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Ultrasound in the diagnosis and management of giant cell arteritis

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Abstract

US has become an important diagnostic tool for musculoskeletal diseases. Because of its wide availability in rheumatology practice, US has also been applied in other rheumatic diseases such as GCA. In acute GCA, US displays a non-compressible, hypoechoic, most commonly concentric arterial wall thickening. Temporal and axillary arteries should be examined in patients with suspected GCA and PMR. Additionally, almost all other large arteries, with the exception of the thoracic aorta, can be easily delineated by US. Many studies and several meta-analyses have been conducted to evaluate the diagnostic performance of US. US is more sensitive than temporal artery biopsy (TAB) because TAB evaluates only a limited anatomical region in a systemic disease. Most US studies arrive at specificities between 90 and 100% compared with the final clinical diagnosis. Reliability for reading US images and videos is excellent and comparable to reliability for reading TAB specimens. The advantage of US over other imaging techniques in GCA is its availability, safety and tolerability and its high resolution of 0.1 mm. Rheumatology departments are increasingly establishing fast-track clinics. Physicians can refer patients with suspected GCA within 24 h. Patients receive clinical and US examination by experienced specialists, establishing a clear diagnosis either before TAB or without the need for TAB. The introduction of fast-track clinics has led to a significant reduction of permanent vision loss. Furthermore, a process that primarily includes US is significantly more cost-effective than TAB.

Key words: ultrasound, giant cell arteritis, large vessel vasculitis, polymyalgia rheumatica, Takayasu arteritis

REVIEW

Rheumatology key messages

- Ultrasound shows a non-compressible, hypoechoic wall thickening of temporal and other arteries in acute GCA.
- Reliability for reading ultrasound images and videos is excellent and comparable to histological reliability.
- Fast-track clinics with clinical and ultrasound examination lead to a decrease in permanent vision loss in GCA.

Introduction

US is a cross-sectional imaging tool that is unique in its potential within clinical examination. US examination is non-invasive and cost-efficient [1, 2]. It can be used as a bedside procedure and is safe, fast and well tolerated by patients [3]. Patients can ask questions, and findings can be explained to the patient during examination [3]. Therefore, the use of US by rheumatologists is widespread in clinical practice, mainly for musculoskeletal indications but also, increasingly, for other rheumatic diseases such as large-vessel vasculitis (LVV) [3]. Characteristic US findings have also been described both in GCA and in Takayasu arteritis [3–5], though most studies to date have addressed GCA.

US findings in GCA

A normal intima–media complex (IMC) of an artery is depicted by US as a homogeneous, hypoechoic or anechoic echo structure delineated by two parallel hyperechoic margins (Fig. 1) [6] (C. Duftner, personal communication).

Four pathological characteristics can be found by US in GCA: wall thickening (halo sign; Fig. 2), non-compressible arteries (compression sign; Fig. 3), stenosis and vessel occlusion. In GCA, cell infiltrates and oedema occur particularly in the media, potentially extending to the intima and the adventitia. US depicts this oedematous wall thickening as material around the artery lumen that contrasts hypoechoic to the surrounding tissue; it is most

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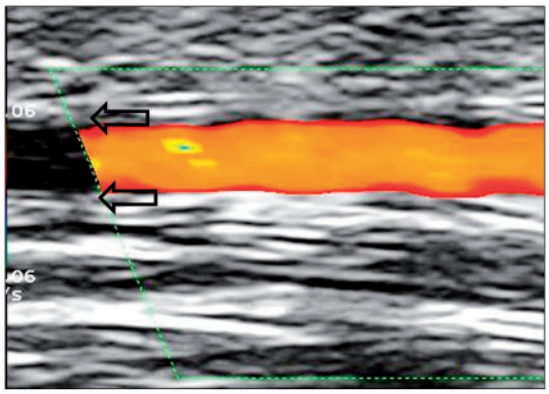
Fig. 1 Normal intima–media complex of a temporal artery parietal branch (22-MHz probe)



commonly concentric in axial views. When first described in temporal arteritis in 1995, this hypoechoic wall thickening was termed the *halo sign* [7]. The echogenicity of synovial proliferation in arthritis and wall thickening in vasculitis is similar. Fluid, as represented by effusion or artery lumen, is anechoic (black).

Several previously published studies have suggested cut-off values for halo diameters of 0.3–1.0 mm for temporal arteries and 1.0–2.0 mm for axillary arteries [8–11]. A recent prospective study to establish cut-off values was performed in patients with GCA and matched controls [12]. Results indicated that though normal IMC has diameters of about 0.2 and 0.6 mm in temporal and axillary arteries, respectively, vasculitic wall swelling most commonly results in diameters of 0.5–0.8 mm in temporal arteries and 1.5–2 mm in axillary arteries (Table 1). Inflammatory tissue is not compressible on application of pressure with the US probe. In contrast, artery lumen and artefacts due to suboptimal filling of the artery lumen with colour are compressible, a phenomenon termed compression sign [13]. Again, this can be compared with arthritis with non-compressible synovial proliferation but compressible effusion.

Histological data have shown that in GCA, the artery lumen may be occluded. During US examination, this is characterized by the absence of colour Doppler signals in a visible artery filled with hypoechoic material, even with low pulse repetition frequency and high colour gain [6] (C. Duftner, personal communication). Furthermore, severe wall swelling in GCA may lead to stenosis, which is characterized by turbulent colour pattern (aliasing) and persistent diastolic flow by colour Doppler US. The maximum systolic flow velocity determined within the stenosis of temporal arteries by pulsed wave Doppler US is two or more times higher than the flow velocity proximal or distal to the stenosis [14].

For accurate diagnosis and monitoring of GCA, it seems clear that sonographers should focus on both the halo sign and the compression sign; however, to date, most published studies have addressed only the halo sign. When occlusions occur in some segments, the halo sign is usually visible in other segments. Acutely occluded arteries are not compressible; in other words, the compression sign is pathological in the case of an occluded artery.

In early studies, inclusion of temporal artery stenosis helped to increase the sensitivity of temporal artery US because resolution was too low for detecting small degrees of wall thickening. With modern $\geqslant$15 MHz transducers, a temporal artery halo is usually detectable in stenotic segments. Furthermore, stenosis may confuse less experienced sonographers; this became obvious particularly in the Role of Ultrasound Compared with Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL) study, in which most sonographers had little experience with temporal artery US [2]. Of note, a new meta-analysis, which will soon be published, shows that evaluating stenosis and/or occlusion in addition to the halo sign does not further increase the sensitivity and specificity of US (C. Duftner, personal communication). Experienced sonographers may, however, consider stenosis of temporal arteries an additional feature for confirming the diagnosis if a halo sign is present. In contrast, for extracranial arteries such as carotid, subclavian, vertebral and axillary arteries, stenosis should be considered only to rate the severity of damage and not to confirm the diagnosis of GCA.

Which arteries should be examined by US?

Temporal and axillary arteries should be routinely examined if GCA is suspected because temporal arteries may be spared in 40% of patients [15, 16]. Examination takes 15–20 min for an experienced sonographer. If temporal and axillary artery US in conjunction with patient history and clinical examination do not reveal a clear diagnosis, other large arteries, except for the thoracic aorta, may be examined. Extracranial involvement has been termed large-vessel GCA [15].

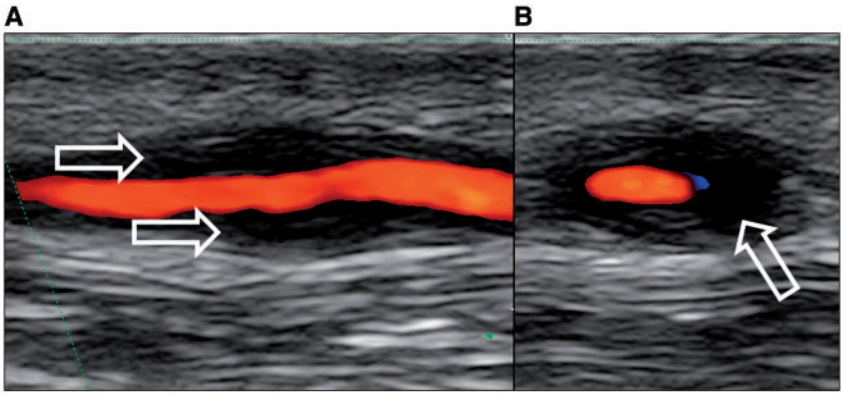
Temporal arteries

Modern high-frequency US probes provide excellent resolution of 0.1 mm, particularly in anatomical areas that localize within 1 cm below the skin surface. Therefore, US is particularly valuable for examining the common superficial temporal arteries, together with their frontal and parietal branches. They should be examined both in longitudinal and in transverse planes bilaterally as completely as possible.

Axillary arteries

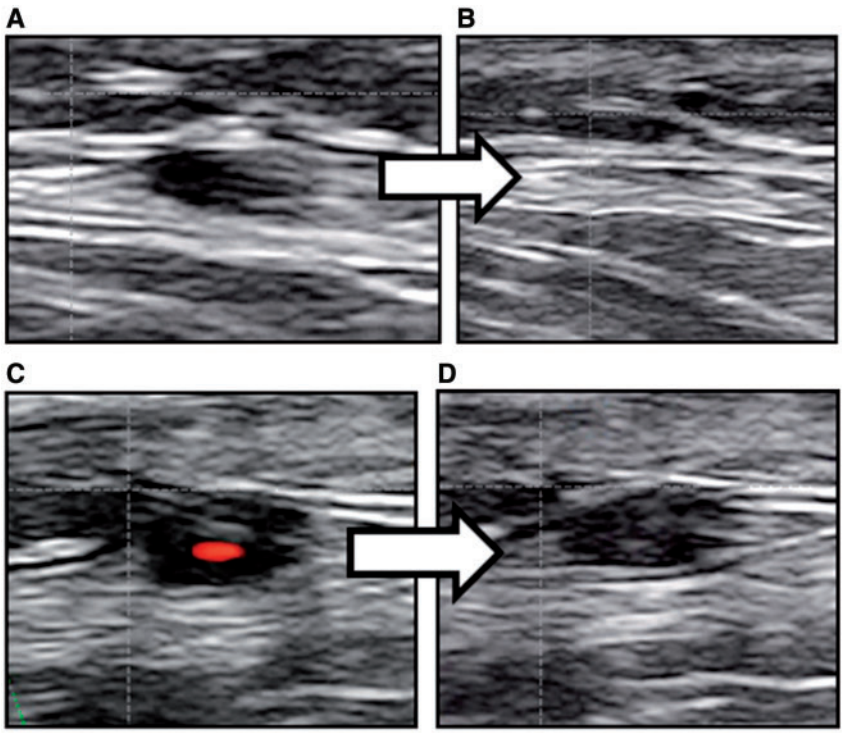
Patients with axillary artery involvement are younger (~66 years of age compared with 72 years of age in those with cranial GCA), and 83–88% are female, compared with 65–78% in those with cranial GCA. The time interval between onset of symptoms and diagnosis is longer, but visual loss is less common [15–20]. The axillary

Fig. 2 Halo sign of temporal artery frontal branch



(**A**) Longitudinal; (**B**) transverse.

Fig. 3 Compression sign of temporal artery branches



(**A** and **B**), normal; (**C** and **D**) abnormal.

arteries can be easily accessed with axillary views; difficulties arise only in severe forms of shoulder immobility.

Occipital and facial arteries

The occipital arteries are located posterior to the ear. The facial arteries wind around the body of the mandible. US detects facial and occipital artery involvement in 41 and 31% of GCA patients, respectively. Jaw claudication (71 *vs* 27%) and permanent blindness (24 *vs* 2%) are more common in patients with facial arteritis compared with those without facial arteritis [21].

Carotid arteries

Common carotid arteries are more often involved than the proximal internal and external carotid arteries. In contrast to temporal, axillary, occipital and facial arteries, arteriosclerosis of carotid arteries is common among the age group of patients with suspected GCA, often with stenosis

Table 1 Cut-off values for US in GCA

Anatomical region	Cut-off value between normal IMT and vasculitis, mm
Common superficial temporal artery	0.42
Frontal branch	0.34
Parietal branch	0.29
Axillary artery	1.0

Summary of results from [12]. IMT: intima–media thickness.

of internal and external carotid arteries. Although arteriosclerosis is characterized by heterogeneous and in part hyperechoic, irregularly delineated, eccentric vessel wall alteration, differentiation from vasculitis may sometimes be difficult. Vasculitic common carotid artery stenoses are uncommon in GCA.

Vertebral arteries

Vertebral arteries can be assessed by shifting the US probe posteriorly from the common carotid arteries, allowing several segments of the artery to be delineated between the vertebral processi transversi. Vasculitis of vertebral arteries may cause cerebral infarctions. If high-grade proximal subclavian artery stenosis or occlusion is present, reverse flow from cranial to caudal may be found in the vertebral arteries as a result of subclavian steal syndrome.

Subclavian arteries

The middle and distal parts of the subclavian arteries can be seen easily with US from above and below the clavicle, respectively. The proximal left common carotid artery and the proximal left subclavian artery can be seen only with a lower resolution because they run deep to the US probe. Stenoses can be determined by Doppler flow curves.

Aorta

US examination of the thoracic aorta is impeded by the lungs. Only the first 4 cm of the ascending aorta and the aortic arch can be examined with low frequency probes; in addition, because of the lower resolution, only major pathology can be seen. Although transoesophageal US can provide excellent, high-resolution images of the thoracic aorta, it is not routinely used for diagnosing GCA because of its invasiveness.

Visibility of the abdominal aorta is generally better with US, though resolution is low in obese patients; meteorism may further decrease image quality. Aortitis is characterized by a circumferential hypoechoic halo. The surrounding tissue is more hyperechoic and heterogeneous in periaortitis (Fig. 4), which commonly is associated with renal obstruction. US is an excellent tool for evaluating stenosis of coeliac, mesenteric and renal arteries; however, typical inflammatory wall thickening of these arteries may be visible only in lean patients.

Femoral arteries

US is the method of choice in the search for arterial occlusive disease in the lower extremities. In almost every elderly patient, these arteries exhibit arteriosclerosis, which sometimes makes it difficult to differentiate from vasculitis. In patients with suspected GCA, the pulse of pedal arteries should be taken. If absent, US is warranted for evaluating the grade of pathology and whether stenosis or occlusions are due to arteriosclerosis or vasculitis.

Technical requirements

Adequate US equipment for diagnosing GCA is widely available in rheumatology practice. Modern high-resolution linear probes that provide Doppler mode should be used, particularly for examining the temporal arteries. Resolution of US increases with higher frequencies, and tissue penetration increases with lower frequencies. Probes with $\geqslant$15 MHz frequency should also be used for examining the temporal arteries to detect minor wall thickening. Probes with frequencies $>$20 MHz are increasingly available, and such probes allow the normal IMC of temporal arteries to be clearly visualized. Detailed information on US settings and scanning techniques is provided in a recently published review article [22].

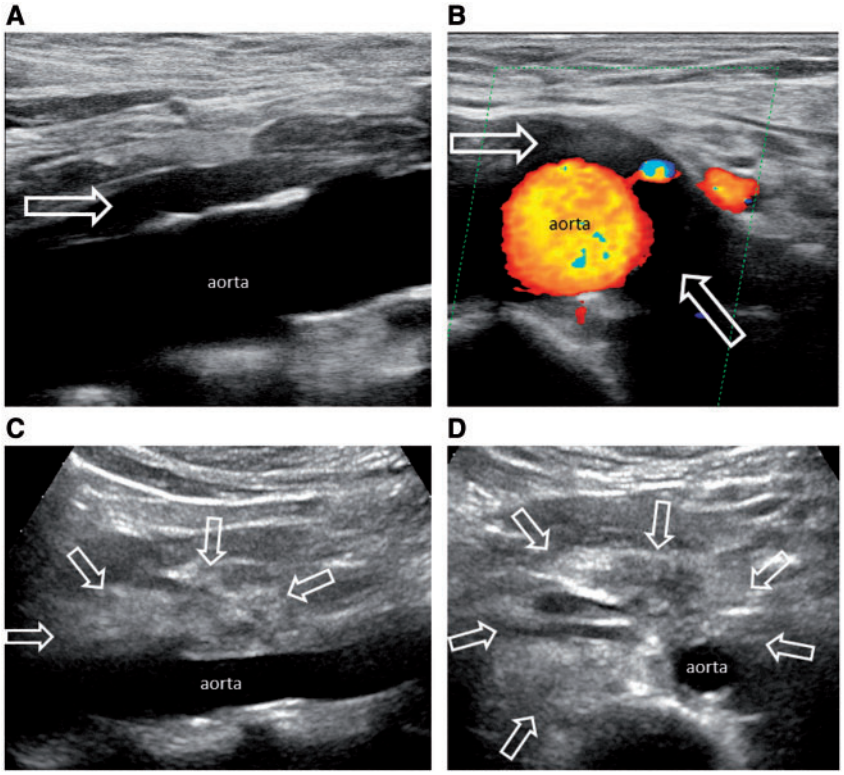
Reliability of US

The use of US is increasingly recommended as a first-line diagnostic test in patients with suspected GCA, and may replace temporal artery biopsy (TAB) in most cases [4, 5, 23, 24]. Conversely, questions have been raised regarding the diagnostic performance and reliability of US and querying the overall clinical usefulness of US in GCA [25].

To address these issues the OMERACT initiative on US in LVV was formed in 2014; it includes members from Europe and the USA. The OMERACT initiative is intended to reach agreement on generally accepted, consistent definitions that can be applied in future clinical trials and to test the reliability of these definitions for image and video interpretation and for image acquisition together with interpretation in patients. The basis for these definitions was a systematic literature review of publications on US and other imaging modalities for the diagnosis of LVV, using Ovid MEDLINE, EMBASE and Cochrane databases up to March 2017 [26]. Full research articles of prospective studies involving more than 20 patients with suspected (diagnostic studies) or established (follow-up studies) primary LVV were included. Case–control studies and studies on continuous wave Doppler and M-mode US for the investigation of vessel wall pulsation were excluded because they were not considered relevant for clinical practice. A meta-analysis was also conducted to synthesize data. This work also forms the basis for EULAR recommendations on imaging in LVV. The EULAR recommendations are expected to be published soon.

Studies that fulfilled the selection criteria for the systematic literature review included US, MRI, CT and PET techniques; however, most selected studies investigated US.

FIG. 4 US appearance of aortitis (**A** and **B**) and periaortitis (**C** and **D**)



The overall sensitivities and specificities of temporal artery US were 77% and 96% compared with the clinical diagnosis of GCA with likelihood ratios of 19 and 0.2 for positive and negative US, respectively. Three older meta-analyses arrived at specificities of 83% [27], 91% [28] and 94% [29] for the halo sign compared with the clinical diagnosis. The first meta-analysis described sensitivities of 55% for the halo sign that increased to 87% when consideration of stenosis and occlusions was included [29]. The other meta-analyses found sensitivities of 68% [28] and 75% [27] for the halo sign. The finding of a bilateral halo sign increased specificity to 100% [28]. In more recent studies, sensitivities are higher because of better technology and increasing experience [30]; this improvement is reflected in the most recent meta-analysis [31, 32]. A recently published study investigating 451 consecutive patients with suspected GCA, among whom 256 patients had a final diagnosis of GCA, arrived at 91.6% sensitivity and 95.8% specificity for US compared with the final clinical diagnosis [33]. Another recent study (TABUL), investigated the diagnostic accuracy and the cost-effectiveness of US compared with TAB. In this multicentre study, the sensitivity of US compared with clinical diagnosis after 6 months was surprisingly low (54%); however, it was higher than the sensitivity of TAB (39%) [2]. It is difficult to define a gold standard for the diagnosis of GCA in order to test any new diagnostic method such as US and other imaging techniques. Despite this caveat, it is clear that TAB is less sensitive than US in most studies, particularly because TAB evaluates only a limited anatomical region in a systemic disease.

How reliable is US? In radiology, it is common to rate reliability for image interpretation but not to rate both image acquisition and image interpretation simultaneously. Despite the absence of scientific data, US is regarded as strongly investigator dependent. To address this, data and interpretation for image acquisition are warranted. A single Spanish study found very high reliability for image and video interpretation and for the examination of patients in workshops for temporal artery US. For all scenarios, κ values were >0.8, suggesting almost perfect agreement [34]. In another study, the inter-observer agreement for the diagnosis of GCA between two sonographers from one institution evaluating the compression sign of temporal arteries was excellent, with the two sonographers disagreeing only in 1 of 60 patients [35]. However, these data must be confirmed in large-scale international studies.

In a web-based reliability test of temporal and axillary artery images and videos of patients with GCA and controls, following the strict rules of OMERACT-related US exercises, the OMERACT US group also arrived at κ values of >0.8 for inter-observer and intra-observer agreements for halo and compression signs [36–40]. The TABUL study applied even stricter rules when assessing the reliability of 12 sonographers for videos randomly

chosen from the study database, irrespective of their quality. Reliability was equal to the reliability of 14 pathologists reading TAB specimens with intraclass correlation coefficients of 0.61 and 0.62, respectively [2]. Sonographers in the TABUL study were less experienced than sonographers in the OMERACT study. Both studies show that US images and videos can reliably document GCA diagnosis. This allows for the use of US as an inclusion criterion for future GCA trials, under the condition that stored US videos are available for subsequent validation.

Reliability has also been tested according to OMERACT rules in patient-based exercises for several other diseases, such as RA [37] and gout [41]. This test is difficult to perform in patients with GCA because GCA responds quickly to treatment. However, we recently conducted investigations with very good reliabilities for the overall diagnosis of GCA (e.g. Light's κ for inter-reader reliability, 0.76–0.86; range, 0.67–1) and moderate to good reliabilities for identifying vasculitis in the respective anatomical segments [42].

Pros and cons of US compared with other diagnostic techniques

Compared with other imaging techniques, US can be performed by the clinician directly in conjunction with the clinical examination. US is widely available and inexpensive, and most arteries can be examined easily. US provides by far the highest resolution of all imaging techniques. Thus, it is particularly useful for small vessels such as temporal arteries.

US *vs* TAB

In centres with experienced staff, clinical examination and US will clearly confirm or exclude a suspected diagnosis of GCA in most patients. TAB may be used if findings are unclear, particularly in patients whose US results are negative and who received glucocorticoid treatment for long durations. If arteries are small or localized deeply, the segment to be biopsied may be marked with the aid of US [43]. A prospective study comparing US-guided TAB with standard TAB, however, found that US guidance did not increase the sensitivity of TAB [44]. Thus, only a few, selected patients with localized halo might benefit from US guidance.

Many studies have shown that TAB is less sensitive than US, primarily because it assesses only a small anatomical region in a generalized disease. US may give a false-negative result in patients with localized adventitial vasculitis and vasculitis limited to vasa vasorum of temporal arteries [45]. Nevertheless, the main benefits of US over TAB are time and cost. It can take 2 weeks or more to receive the results of a biopsy, and a recent publication [2] indicated that the cost per patient was reduced by £485 in favour of temporal and axillary artery US compared with TAB. Thus, new classification criteria for GCA are likely to include US imaging in addition to TAB [46].

US *vs* MRI, CT and PET

Imaging techniques such as MRI, CT and PET in combination with CT (PET-CT) provide an improved overview of large vessels and can better visualize the thoracic aorta compared with US. However, these imaging techniques are more expensive than US and may be unnecessary except for those few patients in whom the thoracic aorta is exclusively affected. In addition, exposure to radiation is particularly high with CT and PET. Angiography is also limited by radiation exposure and invasiveness; as a result, it has no role in the diagnosis of GCA and should be used only when interventions are needed.

Few studies have been published that compare US directly with other imaging modalities. Available data indicate that US correlates well with PET [47–49], although PET might be slightly more sensitive in the vertebral arteries whereas US might detect smaller changes in the axillary arteries. US of temporal and extracranial arteries also seems to correlate well with MRI [1].

Imaging examination should always be performed by a trained specialist using appropriate equipment, operational procedures and settings. Sufficient data are not yet available regarding learning curves for the operation of US in the diagnosis of GCA. The European Federation of Societies for Ultrasound in Medicine and Biology minimum training requirements for rheumatologists performing musculoskeletal US demand a minimum of 300 US examinations to achieve level I competency [50].

US in clinical practice—the fast-track approach

Permanent vision loss, most commonly due to anterior ischaemic optic neuropathy, is a severe, disabling complication of GCA. It occurs almost exclusively in patients with untreated GCA. Therefore, it is mandatory to diagnose and treat patients with suspected GCA without delay. Referring physicians must become aware of key symptoms of GCA and identify a specialist who can be contacted immediately to confirm or exclude the suspected diagnosis. Both delayed initiation of treatment and unnecessary glucocorticoid treatment of conditions mimicking GCA must be avoided.

Glucocorticoid treatment rapidly decreases the sensitivity of imaging. One case report describes the disappearance of a temporal artery halo sign within 2 days [51]. Another study found a decrease in sensitivity from 88 to 85% for temporal artery US and temporal artery MRI, respectively, in patients who were untreated or treated for 1 day only, to 50% and 64% for patients who were treated for 2–4 days and to 50% and 56%, respectively, for patients who were treated for >4 days [52]. Although the halo sign may be seen in temporal arteries within the first 2 weeks of treatment and may persist for months in some patients, both sonography and MRI provide clearer results with a higher sensitivity if performed earlier. Extracranial artery wall swelling may remain detectable for longer durations [17]. It has also been suggested that PET-CT be performed within the first 3 days of treatment

Table 2 Rates of vision loss among consecutive, unselected patients newly diagnosed with GCA from the Medical Centre for Rheumatology Berlin-Buch

Time period	Permanent vision loss (%)	Patients newly diagnosed with GCA
1994–96	27	30
2004–06	11	62
2014–16	8	203

Vision loss includes anterior ischaemic optic neuropathy (80%), central retinal artery occlusion (17%) and branch retinal artery occlusion (3%) [14, 59] (W. A. Schmidt, unpublished observations).

because of decreased sensitivity with treatment [53, 54]. However, histological results from TAB may remain positive longer than that. In a study with serial biopsies, abnormal cell infiltration remained in 70–75% of patients within the first 6 months and in nearly 50% within 9 or 12 months [55].

The need for early diagnosis and treatment led to the introduction of fast-track clinics. When contacting the fast-track clinic, preferably by telephone, the referring physician will receive an appointment for the patient within 24 h and, if possible, on the same day. Glucocorticoid treatment should be started immediately, particularly if the appointment might be delayed for some reason (e.g. by a weekend). Diagnostic tests should not delay initiation of treatment. In the fast-track clinic, a rheumatologist who is experienced in GCA will perform structured medical history and clinical examinations, followed by the US examination. Ideally, the same rheumatologist performs both the clinical and the US examinations, as increasingly practiced [3, 56, 57], allowing the patient to leave the examination room with a report indicating the final diagnosis and to receive immediate treatment if GCA is confirmed. Alternatively, the US examination can be performed in a timely manner by a vascular specialist [4, 58].

The implementation of such GCA fast-track clinics led to a decrease in permanent loss of vision from 37 to 9% [56] and from 19 to 2% [57]. We introduced a GCA fast-track clinic in Berlin, Germany, between 1997 and 2000. The decrease of permanent vision loss in consecutive, unselected patients with newly diagnosed GCA in the years since this introduction is shown in Table 2. Of note, the number of new patients in our institution significantly increased over time as a growing number of physicians used the services of a specialized fast-track clinic. The service is offered by three experienced rheumatologists, who often consult with each other. Only 36 of 1173 patients (3.1%) seen between 2014 and 2016 in the fast-track clinic required TAB to confirm or exclude an otherwise unclear diagnosis.

We also offer the fast-track clinic to all patients with newly diagnosed PMR because US reveals vasculitis of temporal and/or axillary arteries in about 15–20% of patients without cranial symptoms of temporal arteritis [5]. Furthermore, shoulder and hip US typically shows small subdeltoid bursitis, biceps tenosynovitis, glenohumeral and hip joint effusion and/or trochanteric bursitis and helps to differentiate PMR from similar diseases such as shoulder OA and calcifying tendinitis [60–62].

US for disease monitoring

With treatment, the halo becomes brighter and its diameter decreases [2, 3, 63, 64]. In temporal arteries, it may resolve between 2 days [50] and many months [8] after treatment initiation. A small amount of wall thickening may remain visible for years, particularly in patients with temporal artery halo or occlusion; this can be specifically detected with >20-MHz probes. The role of temporal artery US for monitoring disease activity is still unclear, and studies are under way to address this question. Monitoring with US might become more important in the future because new treatments for GCA involving IL-6 inhibition may impair the usefulness of measuring CRP and ESR as follow-up parameters [65].

In extracranial arteries such as the axillary arteries, wall thickening usually remains for months or years [5, 17, 20], probably reflecting a larger oedematous mass of these arteries. In large-vessel GCA, wall thickness can be measured twice yearly [3]. If IMC increases, it suggests that the patient might have been undertreated in the meantime. Still, conventional US can only monitor damage; it cannot predict disease progression. Newer techniques may be of more use in detecting potential markers of disease activity. Neovascularization may be a potential indirect marker of vascular inflammation, and contrast-enhanced ultrasonography can depict small vessels in the artery wall. One study of contrast-enhanced ultrasonography recently showed a correlation between increased vascular flow, disease activity and positive PET results [49]. Further studies are needed, though, before this tool can be considered for clinical practice.

Conclusion

In conclusion, US should be used as a first-line diagnostic test for patients with suspected GCA provided that trained specialists with expertise in clinical diagnosis and vascular US are available. To prevent permanent loss of vision in patients with GCA, centres should offer fast-track clinics that include clinical examination and US to ensure timely diagnosis and treatment initiation.

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