A Case of Lupus Enteritis in Which Multiple Colorectal Ulcers Were the Only Signs of Relapse

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The patient was a 62-year-old woman. She had been treated for systemic lupus erythematosus (SLE) for 15 years and had a stable clinical course with cyclosporine, prednisolone, and ticlopidine. She experienced anal pain, diarrhea, and bloody stools for four months. Colonoscopy showed scattered large and small punched-out ulcers in the colon and deep longitudinal ulcers in the sigmoid colon. Blood test results indicated low SLE activity. Culture of mucosal biopsy did not reveal any findings. Computed tomography showed intestinal membrane arteriovenous dilatation (comb sign), therefore lupus enteritis was suspected. After initiating endoxan pulse therapy, symptoms improved rapidly. Disappearance of ulcers was confirmed by endoscopic images.

Key words: systemic lupus erythematosus, lupus enteritis, intestinal ulcer, Crohn's disease

INTRODUCTION

Systemic lupus erythematosus (SLE) is chronic, refractory, and autoimmune disease that manifests with various inflammatory lesions involving multiple organs throughout the body. Lupus enteritis is known as an enteropathy associated with SLE. Its most common type is ischemic enteritis, which mainly causes inflammation of the small intestine. However, its rare form is the multiple ulcer type of the large intestine, which shows various ulcers in the large intestine. Herein, we report a case of multiple ulcer-type lupus enteritis of the large intestine, which had no hematological deterioration seen in SLE and was difficult to distinguish, along with a literature review.

CASE REPORT

The patient was a 62-year-old woman. She was referred to our hospital due to anemia, thrombocytopenia, and petechiae on both lower limbs. The patient was diagnosed with SLE based on presence of bleeding spots in her nail beds; thrompocytopenia; high levels of antinuclear and anti-ds-DNA antibodies; and positive antiphospholipid antibody levels. She underwent treatment with steroid pulse therapy and cyclophosphamide at the Rheumatology Department of our hospital. However, no improvements were seen. Positive results were then seen after initiation of high-dose endoxan therapy. Endoxan was administered for two years. The patient continued an oral administration of prednisolone (PSL) and cyclosporine, which were gradually tapered during endoxan administration, at doses of approximately 7 mg/d and 100 mg/d, respectively. Serological IgG, complement, and anti-ds-DNA antibody levels remained within the reference range.

Fifteen years after onset, chronic diarrhea and bloody stools appeared. Endoscopy showed scattered redness, edema, erosion, and ulcers from the transverse colon to the rectum. Therefore, the patient was referred to our hospital in April of the same year for suspected inflammatory bowel disease. At the time of visit, the patient had a defecation frequency of 30 times a day and fever (body temperature above 38℃), and she was urgently hospitalized on that same day.

Oral medication history: cyclosporine 100 mg/d, prednisolone 7 mg/d, ticlopidine 200 mg/d, ascorbic acid 2 g/d, risedronic acid 17.5 mg/d, rabeprazole 10 mg/d.

Physical findings: height, 156 cm; weight, 36 kg; body temperature, 38℃; blood pressure, 124/60 mmHg; pulse rate, 76/min; conjunctival pallor; no yellowed conjunctiva of the eyeball; no rash on the face/skin; flat and soft abdomen; tenderness in the lower abdomen without rebound tenderness; the anus was strongly swollen and indurated and tenderness was noted.

Laboratory data results are shown in Table 1.

Abdominal computed tomography (CT) examination: Circumferential colonic wall thickening and small amount of ascites were observed from the descending colon to the rectum.

Colonoscopy; No abnormalities were seen in the

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Table 1

Complete blood count		Blood chemistry	
WBC (/μl, 4000-8000)	15000	Glu (mg/dL, 70-110)	94
RBC (×10⁴/μL, 380-480)	299	TP (g/dL, 6.5-8.0)	6.9
Hb (g/dL, 11.5-15.5)	9.1	Alb (g/dL, 4.1-5.0)	2.4
Ht (%, 34-42)	27.5	BUN (mg/dL, 8-20)	4
MCV (fL, 84.0-99.0)	92.0	Cr (mg/dL, 0.60-1.40)	0.82
Plt (×104/μL, 14.0-40.0)	31.9	Na (mEq/L, 135-145)	135
		K (mEq/L, 3.5-5.0)	4.2
Serology		Cl (mEq/L, 96-109)	105
ANA	1:80	AST (U/L, 0-40)	16
Anti-ds-DNA (IU/mL, 0-12)	<10	ALT (U/L, 0-35)	13
IgG (mg/dL, 870-1700)	1206	LDH (U/L, 100-230)	173
MPO-ANCA (U/L, 0-3.5)	<1.0	ALP (U/L, 100-350)	173
PR3-ANCA (U/L, 0-3.5)	<1.0	γGTP (U/L, 0-60)	39
C1q (μg/mL, 0-3)	<1.5	Amy (U/L, 36-118)	48
Cyclosporin (ng/dL)	<30	CRP (mG/dL, 0-0.3)	10.57
CMV antibody (C10/C11)	negative	C3 (mg/dL, 86-160)	120
		C4 (mg/dL, 17-45)	27

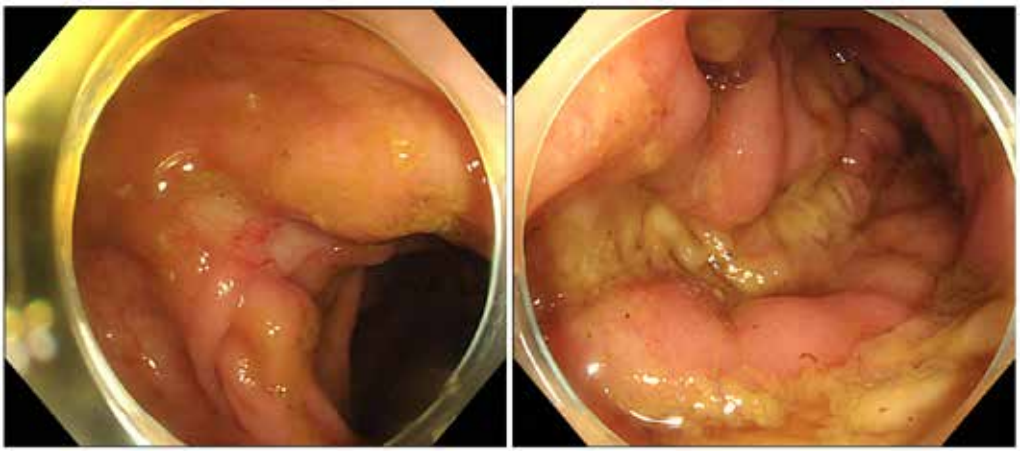

Fig. 1 Lower gastrointestinal endoscopy shows that discontinuous large and small deep ulcers. Longitudinal ulcers with deep groove are observed extending from the sigmoid colon to the rectum. There is no inflammation of mucous membrane between the ulcers.

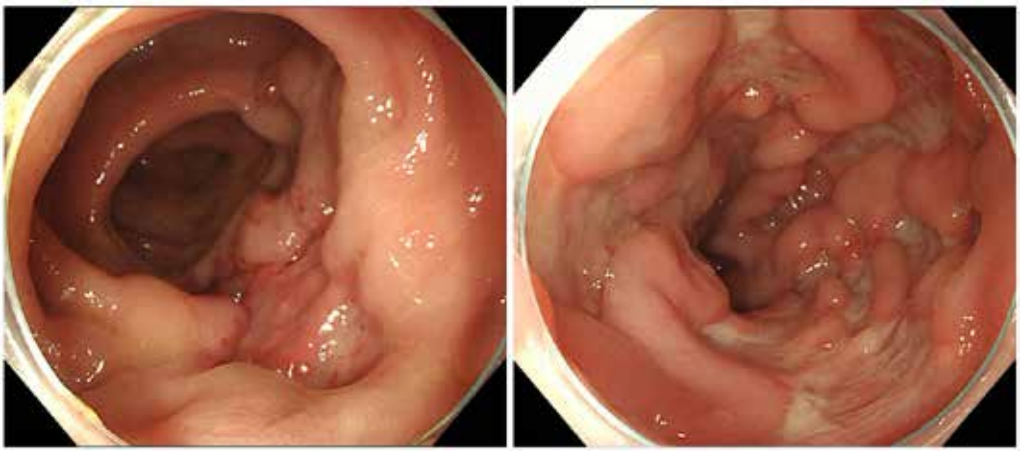

Fig. 2 A second colonoscopy revealed that the ulcers scattered throughout the colon were growing and deepening.

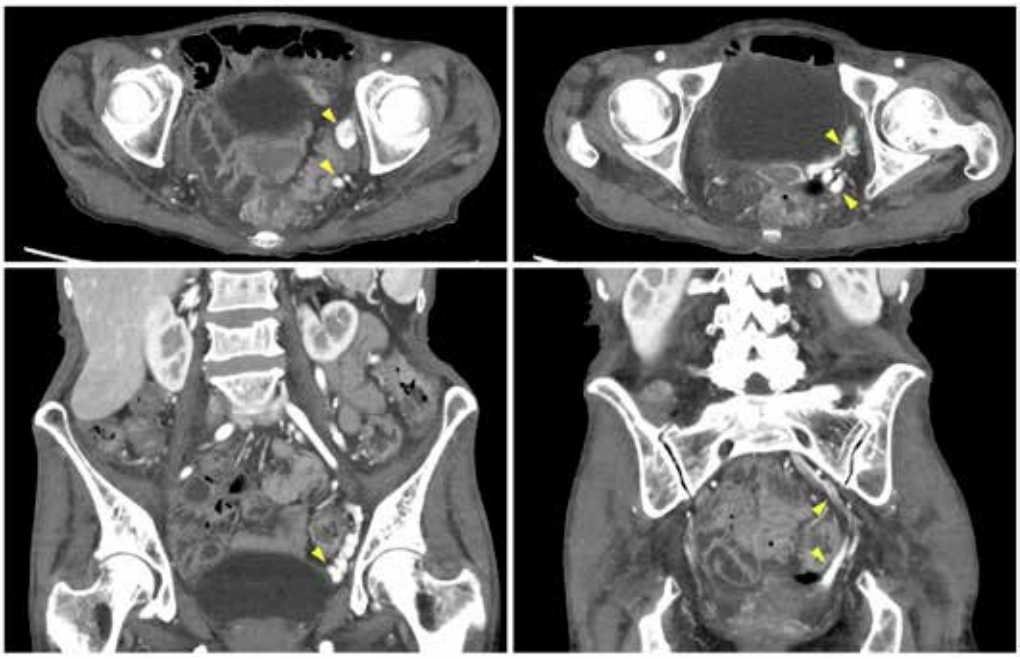

Fig. 3 Computed tomography (CT) shows that strong edema and peripheral wall thickening from the sigmoid colon to rectum. Yellow arrowheads point to the intestinal arteriovenous malformations and vasodialation. This sign is called "comb sign".

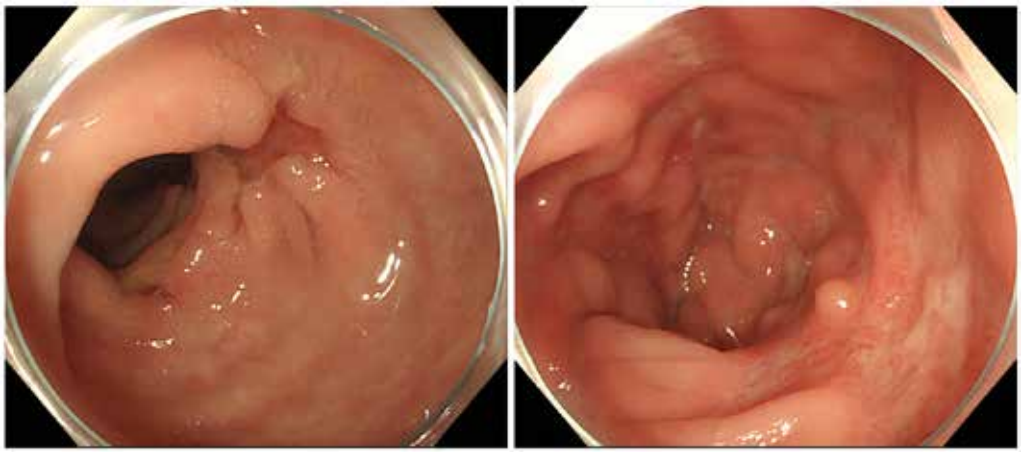

Fig. 4 Four weeks after the start of high-dose cyclophosphamide therapy, ulcers are shrunk and partially scarred.

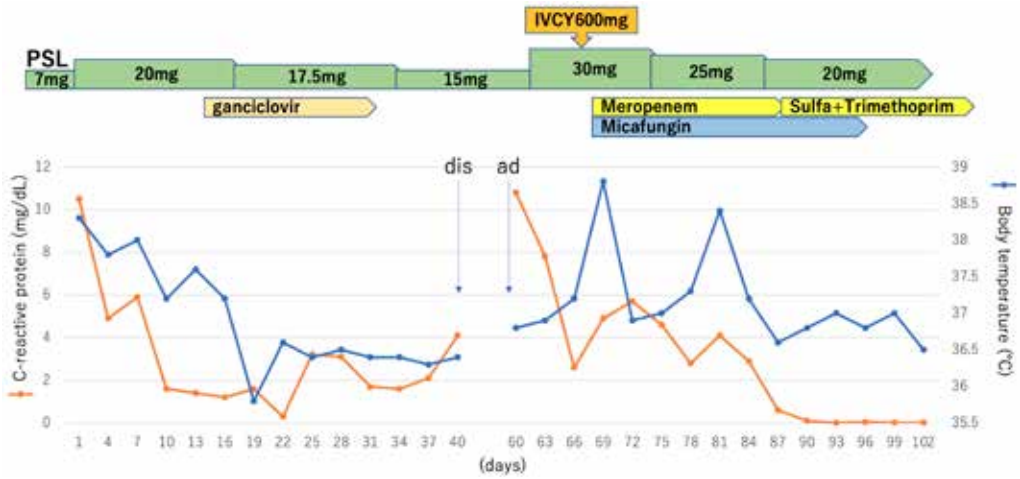

Fig. 5 Fever and C-reactive protein (CRP) improved to some extent by fasting, prednisolone(PSL) 20 mg/d, and denosine. However, both of them relapsed twenty days after discharge. Thirteen days after PSL 30 mg/d and seven days after pulse cyclophosphamide (IVCY), she was treated with antibiotics due to development of pneumonia. Diarrhea improved significantly and she was able to eat without any problems two weeks after IVCY.

terminal ileum. Scattered large and small deep ulcers were detected in the colon. In addition, longitudinal deep ulcers were observed from the sigmoid colon to the rectum (Fig. 1). Biopsies were performed on some ulcers. However, only infiltration of inflammatory cells such as plasma cells was observed, and no granulomatous species or inclusion body structures suggestive of viral infection were observed.

Radiographic contrast study showed no particular abnormalities in the small intestine.

The patient was negative for serum cytomegalovirus (CMV) antigen. However, the possibility of CMV enteritis was considered due to punched-out ulcers in large intestine. Consequently, ganciclovir (200 mg/d) was administered for two weeks. Cyclosporine was discontinued and PSL was increased to 20 mg/d. Both fever and diarrhea improved three weeks after admission, and oral intake was resumed when serum C-reactive protein improved to 1.2 mg/dL. The patient was discharged 48 days after admission and PSL was slowly reduced to 15 mg/d.

However, the patient was readmitted to the hospital four weeks after discharge due to relapse of lower abdominal pain and diarrhea.

A second colonoscopy revealed that the ulcers that were scattered throughout the entire colon increased and also showed an increasing tendency (Fig. 2). Repeated biopsies revealed only crypt abscesses and no particular disease-specific findings.

Contrast-enhanced CT showed mesenteric arteriovenous hyperemia and vasodialation (comb sign), and multiple ulcer-type lupus enteritis was strongly suspected (Fig. 3). The comb sign was not seen on the previous CT. The patient was treated with PSL 30 mg/d and high-dose cyclophosphamide therapy, after which symptoms were markedly improved. A follow-up endoscopy conducted four weeks after the start of treatment showed that ulcer had shrunk and partially scarred (Fig. 4). Fig. 5 shows the course of treatment.

DISCUSSION

We encountered multiple ulcer-type lupus enteritis of the large intestine in a patient with SLE who presented with various ulcers, which was difficult to distinguish from Crohn's disease (CD) or CMV enteritis. It is estimated that 40% of patients with SLE develop gastrointestinal disorders, most often due to gastroduodenal mucosal lesions caused by the side effects of non-steroidal anti-inflammatory drugs, corticosteroids, or cytotoxic drugs. Lupus enteritis is classified into three types according to its clinical features: ischemic enteritis, multiple ulcers, and protein-losing gastroenteritis. However, the ischemic enteritis type accounts for a majority of cases in terms of frequency [1, 2]. The ischemic enteritis type develops with abdominal pain, nausea, vomiting, and diarrhea, and mainly occurs in the small intestine, exhibiting strong diffuse edema. Therefore, the "accordion sign" and "target sign" can be seen on CT scanning. High doses of corticosteroids are used for treatment and prognosis is relatively favorable [3]. The frequency of the multiple ulcer type is rare at approximately 0.4% of all SLE cases. It mainly occurs in the large intestine, especially the rectum and sigmoid colon. It is often seen in cases of long-term SLE after at least 10 years. Moreover, it also develops in cases where disease activity is controlled. Endoscopy reveals frequent round / oval or irregular punched-out lesions with no abnormalities in the surrounding mucosa [4, 5]. Pathological examinations of surgical specimens show inflammatory cell infiltration and interstitial edema, and sometimes identify vasculitis and thrombus formation. However, detection of this rare type via biopsy is difficult. Thickening of the intestinal wall and mesenteric arteriovenous hyperemia (comb sign) on CT scanning are also characteristic features [4, 6, 7].

Diagnosing multiple ulcer-type lupus enteritis requires ruling out other causes of enteritis. In this case, it was particularly difficult to rule out CMV enteritis or CD. The symptoms of CMV enteritis and CD are similar to those of lupus enteritis, both often exhibit fever, abdominal pain, and diarrhea. Punched-out ulcers are typical endoscopic image findings of CMV enteritis. However, CMV enteritis is known to manifest with various lesions, and it may be difficult to distinguish them from those in lupus enteritis. Determining presence of CMV often involves confirming an increase in blood CMV antigen levels. However, the sensitivity of testing for CMV is approximately 50%, and a negative result does not necessarily mean ruling out diagnosis of CMV [8]. Although, there is also a method of confirming presence of intranuclear inclusion bodies by intestinal mucosal biopsy, this testing also has the problem of low sensitivity. In this case, CMV antigen was negative, but CMV enteritis could not be ruled out, so ganciclovir was administered. Since the dose of PSL was increased at the same time, it was difficult to determine which drug was effective. Currently, the real-time PCR method, which has higher sensitivity and specificity than antigen tests, is covered by health insurance. If real-time PCR could be performed in this case as well, it might have been possible to diagnose CMV.

Endoscopic images of CD exhibit presence of Longitudinally aligned aphthae, erosions, and ulcers. In cases of multiple ulcer-type lupus enteritis, this is often difficult to distinguish from CD. There is a report of CD complicated with SLE [9]. However, the present case was 62 years old, and the possibility of CD was ruled out given that there was no granulomatous change even after repeated biopsies, and steroids and immunosuppressants were originally used, which is not a situation where CD would newly appear. Multiple ulcer-type lupus enteritis usually manifests with high activity accompanied by multi-organ lesions and systemic symptoms. Additionally, it rarely develops as an independent symptom of the gastrointestinal tract during SLE remission [10, 11].

Patients with multiple ulcer-type lupus enteritis might be prone to gastrointestinal perforations and bleeding due to presence of large and deep ulcers. Hirata *et al.* indicated that 42% of multiple ulcer-type cases exhibited perforation or penetration, and 19% of cases ended in death [4]. High-dose corticosteroids and cyclophosphamide are used for treatment. However, high-dose corticosteroids are often difficult to be used with endoxan. It has also been reported that high-dose endoxan therapy is recommended because steroids may make perforation more likely to occur. Surgery at an early stage prior to perforation is recommended

if patient is unresponsive to medical treatment [11, 12]. The risk of recurrence of lupus enteritis includes presence of colonic lesions and lupus cystitis, as well as thickening of the intestinal wall exceeding 8–9 mm [13]. The present case is also considered to be at high risk despite no recurrence has been observed for 15 years.

Patients with abdominal symptoms during SLE treatment should undergo careful examination of the entire gastrointestinal tract to detect lesions at an early stage for prompt treatment. If ulcerative lesions of the large intestine are observed, it is important to proceed with the diagnostic process, keeping in mind that multiple ulcer-type lupus enteritis may occur even if disease progression of SLE is suppressed.

CONFLICTS OF INTEREST

The authors have declared no conflicts of interest.

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