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Polymyalgia manifestations in different conditions mimicking polymyalgia rheumatica

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ABSTRACT

Polymyalgia rheumatica (PMR) is a generally benign syndrome involving the neck, shoulder, and hip girdles in the elderly. However, none of the clinical and laboratory findings are specific for this syndrome. Different diseases may present with features suggesting PMR. The consideration of other conditions which in some cases resemble PMR is very important, as their therapy and prognosis differ completely from that of PMR. Four patients presenting with typical PMR manifestations, who were finally diagnosed as having conditions very different from PMR, are described. The importance of the differential diagnosis in patients presenting with polymyalgia symptoms is underlined.

Introduction

Polymyalgia rheumatica (PMR) is a common syndrome in people over the age of 50. Symptoms consist of pain, aching and morning stiffness involving the neck, shoulder girdle, and hip girdle which are generally associated with an elevated erythrocyte sedimentation rate (ESR) (1). Polymyalgia rheumatica is generally a benign and self-limited condition. However, none of the clinical and laboratory findings in PMR are specific. Several others diseases may present with similar musculoskeletal aching and the exclusion of these processes is important as their therapy and prognosis differ greatly from the classic therapy used in PMR.

To further alert clinicians of the importance of considering other conditions that in some cases may resemble PMR, we describe 4 patients with typical polymyalgic syndrome that was the presenting manifestation of very different conditions.

Case reports

Case 1

A 59-year-old man presented at the rheumatology outpatient clinic in 1995 because of a 2-month history of pain involving the neck, shoulder and hips along with asthenia and morning stiffness of more than 1 hour. Clinical examination revealed pain in the shoulder and hip girdles but no synovitis was observed. A diagnosis of PMR was made as no symptoms of giant cell arteritis (GCA) were registered. Treatment with 15 mg/day of prednisone was immediately started with a dramatic response after 24 hours of therapy. However, blood tests performed before the onset of therapy disclosed 3,900/mm^3 leukocytes with 1,200/mm^3 lymphocytes and an elevated ESR (45 mm/1st hr).

Despite clinical improvement, because of the presence of lymphopenia and leukocyte values lower than 4,000/mm^3 a more thorough study was performed. ANA were positive at 1/1280 (by immunofluorescence using as substrate Hep2 cells) with a homogeneous pattern. Anti-nDNA antibodies (by indirect immunofluorescence using as substrate Crithidia lucilae) were also positive at 1/640. Complement C4 values were decreased and slight proteinuria (650 mg/24 hr) was also observed. Other analyses including rheumatoid factor, creatine kinase (CPK), and serum protein electrophoresis were normal except for a slight increase of alpha-2-globulins and a polyclonal elevation of the gammaglobulin fraction. A kidney biopsy yielded a focal segmental glomerulonephritis.

A diagnosis of SLE was made and therapy with chloroquine 250 mg/day was started. A detailed clinical history disclosed a possible photosensitive skin rash related to sun exposure that had occurred at the onset of symptoms. Two and a half years after the diagnosis the patient is symptom-free, receiving 2.5 mg/day of prednisone and 250 mg/day of chloroquine. Slight proteinuria (450 mg/24 hr) is still present but no deterioration of renal function has occurred since the diagnosis.

Case 2

A 73-year-old man presented at the emergency unit because of malaise, asthenia and pain in the pelvic and shoulder girdles along with prominent morning stiffness of 5 weeks' duration. Since the onset of symptoms he had noted oral temperatures between 37° and 38° C. On admission his temperature was 37.4° C. He appeared chronically ill and complained of pain on motion of the neck, shoulders and hips as well as tenderness of the shoulders to palpation. A systolic cardiac murmur was noticed. However, there

was no visceral organ enlargement, synovitis, or skin rash. The ESR on admission was 75 mm/1 hr. Other laboratory parameters were unremarkable.

Despite the patient having typical PMR manifestations, his severe malaise seemed disproportionate to the other findings. Other conditions including infection were considered. Cultures (urine, blood, sputum, and feces) were taken. Also, an intracutaneous tuberculin skin test (PPD) and serologic tests for brucella (rose bengal plate agglutination test, seroagglutinations, and Coombs' test) were performed. All the results were initially negative and a chest radiograph was normal. An M-mode echocardiogram did not disclose vegetation and treatment with 15 mg/day of prednisone was started. No improvement was observed after 8 days of therapy. For this reason a temporal artery (TA) biopsy was performed and prednisone was increased to 40 mg/day. However, the TA biopsy was negative.

Sixteen days after admission all the blood cultures that had been taken at the time of admission became positive for *Haemophilus parainfluenzae* biotype II. A two-dimensional echocardiogram was then performed which disclosed vegetation in the mitral valve. In addition, transesophageal echocardiography showed a large vegetal growth on the anterior mitral leaflet. Treatment with prednisone was rapidly tapered and antibiotic treatment with ampicillin was started with a progressive improvement of symptoms. The patient was followed for 2 years at the outpatient clinic without showing any further symptoms of polymyalgia.

Case 3

An 80-year-old man was admitted to hospital in December 1995 because of a 3-month history of asthenia, weight loss, severe pain and morning stiffness of 30 minutes' duration involving especially the shoulder and hip girdles. Five years previously, at the age of 75, he had been diagnosed as having elderly onset seronegative rheumatoid arthritis (RA) on the basis of acute pain and synovitis in the hips, shoulders, and wrists over a 2-month period. At that time (August 1990) examination revealed tenderness at the gleno-humeral joints, synovitis in wrists, metacarpophalangeal and proximal interphalangeal joints along with edema in hands, severe pain on motion of shoulders and hips, severe morning stiffness (more than 2 hours' duration), high ESR (80 mm/1st hr) and negative serum rheumatoid factor. Treatment with 10 mg/day of prednisone and NSAIDs resulted in a dramatic improvement of symptoms. Due to complete resolution of the rheumatic manifestations this treatment was progressively tapered to complete discontinuation 1 year later (1991). Afterwards, he was periodically followed at our outpatient clinic until December 1992.

However, 5 years after the diagnosis of RA (at the age of 80) he again developed musculoskeletal symptoms involving especially the shoulder and hip girdles. The possibility of either a relapse of RA or the develoment of PMR were considered. However, severe anemia and the presence of diffuse aching symptoms not only limited to the shoulder and hip girdles prompted us to perform a more thorough study. The significant results were as follows: ESR 47 mm/1 hr, hemoglobin 89 g/l, leukocytes 8,300/mm^3, platelet count 276,000/mm^3, creatinine 2.1 mg/dl, urea 111 mg/dl. Serum protein electrophoresis did not disclose any monoclonal peak. However, dipstick proteinuria was at the 3+ level and 24 hr urine protein excretion was 5,283 mg. Urine protein electrophoresis showed a monoclonal peak. Urine immunoelectrophoresis showed lambda light chains. Bone marrow biopsy disclosed massive infiltration by atypical plasmatic cells confirming the diagnosis of multiple myeloma.

The patient was started with melphalan plus prednisone but died two months later because of renal failure and digestive hemorrhage.

Case 4

A 69 year-old woman presented at the outpatient clinic because of pain of 6 weeks' duration along with morning stiffness lasting 1 hour and involving the hip and shoulder girdles. Apart from tenderness and pain on motion of the hips and shoulders the physical examination was unremarkable. No history of symptoms of GCA was obtained and a full blood count, routine laboratory tests including urinanalysis, and chest radiograph were normal except for a slight increase of ESR (42 mm/ 1 hr). A week of treatment with 15 mg/day of prednisone yielded only a mild improvement of symptoms.

A TA biopsy was negative for GCA and a more exhaustive study was performed. An abdominal echo-ultrasound disclosed a mass in the right kidney. Intravenous pyelography showed distorted renal outlines suggesting cancer. Abdominal CT and bone scan were performed to evaluate potential sites of tumor spread. No evidence of metastatic disease was found. A tissue biopsy was positive for renal cell carcinoma and for this reason, radical nephrectomy was performed. Clinical improvement was observed following surgery.

In Table I the criteria for PMR fulfilled by these 4 patients are shown. Both the criteria of Hunder *et al.* criteria (1) and those of Healey (2) were examined. In Table II the data that suggested the presence of conditions other than isolated

Table I. Clinical criteria fulfilled by 4 patients presenting with polymyalgia features.

Criteria	Hunder criteria (1)	Healey criteria (2)
a) Age 50 years and older	Present	Present
b) Bilateral aching and morning stiffness for at least 1 month involving 2 of 3 regions: neck, shoulder girdle, & pelvic girdle	Present	Present
c) ESR of at least 40 mm/1st hour	Present	Present
d) Exclusion of other diseases	Absent	Absent
e) Rapid response to prednisone (20 mg/day or less)	Not applicable	Absent in most cases (cases 2 - 4)

Table II. Data that suggested the presence of a condition different from isolated polymyalgia rheumatica.

Case	Final diagnosis
1) Leukopenia, antinuclear antibodies at a significantly high titer, and proteinuria	Systemic lupus erythematosus
2) Unexplained fever and lack of response to prednisone (at least 15 mg/day)	Infectious endocarditis
3) Diffuse aching symptoms, severe anemia(less than 100 g/l), and renal insufficiency	Hematological disorder
4) Absence of improvement with prednisone (15 mg/day) and renal mass	Renal cell carcinoma

Table III. Differences between 4 patients older than 50 presenting with polymyalgia features and diagnosed as having conditions other than isolated polymyalgia rheumatica and other patients older than 50 with the same diseases but presenting without polymyalgia features.

Case	Typical patient older than 50 years
1) Systemic lupus erythematosus Symptoms resembling polymyalgia rheumatica, renal involvement, hypocomplementemia, and antibody to native DNA	Arthritis, pleurisy, pericarditis, and absence of renal involvement
2) Infectious endocarditis Symptoms resembling polymyalgia rheumatica, blood cultures and echocardiogram initially negative	Pre-existing heart disease, petechiae, splenomegaly, changes in cardiac murmur, and microscopic hematuria
3) Multiple myeloma Symptoms resembling polymyalgia rheumatica, diffuse pain, normal serum electrophoresis with evidence of only light chain excretion in urine	Bone pain from pathologic fractures of the spine, hypercalcemia, lytic bone lesions, and a peak on serum electrophoresis
4) Renal cell carcinoma Symptoms resembling polymyalgia rheumatica without hematuria or flank pain	Gross hematuria, flank pain, and palpable abdominal mass

PMR are described. In Table III differences between these patients presenting with PMR features and other patients of similar age presenting without PMR are displayed.

Discussion

We report 4 patients with very different conditions that presented with polymyalgia manifestations. In general, a diagnosis of PMR is relatively straightforward when typical symptoms are present and in some instances response to corticosteroids is used to support the diagnosis (1). Apart from the frequent association with GCA (3-5) several series have shown no relationship to malignancy or other diseases (5, 6). However, PMR features also may be observed in the context of other well-defined diseases (7). In this regard, in 1999 our group described a work-up for patients presenting with clinical features of PMR in this journal (7). According to this work-up (shown, with minor changes, in Figure 1), patients with classic features of PMR and without any suspicion of any other underlying disease should be treated with 10-20 mg/day of prednisone. In these cases, the absence of improvement after 7 days of therapy would require the search for other conditions, especially GCA. However, the observation of other findings on physical examination, such as synovitis involving the small joints of hands and feet, peripheral enthesitis and/or dactylitis, liver or spleen enlargement, lymphadenopathies, unexplained fever, the presence of hematologic cytopenias, severe anemia, or unexplained biochemistry abnormalities such as hematuria, elevation of muscle enzymes, or positive antinuclear antibodies at high titers should lead to the consideration of the presence of a disease presenting with PMR symptoms.

Healey described patients who had episodes of steroid-responsive conditions, which, at different times, were typical of PMR and seronegative RA (8, 9). More recently, Bahlas *et al.* reported patients with PMR who during their follow-up satisfied 4 of the 1987 ACR criteria for RA (10). Musculoskeletal manifestations, including mono- or oligoarthritis, are not uncommon in PMR (11-13). Also, some patients with PMR present with a benign symmetrical synovitis, satisfy the ACR criteria for RA, have a rapid response to corticosteroids and show a clinical course similar to PMR. These patients have a clinical condition that is different from “classic” RA and most closely resembles PMR (14, 15).

Late-onset SLE presenting as PMR has been previously reported (16, 17). However, a minority of patients with PMR have positive ANA, and the presence of positive ANA in elderly persons by itself does not exclude PMR. Patients with PMR may not routinely have ANA or antiDNA assays done in an effort to keep medical costs under control. As in our first case, the presence of leukopenia with lymphopenia and, in particular, the observation of unexplained high titers of ANA, should lead to a more complete analytical study including assays for anti-nDNA, anti-ENA, C3, and C4.

Although fever may be a symptom of PMR in up to 35% of patients (1), other disease processes presenting with fever and polymyalgia symptoms should be considered when there are some clues pointing to an underlying disease. This is especially true when there is little response to corticosteroids. In this respect, it is of special interest to rule out the possibility of an underlying systemic infection, even when the fever is low grade. The presence of inappropriate malaise and low-grade fever along with musculoskeletal manifestations are good reasons to exclude bacterial endocarditis that may cause musculoskeletal manifestations in up to almost 30% of patients (18).

Malignancies may present with polymyalgia symptoms (19). Hematologic ma-

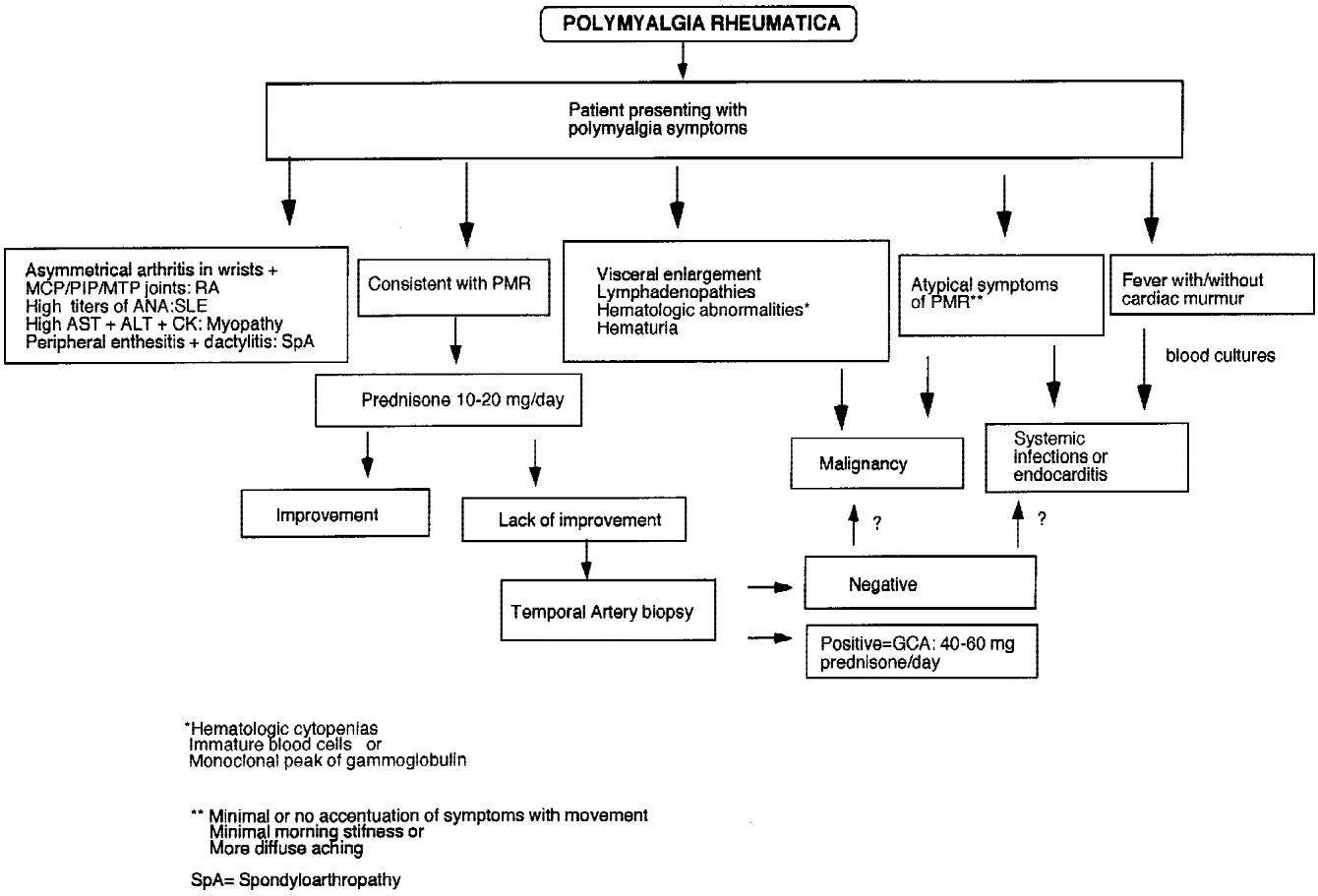

Fig. 1. Chart outlining the diagnosis and management of a patient presenting with polymyalgia.

Table IV. Differential diagnosis in patients presenting with polymyalgia symptoms: summary of the main conditions that may present with polymyalgia symptoms.

Diseases	References
1) Rheumatic diseases	
Rheumatoid arthritis	Healey (9), Bahlas et al (10)
Ankylosing spondylitis	Elkayam et al (25)
Systemic lupus erythematosus	Hutton *et al.* (16), Maragou *et al.* (17)
Polymyositis	Hopkinson *et al.* (26)
Vasculitis	Herrero-Beaumont *et al.* (27)
Fibromyalgia	Wolfe (28)
2) Bacterial endocarditis	Churchill *et al.* (18), Spomer and Ho (29)
3) Amyloidosis	Salvarani *et al.* (22), Gertz *et al.* (30)
4) Hypothyroidism	Bland *et al.* (31)
5) Neoplastic diseases	
Hematologic	
Multiple myeloma	Kalra and Delamere (20)
Lymphoma	Von Knorring (23)
Leukemia	Kohli and Bennett (32)
Myelodysplasia	Kohli and Bennett (32)
Lymphocytoplasmic	Lafforgue *et al.* (33)
Solid tumors	
Renal-cell carcinoma	Sidhom *et al.* (24)
Gastric	Mackenzie (34)
Pancreatic	Olhagen (35)
Prostate, colon	Sheon *et al.* (36)
Uterus	Von Knorring and Somer (37)
Ovary	Sheon *et al.* (36)

lignancies, in particular multiple myeloma or primary systemic amyloidosis, should be considered in elderly patients who present with long-standing asthenia, aches, and muscle pain (20-23). Case 3, because of severe anemia and the presence of diffuse aching symptoms not only limited to the shoulder and hip girdles, along with proteinuria, illustrates the importance of considering multiple myeloma in elderly patients with polymyalgia symptoms. Also, solid malignancies may present with polymyalgia manifestations (24). As described in case 4, the absence of improvement following treatment with doses of prednisone between 15 to 20 mg/day should alert the clinician to the possibility of an underlying condition, including a solid tumor.

In Table IV a differential diagnosis in those patients presenting with polymyalgia symptoms and a summary of the literature on the main conditions that may present with polymyalgia symptoms is shown.

In conclusion, the clinician should be aware of the possibility of other conditions mimicking PMR when additional features are observed or response to PMR treatment is not satisfactory.

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