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Case Report

Immune checkpoint inhibitor-associated linear IgA bullous dermatosis with recalcitrant ocular involvement: a rare presentation

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Abstract

Programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) receptor inhibitors have become imperative in the treatment of advanced solid organ malignancies such as metastatic melanoma. With this disinhibition of certain immune responses to induce an antitumour response, numerous adverse events have been reported, many of which affect the skin. While rare, PD-1/PD-L1 inhibitor-associated severe cutaneous adverse reactions (SCARs) can cause significant morbidity and/or mortality. New SCARs are reported with increasing frequency as immune checkpoint inhibitors become more widely used. Here, we present a rare case of recalcitrant ocular linear IgA bullous dermatosis associated with a PD-1 inhibitor. Awareness of this entity will allow more rapid recognition and initiation of appropriate management and treatment, which would reduce the morbidity and/or mortality associated with these serious adverse reactions.

What is already known about this topic?

- Cutaneous adverse reactions are a commonly encountered side effect of immune checkpoint inhibitors.
- Reports of new adverse reactions are frequently published as these medications become widely utilized.
- Bullous dermatoses secondary to these medications are considered severe adverse reactions as they pose a high risk of morbidity with numerous associated complications and worsen patients' quality of life immensely.
- Thus, raising awareness of these entities and rapid initiation of management and treatment is paramount.

What does this study add?

- To our knowledge, linear IgA bullous disease (LABD) has not been previously reported as an associated adverse reaction to immune checkpoint inhibitors in the literature.
- Given it is a bullous disorder, immune checkpoint-associated LABD would be a severe mucocutaneous adverse reaction.
- Therefore raising awareness that this disease process can occur secondary to these novel medications is imperative for prompt recognition and appropriate management.

Case report

A 77-year-old woman with a history of stage III metastatic melanoma treated with wide local excision and 7 months of adjuvant nivolumab presented to clinic with a 4-month history of tender erosions, initially affecting the oral mucosa and then progressing to her trunk and abdomen. The patient also reported new concurrent onset of photophobia, grittiness and blurred vision in both eyes due to severe bilateral symblepharon, cicatrizing keratoconjunctivitis and limbal stem cell deficiency. The patient was referred to our dermatology department by an ophthalmologist (Figure 1).

A punch biopsy from her upper back revealed an ulcer with numerous neutrophils without eosinophils. The indirect immunofluorescence (IIF) study performed at the commercial immunodermatology laboratory at University of Utah in Salt Lake City revealed linear IgA binding to the basement membrane zone of monkey oesophagus with a titre of 1 : 20 and epidermal staining of the human split skin substrate with a titre of 1 : 640. Enzyme-linked immunosorbent assay (ELISA) tests for IgG antibodies to desmoglein 1/3, bullous

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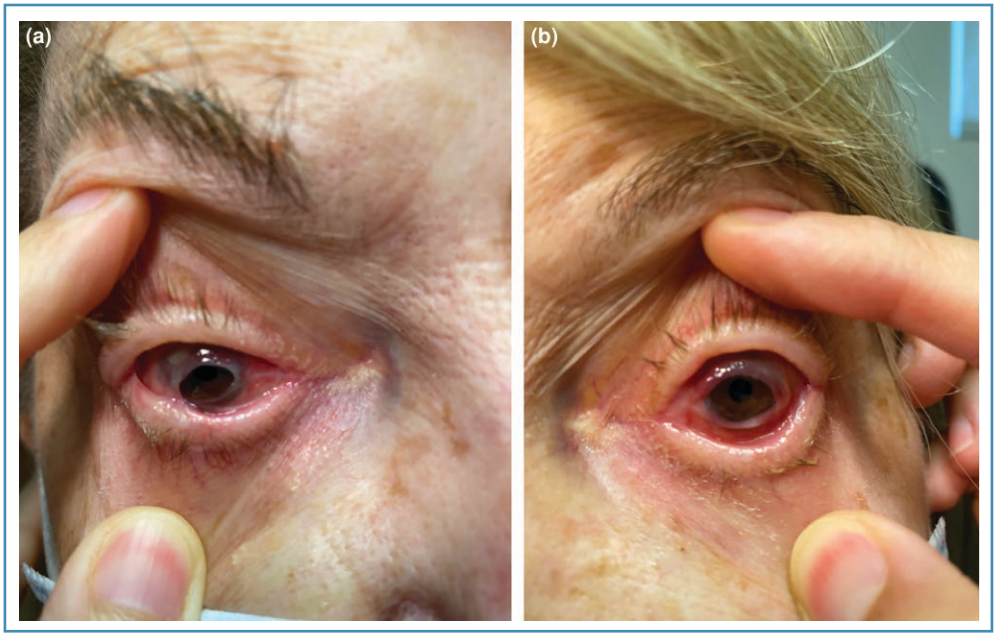

Figure 1 (a) Right eye and (b) left eye. Ocular inflammation and scarring early in treatment course.

pemphigoid 180/230 antigens and collagen VII were negative. These results suggested the diagnosis of linear IgA bullous dermatosis (LABD) affecting skin, as well as oral and ocular mucosal surfaces.

Nivolumab was discontinued and high-dose systemic steroids were initiated with a slow taper over several months. While this regimen halted development of new cutaneous and oral lesions and existing lesions began to heal, her ocular disease continued to progress. Consequently, she was also started on mycophenolate mofetil (2 g daily), doxycycline (200 mg daily), intravenous immunoglobulin (2 g kg monthly), dapsone (100 mg daily) and niacinamide (1500 mg daily), as well as clobetasol topical ointment, tobramycin–dexamethasone and loteprednol ophthalmological steroid suspensions. After 8 months of this regimen, her ocular disease stabilized. She is scheduled for ocular surface reconstructive surgery followed by keratolimbal allograft by ophthalmology, a procedure in which limbal stem cells are transplanted from a cadaveric donor.[1]

Discussion

Therapies targeting the programmed death-1 (PD-1) receptor are used to treat solid malignancies including melanoma.[2,3] Within the tumour microenvironment, programmed death ligand-1 (PD-L1) is overexpressed and engages with PD-1 receptors on CD8 T-cells, subsequently diminishing their killing capacity by causing T-cell dysfunction and inactivation, as well as increasing interleukin-10 (IL-10) production.[2,4] Suppressing this inflammatory and antitumour response is a phenomenon known as adaptive immune resistance.[2] Anti-PD-1/PD-L1 inhibitors are FDA-approved immunotherapies that prevent the overexpressed PD-L1 from interacting with PD-1, thereby allowing cytotoxic T-cells to mount an inflammatory response leading to the death of tumour cells.[4]

PD-1 inhibitors, such as nivolumab, are associated with various immune-related adverse events (irAEs), often involving the skin.[2,4,5] Approximately one-third of patients on a PD-1 inhibitor experience a cutaneous irAE, including bullous disorders such as LABD.[5,6] The time of onset of bullous diseases secondary to PD-1 inhibitors ranges from 4 to 18 months after initiation of treatment.[7]

LABD is characterized by the binding of IgA autoantibodies to LAD-1 and/or LABD97 autoantigens causing subepithelial blistering. Clinically, this presents as grouped or annular papules, vesicles and bullae on an erythematous or urticarial base on the trunk and extensor surfaces. Mucosal involvement is estimated to occur in over 50% of all patients with LABD, commonly affecting the ocular, oral and genital mucosa.[8] Ocular involvement may present as conjunctival redness, sicca-like symptoms, ocular discharge or pain.[8] The most serious consequence of ocular involvement is irreversible scarring of the cornea, development of symblepharon and blindness.[8] Histopathological features of LABD include neutrophil infiltration at the basement membrane zone and, in mature lesions, subepidermal clefting with a predominantly neutrophilic infiltrate.[8,9] Direct immunofluorescence (DIF) of involved and perilesional skin shows IgA and C3 deposition along the basement membrane.[9] IIF demonstrates IgA deposition along the epidermal aspect of human split skin substrate.[9] Indeed, the IIF results revealing exclusively IgA autoantibody support the diagnosis of LABD. Mucous membrane pemphigoid (MMP) was on the differential diagnosis list, but it is typically IgG autoantibody positive. While IgA autoantibodies can be seen in MMP, it is typically in the setting of dual IgG and IgA autoimmunity, which was not the case in our patient, making this entity less likely.[10]

Drug-induced LABD is often associated with vancomycin or captopril, but there have been reports of new-onset LABD that coincide with the initiation immune checkpoint inhibitors (ICIs).[8] Studies suggest there are no significant clinical differences between idiopathic and drug-induced LABD.[9]

Clinician awareness of this potential immune-related adverse event due to PD-1 inhibitors is critical as it can cause significant morbidity, including ectropion and blindness.[8] Immunobullous dermatoses are considered severe cutaneous adverse reactions and often require aggressive treatment and interruption in immunotherapy.[6] While mild disease [body surface area (BSA) <30%] can be managed with ultrapotent topical steroids and anti-inflammatory medications like doxycycline, more severe reactions may require systemic steroids and suspension of immunotherapy.[6] In a retrospective analysis by Siegel *et al.*,[6] almost all of the patients with new immunobullous disease secondary to a PD-1 inhibitor had >30% BSA involvement, requiring initiation of systemic steroid treatment and either temporarily or permanently discontinuing immunotherapy.[6,7] Interruption of anticancer therapies may lead to malignancy progression and death; therefore, early recognition of an immunobullous adverse reaction and prompt initiation of treatment is crucial in order to prevent cessation of oncological treatment and worsening of immunobullous disease.[7]

In summary, we present a rare case of drug-associated LABD with recalcitrant ocular involvement in a patient receiving a PD-1 inhibitor to inform clinicians of this uncommon yet potentially devastating adverse reaction. We conclude that the onset of severe drug-induced/associated immunobullous disorders secondary to immune checkpoint inhibitors necessitates discontinuation of the culprit medication, either temporarily or permanently, and initiation of systemic immunosuppression. If ocular lesions are present, the patient should be referred to ophthalmology for joint management.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

Not applicable.

Patient consent

The patient gave consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

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