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Case Report

Scleroderma Secondary to Pembrolizumab: A Case Report and Review of 19 Cases of Anti-PD-1-Induced Scleroderma

Stephanie Farrugia[a] Liam Mercieca[a] Alexandra Betts[b] Nick Refalo[c] Michael J. Boffa[a]

[a]Department of Dermatology, Mater Dei Hospital, Msida, Malta; [b]Department of Pathology, Mater Dei Hospital, Msida, Malta; [c]Department of Oncology, Sir Anthony Mamo Oncology Centre, Msida, Malta

Keywords
Scleroderma · Pembrolizumab · Nivolumab · Anti-programmed cell death-1 agents · Immunotherapy · Case report

Abstract
Immune checkpoint inhibitors are increasingly being used to treat various malignancies. Despite their efficacy, they are known to potentially cause immune-related adverse effects, including dermatological manifestations. A rare cutaneous immune-related adverse effect is scleroderma, which has been reported to occur with anti-programmed cell death-1 (PD-1) agents such as pembrolizumab and nivolumab. This may present with skin tightening and hardening at any point during or after immunotherapy. We present the case of a 54-year-old Caucasian woman who, following 16 doses of pembrolizumab for breast cancer, developed clinical features of scleroderma confirmed on histology. She was initially treated with oral corticosteroids, followed by oral psoralen-UVA, with poor response, but eventually improved with methotrexate. A literature review revealed 12 other cases of scleroderma following pembrolizumab treatment and 6 cases of scleroderma following nivolumab treatment. Males and females were both affected, and their ages ranged from 33 to 81 years. Scleroderma developed at different stages of pembrolizumab or nivolumab therapy. Although scleroderma is not commonly drug-induced, anti-PD-1 agents may be a rare cause and it is important to elicit an accurate drug history, including immunotherapy, in such cases.

Correspondence to:
Stephanie Farrugia, stephanie.f.farrugia@gov.mt

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Introduction

Immune checkpoint inhibitors (ICIs) are increasingly being used to treat various malignancies. They can potentially cause various dermatological side effects, including vitiligo, morbilliform rash, urticaria, dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis [1, 2]. Scleroderma has also rarely been reported with anti-PD-1 agents such as pembrolizumab and nivolumab [3] and may present with skin tightening and hardening at any point during or after immunotherapy. There are various factors and predictors that are involved in the treatment response and toxicity of immunotherapy, of which there is a need for better comprehension [4]. These include reliable predictors of response to ICIs, which would be vital to modulate their therapeutic responses [4], and better understanding of the role of potential biomarkers [5–7].

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A 54-year-old Caucasian woman was referred by her oncologist to the dermatology clinic with a 2-month history of diffuse, painful, and itchy skin tightening, which started on her distal extremities then gradually also affected her trunk and abdomen. There was no history to suggest Raynaud's phenomenon, difficulty with swallowing or gastrooesophageal reflux, and no history of previous skin problems or autoimmune disease. She had a history of an extra-skeletal osteosarcoma of her left leg when she was 45 years old, which was fully excised and treated with radiotherapy.

She was diagnosed with triple negative (oestrogen receptor, progesterone receptor, HER2 receptor negative) right breast carcinoma in September 2019 and initially received a neoadjuvant treatment regimen of carboplatin-paclitaxel-pembrolizumab, started in December 2019. She was originally planned to receive a total of 4 cycles (carboplatin and paclitaxel administered on days 1, 8, and 15; and pembrolizumab administered on day 21 of each cycle), however, only received three cycles due to severe adverse effects, including lethargy, nausea, vomiting, diarrhoea, headaches, dizziness and paraesthesia in both lower limbs. She underwent right wide local excision with axillary clearance in March 2020, followed by 3 weeks of radiotherapy to the right breast and right axillary lymph nodes. This was followed by a further 13 cycles of 200 mg pembrolizumab every 3 weeks, started in July 2020.

The patient was doing well on pembrolizumab, however, following cycle 9 she developed an erythematous rash with hardness of skin and swelling over her right breast at the site of her previous radiotherapy. This was deemed to be due to radiation recall and was treated with hydrocortisone cream with good effect. The pembrolizumab was continued with no further skin issues and treatment was completed in April 2021, after 13 cycles.

Three months after her final cycle of pembrolizumab, the patient experienced persistent pruritus with skin erythema which initially affected her extremities, but later also the trunk, and was associated with gradually worsening skin induration and discomfort. Low dose oral prednisolone and betamethasone valerate cream were prescribed by her oncologists with minimal effect. In view of this, the patient was referred to the dermatology clinic.

Examination revealed diffuse skin sclerosis with induration, thickening, and erythema in the affected areas (Fig. 1, 2). There were no obvious telangiectasia apart from on the right chest in the same area that was treated previously with radiotherapy. The digits were unaffected with no signs of swelling, ischaemia, or calcinosis. The clinical impression was of scleroderma secondary to pembrolizumab. Investigations including a complete blood count, anti-nuclear antibody (ANA), rheumatoid factor IgM, total extractable nuclear antigen, ANCA, anti-citrullinated peptide, RNA polymerase III antibody, anti-Scl 70, anti-centromere, anti-RO 52, and anti-ribonucleoprotein antibodies were all unremarkable.

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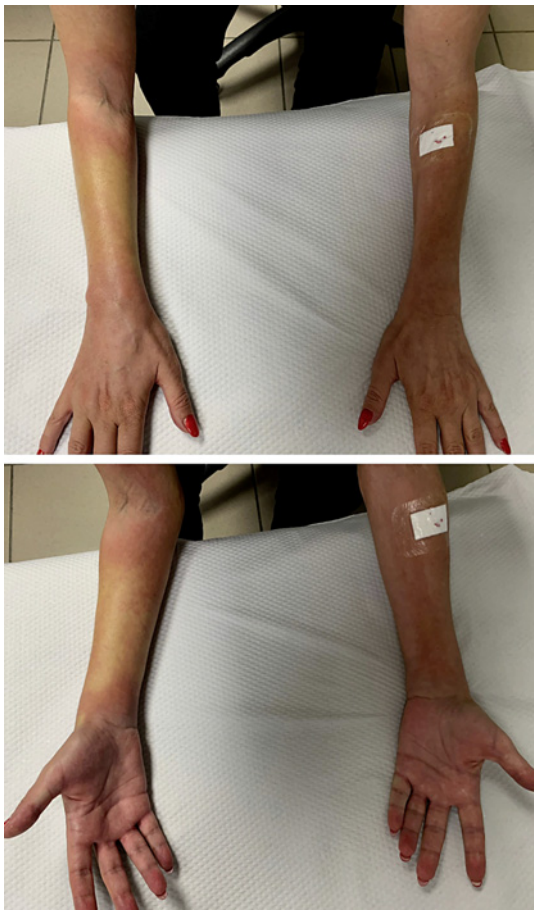

Fig. 1. Skin tightening with erythema, induration and skin thickening affecting the patient's forearms and hands bilaterally.

Skin biopsies from the left forearm and the right side of upper abdomen, respectively, revealed a thickened dermis with hyalinised sclerotic collagen fibre bundles that extended into the subcutis in thick bands. Mild thickening of the blood vessel walls could also be appreciated (Fig. 3). A Hale's colloidal iron stain revealed very focal deposition of scanty mucin between the collagen fibres. These histological features were in keeping with a diagnosis of scleroderma.

Given that the patient had already responded unfavourably to topical and oral corticosteroids, oral psoralen-UVA (PUVA) therapy was added with, however, only minimal improvement after 2 months. PUVA was therefore stopped and methotrexate was prescribed instead (initially 5 mg weekly then increased gradually over 3 months to 15 mg weekly). The patient reported gradual improvement of her pain and erythema, however, significant skin stiffness persisted. The latter was managed further with physiotherapy. The skin fibrosis generally improved, but remained noticeable, especially over her right upper limb. The patient is currently still receiving methotrexate. The patient's timeline of diagnoses and treatment is outlined (shown in Fig. 4). She has also remained well from an oncological point of view and her most recent PET scan was unremarkable.

Discussion

Scleroderma is an autoimmune multisystem connective tissue disorder characterized by skin fibrosis which may be limited or diffuse, causing skin tightening and hardening, and possibly fibrosis of other organ systems such as the lung and vascular involvement [8, 9].

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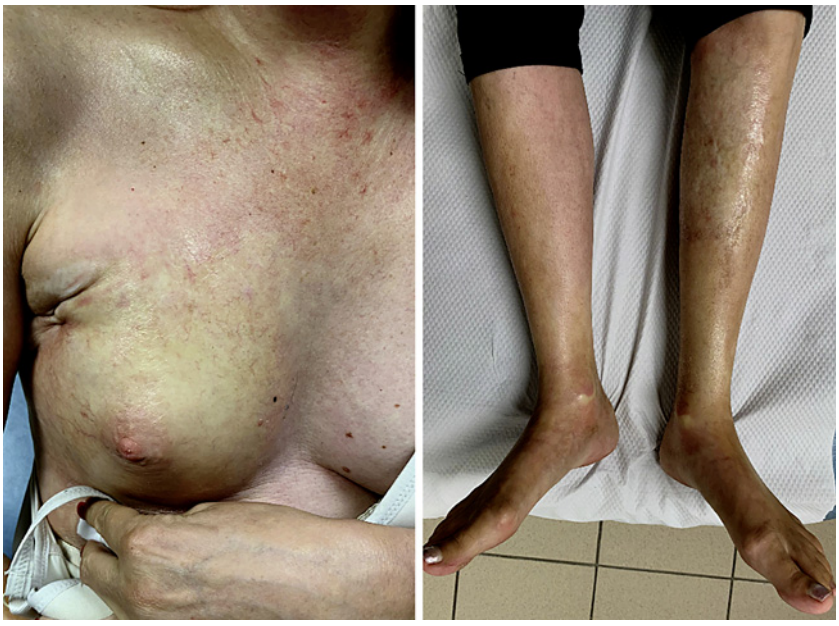

Fig. 2. Skin tightening with erythema, induration and skin thickening affecting the patient's thorax and bilateral lower limbs.

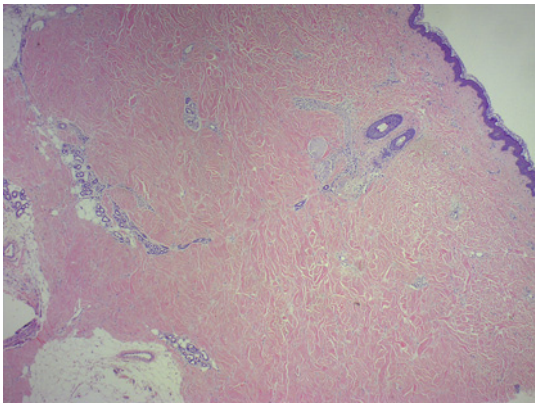

Fig. 3. Low power view showing thickened dermis with hyalinised sclerotic collagen fibre bundles extending into the subcutis in thick bands and mild thickening of the blood vessel walls (Haematoxylin and eosin (H&E) stain ×40).

Aetiopathogenesis is complex and is thought to include genetic and environmental factors [10]. Malignancy may play a role in scleroderma in two main ways. Scleroderma may be triggered through cytokines or hormones secreted by the tumour cells which lead to cytotoxic and autoantibody responses. In such cases, the scleroderma is termed paraneoplastic and this was a differential diagnosis in our case. Scleroderma may also develop secondary to immunotherapy-induced immune disruption [11].

It may be clinically difficult to differentiate with certainty between paraneoplastic scleroderma and ICI-induced scleroderma in an individual patient; however, the literature offers some possible clues which may help distinguish between the two. Raynaud's phenomenon, organ involvement, nailfold capillary abnormality, and ANA and RNA polymerase III antibody positivity do not usually feature in drug-induced scleroderma [10, 12]. The timeline of events may also be indicative, in that paraneoplastic scleroderma usually predates the diagnosis of malignancy or both are diagnosed at around the same time [10]. In our case,

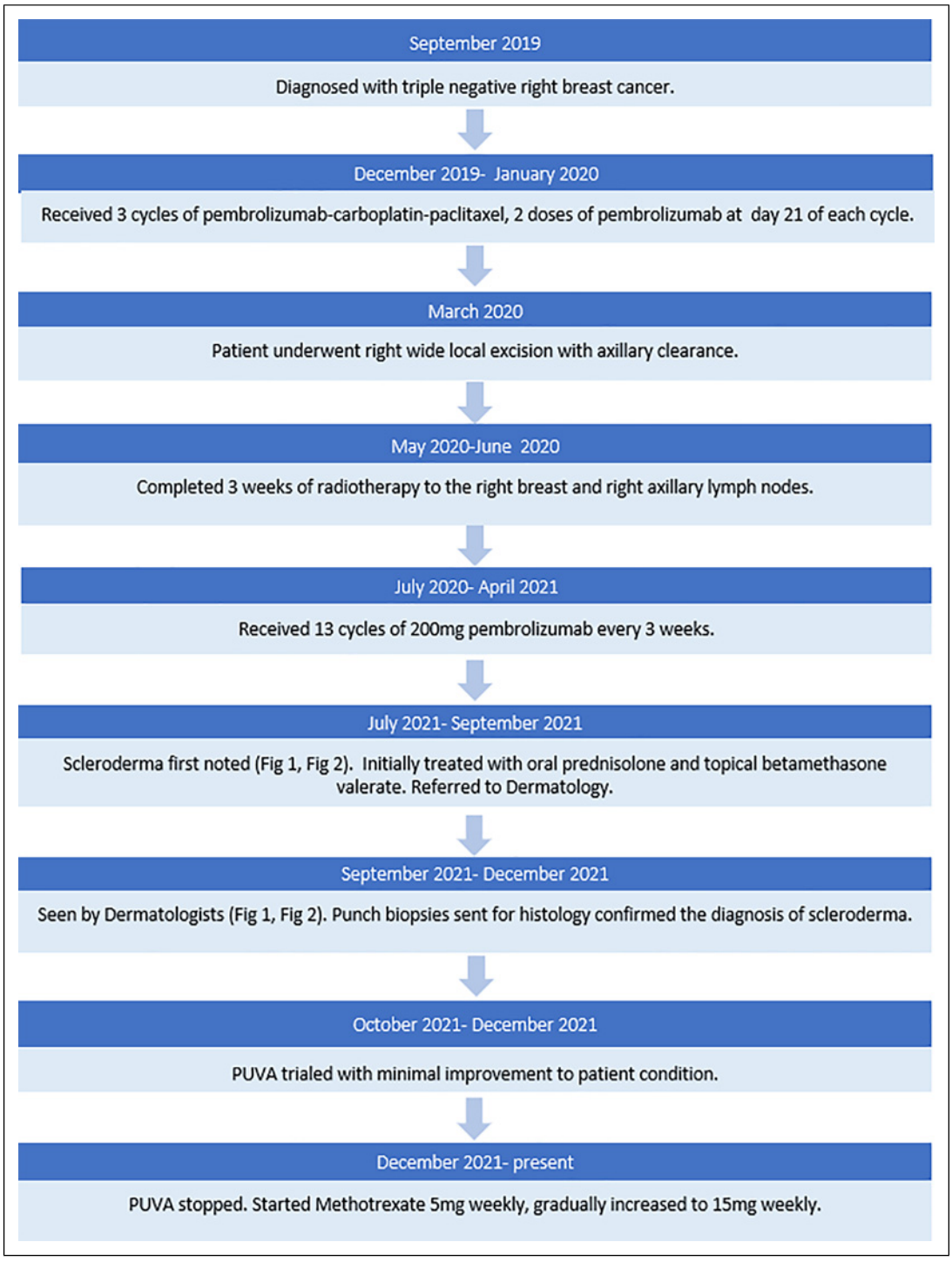

Fig. 4. Timeline outlining the patient's diagnoses and treatment.

scleroderma developed after the patient had already been treated with surgery, radiotherapy and finished a course of planned immunotherapy. She had no Raynaud's phenomenon, no organ involvement elsewhere and her immunology screen (including RNA polymerase III antibody) was negative, making drug-induced scleroderma more likely.

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Table 1. Overview of reported cases of scleroderma secondary to pembrolizumab

Author (year)	Patient gender	Patient age	Cancer type	Other positive findings	Onset of symptoms	Treatment for scleroderma	Outcome
Shenoy et al. [16] (2017)	Male	79 years	Melanoma	NS	After cycle 5	Prednisone	Pembrolizumab was stopped and scleroderma gradually resolved after 6 weeks.
Barbosa et al. [1] (2017)	Male	66 years	Melanoma	Mildly raised C-reactive protein	After cycle 13	Prednisone, Immunoglobulin, mycophenolate mofetil	Pembrolizumab stopped, improvement within 8 weeks of treatment.
	Male	79 years	Melanoma	Raynaud's phenomenon, periungual erythema, mild dilation of nailfold capillaries, inspiratory crackles left base of lung	After cycle 5	Hydroxychloroquine, prednisone	Pembrolizumab stopped, improvement over 12 weeks.
Cheng et al. [17] (2018)	Male	64 years	Melanoma	Elevated ESR (38 mm/h)	After cycle 5	Prednisone 0.8 mg/kg/day	Pembrolizumab stopped. Morphea improved.
Herrscher et al. [18] (2019)	Female	74 years	Melanoma	Vitiligo, arthralgia, ocular dryness, xerostomia	After cycle 6	Colchicine 1 mg/day, topical clobetasol propionate, oral prednisolone 15 mg/day, cyclophosphamide 1 g/3 weeks, infliximab 5 mg/kg/8 weeks.	Pembrolizumab stopped. Improvement of morphea after infliximab.
Connell et al. [19] (2019)	Female	33 years	Melanoma	Nil	After cycle 20	Prednisolone, hydroxychloroquine. Methotrexate	Pembrolizumab stopped. Scleroderma stabilized on methotrexate.
Suraez-Diaz et al. [15] (2020)	Male	75 years	Urothelial carcinoma	Positive ANA 1/160 speckled pattern, anti-Ro 52 positive	After 1 month	Systemic corticosteroids	Pembrolizumab stopped.
Alkilany and Ballou [15] (2020)	Female	60 years	Non-small cell lung carcinoma	Leukopaenia, mildly elevated rheumatoid factor	After 30 cycles	Methotrexate	Pembrolizumab stopped, resolution of scleroderma within 2 months of MTX.

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Table 1 (continued)

Author (year)	Patient gender	Patient age	Cancer type	Other positive findings	Onset of symptoms	Treatment for scleroderma	Outcome
Terrier et al. [20] (2020)	Female	49 years	Non-small cell lung carcinoma	Positive ANA 1/640, nailfold capillaroscopy-mild to moderate microvascular abnormalities	After cycle 1	Prednisone, cyclophosphamide	Extension of scleroderma after 6 weeks of prednisone, hence cyclophosphamide added.
	Female	57 years	Non-small cell lung carcinoma	Abnormal nailfold capillaroscopy, positive ANA, anti-RNA polymerase III positive	After cycle 6	Prednisone, cyclophosphamide	Pembrolizumab stopped. Improvement of scleroderma after 6 cycles of cyclophosphamide.
Salamaliki et al. [21] (2020)	Male	81 years	Non-small cell lung carcinoma	Positive ANA 1/160	NS	Methylprednisolone, mycophenolate mofetil	Pembrolizumab withheld and restarted after 2.5 months. Scleroderma improved but not resolved.
Gambichler et al. [22] (2022)	Female	62 years	Non-small cell lung carcinoma	Elevated lactate dehydrogenase levels, low eosinophils and lymphocytopaenia	After 6 cycles of pembrolizumab-carboplatin-pemetrexed and 27 cycles of pembrolizumab-pemetrexed	Oral prednisolone, ultraviolet-A1 phototherapy	Patient lost to follow up.
Farrugia, 2023 [this case]	Female	54 years	Triple negative breast cancer	Nil	After 3 cycles of pembrolizumab-carboplatin-paclitaxel and 13 cycles of pembrolizumab	Prednisolone, PUVA, Methotrexate	Improvement of pain and erythema. Persistence of skin tightness.

NS, not stated; ANA, anti-nuclear antibody; ESR, erythrocyte sedimentation rate; PUVA, psoralen + ultraviolet A.

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Table 2. Overview of reported cases of scleroderma secondary to nivolumab

Author (year)	Patient gender	Patient age	Cancer type	Other positive findings	Onset of symptoms	Treatment of scleroderma	Outcome
Alegre-Sanchez et al. [23] (2016)	Female	65 years	Non-small cell lung carcinoma	Nil	After 2 months/5 cycles	Nil. of note, this case was a relapse of morphoea after 8 years.	Nivolumab stopped after 6 months due to oncological inefficacy. Morphoea improved.
Cho et al. [24] (2018)	Male	Septuagenarian	Melanoma	Vitiligo	After 18 cycles	Oral prednisolone tapered down over 9 months.	Nivolumab was not discontinued.
Tjarks et al. [25] (2018)	Male	61 years	Renal cell carcinoma	Elevated ESR and C-reactive protein	After 16 cycles	Oral prednisone tapered down to 10 mg daily, then mycophenolate mofetil.	Nivolumab discontinued after 28 cycles. Scleroderma improved.
Dal Bello et al. [26] (2018)	Female	70 years	Melanoma	Oral mucositis.	After 12 cycles	Low dose systemic corticosteroid 12.5 mg/day.	Nivolumab stopped. Morphoea improved, then remission
Acar et al. [27] (2021)	Female	48 years	Melanoma	Hypothyroidism, vitiligo, ANA 1/320 granular and 1/320 homogenous	After 33 cycles	Topical mometasone furoate cream twice daily × 15 days and calcipotriol cream once daily for 15 days alternately.	Nivolumab was not discontinued. Improvement after 9 months
Langan et al. [28] (2021)	Female	61 years	Melanoma	Eosinophilia, elevated C-reactive protein, ANA 1: 160, impaired oesophageal mobility achalasia	10 months after combined nivolumab-ipilimumab	Dexamethasone pulsed intravenous therapy, clobetasone propionate ointment, physiotherapy.	Morphoea improved but not completely resolved.

NS, not stated; ANA, anti-nuclear antibody; ESR, erythrocyte sedimentation rate.

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ICIs are a recent breakthrough in oncology treatment of various malignancies via immune mediated responses against tumour growth [13]. ICIs are monoclonal antibodies and include cytotoxic T-lymphocyte-associated protein 4 (CLTA-4) inhibitors, programmed cell death-1 (PD-1) inhibitors, or programmed cell death ligand-1 (PD-L1) inhibitors [3]. Pembrolizumab is a selective immunoglobulin G4-kappa monoclonal antibody that inhibits PD-1. The use of pembrolizumab as immunotherapy was first approved in 2014 for the treatment of metastatic melanoma [1, 14], and later on for other malignancies such as non-small cell lung cancer [3], urothelial carcinoma [15] and triple-negative breast cancer such as in our case.

An emergent downside of these ICIs is immune-related adverse events (irAEs) which could involve the skin. Cutaneous adverse effects which have been reported with anti-PD-1 agents such as pembrolizumab and nivolumab include dermatoses such as vitiligo, morbilliform rash, urticaria, dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis [1, 2]. Scleroderma is another, but less reported, adverse effect of pembrolizumab and nivolumab [1]. These irAEs occur secondary to erroneous immune system activation against self-antigens. The severity and incidence of irAEs depend on various factors, which include the type of tumour and the type of ICI used, amongst others [5].

We performed an extensive literature review to collate all the reported cases of pembrolizumab- and nivolumab-induced scleroderma up to June 2022. PubMed and Google Scholar were used to search for cases, using the terms "scleroderma," "pembrolizumab," and "nivolumab." In total, 12 other cases of pembrolizumab-induced scleroderma and 6 cases of nivolumab-induced scleroderma were found. These, together with our case, are summarized in Tables 1 and 2.

In our review, eight males and eleven females were affected, with their ages ranging from 33 years old to 81 years old. Skin changes of scleroderma developed at different stages of treatment, in some cases as early as after the first cycle of immunotherapy. Treatment options utilized included corticosteroids, methotrexate, hydroxychloroquine, cyclophosphamide, mycophenolate mofetil, immunoglobulins, and infliximab, with varying response. In most cases, the scleroderma stabilized within a few months of treatment (Tables 1, 2).

The underlying mechanism behind scleroderma secondary to PD-1 inhibitors is not yet fully understood. It is known that through the inhibition of PD-1, pembrolizumab, or nivolumab cause increased CD4 T-cell activity which in turn promotes a T-helper cell response [29]. Several authors have suggested that a profibrotic state is created via type 2 macrophage polarization which promotes fibroblast activation and excessive extracellular matrix production. This may in turn lead to an increase in dermal thickness. ICI-induced scleroderma appears to only occur with PD-1 antagonists and to our knowledge has not been reported with CTLA-4 or PD-L1 inhibitors [20].

Conclusion

Immunotherapy is a relatively new treatment in oncology and further research regarding different factors which play a role in immunotherapy response is still needed. However, so far, immunotherapy has shown great efficacy and potential in the treatment of various malignancies. This report aims to create awareness that pembrolizumab and nivolumab may rarely cause scleroderma. Clinical diagnosis and management of scleroderma in this setting may be challenging, and an accurate drug history and dermatological input are recommended in such cases. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533373).

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.F., L.M., A.B., N.R., and M.J.B. contributed to the management and the reporting of the case, photography, and research involved for this case report.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 Barbosa NS, Wetter DA, Wieland CN, Shenoy NK, Markovic SN, Thanarajasingam U. Scleroderma induced by pembrolizumab: a case series. Mayo Clin Proc. 2017 Jul 1;92(7):1158–63.
2 Le TK, Brown I, Goldberg R, Taylor MT, Deng J, Parthasarathy V, et al. Cutaneous toxicities associated with immune checkpoint inhibitors: an observational, pharmacovigilance study. J Invest Dermatol. 2022 May 20;142(11):2896–908.e4.
3 Alkilany R, Ballou S. Pembrolizumab induced scleroderma. Discussion of Clinical Cases. 2019 May 25;64(4).
4 Rizzo A, Cusmai A, Giovannelli F, Acquafredda S, Rinaldi L, Misino A, et al. Impact of proton pump inhibitors and histamine-2-receptor antagonists on non-small cell lung cancer immunotherapy: a systematic review and meta-analysis. Cancers. 2022 Mar 9;14(6):1404.
5 Santoni M, Rizzo A, Kucharz J, Mollica V, Rosellini M, Marchetti A, et al. Complete remissions following immunotherapy or immuno-oncology combinations in cancer patients: the MOUSEION-03 meta-analysis. Cancer Immunol Immunother. 2023 Jan 12;72(6):1365–79.
6 Rosellini M, Marchetti A, Mollica V, Rizzo A, Santoni M, Massari F. Prognostic and predictive biomarkers for immunotherapy in advanced renal cell carcinoma. Nat Rev Urol. 2023 Mar;20(3):133–57.
7 Rizzo A, Cusmai A, Gadaleta-Caldarola G, Palmiotti G. Which role for predictors of response to immune checkpoint inhibitors in hepatocellular carcinoma? Expert Rev Gastroenterol Hepatol. 2022 Apr 3;16(4):333–9.
8 Lafyatis R. Transforming growth factor β—at the centre of systemic sclerosis. Nat Rev Rheumatol. 2014 Dec;10(12):706–19.
9 Maria ATJ, Partouche L, Goulabchand R, Rivière S, Rozier P, Bourgier C, et al. Intriguing relationships between cancer and systemic sclerosis: role of the immune system and other contributors. Front Immunol. 2018;9:3112.
10 Shah AA, Casciola-Rosen L. Cancer and scleroderma: a paraneoplastic disease with implications for malignancy screening. Curr Opin Rheumatol. 2015 Nov;27(6):563–70.

11 Jedlickova H, Durčanská V, Vasku V. Paraneoplastic scleroderma: are there any clues? Acta Dermatovenerol Croat. 2016 Apr 24;24(1):78–80.
12 Hamaguchi Y. Drug-induced scleroderma-like lesion. Allergol Int. 2022;71(2):163–8.
13 Lewis AL, Chaft J, Girotra M, Fischer GW. Immune checkpoint inhibitors: a narrative review of considerations for the anaesthesiologist. Br J Anaesth. 2020 Mar 1;124(3):251–60.
14 Poole RM. Pembrolizumab: first global approval. Drugs. 2014 Oct;74(16):1973–81.
15 Suárez-Díaz S, Coto-Hernández R, Yllera-Gutiérrez C, Álvarez-Fernández C, Trapiella-Martínez L, Caminal-Montero L. Scleroderma-like syndrome associated with pembrolizumab. J Scleroderma Relat Disord. 2020 Jun;5(2):NP5–6.
16 Shenoy N, Esplin B, Barbosa N, Wieland C, Thanarajasingam U, Markovic S. Pembrolizumab induced severe sclerodermoid reaction. Ann Oncol. 2017 Feb 1;28(2):432–3.
17 Cheng MW, Hisaw LD, Bernet L. Generalized morphea in the setting of pembrolizumab. Int J Dermatol. 2018 Jun 22;58(6):736–8.
18 Herrscher H, Tomasic G, Castro Gordon A. Generalised morphea induced by pembrolizumab. Eur J Cancer. 2019 Jul 1;116:178–81.
19 Connell CM, Welsh SJ, Broderick C, Wallace M, Corrie PG. 13 localized scleroderma in a patient with metastatic melanoma treated with pembrolizumab. Problem Solving Cancer Immunother. 2019 Jan 7:140.
20 Terrier B, Humbert S, Preta LH, Delage L, Razanamahery J, Laurent-Roussel S, et al. Risk of scleroderma according to the type of immune checkpoint inhibitors. Autoimmun Rev. 2020 Aug 1;19(8):102596.
21 Salamaliki C, Solomou EE, Liossis SN. Immune checkpoint inhibitor-associated scleroderma-like syndrome: a report of a pembrolizumab-induced "Eosinophilic Fasciitis-like" case and a review of the literature. Rheumatol Ther. 2020 Dec;7(4):1045–52.
22 Gambichler T, Lee YP, Barras M, Scheel CH, Susok L. Hyperpigmented scleroderma-like lesions under combined pembrolizumab and pemetrexed treatment of non-small lung cancer. Dermato. 2022 Mar 17;2(1):8–13.
23 Alegre-Sánchez A, Fonda-Pascual P, Saceda-Corralo D, de Las Heras-Alonso E. Relapse of morphea during Nivolumab therapy for lung adenocarcinoma. Actas Dermosifiliogr. 2017;108(1):69–70.
24 Cho M, Nonomura Y, Kaku Y, Nakabo S, Endo Y, Otsuka A, et al. Scleroderma-like syndrome associated with nivolumab treatment in malignant melanoma. J Dermatol. 2019 Jan;46(1):e43–4.
25 Tjarks BJ, Kerkvliet AM, Jassim AD, Bleeker JS. Scleroderma-like skin changes induced by checkpoint inhibitor therapy. J Cutan Pathol. 2018 Aug;45(8):615–8.
26 Dal Bello G, Rosina P, Colato C, Girolomoni G. Nivolumab induced morphea. G Ital Dermatol Venereol. 2018 Oct 3;155(5):701–2.
27 Acar A, Oraloglu G, Yaman B, Karaarslan I. Nivolumab-induced plaque morphea in a malign melanoma patient. J Cosmet Dermatol. 2021 Aug;20(8):2645–7.
28 Langan EA, Budner K, Zillikens D, Terheyden P. Generalized morphoea in the setting of combined immune checkpoint inhibitor therapy for metastatic melanoma: a case report. Medicine. 2021 Apr 4;100(16):e25513.
29 Boleto G, Allanore Y, Avouac J. Targeting costimulatory pathways in systemic sclerosis. Front Immunol. 2018 Dec 18;9:2998.