Conditions mimicking polymyalgia rheumatica

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Objective: To examine the main clinical and laboratory data of patients initially diagnosed with polymyalgia rheumatica (PMR), which then developed another condition.

Material and methods: We reviewed the clinical records of patients diagnosed with PMR in three hospitals in Argentina. Patients had a diagnosis of PMR if they met the following criteria: age ≥ 50 years, erythrocyte sedimentation rate (ESR) at the time of diagnosis ≥ 40 mm/h, persistent pain and stiffness of at least one month of evolution in two of the following areas: neck, shoulders or proximal arms, hips or proximal lower limbs. Special attention was paid to symptoms or signs of “alarm” (beginning or during disease progression) for suspecting the presence of other non PMR disease within a period of ≤ 12 months.

Results: Sixteen of the 200 patients (8%) had other diseases during follow up. Malignancies (n = 4) and rheumatic diseases (n = 4) were the most common entities, in addition to infective endocarditis (n = 1), narrow cervical canal (n = 1), Parkinson’s disease (n = 1), statin-related myalgia (n = 1), hypothyroidism (n = 1), vitamin D deficiency (n = 1) and Calcium Pyrophosphate Deposition Disease (CPPD) (n = 2). The average length change of diagnosis was 4.5 ± 3 months. Ten patients had no response to steroids and two had persistently elevated ESR.

Conclusion: In this study we highlight the importance of recognizing signs and symptoms along with laboratory data and lack of response to treatment as suspects for the diagnosis of other disease manifestations in patients with PMR symptoms.

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Enfermedades que simulan polimialgia reumática

Objetivo: Observar las características clínicas y de laboratorio de pacientes con diagnóstico inicial de polimialgia reumática (PMR), que luego desarrollaron otra enfermedad.

Material y método: Se revisaron las historias clínicas de pacientes con diagnóstico de PMR en 3 hospitales de Argentina. Los pacientes tenían diagnóstico de PMR si cumplían con los siguientes criterios: edad ≥ 50 años, velocidad de sedimentación globular (VSG) > 40 mm/h, dolor y rigidez persistente de al menos 1 mes de evolución en dos de las siguientes áreas: cuello o torso, hombros o región proximal de los brazos, caderas o región proximal de los miembros inferiores. Se prestó especial atención a los síntomas o signos de «alarma» que hicieran sospechar la presencia de otra enfermedad no PMR en un período ≤ 12 meses.

Resultados: Se incluyó a 200 pacientes, de los cuales 16 (8%) presentaron otra enfermedad durante el seguimiento. Las enfermedades diagnosticadas fueron neoplasias (n = 4) y enfermedades reumáticas (n = 4), además de endocarditis infecciosa (n = 1), canal estrecho cervical (n = 1), enfermedad de Parkinson (n = 1), mialgias relacionadas con estatinas (n = 1), hipotiroidismo (n = 1), hipovitaminosis D (n = 1) y artritis por depósito de cristales de pirofosfato cálcico dihidratado (PFCD) (n = 2). El tiempo medio ± desviación estándar al cambio de diagnóstico fue 4.5 ± 3 meses. Diez pacientes no tuvieron respuesta a esteroides y 2 sujetos presentaron VSG persistente elevada.

Conclusiones: En este trabajo resaltamos la importancia de reconocer signos y síntomas clínicos, junto con datos de laboratorio y falta de respuesta al tratamiento como sospecha para diagnóstico de otra enfermedad en pacientes con manifestaciones que simulan PMR.

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Introduction

Polymyalgia rheumatica (PMR) is the most common rheumatic inflammatory disease in the elderly population. Even though its clinical characteristics are well known, there is no specific test for its diagnosis. Several studies have described a great variety of diseases that present themselves with polymyalgia symptoms.

The aim of this study was to observe the clinical and laboratory characteristics of patients with initial PMR diagnosis who later developed another disease.

Material and method

The clinical histories of patients from three hospitals in Argentina who were diagnosed with PMR between January 2004 and December 2009 were reviewed; these hospitals were the Hospital J.M. Cullen in Santa Fe, the Hospital E. Tornú in Buenos Aires and Hospital Privado in Mar del Plata.

The patients received a PMR diagnosis if they fulfilled the following criteria:

- Age≥50 years.
- Erythrocyte sedimentation rate (ESR)>40 mm/h.
- Persistent pain and stiffness of at least one month's evolution in two of the following areas: neck or torso, shoulders or proximal arms, hips or proximal region of the lower limbs.

Patients under 50 years old could be included if they had typical PMR symptoms, high ESR and obvious response to steroids.

Demographic characteristics were recorded (gender, age when PMR started), the duration of the symptoms (months) before the PMR diagnosis, morning stiffness (duration) and the initial steroid dose (prednisone or other).

Following the indications of Gonzalez Gay et al. special attention was paid to certain symptoms or "alarm" signs (at the onset or during evolution) that might make us suspect another non-PMR disease:

- Medical history: no worsening of symptoms with movement, widespread pain and minimal morning stiffness.
- Physical examination: fever with or without murmur, arthritis in the wrists, metacarpophalangeal, proximal interphalangeal or metatarsophalangeal joints, dactylitis, heel pain, visceral enlargement and lymphadenopathy.
- Laboratory: cytopenia, monoclonal gammopathy, increased liver transaminases, muscle enzymes, high titres of antinuclear antibodies (ANA), unexplained hematuria and thyrotoxicosis (TSH).

Lack of response was defined as the absence of symptom resolution after 7 days' treatment with low steroid doses (10-20 mg/day).

It was considered that patients had pure PMR if they fulfilled 3 inclusion criteria, as well as a full response to low doses of steroids (10-20 mg/day). Patients were classified as having other conditions different from PMR, if as well as having clinical PMR characteristics, they presented clinical and/or laboratory characteristics of other specific diseases at the time of diagnosis or during a period of≤12 months.

Patients who during evolution developed giant-cell arteritis (GCA) or elderly-onset rheumatoid arthritis (RA) were excluded.

The protocol was presented and approved by the ethics committee of each of hospitals participating in the study.

Results

There were 200 patients included; 16 (8%) who met the classification criteria for PMR presented another illness during follow-up. The main characteristics are present in Table 1. The mean duration of the symptoms before PMR diagnosis was 1.5 months (minimum 1-maximum 6). All patients presented proximal symptoms, together with high ESR at the time of consultation, and only 1 patient was<50 years old. No data regarding the duration of morning stiffness was found for 10 patients; 2 presented stiffness of 1 hr or more and 4 patients of<1 hr. Ten patients did not respond to a mean dose standard deviation (SD) of 15±6 mg of prednisone. The mean time for diagnostic change was 4.5 months.

The most frequently diagnosed diseases were neoplasms and rheumatic diseases, along with infective endocarditis, cervical spinal stenosis, Parkinson's disease and drug-related myalgia, hypothyroidism, vitamin D deficiency and calcium pyrophosphate dihydrate deposition disease (CPPD). The main signs and alarm symptoms are presented in Table 2.

Four patients developed neoplasms, 3 solid and 1 haematological. In the first patient, the characteristics that indicated the presence of another non-PMR condition were the lack of response to steroid treatment, fever and unexplained weight loss. Subsequent imaging studies showed pancreatic adenocarcinoma. Another patient continued with polymyalgia symptoms together with high ESR despite treatment, which led to a total bone scan being carried out; the scan revealed radiopharmaceutical hyper-uptakes for suspected metastasis, finally appertaining to breast cancer. In the third patient, who had a history of smoking, the tomography showed a pulmonary nodule, which a biopsy reported as carcinoma. The fourth patient, a male with typical PMR and good response to 15 mg prednisone, continued with high ESR during the follow-up. After 7 months' treatment, he came to the control consultation with a left inguinal lymph node; a biopsy was performed, which showed Hodgkin lymphoma.

Four patients developed rheumatic diseases, 2 systemic lupus erythematosus (SLE), 1 patient Sjögren's syndrome and the last one psoriatic arthropathy. The patients that developed SLE had polymyalgia symptoms with a good response to steroids, but high ANA titres. One of the patients was 46 years old; the pain was more widespread and he also had leucopenia. Both presented arthritis in their hands during the follow-up.

The third patient presented sicca symptoms after 6 months' treatment for PRA. This led to specific autoantibody identification and a salivary gland biopsy, with a final diagnosis of Sjögren syndrome.

Other diseases were: hypothyroidism, cervical spinal stenosis, infective endocarditis, Parkinson's disease, statin myalgia, CPPD arthropathy and vitamin D deficiency.

A 68-year-old female consulted for pain and stiffness in the neck and shoulder girdle, of 5 weeks' evolution, without systemic symptoms and bilateral knee and right wrist arthritis. The radiological studies showed calcifications (CPPD type) of the triangular wrist ligament, shoulders, knees, hips and symphysis pubis. A computed tomography (CT) of C1 and C2 showed transverse ligament calcification. The other patient presented Crowe syndrome, which was confirmed with a CT. Both were diagnosed with crystal deposition disease (CPPD) and had good response to non-steroidal anti-inflammatory drugs.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Main characteristics of the “non-PMR” patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>6</td>
</tr>
<tr>
<td>Females</td>
<td>10</td>
</tr>
<tr>
<td>Mean age when PMR was diagnosed, years (mean±SD)</td>
<td>67±10</td>
</tr>
<tr>
<td>Initial ESR, mm/h (mean±SD)</td>
<td>78±17</td>
</tr>
<tr>
<td>Initial mean prednisone dose, mg/day (mean±SD)</td>
<td>15±6</td>
</tr>
<tr>
<td>Time at change of diagnosis, months (mean±SD)</td>
<td>4.5±1</td>
</tr>
</tbody>
</table>

ESR indicates erythrocyte sedimentation rate; PMR, polymyalgia rheumatica; SD, standard deviation.
Table 2
Clinical or laboratory data that indicated the presence of another disease (n=16)

<table>
<thead>
<tr>
<th>Neoplasms</th>
<th>n=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rheumatic diseases</th>
<th>n=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>1</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Psoriatic arthropathy</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other diseases</th>
<th>n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>1</td>
</tr>
<tr>
<td>Cervical spinal stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>1</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>1</td>
</tr>
<tr>
<td>Statin myalgia</td>
<td>1</td>
</tr>
<tr>
<td>CPPD crystal disease</td>
<td>2</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>1</td>
</tr>
</tbody>
</table>

ANA indicates antinuclear antibodies; CPPD, calcium pyrophosphate dihydrate; CT, computed tomography; ENA, extractable nuclear antigens; RF, rheumatoid factor; TSH, thyrotropin.

The lack of response to steroids, as well as extreme tiredness and a high TSH, made us suspect the presence of hypothyroidism. This lack of response was also observed in: statin-related myalgias (along with clinical resolution with atorvastatin suspension); vitamin D deficiency (apart from the reduced level vitamin D count and the excellent response to high doses of this) and infective endocarditis from Enterococcus spp. (along with progressive deterioration of the general condition, fever and murmur that led cultures being taken together with an echocardiogram).

Another patient presented pain with cervical and predominantly left shoulder girdle stiffness, which partially improved with steroids. During its evolution, paresthesias and loss of strength in the left hand appeared and the patient was diagnosed with cervical spinal stenosis.

Discussion

When patients present typical PMR symptoms, the diagnosis is obvious. However, PMR continues being a diagnostic challenge. On the one hand, due to differential diagnoses, neither clinical nor laboratory findings are specific for the disease (PMR manifestations can occur in patients with infections, neoplasms and other rheumatic diseases). On the other hand, there are frequent “irregular” findings (peripheral synovitis, distal extremity pain, normal erythrocytes and muscle weakness). A case history and careful physical examination are the most important diagnostic tools.

There are diseases that can cause pain and be confused with PMR, such as elderly-onset RA, inflammatory myositis, late-onset spondyloarthopathies, vasculitis, polymyositis and fibromyalgia. Viral syndromes can cause similar symptoms, but they do not generally last as long. Chronic infections (such as hepatitis C, tuberculosis, brucellosis, human immunodeficiency virus and subacute bacterial endocarditis) as well as paraneoplastic syndromes and endocrine diseases (such as hypothyroidism and hypeparathyroidism) can produce tiredness and myalgia.

Gonzalez-Gay et al were the first to discover clinical and laboratory characteristics of patients with manifestations that mimic PMR, which were diagnosed from another disease, in a well defined population of patients with PMR, with or without GCA. In their study, they found 23/208 (11%) of patients who presented polymyalgia symptoms without evidence of another disease, developed neoplasms within 3 months of the onset of symptoms (10/23 patients, 5 solid and 5 haematological) and rheumatic diseases, with an average delay for diagnosis of 13 months (10/23 patients, 5 seronegative arthritis, 2 SLE, 2 inflammatory myopathy and 1 ankylosing spondylitis, as well as endocarditis, hypothyroidism and Parkinson’s disease).

In this series, 16/200 (8%) patients developed other affectations, in a mean time of 4.5 months of follow-up. Similar to the Gonzalez-Gay et al study, neoplasms and rheumatic diseases were the diseases that were most frequently found. We intentionally excluded patients with elderly-onset GCA and RA, due to the already established relationship between these entities and PMR. Consequently, we will centre the discussion on other entities that are not considered so much.

Arthopathy due to CPPD crystal deposition can present itself with a large variety of clinical syndromes, including symptoms that mimic PMR/GCA (proximal joint compromise can be the clinical presentation of CPPD arthropathy), with high acute phase reactants and response to steroids. Recently, Pego-Reigosa et al analysed patients with pure PMR and PMR-type CPPD disease looking for predictor factors that would differentiate the entities. The presence of tibiofemoral osteoarthritis, tendinous calcifications and ankle arthritis should make us suspect CPPD diseases in patients with symptoms that mimic PMR. Crystal disease should consequently be included in the spectrum of affectations that mimic PMR.

Dieppe et al reported 8 patients with presumed PMR, from a series of 105 patients with pyrophosphate arthropathy. They suggested that CPPD disease could present itself with polymyalgia symptoms or that the treatment with steroids prescribed to these patients with PMR characteristics could lead to chondrocalcinosis development.

Calcification of the transverse ligament was found in 44%-71% of patients with chondrocalcinosis, while Crown’s syndrome was observed in 9%-45% in two of the studies.

In 2004, Aubaa described 3 patients with Crown’s syndrome (association of radiological calcification of the cruciate ligament around the odontoid process and acute cervico-occipital pain, with fever, neck stiffness and biological inflammatory syndrome) and chondrocalcinosis of the wrist and knee, which were mistakenly diagnosed as PMR. Acute cervico-occipital pain, fever and neck stiffness make it essential to eliminate other diagnoses, such as meningitis, spondylitis and PMR/GCA. Identifying this syndrome could avoid unnecessary invasive and expensive investigations, potentially harmful, long unsuitable steroid treatment and prolonged hospitalisation of these patients.

The syndrome that mimics PMR and/or GCA could be the manner a neoplasm presents itself. Haga et al communicate that the interval between PMR and/or GCA diagnosis and neoplasm recording (mean, 6.5 years) is not consistent with a paraneoplastic mechanism.

Haematological neoplasms, such as myelodysplasia, leukaemia, lymphoma, myeloma or amyloidosis, could mimic PMR. It is therefore
important to detect the presence of cytopenia, lymphadenopathy, proteinuria or monoclonal peaks in the electrophoresis run. Likewise, solid neoplasms (kidney, stomach, colon, pancreas, lung, prostate, ovary and uterus) can present themselves as PMR and should be suspected from the history, unusual symptoms (widespread pain, unexplained weight loss, hematuria) and lack of response to steroids.

Generally, myalgias associated to solid tumours do not respond to steroidal treatment; however, those associated to haematological neoplasms can respond to low doses. When high doses are used, this can mask other diseases, such as rotator cuff problems, RA, infection, migraine or tumours.

Elderly patients with unspecific refractory musculoskeletal pains with non-steroidal anti-inflammatory drugs have a high prevalence (30%-90%) of presenting vitamin D deficiency. This is usually defined as levels of 25-hydroxyvitamin D<20 ng/ml (50 nmol/l). The clinical picture may be subtle and not taken into account. The signs and symptoms could be skeletal and/or muscle changes, depending on the seriousness of the deficit, and whether they are due to osteomalacia or secondary hyperparathyroidism. These include widespread pain in the pelvic and shoulder girdle, rib cage, lower back and legs; general fatigue, pain or muscle weakness; and walking disorders. These patients are often mistakenly diagnosed with polymyalgia rheumatica, fibromyalgia or malignant diseases.25

Fever can be seen in 35% of PMR patients; this (even though low), together with the little response to steroids, obliges us to exclude an underlying systemic infection, especially bacterial endocarditis, that can cause musculoskeletal symptoms in 17%-44% of cases.25 This should be taken into account in regions where chronic infectious diseases (Brucellosis, tuberculosis) are endemic.

Hyperthyroidism in its idiopathic form is frequently caused by Hashimoto's thyroiditis, an autoimmune disease that can be associated with connective tissue diseases. The prevalence of skeletal muscle manifestations in patients with hyperthyroidism varies between 30% and 80%. Serious hyperthyroidism could present myxedematous arthropathy that affects the small and large joints. Thyroid myopathy is more common; it is characterised by pain and generalised hardening, but it affects the deltoid and quadriceps muscles more, in a similar way to PMR. This myopathy can also cause muscle weakness, with high muscular enzymes, but with very high TSH.21

The initial symptoms of Parkinson's disease are very varied. Pain in the neck, back and limbs, together with stiffness in the proximal regions that makes walking difficult, can precede the motility disorders and vegetative dysfunction for months. The diagnosis is usually based on clinical data and good response to levodopa.24

It has been reported that several drugs can cause clinical manifestations that suggest PMR (Enalapril, metoprolol, dipyridamole and statins).25 The statins, or hydroxymethylglutaryl-coenzyme A reductase inhibitors (HMG-CoA), are used to decrease cholesterol production and their use is currently very widespread. Although they are generally seen to be safe and well tolerated, we should take myopathy syndromes into account among their adverse effects. Four myopathy syndromes related to statins have been defined: statin myopathic syndromes into account among their adverse effects. Four

In patients with Sjögren’s syndrome, the presence of extraglandular symptoms, such as fibromyalgia, asthenia and fatigue, can confuse the diagnosis. There few communications in the scientific literature on PMR/GCA and primary Sjögren’s syndrome.2829 Improvement with corticoid therapy is not specific for PMR diagnosis, but its absence always requires another diagnostic evaluation. In our series, the lack of response to steroids presented itself in 10/16 (60%) of patients and was one of the main characteristics that alerted to the presence of another infection.

Using ESR is not only for diagnosis, but also for monitoring disease activity. Special attention must be paid to patients in whom ESR starts to increase or remains persistently high during the treatment. This could mean that there is another disease. In our series, 2/16 (12%) of patients had persistent high ESR despite treatment.

In this study, we emphasise the importance of recognising clinical signs and symptoms, laboratory data and lack of response to treatment as diagnostic suspicion of another disease in patients with manifestations that mimic PMR.

**Conflict of interest**

The authors declare no conflict of interest.

References