CLINICAL VIGNETTE

Pembrolizumab and Enfortumab Associated Bullous Pemphigoid

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Case Report

A 67-year-old man with stage II sigmoid colon cancer s/p resection in 2017 who was then diagnosed with right upper tract urothelial carcinoma four years later, with 6 cm right renal lesion on CT imaging. Biopsy confirmed high grade urothelial carcinoma. He received neoadjuvant split dose cisplatin/ gemcitabine followed by robotic nephroureterectomy and LN dissection. Final pathology was ypT4N2 disease with 4 positive nodes up to 3.3cm in size. The primary tumor was 3.7cm with high grade invasion through renal parenchyma into focal perinephretic fat. Renal vein margins were positive. He also found to have increased pulmonary nodules suspicious for worsening pulmonary metastases. He was started on pembrolizumab plus Enfortumab Vendotin (EV). Three-month interval scan showed decreased size of his lung nodules. Six months later he developed a persistent leg rash and his treatment was stopped after 10 cycles. The rash was treated with topical steroids, oral antibiotics without any improvement. He also developed a total body scattered macular rash. A punch biopsy of right forearm skin showed interface dermatitis with superficial/mid dermal perivascular and interstitial inflammation containing lymphocytes and eosinophils. No vasculitis or malignancy was noted, favoring drug eruption. Given slow improvement with steroid treatment, and new development of bullous like lesion near his ankle, a punch biopsy was performed on the ankle lesion ten weeks later. Pathology showed subepidermal clefting with associated superficial dermal inflammation containing eosinophils, lymphocytes and plasma cells. No vasculitis or malignancy was found in the sections examined. The histopathologic findings and the direct immunofluorescence result were consistent with an immunobullous disease, and supported the clinical impression of bullous pemphigoid. The patient remained off both pembrolizumab and EV. His rash and open ulcer improved with time and slow steroid taper. Serial scans showed no evidence of disease progression and he remained off both drugs for nearly a year. A recent scan suggested possible small progression in bones and he resumed pembrolizumab alone. Thus far he has no recurrent skin toxicity. We suspect his initial Bullous Pemphigoid was likely more driven by EV or combination of the drugs.

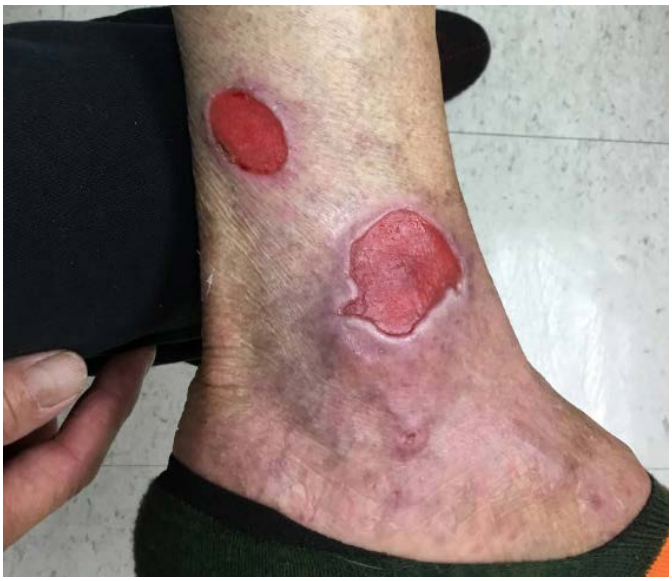

Figure 1. Bullous pemphigoid lesions over right ankle with delayed onset after coming off both pembrolizumab and enfortumab.

Discussion

Bullous pemphigoid is a blistering autoimmune disease which has been rarely reported as skin toxicity with various drugs.[1] Bullous pemphigoid is primarily considered a humorally medicated disease although T cell dysregulation can also contribute to the autoimmunity.

Pembrolizumab is an effective anti-programmed cell death 1 (PD-1) monoclonal antibody which improves survival in melanoma, lung, and other cancers including urothelial cancer. It allows activation of host T cell responses against tumor cells. At the same time, it can trigger immune related adverse reactions by its effect on the patient's immune system. Common immune related adverse reactions of pembrolizumab include pneumonitis, colitis, hepatitis, endocrinopathies and nephritis. Bullous pemphigoid has been reported as a rare side effect of anti-PD1 drugs due to T cell dysfunction.[2]

EV is a nectin-4 directed antibody drug conjugate approved by FDA for the treatment of locally advanced or metastatic urothelial cancer. It carries direct cytotoxic effect as well as bystander effect which occurs when intracellular MMAE

diffuse across cell membranes leading to apoptosis in nearby tumor cells. The delivery of MMAE into nectin4 expressing normal tissues such as epidermis can cause dermatologic complications. EV can cause rare but possibly fatal cutaneous reactions such as Stevens-Johnson syndrome and toxic epidermal necrosis.[3] EV-related skin reactions occurred in 47% of participants in the landmark EV-301 trial, including 0.4% with bullous dermatitis.[3]

In April 2023, the FDA granted accelerated approval to EV with pembrolizumab for patients with locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy. This was based on phase 1/2 EV-103/ KEYNOTE-869 study.[4] In the study, skin reactions occurred in 30 (66.7%) patients. The median time to first onset was 0.7 months. Two patients (4.4%) experience grade 4 dermatitis bullous and toxic epidermal necrolysis. Up to 73.3% of patients had resolution of skin reactions with median time to resolution of one month.

A systematic review reported onset of cutaneous toxicity ranged from 4 to 84 weeks after initiation of pembrolizumab[5] without a dose dependent relationship. Our patient, developed skin toxicity after 10th cycle (week 30) of pembrolizumab and EV. Ongoing monitoring for cutaneous symptoms is needed while on doublet treatment. The skin toxicity has also unpredictable progression. This was seen in in our patient who developed bullous lesions several months after being off both treatments. Early recognition of severe cutaneous toxicity is important as patients need prompt treatment. Most patients with bullous pemphigoid cases can be successfully treated with a combination of systemic and topical steroids. Steroid-sparing drugs, such as methotrexate can be considered for refractory disease.[6]

Although bullous pemphigoid is a rare side effect of anti–PD-1 medication, we now have evidence that it can be seen patients exposed to either EV or EV in combination with immunotherapy. Oncologists need to closely monitor for any cutaneous symptoms because of the unpredictable timeline. It is important to understand the clinical course of skin toxicity to develop more effective and timely therapeutic strategies.

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