Comparison between colour duplex sonography findings and different histological patterns of temporal artery

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Abstract

Objective. To assess the findings of temporal artery colour duplex sonography (CDS) in GCA characterized by a histological pattern of periadventitial small vessel vasculitis (SVV) and/or vasa vasorum vasculitis (VVV) and compare it with those observed in classic GCA with transmural vasculitis.

Methods. We studied 30 patients with SVV and/or VVV, 63 patients with classic GCA and 67 biopsy-negative patients identified over a 9-year period. CDS of the temporal arteries was performed in all patients by one ultrasonographer. Temporal artery biopsy was used as the reference standard. Sensitivities, specificities and likelihood ratios (LRs) were calculated.

Results. The frequency of the halo sign on CDS was significantly lower in the patients with SVV and/or VVV compared with those with classic GCA (20% vs 82.5%, P = 0.0001). The halo sign had a sensitivity of only 20% (95% CI 8.4, 39.1%) and a specificity of 80.6% (95% CI 68.7, 88.9%) for the diagnosis of SVV and/or VVV. The negative LR was 0.992 (CI 0.824, 1.195), and the positive LR was 1.030 (CI 0.433, 2.451). The halo sign for the diagnosis of biopsy-proven classic GCA had a higher sensitivity of 82.5% (CI 70.5, 90.5%), the same specificity of 80.6% (CI 68.7, 88.9%) and a higher positive LR (4.253; CI 2.577, 7.021).

Conclusion. The halo sign is infrequently found in GCA characterized by a histological pattern of SVV and/or VVV. This limits the sensitivity of CDS in correctly identifying patients with GCA.

Key words: giant cell arteritis, ultrasonography, halo, transmural vasculitis, periadventitial small-vessel vasculitis.

Introduction

GCA is a vasculitis that mainly involves the large and medium-sized arteries, especially the branches of the proximal aorta [1]. Temporal artery biopsy (TAB) is the gold standard for the diagnosis of GCA [2]. A positive biopsy result can predict the likelihood of GCA in >90% of cases [3]. Colour duplex sonography (CDS) of the superficial temporal arteries was introduced in the 1990s and is considered the imaging modality of choice for the diagnosis of GCA [4]. Evidence of a hypoechoic halo around the lumen of the temporal arteries, due to edematous thickening of the artery wall, is a quite specific sign for GCA [4-6]. However, no studies have evaluated the findings of CDS in patients with GCA characterized by different histological temporal artery patterns.

The classic histological picture of GCA is a transmural inflammatory infiltrate associated with marked disruption of the internal elastic membrane. A granulomatous inflammation with giant cells at the intima-media junction is observed in 50% of cases, while the remaining 50% have a panarteritis with a mixed-cell inflammatory infiltrate that is predominantly composed of lymphomononuclear cells [7]. However, in some cases the inflammation is...
restricted to the vasa vasorum, to the periadventitial small vessels, or both [8]. Cranial ischemic events are just as common in these patients as in those with classic GCA. Therefore prompt recognition of GCA in these patients with limited vascular inflammation is crucial to start the appropriate glucocorticoid therapy as soon as possible.

In this study we evaluated the findings of temporal artery CDS in a prospective cohort of patients with different histopathological TAB patterns of GCA observed over a 9-year period. The prevalence of the halo sign in patients with SVV and/or VVV was compared with that observed in patients with classic GCA diagnosed in the same time period. We also compared the diagnostic usefulness of CDS in the two groups of patients.

Patients and methods

Patients

Our study was conducted in Santa Maria Nuova Hospital in Reggio Emilia, Italy, where all patients referred by medical practitioners and community-based specialists for suspected GCA are usually assessed by rheumatologists in the rheumatology unit. Routine CDS of the temporal arteries for patients with suspected GCA has been performed as part of a standard screening since 1998. Standardized reports for all US examinations are stored in a computerized database. All patients seen in the rheumatology unit in the 2002–2010 period who had TAB and CDS of temporal arteries for suspected GCA were included in this study. Globally, 352 TABs were performed in the study period in Reggio Emilia Hospital; 163 patients (46.3%) were seen in the rheumatology unit had CDS before TAB. In three patients TAB did not show temporal artery. Therefore 160 patients were included in the study. These patients followed a standardized protocol: initially they underwent CDS of the temporal arteries performed by an ultrasonographer who was blinded to the clinical diagnosis, and subsequently TAB was performed at the site highlighted by the ultrasonographer.

The pathologist who examined the biopsies had no knowledge of the clinical or ultrasonographic findings. The final diagnosis of GCA or another disorder was made after the results of the investigations became available and the clinical course had been assessed.

Temporal artery CDS was performed using an ATL HDI 5000 device (ATL Ultrasound, Bothell, WA, USA) with a linear 5–12 MHz probe for the common superficial temporal arteries and their branches. These vessels were examined as thoroughly as possible in a longitudinal and transverse plane to evaluate whether a halo was present around the lumen. A dark, hypoechoic circumferential wall thickening (halo sign) with a diameter >0.4 mm was considered consistent with vasculitis. CDS was carried out by one ultrasonographer (A.N.) with longstanding expertise in vessel CDS who was unaware of the patients’ clinical data.

Thirty patients had biopsy-proven SVV and/or VVV, 16 patients had SVV, 11 VVV and 3 associated SVV and VVV. Fourteen patients (46.6%) satisfied the ACR criteria for the classification of GCA [9]. None of the 30 patients with SVV and/or VVV had clinical manifestations suggesting a systemic vasculitis other than GCA or another unrelated disorder when TAB was performed and during the follow-up [mean 86 months (s.d. 48 months)]. CDS findings in these 30 patients were compared with those of 63 patients with classic GCA [transmural infiltration predominantly of lymphomononuclear cells in the temporal artery wall, with or without giant cells] and 67 biopsy-negative patients who had TAB for suspected GCA in the same time period. Of these 67 biopsy-negative patients, 29 satisfied the ACR criteria for GCA, 12 the Healey criteria for PMR [10], 2 had fever of unknown origin, 3 had non-arteritic anterior ischaemic optic neuropathy and the other 21 satisfied two ACR criteria for GCA. Sixty of the 67 (89.5%) biopsy-negative patients underwent CDS of the epiaortic vessels and of the aorta. Three patients showed the characteristic halo sign indicative of large-vessel vasculitis in at least one vessel examined.

All TABs were reviewed by a pathologist (A.C.) with an expertise in vasculitides who had no access to clinical data nor knowledge of the previous pathology report. The length of the TAB specimen was at least 0.5 cm in all cases. Biopsy specimens were classified as SVV and/or VVV according the criteria defined in a recent article by our group [8]. The paraffin blocks of all 69 TABs with negative findings and 30 TABs showing SVV and/or VVV were retrieved from the pathological archive and additional multiple transverse sections were cut and stained with haematoxylin and eosin. No classic wall transmural inflammation was observed after the additional sections were cut.

All inpatient and outpatient medical records of these 162 patients were reviewed. Additional information was also obtained by interviews with patients and/or relatives whenever required. A standardized data collection form was completed for all cases. This form includes comprehensive information about clinical manifestations at presentation and during the follow-up, other medical conditions, laboratory investigations, imaging findings, treatment regimen, response to treatment, number of relapses or recurrences and status of the patient at the last follow-up visit. Patients were seen by rheumatologists at the Reggio Emilia Hospital and were not treated according to a specific protocol.

The ESR was determined using the Westergren method (because most of our patients were females over the age of 50 years, the upper limit of the normal reference range was considered 30 mm/1st hour). CRP was measured by nephelometry (NA latex CRP kit, Behringwerke, Marburg, Germany; upper limit of the normal reference range was 0.5 mg/dl).

Systemic signs and/or symptoms were identified by at least one of the following: fatigue, anorexia, weight loss of at least 4 kg or fever. PMR was defined as marked bilateral aching and stiffness without other apparent cause in at least two of the three regions, namely shoulder girdle, hip girdle or neck [10]. The endpoint of patient follow-up was the date of the last visit or the date of death. The
patients were followed up until July 2012. The study was approved by the ethics committee of Reggio Emilia Hospital and informed consent was obtained from all patients or their relatives.

Statistical analysis
Statistical analysis was performed using the SPSS statistical package, version 18.0. Differences between the patients were analysed using Student's two-tailed t-test, Kruskal-Wallis non-parametric test for continuous variables and χ² test (or Fisher's exact test whenever indicated) for categorical variables. P-values <0.05 were considered significant.

We calculated sensitivities, specificities, predictive values and likelihood ratios (LRs) with 95% CIs [11]. A positive LR (defined as sensitivity/1 − specificity) is the increase in the odds of having SVV and/or VVV, or classic GCA when there is evidence on CDS of the halo sign. A negative LR (defined as 1 − sensitivity/specificity) is the decrease in the odds of having SVV and/or VVV, or classic GCA when there is no evidence on CDS of the halo sign.

Results
Table 1 shows the comparisons between the patients with SVV and/or VVV and those with classic transmural GCA. Cranial signs/symptoms such as headache, scalp tenderness, abnormalities of temporal arteries on examination and jaw claudication were significantly less common in patients with SVV and/or VVV compared with those with classic transmural GCA. In contrast, no differences in the frequencies of systemic manifestations, visual loss and PMR were observed between the two groups of patients. Peripheral synovitis was significantly more frequent in patients with SVV and/or VVV. ESR and CRP values at diagnosis were lower in patients with SVV and/or VVV, however, the differences were not significant. A greater proportion of patients with classic GCA had an elevated value of CRP at diagnosis compared with those with SVV and/or VVV (100% vs 85.2%; P = 0.014).

Seven of 29 patients (24.1%) with SVV and/or VVV and 25 of 60 patients (41.7%) with transmural classic GCA, and 31 of 67 biopsy-negative patients (46.3%) received prednisone before CDS. The difference was not statistically significant (P = 0.123). All these patients received prednisone for <7 days at the following mean dosages: 18.7 ± 12.1 mg/day for SVV and/or VVV, 33.1 ± 22.1 mg/day for classic GCA, 22.1 ± 17.1 mg/day for biopsy-negative patients. The differences were not significant (P = 0.148). The mean time intervals between CDS and TAB were 5.6 ± 11.7 days for patients with SVV and/or VVV, 4.4 ± 6.5 days for patients with classic GCA and 4.6 ± 9.7 days for biopsy-negative patients. The differences were not statistically significant (P = 0.629). In the treated patients, the prednisone dose at diagnosis (after CDS and TAB) was significantly lower in patients with SVV and/or VVV compared with those with classic transmural GCA. Representative findings of temporal artery CDS in a case with classic transmural GCA and in a case with periadventitial small-vessel vasculitis are shown in Fig. 1.

The frequency of the halo sign on CDS was significantly lower in the patients with SVV and/or VVV compared with those with classic GCA (20% vs 82.5%; P = 0.0001). The halo sign was bilateral in 1 of the 6 patients (16.7%) with SVV and/or VVV compared with those with classic transmural GCA. Representative findings of temporal artery CDS in a case with classic transmural GCA and in a case with periadventitial small-vessel vasculitis are shown in Fig. 1.

Table 1 Characteristics of the 30 patients with SVV and/or VVV and 63 with classic GCA

<table>
<thead>
<tr>
<th>Variable</th>
<th>SVV and/or VVV (n = 30)</th>
<th>Classic GCA (n = 63)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Male/female, n (%)</td>
<td>11 (36.7)/19 (63.3)</td>
<td>16 (24.5)/47 (74.6)</td>
<td>0.263</td>
</tr>
<tr>
<td>Age at disease onset, mean (s.d.), years</td>
<td>74 (7)</td>
<td>75 (8)</td>
<td>0.550</td>
</tr>
<tr>
<td>Headache</td>
<td>17/30 (56.7)</td>
<td>49/63 (77.8)</td>
<td>0.036</td>
</tr>
<tr>
<td>Scalp tenderness</td>
<td>4/30 (13.3)</td>
<td>20/52 (38.5)</td>
<td>0.023</td>
</tr>
<tr>
<td>Abnormalities of temporal arteries</td>
<td>8/24 (33.3)</td>
<td>39/61 (63.9)</td>
<td>0.011</td>
</tr>
<tr>
<td>Visual loss</td>
<td>2/30 (6.7)</td>
<td>11/63 (17.5)</td>
<td>0.211</td>
</tr>
<tr>
<td>Jaw claudication</td>
<td>1/30 (3.3)</td>
<td>31/63 (49.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systemic signs/symptoms</td>
<td>19/30 (63.3)</td>
<td>32/63 (50.8)</td>
<td>0.256</td>
</tr>
<tr>
<td>PMR</td>
<td>18/30 (60.0)</td>
<td>25/63 (39.7)</td>
<td>0.066</td>
</tr>
<tr>
<td>Peripheral synovitis</td>
<td>9/30 (30.0)</td>
<td>4/63 (6.3)</td>
<td>0.004</td>
</tr>
<tr>
<td>Halo on CDS</td>
<td>6/30 (20.0)</td>
<td>52/63 (82.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Bilateral halo on CDS</td>
<td>1/6 (16.7)</td>
<td>36/49 (69.5)</td>
<td>0.012</td>
</tr>
<tr>
<td>ESR, mean (s.d.), mm/h</td>
<td>70 (33)</td>
<td>80 (28)</td>
<td>0.165</td>
</tr>
<tr>
<td>ESR &gt; 40 mm/h</td>
<td>24/30 (80.0)</td>
<td>52/56 (92.9)</td>
<td>0.090</td>
</tr>
<tr>
<td>CRP, mean (s.d.), mg/dl</td>
<td>5.2 (5.3)</td>
<td>7.7 (5.5)</td>
<td>0.055</td>
</tr>
<tr>
<td>CRP &gt; 0.5 mg/dl</td>
<td>23/27 (85.2)</td>
<td>49/49 (100.0)</td>
<td>0.014</td>
</tr>
<tr>
<td>Prednisone dose at GCA diagnosis, mean (s.d.), mg/day</td>
<td>32 (19)</td>
<td>48 (11)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Patients taking prednisone at the time of CDS</td>
<td>7/30 (23.3)</td>
<td>24/63 (38.1)</td>
<td>0.158</td>
</tr>
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</table>

Except where indicated otherwise, values are the number of patients who were positive/number of patients for whom data were available (%).
Fig. 1 Representative histopathological and colour Doppler sonography findings of GCA.

Patient with classical GCA. (A) shows a dense transmural inflammatory infiltrate; haematoxylin–eosin, 20x. (B) colour Doppler sonography of the frontal branch of temporal artery of the same patient; the scan shows typical concentric hypoechogenic inflammatory thickening of the artery wall (halo sign). Patient with periadventitial small-vessel vasculitis. (C) shows a subtle cuffing of lymphocytes surrounding periadventitial small vessels; the temporal artery is spared (bottom); haematoxylin–eosin, 100x. (D) Colour Doppler sonography of the frontal branch of temporal artery of the same patient; the scan shows normal appearance of the artery wall.

Table 2 Ultrasonographic evidence of halo sign for the diagnosis of GCA in patients with SVV and/or VVV and in patients with classic GCA

<table>
<thead>
<tr>
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<th>Sensitivity, n/n (%) (95% CI)</th>
<th>Specificity, n/n (%) (95% CI)</th>
<th>Positive predictive value, %</th>
<th>Negative predictive value, %</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVV and/or VVV Halo</td>
<td>6/30 (20.0) (8.4, 39.1)</td>
<td>54/67 (80.6) (68.7, 88.9)</td>
<td>31.6 (13.5, 56.5)</td>
<td>69.2 (57.6, 78.9)</td>
<td>1.030 (0.433, 2.451)</td>
<td>0.992 (0.824, 1.195)</td>
</tr>
<tr>
<td>Classic GCA Halo</td>
<td>52/63 (82.5) (70.5, 90.5)</td>
<td>54/67 (80.6) (68.7, 88.9)</td>
<td>80.0 (67.9, 88.5)</td>
<td>83.1 (71.3, 90.8)</td>
<td>4.253 (2.577, 7.021)</td>
<td>0.216 (0.125, 0.373)</td>
</tr>
</tbody>
</table>

Sensitivity: positive test results/total tests; specificity: negative test results/total tests. SVV and/or VVV: periadventitial small-vessel vasculitis and/or vasa vasorum vasculitis.
The halo sign was also present in 13 of 67 patients (19.4%) who had negative TAB results. In none of these patients was it bilateral. The difference was statistically different compared with that observed in patients with classic GCA (19.4% vs. 82.5%; \( P = 0.0001 \)), but not with that observed in patients with SVV and/or VVV (19.4% vs. 20%; \( P = 0.945 \)). Ten of the 13 biopsy-negative patients with a positive halo sign on CDS satisfied the ACR criteria for GCA.

Table 2 shows the sensitivities, specificities and LRs (with 95% CIs) of the halo sign for the diagnosis of GCA in patients with SVV and/or VVV and in patients with classic GCA. The sensitivity and specificity of the halo sign for the diagnosis of biopsy-proven classic GCA were 82.5% and 80.6% respectively, while the positive LR was 4.253. The sensitivity for the halo sign in patients with SVV and/or VVV was much lower (20%) compared with that observed in patients with classic GCA, while the specificity was the same (80.6%). The positive LR was 1.030.

Because a source of potential bias is glucocorticoid therapy before CDS, we also ran an analysis excluding all patients treated with glucocorticoids before CDS. We did not find significant differences compared with the results presented in this article (data not shown).

Discussion

We have previously shown that SVV and/or VVV are part of the histopathological spectrum of GCA, however, GCA patients with SVV and/or VVV show some distinctive clinical features compared with those with classic GCA, i.e. GCA characterized by transmural inflammatory infiltrates on TAB [8]. Specifically, cranial and constitutional manifestations are significantly less common and levels of ESR and CRP at diagnosis lower in GCA patients with SVV and/or VVV compared with those with classic GCA. In contrast, the frequency of cranial ischemic events appears to be comparable in patients with SVV and/or VVV and those with classic GCA. Therefore glucocorticoid therapy should be initiated as soon as the diagnosis of GCA is established, regardless of the histological pattern of GCA, to prevent visual loss.

CDS of the temporal arteries is a cheap, easy-to-arrange, non-invasive diagnostic tool for patients with suspected GCA. A recent meta-analysis reported a sensitivity of 75% (95% CI 67%, 82%) and a specificity of 83% (95% CI 78%, 88%) of the halo sign, respectively, compared with TAB for the diagnosis of GCA [12]. In clinical practice, because of its high specificity for GCA, a positive halo sign may justify starting glucocorticoids in patients with clinical manifestations consistent with GCA [4, 13–15], pending the results of TAB. However, a negative halo sign does not exclude the presence of GCA [5].

In agreement with previous studies and meta-analyses [12, 16], in this study we showed that the halo sign had a sensitivity of >80% (82.5%) for the diagnosis of classic biopsy-proven GCA. Patients with a positive halo sign have a positive LR of 4.253, indicating that the presence of the halo sign increased 4-fold the likelihood of having GCA. As shown by other studies, the halo sign was also relatively specific for GCA compared with the reference standard of TAB [4, 5, 15]. In particular, the presence of a positive halo sign had a specificity of 80.6% in our study.

When the ACR classification criteria for GCA [9] were applied as the reference standard [12, 16], the meta-analyses reported a lower sensitivity and a higher specificity of the halo sign for the diagnosis of GCA. However, these criteria were designed for research, and they are inadequate for diagnosing GCA in clinical practice [17]. Therefore we did not use ACR criteria as the reference standard in this study.

However, no studies have evaluated the findings of CDS in GCA patients with different histological temporal artery patterns. In a small study, Schmidt et al. [14] observed that four of eight patients with false-negative CDS findings had only minor inflammatory infiltration confined to one vessel layer or the vasa vasorum. These authors suggested that these patients might represent an early stage of the inflammatory process in GCA. However, in all likelihood SVV and/or VVV do not represent an early phase of GCA, but identify a subgroup of patients that, if not adequately treated, are at risk of developing cranial ischemic events as frequently as those with classic GCA [8]. Nevertheless, in clinical practice these patients may be undertreated or not treated at all because clinicians may feel that they do not have GCA or, alternatively, that their disease is milder. Theoretically, CDS may be particularly useful to support the diagnosis of GCA in this subgroup of patients who present with more vague cranial manifestations, but the presence of the characteristic halo on the CDS of patients with SVV and/or VVV has not been investigated. Therefore the main objective of our study was to evaluate the findings of CDS in patients with GCA characterized by a histology pattern of SVV and/or VVV. We found that the presence of the halo sign had a sensitivity of only 20% with a negative LR of 0.992. In other words, the absence of a hypoechoic halo on CDS neither rules out nor decreases the likelihood of SVV and/or VVV. On the other hand, the positive LR of the halo sign was also around 1. Therefore a positive halo sign does not increase the probability that a patient with suspected SVV and/or VVV will have a positive TAB result. Taken together, these data indicate that there is no association between the halo sign and the histology pattern of GCA characterized by SVV and/or VVV. Therefore TAB remains the only reliable method to confirm a diagnosis of GCA, particularly in patients with the absence of the halo on CDS.

The second objective of our study was to compare the prevalence of the halo sign and the diagnostic usefulness of CDS in patients with classic transmural GCA vs those with SVV and/or VVV. The halo sign was present in 82.5% of our patients with classic transmural GCA, but in only 20% of patients with SVV and/or VVV. The difference was highly significant. We think that the lower frequency of a
positive halo sign in patients with SVV and/or VVV is probably due to the fact that in these patients the inflammatory reaction is less pronounced and confined to the vasa vasorum or small capillaries located in the connective tissue surrounding the adventitia. Therefore CDS may not be sufficiently sensitive to show active inflammation in patients with SVV and/or VVV as it is in patients with classic GCA with transmural inflammation.

Karahaliou et al. [15] showed that the halo sign was bilateral in 50% of GCA patients. These authors suggested that this finding is highly specific for the diagnosis of GCA. We evidenced bilateral halos in 69.5% of the patients with classic GCA, but in only 16.7% of the patients with SVV and/or VVV. Only 1 of the 30 patients (3.3%) with SVV and/or VVV GCA had bilateral halo signs. Therefore this specific ultrasonographic sign is not of value in patients with SVV and/or VVV.

Our study has several limitations. A source of potential bias is glucocorticoid therapy. Hauenstein et al. [18] showed that the sensitivity of CDS for detection of GCA decreases rapidly under glucocorticoid therapy. However, almost all treated patients in this study had been receiving glucocorticoid therapy for <7 days at the time of CDS, while there were no differences in the percentages of treated patients and in the mean prednisone dosages between patients with SVV and/or VVV, classic GCA and biopsy-negative controls. Furthermore, when we considered only patients not treated with glucocorticoid at the moment of CDS, the data were very similar to those shown in this article. Therefore glucocorticoid therapy is very unlikely to have significantly influenced the results of our study.

We considered a positive TAB as the gold standard for the diagnosis of GCA. Due to the segmental distribution of the inflammation, a diagnosis of GCA cannot always be excluded by a negative TAB. However, the length of the TAB specimen was adequate for histological examination, and several histological sections from patients with negative TAB findings and from those with SVV and/or VVV were examined by a pathologist expert in vasculitis, minimizing the risk of false-negative results and the misclassification of patients.

In conclusion, our study shows that the halo sign is not useful to identify all patients with GCA, particularly the subgroup with histological evidence of SVV and/or VVV. Therefore TAB remains the only reliable method to confirm GCA. Finally, it is crucial that clinicians are aware that all different histological TAB patterns in GCA patients are associated with a risk of vascular complication, thus requiring prompt glucocorticoid treatment.

Disclosures statement: C.S. has received honoraria from Abbott, BMS, MSD, Pfizer, UCB and Roche to attend scientific meetings. All other authors have declared no conflicts of interest.

References
