Severe recalcitrant morbilliform eruption from dual immune checkpoint blockade

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INTRODUCTION

Immune checkpoint inhibitors represent one of the newest and most promising therapies for malignancy, but they place patients at risk for autoimmune sequelae, including cutaneous eruptions. M7824, a novel bifunctional fusion protein currently in clinical trials, is directed against both programmed cell death ligand 1 (PD-L1) and transforming growth factor beta (TGF-β). It is well known that PD-1 checkpoint inhibition may lead to symptomatic cutaneous eruptions that most often can be effectively managed without discontinuation of antitumor therapy. Here we report a case of a severe, recalcitrant morbilliform eruption that began after dual immune checkpoint blockade with M7824 infusion.

CASE REPORT

A 54-year-old man with a history of glioblastoma after resection presented to the oncology department with a severely pruritic, nontender, erythematous papular and macular eruption involving his back, bilateral ankles, and upper extremities 4 weeks after beginning clinical trial treatment with M7824, an immune checkpoint inhibitor directed against PD-L1 and TGF-β (Fig 1, A). He was on no other treatments at that time. The oncology department classified the eruption as a grade I rash and started him on hydrocortisone 1% cream and oral diphenhydramine as needed for itching, which failed to control progression of the rash and associated pruritus. One month later, the rash progressed to grade II status, at which time treatment with doxycycline was initiated by the oncology team for suspected acneiform eruption. The patient was referred for dermatologic evaluation, with the consensus diagnosis being morbilliform drug eruption related to M7824 therapy. The differential diagnosis at that time included drug-induced hypersensitivity syndrome, which was less likely given the lack of associated liver enzyme elevations, eosinophilia, or lymphadenopathy. It was determined that the best course of action would be to treat through the eruption with triamcinolone 0.1% ointment and hydroxyzine for associated severe pruritus. Over the next 2 weeks, the rash progressed to grade III status (Fig 1, B) with worsening pruritus. Further M7824 therapy was held, and the patient was started on systemic corticosteroids with prednisone, 40 mg/d per National Comprehensive Cancer Network guidelines, which failed to control his symptoms. Twenty days later, a biopsy of an abdominal skin lesion was taken, which showed epidermal spongiosis with a superficial perivascular infiltrate composed of lymphocytes and numerous eosinophils. Rare necrotic keratinocytes were also observed. Direct immunofluorescence of perilesional skin was negative. This was consistent with the clinical suspicion of morbilliform drug eruption.

The patient was referred to the dermatology day hospital for daily office-based treatment with triamcinolone 0.1% ointment wet wraps and continued prednisone, 40 mg/d. At that time, his last infusion of M7824 had been 1 month prior. After receiving

Abbreviations used:
PD: programmed cell death
PD-L1: programmed cell death ligand 1
TGF-β: transforming growth factor β

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1 week of triamcinolone wet wrap treatment at the day hospital, the rash began to regress with improvement in his pruritus. Together with input from the oncology department, the patient determined that the severity of the eruption and pruritus outweighed the benefit of trying to proceed with further M7824 therapy, as his tumor had not responded to treatment, and there were alternative trial drugs available.

**DISCUSSION**

Immune checkpoint inhibitors are at the forefront of cancer immunotherapy, with new targets continuously emerging. PD-1 and its ligand PD-L1 are currently the most prevalent targets, which act as immune inhibitory surface molecules on T cells and other immune cells. Although beneficial in their antitumor effects, these therapies have been associated with a higher incidence of autoimmune reactions, particularly mucocutaneous eruptions and pruritus. A recent review noted that up to 40% of patients treated with PD-1 inhibitors had cutaneous adverse events ranging from maculopapular eruptions, eczematous eruptions, lichenoid dermatoses, pruritus, vitiligo, and bullous pemphigoid to severe life-threatening reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. These cutaneous adverse effects have been successfully treated through therapy with emollients, topical steroids, and oral corticosteroids in most patients, with few cases necessitating treatment cessation.

Fig 1. Drug eruption secondary to M7824 therapy. **A**. Erythematous papules coalescing into plaques on the patient’s back, 4 weeks after initiation of M7824 therapy. **B**. Progression of the rash despite treatment with antihistamines, doxycycline, topical steroids, and prednisone.

Fig 2. Drug eruption secondary to M7824 therapy. Biopsy specimen of an abdominal skin lesion shows epidermal spongiosis with a superficial perivascular infiltrate composed of lymphocytes and numerous eosinophils. (Hematoxylin-eosin stain; original magnification: ×200.)

M7824, a bifunctional IgG1 antibody targeting PD-L1 and TGF-β, is a novel drug currently in trials for treatment of solid tumors. Results from a phase 1 trial found grade ≥ 3 adverse events (dose-limiting toxicity) in 4 of 19 patients (skin infection secondary to bullous pemphigoid, asymptomatic lipase increase, colitis with associated anemia, and gastro-paresis with hypokalemia). No grade 5 adverse events occurred. The colitis and bullous pemphigoid responded well to corticosteroids. The second target of M7824, TGF-β, has an inhibitory effect on many proinflammatory responses as well as antitumor immunity, which makes it a prime candidate for immune checkpoint blockade. TGF-β inhibits natural killer cells, type I macrophage and neutrophil development, and activation of cytotoxic T-cells and induces tolerogenic dendritic cells. Clinical studies assessing various TGF-β inhibitors found the most significant side effects were drug rashes and non-eruptive keratoacanthomas and squamous cell carcinoma.

Targeting both PD-L1 and TGF-β, M7824 is a novel therapeutic approach of immune checkpoint inhibition. Cutaneous adverse reactions are reported for each target individually, raising the question of a possible summative reaction of targeting both molecules simultaneously and whether the rash can be treated through therapy as previously described with mono checkpoint inhibition. We present a case of a severe morbilliform drug eruption caused by a dual checkpoint inhibitor that failed to respond to topical and systemic corticosteroids after the drug was held, necessitating cessation of therapy and extended topical steroid wet wraps for resolution.
Per National Comprehensive Cancer Network guidelines, patients with a grade II maculopapular rash caused by immunotherapy should consider having treatment held and begin topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids, while considering the addition of systemic steroids. It is uncertain if earlier initiation of systemic steroids when the patient first developed a grade II rash would have led to a less severe or manageable rash, as this patient progressed from grade II to III within 2 weeks on topical steroids. This finding highlights the importance of close monitoring to treat more aggressively if required. The choice to discontinue therapy in this case was straightforward, as the patient had disease progression and severe rash, and alternative trial drugs were available. However, if a patient was responding to treatment, a more in-depth risk-versus-benefit conversation relative to quality of life and prognosis would be required.

As novel tumor immunotherapy treatments continue to develop, and multichannel inhibition is more frequently used, it is important to be aware of the possible immune sequelae that may arise, and various treatment options that are available, and when cessation of therapy should be considered.

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