Mucosal linear IgA disease with esophageal involvement responsive to ustekinumab

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Key words: immunobullous dermatosis; linear IgA bullous dermatosis; treatment; ustekinumab.

INTRODUCTION

Linear IgA bullous dermatosis (LABD), or linear IgA disease, is a rare autoimmune mucocutaneous blistering disease with vesicles and bullae characteristically arranged in an annular or arciform pattern on the skin and, less common, mucosal involvement manifesting as vesicles, erosions, and/or ulcers. We present a rare case of a patient who had Crohn's disease and LABD with primarily mucosal involvement, including oral, esophageal, and vaginal lesions, who responded well to ustekinumab therapy.

CASE REPORT

A 58-year-old woman presented with a several-year history of recurrent painful oral and genital ulcers. Her medical history was notable for Crohn's disease and common variable immune deficiency. Lesions had developed in most regions of her oral mucosa—including lingual, gingival, labial, buccal, and pharyngeal. She had previously been treated with adalimumab, with a temporary resolution of mucosal lesions and improvement in Crohn's disease symptoms; however, the treatment was discontinued due to sepsis. Subsequent therapies with prednisone, sulfasalazine, monthly intravenous immunoglobulin, allopurinol, 6-mercaptopurine, and viscous lidocaine were inadequate in controlling her disease. Her symptoms included occasional sore throat, hoarse voice, and dysphagia as well as intermittent development of vesicles on her face and arms. She denied eye or other skin involvement. Dermatologic examination revealed multiple erythematous papules scattered throughout the patient's oral mucosa without genital or ocular mucosal lesions or other skin involvement. Subclinical ocular disease also was ruled out by ophthalmologic examinations.

Abbreviations used:

BMZ:	basement membrane zone
DIF:	direct immunofluorescence
LABD:	linear IgA bullous dermatosis

A 3-mm punch biopsy specimen of an oral papule was obtained for direct immunofluorescence (DIF) testing, and her serum was submitted for epithelial antibody testing using indirect immunofluorescence assay and enzyme-linked immunosorbent assay. She also underwent endoscopy that included obtaining biopsy specimens from the upper and lower portions of the esophagus for DIF. DIF demonstrated linear IgA basement membrane zone (BMZ) antibody localization on the oral and esophageal specimens (Fig 1). Less intense, discontinuous linear IgG BMZ reactivity was also observed in the oral specimen. C3 staining was negative. Serum indirect immunofluorescence assay demonstrated positive IgA BMZ antibodies, epidermal pattern (roof) on human split skin substrate, in a limiting-dilution, end-point titer of 1:40; IgG BMZ and cell surface antibodies were negative on monkey esophagus, human split skin, and intact human skin substrates with indirect immunofluorescence assay. Enzyme-linked immunosorbent assays showed normal levels of IgG bullous pemphigoid antigen BP180, IgG bullous pemphigoid antigen BP230, IgG desmoglein 1, and IgG desmoglein 3 antibodies. Therefore, the findings

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Funding sources: None.
IRB approval status: University of Utah Institutional Review Board Exemption Umbrella: Clinical-pathologic correlation of dermatologic disorders.

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JAAD Case Reports 2021;15:4-6.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.06.021

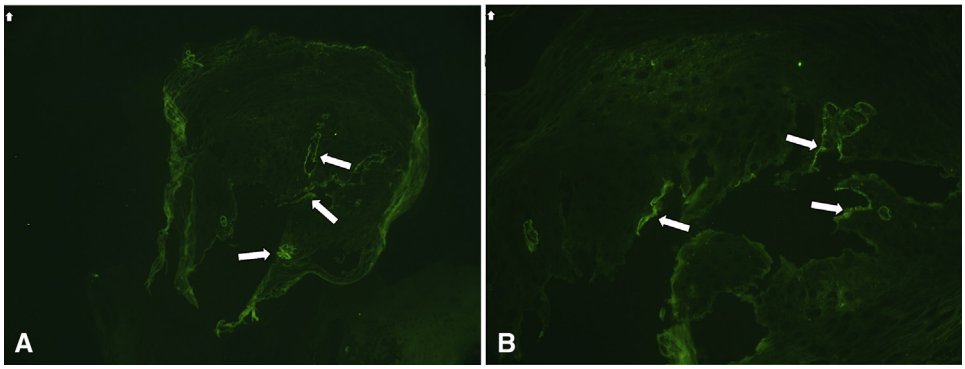

Fig 1. Direct immunofluorescence photomicrographic images of biopsy tissue from the distal portion of the esophagus demonstrated linear IgA basement membrane zone reactivity (*arrows*) at 2 magnifications (images courtesy of Immunodermatology Laboratory, University of Utah). (Original magnifications: **A**, ×100; **B**, ×200.)

of the tissue and serum testing supported the diagnosis of linear IgA disease.

The patient was started on oral dapsone (25 mg twice daily), "swish and spit" dexamethasone solution for her oral ulcers, and topical clobetasol ointment for her vulvar lesions. Attempts to taper oral prednisone dose resulted in flaring of her Crohn's disease symptoms and mucosal lesions. She could not tolerate increases in dapsone dosage above 25 mg due to the development of shortness of breath despite a complete blood cell count within normal limits and a normal glucose-6-phosphate dehydrogenase level. She also failed to respond to the addition of 6-mercaptopurine and continued topical glucocorticoid therapy. Ustekinumab therapy was initiated at 90 mg every 8 weeks, with continued administration of dapsone 25 mg daily and dexamethasone solution. At the 2-month follow-up, she reported remarkable improvement in both her Crohn's disease symptoms and mucosal lesions. The examination did not reveal new or active oral lesions or other mucocutaneous involvement. Prednisone was successfully tapered to 2 mg daily. She maintained satisfactory clinical response to ustekinumab at the 1-year follow-up, reporting only mild flareups manifesting as 1 to 2 oral lesions. Her dysphagia resolved shortly after the initiation of ustekinumab, although she had not undergone repeat endoscopic examination to visually assess esophageal response.

DISCUSSION

Mucosal involvement, in addition to the skin, develops in 80% of adults affected with LABD.[1] Rarely, LABD spares the skin and is limited to mucous membranes.[2] Manifestations of LABD may develop on any mucosal surface as painful erosions and/or ulcers.[1,2] Esophageal lesions are often considered in patients with mucous membrane pemphigoid experiencing dysphagia and should also be considered in patients with LABD who describe symptoms of dysphagia. DIF is a diagnostic standard for LABD, demonstrating linear IgA deposition (from which the disease name has been derived) along the mucosal and skin BMZ.[3] As observed in this patient, concomitant IgG BMZ antibodies develop and are found in 20% of patients, although characteristically less strong DIF BMZ staining intensity and lesser serum BMZ antibody titer than IgA are observed.[4]

This patient also had Crohn's disease and common variable immune deficiency. Reports have demonstrated an association between immunobullous disease and inflammatory bowel disease, particularly ulcerative colitis.[5] Immunobullous disease has been shown to resolve with colectomy in several reports, indicating that bowel disease may contribute to the pathogenic activity promoting the skin disease, a phenomenon postulated to result from immunopathologic cross reactivity of colonic inflammatory stimuli with cutaneous epithelial BMZ and cell surface antigens.[5] The ustekinumab dosing was based on that recommended for treating Crohn's disease, reflecting the goal to improve LABD through controlling her bowel disease. Common variable immune deficiency is associated with autoimmunity in approximately 30% of patients. Cytopenias are the best characterized association; however, common pathophysiology may contribute to the expression of epithelial antibody-associated disease.[6]

Dapsone and topical therapies are considered first-line agents for treating linear IgA disease; various second-line agents are used for refractory

disease.[4] Patients with LABD successfully treated with infliximab and rituximab have been reported; however, the use of biologics has been sparsely documented.[7,8] The patient presented herein experienced remarkable improvement in her symptoms within 2 months of beginning ustekinumab therapy, and although she has not achieved complete disease remission, her symptoms have remained mild and tolerable with successful reduction of prednisone dosage. Ustekinumab is a monoclonal antibody targeting the p40 subunit of interleukin 12/23. Ustekinumab has been approved for the treatment of inflammatory bowel disease and psoriasis/psoriatic arthritis, and it has been used for the treatment of multiple autoimmune and autoinflammatory skin disorders, including 1 reported case of a patient with bullous pemphigoid.[9] Although this patient's disease was not drug-induced, consideration should be given to drugs associated with new-onset LABD, including in a report of a patient with psoriasis taking ustekinumab.[10]

This patient with mucosal linear IgA disease responded to ustekinumab therapy when multiple other therapies were ineffective. With the recognition that responsiveness may be related to the distinctive presentation in this patient with comorbid conditions, the finding prompts consideration for investigating its use in trials, especially in the setting of Crohn's disease unresponsive to other treatments.

Conflicts of interest

None disclosed.

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