CASE STUDY SERIES IN IBD

Treatment of Genital Crohn's Disease With Upadacitinib in a Male Child: A Case Report

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The prevalence of Crohn's disease is increasing in young children.[1] However, much of the current pediatric medical treatment for refractory inflammatory bowel disease (IBD), including Crohn's disease, involves off-label use of medication, unlike in adult IBD.[2] Currently, only 2 anti–tumor necrosis factor (TNF) agents (infliximab and adalimumab) have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of Crohn's disease in children.[3] Other agents, including vedolizumab (Entyvio, Takeda), ustekinumab (Stelara, Janssen), and Janus kinase (JAK) inhibitors, have been used off-label.[4,5] Pediatricians often prescribe medically necessary medications off-label, but off-label prescribing may carry additional risk owing to the lack of high-quality safety, efficacy, and dosing data.[6,7] This case report describes a child who developed a rare extraintestinal manifestation of Crohn's disease (Crohn's disease of the penis and scrotum) and did not respond to multiple maintenance medications for IBD, but ultimately improved after treatment with the JAK inhibitor upadacitinib (Rinvoq, AbbVie).

Case Report

A 12-year-old boy with a 5-year history of Crohn's disease who was being treated with ustekinumab presented with penile and scrotal swelling (Figure 1). His prior history was pertinent for refractory Crohn's ileocolitis that had been previously treated with multiple medications, including infliximab, adalimumab, and vedolizumab. On vedolizumab, he had continued to have active Crohn's colitis, and so had been transitioned to ustekinumab 6 months prior to the current presentation. His colonoscopy prior to the initiation of ustekinumab therapy had demonstrated active Crohn's colitis in the rectosigmoid colon, with 1 granuloma noted on biopsy. He had required dose escalation to 90 mg of ustekinumab monthly owing to ongoing symptoms. On the escalated monthly dosage of ustekinumab, his gastrointestinal symptoms were subsequently well controlled, and he was thought to be in clinical remission. At the time of the current presentation, however, the patient was complaining of difficulty urinating, mild pruritus, and pain in the penis and scrotum. He was referred to the urology department and underwent a scrotal biopsy, which was used to establish a diagnosis of extraintestinal Crohn's disease. The biopsy demonstrated inflammation of the scrotal skin with noncaseating granulomas in the superficial and deep dermis (Figure 2).

The patient was initially treated with corticosteroids, which reduced the swelling within 1 week. Subsequently, methotrexate was added as a maintenance medication, and the patient was continued on ustekinumab. We initially wished to treat him using combination therapy with ustekinumab (for his Crohn's colitis) and adalimumab (for his Crohn's disease of the scrotum and penis). However, the dual biologic therapy was denied by his insurance plan. Because the corticosteroid treatment was tapered, the patient's penile and scrotal swelling recurred. Six months after his initial presentation with genital Crohn's disease, the patient underwent a follow-up colonoscopy. The colonoscopy findings continued to demonstrate active Crohn's colitis of the left colon, now with the development of a stricture in the rectosigmoid colon. At this point, after extensive discussion with our colleagues and the patient's family, we decided to discontinue ustekinumab therapy and begin upadacitinib treatment.

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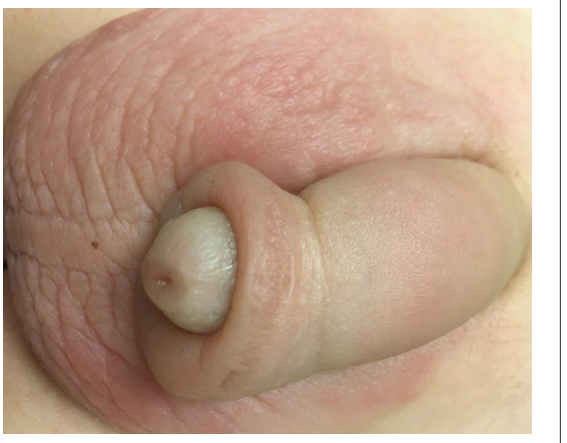

Figure 1. Penile and scrotal swelling at initial presentation.

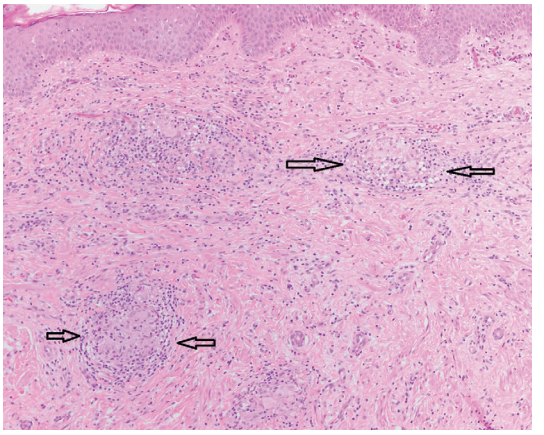

Figure 2. Scrotal skin biopsy demonstrating noncaseating granulomas (arrows).

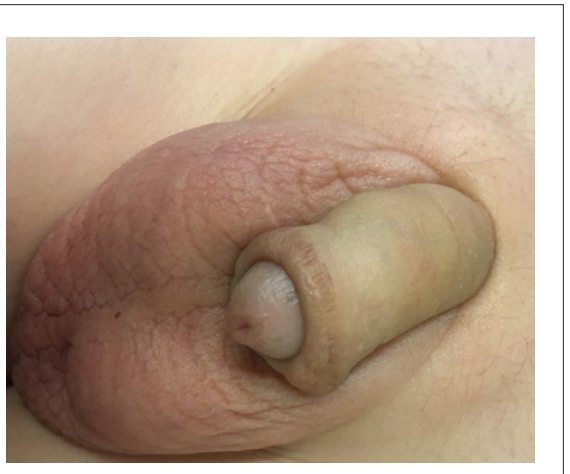

Figure 3. Reduction in penile and scrotal swelling after treatment with corticosteroids and upadacitinib for 3 weeks.

The patient was started on the induction dose of upadacitinib (45 mg daily) and almost immediately noted improvement in his bowel habits, with his bowel movements decreasing from 5 per day to 1 to 2 per day. However, about 5 days after the initiation of this medication, he developed a rash in his trunk and scrotum. Dermatologic evaluation raised the question of a drug reaction, and the patient was restarted on corticosteroid therapy. The combination of upadacitinib and corticosteroids resulted in marked improvement in his penile swelling, and the swelling essentially resolved within 1 month (Figure 3). Four months after initiation of treatment, the patient's upadacitinib dose has been reduced to a maintenance dose of 15 mg daily. However, the patient continues to require 5 mg daily of prednisone to maintain remission.

Discussion

Genital inflammation is an uncommon extraintestinal manifestation of Crohn's disease that is largely limited to individual case reports and case studies. In males, the classic presentation includes marked scrotal and penile swelling, whereas the most common presentation in females is vulvar swelling. Biopsy of the affected area can demonstrate a mixed inflammatory infiltrate of the skin, as well as multinucleated giant cells and epithelial granulomas.[8-16] The term *granulomatous lymphangitis* has been utilized to describe a subset of these cases. It is suspected that lymphatic obstruction, in addition to inflammation, may result in the marked penile and scrotal edema seen in these patients. Penile inflammation may precede the formal diagnosis of Crohn's disease. Owing to the atypical initial presentation, patients with penile Crohn's disease may present not to a gastroenterologist, but to a dermatologist or urologist. The differential diagnosis of penile swelling and granulomatous lymphangitis can include infections such as tuberculosis. Therefore, a high degree of clinical acumen is required to establish the diagnosis of Crohn's disease and exclude other conditions. If the condition is untreated, complications including penile necrosis may occur.[17]

Barrick and colleagues from the Mayo Clinic reported the largest case series of penile Crohn's disease in children. The researchers identified 8 patients, ranging from 7 to 16 years of age (mean age 11 years). Seven of the 8 patients experienced dermatologic symptoms before a diagnosis of Crohn's disease was made. These 7 patients underwent colonoscopy and biopsy, and in 5 of these patients, intestinal biopsy findings were consistent with Crohn's disease.

Treatment of this group of patients included prednisone, mercaptopurine, azathioprine, mesalamine, ciprofloxacin, topical tacrolimus, and anti-TNF therapy. Anti-TNF therapy was described as the most effective treatment, with either improvement or resolution of scrotal swelling in most patients. However, intermittent penile swelling persisted in a subset of the patients.[18]

Upadacitinib is a new medication that is approved by the FDA for the treatment of ulcerative colitis in adults. Recently, upadacitinib was also approved for the treatment of Crohn's disease in adults, with phase 3 induction and maintenance trials showing positive findings in this patient population.[19] Given the lack of response to multiple other medications, and the denial from the patient's insurance for using 2 biologics, we decided to try upadacitinib monotherapy to treat both the patient's Crohn's colitis as well as his penile and scrotal inflammation. Although follow-up has been less than 6 months thus far, the dramatic response of both the gastrointestinal symptoms and the penile swelling to upadacitinib and corticosteroids suggests that these medications may be efficacious in the treatment of colonic and penile Crohn's disease. Additional long-term follow-up, including repeat colonoscopy, will help determine if we can achieve a corticosteroid-free remission and whether this approach will be useful in this patient and other patients.

Conclusion

Although data on the use of JAK inhibitors to treat pediatric IBD are limited, the fact that these are small molecules with wide systemic effects suggests that JAK inhibitors may be useful in the treatment of extraintestinal manifestations of IBD. Although anti-TNF agents are most commonly used in children to treat moderate to severe Crohn's disease, and are also effective in treating extraintestinal manifestations, a subset of patients will fail anti-TNF agents. Our case report suggests that JAK inhibitors such as upadacitinib may play an important role in the treatment of such refractory patients. Hopefully, case reports such as this one will stimulate the additional reporting of clinical experience with JAK inhibitors in children. More importantly, we hope that definitive industry-sponsored clinical trials will be conducted to examine the safety and efficacy of upadacitinib and the JAK inhibitor tofacitinib (Xeljanz, Pfizer) in children with IBD and, if appropriate, lead to regulatory approval of these drugs in children as well as adults.

Disclosures

The authors have no relevant conflicts of interest to disclose pertaining to the content of this case report. Dr Bousvaros did participate in a safety registry of adalimumab (a drug made by AbbVie) in the past.

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