

Seronegative polymyalgia rheumatica: an update

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Dear Editor,

The possibility that patients with polymyalgia rheumatica (PMR) may have normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values before starting treatment with glucocorticosteroids has been considered an oxymoron in the literature. As an example, according to the 2012 European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) classification criteria, elevation of ESR and CRP values is required for classifying a patient older than 50 years presenting with bilateral shoulder pain as having PMR [1].

In 2018, an editorial published in *Reumatologia* stressed isolated PMR is possible even when ESR and CRP are within normal ranges. A four-point guide was proposed for correct identification of these patients [2]. Until then, PMR with normal values of both ESR and CRP concentrations was little more than a curiosity [3, 4]. Several articles were then published on this topic, confirming that seronegative PMR exists [5–11]. Interestingly, in accordance with the 3 main cohort studies, the patients with seronegative PMR almost never developed giant cell arteritis (GCA) during their follow-ups: only 2% of the Netherlands cohort developed GCA [7], and no cases of GCA were present in the Italian-Polish [6] and Turkish [8] cohorts. More recently, a narrative review discussed seronegative PMR as a subset of the disease [12].

A few hypotheses have been proposed to explain why ESR and CRP are not elevated in an autoinflammatory disease such as PMR. For example, a lower prevalence of systemic manifestations in patients with seronegative PMR has been discussed as a possible explanation. To date, however, all the proposed hypotheses are only speculative [13].

In the literature, the percentage of seronegative PMR varied from 1 [11] to 14.8% [8]. Such very different percentages can generate confusion in an already difficult topic. In other words, is seronegative PMR an uncommon condition or not? Only multi-centre studies with a shared design could perhaps provide a definitive answer, finding a way

to address the main differences among published studies, which include differing inclusion and exclusion criteria, instrumental assessments, and follow-up durations.

Ultrasound (US) and 18-fluorodeoxyglucose positron emission associated with total body computed tomography (18-FDG PET/CT) evaluations are essential in improving identification of seronegative PMR. There are no significant differences, indeed, in the distribution of FDG uptake between patients with normal and elevated inflammatory markers [5]. Similarly, PMR patients with normal or elevated ESR and CRP exhibit comparable US findings validated by the 2012 EULAR/ACR collaborative initiative [2, 6–8]. Moreover, US and 18-FDG PET/CT are very useful in differential diagnosis with PMR-mimicking conditions where ESR and CRP are normal [14, 15]. In short, in patients with suggestive clinical features but normal inflammatory markers, whole body PET/CT and/or US should always be performed to confirm a diagnosis of PMR. Difficulty in accessing 18-FDG PET/CT and US might favour an underdiagnosis of seronegative PMR in some healthcare settings.

As is the case for patients with classic, isolated PMR, patients with seronegative PMR are to be periodically reassessed because some patients initially diagnosed with PMR may be reclassified as having a different disease during follow-ups [15]. This means that the initial diagnosis of seronegative PMR must be confirmed over time.

What impacts can normal values of ESR and CRP have on treatment of PMR? Published data are not unique. Most authors suggest starting with 12.5–25 mg/day of prednisone and to follow the tapering schedule proposed by the 2015 EULAR/ACR recommendations [16]. According to these authors, the treatment of seronegative PMR is the same as the classic form, indirectly confirming that seronegative PMR can be a disease subset [6, 7, 12]. Starting with a lower dose of prednisone or adopting a shorter tapering scheme was also proposed [11].

In conclusion, when evaluating a patient older than 50 years presenting with bilateral shoulder and hip girdle pain with normal ESR and CRP, it is reasonable

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to assume that PMR is unlikely. However, seronegative PMR remains a possibility that should be taken into account, especially when excluding alternative diagnoses and treatment with non-steroidal anti-inflammatory drugs and painkillers failed to improve shoulder/hip girdle pain and function. Ultrasound and/or 18-FDG PET/CT evaluations and a long follow-up are mandatory.

I hope that greater attention to this diagnostic possibility in everyday clinical practice will foster further, useful contributions.

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