

## Giant Cell Arteritis: Diagnosis and Management

Case Study and Commentary: Jazibeh Qureshi, MD, and William S. Wilke, MD

### DR. LIANG:

Giant cell arteritis (GCA), also known as *temporal* or *cranial arteritis*, is a systemic vasculitis of adults that is the most common arteritis in western countries.<sup>1</sup> The general disease state has been known for over a century, after a “peculiar form of arteritis in the aged” was reported in 1890.<sup>2</sup> GCA was pathologically confirmed in 1932.<sup>3</sup> The disorder is generally a panarteritis limited to vessels with an internal elastic component,<sup>4</sup> and it usually affects the extracranial branches of the carotid artery, although it may extend to other vessels as well.<sup>5-7</sup> Temporal arteritis, which affects the temporal artery, is the most common form of GCA.<sup>8</sup>

There is a wide array of clinical characteristics associated with the disease. The single greatest risk factor for GCA in its various forms is advancing age<sup>9,10</sup>; the disease almost exclusively affects persons older than 50 years, with an average of onset of age 72 years and an average incidence of 1.54 per 100,000 persons during the sixth decade of life.<sup>11</sup> The annual incidence rises steadily after the sixth decade, reaching 20.7 per 100,000 persons by the eighth decade of life<sup>11</sup> and then 1100 per 100,000 persons by age 85 or older.<sup>12</sup> By gender, age-adjusted estimates indicate a female preponderance; for persons older than 50 years, the incidence in women is 24.2 per 100,000 and in men is 8.2 per 100,000.<sup>13</sup> These figures, combined with a recognition of the aging US population,<sup>14</sup> suggest the significant cost that the morbidity associated with the disorder represents.

Although GCA affects patients in all cultural and racial groups, it has been reported as particularly common in patients with Scandinavian and other northern European backgrounds.<sup>5</sup> Prevalence increases as residence moves from southern latitudes to northern ones.<sup>15</sup> White persons are much more affected by the disease than are black, Hispanic, or Asian persons.

The exact mechanism of the disease process in GCA is unknown but is thought to be T-cell dependent and

antibody mediated.<sup>16</sup> There is also evidence of a genetic component; genes associated with HLA-DR4 haplotypes 0401 and 0404/8, contained on the HLA-DRB1 locus, are thought to be associated with increased risk for development of temporal arteritis.<sup>17</sup> It has been postulated that deposition of immune complexes results in a local immune response on the affected vessels. However, the cause of this complex formation and immune response is not well known.<sup>18,19</sup>

The classic presentation of the disease is directly related to an inflammatory process and localized damage associated with the inflammation, which may cause endovascular damage, stenosis, and occlusion. Patients report a constellation of symptoms, including headache, jaw claudication, polymyalgia rheumatica, and visual symptoms, with headache being the most common feature. In fact, headache occurs in more than 70% of all patients with GCA,<sup>20</sup> as it did with the patient in this case study. However, approximately 40% of patients with GCA do not present with classic symptoms<sup>21-23</sup>; indeed, headache was not recognized as a common part of the presentation until 5 years after initial pathologic description of the disease.<sup>24</sup> Although a deep aching headache over the temporal region is the classic presentation, the headache of GCA may be extremely variable in location, quality, and intensity and may be noteworthy only because of its new or recent onset.<sup>25,26</sup>

It should also be noted that jaw claudication may be a confusing finding. Jaw claudication associated with GCA results from ischemic pain of the affected muscles and occurs with chewing foods that are tougher (eg,

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meat). This pain differs from that of temporomandibular joint syndrome, which produces pain on initiation of chewing or with chewing soft foods.<sup>8</sup> Furthermore, many patients with GCA only experience a vague discomfort in the jaw area. Other related but unspecific findings, such as malaise, fever, and/or weight loss, may also be seen with GCA and may be result from specific cytokines associated with the inflammatory process occurring in the disease.<sup>27</sup>

As noted in this case study, polymyalgia rheumatica is closely related to GCA and may be a manifestation of the same disease process. This disease state is associated with pain and stiffness in the hip girdle area, shoulders, and neck; symptoms are generally worse in the morning, with improvement during the day. The pain usually is associated with bursae inflammation in the hip region as well as the shoulders and with synovitis in nearby joints.<sup>28</sup> There also may be referred pain to the proximal arms and thighs.<sup>29</sup>

The most severe complication of GCA and the one of greatest concern to those diagnosing and treating the condition is visual disturbance, especially diplopia and blindness. The mechanism of blindness in patients with GCA typically involves an anterior ischemic optic neuropathy; this neuropathy is usually caused by posterior ciliary artery occlusion, which results in a decreased blood flow to the optic nerve head.<sup>30</sup> Untreated reduction of flow then leads to blindness. Because blindness is virtually never the first presenting sign of GCA, early recognition of the potential for this outcome is key to averting it by initiating corticosteroid treatment for the disorder.<sup>31,32</sup> Ophthalmologic consultation may be helpful in preventing visual disturbances and permanent loss of vision.<sup>33,34</sup>

Finally, as seen in this case study, large artery involvement can occur in GCA. It has been reported that patients with confirmed temporal arteritis have been found to have involvement of the carotid, vertebral, and subclavian arteries in 14% of cases.<sup>35</sup> Additionally, aortic involvement has also been noted, as with the patient in this case study; in one study, 18% of patients had aortic involvement, including thoracic aortic aneurysm.<sup>36</sup> The use of positron emission tomographic scans in more recent studies has indicated that patients with temporal arteritis may have involvement of the aorta and/or its major branches in as many as 50% of cases.<sup>37</sup> These scans may have utility in noninvasive diagnosis of the disorder and in prognosticating its extent, its response to therapy, and the likelihood of disease recurrence.<sup>38</sup>

Overall, GCA is a major disease of elderly persons. The most devastating complication is the loss of vision that can accompany the disease. A high index of suspi-

cion for elderly patients with new or recent onset of headache should be maintained, and empirical therapy should be initiated to treat affected patients and avoid potential visual adverse effects, particularly blindness.

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GCA, also known as temporal arteritis, is a form of vascular inflammation that preferentially affects medium and large arteries, including the vessels originating from the aorta. It is rarely encountered in patients younger than 50 years. In persons of northern European descent who are older than 50 years, the mean annual incidence is approximately 20 to 25 cases per 100,000 persons, but the incidence is somewhat lower for other populations.<sup>39</sup> GCA is more common in women, with a female-to-male ratio of 4:1. This article discusses methods for evaluating patients with signs and symptoms of GCA and presents an approach to the management of this disease.

#### CASE STUDY

##### Initial Presentation

A 78-year-old man goes to his primary care physician because of a 2-week history of extreme fatigue, fevers and chills, and headaches.

**History.** The patient reports that he was in his usual state of health until 2 weeks ago, when he experienced sudden onset of right-sided temporal pain, extreme fatigue with fevers and chills, and scalp tenderness. He reports no vision abnormalities, jaw and tongue claudication, odynophagia, or shoulder or pelvic girdle stiffness.

**Physical examination.** On physical examination, the patient has normal blood pressure in all 4 extremities and is afebrile. The right temporal artery is pulsatile and tender, and scalp tenderness is present. There is no evidence of synovitis, and strength is normal. Active range of motion of the shoulders is full and not painful. Cardiovascular examination reveals an aortic regurgitation murmur at the left sternal border and no systemic bruits.

- **What are the clinical manifestations of GCA?**
- **What is the differential diagnosis?**

GCA can produce a wide range of clinical manifestations that span multiple organ systems (**Table 1**). GCA should be considered in patients age 50 years and older who have 1 or more of the following symptoms or signs: new, localized headache; scalp tenderness or nodules; jaw, tongue, or deglutition-related claudication; signs or symptoms of polymyalgia rheumatica (PMR); an abnormal temporal artery; and vision

**Table 1.** Symptoms of Giant Cell Arteritis Present at Diagnosis in 4 Epidemiologic Studies

	Hamilton et al <sup>40</sup>	Houston et al <sup>41</sup>	Smith et al <sup>42</sup>	Hunder et al <sup>39</sup>
No. of patients	25	42	24	31
Year	1971	1978	1983	1985
Features present, % of patients				
Headache	48	90	83	71
Scalp tenderness	16	69	62	42
Myalgia	28	48	25	29
Malaise	8	48	62	45
Fatigue	12	48	62	NS
Anorexia	12	NS	NS	NS
Weight loss	16	55	21	29
Fever	16	21	29	3
Vision change	8	53	12	6
Vision loss	54	10	21	42
Jaw claudication	8	67	25	NS
Arthralgia	4	21	NS	16
Anemia	4	NS	NS	NS
First symptom to diagnosis, mo	NS	1	NS	NS

NS = not stated.

abnormality (eg, diplopia, optic atrophy/neuritis, loss of vision).

Symptoms and signs of GCA overlap considerably with those of PMR, but the conditions do not necessarily occur concurrently (**Table 2**). Patients with PMR usually have chronic symmetrical aching and stiffness of the proximal muscles (commonly in the shoulders, neck, and pelvic girdle), with constitutional symptoms of malaise and fatigue and elevated levels of acute phase reactants on laboratory testing. In a population-based survey of 126 patients with GCA in Sweden, 21% of those studied had a clinical presentation of temporal arteritis, 18% had both temporal arteritis and PMR, 53% had PMR without temporal symptoms, and 8% had constitutional symptoms only.<sup>44</sup> Constitutional symptoms associated with GCA and PMR might mistakenly be attributed to occult neoplasm or infection.<sup>45</sup>

The differential diagnosis of GCA includes other vasculitides (eg, Wegener’s granulomatosis, Churg-Strauss syndrome, polyarteritis nodosa), systemic infections, causes of severe headaches (eg, migraines, tension

**Table 2.** Clinical Findings in 96 Patients with Polymyalgia Rheumatica

Clinical Finding	No. of Patients (%)
Pain and morning stiffness	96 (100)
Shoulder	92 (96)
Hip	74 (77)
Neck	63 (66)
Upper arms	60 (63)
Thighs	52 (54)
Torso	43 (45)
Peripheral pain and stiffness	80 (83)
Lower extremities	70 (73)
Upper extremities	54 (56)
Systemic symptoms and signs	52 (54)
Fever*	12 (13)
Malaise, fatigue	29 (30)
Depression	14 (15)
Weight loss	14 (15)
Anorexia	13 (14)
Tenderness	37 (39)
Shoulder	25 (26)
Upper arms	23 (24)
Bicipital tendon groove	16 (17)

Data from Chuang et al.<sup>43</sup>

\*Temperature > 38°C (100.4°F).

headaches, subdural hematoma, intraparenchymal hemorrhage, stroke), tumors, and depression states. A case-control study compared patients with biopsy-proved GCA with patients in whom GCA was suspected but whose temporal artery biopsy results revealed no abnormalities.<sup>46</sup> During the 16-year follow-up period, 9 (11%) of the 88 patients with a negative initial temporal artery biopsy result had infectious diseases, 8 (9%) were diagnosed with an inflammatory disease other than GCA (eg, rheumatoid arthritis), and 2 had a malignancy. Similarly, in a case series of 68 patients with negative results on temporal artery biopsy, other inflammatory rheumatic diseases were diagnosed in 10% of patients, and a primary neurologic disease was subsequently diagnosed in 15% of patients.<sup>47</sup>

- **What tests are included in the diagnostic work-up of suspected GCA?**

## Diagnostic Evaluation

GCA is a corticosteroid-responsive disease, and corticosteroid therapy results in rapid and complete control of symptoms in most cases. When a patient has typical symptoms of GCA, such as those described previously, and has elevated levels of acute-phase reactants, corticosteroid therapy should be initiated. If the patient has an appropriate response to corticosteroids, then a temporal artery biopsy is not needed.<sup>48</sup> However, it is necessary to confirm the diagnosis of GCA with a temporal artery biopsy when the clinical picture is not entirely consistent with the diagnosis. Definitively excluding GCA with a biopsy can avert unnecessary exposure to prolonged, potentially toxic corticosteroid therapy.

**Erythrocyte sedimentation rate and C-reactive protein level.** Laboratory evidence of systemic inflammation can support the diagnoses of GCA and PMR and can help determine whether temporal artery biopsy is appropriate. Measurement of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level together provide the best sensitivity for GCA. Baseline laboratory indices also help in assessing response to and need for continued corticosteroid therapy. In a case-control study of 214 patients with GCA and 513 patients with other forms of vasculitis, an ESR of 50 mm/hr or greater was 86.5% sensitive and 47.7% specific in predicting positive biopsy results.<sup>39</sup> Adjusting the ESR for the patient's age (men:  $17.3 + 0.18 \times \text{age}$ ; women:  $22.1 + 0.18 \times \text{age}$ ) improved the sensitivity and specificity of this test in diagnosing GCA.<sup>49</sup> However, the ESR is within normal limits in an estimated 2% to 8.7% of cases of biopsy-proved temporal arteritis,<sup>50</sup> which reinforces the importance of history and physical examination in determining the need for biopsy. In addition, patients may have typical symptoms of GCA but have normal levels of acute phase reactant. In such cases, a corticosteroid trial is initiated, and if the response is appropriate with symptom improvement, a temporal artery biopsy is not pursued. The ESR may be within normal limits during active arteritis because of prior corticosteroid treatment, impaired hepatic protein synthesis, hematologic disorders (eg, polycythemia, hemoglobinopathy, hypofibrinogenemia), or congestive heart failure.<sup>49</sup>

The level of CRP, like other acute-phase reactants, rises and falls more quickly in response to changes in inflammatory activity. Levels rise with tissue necrosis, infection, myocardial infarction, and inflammatory and rheumatic diseases in response to interleukin 6. Unlike the ESR, the CRP level is not influenced by hematologic factors or age.

**Temporal artery biopsy.** Biopsy distinguishes between GCA and other forms of systemic vasculitis that may very rarely involve the temporal artery (eg, polyarteritis nodosa, Wegener's granulomatosis, Churg-Strauss syndrome, hypersensitivity vasculitis).<sup>51</sup> In a retrospective case-control study of 134 patients in whom a temporal artery biopsy was performed, a negative initial biopsy result correctly predicted no need for corticosteroid therapy in 91% of cases, and a positive initial biopsy result correctly predicted need for corticosteroids in 94% of cases.<sup>46</sup> Overall clinical features were remarkably similar in the negative and positive biopsy groups, with almost equal frequencies of PMR (38%/40%), malaise (28%/25%), fever (33%/30%), and weight loss as well as more specific symptoms such as headaches of recent onset (70%/57%) and visual disturbances (23%/24%). In 88 patients with a negative temporal artery biopsy result, 31 had PMR, 9 had infections, 8 had other connective tissue diseases, and 2 had malignancies. Superficial temporal artery biopsy should be obtained in patients with signs and symptoms of GCA who fail to respond to a prednisone dose of at least 20 mg per day and in patients with unexplained visual symptoms, malaise, weight loss, and elevated levels of acute phase reactants in whom a diagnosis of infection, malignancy, or other connective tissue disease is lacking.

Bilateral biopsy improves the diagnostic yield in only 3% of cases; therefore, unilateral biopsy is recommended. Unilateral biopsy is usually sufficient to confirm a diagnosis of GCA if the specimen is of adequate length (ie, at least 2 cm) and is sectioned in a manner that accounts for the discontinuous distribution observed in as many as 28% of patients in one case series.<sup>52</sup>

**Noninvasive imaging.** Color Doppler ultrasonography with simultaneous duplex mode allows visualization of the entire temporal artery and yields information regarding the appearance of the vessel wall and blood flow velocity of the arteries examined.<sup>53</sup> However, the accuracy of ultrasonography depends largely on the expertise of the sonographer, and this modality lacks the specificity required to discern inflammatory from degenerative or atheromatous changes of vessels involved in GCA. Ultrasonography may prove useful in helping to further identify which patients should undergo temporal artery biopsy.<sup>54</sup> Gadolinium-contrast magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (PET) may also provide useful information.<sup>55,56</sup> The test performance characteristics of MRI and PET scans in diagnosing GCA have not been determined.

- **What are the characteristic histologic findings on temporal artery biopsy in GCA?**

### Histology

A positive temporal artery biopsy specimen in GCA shows panarteritis and endothelial proliferation on microscopy. Inflammatory cells, predominantly macrophages and CD4-positive T lymphocytes, and multinucleate giant cells are present. Langhans' giant cells form by the fusion of macrophages in the diffuse inflammatory infiltrate. Temporal arteries are small muscular arteries without a distinct external elastic lamina, and they display a spectrum of aging changes similar to that observed in coronary arteries, although they do not develop atheroma. Senile changes in temporal arteries are not associated with giant cell reaction and should not be confused with the active phase of GCA. The single most helpful feature in distinguishing GCA from senile changes appears to be zonal arrangements of intimal proliferation that differ from arrangements seen in senescent arteries.<sup>57</sup>

Corticosteroid treatment administered prior to biopsy may modify temporal artery histologic characteristics. A retrospective study of 535 patients found that the rate of positive results in patients who received corticosteroids before biopsy was not significantly different from the rate in patients who did not receive treatment, but there was a trend toward more atypical biopsy results in patients who had had corticosteroid treatment for more than 14 days.<sup>58</sup> However, the results of this study may have been biased by a greater likelihood that patients with clinical features strongly suggestive of GCA would have received treatment prior to biopsy. Other studies report that temporal artery biopsies may remain unaffected by corticosteroid treatment up to and perhaps longer than 14 days before biopsy is performed.<sup>47</sup> One study found that patients who had not received treatment had the highest incidence (82%) of a positive temporal artery biopsy result; the rate of positive results decreased to 60% in patients who had received therapy for less than 1 week and to 10% in patients treated for 1 week or longer.<sup>59</sup>

### Diagnosis and Treatment

Laboratory testing in the case patient reveals an elevated ESR of 100 mm/h (normal, 0–20 mm/h) and a CRP level of 4.5 mg/dL (normal, 0–2 mg/dL). A right temporal artery biopsy is performed, and the results are suggestive of GCA, including an inflammatory infiltrate composed of predominantly mononuclear cells, fragmentation of internal elastic lamina by giant cells, and marked intimal proliferation. Based on the labora-

tory findings and these biopsy results, the physician makes a diagnosis of GCA. The patient is prescribed prednisone 60 mg daily. Calcium supplements (1500 mg) and vitamin D are prescribed along with the prednisone.

- **What is the approach to treating GCA with corticosteroids?**

### Corticosteroid Therapy

Corticosteroids provide very rapid control of common signs and symptoms of GCA, including headache, stiffness, and musculoskeletal pains. If the anticipated response to initiation of corticosteroid therapy is not prompt or is not achieved, other diagnoses, such as polyarteritis nodosa and Wegener's granulomatosis, should be reconsidered. Rapid control of symptoms is desired in GCA, but the compelling reason to treat with corticosteroids in GCA is to prevent blindness and stroke. Moreover, although corticosteroids are effective, they have a broad range of toxic effects that include infection, hyperglycemia, hypertension, cataracts, myopathy, psychosis, sleep disturbance, poor wound healing, acne, striae, weight gain, change in fat distribution, avascular necrosis, and osteoporosis. The challenge of treating GCA with corticosteroids is to prescribe an initial dose high enough to quickly control GCA symptoms but low enough to reduce these potential toxic effects.

Dividing the corticosteroid dose throughout the day appears to result in greater anti-inflammatory effects but is associated with a higher risk for adverse effects. Therefore, the use of split-dose corticosteroids should be reserved for acute settings, and consolidation to a single daily dose should be made as soon as possible. Tapering of corticosteroids to an alternate-day schedule is associated with a lower risk for toxicity, particularly infection, and is recommended only following the initial 4 to 6 weeks of therapy.<sup>60</sup> A plan for monitoring and minimizing corticosteroid-induced osteoporosis should be actively pursued in all patients treated with corticosteroids. Baseline bone mineral density measurement is recommended prior to or within 6 months of initiating corticosteroid therapy. These patients should take up to 1500 mg of calcium per day and maintain serum 25-hydroxyvitamin D<sub>3</sub> in the upper third of the normal range.<sup>61</sup>

**Initial dosing.** There is no clear consensus regarding an appropriate initial dose of corticosteroids for the treatment of GCA.<sup>62</sup> Only a few well-designed prospective series have studied the initial dose of corticosteroids. In 2 series, a starting dose of 11 to 20 mg of

prednisolone daily controlled symptoms in 95% to 97% of patients.<sup>63,64</sup> Patients given an initial dose of prednisolone of less than 20 mg daily had a much lower rate of remission and experienced a significantly higher frequency of disease flare than did patients given a daily prednisolone dose of 20 mg or more. Another study found that 12 of 15 patients were well controlled on 20 mg of prednisolone per day when given an initial dose of 40 mg daily for the first 5 days.<sup>65</sup> In these 3 series, 128 of 196 patients were treated initially with prednisolone doses of 20 mg per day or less, and none experienced cerebrovascular morbidity or blindness. Of the entire cohort of 196 patients, only 1 patient experienced blindness, which occurred after 4 weeks of prednisolone therapy at the higher dose of 60 mg daily.

Other studies show that adverse effects increase with the dosage. In a retrospective review of 77 patients who were given varying initial doses of prednisolone (daily doses of 30–40 mg, 41–60 mg, or more than 60 mg), patients taking more than 40 mg per day had statistically and clinically significant increases in adverse effects.<sup>66</sup> The group that received the lowest dose experienced a 36% frequency of adverse effects versus 80% in the 2 higher-dose groups. In addition, life-threatening adverse effects occurred in 14% of the lower-dose group versus 34% of the 2 higher-dose groups. The frequency of relapse and adverse outcomes caused by GCA was not significantly different among the groups.

A randomized trial compared the effectiveness of prednisone in suppressing arteritis symptoms when given on an alternate-day dosing schedule (90 mg every other morning) and daily dosing schedules (45 mg per day and 15 mg every 8 hours).<sup>67</sup> The 2 daily dosing schedules were equally effective, with the 45 mg daily dose suppressing arteritis symptoms in 18 of 20 patients and the split-dose regimen suppressing symptoms in 16 of 20 patients. In the alternate-day group, only 6 of 20 patients achieved remission. Thus, an alternate-day schedule should not be used for initial dosing.

We recommend treatment of uncomplicated GCA with a starting dose of prednisone never lower than 20 mg/day. The patient should be instructed to call back in 3 days to report response to corticosteroids. If symptoms are entirely controlled, we continue the prednisone at the initial dose for 2 to 4 weeks and then taper to 5 to 7.5 mg per day over the next 1 to 3 months. If the symptoms are not controlled, we raise the dose to 40 mg per day and provide a facilitated visit within the next 2 to 3 days. Prednisone doses of 60 mg per day are reserved for patients who have ocular or central nervous system involvement.

**Maintenance dosing.** A prospective 2-year study from Norway described the maintenance dose and annual cessation rate of oral corticosteroids in relation to the starting dose in patients with PMR and GCA.<sup>68</sup> This study showed that initial daily prednisone doses of 15 mg for PMR and 40 mg for GCA should be sufficient to relieve symptoms, improve general status, and prevent disease complications. A close positive correlation between the initial dose and the maintenance doses of corticosteroids during the first 2 years of treatment was found. Thus, the use of a low initial dose of corticosteroids and regular follow-up should facilitate a low maintenance dose of corticosteroids, thereby reducing the unwanted effects of such treatment. In this study, only 34% of PMR patients and 22% of GCA patients succeeded in stopping drug treatment after 2 years. The majority of patients need drug treatment for more than 2 years, but cases with PMR involving only mild elevation of ESR prior to therapy may represent a milder condition in which early termination of therapy is possible. Patients exhibiting clinical manifestations of both PMR and GCA may require therapy of a longer duration.

#### **Tapering of Corticosteroids**

The patient's symptoms of scalp tenderness, headaches, and fatigue subside with prednisone therapy. His initial prednisone dose is tapered after 4 to 6 weeks of treatment, and over the next 6 months the dose is tapered and stopped. One week following cessation of prednisone therapy, the patient's symptoms of fatigue return, and his ESR and CRP level increase to 65 mm/hr and 3 mg/dL, respectively, from normal baseline values. The physician prescribes prednisone 5 mg daily, with which the patient's fatigue subsides.

- **What agents can be used to achieve a corticosteroid-sparing effect in cases of GCA?**

#### **Corticosteroid-Sparing Agents**

Publications describing the use of corticosteroids and a second immunosuppressive agent are of 2 kinds: those that address so-called corticosteroid-resistant disease, in which a second agent is added after resistance is recognized, and those that attempt to demonstrate the superiority of initiation of therapy with 2 agents rather than with corticosteroids alone. Four small prospective and retrospective series describe the use of 2 immunosuppressive agents in 16 patients with corticosteroid-resistant GCA and 1 patient with corticosteroid-resistant PMR.<sup>69–72</sup> The second agents differed among the patients and included cyclophosphamide, dapsone, and methotrexate. Only 3 of these reports provided

information about diagnostic criteria and measures of disease activity. Methotrexate (7.5 to 12.5 mg per week) was given to 3 patients with GCA who initially responded to prednisone (40 to 60 mg daily) but whose symptoms recurred when the dose was reduced. When weekly methotrexate was added to the reduced prednisone dose, the patients' symptoms improved and the ESR returned to normal.<sup>69</sup>

A randomized, double-blind, placebo-controlled trial analyzed the safety and efficacy of combined therapy with corticosteroids and methotrexate in GCA.<sup>73</sup> Compared with combined corticosteroid and placebo therapy, treatment with corticosteroids and methotrexate significantly reduced the proportion of patients who experienced at least 1 relapse (45% versus 84.2%) and the proportion of patients who experienced multiple relapses. This study suggests that treatment with methotrexate plus corticosteroids is a safe alternative to corticosteroid therapy alone in patients with GCA and is more effective in controlling disease. However, a prospective, double-blind, randomized, placebo-controlled study argues against this finding.<sup>74</sup> This study compared methotrexate with placebo in addition to corticosteroid therapy in patients with newly diagnosed GCA. A total of 21 patients were enrolled, with 12 randomized to methotrexate (treated with high-dose prednisolone as well as methotrexate starting at 7.5 mg per week) and 9 to placebo. After a clinically defined remission and corticosteroid discontinuation, methotrexate or placebo was tapered monthly to 0 by 2.5 mg per week. There was no statistically significant difference between methotrexate- and placebo-treated patients with regard to cumulative corticosteroid dose. Therefore, no corticosteroid-sparing benefit could be attributed to the combination of methotrexate with corticosteroid therapy for the treatment of GCA. In this study, the corticosteroids were tapered very quickly after patients reached 10 mg per day, and the average dose of methotrexate was low, at 8.4 mg per week.

We recommend considering methotrexate for patients with biopsy-proved GCA who do not respond to low-dose prednisone. Patients selected to receive this therapy should have normal renal function for their age, be without evidence of liver disease, abstain from alcoholic beverages, and be able to comply with medication instructions.<sup>75</sup>

• **How should patients with GCA be monitored?**

Patients diagnosed with GCA should be assessed for clinical evidence of active GCA or PMR and complications due to GCA at each follow-up visit. They also should be screened for active disease and disease-related complications by history and physical examina-

tion and for ophthalmologic, neurologic, cardiac, and large vessel disease. Examinations should include careful cardiac auscultation to detect any new aortic insufficiency murmur, palpation and auscultation of abdominal aorta to evaluate for aneurysm formation, and palpation of upper and lower extremities to evaluate for signs of vascular insufficiency. Chest radiographs should be obtained annually, including a lateral view to detect aortic widening. Four-extremity blood pressures should be monitored to facilitate early detection of large vessel involvement.

ESR and CRP level may be used to detect subclinical inflammation and to confirm ongoing or reactivation of systemic inflammation. In a case-control study of 32 patients with biopsy-proved GCA and 32 patients with negative results on temporal artery biopsies, the CRP level was more sensitive than was ESR in following response to corticosteroid therapy in cases of GCA.<sup>76</sup> In a prospective serial study, 13 patients with PMR were followed to assess the behavior of ESR and CRP level during the course of the illness.<sup>77</sup> CRP level and ESR were elevated prior to corticosteroid therapy. With treatment, CRP level returned to normal at a rate that paralleled clinical improvement. The ESR also decreased but was still not normal after 2 weeks of therapy in half of the patients. Therefore, assay of serum CRP provides a precise means of objectively assessing the course of PMR during initial therapy with corticosteroids and suggests that routine measurements of CRP may make a useful contribution to the management of the disease.

**3 Years Later**

Three years after receiving the diagnosis of GCA, the patient is hospitalized because of a ruptured appendix, which leads to an exploratory laparotomy. Results of follow-up computed tomography (CT) scans of his abdomen demonstrate an asymptomatic abdominal aortic aneurysm more than 4 cm in diameter. Transthoracic echocardiography at that time shows moderate aortic regurgitation. The patient has been maintained on prednisone 1 mg daily and has had no GCA symptoms. He undergoes surgical repair of the aortic aneurysm. Biopsy of the aortic tissue is performed and reveals active giant cell aortitis.

- **How common is aortitis in cases of GCA?**
- **How is aortitis diagnosed and treated?**

**Aortitis**

Vascular inflammation in GCA can be widespread. Branches of the proximal aorta, especially those supplying the neck, extracranial structures of the head,

and upper extremities, tend to be affected most prominently. Inflammatory lesions are usually scattered along the courses of affected arteries in an irregular pattern, but in some instances longer segments ( $\geq 2$  cm) may be continuously involved.<sup>78</sup> Extracranial vascular involvement is clinically detectable in 10% to 15% of patients with GCA. It often presents dramatically as an unsuspected cause of aortic dissection or ruptured aortic aneurysm in the elderly.<sup>35</sup>

In a study involving 248 patients with GCA, 34 patients had evidence of involvement of the aorta or its major branches.<sup>35</sup> Symptoms suggestive of large vessel involvement included intermittent claudication of extremities, paresthesias, and Raynaud's phenomenon. Physical findings included absent or decreased large artery pulses and bruits over large arteries. Angiography was performed in 10 patients and was helpful in indicating arteritis. Three patients died as a result of aortic rupture. However, when corticosteroids were given in adequate doses, the response was favorable in most patients, intermittent claudication decreased, and pulses improved.

A review of 72 cases of aortic and extracranial GCA with histopathologic verification of the disease revealed that 25% of patients with aortic and extracranial large vessel GCA had asymptomatic GCA.<sup>79</sup> The ascending aorta and the aortic arch were most frequently involved (39%), followed by the subclavian and axillary arteries (26%) and femoropopliteal arteries (18%). Of the 18 patients whose deaths were directly attributable to extracranial GCA, the causes were ruptured aortic aneurysm (6), aortic dissection (6), stroke (3), and myocardial infarction (3). Given these findings, physicians should be cautious about attributing all aortic and large vessel arterial disease in the elderly to atherosclerosis and should remember that timely surgical intervention may be necessary and life-saving in patients with aortic and extracranial GCA.

**Diagnostic methods.** Methods used to diagnose arteritis include CT scans, MRI with T2-weighted images showing enhancement in areas of inflammation, angiograms of the aorta, and biopsy specimens at time of surgery or autopsy. In a study that used MRI to evaluate disease activity in Takayasu's arteritis, 77 MRI scans were performed in 24 patients.<sup>80</sup> In patients thought to have unequivocally active disease, 94% (17/18) of MRI studies revealed evidence of vessel wall edema. During periods of uncertain disease activity and during periods of apparent clinical remission, 81% (13/16) and 56% (24/43) of studies revealed vessel wall edema. The presence of edema within vessel walls

did not consistently correlate with the occurrence of new anatomic changes found on subsequent studies. Therefore, inconsistencies in the presence or absence of vessel wall edema and subsequent anatomic change have cast doubt on the utility of MRI findings as a sole guide in assessing activity of aortitis. MRI scans can be used to assess degree of inflammation on follow-up as well, but this method has its limitations, including several occasions in our experience in which MRI findings have not correlated with active aortitis on biopsy.

**Treatment.** There is no standardized approach to medical therapy following recognition of aortitis. In a study of 52 patients with idiopathic aortitis, 36 were followed between 1 and 144 months (mean, 42 months).<sup>81</sup> Of these, 11 patients received corticosteroids in varying dosages (range, 5–60 mg prednisone daily, with 1 patient receiving 1 g of intravenous methylprednisolone daily for 3 days) for varying periods of time (range, 3 days to 144 months). None of the 11 patients treated with corticosteroids (mean follow-up, 35.5 months) developed new aneurysms, while 6 of 25 who did not receive corticosteroid therapy (mean follow-up, 41.2 months) developed additional aneurysms. Nonetheless, therapy was not standardized among patients treated with corticosteroids, and several patients received very brief courses of treatment with very low doses of questionable utility. Some recommendations can be drawn from this study. Incidental aortitis may be a focal lesion, which—once surgically removed—does not recur. These patients should not be routinely provided with corticosteroids or other forms of immunosuppressive therapy. Evaluation for other large vessel abnormalities should be made by MRI with enhancement techniques that may identify sites of morphologic abnormalities and inflammation within the aorta. These techniques also may be of value in the assessment of patients with aortic diseases that do not require surgery or for which surgery is planned. If there is proof of inflammation, treatment with corticosteroids is probably indicated. This recommendation is derived from experience with Takayasu arteritis and GCA.

There have been other case reports in which patients have been treated with prednisone 60 mg per day when aortitis has been diagnosed.<sup>35,82</sup> In practice, if there is evidence of aortitis, we prescribe prednisone 20 mg per day, because this dose usually controls GCA; we then repeat MRI in 6 weeks along with measurement of acute phase reactants. If no response is seen at that time, we consider increasing the prednisone dose or adding a second agent.

### Follow-up

Following the diagnosis of active aortitis, the patient is prescribed prednisone 20 mg per day. Follow-up MRI scans performed 2 and 3 months later show decreased vessel wall edema. Because the patient is free of GCA symptoms and is doing well, the physician tapers the corticosteroids to 5 mg over the next 2 months. When last seen, the patient was doing well on this dose, and it was decided to further taper to 2.5 mg over the next month.

### SUMMARY

Although PMR and GCA are 2 different pathologic clinical entities, they are probably closely related pathophysiologically and often coexist. Temporal artery biopsy is indicated to confirm the diagnosis of GCA in patients with clinical findings suggestive of PMR or GCA who do not respond to prednisone of at least 20 mg per day and in those with unexplained constitutional symptoms and visual symptoms. Aortitis is a manifestation of GCA that must be considered during follow-up of patients even after treatment with corticosteroids is no longer necessary, because it can appear years after the diagnosis of GCA.

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