CLINICAL PRACTICE

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Giant-Cell Arteritis and Polymyalgia Rheumatica

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

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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.[1] 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.[2] Vasculitis leads to luminal occlusion and therefore ischemic complications, such as ischemic optic neuropathy, which causes vision loss in 10 to 15% of patients.[3] Aortitis can be complicated by dissection and aneurysm formation.[4]

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Polymyalgia rheumatica causes aching and stiffness in selected muscle groups, predominantly in the neck, shoulders, upper arms, and pelvic girdle.[5] 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.[6] Furthermore, the interstitial fluids from painful muscles contain high cytokine levels.[7,8] Typically, these myalgias are associated with robust systemic inflammation, as indicated by markedly elevated levels of acute-phase reactants in the blood.

Giant-cell arteritis and polymyalgia rheumatica have multiple risk factors and pathogenic abnormalities in common.[1,5] 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.

Both giant-cell arteritis and polymyalgia rheumatica are diseases that affect the elderly, with peak incidences at the age of 70 to 80 years[9]; 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.[10] Disease risk varies according to race and geographic region. The incidence

KEY CLINICAL POINTS

GIANT-CELL ARTERITIS AND POLYMYALGIA RHEUMATICA

The immune-mediated diseases giant-cell arteritis and polymyalgia rheumatica occur in patients 50 years of age or older and are now recognized as chronic conditions.

- The diagnosis of giant-cell arteritis should be confirmed on the basis of histologic findings when possible.
- Glucocorticoids are the standard therapy for both giant-cell arteritis and polymyalgia rheumatica, with higher doses used for giant-cell arteritis.
- Disease flares in patients with giant-cell arteritis and polymyalgia rheumatica are common during the tapering of glucocorticoids and often respond to a 10 to 20% increase in dose.
- Arteritic ischemic optic neuropathy, which can result in blindness, should be treated as an emergency and requires prompt diagnosis and initiation of high-dose glucocorticoid therapy.
- In one quarter of patients with giant-cell arteritis, the aorta and its major branches are involved. Large-vessel disease is reliably diagnosed with computed tomography or magnetic resonance imaging.
- Longevity is generally not reduced by giant-cell arteritis or polymyalgia rheumatica, but glucocorticoid treatment often has adverse effects. Patients should be closely monitored, with attention to bone loss and consideration of prophylaxis against pneumocystis pneumonia.

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 vasculitis[15] 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 tree[16] 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 axis[17]; 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.

STRATEGIES AND EVIDENCE

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

(CRP) are common in giant-cell arteritis and polymyalgia rheumatica, as are the presence of thrombocytosis and anemia. In a cohort of 764 patients with suspected giant-cell arteritis who underwent biopsy, with the diagnosis confirmed in 177 patients, the sensitivity of an elevated ESR was 84% and that of an elevated CRP level was 86%; the specificity of these markers was low, however, at 30%. Only 4% of patients with confirmed giant-cell arteritis had both a normal ESR and a normal CRP level at the time of diagnosis.[19] Assessment of inflammatory markers is helpful during diagnostic evaluation and long-term monitoring, but 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.[20-22] 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.[14] 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[6] (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 ^{18}F-fluorodeoxyglucose (^{18}F-FDG) with positron-emission tomography and computed tomography (PET–CT), which detects hypermetabolic cells, has been proposed for quantifying the inflammatory burden.[23] The sensitivity and specificity of this high-cost imaging method for diagnosing and monitoring giant-cell arteritis have not been established. ^{18}F-FDG with PET–CT cannot be relied on to distinguish vasculitis from nonvasculitic inflammatory lesions (e.g., atherosclerotic changes in vessel walls), and its sensitivity for smoldering and treated vasculitis is limited[24]; 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%.[25] 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.[26,27]

In polymyalgia rheumatica, ultrasonography or MRI may identify subacromial, subdeltoid, trochanteric, and cervical bursitis and tenosynovitis of the long biceps head.[5,6] 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.[28]

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.[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,[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.[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).

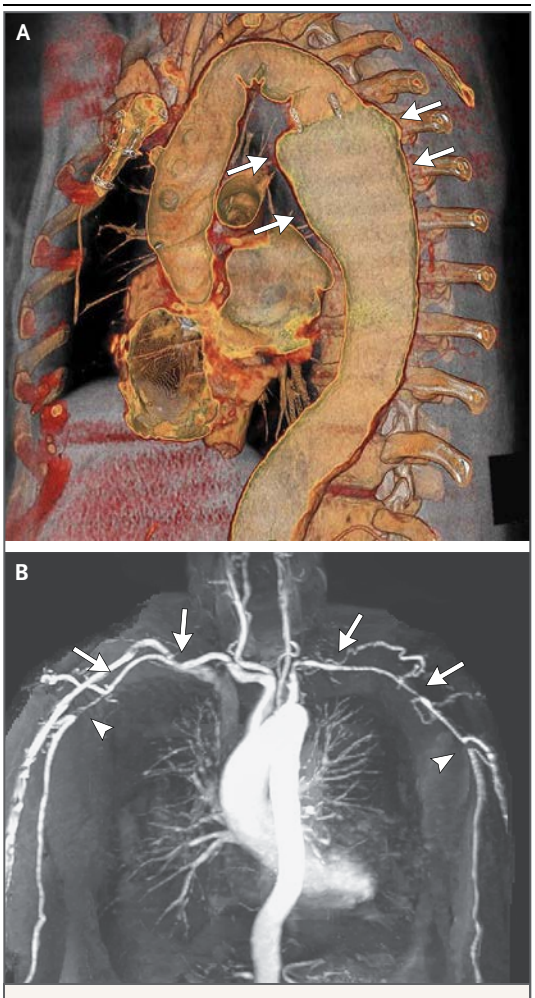

Figure 1. CTA and MRA of the Aortic Arch in Two Patients with Giant-Cell Arteritis.

Computed tomographic angiography (CTA) (Panel A) shows the results of aortic-root repair and aortic-arch replacement with an "elephant trunk graft" in a 71-year-old woman who had biopsy-confirmed giant-cell arteritis. The graft terminates in the proximal descending thoracic aorta. Arrows indicate an aneurysm that is maximally dilated at the proximal descending thoracic aorta. The image was created with data from contiguous axial images reformatted in the sagittal and coronal planes. Contrast-enhanced magnetic resonance angiography (MRA) (Panel B) shows the aortic arch and its branches in a 72-year-old woman with biopsy-positive giant-cell arteritis. Arrows indicate stenotic lesions in the bilateral subclavian and axillary arteries, and arrowheads indicate long-segment occlusions of the proximal brachial arteries. Images courtesy of Dr. D. Fleischmann (Panel A) and Dr. F. Chan (Panel B), Department of Radiology, Stanford University.

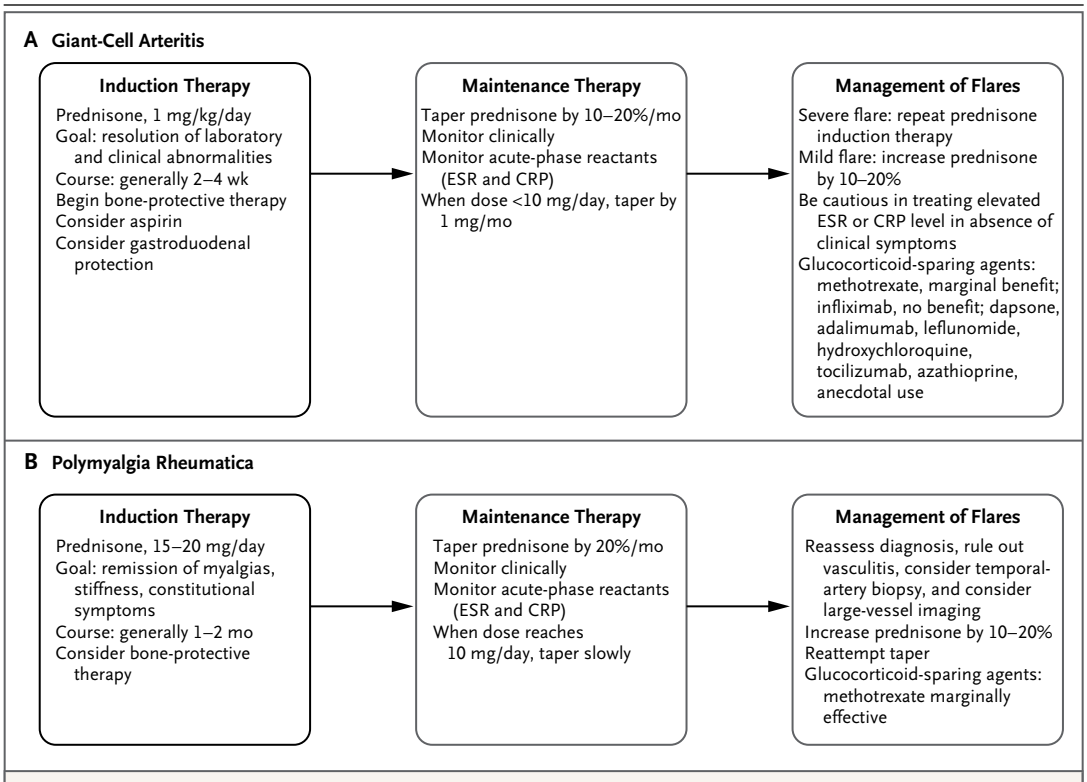

Figure 2. Therapeutic Approaches to Giant-Cell Arteritis and Polymyalgia Rheumatica.

The management of giant-cell arteritis (Panel A) depends on the disease stage. Therapeutic interventions for newly diagnosed disease (induction therapy), chronic disease (maintenance therapy), and disease flares (management of flares) are outlined. Glucocorticoids remain the cornerstone of therapy. Other immunosuppressive agents tested to date provide only marginal or no glucocorticoid-sparing benefits. The management of polymyalgia rheumatica (Panel B) has much lower glucocorticoid dose requirements. CRP denotes C-reactive protein, and ESR erythrocyte sedimentation rate.

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.

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.[34] Patients must be monitored for hypertension, hyperglycemia, and bone loss. Measures that are protective against bone loss should be provided.[35] Prophylaxis against *Pneumocystis jirovecii* pneumonia should be considered in patients receiving doses of prednisone of 20 mg or more daily.[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.[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,[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,[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.[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.[40] Whereas open-label studies of anti–tumor necrosis factor (TNF) agents initially suggested a benefit,[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.[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.[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.[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.[46]

AREAS OF UNCERTAINTY

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.[22] The best way to manage the postacute phase of disease remains to be determined. It is not clear whether

Table 1. Classification Criteria for Giant-Cell Arteritis and Polymyalgia Rheumatica.*

ACR classification criteria for giant-cell arteritis, 1990[47]

At least three criteria must be met:

- Age at disease onset ≥50 yr
- New headache, either new onset or new type of localized pain in the head
- Abnormal temporal artery, with tenderness to palpation or decreased pulsation
- Elevated ESR, >50 mm/hr during first hr of testing (Westergren method)
- Biopsy evidence of vasculitis with predominance of mononuclear-cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

Provisional ACR–EULAR classification criteria for polymyalgia rheumatica, 2012[28]

Mandatory criteria:

- Age ≥50 yr
- Aching in both shoulders
- Abnormal C-reactive protein level, ESR, or both

Additional criteria†

- Morning stiffness lasting >45 min (2 points)
- Hip pain or reduced range of motion (1 point)
- Negative rheumatoid factor or antibodies to cyclic citrullinated peptides (2 points)
- Absence of peripheral synovitis (1 point)
- Ultrasonographic findings
  - At least one shoulder with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis, or at least one hip with synovitis or trochanteric bursitis (1 point)
  - Subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis in both shoulders (1 point)

* ACR denotes American College of Rheumatology, ESR erythrocyte sedimentation rate, and EULAR European League against Rheumatism.

† According to the provisional ACR–EULAR classification criteria for polymyalgia rheumatica, diagnosis requires that in addition to the mandatory criteria, there must be a score of 4 or more points for additional criteria without ultrasonographic findings (diagnostic sensitivity and specificity, 68% and 78%, respectively) and a score of more than 5 points with ultrasonographic findings (diagnostic sensitivity and specificity, 66% and 81% respectively).

more aggressive, longer-term immunosuppression improves outcomes.

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.

GUIDELINES

The American College of Rheumatology (ACR) and the Chapel Hill Consensus Conference have developed criteria to distinguish giant-cell arteritis from other vasculitides (Table 1).[47] The specificity of these criteria for diagnostic purposes in a general population is undetermined. The EULAR and ACR have suggested provisional classification criteria for polymyalgia rheumatica,[28] but even a score of 5 or more (Table 1)[28] has a sensitivity of only 66% and a specificity of only 81% for the purpose of distinguishing polymyalgia rheumatica from nonpolymyalgic rheumatic conditions. The BSR has published guidelines for the management of giant-cell arteritis[31] and polymyalgia rheumatica,[48] and the EULAR has published guidelines for the management of large-vessel vasculitis.[32] The recommendations in this article are generally consistent with the available guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette has biopsy-confirmed giant-cell arteritis, which has responded well to high-dose glucocorticoid therapy and subsequent tapering. As is common in such patients, the patient now presents with symptoms of polymyalgia rheumatica, without evidence of recurrent ischemic manifestations. In this case, the dose of prednisone should be temporarily increased to 10 mg per day to suppress myalgias. Once there are clinical indications of improvement, an attempt should be made to taper the dose again while monitoring the clinical response and levels of inflammatory markers. Additional disease recurrences would raise the possibility of large-vessel involvement, which should be assessed with MRA or CTA. Careful follow-up is required to monitor the patient for any adverse effects of treatment with glucocorticoids.

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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