Programmed cell death protein 1 inhibitor-induced recalcitrant mixed small and medium vessel vasculitis

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Abstract

Pembrolizumab, a programmed cell death protein 1 (PD1) inhibitor, has been known to be associated with several adverse reactions, including immune related adverse events. In less than one percent of patients, PD1 inhibitors have been linked to the development of connective tissue disease. Patients with previously known connective tissue disease are hypothesized to be at increased risk of flares in as many as 40% of cases. A 70-year-old man with a past medical history significant for rheumatoid arthritis in remission and stage IV lung adenocarcinoma presented to the dermatology clinic after one cycle of nivolumab and eight cycles of pembrolizumab exhibiting worsening, painful bilateral lower extremity ulcers for approximately one month. On the lower legs, three large black retiform eschars and bullous purpuric plaques were observed. Vasculitis is a rare complication of PD1 inhibitor therapy, with the majority of cases reported in literature either medium vessel or large vessel vasculitis. Only glucocorticoids have proven effective for PD1-induced vasculitis and these patients generally require multi-specialty management.

Keywords: vasculitis, programmed cell death protein 1, PD1, inhibitors, check point, immune related adverse events, IRAE

Introduction

Pembrolizumab, a programmed cell death protein 1 (PD1) inhibitor, is known to be associated with adverse reactions including immune related adverse events (IRAE), including autoimmune thyroiditis, adrenal insufficiency, autoimmune pancreatitis, autoimmune hypophysitis, myocarditis, endophthalmitis, pneumonitis, colitis, inflammatory arthritis, and dermatologic eruptions [1,2]. Rarely, in less than one percent of patients, PD1 inhibitors have also been associated with the onset of connective tissue disorders, including systemic sclerosis, sarcoidosis, Sjogren syndrome, and myasthenia gravis [1,3,4]. Patients with a history of connective tissue disease, such as systemic lupus erythematosus, rheumatoid arthritis (RA), and sarcoidosis, are hypothesized to be particularly vulnerable to experiencing a flare of their disease as a result of initiating these therapies in as many as 40% of cases [5].

Vasculitis is a rare complication of PD1 inhibitor therapy. In a large, multicenter, prospective study, one case of cryoglobulinemic vasculitis in a patient with previously suspected Sjogren syndrome was reported out of a total of 447 patients studied [3]. The majority of cases reported in the literature have been either medium vessel or large vessel vasculitis. Most of the medium vessel vasculitides reported in the literature have been predominantly primary angiitis of the nervous system [6]. Cases of PD1 inhibitor-induced cutaneous small vessel and medium vessel cutaneous vasculitis have been reported but are rare [2]. Herein, we present a novel case of acute activation of rheumatoid vasculitis related to

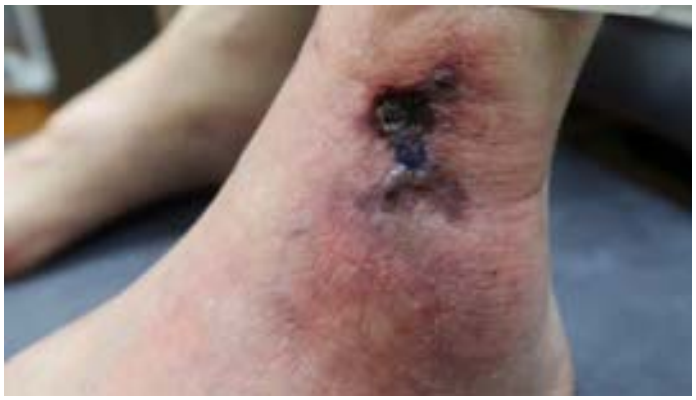

Figure 1. *Retiform purpuric plaque on left distal lateral lower leg at time of presentation to dermatology clinic.*

pembrolizumab therapy in a patient with a history of seropositive RA.

Case Synopsis

A 70-year-old man with a past medical history significant for diabetes mellitus, RA in remission, and stage IV lung adenocarcinoma presented to the outpatient dermatology clinic after one cycle of nivolumab and eight cycles of pembrolizumab. He exhibited worsening, painful bilateral lower extremity ulcers. The ulcers had been present for approximately one month prior to presentation. He denied any other associated symptoms including fevers, joint pains, dry eyes or mouth, dysphagia, or Raynaud phenomenon. Prior treatment for his ulcers included a two-week course of cephalexin 500mg four times per day, with no improvement in his symptoms. On examination, two large black retiform eschars were present on the right lateral lower leg and a retiform, bullous, purpuric plaque (14mm×12mm) was observed on the left distal lateral lower leg, just proximal to the lateral malleolus (**Figure 1**). Bilateral lower extremity pulses were strong and symmetric. No other significant lesions were noted on examination.

Laboratory examination was significant for elevated inflammatory markers (erythrocyte sedimentation rate 97mm/hr and C-reactive protein 43.8mg/L), trace cryoglobulins, rheumatoid factor (RF) >6,000IU/mL (previously 1,820-2,020), cyclic citrullinated peptide (CCP) antibody >250units/mL (previously 107.5units/mL), cardiolipin IgM 44 MPL units, and a low C4. All other laboratory tests including serum protein electrophoresis, β2 glycoprotein autoantibody, anti-cardiolipin autoantibody, viral hepatitis serologies, antinuclear antibody, antineutrophil cytoplasmic antibody (ANCA), C3, liver function tests, creatinine, blood cultures, and coagulation function tests were all negative or within normal limits. A punch biopsy of the retiform purpuric plaque was obtained and demonstrated a mixed small and medium vessel vasculitis with leukocytoclasia and focal thrombosis of vessels (**Figure 2**).

The differential diagnosis proposed was pembrolizumab-associated mixed small and medium vessel vasculitis, rheumatoid vasculitis, or a combination of the two. Cryoglobulinemia was considered less likely because only trace amounts were found in the serum. Although the patient did

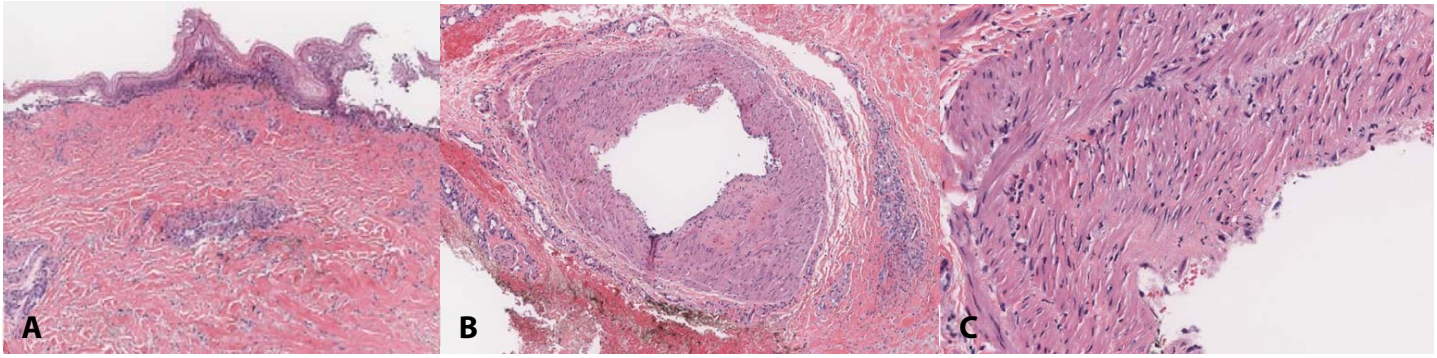

Figure 2. *Pathologic features.* ***A)*** *Skin biopsy specimen shows a perivascular infiltrate surrounding capillary-sized vessels, rich in neutrophils; although definite endothelial necrosis is not present, leukocytoclastic debris is prominent. H&E, 55×.* ***B)*** *This medium-sized, muscular arteriole exhibits medial infiltration by neutrophils and endothelial damage. A mixed lymphohistiocytic and neutrophilic infiltrate is present in the nearby deep dermis. H&E, 70×.* ***C)*** *Close-up view of medial infiltration by neutrophils, with foci of vascular smooth muscle necrosis. H&E, 210×.*

not develop a reactivation of inflammatory arthritis, given the history of seropositive arthritis, the dramatic rise in RF and CCP, and the small and medium vessel involvement of the vasculitis, the diagnosis of pembrolizumab-associated rheumatoid vasculitis was made.

The patient was started on high-dose prednisone and pembrolizumab was discontinued. Since time of diagnosis, his course has been complicated by acute onset heart failure with reduced ejection fraction as well as interstitial lung disease, both believed to be induced by checkpoint inhibitor. He additionally was hospitalized and treated for *Pneumocystis jirovecii* pneumonitis. Approximately six months after discontinuation of the pembrolizumab he was found to have progression of his lung cancer and was started on a chemotherapy regimen of C1 carboplatin and pemetrexed. He has been unable to taper his prednisone below 60mg daily owing to recurrence of pain and onset of new lesions with tapering even after six months.

Case Discussion

Mixed small and medium vessel vasculitis has been associated with several underlying conditions, including ANCA-associated vasculitis, cryoglobulinemic vasculitis, polyarteritis nodosa, Behcet disease, septic vasculitis, rheumatoid vasculitis, and several connective tissue diseases including systemic lupus erythematosus and Sjogren syndrome [7]. In this case, our diagnosis was pembrolizumab-activated rheumatoid vasculitis in a patient that would otherwise be unlikely to develop rheumatoid vasculitis. Classically, rheumatoid vasculitis occurs in patients with erosive and long-standing (>10 years) RA [8]. Our patient, described herein, had a fairly mild course of RA that had burnt-out 4.5 years prior. Since vasculitis as a consequence of PD1 inhibitors is rare and more often a medium to large vessel vasculitis [6], it was most likely that the pembrolizumab resulted in acute activation of typical rheumatoid vasculitis in an atypical patient. It is hypothesized that pembrolizumab and PD1 checkpoint receptor blockade can result in an amplified immune response from T cells as well as natural killer cells, leading to upregulation in IL17, IL21, and IFNγ, which together can promote uncontrolled vascular destruction and resultant remodeling [9].

There is limited data in the literature on treatment options for PD1 associated vasculitis. To date, only glucocorticoids have been reported as a treatment for this rare complication [6]. Other treatment options recommended for immune-related adverse events related to checkpoint inhibitors include methotrexate, hydroxychloroquine, rituximab, leflunomide, sulfasalazine, TNF inhibitors, and IL6 inhibitors such as tocilizumab [2,4,10].

Conclusion

In summary, vasculitis is a rare but known complication of check point inhibitors. Patients with a previously diagnosed autoimmune disease, such as rheumatoid arthritis in our patient, may be at increased risk for this complication. Further research in this area is needed. Although several types of immunosuppressive and immunomodulator medications have been used to treat the complications related to check point inhibition, only glucocorticoids have been used and shown to be effective in cases of vasculitis reported in the literature. Additional research is also needed to determine the best management options for patients with vasculitis related to checkpoint inhibition. We recommend a multidisciplinary approach to this complication.

Potential conflicts of interest

The authors declare no conflicts of interests.

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