CASE REPORTS AND CLINICAL VIGNETTES

Delayed Diagnosis of Biopsy-Negative Giant Cell Arteritis Presenting as Fever of Unknown Origin

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Fever of unknown origin (FUO) presents a diagnostic challenge. Giant cell arteritis (GCA) may present with FUO and this entity should be included in the differential of elderly patients who present with constitutional symptoms. While a temporal artery biopsy is considered the gold standard for the diagnosis of GCA, a subset of patients with large vessel involvement by GCA may have a negative temporal artery biopsy and no cranial symptoms. We present a 79 year-old woman with FUO and negative temporal artery biopsies in whom diagnosis of GCA was delayed. Further imaging with CT-angiogram and positron emission tomography/computed tomography (PET/CT) scan showed diffuse extensive active vasculitis. The above case underscores the value of imaging studies in the evaluation of patients with FUO from occult large vessel vasculitis.

KEY WORDS: giant cell arteritis; fever of unknown origin; large vessel vasculitis.

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INTRODUCTION

Giant cell arteritis (GCA), also known as temporal arteritis, is a granulomatous vasculitis of large and medium-sized arteries. It represents the most common systemic vasculitis in adults, with an average annual incidence of 18.8 cases per 100,000 persons over the age of 50 years.¹ GCA predominantly affects elderly individuals of Northern European descent and is more common in women.² The vasculitic process in GCA preferentially involves the extra-cranial branches of the carotid artery and temporal artery biopsy is considered the gold standard for establishing a diagnosis of GCA. However, it is well recognized that GCA is often not limited to the cranial arteries and may involve the aorta and its major branches.³ In a prospective study of patients with newly diagnosed GCA, up to 45% of cases had thickening of the aorta on CT.⁴

Patients often present with classic cranial symptoms but a subset of patients may present with only constitutional

symptoms. Vasculitis (including GCA) is in the differential of elderly patients who present with fever of unknown origin (FUO). Positron emission tomography scans with 18F-Fluorodeoxyglucose (FDG-PET) and computed tomography (CT) may be useful in evaluation of FUO. In limited prospective studies, PET scans contributed to the final diagnosis in 25-69% of cases of FUO.⁵

We report an unusual case of a patient presenting with FUO and negative temporal artery biopsies in whom large vessel vasculitis was diagnosed by CT-angiogram and FDG-PET/CT. This case illustrates the value of imaging studies in the evaluation of patients with atypical or biopsy-negative GCA.

REPORT OF CASE

A 79 year old woman was referred to us with an 8-month history of fatigue, fever and a 17-pound weight loss. Her illness began with cough and fever for which a presumptive diagnosis of pneumonia was initially made. During the first few months of symptoms, she was treated with several courses of antibiotics without any improvement. Four months into her illness, she was re-evaluated by her local physician for persistent fevers, cough, fatigue and a progressive weight loss. At this point, further investigation was pursued. On laboratory evaluation, she was found to have a normocytic anemia with hemoglobin 11.2 g/dL and an erythrocyte sedimentation rate (ESR) of over 100 mm/hour (0-29 mm/hour). She had no cranial symptoms of GCA. However, in view of the laboratory abnormalities, bilateral temporal artery biopsies were performed, and were negative for GCA. This was followed by an extensive evaluation for infection and malignancy, including a bone marrow biopsy, all of which were unremarkable. Several sets of blood cultures and urine cultures were obtained and were negative. Given the lack of diagnosis and persistent constitutional symptoms, she was then referred to a tertiary care center 8 months after her illness began.

On evaluation at this institution, she complained of cough, 17 pound weight loss over the 8-month duration of her illness, low grade fevers and intermittent right hip/buttock pain and stiffness. She denied night sweats. She had not experienced cranial symptoms of GCA, including headache, jaw claudication, sudden visual changes, and carotidynia. She did not report typical symptoms of polymyalgia rheumatica. The patient also denied symptoms of upper or lower extremity claudication. Gastrointestinal review of systems was negative for symptoms of mesenteric ischemia.

On physical examination, she appeared chronically ill but in no acute distress. She was alert, oriented and had an

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appropriate affect. She was afebrile with temperature 36.5 degrees celsius. Blood pressure was equal in both arms and pulse was 60 beats per minute and regular. Skin examination did not reveal rashes. There was no lymphadenopathy or hepatosplenomegaly. Lungs were clear to auscultation bilaterally. Vascular examination was negative for carotid, subclavian, abdominal or femoral bruits and peripheral pulses were all present and symmetric. Musculoskeletal examination was also normal with full range of motion and no evidence of synovitis of the peripheral joints. Cranial nerve examination was normal. Upper and lower extremity sensory and motor examination was also normal with no focal deficits noted.

Further laboratory investigations were pursued. CBC revealed normocytic anemia with a hemoglobin of 11.1 g/dL (12–15.5 g/dL), elevated sedimentation rate of 81 mm/hour (0–29 mm/h) and C-reactive protein 18 mg/L (≤ 8.0 mg/L). Peripheral smear showed rouleaux formation. Iron, total iron binding capacity (TIBC), vitamin B12 and folate were normal. Serum protein electrophoresis revealed a polyclonal hypergammaglobulinemia. No monoclonal protein was detected on immunofixation. Outside bone marrow biopsy was reviewed at our institution and was normocellular with normal trilineage hematopoiesis. Urinalysis was normal. Repeat cultures were not obtained given the negative blood and urine cultures at the outside facility. All other laboratory evaluations, including rheumatoid factor, antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), cryoglobulins, total complement level, fungal serologies, hepatitis serologies, and serologies for Lyme disease and syphilis were negative or normal. TSH was 1.1 mIU/L (normal 0.3–5.0 mIU/L). QuantiFERON-TB Gold assay for mycobacterium tuberculosis was negative. Given the absence of risk factors, testing for HIV was not performed. The temporal artery biopsies and bone marrow biopsy performed at the outside institution were reviewed and read as normal. Plain films to evaluate the right buttock pain showed mild degenerative arthritis of both hips.

CT angiogram of the chest and abdomen showed multiple areas of thickened arterial walls of the great vessels, throughout the descending thoracic aorta (Fig. 1A), and the superior mesenteric artery (SMA) (Fig. 1B). There was evidence of significant stenosis in the proximal SMA as well as mild stenoses at the origin of the right vertebral artery and left subclavian artery at the subclavian-axillary junction. An FDG-PET/CT scan was then performed to rule out occult malignancy. This study showed no evidence of malignancy, but there was increased FDG uptake along the entire aorta, subclavian arteries, proximal brachial arteries, carotid arteries, iliac and femoral arteries bilaterally, consistent with a severe inflammatory process of the aorta and the great branches (Figs. 2A and 2B).

Based on the findings of the CT-angiogram and FDG-PET/CT, a diagnosis of large vessel vasculitis, most consistent with GCA, was made. Treatment with prednisone 60 mg daily for 4 weeks was initiated with resolution of the patient's symptoms. Prednisone was gradually tapered based on her clinical course. Repeat FDG-PET/CT scan 6 months later showed marked reduction in the extensive FDG uptake within the large vessels in the neck, chest, abdomen and pelvis (Fig. 2C). At a follow-up visit 1 year from diagnosis, a repeat CT angiogram revealed only mild residual thickening of the involved vessels. The focal narrowing of the SMA had decreased considerably and no new areas of vascular stenosis had developed. The patient was on 10 mg of prednisone at this time. At the time of

Figure 1. CT angiogram showing diffuse thickening of the walls of the descending portion of the thoracic aorta (sagittal view) (A) and the origin of the superior mesenteric artery (sagittal view) (B) as indicated by the arrows.

last follow-up, 2 years from initial presentation, the patient's vasculitis was in clinical and biochemical remission while on 5 mg prednisone daily. Unfortunately she has developed corticosteroid-related adverse effects including diabetes, weight gain, cataracts and glaucoma.

DISCUSSION

The predominant type of large-vessel vasculitis that affects the aorta and its major branches in patients over the age of

Figure 2. FDG-PET scan shows diffuse increased uptake along the entire aorta, subclavian arteries, proximal brachial arteries, carotid arteries, iliac arteries and femoral arteries bilaterally (Panel A). PET scanned images with fused axial CT images demonstrate uptake in the vessel wall of the aortic arch (Panel B). FDG/PET six months later shows interval improvement with minimal residual uptake evident in the subclavian arteries bilaterally (Panel C).

50 years is GCA. The above case highlights the challenges in the diagnostic work-up of patients with large-vessel vasculitis who present with FUO. Our patient presented with fevers and weight loss but denied any typical cranial symptoms of GCA. Furthermore, symptoms or clinical findings of vascular insufficiency that would have prompted suspicion for large-vessel vasculitis were also absent, further delaying diagnosis.

The presence of classic symptoms of GCA such as headache, scalp tenderness, visual disturbances or jaw claudication usually lead to prompt evaluation, diagnosis and treatment. However, a subset of GCA patients may present with constitutional symptoms such as fever, while cranial symptoms may be absent. In a study comparing patients with large-vessel GCA to those with cranial GCA, temporal artery biopsy was normal in 42% of 57 patients with large-vessel vasculitis who underwent biopsy.⁶ This suggests low sensitivity of temporal artery biopsy in patients who present with predominantly large-vessel involvement. In this subset of patients, radiologic vascular imaging studies are often essential in establishing the diagnosis.

Conventional angiography can demonstrate vascular stenoses in branches of the aortic arch in patients with GCA, but does not provide information regarding the vessel wall and is invasive. CT angiography can evaluate both the blood vessel wall for thickening as well as the lumen and is therefore helpful in early diagnosis, particularly if significant vascular stenoses are absent.⁷ Magnetic resonance angiography (MRA) can also show increased vessel wall thickness and post-contrast enhancement on T1 sequences in patients with GCA.⁷ More recently [18], FDG-PET is being increasingly used for the diagnosis and monitoring of response to therapy in large-vessel vasculitis.

18-Fluoride labeled FDG is a structural analogue of 2-deoxyglucose. It follows the same metabolic route as glucose and is taken up predominantly by metabolically active cells such as malignant cells, but also by inflammatory cells.⁸ PET scans may be helpful in diagnosis of early large vessel vasculitis since an early change in arteritis is infiltration of the vessel wall by inflammatory cells.^{8,9} Limitations of PET include expense and potential difficulty in discriminating between atherosclerotic and vasculitic lesions. However, these

can usually be distinguished based on more intense FDG uptake in vasculitis and also by the distribution of uptake in areas that are usually spared in atherosclerosis.⁷

Our patient presented with cough, buttock pain and constitutional symptoms of fever and weight loss. This was in the absence of other typical symptoms of GCA or vascular insufficiency. In retrospect, the cough was possibly an initial manifestation of GCA. It is estimated that 10% of patients with GCA have prominent respiratory tract symptoms such as a cough, sore throat or hoarseness.^{3,10} The persistent cough, poor response to antibiotics, and its resolution with prednisone all suggest that the cough was related to GCA. The right hip/buttock pain and stiffness may have been due to low grade articular inflammation. Physical examination was normal and PET did not show significant uptake at the hip. However, these symptoms also improved with prednisone therapy and therefore may have been an incomplete manifestation of PMR, which is seen in about 40%-60% of patients with GCA.³ The patient also had several non-specific laboratory abnormalities including a normocytic anemia and elevated markers of inflammation. The ESR was markedly elevated while the CRP was modestly elevated. SPEP obtained to evaluate for monoclonal protein showed hypergammaglobulinemia and peripheral smear showed rouleaux formation, which can spuriously elevate the ESR. This may partly explain the discrepancy between the markedly elevated ESR and modest elevation of the CRP. GCA was initially considered given the FUO and elevated inflammatory markers. Appropriate evaluation was pursued with bilateral temporal artery biopsies, but these were negative. The final diagnosis remained elusive until further imaging was pursued.

A CT angiogram was obtained for further evaluation of the patient's symptoms. This showed diffuse thickening of the aorta suggestive of vasculitis. Atherosclerosis can also result in vessel wall thickening, although usually not to the degree seen in this case. Additionally, an FDG-PET/CT scan was performed to rule out malignancy, but was useful in confirming that the vessel wall thickening noted on CT was due to inflammation. It was also helpful in monitoring the disease activity in this patient. The minimal residual uptake noted on FDG-PET/CT at six months may be due to tissue repair and remodeling rather than active vasculitis.

Table 1. Infectious Organisms and Inflammatory Diseases that May Cause Aortitis

Infectious organisms
<i>Bacterial</i>
Treponema pallidum
Salmonella spp.
Staphylococcus spp.
Mycobacterium
Streptococcus pneumoniae
<i>Fungal</i>
Candida
Aspergillus
Cryptococcus
<i>Viral</i>
HIV
<i>Inflammatory diseases</i>
Takayasu arteritis
Giant cell arteritis
Cogan's syndrome
Behçet's disease
Relapsing polychondritis
Rheumatoid arthritis
Inflammatory bowel disease
Systemic lupus erythematosus
ANCA-associated vasculitis
Ankylosing spondylitis

The differential diagnosis of aortitis is broad and includes infectious and inflammatory etiologies.^{11,12} Table 1 lists rheumatic diseases with aortic involvement and the main infectious causes of mycotic aneurysms. A detailed history and laboratory evaluations can help in distinguishing between the different causes of large-vessel vasculitis.

In the above case, there were no features in the patient's history to suggest an associated condition. Clinical and

laboratory evaluations were helpful in ruling out an alternate disorder such as a connective tissue disease, rheumatoid arthritis or ANCA-associated vasculitis. Serologies for infectious diseases including syphilis were negative. Therefore, in the absence of findings to suggest another diagnosis, the most likely diagnosis in a person of this age is GCA. While histologic confirmation is desirable, vessels other than the temporal arteries are not readily accessible for diagnostic biopsy. Therefore, increasingly, imaging findings have been useful in the diagnosis of large vessel involvement from GCA. In a study by Blockmans et al., the sensitivity and specificity of thoracic vascular ¹⁸F-glucose uptake for the diagnosis of GCA or PMR was 56% and 98% respectively.⁸ The positive predictive value of PET in the same study for these two diagnoses was 93%. Therefore, a diagnosis of large-vessel vasculitis can often be confidently made even in the absence of a histologic diagnosis. Furthermore, the patient's positive response to prednisone and the clinical outcome at 2 years of follow up essentially excludes another diagnosis such as a malignancy or infection as the cause of the patient's initial symptoms and imaging findings.

This case illustrates several important clinical pearls. Primarily, it emphasizes the importance of considering GCA in the work-up of elderly patients with FUO. Indeed, GCA may contribute up to 17% of cases of FUO in elderly patients.¹³ In another study of an unselected population of patients with FUO, large vessel vasculitis was diagnosed in 6% of the cases.¹⁴ Second, clinicians should be aware of a subset of patients with GCA in whom cranial symptoms are absent and constitutional symptoms may be the only presenting feature. Third, negative temporal artery biopsies do not exclude the diagnosis of GCA. If clinical suspicion for GCA is high and biopsies are negative, we suggest pursuing imaging studies such as CT or MR angiography of the aorta and great vessels.

Figure 3. Suggested algorithm in evaluation of a patient in whom large vessel vasculitis is suspected.

Imaging studies may help to identify changes of vasculitis or may reveal other causes of an elevated ESR such as occult malignancy or infection. Figure 3 summarizes our recommended approach for workup in patients in whom GCA is suspected. Fourth, in patients with a systemic inflammatory process, FDG-PET can be useful to localize the inflammatory process to the blood vessel wall, therefore confirming the diagnosis of vasculitis. Finally, we suggest that whenever possible, a diagnosis of GCA be established with objective evidence since glucocorticoid therapy, while effective, is associated with serious adverse effects.¹⁵ The importance of establishing a diagnosis becomes apparent since markers of inflammation are often used in conjunction with patient's clinical course to guide duration and effectiveness of therapy. Without a specific diagnosis at disease onset, it is challenging for a physician to recommend prolonged use of corticosteroids, especially when there is discordance between the patient's symptoms and laboratory findings.

Conflict of Interest: None disclosed.

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