

Review Article

*Medical Progress***POLYMYALGIA RHEUMATICA
AND GIANT-CELL ARTERITIS**CARLO SALVARANI, M.D., FABRIZIO CANTINI, M.D.,
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POLYMYALGIA rheumatica and giant-cell arteritis are closely related conditions that affect persons of middle age and older and frequently occur together. Many authorities consider them to be different phases of the same disease. Polymyalgia rheumatica is an inflammatory condition of unknown cause characterized by aching and morning stiffness in the cervical region and shoulder and pelvic girdles. It usually responds rapidly to low doses of corticosteroids and has a favorable prognosis.

The first description of polymyalgia rheumatica was provided by Bruce in 1888, who called this condition "senile rheumatic gout," thus emphasizing its occurrence in the elderly.¹ In 1957, Barber proposed the use of the term "polymyalgia rheumatica."² In 1963, Bagratuni outlined the nonerosive articular nature of polymyalgia rheumatica,³ and in the 1990s, diffuse swelling of the hands and edema were reported in some patients.⁴

Giant-cell arteritis is a chronic vasculitis of large and medium-sized vessels. Although it may be widespread, symptomatic vessel inflammation usually involves the cranial branches of the arteries originating from the aortic arch. The first clinical description of giant-cell arteritis was presented by Hutchinson in 1890.⁵ However, it was not reported again until the 1930s, when Horton and colleagues⁶ described the histologic appearance of granulomatous arteritis of the temporal vessels. The relation between polymyalgia rheumatica and giant-cell arteritis was not widely accepted until more than 20 years later, and Paulley and Hughes were among the first to recognize the association.⁷

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**EPIDEMIOLOGY AND DIAGNOSTIC
CRITERIA**

Polymyalgia rheumatica is a common illness in certain populations, with a prevalence of 1 case for every 133 people over the age of 50 years.⁸ Giant-cell arteritis is less frequent than polymyalgia rheumatica. In Olmsted County, Minnesota, the average annual incidence was 17.8 cases per 100,000 persons 50 years of age and older.⁹ However, autopsy studies suggest that giant-cell arteritis may be more common than is clinically apparent.¹⁰ Women are affected twice as often as men.

The incidence of polymyalgia rheumatica and giant-cell arteritis increases after the age of 50 years and peaks between 70 and 80 years of age. Population surveys show higher frequencies of polymyalgia rheumatica and giant-cell arteritis at higher latitudes.^{8,9,11-15} The incidence of polymyalgia rheumatica appears to have been relatively stable in recent years; in contrast, the incidence of giant-cell arteritis appears to have increased. In addition, there is evidence of periodic clustering of cases of giant-cell arteritis.⁹ The mortality rate in patients with polymyalgia rheumatica and giant-cell arteritis is similar to that expected in general populations of similar age and sex, although thoracic aortic aneurysms and dissection of the aorta are important late complications of giant-cell arteritis.¹⁶

The current diagnostic criteria for polymyalgia rheumatica were empirically formulated by Chuang et al.¹⁷ and Healey¹⁸ (Table 1). The two sets of criteria

**TABLE 1. TWO SETS OF DIAGNOSTIC CRITERIA
FOR POLYMYALGIA RHEUMATICA.***

Criteria of Chuang et al., ¹⁷ 1982
Age of 50 years or older
Bilateral aching and stiffness for one month or more and involving two of the following areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs
Erythrocyte sedimentation rate greater than 40 mm/hour
Exclusion of all other diagnoses except giant-cell arteritis
Criteria of Healey, ¹⁸ 1984
Pain persisting for at least one month and involving two of the following areas: neck, shoulders, and pelvic girdle
Morning stiffness lasting more than one hour
Rapid response to prednisone (≤ 20 mg/day)
Absence of other diseases capable of causing the musculoskeletal symptoms
Age of more than 50 years
Erythrocyte sedimentation rate greater than 40 mm/hour

*For each set of criteria, all the findings must be present for polymyalgia rheumatica to be diagnosed.

are similar, the only difference being the inclusion in the Healey criteria of responsiveness to corticosteroids. Criteria for the classification of giant-cell arteritis were formulated by the American College of Rheumatology in 1990 (Table 2).¹⁹ These criteria were designed for use in investigative studies to help distinguish giant-cell arteritis from other types of vasculitis; they are not useful for making the diagnosis in individual patients.²⁰

Temporal-artery biopsy is recommended in all patients who are suspected of having giant-cell arteritis. The inflammatory involvement of affected arteries is often intermittent rather than continuous. If the temporal artery is clearly abnormal on physical examination, only a small specimen needs to be removed for histopathological review. When extracranial arteries are normal on palpation and giant-cell arteritis is suspected, it is important to obtain a biopsy of a longer segment of temporal artery (3 to 5 cm) and consider performing a contralateral biopsy if the results of the first biopsy are normal. We used this approach and found that only 10 percent of patients had negative findings on biopsy.²¹ When possible, temporal-artery biopsy should be performed before treatment is initiated; however, examination of temporal-artery–biopsy specimens may reveal evidence of arteritis after more than two weeks of corticosteroid therapy.²²

Population-based studies of polymyalgia rheumatica have demonstrated the presence of biopsy-proved giant-cell arteritis in 16 to 21 percent of patients.^{8,11} Conversely, symptoms of polymyalgia rheumatica have been observed in 40 to 60 percent of patients with giant-cell arteritis in clinical series.⁹ Polymyalgia rheumatica may thus begin before, at the same time as, or after giant-cell arteritis.

Patients with polymyalgia rheumatica who do not have symptoms of claudication or abnormalities of temporal arteries on examination have a very high probability of having normal findings on biopsy.²³ Consequently, we perform temporal-artery biopsy only in patients with polymyalgia rheumatica who present with cranial symptoms or signs.

PATHOGENESIS

Polymyalgia rheumatica and giant-cell arteritis are probably polygenic diseases in which multiple environmental and genetic factors influence susceptibility and severity. The increased incidence at higher latitudes and in Scandinavian countries and U.S. communities with a strong Scandinavian ethnic background and the occasional familial cases support the evidence suggesting environmental and genetic causes.^{8,9,11-15}

A viral cause has been suspected but not confirmed in polymyalgia rheumatica and giant-cell arteritis. An increased prevalence of antibodies against parainfluenza virus type 1 was reported in patients with polymyalgia rheumatica and giant-cell arteritis.²⁴ A close temporal relation between the observed incidence peaks of polymyalgia rheumatica and giant-cell arteritis and epidemics of *Mycoplasma pneumoniae*, parvovirus B19, and *Chlamydia pneumoniae* infections has been found.¹⁴ However, other studies were unable to find any association between infection and the onset of polymyalgia rheumatica and giant-cell arteritis.²⁵ The epidemiologic evidence that there is a similar cyclic fluctuation (every six to seven years) in the incidence of giant-cell arteritis and parvovirus B19 infection suggests that this virus has a role.⁹ A significant association between histologic evidence of giant-cell

TABLE 2. TRADITIONAL CRITERIA FOR THE CLASSIFICATION OF GIANT-CELL (TEMPORAL) ARTERITIS.*

CRITERION	DEFINITION
Age at onset of disease ≥ 50 yr	Development of symptoms or findings beginning at the age of 50 or older
New headache	New onset of or new type of localized pain in the head
Temporal-artery abnormality	Tenderness of temporal artery to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
Elevated erythrocyte sedimentation rate	Erythrocyte sedimentation rate ≥ 50 mm per hour according to the Westergren method
Abnormal findings on biopsy of temporal artery	Artery-biopsy specimen shows vasculitis characterized by a predominance of mononuclear-cell infiltrates or granulomatous inflammation, usually with multinucleated giant cells

*The criteria were formulated in 1990 by the American College of Rheumatology.¹⁹ For the purposes of classification, a patient with vasculitis is said to have giant-cell (temporal) arteritis if at least three of these five criteria are met. The presence of three or more criteria yields a sensitivity of 93.5 percent and a specificity of 91.2 percent.

arteritis and the presence of parvovirus B19 DNA in temporal-artery specimens has been reported.²⁶

The most commonly studied genetic association is with the genes of the HLA complex. As is the case in rheumatoid arthritis, HLA-DRB1*04 and DRB1*01 alleles are associated with susceptibility to polymyalgia rheumatica and giant-cell arteritis.^{27,28} These alleles may influence the severity of disease.²⁹

A model for the pathogenesis of giant-cell arteritis has been proposed by Weyand and Goronzy.³⁰ Antigen is recognized in the adventitia by T cells that enter the artery through the vasa vasorum, undergo clonal expansion, and are stimulated to produce interferon- γ . This results in the differentiation and migration of macrophages and the formation of giant cells. In the adventitia macrophages produce the inflammatory cytokines interleukin-1 and interleukin-6, whereas in the media and intima, they contribute to arterial injury by producing metalloproteinases and nitric oxide, respectively. This destructive mechanism of the arterial wall is associated with a repair mechanism that includes the secretion of growth and angiogenic factors (platelet-derived growth factor and vascular endothelial growth factor) through the infiltration of mononuclear cells and multinucleated giant cells. These changes ultimately lead to the degradation of the internal elastic lamina and to occlusive luminal hyperplasia.

Variations in the clinical presentation of giant-cell arteritis may be correlated with the expression of cytokine messenger RNA (mRNA) in the affected temporal arteries. Patients with ischemic symptoms have higher concentrations of interferon- γ mRNA and interleukin-1 β mRNA, fever is correlated with low concentrations of interferon- γ , and polymyalgia rheumatica and large-vessel giant-cell arteritis are correlated with the up-regulation of interleukin-2 mRNA.³⁰

In situ production of cytokines can be documented in the temporal arteries of patients with polymyalgia rheumatica who do not have histologic evidence of arteritis, even though these patients do not produce interferon- γ , unlike those with giant-cell arteritis.³¹ These data suggest that a subclinical vasculitis may be present in the temporal arteries of patients with polymyalgia rheumatica and that the production of interferon- γ may be crucial for the development of overt vasculitis.

Recently, studies involving positron-emission tomography have provided evidence of vascular involvement in patients with polymyalgia rheumatica who do not have clinical signs of vasculitis.³²

PATHOLOGICAL FINDINGS

Arthroscopic, radioisotopic, and magnetic resonance imaging (MRI) studies of patients with polymyalgia rheumatica all have indicated the presence of

a synovitis in proximal joints and periarticular structures.³³⁻³⁵ The synovitis associated with polymyalgia rheumatica is histologically mild and is characterized by a predominance of macrophages and T cells, mostly CD4+ helper T cells³³ (Fig. 1A and 1B). These features are very similar to those of the vascular lesions of giant-cell arteritis.³⁶

In giant-cell arteritis, arteries originating from the aortic arch are usually affected by an inflammatory infiltrate associated with marked disruption of the internal elastic lamina. This infiltrate is usually focal and segmental. The classic histologic picture of giant-cell arteritis, observed in 50 percent of the cases, is one of granulomatous inflammation in which giant cells are usually located at the junction between the intima and media (Fig. 1C). The other 50 percent have pan-arteritis with a mixed-cell inflammatory infiltrate that is predominantly composed of lymphomononuclear cells, with occasional neutrophils and eosinophils but without giant cells (Fig. 1D).³⁷ In rare patients the only histologic abnormality may be a small-vessel vasculitis surrounding a normal temporal artery.³⁸

CLINICAL MANIFESTATIONS

Polymyalgia Rheumatica

The combination of persistent pain for at least one month with aching and morning stiffness in the neck, shoulder girdle, and pelvic girdle that lasts at least 30 minutes and an increase in the erythrocyte sedimentation rate to at least 40 mm per hour is strongly suggestive of polymyalgia rheumatica.^{17,18} Patients with polymyalgia rheumatica have bilateral discomfort involving the proximal limb and joint areas. The musculoskeletal pain worsens with movement of the affected area and typically interferes with usual daily activities.

On examination, limitation of active and, often, passive movements of the shoulders due to pain is present. Shoulder pain is the presenting finding in the majority of patients (70 to 95 percent). The hips and neck are less frequently involved (between 50 and 70 percent). In both the shoulder and pelvic girdles the pain usually radiates distally toward the elbows and knees. The discomfort may begin on one side, but it soon becomes bilateral. Systemic symptoms and signs are present in approximately one third of patients and include fever, malaise or fatigue, anorexia, and weight loss. The diagnosis is usually made within two to three months after the onset of symptoms.^{17,39,40}

The prominent and diffuse shoulder discomfort may be due more to periarticular structures than to the glenohumeral joint itself. Physical examination reveals little evidence of swelling or tenderness of proximal joints that could account for the patients' often marked symptoms. An MRI study of patients with polymyalgia rheumatica identified subdeltoid and subacromial

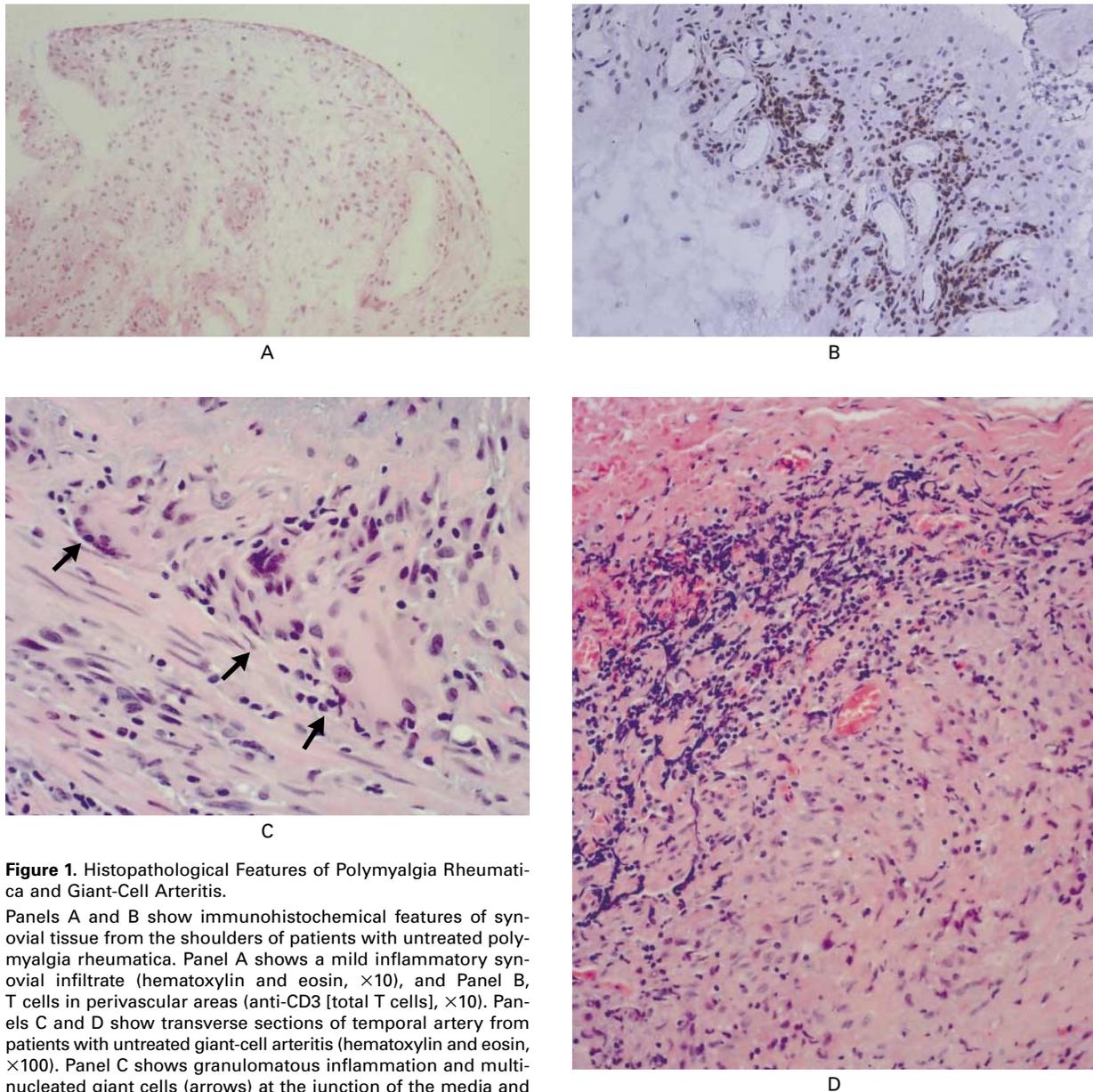


Figure 1. Histopathological Features of Polymyalgia Rheumatica and Giant-Cell Arteritis. Panels A and B show immunohistochemical features of synovial tissue from the shoulders of patients with untreated polymyalgia rheumatica. Panel A shows a mild inflammatory synovial infiltrate (hematoxylin and eosin, $\times 10$), and Panel B, T cells in perivascular areas (anti-CD3 [total T cells], $\times 10$). Panels C and D show transverse sections of temporal artery from patients with untreated giant-cell arteritis (hematoxylin and eosin, $\times 100$). Panel C shows granulomatous inflammation and multinucleated giant cells (arrows) at the junction of the media and intima. Panel D shows a predominantly lymphocytic infiltrate.

bursitis as more prominent and common than joint synovitis and bicipital tenosynovitis³⁵ (Fig. 2).

Distal manifestations are present in about half of the cases.^{4,8,41,42} They include nonerosive, self-limited, asymmetric peripheral arthritis (predominantly affecting the knees and wrists), carpal tunnel syndrome, and swelling and pitting edema of the dorsum of the hands and wrists (Fig. 3A), as well as of the ankles and the tops of the feet.

Giant-Cell Arteritis

The onset of giant-cell arteritis tends to be gradual, but it can be abrupt. Systemic symptoms are present in about half of patients.^{39,43} Although the fever is usually low grade, it can reach 39° to 40°C in about 15 percent of patients and may be the presenting clinical manifestation.⁴⁴

A headache is probably the most frequent symptom and occurs in two thirds of patients.^{39,45} The pain is

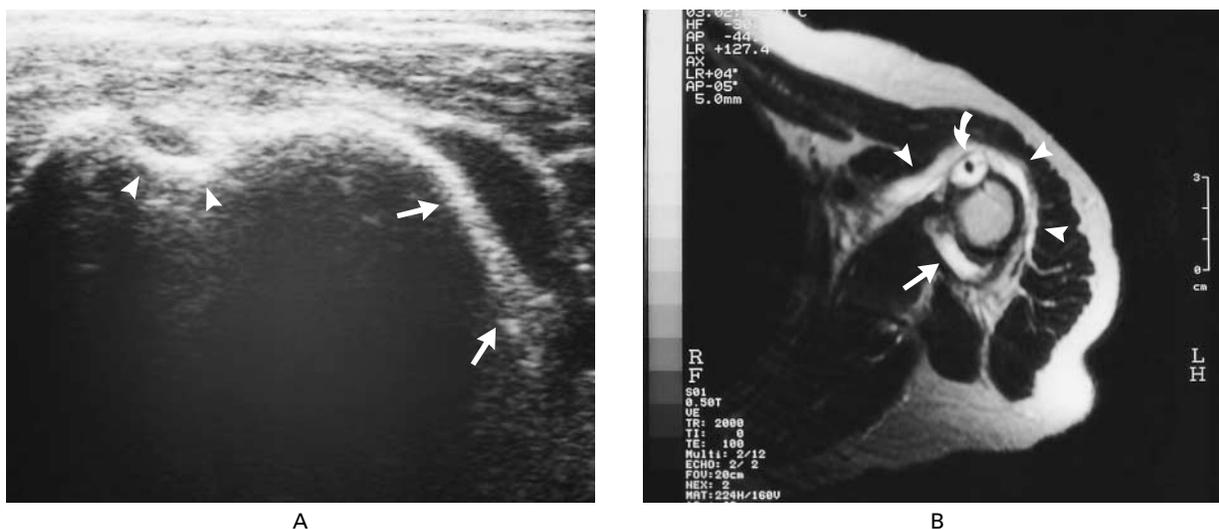


Figure 2. Ultrasonography (Panel A) and Magnetic Resonance Imaging (Panel B) of the Shoulder of a Patient with Untreated Polymyalgia Rheumatica.

In Panel A, ultrasonography reveals the presence of fluid within the subacromial bursa (arrows) and surrounding the long biceps-tendon groove (arrowheads). In Panel B, an axial T₂-weighted section shows subacromial and subdeltoid bursitis (arrowheads), joint effusion (arrow), and tenosynovitis of the long head of the biceps (curved arrow).

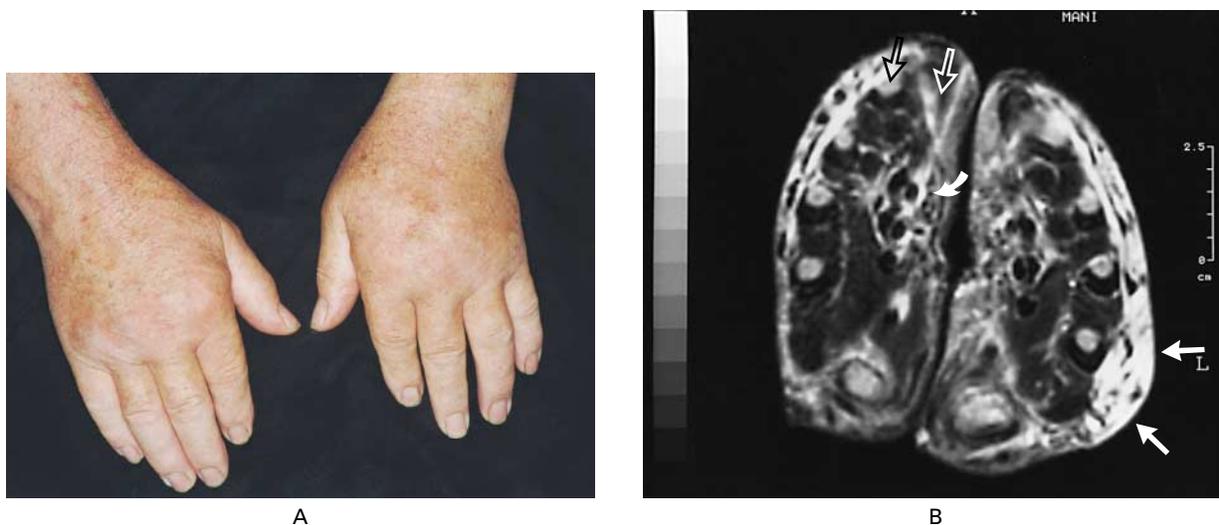


Figure 3. The Hands of a Patient with Untreated Polymyalgia Rheumatica.

Panel A shows bilateral, diffuse swelling of the hands and fingers with pitting edema. Panel B shows a bilateral magnetic resonance image of the patient's hands in a praying position. An axial T₂-weighted section through the midpoint of the palm shows subcutaneous edema in the dorsum (arrows), as well as fluid collection in the extensor synovial sheaths (open arrows) and the flexor synovial sheaths (curved arrow).

frequently marked and tends to be located over the temporal or occipital areas but may be less well defined. Scalp tenderness is usually confined to the temporal and, less commonly, the occipital arteries, but it may be diffuse. It is seen most often in those with headaches.

On physical examination, the frontal or parietal branches of the superficial temporal arteries may be thickened, nodular, tender, or occasionally erythematous (Fig. 4A). Pulses may be decreased or absent. The occipital arteries and, less often, the postauricular or facial arteries may be enlarged or tender. Nearly half of patients suffer from jaw claudication.⁴³ Occasionally, intermittent claudication may occur in the muscles of the tongue or those involved in swallowing. In rare cases, more marked vascular narrowing may lead to infarction of the scalp or the tongue.

Permanent partial or complete loss of vision in one or both eyes occurs in up to 20 percent of patients and is often an early manifestation of the disease.^{43,45-47}

Affected patients typically report partially obscured vision (“a shade covering one eye”), which may progress to total blindness. If untreated, the other eye is likely to become affected within one to two weeks. Once established, visual impairment is usually permanent. Amaurosis fugax is an important visual symptom that precedes permanent visual loss in 44 percent of patients.⁴⁷ Diplopia or visual hallucinations occur less frequently.⁴⁶⁻⁴⁸ Visual loss is caused by ischemia of the optic nerve or tracts as a result of arteritis of the branches of the ophthalmic or posterior ciliary arteries and, less commonly, by occlusion of the retinal arterioles. The early fundusoscopic findings consist of ischemic optic neuritis with a slight pallor and edema of the optic disk and scattered cotton-wool patches and small hemorrhages. These retinal changes usually follow the loss of vision.

Approximately 30 percent of patients have neurologic manifestations.⁴⁹ The most common are neuropathies (14 percent), including mononeuropathies and

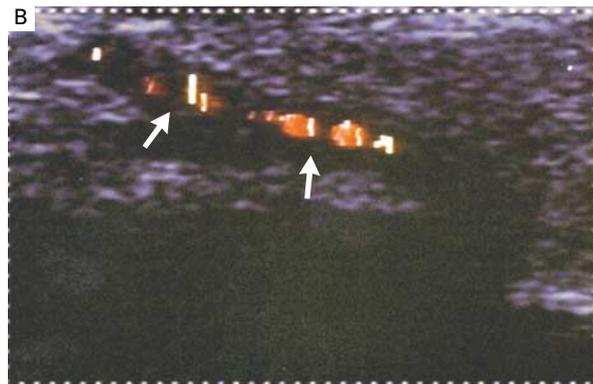


Figure 4. The Temporal Artery of a Patient with Giant-Cell Arteritis.

On physical inspection, a segment of the frontal ramus is thickened, nodular, and tender (Panel A). On color duplex ultrasonographic examination, a hypoechoic, dark halo surrounds the lumen of the temporal artery (arrows), most likely reflecting edema of the vessel wall (Panel B).

peripheral polyneuropathies of the arms or legs.⁵⁰ Less common neurologic findings are transient ischemic attacks or strokes in the territory of the carotid or vertebrbasilar artery.

Respiratory tract findings, including cough with or without sputum, sore throat, and hoarseness, occur in about 10 percent of patients.⁵¹ Musculoskeletal manifestations are common in patients with giant-cell arteritis. Polymyalgia rheumatica is the most frequent, occurring in around 40 percent of patients, but distal symptoms, such as peripheral arthritis and swelling and pitting edema of the hands and feet, may occur in 25 percent of patients.⁵²

In approximately 10 to 15 percent of patients, the branches of the aortic arch, particularly the subclavian and axillary arteries, become narrowed and result in claudication of the arms.⁵³ Bruits may be heard on auscultation over the carotid, subclavian, axillary, and brachial arteries. Pulses in the neck or arms may be decreased or absent. Patients with such symptoms may have few of the usual symptoms of giant-cell arteritis, so the diagnosis may initially be overlooked.

Thoracic aortic aneurysm is 17 times as likely in patients with giant-cell arteritis as in those without the disease.¹⁶ This complication occurs as a late event, usually several years after the diagnosis and often after other symptoms have subsided. The aneurysm may rupture and result in death. A yearly chest radiograph is adequate to screen for thoracic aortic aneurysm.

Laboratory Findings

An erythrocyte sedimentation rate of at least 40 mm per hour is considered an important diagnostic finding in patients with polymyalgia rheumatica. Some studies have reported that 7 to 20 percent of patients with polymyalgia rheumatica have a normal erythrocyte sedimentation rate at the time of diagnosis.⁵⁴ A markedly elevated erythrocyte sedimentation rate is also a hallmark of giant-cell arteritis. The criteria of the American College of Rheumatology include an erythrocyte sedimentation rate of at least 50 mm per hour as one of the five criteria found to be useful in the classification of giant-cell arteritis.¹⁹ However, up to 22.5 percent of patients with giant-cell arteritis have a normal erythrocyte sedimentation rate before treatment.²¹

A recent population-based study from the Mayo Clinic has reported that 5.4 percent of patients had an erythrocyte sedimentation rate of less than 40 mm per hour at diagnosis and that 10.8 percent had an erythrocyte sedimentation rate of less than 50 mm per hour.²¹ Therefore, the finding of a normal erythrocyte sedimentation rate is not incompatible with a diagnosis of active polymyalgia rheumatica or giant-cell arteritis when other clinical findings suggest these diagnoses and should not constitute a reason to delay

corticosteroid therapy if other features of polymyalgia rheumatica or giant-cell arteritis are present.

The C-reactive protein level has been found to be a more sensitive indicator of disease activity than the erythrocyte sedimentation rate both at diagnosis and during relapse.⁵⁴⁻⁵⁶ Levels of interleukin-6 appear to be a sensitive indicator of active disease, but most clinical laboratories do not yet have the means to measure these levels.⁵⁶ Most patients have a mild-to-moderate anemia of chronic disease, and approximately one third of patients have mildly abnormal liver-function tests. Tests for rheumatoid factor and antinuclear antibodies are usually negative.^{17,39,45}

IMAGING

Scintigraphy, MRI, and ultrasonography are all useful in identifying proximal synovitis in patients with polymyalgia rheumatica.^{34,35,57} Ultrasonography and MRI studies have shown that subacromial and subdeltoid bursitis is the most frequent lesion, present in almost all patients with polymyalgia rheumatica (Fig. 2A and 2B), and that these two techniques are equally effective in confirming the presence of bilateral subacromial and subdeltoid bursitis in such patients.⁵⁷ We have found that ultrasonography of the shoulders is sometimes useful to confirm the diagnosis in patients with atypical cases.⁵⁸

MRI has demonstrated that tenosynovitis is the prominent lesion in patients with polymyalgia rheumatica who have swelling and pitting edema of the hands and feet⁵⁹ (Fig. 3B). A role for color duplex ultrasonography in the diagnosis of giant cell arteritis has been proposed by Schmidt et al.,⁶⁰ who found that a dark halo around the lumen of temporal arteries was specific for the diagnosis of giant-cell arteritis (Fig. 4B). However, we found that ultrasonography does not increase the diagnostic accuracy of a careful physical examination⁶¹; therefore, we do not routinely use this technique.

If a diagnosis of extracranial giant-cell arteritis is suspected, arteriography, computed tomography (CT), and magnetic resonance angiography are the required diagnostic tests. On arteriography, the typical finding is bilateral stenosis or occlusion of the subclavian, axillary, and proximal brachial arteries, and these arteries have a smooth, tapered appearance (Fig. 5A). Femoral arteries and their branches are less commonly involved. The best imaging technique to detect aortic aneurysms or dissections is CT (Fig. 5B) or MRI (Fig. 5C). The finding of a thickened aortic wall on CT or MRI is a direct indication of inflammation of the aortic wall (Fig. 5C) and thus of active disease.⁶²

TREATMENT AND COURSE

Corticosteroids are the drug of choice to treat polymyalgia rheumatica and giant-cell arteritis. An initial

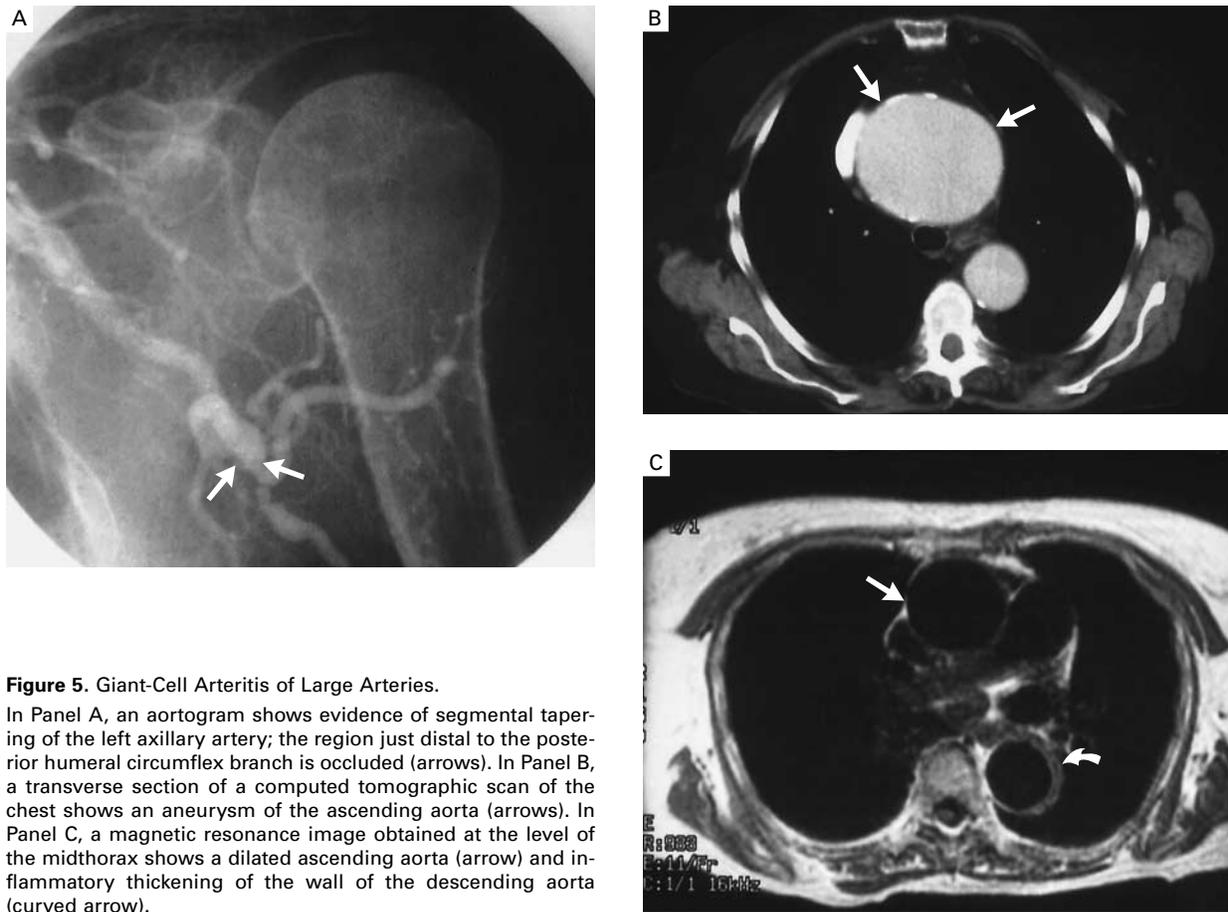


Figure 5. Giant-Cell Arteritis of Large Arteries.

In Panel A, an aortogram shows evidence of segmental tapering of the left axillary artery; the region just distal to the posterior humeral circumflex branch is occluded (arrows). In Panel B, a transverse section of a computed tomographic scan of the chest shows an aneurysm of the ascending aorta (arrows). In Panel C, a magnetic resonance image obtained at the level of the midthorax shows a dilated ascending aorta (arrow) and inflammatory thickening of the wall of the descending aorta (curved arrow).

dose of 10 to 20 mg of prednisone or its equivalent per day is adequate in most cases of polymyalgia rheumatica. Giant-cell arteritis requires an initial dose of prednisone of at least 40 to 60 mg as a single or a divided dose. Initial pulsed intravenous doses of methylprednisolone (1000 mg every day for three days) may be given to patients with recent or impending visual loss. Corticosteroids may prevent but usually do not reverse visual loss.

The response to corticosteroids is rapid, with the resolution of many symptoms after a few days of therapy. A lack of improvement should alert physicians to question the diagnosis. The initial dose of corticosteroids is usually given for two to four weeks; then, it can be gradually reduced each week or every two weeks by a maximum of 10 percent of the total daily dose. If the doses of corticosteroids are reduced or withdrawn too quickly, a relapse or recurrence of symptoms usually occurs. However, about 30 to 50 percent of the patients have spontaneous exacerbations of disease, es-

pecially during the first two years, that are independent of the corticosteroid regimen.^{39,63}

Regular assessment of clinical symptoms, the erythrocyte sedimentation rate, or the C-reactive protein value is the most useful way of monitoring the patients.^{39,54} An isolated finding of an increased erythrocyte sedimentation rate during therapy is not a valid reason to increase the dose of corticosteroids. A treatment course of one to two years is often required. However, some patients have a more chronic, relapsing course and may require low doses of corticosteroid for several years.^{39,54,63,64} No consistently reliable predictors of the duration of corticosteroid therapy have been found. One study suggested that measurement of interleukin-6 levels after four weeks of therapy was helpful in identifying patients with more severe disease.⁵⁶ Corticosteroid-related adverse events are common. A long-term follow up study found that 65 percent of patients with polymyalgia rheumatica had at least one adverse event.⁶⁵ The risks of diabetes

mellitus and osteoporotic fractures were two to five times as great among patients with polymyalgia rheumatica as among persons of similar age from the same population. Increasing age at diagnosis, a cumulative dose of prednisone of at least 2 g, and female sex independently increased the risk of adverse events. In a 15-year survey, 58 percent of patients with temporal arteritis had serious corticosteroid-related complications, and these complications were more frequent among patients over 75 years of age and among those given an initial dose of prednisone of more than 40 mg per day.⁶⁶

Calcium and vitamin D supplementation should be given with corticosteroid therapy in all patients with polymyalgia rheumatica or giant-cell arteritis. In patients with reduced bone mineral density, bisphosphonates are indicated.⁶⁷

In studies of cytotoxic agents, methotrexate has been used as a corticosteroid-sparing drug in patients with polymyalgia rheumatica and giant-cell arteritis, with conflicting results.^{68,69} However, this drug may be given to patients who need high doses of corticosteroids to control active disease and who have serious side effects. Alternate-day oral corticosteroid therapy is generally less effective in suppressing symptoms of polymyalgia rheumatica and giant-cell arteritis than is daily administration.⁷⁰

DIFFERENTIAL DIAGNOSIS

A wide variety of conditions may mimic polymyalgia rheumatica.⁷¹ When present, distal-limb symptoms may initially make it difficult to differentiate polymyalgia rheumatica from rheumatoid arthritis or other, similar syndromes. Pronounced symmetric involvement of peripheral joints, seropositivity for rheumatoid factor, and the development of joint erosions and extra-articular manifestations clearly differentiate rheumatoid arthritis from polymyalgia rheumatica. It may be difficult to differentiate polymyalgia rheumatica with swelling and edema of the hands and feet from the uncommon syndrome of remitting seronegative, symmetric synovitis with pitting edema (RS3PE).^{4,59,72} The latter condition is characterized by the acute onset of bilateral, diffuse, symmetric swelling of the wrists and hands associated with marked, pitting edema of the dorsum of the hands and, less frequently, of the feet.⁷² Affected patients are persistently seronegative for rheumatoid factor and do not have rheumatoid arthritis. Articular symptoms of RS3PE respond rapidly to small doses of corticosteroid. MRI of the hands and feet has shown tenosynovitis to be the cause of diffuse swelling in some cases of RS3PE.⁵⁹ Some studies have suggested that polymyalgia rheumatica and RS3PE are part of the clinical spectrum of the same disease.⁴²

In the elderly, systemic lupus erythematosus may

sometimes present as polymyalgia rheumatica.⁷³ The presence of pleuritis or pericarditis (which are common in late-onset systemic lupus erythematosus), leukopenia or thrombocytopenia, and antinuclear antibodies should raise the clinical suspicion of systemic lupus erythematosus. The predominant proximal muscular weakness demonstrated with movement, rather than pain and an increase in muscular enzyme levels, differentiate polymyositis from polymyalgia rheumatica.⁷⁴

The presence of peripheral enthesitis, dactylitis, anterior uveitis, and radiologic evidence of sacroiliitis differentiate late-onset spondyloarthropathy from polymyalgia rheumatica.⁷⁵ The younger age at the onset of symptoms, the presence of other, related conditions, such as irritable bowel syndrome, the presence of multiple, small, localized areas of muscle tenderness ("trigger points"), and a normal erythrocyte sedimentation rate clearly differentiate fibromyalgia from polymyalgia rheumatica.

Bacterial endocarditis and solid-organ cancers (of the kidneys, ovaries, or stomach) or hematologic (myeloma) cancers may also cause conditions mimicking polymyalgia rheumatica.⁷¹ The lack of an adequate response to prednisone and the presence of atypical features (the absence of the accentuation of symptoms with motion, the absence of morning stiffness or the presence of minimal stiffness, and a diffuse pattern of aches) should suggest the need for further investigations. In patients with typical signs and symptoms of polymyalgia rheumatica, a systemic search for occult cancer or infection is not routinely advised.

Primary systemic amyloidosis may have features mimicking polymyalgia rheumatica, giant-cell arteritis, or both.⁷⁶ In patients with a monoclonal band on immunoelectrophoresis who have no response to corticosteroid therapy, staining of temporal-artery specimens for amyloid should be performed.

Generally, there is little difficulty in distinguishing giant-cell arteritis from other types of vasculitis, because of the difference in the distribution of lesions, histopathological findings, and organ involvement. The histopathological and radiographic findings of giant-cell arteritis may sometimes be indistinguishable from those observed in Takayasu's arteritis or isolated angiitis of the central nervous system. The age at onset and the distribution of lesions allow the proper diagnosis to be made.

FUTURE PERSPECTIVES

Standardized diagnostic and classification criteria are needed for polymyalgia rheumatica. We believe that ultrasonographic evidence of bilateral shoulder bursitis and elevated C-reactive protein levels could be included as diagnostic criteria. Some studies have shown that serum levels of interleukin-6 are persistently in-

creased in patients with polymyalgia rheumatica or giant-cell arteritis after months of corticosteroid treatment, despite the rapid control of symptoms. Future studies will clarify whether this marker of inflammation can be used to monitor disease activity and to gauge the rate of reduction in the corticosteroid dose.

Large, multicenter, randomized, double-blind, placebo-controlled studies are required to define the role of methotrexate or other immunosuppressants as corticosteroid-sparing drugs in polymyalgia rheumatica and giant-cell arteritis. A recent pilot study found that infliximab was efficacious in patients with corticosteroid-resistant giant-cell arteritis.⁷⁷ Finally, a better understanding of the molecular mechanisms involved in the pathogenesis of polymyalgia rheumatica and giant-cell arteritis should provide targets for therapy as well as help determine whether there is a relation between these two conditions and an infectious cause or triggering mechanism.

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REFERENCES

- Bruce W. Senile rheumatic gout. *Br Med J* 1888;2:811-3.
- Barber HS. Myalgic syndrome with constitutional effects: polymyalgia rheumatica. *Ann Rheum Dis* 1957;16:230-7.
- Bagratuni L. Prognosis in the anarthritic rheumatoid syndrome. *BMJ* 1963;1:513-8.
- Salvarani C, Gabriel S, Hunder GG. Distal extremity swelling with pitting edema in polymyalgia rheumatica: report on nineteen cases. *Arthritis Rheum* 1996;39:73-80.
- Hutchinson J. On a peculiar form of thrombotic arteritis of the aged which is sometimes productive of gangrene. *Arch Surg* 1890;1:323-9.
- Horton BT, Magath TB, Brown GE. An undescribed form of arteritis of the temporal vessels. *Proc Mayo Clin* 1932;7:700-1.
- Paulley JW, Hughes JP. Giant-cell arteritis, or arteritis of the aged. *BMJ* 1960;2:1562-7.
- Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. Epidemiology of polymyalgia rheumatica in Olmsted County, Minnesota, 1970-1991. *Arthritis Rheum* 1995;38:369-73.
- Idem*. The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. *Ann Intern Med* 1995;123:192-4.
- Östberg G. An arteritis with special reference to polymyalgia arteritica. *Acta Pathol Microbiol Scand [A]* 1973;237(Suppl):1-59.
- Franzén P, Sutinen S, von Knorring J. Giant cell arteritis and polymyalgia rheumatica in a region of Finland: an epidemiologic, clinical and pathologic study, 1984-1988. *J Rheumatol* 1992;19:273-6.
- Gonzalez-Gay MA, Alonso MD, Aguero JJ, Bal M, Fernandez-Cambor B, Sanchez-Andrade A. Temporal arteritis in a northwestern area of Spain: study of 57 biopsy proven patients. *J Rheumatol* 1992;19:277-80.
- Noltorp S, Svensson B. High incidence of polymyalgia rheumatica and giant cell arteritis in a Swedish community. *Clin Exp Rheumatol* 1991;9:351-5.
- Elling P, Olsson AT, Elling H. Synchronous variations of the incidence of temporal arteritis and polymyalgia rheumatica in different regions of Denmark: association with epidemics of *Mycoplasma pneumoniae* infection. *J Rheumatol* 1996;23:112-9.
- Salvarani C, Macchioni PL, Zizzi F, et al. Epidemiologic and immunogenetic aspects of polymyalgia rheumatica and giant cell arteritis in northern Italy. *Arthritis Rheum* 1991;34:351-6.
- Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis. *Ann Intern Med* 1995;122:502-7.
- Chuang T-Y, Hunder GG, Ilstrup DM, Kurland LT. Polymyalgia rheumatica: a 10-year epidemiologic and clinical study. *Ann Intern Med* 1982;97:672-80.
- Healey LA. Long-term follow-up of polymyalgia rheumatica: evidence for synovitis. *Semin Arthritis Rheum* 1984;13:322-8.
- Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990;33:1122-8.
- Rao JK, Allen NB, Pincus T. Limitations of the 1990 American College of Rheumatology classification criteria in the diagnosis of vasculitis. *Ann Intern Med* 1998;129:345-52.
- Salvarani C, Hunder GG. Giant cell arteritis with low erythrocyte sedimentation rate: frequency of occurrence in a population-based study. *Arthritis Rheum* 2001;45:140-5.
- Achkar AA, Lie JT, Hunder GG, O'Fallon WM, Gabriel SE. How does previous corticosteroid treatment affect the biopsy findings in giant cell (temporal) arteritis? *Ann Intern Med* 1994;120:987-92.
- Gabriel SE, O'Fallon MW, Achkar AA, Lie TT, Hunder GG. The use of clinical characteristics to predict the results of temporal artery biopsy among patients with suspected giant cell arteritis. *J Rheumatol* 1995;22:93-6.
- Duhaut P, Bosshard S, Calvet A, et al. Giant cell arteritis, polymyalgia rheumatica, and viral hypotheses: a multicenter, prospective case-control study. *J Rheumatol* 1999;26:361-9.
- Narvaez J, Clavaguera MT, Nolla-Sole JM, Valverde-Garcia J, Roig-Escofet D. Lack of association between infection and onset of polymyalgia rheumatica. *J Rheumatol* 2000;27:953-7.
- Gabriel SE, Espy M, Erdman DD, Bjornsson J, Smith TF, Hunder GG. The role of parvovirus B19 in the pathogenesis of giant cell arteritis: a preliminary evaluation. *Arthritis Rheum* 1999;42:1255-8.
- Weyand CM, Hunder NN, Hicok KC, Hunder GG, Goronzy JJ. HLA-DRB1 alleles in polymyalgia rheumatica, giant cell arteritis, and rheumatoid arthritis. *Arthritis Rheum* 1994;37:514-20.
- Haworth S, Ridgeway J, Stewart I, Dyer PA, Pepper L, Ollier W. Polymyalgia rheumatica is associated with both HLA-DRB1*0401 and DRB1*0404. *Br J Rheumatol* 1996;35:632-5.
- Salvarani C, Boiardi L, Mantovani V, et al. HLA-DRB1 alleles associated with polymyalgia rheumatica in northern Italy: correlation with disease severity. *Ann Rheum Dis* 1999;58:303-8.
- Weyand CM, Goronzy JJ. Arterial wall injury in giant cell arteritis. *Arthritis Rheum* 1999;42:844-53.
- Weyand CM, Hicok KC, Hunder GG, Goronzy JJ. Tissue cytokine patterns in patients with polymyalgia rheumatica and giant cell arteritis. *Ann Intern Med* 1994;121:484-91.
- Blockmans D, Maes A, Stroobants S, et al. New arguments for a vasculitic nature of polymyalgia rheumatica using positron emission tomography. *Rheumatology (Oxford)* 1999;38:444-7.
- Meliconi R, Pulsatelli L, Ugucioni M, et al. Leukocyte infiltration in synovial tissue from the shoulder of patients with polymyalgia rheumatica: quantitative analysis and influence of corticosteroid treatment. *Arthritis Rheum* 1996;39:1199-207.
- O'Duffy JD, Wahner HW, Hunder GG. Joint imaging in polymyalgia rheumatica. *Mayo Clin Proc* 1976;51:519-24.
- Salvarani C, Cantini F, Olivieri I, et al. Proximal bursitis in active polymyalgia rheumatica. *Ann Intern Med* 1997;127:27-31.
- Cid MC, Campo E, Ercilla G, et al. Immunohistochemical analysis of lymphoid and macrophage cell subsets and their immunological activation markers in temporal arteritis: influence of corticosteroid treatment. *Arthritis Rheum* 1989;32:884-93.
- Lie JT. Illustrated histopathologic classification criteria for selected vasculitis syndromes. *Arthritis Rheum* 1990;33:1074-87.
- Esteban M-J, Font C, Hernandez-Rodriguez J, et al. Small-vessel vasculitis surrounding a spared temporal artery: clinical and pathological findings in a series of twenty-eight patients. *Arthritis Rheum* 2001;44:1387-95.
- Salvarani C, Macchioni PL, Tartoni PL, et al. Polymyalgia rheumatica and giant cell arteritis: a 5-year epidemiologic and clinical study in Reggio Emilia, Italy. *Clin Exp Rheumatol* 1987;5:205-15.
- Salvarani C, Macchioni L, Boiardi L. Polymyalgia rheumatica. *Lancet* 1997;350:43-7.
- Salvarani C, Cantini F, Macchioni L, et al. Distal musculoskeletal manifestations in polymyalgia rheumatica: a prospective follow-up study. *Arthritis Rheum* 1998;41:1221-6.

42. Salvarani C, Cantini F, Olivieri I, Hunder GG. Polymyalgia rheumatica: a disorder of extraarticular synovial structures? *J Rheumatol* 1999;26:517-21.
43. Calamia KT, Hunder GG. Clinical manifestations of giant cell (temporal) arteritis. *Clin Rheum Dis* 1980;6:389-403.
44. *Idem*. Giant cell arteritis (temporal arteritis) presenting as fever of undetermined origin. *Arthritis Rheum* 1981;24:1414-8.
45. Huston KA, Hunder GG, Lie JT, Kennedy RH, Elveback LR. Temporal arteritis: a 25-year epidemiologic, clinical, and pathologic study. *Ann Intern Med* 1978;88:162-7.
46. Aiello PD, Trautmann JC, McPhee TJ, Kunselman AR, Hunder GG. Visual prognosis in giant cell arteritis. *Ophthalmology* 1993;100:550-5.
47. Gonzalez-Gay MA, Blanco R, Rodriguez-Valverde V, et al. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. *Arthritis Rheum* 1998;41:1497-504.
48. Neshet G, Neshet R, Rozenman Y, Sonnenblick M. Visual hallucinations in giant cell arteritis: association with visual loss. *J Rheumatol* 2001;28:2046-8.
49. Caselli RJ, Hunder GG, Whisnant JP. Neurologic disease in biopsy-proven giant cell (temporal) arteritis. *Neurology* 1988;38:352-9.
50. Caselli RJ, Daube JR, Hunder GG, Whisnant JP. Peripheral neuropathic syndromes in giant cell (temporal) arteritis. *Neurology* 1988;38:685-9.
51. Larson TS, Hall S, Hepper NG, Hunder GG. Respiratory tract symptoms as a clue to giant cell arteritis. *Ann Intern Med* 1984;101:594-7.
52. Salvarani C, Hunder GG. Musculoskeletal manifestations in a population-based cohort of patients with giant cell arteritis. *Arthritis Rheum* 1999;42:1259-66.
53. Klein RG, Hunder GG, Stanson AW, Sheps SG. Large artery involvement in giant cell (temporal) arteritis. *Ann Intern Med* 1975;83:806-12.
54. Cantini F, Salvarani C, Olivieri I, et al. Erythrocyte sedimentation rate and C-reactive protein in the evaluation of disease activity and severity in polymyalgia rheumatica: a prospective follow-up study. *Semin Arthritis Rheum* 2000;30:17-24.
55. Hayreh SS, Podhajsky PA, Raman R, Zimmerman B. Giant cell arteritis: validity and reliability of various diagnostic criteria. *Am J Ophthalmol* 1997;123:285-96.
56. Weyand CM, Fulbright JW, Evans JM, Hunder GG, Goronzy JJ. Corticosteroid requirements in polymyalgia rheumatica. *Arch Intern Med* 1999;159:577-84.
57. Cantini F, Salvarani C, Olivieri I, et al. Shoulder ultrasonography in the diagnosis of polymyalgia rheumatica: a case-control study. *J Rheumatol* 2001;28:1049-55.
58. Cantini F, Salvarani C, Olivieri I, et al. Inflamed shoulder structures in polymyalgia rheumatica with normal erythrocyte sedimentation rate. *Arthritis Rheum* 2001;44:1155-9.
59. Cantini F, Salvarani C, Olivieri I, et al. Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome: a prospective follow up and magnetic resonance imaging study. *Ann Rheum Dis* 1999;58:230-6.
60. Schmidt WA, Kraft HE, Vorpahl K, Völker L, Gromnica-Ihle EJ. Color duplex ultrasonography in the diagnosis of temporal arteritis. *N Engl J Med* 1997;337:1336-42.
61. Salvarani C, Silingardi M, Ghirarduzzi A, et al. Is duplex ultrasonography useful for the diagnosis of temporal arteritis? *Ann Intern Med* (in press).
62. Stanson AW. Imaging findings in extracranial (giant cell) temporal arteritis. *Clin Exp Rheumatol* 2001;18:Suppl 20:S43-S48.
63. Andersson R, Malmvall B-E, Bengtsson B-A. Long-term corticosteroid treatment in giant cell arteritis. *Acta Med Scand* 1986;220:465-9.
64. Ayoub WT, Franklin CM, Torretti D. Polymyalgia rheumatica: duration of therapy and long-term outcome. *Am J Med* 1985;79:309-5.
65. Gabriel SE, Sunku J, Salvarani C, O'Fallon WM, Hunder GG. Adverse outcomes of anti-inflammatory therapy among patients with polymyalgia rheumatica. *Arthritis Rheum* 1997;40:1873-8.
66. Neshet G, Sonnenblick M, Friedlander Y. Analysis of steroid related complications and mortality in temporal arteritis: a 15-year survey of 43 patients. *J Rheumatol* 1994;21:1283-6.
67. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. *N Engl J Med* 1998;339:292-9.
68. van der Veen MJ, Dinant HJ, van Booma-Frankfort C, van Albeda-Kuipers GA, Bijlsma JW. Can methotrexate be used as a steroid sparing agent in the treatment of polymyalgia rheumatica and giant cell arteritis? *Ann Rheum Dis* 1996;55:218-23. [Erratum, *Ann Rheum Dis* 1996;55:563.]
69. Jover JA, Hernandez-Garcia C, Morado IC, Vargas E, Banares A, Fernandez-Gutierrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;134:106-14.
70. Hunder GG, Sheps SG, Allen GL, Joyce JW. Daily and alternate-day corticosteroid regimens in treatment of giant cell arteritis: comparison in a prospective study. *Ann Intern Med* 1975;82:613-8.
71. Gonzalez-Gay MA, Garcia-Porrúa C, Salvarani C, Olivieri I, Hunder GG. The spectrum of conditions mimicking polymyalgia rheumatica in northwestern Spain. *J Rheumatol* 2000;27:2179-84.
72. McCarty DJ, O'Duffy JD, Pearson L, Hunter JB. Remitting seronegative symmetrical synovitis with pitting edema: RS3PE syndrome. *JAMA* 1985;254:2763-7.
73. Hutton CW, Maddison PJ. Systemic lupus erythematosus presenting as polymyalgia rheumatica in the elderly. *Ann Rheum Dis* 1986;45:641-4.
74. Hopkinson ND, Shawe DJ, Gumpel JM. Polymyositis, not polymyalgia rheumatica. *Ann Rheum Dis* 1991;50:321-2.
75. Olivieri I, Salvarani C, Cantini F. Remitting distal extremity swelling with pitting edema: a distinct syndrome or a clinical feature of different inflammatory rheumatic diseases? *J Rheumatol* 1997;24:249-52.
76. Salvarani C, Gabriel SE, Gertz MA, Bjornsson J, Li C-Y, Hunder GG. Primary systemic amyloidosis presenting as giant cell arteritis and polymyalgia rheumatica. *Arthritis Rheum* 1994;37:1621-6.
77. Cantini F, Niccoli L, Salvarani C, Padula A, Olivieri I. Treatment of longstanding active giant cell arteritis with infliximab: report of four cases. *Arthritis Rheum* 2001;44:2933-5.

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