

Case report

Cranial giant cell arteritis evolving into early large-vessel vasculitis

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Introduction

Polymyalgia rheumatica (PMR) is an inflammatory disorder characterized by pain and prolonged early morning stiffness affecting mainly the articular and periarticular structures of the neck, shoulder and pelvic girdle (1). In 16-21% of cases, PMR is associated with biopsy-proven giant cell arteritis (GCA) (1). GCA typically involves the temporal arteries, but widespread large-vessel involvement, particularly of the aorta and of the arteries originating from the aortic arch, can occur (2-4). In one study, large-vessel arteritis has been demonstrated using ¹⁸Fluorodeoxyglucose positron emission tomography (PET) in as many as 83% of untreated GCA patients at disease onset (5). By contrast, large vessel involvement characterized by stenoses, aneurysms, and dissection of the aorta and of its proximal branches occurs in only one third of patients, usually years after the onset of the disease (6). In addition to symptoms related to vessel involvement, patients with GCA can also present with a variety of constitutional symptoms including fatigue, fever, and weight loss.

Relapses and flares of GCA can occur as a consequence of rapid tapering of glucocorticoid dose (7), but also independently of the treatment regimen (1). Herein, we report a patient with PMR who developed biopsy-proven GCA with cranial symptoms. She responded well to glucocorticoid therapy, however, upon tapering of the glucocorticoid dose she suffered a relapse of GCA characterized by large vessel but not temporal artery involvement. The unusual features of this case and its implications are discussed.

Case report

A 79-year-old woman presented to our rheumatology outpatients clinic

with a two-month history of pain in the neck, shoulder and pelvic girdle, which became worse at night and responded only partially to non-steroidal anti-inflammatory drugs. She also reported early morning stiffness of approximately three hours' duration and a two-kg weight loss over the previous two months. Physical examination revealed neck and girdle stiffness on active movements, while laboratory investigations disclosed a raised ESR (75 mm/1st hour) and C-reactive protein (CRP) (84.1 g/dl, normal values <6) with a hemoglobin of 12.1 g/dl. The patient responded promptly to methylprednisolone treatment (16 mg/day for three days tapered down by 4 mg decrements every three weeks to a maintenance dose of 4 mg daily), while the ESR and CRP decreased to 11 mm/1st hour and 4.9 g/dl, respectively. However, eleven months after the onset of PMR she developed bilateral headache worse at night, pain on chewing, and "flashes" in the left eye. At this time, the ESR was 40 mm/1st hour and the CRP 80.8 g/dl. Her methylprednisolone dose was increased to 8 mg/day with some improvement of her headache although not of her visual disturbances. She was admitted shortly thereafter to the rheumatology day hospital with a suspicion of GCA for further investigations.

On examination, the temporal arteries were pulsatile and only slightly tender. Color-Doppler ultrasonography (CDS) showed no inflammatory halo or stenoses of the temporal arteries, of the aortic arch and its major branches, or of the abdominal aorta (Fig. 1), whereas temporal artery biopsy demonstrated vessel wall inflammatory infiltration with granulomata. GCA was diagnosed, and treatment with prednisone 50 mg/day with a tapering scheme associated with low-dose aspirin and osteoporosis

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prophylaxis commenced. The patient's complaints resolved within a few days and the inflammatory markers normalized entirely. However, twelve months later, while on a maintenance dose of 2 mg methylprednisolone daily, the patient reported mild fatigue in the absence of headache or other disturbances or constitutional symptoms. Laboratory investigations showed an increased ESR (46 mm/1st hour) and CRP (87.2 g/dl). A flare of GCA was suspected. A repeat CDS showed the presence of an inflammatory halo in the subclavian, axillary, and iliac arteries but not in the temporal arteries (Fig. 2), while ¹⁸Fluorodeoxyglucose positron emission tomography disclosed increased tracer uptake in the subclavian arteries and in the entire aorta (Fig. 3), consistent with GCA with large-vessel involvement. The prednisone dose was put up again to 50 mg/day with a tapering scheme and methotrexate 15 mg/weekly orally with folic acid supplementation (later switched to azathioprine 150 mg/day because of intolerance) added to her medications. At the last follow-up visit three months later the patient was doing well on methylprednisolone 6 mg daily and azathioprine 150 mg daily, while the ESR was 14 mm/1st hour and the CRP 1.2 g/dl.

Discussion

Herein, we have reported a patient with PMR who developed biopsy-proven GCA with cranial symptoms but no large-vessel inflammation of the aortic arch, of the supra-aortic vessels, or of the abdominal aorta as assessed by CDS performed at disease onset before treatment. However, a subsequent flare of GCA was characterized by large-vessel inflammation (documented by CDS and PET) in the absence of cranial symptoms. To our knowledge, this is the first reported case of cranial GCA progressing shortly after disease onset into large-vessel vasculitis. This case also highlights the role of imaging in GCA.

Imaging techniques such as PET, CDS, magnetic resonance imaging (MRI), and computerized tomography scan, play an increasingly important role both in the diagnosis and in the follow-

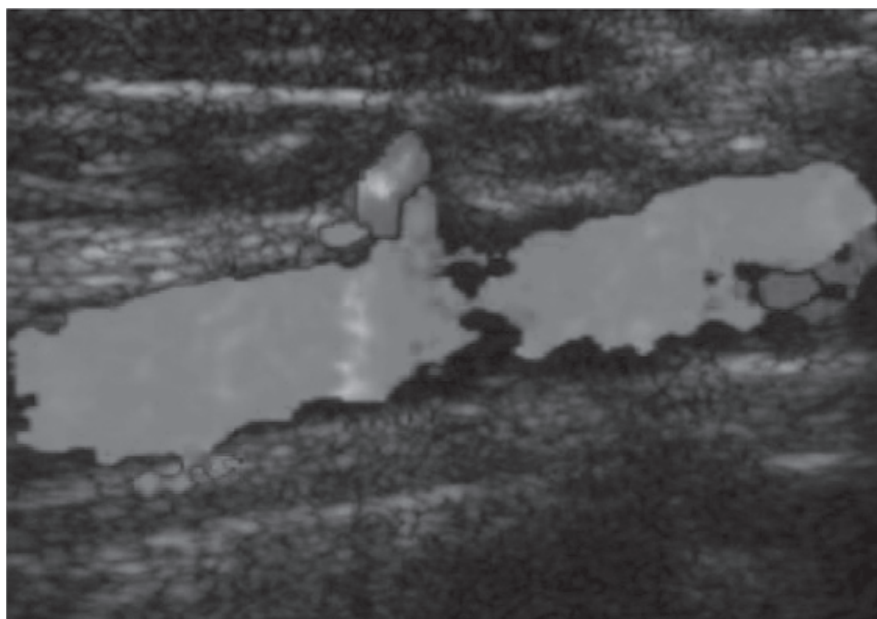


Fig. 1. Color-Doppler sonography performed at baseline showing absence of an inflammatory halo or stenoses of a subclavian artery. No other vessels examined by Color-Doppler sonography at this stage including the temporal arteries showed evidence of an inflammatory halo or stenoses

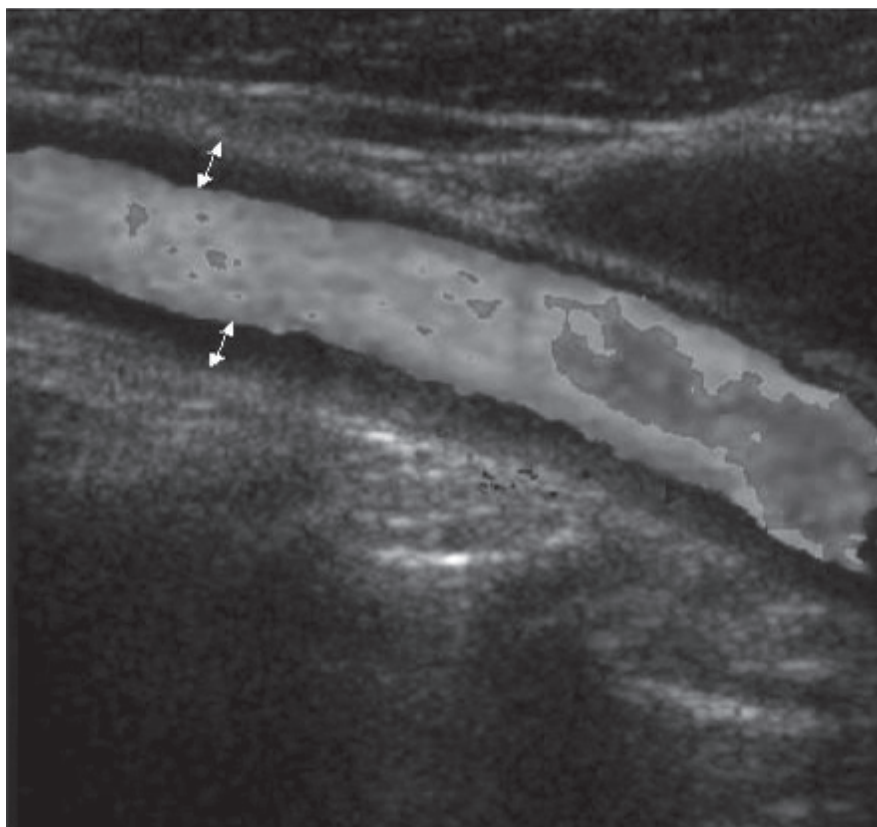


Fig. 2. Color-Doppler sonography performed at relapse showing the presence of a halo (arrows) around a subclavian artery. An inflammatory halo on Color-Doppler sonography was also observed at relapse around the axillary and iliac arteries, but not in the temporal arteries

up of patients with large-vessel vasculitis including GCA.

In GCA, imaging techniques can be

used to investigate the temporal arteries, the large vessels, or both. CDS is a rapid, easy to repeat, non-invasive

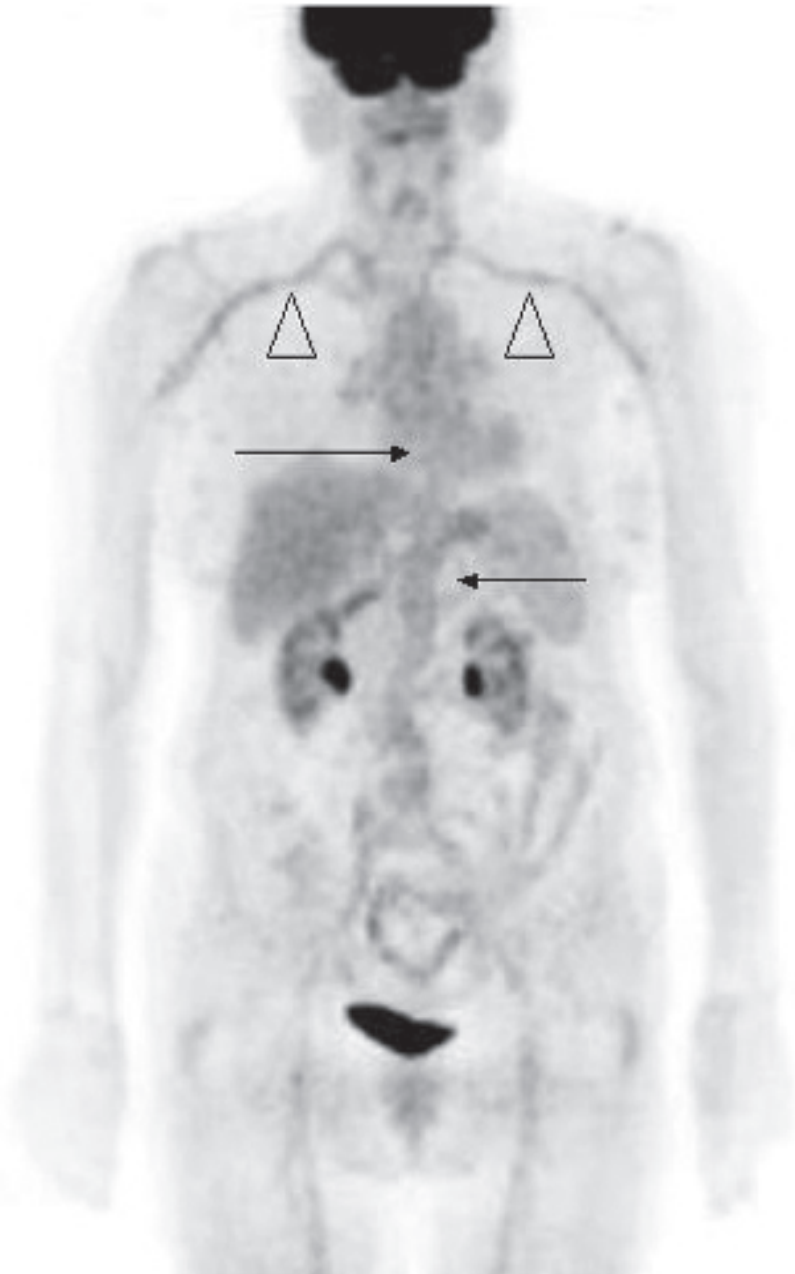


Fig. 3. ^{18}F Fluorodeoxyglucose positron emission tomography at relapse showing increased tracer uptake in the subclavian arteries (arrowheads) and in the entire aorta (arrows)

method, with a high specificity although somehow lower sensitivity for the diagnosis of GCA (8). In particular, the presence of a halo around the temporal artery wall is considered quite specific for GCA (9), whereas flow abnormalities including stenoses appear to be less specific (10). A limitation of CDS is the inability to image some arterial segments, such as the left proximal subclavian artery and the thoracic aorta because of overlying structures (11) and sometimes the abdominal vessel

because of superimposed bowel gases and fat (12). MRI of the temporal arteries has also been shown in preliminary studies to be very sensitive and specific for the diagnosis of GCA (13, 14). By contrast, PET is unable to visualize the temporal arteries (15, 16).

Large-vessel involvement in GCA can also be demonstrated using imaging procedures. CDS, MRI and computerized tomography can show arterial wall alterations suggestive of active inflammation such as mural thickening and

edema (11), while PET can demonstrate inflamed vessel segments although not clearly delineate the vessel wall (17).

Large-vessel involvement has been documented in 83% of untreated GCA patients and in 30% of both treated and untreated GCA patients using PET and CDS, respectively (5, 18). However, in these studies imaging procedures were only repeated at follow-up in those patients who had abnormal findings at baseline. Therefore, from these data it is impossible to establish whether any patient without large-vessel vasculitis at disease onset developed shortly thereafter large-vessel involvement. Bley *et al.* described a patient with cranial GCA who was shown eight months after the diagnosis to have vasculitis of the subclavian arteries on magnetic resonance imaging (19). Again, since no baseline investigations had been performed to investigate large vessel involvement, it is unclear whether large-vessel disease was a later complication of GCA or was already present at disease onset.

We routinely perform CDS of the temporal arteries, of the aortic arch and its main branches, and of the abdominal aorta in all patients with a clinical suspicion of GCA. These vessels have been demonstrated to be involved in the vast majority of GCA cases (5, 18). Therefore, we believe that it is quite unlikely that our patient had large vessel vasculitis at the onset of GCA, although this possibility cannot be entirely discarded since no baseline PET was carried out. On the other hand, CDS (performed by the same operator (A.N.), who has longstanding expertise in vascular ultrasonography) unequivocally demonstrated involvement of multiple large vessels during a flare that were not affected at disease onset. These findings provide evidence that large-vessel vasculitis may develop during relapses/recurrences of GCA.

Complications related to large-vessel vasculitis have been reported as occurring (usually late in the disease course) in 27% of GCA patients (6). Recognition of large-vessel vasculitis in GCA is important since large-vessel disease has been shown to be associated with increase mortality, mainly due to thoracic

aortic dissection (20, 21). Imaging techniques could be potentially valuable in detecting and monitoring early arteritis before overt changes occur (12, 22).

Serial imaging studies have been proposed to monitor GCA patients over time (10). CDS lends itself well to sequential studies because it is relatively inexpensive and entails no radiation exposure, however, there is limited evidence on its role in the follow-up of patients with GCA. In one study, halos around the temporal arteries disappeared in all patients investigated (in nine at two and in further nine patients at four weeks) after initiation of glucocorticoid treatment (10). In four patients in whom GCA relapsed during tapering of glucocorticoid treatment, halos reappeared and regressed again when the glucocorticoid doses increased. With regard to MRI, a patient has been reported in whom marked improvement of MRI inflammatory changes of the temporal arteries was observed after commencing glucocorticoid therapy (23). On a note of caution, vessel wall thickness and a positive halo sign have been linked not only to inflammatory edema but also to hypervascularity (22, 24). In addition, affected vascular segment on imaging may not develop later luminal changes and, conversely, seemingly unaffected vessels may become involved later on (11). Therefore, increased vessel wall thickness and edema may not invariably be construed as evidence of active arteritis. Finally, although PET is considered very sensitive in detecting inflamed large vessels (17), in a large study on thirty-five GCA patients no correlation was found between vascular uptake decrease following treatment and the risk of subsequent clinical relapse (5).

The case presented herein suggests that large-vessel involvement may develop as an early complication of cranial GCA, and that vigilant monitoring of GCA patients is thus required to detect and treat large-vessel vasculitis at any time during the disease course. A further point suggested by this case is

the need to investigate in clinical studies the early occurrence of large-vessel vasculitis instead of simply documenting clinically overt late complications, in line with the approach recommended by Schmidt *et al.* (18). A correct use of the imaging techniques currently available can enable the clinician to precociously assess the presence and extent of large-vessel involvement in GCA before late, potentially lethal complications may occur.

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