SHORT REPORT

Impact of ultrasound limitation to assess aortitis in patients with giant cell arteritis: comparative study with FDG-PET/CT

Juan Molina-Collada,1,2 Isabel Castrejón,1,2,3 Irene Monjo-Henry,3,4 Elisa Fernández-Fernández,4 Gabriela Torres Ortiz,4 Julia Martínez-Barrio,1,2 José María Álvaro-Gracia,1,2,3 Eugenio de Miguel1,4

ABSTRACT

Objective To determine the impact of ultrasound (US) intrinsic limitation to assess aortitis versus FDG-PET/CT in patients with US-proven giant cell arteritis (GCA) and to identify factors associated with aortic involvement.

Methods Retrospective observational study of patients referred to US fast-track clinics at two academic centres over a 4-year period. Only patients with GCA confirmed by US were included. Temporal arteries (TA) and extracranial arteries US were performed at baseline. FDG-PET/CT was performed according to clinician’s criteria. An FDG artery uptake at the aorta higher than liver uptake was considered positive for aortitis.

Results Seventy-two of 186 patients with US-proven GCA underwent an FDG-PET/CT; 29 (40.3%) had a positive FDG-PET/CT and 24 (33.3%) presented aortitis. Only 6 (20.7%) patients with positive FDG-PET/CT had negative US findings of large vessel (LV)-GCA. Among patients with aortitis in FDG-PET/CT, only two (8.3%) had negative US findings of LV-GCA. Patients with aortitis were younger (68.9 vs 81;p<0.001), more frequently females (79.2% vs 39.6%;p=0.002) and had higher platelets count (413.4 vs 311.1;p=0.001). Patients with aortitis presented positive TA US less frequently (41.7% vs 83.3%;p<0.001), but more LV US involvement (91.7% vs 41.7%;p<0.001) versus patients without aortitis. None of the patients with aortitis exhibited visual symptoms (0% vs 31.2%;p=0.001).

Conclusions FDG-PET/CT can detect aortitis in one out of every three patients with US-proven GCA. However, a negative US examination for LV-GCA suggests a low risk of aortitis. Younger and female GCA patients with thrombocytosis, absence of visual manifestations and LV-GCA on US may more frequently present aortitis by FDG-PET/CT.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Aortitis is a serious potential complication of patients with giant cell arteritis (GCA) and may lead to dilation, aneurysms or dissection.

Since ultrasound (US) has limited access to detect aortitis, comparative studies with other imaging modalities to determine the clinical impact of this limitation and the specific situations warranting their use are needed.

WHAT THIS STUDY ADDS

A negative US examination for large vessel-GCA (LV-GCA) suggests a low risk of aortitis detected by FDG-PET/CT.

Younger and female GCA patients with thrombocytosis, absence of visual manifestations and LV-GCA on US may more frequently present aortitis by FDG-PET/CT in comparison with patients without aortitis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

These findings may guide decisions on when and how to investigate the presence of aortitis in patients with US-confirmed GCA. Further research in at-risk populations is needed to confirm these results.

INTRODUCTION

Giant cell arteritis (GCA) is the most common form of vasculitis in the older adults.1 In the last decades, the increasing availability of modern imaging techniques has shown that involvement of extracranial arteries, known as large vessel (LV)-GCA, may be present in up to 50% of patients.2–5 Aortitis is a serious potential complication of patients with giant cell arteritis (GCA) and may lead to dilation, aneurysms or dissection.6 According to European Alliance of Associations for Rheumatology (EULAR) recommendations on the use of imaging in LV vasculitis, ultrasound (US), fluorodeoxyglucose-positrion emission tomography/computed tomography (FDG-PET/CT), MRI or CT can be useful for detecting mural inflammation or luminal changes in extracranial arteries to support a diagnosis of LV-GCA.6 US can detect signs of LV-GCA in axillary, subclavian or carotid arteries among other regions, but has limited access to the thoracic aorta. The
first portion of the ascending aorta, the aortic arch and the abdominal aorta may be visible with appropriate probes (sector or convex). The prevalence of aortic stenosis, the most frequent region affected in LV-GCA, has been estimated at 45%–65%, although the exact incidence is unknown as it is not routinely evaluated in all patients at diagnosis or during follow-up. Aortitis is a serious diagnosis as it can result in a life-threatening situation due to serious complications such as dilation, aneurysms or dissection. Some cohort studies have shown that LV-GCA patients have a higher risk of developing aortic dilation,\(^4\) giving the limitation of US to assess the aorta, comparative studies on the usefulness of different imaging tools in clinical practice and the specific situations warranting their use are needed.

The primary objective of this study was to investigate the impact of US limitation to detect aortitis versus FDG-PET/CT examination in patients with US-proven GCA. Secondary objectives included the identification of factors associated with aortic involvement.

**METHODS**

**Patient selection and data collection**

This was a retrospective cross-sectional study including a cohort of patients referred to GCA fast-track clinics at two academic centres over a 4-year period (January 2018–January 2022). US vascular assessment within 24–48 hours was performed on all patients with suspected GCA. For the purpose of this study, only those patients with a GCA diagnosis confirmed by the clinicians and positive US in whom an FDG-PET/CT was performed were selected. We retrospectively collected patients’ data from their electronic health records: demographics, symptoms including headache, scalp tenderness, jaw claudication, visual loss or ischaemic complications such as ocular ischaemia diagnosed by an ophthalmologist, morning stiffness, fever and abnormal findings on the temporal artery (TA) examination. Laboratory tests such as C reactive protein, erythrocyte sedimentation rate, haemoglobin and platelets, and TA biopsy findings (if available) were collected. The study was performed under routine clinical practice conditions.

**Imaging assessment**

All patients underwent a protocolised vascular bilateral US examination of the cranial arteries (common superficial TA, its parietal and frontal branches) and extracranial arteries (carotid, subclavian and axillary). The entire axillary artery was evaluated including its three parts from the anterior side or the axillary fossa. The proximal region of the brachial artery was also scanned. The US examination was performed by three experienced ultrasonographers (EdM, IM and JM-C) with two sets of US equipment including an Esote MyLab8 (Esote, Genoa) with a 12–18 MHz (for TA) and 6–15 MHz transducer (for extracranial arteries) and an Esote MylabTwice with a 10–22 MHz (for TA) and 4–13 MHz transducers (for extracranial arteries). The presence of a halo and/or compression sign in TA or the presence of a halo in the extracranial arteries in the absence of atherosclerosis was considered sufficient for a positive US examination.\(^9\) The ultrasonographers were not blinded to the clinical information of the patients.

FDG-PET/CT was performed per clinician’s criteria according to routine clinical care if considered necessary to support diagnosis, despite the positive US examination, usually in patients with high suspicion of extracranial involvement (fever, constitutional symptoms, bruises or arm claudication). Additionally, clinician experience interpreting US or FDG-PET/CT may also guide the decision of performing the latest, despite the absence of LV symptoms. All FDG-PET/CT scans were assessed by expert nuclear medicine physicians and performed at the two centres included in the study, using a Siemens Biograph 6–4R TruePoint PET/CT Scanner and a Siemens Biograph Vision PET/CT Scanner 128 slices (Siemens Medical Systems, Knoxville, Tennessee, USA). An FDG artery uptake at the thoracic or abdominal aorta higher than liver uptake was defined as aortitis. The qualitative FDG uptake in the aortic branches (carotid, axillary and subclavian arteries), iliofemoral and cranial arteries was also registered.

**Statistical analysis**

Simple descriptions are presented as mean (SD) or total number (%). A \(\chi^2\) test or Fisher’s exact test was used to analyse differences between proportions; a Student’s t-test was used for comparisons between means. All tests were two sided; \(p\) values <0.05 were considered statistically significant.

**RESULTS**

**Patient characteristics**

A total of 186 patients with US-proven GCA were evaluated at the two US fast-track clinics during the study period. Of these, 72 patients underwent an FDG-PET/CT and were included for analysis. Mean age was 77 years and 52.8% were females. The clinical, laboratory and histology findings of patients with or without aortic involvement are depicted in table 1. A total of 38 (52.8%) and 68 (94.4%) patients fulfilled the 1990 American College of Rheumatology (ACR) and the 2022 ACR/EULAR classification criteria for GCA, respectively, and 15 (20.8%) had been diagnosed with PMR before the US examination.

**Imaging findings**

A total of 48 (66.7%) patients had LV-GCA imaging findings based on US or FDG-PET/CT examinations. US revealed cranial involvement in 50 (69.4%) patients and LV-GCA in 42 (58.3%) (table 2). Twenty-one (29.2%) had carotid, 29 (40.3%) subclavian and 35 (48.6%) axillary involvement. A mixed pattern...
Imaging

of cranial and extracranial US involvement was found in 20 (27.8%) patients. A total of 29 (40.3%) patients had positive FDG-PET/CT findings for LV-GCA, 24 (33.3%) presenting aortitis. Moreover, 21 (29.2%) had subclavian, 15 (20.8%) carotid, 9 (12.5%) iliofemoral, 7 (9.7%) axillary, 3 (4.2%) vertebral and 1 (1.4%) TA involvement, based on FDG-PET/CT findings. Mean time from glucocorticoid initiation and FDG-PET/CT was 46.4 days. Taking FDG-PET/CT as the reference standard, six (20.7%) patients had negative US findings for LV-GCA but positive FDG-PET/CT. Among patients with aortitis in FDG-PET/CT, two (8.3%) presented negative US findings of LV-GCA (one patient presented with isolated aortitis and the other had aortic and iliac involvement). None of these patients had supraaortic arteries involvement reported in FDG-PET/CT.

Table 1 Clinical, laboratory and histology findings of patients with and without aortic involvement

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total n=72</th>
<th>Patients with aortic involvement in FDG-PET/CT n=24 (33.3%)</th>
<th>Patients without aortic involvement in FDG-PET/CT n=48 (66.7%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>77 (9.1)</td>
<td>68.9 (8.1)</td>
<td>81 (6.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>38 (52.8)</td>
<td>19 (79.2)</td>
<td>19 (39.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMR diagnosis before US exam</td>
<td>15 (20.8)</td>
<td>3 (12.5)</td>
<td>12 (25)</td>
<td>0.432</td>
</tr>
<tr>
<td>Headache, n (%)</td>
<td>49 (68.1)</td>
<td>14 (58.3)</td>
<td>35 (72.9)</td>
<td>0.211</td>
</tr>
<tr>
<td>Scalp tenderness, n (%)</td>
<td>16 (22.2)</td>
<td>3 (12.5)</td>
<td>13 (27.1)</td>
<td>0.232</td>
</tr>
<tr>
<td>Jaw claudication, n (%)</td>
<td>16 (22.2)</td>
<td>4 (16.7)</td>
<td>12 (25)</td>
<td>0.423</td>
</tr>
<tr>
<td>Visual symptoms, n (%)</td>
<td>15 (20.8)</td>
<td>0 (0)</td>
<td>15 (31.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ocular ischaemia, n (%)</td>
<td>6 (8.3)</td>
<td>0 (0)</td>
<td>6 (12.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Constitutional symptoms, n (%)</td>
<td>42 (58.3)</td>
<td>17 (70.8)</td>
<td>25 (52.1)</td>
<td>0.128</td>
</tr>
<tr>
<td>Fever, n (%)</td>
<td>19 (26.4)</td>
<td>9 (37.5)</td>
<td>10 (20.8)</td>
<td>0.130</td>
</tr>
<tr>
<td>Morning stiffness in shoulders/neck, n (%)</td>
<td>38 (52.8)</td>
<td>10 (41.7)</td>
<td>28 (58.3)</td>
<td>0.182</td>
</tr>
<tr>
<td>Abnormal TA clinical examination, n (%)</td>
<td>11 (15.3)</td>
<td>3 (12.5)</td>
<td>8 (16.7)</td>
<td>0.643</td>
</tr>
<tr>
<td>Fulfilled 1990 ACR GCA classification criteria, n (%)</td>
<td>38 (52.8)</td>
<td>9 (37.5)</td>
<td>29 (60.4)</td>
<td>0.066</td>
</tr>
<tr>
<td>Fulfilled 2022 ACR/EULAR GCA classification criteria, n (%)</td>
<td>68 (94.4)</td>
<td>22 (91.7)</td>
<td>46 (95.8)</td>
<td>0.467</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L), mean (SD)</td>
<td>85.8 (79.6)</td>
<td>101.8 (77.8)</td>
<td>77.8 (80.4)</td>
<td>0.230</td>
</tr>
<tr>
<td>ESR (mm/hour), mean (SD)</td>
<td>68.6 (33.6)</td>
<td>69.7 (31.8)</td>
<td>68 (34.7)</td>
<td>0.839</td>
</tr>
<tr>
<td>Haemoglobin (g/L), mean (SD)</td>
<td>119 (16)</td>
<td>115 (15)</td>
<td>121 (17)</td>
<td>0.139</td>
</tr>
<tr>
<td>Platelets 10⁶/L, mean (SD)</td>
<td>345.7 (152.4)</td>
<td>413.4 (169.7)</td>
<td>311.11 (131.1)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

ACR, American College of Rheumatology; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; TA, temporal artery.

Table 2 US patterns of vascular involvement in patients with or without aortitis in FDG-PET/CT

<table>
<thead>
<tr>
<th></th>
<th>Total n=72</th>
<th>Patients with aortic involvement in FDG-PET/CT n=24 (33.3%)</th>
<th>Patients without aortic involvement in FDG-PET/CT n=48 (66.7%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive cranial GCA US, n (%)</td>
<td>50 (69.4)</td>
<td>10 (41.7)</td>
<td>40 (83.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive LV-GCA US, n (%)</td>
<td>42 (58.3)</td>
<td>22 (91.7)</td>
<td>20 (41.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative LV-GCA US, n (%)</td>
<td>30 (41.7)</td>
<td>2 (8.3)</td>
<td>28 (58.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Isolated positive LV-GCA US, n (%)</td>
<td>22 (30.6)</td>
<td>14 (58.3)</td>
<td>8 (16.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive cranial+LV GCA US, n (%)</td>
<td>20 (27.8)</td>
<td>8 (33.3)</td>
<td>12 (25)</td>
<td>0.457</td>
</tr>
</tbody>
</table>

GCA, giant cell arteritis; LV, large vessel; US, ultrasound.
CT. In contrast, 19 (45.2%) patients with US findings of LV-GCA had a negative FDG-PET/CT.

Factors associated with aortitis on FDG-PET/CT
Patients with aortitis were younger (68.9 vs 81; \(p<0.001\)) and more frequently females (79.2% vs 39.6%; \(p=0.002\)) compared with patients without aortitis. Regarding laboratory markers, patients with aortitis had higher (mean) platelet count (413.4 vs 311.1×10^9/L; \(p=0.014\)). The best threshold to differentiate between aortic and non-aortic involvement was 354.5×10^9/L (AUC 0.663; Sens 58.3%; Spec 66%). The absence of visual symptoms was the only clinical variable associated with aortitis (0% vs 31.2%; \(p=0.001\)) (Table 1). US comparison between groups showed that when aortitis was present by FDG-PET/CT, positive TA US was less frequent (41.7% vs 83.3%; \(p<0.001\)), whereas US signs of LV-GCA were more frequent (91.7% vs 41.7%; \(p<0.001\)) in comparison with patients without aortic involvement (Table 2).

DISCUSSION
According to EULAR recommendations, in patients in whom there is a high clinical suspicion of GCA and a positive imaging result, the diagnosis of GCA may be made without additional tests (biopsy or further imaging).6 LV involvement, particularly the aorta, is frequent in patients with GCA.2–5 Indeed, the screening of LV-GCA by US, at least the axillary arteries, is recommended in patients with suspected GCA.4 However, US is of limited value for assessing the thoracic aorta, although the first portion of the ascending aorta, the aortic arch and the abdominal aorta may be visible depending on the characteristic of the patient with appropriate probes (sector or convex) and adequate training. Nowadays, an increased number of fast-track clinics use US as their preferred diagnostic tool when GCA is suspected. Consequently, our study sought to investigate the usefulness of performing FDG-PET/CT in patients with US-confirmed GCA, as the presence of aortitis have an increased risk for the development of aortitis dilatation, aneurysms, dissection or rupture.9–12 Moreover, GCA patients with an aortic aneurysm have a higher mortality compared with those without aortic complications or with the general population.14-17 Therefore, it is necessary to determine the clinical impact of US intrinsic limitations to assess aortitis. Our results demonstrate that FDG-PET/CT may be useful for detecting aortitis in certain patients with US-confirmed GCA, although a negative US examination for LV-GCA suggests a low risk of aortitis.

Several studies have compared the ability of US and FDG-PET/CT to detect LV-GCA, showing good, but not excellent agreement between both techniques.18–20 However, for most studies comparing different imaging tools, the patients included are usually investigated based on either clinical or imaging findings of LV-GCA, which could potentially lead to circularity. To our knowledge, no studies have been specifically designed to assess the added value of FDG-PET/CT in patients with GCA and positive US findings. According to our results, 33.3% of patients with US-confirmed GCA have aortitis in FDG-PET/CT. These results are of value, not only for diagnostic and prognostic purposes, but also for monitoring activity during treatment, as baseline assessment of involved vascular regions are helpful for detecting new or recurrent involvement during follow-up.21 However, it is important to note that the majority of patients with aortitis had signs of LV involvement on US examination (only two patients had negative US findings of LV-GCA but positive aortitis in FDG-PET/CT). Thus, it seems an unfeasible screening strategy. Thus, it would be necessary to investigate factors associated with aortic involvement and then select those patients who would most benefit from undergoing FDG-PET/CT. In this context, we have identified several variables associated with the presence of aortitis in patients with US-confirmed GCA such as female gender, younger age, thrombocytosis and the absence of visual manifestations. Our results should be confirmed by other studies. These variables may be helpful for identifying which patients can benefit from an additional FDG-PET/CT in order to properly identify aortitis, especially in patients with low or intermediate pretest probability.22 On the other hand, some US findings may indicate the need for FDG-PET/CT in this specific population due to the US pattern of LV-GCA, which was significantly more frequent in patients with aortitis.

Some limitations of our study should be noted. First, the sensitivity of FDG-PET/CT may be affected by glucocorticoid treatment.23-24 Thus, sensitivity results of FDG-PET/CT should be interpreted with caution and in keeping with the context of this study, which was conducted under clinical practice conditions where delays in performing FDG-PET/CT may occur and patients can be undergoing glucocorticoid treatment at the time of the imaging study. Second, due to the absence of an appropriate gold standard, either for GCA or for LV-GCA diagnosis, diagnostic studies of LV-GCA are always limited by the fact that one imaging method is usually required to verify the presence of vasculitis, serving as the gold standard. In our study, since US-confirmed GCA was selected as an inclusion criterion, the exact sensitivity of FDG-PET/CT in all GCA patients (including also those with negative US)
was not investigated. Third, the decision of performing FDG-PET/CT was made per clinician’s criteria, usually in patients with high suspicion of LV involvement, what may lead to a selection bias with a higher probability of aortitis. Finally, the inclusion of other extracranial arteries (as the vertebral arteries or the visible regions of the aorta) in the US examination could potentially increase the sensitivity for extracranial GCA.

In summary, FDG-PET/CT may detect aortitis in patients with US-confirmed GCA in certain situations. However, US is able to detect signs of LV-GCA in the majority of patients presenting with aortitis, thus minimizing the need for routinely FDG-PET/CT, especially in negative US patients for LV-GCA. Female gender, younger age, thrombocytosis, absence of visual manifestations and an US-pattern of LV-GCA are all associated with the presence of aortitis in FDG-PET/CT.

REFERENCES