INTRODUCTION

Under physiologic conditions, immune checkpoints provide negative signals to control T-cell activation and prevent inflammation-associated tissue destruction. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a principal negative regulator of T-cell activation, binds to CD80/CD86 on antigen-presenting cells, dampening the stimulatory signal of CD28 on T cells. Programmed cell death 1 receptor (PD-1) is another inhibitive co-regulator of the CD28/CTLA4 pathway. Excessive activity of either of these checkpoints is one of the underlying mechanisms for cancers, such as melanoma, to evade the immune system. The negative feedback of T cells causes a down-regulation of a normal immune surveillance activity allowing cancer cells to avoid detection.1,2 Thus, the aim of therapeutically targeting CTLA-4 and PD-1 with pharmacologic checkpoint inhibitors is to restrict the negative feedback of T cells so that malignant cells can be recognized and destroyed. This immunotherapy may come with a risk of T-cell overstimulation and immunotoxicity. We present a case of cutaneous small vessel vasculitis associated with dual checkpoint inhibitor therapy.

CASE REPORT

The patient is a man in his 40s with a history of stage IV desmoplastic melanoma, who was originally treated with radical re-excision, adjuvant radiation therapy, and 5 cycles of pembrolizumab, without significant complication, but with disease progression. He began therapy with pembrolizumab (200 mg) and ipilimumab (1 mg/kg). One week after this infusion, he noticed malaise and a progressively worsening pruritic rash on his legs. He denied any new medications other than ipilimumab and had no known allergies.

Upon examination, vital signs were stable, and palpable purpura was present primarily on his lower extremities (Fig 1) with some involvement of the abdomen and buttocks. There was bilateral lower extremity edema but no appreciable lymphadenopathy. Punch biopsies findings showed fibrin deposition within the superficial cutaneous vessels surrounded by red blood cell extravasation, numerous neutrophils demonstrating leukocytoclasis, and a few eosinophils (Fig 2). Direct immunofluorescence findings showed a perivascular deposition of C3 and fibrinogen, with negative IgG, IgM, and IgA. PD-1 and PD-1 ligand (PD-L1) immunohistochemical stains were negative. Full blood counts, renal and liver function test results, and urinalysis results were normal. Complement levels, antinuclear antibody, rheumatoid factor, cryoglobulins, hepatitis B and C serology, and antineutrophilic cytoplasmic antibodies were negative. C-reactive protein was 0.79 mg/dL (normal, <0.49 mg/dL).

The clinicopathologic findings combined with the temporal association with the initiation of ipilimumab to the regularly scheduled pembrolizumab infusions are consistent with an adverse drug reaction associated with dual checkpoint inhibitor therapy.

Abbreviations used:

- CTLA-4: cytotoxic T-lymphocyte–associated antigen 4
- GPA: granulomatosis polyangiitis
- PD-1: programmed cell death 1 receptor
- PD-L1: PD-1 ligand

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support the diagnosis of drug-induced cutaneous small vessel vasculitis. Pembrolizumab and ipilimumab were held. An initial 4-week taper of high-dose steroids (prednisone, 1 mg/kg/d) was attempted, but he had severe ulcerating disease during the taper (Fig 3). Dapsone and topical silver sulfadiazine were then added. Dapsone was discontinued after 1 week because of an acute kidney injury that did not have a clear alternative etiology. Although vasculitic involvement of the kidney was considered, timing during high-dose immunosuppressive therapy argued against this therapy. Kidney biopsy was not performed, as the renal injury improved with supportive measures. Prednisone was maintained at a high dose for 2 months and tapered slowly over 3 additional months. During this time, he was hospitalized for superimposed cellulitis. At the 6-month follow up, his ulcerative disease was mild, and he continued to use silver sulfadiazine in the remaining erosions. At no point during his this disease process did the patient complain of diarrhea, nor was there concern for colitis that necessitated abdominal imaging or colonoscopy.

DISCUSSION

Ipilimumab is a CTLA-4 inhibitor, approved for therapeutic use of advanced melanoma. Cutaneous eruptions are a common side effect of ipilimumab, with all-grade rash occurring in approximately 25% of patients and high-grade rash in 2.4%. Vasculitis is an adverse event that can occur in less than 1% of patients. Ipilimumab has been previously associated with giant cell arteritis and lymphocytic vasculitis of the uterus.

Pembrolizumab is a PD-1 inhibitor also approved for therapeutic use of advanced melanoma. This immunomodulator is less commonly associated with cutaneous eruptions, mostly as maculopapular rashes at an incidence of up to 14.4%. Immune-mediated cutaneous conditions such as Stevens-Johnson syndrome and bullous pemphigoid have each been reported with pembrolizumab. In a case report, pembrolizumab was implicated in the development of antineutrophilic cytoplasmic antibody–positive granulomatosis polyangiitis (GPA). The authors hypothesized that the patient likely had subclinical GPA before receiving the medication, which was then unveiled with the introduction of pembrolizumab. Interestingly, aberrant expression of PD-1 on T helper cells has been previously implicated in the pathogenesis of GPA. On the other hand, PD-L1 deficiency within dendritic cells of vessels affected by giant cell arteritis has been connected to the pathogenesis of giant cell arteritis.

Our patient had no complications while only on pembrolizumab. Although we did not find PD-1–positive T cells in the vasculitic infiltrate in our patient, it remains to be elucidated whether the lack of PD-L1 expression in small vessels may act as an amplification loop leading to immune recognition of otherwise ignored self-antigens in a susceptible patient. These deficiencies may not result in abnormal immune responses until they are
overwhelmed by excessive T cell activation, perhaps unmasked by pharmacologic immunomodulators. Other monoclonal antibodies, such as tumor necrosis factor-α inhibitors and rituximab have been associated with small vessel vasculitis,13,14 which begs the questions: “Can monoclonal antibodies themselves cause immune complex formation and deposition?” and, if so, “Can this deposition be a nidus for a neutrophilic chain of events causing vasculitis?”

A strong temporal relationship existed in our case with the onset of vasculitis and the administration of checkpoint inhibitors and with the resolution of vasculitis with the discontinuation of the implicated drugs and initiation of appropriate medical management (Naranjo score of 7).15 Furthermore, the biopsy specimen showed eosinophils, which suggest a drug-induced reaction.16 We hypothesize that the combinatorial effect of dual checkpoint inhibition, with the therapeutic addition of ipilimumab to pembrolizumab in our patient, resulted in drug-induced cutaneous small vessel vasculitis. The pathogenesis has yet to be elucidated; however, we hope this addition to the literature will spur curiosity in the medical community to delve deeper into the rare vasculitic complications of checkpoint inhibitors and, more broadly, monoclonal antibodies.

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