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Original contribution

Paradoxical gastrointestinal reactions in patients taking tumor necrosis factor inhibitors: a rare event that broadens the histologic spectrum of medication–associated injury☆

Danielle Hutchings MD*, James A. Miller MD, Lysandra Voltaggio MD

Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD 21287

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Summary Tumor necrosis factor (TNF) inhibitors are widely used in the therapy of certain autoimmune disorders. Paradoxical immunologic reactions manifesting as new-onset autoimmune disease or exacerbation of the underlying condition have been reported in association with these drugs. In this study, we reviewed gastrointestinal biopsies and clinical findings in patients with rheumatologic disease on TNF inhibitor therapy and compared to patients with rheumatologic disease not on TNF inhibitors. Eighteen biopsies from 9 patients treated with TNF inhibitor therapy and 249 biopsies from 120 control patients not treated with TNF inhibitors were included. Among patients taking a TNF inhibitor, 55.6% were female, and the median age was 47 (range, 30-67 years). Four (44.4%) patients were taking etanercept, 4 (44.4%) adalimumab, and 1 (11.1%) certolizumab pegol. Of the 120 control patients, 75 (62.5%) were female and the median age was 62 (range, 26-85 years). Paradoxical reactions were observed in 3 (33.3%) of 9 patients on TNF inhibitors, including 2 (22.2%) with inflammatory bowel disease–like changes and 1 (11.1%) with sarcoid-like granulomas. All 3 patients showed symptomatic and histologic improvement or resolution after discontinuation of therapy. These reactions were not observed in any of the control patients ($P = .0002$). Our results indicate that among patients with rheumatologic disease, paradoxical reactions of the gastrointestinal tract are associated with TNF inhibitor therapy. Knowledge of this association is important because symptoms and histologic features may improve following medication switch.

1. Introduction

Tumor necrosis factor (TNF) inhibitor therapy is an important treatment modality for inflammatory conditions such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis, sarcoidosis, and ankylosing spondylitis (AS). Currently, there are 5 TNF inhibitors; 4 are monoclonal antibodies including infliximab, adalimumab, certolizumab pegol, and golimumab. The fifth, etanercept, is a soluble TNF receptor fusion protein.

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* Corresponding author at: Department of Pathology, Johns Hopkins University School of Medicine, 600 N Wolfe St, Baltimore, MD 21287.
E-mail address: dhutch15@jhmi.edu (D. Hutchings).

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The use of TNF inhibitors has been associated with new onset or exacerbation of the very diseases these drugs are intended to treat. These paradoxical reactions often show improvement on discontinuation of the medication or switch to another anti-TNF agent [1,2]. Specifically, new onset or exacerbation of IBD, psoriasis, uveitis, vasculitis, and sarcoidosis among patients taking TNF inhibitors has been reported [1,2]. The most commonly reported manifestation of IBD is Crohn disease [3-7]. Sarcoid-like granulomas have been described in the lungs, lymph nodes, skin, brain, and bone marrow [8-12]. Vasculitis most commonly involves the skin, but systemic vasculitis involving the kidney, lung, and central nervous system has been identified [2,13]. To date, no cases of sarcoidosis or vasculitis have been reported in the gastrointestinal (GI) tract.

In this study, we reviewed the gastrointestinal biopsies and clinical findings of patients with rheumatologic disease on TNF inhibitor therapy and compared these to those of patients with rheumatologic disease not treated with TNF inhibitors.

2. Materials and methods

2.1. Case selection

After approval by the Institutional Review Board, 259 patients with active prescriptions for TNF inhibitors including etanercept, adalimumab, certolizumab pegol, golimumab, and infliximab were identified through the outpatient pharmacy. A search of our electronic pathology database revealed that 48 patients had GI mucosal biopsies taken while on the medication. Electronic medical records were reviewed for clinicopathologic characteristics including age, sex, indication for endoscopy, rheumatologic condition, and additional medications. One patient was identified during routine GI mucosal sign out. After excluding patients with a prior history of IBD or sarcoidosis, 9 patients with GI mucosal biopsies taken during anti-TNF therapy were included.

We queried our electronic medical record system and identified 120 control patients with rheumatologic disease (RA, psoriasis, spondyloarthropathy, and Still disease) without a history of TNF inhibitor therapy and who underwent upper and/or lower GI endoscopies with biopsies at our institution. Those with a prior history of IBD and/or sarcoidosis were excluded.

2.2. Histologic review

For patients on TNF inhibitor therapy, the authors reviewed all available hematoxylin eosin (H&E) stained sections from GI biopsies taken from the upper tract (esophagus, stomach, or duodenum) and/or lower tract (terminal ileum and colon), which were performed during and after the discontinuation of therapy. After reviewing reports for all controls, a subset of the cases was selected for histologic examination, namely, those diagnosed as (1) "mildly increased gastric lamina propria chronic inflammation," (2) "inactive gastritis," (3) "active chronic gastritis without *Helicobacter pylori*," (4) "celiac disease–related changes," 5) "Common variable immunodeficiency (CVID)-associated changes," (6) "focal active colitis," (7) "acute colitis," (8) "collagenous colitis," (9) "lymphocytic colitis," and (10) "ischemic colitis."

2.3. Statistical analysis

Statistical analyses were performed using R statistical programming language (R Foundation, Vienna, Austria). A Fisher exact test was used to compare cases with paradoxical reactions in patients treated with TNF inhibitor therapy versus control patients.

3. Results

3.1. Clinicopathologic characteristics

The clinicopathologic characteristics of patients treated with TNF inhibitor therapy are summarized in Table 1. Briefly, 55.6% were female and the median age was 47 (range, 30-67 years). The underlying condition requiring anti-TNF therapy was spondyloarthropathy in 4 (44.4%) patients, RA in 3 (33.3%), and psoriasis in 2 (22.2%). Four (44.4%) patients were taking etanercept, 4 (44.4%) adalimumab, and 1 (11.1%) certolizumab pegol. Eight (88.9%) patients underwent endoscopy and biopsy because of GI-related symptoms, whereas 1 (11.1%) had routine screening colonoscopy. All 9 (100%) patients were taking 1 or more medications in addition to the anti-TNF agent.

Table 2 summarizes the clinicopathologic characteristics of control patients. Seventy-five (62.5%) patients were female, and the median age was 62 (range, 26-85 years). Seventy-five (62.5%) had psoriasis, 41 (34.2%) had RA, 2 (1.7%) had both psoriasis and RA, 1 (0.8%) had AS, and 1 (0.8%) had Still disease. Of the 78 patients with upper GI biopsies taken, 72 (92.3%) were symptomatic and 6 (7.7%) were on surveillance for esophageal varices. Of the 86 patients with lower GI biopsies taken, 29 (33.7%) were symptomatic and 57 (66.3%) were routine screening colonoscopies.

Three (33.3%) patients, all on etanercept, developed clinical and histologic paradoxical reactions, including 2 (22.2%) with IBD-like changes and 1 (11.1%) with sarcoid-like granulomas. These reactions were not observed in any of the control patients ($P = .0002$). Brief case reviews of these 3 patients are presented in Section 3.2.

Among control patients, the majority of upper tract biopsies were normal (n = 37, 29.3%) or showed a chemical gastritis pattern (n = 37, 29.3%). There were 44 (34.6%) of 126 total upper tract biopsies with a variety of inflammatory histologic patterns. Fifteen (11.9%) had acute and/or chronic gastritis due to current or prior *H. pylori* infection, 3 (2.4%) had active chronic gastritis in the absence of clinical or histologic

Table 1 Case characteristics and histopathologic findings in patients taking TNF inhibitors

Patient	Age	Sex	TNF inhibitor drug (duration of therapy)	Underlying condition	Indication for biopsy	Other medications	Upper GI biopsy findings	Lower GI biopsy findings
1	30	F	Etanercept (8.5 y)	Juvenile RA	Diarrhea	Methotrexate, folic acid, naproxen, metoprolol, alendronic acid, rizatriptan	▪ Duodenum with gastric mucin cell metaplasia.	▪ Terminal ileum with active inflammation, architectural distortion, and pyloric gland metaplasia. ▪ Sigmoid colon and rectum normal.
1 [a]	31	F	Adalimumab (0.9 y)	Juvenile RA	Follow-up (asymptomatic)	Methotrexate, folic acid	▪ Not performed	▪ Terminal ileum with focal active inflammation and persistent pyloric metaplasia. Restored villous architecture. ▪ Rectal mucosa with focal cryptitis.
2	50	M	Etanercept (8.2 y)	AS	Abdominal pain	Atorvastatin, losartan, metoprolol	▪ Not performed	▪ Terminal ileum with focal active enteritis with erosion. ▪ Rectal mucosa with active colitis with architectural distortion and focal Paneth cell metaplasia.
2 [a]	51	M	Adalimumab (0.3 y)	AS	Persistent abdominal pain	Atorvastatin, losartan, metoprolol, cholecalciferol	▪ Not performed	▪ Normal
3	47	M	Etanercept (6.2 y)	AS	Protein-losing enteropathy	Amlodipine/ benazepril, naproxen	▪ Distal duodenum with active duodenitis, villous attenuation, and gastric mucin cell metaplasia. ▪ Duodenal bulb with active duodenitis, reactive epithelial changes, and villous blunting. ▪ Active chronic antral and oxyntic gastritis with non-necrotizing granulomas. *H. pylori* immunostain negative. AFB and GMS stains negative. *T. whipplei* immunostain negative.	▪ Descending colon with reactive epithelial changes and focal non-necrotizing granulomatous inflammation. ▪ Rectosigmoid colon with non-necrotizing granulomas. AFB and GMS stains negative.
3 [a]	48	M	None (0.9 y)	AS	Follow-up (asymptomatic)	Amlodipine/ benazepril, naproxen, ferrous sulfate, omeprazole	▪ Active chronic duodenitis in duodenal bulb with granulation tissue and fibrinopurulent exudate. ▪ Antrum with chronic focally active gastritis and poorly formed granuloma. *H. pylori* immunostain negative.	▪ Ascending and sigmoid colon with focal acute colitis. No granulomas.

4	57	F	Certolizumab pegol (4.8 y)	RA	Screening colonoscopy	Alendronate, bupropion, folic acid, lisinopril, methotrexate, prednisone, ranitidine, atenolol	▪ Not performed	▪ Normal
5	49	F	Adalimumab (3.1 y)	RA	Abdominal pain	Prednisone, hydroxychloroquine, vitamin D, ferrous sulfate	▪ Normal	▪ Normal
6	34	F	Etanercept (1.7 y)	RA	Diarrhea and weight loss	Ibuprofen, methotrexate, hydroxychloroquine, folic acid, tramadol, valacyclovir	▪ Duodenum normal. ▪ Stomach with active chronic *H. pylori* gastritis in antral, oxyntic, and cardiac mucosa.	▪ Descending colon normal
7	67	M	Adalimumab (1.2 y)	AS	Abdominal pain	Aspirin, celecoxib, atorvastatin, esomeprazole, metoprolol, levothyroxine, magnesium oxide, cholecalciferol	▪ Second portion of duodenum normal. ▪ Antral mucosa with reactive epithelial changes. No *H. pylori* identified on Diff-Quik stain.	▪ Not performed
8	46	F	Adalimumab (0.2 y)	Psoriasis	Gastroesophageal reflux disease and diarrhea	Cetirizine, ergocalciferol, fluoxetine, levothyroxine, loperamide	▪ Duodenal bulb normal.	▪ Terminal ileum normal
9	41	M	Adalimumab (4.8 y)	Psoriasis	Screening colonoscopy	Atorvastatin, hydrochlorothiazide, losartan, clobetasol	▪ Not performed	▪ Tubular adenoma

[a] Indicates follow-up data.

Table 2 Clinicopathologic characteristics of control patients not treated with TNF inhibitor therapy

Underlying disease (n = 120)	
Psoriasis, % (n)	62.5% (75)
RA, % (n)	34.2% (41)
Psoriasis and RA, % (n)	1.7% (2)
AS, % (n)	0.8% (1)
Still disease, % (n)	0.8% (1)
Sex (n = 120)	
Female, % (n)	62.5% (75)
Male, % (n)	37.5% (45)
Histologic diagnosis upper GI tract (n = 126) [a]	
Normal, % (n)	29.3% (37)
Chemical gastritis, % (n)	29.3% (37)
H pylori infection, % (n)	11.9% (15)
Isolated intestinal metaplasia, % (n)	7.1% (9)
Benign polyps, % (n)	6.3% (8)
Mild increase in chronic inflammation, % (n)	7.9% (10)
Inactive chronic gastritis, % (n)	4.0% (5)
Active chronic gastritis without *H pylori,* % (n)	2.4% (3)
Adenocarcinoma, % (n)	0.8% (1)
Chronic peptic duodenitis, % (n)	6.3% (8)
Celiac disease associated changes, % (n)	0.8% (1)
CVID-associated changes, % (n)	0.8% (1)
Histologic diagnosis lower GI tract (n = 123) [a]	
Normal, % (n)	20.3% (25)
Benign polyp(s)	67.5% (83)
Focal active colitis	1.6% (2)
Acute colitis	1.6% (2)
Lymphocytic colitis	1.6% (2)
Collagenous colitis	1.6% (2)
Ischemic colitis	0.8% (1)
Isolated focal erosion	0.8% (1)

[a] If multiple discrete diagnoses per case, each diagnosis categorized separately.

evidence of *H. pylori* infection, and 5 (4.0%) had inactive chronic gastritis. Ten (7.0%) showed mildly increased lamina propria chronic inflammation. One (0.8%) biopsy showed changes consistent with celiac disease, which was confirmed by positive IgA tissue transglutaminase. One (0.8%) biopsy from a patient with RA and CVID showed duodenal and gastric changes previously described in association with this condition. None showed granulomas.

Most lower GI biopsies in controls showed benign polyps (n = 83, 67.5%) or were normal (n = 25, 20.3%). Inflammatory patterns were identified in 9 (7.3%) of 123 total biopsies including 2 (1.6%) with focal active colitis, 2 (1.6%) with lymphocytic colitis, 2 (1.6%) with collagenous colitis, and 1 (0.8%) with ischemic colitis. Two (1.6%) biopsies showed isolated active colitis. None showed granulomas or other features of IBD.

3.2. Case reviews of patients with paradoxical reactions

3.2.1. Patient 1

This 30-year-old woman had a history of juvenile RA, diarrhea, and an 8.5-year history of etanercept use. Biopsies were taken from the duodenum, terminal ileum, and colon and were significant for active inflammation, architectural distortion, and pyloric gland metaplasia (Fig. 1). No granulomas were identified. The pathologic results were clinically interpreted as Crohn disease, and her medication was switched from etanercept to adalimumab with improvement of symptoms. Follow-up endoscopy was performed 1 year later with biopsies taken from the terminal ileum and colon. The small bowel showed persistent focal active inflammation and pyloric metaplasia but with overall inflammatory and architectural improvement.

3.2.2. Patient 2

A 49-year-old man with AS had been treated with etanercept for 8.2 years and presented with chronic right lower quadrant abdominal pain. Biopsies of the terminal ileum showed focal active enteritis with erosion. The rectum presented active colitis with architectural distortion and focal Paneth cell metaplasia. No granulomas were identified. The changes were interpreted clinically as emerging Crohn disease, and the patient was started on mesalamine and switched to adalimumab. Mesalamine was discontinued 6 months later due to adverse effects. Follow-up biopsies from the terminal ileum were taken 9 months later and showed no histologic abnormalities. Notably, because of worsening of AS symptoms, the patient had been switched back to etanercept approximately 2 weeks before follow-up biopsies were taken. No further clinical or pathologic follow-up was available at the time of this writing.

3.2.3. Patient 3

This 47-year-old man with AS had a 6-year history of etanercept use and presented with persistent hypoalbuminemia and protein-losing enteropathy with elevated stool fat and α-1 antitrypsin. A serum gastrin was within normal limits. Results of serum tissue transglutaminase IgA, anti-gliadin antibody, and blood polymerase chain reaction for *Tropheryma whipplei* were negative. Results of stool ova, parasite, and giardia antigen studies were negative. Tuberculosis testing was not performed. Biopsies from the stomach, duodenum, terminal ileum, and colon were obtained. Histologic examination revealed active chronic antral and oxyntic gastritis with well-formed, non-necrotizing granulomas within the antrum and body of the stomach (Fig. 2). No *H. pylori* organisms were identified on immunostain. The duodenal bulb showed active duodenitis with reactive epithelial changes and villous blunting. The distal duodenum showed active duodenitis with villous attenuation and gastric mucin cell metaplasia. There were well-formed, non-necrotizing granulomas in the descending and rectosigmoid colon (Fig. 2). Acid fast bacilli (AFB) and Grocott methenamine silver (GMS) stains performed on stomach and colon were negative. Infectious etiologies and celiac disease were considered clinically unlikely, as was IBD given the atypical clinical symptoms and absence of histologic features of chronicity. A serum angiotensin-converting enzyme performed on follow-up was within normal limits. The findings were clinically interpreted as an adverse reaction to etanercept, and the medication was discontinued.

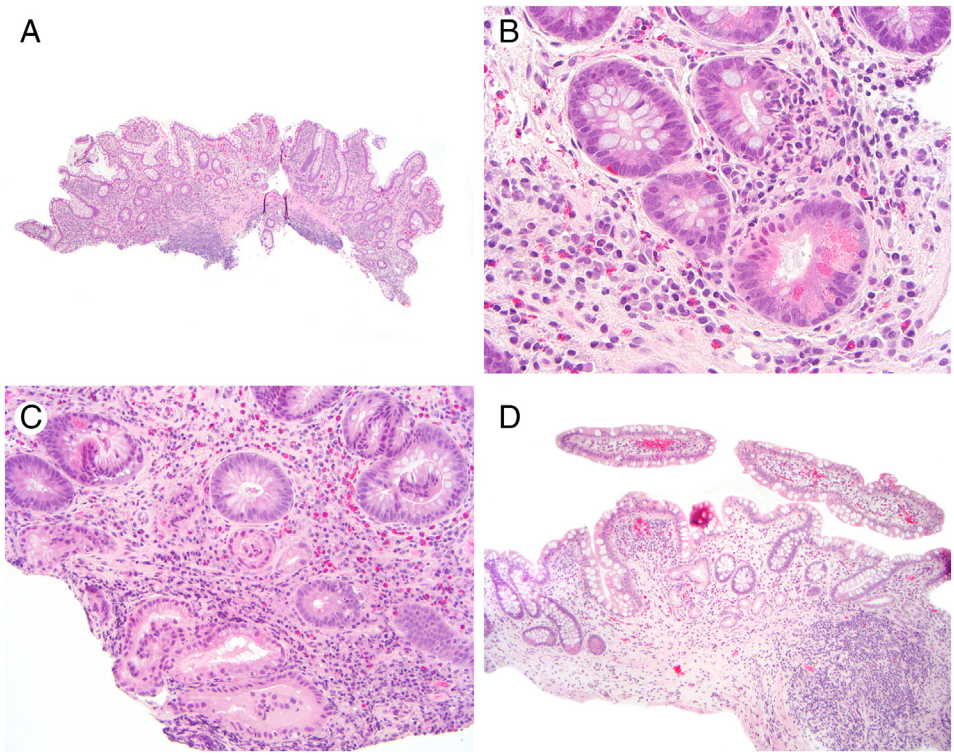

Fig. 1 Inflammatory bowel disease–like changes in a patient taking TNF inhibitor therapy. A-C, Biopsies showed chronic active ileitis with pyloric metaplasia. D, One-year follow-up biopsies after medication switch showed well-formed villi with focal active inflammation and persistent pyloric metaplasia. Hematoxylin and eosin stain, original magnification ×40 (A), ×400 (B), ×200 (C), and ×100 (D).

His protein losing-enteropathy resolved as evidenced by normalization of serum albumin and stool α-1 antitrypsin. Follow-up biopsies 1 year later showed focally active antral gastritis with a persistent but poorly formed granuloma (Fig. 2). *H. pylori* immunostain was negative, as was serum *H. pylori* IgG antibody. The duodenal bulb showed active chronic duodenitis with granulation tissue. There was additionally focal acute colitis in the ascending and sigmoid colon but no granulomas or architectural distortion. He was started on adalimumab given worsening of his AS symptoms and has been maintained on that medication for 2 years with no reported GI symptoms and normal serum albumin levels.

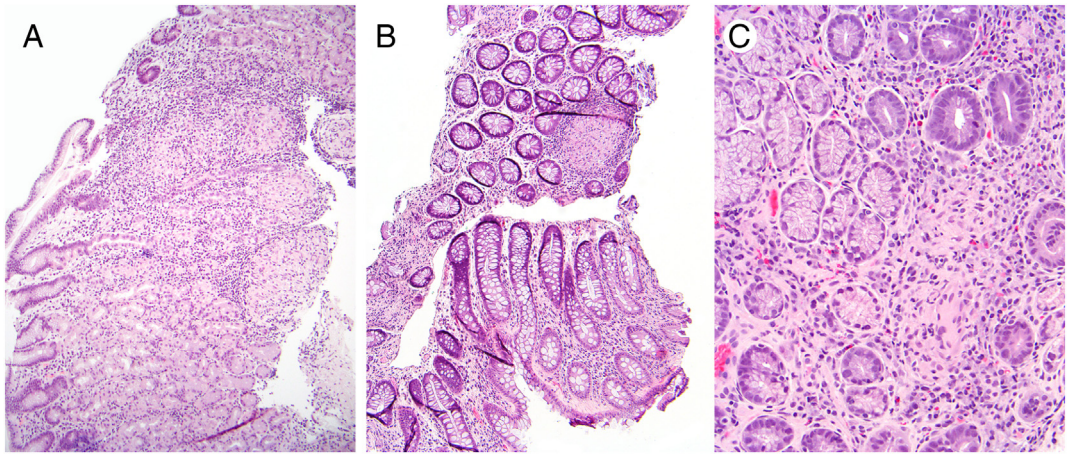

Fig. 2 Sarcoid-like granulomas in a patient taking TNF inhibitor therapy. Biopsies showed well-formed, compact, non-necrotizing granulomas in the stomach (A) and colon (B). C, Follow-up gastric biopsy at 1 year showing a single, poorly formed granuloma. Hematoxylin and eosin stain, ×100 (A-B) and ×200 (C).

4. Discussion

Tumor necrosis factor inhibitors have revolutionized the field of rheumatology since their development in the 1990s. Since then, they have been used widely to treat a variety of immune-mediated conditions including RA, psoriatic arthritis, AS, plaque psoriasis, polyarticular juvenile idiopathic arthritis, Crohn disease, and ulcerative colitis. Their mechanism of action involves binding to TNF and thereby suppressing the body's immune response.

As with most medications, adverse reactions are well documented with the use of TNF inhibitors. These range from infections to new-onset autoimmune conditions to malignancies. New-onset immune-mediated conditions paradoxically include some of the very diseases these drugs are intended to treat. Psoriasis, eosinophilic gastroenteritis, sarcoid-like granulomas, vasculitis, interstitial lung disease, and new-onset IBD have been reported [2,5,8-12,14-18]. On the other hand, Braun et al. studied 419 patients with AS treated with TNF inhibitors and found no statistically significant differences in new-onset IBD between patients treated with placebo and those treated with anti-TNF agents [4]. In a similar fashion, Fouache et al. found no statistically significant differences in paradoxical adverse effects (psoriasis, acute anterior uveitis, IBD) in patients taking these drugs versus their control group [3]. These paradoxical events are rare, and the underlying mechanism is not well understood. They may represent reactions intrinsic to the drug or more likely are the result of an altered inflammatory milieu due to TNF blockade.

We identified 2 salient histologic patterns of GI tract inflammation in 3 individual patients who were taking etanercept: an IBD-like pattern and a sarcoid-like pattern. Control patients featured an inflammatory pattern in 34.6% and 7.3% of upper and lower GI tract biopsies, respectively, none showed sarcoid- or IBD-like morphology. Although 4 of our control patients showed lymphocytic or collagenous colitis patterns and TNF inhibitors are used in the treatment of refractory microscopic colitis, to the best of our knowledge, no reports of such anti-TNF–related paradoxical reactions have been reported as of this writing.

Sarcoid-like granulomas have been well documented in association not only with etanercept but also with the use of infliximab and adalimumab [8,9,12,19-22]. More recently, sarcoid-like granulomas have been reported with the use of antibodies to programmed death-1 [23,24]. Reported sites of involvement associated with TNF inhibitor use include bone marrow, lymph nodes, kidney, lung, salivary glands, and eye. Time from initiation of therapy to diagnosis ranged from 1 to 51 months (median, 18 months) in 1 study [8]. To our knowledge, this is the first report of TNF inhibitor–related sarcoid-like granulomas in the GI tract. The patient presented with protein-losing enteropathy, a rare yet documented manifestation of sarcoidosis [25-27]. The mechanism of this rare presentation is unknown, although some have proposed involvement of the mesenteric lymph nodes by the granulomatous process [27]. Our patient had no history of bloody diarrhea or abdominal pain and no architectural distortion on histology to suggest Crohn disease. Likewise, infectious processes were considered unlikely from a clinical standpoint. Resolution of the protein-losing enteropathy after drug discontinuation argues for (but admittedly does not prove) a role of etanercept in this process. Twelve months after drug discontinuation, our patient had follow-up biopsies, which showed no colonic granulomas and a single, poorly formed granuloma in the stomach. This is not surprising when one takes into account the report by Daïen et al. who studied 10 patients who developed pulmonary, cutaneous, nodal, and salivary gland sarcoid-like granulomas during treatment with TNF blockers. In their report, the median delay between drug withdrawal and radiologic remission was 6 months (range, 2-12 months) [8]. The duodenal ulcer seen on follow-up biopsies may be explained by his continued intake of naproxen to control his AS symptoms.

New-onset IBD (Crohn disease, ulcerative colitis, and indeterminate colitis) and IBD flares during treatment with TNF blockers are documented and have been reported to occur from 4 to 40 months after initiation of TNF blocker therapy [5-7,14,17,28,29]. Cases have been reported in association with etanercept [5,7,14,17,28,29], infliximab [3,5], and adalimumab [6] and with underlying conditions such as AS [7,14], RA [6,17], juvenile idiopathic arthritis [28,29], and psoriatic arthritis [5]. Toussirot et al. reported favorable outcomes for most patients after replacement of one TNF agent by another [5]. Both patients in this present study had available follow-up information in our study and improved clinically, endoscopically, and histologically after switching medication from etanercept to adalimumab.

It is admittedly difficult to draw solid conclusions from this study because our cohort is small and, in addition, polypharmacy is a potential confounding factor because all of the patients were taking drugs in addition to the anti-TNF agent, including methotrexate (3 patients) and/or nonsteroidal anti-inflammatory drugs (4 patients). Among the 3 patients with paradoxical reactions, only 1 had significant medication change at follow-up, specifically discontinuation of nonsteroidal anti-inflammatory drug in patient 1, which may have contributed to this patient's clinical and histologic improvement. Nevertheless, knowledge of these associations is important and may help guide clinical management as patients experience clinical and histologic improvement after discontinuation or switch of the TNF agent [6,8,13,15,28].

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