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【 CASE REPORT 】

Rituximab-induced Ileocolitis in a Patient with Gastric MALToma: A Case Report and Literature Review

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Abstract:
Rituximab (RTX) is effective for treating cancer, but reports of RTX-associated enterocolitis are limited. We herein report the case of a 65-year-old man who developed RTX-induced ileocolitis. He was diagnosed with gastric mucosa-associated lymphoid tissue lymphoma (MALToma) and treated with RTX. He complained of bloody diarrhea after RTX. Mucosal inflammation on colonoscopy indicated RTX-induced ileocolitis. He was treated with corticosteroids, and his symptoms improved. We reviewed the RTX-associated gastrointestinal adverse events and classified the features into ulcerative colitis, Crohn's disease, microscopic colitis, and ileocolitis. To our knowledge, this is the first case of a Japanese patient who developed RTX-induced ileocolitis.

Key words: rituximab, ileocolitis, MALToma, B cells, T cells, inflammatory bowel disease

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Introduction

Rituximab (RTX), the anti-cluster of differentiation (CD)20 chimeric antibody, depletes both CD19-positive and CD20-positive B cells via various mechanisms (1). This B-cell depletion therapy is effective for treating CD20-positive hematological malignancies, including mucosa-associated lymphoid tissue lymphoma (MALToma), non-Hodgkin lymphoma, and chronic lymphocytic leukemia (2); as well as autoimmune disorders, including rheumatoid arthritis, multiple sclerosis, and nephrotic syndrome.

Gastric lymphomas are classified into mainly MALToma and diffuse large B cell lymphoma, accounting for over 95% of cases, with others including follicular lymphoma, Mantle lymphoma, etc. Among MALTomas, gastric MALToma is primarily induced by *Helicobactor pylori* infection. Therefore, the first-line therapy is *H. pylori* eradication (3). When first-line therapy fails, chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and/or RTX are considered as second- or third-line therapy in advanced cases. In addition, radiation therapy is also considered for low-grade primary gastric MALToma.

RTX is well-tolerated in most cases. However, relatively rare and late-onset adverse events have been reported, including gastrointestinal tract issues (4, 5). Among patients who received RTX and underwent colonoscopy, 4% were reported to develop RTX-associated colitis (4).

A diagnosis of biologics-induced enterocolitis is based on clinical manifestations, the endoscopic appearance, and histological features. The endoscopic features of immunosuppressive agent-induced enterocolitis have been reported to include ulcerative colitis (UC) (6) and Crohn's disease (7). Microscopic colitis (MC) (8) and ileocolitis induced by RTX (9) have also been reported. To date, only 35 cases of RTX-associated enterocolitis have been reported.

To our knowledge, this is the first reported case of a Japanese man who received RTX for gastric MALToma, developed ileocolitis, and was successfully treated with corticosteroids (CSs).

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Table. **Laboratory Examination Findings.**

Peripheral blood		Biochemistry		Hormone and tumor markers		Viral antibodies	
WBC	10,680 U/μL	TP	7.3 g/dL	TSH	1.16 μIU/mL	CMV-Ag	negative
neutrophils	67.8 %	Alb	4.2 g/dL	free T3	2.24 pg/mL	HIV	negative
lymphocytes	20.0 %	AST	13 U/L	free T4	1.18 pg/mL		
monocytes	12.1 %	ALT	10 U/L	sIL-2R	962 U/mL		
eosinophils	0.0 %	LDH	128 U/L				
basophils	0.1 %	Cr	0.63 mg/dL				
RBC	467 U/μL	BUN	5.9 mg/dL				
Hb	12.3 g/dL	Na	138 mEq/L				
Plt	25.7 U/μL	Cl	98 mEq/L				
ESR	36 mm/h	K	3.9 mEq/L				
		CRP	1.2 mg/dL				

WBC: white blood cell count, RBC: red blood cell count, Plt: platelets, ESR: erythrocyte sedimentation rate, TP: total protein, Alb: albumin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, Cr: chromium, BUN: blood urea nitrogen, Na: sodium, Cl: chlorine, K: potassium, CRP: C-reactive protein, TSH: thyroid-stimulating hormone, sIL-2R: soluble form of interleukin 2 receptor, CMV: cytomegalovirus, HIV: human immunodeficiency virus

Case Report

A 65-year-old man was referred to the Department of Gastroenterology at our hospital complaining of bloody diarrhea after RTX therapy for gastric MALToma.

Related medical history and presentation of current illness

He had a history of gastric ulcer with *H. pylori* infection, which was treated with the standard triple eradication regimen (amoxicillin/clarithromycin/lansoprazole).

He was diagnosed with gastric MALToma following a histological examination of the biopsy specimens from the antral gastric ulcer 4 years after *H. pylori* eradication. He was admitted to the hematology unit at our hospital. Bone marrow aspiration revealed no lymphoma cells. He was diagnosed with stage IV lymphoma under both the Ann Arbor classification and Lugano International classification due to metastasis in the cervical, subclavian, and mesenteric lymph nodes, as evaluated by computed tomography (CT), abdominal ultrasound, magnetic resonance imaging, and positron emission tomography (PET)-CT.

He was treated with four courses of RTX monotherapy with subsequent treatment of yttrium-conjugated ibritumomab tiuxetan (genetic recombination) and exhibited a partial response (PR). However, four months after the PR, follow-up PET-CT indicated the recurrence of lymphoma in the right cervical lymph nodes. He was treated with another four courses of RTX as the second-line therapy, which resulted in a complete response as evaluated by enhanced CT (data not shown). He complained of watery diarrhea occurring 20 times/day and bloody stool 2 days after the commencement of the second-line RTX therapy. No disease-related family history was reported.

Physical examination findings

A physical examination revealed no anemia, superficial lymph node swelling, or abdominal abnormalities.

Laboratory examination findings

The laboratory examination findings are presented in Table. A blood examination revealed leukocytosis (white blood cell count of 10,680/μL), mild anemia (Hb, 12.3 g/dL), hypersensitive C-reactive protein (CRP) (1.2 mg/L), a high erythrocyte sedimentation rate (ESR) (36 mm/h), cytomegalovirus (CMV) negativity, and human immunodeficiency virus (HIV) negativity. Biochemistry demonstrated no abnormality. His serum interleukin (IL)-2 level was 962 U/mL. The fecal occult blood test was positive. In addition, the fecal culture detected no significant microbiome (bacteria: negative).

Imaging and endoscopic examination findings

Contrast enhanced-CT revealed consecutive circumferential hypertrophy in the terminal ileum through the rectum (Fig. 1). Reddish changes with multiple erosions in gastric antrum were observed by esophagogastroduodenoscopy (EGD) in January 201X before RTX monotherapy with subsequent treatment of yttrium-conjugated ibritumomab tiuxetan treatment (Fig. 2A). A pathological examination with biopsy specimens from the gastric antrum revealed MALToma. EGD revealed atrophic gastritis after *H. pylori* eradication, whereas ileocolonoscopy (ICS) revealed mild reddish mucosa in the terminal ileum (Fig. 2B), which differed from diffuse consecutive backwash ileitis as occasionally observed in severe UC. ICS showed scattered aphtha and diffuse consecutive inflammation throughout the transverse colon with normal mucosa in some regions (Fig. 2C). In addition, ICS revealed severe erosion and diffuse consecutive inflammation throughout the sigmoid colon and rectum (Fig. 2D).

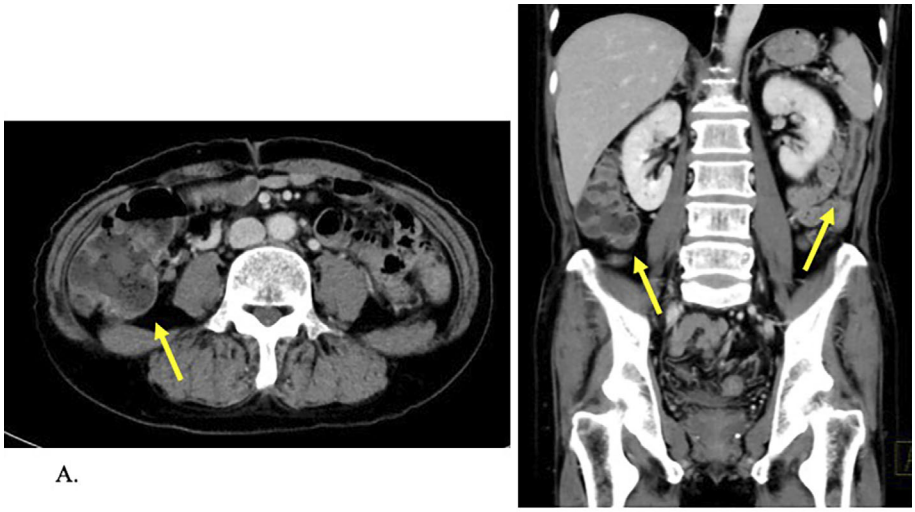

Figure 1. **A, B: Contrast-enhanced computed tomography revealed continuous circumferential hypertrophy from the terminal ileum to the rectum.**

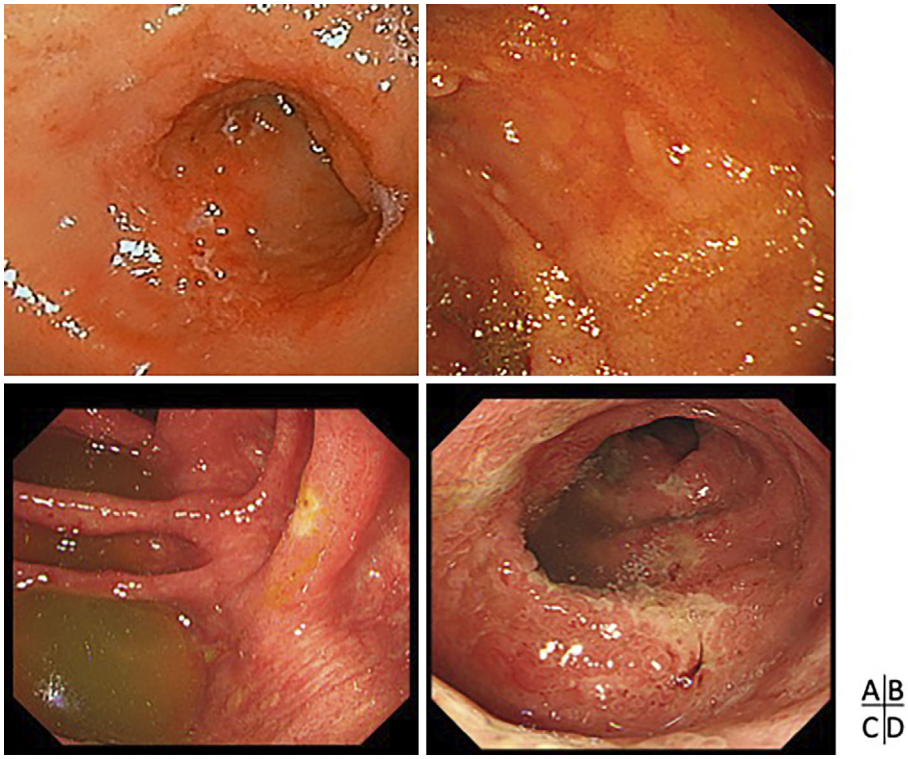

Figure 2. **Esophagogastroduodenoscopy (EGD) and ileocolonoscopy findings. A: Reddish changes with multiple erosions in the gastric antrum in January 201X before R-CHOP treatment. B: Ileocolonoscopy (ICS) revealed mild reddish mucosa in the terminal ileum. C: ICS revealed scattered aphtha and diffuse consecutive inflammation throughout the transverse colon. D: ICS revealed severe erosion and diffuse consecutive inflammation throughout the sigmoid colon and rectum.**

Histological examination findings

Hematoxylin and Eosin (H&E) staining of specimens from the colonic mucosa revealed that plasma cells were dominant in this segment (Fig. 3A), which was consistent with descriptions of RTX-induced colitis in the literature (10).

H&E staining of the colorectal mucosa demonstrated diffuse and circumferential erosions, epithelial atrophy, goblet cell reduction, and extensive intestinal inflammation. Furthermore, cryptitis and crypt abscess, but not granuloma, were observed in the colonic mucosa. Cytomegalovirus and pathogenic bacteria were not detected in biopsy specimens. In addition, the ileal erosion specimens indicated lympho-

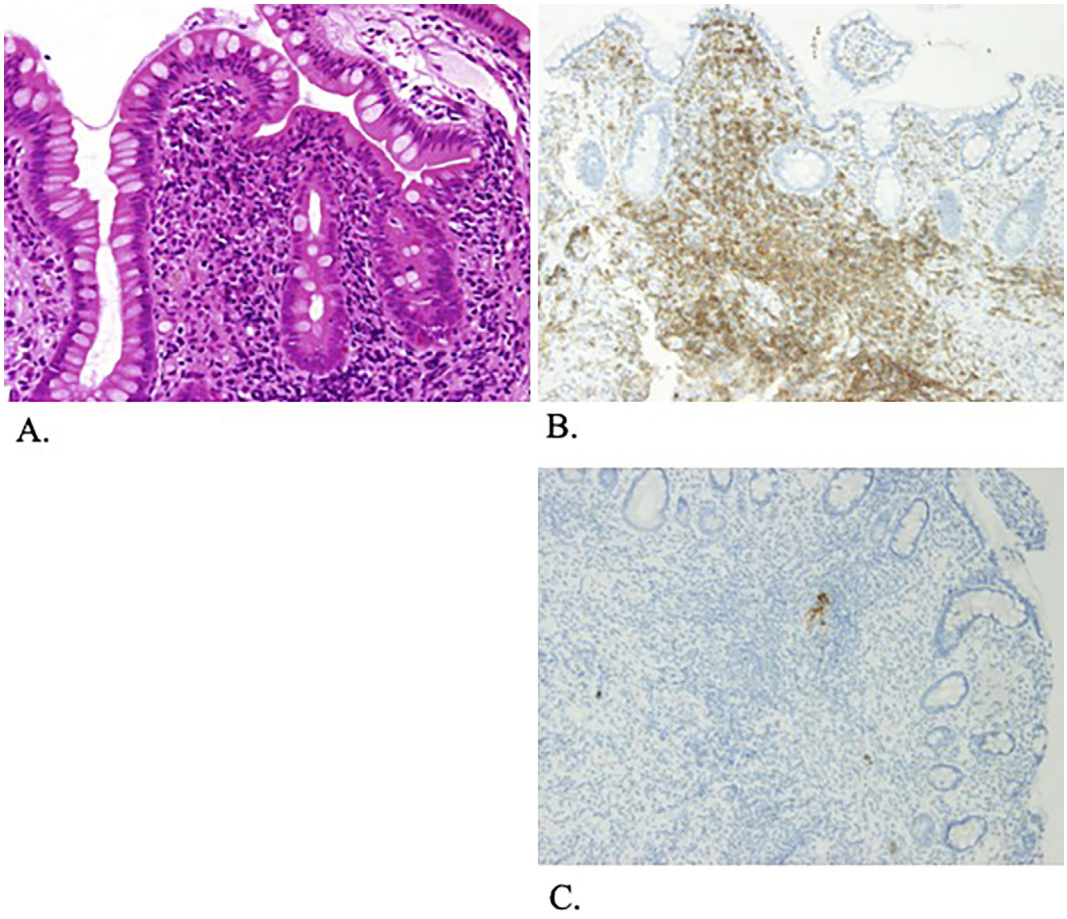

Figure 3. **Histopathological and immunohistochemical findings in colonic mucosa specimens (before treatment) (×100). A: Hematoxylin and Eosin staining of the specimens from the colonic mucosa exhibited diffuse and circumferential erosions, epithelial atrophy, goblet cell reduction, and extensive intestinal inflammation. Furthermore, cryptitis and crypt abscess but not granuloma were observed in the colonic mucosa. B: Immunohistochemistry demonstrated increased CD3+ lymphocytes. C: The complete depletion of CD20+ lymphocytes in the colonic mucosa was demonstrated.**

cyte infiltration, and these lymphocytes had little atypia (data not shown). Although the presence of a thickened subepithelial collagen band and marked increase in intraepithelial lymphocytes (IELs) were not evaluated, microscopic colitis (MC) was denied, as MC shows endoscopically normal mucosa, in contrast to the present findings.

Immunohistochemistry demonstrated increased CD3-positive lymphocytes and complete depletion of CD20-positive lymphocytes in the colonic mucosa (Fig. 3B, C). In addition, specimens from the ileal erosions revealed CD3+T lymphocytes>CD79alpha+B lymphocytes infiltration. Furthermore, κ and λ chains were equivalent, suggesting no residual MALToma cells.

Differential diagnoses

Crohn's disease, Behçet's disease (BD), non-steroidal anti-inflammatory drug (NSAID)-induced ulcers, and infectious colitis, including bacterial, tuberculosis, and viral colitis, were considered as differential diagnoses.

The final diagnosis

Crohn's disease was excluded due to the absence of longitudinal ulcers or a cobblestone appearance. BD was excluded because no typical round ulcers were observed in the terminal ileum, and the BD diagnostic criteria were not met. The patient had no recent history of NSAID intake. The diagnosis of RTX-induced ileocolitis in the presented patient was thus confirmed based on the clinical, radiological, endoscopic, and histological criteria.

Treatment

The patient was treated with CSs (prednisolone) at a dose of 50 mg/day for 2 weeks. Subsequently CSs were tapered by 5 mg/2-3 weeks (Fig. 4).

Outcome and follow-up

The reported bloody diarrhea gradually improved despite CS tapering, and the symptoms had completely disappeared by three months' treatment with CSs. The mucosal and submucosal inflammation (Fig. 5) after additive CS treatment

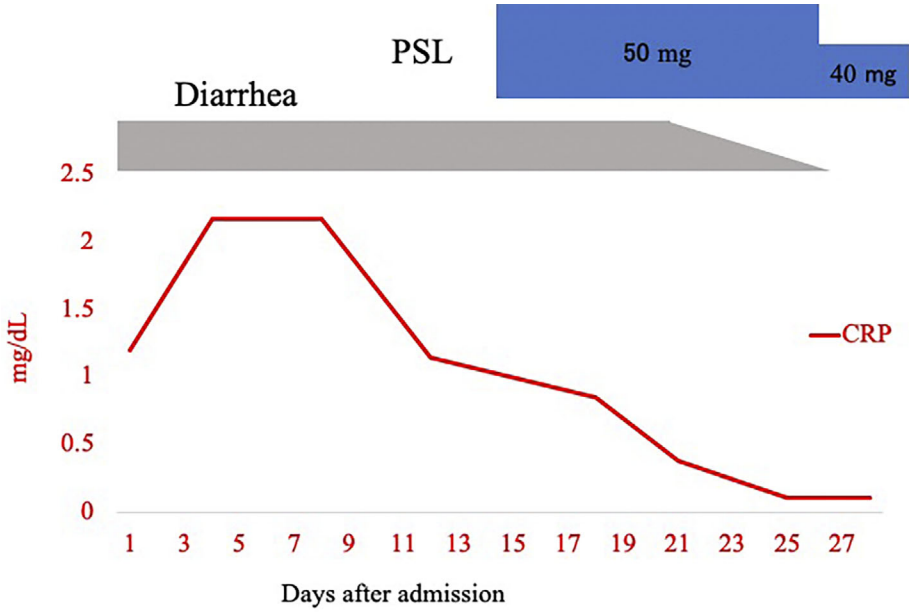

Figure 4. **Clinical findings. The clinical findings indicate that corticosteroid therapy was effective in ameliorating diarrhea and reducing inflammatory markers. PSL: prednisolone**

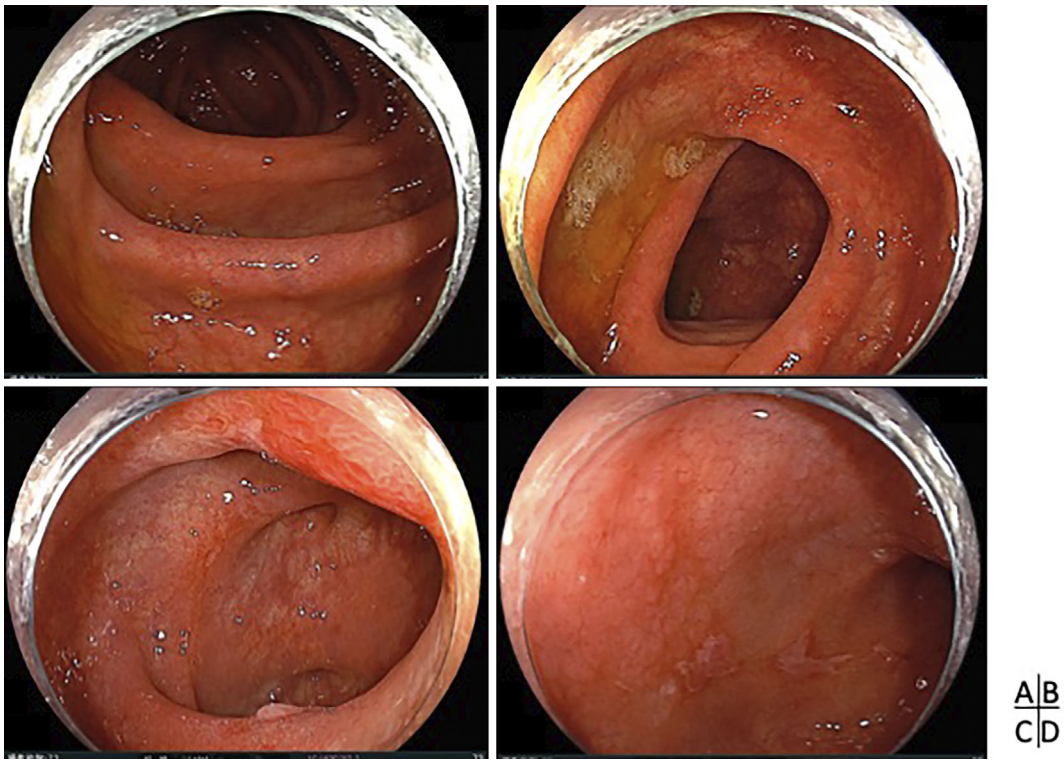

Figure 5. **Endoscopy findings. The endoscopic appearance of mucosal inflammation improved after 5-month corticosteroid treatment. A: Ascending colon, B: transverse colon, C: sigmoid colon, and D: rectum.**

for two months had improved by five months after the start of CS therapy (Fig. 6). At the time of writing, gastric MALToma had not recurred. However, the swelling cervical lymph node was biopsied to reveal the CD30-positive, CD15-positive, pax-5-positive, and EBER-positive lymphoma. The patient was diagnosed with Hodgkin's lymphoma. Two cycles of an ABVD regimen and three cycles of Brentuximab vedotin therapy were administered, and complete remission was achieved. No recurrence had been observed at the time of writing this report.

Discussion

We herein report the case of a Japanese man who pre-

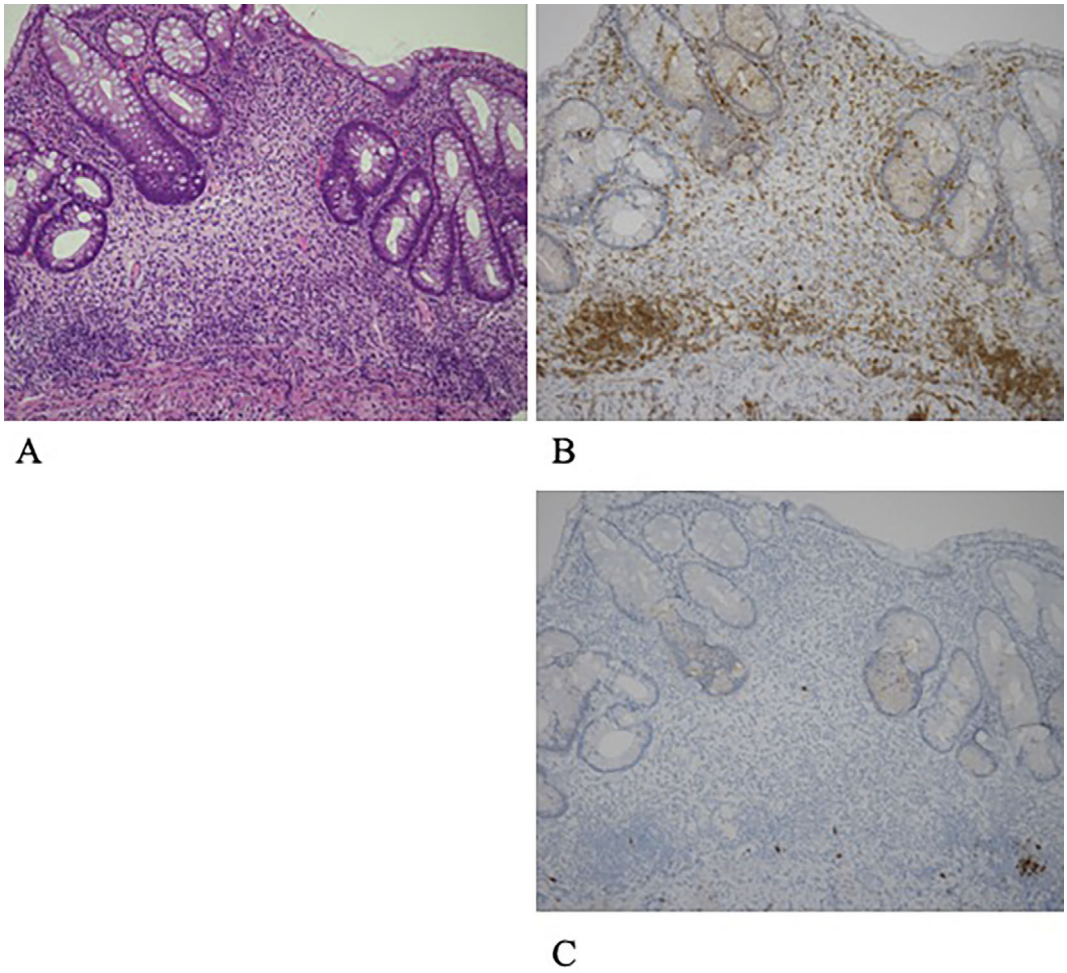

Figure 6. Histopathological and immunohistochemical findings (after treatment) (×100). A: Hematoxylin and Eosin staining of the colonic specimens after additive corticosteroid treatment demonstrated a significant reduction in the number of infiltrating inflammatory cells. B: Immunohistochemistry for CD3+ cells indicated a reduction in the infiltration of T cells. C: Immunohistochemistry for CD20+ cells demonstrated the recovery of the scattered infiltration of B cells in colonic mucosa.

sented with RTX-induced ileocolitis. The patient had been treated for gastric MALToma with four courses of RTX monotherapy with subsequent treatment of yttrium-conjugated ibritumomab tiuxetan (genetic recombination) and exhibited a partial response because the swelling of the right cervical lymph nodes remained, which was indicated by follow-up PET-CT. He was treated with an additional four courses of RTX as third-line therapy, which resulted in a complete response. Thereafter he presented with severe watery diarrhea approximately five months (five doses) after the commencement of the first round of RTX with yttrium-conjugated ibritumomab tiuxetan therapy. The median period and median doses of RTX administered between the first RTX exposure and onset of diarrhea has been reported to be 8 months (4.5-29 months) and 6 doses (5-12 doses), respectively (8); therefore, the median time and administered doses in our case were consistent with those reported previously.

Our patient was 65 years old at the diagnosis. Eckmann et al. reported that the median age of patients diagnosed with inflammatory bowel disease (IBD) after RTX was 52.5 years old (8), which is older than the susceptible age of IBD in the general population, suggesting that the pathogenesis of RTX-associated colitis differs from that of IBD.

Colonoscopy demonstrated moderate-to-severe ileitis and pancolitis. His ileitis resembled Crohn's disease in terms of scattered erosions, and the colitis was similar to UC in terms of the diffuse consecutive circumferential inflammation from the cecum to the rectum. However, no longitudinal ulcers, cobblestone appearance, or skip lesions were observed in the intestine. In addition, the colitis in our patient differed from typical UC in that there was sparse visible vasculature throughout the colon and rectum. Furthermore, the surface appearance of the inflammatory colonic mucosa in this patient indicated the aggregation of small granules. However, small white hues representing cryptitis or crypt abscess are typical findings in UC. Therefore, there is a discrepancy in the mucosal appearance between this patient and typical UC patients. Colonoscopy revealed no punched-out ulcers in the terminal ileum or aphthoid lesions in the colon. Taken together, the colonoscopy findings indicated that our patient did not exhibit typical Crohn's disease, UC, or BD features.

A histological examination of the colonic biopsy specimens demonstrated epithelial atrophy and inflammatory cell infiltration composed of lymphocytes and plasma cells in the epithelium and lamina propria in the focal area. Immunohistochemistry revealed that these infiltrated cells were primarily CD3-positive T cells. CD20-positive B cells were depleted both immediately after RTX treatment and five months after treatment. Ardelean et al. reported a case of RTX-induced severe UC with the infiltration of mature CD3 T cells, cytotoxic CD8 T cells, and forkhead box P3 gene+ regulatory T cells, suggesting that their case was an adverse effect of RTX (11). This evaluation might confirm that the inflammation in the terminal ileum and colon in our case was also an adverse effect of RTX. Although the CD68+ histiocytes and CD68+ small granuloma in the lamina propria suggest the diagnosis of Crohn's disease (7), this finding is not specific to Crohn's disease. In addition, no multinucleate giant cell granuloma, which is typically observed in Crohn's disease, was found in our case. CMV was negative in the biopsy specimens.

Eckmann et al. reported nine cases of MC induced by RTX (8). Collagenous colitis and lymphocytic colitis are included in MC. However, collagen bands in the submucosa and an increase in intraepithelial lymphocytes were not observed in our case, suggesting this was not a case of MC.

With regard to the diagnosis, infectious enterocolitis, including bacterial, viral, and tuberculosis, and the recurrence of MALToma were excluded based on the findings of culture and a histopathological examination. Although yttrium-conjugated ibritumomab tiuxetan might induce or affect ileocolitis, no case of yttrium-conjugated ibritumomab tiuxetan-induced ileocolitis has been reported. Given the present findings, we diagnosed the patient with RTX-induced T cell-mediated ileocolitis.

RTX therapy induced complete depletion of both peripheral and intestinal CD19+ and CD20+ B cells (12). Thereafter, the patient may have developed T cell-mediated intestinal inflammation manifesting as ileocolitis. RTX reportedly exacerbates UC, and B cells can modulate T cell proliferation or activation and induce anti-inflammatory effects via B cell-T cell interaction, as demonstrated by the recovery of mucosal regulatory T cells with the adaptive transfer technique in B cells (13). In our case, the complete depletion of B cells might have caused the downregulation of regulatory cytokines, such as IL-4, transforming growth factor-beta secreted from B cells in gut-associated lymphoid tissue and leading to the upregulation of inflammatory cytokines by activated T cells.

A total of 35 cases of UC, Crohn's disease, MC, and ileocolitis induced by RTX have been reported. Thirteen patients had RTX-induced UC (6, 8, 11, 14), 11 had RTX-induced Crohn's disease (7, 8, 15, 16), 9 had RTX-induced MC, and patients had ileocolitis (9), including our case.

The reason why different RTX-induced diseases (i.e., UC, Crohn's disease, MC, and ileocolitis) present in different patients has not been clarified. However, the loss of B cells might have caused cellular immune dysregulation, followed by the activation of cytotoxic T cells. Indeed, the association of RTX and ileocolitis or enterocolitis was suggested in one study demonstrating the development of severe colitis in B-cell-depleted double-knockout mice (17). In addition, one of the immunosuppressive roles of B cells is the control of pathogenic CD4+ T cells via the production of the regulatory cytokine IL-10 (10, 17) and the regulation of circulating self-antigens in autoimmune diseases, such as IBD. Therefore, one potential mechanism is that the depletion of B cells induced regulatory T cell dysfunction and the activation of cytotoxic T cells, resulting in mucosal damage. The differential magnitude of the suppression of regulatory T cells and the activation of Th1 and Th17 induced by B cell depletion after RTX may lead to differences in both the degree of inflammation and affected region in the intestinal mucosa. Determining this mechanism may clarify the pathogenesis of IBD.

Why ileocolitis did not occur when RTX was used in the first line but did occur when used in the third line remains unclear. However, the accumulation of damage to the ileocolic mucosa or additive damage of the combination with yttrium-conjugated ibritumomab tiuxetan may be involved.

Treatments for RTX-induced enterocolitis have not yet been established. However, several agents suggested in the IBD guideline, such as 5-ASA, CSs, azathioprine, and biologics were effective in some cases. Indeed, Shahmohammadi et al. reported that the concomitant use of 5-ASA and CSs was effective in 43% (3/7) of patients (6). Biologics can be added because the efficacy of ustekinumab for RTX-induced Chron's disease has been reported (18).

CSs were effective in our case; however, after ileocolitis remission and B cell recovery in the intestinal mucosa, the MALToma recurred, which is consistent with the case of recurrent autoimmune hepatitis reported by Shahmohammadi et al. and NS reported by Ardelean et al. (6, 11). Medications other than RTX may be added if they are confirmed to be effective for controlling the original diseases.

Conclusion

We herein report what is to our knowledge the first case of a Japanese man treated with RTX who developed ileocolitis diagnosed by endoscopy and histological findings and was successfully treated with CSs. RTX-induced ileocolitis should be considered as a differential diagnosis for patients experiencing bloody stool or watery diarrhea after RTX treatment. Furthermore, we should accumulate cases to establish diagnostic criteria and the ideal treatment for RTX-induced ileocolitis.

The authors state that they have no Conflict of Interest (COI).

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