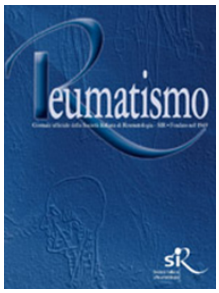

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After what time interval are we justified to diagnose immune checkpoint inhibitor-mediated polymyalgia rheumatica?

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Dear Editor,
the number of cases of cancer patients diagnosed as having immune checkpoint inhibitor-mediated polymyalgia rheumatica (ICI-PMR) has been steadily rising in published reports. However, the lack of a validated scale or algorithm is still a relevant methodological limit in diagnosing this nosologic entity.
A recent systematic literature review well illustrates this diagnostic limitation. The authors found a wide onset range - from one day to 213 weeks (about 4 years) - after the initiation of ICI treatment [mean time of onset ± standard deviation (range): 15.40±10.54 weeks]. The diagnosis of ICI-PMR was never based on validated algorithms. Clinical judgment only was preferred. Several articles included in this review were published after 2021 (1).
In 2021, a European Alliance of Associations for Rheumatology task force suggested the use of validated scales or algorithms (such as the so-called Naranjo scale) for assessing the causal link between immune-mediated adverse events and ICI therapy (2). The Naranjo scale is based on a list of 10 weighted questions and classifies the probability that an event is related to drug therapy, as an adverse drug reaction. The higher the score (the range is from -4 to +13), the higher the probability that an adverse event is related to the drug itself rather than a disease. According to the Naranjo's algorithm, the time between drug administration and event occurrence must be plausible for the specific event (3).
Pathogenesis of ICI-PMR is still a matter of more or less fascinating speculations. It could be hypothesized that in ICI-PMR, the first trigger is represented by an antigenic stimulus (potentially activated by the primary or metastatic tumour mass) recognized by the antigen-presenting macrophages. Subsequent activation of T-lymphocytes induced by ICIs could favour their infiltration in the anatomical sites where PMR starts (4). Could the variability of these steps, if confirmed, justify a temporal unpredictability of ICI-PMR?
As of today, what is the "plausible time interval" that can justify diagnosis of ICI-PMR seems entirely subjective (5). The duration of this time interval should instead be defined, as it cannot be dilated *ad libitum*. Are we willing to accept diagnosis of ICI-PMR when PMR manifestations occur after several months or even years of ICI treatment?

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