

Polymyalgia rheumatica without elevated baseline acute phase reactants

Sirs,

We read with great interest the article “Polymyalgia rheumatica patients with and without elevated baseline acute phase reactants: distinct subgroups of polymyalgia rheumatica?” written by Marsman *et al.*, currently in press (1).

Among 454 patients with polymyalgia rheumatica (PMR), the authors found 62 (14%) with normal baseline values of acute phase reactants (APR); specifically, normal baseline values of both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentrations. In a retrospective cohort study published in 2019, we found only 7 with normal baseline APR among 460 PMR patients (1.5%) (2).

The different inclusion and exclusion criteria used in the two studies can explain the different percentages. For instance, no formal classification criteria were used as inclusion criteria in Marsman’s study, whereas we used them. Furthermore, the duration of follow-up was from 29 to 120 months in our study, whereas was up to 24 months in Marsman’s study. It is a common knowledge that in some patients initially diagnosed as PMR, the first diagnosis can change even after 9 months, while still influenced by longitudinal treatment with glucocorticoid (3, 4). In Marsman’s study, patients were not included if the PMR diagnosis changed within the first 9 months of follow-up. Moreover, only 2% of Marsman’s cohort developed giant cell arteritis (GCA) during follow-up. As the authors highlighted, this was far less than the usual reported GCA incidence of 16–20%. Is it possible that many GCA overlapping PMR could be not diagnosed in Marsman’s study because the included follow-up duration and the high percentage of excluded patients? (5). It could be interesting to compare the APR in patients included into study group with patients excluded from the analysis.

Three hypotheses were proposed to explain the lack of APR increase in patients with PMR. The possibility that these patients might just caught earlier in the disease

course with an increased APR at a later stage is unconvincing. Typically, PMR has an abrupt onset, and many patients remember the exact day and the hour when the clinical manifestations started (6, 7).

We agree with Marsman *et al* that a specific pathophysiologic pathway can be present in PMR patients with normal baseline APR. Recently, we speculated on the role of the so-called “immune checkpoints” (8). In some of these patients, clinical and/or laboratory findings have been considered atypical, so that PMR-like syndrome was diagnosed. According to our best knowledge, the expression of the immune checkpoints (ICs) in PMR has not yet been studied, but the onset of PMR following immune checkpoint inhibitors (ICIs) therapy might suggest a potential role of IC signal in PMR pathogenesis. In 2019, Calabrese *et al.* published the characteristics of 20 patients from three centers: 6/20 (30%) had normal inflammatory markers at the time of PMR diagnosis (9). Is it possible that an auto-immunisation triggered by ICIs could happen instead of being triggered by innate immunity activation with its traditional inflammatory markers? Innate immunity may trigger fever, fatigue, general malaise, and other constitutional manifestations: they were infrequently reported both in Marsman’s and in our cohort of PMR patients without elevated baseline APR. We are looking forward to comparative MRI studies in ICI-induced PMR.

Nevertheless, our considerations and the differences between Marsman’s and our study must not minimise the key-messages that Marsman’s study reposed: normal ESR and CRP should not stop to include PMR in differential diagnosis, because PMR without elevated baseline APR exists. Moreover, if the high percentages found by Marsman *et al* will be confirmed in other large-sized studies, one of the three preliminary required criteria (abnormal ESR/CRP) proposed by 2012 EULAR/ACR collaborative initiative (10) should be revised. In any case, a new conceptual approach to PMR is necessary.

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Competing interests: none declared.

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