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Concise report

False positives in the ultrasound diagnosis of giant cell arteritis: some diseases can also show the halo sign

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Abstract

Objectives. To describe the frequency and causes for the presence of a halo sign on the ultrasound of patients without a diagnosis of GCA.

Methods. In total, 305 patients with temporal artery colour Doppler ultrasound showing the presence of halo sign (intima-media thickness $\geq$0.34 mm for temporal arteries [TAs] and $\geq$1 mm for axillary arteries) were included, and their medical records were reviewed. The clinical diagnosis based on the evolution of the patient over at least one year was established as the definitive diagnosis.

Results. Fourteen of the 305 (4.6%) patients included showed presence of the halo sign without final diagnosis of GCA: 12 patients in the TAs (86%), and two patients with isolated AAs involvement (14%). Their diagnoses were PMR ($n = 4$, 29%); atherosclerosis ($n = 3$, 21%); and non-Hodgkin lymphoma type T, osteomyelitis of the skull base, primary amyloidosis associated with multiple myeloma, granulomatosis with polyangiitis, neurosyphilis, urinary sepsis and narrow-angle glaucoma ($n = 1$ each, 7%).

Conclusion. The percentage of halo signs on the ultrasound of patients without GCA is low, but it does exist. There are conditions that may also show the halo sign (true positive halo sign), and we must know these and always correlate the ultrasound findings with the patient's clinic records.

Key words: giant cell arteritis, ultrasound, temporal arteritis, false positives, vasculitis, ultrasonography, specificity, halo sign

Rheumatology key messages

- The percentage of false positives in the CDUS diagnosis of GCA is low (4.6%).
- Most false positives occur in GCA patients with only one affected branch.
- There are some systemic diseases that show halo sign non-related with GCA.

Introduction

GCA is the most common systemic vasculitis in the elderly. It is associated with high mortality and morbidity due to ischaemic complications, such as stroke or visual loss. Therefore, a quick and correct diagnosis is essential to prevent its serious consequences. Over time, the role of imaging as a diagnostic tool in GCA has increased, especially with the widespread use of colour Doppler ultrasound (CDUS) [1–4]. Since the establishment of fast-track outpatient clinics where CDUS is the main diagnostic tool, the rate of arterial-related permanent blindness has been reduced by 76–88% [5, 6].

In the latest EULAR recommendations of 2018 for the use of imaging in GCA, CDUS is recognized as the first diagnostic tool to be applied in centres with experience as it is less invasive, more cost-effective and has a lower rate of false-negative findings than temporal artery biopsy (TAB) [7]. In the OMERACT definitions of elemental ultrasonographic lesions of GCA, the halo sign has been shown to be the most valuable and accurate for

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diagnosing the disease [8], with a mean sensitivity and specificity in a review of the evidence of 77% and 96%, respectively [9]. However, published results from centres specializing in this pathology are better, with a sensitivity of 91% and a specificity of 96% [10]. Nevertheless, these specificity data indicate that some patients are incorrectly diagnosed with GCA.

A false-positive halo sign for GCA may occur due to errors in the interpretation of the images or due to other diseases that also show the halo sign. In this context, our group published data indicating that atherosclerosis can cause a false-positive GCA diagnosis by increasing the intima-media thickness (IMT), but knowledge about the presence of the halo sign in other diseases remains scarce [11].

The aim of this study was to describe the frequency and possible causes for the presence of halo sign on CDUS without final diagnosis of GCA seen in our patient cohort, which could be relevant for the application of this diagnostic method in clinical practice.

Methods

We conducted a retrospective observational study of a longitudinal cohort of consecutive patients with suspected GCA who had undergone CDUS. All patients with CDUS findings compatible with GCA were included. The medical records of these patients were reviewed, and the clinical diagnosis based on the evolution of the patient over at least one year was established as the definitive diagnosis. The study was approved by the ethics committee of La Paz University Hospital (HULP: PI-2676).

Ultrasonography

A baseline CDUS examination of the temporal superficial arteries (TSAs) was performed. The common trunks, frontal and parietal branches were explored bilaterally, including the longitudinal and transverse views. The axillary arteries (AAs) were explored systematically in the last 39 patients. An ultrasound diagnosis of GCA was made if the halo sign appeared in at least one vessel segment. In agreement with the OMERACT guidelines, we defined the halo sign as a homogeneous, hypoechoic wall thickening, well-delineated towards the luminal side, visible in both the longitudinal and transverse planes, most commonly concentric in transverse scans [8]. To increase the accuracy of the diagnosis, we measured the IMT on a grey scale using a cut-off of 0.34 mm for the TSAs and 1 mm for the AAs, in agreement with previous studies [10–12]. The examinations were done by two expert sonographers who had performed >300 GCA CDUS exams each. They were blinded to the clinical and laboratory data. Each patient's ultrasound examination was performed by just one sonographer. For reliability purposes, the two readers reviewed videos of 50 patients, with a mean of six videos per patient. The device used was a Mylab Twice Esaote system (Genoa, Italy). For exploration of the TSAs, a frequency of 22 MHz for the grey scale and 12.5 MHz for colour Doppler, a colour gain of 60 and a pulse repetition frequency of 2 kHz were used. For the AAs, a frequency of 13 MHz for the grey scale and 7.2 MHz for colour Doppler with a pulse repetition frequency of 3.5 kHz and a colour gain of 61 were used.

Statistical analysis

Absolute and relative frequencies were calculated for the qualitative variables and the median and interquartile range were calculated for the quantitative variables. SPSS version 23 was used.

Results

A total of 305 patients with CDUS findings compatible with GCA were included. Among them, 14 (4.6%) were considered to have false-positive findings for GCA by the clinician at the time of the diagnosis or during follow-up. The characteristics of these 14 patients and their final diagnoses are shown in Table 1. Nine of the 14 (64%) were women. The median age was 72 (interquartile range, 11) years. The median ESR, CRP level and haemoglobin level at the time of diagnosis were 55 (78) mm/h, 15.1 (93.6) mg/l and 13.3 (2.8) g/Dl, respectively. Five patients (36%) fulfilled the ACR 1990 classification criteria. TAB was performed in 9 of the 14 patients (64%), which was not compatible with GCA in none of the patients. Twelve patients (86%) showed involvement of the TSAs on ultrasound; five showed one branch involved (42%), three showed two branches involved (25%), two showed three branches involved (17%) and two showed four branches involved (17%). In addition, two patients (14%) showed an isolated halo sign in the AAs; the sign was unilateral in one patient and bilateral in the other. Regarding the definitive diagnosis, four patients were diagnosed with PMR (29%), three were diagnosed with atherosclerosis (21%), and one patient each was diagnosed with non-Hodgkin lymphoma type T, osteomyelitis of the skull base, primary amyloidosis associated with multiple myeloma, granulomatosis with polyangiitis, neurosyphilis, urinary sepsis and narrow-angle glaucoma (Fig. 1).

Discussion

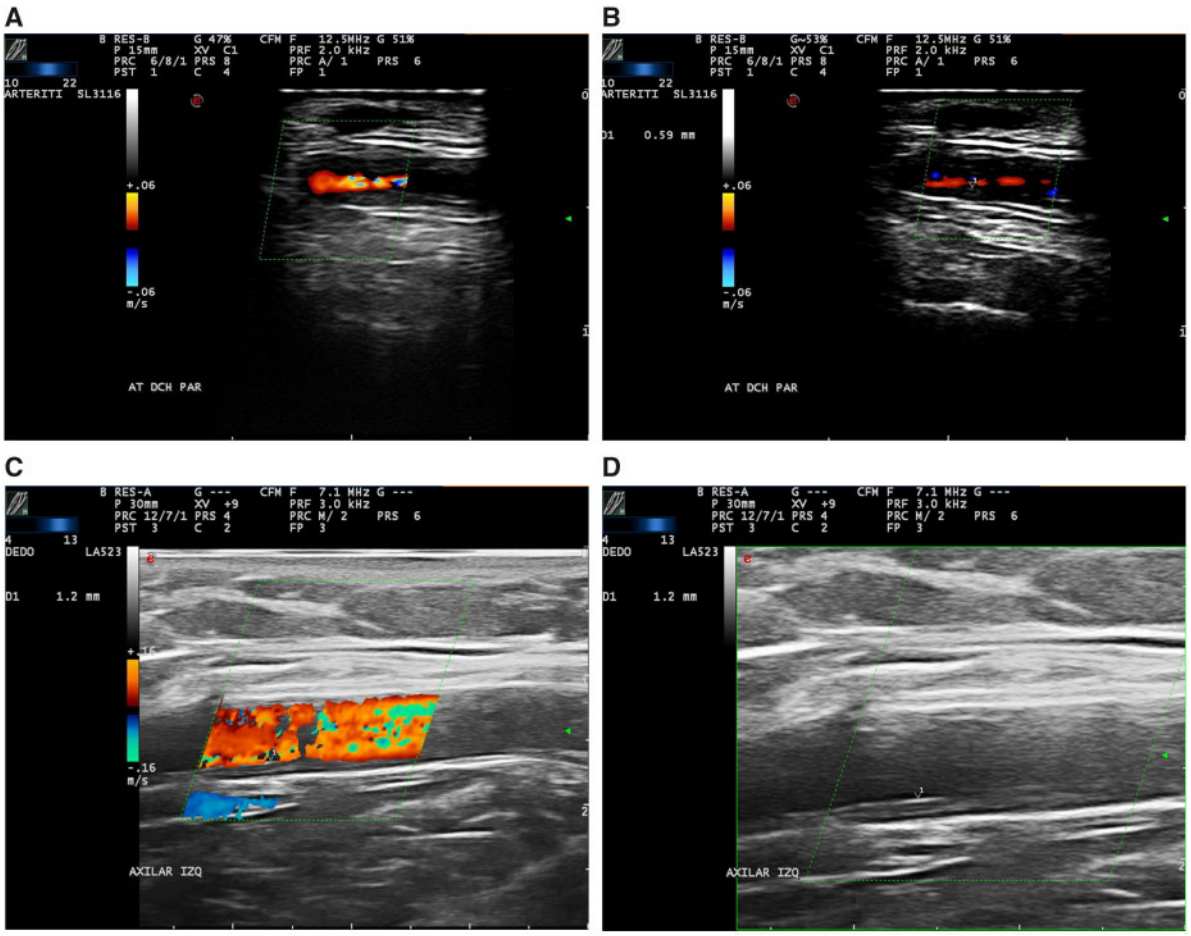
In recent years, TSAs CDUS has been shown to have a high sensitivity and specificity for diagnosing GCA. However, like all diagnostic tools, it can yield false-positive findings. In a previous paper, our group showed that atherosclerosis could generate an increase in the IMT that mimics the halo sign [11], but thus far, only a few case reports or small cohort studies have been published on other conditions that could also mimic the halo sign. Our study shows a rate of positive ultrasound findings without a final diagnosis of GCA of 4.6%, which is consistent with previously published specificity rates

Table 1 Final diagnoses and ultrasound involvement

Patient	Definitive diagnosis	Biopsy result	Artery involved	Number of involved arterial branches
1	PMR[a]	Negative	Temporal	2
2	PMR[a]	Negative	Temporal	1
3	PMR[a]	Negative	Temporal	1
4	PMR	Negative	Temporal	1
5	Atherosclerosis	Not done	Axillary	1
6	Atherosclerosis	Not done	Axillary	2
7	Atherosclerosis	Negative	Temporal	2
8	Narrow-angle glaucoma	Not done	Temporal	1
9	Urinary sepsis[a]	Negative	Temporal	1
10	Non-Hodgkin's T-cell lymphoma[a]	Negative	Temporal	3
11	Osteomyelitis of the skull base[a]	Not done	Temporal	4
12	Granulomatosis with polyangiitis	Not done	Temporal	2
13	Amyloidosis due to multiple myeloma	Negative (deposit of amyloid material)	Temporal	4
14	Neurosyphilis[a]	Negative	Temporal	3

[a]Axillary arteries were not explored.

Fig. 1 Ultrasound images of right parietal branch of patient 13 (**A, B**) and left axillary artery of patient 5 (**C, D**)



[9, 10, 13]. The reliability values are also in agreement with data previously reported by our group [11, 14] and OMERACT [8].

By critically reviewing the ultrasound results of patients without a final diagnosis of GCA but in whom the halo sign was found, we believe that two different categories can be distinguished. The first category consists of those patients in whom there was probably a misinterpretation of recorded images; in these cases, the halo sign could be considered a 'not true halo sign'. In contrast, the second category consists of those patients in whom a condition other than GCA increased the IMT; in these cases, the halo sign could be classified as a false-positive halo sign for GCA but a 'true halo sign' on the ultrasound image.

In some patients with a 'true halo sign', a histopathological study could be helpful to reveal the true aetiology. The hypoechoic thickening of the arterial wall could be due to cellular infiltration and related oedema, as would be the case in our patients with ANCA-associated vasculitis, osteomyelitis of the skull base, neurosyphilis and non-Hodgkin lymphoma. Patients with other systemic vasculitis, malignant and infectious processes have already been described to show the halo sign on ultrasound examination [15, 16]. Another possibility is that the hypoechoic area could be due to the deposition of material in the arterial wall [17], which could apply to our patients with atherosclerosis and multiple myeloma. De Miguel *et al.* analysed a cohort of 40 patients with high or very high vascular risk and found the halo sign in 10% [11]. In our patient with multiple myeloma, TAB showed the presence of amyloid material in the vessel wall [18]. Similar false-positive findings have also been reported in other biopsy studies. In 1999, Hachulla *et al.* observed that in 4% of cases, TAB performed due to the suspicion of GCA revealed other systemic necrotizing vasculitis [19]. In 2014, Cavazza *et al.* reviewed the histopathology findings of 322 positive TAB samples and found that five corresponded to pathologies other than GCA, such as ANCA-associated vasculitis, polyarteritis nodosa and primary systemic amyloidosis [20].

Regarding the so-called 'not true halo sign', an operator-dependent error was probably made when locating the intima or when measuring the IMT. This would be the case in our patients with PMR, urinary sepsis and narrow-angle glaucoma. We believe it is important to emphasize that all of these patients except one (patient 4) showed the involvement of a single branch on CDUS. Therefore, we consider that when only one branch is affected, performing TAB is justified to confirm the diagnosis [2, 16].

Our study has some limitations. The AAs were explored in only 39 of the 305 patients included because until a few years ago, the AAs were not systematically explored in all patients referred to the fast-track outpatient clinic. This may have an impact on our results because other false-positive cases of large vessel vasculitis could have been detected. Another issue is the four cases of PMR among the false-positive cases. It is known that PMR may cause some degree of arterial inflammation, because GCA and PMR are associated pathologies. However, clinicians, whose diagnosis was the gold standard in our study, did not consider these cases as PMR associated with GCA. To support this definitive diagnosis, the medical records of these patients were reviewed, and it was confirmed that all of them responded to low doses of corticosteroids recommended for PMR and did not have refractory PMR or develop suggestive symptoms of GCA during a long follow-up period of at least one year. In addition, three of the four patients with PMR showed imaging findings compatible with the halo sign in a single cranial branch, and in these cases, the specificity of CDUS is lower.

In conclusion, the percentage of false-positive halo signs for GCA is low. However, it is important to be aware of the possible causes and always correlate the results of CDUS with the clinical data to minimize the rate of false-positive results.

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