

Pembrolizumab-Induced Hypertrophic Lichen Planus in Patient with Hepatocellular Carcinoma

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ABSTRACT:

Pembrolizumab, an anti-programmed cell death-1 (PD-1) antibody, is a highly effective targeted therapy for many cancers, including hepatocellular carcinoma (HCC). Besides the excellent efficacy, one of the major reported downsides of this drug are the cutaneous adverse events, which can be presented in various forms. In this case report, we demonstrate a case of hypertrophic lichen planus (LP) after receiving pembrolizumab for 1 month. The initial diagnosis was made using dermoscopy and the diagnosis was confirmed by skin biopsy. Our patient was treated with intralesional corticosteroid which provided an excellent outcome. After the treatment, this patient can resume HCC treatment, using pembrolizumab. Hypertrophic LP is an unusual AE of pembrolizumab, the correct diagnosis and early treatment are critical for drug continuation.

Key words: Hypertrophic lichen planus, Pembrolizumab, Cutaneous adverse event, Anti-PD-1 receptor

Introduction

Pembrolizumab, a humanized monoclonal anti- PD-1 antibody, is a novel therapeutic option for treating various cancers, including hepatocellular carcinoma (HCC). Among those side effects, cutaneous adverse events (AEs) were one of the most common, which can be found in up to 42% of patients¹. In this case report, we present an unusual form of cutaneous AE, hypertrophic lichen planus (LP), in a patient receiving pembrolizumab for HCC treatment.

Case report

A 76-year-old male patient was referred from an oncologist to a dermatologist for multiple pruritic skin lesions. He had been receiving pembrolizumab for HCC treatment. These lesions occurred after he received pembrolizumab for 4 weeks with accumulative dose of 300 mg. Because of the worsening cutaneous AEs, the oncologist decided to

terminate the treatment after using the drug for 4 months. However, the lesions persisted despite the discontinuation of the drug. His previous treatments for HCC were radiofrequency ablation and sorafenib, but the result was unsatisfying. He had also been diagnosed with hepatitis B viral (HBV) infection with cirrhosis for 10 years. His latest HBV viral load was < 10 IU/ml. Physical examinations revealed multiple symmetrically distributed erythematous to violaceous hypertrophic plaques with fine adherent scales on both hands, legs, and ankles (Figure 1). The patient also noticed the linear expansion on the lesion of lower leg after being scratched (Figure 1). Dermoscopic findings demonstrated blue-gray globules, comedo-like opening and follicular plugging (Figure 2). The mucosa or other typical sites for LP were not affected.

The skin biopsy, performed on left lower leg, showed dense lichenoid infiltrate on an area with acanthotic epidermis. Hypergranulosis and hyperkeratosis were also presented (Figure 3). A diagnosis of hypertrophic lichen planus-like drug eruption from pembrolizumab was made. Intralesional corticosteroid injection was

performed on the lesions of both hands. At 2-week follow-up, the itchiness and thickness of all injected lesions were drastically improved (Figure 4). After the improvement of lesions, oncologist decides to resume the pembrolizumab for HCC treatment.



Figure 1 Multiple symmetrical erythematous to violaceous hypertrophic plaques with fine adherent scales on both hands, legs, and ankles.

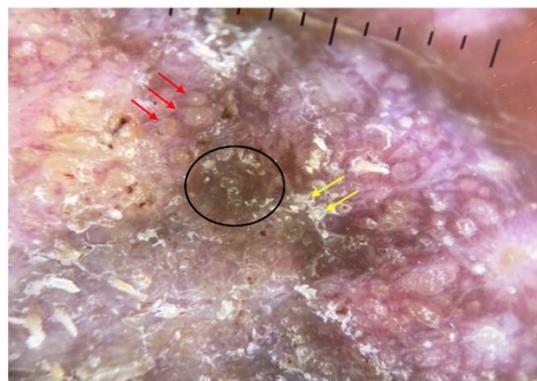


Figure 2 Dermoscopic findings demonstrated blue-gray globules (black circle), comedone-like opening (red arrow) and follicular plugging (yellow arrow)

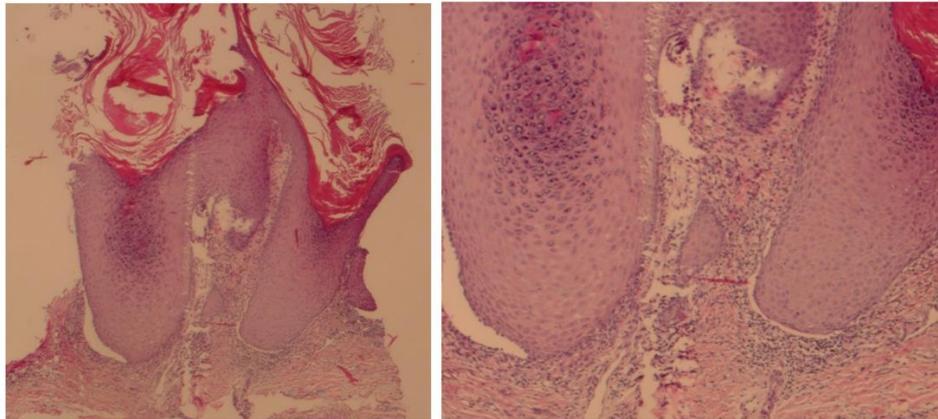


Figure 3 Histopathological finding showed hyperkeratosis, hypergranulosis, acanthosis of the epidermis and dense lichenoid infiltrate of lymphohistocytes along the acanthotic area (10X, 40X)



Figure 4 Dramatic improvement of the lesions on both hands after intralesional corticosteroid injection.

Discussion

Immune check point inhibitors (ICIs) have been used to target on specific proteins on the surface of cancer cells. The most well-known targets are programmed cell death protein 1 (PD-1) and its ligand, which upregulate on cancer cells. The presence of these proteins leads to downregulation of cancer surveillance by cytotoxic T cells, which results in cancer invasion and proliferation². However, using ICIs to block these targeted molecules can result

in enhanced functions and lack of inhibition of T cells, which may result in immune-related AEs, including cutaneous AEs. Wide range of PD-1 receptor inhibitors-related cutaneous AEs have been reported. These cutaneous AEs have significant effects on the quality of life of the patients, which can result in dose reduction or even discontinuation of the treatment¹. Pembrolizumab is an ICI, targeting PD-1 receptor. It has been approved by USA food and drug administration for treatment of many

malignancies including melanoma, non-small cell lung cancer and HCC. Particularly in HCC, pembrolizumab is only recommended in those patients with advanced disease who have failed to response to sorafenib³.

Among ICIs-related cutaneous AEs, maculopapular rash is the most common. However, lichenoid reaction is also found to be quite common amongst these patients with a prevalence of 17%⁴. This lichenoid reaction ranges from typical LP to hypertrophic and vesiculobullous lesions, which may occur during the first week or several months after the drug initiation⁵. The occurrence of the lichenoid eruption may be explained by its immunological mechanism, which is thought to be T-cell mediated response. By blocking PD-1 activity, it can unleash the previously suppressed T-cells, causing widespread non-specific T-cell activation and eventually, carrying out their inflammatory attack on autoantigens in response. This theory has been further supported by the previous report, which skin biopsy showed an abundant proliferative CD8+ PD-1+ T cells infiltration⁶. It has been suggested that the lichenoid reactions can be the result of the blocking the interaction between PD-L1 on keratinocytes and PD-1 on T-cells.

Our patient developed hypertrophic LP, after receiving pembrolizumab for 4 weeks. The typical clinical presentation of hypertrophic LP, including Koebner's phenomenon, dermoscopic findings and histopathological findings help to confirm the diagnosis. Besides the histological finding which requires skin biopsy, dermoscopy can be useful as a supportive diagnostic tool. Dermoscopic findings in our patients showed blue-gray globules, comedo-like opening and follicular plugging, which correlated with the previously described characteristic finding of hypertrophic LP⁷. Only a few previous reports have described a hypertrophic LP in this setting^{1,5}. What concerns dermatologist the most is that, sometimes these lesions can mimic squamous

cell carcinoma (SCC). Unlike SCC, which dermoscopic findings largely depend on the degree of differentiation of the tumor. However, the prominent keratin components and polymorphism of the vessels are the key features⁸. Besides the similarity of clinical appearance, occasionally SCCs can arise on the long-standing LP, with average lag time of 12 years⁹. But there is no report regarding this malignant transformation from drug-induced hypertrophic LP. This can be due to the limited number of cases and shorter duration of lesions due to drug discontinuation in patients who developed drug-induced hypertrophic LP.

For the treatment of the ICIs-induced lichenoid eruptions, there are reports of the successful treatments using acitretin and corticosteroids in many forms: topical, intralesional and oral¹⁰. Our patient responded well to the intralesional corticosteroid injection, as the symptoms and the appearance of the lesions improved drastically after the injection. By treating the cutaneous AEs, patient could resume the anti-PD-1 treatment. This emphasizes the importance of management of cutaneous AEs since it could improve the oncological outcomes.

Conclusion

While lichenoid reaction is common AE in patients receiving anti-PD-1 receptor, hypertrophic LP is a rare cutaneous AE. The treatment should be addressed on the T cell reactivation. In order to prevent the patient from treatment cessation, collaboration between oncologists and dermatologists is crucial in order to make an early diagnosis with prompt treatment that can result in better outcome. Further investigation on molecular basis will be important to elucidate the pathogenesis of pembrolizumab-induced hypertrophic LP.

References

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