

Case Report

Hyperpigmented Scleroderma-like Lesions under Combined Pembrolizumab and Pemetrexed Treatment of Non-Small Lung Cancer

Thilo Gambichler * , Yi-Pei Lee, Milan Barras, Christina H. Scheel and Laura Susok

Skin Cancer Center, Department of Dermatology, Ruhr-University, 44801 Bochum, Germany; yi-pei.lee@klinikum-bochum.de (Y.-P.L.); m.barras@klinikum-bochum.de (M.B.); christina.scheel@klinikum-bochum.de (C.H.S.); l.susok@klinikum-bochum.de (L.S.)

* Correspondence: t.gambichler@klinikum-bochum.de

Abstract: Immune checkpoint inhibitors (ICI) and other antineoplastic treatment regimens can trigger cutaneous immune-related adverse events (irAEs). There is a tendency for underreporting of such cases, as cutaneous irAEs are typically perceived as mild and transient. However, more serious cutaneous irAEs can occur which, despite their lower frequency, deserve attention and require specific care. Here, we report a case of extensive hyperpigmented scleroderma-like lesions (SLL) on the lower extremities under combination treatment with pembrolizumab and pemetrexed in a patient with metastatic non-small cell lung cancer. The present case in conjunction with a review of the current literature underscores the potential risk of developing SLL under treatment with anti-PD-1 antibody and/or pemetrexed. Moreover, it is possible that this particular combination treatment synergistically increases the risk of SLL. As a result, more such cases may arise in the future, as ICI/pemetrexed combination treatment might be employed more often. As drug-induced SLL usually require systemic treatment with high dose-corticosteroids, physicians should be aware of SLL as an irAE when cancer patients present with sclerotic and/or fibrotic skin lesions.

Keywords: immune checkpoint inhibitors; immune-related adverse events; morphea; skin fibrosis



Citation: Gambichler, T.; Lee, Y.-P.; Barras, M.; Scheel, C.H.; Susok, L. Hyperpigmented Scleroderma-like Lesions under Combined Pembrolizumab and Pemetrexed Treatment of Non-Small Lung Cancer. *Dermato* **2022**, *2*, 8–13. <https://doi.org/10.3390/dermato2010002>

Academic Editor: Adam Reich

Received: 7 January 2022

Accepted: 15 March 2022

Published: 17 March 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Regarding immune-related adverse events (irAEs) that occur under immune checkpoint inhibitors (ICIs), the majority of physicians are aware of typical irAEs affecting internal organs (e.g., colitis, thyroiditis, pneumonitis). By contrast, cutaneous irAEs may be underrated and, as a consequence, underreported, as they are often perceived as benign in nature [1–3]. In fact, ICI therapy can induce a variety of cutaneous irAEs, including macular/papular, psoriasiform, eczematous, and lichenoid lesions. While most of these skin conditions are indeed transient and mild, more severe ICI-related cutaneous irAEs, including autoimmune blistering diseases, acral necroses, and even life-threatening severe cutaneous adverse drug reactions, have also been reported [1–3]. Additionally, fibrosing conditions ranging from localized scleroderma (morphea) to more generalized scleroderma-like syndromes have also been observed under ICI treatment, albeit rarely [4,5]. Apart from ICI treatment modalities, other antineoplastic agents (e.g., taxane-based substances, bleomycin, gemcitabine, pemetrexed) have anecdotally been reported as triggers for new-onset scleroderma-like lesions (SLL) [5,6]. However, taken together, drug-induced SLL are relatively rare. Here, we report a case of widespread hyperpigmented SLL on the lower extremities under combination treatment with pembrolizumab and pemetrexed in a patient with metastatic non-small cell lung cancer.

2. Case Report

A 62-year-old female presented with a 4-year history of non-small lung cancer. At presentation in November 2021, she was stage IVa according to the 7th edition IASLC/UICC [pT3, pN0(0/11), cM1a(Pul)]. She had received 27 cycles pembrolizumab (200 mg 3-weekly) combined with pemetrexed (500/m²) when she noticed gradually increasing hyperpigmentation and skin hardening on her lower legs. Prior to pembrolizumab/pemetrexed maintenance therapy, she had also received 6 cycles of carboplatin in combination with pembrolizumab/pemetrexed. Clinical evaluation revealed weakly demarcated erythematous and violaceous hyperpigmented skin on the lower legs and feet sparing the forefoot and toes. There was a non-pitting edema as well as xerosis cutis with rhomboid-like, small lamellar desquamation on both lower legs. On palpation, the skin was pathologically firm to the touch (Figure 1). Additionally, a pattern of livedo reticularis was observed on the legs, which the patient reported to have had since childhood. Of note, there was no history for Raynaud's syndrome. In addition, the patient showed no evidence for other signs of systemic sclerosis such as vascular changes in the nail fold, sclerodactyly or conditions such as scleromyxedema and eosinophilic fasciitis.



Figure 1. (a–c) Overview and detail of erythematous and violaceous hyperpigmented and edematous/xerotic skin on the lower legs sparing the toes in a patient with pembrolizumab/pemetrexed-induced SLL.

A skin biopsy revealed sclerotizing dermatitis with homogenized collagen fibers and rarefaction of skin appendages throughout the dermis (Figure 2). Moreover, the epidermis showed basal hyperpigmentation and an abundance of melanophages in the upper corium. Taken together, histopathological findings were consistent with hyperpigmented SLL such as morphea.

Serology revealed slightly elevated lactate dehydrogenase levels, and blood counts showed a decrease in eosinophils and a slight decrease in lymphocytes. Other parameters for SLL, such as elevated immunoglobulins and increased titers of antinuclear autoantibodies (ANA), extractable nuclear autoantibodies (ENA), anti-citrullin autoantibodies, and anti-ds-DNA autoantibodies, were all negative. Treatment with pembrolizumab/pemetrexed was withheld and a tapered oral prednisolone regimen was prescribed by the attending oncologist. In addition, we recommended ultraviolet (UV-A1) phototherapy three times weekly as reported previously [7]. However, the patient was subsequently lost on follow-up.

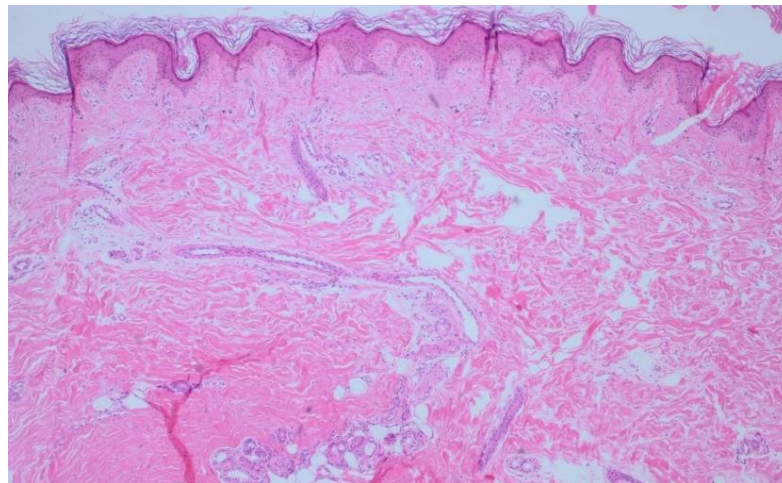


Figure 2. Hematoxylin and eosin staining of a skin biopsy revealing sclerotizing dermatitis with homogenized collagen fibers and rarefaction of skin appendages throughout the dermis.

3. Discussion

A wealth of evidence indicates that ICI can induce a broad spectrum of autoimmune diseases in cancer patients [1–3,8]. To our best knowledge, eleven case reports of ICI-induced SLL have been published to date [9–19]. In nine of these cases, ICI therapy consisted of the anti-programmed cell death protein (PD-1) agents, nivolumab or pembrolizumab, for the treatment of different neoplasms such as melanoma, non-small cell lung cancer, and renal cell carcinoma (Table 1). Here, we also included a case of eosinophilic fasciitis-like condition under Pembrolizumab therapy that falls within the spectrum of SLL manifestations [17]. Of note, this article also identifies twelve additional, similar cases [17]. In most of these cases, treatment elicited an anti-tumor response and indeed, the occurrence of irAEs is currently discussed as a predictor of responsiveness to PD-1 and PD-L1 inhibitors [20].

Table 1. A list of SLL-cases cited, auto-antibody status, and summary of treatment.

Target	ICI	Entity	Auto-ab	Treatment	Ref.
PD-1	Nivolumab	Melanoma	negative	topical steroids + calcipotriol	[9]
		Melanoma	negative	systemic steroids	[10]
		RCC	negative	systemic steroids	[11]
		NSCLC	not reported	spontaneous remission	[12]
	Pembrolizumab	Melanoma	not reported	systemic steroids	[13]
		Melanoma	negative	hydroxychloroquine + systemic steroids	[14]
		Choroidal melanoma	not reported	systemic steroids	[15]
		Melanoma	negative	colchicine, topical steroids, systemic steroids, cyclophosphamide, infliximab	[16]
		NSCLC	ANA	systemic steroids	[17]
PD-1 + CTLA-4	Pembrolizumab + ipilimumab	Melanoma	ANA	systemic followed by topical steroids	[18]
PD-L1	Atezolizumab	NSCLC	PM/SCL-75	mycophenolate mofetil	[19]

ICI = Immune Checkpoint Inhibitor, Auto-ab = Autoantibodies, NSCLC = non-small cell lung cancer, RCC = renal cell carcinoma.

Moreover, a case of generalized morphea under double-immunotherapy with anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) in combination with anti-PD1-antibody was reported (Table 1). Finally, we identified one case of scleroderma-like manifestation induced

by Atezolizumab, an anti-programmed cell death protein ligand 1 (PD-L1) agent (Table 1). Importantly, in many of these cases, autoantibody titers were not increased. Moreover, Terrier et al. identified 38 additional cases of SLL associated with ICI by searching among 2527 scleroderma patients in the WHO pharmacovigilance database [4]. Importantly, in this context, only the PD-1 inhibitors nivolumab and pembrolizumab were reported as possible triggers. However, despite this growing body of literature suggesting that SLL as an irAE under ICI-therapy might represent an underreported event, a large case series reported by Panhaleux et al. [21], suggests that anti-PD1 or PD-L1 treatments are nonetheless suitable options for cancer patients with preexisting systemic sclerosis.

Similar to methotrexate, pemetrexed is an antifolate compound that inhibits thymidylate synthetase and other folate enzymes and is particularly useful for the treatment of NSCLC. Dermatological AEs induced by pemetrexed are observed in about 20% of patients [5,22–24]. Specifically, more than 10 pemetrexed-induced SLL cases have been reported [5,6,23,25–29]. In almost all cases, lower extremities were affected exclusively, and hyperpigmentation, as described previously in scleroderma [30,31], was noticed frequently [6,29]. Onset of SLL under pemetrexed occurred after 2 to 18 cycles. Notably, three of the aforementioned cases were reported as lipodermatosclerosis secondary to pemetrexed use and should be reassigned to the spectrum of drug-induced SLL [28].

Although investigations are being performed with respect to vasculopathy, (auto)immune abnormalities, and different aspects of sclerosis/fibrosis, the pathomechanisms of drug-induced SLL remain uncertain [5]. Pathophysiology very likely differs depending on which drug triggered the condition. As observed in the present case, SLL are frequently observed on the lower legs and usually do not spread to other body sites. The initial phase of drug-induced SLL is predominantly characterized by swelling and erythema, followed by an edematous fibrotic/sclerotic phase [5]. Lesions often begin deep in the dermis and, clinically, can mimic panniculitis and even eosinophilic fasciitis as discussed above [17]. Thus, taken together, in contrast to systemic sclerosis, SLL has no predominance in females, almost exclusively affects the lower limbs, is not associated with autoantibodies, and is usually not combined with sclerodactyly, ulceration of the fingertips, and Raynaud's phenomenon [5,32]. With respect to treatment of SLL, all patients with widespread skin lesions required high-dose corticosteroids, with most of them subsequently experiencing an improvement of skin fibrosis [5].

For the present case, it is impossible to determine whether SLL were induced by long-term treatment with pembrolizumab and/or pemetrexed. As discussed above, both agents have the potential for triggering sclerotic/fibrotic skin lesions. A synergistic effect by both agents in causing SLL in cancer patients is not implausible. As experience with combined treatment using anti-PD1 and pemetrexed is limited to only a few years, time will tell whether the incidence of SLL will increase in this setting [33]. Finally, while it is highly likely that pembrolizumab and/or pemetrexed caused SLL in the present case, we cannot fully exclude that the trigger for SLL development was the underlying malignancy. Indeed, the temporal clustering between cancer diagnosis and onset of SLL observed in some patients raises the possibility that systemic sclerosis may present as a paraneoplastic syndrome, as described for other autoimmune conditions such as dermatomyositis [34]. However, as discussed above, there are significant differences in clinical presentation and course of the disease between the spectrum of systemic sclerosis and treatment-induced SLL, independently of whether they occurred under immuno- or chemotherapy.

4. Conclusions

The present case underscores the potential risk of developing SLL under treatment with ICI, pemetrexed or combination treatment. Moreover, a synergistic effect on the frequency of treatment-induced SLL by this particular combination cannot be ruled out. Clinicians treating patients with sclerotic/fibrotic skin lesions should be aware that such symptoms can represent immuno- or chemotherapy-induced SLL.

Author Contributions: Conceptualization, T.G. and L.S.; data interpretation, T.G., investigation, L.S., M.B., C.H.S. and T.G.; writing—original draft preparation, T.G.; visualization, T.G., Y.-P.L. and L.S.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This case study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Ruhr-University Bochum (#4222-12, date of the approval: 30 November 2015).

Informed Consent Statement: Informed consent was obtained from the patient presented.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Apalla, Z.; Nikolaou, V.; Fattore, D.; Fabbrocini, G.; Freites-Martinez, A.; Sollena, P.; Lacouture, M.; Kraehenbuehl, L.; Stratigos, A.; Peris, K.; et al. European Recommendations for Management of Immune Checkpoint Inhibitors-Derived Dermatologic Adverse Events. The EADV Task Force “Dermatology for Cancer Patients” Position Statement. *J. Eur. Acad. Dermatol. Venereol. Jeadv.* **2021**, *36*, 332–350. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Gambichler, T.; Scheel, C.H.; Reuther, J.; Susok, L. Management of Immune-related Adverse Events in Anti-PD-1-treated Patients with Advanced Cutaneous Squamous Cell Carcinoma. *J. Eur. Acad. Dermatol.* **2022**, *36*, 23–28. [\[CrossRef\]](#)
3. Le, T.K.; Kaul, S.; Cappelli, L.C.; Naidoo, J.; Semenov, Y.R.; Kwatra, S.G. Cutaneous Adverse Events of Immune Checkpoint Inhibitor Therapy: Incidence and Types of Reactive Dermatoses. *J. Dermatol. Treat.* **2021**, 1–5. [\[CrossRef\]](#)
4. Terrier, B.; Humbert, S.; Preta, L.-H.; Delage, L.; Razanamahery, J.; Laurent-Roussel, S.; Mestiri, R.; Beaudeau, L.; Legendre, P.; Goupil, F.; et al. Risk of Scleroderma According to the Type of Immune Checkpoint Inhibitors. *Autoimmun. Rev.* **2020**, *19*, 102596. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Hamaguchi, Y. Drug-Induced Scleroderma-like Lesion. *Allergol. Int.* **2021**. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Ishikawa, K.; Sakai, T.; Saito-Shono, T.; Miyawaki, M.; Osoegawa, A.; Sugio, K.; Ono, A.; Mori, H.; Nishida, H.; Yokoyama, S.; et al. Pemetrexed-induced Scleroderma-like Conditions in the Lower Legs of a Patient with Non-small Cell Lung Carcinoma. *J. Dermatol.* **2016**, *43*, 1071–1074. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Gambichler, T.; Schmitz, L. Ultraviolet A1 Phototherapy for Fibrosing Conditions. *Front. Med.* **2018**, *5*, 237. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Gambichler, T.; Doerler, M.; Scheel, C.H. Onset of Subacute Cutaneous Lupus Erythematosus after the Initiation of Immune Checkpoint Inhibitor Therapy of Cancer. *Lupus* **2001**, *30*, 531–533. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Acar, A.; Oraloglu, G.; Yaman, B.; Karaarslan, I. Nivolumab-induced Plaque Morphea in a Malign Melanoma Patient. *J. Cosmet. Dermatol.* **2021**, *20*, 2645–2647. [\[CrossRef\]](#) [\[PubMed\]](#)
10. Cho, M.; Nonomura, Y.; Kaku, Y.; Nakabo, S.; Endo, Y.; Otsuka, A.; Kabashima, K. Scleroderma-like Syndrome Associated with Nivolumab Treatment in Malignant Melanoma. *J. Dermatol.* **2019**, *46*, e43–e44. [\[CrossRef\]](#) [\[PubMed\]](#)
11. Tjarks, B.J.; Kerkvliet, A.M.; Jassim, A.D.; Bleeker, J.S. Scleroderma-like Skin Changes Induced by Checkpoint Inhibitor Therapy. *J. Cutan. Pathol.* **2018**, *45*, 615–618. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Alegre-Sánchez, A.; Fonda-Pascual, P.; Saceda-Corrado, D.; de las Heras-Alonso, E. Relapse of Morphea during Nivolumab Therapy for Lung Adenocarcinoma. *Actas Dermo-Sifiliográficas Engl. Ed.* **2017**, *108*, 69–70. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Shenoy, N.; Esplin, B.; Barbosa, N.; Wieland, C.; Thanarajasingam, U.; Markovic, S. Pembrolizumab Induced Severe Sclerodermoid Reaction. *Ann. Oncol.* **2017**, *28*, 432–433. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Barbosa, N.S.; Wetter, D.A.; Wieland, C.N.; Shenoy, N.K.; Markovic, S.N.; Thanarajasingam, U. Scleroderma Induced by Pembrolizumab: A Case Series. *Mayo Clin. Proc.* **2017**, *92*, 1158–1163. [\[CrossRef\]](#)
15. Cheng, M.W.; Hisaw, L.D.; Bernet, L. Generalized Morphea in the Setting of Pembrolizumab. *Int. J. Dermatol.* **2019**, *58*, 736–738. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Herrscher, H.; Tomasic, G.; Gordon, A.C. Generalised Morphea Induced by Pembrolizumab. *Eur. J. Cancer* **2019**, *116*, 178–181. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Salamaliki, C.; Solomou, E.E.; Liossis, S.-N.C. 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**, *7*, 1045–1052. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Langan, E.A.; Budner, K.; Zillikens, D.; Terheyden, P. Generalized Morphoea in the Setting of Combined Immune Checkpoint Inhibitor Therapy for Metastatic Melanoma. *Medicine* **2021**, *100*, e25513. [\[CrossRef\]](#)
19. Grant, C.; Chalasani, V.; Uchin, J.M.; Dore, A. Atezolizumab-Induced Scleroderma: A Rare Complication. *BMJ Case Rep.* **2021**, *14*, e244968. [\[CrossRef\]](#) [\[PubMed\]](#)
20. Das, S.; Johnson, D.B. Immune-Related Adverse Events and Anti-Tumor Efficacy of Immune Checkpoint Inhibitors. *J. Immunother. Cancer* **2019**, *7*, 306. [\[CrossRef\]](#) [\[PubMed\]](#)

21. Panhaleux, M.; Espitia, O.; Terrier, B.; Manson, G.; Maria, A.; Humbert, S.; Godbert, B.; Perrin, J.; Achille, A.; Arrondeau, J.; et al. Anti-Programmed Death Ligand 1 Immunotherapies in Cancer Patients with Pre-Existing Systemic Sclerosis: A Postmarketed Phase IV Safety Assessment Study. *Eur. J. Cancer* **2021**, *160*, 134–139. [[CrossRef](#)] [[PubMed](#)]
22. Shih, C.; Chen, V.J.; Gossett, L.S.; Gates, S.B.; MacKellar, W.C.; Habeck, L.L.; Shackelford, K.A.; Mendelsohn, L.G.; Soose, D.J.; Patel, V.F.; et al. LY231514, a Pyrrolo[2,3-d]Pyrimidine-Based Antifolate That Inhibits Multiple Folate-Requiring Enzymes. *Cancer Res.* **1997**, *57*, 1116–1123.
23. Piérard-Franchimont, C.; Quatresooz, P.; Reginster, M.-A.; Piérard, G.E. Revisiting Cutaneous Adverse Reactions to Pemetrexed. *Oncol. Lett.* **2011**, *2*, 769–772. [[CrossRef](#)]
24. Racanelli, A.C.; Rothbart, S.B.; Heyer, C.L.; Moran, R.G. Therapeutics by Cytotoxic Metabolite Accumulation: Pemetrexed Causes ZMP Accumulation, AMPK Activation, and Mammalian Target of Rapamycin Inhibition. *Cancer Res.* **2009**, *69*, 5467–5474. [[CrossRef](#)] [[PubMed](#)]
25. Vitiello, M.; Romanelli, P.; Kerdel, F.A. Painful Generalized Erythematous Patches: A Severe and Unusual Cutaneous Reaction to Pemetrexed. *J. Am. Acad. Dermatol.* **2011**, *65*, 243–244. [[CrossRef](#)]
26. Eguia, B.; Ruppert, A.-M.; Fillon, J.; Lavolé, A.; Gounant, V.; Epaul, C.; Milleron, B.; Moguelet, P.; Wislez, M.; Frances, C.; et al. Skin Toxicities Compromise Prolonged Pemetrexed Treatment. *J. Thorac. Oncol.* **2011**, *6*, 2083–2089. [[CrossRef](#)] [[PubMed](#)]
27. Merklen-Djafri, C.; Imbert, E.; Courouge-Dorcier, D.; Schott, R.; Méraud, J.-P.; Muller, C.; Tebacher, M.; Springinsfeld, G.; Cribier, B.; Lipsker, D. Pemetrexed-Induced Skin Sclerosis. *Clin. Oncol.* **2012**, *24*, 452–453. [[CrossRef](#)] [[PubMed](#)]
28. Corbaux, C.; Marie, J.; Meraud, J.-P.; Lacroix, S.; Delhoume, J.-Y.; Jouary, T.; Madoui, S. Pemetrexed-Induced Scleroderma-like Changes in the Lower Legs. *Ann. De Dermatol. Et De Vénéréologie* **2014**, *142*, 115–120. [[CrossRef](#)]
29. Shuster, M.; Morley, K.; Logan, J.; Sequist, L.V.; Shaw, A.; Fidias, P.; Kroshinsky, D. Lipodermatosclerosis Secondary to Pemetrexed Use. *J. Thorac. Oncol.* **2015**, *10*, e11–e12. [[CrossRef](#)] [[PubMed](#)]
30. Szczepanek, M.; Frątczak, A.; Lis-Święty, A. Narrow-Band Reflectance Spectrophotometry for the Assessment of Erythematous and Hyperpigmented Skin Lesions in Localized Scleroderma: A Preliminary Study. *Clin. Cosmet. Investig. Dermatol.* **2021**, *14*, 575–580. [[CrossRef](#)] [[PubMed](#)]
31. Pope, J.E.; Shum, D.T.; Gottschalk, R.; Stevens, A.; McManus, R. Increased Pigmentation in Scleroderma. *J. Rheumatol.* **1996**, *23*, 1912–1916. [[PubMed](#)]
32. Tiniakou, E.; Crawford, J.; Darrah, E. Insights into Origins and Specificities of Autoantibodies in Systemic Sclerosis. *Curr. Opin. Rheumatol.* **2021**, *33*, 486–494. [[CrossRef](#)] [[PubMed](#)]
33. Morimoto, K.; Yamada, T.; Yokoi, T.; Kijima, T.; Goto, Y.; Nakao, A.; Hibino, M.; Takeda, T.; Yamaguchi, H.; Takumi, C.; et al. Clinical Impact of Pembrolizumab Combined with Chemotherapy in Elderly Patients with Advanced Non-Small-Cell Lung Cancer. *Lung Cancer* **2021**, *161*, 26–33. [[CrossRef](#)]
34. Maria, A.T.J.; Partouche, L.; Goulabchand, R.; Rivière, S.; Rozier, P.; Bourgier, C.; Quéllec, A.L.; Morel, J.; Noël, D.; Guilpain, P. Intriguing Relationships Between Cancer and Systemic Sclerosis: Role of the Immune System and Other Contributors. *Front. Immunol.* **2019**, *9*, 3112. [[CrossRef](#)] [[PubMed](#)]