

# Bullous pemphigoid secondary to bintrafusp alfa, a bifunctional fusion protein targeting TGF-beta and PD-L1



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## INTRODUCTION

Immune checkpoint inhibitors targeting the programmed cell death-1 receptor (PD-1) and the programmed cell death ligand-1 (anti-PD-L1) have emerged as effective therapies for some patients with unresectable cancers.<sup>1</sup> However, by amplifying the body's natural antitumor defenses, normal cells can be affected, resulting in autoimmune-like side effects. Cutaneous immune-related adverse events (irAEs) are observed in 39% to 49% of patients receiving anti-PD-1 therapy.<sup>2,3</sup> Anti-PD-L/anti-PD-L1-induced bullous disorders make up a rare but recognized class of cutaneous irAE.<sup>4</sup> Bullous cutaneous irAEs requiring systemic treatment can cause delays in the delivery of cancer therapy, making prompt diagnosis and treatment essential to preventing undue morbidity and mortality.

Despite the success of antibodies targeting PD-1/PD-L1, many patients do not have an adequate response. This has led to the development of combination therapies, such as the addition of transforming growth factor beta (TGF- $\beta$ ). Upregulation of TGF- $\beta$  signaling has been associated with immunosuppression in the tumor microenvironment and development of resistance following initial response to anti-PD-1/PD-L1 treatments for patients with metastatic melanoma and urothelial cancers.<sup>5,6</sup> Bintrafusp alfa is a bifunctional fusion protein, which blocks PD-L1 and sequesters TGF- $\beta$  from the systemic circulation via a TGF- $\beta$ RII component, offering

### Abbreviations used:

BP:	bullous pemphigoid
irAE:	immune-related adverse events
PD-1:	programmed cell death-1
PD-L1:	programmed cell death ligand-1
TGF- $\beta$ :	transforming growth factor beta
Treg:	T regulatory cell

a novel approach to alter the immune cell compartment in tumors by seeking to prevent TGF- $\beta$ -mediated resistance to immunotherapy. Here, we present a case of a patient with metastatic colorectal cancer with prior progression on pembrolizumab who participated in a clinical trial (NCT03436563) with bintrafusp alfa and developed treatment-related bullous pemphigoid (BP).

## CASE REPORT

A 59-year-old man had initially been diagnosed with stage IV cecal adenocarcinoma metastatic to the peritoneum 2 years prior to presenting to our institution. He received systemic chemotherapy with 5-fluorouracil/oxaliplatin in combination in the frontline setting. Subsequently, he received pembrolizumab for 12 months until demonstration of disease progression. Next, he was treated in a clinical trial with 1200 mg bintrafusp alfa intravenously every 2 weeks. Following 4 months of this investigational therapy, he reported mild bilateral

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forearm pruritus. On initial physical examination, excoriations without primary skin lesions were noted. He was treated with triamcinolone cream 0.1% without improvement. Three weeks later, he developed pruritic intact and ruptured bullae scattered across the trunk, scalp, and bilateral upper and lower extremities (Fig 1). The palms, soles, and mucous membranes were not involved. A 4-mm punch biopsy of the left thigh revealed a subepidermal cleft filled with serum, neutrophils, eosinophils, lymphocytes, and histiocytes (Fig 2). Direct immunofluorescence revealed linear deposits of IgG and C3 (Fig 3). Taken together with his clinical presentation, he was diagnosed with drug-induced BP. The bintrafusp alfa was held per protocol, and he was initiated on betamethasone ointment and prednisone (1 mg/kg/day). His prednisone dose was tapered over a course of 6 weeks, with complete resolution of the bullae and pruritus. He remained off bintrafusp alfa and began a new immunotherapy regimen of nivolumab and ipilimumab. There was no recurrence of BP on this dual immune checkpoint inhibitors regimen.

## DISCUSSION

Bintrafusp alfa is a bifunctional fusion protein of an anti-PD-L1 moiety fused with 2 TGF- $\beta$ R2 molecules, functioning to block PD-L1 and sequester TGF- $\beta$  in an attempt to promote an antitumor response.<sup>6</sup> BP is a well-documented irAE in anti-PD-1/PD-L1 therapy, which may flare during rechallenge with the same or alternative immune checkpoint inhibitors therapy.<sup>4</sup> In this case, BP did not arise during 12 months of anti-PD-1 therapy with pembrolizumab preceding treatment with bintrafusp alfa, nor did it recur during subsequent treatment with nivolumab/ipilimumab. Although it was plausible that BP in this case arose solely because of the PD-L1 blockade, the dual targeting of PD-L1 and TGF- $\beta$  may increase the likelihood of this irAE.

BP is characterized by autoantibodies to the basement membrane zone self-antigens BP180 (collagen XVII) and BP230. Beyond the humoral response, there is growing evidence of a role of a T cell-mediated autoimmune response. The mechanism of PD-L1/PD-1 blockade-induced BP has not been fully elucidated. One hypothesis suggests a role for T cell activation against the BP antigen, which may be expressed on the surface of certain cancer cells, including colon cancer cells.<sup>7,8</sup>

TGF- $\beta$  exhibits potent immune-suppressive activity, as it negatively regulates both innate and adaptive immune responses. Single-agent anti-TGF- $\beta$

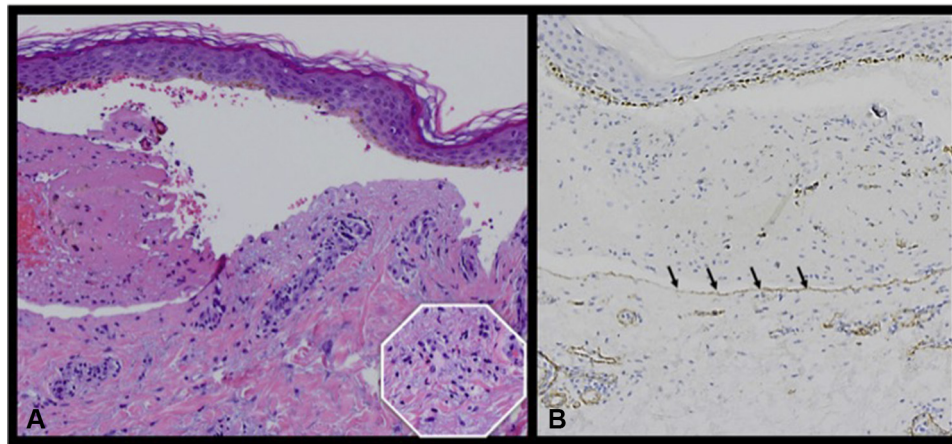


**Fig 1.** Bilateral lower extremities with scattered ruptured and intact tense bullae.

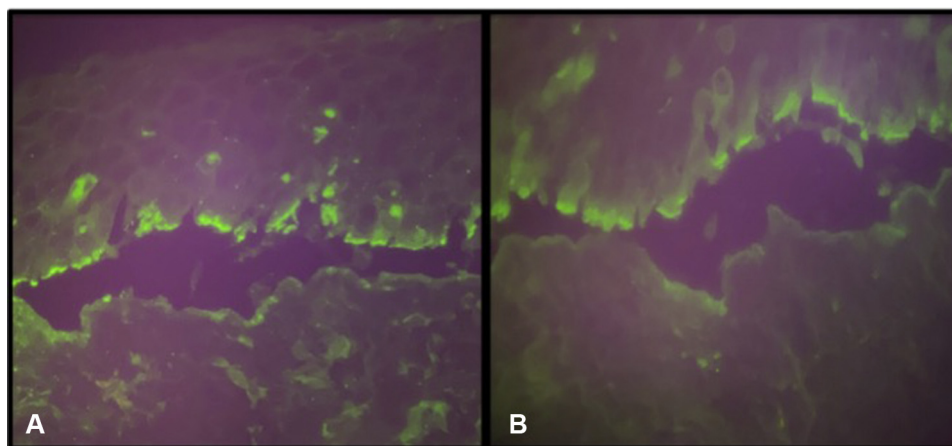
therapies have been investigated in oncology trials with low efficacy. Cutaneous side effects include keratoacanthomas and hyperkeratosis.<sup>6</sup> Only 1 previous report of BP associated with bintrafusp alfa was reported in a phase 1 trial.<sup>9</sup> While a dual-targeted therapy promotes an antitumor response, an increase in irAEs would not be unexpected.

T regulatory (Treg) cells regulate the maintenance of self-tolerance and have a suppressive effect on B cells. It has been shown that the number of Treg cells is reduced in the skin and peripheral blood in patients with BP.<sup>10</sup> It has been postulated that, in BP, a reduction of Treg cells in turn leads to the proliferation of autoantibody-secreting B cell clones.<sup>7</sup> TGF- $\beta$  has numerous roles, including induction of Treg cells.<sup>9</sup> Therefore, sequestration of TGF- $\beta$ , by reducing the induction of Treg cells, reduces the inhibition of autoantibody-secreting B cell clones. This creates a prime environment for BP development. By combining PD-L1 blockade with TGF- $\beta$  sequestration, there is a dual hit on the immune system that may facilitate development of BP.

Bintrafusp alfa is in the early phases of clinical trials, and the incidence of irAEs, including BP, is not yet known. As new combination therapies for the treatment of cancer become available, it is important that oncologists and dermatologists are aware of the risk of irAEs, including BP. Early recognition and treatment are essential to reduce morbidity and mitigate disruptions of oncologic treatments.



**Fig 2.** **A**, Bullous pemphigoid (BP) with subepidermal blister and associated lymphocytic and eosinophilic inflammation. (*inset*) (Hematoxylin-eosin stain; original magnification  $\times 100$  [*inset*,  $\times 400$ ]). **B**, Immunohistochemical study with anti-type IV collagen antibody highlights the basement membrane zone at the floor (*arrows*) of the blister cavity. (Immunohistochemical stain; original magnification;  $\times 100$ ).



**Fig 3.** C3 (**A**) and IgG (**B**) immunofluorescence staining at the roof of the blister.

#### Conflicts of interest

Dr Van K Morris has received research support from EMD Serono. No conflicts of interest were declared for the remaining authors.

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