CME CREDIT

TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Polymyalgia rheumatica: Clinical presentation is key to diagnosis and treatment

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ABSTRACT

Polymyalgia rheumatica should be considered in the differential diagnosis in patients over 50 years old who present with bilateral achiness and stiffness in the shoulders or hips or both. It usually responds quickly to once-daily, low-dose prednisone, but some patients require treatment for several years. Polymyalgia rheumatica frequently overlaps with giant cell arteritis, and patients must be followed closely for development of complications from this condition, especially aortitis.

DIAGNOSING polymyalgia rheumatica can be likened to the saying, "If it looks like a duck and quacks like a duck, it probably is a duck." Because there is no specific test for the condition, the clinician must keep the diagnosis in mind when the characteristic symptoms and history present in a patient of the right age.

CAUCASIANS OVER 50 AT RISK

Polymyalgia rheumatica is more common in:

- Older age groups (the estimated annual incidence is 12 to 50 per 100,000 people over age 50)
- Scandinavians (the prevalence is 1/133 in Olmsted County, Minnesota)
- Women (2:1 ratio).

INFECTIOUS AND GENETIC CAUSES

The exact cause of the condition is unknown, but there is circumstantial evidence for an infectious trigger—the disease tends to arise in seasonal clusters, and symptoms frequently develop suddenly.

Genetic factors also seem to play a role. The condition is associated with HLA-DR4 antigens, which seem to affect how the body responds immunologically to certain proteins. This is the same haplotype common in patients with rheumatoid factor-positive rheumatoid arthritis, who are more likely to run a severe, progressive course.

If it walks like a duck, it often is a duck

Not rheumatoid arthritis

Although patients with polymyalgia rheumatica may share the DR4 haplotype and sometimes present similarly to those with rheumatoid arthritis, the two conditions seem to be distinct entities. Unlike rheumatoid arthritis, polymyalgia rheumatica does not destroy joints over time and is more likely to go into complete drug-free remission.

DIAGNOSE BY CLINICAL FEATURES

In 1979, Bird et al proposed a set of criteria to diagnose the condition, which included:

- Bilateral pain and stiffness in the shoulders
- Acute or subacute onset (symptoms develop over less than 2 weeks)

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- Elevated erythrocyte sedimentation rate (ESR)
- Morning stiffness lasting longer than 1 hour
- Age over 65 years
- Depression and weight loss
- Bilateral tenderness in arm muscles.

Bird et al also linked giant cell arteritis with the diagnosis of polymyalgia rheumatica. If giant cell arteritis is documented by temporal artery biopsy, they suggested that only one additional criterion is needed to diagnose polymyalgia rheumatica. Although we don't generally use these criteria, the authors nicely defined the features of the disease.

In 1984, Healey[1] proposed a slightly different set of criteria. He required that patients be over 50 years old, be seronegative for rheumatoid factor, and have at least three of the following:

- Neck, shoulder, or pelvic girdle pain
- Morning stiffness
- Elevated ESR
- Rapid response to daily, low doses of a steroid (eg, prednisone ≤ 20 mg).

In the future we might consider additional factors (although no one factor would be sufficient on its own to determine the diagnosis), eg:

- Ultrasonographic evidence of low-level synovitis and/or bursitis in the shoulders or hips
- An elevated blood level of interleukin 6 (IL-6) as an alternative to an elevated ESR or C-reactive protein (CRP) level. In some studies, IL-6 has been found to be a better indicator of active disease than elevated ESR or CRP.

Many patients describe 'a flu that won't go away'

There is no diagnostic test for polymyalgia rheumatica. Instead, we rely on the history and clinical evidence in patients of the right age, and actively exclude disorders that could mimic this disease. In addition, a positive response to low doses of corticosteroids supports the diagnosis—polymyalgia rheumatica tends to dramatically improve within a few days of initiation of corticosteroid therapy.

HALLMARK FEATURES

Age older than 50. Polymyalgia rheumatica is unusual in young patients—another diagnosis should be sought in those younger than 50.

Proximal pain and stiffness. Patients typically present with the acute onset of proximal myalgias and stiffness. They describe this in different ways, commonly as the achiness of having "a flu that won't go away."

Polymyalgia rheumatica should be considered in patients who present acutely with unexplained bilateral periarthritis of the shoulder. People rarely develop acute bursitis or rotator cuff tendinitis on both sides unless they have suddenly initiated some unusual physical activity.

Nighttime and morning worsening. Nighttime symptoms are common. Patients often are awakened due to pain and stiffness in the early morning hours. Bed partners often note more restless sleeping or even moaning during sleep.

Normal strength. Objective strength testing should be normal. If weakness is found on physical examination, it is either unrelated to the condition or secondary to discomfort during the examination.

Systemic symptoms. Features of systemic inflammatory disease, such as fatigue, weight loss, fever, and sweats, are often present and can occasionally be striking. In some cases, they appear before proximal pain symptoms develop.

LABORATORY TESTS PROVIDE SECONDARY EVIDENCE

ESR and CRP levels are usually elevated but are normal in up to 20% of patients. A normal value should not dissuade the clinician from entertaining the diagnosis if the clinical picture is otherwise compatible.

Anemia is usually mild.

'Liver enzymes' may have a cholestatic pattern—alkaline phosphatase and gamma-glutamyl transpeptidase levels may be slightly elevated. If transaminase levels are increased, one should measure creatine kinase (CK) in order to exclude polymyositis or other painful myopathies (eg, statin-induced myopathy) that can occasionally mimic polymyalgia rheumatica.

SYNOVITIS OR BURSITIS OR BOTH ARE PRESENT

The pain of polymyalgia rheumatica is probably due to proximal synovitis and/or bursitis.

Evidence of this has been found using tests that are not normally performed in routine clinical practice:

Synovial biopsies of the shoulders of 19 patients with polymyalgia rheumatica[2] revealed low-level synovitis in 17.

Three-phase bone scans in the early uptake phase showed increased vascular flow in the hip and shoulder girdles.

Ultrasound studies showed shoulder or hip effusions in 68% of patients as well as fluid in the subacromial bursa in 96% of patients with polymyalgia rheumatica vs 26% of controls.[3]

Magnetic resonance imaging (MRI) studies of 13 patients with polymyalgia rheumatica revealed evidence of bursitis and synovitis.[4]

UNUSUAL PRESENTATIONS

Polymyalgia rheumatica does not always present classically, with symptoms of the proximal shoulder or hip girdle. Sometimes patients present with synovitis elsewhere.

Peripheral synovitis. Some authors have speculated that peripheral synovitis is a different disease, and that patients with it are less likely to also have giant cell arteritis. These assertions remain, in my mind, preliminary. Rheumatoid arthritis of the elderly with a prominent proximal component should, however, always be considered.

Sternoclavicular synovitis. The sternoclavicular joint is not usually affected in inflammatory diseases, but it is sometimes involved in polymyalgia rheumatica, rheumatoid arthritis, or spondylitis.

Carpal tunnel syndrome. Because the carpal tunnel is such a small canal, it easily fills with synovial fluid or swollen tissue and causes symptoms in many conditions. Mild wrist synovitis associated with polymyalgia rheumatica can cause distal dysesthesias, prompting a search for primary amyloidosis, neuropathy, or radiculopathy.

Distal swelling with pitting edema. Another unusual syndrome is known as RS3PE (remitting seronegative symmetrical synovitis with pitting edema). It presents as the dramatic onset of swelling and pitting edema of both hands and sometimes the feet.

Asymmetric pain. When a patient presents with strikingly asymmetric pain, polymyalgia rheumatica should not be considered as a likely diagnosis. However, such a case may in time prove to be an unusual presentation of the syndrome.

ASSOCIATION WITH GIANT CELL ARTERITIS

Polymyalgia rheumatica and giant cell arteritis are related conditions. About 20% of patients with polymyalgia rheumatica without any symptoms of giant cell arteritis may have biopsy-confirmed giant cell arteritis involving the superficial temporal arteries. Conversely, about 40% of people with known giant cell arteritis have symptoms compatible with polymyalgia rheumatica.

Because the two conditions often overlap, if a physician suspects giant cell arteritis in a patient with new onset of headache or visual symptoms, the presence of symptoms of polymyalgia rheumatica strengthens the clinical diagnosis. Because of this overlap, patients with polymyalgia rheumatica need to be followed as if they have giant cell arteritis. Physicians should be vigilant regarding the development of aortitis or symptoms of aortic branch occlusion.

Polymyalgia rheumatica and giant cell arteritis often overlap

On the other hand, there are no data to justify performing a temporal artery biopsy on a patient with polymyalgia rheumatica who has no clinical indications of giant cell arteritis. Instead, I recommend regular follow-up to detect symptoms or findings of occult giant cell arteritis if they develop.

Pathogenesis of giant cell arteritis

Weyand et al[5] proposed that in giant cell arteritis, recruited T lymphocytes enter from feeder vessels (vasa vasorum) rather than via the lumen, and work their way into the adventitia—the connective tissue layer of the artery. There, some T cells become activated and start a cascade of events involving clonal proliferation. The fact that a specific set of T cells becomes activated suggests that this is an antigen-driven response (although the specific antigen has not been identified).

The activated T cells produce interferon gamma, which leads to the activation and differentiation of macrophages. The macro-

TABLE 1

Conditions that can mimic polymyalgia rheumatica

Bacterial endocarditis
Cervical myelopathy and bilateral radiculopathy
Fibromyalgia/depression
Hepatitis
Hypothyroid myopathy
Malignancy
Myopathic drug reactions—statins, colchicine
Parkinson disease
Polymyositis
Rheumatoid disease
Rotator cuff disease

phages produce other mediators, including nitrous oxide, metalloproteinases, and transforming growth factor beta, which lead to arterial injury in the media, intimal proliferation, and elastic membrane disruption.

Giant cells may form in response to this inflammation in an attempt to repair the damaged artery. The giant cells produce growth factors that may lead to more intimal proliferation, occluding the superficial temporal artery and other vessels downstream, causing the characteristic visual and other ischemic symptoms.

The macrophages also produce IL-1 and IL-6, which may cause the systemic features of the acute inflammatory phase, including fever and wasting and the elevated ESR and CRP.

In polymyositis, weakness is more prominent than pain, CPK is usually elevated, and interstitial lung disease may be present

Macrophages key to relationship

Weyand et al[6] performed biopsies of superficial temporal arteries from 15 patients with biopsy-proven giant cell arteritis, 9 patients with polymyalgia rheumatica without biopsy evidence of vasculitis, and 10 patients with suspected giant cell arteritis who eventually proved to have neither polymyalgia rheumatica nor giant cell arteritis who served as controls. Levels of IL-1, IL-2, and transforming growth factor mRNA were greater in the lesions from patients with giant cell arteritis and polymyalgia rheumatica than from controls. Only patients with giant cell arteritis, however, had significantly elevated interferon gamma and intimal occlusion.

Apparently, while patients with polymyalgia rheumatica may have abnormal vessels, they do not seem to have the complete interferon-mediated inflammatory response that leads to the occlusion that occurs in giant cell arteritis. Why some people get one condition and not the other is unclear—perhaps there is something different about the localization or clearance of the triggering antigen, the individual genetic makeup, or the capacity of an individual to respond to antigenic stimulation in the vessel wall.

MIMICS

Gonzalez-Gay et al[7] studied patients retrospectively who had been diagnosed "incorrectly" with polymyalgia rheumatica. The correct diagnosis was generally found within 3 months of the initial diagnosis and included a broad spectrum of other problems. Red flags indicating the diagnosis was incorrect included continuous pain rather than nighttime and morning worsening, and pain that did not rapidly improve with corticosteroid treatment. Their data also indicate that the clinical diagnosis of polymyalgia rheumatica by experienced clinicians is usually correct.

There are multiple conditions that can mimic polymyalgia rheumatica (TABLE 1).

Distinguishing polymyositis from polymyalgia seems to be particularly confusing for physicians who are infrequently confronted with these diseases. In polymyositis, weakness is more prominent than pain, CK is elevated in most cases, and interstitial lung disease is sometimes present. As is also true for polymyalgia rheumatica, elevated ESR and the presence of anemia or fever do not help determine the specific diagnosis.

"Bilateral rotator cuff disease" is sometimes mistakenly diagnosed and is treated with local steroid injections. The patient typically responds, but then returns wanting another injection. One clue that the real diagnosis is polymyalgia rheumatica is if the patient mentions that a unilateral injection not only helped the shoulder pain but also relieved pains in the hips and thighs (which had not

been previously reported) or in the contralateral arm, due to the systemic effects of absorbed steroid.

TREAT WITH LOW-DOSE STEROIDS

Treatment of polymyalgia rheumatica is low-dose prednisone (10–15 mg in the morning). Some patients with polymyalgia rheumatica will need more than 20 mg a day or rarely even split doses, but one should keep an open mind and suspect another diagnosis if a patient needs more than a small dosage.

When the patient is pain-free and steroid treatment is being tapered, distinguishing between a relapse and steroid withdrawal syndrome can be challenging. There are no laboratory tests to reliably serve as a guide. The corticotropin (ACTH) stimulation test is not useful for diagnosing all steroid withdrawal syndromes because biochemical adrenal insufficiency is not uniformly the pathophysiology of all of these syndromes.

Unproven treatments

"Steroid-sparing" drugs such as methotrexate are not proven to be effective for polymyalgia rheumatica, particularly over the long term.

Nonsteroidal anti-inflammatory drugs may provide a limited response, but the response is usually not complete or lasting.

An initial alternate-day regimen of low-dose glucocorticoids is usually inadequate for the treatment of polymyalgia rheumatica.

FOLLOW COURSE CLINICALLY

The ESR is only somewhat useful for diagnosis and measuring treatment response. A significant percentage of patients have an age-appropriate ESR when diagnosed, and while only half of patients have an elevated ESR during a relapse, nearly half also have increased rates when there is no clinical indication of relapse.[8] Clinical indicators should be the deciding factor to guide treatment.

It is important to monitor for complications of both the disease itself and of steroid therapy over time. The routine care of patients with polymyalgia rheumatica includes:

- Clinical screening for giant cell arteritis. Patients with polymyalgia rheumatica need to be followed as if they had giant cell arteritis: at every examination the physician should ask about eye symptoms and headache, check blood pressure in both arms, and listen for bruits throughout the vasculature.
- Screening for hyperlipidemia and treating it aggressively. The combination of age, underlying vascular disease, and possible vascular inflammatory disease puts patients with polymyalgia rheumatica at high risk.
- Screening for osteoporosis and treating prophylactically if indicated with calcium, vitamin D, and antiresorptive agents.
- Screening for steroid-induced glaucoma and diabetes mellitus.
- Asking about steroid-induced sleep disturbances and mood disorders.
- Screening for development of mucosal candidiasis.

PROGNOSIS AND TREATMENT DURATION VARY

Although textbooks often portray polymyalgia rheumatica as a short, self-limited disease with a favorable outcome, this is not true in many cases. In one study,[9] only about half of patients had symptoms that completely resolved after steroid treatment, and about 10% required steroids for more than 5 years.

In another study, Weyand et al[10] prospectively put 27 patients on a rigidly defined protocol, starting with 20 mg prednisone. If symptoms did not resolve, the dosage was increased incrementally up to 30 mg. If the patient was doing well, the dosage was progressively tapered by 2.5 mg every 2 weeks. A large variation in treatment time was observed—from 18 weeks to more than 800 days. Only 8 patients needed less than a year of treatment; 12 others responded well initially but had remitting disease for longer than 1 year.

Polymyalgia rheumatica should rapidly respond to low oral doses of a steroid

CASE STUDIES

The following case studies illustrate some of the issues discussed.

Case 1: A woman with polymyalgia rheumatica and mid-back pain

A 63-year-old woman was diagnosed with polymyalgia rheumatica after 2 weeks of flu-

like myalgias in the shoulders, neck, and thighs, which were worse during the night and upon awakening. She had no headache, fever, eye symptoms, jaw pain, or scalp tenderness. Her blood pressure was 162/94 mm Hg. Laboratory findings included low-grade anemia and an elevated ESR. She responded dramatically to prednisone 15 mg once daily and was treated for 6 months. When prednisone was tapered to 7.5 mg per day, symptoms returned but were relieved when the dosage was increased to 12.5 mg.

The patient now presents to the emergency room at 3:00 AM with severe mid-back pain and sweating, blood pressure 102/46 mm Hg, and heart rate 134 beats per minute. The pain is constant and cannot be reproduced or worsened with spine pressure or motion. The abdomen is nontender. While in the emergency room she vomits twice. Vomit and stool are heme-negative, urine is normal, and the pulses are intact with bilateral iliac bruits. Her electrocardiogram is unchanged from baseline, hemoglobin is 9.6 mg/dL, and ESR is 42 mm/hour.

Consider the possibility of clinically silent giant cell arteritis

1 Choose the best option:

- ❑ Order a thoracic lumber spine radiograph to look for compression fractures
- ❑ Order magnetic resonance imaging (MRI) of the chest and abdomen
- ❑ Treat with a proton pump inhibitor and request an endoscopy
- ❑ Order amylase and lipase levels, insert a nasogastric tube, and stop oral intake

The second option (MRI) is best. She is at risk for an aortic dissection (which is what she had) because of the possibility of clinically silent giant cell arteritis, which may cause inflammation of large vessels, aneurysms, and dissections. Aortic branch stenoses are, however, more common than dissection of the aorta.

As for the other possibilities, a compression fracture would not be expected to cause hypotension and should be tender on examination. Gastric perforation is possible, including posterior perforation into the pancreas, but the patient has no specific risk factors for this. The MRI scan may assist in this diagnosis as well.

Case 2: A 64-year-old woman with bilateral arm pain

One month ago, a 64 year-old woman presented to her family physician with bilateral arm pain exacerbated by performing housework. She had been treated for polymyalgia rheumatica for 2 years and was still taking prednisone 2.5 mg/day. Until recently, she had felt well and had no nighttime or morning pain.

Electrocardiographic and stress thallium tests are normal, ESR 28 mm/hour, hemoglobin 11.4 mg/dL.

At this time she is seen by a rheumatologist. Her blood pressure is 93 mm Hg by palpation in both arms with bilateral subclavian bruits, a right carotid bruit, and radial and ulnar pulses not palpable. She has a left femoral bruit and barely palpable leg pulses. No bruits or any pulse examination were previously noted in her chart. There is no evidence of synovitis on examination. Ultrasonography and computed tomography of the aorta show no aneurysm.

2 What is the next step in checking for other complications?

- ❑ Perform a retinal eye examination
- ❑ Order an ultrasensitive CRP level
- ❑ Order an echocardiogram
- ❑ Order an aortic arch angiogram

A retinal examination and an aortic arch angiogram are both appropriate. Looking for hypertensive retinopathy can easily and rapidly be performed. We do not know her true blood pressure because of the bilateral subclavian disease. One can have central aortic hypertension that is undetectable because of decreased perfusion in the arms!

At the time of angiography, a central arterial blood pressure must be obtained. Neither a CRP level nor an echocardiogram will provide as much useful information, although the echocardiogram could detect either left ventricular hypertrophy due to chronic hypertension or aortic root dilatation. Older autopsy studies have suggested an extremely high prevalence of inflammatory aortic branch disease in patients with polymyalgia rheumatica or giant cell arteritis.

Case 3: A 76-year-old man with sudden onset of pain and bilateral stiffness

A 76-year-old retired carpenter complains of the sudden onset 7 weeks ago of pain and stiffness bilaterally in the shoulders and knees. The stiffness lasts several hours in the morning. He also complains of mild fatigue. Symptoms are severe enough to limit his ability to wield a hammer and has forced him to stop work as a handyman.

Arthrocentesis of both knees reveals no crystals. Synovial fluid contains white blood cells (42,000 cells/mm^3 on one side, 36,000 on the other) with 48% polymorphonuclear neutrophils and negative cultures.

3 The differential diagnosis includes all of the following except which one?

- ❑ Rheumatoid arthritis
- ❑ Polymyalgia rheumatica
- ❑ Polymyositis
- ❑ Hypothyroidism
- ❑ Hepatitis C infection

Although this is a classic clinical presentation of polymyalgia rheumatica, rheumatoid arthritis can also begin this way and is probably more likely than polymyalgia rheumatica to produce such inflammatory knee effusions. Polymyositis is another possibility, as it may cause arthritis, aching, and pain, and the patient's inability to work may be due to weakness. Hepatitis C infection can mimic polymyalgia rheumatica and rheumatoid arthritis.

The one diagnosis that does not fit is hypothyroidism, which may cause fatigue, myalgias, and arthralgias, but does not cause such inflammatory joint fluid.

4 How can we distinguish rheumatoid arthritis from polymyalgia rheumatica at this early stage?

- ❑ ESR, which is much higher in polymyalgia rheumatica
- ❑ Radiographic studies of the wrists
- ❑ Test for rheumatoid factor
- ❑ Test for antinuclear antibody
- ❑ Check for acute carpal tunnel syndrome with electromyography

Neither the ESR nor the antinuclear antibody titer is specific enough to help determine the diagnosis. Radiographic studies of the wrist to detect erosive disease may be useful later, but are insensitive very early in the course of rheumatoid arthritis. Acute carpal tunnel syndrome could be present in either condition.

Testing for rheumatoid factor is best. If the titer is high, rheumatoid arthritis is the more likely diagnosis, although a high titer can be found in hepatitis C as well. In this case the titer was low: the patient had polymyalgia rheumatica.

Hypothyroidism does not cause such inflammatory joint fluid

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