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Jonathan Kay

University of Massachusetts Medical School Worcester

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CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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Case 4-2006: A 79-Year-Old Woman with Myalgias, Fatigue, and Shortness of Breath

Jonathan Kay, M.D., David S. Finn, M.D., and James R. Stone, M.D., Ph.D.

PRESENTATION OF CASE

Dr. Celine R. Gounder (Department of Medicine): A 79-year-old woman was admitted to the hospital because of myalgias, fatigue, and shortness of breath.

Hyperlipidemia had been diagnosed six years earlier and had been controlled with simvastatin. Three years before admission, treatment with simvastatin was discontinued because of myalgias, and atorvastatin was started. Seven months before admission, pain developed over the lateral aspect of the chest wall bilaterally, extending from the axillas to the middle of her rib cage. The area was sore to the touch, but the pain was not affected by activity or changes in position. It did not awaken her from sleep. She also felt a lump in her throat when swallowing and had pain that radiated to her right ear. She discontinued atorvastatin, and the symptoms gradually resolved. One to two months later, she resumed atorvastatin, and the symptoms recurred, along with fatigue and reduced tolerance for exercise. Because of this, one month before admission, ezetimibe was added to her medications, and the dose of atorvastatin was reduced from 20 mg to 10 mg per day. Two days later, bilateral shoulder aches and neck and back pain developed. She stopped taking both ezetimibe and atorvastatin, but the symptoms persisted.

Eleven days before admission, she saw her primary care physician. She had what she described as “unbearable” pain in the morning and difficulty arising from her bed and from chairs, a sore throat, and pain over the lateral aspect of the chest wall bilaterally, extending from the axillas to the middle of her rib cage. On examination, there was normal range of motion of all joints. There was tenderness with abduction of the shoulders at about 45 degrees, worse on the left than the right. Motor strength was 4+ out of 5+ in all muscle groups of the arms and legs. There was no muscle tenderness. The results of liver- and renal-function tests and the levels of serum electrolytes, creatine kinase, aldolase, and aminotransferase were normal. Hematologic test results are shown in Table 1.

During the next week, the pain and fatigue persisted, and weakness worsened. The patient reported continuing difficulty arising from a chair and difficulty combing her hair. She did not have headaches, visual changes, jaw claudication, difficulty chewing food, fevers, night sweats, or a change in weight. Four days before admission, she again saw her primary care physician, who documented increased proximal muscle weakness; the findings on physical examination were otherwise unchanged.

From the Department of Rheumatology, Allergy, and Immunology (J.K.) and the Departments of Medicine (D.S.F.) and Pathology (J.R.S.), Massachusetts General Hospital; and the Departments of Medicine (J.K., D.S.F.) and Pathology (J.R.S.), Harvard Medical School — both in Boston.

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Table 1. Hematologic Laboratory Values.

| Variable | 11 Days before Admission | On Admission | Normal Range |
|--|--------------------------|--------------|---------------------|
| White-cell count (per mm ³) | 7,400 | 9,400 | 4,500–11,000 |
| Hematocrit (%) | 35.2 | 34.4 | 36.0–46.0 |
| Hemoglobin (g/dl) | 11.4 | 11.5 | 12.0–16.0 |
| Red cells (per mm ³) | 3,850,000 | 3,880,000 | 4,000,000–5,200,000 |
| Platelet count (per mm ³) | 360,000 | 402,000 | 150,000–350,000 |
| Mean corpuscular volume (μm ³) | 92 | 89 | 80–100 |
| Mean corpuscular hemoglobin (pg/cell) | 29.7 | 29.6 | 26.0–34.0 |
| Mean corpuscular hemoglobin concentration (g/dl) | 32.4 | 33.4 | 31.0–37.0 |
| Erythrocyte sedimentation rate (mm/hr) | 90 | Unavailable | Unavailable |

Prednisone was started at a dose of 20 mg per day. The pain and weakness improved, but two days before admission progressively worsening shortness of breath developed with minimal exertion and with prolonged speaking. She did not have chest pain or palpitations. She was admitted to this hospital.

The patient had had a myocardial infarction six years before admission that had required placement of a stent in the right coronary artery. Ten years before admission, a diagnosis of breast cancer had been made; the cancer had been treated by lumpectomy and radiation therapy, with no recurrence. The patient had had several admissions to the hospital for management of pancreatitis and pseudocyst formation. Eight months before admission, an endoscopic ampullectomy had been performed for treatment of an ampullary adenoma. Six weeks before admission, an episode of atrial fibrillation occurred, which was controlled with metoprolol. A cardiac ultrasonographic examination at that time showed trace mitral regurgitation and an ejection fraction of 67 percent.

There was a history of anxiety, depression, osteoarthritis, and gastroesophageal reflux. The patient's mother and an aunt had had breast cancer; her father and two brothers had had coronary artery disease, and a sister had died of lung cancer. She was a retired widow who lived alone; a son and daughter were well. She had never smoked, and she drank alcohol rarely. Her medications on admission were prednisone, aspirin, venlafaxine, esomeprazole, lorazepam, ranitidine, and metoprolol.

On physical examination, the patient was alert and in no distress. The temperature was 36.7°C,

the blood pressure 130/70 mm Hg, and the pulse 78 beats per minute with a regular rhythm; the respiratory rate was 16 breaths per minute. The head and neck appeared to be normal without areas of tenderness; the temporal arteries were not palpable or tender. There was no cervical or axillary lymphadenopathy. Inspiratory crackles were heard at both lung bases. The heart sounds were normal without murmurs. The abdomen was soft and nontender without masses or organomegaly. There was pitting edema (+) of the legs extending proximally to 3 cm below the knees. The peripheral pulses were easily felt, and the distal extremities were warm. The motor strength was rated 5 out of 5 in all muscle groups. An electrocardiogram demonstrated a normal sinus rhythm with a rate of 90 beats per minute and Q waves in leads II, III, and aVF. A chest radiograph demonstrated patchy bibasilar atelectasis. Hematologic laboratory results are listed in Table 1. Her symptoms improved over the next two days while she was receiving the same dose of prednisone, and she was discharged on the third hospital day.

Shortly after discharge, the patient's sore throat and hoarseness recurred. A diagnostic procedure was performed one week later.

DIFFERENTIAL DIAGNOSIS

Dr. Nancy Lee Harris (Pathology): Dr. Finn will give us the general internist's perspective on this case.

Dr. David S. Finn: This patient initially presented to my office with generalized muscle aches. She had a known history of coronary artery disease; her low-density lipoprotein cholesterol level was above 70 mg per deciliter (1.80 mmol per liter),

and she had not been able to tolerate doses of atorvastatin greater than 10 to 20 mg in the past; these doses caused myalgias with normal creatine kinase levels. One week before her presentation at my office, ezetimibe, at a dose of 10 mg per day, had been added to her regimen in accordance with the 2004 National Cholesterol Education Program guidelines.¹

The patient had stopped taking the ezetimibe several days before the office visit after reading the package insert, which listed all her symptoms as possible side effects from the medication. An examination revealed mild weakness of the upper and lower extremities that was greater proximally than distally. There was no synovitis on examination, and she had full range of motion of all her joints without pain. The initial intervention was to continue to withhold her lipid-lowering medications, on the assumption that these were responsible for her symptoms.

The incidence of statin-associated myalgias ranges from 1 to 5 percent in the randomized, controlled trials in which the symptom is reported.² This level did not differ markedly from that of placebo in most trials. This small percentage, however, is in vast contrast to the clinical experience; 25 percent or more of patients in surveillance databases report myalgias, with the average between 5 to 10 percent.² The cause of this large discrepancy between the clinical-trial experience and the outpatient-practice experience is unclear, but there is some evidence that patients can have a statin-associated myopathy with normal levels of creatine kinase.³ Ezetimibe has also been reported to cause myalgias in up to 4 percent of patients, and there have been additional case reports of myositis associated with the combination of atorvastatin and ezetimibe.⁴

My initial differential diagnosis also included polymyalgia rheumatica, temporal arteritis, a viral infection, subacute bacterial endocarditis, hypothyroidism, inflammatory arthritis, and even a recurrence of breast cancer in the form of a paraneoplastic syndrome. A recent test showed a normal level of thyroid-stimulating hormone. I ordered routine laboratory tests, and the patient was instructed to return to the office in one week. At the time of her return, she had increased weakness, much greater proximally than distally, as well as fatigue. On examination, there was increased proximal muscle weakness, but no other abnormalities were evident, and no abnormality

was noted on palpation of the temporal arteries. The laboratory-test results were normal except for an elevated erythrocyte sedimentation rate and a decrease in the hematocrit from her usual level of 38 percent to 35 percent. The combination of her symptoms, her elevated sedimentation rate, and the general lack of an alternative cause led me to a diagnosis of polymyalgia rheumatica.

I prescribed 20 mg per day of prednisone, with the expectation that the patient would have a dramatic improvement in her symptoms over the next 48 to 72 hours. When I spoke with her on the telephone four days later, she reported that the myalgias had improved, but increasing dyspnea had developed, to the extent that she was unable to perform her activities of daily living.

At this point, she clearly had a systemic inflammatory condition with fatigue, weakness, dyspnea, pharyngitis, elevated inflammatory markers, and a new anemia. Although she did not have many of the typical symptoms of giant-cell arteritis (headache, jaw claudication, and visual changes), many patients do not present with typical symptoms, and 4 percent of patients present with chiefly respiratory symptoms. Although the patient had some improvement while taking low-dose corticosteroids, it was not the dramatic improvement I had expected to see in a patient with polymyalgia rheumatica. The alternative diagnoses (subacute bacterial endocarditis, cancer, and other infections) all seemed unlikely. I began to suspect the diagnosis of giant-cell arteritis and admitted her to the hospital for further evaluation. I asked for consultation from the rheumatology service.

Dr. Jonathan Kay: This 79-year-old woman presented with fatigue and the relatively sudden onset of bilateral shoulder, neck, and back pain, which were most pronounced on awakening and did not improve with discontinuation of ezetimibe and atorvastatin. She experienced difficulty arising from chairs but had normal levels of muscle enzymes, suggesting that her symptoms were not due to a primary myopathic process. However, she had a mild anemia, and her erythrocyte sedimentation rate was markedly elevated at 90 mm per hour. Four days before admission, she had been started on oral prednisone (20 mg daily).

Her clinical presentation is typical of polymyalgia rheumatica, for which two sets of diagnostic criteria have been formulated empirically — by Chuang et al.⁵ and Healey.⁶ Both sets of criteria

require the presence of pain and stiffness persisting for at least one month and involving two of the following areas: neck, shoulders, and pelvic girdle. Patients must be 50 years of age or older and have an erythrocyte sedimentation rate elevated to more than 40 mm per hour. All other diseases that might cause these musculoskeletal symptoms, other than giant-cell arteritis (which can be associated with polymyalgia rheumatica), must be ruled out. In addition, Healey's diagnostic criteria require a rapid response to prednisone therapy at a daily dose no higher than 20 mg; despite some initial improvement, this patient's symptoms worsened while she received this therapy.

What other conditions might cause this woman's musculoskeletal symptoms? As Dr. Finn has mentioned, statin drugs may cause a painful myopathy, but there was no elevation of the level of muscle enzymes and her symptoms did not improve with the discontinuation of her lipid-lowering medications. Idiopathic inflammatory myopathies, such as polymyositis, dermatomyositis, and inclusion body myositis, also would be accompanied by elevated levels of muscle enzymes and usually by painless muscle weakness. About 15 percent of patients with rheumatoid arthritis present with polymyalgia rheumatica, with neck, shoulder, and pelvic-girdle pain and stiffness. However, this patient had no joint swelling or tenderness. Patients with degenerative arthritis may perceive pain above or below involved joints, but the morning stiffness that this woman had is more characteristic of an inflammatory process.

A patient with hypothyroidism may present with fatigue and muscle pain. However, these clinical manifestations usually are accompanied by elevated levels of muscle enzymes and other features of hypothyroidism, such as abnormal reflexes, low levels of thyroid hormone, and elevated levels of thyroid-stimulating hormone. Patients with fibromyalgia and other diffuse pain syndromes — which often accompany sleep disorders,⁷ depression,⁸ and past physical or sexual abuse⁹ — may present with fatigue and neck, shoulder, and pelvic-girdle pain and stiffness that are more pronounced on awakening. However, patients with hypothyroidism or diffuse pain syndromes also perceive pain in other areas and usually do not have anemia or a marked elevation of the erythrocyte sedimentation rate.

With this woman's history of breast cancer,

one must take into consideration that her neck, shoulder, chest-wall, and low-back pain might herald metastatic breast cancer. Furthermore, some cancers may be accompanied by a paraneoplastic syndrome that resembles polymyalgia rheumatica, with an elevation of the erythrocyte sedimentation rate that is associated with the presence of the cancer.¹⁰ However, the onset of polymyalgia rheumatica is often so sudden that the patient may recall the exact date when symptoms first began, whereas that of a paraneoplastic syndrome mimicking polymyalgia rheumatica is much more gradual. The most reliable feature that differentiates polymyalgia rheumatica from a paraneoplastic syndrome is the response to therapy: patients with polymyalgia rheumatica usually experience marked and rapid improvement of their pain within four to five days of beginning treatment with daily oral prednisone at doses of 20 mg or less, whereas those with underlying malignant tumors do not have improvement until the cancer is treated successfully.

Giant-cell arteritis and polymyalgia rheumatica are part of a single disease spectrum. Patients with giant-cell arteritis and polymyalgia rheumatica have a low frequency of the HLA-DRB1*01 allele. As with rheumatoid arthritis, there is an association with the HLA-DRB1*04 allele.¹¹ A sequence polymorphism in the second hypervariable region of the HLA-DR molecule antigen-binding site has been identified.¹² The disease occurs more commonly in people of northern European ancestry than in other ethnic groups and may aggregate in families.¹³

This woman reported no constitutional symptoms, such as fever, night sweats, or weight loss. She reported no headache, visual changes, or jaw claudication, which might be symptoms of giant-cell arteritis, a large-vessel vasculitis that occurs in some patients with polymyalgia rheumatica. We are told that she had no areas of tenderness on her head or neck, nor did she have thickening of her temporal arteries, which is a typical physical sign of giant-cell arteritis. The true prevalence of giant-cell arteritis among patients with polymyalgia rheumatica is not defined, because patients presenting with polymyalgia rheumatica do not routinely undergo temporal-artery biopsy. In one report,¹⁴ giant-cell arteritis was demonstrated in temporal-artery-biopsy samples from 41 percent of patients with a clinical diagnosis of polymyalgia rheumatica. Of these, 47 percent presented

without cranial symptoms. Thus, in the setting of polymyalgia rheumatica and an elevated erythrocyte sedimentation rate, one cannot rely on the absence of cranial symptoms to rule out a diagnosis of giant-cell arteritis.

Up to 10 percent of patients with giant-cell arteritis have pulmonary symptoms.¹⁵ This patient noted a sore throat; subsequently, progressively worsening shortness of breath developed with minimal exertion and with prolonged speaking. Inspiratory crackles were heard at both lung bases and patchy bibasilar atelectasis was evident on a chest radiograph. Cough is the most common presenting pulmonary symptom of giant-cell arteritis. Sore throat, presumed to be a symptom of ischemia involving the arteries that supply the laryngeal and pharyngeal tissues, occurs almost as frequently as cough. Peribronchial and interstitial granulomas that have been found in tissue obtained by transbronchial lung biopsy from a patient with giant-cell arteritis have been interpreted as being consistent with pulmonary involvement by giant-cell arteritis.¹⁶

The diagnostic procedure in this case should have been a temporal-artery biopsy to look for evidence of giant-cell arteritis. Although all attempts should be made to perform the temporal-artery biopsy before or soon after the initiation of prednisone therapy, findings diagnostic of giant-cell arteritis still may be observed even after more than 14 days of prednisone therapy.¹⁷

Dr. Finn: The patient was seen in consultation by the surgical service; a temporal-artery biopsy was performed.

CLINICAL DIAGNOSIS

Giant-cell arteritis (temporal arteritis).

DR. JONATHAN KAY'S DIAGNOSIS

Giant-cell arteritis (temporal arteritis).

PATHOLOGICAL DISCUSSION

Dr. James R. Stone: Histologic examination of the biopsy specimen of the temporal artery revealed a muscular artery with fragmentation of the internal elastic lamina, as well as intimal hyperplasia (Fig. 1A). In addition, there was a patchy lymphocytic infiltrate in the adventitia (Fig. 1B). Careful examination revealed the presence of fo-

cal histiocytic giant cells at the level of the internal elastic lamina (Fig. 1C). The macrophages at this location were also highlighted by immunohistochemical staining for the histiocytic marker CD68 (Fig. 1D). These findings are diagnostic of active giant-cell (temporal) arteritis.

The current approach to the subclassification of systemic vasculitis starts with consideration of the sizes of the vessels involved.¹⁸⁻²⁰ Large-vessel vasculitis often involves the aorta and major arterial branches to the head and arms and legs, as well as medium-sized vessels (small to medium-sized arteries), and is characterized histologically by granulomatous inflammation. The primary examples are giant-cell arteritis and Takayasu's arteritis. Medium-sized-vessel vasculitis occurs in small and medium-sized arteries without the involvement of small vessels (arterioles, capillaries, and venules). Primary examples include polyarteritis nodosa and Kawasaki's disease. Small-vessel vasculitis involves small vessels but can also affect medium-sized vessels²⁰; examples include diseases associated with the antineutrophil cytoplasmic antibody (ANCA), such as microscopic polyangiitis, Wegener's granulomatosis, and the Churg–Strauss syndrome, as well as immune-complex vasculitis, that are not associated with ANCA, including Henoch–Schönlein purpura, cryoglobulinemic vasculitis, drug-induced immune complex vasculitis, and immune-complex vasculitis secondary to infection, cancer, or collagen vascular disease.

In the case under discussion, the nature of the inflammatory infiltrate and the vessel involved are both characteristic of giant-cell arteritis. This disease most commonly affects the medium-sized extracranial arteries as well as other arteries of the head, the aorta and its major branches, and the arteries of the arms. Histologically, the condition can usually be identified by the presence of a lymphocytic infiltrate in the adventitia or media, or both, as well as a granulomatous infiltration of macrophages with giant-cell formation directed at elastic fibers.²¹ Thus, the giant cells will typically be located at the level of the internal elastic lamina in muscular arteries such as the temporal artery, but they may be dispersed throughout the media of elastic arteries and the aorta. The intensity and location of these two inflammatory components are highly variable and do not correlate with clinical symptoms. In giant-cell arteritis, in contrast to other forms of

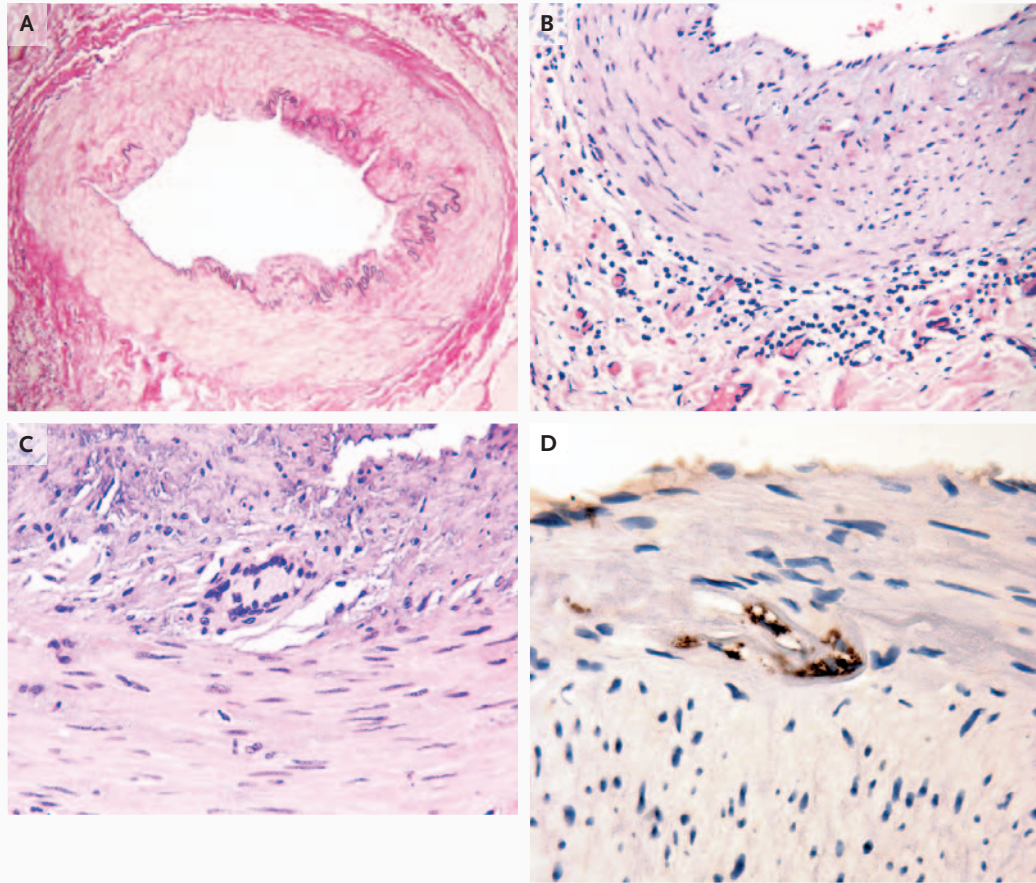


Figure 1. Biopsy Specimen of the Temporal Artery.

Panel A shows fragmentation of the internal elastic lamina and intimal hyperplasia (elastic tissue stain). In Panel B, lymphocytic infiltration of the adventitia is shown (hematoxylin and eosin). Panel C shows a histiocytic giant cell located at the internal elastic lamina (hematoxylin and eosin). In Panel D, immunoperoxidase stain for the macrophage marker CD68 shows macrophages at the internal elastic lamina.

vasculitis, necrosis of the vessel wall is not required for the diagnosis. The infiltrates have been shown to persist despite corticosteroid therapy.^{17,22} Fragmentation of the internal elastic lamina and intimal hyperplasia are both typically present; however, these findings are not by themselves diagnostic of arteritis. In giant-cell arteritis, arterial occlusion and subsequent ischemia of distal tissue typically result from intimal hyperplasia and not necessarily from thrombosis, as is often found with other forms of vasculitis. Because of the segmental nature of the disease, a negative biopsy result does not rule out the presence of giant-cell arteritis.

Giant-cell arteritis is one of the most common types of vasculitis, with an overall clinical preva-

lence of 0.2 percent among people more than 50 years of age.²³ However, autopsy studies have indicated the pathological prevalence to be closer to 1.7 percent among people in this age group,²⁴ indicating that many cases are subclinical. In fact, it is not uncommon for giant-cell arteritis to be diagnosed unexpectedly on resection of thoracic aortic aneurysms. The cause of this disease is not known.

Dr. Harris: Dr. Kay, would you discuss the management of this patient's condition?

Dr. Kay: Because not all patients who receive a pathological diagnosis of giant-cell arteritis have the clinical syndrome, the decision to treat is based on a combination of clinical and pathological findings. The diagnostic criteria for the

clinical syndrome of giant-cell arteritis include three or more of the following: an age of 50 years or older at disease onset, new-onset headache, a temporal-artery abnormality (tenderness or decreased pulse), an erythrocyte sedimentation rate of 50 mm per hour or higher, and a temporal-artery–biopsy specimen showing vasculitis with a mononuclear-cell infiltrate or granulomatous inflammation, usually with multinucleated giant cells. Does this patient without cranial symptoms or abnormalities on physical examination meet the classification criteria for giant-cell arteritis? She was older than 50 years of age, she had an elevated sedimentation rate, and her biopsy demonstrated the specific features associated with giant-cell arteritis. Thus, we can make a diagnosis of the clinical syndrome of giant-cell arteritis.

Whereas polymyalgia rheumatica is effectively treated with low doses of oral prednisone, giant-cell arteritis requires doses of oral prednisone of 40 to 60 mg, or the equivalent, administered as a single or divided daily dose.²⁵ Pulsed intravenous methylprednisolone (1000 mg daily for three days) may be given to patients with visual loss.²⁶ After at least two to four weeks, prednisone may be tapered gradually to a maintenance dose that controls the associated symptoms of polymyalgia rheumatica. Patients with giant-cell arteritis or polymyalgia rheumatica may require low-dose corticosteroid therapy for several years to control disease activity. Because of the risk of corticosteroid-induced osteoporosis, calcium and vitamin D supplementation should be administered, and consideration should be given to prophylactic bisphosphonate therapy.

A recent randomized, controlled clinical trial²⁷ demonstrated that low-dose weekly methotrexate is an effective corticosteroid-sparing agent for the treatment of polymyalgia rheumatica. However, low-dose weekly methotrexate is not effective in the treatment of giant-cell arteritis.²⁸

Dr. Harris: What causes the pain in patients with polymyalgia rheumatica?

Dr. Kay: The pain in polymyalgia rheumatica is caused by synovitis. The biologic process is similar to that in rheumatoid arthritis, but in polymyalgia rheumatica it predominantly involves the proximal joints and not the distal peripheral joints.²⁹

Dr. Harris: The patient had been having pain on swallowing for several months. Could this disease have been smoldering during that time before the acute presentation? Would this symptom argue against a diagnosis of polymyalgia rheumatica?

Dr. Kay: The sore throat could have been a clue to the presence of giant-cell arteritis that involved her laryngeal arteries.

Dr. Finn: After the biopsy, the patient was started on prednisone (60 mg per day). She was referred to a neuro-ophthalmologist as well as a rheumatologist for assistance in corticosteroid management. An ophthalmologic examination was normal. She began taking trimethoprim–sulfamethoxazole prophylaxis and a proton-pump inhibitor for gastric protection, and she was referred to a nutritionist for management of her hyperglycemia. She was also referred to the bone clinic for consideration of intravenous bisphosphonates, because she had been intolerant of alendronate when treated in the past. The prednisone dosage was tapered to 5 mg per day, but symptoms recurred; methotrexate (10 mg weekly) has recently been added. She currently feels well, 15 months after her original presentation.

ANATOMICAL DIAGNOSIS

Active giant-cell (temporal) arteritis.

No potential conflict of interest relevant to this article was reported.

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