Pembrolizumab-Induced Lichen Planus: A Rare Immune-Related Adverse Side Effect

Abstract

Pembrolizumab is the first anti-programmed death protein-1 agent approved by the US Food and Drug Administration. It has demonstrated efficacy in melanoma, lung cancer, and other advanced solid tumours and hematologic malignancies. Various dermatological side effects including pruritus, maculopapular rash, vitiligo, lichenoid skin reactions, psoriasis, and rarely life-threatening conditions like bullous pemphigoid, Stevens-Johnson syndrome, and drug rash with eosinophilia and systemic symptoms have been reported. We report a case of pembrolizumab-induced lichen planus in a 54-year-old female who was receiving pembrolizumab for management of lung metastasis from squamous cell carcinoma of the buccal mucosa. The lichen planus responded to acitretin and pembrolizumab was continued safely.

Keywords: *Acitretin, dermoscopy, lichen planus, pembrolizumab*

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Access this article online

Website: www.idoj.in

DOI: 10.4103/idoj.idoj_377_22

Quick Response Code:

Introduction

Programmed cell death protein-1 (PD-1) is a checkpoint protein on T cells that acts as a type of "off switch" that prevents T cells from attacking other cells in the body by attaching to programmed death-ligand-1 (PD-L1).[1] Monoclonal antibodies that target either PD-1 or PD-L1 can block this binding and boost the immune response against cancer cells. These drugs have demonstrated efficacy in melanoma, lung cancer, and other advanced solid tumours.[1,2] Activating the patient's innate immune system to recognize and act against cancer cells has led to improved outcomes with less toxicity than traditional chemotherapy in various malignancies. However, this has also led to a new class of side effects known as immune-related adverse events (IRAEs). Of these IRAEs, dermatological reactions observed include pruritus, maculopapular rash, vitiligo, lichenoid skin reaction, psoriasis, and rarely life-threatening conditions like bullous pemphigoid, Stevens-Johnson syndrome, and drug rash with eosinophilia and systemic symptoms.[1,2] We report a case of pembrolizumab-induced lichen planus in a 54-year-old female with lung metastasis from squamous cell carcinoma of the buccal mucosa.

Case Report

A 54-year-old female presented with an itchy skin rash over her feet for two weeks. She also had dry lips, pigmentation, and burning sensation in the oral cavity. Her medical history was also significant for hypertension and hypothyroidism, for which she was on telmisartan and thyroxine, respectively. The patient was a case of locally recurrent squamous cell carcinoma in the left buccal mucosa, for which she underwent multiple excisions over the last 7 years. Recently, she underwent wide local excision of the left buccal mucosa in March 2020, which was diagnosed as sarcomatoid carcinoma (pT_3 N_{2b} M_0). Treatment with adjuvant chemotherapy (cisplatin + nimotuzumab) and intensity-modulated radiation therapy to the left face and neck was initiated. Subsequently, the patient developed breathlessness and fever, and investigations revealed gross left pleural effusion with multifocal enhancing solid pleural deposits and nodules in lung fields, along with hilar lymphadenopathy. A trucut soft tissue biopsy of left lung mass confirmed lung metastasis from the malignancy. Immunohistochemistry revealed positivity for Ck (AE1 and AE3), p40, and vimentin, while staining for p16 was negative. Sixty

How to cite this article: Bansal A, Singla A, Paul D, Kaur S. Pembrolizumab-induced lichen planus: A rare immune-related adverse side effect. Indian Dermatol Online J 2023;14:391-4.

Received: 07-Jul-2022. **Revised:** 02-Nov-2022. **Accepted:** 11-Dec-2022. **Published:** 04-Apr-2023.

percent of tumour cells showed membranous staining of moderate intensity for PD-L1. DNA analysis showed clinically relevant mutations in the *HRAS* and *EP300* genes of the subject. Immunotherapy with 3-weekly pembrolizumab was initiated from July 2020 onwards.

The patient presented to dermatology outpatient with cheilitis and burning in oral mucosa in October 2020, and a few itchy pinkish red papules on both feet. Cutaneous examination revealed multiple, well-defined, pink to violaceous, flat-topped papules over bilateral feet. On examination of the oral cavity, there were well-defined erosions with Wickham striae over buccal mucosa and lips, with a violaceous hue and crusting at places [Figure 1]. On dermoscopic examination of lips, there were leaf venation-like Wickham striae, scaling, dotted vessels, pigmented dots, and globules over a violaceous background [Figure 2]. Over soles, Wickham striae with central yellow dots over violaceous background were seen. Skin biopsy revealed hyperkeratosis, parakeratosis and acanthosis of the epidermis with wedge-shaped hypergranulosis, in addition to vacuolar degeneration of the basal layer with dense band-like chronic inflammatory infiltrate at the dermoepidermal junction [Figure 3].

On clinicopathological correlation, she was diagnosed with pembrolizumab-induced lichen planus. Although it is possible that our patient exhibited a delayed lichenoid drug eruption from telmisartan, it is noteworthy that she did not experience a single episode of lichen planus (LP) during her previous history of taking telmisartan. Instead, she developed LP eruption shortly after the addition of pembrolizumab. This temporal relation led us to consider that the more likely causative agent of lichenoid rash is pembrolizumab. Also, based on the Naranjo probability scale, a method to assess the causality of the adverse drug reaction by the drug, the causality assessment score (9) was found to be definite.

She was managed with topical corticosteroids and oral antihistamines. Pembrolizumab injections were continued 3-weekly and the patient was kept on a regular follow-up. She was observed to develop fresh papules over bilateral feet, soles and wrists, which were extremely itchy [Figures 4a and 5a]. The lesions over the soles were ulcerated and painful. However, a good response to immunotherapy with regression of metastatic bilateral lung masses on sequential ^{18}FDG-PET-CECT scans were seen, and so, it was continued. For the cutaneous lesions, acitretin was prescribed at a dose of 10 mg once daily, which ultimately led to clinical improvement [Figures 4b and 5b].

Remission in lichen planus was achieved with acitretin and pembrolizumab was continued safely for the next 6 months. Unfortunately, she succumbed to infection with COVID-19 in January 2022 during the third wave in India as she had developed COVID-19 pneumonia.

Discussion

Our immune system recognizes and destroys mutant cells, thus protecting against the development of cancer.[3] These cancer cells develop mechanisms to evade this immunosurveillance response, leading to the development of malignancies.[3] Interaction between PD-1 (on T cells) and PD-L1/2 (on tumour cells) leads to

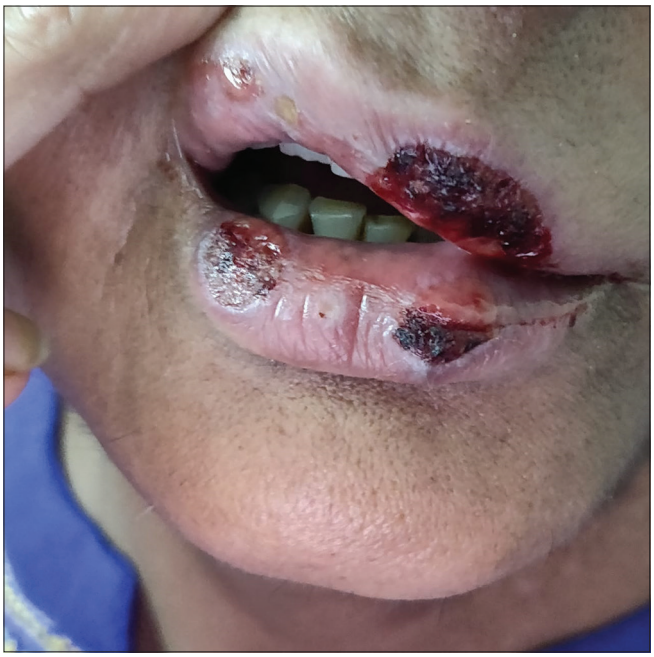

Figure 1: Well-defined erosions with Wickham striae over upper and lower lips with violaceous hue and crusting at places

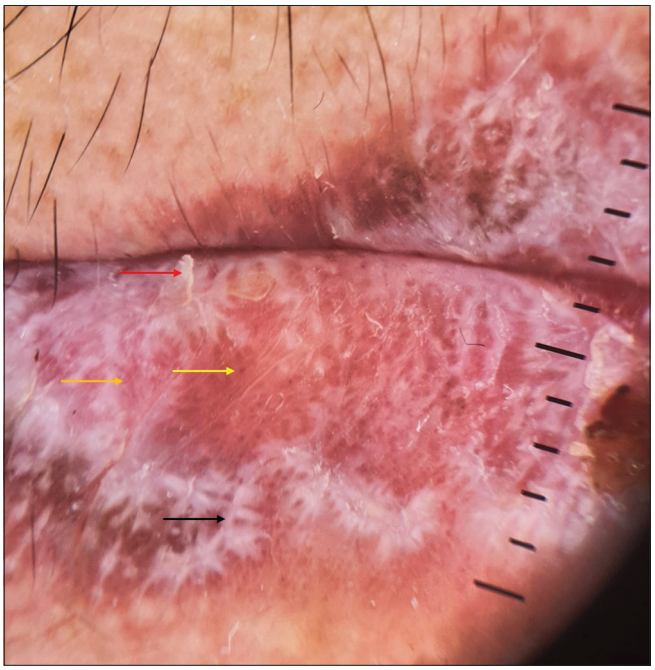

Figure 2: Non-contact dermoscopy under polarised mode using DermLite DL4 (10X) showing leaf venation-like Wickham striae (black arrow), scaling (red arrow), dotted vessels (orange arrow), pigmented dots, and globules over a violaceous background (yellow arrow)

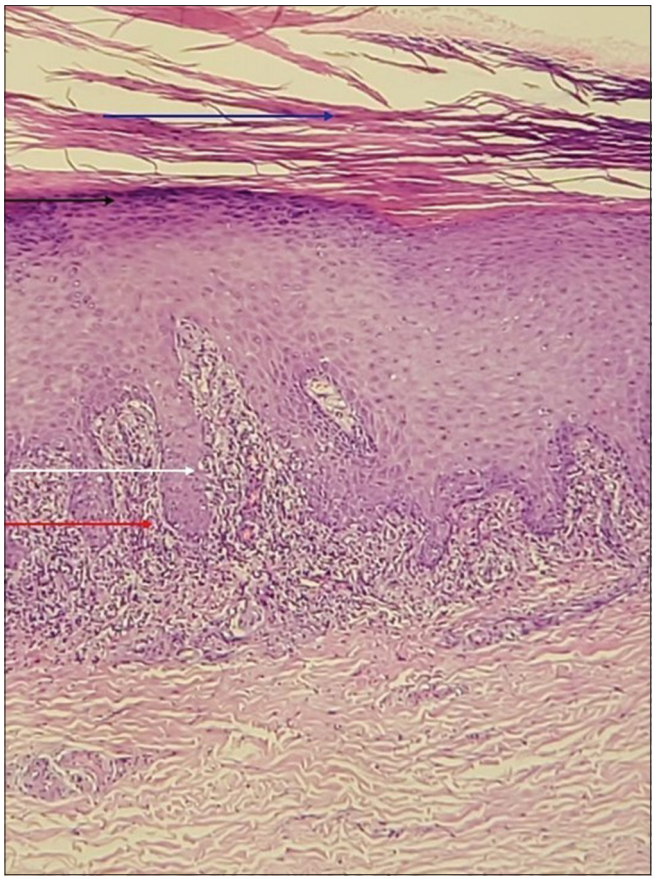

Figure 3: Photomicrograph showing hyperkeratosis, parakeratosis (blue arrow), acanthosis of the epidermis with wedge-shaped hypergranulosis (black arrow), along with vacuolar degeneration of basal layer (white arrow) with dense band-like chronic inflammatory infiltrate (red arrow) at the dermo-epidermal junction (H and E, 400X)

T cell exhaustion. This can now be inhibited by antibodies against PD-1 or PD-L1.

Anti-PD-1 drugs have been approved for the treatment of unresectable or metastatic melanoma, metastatic non-small cell lung cancer, and renal cell carcinoma.[4] Even though these drugs have a better safety profile than the traditional ones owing to their targeted therapeutic response, they can have significant adverse effects on various organs. These IRAEs are thought to be due to treatment-related non-specific hyperfunctioning of our immune system, skin being the major organ affected by this enhanced autoimmunity.[5] In a retrospective review of 83 patients, 42% developed cutaneous adverse effects (AEs) attributed to pembrolizumab, the most common of which were maculopapular eruptions, pruritus, and vitiligo.[6]

Lichenoid reactions, ranging from typical lichen planus-like lesions to hypertrophic or papulosquamous lesions associated with severe pruritus, have been reported as rare cutaneous AEs, which may develop weeks to months after treatment.[6,7]

In lichenoid reactions, keratinocytes expressing PD-L1 are specifically affected, leading to dense CD4/CD8 positive lymphocytic infiltration in basal membrane and

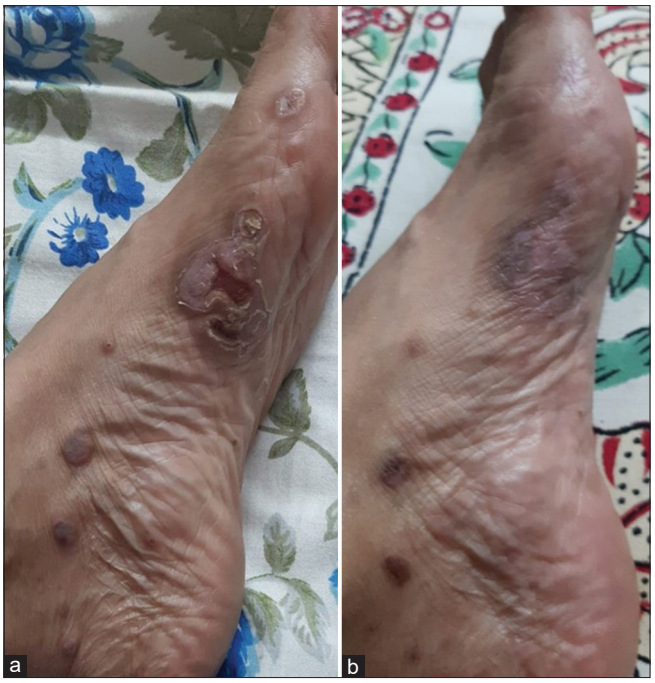

Figure 4: Multiple, well-defined, pink to violaceous, flat-topped papules and ulcerated plaques over the left foot (a), post-treatment resolution (left foot) (b)

sub-epithelium, necrosis of keratinocytes, acanthosis, and hypergranulosis.[8] This indicates that the cutaneous reactions are a target effect of the PD-1/PD-L1 pathway, rather than a non-specific hypersensitivity reaction. Kwon *et al*.[9] concluded that cutaneous toxicities may serve as surrogate markers for the efficacy of treatment with immune checkpoint inhibitors.

Although none of the Indian studies have reported lichenoid reactions or lichen planus as a cutaneous adverse drug reaction due to pembrolizumab, lichen planus pemphigoides following pembrolizumab and nivolumab have been reported otherwise.[9]

Treatment for cutaneous IRAEs is primarily based on severity grading, which is referred to most commonly by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).[10] Furthermore, there is no standardized treatment for many IRAEs, and management is based on case reports, case series, and expert consensus and opinions.[5] Generally, Grade 1-2 cutaneous reactions are treated with topical corticosteroids and oral antihistamines.[3,7] For Grade 3-4, a skin biopsy is needed for classification, and systemic steroids are planned for at least 2-4 weeks, which are gradually tapered, along with temporary or permanent cessation of immunotherapy.[4] Lastly, in the cases refractory to steroids, newer agents such as tumour necrosis factor-alpha inhibitors, azathioprine, acitretin, and mycophenolate mofetil can be used. Sibaud V in his review of AEs of checkpoint inhibitors mentioned the role of acitretin, steroids, and phototherapy in the management of pembrolizumab-induced lichenoid reactions.[6]

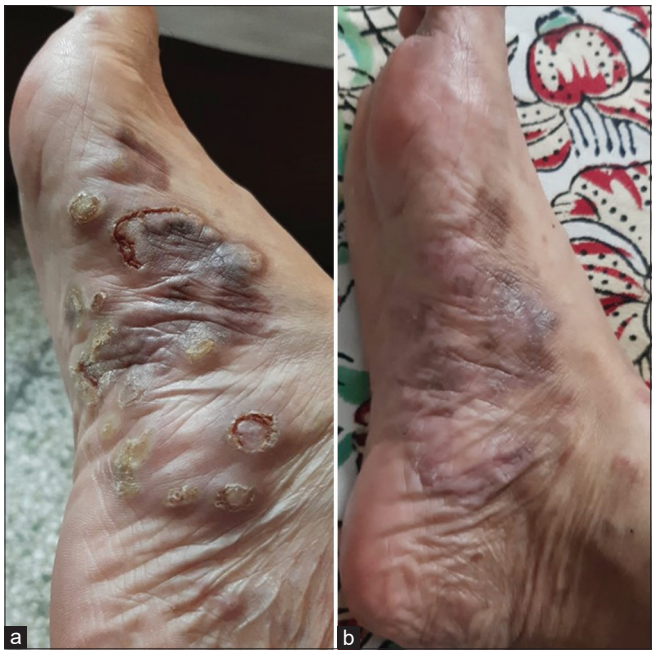

Figure 5: Multiple, well-defined, pink to violaceous, flat-topped papules and ulcerated plaques over the right foot (a), post-treatment resolution (right foot) (b)

In the present case, the patient presented with violaceous papules over the feet and mucosal lesions, following the start of treatment with pembrolizumab, after detection of pulmonary metastasis on PET-CT. The consecutive scans conducted every 6 months showed a constant regression of the underlying metastatic lesion with immunotherapy. In our case, pembrolizumab was continued even after the development of lichenoid rash, which increased in severity in the form of ulcerations over soles and oral erosions. Remission in lichen planus was achieved with acitretin, thus allowing pembrolizumab to be continued safely.

Conclusion

In the nutshell, all the immune checkpoint inhibitors can induce dermatological adverse events, and with their increasing use to manage malignancies, greater awareness is required among dermatologists to diagnose, manage, and report more such cases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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