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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Crohn's Disease Associated With IgA Nephropathy Effectively Treated With the Interleukin-23 Inhibitor Risankizumab

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ABSTRACT

Extraintestinal manifestations (EIMs) are common in inflammatory bowel disease (IBD). Renal EIMs, including immunoglobulin A nephropathy (IgAN), are relatively rare. EIMs are important to consider when developing a treatment plan for IBD. Studies differ on whether IBD disease activity correlates with IgAN disease activity. Published guidance on effective therapies for IBD-associated IgAN is limited. This case report suggests that risankizumab, an effective therapy for Crohn's disease, may also be effective in treating Crohn's disease–associated IgAN.

KEYWORDS: inflammatory bowel disease; Crohn's disease; extraintestinal manifestiations; IgA nephropathy; diagnosis; management; interleukin-23 inhibitor

INTRODUCTION

Extraintestinal manifestations (EIMs) are a common feature of inflammatory bowel disease (IBD), with prevalence estimates ranging from 6% to 47%.[1] Management of EIMs is important when developing an effective treatment plan for IBD. Renal disease is a rare EIM, with immunoglobulin A nephropathy (IgAN) and tubulointerstitial nephritis being the most common associated renal disorders.[2,3] We present a patient who was diagnosed with both IgAN and Crohn's disease (CD) within 1 month. Treatment with risankizumab, an interleukin (IL)-23 inhibitor, effectively treated both his CD and IgAN.

CASE REPORT

A 63-year-old man with no previous renal or gastrointestinal disease presented with 1 month of tea-colored urine and hematuria on urine dipstick. Cystoscopy and computed tomography urogram were unremarkable. Twenty-four-hour protein was elevated at 606 mg, and a spun urine sediment showed dysmorphic red cells. Renal biopsy demonstrated 2+ IgA mesangial deposits seen on immunofluorescence with intermediate density and minimal chronicity (Figure 1). The patient was diagnosed with IgAN, suspected to be an EIM of CD. The lack of chronicity in his age group suggested against primary IgAN.[4] The density of mesangial deposits was higher than expected for incidental IgA renal deposits, and the presence of red blood cell casts further argued against this diagnosis.[4]

Concurrently, the patient was evaluated for new-onset iron deficiency anemia. Initial upper endoscopy was negative. Because of persistent anemia, a colonoscopy was completed and showed aphthous ulcers throughout the colon without rectal or ileal involvement. Histology demonstrated active chronic patchy colitis with scattered granulomas, consistent with a diagnosis of CD. A

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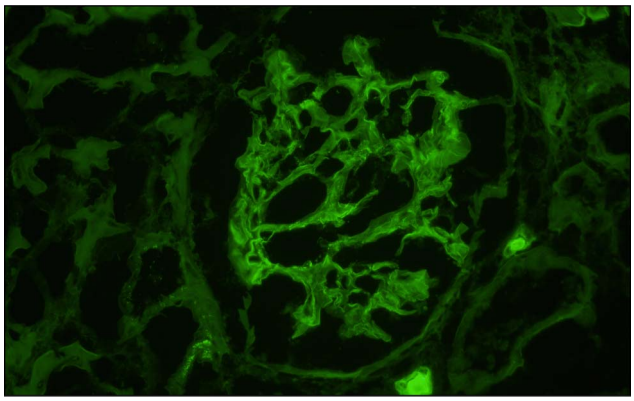

Figure 1. Renal biopsy demonstrating 2+ immunoglobulin A mesangial deposits seen on immunofluorescence with intermediate density and minimal chronicity.

screening colonoscopy 3 years earlier had been grossly normal. The only notable bowel symptoms were mild, intermittent fecal urgency and a slight increase in loose stools over the past 5 months, without hematochezia.

Once CD was suspected, budesonide 9 mg was started. After discussing treatment options, risankizumab was chosen because of its favorable safety profile and the patient's preference for subcutaneous injections. The induction dose was 600 mg intravenously (IV) at weeks 0, 4, and 8, followed by a maintenance dose of 360 mg at week 12 and every 8 weeks thereafter. The patient reported significant symptomatic improvement in gastrointestinal and renal symptoms within 1–2 months of initiating risankizumab. Within 5 months, his 24-hour total urine protein had decreased from 606 to 157 mg, his urine analysis was negative for blood, and his urine red blood cells had decreased from >50 to 0–3 cells per high-power field. Repeat colonoscopy approximately 1 year into treatment showed quiescent disease, which correlated with fecal calprotectin of <50 mcg/g.

DISCUSSION

Although IgAN is a rare EIM of CD, its association with CD and other forms of IBD has been substantiated in previous retrospective case-control studies.[5,6] This case report illustrates a novel treatment approach that reduced disease severity in both IgAN and CD.

A 2021 retrospective case-control study showed an increased prevalence of IBD in patients with IgAN.[6] Furthermore, in a series review of 23 patients with both CD and IgAN, 17 had simultaneous development of both conditions.[2] There is inconsistency in the literature as to whether UC or CD is more commonly associated with IgAN.[2,4,5] The same 2021 study also showed a higher risk of IgAN progressing to end-stage renal disease in patients with IBD: 50% of patients with IBD compared with 25% of patients with primary IgAN progressed to end-stage renal disease (odds ratio [OR]: 2.6 [95% confidence interval [CI] 2.02–3.35]).[5] In addition, it is unclear whether IgAN disease activity is associated with IBD disease activity. In 1 study of patients with active IgAN, only 26.3% of patients with CD and no patients with UC had any signs of active IBD.[4] However, in our case and another published case report, improvement of IgAN was achieved with treating the underlying CD.[7]

The pathophysiology of IBD-associated IgAN is not fully elucidated, but several mechanisms have been proposed. Abnormal O-linked glycosylation of IgA, the suspected initial IgAN trigger, occurs in CD because of reduced *N*-acetylgalactosamine.[5] In IBD, heightened mucosal B-cell activity shifts IgA production from IgA2 to IgA1, which favors renal deposition.[5] Apoptosis inhibitor of macrophages and abnormal T cells may also contribute, and IgAN is typically characterized higher proportions of Th2 and Th17 but lower proportions of Th1.[7–9] TNFα antagonists, such as adalimumab and infliximab, induce a shift from Th1 to Th2, which could explain rare cases of TNFα antagonists inducing IgAN.[10–13] The only literature on treating a patient with risankizumab who has IgAN is a case report of a patient with guttate psoriasis and IgAN, whose psoriasis improved without flaring of her IgAN during treatment.[14] Given that IgAN nephropathy has a higher proportion of Th17, a plausible explanation of risankizumab's efficacy in treating IgAN in our case is inhibition of IL-23, leading to downregulation of Th17. However, there has been some literature to suggest that IgAN can be precipitated by IL-23 inhibitors.[15,16] Further research could help clarify the complicated relationship between IL-23 and IgAN.

Although no published literature investigates the efficacy of risankizumab for treating IBD-associated IgAN, using a systemic biologic to treat EIMs, as opposed to a luminal agent such as vedolizumab, is well established. For example, ustekinumab, a monoclonal IgG1 antibody against IL-12 and IL-23, effectively treats CD associated with psoriatic arthritis, arthralgias, psoriasis, pyoderma gangrenosum, and erythema nodosum.[17–19] It is believed that some EIMs of IBD may not respond to treatment aimed at decreasing intestinal inflammation. For instance, although the disease activity of arthritis, aphthous ulcers, episcleritis, and erythema nodosum generally correlates with endoscopic luminal inflammation, anterior uveitis, ankylosing spondylitis, and primary sclerosing cholangitis do not.[1] Given this report, further work should be conducted to investigate the relationship between renal EIMs and intestinal inflammation to better understand the natural course of disease and to help guide the optimal therapeutic approach.

This case report supports the use of risankizumab as a potential treatment for IBD-associated IgAN. It also suggests that IgAN activity may correlate with luminal inflammation.

DISCLOSURES

Author contributions: C. Larson: lead author, literature review, manuscript writing, and editor. N. Munir: clinical contributor and editor. NP Rao: nephrology clinical contributor and editor. E. Farkash: Pathology clinical contributor and editor. D. Roman and P. Kathuria: editor. J. Berinstein: senior author, conception, assistance with literature review, and editor. J. Berinstein is the article guarantor.

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