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A Case of Right-Sided Ulcerative Colitis with Mesalamine-Induced Hypersensitivity Reactions

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 56
Final Diagnosis: Right-sided ulcerative colitis • mesalamine-induced hypersensitivity
Symptoms: High fever • vague discomfort of the upper abdomen
Medication: Mesalamine
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology

Objective: Unusual clinical course

Background: Ulcerative colitis (UC) is a chronic inflammatory bowel disease, affecting the colon continuously from the rectum proximally. However, a clinical type with right-sided colitis sparing the anal side of the colon is also known. Mesalamine, which is generally used to treat UC, can rarely aggravate the disease.

Case Report: A 56-year-old woman with no history of colonic diseases visited our hospital because of a positive fecal occult blood test. The first colonoscopy showed inflamed and edematous mucosa extending from the ascending colon to the right-half of the transverse colon. Colonic biopsy specimens demonstrated infiltrations of chronic inflammatory cells in the mucosa and crypt abscesses, but no epithelioid granulomas, compatible with UC. She was highly positive for PR3-ANCA, confirming the diagnosis of UC. After starting mesalamine, she had hypersensitivity reactions and aggravations of UC, which were confirmed endoscopically.

Conclusions: Right-sided colitis may be a subgroup of UC, and this is the first report of this type of disease complicated by aggravation due to mesalamine hypersensitivity.

MeSH Keywords: Antibodies, Antineutrophil Cytoplasmic • Colitis, Ulcerative • Colon, Ascending • Drug Hypersensitivity • Mesalamine

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Background

Ulcerative colitis (UC) is an idiopathic, chronic inflammatory bowel disease in which the inflammation is mainly located in mucosal layers, affecting the bowel continuously from the rectum to the proximal side [1,2]. The Montreal classification divides the extent of UC into 3 types: E1 (proctitis), E2 (left-sided; distal), and E3 (pancolitis) [2]. However, it has been known that some patients with proctitis or left-sided colitis have a cecal patch of inflammation [3,4], and UC with right-sided or segmental colitis with no recto-sigmoid inflammation has been reported [5,6]. Mesalamine and other 5-aminosalicylic acid (5-ASA) compounds are mainstay drugs for induction and maintenance treatment of UC because of their safety and usefulness [7]. However, it is known that mesalamine-induced hypersensitivity reactions can occur and cause aggravation of UC [8,9]. In this report, a case of UC that presented with right-sided colitis complicated by aggravation due to mesalamine-induced hypersensitivity reactions is described. Moreover, changes in the endoscopic findings of mesalamine-induced hypersensitivity reactions are also presented.

Case Report

A 56-year-old woman with no history of UC visited our hospital because of a positive fecal occult blood (FOB) test. She had felt vague discomfort in her upper abdomen for the past few years. However, she had no bloody mucoid diarrhea, abdominal pain, or fever. On examination, there were no abdominal findings except for mild tenderness of the right upper quadrant. Routine laboratory tests were normal other than slight elevation of inflammatory markers, with the erythrocyte sedimentation rate (ESR) at 58 mm/h and C-reactive protein (CRP) of 0.47 mg/dL. The first colonoscopy showed that inflamed and edematous mucosa was confined from the ascending to the right-half of the transverse colon, with mucosal friability, multiple shallow ulcerations, erosions, erythema, and loss of typical vascular patterns (Figure 1). Patchy inflammation in other lesions or backwash ileitis was not seen. There were no significant bacteria on stool culture results. Colonic biopsy specimens of the inflamed mucosa demonstrated infiltrations of chronic inflammatory cells in the lamina propria, cryptitis, crypt abscesses, and architectural distortions, but there were no epithelioid granulomas, which were pathologically compatible with UC (Figure 2). The rectum and left-sided colon with intact colonoscopic findings did not show any inflammation on histological examination (data not shown).

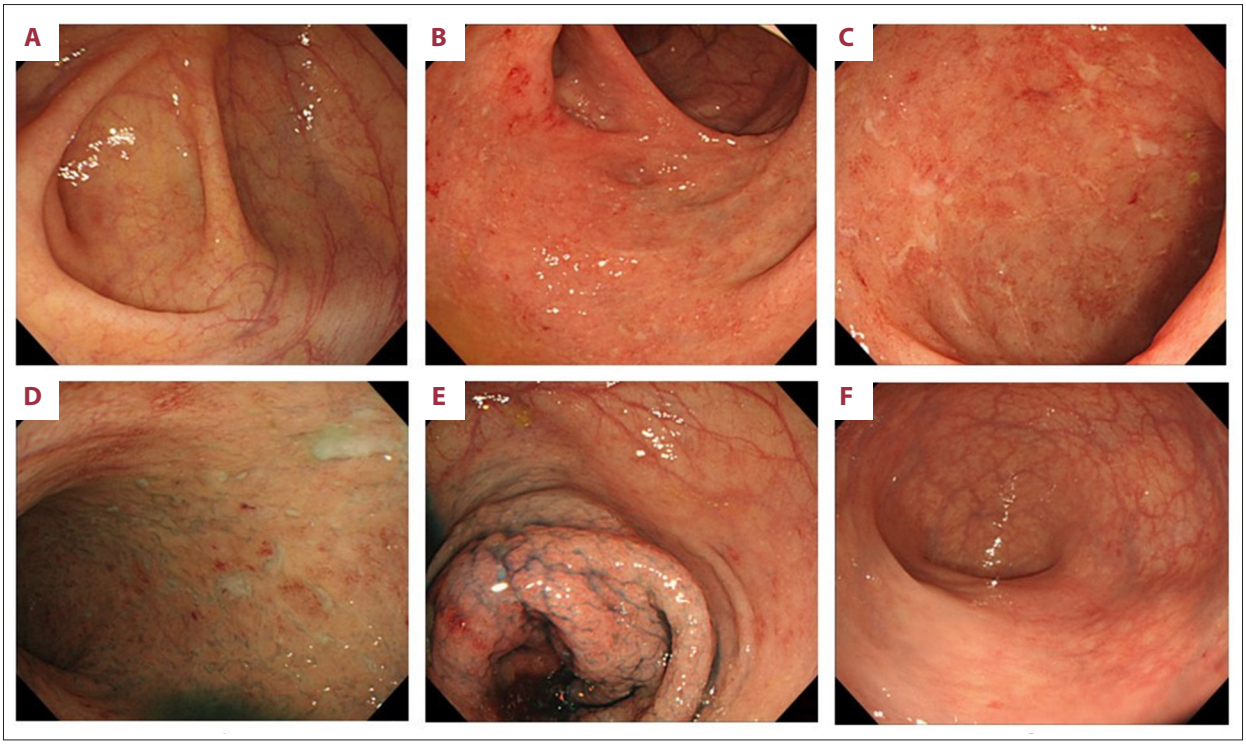

Figure 1. Representative lesions on colonoscopy 1. (**A**) No inflammation at the cecum and the appendiceal orifice. (**B–D**) Mucosal friability, multiple shallow ulcerations, erosions, erythema, and loss of typical vascular patterns are seen at the ascending colon and the right-half of the transverse colon. (**E**) The border between the inflamed and normal mucosa, with indigo carmine dye spraying at the right-half of the transverse colon. (**F**) No inflammation at the rectum.

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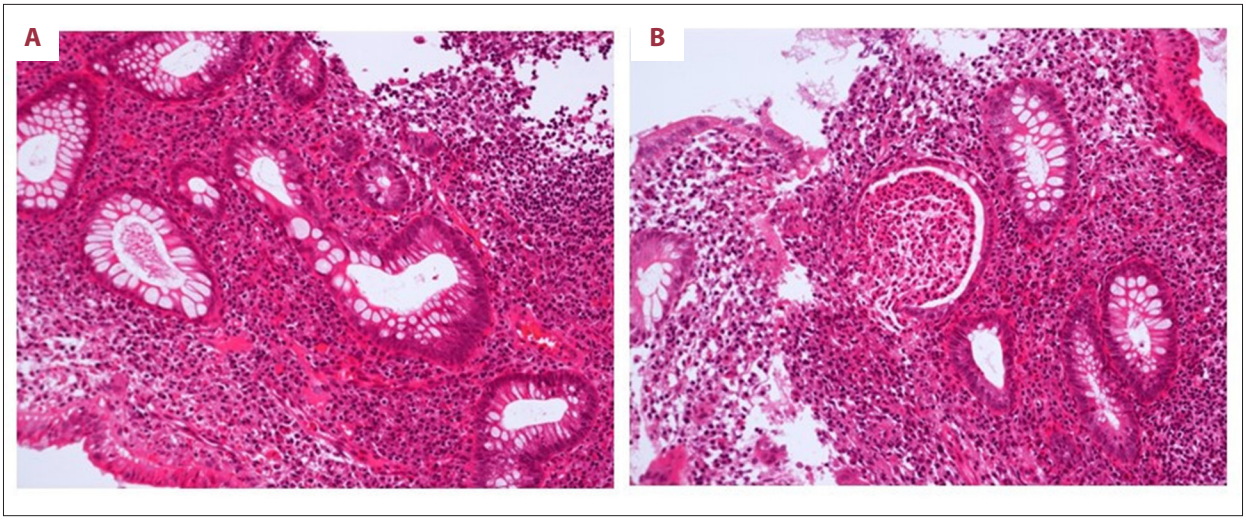

Figure 2. Microscopic features of a biopsy specimen at colonoscopy 1. (**A**) High-power view of the histological features of the biopsy specimen from the active colitis of the transverse colon shows a diffuse mononuclear inflammatory infiltrate in the lamina propria and architectural glandular distortion. (**B**) The right-half of the transverse colon shows a diffuse mononuclear inflammatory infiltrate in the lamina propria and a crypt abscess (H and E stain, ×100).

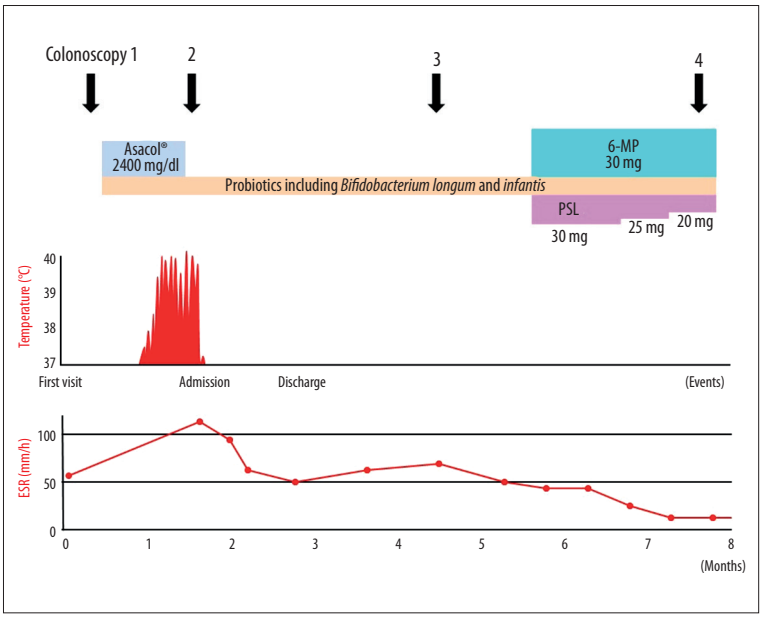

Figure 3. The clinical course of the patient. Body temperature and ESR improved immediately after the withdrawal of mesalamine. In particular, ESR improved after the introduction of PSL and 6-MP.

Therefore, the right-sided colitis type of UC was diagnosed. The activity of UC was evaluated by the Mayo scoring system [10], which resulted in a score of 3. Mesalamine (Asacol® tablets; Tillotts Pharma AG, Ziefen, Switzerland) at 2400 mg/day was then started (Figure 3). However, approximately 1 week later, a slight fever occurred, and it increased to over 39°C in an intermittent manner. Exacerbation of the diarrhea and abdominal pain did not occur. She was admitted to our hospital 16 days after the start of mesalamine treatment. Although physical examination on admission only showed high fever and mild tenderness of the right upper quadrant, as at the first examination, no other abdominal symptoms or drug allergy findings such as a skin rash could be seen. Blood examinations showed higher levels of inflammation markers, with the ESR at 119 mm/h and a CRP of 18.3 mg/dL. Eosinophilia was not observed (4% of 5.73×10^9/L white blood cells). However, liver and pancreatic enzyme levels were normal. With a normal level of serum procalcitonin and negative results on blood culture and for cytomegalovirus (CMV) antigenemia, infections were ruled out. Although anti-nuclear antibody (ANA) and myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) were negative, proteinase-3 ANCA (PR3-ANCA) was positive (55.2 U/mL, CLEIA method, SRL Inc, Tokyo, Japan). Primary sclerosing cholangitis (PSC) was not seen on magnetic resonance

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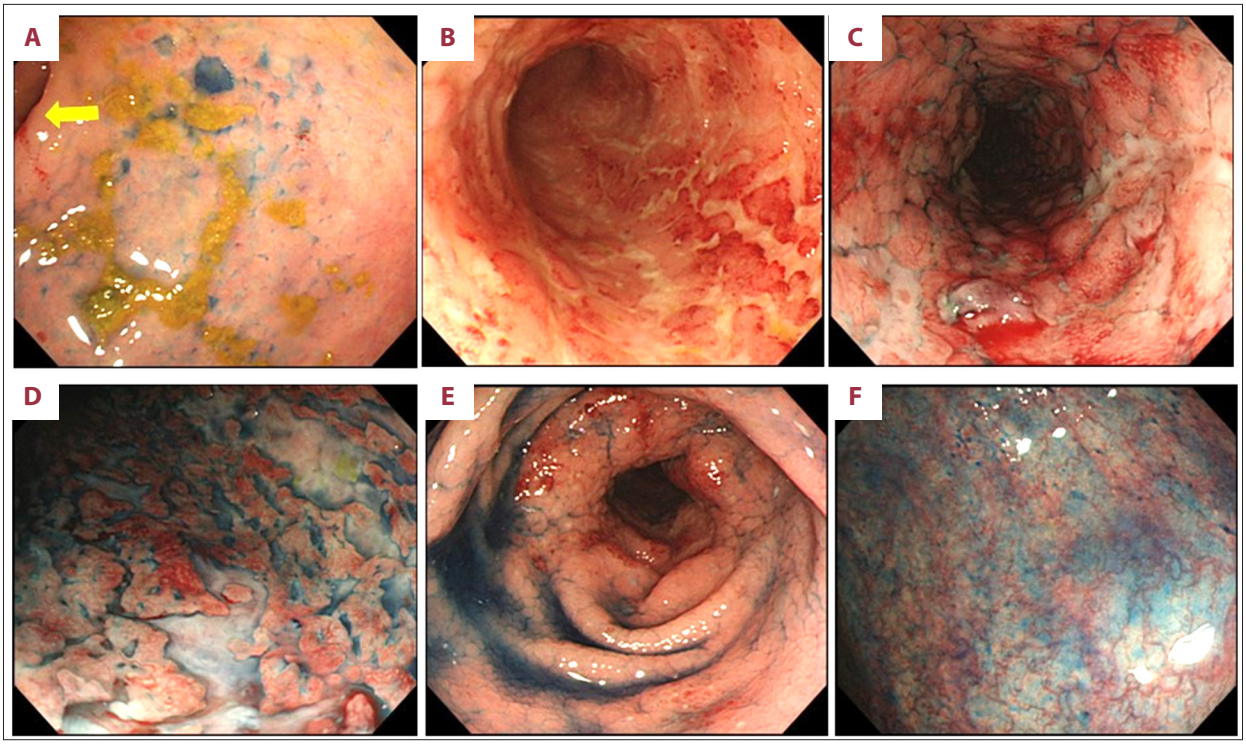

Figure 4. Colonoscopy 2. (**A**) Scattered erosions appear in the cecum and around the appendiceal orifice (arrow). (**B, C**) Aggravation of inflammation in the ascending colon showing more edema, purulent erosions, and an increased number of deeper multiple ulcerations. (**D**) Inflammation of the right-half of the transverse colon has also worsened, showing an increased number of deeper ulcerations. (**E**) The border between severe and mild inflamed mucosa in the right-half of the transverse colon is observed. (**F**) Similar to the cecum, scattered erosions appear in the left-half of the transverse colon.

cholangiopancreatography (MRCP). On the basis of these results, mesalamine-induced hypersensitivity reactions were suspected. A lymphocyte transformation test (LTT) for mesalamine showed a positive result (220 cpm, 207%; control 106 cpm). Therefore, the diagnosis was right-sided or segmental colitis type UC with mesalamine-induced hypersensitivity reactions. Mesalamine treatment was immediately withdrawn, and a second colonoscopy was performed (Figure 4). It showed more intensely inflamed mucosa at the same inflamed colonic segments as at the first colonoscopy, from the ascending colon to the right-half of the transverse colon, with more edematous mucosa, bowel stenosis, and much more purulent erosions and ulcerations. In addition, mucosal inflammation expanded toward the oral and anal sides. Scattered erosions appeared in the cecum and around the appendiceal orifice and in the left-half of the transverse colon. However, the left-sided colon from the descending colon to the rectum showed no inflammation, as before. Histopathologic examination of biopsy specimens of the inflamed mucosa showed more severe inflammation (data not shown). After drug withdrawal, the high fever and inflammatory findings disappeared promptly. Only probiotics including *Bifidobacterium longum* and *infantis* were then prescribed. After discharge, the patient still felt vague discomfort of her right upper abdomen. Three months after withdrawal of mesalamine treatment, a third colonoscopy was done as follow-up (Figure 5). It showed that the inflamed mucosa was again restricted from the ascending colon to the right-half of the transverse colon, and the inflammation of the mucosa was ameliorated; the edematous mucosa and the bowel stenosis of the inflamed colonic segment were improved, the ulcerations of the ascending colon had improved and changed to multiple ulcer scars, and the purulent erosions and shallow ulcerations had improved. Scattered erosions at the cecum and the left-half of the transverse colon, appearing at the second colonoscopy, were no longer seen. The border between the inflamed and non-inflamed mucosa at the right-side of the transverse colon became clear because the edematous mucosa improved. After the third colonoscopy, oral prednisolone (PSL) was started at 30 mg/day along with 6-mercaptopurine (6-MP) at 30 mg/day, in addition to the probiotics, and the dose of PSL was tapered over a period of 1 year (Figure 3). A fourth colonoscopy was done after nearly 3 months of combination therapy with PSL and 6-MP (Figure 6). It showed that the edema of the inflamed mucosa from the ascending to the right-half of the transverse colon had improved even more and disappeared, resulting in multiple reticular scars. The active erosions and ulcers were not seen, but instead, the regenerating epithelium was seen at

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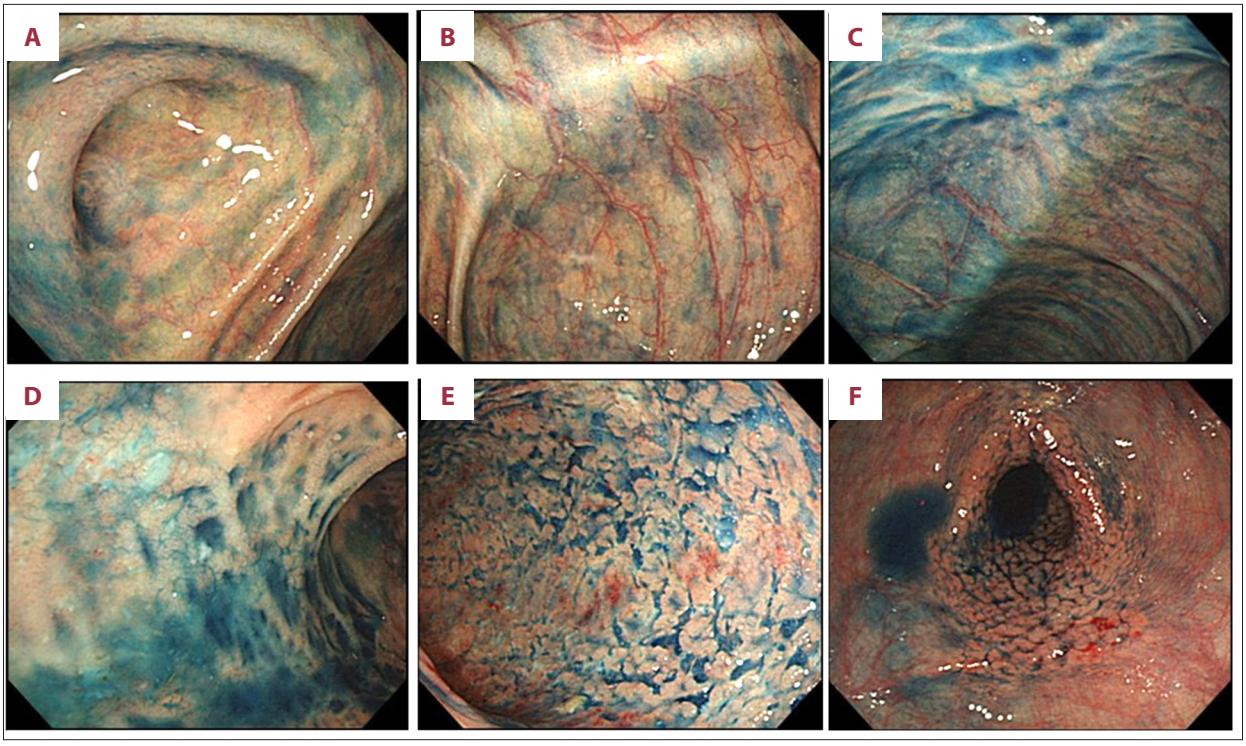

Figure 5. Colonoscopy 3. (**A, B**) Scattered erosions have disappeared in the cecum and around the appendiceal orifice, respectively. (**C, D**) Inflammation of the ascending colon has improved, resulting in multiple ulcer scars and erosions. (**E**) Multiple ulcer scars of the right-half of the transverse colon have improved, and the edematous mucosa has disappeared. (**F**) The border between inflamed and non-inflamed mucosa is clearly seen at the right-half of the transverse colon. The erosions in the left-half of the transverse colon have disappeared.

the same colonic segment. The border between the inflamed and non-inflamed mucosa at the right-side of the transverse colon could be seen more clearly. The inflammatory markers of UC were also improved, with ESR at 17 mm/h and CRP of 0.03 mg/dL. The patient has maintained her good general condition since she was discharged from the hospital.

Discussion

UC is a chronic inflammatory disease characterized by involvement of the rectum with extension to the proximal colon in a continuous manner. On the other hand, involvement of the appendiceal orifice as a discontinuous lesion is well known [3,4]. In Japan's diagnostic and therapeutic guidelines in 2017, the right-sided or segmental type of UC is classified as one disease type along with total, left-sided colitis, and proctitis. It is considered to be a subtype of UC in which the anal side is spared. So far, this subtype has been described in very few reports from Western countries [5]. Although the cause of this discrepancy has not been well elucidated, the subgroup of patients with an uncertain diagnosis has been classified as "indeterminate colitis"[11]; it accounts for about 5% of inflammatory bowel disease (IBD) cases in Japan [12]. The present case could be classified into this type of IBD because of the atypical location of the colonic lesion. However, while the colonic lesion was restricted to the right side of the colon, it was continuous. There were no lesions suggestive of Crohn's disease, such as longitudinal ulcers and a cobblestone appearance. Moreover, the histological lesions showed typical features of UC, without any granulomatous lesions. Given these findings, UC was diagnosed in this patient.

ANCAs are the most frequently studied serological markers for IBD [13]. A combination of both tests could help make the diagnosis of inflammatory bowel disease. The present case was negative for MPO-ANCA, which constitutes a large part of P-ANCA, but was positive for PR3-ANCA, which targets the serine protease proteinase-3 [14]. Several studies reported that PR3-ANCA positivity was useful in differentiating UC from CD [15]. In particular, Arias-Loste et al. reported that a cut-off PR3-ANCA titer of 11.8 chemiluminescent units showed 97.3% specificity for UC (it was 55.2 in the present case), strongly supporting the diagnosis of UC in the present patient [16]. Although PR3-ANCA is frequently detected in primary sclerosing cholangitis [17], this disease was not detected with MRCP.

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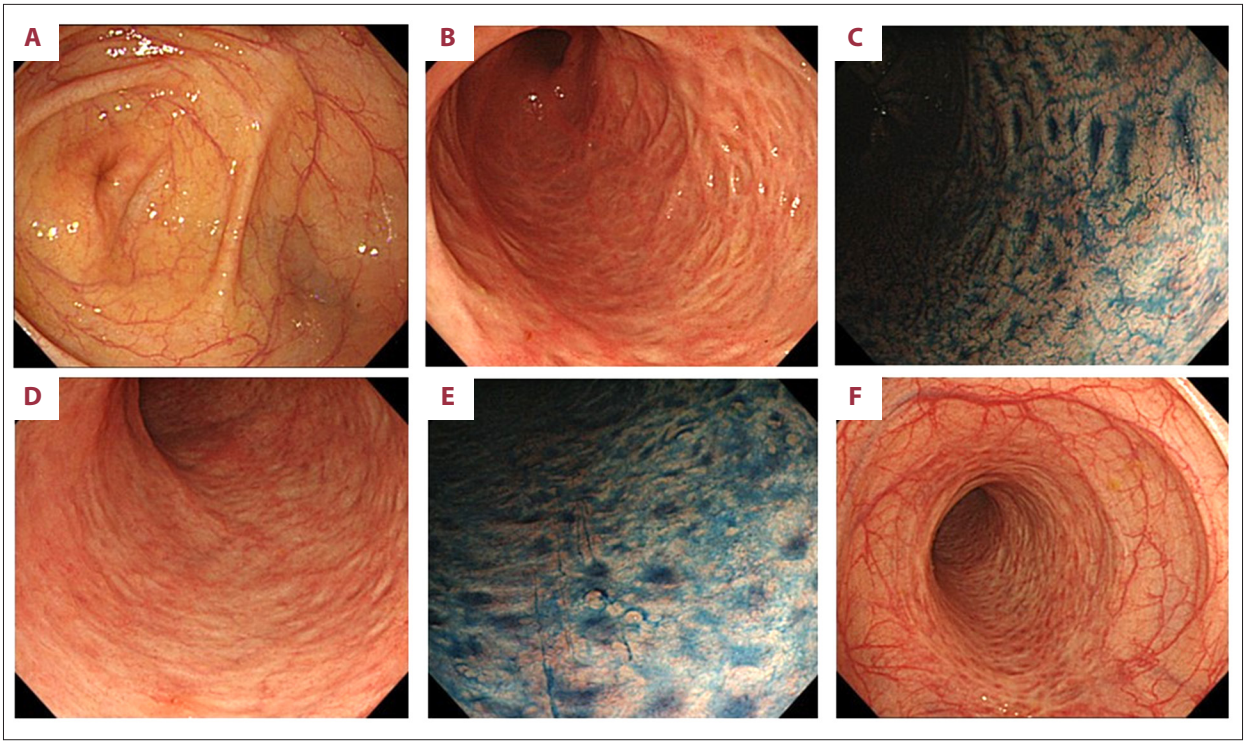

Figure 6. Colonoscopy 4. (**A**) Inflamed mucosa such as erosions is not seen in the cecum. (**B, C**) Active erosions are not seen in the ascending colon, resulting in multiple reticular ulcer scars and regenerative mucosa. (**D, E**) Similar findings in the right-half of the transverse colon. (F) The border between inflamed and non-inflamed mucosa is more clearly seen at the right-half of the transverse colon, presenting a mesh tubing appearance.

Our patient was diagnosed at a regular health screening with the FOB test. Howarth et al. investigated subjects who were found to be FOB-positive on screening for colorectal cancer. Among 44 838 cases, 52 were previously undetected UC, for an estimated rate of 116 per 100 000 (95%CI=85–147/10^5), and 17% (9/52) was asymptomatic. Among them, 52% (27/52) had only proctosigmoiditis, and 25% (13/52) had total colitis. However, the right-sided or segmental colitis type of UC was not found [18]. On the other hand, among 236 000 healthy Japanese who underwent FOB test screening, 19 were diagnosed as having asymptomatic or minimally symptomatic UC on colonoscopy, and 4 had asymptomatic right-sided or segmental type [19]. These studies suggested that UC, including right-sided or segmental colitis type, can exist in healthy individuals.

Another important aspect of this patient was aggravation of the colitis by hypersensitivity reactions to mesalamine. Although 5-ASA agents like mesalamine are thought to be safe and are the first-line drugs for inducing remission and preventing UC [7], hypersensitivity reactions such as fever and rash occur in some patients [20]. Although aggravation of UC with mesalamine has also been reported [8,9,21–23], there have been very few reports of the changes in the endoscopic findings caused by hypersensitivity reactions. More edematous mucosa, much more purulent erosions, and ulcerations were seen. However, it is interesting that, despite some extensions of lesions to both oral and anal sides, the left-sided colon remained intact. Mesalamine-induced aggravation was diagnosed by the dramatic amelioration of symptoms after cessation of the drug, and the positive LTT result confirmed the diagnosis [24]. To the best of our knowledge, this is the first report to show changes in the endoscopic findings during mesalamine-induced hypersensitivity reactions in a case of right-sided colitis type of UC.

Conclusions

We report a rare case of right-sided colitis with mesalamine-induced aggravation with unusual overlapping clinical features.

Conflict of interest

None.

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