Giant-Cell Arteritis and Polymyalgia Rheumatica

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A 79-year-old woman presents with new-onset pain in her neck and both shoulders. She takes 7.5 mg of prednisone per day for giant-cell arteritis. Occipital tenderness and diplopia developed 11 months before presentation. At that time, her erythrocyte sedimentation rate was elevated, at 78 mm per hour, and a temporal-artery biopsy revealed granulomatous arteritis. The diplopia resolved after 6 days of treatment with 60 mg of prednisone daily. Neither headache nor visual symptoms developed when the glucocorticoids were tapered. How should this patient's care be managed?

**The Clinical Problem**

Giant-cell arteritis is an inflammatory vasculopathy that typically occurs in medium and large arteries with well-developed wall layers and adventitial vasa vasorum. The vascular beds that are usually affected include the external carotid branches (e.g., temporal and occipital arteries), the ophthalmic, vertebral, distal subclavian, and axillary arteries, and the thoracic aorta. Vasculitis leads to luminal occlusion and therefore ischemic complications, such as ischemic optic neuropathy, which causes vision loss in 10 to 15% of patients. Aortitis can be complicated by dissection and aneurysm formation.

Polymyalgia rheumatica causes aching and stiffness in selected muscle groups, predominantly in the neck, shoulders, upper arms, and pelvic girdle. Symptoms are most pronounced in the morning. The source of the myalgias is insufficiently defined. Imaging studies have revealed inflammation of the bursas and periarticular structures. Furthermore, the interstitial fluids from painful muscles contain high cytokine levels. Typically, these myalgias are associated with robust systemic inflammation, as indicated by markedly elevated levels of acute-phase reactants in the blood.

Both giant-cell arteritis and polymyalgia rheumatica have multiple risk factors and pathogenic abnormalities in common. These conditions may occur simultaneously or in isolation. Symmetric proximal myalgias combined with laboratory abnormalities underlie the diagnosis of polymyalgia rheumatica. Since some patients with polymyalgia rheumatica have subclinical vasculitis and are subject to vasculitic complications, follow-up evaluation is needed. Approximately 50% of patients with giant-cell arteritis present with polymyalgia rheumatica before, at the time of, or after the diagnosis of vasculitis. Symptoms of polymyalgia rheumatica often appear when the therapy for giant-cell arteritis is being tapered.

Giant-cell arteritis and polymyalgia rheumatica are diseases that affect the elderly, with peak incidences at the age of 70 to 80 years; age (50 years or older) is considered a criterion for the diagnosis. Women account for 65 to 75% of patients. Polymyalgia rheumatica occurs at a frequency that is 3 to 10 times that of giant-cell arteritis. Disease risk varies according to race and geographic region. The incidence...
is highest among whites in northern European populations (about 20 cases per 100,000 persons older than 50 years of age); it is lower in southern European populations (about 10 cases per 100,000) and is markedly lower in American populations of Asian or African descent (about 1 case per 100,000). HLA polymorphisms modulate the risk of disease. An onset of disease late in life suggests that environmental exposures influence susceptibility factors; socioeconomic status has no noticeable effect.11

Longevity is not reduced in patients with giant-cell arteritis and polymyalgia rheumatica unless severe aortitis is also present.12-14 Contrary to the previously held belief that giant-cell arteritis and polymyalgia rheumatica are self-limiting conditions, vasculitis persists in many, if not all, patients, although in most instances it does not cause life-threatening complications.

PATHOPHYSIOLOGICAL FEATURES

Molecular studies of large-vessel vasculitis15 suggest that dendritic cells residing in the vessel wall initiate the pathogenic cascade and recruit T cells and macrophages to form granulomatous infiltrates. Dendritic cells have a territorial distribution in the vascular tree16 that may determine the pattern of vasculitis. Vascular lesions in inflamed temporal arteries contain an array of cytokines and inflammatory mediators.15 Two major immune-response networks have been identified: the interleukin-12–type 1 helper T-cell (Th1)–interferon-γ axis and the interleukin-6–type 17 helper T-cell (Th17)–interleukin-17 or interleukin-21 axis17; the latter (but not the former) is effectively suppressed with glucocorticoid treatment.18 Effector cytokines released into the arterial wall activate inflammatory cells and target endothelial cells, vascular smooth-muscle cells, and fibroblasts, leading to lumen-obstructive intimal hyperplasia. Elastolytic and proteolytic enzymes (e.g., matrix metalloproteinases) and proangiogenic and growth-promoting factors (e.g., vascular endothelial growth factor and platelet-derived growth factor) promote remodeling of the arterial wall, giving rise to the characteristic findings on imaging and clinical manifestations.

EVALUATION AND MANAGEMENT

The diagnosis of giant-cell arteritis is considered on the basis of the medical history, clinical evaluation, and laboratory and imaging tests, and it is confirmed on the basis of histologic findings. The absence of pathognomonic clinical and laboratory characteristics makes polymyalgia rheumatica more difficult to diagnose, unless it is accompanied by giant-cell arteritis.

Laboratory Testing

Marked elevations in the erythrocyte sedimentation rate (ESR) and the level of C-reactive protein
**Immunologic Markers**

Serum electrophoresis can be used to detect monoclonal gammopathy. Blood cultures are recommended to evaluate fever of unknown origin. Antineutrophil cytoplasmic antibodies (ANCA) or anti–cyclic citrullinated peptide antibodies (e.g., antineutrophil cytoplasmic antibodies [ANCA] or anti–cyclic citrullinated peptide antibodies) can be used to rule out other rheumatic diseases, and elevated levels of these markers should not be the only indication for immunosuppressive therapy.

No highly specific biomarkers for giant-cell arteritis and polymyalgia rheumatica have been validated. Levels of interleukin-6, a major inducer of CRP production, are characteristically elevated in untreated patients, transiently suppressed by therapy, and often higher than normal in patients with chronic disease. There is no evidence that the measurement of interleukin-6 levels is superior to the measurement of CRP levels in guiding clinical decisions, and its measurement is not recommended in routine practice.

If clinically indicated, assays for autoantibodies (e.g., antineutrophil cytoplasmic antibodies [ANCA] or anti–cyclic citrullinated peptide antibodies) can be used to rule out other rheumatic diseases, and serum electrophoresis can be used to detect monoclonal gammopathy. Blood cultures are recommended to evaluate fever of unknown origin.

**Imaging**

Large-vessel vasculitis occurs in 25% of patients with giant-cell arteritis. Magnetic resonance angiography (MRA) or computed tomographic angiography (CTA) of the aortic arch and its major branches is useful in patients in whom giant-cell arteritis has been confirmed on biopsy, in order to assess the extent of arterial involvement (including the presence of stenosis, dissection, and aneurysms) and to monitor vascular lesions for any signs of progression (Fig. 1). MRA or CTA may also be used to identify large-vessel involvement in patients with suspected giant-cell arteritis that has not been confirmed on biopsy and in whom there is clinical evidence of peripheral ischemic disease. Intramural leaky microvessels give rise to delayed enhancement of the arterial wall, which is consistent with but not specific for inflammatory activity. Wall thickening and increased intrawall blood pooling may not be reversible with treatment and should not be used to assess the inflammatory burden or disease activity. Given the effective use of MRA and CTA, traditional angiography is now reserved for planning revascularization procedures, when required.

The use of 18F-fluorodeoxyglucose (18F-FDG) with positron-emission tomography and computed tomography (PET–CT), which detects hypermetabolic cells, has been proposed for quantifying the inflammatory burden. The sensitivity and specificity of this high-cost imaging method for diagnosing and monitoring giant-cell arteritis have not been established. 18F-FDG with PET–CT cannot be relied on to distinguish vasculitis from non-vasculitic inflammatory lesions (e.g., atherosclerotic changes in vessel walls), and its sensitivity for smoldering and treated vasculitis is limited; routine use is not recommended.

Color Doppler ultrasonography can be used to visualize superficial arteries, such as the temporal artery, but its usefulness in evaluating the walls of deeper-seated vessels is limited. Vessel-wall edema produces a hypoechoic signal on color Doppler ultrasonography that is referred to as a halo sign. In a meta-analysis involving a total of 998 patients in 17 studies, the sensitivity of the halo sign for biopsy-positive giant-cell arteritis was only 75%, and the specificity was only 83%. High-field-strength MRI may emerge as a method that is sensitive to the detection of temporal-artery inflammation, but neither ultrasonography nor MRI has yet replaced temporal-artery biopsy, which is highly sensitive for even minor inflammatory changes.

In polymyalgia rheumatica, ultrasonography or MRI may identify subacromial, subdeltoid, trochanteric, and cervical bursitis and tenosynovitis of the long biceps head. Peripheral-joint synovitis should raise suspicion of an alternative diagnosis, such as rheumatoid arthritis or inflammatory osteoarthritis. Current classification criteria do not require ultrasonography as a means of establishing the diagnosis of polymyalgia rheumatica.

**Pathological Analysis**

In cases of suspected giant-cell arteritis, histologic verification of vasculitis should be sought by means of a temporal-artery biopsy with assessment of a vascular segment that is 1.5 to 2.0 cm in length. Histologic analysis is the standard for diagnosis; it can detect small inflammatory infiltrates and can also distinguish giant-cell arteritis from non–giant-cell arteritis arteritides (e.g., ANCA-associated vasculitis). A negative biopsy finding does not rule out
giant-cell arteritis; however, biopsy identifies 85 to 95% of cases.\textsuperscript{14} Temporal arteries are frequently not involved in patients with giant-cell arteritis who have predominantly subclavian involvement. Biopsy of a second site should be performed if there is a strong clinical suspicion in spite of negative findings at the site of the first biopsy and negative results of imaging. Routine bilateral biopsies are discouraged. Interpreting biopsy findings as false negative results and treating patients in the absence of strong diagnostic evidence is problematic, yet appears to be frequent in current practice. In a recent study, giant-cell arteritis was diagnosed clinically in 61% of 112 patients,\textsuperscript{29} despite negative findings on temporal-artery biopsy. In such cases, patients may be unnecessarily exposed to the risk of glucocorticoid therapy.

Arteritic optic neuropathy is a true emergency, and therapy should not be delayed because of the risk of vision loss. The diagnostic sensitivity of temporal-artery biopsy remains high even after glucocorticoid therapy has been initiated; the sensitivity declines after several weeks of therapy.\textsuperscript{18,30}

**TREATMENT**

**Immunosuppressive Therapy**

Giant-cell arteritis and polymyalgia rheumatica are responsive to glucocorticoids, and although there is no specific indication for their use in the treatment of these conditions, most cases are managed effectively with glucocorticoid monotherapy (Fig. 2A). Most treatment recommendations are based on clinical experience rather than the results of randomized, controlled trials. Therapy for giant-cell arteritis is initiated with prednisone at a dose of 1 mg per kilogram of body weight per day. Given the risk of irreversible ischemic complications, new-onset clinical manifestations of disease indicating an unstable supply of blood to the eyes or the central nervous system (e.g., arteritic optic neuropathy) are typically managed with intravenous pulse therapy (e.g., 1000 mg of methylprednisolone per day for 3 consecutive days) to optimize immunosuppression and suppress tissue edema. Once tissue necrosis occurs (e.g., optic-nerve ischemia with blindness for several hours), it is irreversible.

In most patients, the administration of high-dose glucocorticoids is followed by rapid improvement of systemic inflammatory signs, presumably due to the effective suppression of interleukin-6 and the acute-phase response. In current practice, the tapering of glucocorticoids is generally started once reversible clinical signs have abated and laboratory values have normalized. The dose is initially reduced by 10 to 20% every 2 weeks; once the dose falls below 10 mg of prednisone per day, tapering is usually slowed (generally by 1 mg per month).
These recommendations match those developed by the British Society for Rheumatology (BSR).31 Guidelines from the European League against Rheumatism (EULAR) suggest a faster initial tapering to a dose of 10 to 15 mg per day within 3 months after treatment initiation.32 Inflammatory markers are monitored monthly during the first year of treatment, bimonthly during the subsequent year, and at intervals of 3 to 6 months during long-term follow-up.

When glucocorticoids are tapered, disease flares may occur frequently (an average of one to two episodes per person-year) and are often manifested as new-onset or recurrent polymyalgia rheumatica.22,33 Relapses are rarely manifested as ischemic complications and often respond to slight increases in the dose of glucocorticoids. Elevated levels of laboratory markers alone, without concomitant clinical signs, should not automatically trigger substantial intensification of immunosuppression. Some patients do not fare well when glucocorticoids are discontinued, which may indicate continuous, smoldering disease activity.

The doses of glucocorticoids used to treat polymyalgia rheumatica are much lower than those used for the treatment of giant-cell arteritis.5 In the majority of patients, a dose of 15 to 20 mg of prednisone per day is sufficient to control myalgias. Clinical findings should be used to guide a slow tapering of glucocorticoids (Fig. 2B). The BSR recommendations suggest the administration of 10 to 15 mg of prednisolone daily over a period of about 10 weeks, followed by a slow taper.31 Recurrent myalgias are common and require dose adjustment. Repetitive flares should prompt diagnostic reassessment, including evaluation for full-blown giant-cell arteritis and for nonvasculitic conditions.34 The use of glucocorticoids calls for careful monitoring for adverse effects, especially with the prolonged use of supraphysiologic doses. During a 10-year follow-up of a population-based cohort of patients with giant-cell arteritis,
more than 80% had at least one complication related to glucocorticoid treatment.\textsuperscript{34} Patients must be monitored for hypertension, hyperglycemia, and bone loss. Measures that are protective against bone loss should be provided.\textsuperscript{35} Prophylaxis against 	extit{Pneumocystis jirovecii} pneumonia should be considered in patients receiving doses of prednisone of 20 mg or more daily.\textsuperscript{36} Physical activity and, if indicated, physical therapy aid in maintaining muscle strength and minimizing the side effects of glucocorticoids. Efforts should be made to minimize the duration of treatment and the cumulative glucocorticoid dose.

**Glucocorticoid-Sparing Therapy**

No glucocorticoid-sparing agents have been approved for the treatment of giant-cell arteritis or polymyalgia rheumatica. Retrospective case series and open-label trials have not shown responses to other immunosuppressive agents that are similar to those obtained with glucocorticoids. Despite the lack of rigorous data, a broad spectrum of secondary agents are used in patients with giant-cell arteritis. These include infliximab, methotrexate, cyclophosphamide, azathioprine, and antimalarial agents.\textsuperscript{37} The findings of a recent meta-analysis of 10 studies with a total of 638 participants indicate that the use of immunosuppressive agents in addition to glucocorticoids did not improve therapeutic efficacy or safety as compared with the use of glucocorticoids alone,\textsuperscript{38} raising doubts about whether such adjunctive therapy is appropriate.

Recommendations from the EULAR include the use of methotrexate as a potential adjunct to glucocorticoids in patients with large-vessel vasculitis,\textsuperscript{32} but supporting evidence is limited. A meta-analysis of three placebo-controlled randomized trials involving patients with newly diagnosed giant-cell arteritis showed that a regimen of glucocorticoid therapy plus methotrexate as compared with glucocorticoids alone conferred a significant but modest benefit in lowering the relapse rate and in reducing the cumulative dose of glucocorticoids, without reducing the side effects of the glucocorticoids.\textsuperscript{39} Data supportive of the adjunctive use of other immunosuppressive agents are even more limited. In a small randomized, controlled trial, the administration of 2 mg of azathioprine per kilogram per day modestly reduced requirements for glucocorticoid therapy in patients with giant-cell arteritis and polymyalgia rheumatica.\textsuperscript{40} Whereas open-label studies of anti-tumor necrosis factor (TNF) agents initially suggested a benefit,\textsuperscript{41} subsequent placebo-controlled, randomized trials have not supported the use of TNF blockers as glucocorticoid-sparing agents in patients with giant-cell arteritis or polymyalgia rheumatica.\textsuperscript{42,43}

Therapy targeted at disrupting the function of interleukin-6 is currently undergoing clinical testing. In a series of patients with large-vessel vasculitis, including five patients with giant-cell arteritis, treatment with the interleukin-6 receptor antagonist tocilizumab at a dose of 8 mg per kilogram per month resulted in rapid suppression of systemic inflammation.\textsuperscript{44} However, it is not certain whether interleukin-6 blockade is effective for the treatment of vascular inflammation. In one patient with large-vessel vasculitis who had a clinical response to tocilizumab, persistent vasculitis was identified at autopsy.\textsuperscript{45}

**Other Therapies**

Aspirin (75 to 150 mg per day), which is used in other high-risk populations to reduce the risk of cardiovascular events, has been suggested as a possible means of reducing the risk of ischemic complications of giant-cell arteritis, but data from randomized trials showing a benefit in this patient population are lacking. If indicated, gastroduodenal mucosal protection should be added whenever aspirin is used. Whereas hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) reduce inflammation, there are no data supporting their use in the management of giant-cell arteritis or polymyalgia rheumatica. Observational data indicate a similar disease course and similar requirements for glucocorticoid therapy in patients who do and those who do not take statins.\textsuperscript{46}

### A R E A S O F U N C E R T A I N T Y

Validated diagnostic criteria for giant-cell arteritis and polymyalgia rheumatica are not available. The diagnosis of polymyalgia rheumatica is particularly challenging, since objective and disease-specific findings are often absent. Randomized trials are needed to determine the best course of treatment for both conditions. The role of imaging studies in diagnosis and follow-up has been insufficiently defined.

Giant-cell arteritis and polymyalgia rheumatica are now recognized as chronic conditions. Often, inflammatory markers remain abnormally elevated, even after a 2-year treatment course.\textsuperscript{22} The best way to manage the postacute phase of disease remains to be determined. It is not clear whether...
The coexistence of several vasculogenic immune abnormalities has complicated the development of new, glucocorticoid-sparing therapies. Current therapy offers prompt suppression of some inflammatory pathways, but resistant pathways sustain chronic vascular remodeling.

**Disclosures.**

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

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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