

Tubulointerstitial Nephritis as the Initial Presentation of Crohn's Disease and Successful Treatment with Infliximab

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ABSTRACT

Tubulointerstitial nephritis (TIN) is not commonly associated in aminosalicylate-naïve patients with Crohn's disease (CD). Our case describes the initial presentation, diagnosis, and management of an adolescent presenting with TIN and underlying CD. Our case emphasizes that CD should be considered in the differential diagnosis of interstitial nephritis as not only a medication-related effect, but also as an extraintestinal manifestation of CD. We also describe successful management of undiagnosed recurring and symptomatic CD-related TIN with infliximab.

INTRODUCTION

Tubulointerstitial nephritis (TIN) is known to be associated with Crohn's disease (CD), but only rarely as one of the prominent features of the initial presentation of CD. Although many cases have shown acute interstitial nephritis as a result of aminosalicylates, few cases have been reported to include TIN among initially presenting adults.¹⁻³ Only 3 reports of TIN or acute interstitial nephritis have been reported as part of initial presentation in adolescents with CD.³ This case accentuates why CD should be considered in the differential diagnosis of TIN as an extraintestinal manifestation of CD rather than due to other causes, including medications.

CASE REPORT

A 14-year-old adolescent boy presented to an outside emergency department with 4 weeks of intermittent low-grade fever, fatigue, headache, congestion, generalized abdominal pain, tenesmus, bloody diarrhea, and bilateral flank pain. He was treated initially with doxycycline and metronidazole for presumed infectious gastroenteritis and urinary tract infection. He did not receive any nonsteroidal anti-inflammatory drugs prior. Three weeks later, there was no improvement in his symptoms, and he presented to our emergency department. He had no gross hematuria or oliguria, nor did he have any pertinent past medical or surgical history. Family history included a maternal uncle with CD.

Physical exam demonstrated a 52-kg adolescent with blood pressure 143/97 mm Hg and heart rate 80 bpm. The patient was afebrile, appeared tired, and had mild cervical lymphadenopathy. He showed no signs of uveitis. Labs revealed leukocytosis (14.1/ μ L), mildly decreased hemoglobin (12.5 g/dL), and elevated creatinine (1.3 mg/dL), erythrocyte sedimentation rate (70 mm/hr), and C-reactive protein (7.7 mg/L). Microscopic urinalysis showed 62 leukocytes per high-power field and 3 red blood cells per high-power field, and was negative for protein and glucose. Hemocult stool sample was positive. Stool cultures were negative. Renal ultrasound showed mild bilateral kidney enlargement and increased parenchymal echogenicity. The patient was admitted, treated with supportive

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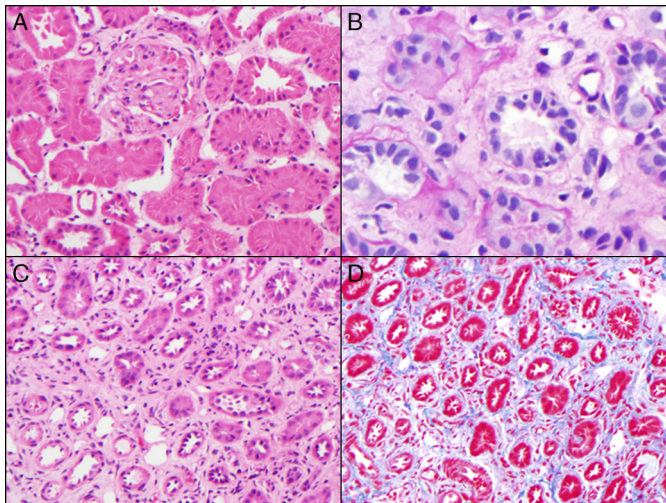


Figure 1. Histopathology of renal biopsy demonstrating acute tubulointerstitial nephritis with some chronicity. (A) Glomerulus showing ischemic change and periglomerular fibrosis. Hematoxylin & eosin (H&E) stain, 200x. (B) Lymphocytic tubulitis, 500x, Periodic acid-Schiff stain. (C) Interstitial inflammation in the medulla, predominantly chronic, with interstitial fibrosis, tubular atrophy, and regeneration. H&E stain, 200x. (D) Interstitial fibrosis highlighted with Masson-trichrome stain, 200x. Sclerotic collagen is highlighted in blue.

care, and started on amlodipine by the nephrology specialist. The gastroenterological specialist recommended panendoscopy; however, the gastrointestinal (GI) symptoms improved with supportive care, and outpatient follow-up was scheduled. The patient's creatinine levels improved from 1.3 to 1.0 mg/dL over 7 days, and urine leukocyte esterase became negative within 2 days without steroids. He was discharged on amlodipine with presumed TIN.

One month later, pyuria recurred, with creatinine rising to 1.5 mg/dL, as well as fluctuating symptoms of sinusitis. Computed tomography sinus imaging demonstrated pansinusitis with early erosion of the uncinata process. Antinuclear antibody was slightly elevated (1:250 speckled pattern). Anti-dsDNA antibodies and previous anti-neutrophil cytoplasmic antibodies were negative. With hydration, creatinine initially improved to 1.2 mg/dL in 2 weeks but rebounded to 1.5 mg/dL in 2 months. Renal biopsy showed non-specific TIN and some interstitial fibrosis (Figure 1). The patient was treated with prednisone (60 mg daily) for TIN with improvement of creatinine to 1.0 mg/dL. During steroid weaning, abdominal pain and diarrhea with intermittent hematochezia recurred. Labs revealed persisting hypochromic and microcytic anemia. Stool calprotectin results returned after discharge and were elevated at 779 $\mu\text{g/g}$. Colonoscopy confirmed ileocolonic CD (Figure 2). Infliximab was started at 5 mg/kg. With this treatment, the patient was able to wean off oral prednisone within 3 months of infliximab. Nine months into infliximab therapy, the patient remains symptom free. Renal function stabilized at creatinine 1.0

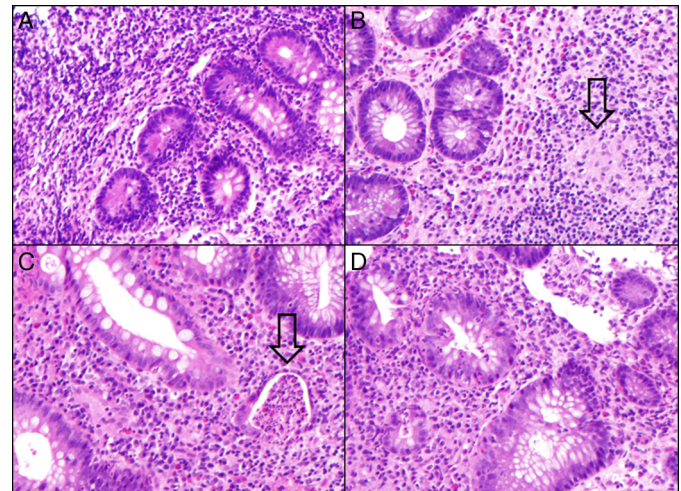


Figure 2. Histopathology of lower GI biopsies demonstrating Crohn's disease. (A) Terminal ileum showing mild active ileitis, with lymphocytic and neutrophilic infiltration into glands and mild architectural distortion. H&E stain, 50x. (B) Chronic active colitis with granuloma formation (arrow) in the ascending colon. H&E stain, 200x. (C, D) Descending colon with chronic active colitis with crypt abscess (arrow) formation (C) and cryptitis (D). H&E stain, 200x.

mg/dL. Blood pressure was well controlled with daily amlodipine (10 mg) and lisinopril (20 mg).

DISCUSSION

CD is an inflammatory process that not only affects the GI tract, but other organ systems as well.⁴ Chronic granulomatous nephritis has been described as an extraintestinal manifestation of inflammatory bowel disease, and TIN has been described as a result of treatment of CD with aminosaliclates.^{2,3} Aminosaliclates, non-steroidal anti-inflammatory drugs, antibiotics, and other drugs have been implicated in TIN. However, non-granulomatous TIN is not a widely known result of CD. In our case, the patient had no prior exposure to medications other than a course of metronidazole and doxycycline after his initial symptoms had begun. Renal biopsy did not demonstrate significant eosinophilic infiltration, which one would expect to see in drug-induced TIN.

The clinical course our patient followed suggests that the TIN and subsequent chronic kidney disease was likely an early extraintestinal manifestation of CD. His initial presentation with enlarged kidneys and initial recovery of renal function support an acute process. With subsequent fluctuation of symptoms, he eventually developed chronicity. At the time of the renal biopsy, we see active prominent mononuclear infiltration with lymphocytic tubulitis, along with areas of interstitial fibrosis as expected.

With the understanding of the potential nephrotoxicity of aminosaliclates and the longer time to recovery with immunosuppressants, a biologic agent was chosen in this case.¹

Infliximab is a chimeric monoclonal antibody that functions to decrease tissue necrosis factor α (TNF- α), which is very effective in a granulomatous disease like CD. In granulomatous nephritis, infliximab may have possible effects on the renal tubules. In non-granulomatous TIN, as in our case, we believe that infliximab improved the underlying CD, which reciprocally lifted its burden on the kidneys. The patient's GI and renal symptoms improved with infliximab; hypertension was well managed pharmacologically.

This is not always the case in CD-associated TIN. Classically, TIN will improve once the underlying condition is controlled, though interstitial fibrosis is irreversible. Some cases of simultaneous CD and TIN are reported in which pediatric patients had variable responses to infliximab.⁵ In one case, only a GI response was seen, while renal symptoms persisted.⁵ Another case demonstrated both renal and GI response to infliximab, though with eventual relapse.⁵ Treatment-resistant CD with relapse of intestinal symptoms will likely also be followed by recurrence of renal manifestations. This highlights the general clinical course of TIN: If the underlying condition is controlled prior to permanent damage, the kidney will improve. As for the chronic renal effects, patients may require long-term anti-hypertensive treatment due to interstitial fibrosis.

In this case, endoscopy was not performed during the first admission due to the patient's clinical improvement. He was scheduled for outpatient follow-up, and when endoscopy was then recommended he was found to be a poor candidate for anesthesia due to his recurrent sinusitis and respiratory symptoms. After initially rescheduling, the family canceled the endoscopy. Perhaps if an association with acute TIN and initial presentation of CD was more readily acknowledged, the argument for inpatient endoscopy would have been stronger. Earlier endoscopic exam in patients who present with a similar constellation of symptoms including acute TIN, bloody diarrhea, and a

family history of inflammatory bowel disease should be explored in management. In treatment options, potential nephrotoxins and the length of time for medication effect are important to consider in therapeutic decisions.

This case highlights TIN as an extraintestinal manifestation in the initial presentation of CD. As untreated or undiagnosed CD may lead not only to poor GI outcomes, but also poor renal outcomes, we emphasize the importance of considering prompt, synergic involvement of pediatric GI and nephrology in similar cases.

DISCLOSURES

Author contributions: B. Stanton compiled the manuscript. T. Caza obtained and interpreted the pathology images and created the figures. D. Huang interpreted the renal findings and edited the manuscript. MB Beg edited the manuscript and is the article guarantor.

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Informed consent was obtained for this case report.

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