

# Patient with Giant Cell Arteritis Who Presents with Fever of Unknown Origin

Mark A. Marinella, MD

**G**iant cell arteritis (GCA) is a systemic inflammatory disorder that typically occurs in persons older than age 50 years. GCA classically presents with headache, visual changes, masticatory claudication, and symptoms of polymyalgia rheumatica.<sup>1,2</sup> On rare occasion, however, GCA may present with fever as the only dominant symptom and thus lead to diagnostic difficulty that may result in invasive diagnostic testing. Fever of unknown origin (FUO) is an uncommon manifestation of GCA, which occurs in 2% to 15% of patients in some series of FUO.<sup>3,4</sup>

The definitive diagnostic procedure in the diagnosis of GCA is temporal artery biopsy, which typically reveals granulomatous inflammation, fibrosis, and disruption of the internal elastic lamina.<sup>5</sup> Laboratory abnormalities may also aid in the diagnosis of this disease and include an elevated erythrocyte sedimentation rate (ESR), anemia, and elevated liver enzymes.<sup>4</sup>

This report describes the case of a 61-year-old man with prolonged fever and an absent serum iron level. Clinical presentation, laboratory findings, diagnosis, and treatment of GCA as a manifestation of FUO are also discussed.

## CASE PRESENTATION

A 61-year-old man with congenital deafness caused by maternal rubella infection presents to the emergency department (ED) with transient dysarthria and prolonged fevers.

## History

**Initial presentation to a primary care physician.** The patient had been well until approximately 2 months prior to presentation when he developed daily fevers and night sweats accompanied by occasional headache and a 10-lb weight loss. The patient was initially treated by his primary care physician with several empiric courses of antibiotics without improvement.

**Referral to an infectious diseases specialist and hospital admission.** The patient continued to experience the previously noted symptoms for approximately 4 weeks. He was then referred to an infectious diseases

specialist who hospitalized the patient for further evaluation. Physical examination at that time was reported as unremarkable except for a low-grade fever. The ESR was 70 mm/hr, and a normochromic, normocytic anemia was present. Normal results were noted on a chest radiograph and an abdominal ultrasound, as well as on computed tomographic scans of the brain, sinuses, chest, abdomen, and pelvis.

Esophagogastroduodenoscopy, colonoscopy, and a barium small bowel follow-through examination were also normal. A lumbar puncture revealed normal values for protein and glucose with 1 leukocyte/mm<sup>3</sup>; cryptococcal antigen was negative, as was the spinal fluid culture. Multiple blood cultures (held for 2 weeks) and a urine culture were sterile. Thyroid and adrenal function studies were normal. Rheumatoid factor and antinuclear antibody were negative. Serologic tests for syphilis and antibodies to *Brucella* species were negative, as was a skin test for tuberculosis.

**Tentative diagnosis and hospital discharge.** The patient was thought to have a non-specific inflammatory disease and was discharged on non-steroidal anti-inflammatory agents; his intermittent headache was thought to be caused by muscle contraction. He was scheduled for outpatient bone marrow biopsy if the fevers persisted. Following discharge, the patient continued to experience daily fevers up to 102°F and occasional headaches.

## Presentation to the Emergency Department

Two weeks after discharge, the patient develops a transient episode of dysarthria and presents to the ED for evaluation. He denies other neurologic symptoms or visual changes. Except for a temperature of 100.6°F, vital signs are normal.

Physical examination, including fundoscopic examination, is unremarkable except for minimal bilateral temporal area tenderness. No cords are palpated over

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*Dr. Marinella is Assistant Clinical Professor of Internal Medicine, Wright State University School of Medicine, Dayton, OH, and a Hospitalist, Miami Valley Hospital, Dayton.*

**Table 1.** Laboratory Abnormalities Associated with Giant Cell Arteritis

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Elevated alkaline phosphatase
Anemia
Elevated erythrocyte sedimentation rate and C-reactive protein
Hyperglobulinemia
Hypoalbuminemia
Increased fibrinogen
Leukocytosis
Elevated liver aminotransferases
Increased serum complement levels
Increased serum ferritin
Increased serum haptoglobin
Decreased serum iron
Thrombocytosis

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the temporal arteries. The blood hemoglobin level is 11.3 g/dL with a normal mean corpuscular volume; leukocyte and platelet counts are normal.

**Hospital admission.** The patient is admitted to the hospital with a diagnosis of a transient ischemic attack in the setting of FUO, thought to be caused by GCA. Aspirin is administered immediately. Because no visual changes are present and because symptoms were present for several weeks, prednisone is not empirically administered.

**Laboratory and radiographic evaluation.** Further evaluation reveals a normal result on carotid ultrasound, echocardiogram, and magnetic resonance angiography of the cerebral vasculature. A repeat ESR is 84 mm/hr. Results of liver function studies, including alkaline phosphatase, are normal. Serum protein electrophoresis reveals hypoalbuminemia and evidence of chronic inflammation. Serum iron level is 0 µg/dL as is the iron saturation. Ferritin is 231 ng/mL, and haptoglobin is 575 mg/dL. Serum C3 is 212 mg/dL (normal, 75 to 161 mg/dL) and C4 is 51 mg/dL (normal 16 to 47 mg/dL).

**Biopsy, ophthalmology consultation, and hospital discharge.** Bilateral temporal artery biopsies are obtained 2 days after hospital admission and reveal changes consistent with GCA. An ophthalmology consultant performs a detailed retinal examination, the results of which are normal. The patient is administered oral prednisone (60 mg/day), with resolution of fever in 3 days. He is discharged from the hospital on day 5. At 2-week follow-up, the patient is afebrile with a decline in the ESR and a resolution of his symptoms.

## DISCUSSION

FUO, as defined by Petersdorf and Beeson,<sup>6</sup> is characterized by the following three criteria: 1) an illness of at least 3 weeks duration, 2) fever of 101°F or greater on three or more occasions, and 3) no clear diagnosis after 1 week of inpatient investigation.<sup>3</sup> A recent modification of these criteria suggests that hospitalization is not necessary if 1 week of intensive evaluation occurs as an outpatient.<sup>7,8</sup>

A recent study found that approximately 24% of cases of FUO are caused by noninfectious inflammatory disorders,<sup>3</sup> which is similar to rates previously cited in the literature.<sup>7</sup> GCA as a manifestation of FUO is uncommon but has been reported previously.<sup>4,5,9-12</sup> It was not uncommon for patients in these reports to undergo several diagnostic tests, including costly and invasive procedures, to look for infectious and neoplastic conditions before arriving at a diagnosis of GCA.<sup>10-12</sup>

## Clinical Presentation

Headache is the most common symptom of GCA but may be minimal or absent.<sup>12</sup> Symptoms of polymyalgia rheumatica may occur in up to 25% of patients with GCA,<sup>13</sup> and symptoms of jaw claudication and lingual pain occur less commonly.<sup>13,14</sup> The most feared complication of GCA is visual loss, which is typically caused by ischemic optic neuropathy from vasculitic occlusion of the posterior ciliary artery.<sup>15</sup> Some patients, however, may not present in the "classic" fashion, but instead, experience nonspecific, systemic symptoms. Fever, night sweats, fatigue, anorexia, and weight loss may predominate in a minority of patients with GCA and lead to a delay in diagnosis.<sup>4,9,13</sup>

Neurologic symptoms have been reported and may include cerebrovascular accident caused by vascular occlusion.<sup>15</sup> Ischemic symptoms of the carotid and vertebral basilar systems may occasionally occur and give rise to a variety of symptoms, including transient diplopia, dysarthria, vertigo, tinnitus, syncope, and aphasia.<sup>16,17</sup> Hence, the diagnosis of GCA must be considered in the elderly patient with new-onset cerebrovascular symptoms, especially in the setting of systemic illness. The patient in this case report experienced systemic symptoms for several weeks with only intermittent headache, before developing transient dysarthria. Evaluation for atherosclerotic cerebrovascular disease was unrevealing for this patient, supporting the idea that GCA was the cause of his transient dysarthria.

## Laboratory Findings

Laboratory findings in GCA are nonspecific and reflect the underlying chronic inflammatory state (**Table 1**).

Leukocytosis, thrombocytosis, anemia of chronic disease, and hypoalbuminemia are commonly observed in patients with GCA.<sup>11,13</sup> A study of 100 patients with FOU found that the 15 patients with GCA had significantly lower values for hemoglobin and albumin and significantly higher platelet counts, sedimentation rates, and alkaline phosphatase levels than the 85 patients without GCA.<sup>9</sup> An elevation of serum alkaline phosphatase, though not specific for GCA, has been reported in 29% to 65% of patients.<sup>12,13,18</sup> Elevated liver aminotransferases may occur as well, with reported abnormalities on liver biopsy specimens such as mononuclear cell infiltration, hepatocellular necrosis, and granuloma formation.<sup>12</sup> The anemia of GCA is typically an anemia of chronic disease, with occasional hypochromia and microcytosis. Serum iron levels and iron saturation are typically low, with a normal or increased serum ferritin.<sup>12,19</sup> The patient in this case report had an absent serum iron level with a normal ferritin, likely indicating anemia of chronic disease. Other laboratory features of GCA include elevated complement levels, increased serum haptoglobin, and hyperglobulinemia.<sup>13</sup>

#### Diagnosis

The most useful initial diagnostic test for GCA is the ESR, which is typically greater than 50 mm/hr. However, the ESR may be normal in up to 15% of patients with GCA.<sup>15</sup> A recent study by Hayreh et al<sup>20</sup> noted a sensitivity of 92% of the ESR for the diagnosis of GCA, but a sensitivity of 100% for an elevated C-reactive protein, which suggests that the protein test may prove useful in patients with a normal ESR but symptoms suggestive of GCA.

The gold standard for the diagnosis of GCA, however, is temporal artery biopsy.<sup>5,12,13,15</sup> Sensitivity ranges between 67% to 97%, with an increase in sensitivity of 5% to 10% if bilateral biopsies are obtained because pathologic changes may be noncontiguous.<sup>5</sup> Biopsy findings include granuloma formation, disruption of the internal elastic lamina, inflammatory infiltrate of the vascular wall, and obliteration of the vascular lumen caused by intimal fibrosis.<sup>2,5,12,20</sup> Granulomas may be absent in up to one third of specimens and are not necessary for the diagnosis.<sup>5,20</sup>

#### Treatment

Treatment for suspected or confirmed GCA is systemic corticosteroids, typically prednisone at a dose of 1 mg/kg/day with a slow taper.<sup>20</sup> Response to treatment may be dramatic, with improvement of symptoms within a few days.

#### SUMMARY

After an exhaustive evaluation for infectious, neoplastic, and autoimmune diseases, the patient in this case study was determined to have GCA. The patient had a favorable clinical response to prednisone therapy. Clinicians caring for elderly patients should be aware of the atypical presenting features of GCA in order to avoid unnecessary testing and because corticosteroid therapy has a favorable effect on this disease. **HP**

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