Polymyalgia rheumatica with normal values of both erythrocyte sedimentation rate and C-reactive protein concentration at the time of diagnosis: a four-point guidance

Ciro Manzo¹, Marcin Milchert²

¹Internal and Geriatric Medicine Department, Rheumatologic Outpatient Clinic and Gerontorheumatological Ambulatory, Hospital "Mariano Lauro", Sant’Agnello, Naples, Italy
²Department of Rheumatology, Internal Medicine, and Geriatrics of Pomeranian Medical University in Szczecin, Poland

Raised values of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentration are typical findings in patients with polymyalgia rheumatica (PMR) at the time of diagnosis. In 1979 Bird et al. proposed an ESR of 40 mm/h or higher as a diagnostic criterion, and in 1981 Jones and Hazleman considered a CRP concentration of more than 6 mg/l as an additional criterion. In a sizable proportion of PMR patients – from 7% to 22% – ESR is not raised at the time of diagnosis. However, in these patients, CRP is usually raised [1].

The normal values of both of these biomarkers at the time of diagnosis were rarely reported. Myklebust and Gran [2] found normal both ESR and CRP in 1.2% of 178 PMR patients, and only one patient amongst 177 had normal ESR and normal CRP in a prospective follow-up study conducted in two Italian secondary referral centres of rheumatology [3]. In our medical records (data unpublished), six amongst 265 PMR patients had normal values of both ESR and CRP at diagnosis. The vast majority of these patients had no constitutional manifestations.

The reasons why this can be possible in an auto-inflammatory disease are only speculative. The absence of constitutional manifestations could realise a first-favouring element. PMR with low ESR is considered a more benign form of disease, with lower frequency of constitutional manifestations compared to PMR with high ESR [4]. Innate immunity may trigger fever, general malaise, fatigue, and depressive reaction. In patients with PMR, their absence can be a result of interactions between innate and adaptive immunity within a specific genetic background [5].

Some speculated that PMR might be an incomplete form of giant cell arteritis (GCA), manifested in the regions in the proximity of axillary, subclavian, and/or femoral arteritis. A biopsy-proven GCA can be present without elevation of ESR and CRP [6], and in the literature GCA with normal ESR and CRP at diagnosis is much more frequent than PMR with normal values of inflammatory markers. Accordingly, it might be hypothesised that PMR patients with normal values of both ESR and CRP have an occult GCA.

In individuals aged 50 years or older, in the presence of: persistent pain involving shoulders, pelvic girdle, and/or neck plus morning stiffness lasting for more than 1 hour plus absence of other different diseases (with the exception of giant cell arteritis), the diagnosis of PMR is possible. The rapid response (seven days, on average) to low-dosed prednisone (< 20 mg per day), together with watchful observation to ensure that no alternative diagnosis appear during follow-up, can confirm the first diagnosis. However in the clinical practice we must take into account that several patients fail to achieve a complete response after one week, and – on the other hand – some diseases can mimic PMR not only in the clinical features but also in a fast response to low-dosed systemic glucocorticoids. Some of these diseases fail to maintain the first positive response in a short time (with reappearance of manifestations despite glucocorticoid therapy) but others (such as solid or haematological tumours) can do it [7].

In recent years, ultrasound (US) imaging has become an integral element of the diagnostic process in PMR. Even if there are no pathognomonic findings, subdeltoid
Bursitis and tenosynovitis of the long head of the biceps tendon are highly characteristic, especially when bilateral. In 2009, Zaccaria et al. [8] highlighted that there are no significant differences in the US pictures of the shoulders between a group of PMR patients with low ESR and a group with elevated one. A systematic review published in 2015 confirmed that there is no correlation between US findings and levels of ESR and CRP [9].

Other biomarkers in adjunct to ESR and CRP can be useful. Among these is plasma fibrinogen. Its level correlates with interleukin 6 (IL-6) production, a cytokine typically raised in patients with PMR, before starting with low-dosed prednisone. Its measurement is inexpensive and readily assayed in all laboratories (whereas IL-6 concentrations are not), and some investigators consider it to be an accurate marker of disease activity [10]. Despite that, there is no study that has evaluated the utility of plasma fibrinogen levels for first-time diagnosis when normal values of ESR and CRP coexist. To the best of our knowledge, studies on further different biomarkers in PMR are anecdotal and pending confirmation.

**Conclusion**

Polymyalgia rheumatica can still be a very surprising disease: the diagnosis is possible even if normal values of both ESR and CRP are present. This eventuality is highly infrequent, so when we visit an older person complaining of chronic bilateral shoulder and hip girdle pain associated with normal inflammatory indices, it is reasonable to think in the first instance of an alternative diagnosis. However, a possible PMR must be considered when we are not able to piece the “puzzle” together. In this case, a four-point guidance can be useful (Table I).

**Table I. A four-point guidance on how to investigate PMR when normal ESR and CRP coexist**

| 1. | In an older person complaining of chronic bilateral shoulder and hip girdle pain associated with inflammatory morning stiffness, a possible PMR can be considered (even if ESR and CRP are both normal) if the proposed therapies do not improve pain and self care |
| 2. | An ultrasound examination of shoulder and hip girdle as well as the measurement of other biomarkers in adjunct to ESR and CRP can give additional information |
| 3. | A fast and significant improvement after a few days (seven days, on average) of low-dosed prednisone can confirm the first diagnostic suspicion, but it should be kept in mind that a watchful follow-up is mandatory |
| 4. | Several diseases can mimic PMR in some clinical features and in positive response to low-dose prednisone. They must be carefully excluded (not only at the beginning but also after follow-ups). The possibility of occult GCA should be investigated |

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The authors declare no conflict of interest.