Immune checkpoint inhibitor lichenoid eruption due to pembrolizumab

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SUMMARY
Pembrolizumab is an immune checkpoint inhibitor used in many cancer types, including genitourinary cancers. Although immunotherapies have dramatically changed the landscape of cancer treatment by providing an alternative to traditional chemotherapy, they have been associated with significant immune-related adverse events (IRAEs) with wide-ranging clinical manifestations. We present the case of an elderly woman on pembrolizumab for metastatic bladder cancer who developed cutaneous IRAE with lichenoid eruptions that responded to high-dose intravenous glucocorticoids.

BACKGROUND
Immune checkpoint inhibitor (ICI) therapies have dramatically changed the landscape of cancer treatment by providing an alternative to chemotherapy. However, ICI therapies, such as pembrolizumab, are associated with significant immune-related adverse events (IRAEs) affecting all organ systems. Cutaneous manifestations are common with clinical presentations including maculopapular rash, psoriasisform rash, bullous dermatitis, lichenoid eruption, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). ICI lichenoid eruptions present later than maculopapular and psoriasisform rashes, most commonly 6–12 weeks after initiation of immunotherapy.1 Lichenoid eruptions have been reported in 0.5%–6% of patients treated with anti-PD-1/PD-L1 immunotherapies.2 Systemic glucocorticoids are the mainstay of therapy for most high-grade IRAEs. High-potency topical steroids can be considered for grade 1 ICI bullous dermatitis—when the disease involves <10% body surface area (BSA)—but for grades 2–4, systemic corticosteroids are recommended.3-5 However, the current National Comprehensive Cancer Network (NCCN) guidelines do not address management recommendations for ICI lichenoid eruptions.

CASE PRESENTATION
A woman in her 80s presented to the emergency department for a diffuse, progressive rash with pruritus. She had active metastatic bladder cancer and developed a rash 92 days after the initiation of immunotherapy with pembrolizumab. Two weeks before admission, the patient’s skin lesions evolved into a diffuse vesiculobullous rash covering all extremities, despite conservative management with topical triamcinolone, oral antihistamines and holding pembrolizumab. She denied constitutional symptoms, abdominal pain, nausea, vomiting, dyspnoea or chest pain.

On admission, she was afebrile and normotensive with a pulse rate of 74 beats per minute and SpO2 of 95% on room air. A physical examination of the patient revealed cachexia, mild oropharyngeal mucositis, angular cheilitis and a right subclavian port without surrounding erythema or purulence. A focused dermatological examination was significant for diffuse violaceous plaques and erosions with adherent haemorrhagic crusting on her face, bilateral upper and lower extremities, and dorsal surfaces of her hands (figure 1). Multiple lesions on the upper and lower extremities exhibited purulence. The left lower extremity also had erosions with a negative Nikolsky sign. There were no targetoid or dusky lesions, facial swelling, conjunctivitis or lymphadenopathy. The patient’s laboratory findings were notable for a normal leucocyte count with an elevated erythrocyte sedimentation rate and C reactive protein at 39 mm/hour (normal range: 0–29 mm/hour) and 9.59 mg/L (0–8.0 mg/L), respectively. Due to our concern for secondary impetiginisation of the lesions, the patient was started empirically on empiric antibiotic therapy.

INVESTIGATIONS
We obtained multiple skin biopsies for pathological examination, including perilesional direct immunofluorescence (DIF) and tissue culture. The fluid cultures grew Proteus mirabilis and Methicillin-resistant Staphylococcus aureus (MRSA). The skin biopsies demonstrated lichenoid dermatitis with eosinophils and focal subepidermal clefting (figure 2). Additionally, we obtained multiple serologies, including bullous pemphigoid antigens, desmogleins, paraneoplastic antibodies and indirect immunofluorescence, which were all negative.

DIFFERENTIAL DIAGNOSIS
Our differential diagnoses for this patient’s rash prior to biopsy results included neutrophilic dermatoses, immunobullous disorders and drug eruption. The clinical presentation was inconsistent with life-threatening drug-related dermatoses, such as SJS or drug rash with eosinophilia and systemic symptoms based on the absence of significant truncal involvement, painful or dusky skin lesions, Nikolsky sign, odynophagia, facial swelling, atypical lymphadenopathy, fevers or eosinophilia. Destruction of the basal layer of the epidermis is characteristic of lichenoid interface dermatitis and may result in focal subepidermal clefting. Although subepidermal...
Clefting with eosinophils is characteristic of certain immunobullous disorders, such as bullous pemphigoid, the presence of lichenoid interface dermatitis seen in this case is most consistent with lichenoid drug eruption as DIF was negative for any specific dermatosis, which supports the diagnosis of drug eruption over immunobullous disorder.3

**TREATMENT**

The patient was started empirically on intravenous vancomycin and cefepime due to our concern for purulent cellulitis and bacterial superinfection of progressive cutaneous eruptions in an immunocompromised host. Following pathology results demonstrating a lichenoid eruption attributed to immunotherapy, the patient was started on prednisone 1 mg/kg daily with a plan for the continuation of systemic steroids for 4–6 weeks pending clinical improvement to ≤grade 1 symptoms. The patient completed a 7-day course of oral antibiotics for superimposed cellulitis.

**OUTCOME AND FOLLOW-UP**

At a follow-up visit with dermatology 1 week after discharge, the patient had clinical improvement of all lesions. Based on recommendations from dermatology and oncology, pembrolizumab was permanently discontinued. One month after hospital discharge, the patient experienced complete resolution of her cutaneous lesions. Due to the progression of metastatic disease and extensive side effects of previously attempted therapies, the patient elected to pursue palliative therapies without further oncological treatment.

*Figure 1* Violaceous plaques and erosions involving the right hand (top) and right upper extremity (bottom) at the time of admission.
Lichenoid dermatitis with eosinophils may be seen in a variety of clinical syndromes, including lichenoid drug eruptions. Although subepidermal clefting with eosinophils is characteristic of certain immunobullous disorders (eg, bullous pemphigoid), interface dermatitis, intraepidermal acantholysis and keratinocyte necrosis are most specific for paraneoplastic pemphigus.1 The patient was diagnosed with a lichenoid eruption due to ICI toxicity from pembrolizumab and superimposed soft tissue infection.

Corticosteroids are the mainstay of treatment for IRAEs and do not reduce the anti-tumour effects of checkpoint inhibitors.3–5 Although the current NCCN guidelines do not explicitly address lichenoid eruptions related to ICI therapy, they recommend treating grades 3–4 bullous dermatitis and other severe IRAEs with prednisone or methylprednisolone 1–2 mg/kg daily until clinical improvement to ≤grade 1 symptoms.3 Additionally, infliximab, rituximab and intravenous immunoglobulin are supportive therapies that can be used for clinically refractory disease, but they are not used as first-line therapies.

No studies have shown a consistent correlation between checkpoint inhibitor side effects and anti-tumour effects. The NCCN recommends resuming immunotherapy agents in patients with grades 1–2 ICI bullous dermatitis once lesions are mild/localised, requiring only topical steroids (grade 2 disease involves 10%–30% BSA with painful blisters). Further immunotherapy is contraindicated in all grade 4 dermatological toxicity cases, including SJS and TEN.3 This patient exhibited grade 3 symptoms (>30% BSA involvement without electrolyte/fluid abnormalities); therefore, resuming pembrolizumab at any dose or transitioning to a different immunotherapy agent would not be recommended due to the concern for life-threatening complications. Accordingly, pembrolizumab was permanently discontinued in this patient.

Learning points

- Immune checkpoint inhibitor (ICI) lichenoid eruptions present later than maculopapular and psoriasiform rashes, most commonly 6–12 weeks after initiation of immunotherapy.
- Immune-related adverse events (IRAEs) include a broad spectrum of cutaneous reactions (eg, maculopapular, psoriasiform, eczematous and lichenoid eruption subtypes). Lichenoid eruptions have been reported in 0.5%–6% of patients treated with anti-PD-1/PD-L1 immunotherapies.
- Steroids are the mainstay of treatment for IRAEs. Individuals with grade 1 ICI bullous dermatitis can receive high-potency topical steroids, whereas individuals with grades 2–4 IRAEs should be treated with systemic steroids.
- Severe ICI toxicity (grades 3–4) is a contraindication to further immunotherapy; however, little prospective research exists on this subject. Additional trials should be performed to evaluate the risks and benefits of ongoing immunotherapy following severe ICI toxicity, especially in the absence of Stevens-Johnson syndrome or toxic epidermal necrolysis.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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