INTRODUCTION

Chilblain lupus erythematosus (CHLE) is a rare form of chronic cutaneous lupus erythematosus characterized by purple plaques/nodules and edematous skin, mainly around the acral regions of the body. The familial form is due to a heterozygous mutation in the TREX1 gene, a widely expressed gene that encodes 3' to 5' exonuclease to remove unneeded fragments that may form during DNA replication and has also been found to be implicated in immune regulation and viral infection. The sporadic form remains with unknown etiopathogenesis. Drug-induced chilblain lupus is rare and has previously been reported predominantly in patients on tumor necrosis factor inhibitors and abatacept. We herein report a case of a man with a recent renal transplant who was started on belatacept and subsequently developed CHLE. The rash resolved with the discontinuation of the medication.

CASE REPORT

A 60-year-old man with a history of Crohn’s disease and end-stage renal disease due to enteric oxalosis underwent uncomplicated living donor kidney transplantation with thymoglobulin and methylprednisolone induction. He was initially treated with tacrolimus and mycophenolate mofetil maintenance immunosuppression, but the mycophenolate mofetil was replaced with azathioprine one week after the transplant due to persistent diarrhea. Because of the worsening of the diarrhea, induction dosing of belatacept 10 mg/kg was initiated 2 months posttransplant, with reduced-dose azathioprine and tacrolimus (he was previously intolerant to maintenance corticosteroids).

One month after belatacept initiation, in the autumn, he developed an eruption, which began as a “blister” on the left second toe and continued to spread to other toes. The patient noted a burning sensation, especially at nighttime, when he was unable to warm his feet despite the use of socks. Other than his immunosuppression changes mentioned earlier, he had had no other changes in his medication regimen since the transplant. The regimen included atovaquone, gabapentin, omeprazole, tamsulosin, nystatin, and valganciclovir.

On physical examination, he was noted to have blanching red-purple erythematous toes with overlying scale (Fig 1). Serology showed negative anti-nuclear antibodies, anti-RNA, and anti-Smith antibodies. His C3 and C4 levels were within normal limits. COVID-19 serologies were negative. A skin biopsy performed on the right third toe revealed a mild perivascular lymphocytic infiltrate, conspicuous interface change with vacuolar alteration of the basal layer, and singly scattered necrotic keratinocytes in the lower epidermis (Fig 2, A and B). A colloidal iron stain (Fig 2, C) highlighted the increased amount of mucin in the interstitial dermis.
Direct immunofluorescence was declined by the patient. Based on the above findings, the patient was diagnosed with CHLE, possibly caused by belatacept. The patient was started on hydroxychloroquine 200 mg twice daily for 2 months and 0.05% betamethasone dipropionate ointment. Furthermore, conservative measures were taken, including keeping the toes warm with socks, with initial improvement in the symptoms. However, the rash returned after hydroxychloroquine discontinuation 2 months later. Other therapies, such as nifedipine, were contraindicated. Belatacept was, therefore, discontinued, resulting in the total, sustained resolution of symptoms (Fig 3, A to B).

**DISCUSSION**

Belatacept, a second-generation fusion protein that is composed of the fragment crystallizable region of human IgG1, linked to the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and inhibits the CD28-CD80/86 pathway, is the first fusion protein approved by the Food & Drug Administration for use in transplantation and the first biologic agent to be incorporated into standard transplantation maintenance immunosuppression protocols. This fusion protein inhibits T-cell activation by blocking costimulatory signals from antigen-presenting cells while avoiding both the renal and nonrenal toxicities associated with calcineurin inhibitors. Belatacept was developed to be a higher-avidity variant of abatacept through 2 amino acid substitutions, CD80 and CD86, because abatacept does not sufficiently inhibit alloreactivity in pancreatic and kidney transplants.

Herein, we present a case of belatacept-associated CHLE. CHLE is a rare form of cutaneous lupus erythematosus that is typically triggered by cold exposure, leading to ulceration. A set of diagnostic criteria have been proposed by the Mayo Clinic and include 2 major criteria of (1) skin lesions of the acral sites induced by exposure to cold or a drop in temperature and (2) evidence of lupus erythematosus in the skin lesions as determined by histopathologic examination or direct immunofluorescence. The 3 minor criteria include the following: (1) coexistence of systemic lupus erythematosus or other skin lesions of discoid lupus erythematosus, (2) response to antilupus therapy, and (3) negative cryoglobulin and cold agglutinin studies. Both major criteria and 1 minor criterion are needed to diagnose CHLE. The reported patient fulfilled both major criteria and showed a response to antilupus therapy, with marked improvement in the skin lesions using a regimen of hydroxychloroquine and topical steroids. Further evidence of belatacept as the causative agent include the onset of the rash approximately one month after belatacept initiation, recurrence of the rash until belatacept was discontinued, and permanent resolution after belatacept cessation despite the withdrawal of hydroxychloroquine. The onset and resolution of drug-induced cutaneous lupus can vary widely. The duration between drug exposure and the onset of skin lesions ranges from 3 days to 10 years, and the resolution time after withdrawal of medication ranges between 1 week and 1 year.

The pathogenesis of sporadic CHLE is not well understood, but is thought to be due to vasoconstriction or microvascular injury provoked by the cold. A type 1 interferon response may be provoked locally, leading to cutaneous findings. Drug-induced chilblain lupus is rare and predominantly reported in patients on tumor necrosis factor inhibitors. Although there have not been reports of belatacept-induced lupus, there have been 3 prior reports on abatacept, belatacept’s parent compound, causing drug-induced subacute cutaneous lupus erythematosus (SCLE) and 1 report on systemic lupus erythematosus with membranous nephropathy associated with abatacept. In all of these cases, as with our patient, a longstanding history of autoimmune disease preceded the initiation of the costimulatory blockade. Each case of SCLE resolved after abatacept discontinuation, though the case of systemic lupus erythematosus did not. Although the putative mechanism of the development of SCLE is not certain, a proposed pathogenesis is the development of antibodies to the CTLA-4 portion of the abatacept molecule, which subsequently interfere with the CTLA-4 antigen on T-regulatory cells, inducing SCLE or other
autoimmune syndromes. However, the resolution of cutaneous lesions in our patient and prior cases of abatacept-associated SCLE after the discontinuation of costimulatory blockade call this proposed mechanism into question, given that we may not necessarily expect the rapid disappearance of anti–CTLA-4 antibodies. We hope this report encourages further investigation into these reactions and the potential role of the CTLA-4/CD28-CD80/86 pathway in triggering de novo autoimmune disease. Given that this complication may occur in an existing autoimmune milieu, further studies are needed to better identify the risk factors for CHLE induced by belatacept.

Fig 2. Punch biopsy from dorsal right third toe. A, B, Hematoxylin-eosin stains (original magnifications: A, ×40; B, ×400) show a mild perivascular lymphocytic infiltrate and prominent interface change with vacuolar alteration of the basal layer and singly scattered necrotic keratinocytes. C, Colloidal iron stain (original magnification: ×200) highlights the increased amount of dermal mucin.

Fig 3. Resolution of lesions after discontinuation of belatacept on the (A) left foot and (B) right foot.

Conflicts of interest
None disclosed.

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