

Rituximab-Induced Colitis and Esophagitis in a Patient With Granulomatosis With Polyangiitis

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Abstract

Granulomatosis with polyangiitis (GPA) is a small vessel vasculitis that affects many organ systems with varying disease severity. GPA commonly affects the sinuses and lung parenchyma. However, GPA can affect the gastrointestinal tract and may present as colitis. Immunosuppressive therapy, like rituximab (RTX), is used for the management of this disease. Rituximab is generally well-tolerated but has rare side effects that have been shown to mimic colitis in inflammatory diseases. Our case is a 44-year-old female with a history of GPA who presented with dysphagia, abdominal pain, and diarrhea. The patient received a maintenance dose of RTX six months before the presentation. The patient was seronegative for anti-neutrophilic cytoplasmic antibodies against proteinase 3 (PR3 ANCA). Infectious etiology was ruled out. Esophagogastroduodenoscopy (EGD) and colonoscopy showed esophageal bleeding ulcers and diffuse colonic inflammation, respectively. Pathology was consistent with esophagitis and colitis. Colonic mucosal biopsy failed to show evidence of vasculitis. The patient was treated with sucralfate and intravenous pantoprazole with an improvement in the symptoms. The repeat endoscopy on an outpatient basis showed the patient had full mucosal healing, including histological healing. Our patient likely had rituximab-induced colitis and esophagitis.

Categories: Internal Medicine, Gastroenterology, Rheumatology

Keywords: immune-mediated colitis, side effects of medical treatment, rituximab, colitis, granulomatosis with polyangiitis (gpa)

Introduction

Granulomatosis with polyangiitis (GPA) is a rare blood vessel disease affecting many organ systems with varying disease severity. Immunosuppressive therapy has been the cornerstone in the management of this disease, with a significant decrease in mortality following appropriate treatment. However, these agents are not without side effects, thereby posing a diagnostic dilemma between medication side effects and disease progression. Rituximab (RTX) is known to be well-tolerated, but on rare occasions, RTX-induced colitis can present as a complication of treatment [1]. Esophagitis caused by RTX is also an uncommon complication [2]. There are unique occasions where GPA presents gastrointestinal manifestations such as esophagitis and colitis [3,4]. When a patient with GPA who was treated with RTX develops these symptoms, it is often difficult to discern the underlying etiology.

Herein, we describe a case where RTX induces colitis and esophagitis in a patient with a history of GPA.

Case Presentation

We present a 44-year-old female with a history of granulomatosis with polyangiitis (GPA) that came in after a five-week history of abdominal pain and diarrhea.

The patient was diagnosed with limited GPA in 2017. She had a GPA history that was significant for lung granulomatous inflammation and positive anti-neutrophilic cytoplasmic antibodies against proteinase 3 (PR3 ANCA). She received treatment with an anti-CD20 antibody, rituximab (RTX). Her symptoms improved and eventually achieved remission.

On presentation, the patient stated that her abdominal pain was postprandial, crampy, located in the periumbilical region, and usually preceded diarrhea. She reported having between three and five episodes of mucoid non-bloody stools, anorexia, and a nine-pound weight loss in two weeks. Her symptoms were associated with a sensation of food getting stuck in her throat and pain when she swallowed two days before admission. She denied fever, nausea, vomiting, or dark-colored stool. She reported worsening sinus congestion for which she had been seeing an otolaryngologist. She was referred to a gastroenterologist because of the dysphagia one week before the presentation. The patient states that an esophagogram was done and was shown to be within normal limits.

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At this time, the patient's gastrointestinal symptoms persisted, and she decided to come to the emergency department (ED) for evaluation. In the ED, a computerized tomography scan showed colonic wall thickening, suggestive of infectious or inflammatory colitis. It also showed a patulous esophagus and possible mild reflux esophagitis. After admission, the patient was treated with oral sucralfate and intravenous pantoprazole for esophagitis. Gastroenterology and rheumatology were consulted. Laboratory investigations showed a negative anti-neutrophilic cytoplasmic antibody (ANCA) profile, blood and stool culture, herpes simplex virus (HSV), and human immunodeficiency virus (HIV) serology. C-reactive protein, erythrocyte sedimentation rate, and stool calprotectin were all elevated. Esophagogastroduodenoscopy (EGD) showed non-bleeding esophageal ulcers as depicted in Figure 1. A colonoscopy showed pancolitis with diffuse mild inflammation found in the entire colon (Figure 2).

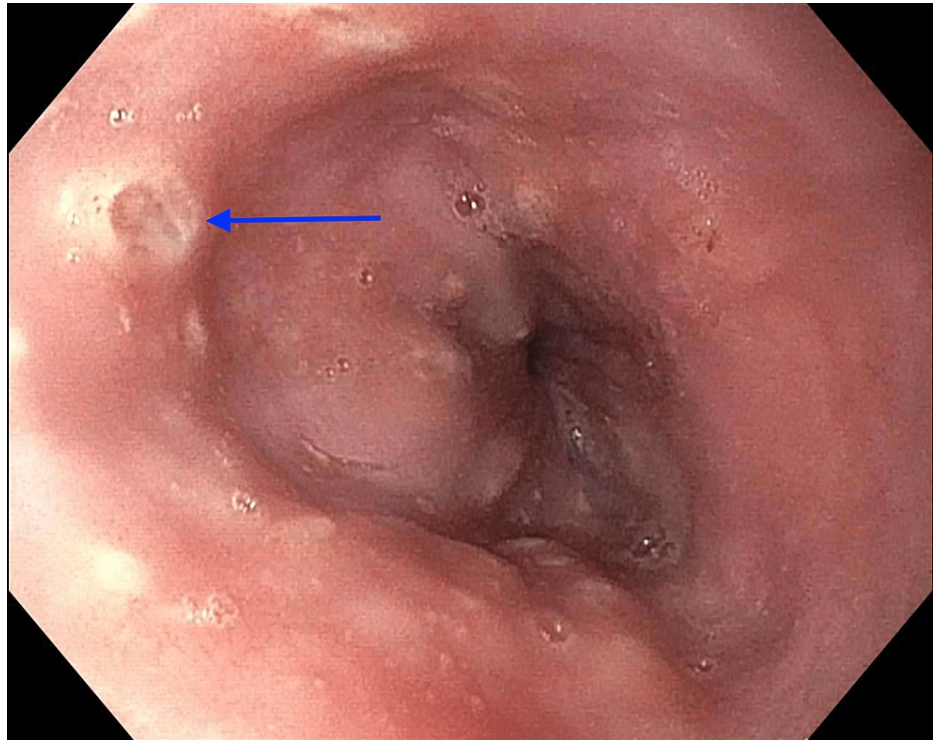


FIGURE 1: EGD finding of large bleeding ulcers in the third part of the esophagus

EGD: esophagogastroduodenoscopy

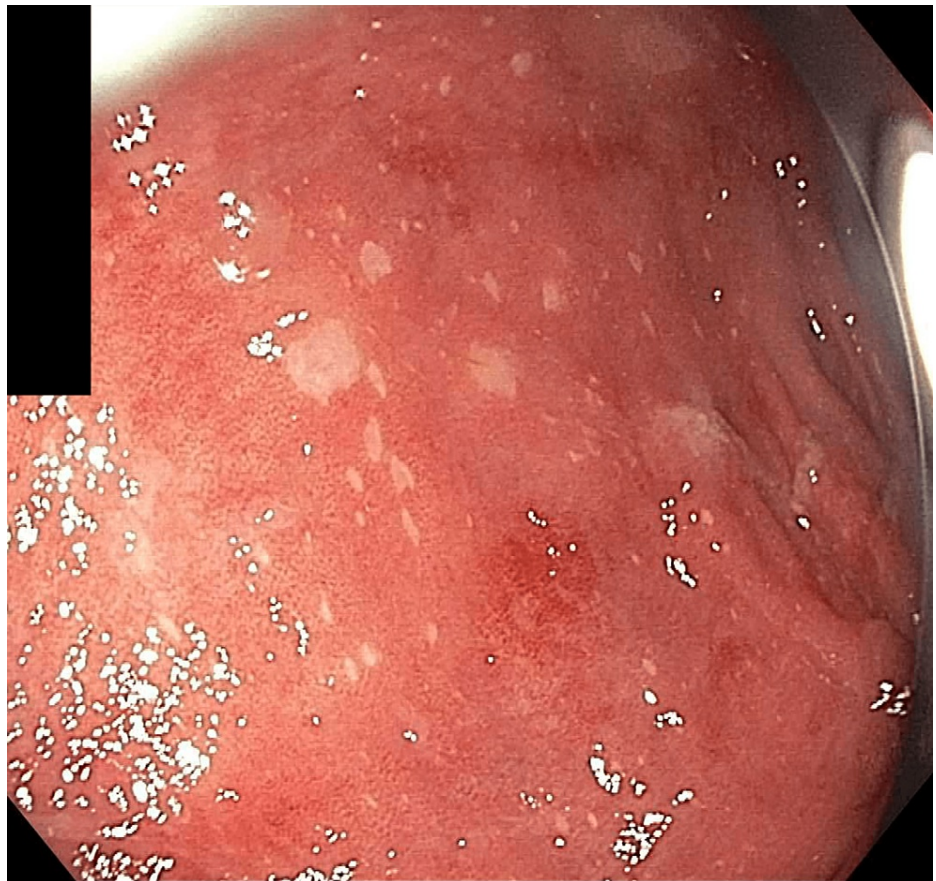


FIGURE 2: Colonoscopy finding of diffuse mild inflammation in the sigmoid colon

A biopsy of the esophagus showed acute and chronic esophagitis. It was negative for Cytomegalovirus and HSV I/II and negative for fungi by periodic acid-Schiff stain as depicted in Figure 3. A biopsy of the colon showed active colitis and granulomas depicted in Figure 4. There was also encompassing cryptitis throughout most of the colon. No necrosis or vasculitis was seen as depicted in Figure 5.

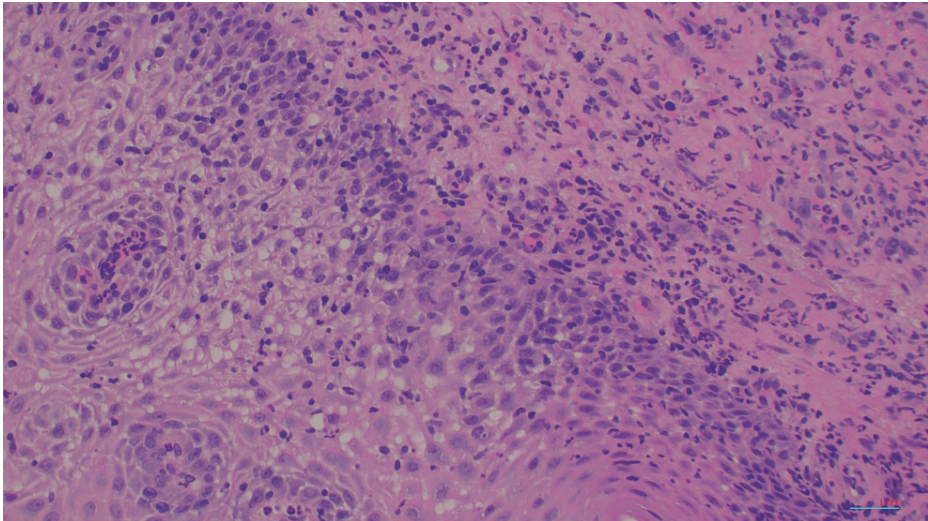


FIGURE 3: H&E histology stain, 100x magnification

Esophageal squamous mucosa with acute and chronic esophagitis showing neutrophils and infiltrating squamous epithelium and underlying stroma

H&E: hematoxylin and eosin

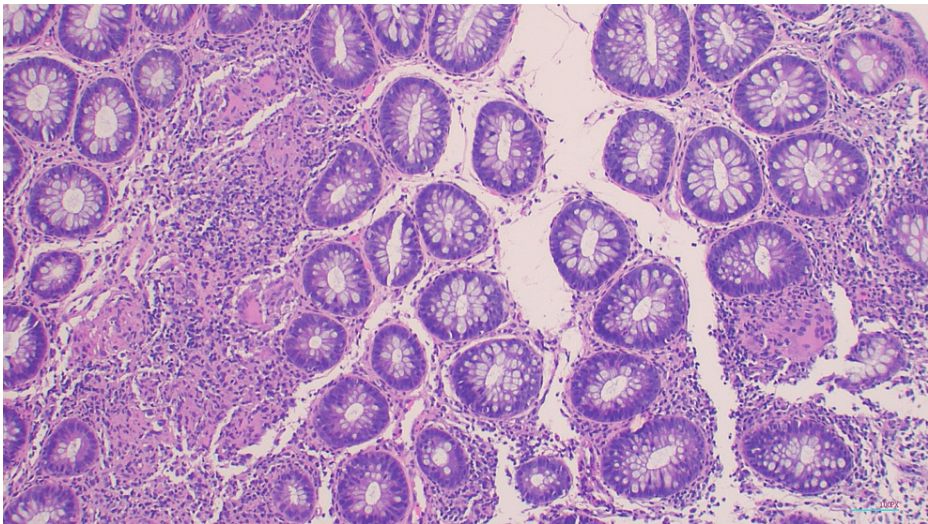


FIGURE 4: H&E histology stain, 100x magnification

Transverse mucosa shows many non-caseating granulomas forming coalescent lesions in lamina propria and one single granuloma in the right mid-field.

H&E: hematoxylin and eosin

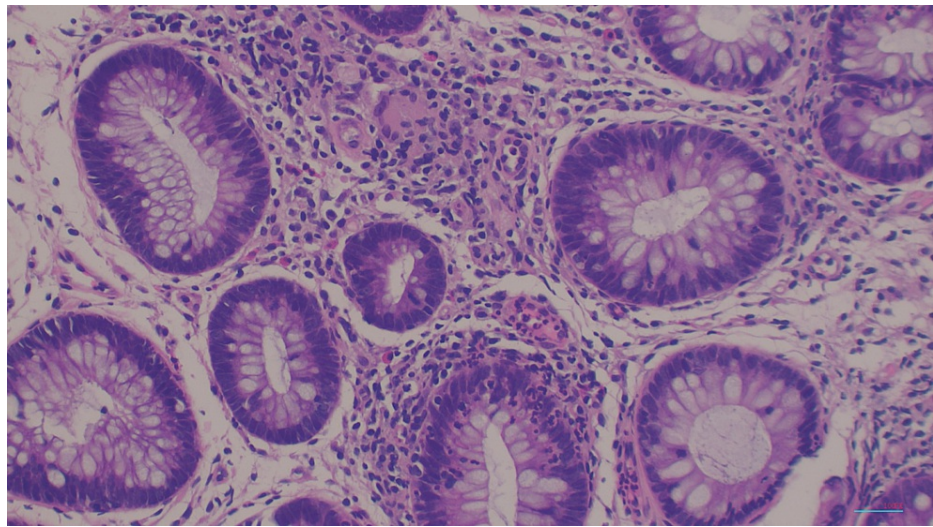


FIGURE 5: H&E histology stain, 100x magnification

Rectal mucosa with active colitis showing cryptitis and adjacent non-caseating granulomas

H&E: hematoxylin and eosin

The patient had a favorable response to symptomatic treatment with intravenous pantoprazole and sucralfate and was discharged home with significant improvement. In subsequent outpatient visits, she remained asymptomatic. The repeat endoscopy was benign and showed she had full mucosal healing, including histological healing.

Discussion

GPA is a small vessel vasculitis that affects multiple organs. The full scope of the pathogenesis of GPA is still unknown. Genetic, environmental, and epigenetic factors all play a role. Anti-neutrophil cytoplasmic antibodies (ANCA) that primarily target proteinase 3 (PR3), which are found within neutrophils, are believed to play a role in the pathophysiology. The evidence is circumstantial, and opinions are divided among experts.

GPA is commonly treated with RTX, which is a monoclonal antibody that targets the CD20 marker present in most of the mature B lymphocytes. RTX was approved by the United States Food and Drug Administration (FDA) for the treatment of ANCA-related vasculitis after a successful randomized control trial [5]. It is generally well-tolerated, but on rare occasions, treatment results in adverse reactions. De novo colitis was associated with RTX infusion in a study conducted by Eckmann et al. [1]. A few patients with diseases treated with RTX developed colitis resembling inflammatory bowel disease. Our patient's last exposure to RTX was six months before the presentation, and she received maintenance-level dosing (a single infusion of 500 mg). We hypothesize that at the time of presentation in the ED, the immunologic activity of RTX would have been at the tail end of any significant immunomodulatory effects. However, according to a study done by Mallepally et al., RTX-induced colitis should be considered in patients who received RTX treatment with GI symptoms for up to two years after patients receive the last dose of rituximab [6]. There are reported cases of colitis presentation from immediately after infusion to two years after RTX administration [3,7-12]. It is important to note that most case reports of colitis induced by RTX were either diagnosed as Crohn's disease or ulcerative colitis based on clinical presentation and histology [7-12]. Our patient's histology showed cryptitis and non-caseating granulomas, similar to the pathology found in Crohn's disease. The pathogenesis of RTX-induced colitis may involve the role RTX plays in the depletion of CD20+ B cells. B and T lymphocytes are responsible for the mucosal immunoregulation in the GIT, increasing immune tolerance [11]. The colitis found after RTX may be due to CD20+ B cell depletion and infiltration of T lymphocytes in the mucosa, leading to immune dysregulation [6,11]. We found only one reported case of RTX causing esophagitis [2]. The patient in the case had an esophageal ulcer that was ultimately responsive to steroids after a failed trial of proton pump inhibitors.

During our patient's course, we were able to rule out infectious causes of colitis and esophagitis. Our patient had worsening sinusitis for two days before the presentation. There may have been a possibility that colitis, esophageal ulcers, and worsening sinusitis emerged as a GPA flare after the therapeutic effects of RTX faded. Serology tests, however, were negative for PR3 and anti-myeloperoxidase ANCA. Chest imaging did not reveal any pulmonary parenchymal disease that was indicative of this patient's usual flare. The patient's nodules and lung interstitials were improved. The colonic mucosal biopsy failed to show evidence of

vasculitis or necrosis.

The clinical manifestations of GPA vary greatly. When our patient was initially diagnosed, the GPA symptoms presented as sinusitis, pulmonary nodules, and infiltrates. These symptoms are among the most common presentations in GPA [13]. Gastrointestinal tract (GIT) involvement in GPA is uncommon and can be an elusive presentation in the setting of RTX treatment.

GPA can affect any part of the gastrointestinal tract. Though uncommon, there are reports of patients with GPA presenting with colitis and esophagitis [2,14-17]. Some clinical manifestations include bloody diarrhea, melena, and abdominal pain [15,17]. Endoscopy often reveals the inciting damage along with a biopsy to determine the pathological characteristics of the inflammation. There are only a few reported cases of esophageal involvement with GPA. Similarly, in these cases, patients presented dysphagia, odynophagia, and reflux symptoms [4,16]. Moreover, patients with GPA tend to have evidence of active vasculitis elsewhere and are not just limited to the GIT. In all GPA cases that we reviewed, PR3 ANCA titers were positive [4,14-17].

Conclusions

The etiology of colitis and esophageal ulcers, in this case, is unique. Gastrointestinal manifestations in GPA are rare and all other etiologies, such as treatments and infections, must be ruled out. Exposure to RTX has been shown to cause inflammation in the gastrointestinal tract at variable times of onset. It is important to be aware of the potentially rare side effects of immunosuppressants, as some can mimic the very disease they are intended to treat.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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