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【 LETTERS TO THE EDITOR 】

Paraneoplastic Remitting Seronegative Symmetrical Synovitis with Pitting Edema Syndrome Should Be Treated with Low-dose Prednisolone During Pembrolizumab Therapy

Key words: RS3PE syndrome, pembrolizumab, immune checkpoint inhibitor, paraneoplastic syndrome, corticosteroid, immune-related adverse event

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To the Editor Aoshima et al. (1) described an intriguing case of two paraneoplastic syndromes in a patient with lung cancer. The authors described the importance of the proper diagnosis of paraneoplastic syndromes before initiating immune checkpoint inhibitor (ICI) therapy. They also mentioned that the treatment of lung cancer with pembrolizumab (anti-PD-1 antibody) improved, at least somewhat, the paraneoplastic syndromes without requiring immunosuppressive treatment. We would like to comment on their article from a rheumatologist's perspective.

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome can develop as an immune-related adverse event during ICI therapy (2). Recently, we treated a case of RS3PE syndrome that developed during pembrolizumab therapy. The patient in our case was a 76-year-old man in whom RS3PE syndrome developed after 17 cycles of pembrolizumab to treat advanced urothelial carcinoma. The patient exhibited extensive swelling of both his hands and feet, resulting from synovitis (Figure). The administration of low-dose prednisolone (15 mg/day) dramatically improved his symptoms within 2 weeks. This case suggests that ICIs can modulate the immune responses that cause RS3PE syndrome. Based on our experience, when we read the manuscript by Aoshima et al. (1), we anticipated that the paraneoplastic RS3PE syndrome would worsen after the initiation of ICI. Contrary to our expectations, the ICI therapy improved the RS3PE syndrome in this case. As the authors discussed, the improvement of the RS3PE syndrome might have been due to the tumor-regressing effect of the ICI therapy, which would overwhelm any potential exacerbating effect of the ICI in the patient. Because the balance between the improving and exacerbating effects of ICIs on paraneoplastic syndromes might vary depending on the patient's pathological condition, careful monitoring is required during ICI therapy.

We would like to ask the authors why they did not administer systemic corticosteroid to treat RS3PE syndrome. Corticosteroids are reported to be effective for treating RS3 PE syndrome, regardless of the presence of malignancies (3). In the present case, RS3PE syndrome-related symptoms persisted after partial improvement during ICI therapy. While we agree that tumor regression partially improved the symptoms, we believe that corticosteroid administration should have been considered in order to induce the remission of RS3PE syndrome. Since low-dose prednisolone has been reported to not affect the anti-tumor effect of ICIs (4, 5), clinicians should not hesitate to use it. Therefore, we believe that the administration of low-dose prednisolone would further improve RS3PE syndrome without affecting the cancer prognosis.

The authors state that they have no Conflict of Interest (COI).

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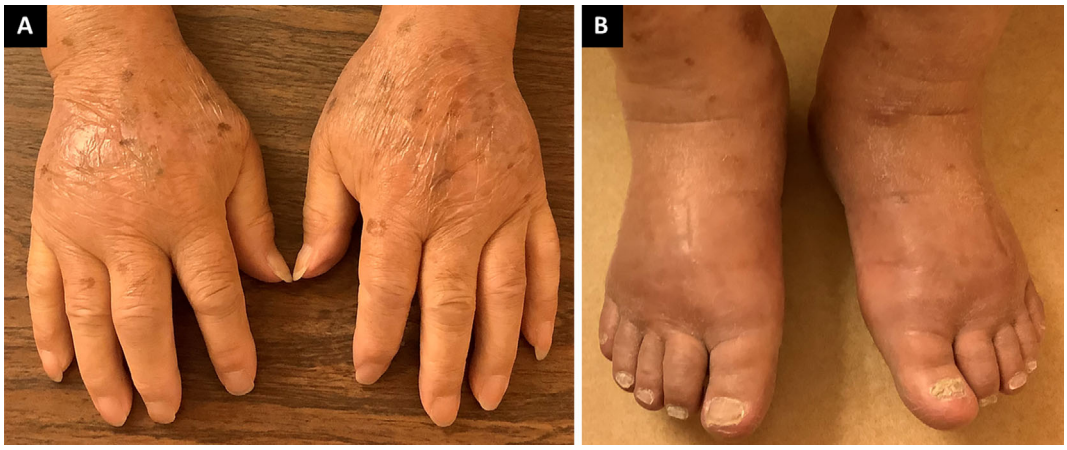

Figure. **Diffuse swelling on the dorsum of the bilateral hands (A) and feet (B).**

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