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Letter to the Editor

Generalised morphea induced by pembrolizumab

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Letter to the editor

We want to report the case of a severe generalised morphea induced by pembrolizumab and discuss this association.

Anti-PD1 monoclonal antibodies are associated with immune-related adverse events. The commonly reported skin adverse events are non-specific erythema or pruritus, psoriatic or lichenoid-like rashes. Less frequently, they can present as autoimmune skin diseases such as vitiligo, cutaneous erythematosus lupus or bullous pemphigoids. Cutaneous scleroderma has rarely been reported with only five cases found in the literature.

A 74-year-old woman was referred to our hospital for a stage IV melanoma involving the lymph nodes, liver and brain without any known primary melanoma. Her melanoma harboured a *NRAS* mutation and was wild type for *BRAF* and *KIT*. After surgical resection of her unique brain metastasis, she received pembrolizumab 2 mg/kg every 3 weeks. After five infusions of pembrolizumab, she was in complete response (CR). After 21 weeks of treatment, she was diagnosed with a grade II diffuse vitiligo. She also complained of a grade II pruritus, a burning skin sensation and ocular dryness, as well as a grade II articular pain (right shoulder, knees and hands). She was treated symptomatically and received three additional infusions of pembrolizumab. Thirty weeks after treatment initiation, she presented with painful and atrophic skin areas on her neck, chest and shoulders (Fig. 1). A cutaneous biopsy showed thickened and horizontalised collagen fibres in the dermis associated with a dermal lymphocytic infiltration (Fig. 2) without any epidermal abnormality. She had no vascular, respiratory or digestive symptoms. Circulating autoantibodies were absent. Renal function was normal, and there was no sign of pulmonary involvement on the computed tomography (CT) scan. Pulmonary function testing was normal. She was diagnosed with a cutaneous generalised morphea induced by immunotherapy. Pembrolizumab was definitively discontinued. Colchicine 1 mg/d was first initiated in association with topical clobetasol propionate. After 1 week, the patients' skin condition continued to worsen with an extension of skin infiltration. Colchicine was discontinued, and she was initiated oral prednisone 15 mg/day. After 3 weeks of systemic corticotherapy, her symptoms continued to

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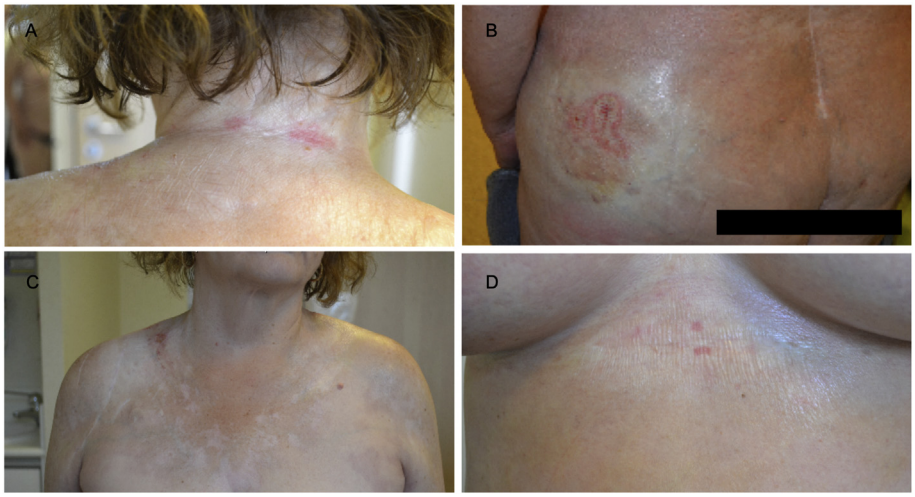

Fig. 1. Clinical presentation of scleroderma. A: Skin atrophy and stiffness on the neck. B: Skin atrophy with ulceration. C: Skin atrophy and stiffness associated with vitiligo. D: Morphea on the abdomen.

worsen. She then received three infusion of cyclophosphamide high dose (1000 mg = 584 mg/m^2) that did not improve her symptoms. After 40 days, cyclophosphamide was discontinued, and she received infliximab 5 mg/kg every 8 weeks. After three infusions, she felt a real improvement of her symptoms, and her skin condition was objectively ameliorated with a significant skin softening.

A new CT scan evaluation performed 7 months after pembrolizumab discontinuation showed a persistence of the CR.

Only five cases of scleroderma induced by immune checkpoint inhibitors (ICI) have been reported in the literature [1–5] (Table 1). They were all men. All but one were treated for metastatic melanoma. Pembrolizumab was used for three patients and nivolumab for the two others. In all cases, scleroderma appeared after at least 3 months of treatment (between 15 and 54 weeks). Three had a generalised scleroderma, and the two others had a limited scleroderma. Autoantibodies were constantly negative. Two patients had a stable disease, one had a CR, and data are missing for the two others.

All patients were treated with systemic corticosteroids for the scleroderma. Two patients received mycophenolate mofetil, and one of them also received intravenous immunoglobulins. One patient received hydroxychloroquine.

All patients experienced an improvement of their symptoms and skin changes within the first weeks of the treatment for scleroderma.

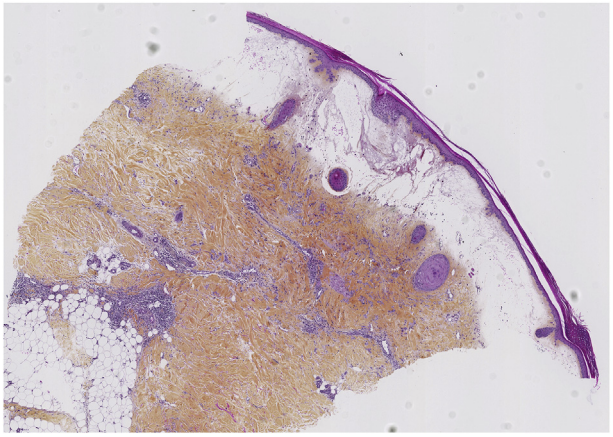

Fig. 2. Histological aspect of scleroderma. Dermal fibrosis with thickening and horizontalisation of collagen fibres. Haematoxilin-eosin x25.

Table 1
Characteristics of patients with immune-related scleroderma.

Cases	Gender/age	Tumour	Previous treatment	Drug	No of cycles	Modified Rodnan skin score (mRSS)	Scleroderma extra-skin symptoms	Extra-skin irAE	Scleroderma subtype	Tumour response	Treatment for scleroderma	Evolution of scleroderma
Barbosa et al.	M/66	Melanoma	0	Pembrolizumab 2 mg/kg /3 weeks	13	36	0	- Fatigue - Joints swelling - Muscle weakness - Sensorimotor axonal polyneuropathy	Diffuse scleroderma	Complete response	- Prednisone 1 mg/kg - IV immunoglobulins - Mycophenolate mofetil 1000 mg bid	Symptoms improvement within 8 weeks without objective skin changes
	M/79	Melanoma	0	Pembrolizumab 2 mg/kg /3 weeks	5	12	- Raynaud phenomenon - Periungual erythema - Dilated nail-fold capillaries	- Weakness - Pneumonitis	Limited scleroderma	NA	- Hydroxy-chloroquine 200 mg bid - Prednisone 1 mg/kg	Symptoms and skin changes improvement within 3 weeks
Tjarks et al.	M/61	Renal cell carcinoma	Radiation therapy Pazopanib	Nivolumab /2 weeks	16	28	0	0	/	Stable disease	- Prednisone 1 mg/kg - Mycophenolate mofetil	Symptoms improvement and objective skin changes improvement
Cho et al.	M/70	Melanoma	Interferon	Nivolumab 2 mg/kg /3 weeks	18	2	0	- Vitiligo	/	NA	- Prednisolone 0,3 mg/kg	Symptoms and skin changes improvement in a few days
Cheng et al.	M/64	Choroidal melanoma	Ipilimumab 3 mg/kg /3 weeks	Pembrolizumab 200 mg /3 weeks	5	NA	0	- Hypothyroidism - Vitiligo - Colitis	Generalised morphea	Stable disease	- Prednisone 0,8 mg/kg	Skin changes improvement
Our case	F/74	Melanoma	Radiation therapy	Pembrolizumab 2 mg/kg /3 weeks	6	22	0	- Vitiligo - Joint pain - Ocular dryness - Xerostomia	Generalised morphea	Complete response	- Topical steroids - Colchicine - Prednisone 15 mg/d - Cyclophospha-mide 1000mg/3 weeks - Infliximab 5 mg/kg/8 weeks	Symptoms and skin changes improvement after infliximab

Scleroderma is a rare and potentially serious dermatologic immune-related adverse events that can occur in patients treated with anti-PD1 therapy. The number of reported cases is too small to know whether there is a relationship between the occurrence of scleroderma and response to ICI therapy. Anti-tumour necrosis factor-alpha therapy was remarkably effective in our patients as it frequently also the case for colitis induced by immune checkpoint blockade.

Conflict of interest statement

Authors do not declare disclosures for this work.

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