Back to the future: identification and classification of polymyalgia rheumatica and polymyalgia rheumatica-like syndromes following cancer immunotherapy with checkpoint inhibitors

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Abstract

Polymyalgia rheumatica (PMR) and PMR-like syndromes are among the most frequent rheumatologic immuno-related adverse events (IRAEs) induced by cancer immunotherapy with "checkpoint inhibitors" (ICIs). Our short communication addresses two key methodological issues laid bare by published literature : 1) how to diagnose PMR and PMR-like syndromes following ICI therapy, 2) how PMR/PMR-like syndromes following ICI therapy are described as adverse drug reactions (ADRs).

Key words: polymyalgia rheumatica, cancer immunotherapy, diagnostic and classification criteria, adverse drug reactions.

Immunotherapy with checkpoint inhibitors

Since 2011, when the US Food and Drug Administration (FDA) approved the use of ipilimumab – a fully human monoclonal antibody against cytotoxic T-lymphocyte antigen-4 (CTLA4) – for patients with metastatic melanoma, immunotherapy with checkpoint inhibitors (ICIs) has been recommended for an increasing variety of cancers, both in metastatic and adjuvant settings [1].

It is well documented that the ICIs' mechanisms of action can promote immune-related adverse events (IRAEs), which can affect multiple organ systems, and this risk increases when two ICIs are used in combination [2]. Among rheumatologic IRAEs, polymyalgia rheumatica (PMR) and PMR-like syndromes are, together with inflammatory arthritis, the most frequent clinical presentations [3].

Polymyalgia rheumatica/PMR-like syndromes following ICI therapy

To date, a few dozen instances of ICI-linked PMR and PMR-like syndromes have been reported in published literature, but, as the use of ICIs is significantly increasing in clinical practice, it is highly probable that cases will increase over time [4].

Two key methodological issues need to be addressed. The first one centers on how to diagnose PMR and PMR-like syndromes following ICI therapy. Over time, several diagnostic and classification criteria – of varying specificity and sensitivity – have been proposed and validated for PMR [5, 6]. Nevertheless, the risk that PMR could be used as an umbrella label for every glucocorticoid-responsive syndrome of shoulder and pelvic girdle pain and stiffness is always present [7].

A 2019 review reported on data from 49 patients enrolled via two sources: 20 patients from three col-

laborative centers, and 29 case reports from published literature. The 2012 EULAR/ACR classification criteria were applied, but not across the whole sample, due to inadequate data for 25% of patients [8]. More recently, a systematic review highlighted that in other case reports and case series, diagnosis of PMR was made only according to clinical judgment, without specifying which diagnostic or classification criteria were used. Moreover, in some patients this diagnosis was made by a managing non-rheumatologist [4].

We wonder how it was possible to diagnose a PMR-like syndrome when the boundaries of "primary/idiopathic" PMR had not been stated. Also, some cases described as PMR could indeed be new distinct clinical entities. The question is, if these diagnostic boundaries are not predetermined, how can we establish whether PMR following ICI therapy is a new entity or a subset of this disease?

The second issue revolves around defining PMR/PMR-like syndromes following ICI therapy as an adverse drug reaction (ADR). A commonly used algorithm is the ADR Probability Scale developed in 1981 by Naranjo and colleagues to standardize causality assessments. This scale estimates the probability that an adverse event is related to drug therapy.

A list of 10 weighted questions examines factors such as temporal association with the drug administration and event occurrence; alternative causes if any; drug levels; and previous patient experience with the same drug. The sum of the scores ranges from –4 to +13: a score > 9 is indicates that the drug "definitely" caused the ADR; a score between 5 and 8 indicates that the drug "probably" caused the ADR; a score between 1 and 4 indicates that the ADR was "possibly" caused by the drug; and a score < 1 indicates a "doubtful" association with the drug [9]. The key advantages of Naranjo's scale are its simplicity of use and clarity, and a significant increase in inter- and intra-rater agreement compared with standard clinical examination alone.

As recently confirmed by an EULAR/ACR task force, using the Naranjo scale may help to assess the causal link between rheumatologic IRAEs and ICI therapy [3]. Nevertheless, the absence of Naranjo's or other validated scales for ADR assessment in publications around PMR/PMR-like syndromes following ICI therapy is still a key critical point. In fact, ADR identification is based on clinical judgment only. When we were able to apply Naranjo's scale to the published reports' data [4], total Naranjo scores were almost never higher than 4.

We wonder, are PMR/PMR-like syndromes following ICI therapy true ADRs? Is the deductive-type methodology described in published case reports and case series the correct approach? In patients affected with malignancies, these questions are extremely relevant. Indeed, PMR can be a paraneoplastic syndrome, though not commonly [10, 11], and in cancer patients on ICIs this potential association should be carefully excluded. In short, is PMR caused by ICIs or by malignancy?

Conclusions

A more rigorous methodologic approach seems necessary and indeed mandatory for identification of PMR and PMR-like syndromes following ICI therapy, and for their classification as ADRs. Otherwise, there is a risk of mixing all the data in a "kind of cauldron".

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