# Remitting seronegative symmetrical synovitis with pitting edema and polymyalgia-like syndromes following cancer immunotherapy with checkpoint inhibitors: causal link, potential association or else?

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Dear Editors,

I read with interest the manuscript entitled *Rheumatic immune-related adverse events from checkpoint inhibitor therapy: a case series*, recently published in Beyond Rheumatology, where Laria *et al*. reported three patients with rheumatologic immuno-related adverse events (r-IRAEs) following cancer immunotherapy with checkpoints inhibitors (ICIs). Their case-series gives food for thought. No doubt.

In particular, their case 3 described a 58-year-old man with metastatic melanoma who reported remitting seronegative symmetrical synovitis with pitting edema (RS3PE) associated with polymyalgia rheumatica-like (PMR-like) manifestations following 11 treatment cycles with pembrolizumab.[1]

I wish to share two considerations, that could be useful to readers in their clinical practice.

The first consideration revolves around the definition of rheumatic manifestations 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 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.[2] As recently confirmed by an EULAR/ACR task force, the use of Naranjo scale may help the assessment of the causal link between r-IRAEs and ICI therapy.[3] Nevertheless, the absence of Naranjo's or other validated scales for ADR assessment in publications around r-IRAEs following ICI therapy is still a key critical point. In fact, ADR identification is often based on clinical judgment only. In a recent systematic review on PMR and PMR-like syndromes following ICIs therapy, when we were able to apply Naranjo's scale to the published report data, the total scores were almost never higher than 4.[4] Therefore, a rigorous methodologic approach seems necessary and indeed mandatory (obviously, not only for PMR-like syndrome following ICIs therapy) to avoid a kind of *all-inclusive cauldron*.[5,6]

The second consideration revolves around the possibility that RS3PE syndrome may be a paraneoplastic warning in patients with PMR (or PMR-like manifestations). Indeed, RS3PE syndrome is a neoplastic marker in elderly patients with rheumatic diseases in up to 20% of cases.[7] According to our experience, the appearance of RS3PE syndrome in patients with PMR can be considered a neoplastic warning.[8] Therefore, in patients affected with malignancies, the possibility that the association of RS3PE + PMR may be a paraneoplastic finding should be carefully excluded. This question is extremely relevant. In short, is RS3PE + PMR caused by ICIs or a malignancy?

In conclusion, as Laria *et al.* highlighted, there are scarce and conflicting data in published literature on r-IRAEs following ICIs therapy. The road is still long. However, some points need to be very clear in everyday clinical practice.

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