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

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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

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, thyreoiditis, 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 forehead 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.](image)

A skin biopsy revealed sclerotizing dermatitis with homogenized collagen fibers and rarefication 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.
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 search.

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

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

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

ICI = Immune Checkpoint Inhibitor, Auto-ab = Autoantibodies, NSCLC = non-small cell lung cancer, RCC = renal cell carcinoma.
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.
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Data Availability Statement: Not applicable.

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References


