

Polymyalgia rheumatica with normal inflammatory indices at the time of diagnosis: can we just move a step forward?

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Abstract

The existence of polymyalgia rheumatica (PMR) with normal inflammatory indices at the time of diagnosis still represents a diagnostic conundrum. According to the literature, some patients with PMR following immune checkpoint inhibitory therapy had normal values of both erythrocyte sedimentation rate and C-reactive protein concentrations at the time of diagnosis.

In this short communication we investigated the possibility that in some patients with PMR the main pathogenic mechanism is constituted by inhibition of some checkpoints, such as programmed death receptor-1, programmed death ligand 1, and “cytotoxic” lymphocyte antigen 4. In these patients, the pathogenetic mechanisms underlying PMR can act much more upstream than commonly suggested. Also, we addressed the question of whether these patients should be considered as affected by PMR-like syndromes or by PMR subset.

Key words: polymyalgia rheumatica, checkpoint inhibitory therapy, checkpoint inhibitors, inflammatory indices.

Initial raised values of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentrations are typical findings in patients with polymyalgia rheumatica (PMR), and they are present in all its diagnostic and classification proposed criteria [1]. An international collaborative initiative between the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) proposed new classification criteria in 2012. According to them, the age of 50 years or older, bilateral shoulder aching and abnormal CRP and/or ESR were considered required criteria [2].

In an editorial published in *Reumatologia* in 2018, we highlighted the possibility that, in an older person complaining of chronic bilateral shoulder and hip girdle pain associated with inflammatory morning stiffness, PMR can be considered even if ESR and CRP are both normal, and we proposed a four-point guidance [3]. In a case series published in 2019, among 460 PMR patients we identified seven (1.52%) with normal values of

both ESR and CRP concentrations at the time of diagnosis. In these seven patients, all PMR-mimicking diseases were excluded during follow-ups lasting from 29 to 120 months [4].

Since 2011, when ipilimumab was first approved for metastatic melanoma, immune checkpoint inhibitors (ICIs) have been receiving an increasing number of indications in cancer patients [5–7]. As is known, ICIs act by blocking some co-stimulatory molecules such as cytotoxic lymphocyte antigen 4 (CTLA-4), programmed death protein 1 (PD-1), programmed death ligand 1 (PD-L1), localized on T cells, antigen presenting cells and cancer cells. As a consequence of such inhibition, T cell activation and development of regulatory T cells (Tregs) are suppressed [8].

Among immune rheumatic adverse events associated with ICIs, PMR is frequently reported both as case reports and case series [9–14]. In a recent study on pharmacovigilance, a fivefold elevated risk for developing

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Submitted: 13.02.2020; Accepted: 20.04.2020

PMR was highlighted in cancer patients treated with ICIs versus those not treated [15]. In some of these patients, clinical and/or laboratory findings have been considered atypical, so that PMR-like syndrome was diagnosed. For example, in 2019 Calabrese et al. [9] published the characteristics of 20 patients from three centres: 6/20 (30%) had normal inflammatory markers at the time of PMR diagnosis. However, it must be highlighted that in three of these (patients no. 4, 9, 14) there were other findings (i.e. positivity for rheumatoid factor, knee involvement, treatment with prednisone 60 mg/day) that could not be compatible with this diagnosis [16].

Pathogenesis of PMR is debated [17–20]. According to our best knowledge, the activation of the immune checkpoints in PMR has not yet been studied. Nevertheless, the onset of PMR manifestations following ICIs might suggest their potential role in its pathogenesis.

On the other hand, an impaired PD-1 immune checkpoint has been proved again and again in giant cell arteritis (GCA). Indeed, in GCA-affected arteries a deficiency of the PD-1 immune checkpoint on dendritic cells (DCs) fails to inhibit interacting PD-1+T cells. As a consequence, uninhibited T cells overexpress [21, 22]. GCA is a vasculitis frequently associated with PMR, in most studies estimated between 10% and 30% [23]. However, the pathogenetic link between PMR and GCA is still not fully elucidated [24, 25], and all that is known for GCA cannot be applied to isolated PMR.

Recently there was an intriguing proposal to redefine PMR from inflammatory musculoskeletal syndrome to “inflammatory disease of musculotendinous structures” originating from peritendineum and perimysium [26]. The questions arises whether such localised auto-immunisation, possibly triggered by checkpoints inhibitors, could happen instead of being triggered by innate immunity activation with its traditional inflammatory markers. We are looking forward to comparative MRI studies in checkpoint inhibitor induced PMR.

Hence, future appropriately designed studies are needed. In the meantime, we can speculate that in some PMR patients the pathogenetic mechanisms act much more upstream than commonly considered. If this working hypothesis were proved correct, a new subset of disease having normal inflammatory indices (and not PMR-like syndrome) would be possible.

However, detailed definition of such a subset of disease must be provided to avoid overdiagnosis, as “secondary PMR” currently does not exist. A validation of musculoskeletal imaging utility in inflammatory marker negative PMR cases could be advocated as well as possibly higher cut-off values for PMR in classification criteria scores.

Conclusions

The onset of PMR cases in patients treated with ICI therapy suggests a potential role of immune checkpoint signals (PD-1 and PD-L1, above all) in PMR pathogenesis.

The fact that some of these cases had normal inflammatory indices at the time of diagnosis, as PMR patients (not treated with ICI therapy), in our case series suggests that a subset of disease, in which the impairment of these signals is relevant, can exist.

The authors declare no conflict of interest.

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