Cutaneous IgG4-related disease associated with lymphocytic colitis

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INTRODUCTION

Cutaneous IgG4-related disease (lgG4-RD) is a rare and emerging clinical entity. It predominantly affects middle-aged and older Asian men, especially those with a history and/or exposure to hepatitis B.[1,2] Lesions display an IgG4-positive plasma cell infiltrate that drives the fibroinflammatory process within the dermal and subdermal components.[3,4] Lesions often affect the face, neck, upper extremities, and torso,[1,5,6] whereas the buttocks and waist each represent 1.25% of cutaneous presentations.[5] Although elevated levels of IgG-subtype 4 in blood/serum alone may not necessarily be indicative of disease activity in internal organs, studies suggest that the presence of cutaneous IgG4-RD heralds internal organ involvement within 4 years after the skin lesions are identified.[7] Thus, we present a rare case of cutaneous IgG4-RD in a young adult Indian American man with exclusively lower-body involvement in the setting of lymphocytic colitis (LC).

Abbreviations used:

IgG4-Rd:	IgG4-related disease
GI:	gastroenterology
LC:	lymphocytic colitis

CASE REPORT

A 25-year-old Indian American man presented with a 3-year history of a persistent pruritic eruption extending from the lumbar area distally to the feet for several months. He reported chronic diarrhea with abdominal pain and weight loss for 4 years. He denied fever or chill. He reported no sick contacts, and there were no household members with similar complaints. He also denied the recent travel. An extensive review of the systems to identify other symptoms was negative. Medical history included type 1 diabetes mellitus since childhood, which was uncontrolled for many years resulting in peripheral neuropathy, bilateral ankle ulcers, bilateral cataracts, major depressive disorder, and medications including insulin. Prior treatments included mometasone, betamethasone, triamcinolone, hydrocortisone valerate, tacrolimus, and mupirocin with a lack of improvement and subsequent relapse.

On examination, he was afebrile, and his vital signs were normal. Skin examination demonstrated one erythematous papule admixed with scattered erosions on background hyperpigmented patches on the lower back and the right buttock (Fig 1). The lymph node examination was unremarkable. A punch biopsy sample of the erythematous papule revealed an acanthotic epidermis with the extensive perifollicular proliferation of plasma cells (Fig 2). At low magnification, hematoxylin and eosin staining results showed extensive storiform fibrosis with dermal inflammatory infiltrate predominantly in the perifollicular distribution (Fig 2). At high magnification, hematoxylin and eosin results revealed that the inflammatory infiltrate consisted of ovoid cells with prominent perinuclear hof and coarse chromatin in the eccentrically placed nucleus (Fig 2). Immunohistochemical analysis showed polyclonality of these plasma cells with retained

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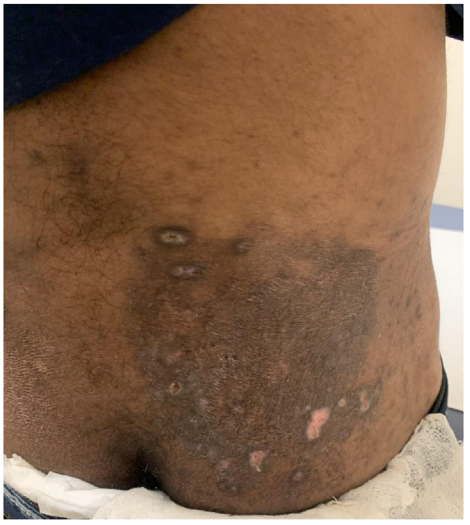

Fig 1. Cutaneous IgG4 disease. A clinical photograph of a 25-year-old Indian American man shows a well-demarcated hyperpigmented patch with healing erosions and admixed excoriations on the right side of the lower portion of the back and upper portion of the buttock. This picture is lacking the erythematous papule that was biopsied, as it was obtained after the biopsy result.

kappa and lambda expression (Fig 3, *A* and *B*). Anti-IgG4 antibodies stained >90% of the plasma cell infiltrate (Fig 3, *C*). Anti-treponemal antibodies, Steiner stain, and PCR for Herpes Simplex and Herpes Zoster viruses were negative. Direct immunofluorescence analyses performed on the biopsy were negative. The morphologic and immunohistochemical profiles were consistent with the cutaneous IgG4 disease. Serum antibody panel demonstrated elevated IgE (1720 kU/L; normal, ≤100 kU/L), Total IgG (1826 mg/dL; normal, 610-1660 mg/dL), IgG Subset-4 (322 mg/dL; normal, 2-9 6 mg/dL). The hepatitis panel demonstrated immunity to hepatitis B and was otherwise negative. He was managed with topical clobetasol and referred to rheumatology and gastroenterology (GI) to rule out systemic disease. Extensive work-up by GI revealed positive *Helicobater pylori* infection and positive colonic crypt lymphocytosis consistent with LC. Immunohistochemistry revealed no increase in lgG4+ plasma cells in the GI biopsy sample.

Anti-endomysial IgA, normal anti-TG IgA, total IgA, anti-Gliadin, complement C3, and C4 were normal. He was treated with GI with budesonide for LC and triple therapy for *H. pylori* infection. His pruritus and skin lesions were managed with clobetasol and resolved following budesonide treatment for his lymphocytic-plasmacytic colitis. The rheumatologic work-up was unremarkable.

DISCUSSION

This case highlights an unusual presentation of cutaneous IgG4-RD due to the patient's young age, lack of head and neck involvement, and concurrent LC. LC is an inflammatory disease of the colon and a common cause of chronic watery diarrhea with weight loss.[8] The pathophysiology of IgG4-RD and LC is yet to be elucidated. However, genetic predisposition, environmental triggers, and infections are thought to prompt aberrant immune pathways to perpetuate disease in both.[2,7,9] Exposure to hepatitis B>C>A is a well-established risk factor for IgG4-RD.[10] In our case, hepatitis serologies were negative. His uncontrolled diabetes mellitus 1 is also a well-established risk factor for LC.[8] Given that his LC preceded his cutaneous IgG4-RD, it is possible that it prompted aberrant immune dysregulation leading to cutaneous IgG4-RD.[9] Cutaneous IgG4-RD should be considered in Asian patients with a persistent pruritic papular eruption, especially in the presence of certain clinical features, such as older age, male sex, presence of other autoimmune conditions, and history of hepatitis.

Although inflammatory bowel disease (Crohn, Ulcerative Colitis) at times presents with cutaneous manifestations, such as erythema nodosum and pyoderma gangrenosum, these are predominantly neutrophilic dermatoses, which differ from the lymphocytic infiltrate observed in our patient's skin and colon biopsy samples. Similarly, case reports have associated other forms of microscopic colitis, such as the collagenous subtype, with neutrophil-predominant dermatoses. However, to our knowledge, LC is yet to be associated with cutaneous manifestations to date. In our patient, cutaneous IgG4-RD appeared to worsen during periods of colitis activity, which suggests that his intestinal and cutaneous manifestations may be related, to a phenomenon previously observed in collagenous colitis. We also observed that cutaneous and intestinal, symptoms resolved after steroid therapy, further suggesting an association between the skin and intestinal processes in our patient.

Overall, our case report highlights the role of dermatologists in recognizing cutaneous IgG4-RD as part of the differential diagnosis of pruritic papules. Prompt management can prevent the detrimental consequences of irreversible end-organ fibrosis, especially if systemic involvement is present. Further studies are needed to characterize the potential cutaneous manifestations of LC.

Conflicts of interest

None disclosed.

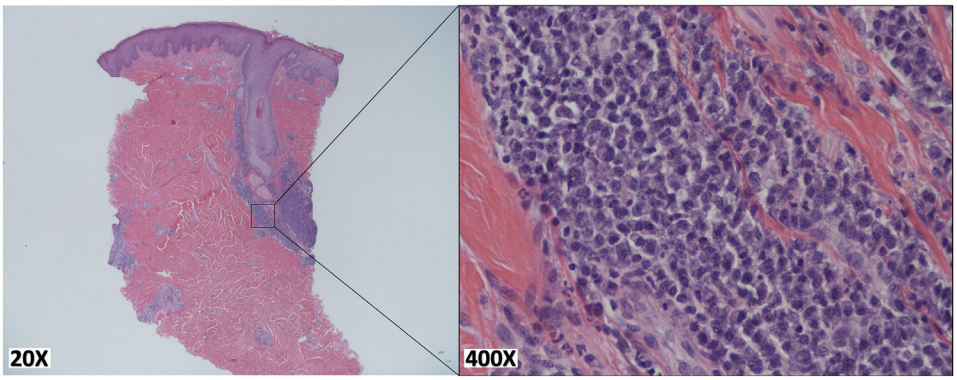

Fig 2. A, Low magnification photomicrograph shows extensive storiform fibrosis with dermal inflammatory infiltrate predominantly in the perifollicular distribution. **B,** The inflammatory infiltrate was consistent with ovoid cells with prominent perinuclear hof (clearing) and coarse chromatin in the eccentrically placed nucleus (**A** and **B**, Hematoxylin-eosin: original magnifications: **A**, ×20; **B**, ×400).

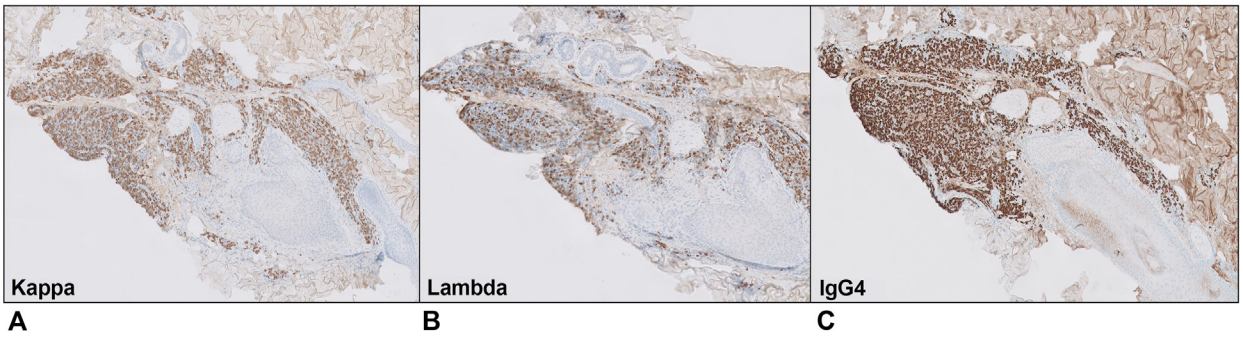

Fig 3. Immunohistochemical analyses with kappa and lambda showed polyclonality of plasma cells. The anti-IgG4 antibody tagged >90% of the plasma cell infiltrate.

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