Linear IgA dermatosis after infliximab infusion for ulcerative colitis

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INTRODUCTION

Linear IgA dermatosis (LAD) is an idiopathic or drug-induced autoimmune subepidermal blistering disease characterized by linear deposition of IgA antibodies along the dermoepidermal junction. The pathogenesis, although incompletely understood, involves the formation of dermal papillary microabscesses that lead to subepidermal clefts and blistering. The tissue injury likely results in part from the release of proteolytic enzymes by neutrophils composing the abscess.[1,2] LAD can occur in both children and adults, with lesions classically described as round or oval vesicles or bullae on normal, erythematous, or urticarial skin.[1] Definitive diagnosis requires the use of direct immunofluorescence to show the distinctive band of IgA at the dermoepidermal junction. In most cases of LAD, the inciting factor is unknown, although several reports implicate various medications in the development of the disease.[3] Vancomycin is the most frequently reported medication in drug-induced LAD, with nonsteroidal anti-inflammatory agents, penicillins, cephalosporins, and captopril also commonly cited.[3] Herein, we present an uncommon case of LAD after the administration of the anti–tumor necrosis factor (TNF) monoclonal antibody, infliximab.

Abbreviations used:

IBD:	inflammatory bowel disease
LAD:	linear IgA dermatosis
TNF:	tumor necrosis factor
UC:	ulcerative colitis

CASE REPORT

A 54-year-old man with a 4-year history of ulcerative colitis (UC) presented for evaluation of pruritic vesiculobullous eruptions on his thighs, abdomen, feet, and flexor surfaces of both forearms, which arose 2 to 3 weeks after initiating infliximab treatment at a dose of 5 mg/kg body weight (total weight-based dose of 500 mg administered per infusion). At that time, the patient received the first 2 infusions of the induction regimen. Physical examination found scattered tense bullae with areas of erosion and crusting without any mucosal involvement (Fig 1). Light microscopy of a lesional punch biopsy specimen found subepidermal bulla formation with predominately neutrophilic infiltration (Fig 2, *A* and *B*) and direct immunofluorescence studies of a perilesional punch biopsy exhibited linear deposition of IgA along the basement membrane zone, confirming a diagnosis of LAD. The lesions dissipated 2 weeks later on oral prednisone, with only fading erythema and scale remaining before the next scheduled infliximab

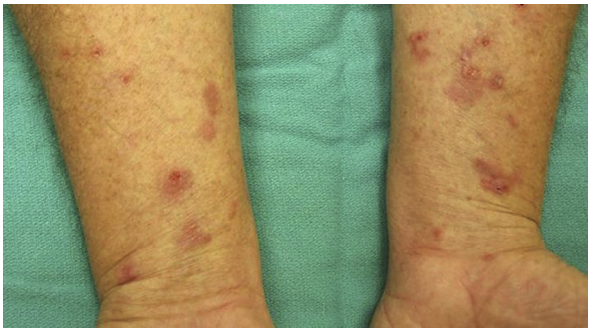

Fig 1. Vesiculobullous lesions on patient's forearm after infliximab therapy for the treatment of UC.

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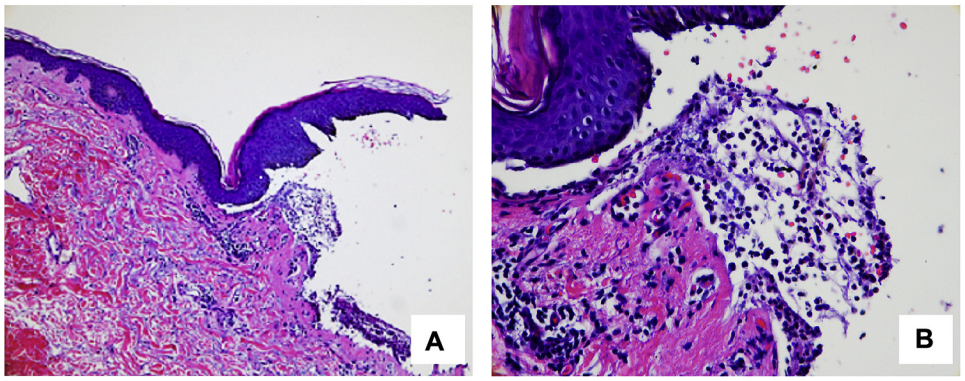

Fig 2. Skin biopsy shows a subepidermal bulla with predominately neutrophilic infiltration (volar forearm). A mild superficial perivascular lymphohistiocytic infiltrate is present in the underlying dermis. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×100; **B**, ×200.)

infusion. Because the patient's previously refractory colitis symptoms had improved on infliximab, with the patient reporting normal bowel movements without urgency or bleeding after the first infusion, he underwent the third infusion (week 6) after pretreatment with intravenous hydrocortisone sodium succinate and diphenhydramine. Despite these measures, a vesiculobullous eruption, worse than the initial outbreak, recurred 3 days later with biopsy findings consistent with those of LAD. Ultimately, the patient's UC was put into remission with the use of adalimumab, another TNF inhibitor, without any reappearance of LAD over the last 2 years.

DISCUSSION

Linear IgA dermatosis has been reported in association with drugs, malignancy, infections, connective tissue diseases, and inflammatory bowel disease (IBD), with UC being the most commonly reported systemic disorder linked to its development.[4] The pathogenesis of LAD in the setting of IBD remains uncertain but may involve a humoral immune response to antigens crossing inflamed bowel mucosa, leading to the production of cross-reactive IgA autoantibodies against cutaneous antigens.[4,5] Drug-associated LAD typically presents similarly to the idiopathic form, with analogous lesion morphology and distribution. Most reported cases occur within 1 month of drug initiation and typically dissipate within 3 weeks of drug cessation.[3] Re-exposure to the offending drug often results in recurrence of the blistering eruption, which may be more severe with a shorter latency period and a longer time to clearance. Given the temporal relation between initiating infliximab therapy and the development of the patient's eruption and diagnostic findings, along with the reappearance of lesions immediately after re-exposure, we assert that LAD was a consequence of exposure to infliximab. This case supports the suggestion made by Hoffman et al[6] and Sundlass et al[7] that infliximab may be a new drug implicated in the development of LAD, with the added evidence of rechallenge with the drug precipitating a second LAD eruption. We also documented sustained remission of both LAD and UC in this patient while undergoing treatment with adalimumab, another TNF inhibitor. This finding suggests that infliximab in particular, and not necessarily the TNF inhibitor class in general, has a causal role in LAD pathogenesis. This TNF inhibitor intraclass dissociation is an important finding, as many patients with refractory IBD depend on these biologic agents to treat their disease and often have limited or no alternative options. Furthermore, there are reports of other autoimmune bullous skin diseases occurring in patients undergoing treatment with infliximab, namely, bullous pemphigoid and pemphigus foliaceus.[8] The formation of a secondary autoimmune condition in patients undergoing treatment with TNF inhibitors has been described as a "paradoxical" reaction in which the biologic agent can both treat and induce the disease. The favored hypothesis to explain the development of these paradoxical adverse events involves a disequilibrium in cytokine balance created by TNF inhibition.[9] Interestingly, Yamada et al[10] has also published a case report of dramatic symptom improvement after infliximab therapy in UC-associated LAD. Whether this shows a direct therapeutic benefit of infliximab on LAD or, alternatively, an indirect effect mediated by a reduction in UC disease severity remains unclear. We present this case to show an unusual reaction to a class of medication that is increasingly used to treat a growing number of autoimmune diseases. The role of TNF inhibitors in the development of autoimmune

skin diseases is unquestionably complex and multifactorial. Nevertheless, emerging evidence strongly implicates these biologic agents as occasional causes of immunobullous disease.

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