Bullous pemphigoid limited to the primary site of cutaneous squamous cell carcinoma in two patients treated with anti-PD-1 therapy

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Background

- Immune checkpoint inhibitors such as cemiplimab or pembrolizumab are increasingly used for patients with unresectable or metastatic cutaneous squamous cell carcinoma
- Cutaneous inflammatory effects have been frequently reported with immune checkpoint inhibitors, including psoriasis, lichen planus, eczematous dermatitis and bullous pemphigoid
- Management of these adverse effects is nuanced and involves a delicate balance between therapeutic immunosuppression and optimal anti-tumor effect of immune checkpoint inhibitors
- Bullous pemphigoid is an autoimmune subepidermal blistering disorder that presents with tense bullae and generalized pruritic
- Although immune checkpoint inhibitor-induced bullous pemphigoid generally presents during immunotherapy, it may also present several months after discontinuing treatment and lack classic bullous lesions
- We present two cases of patients with cutaneous squamous cell carcinoma who developed bullous pemphigoid lesions limited to the primary malignancy site

Case 1

- We present the case of a 77-year-old male diagnosed with moderately differentiated cSCC of the left arm in January 2018
- After primary excision, he was found to have metastatic disease to the left axillary lymph nodes in January 2020 and underwent six months of immunotherapy with cemiplimab and two months of radiation therapy with 55 Gy to the left upper arm
- This was followed by radiation to the left axillary and infraclavicular lymph node metastases
- He then developed pulmonary metastases two years later for which he started pembrolizumab
- Four months into treatment, he developed pruritus and bullae on his left arm in the area of prior radiation therapy, clinically suspicious for BP (Figure 1)
- Serum eosinophils were unknown and his BP230 IgG was within normal limits (BP 180 IgG was unavailable)
- Given the high index of suspicion and presumed diagnosis of BP, he was treated with doxycycline and prednisone with significant improvement in the rash
- Pembrolizumab was held, and the patient was found to have evidence of disease progression on PET-CT scan three months later
- He received cetuximab for four months and was then switched to palliative carboplatin and paclitaxel due to disease progression
- The patient's ctDNA levels became undetectable, and due to chemotherapy-related neuropathy, he has been on a treatment break with no progression of disease

Case 2

- A 78-year-old male presented in December 2020 with a new subcutaneous nodule on his right cheek at the site of a previous cSCC treated with Mohs surgery 10 years prior
- Biopsy of the nodule was positive for well to moderately differentiated invasive squamous cell carcinoma
- The patient underwent wide local excision which revealed an invasive moderately differentiated cSCC measuring 1.9 cm with ulceration, a depth of invasion of 13 mm, perineural invasion and lymphovascular invasion and was treated with adjuvant proton external beam radiotherapy in May 2021
- Three months later, he developed a new right facial mass
- Wide local excision revealed recurrent moderately to poorly differentiated cSCC with extension into skeletal muscle and perineural invasion
- The patient was started on pembrolizumab in September 2021, which he continued for 18 cycles
- In June 2023, he developed a blistering rash on his right cheek within the prior irradiated field and excoriations on the torso, with punch biopsy revealing a subepidermal vesiculation with eosinophils
- Direct immunofluorescence demonstrated a linear granular deposition of IgG1 and IgG4 at the dermal epidermal junction (Figure 2)
- Enzyme-linked Immunosorbent Assay revealed a BP180 level of 28.2 U/mL (normal <15 U/mL) and BP230 level of 1.2 U/mL (normal <9 U/mL), consistent with BP
- The patient was simultaneously treated with clobetasol and dupilumab, leading to clearance of active bullae
- Due to absence of disease progression on imaging, he was given a treatment break

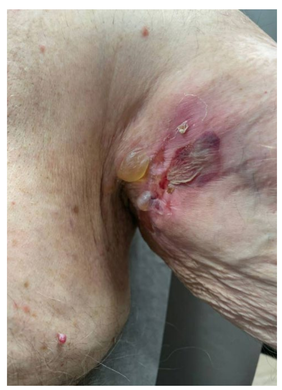

Figure 1. Intact bullae at the prior site of radiation on the left upper extremity near the axilla.

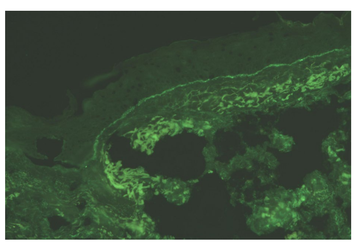

Figure 2. Direct immunofluorescence with a linear granular deposition of IgG1 and IgG4 at the dermal epidermal junction.

Discussion

- Both patients experienced significant improvement after discontinuing immunotherapy and receiving a combination of steroids and steroid-sparing agents
- Notably, the patients had also previously received radiation therapy in the area, which is related to the phenomenon of locus minoris resistentiae
- The development of adverse effects localized to the site of prior malignancy is likely due to changes in the skin microenvironment and may represent an important prognostic factor for patients with metastatic or unresectable disease
- Histologically, drug-induced BP presents with subepidermal cleft with eosinophils within the blister cavity and dermis
- Immunofluorescence generally demonstrates linear C3 or C3 and IgG along the basement membrane
- In pembrolizumab-induced BP, anti-BP230 autoantibodies are frequently negative, especially when compared to anti-BP180 autoantibodies
- Previous studies have shown that cutaneous immune related adverse effects may be associated with decreased mortality rates, suggesting a possible protective effect

Conclusions

- Our cases highlight negative anti-BP230 autoantibodies in pembrolizumab-induced bullous pemphigoid and the use of targeted treatment regimens in order to preserve anti-tumor immunity and minimize global immunosuppression with dupilumab
- Future studies should explore the potential role of localized cutaneous immune-related adverse effects on cSCC prognosis and management

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