CASE STUDY IN GASTROENTEROLOGY & HEPATOLOGY

Fulminant Colitis Following Rituximab Therapy

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Rituximab (RTX; Rituxan, Genentech) is the clinical formulation of a murine immunoglobulin G (IgG) 1 monoclonal anti-CD20 antibody and is widely used in the initial treatment of CD20-positive hematologic malignancies and a variety of autoimmune disorders. Rarely, fulminant colitis has been reported with the use of RTX (Table).[1-7] We report a patient who developed 2 episodes of fulminant colitis after 2 infusions with RTX for the treatment of disseminated B-cell marginal lymphoma. The first episode of colitis required subtotal colectomy, and the second episode required completion proctectomy.

A 62-year-old woman presented in October 2002 with a left lower abdominal wall mass. The patient's peripheral blood smear showed atypical lymphocytes. After an excisional biopsy and histologic and flow cytometry, the patient was diagnosed with marginal zone B-cell lymphoma. The patient was offered a combination treatment of CHOP chemotherapy with RTX or RTX alone. The patient decided to undergo therapy with RTX alone.

After receiving several cycles of RTX therapy from 2002 to 2005 and another 4 doses in September 2005, the patient developed severe abdominal pain and diarrhea. Her stool studies were negative for an infectious etiology. A computed tomography scan showed diffuse wall thickening and distention of the entire colon with areas of pneumatosis. The patient's condition deteriorated and required a subtotal colectomy with ileostomy. Three months later, the ileostomy was closed.

In September 2010, after receiving a second course of 4 cycles of RTX therapy for recurrent lymphoma, the patient developed severe abdominal pain and diarrhea. Her stool studies were again negative for an infectious source. Diffuse severe colitis was noted on a sigmoidoscopy. The biopsies revealed severely inflamed tissue (Figure). The patient's clinical course worsened later, requiring a proctectomy.

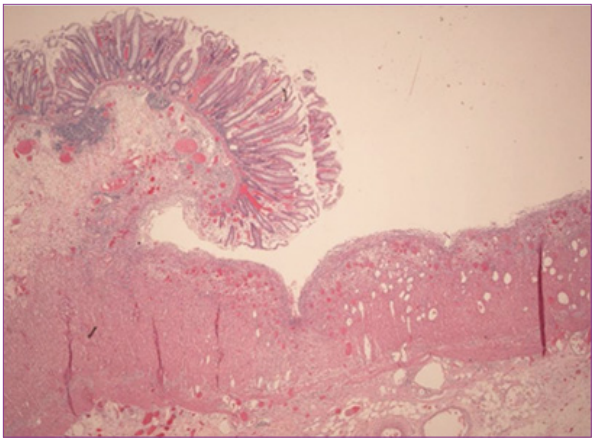

Figure. Colonic mucosa, submucosa, and muscularis propria on the left show the lateral edge of an ulcer on the right that undermines residual mucosa and submucosa. Ulceration extends to the level of the muscularis propria with partial penetration of the ulcer into it (100× magnification, hematoxylin and eosin stain).

Discussion

Recent case reports have cited RTX as a trigger for severe colitis.[1-7] RTX is a murine IgG 1 monoclonal anti-CD20 antibody that has become a successful treatment for several hematologic malignancies. The CD20 antigen is expressed on more than 90% of B-cell lymphomas.[8] B cells regulate a number of immune functions, including production of both cytokines and immunoglobulins as well as antigen presentation.[9-11]

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Table. Cases of RTX and Colitis

Case	Age, Sex	Indication(s)	Treatment(s)/Outcome
1	67, M	Relapse of follicular lymphoma	Subtotal colectomy; died of recurrent bacterial pneumonia 4 months after surgery[1]
2	26, F	Non-Hodgkin lymphoma treatment	Colectomy[2]
3	45, F	Clinical trial for Grave's disease	Mesalamine-induced remission[3]
4	58, M	Long-standing ulcerative colitis unresponsive to corticosteroids, immunosuppressants, and biologics	5-ASA, corticosteroids, and ciprofloxacin; patient suffered from 10-15 loose stools/day and was considered for proctocolectomy[4]
5	4, M	Refractory minimal-change disease nephrotic syndrome	Corticosteroid-induced remission. Eventually, the nephrotic syndrome relapsed[5]
6	34, unknown	Corticosteroid-, cyclophosphamide-, and methotrexate-resistant bullous systemic lupus erythematous	Episode of acute appendicitis with appendectomy. Later developed ulcerative colitis. When RTX was withdrawn, symptoms resolved[6]
7	38, F	Refractory seronegative rheumatoid arthritis	Corticosteroid- and 5-ASA–induced remission[7]
8	62, F	Disseminated marginal zone B-cell lymphoma	Initially patient underwent subtotal colectomy and on subsequent RTX re-exposure patient experienced active proctitis requiring completion proctectomy[a]

5-ASA, 5-aminosalicylic acid; F, female; M, male; RTX, rituximab. [a]The current case.

The normal mucosal immunity of the gastrointestinal tract maintains an equilibrium between proinflammatory and anti-inflammatory stimuli from the innate immune system, T cells, B cells, and their associated cytokines. Although the complete pathogenesis of ulcerative colitis (UC) is not understood, the presence of antigoblet cell antibodies, perinuclear antineutrophil cytoplasmic antibodies, and antihuman tropomyosin 5 hints toward B-cell involvement.[12] RTX was reported to exacerbate UC in a patient with refractory disease, leading to a hypothesis that B cells may play a protective role.[4] Mizoguchi and colleagues revealed that B-cell–depleted T-cell receptor alpha mu double-knockout mice developed severe colitis.[13] B cells produce interleukin-10, a regulatory cytokine that maintains immune equilibrium and prevents the development of autoimmune disease.[14,15] B cells in gut-associated lymphoid tissue were shown to protect against autoimmune disease through the promotion of transforming growth factor beta and interleukin-4 in mice.[16] B-cell regulation of CD4 T-cell activity or B-cell effect on mucosal clearance of apoptotic cells plays a role in the development of inflammatory bowel disease in murine models.[17,18] B-cell depletion may lead to T-regulatory cell dysfunction with subsequent stimulation of autoreactive T cells.[19] This disequilibrium of the innate immune system of the gastrointestinal tract may lead to the activation of cytotoxic T cells and colitis in susceptible RTX patients. In corticosteroid-refractory UC, RTX was well tolerated with no reported cases of fulminant colitis; however, RTX failed to show a significant effect on inducing remission in 24 UC patients in a double-blind, randomized, controlled trial.[20]

In conclusion, RTX therapy is extensively used in a variety of hematologic malignancies and autoimmune diseases, but acute severe colitis is an underappreciated complication. B cells have both an inflammatory and anti-inflammatory function in humans, and disruption of this equilibrium in susceptible individuals may result in severe colitis.

The authors have no relevant conflicts of interest to disclose.

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