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CASE REPORT
ΕΝΔΙΑΦΕΡΟΥΣΑ ΠΕΡΙΠΤΩΣΗ

What is behind the diagnostic curtain? A teaching case of polymyalgia rheumatica

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2024, 41(2):270–274

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An 81-year-old female was admitted to the Department of Internal Medicine with generalized weakness and arthralgia with a predilection to the spine and shoulder girdle, walking difficulty and mild memory loss of one week's duration. Symptomatology spontaneously resolved after two weeks of admission but recurred at follow-up along with a mixed disease impression, where an exhaustive list of diagnoses was ruled out. Polymyalgia rheumatica (PMR) is an aseptic inflammatory condition that may be diagnostically challenging, especially in patients with multiple comorbidities, and therefore, critical clinical thinking is imperative. Our case elucidated that the cornerstone of differential diagnosis and patient treatment is an excellent retrieval of medical history, in combination with reinforcement from the physical exam and radiological-laboratory work-up.

Μια διδακτική περίπτωση ρευματικής πολυμυαλγίας

Περίληψη στο τέλος του άρθρου

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Polymyalgia rheumatica (PMR) is a non-septic inflammatory disorder characterized by severe pain and stiffness affecting the proximal muscles of the musculoskeletal system, namely those of the cervical region and shoulder girdle and may also be associated with constitutional symptoms.[1] Caudal muscles such as those of the lumbar spine, pelvis and lower limbs are rarely involved. Notably, the symptom constellation of PMR may be self-limiting, but can also manifest for several months.[2] Epidemiological evidence suggests a grander predilection to the white population and less so in Black, Asian, and Hispanic populations.[1] In addition, a predilection also exists in individuals in their seventh decade of life and older, with a lesser occurrence in the fifth decade of life and older. Specifically, it is considered a rather common disease witnessed in 19.8/100,000 people and 112.2/100,000 in the 50- to 59-year-old age group, and 70- to 79-year-old age group, respectively.[2]

Laboratory findings concerning the acute phase reactants may raise suspicion for PMR and typically include elevated C-reactive protein (CRP) levels and a raised erythrocyte sedimentation rate (ESR),[3] but both may even be normal or only slightly raised in 7–22% of cases.[4,5] Importantly, findings of normocytic anemia of chronic disease and left shift of the white blood cell (WBC) count may also be demonstrated in PMR.[1] Treatment of PMR involves a regimen with a low-dose corticosteroid,[6] which carries special considerations discussed later in the manuscript.

We present a case of a patient with constitutional symptomatology and non-specific semiology and discuss the diagnostic and therapeutic implications involved during our clinical work-up until diagnosis.

CASE PRESENTATION

An 81-year-old female was admitted to the Department of Internal Medicine of Troodos Hospital with generalized weakness and bone pain with a predilection to the spine and shoulders, difficulty in walking and mild memory loss for the past week. Headache, visual impairment or jaw pain with mastication were not reported. Past medical and surgical history of significance includes hypothyroidism, arterial hypertension, transient ischemic attack, osteoarthritis, beta-thalassemia trait, right shoulder arthroplasty,

right knee arthroplasty, vaginal prolapse, and penicillin allergy. Current medication regimen included thyroxine, lisinopril and lorazepam.

Upon initial clinical examination, the patient was afebrile and hemodynamically stable. System examination revealed mild tenderness of the thoracic spine and no sign of joint inflammation was noted. Temporal arteries were pulsating normally without tenderness on palpation. Laboratory findings are listed in table 1. Radiological imaging included computer tomography (CT) studies of the brain, and cervical and thoracic spine. CT of the brain demonstrated ischemic lesions of the periventricular white matter. CT of the cervical and thoracic spine revealed severe degenerative lesions and a significant degree of stenosis of the intervertebral spaces (especially C6–C7, C7–T1 and T10–T11).

The patient remained afebrile throughout her hospitalization but had gait difficulty and slight muscle weakness in both upper and lower extremities. She showed significant self-resolving clinical improvement and as such, was discharged after 15 days. During follow-up 10 days later, the patient reported fatigue and bone pain in her spine and knees. No new clinical finding was noted, while laboratory tests showed worsening anemia, mild leukocytosis, with raised CRP. Re-admission occurred a week later due to report of fever, dizziness and difficulty in walking. During the clinical examination, the patient was febrile (39 °C), but hemodynamically stable. System examination was normal and temporal arteries were pulsating normally without tenderness on palpation. Laboratory investigation demonstrated marked leukocytosis with neutrophil predominance, chronic anemia, and markedly high CRP, with double-digit ESR; and microbiological work-up did not yield findings in concordance with infection. Echocardiography revealed mild concentric hypertrophy and an ejection fraction above 55%, without signs of pericardial effusion or vegetations. CT of the cervical region performed did not reveal any pathological findings. CT of the thorax revealed fibrous parenchymal bands of the lung bases bilaterally, as well as a hiatal hernia. Abdominal CT showed fatty infiltration of the liver, which may explain the liver function test derangement the patient had been exhibiting.

Table 1. Patient's laboratory findings during diagnostic work-up.

	Laboratory results
First admission (day 0, week 1)	
Hematology	WBC 25,940/μL (neutrophils 76.6%, lymphocytes 9.2%), Hct 30.2%, Hb 10.4 g/dL, PLTs 680×10^3/μL
	ESR 77 mm/hour
	Peripheral blood smear: Left shift and few reactive lymphocytes
	Molecular test for *BCR/ABL*, *JAK2* gene: *Negative*
Biochemistry	Urea 45 mg/dL, Creatinine 0.68 mg/dL
	ALT 88 U/L, AST 77 U/L, ALP 138 U/L, γ-GT 48 U/L, CRP 236 mg/L, ferritin 360 μg/L
Rheumatology panel	RF 3 IU/mL, C3 203 mg/dL, C4 46 mg/dL
	ANA, anti-dsDNA, anti-CCP, anti-RP3, anti-MPO, AMA2, anti-Ro, anti-La, anti-SmD3p, anti-U1RNP, anti-RNP70, anti-Scl70, anti-CENP-B, anti-Jo1: *Negative*
Serology and other specialised tests	IgG 1,590 mg/dL, IgA 474 mg/dL, IgM 136 mg/dL, protein electrophoresis: *No* monoclonal fraction
	TSH 6.39 mIU/L
	HIV, HBV, HCV serology studies: *Negative*
Microbiology	×2 sets of peripheral blood cultures: *No growth*
Follow-up as outpatient (10 days post-first discharge, week 3+)	
Hematology	WBC 11,000/μL, Hct 27.8%, Hb 9.1 g/dL, PLTs 558×10^3/μL
Biochemistry	ALT 65 U/L, AST 54 U/L, ALP 160 U/L, γ-GT 43 U/L, CRP 90 mg/L
Second admission (weeks 4–5)	
Hematology	WBC 20,570 μL (neutrophils 78.9%, monocytes 15.6%), Hct 27.9%, Hb 9.2 g/dL, PLTs 577×10^3/μL
	ESR 74 mm/hour
	Peripheral blood smear: Left shift
Biochemistry	ALP 157 U/L, γ-GT 46 U/L, ALT 63 U/L, AST 63 U/L, CRP 202 mg/L
Serology	*Rickettsia typhi* IgM 1/2,048 (IgG negative)
	Rickettsia conori IgM 1/2,048 (IgG negative)
Microbiology	Urine microscopy and culture: WBCs absent, no growth
	Multiple sets of blood cultures for anaerobic bacteria: No growth
	Mantoux test: Negative

During the following days, the patient presented significant clinical deterioration. Initially, there was clinical worsening of both upper and lower limb weakness to the extent that she was unable to maintain daily activities, such as showering or combing her hair. Eventually, she was unable to walk. The patient was commenced on ciprofloxacin and metronidazole without clinical improvement. As such, further serology investigations took place. Tests for *Rickettsia typhi* revealed IgM 1/2,048 (IgG negative) and for *Rickettsia conori* IgM 1/2,048 (IgG negative). Treatment was switched to oral doxycycline, without complete resolution of the fever and any other clinical improvement. Rheumatological assessment was then requested upon suspicion of PMR and 32 mg oral methylprednisolone was commenced, which resulted in remission of the fever, rapid clinical improvement, and discharge 4 days later with an improved gait.

During the weeks that followed, the patient's gait improved further with excellent and independent mobility and functionality in the upper extremities, with normalization of her inflammatory markers. However, the patient had a fracture of her ribs and hip after a fall, for which surgical management was deemed necessary but fully recovered thereafter. An attempt was made to completely withdraw corticosteroids but a slight increase in the inflammatory markers (ESR, CRP) was noted, and she complained of shoulder pain, so the corticosteroid regimen was resumed. Currently, she is being treated with 2 mg of methylprednisolone orally, and is in excellent clinical and laboratory condition four years after PMR diagnosis.

DISCUSSION

PMR is a steroid-responsive inflammatory disease,[7] sometimes associated with giant cell arteritis (GCA). PMR usually affects elderly Caucasians with symptoms, such as back pain, morning joint stiffness and flu-like symptoms. Furthermore, PMR may also increase susceptibility to infections, causing immunological changes and hormonal disturbances.[8] Many diseases can present with symptoms that resemble PMR, and as such, it can be thought of as a diagnostic chameleon. Specifically, it may mimic a wide span of musculoskeletal, rheumatological, infectious, and hematological diseases –examples including traumatic muscle injury, myositis, rheumatoid arthritis (RA), fibromyalgia, viral myalgia, osteoporosis, multiple myeloma and hypothyroidism– all of which were considered in our differential work-up.

From an academic and clinical standpoint, it is important to develop a thoughtful differential diagnosis. The initial stage of any differential diagnosis development is the consideration of the patient history. In our case, our patient presented with symptomatology of shoulder and hip pain of one week that spontaneously relieved after two weeks of admission, but was accompanied by a relapse of this pain a few weeks later. Our patient's complaints, as well as their temporal relation were significant in this endeavor. Additionally, the demographic characteristics, such as age and gender of the patient must be considered – for example, there is a known predilection for older women with regards to PMR.[2] Furthermore, the differential diagnosis may also be categorized depending on the nature of the disease itself, as depicted in the example of our case breakdown (fig. 1). It must be emphasized that the cornerstone of differential diagnosis and patient treatment is an excellent retrieval of medical history, in combination with reinforcement from the physical exam and radiological-laboratory work-up (fig. 2).

Notably, the especially confusing findings in the work-up of our case were the laboratory and clinical (fever) evidence consistent with infection – albeit negative cultures, the patient had reactive IgM antibodies to *Rickettsia* and was commenced on doxycycline without fever remission. This non-responsiveness to antibiotics further drove us away from an infectious cause of the patient's malady. Interestingly, although in the literature *Rickettsia* is not associated nor a trigger to PMR, there have been reports

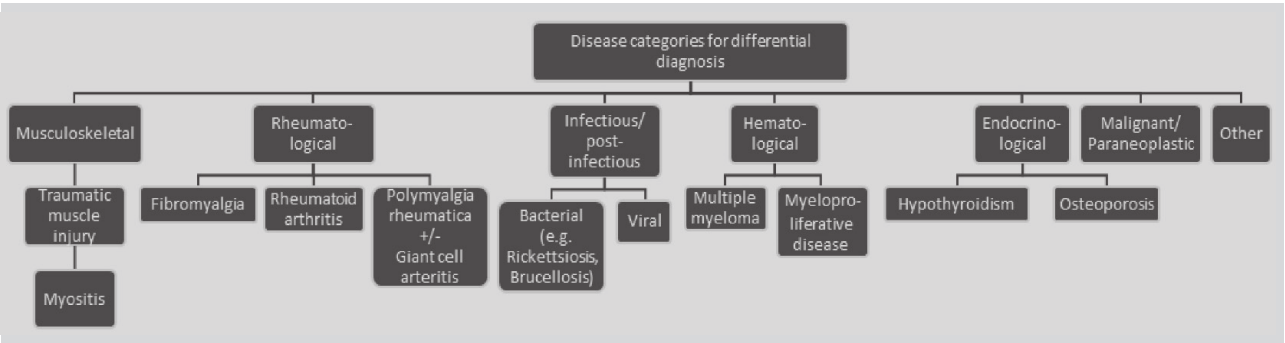

Figure 1. Breaking down our patient's differential diagnosis – categorization based on nature of disease.

that patients with chronic illness might have false positive antibodies.[9]

Our next step, since imaging was unrevealing, was to investigate for autoimmune diseases. RA (common in older patients), myositis and seronegative spondyloarthropathies were disqualified due to negative tests and incompatible clinical presentation. As such, PMR was a remaining diagnostic pawn, and a corticosteroid regimen was initiated for our patient, with good clinical response – a characteristic trait of PMR. Although GCA often coexists with PMR, no compatible clinical findings such as pain with mastication, palpable temporal artery or pounding temporal headache were exhibited in our patient. Moreover, GCA (as in PMR) may also exhibit a range of ESR levels and may not always be a triple-digit figure.[10] Nevertheless, around one fifth of patients with PMR may develop concomitant GCA in the future.[11]

Pathophysiology of PMR has not yet been fully elucidated; however, aging might be a key element involved, as PMR occurs in patients over 70 years old.[8] Nearly all patients with PMR develop shoulder pain, while neck and pelvic girdle are involved in approximately 70% and 50% of patients, respectively. Interestingly, interleukin-6 (IL-6) activity is significantly elevated in all untreated patients with PMR.[12] Elevated IL-6 levels might lead to leukocytosis as a part of a generalized inflammatory response, but evidently this condition must be differentiated from other inflammatory processes of infectious and iatrogenic cause.[12,13]

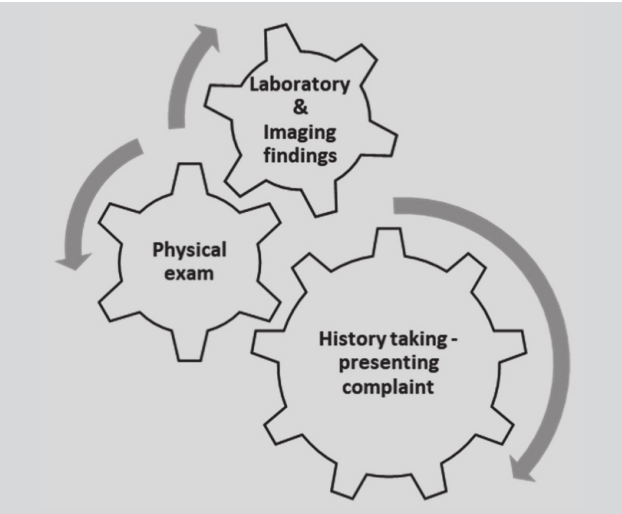

Figure 2. The importance of a complete work-up represented as a cogwheel mechanism. Note that the biggest cogwheel in the group signifies the most important – history retrieval.

Although strict diagnostic criteria have not yet been established for PMR, a team of researchers from international work groups released provisional classification criteria for the disease for the first time a decade ago.[14] Of note, individuals in their fifth decade of life or older that complain of new bilateral shoulder pain (otherwise unexplained), along with elevated acute phase reactants such as CRP and or ESR rate, morning stiffness lasting longer than 45 minutes, and new complaints of hip pathology such as pain, tenderness, or limited mobility are thought to display PMR. Of interest, the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) study also touches upon the value of utilizing imaging such as ultrasonography to further decipher the PMR diagnosis, as various pathological findings of bilateral shoulder girdles, or, alternatively, one shoulder and hip; raise suspicion of PMR even further.[14,15] Specifically, ultrasonography had 89% specificity at distinguishing PMR from other shoulder pathologies; however this dropped to 70% when it came to a respective comparison with RA.

A low-dose glucocorticoid (GC) regimen administration is the cornerstone of managing PMR; however initial GC dose and exact chronicity of tapering duration are disputed.[11] Nevertheless, prednisolone dose can be decreased upon evidence of timely improvement in the patient's symptomatology, and laboratory markers such as ESR are within normal limits. In the event of relapse, slower tapering must take place.[11]

Importantly, careful consideration is negated regarding corticosteroidal potentiation of osteoporosis, especially in elderly females that may concomitantly be at an increased risk for falls. In addition, this side effect can also be dose-dependent, as evidenced by a higher risk of fractures in doses over 5 mg prednisolone.[16] Bisphosphonate prophylaxis for patients with moderate-to-high fracture risk or Frax score >1% is applicable in this population.[17] Finally, nonpharmacological pathways should also be pondered and discussed with patients, as physical therapy and rehabilitation have shown to improve mobility and quality of life in various rheumatological diseases.[18]

As supported by the 2015 EULAR/ACR group, further thoughtfully designed, multi-center trials are needed to establish many of the missing pieces of PMR, including but not limited to the efficacy and safety of different routes of GC administration (oral, intramuscular, intra-articular), different initial GC doses, various GC tapering regimens, and different GC flare doses. Furthermore, investigation as to why some patients respond more favorably and how patients can be more implicated in treatment decisions is also pertinent.[6]

ΠΕΡΙΛΗΨΗ

Μια διδακτική περίπτωση ρευματικής πολυμυαλγίας

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Η ρευματική πολυμυαλγία είναι μια άσηπτη, φλεγμονώδης κατάσταση που καθίσταται διαγνωστικά δύσκολη, ειδικά σε ασθενείς με πολλαπλές συννοσηρότητες, και ως εκ τούτου η κριτική κλινική σκέψη είναι επιτακτική. Η περίπτωσή μας καταδεικνύει ότι ο ακρογωνιαίος λίθος της διαγνωστικής προσπέλασης ενός ασθενούς είναι η άριστη ανάκτηση του ιατρικού ιστορικού, σε συνδυασμό με τα ευρήματα της κλινικής εξέτασης και των παρακλινικών εξετάσεων.

Λέξεις ευρετηρίου: Γιγαντοκυτταρική αρτηρίτιδα, Μυοσκελετική νόσος, Ρευματική νόσος, Ρευματική πολυμυαλγία

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