications and is well integrated in the majority of healthcare systems. The length of the specimen, the number of the examined sections and the prolonged use of glucocorticoids before the biopsy may affect the outcome of the TAB as diagnostic tool. The typical histological findings in GCA are often characterized by granulomatous inflammation with infiltration of mononuclear cells with or without the presence of giant cell, varying degrees of external and internal elastic lamina damage and intimal thickening. Overlooking signs of inflammation in the adventitia and in connective tissue surrounding the temporal artery may lead to false negative results. The distinction between healed arteritis and age-related atherosclerosis may be challenging.

KEYWORDS

giant cell (temporal) arteritis, temporal artery biopsy, histology, specimen length, arteritis, adventitial inflammation, transmural inflammation, polymyalgia rheumatica (PMR)

Introduction

Since 1932, when Bayard Horton reported the outcomes of the first two temporal artery biopsies (TABs) of patients with giant cell arteritis (GCA) and until the very recent past, TAB was the only diagnostic procedure which could confirm the diagnosis of GCA (1, 2). During the last two decades, the increased recognition of the extracranial features of the disease and the use of imaging studies, including ultrasound, for the diagnosis of both cranial and extracranial GCA have challenged the role of TAB for the diagnosis of GCA. Currently, there is a discrepancy between the recommendations of the European Alliance of Associations of Rheumatology (EULAR) and the recommendations of the American College of Rheumatology (ACR) for the diagnostic role of TAB. EULAR recommends imaging, particularly temporal and axillary ultrasound, as first diagnostic modality to investigate mural inflammatory changes (3). On the other hand, ACR recommends TAB over temporal artery ultrasound (4). Differences in the technical expertise of healthcare professionals between different healthcare systems and the severe consequences of missing the diagnosis (visual complications, stroke) as well as the burden of the side effects due to unnecessary long-term treatment with glucocorticoids (GCs) in cases of false positive findings may explain this discrepancy. A recent Cochrane meta-analysis could not draw any conclusions on whether the halo sign on temporal

artery can replace TAB for diagnosing GCA as data were heterogeneous and the included studies did not use the same halo thickness threshold or did not report it (5).

It has been reported that in areas with high availability of trained ultrasonographers, the proportion of GCA patients diagnosed using TAB has decreased in recent years (6). If TABs are reserved for atypical cases, this might lead to a reduction in the sensitivity of GCA. On the other hand, if patients are selected for TAB based on clinical expertise and ultrasound findings suggesting vasculitis, this would increase sensitivity.

The aims of this narrative review are (1) to provide an update on some important clinical parameters regarding TAB in GCA (such as rate of complications, unilateral vs. bilateral biopsy, specimen length, number of examined sections, predictors of positive TAB and effect of therapy on the specimen) and (2) to describe the histological patterns seen in GCA in order to assist clinicians in the interpretation of TAB findings, with optimization of the TAB use in every day clinical praxis as the ultimate goal.

Methods of literature search

We conducted a PubMed search on May 12, 2024, for English-language articles, using the following keywords: giant cell arteritis, biopsy, histolog* and temporal artery. Reference lists of retrieved articles were also manually reviewed to identify additional relevant studies. The initial search revealed 114 studies. A careful review of the most relevant studies ($n = 23$) formed the basis for this narrative review.

Clinical perspectives

TAB has been considered the gold standard for diagnosis of GCA, especially for the cranial phenotype. A meta-analysis comprising 32 studies conducted from 1993 to 2015 reported TAB sensitivity of 77% for GCA (7). Two studies after this meta-analysis have reported significantly lower sensitivity 33% (95%CI; 19–51%) and 39% (95%CI; 33–46%) (8, 9). It is possible that patient selection (ophthalmology center, low proportion with headache) (8) and lack of structured training of surgeons and pathologists (9) may partly explain these results. The specificity of TAB is excellent and up to 100% in several studies (9–13). The likelihood of a positive biopsy increases with better selection of patients with high probability of cranial GCA. We reviewed reports on more than 6,500 TABs performed between 1997 and 2019 in southern Sweden and found that only 21% were positive for GCA (14). The proportion of positive TABs in our study should be interpreted cautiously as it was originated from an unselected population (all patients in our region who underwent TAB for any reason between 1997 and 2019). However, in studies of patients in whom diagnosis was confirmed by clinical and laboratory characteristics and who fulfilled the classification criteria for GCA (15), proportions with positive TAB have been reported to be 77% (16) and 87% (17), respectively, in two studies of populations with a high incidence of GCA from Malmö, Sweden and Minnesota, USA (16, 17).

In the TABUL study (The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis), 14 pathologists evaluated 30 TABs from patients with suspected GCA (9). In 11 cases the pathologists agreed unanimously, in 13 cases there were only one or two pathologists with different opinion from the majority but in 6 cases the opinion was divided. The results from the TABUL study imply that despite the long-established use of TAB for the diagnosis of GCA, there still exist areas for continued improvement. A better selection of patients undergoing TAB, an adequate specimen length and a sufficient number of examined sections are modifiable factors which may increase the diagnostic accuracy of TAB. Standardization of terminology and a consensus among healthcare professionals who are involved in the management of patients with GCA on processing, interpretation and reporting of TAB specimens are also key components of the real-world application of TAB in every day clinical praxis (18, 19).

The involvement of a specialist team in investigation of suspected GCA, as recommended by EULAR (20), likely reduces the number of TABs performed with a low pre-test probability of GCA.

Procedural aspects

A TAB is usually performed under local anaesthesia as an outpatient procedure. It is recommended that it should be performed by an experienced surgeon. The rate of complications is low in such cases (0.5%), with the most serious complications being facial palsy and scalp necrosis (21–25). In some cases, sampling errors may arise when a vein or other anatomical structure is sampled instead of an artery (9).

Clinical features predicting of positive biopsy

Reported weight loss at baseline, age ≥ 75 years, female sex, headache, jaw claudication, neck pain, elevated ESR, and elevated platelet levels have been reported as predictors of a positive TAB in patients with suspected GCA (26–29). A study of 459 positive for GCA TABs (out of 3,001 individuals who underwent TAB) found that the odds of a positive TAB were 1.5 times greater with an ESR ranging from 47 to 107 mm/h, 5.3 times greater with CRP > 2.45 mg/dL and 4.2 times greater with platelets >400.000/μL (30). Among patients with a negative biopsy, fulfillment of the ACR criteria, PMR and high platelet count have been reported to be the best predictors for GCA diagnosis (31).

Unilateral versus bilateral TAB

Several observational studies have shown that a bilateral TAB increases diagnostic accuracy by 3–14% (25, 32–37). A large retrospective study over all three Mayo Clinic campuses included 3,817 TABs. Of the 603 patients with bilateral biopsy within 3 months from the initial biopsy, 43 (7%) had a negative initial biopsy followed by a positive on the other side (38). Although this indicates some improvement in the diagnostic yield, it seems to be moderate, and therefore a bilateral temporal artery is recommended only for selected cases with discordance between the clinical findings and the findings described in the initial TAB report.

Specimen length

Skip lesions are reported to occur in 8.5–28% of TAB+ GCA (39, 40). The optimal length of a TAB to minimize the risk of a false negative result is a matter of debate. EULAR recommends a specimen of at least 10 mm in length, which corresponds to a post-fixation length of at least 7 mm (20). A recent study from Sweden showed that the temporal artery contracted by about 12% after surgical excision, both in positive and negative TABs, while formalin fixation caused no further shrinkage (41). Another study from the US, found a 20% mean percentage of contraction, 12% (SD 7%, range 0–25%) in TAB+ specimens and 22% (SD 9%, 7–45%) in TAB- specimens (42). Taken altogether, and based on several observational studies, a post-fixation length of 5–10 mm, which corresponds to a prefixation surgical specimen length of 10–15 mm, is considered sufficient for diagnosis (27, 32, 43, 44).

Multiple sectioning

After the TAB, the extracted temporal artery specimens are transversally sectioned into smaller pieces (measured in mm), fixed with formalin and completely embedded in paraffin (usually transversally) (32, 45). Then, sections measured in μm are cut from paraffin blocks and stained most commonly with hematoxylin–eosin (32, 45). As the first section could be negative, at least three sections at deeper levels should be examined (32, 44). Muratore et al. reviewed 662 TABs performed for suspected GCA with 65% of the specimens classified as negative (44). The authors found that 26 out of 408 TAB specimens (6.4%) reported initially as uninflamed, had inflamed sections, after cuts of additional biopsy sections at deeper levels (44). In 14/26 specimens the inflamed section was the second, in 9/26 specimens the inflamed section was the third and in 3/26 specimens the inflamed section was the fourth (44). Examination of multiple sections at deeper levels is of importance especially in cases of inflammation restricted to periadventitial and/or adventitial tissue (32, 44).

Impact of treatment on histological findings

Existing evidence suggests that the inflammatory findings in TAB subside more slowly than do imaging findings. When the temporal artery is affected, histological evidence of ongoing inflammation is present in the TAB for at least a month after therapy initiation (16, 46), and positive histological findings have been reported up to 12 months after GCA diagnosis, especially when symptoms are present (45, 47, 48). In a study with repeated TABs, 44% of patients with initial positive biopsies also had positive biopsies when having symptoms of active disease between 9 and 12 months after therapy initiation (45). In our clinical practice, we aim to obtain a TAB within 2 weeks of treatment initiation to confirm or rule out the diagnosis and to avoid unnecessary medication toxicity in patients with negative TAB and low clinical suspicion for GCA. This timeframe is also recommended, with low level of evidence, in the 2021 ACR/Vasculitis Foundation guidelines for the management of GCA (4). On the other hand, when a TAB has not been previously conducted, and there is high clinical suspicion of GCA with typical symptoms present, the results of a TAB could be informative, even if the patient has received GC treatment for more than 2 weeks (16, 45, 46). Low GC doses in GCA patients with prior PMR seem to not affect histological findings of vasculitis (46).

Histological patterns in GCA

The typical pattern

Granulomatous inflammatory infiltrate comprised mainly of CD4+ lymphocytes and macrophages, usually affecting all three artery layers, is considered to be the hallmark of a positive TAB. Transmural inflammation is the most common pathological pattern in inflamed temporal arteries of patients with GCA. In artery cross-section, the inflammatory infiltrate appears as concentric rings, with a thicker inflammatory ring adjacent to external elastic lamina and a thinner ring along the internal elastic lamina (32). Mono- and multi-nucleated giant cells are present along the internal elastic lamina in the majority of positive TABs (32, 45, 46), but the absence of giant cells does not preclude a GCA diagnosis. In a study of patients with evidence of inflammation indicating GCA in TAB, absence of reported giant cells was associated with involvement of the aorta and its branches, suggesting that cranial arteritis with typical TAB findings and large vessel involvement are different parts of the spectrum of GCA (49).

Although inflammation affecting the media is traditionally considered a defining feature of a positive TAB, the media is relatively spared except for severe cases in which the inflammatory infiltrate is diffuse, severely affecting all three arterial layers (panarteritis). The intima becomes progressively thicker due to myofibroblastic proliferation, resulting in varying degrees of occlusion of the lumen. The grade of intimal thickening correlates with the severity and intensity of the inflammatory infiltration (46). Occlusion due to thrombosis occurs rarely (32). Fragmentation of internal elastic lamina and neo-angiogenesis are commonly seen in positive TABs (32, 50). Table 1 summarizes reported histological findings in patients with TAB+ GCA from 5 studies (32, 45, 46, 50, 51).

Investigation of cellular markers or cytokines is not currently part of standard evaluation of TABs. Detailed studies have revealed expansions of T cell subsets, with reduction of Th17 but not Th1 pathways after GC therapy (52). Such findings may have implications for future targeted therapies and possibly also for disease monitoring.

Periadventitial and adventitial inflammation

Temporal artery biopsies with mild inflammatory lesions and biopsies from patients with early GCA may lack the described typical features. The inflammation occurs as a dynamic process in which the inflammatory infiltrate spreads through the wall of the temporal artery from the adventitia toward the intima (46). Consequently, at the time of temporal artery excision, inflammation may be restricted to the periadventitial or adventitial tissue, as the small vessels around the temporal artery and the adventitial vasa vasorum are considered the gates through which the invading inflammatory cells initiate the inflammatory process, as well as the primary field in which it takes place. A series of 354 TABs showing inflammation included 80

TABLE 1 Histological findings in patients with positive TAB with transmural inflammation or panarteritis.

	Cavazza et al. (32)	Hernandez-Rodriguez et al. (46)	Maleszewski et al. (45)	Putman et al. (50)	Font and Prabhakaran (51)
Number of + Biopsies	354	285	40	705	35
Cell types					
Lymphocytes	100%	NR	100%	NR	100%
Plasma cells	Inconspicuous	NR	83%	NR	NR
Giant cells	74.8%	61.4%	55%	51%	42.9%
Eosinophils (%)	8%	NR	18%	NR	NR
Neutrophils (%)	1.8%	NR	3%	NR	NR
Isolated adventitial or periadventitial inflammation	22.5%	5.6%	NR		22.9%
Disruption of internal elastic membrane	Very common	NR	100%	41%	100
Intimal thickening	100%[a]	72.3%	93%	33%	NR
Thrombus	9.5%	NR	NR	4%	NR

[a]In patients with transmural inflammation ($n = 274$).
NR, not reported. Data derived from quantitative studies.

(22.5%) with inflammatory cell infiltrates restricted to the adventitia or the periadventitial tissue (32). Such isolated inflammation may escape the pathologist's attention (9, 32, 53). As mentioned, the first section of a specimen may occasionally be negative, and examination of deeper sections may be necessary to detect inflammation, especially when it is limited to adventitia and the surrounding connective tissue (32, 53). A negative first section appears to be infrequent in TABs of patients with transmural inflammation, whereas it occurs in 32–50% of biopsies of patients with isolated periadventitial or adventitial inflammation (32). Table 2 presents the most frequent histological patterns in inflamed TAB and some of its clinical significance (32, 45, 46, 50, 51, 53–57).

Small vessel vasculitis (SVV) of capillaries in the connective tissue that surrounds an uninflamed temporal artery is an infrequently reported, but probably underestimated, histological pattern. Every TAB includes a portion of the connective tissue surrounding the biopsied artery that may contain capillaries, arterioles, small nerves and, occasionally, small veins (53). The pattern suggestive of vasculitis consists of an aggregate of mononuclear inflammatory cells (≥15) without polynuclear neutrophils and eosinophils and without the presence of fibrinoid necrosis, surrounding a capillary 0.5–1.5 mm from the arterial wall of an inflammation-spared temporal artery. The small nerves may also be affected (53).

The prevalence of SVV and its clinical significance was investigated in a multicentre prospective study of a cohort of 397 patients with GCA (280 biopsy-confirmed) and 101 patients with isolated PMR (53). Isolated SVV was present in 35 (7%) of 498 patients with clinical GCA or PMR diagnosis. Patients with SVV were more often male and showed fewer systemic and cranial ischemic symptoms and lower inflammatory response compared with patients with biopsy-confirmed GCA (53). Symptoms of PMR were also more frequently observed in patients with SVV in this study as well as in a small retrospective observational study including 28 patients with SVV (54), whereas PMR symptomatology was equally distributed among histological patterns as shown by Cavazza et al. (32) Blindness occurred in one of the 35 patients with SVV (53). Of note, SVV was reported in only 3/35 cases (9%) of the initial pathology reports (53).

Although the histological features of GCA are more varied than previously thought, the finding of SVV should be interpreted with caution, as SVV surrounding an uninflamed temporal artery can also be seen in other vasculitides and malignant disease (57). Cavazza et al. found three of 32 patients to exhibit isolated SVV positive for ANCA-associated vasculitis and one with amyloidosis (32). Thus, when TAB features atypical of GCA histology, such as fibrinoid necrosis or leukocytoclasia, are present, alternative diagnoses may be considered based on clinical, laboratory, and imaging findings (58). On the other hand, the presence of PMR or of other clinical features typical of GCA favours the diagnosis of GCA.

Healed arteritis vs. atherosclerosis

Caution is advised in interpretation of the TAB when histological evidence of active ongoing arteritis is absent, and the primary findings include healed (quiescent) arteritis. This pattern of histological findings may also be present in atherosclerosis and in normal temporal arteries because of aging. This topic is an area of debate among pathologists (32, 55, 56). It seems that scarring and neovascularization affecting media and adventitia in a temporal artery with no detectable inflammation suggests healed arteritis, whereas isolated effects on intima and internal elastic lamina (Table 2) indicate atherosclerotic or age-related changes (55, 56). A retrospective observational study from the USA examined 400 TABs to investigate the clinical course of healed arteritis (55). Forty-seven biopsies (11.8%) were identified as healed arteritis in the initial pathology report. When published criteria of healed arteritis were applied, only 15 of the 47 cases were confirmed to be healed arteritis (55, 59). Thirty of 47 were categorized as normal or age related/atherosclerotic changes and two as active arteritis (55).

TABLE 2 The most frequent histological patterns seen in TABs of patients with biopsy-confirmed GCA based on selected studies.

Pattern	Description	Clinical significance
Normal artery	The three arterial layers are separated by the external elastic lamina (adventitia-media) and internal elastic lamina (media-intima). The vasa vasorum is located in the adventitia. At the outer limit of the adventia, connective tissue consisting of adipose tissue contains small vessels with or without a muscle layer. Small nerves may exist in the periadventitial tissue.	Normal arterial segments may be present between the arteritis-affected sections of the artery.
Periadventitial inflammation	Aggregates of mature lymphocytes (≥15) are localized around small vessels in the periadventitial connective tissue with no inflammation of the temporal artery.	This pattern may be the only histological evidence of inflammation in a small subset of patients with GCA (<9%). Male sex, absence of halo sign in ultrasound, and PMR symptoms are more likely to occur in patients presenting this pattern. Cranial ischemic manifestations, including blindness, may occur.
Adventitial inflammation	Inflammation in the vasa vasorum and/or inflammation extended to the adventitia without detectible inflammatory infliltrate crossing the external elastic lamina into the media.	May appear as isolated adventitial inflammation in early/mild stages of the disease. Frequently coexists with periadventitial and transmural inflammation.
Transmural inflammation	Concentric rings consisting of mature lymphocytes and macrophages, with a thicker ring in proximity to the external elastic lamina and a thinner ring adjacent to internal elastic lamina. The bulk of inflammation is localized at the adventitia media border. The rings extend from the adventitia to the intima (or the intima-media junction). The adjacent media is relatively spared except in severe cases. Giant cells are usually seen along the internal elastic lamina. Some cases involve laminar necrosis consisting of acellular eosinophilic material along the internal elastic lamina, surrounded by histocytes, whereas fibrinoid necrosis is rare in GCA.	With panarteritis, this pattern is the most frequently seen in TABs. The absence of giant cells does not preclude GCA diagnosis.
Panarteritis	Inflammatory infliltrate in all three arterial layers. The severity and the extent of inflammation is greater than in transmural inflammation.	Indicates severe inflammation. Jaw claudication and scalp tenderness are more likely to occur in patients exhibiting this pattern.
Healed arteritis	Irregular intimal thickening, intimal and medial fibrosis, focal areas of persistent chronic inflammation, multifocal to complete loss of elastic lamina, medial neovascularization, and adventitial fibrosis.	Cautious interpretation of this pattern is required since, as well as indicating healed arteritis, it may be a consequence of normal aging and arteriosclerosis/atherosclerosis.
Atherosclerosis	Regular intimal proliferation, focal loss of internal elastic lamina, calcification of the media (Monkeberg's calcifications). Absence of significant medial pathology.	These findings may be also be present between arteritis affected sections, and in healed arteritis.

Different patterns may coexist in the same temporal artery specimen.

Maleszewski et al. in their study of repeat temporal biopsies in patients with GCA under GC treatment observed active arteritic lesions in 60%. Even among those biopsied 9 and 12 months after the initial biopsy, 44% were positive, mostly patients symptomatic at the time of the second biopsy. Thus, histological evidence of active arteritis may be present weeks or even months after the initiation of therapy with GCs and therefore, TAB reports describing findings consistent with healed arteritis a few weeks or months after the initiation of treatment should be interpreted cautiously, as these findings may be primarily related to age-related changes and/or atherosclerosis (45–48, 51, 55, 56, 60).

Conclusions and future perspectives

Although useful alternatives have emerged, TAB remains the gold standard for cranial GCA. It is a well-established outpatient procedure with very low rates of complications. Modifiable factors as the specimen length and the number of examined sections could increase the sensitivity of the procedure as the specificity is already high. Recent insights in the disease's pathophysiology, which have elucidated the course of the inflammatory infiltrate within the artery with a clear direction from the vasa vasorum in adventitia to intima, may increase the diagnostic yield of TAB by identifying early stages of the disease with isolated affection of adventitia and/or small vessel vasculitis of the capillaries in the connective tissue surrounding the temporal artery (32, 46, 53). Looking for traces of previous inflammation in the adventitia and in media may be helpful to distinguish a healed arteritis from age-related changes (51, 55). In rare cases, TAB could be helpful tool to identify other diseases which can be presented with cranial symptoms and features of systemic inflammation mimicking GCA such as ANCA-associated vasculitis and amyloidosis (32).

TABs have, together with large vessel imaging, been used to identify patients with definite GCA for clinical trials with

bDMARDs, e.g., tocilizumab (61). Additional novel therapies are currently investigated in phase III studies (62). The findings in the TAB may be used in future studies to predict response rates to specific treatments, based on improved understanding of the underlying mechanisms.

Author contributions

PS: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. CT: Writing – original draft, Writing – review & editing. AM: Writing – original draft, 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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