Systemic sclerosis and inflammatory myopathy after treatment with durvalumab in a patient with rectal neoplasm

Sirs,

This case report details a 74-year-old male patient who developed systemic sclerosis (SSc) and inflammatory myopathy after receiving durvalumab, an anti-PD-L1 immune checkpoint inhibitor (ICI) used in the treatment of his rectal neoplasm.

The patient had a history of hypertension, dyslipidaemia, and long-term autoimmune hypothyroidism managed with levothyroxine. In March 2022, he was diagnosed with infiltrating adenocarcinoma of the rectum, staged cT3pN1. Neoadjuvant treatment followed by surgery was decided. He was enrolled in a clinical trial where he received durvalumab combined with FOLFOX chemotherapy (folinic acid, fluorouracil, and oxaliplatin) starting in April 2022.

Within a week of starting durvalumab, the patient developed severe polyarthritis, mucositis, and a desquamative rash, managed with prednisone. Durvalumab was discontinued due to these adverse effects. By July 2022, he exhibited progressive myalgia, weakness, dyspnoea, and bulbar symptoms. Blood tests revealed elevated markers of muscle and myocardial damage, and he tested positive for antinuclear antibodies (ANA) and anti-PM-Scl antibodies. Subpleural ground glass infiltrates were found in his lungs. Treatment included methylprednisolone bolus, intravenous immunoglobulins (IVIG), and mycophenolic acid (MPA).

After discontinuation of durvalumab, the patient continued with FOLFOX chemotherapy, achieving partial tumour remission. He then underwent sequential radiotherapy and surgery in December 2022, leading to total tumour resection.

In April 2023, he was readmitted with worsening dyspnoea and muscular symptoms. Imaging showed organising pneumonia and acute inflammatory myopathy, treated with increased prednisone up to 40 mg/day and rituximab (1g x 2).

In November 2023, the patient was evaluated for the first time in our hospital. He had mild muscular involvement without any cutaneous toxicity or dyspnoea. Laboratory results indicated mildly elevated CK, LDH, transaminases, and high-titre ANA (7-8 Hep2) with a nucleolar pattern and moderate positivity for PM-Scl-75. He was on prednisone 20 mg/day, MPA 720 mg every 12 hours, and monthly IVIG. Muscle biopsy confirmed necrotising myositis and focal perifascicular atrophy (Fig. 1), and high-resolution CT showed stable organising pneumonia. Capillaroscopy revealed dilated capillaries, tortuosity, and avascular areas (Fig. 2). A slow tapering of prednisone was initiated, with maintenance of MPA and IVIG.

In February 2024, the patient developed Raynaud's phenomenon (RP), telangiectasias, sclerodactyly, and puffy fingers (Fig. 3). Muscular symptoms such as myalgia and weakness persisted so RTX maintenance therapy (500 mg every 6 months) was considered. By April 2024, the patient remained free of oncologic disease.

This case illustrates a possible durvalumab-induced toxicity affecting multiple organs and subsequent development of systemic sclerosis. The emergence of ANA and anti-PM-Scl antibodies, alongside clinical symptoms like RP and sclerodactyly, suggest an autoimmune response potentially triggered by durvalumab.

The onset of SSc in this patient raises the question of whether it is an ICI-associated condition, has a paraneoplastic origin or it is just a casual coincidence. The literature indicates a known association between SSc and neoplasia, particularly with certain antibodies (1). However, the association with anti-PM-Scl antibodies is less clear (2, 3).

The relationship between ICIs and the onset of SSc remains complex and not fully understood. Particularly PD-1 inhibitors have been associated with SSc development, with a possible role of T-cell co-stimulation signals in SSc pathogenesis (4, 5).

Durvalumab, which enhances T-cell activation by blocking PD-L1 interactions, has been linked to various immune toxicities but not definitively to SSc (4, 6-8). Reports of similar cases are emerging, suggesting a need for heightened awareness (9).

The case underscores the necessity for vigilant monitoring of patients on durvalumab for potential autoimmune adverse effects, particularly those with pre-existing autoimmune conditions (4). Further research is needed to elucidate the mechanisms behind ICI-induced autoimmune diseases and to establish guidelines for managing such complex cases. Multidisciplinary care and thorough reporting of adverse events are crucial for optimising patient outcomes in oncology and autoimmune disease management.

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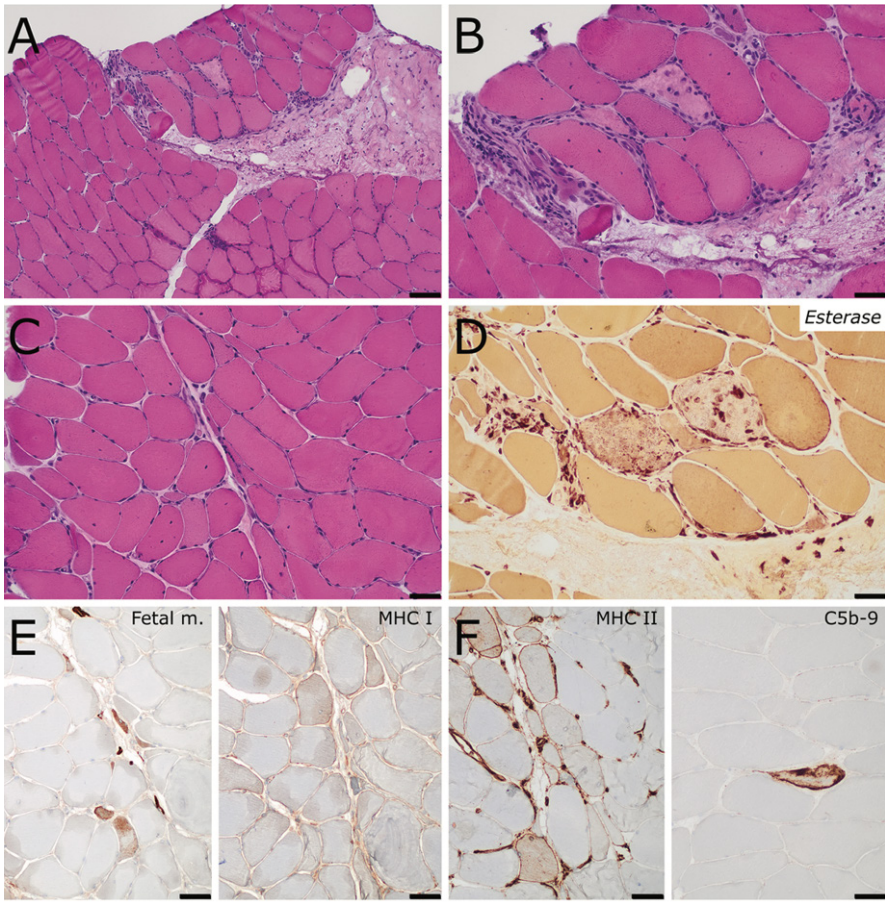

Fig. 1. Muscle biopsy showed scattered images of necrosis (**A** and **B**), while there were focal areas of perifascicular atrophy (**C**). Esterase highlighted the foci of macrophagic necrosis (**D**). Foetal myosin showed fibre regeneration in perifascicular areas (**E** left). Major histocompatibility complex type I had a diffuse membrane positivity (**E** right), while type II was mainly limited to perifascicular areas (F left). Necrotic fibres were positive for C5b-9 complement complex (**F** right). Scale bars: A 100 µm, B to F 50 µm.

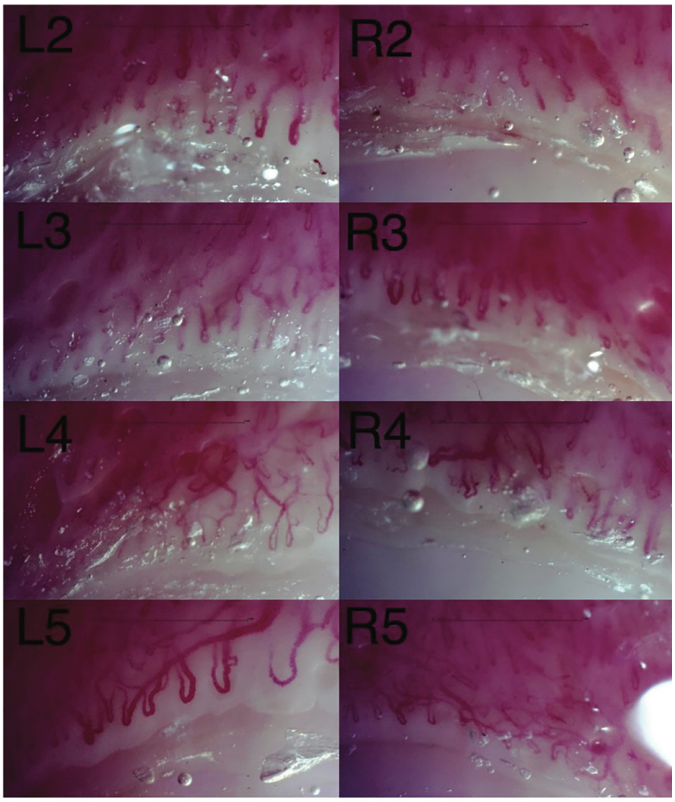

Fig. 2. Capillaroscopy of left (L2-L5) and right (R2-R5) nailfolds, showing very decreased capillary density, with an average of 6.0 capillaries/mm. Capillary dilation was found in 68.6% of observed capillaries, with an average apical diameter of 27.4 µm. There was the presence of giant capillaries with a percentage of 4.3%. Tortuosities and abnormal shapes were infrequent, with an involvement of 14.8% and 2.1% of observed capillaries, respectively. There was the presence of haemorrhages with an average density of 0.1 haemorrhages/mm and an average surface area of 17516.3 µm^2.
Quantitative analysis performed with the software Capillary.io ®".

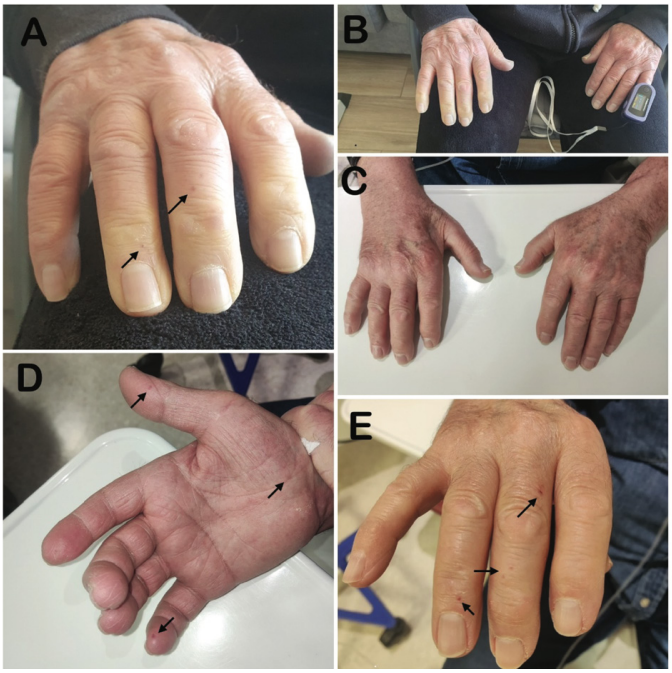

Fig. 3. Patient's hands, showing Raynaud's phenomenon (**A** and **B**), puffy fingers (**C**), and sclerodactyly (**D**), with inability to open the hands. Note round telangiectasias, marked with arrows (**A, D, E**).

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