# Fever of unknown origin as initial manifestation of large vessel giant cell arteritis: diagnosis by colour-coded sonography and 18-FDG-PET

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## ABSTRACT

**Objectives.** *To evaluate the clinical characteristics and imaging results (CDS, 18-FDG-PET) of patients with large vessel giant cell arteritis (LV-GCA) presenting as fever of unknown origin (FUO).*

**Methods.** *From a series of 82 patients with GCA we identified 8 patients with FUO as initial disease manifestation. Clinical characteristics and results of CDS and 18-FDG-PET were analysed. Patients with FUO and those with other clinical manifestations of GCA were compared.*

**Results.** *18-FDG-PET-scans were available for 6/8 patients, revealing enhanced tracer uptake of the thoracic aorta and the aortic branches in all patients. CDS was performed in 8/8 patients, with detection of hypoechogenic wall thickening related to LV-GCA in 7/8 patients. Subjects with FUO were significantly younger (60.9 vs. 69.3 years, p<0.01) and had a stronger humoral inflammatory response (CRP 12.6 vs 7.1 mg/dl, p<0.01; ESR 110 vs. 71 mm/hour, p<0.01), when compared to the other GCA-patients.*

**Conclusion.** *LV-GCA should be considered as important differential diagnosis in patients with FUO. In addition to 18-FDG-PET, which is known to be a valuable method in the diagnostic work-up of FUO, we recommend CDS of the supraaortal and femoropopliteal arteries for the initial diagnostic work-up.*

## Introduction

Fever of unknown origin (FUO) is characterised by fever of at least 38.3°C on several occasions and lasting longer than 3 weeks, with the diagnosis remaining uncertain after 3 days of appropriate in-hospital investigation or three outpatient visits (1). Giant cell arteritis (GCA) is known to account for up to 17% of FUO in the elderly (>55 years), and conversely, 15% of GCA patients fulfill criteria for FUO (2, 3). There is growing evidence for involvement of extracranial large arteries in GCA, such as the aorta, the proximal arm arteries and also the leg arteries (4). For this disease pattern, the term large vessel-GCA (LV-GCA) was introduced (5). Colour-coded duplex sonography (CDS) and $^{18}$F-fluoro-2-deoxy-D-glucose positron emission tomography (18-FDG-PET) are valuable methods to detect extracranial vasculitic changes in LV- GCA, and FUO related to large artery inflammation detected by 18-FDG-PET has been repeatedly reported in GCA (6-9). We sought to analyse the clinical characteristics and imaging results of patients initially presenting with FUO out of a cohort of GCA-patients.

## Patients and methods

From 82 patients seen at our institution with the diagnosis of GCA between 01/2002 and 05/2009, we retrospectively identified all patients who fulfilled the revised criteria of FUO (1). GCA was diagnosed based on the criteria of the American College of Rheumatology (ACR) for cranial arteritis and/or by imaging results suggesting extracranial LV-GCA (4, 6, 7, 10). Clinical and laboratory data were obtained and results of CDS and 18-FDG-PET studies performed prior to treatment initiation were analysed. Patients with FUO (n=8) and those with other clinical manifestations of GCA (n=74) were compared using the Fisher's exact test (categorical variables) and the unpaired *t*-test (continuous variables). *P*-values <0.05 were considered significant.

Results from 18-FDG-PET-studies at initial presentation were available for 6 patients. All patients fasted prior to 18-FDG-PET-scans and had normal serum glucose levels at the time of 18-FDG-injection (5MBq/kg). Images were obtained in a 3D-aquivistion mode using a Philips Allegro PET scanner. Vascular enhancement was visually graded in relation to liver uptake using a four-point scale as follows: 0=no uptake; 1=low grade (lower than liver uptake); 2=intermediate (similar to liver) uptake; 3=high grade (higher than liver uptake). Intermediate and high grade uptake was regarded suggestive for vasculitis (6).

All patients identified underwent CDS of the superficial temporal, carotid, subclavian, axillary and proximal brachial arteries at time of diagnosis, and in 7/8 patients the femoropopliteal arteries also were evaluated by CDS.

CDS was performed with 5-10 MHz linear transducers (extracranial large arteries) and 8-14 MHz linear transducers (superficial temporal arteries). The Acuson ASPEN™ (Siemens AG, Medical Solutions, Erlangen, Germany) and the LOGIC™9 (General Electric Medical Systems, Milwaukee, Wisconsin, USA) ultrasound device were applied. Long segmental, concentric, hypo- or midechoic wall thickening was regarded a typical sign for LV-GCA (4, 7).

## Results

*Clinical presentation*

Seven women and one man aged between 54 and 67 years (mean age 60.9 years) presented with FUO, with a mean symptom duration of 18.4 weeks (3 to 31 weeks). Accompanying symptoms were night sweat in 6 patients and substantial weight loss in 7 patients. None of the patients complained of jaw claudication, symptomatic arm or leg ischemia or symptoms of polymyalgia rheumatica. In the disease course, 2 of 8 patients developed headache (4 and 20 weeks after fever onset, respectively). Visus disturbances did not occur.

Physical examination was abnormal in only two patients, revealing diminished bilateral upper extremity pulses and axillary artery bruits. Laboratory analysis showed markedly elevated erythrocyte sedimentation rate (ESR) and C-reactive-protein (CRP) in all patients. None of the patients had an elevated leukocyte count, but thrombocytosis was present in 6 cases and normochrome anemia in 7 patients.

Only the 2 women who developed headache in the course of the disease met the ACR-criteria for diagnosis of cranial GCA (10). Notably, superficial temporal artery biopsy was performed in only one patient, with a negative result. A halo of the superficial temporal arteries was not seen in any of the patients described here.

*Comparison between patients with FUO and other manifestations of GCA*

Patients presenting with FUO as initial clinical manifestation of LV-GCA were significantly younger (60.9 *vs.* 69.3 years, $p<0.01$), had a more severe mean weight loss (6.8 *vs.* 3.1 kg, $p=0.03$) and a stronger humoral inflammatory response (CRP 12.6 *vs.* 7.1 mg/dl, $p=0.01$; ESR 110 *vs.* 71 mm/hour, $p<0.01$) compared to GCA patients with other clinical symptoms. There were no significant differences between patients with and without FUO regarding frequency of anemia, leuko- or thrombocytosis as well as traditional cardiovascular risk factors. We observed a non-significant trend towards a delayed diagnosis in GCA patients presenting with FUO (18.4 *vs.* 14.9 weeks, $p=0.59$).

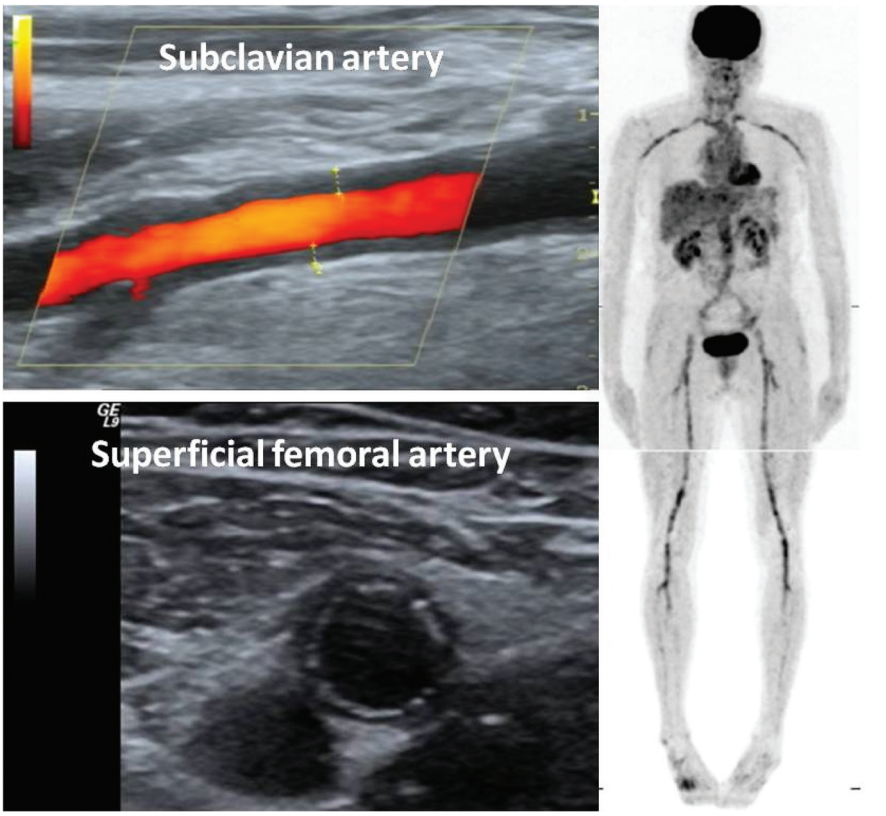


**Fig. 1.** Vascular inflammation (18-FDG-PET) and hypoechogenic wall thickening (CDS) of the extremity arteries related to LV-GCA in a 59 year-old woman with FUO

*Large vessel giant cell arteritis documented by vascular imaging*

Intermediate and high grade vascular tracer uptake suggesting vasculitis was seen in 6/6 18-FDG-PET-scans, involving the carotid arteries (3/6), the proximal arm arteries (6/6), the thoracic aorta (6/6) and the leg arteries (5/6). Tracer uptake in the arm and leg arteries appeared symmetrically in all cases (Fig. 1).

CDS showed concentric, long segment, hypoechogenic wall thickening of the common carotid arteries (3/8), subclavian and/or axillary arteries (7/8) and superficial femoral arteries (4/8) (Fig. 1). Common femoral artery, deep femoral artery and popliteal artery were affected in one patient (patient 2 in Table I). CDS-findings were bilateral in all vascular regions involved. Significant arterial stenoses were only present in the proximal arm arteries (4/8, bilateral stenoses in 3 patients). In 5 of 6 PET-positive patients CDS revealed typical findings in at least one of the vascular regions investigated. In one female patient with a positive 18-FDG-PET-scan CDS of the supraaortal and femoropopliteal arteries was negative (patient 8 in Table I). The two patients in whom an initial 18-FDG-PET-scan at time of diagnosis was not available both exhibited bilateral stenoses of the proximal arm arteries due to hypoechogenic, concentric wall thickening depicted by CDS (patients 4 and 7 in Table I).

## Discussion

GCA is the predominant type of large vessel vasculitis in patients above the age of 50 (11). As documented by our case series as well as by Calamia *et al.*

**Table I.** Clinical characteristics and imaging results of the 8 patients with large vessel-GCA presenting as FUO.

| Patient/sex/age (years) | Weight loss (kg) | Headache | ESR* (mm/hour) | CRP** (mg/dl) | Time to diagnosis (weeks) | Aorta (PET) | Carotid arteries | | Proximal arm arteries | | Leg arteries | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | PET | CDS | PET | CDS | PET | CDS |
| 1/F/59 | 5 | – | 120 | 12.2 | 18 | + | + | + | + | + | – | + |
| 2/F/67 | 4 | – | 90 | 10.1 | 21 | + | – | – | + | +S | + | + |
| 3/F/64 | 4 | – | 120 | 16.5 | 3 | + | – | – | + | + | + | – |
| 4/M/54 | 14 | – | 120 | 10.6 | 31 | fu. | fu. | – | fu. | +S | fu. | nd. |
| 5/F/59 | 6 | – | 120 | 18.5 | 14 | + | + | – | + | +S | + | + |
| 6/F/52 | 6 | + | 120 | 10.3 | 6 | + | + | + | + | + | + | + |
| 7/F/65 | 15 | – | 120 | 19.0 | 34 | fu. | fu. | + | fu. | +S | fu. | – |
| 8/F/67 | 0 | + | 66 | 13.8 | 21 | + | – | – | + | – | + | – |

*ESR: reference range <20mm/hour; **CRP: reference range <0.5mg/dl.
fu: 18-FDG-PET during follow-up; nd: not done; S: stenosis.

30 years ago, FUO may be an important initial clinical manifestation of GCA (3). Patients presenting with FUO were characterised by a younger age and a more severe inflammatory response when compared to subjects with other heralding symptoms. Fever in patients with GCA is known to be associated with higher inflammatory markers and less ischemic complications (12). Likewise, visual loss was not noticed in any patient presenting with FUO in our study. The observed delay in diagnosis is probably caused by the lack of cranial symptoms in most of these patients (13).

Related to the retrospective design of our study, temporal artery biopsy was at the discretion of the responsible physician and was consequently performed in only one patient presenting with FUO. This may be mainly related to the fact that CDS of the temporal arteries was unremarkable in all patients with FUO, indicating a low pretest-probability for positive biopsy results. A low rate of positive temporal artery biopsies is known for LV-GCA, and our results suggest that the extracranial large arteries are preferentially affected in GCA-patients presenting with FUO (5, 7). To date, imaging modalities are of paramount importance for the diagnosis of LV-GCA (4).

18-FDG-PET is an established method in the diagnostic work up of FUO, contributing to the final diagnosis in up to 70% of cases and frequently disclosing vasculitis as the cause of FUO (14). Although the role of 18-FDG-PET in the diagnosis of GCA is still under discussion results obtained in our patients presenting with FUO demonstrate its high diagnostic potential for detecting LV-GCA in this subgroup of patients. Regularly, the thoracic aorta and the arm arteries were affected which has been proven to be highly specific for LV-GCA in elderly patients (6). In future, functional and morphological imaging of the extracranial large vessels will increasingly be combined using PET/CT-Scanners, with promising preliminary results already been published (15).

Hypoechogenic vessel wall thickening of extracranial arteries has been detected by CDS in up to 30% of patients with GCA (7). CDS is the most valuable noninvasive diagnostic method for the detection of vessel wall alterations of the extrathoracic aortic branches (4, 7). In 7 of our 8 patients with FUO typical findings were documented in the arm, carotid and/or lower extremity arteries. In combination with clinical and laboratory findings, CDS of these arteries appears to be a rapid and cost-effective way to diagnose LV-GCA in FUO-patients without exposure to radiation. Involvement of multiple vessel regions including the lower extremity arteries in our patients strongly refers to the current concept of GCA being regarded as a systemic vascular disease (4).

In summary, LV-GCA should be considered as an important differential diagnosis in patients above the age of 50 presenting with FUO. 18-FDG-PET is known to be a valuable tool in the diagnostic work up of FUO and may early detect vessel wall inflammation. Our study suggests that CDS of the supraaortal and femoropopliteal arteries is a promising alternative for the initial diagnostic approach to elderly patients with FUO.

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