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Rare cutaneous toxicity of immune checkpoint inhibitors: A case of durvalumab-induced dermatomyositis

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KEYWORDS

Immune checkpoint inhibitors;
Hepatocarcinoma;
Paraneoplastic syndrome;
Dermatomyositis;
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Dear editor,

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Cutaneous reactions are among the most frequent immune-related adverse events (irAEs) with immune checkpoint inhibitor (ICI) therapies targeting cytotoxic T-lymphocyte antigen 4 or programmed death (ligand)-1 (PD-1/PD-L1). Most reactions present as maculopapular rash, pruritus, vitiligo, lichen, or bullous diseases. There are few observations about sarcoidosis, lupus, or sclerosis. We report here a dermatomyositis revealed by anti-PD-L1 immunotherapy.



Fig. 1. Clinical features. (A) Voluminous oedema of eyelids. (B) Superficial erosions on heliotrope rash few days later.

A 66-year-old man was referred to our hospital for a stage B hepatocellular carcinoma (HCC) with three intrahepatic lesions, on a CHILD A5 liver, and AFP-score of 6. He had no personal or familial history of autoimmunity, but his brothers were diagnosed with haemochromatosis. Because hepatocarcinoma was unresectable, he underwent two chemoembolisations with idarubicin, followed by an infusion of durvalumab. Eighteen days later, he was referred to dermatology department for the rapid onset of symmetrical erythematous oedema of the eyelids, associated with subsequent erosive lesions that extended to the forehead (Fig. 1), and ulcerative cheilitis. No other lesion was present upon comprehensive skin and mucosae examination, nor pathological lymph nodes, nor myositis symptoms. Herpes simplex virus (HSV) infection was ruled out and 0.5 mg/kg oral prednisone was prescribed. Upon a recent sun exposure, idarubicin phototoxicity was first suspected. Two days later, he reported a slight improvement, and received a second infusion of durvalumab. However, 48 h later, he presented to the emergency ward for a left leg oedema, with negative screening for venous thrombosis. Clinical examination revealed proximal muscular weakness, while creatine kinase reached the level of 3816 UI/l (20N), with myoglobin level of 2580 UI/l (35N) and a mildly elevated troponin (Troponin T-HS 130 ng/l). Immunology revealed antinuclear antibodies titre of 1/1280, and positivity of anti-transcriptional intermediary factor-1-gamma (anti-TIF1 γ) autoantibodies, consistent with the diagnosis of dermatomyositis. Cardiac magnetic resonance imaging excluded myocarditis, while angiography revealed a severe coronary artery disease with mainly a significant stenosis on the left main coronary artery. Because of immune haemolytic anaemia and thrombocytopenia, angioplasty was postponed and he received three pulses of methylprednisolone with subsequent oral prednisone 1 mg/kg. Few days later, he exhibited a septic discharge on the

peripherally inserted central catheter of the left arm, which lead us to introduce antibiotics (daptomycin/cefazolin/gentamicin). Unfortunately, he presented sudden respiratory failure complicated by cardiac arrest a few hours later and died from subsequent multiorgan failure in spite of adapted reanimation. Post-mortem analyses revealed positivity for anti-acetylcholine receptor antibodies, leading to the diagnosis of ICI-induced myasthenia gravis (MG). Myasthenic crises may be a possible explanation for the sudden respiratory distress that may have been triggered by minoglycosides.

A literature review in 2018 found 10 cases of HCC associated with dermatomyositis [1], an inflammatory myopathy which is known to be associated with cancer in up to 20–30% of cases (paraneoplastic syndrome). This association is strongly dependent on the subtype of myopathy-specific autoantibody involved, like anti-TIF1 γ . Interestingly, there is a literature supporting the role of TIF1 γ in the regulation of transforming growth factor-beta superfamily signalling, which is involved in the control of cellular proliferation, and thereby in cancer inhibition. A study even found a reduced expression of TIF1 γ in HCC, especially in advanced HCC [2]. The authors mentioned a poor prognosis of decreased level of TIF1 γ , as a significant risk factor for recurrence, and associated with more metastases [2].

There are few cases of ICI-induced dermatomyositis, and only one with anti-TIF1 γ antibodies, triggered by ipilimumab [3,4]. The clinical signs were unusual, leading us to misdiagnose, because if heliotrope rash of the upper eyelids is classical, this intensity remains exceptional. We were also surprised by the migrating oedema of the limbs that the patient presented. Unilateral oedema of the limbs is uncommon, but possible, in inflammatory myopathy, with a recent article outlining the association with the antibodies of dermatomyositis, rather than other inflammatory myopathies [5]. Interestingly, ICI-induced myositis may also be associated with MG and myocarditis (3M syndrome) in 11.9% and 11.3% of cases respectively [6], with worse prognosis and higher mortality rates. Of note, paraneoplastic syndromes are known to be a risk factor for irAEs [7].

As a conclusion, we describe for the first time the co-occurrence of TIF-1 gamma dermatomyositis and MG under anti-PD-L1 therapy with fatal outcome in a patient with hepatocarcinoma. This unfortunate observation prompts to more vigilance in the follow-up of patients under ICIs, and systematic biological screening on creatine kinase. Immunological work-up should also include anti-acetylcholine receptor antibodies.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ATJM received fees from Abbvie, Actelion, CSL Behring, Experf, Novartis, and Shire and declares speaking fees from Astra-Zeneca, Sanofi-Aventis, and BMS in the last 5 years. Other authors declare they have no known competing financial interests.

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