Pembrolizumab-Induced Hypertrophic Lichenoid Dermatitis and Bullous Pemphigoid in One Patient

Dear Editor,

Pembrolizumab is approved to treat multiple types of cancer. It is an immune checkpoint monoclonal antibody inhibiting (ICI) the interaction between programmed cell death (PD)-1 receptor and its ligand (PD-L1).[1] Multiple cutaneous immune-related adverse events (CirAEs) were reported with Pembrolizumab use.[2] To the best of our knowledge, only two cases of multiple CirAEs in a single patient have been reported.[3,4] We are reporting a 68-year-old male patient who developed Pembrolizumab-induced hypertrophic lichenoid dermatitis (HLD) and bullous pemphigoid (BP).

The patient with a known history of hypertension and hyperlipidemia was diagnosed with urinary bladder cancer in 2009 and underwent multiple surgical procedures.

In 2020, he was diagnosed with local metastatic urinary bladder cancer, and in May 2021, he was started on the Bacillus Calmette–Guérin vaccine (BCG) and Pembrolizumab at a dose of 200 mg intravenous infusion every 3 weeks. He was referred to the dermatology clinic in December 2021 with a four-month history of mildly pruritic, thick lesions over the extremities [Figure 1]. The examination revealed thick lichenified plaques and nodules on legs. Few lesions were already healing after self-prescription of betamethasone cream. The biopsy findings were consistent with drug-induced lichenoid dermatitis [Figure 2a], and the patient was prescribed topical steroids in the form of mometasone cream. He responded well to the treatment with no recurrence.

In May 2022, the patient presented to the Emergency Room with a five-day history of severely pruritic generalized rashes and scattered blisters. He denied taking any new medication or using new skin care products. Examination revealed multiple large targetoid plaques and wheels with central bullae involving the head, trunk, and extremities without mucosal involvement [Figure 3]. Investigations revealed positive BP (Bullous Pemphigoid) 180 IgG antibodies and negative BP 230 IgG. The biopsy showed subepidermal blister with inflammatory infiltrate composed of lymphocytes, eosinophils, and fibrin. Direct IF (immunofluorescence) revealed subepidermal linear deposition for IgG and C3, negative for IgA, IgM, C1q, and fibrinogen. Unfortunately, we were not able to provide BP histology and DIF images as it was not performed in our laboratory.

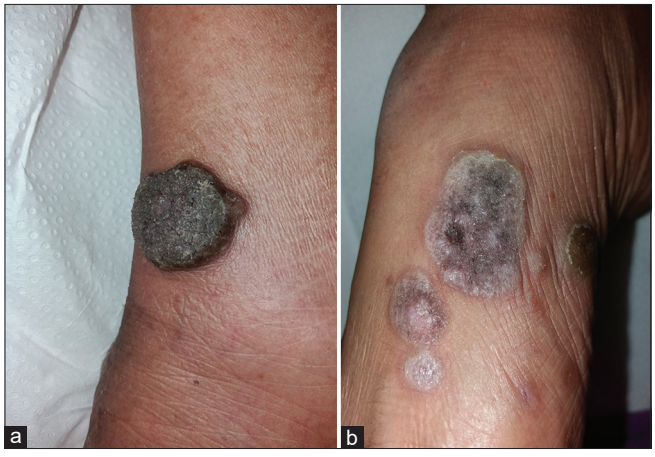

Figure 1: (a) Hypertrophic lichenoid nodule on the posterior leg (b) healing nodules after applying topical steroids on dorsum of the right foot

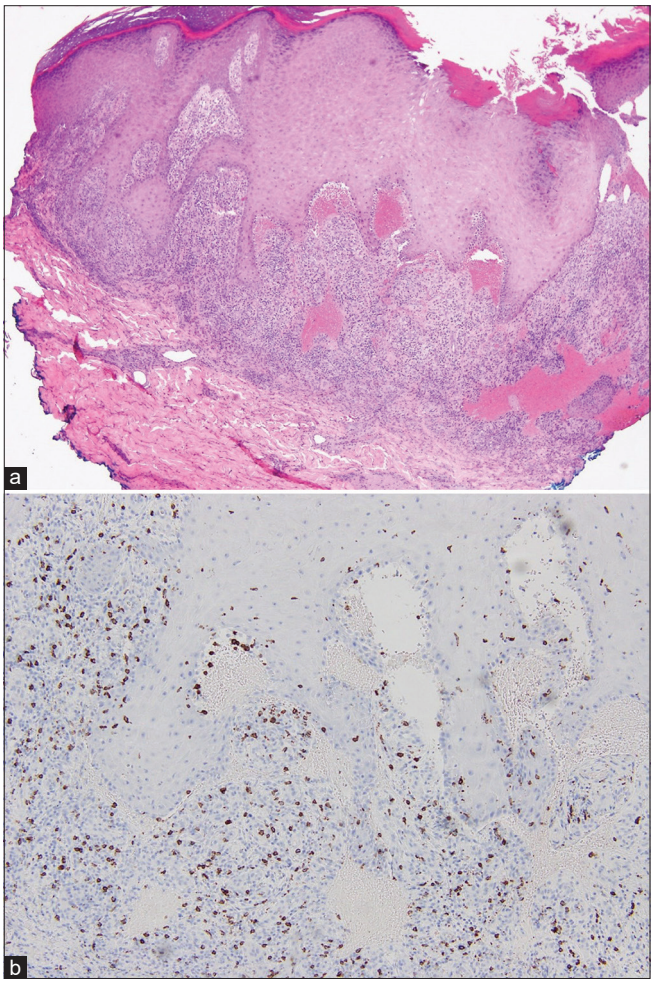

Figure 2: (a) Microphotograph showed orthokeratosis, wedge-shaped hypergranulosis, acanthosis with band like inflammatory infiltrate comprised of lymphocytes and eosinophils at dermo-epidermal junction with pigment incontinence. (H and E, 40×) (b) Microphotograph showed CD8-positive lymphocytes at dermo-epidermal junction on immunohistochemistry

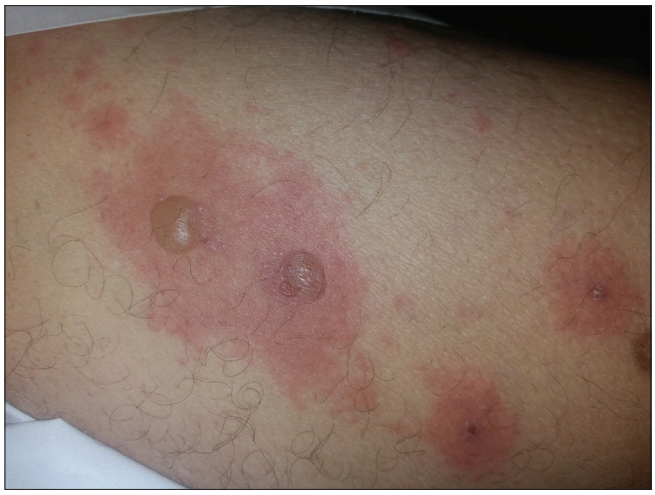

Figure 3: Large wheels with central bullae on the anterior thigh

The diagnosis of BP was made, Pembrolizumab was withheld, and a tapering prednisolone course (0.5 mg/kg/day) was initiated along with topical steroid. All lesions healed within two months with no recurrence.

Lichen planus pemphigoides, which is considered by some authors as a BP subtype, was excluded based on a negative history of lichen planus, absence of lichen planus lesions, and bullous formation on urticarial lesions. Paraneoplastic pemphigus was also excluded absent mucosal lesions, complete healing with systemic steroids with no recurrence after stopping Pembrolizumab, and negative BP 230 IgG.[5]

Later, the patient was found to have hypersensitivity pneumonitis secondary to ICI. The decision of resuming Pembrolizumab was cancelled based on pulmonology recommendations. Currently, he is on Gemcitabine–Cisplatin.

CirAEs are one of the most common adverse events seen with ICI.[6] They typically occur within weeks after initiating ICI and continue even after ICI discontinuation.[6] The management of CirAEs depends on their severity. According to the National Comprehensive Cancer Network (NCCN) guidelines, bullous dermatitis involving 10–30% of the body surface area and limiting daily living activities is considered grade 2 that requires stopping the ICI and initiating systemic steroids in the form of prednisolone or methylprednisolone 0.5–1.0 mg/kg/day tapered over eight weeks.[6,7] This protocol was followed in managing our patient. From oncology perspective, the administration of systemic steroids in the management of CirAEs does not appear to have a negative effect on the patient outcome.[8]

The decision of stopping Pembrolizumab and initiating Gemcitabine–Cisplatin was made by the oncologist. However, combining ICI with paclitaxel can decrease the risk of developing CirAEs compared with ICI alone.[9] This combination showed a favorable safety profile when used as a second or a third-line chemoimmunotherapy for urothelial carcinoma.[10] A recent systematic review showed no difference between Paclitaxel and Pembrolizumab in response rate in treating gastro-esophageal junction cancer.[11]

The exact mechanism of developing CirAEs is not fully understood. ICIs help in reviving T cells and thus increasing the immune system activity by improving the antitumor action. Subsequently, CirAEs may occur. This may include inducing new autoimmune inflammatory diseases or exacerbating pre-existing conditions.[6] Recurrence of CirAEs has been also observed upon rechallenge as well as the formation of new distinct CirAEs, which is thought to be due to predisposition to subsequent toxicity and delayed presentation.[7]

Multiple theories were suggested explaining the development of drug-induced BP and with ICI intake. Depletion of CD4+CD25+Foxp3+ regulatory T cells leading to autoantibody-secreting B-cell clones' proliferation was suggested. It has been also proposed that anti-PD-1/PD-L1 therapy can induce an interaction between PD-1/PD-L1-expressing B cells and PD-1+ follicular helper T cells, causing a B-cell germinal center response.[12]

Immuno-bullous diseases may exhibit epitope spreading phenomenon where chronic inflammation at the dermo-epidermal junction may expose the antigens to T cells causing a secondary immune reaction.[5] In our patient, BP was proceeded by HLD.

HLD is rarely reported as a side effect of Pembrolizumab and its exact pathogenesis remains unknown.[13-15] Honda *et al*., (2021) reported CD8+ T cell infiltration in the upper dermis with the expression of PD-L1 on the epidermal keratinocytes.[14] Those findings suggest that inhibiting the interaction between PD-L1 on keratinocytes and PD-1 on dermal T cells may cause epidermal hypertrophy.[14] In our patient, the T cells stained positive for CD8+ [Figure 2b]. This may support the previous hypothesis.

Another possible pathway suggested by Curry *et al*., (2019) is the activation of the innate immune response through CD14/TLR signaling of CD14+CD16+ monocytes. Unfortunately, the latter stains were not available in our institute.[15]

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.

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Conflicts of interest

There are no conflicts of interest.

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