

A case of nivolumab-induced scleroderma-like syndrome successfully treated with intravenous immunoglobulin



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Key words: checkpoint inhibitor; immune-related adverse event; IVIG; scleroderma-like syndrome.

INTRODUCTION

Checkpoint inhibitors are monoclonal antibodies used in cancer therapy to stimulate the immune system's antitumor activity by preventing T-cell inhibition through targets such as PD-1/PD-L1 and CTLA-4. The increased immune activity is not tumor-specific, and immune-related adverse events (irAEs) are common. Cutaneous reactions are some of the most frequent irAEs described, making up a broad spectrum of reactions, including acneiform, lichenoid, psoriasiform, and immunobullous eruptions,^{1,2} as well as rare checkpoint inhibitor-induced morphea or scleroderma-like syndrome (SLS).^{3,4} Some reported immunotherapy-induced SLS cases were severe and refractory to corticosteroid treatment, causing significant morbidity.⁴ This case describes the successful treatment of PD-1 inhibitor nivolumab-induced SLS with intravenous immunoglobulin (IVIG).

CASE REPORT

A 69-year-old woman with metastatic small-cell lung cancer on nivolumab for 2.5 years and a remote history of follicular lymphoma in remission initially presented to rheumatology with debilitating joint pain and swelling of the hands, wrists, feet, and ankles. She had a positive rheumatoid factor, which was negative the year prior. The patient was diagnosed with immunotherapy-induced rheumatoid arthritis, prompting the discontinuation of

Abbreviations used:

irAE:	immune-related adverse event
IVIG:	intravenous immunoglobulin
SLS:	scleroderma-like syndrome
NBUVB:	narrow-band ultraviolet B

nivolumab. Sulfasalazine, methotrexate, hydroxychloroquine, and adalimumab were initiated with a 3-month course of prednisone. Two months into this regimen, the patient was referred to dermatology for skin tightening, dysphagia, and increasing fatigue. She denied symptoms of Raynaud's phenomenon. On examination, she had indurated and sclerotic plaques over her chest, arms, abdomen, and back with a limited range of motion (Fig 1). She had no nailfold capillary changes or sclerodactyly. Biopsy showed increased dermal collagen and entrapment of the eccrine glands consistent with morphea (Fig 2). Antinuclear antibody and extractable nuclear antigen panel were negative. Pulmonary function tests were consistent with restrictive lung disease. Mycophenolate mofetil and psoralen UV-A were added to the patient's treatment regimen of sulfasalazine, methotrexate, hydroxychloroquine, adalimumab, and prednisone, but both were discontinued after 3 months because of intolerable nausea and vomiting. After about a year of treatment, persistent cytopenia resulted in the discontinuation of

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Fig 1. Indurated, sclerotic plaques on the chest and back with markedly reduced range of motion.

methotrexate. Her skin disease progressed with sclerotic plaques involving most of her upper body, with an associated decreased range of motion limiting her daily activities. She was started on IVIG and narrow-band UV-B (NBUVB). After 2 months, her cutaneous induration and tightening had improved, and the cobblestone texture of her lower extremities was less prominent. Ten months after starting IVIG and NBUVB, she had a dramatic improvement in her skin and range of motion (Fig 3). Because of COVID-19 exposure concerns, NBUVB therapy was tapered to once weekly and was eventually stopped. After stopping NBUVB, her skin disease remained well controlled for more than 15 months on monthly IVIG, adalimumab, and hydroxychloroquine. Palliative radiotherapy and cryoablation of a single adrenal tumor were the only treatments she received during this time for her lung cancer. The patient died suddenly from a myocardial infarction.

DISCUSSION

The patient presented here developed immunotherapy-induced SLS with overlapping features of generalized morphea and systemic sclerosis. Her cutaneous disease lacked some classic clinical features of scleroderma, including sclerodactyly, Raynaud's phenomenon, and nailfold capillary changes. However, her dysphagia and restrictive



Fig 2. Improved range of motion and reduction of induration and skin tightening after 10 months of IVIG therapy.

lung disease coincided with the onset of her skin disease and were felt to be part of the same irAE. Given these overlapping features, we believe the best term for this irAE is nivolumab-induced SLS, a term used first in the description of another nivolumab-associated sclerotic skin disease that lacked some classic features of scleroderma.³ While a paraneoplastic SLS diagnosis was also taken into consideration, these patients typically do not improve without treatment of their underlying malignancy.⁵ Our patient improved on IVIG while treatment of her lung cancer was limited to palliative radiation before cryoablation of an individual metastasis. Therefore, a delayed nivolumab-induced SLS was thought more likely.

Current understanding of checkpoint inhibitor-induced fibrotic skin disease is limited but may involve upregulation of transforming growth factor β and the creation of a profibrotic state.² Cutaneous irAEs may resemble other dermatologic conditions like morphea or scleroderma, but nuanced differences in the pathogenesis may impact patient presentation and response to therapy, shown by the contrasting degree of response to steroid therapy alone versus the requirement of additional therapies in sclerodermatous irAEs.²⁻⁴ In this case, steroid

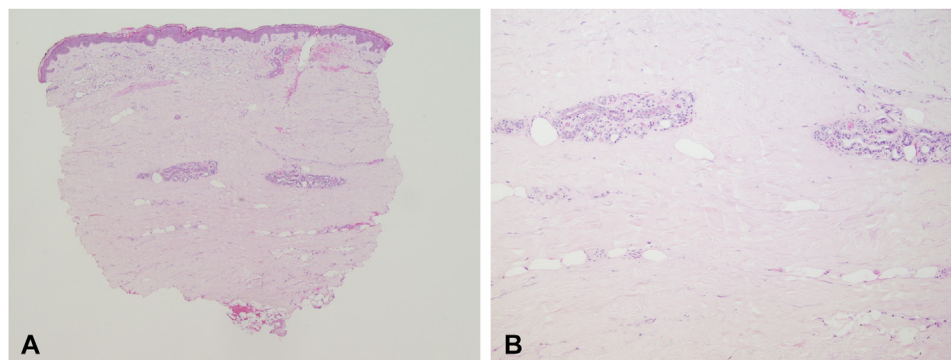


Fig. 3. Square biopsy sign with increased dermal collagen and entrapment of the eccrine glands consistent with morphea.

Table I. Other cases of immunotherapy-induced sclerotic skin disease

Drug(s)	Target	Patient sex, age, and indication	irAE	Time from drug onset to irAE	Treatment of SLS and result	SLS treatment response outcome
Pembrolizumab Ipilimumab Nivolumab	PD-1, CTLA-4	61 M, Melanoma	Generalized morphea associated with eosinophilia ⁴	10 mos (from combined immunotherapy onset)	Dexamethasone pulse dosing and clobetasone propionate	Improvement but not resolution
Nivolumab	PD-1	70 (s) M, Melanoma	SLS with no system symptoms ⁵	54 wks	Prednisolone, 20 mg/d (0.3 mg/kg)	Resolution after 9-mo prednisone taper
Nivolumab	PD-1	61 M, Oligometastatic renal cell carcinoma	Scleroderma-like skin changes ⁶	32 wks	Prednisone, mycophenolate mofetil	Improved; flared after prednisone taper requiring mycophenolate mofetil

irAE, Immune-related adverse event; SLS, scleroderma-like syndrome.

therapy was insufficient; the patient failed several additional therapies before responding to IVIG. As more checkpoint inhibitors are developed and used, the incidence of drug-induced fibrotic conditions will likely increase. Sclerodermatous irAEs have been reported after the use of dacarbazine,² nivolumab,^{3,4} and pembrolizumab.² However, it remains unclear whether the clinical presentation and treatment response of irAEs will be related to the specific offending drug. While most irAEs occur within a few months of therapy, delayed reactions are becoming increasingly recognized.⁶ Our patient developed SLS 2.5 years after starting nivolumab, adding to this growing list of delayed irAEs. For other cases of immune-related sclerotic skin disease see [Table I](#).

Sclerotic conditions can have a profound impact on wellbeing, and no universally effective therapy exists. Systemic immunosuppressive therapies are often used, including methotrexate, mycophenolate

mofetil, cyclophosphamide, prednisone, and rituximab, among others. IVIG offers a nonimmunosuppressive therapeutic option, which may be preferable during ongoing cancer treatment. The successful use of IVIG for systemic sclerosis was reported as early as 2000,⁷ and there are several reports of morphea demonstrating a positive response to IVIG therapy.⁸⁻¹⁰ Due to the relatively recent phenomenon of immunotherapy-induced SLS, it is unknown whether this condition will respond to the same therapies as systemic sclerosis and morphea. We present this case as an example of nivolumab-induced SLS responding to IVIG with marked improvement in disease burden and quality of life. It is worth noting that NBUVB may have initially contributed to improvement in our patient's disease, however, IVIG likely had the greatest benefit as our patient did not experience a relapse when NBUVB was discontinued.

Though more research is needed to document the response rate and time until clinical improvement, we believe select patients may benefit from the addition or substitution of IVIG therapy for their SLS disease.

Conflicts of interest

None disclosed.

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