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CASE REPORT

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# Corticosteroid-resistant multiple colonic ulcers in a patient with systemic lupus erythematosus/systemic sclerosis overlap syndrome effectively treated with intravenous cyclophosphamide pulse therapy

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**Abstract** We report a rare case of a 17-year-old female with overlap syndrome (systemic lupus erythematosus and systemic sclerosis) who developed severe abdominal pain and bloody diarrhea accompanied by central nervous system lupus. Colonoscopy revealed multiple irregular and linear ulcers throughout the colon, which were resistant to corticosteroid pulse therapy and plasma exchange. The patient finally recovered after treatment with a relatively low dose of monthly intravenous cyclophosphamide (250 mg/m$^2$) pulse therapy.

**Key words** Colonic ulcers · Cyclophosphamide pulse therapy (IV-CY) · Overlap syndrome · Systemic lupus erythematosus (SLE) · Systemic sclerosis (SSc)

## Introduction

Gastrointestinal manifestations of systemic lupus erythematosus (SLE) are common. For example, Dubois and Tuffanelli[1] reported that almost half of the 520 SLE patients in their study had gastrointestinal symptoms. However, it is often unclear whether the etiology of these symptoms is really due to SLE or to a different cause, such as a complication of inflammatory bowel disease or a medication-induced effect. Although the term "lupus enteritis" is generally used to refer to lupus-induced intestinal lesions, this term is not specific and may include many types of lesion, such as ulcers, perforation, bleeding, ileus, and protein-losing enteropathy. While the mechanism of some types of lupus enteritis have been reported[2,3] as mesenteric vasculitis or thrombosis, the mechanism of malabsorption and dysmotility are still under investigation. In addition, the effect of intravenous monthly cyclophosphamide pulse therapy (IV-CY) for treating lupus enteritis has not been well discussed.[4–6] To our knowledge, multiple colonic ulcers occurring with systemic sclerosis (SSc) or overlap syndrome (SLE and SSc) have not been reported. Here, we report the case of a patient with overlap syndrome accompanied by central nervous system (CNS) lupus who developed corticosteroid-resistant enteritis, but was effectively treated with a relatively low dose of monthly IV-CY.

## Case report

A 17-year-old female was diagnosed with overlap syndrome accompanied by CNS lupus in March 1997, when she was hospitalized because of persistent fever, polyarthralgia, proteinuria, pericarditis, generalized seizure, Raynaud's phenomenon, and proximal scleroderma. She was positive for antinuclear antibodies, anti-dsDNA antibodies, and antiscleroderma 70 antibodies. The patient was successfully treated with methylprednisolone pulse therapy (1 g for 3 days) followed by prednisolone, which was gradually tapered to 20 mg. After discharge from hospital, her progress was followed at an outpatient clinic.

The patient was readmitted to the same hospital owing to severe abdominal pain and bloody diarrhea on June 15, 1997. A complete colonoscopy revealed multiple irregular and linear ulcers throughout the entire colon. The histological findings of the biopsy specimens showed nonspecific colitis without vasculitis. A complication of ulcerative colitis, or viral-induced colitis such as cytomegalovirus, was ruled out because of histological findings and several laboratory tests, including a negative cytomegalovirus antigenemia assay. In addition, the patient showed symptoms of CNS lupus, including generalized seizure, indicating an increase in SLE disease activity. Based on this information, a diagnosis of enteritis due to overlap syndrome was made

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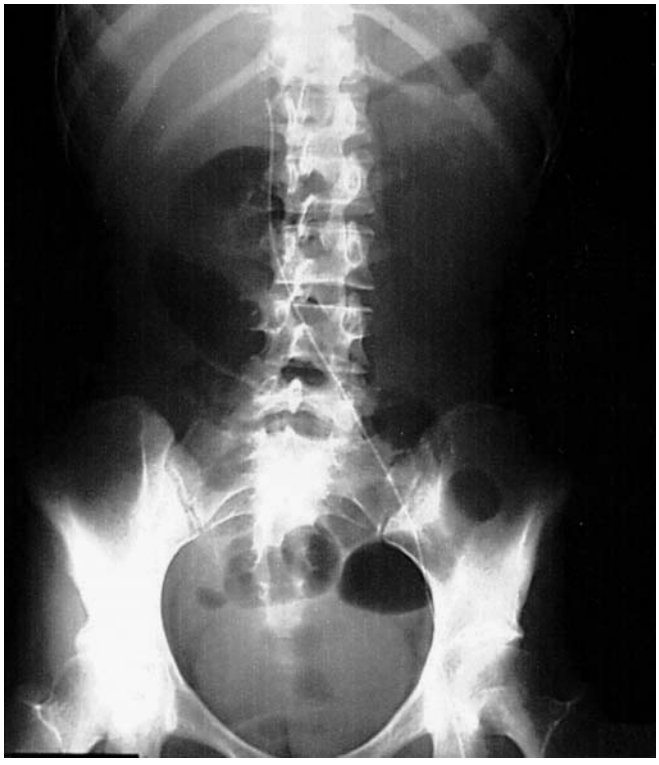

**Fig. 1.** Abdominal X-ray (supine position) on admission to this hospital showing dilatation of the small intestine

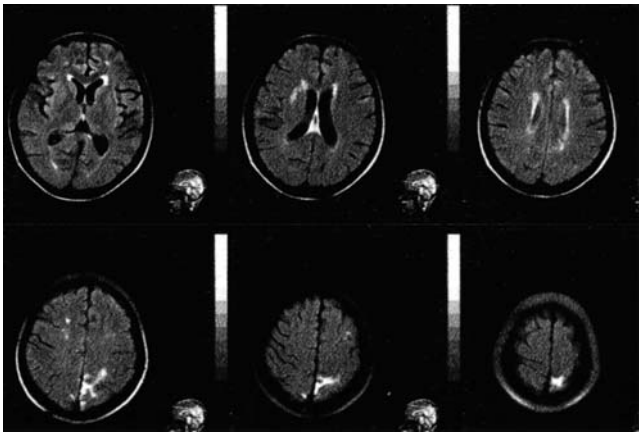

**Fig. 2.** Magnetic resonance imaging of the brain (August 25, 1997, $T_2$-weighted imaging) showing multiple high-intensity lesions in the cortex or subcortical white matter of the left occipital and parietal lobes, the white matter of both frontal lobes, and the deep white matter around the right ventricle

even though the histopathological findings failed to show vasculitis. The patient was treated with methylprednisolone pulse therapy (1 g for 3 days), followed by 125 mg intravenous methylprednisolone. However, she was referred to our hospital on August 6, 1997, because both the enteritis and CNS lupus were uncontrollable.

A physical examination showed that her height was 154 cm and her weight was 31.8 kg. Her pulse rate was 112 beats/min, blood pressure 120/70 mmHg, and body temperature 35.6°C. A mild moon-faced appearance, anemia, and scleroderma on her face, forearms, and fingers were observed. Shortening of the tongue frenum, limitation of the oral aperture, pitting ulcer scars on her fingers, and limitations of both fist closure and finger extension were noted. No abnormal cardiopulmonary findings were detected, but mild abdominal tenderness around the umbilicus with a slight increase in bowel sounds were observed. A neurological examination was unremarkable except for muscle atrophy and weakness of the lower limbs caused by staying in bed for about 2 months. An abdominal X-ray showed dilatation of the small intestine (Fig. 1). Magnetic resonance imaging of the brain (August 25, 1997, $T_2$-weighted imaging) revealed multiple high-intensity lesions in the cortex or subcortical white matter of the left occipital and parietal lobes, the white matter of both frontal lobes, and the deep white matter around the right ventricle (Fig. 2). An electroencephalogram on admission revealed no epileptic discharge while taking 300 mg zonisamide daily. Initial laboratory results were as follows: urinalysis normal; white blood cell count 2100/mm$^3$ (neutrophils 86.8%, eosinophils 0.5%, basophils 0%, lymphocytes 10.8%, monocytes 1.9%); red blood cell count 346 $\times$ 10$^4$/mm$^3$; hemoglobin 10.1 g/dl; hematocrit 32.5%; platelet count 29.0 $\times$ 10$^4$/mm$^3$; erythrocyte sedimentation rate 46 mm/h; total protein 3.5 g/dl; albumin 2.2 g/dl; billirubin 0.2 mg/dl; aspartate aminotransferase 22 U/l (normal 5–37 U/l); alanine aminotransferase 28 U/l (normal 3–35 U/l); lactate dehydrogenase 526 IU/l (normal 180–460 IU/l); alkaline phosphatase 302 U/l (normal 105–320 U/l); amylase 118 U/l (normal 54–168 U/l); creatine phosphokinase 25 U/l (normal less than 190 U/l); blood urea nitrogen 3 mg/dl; creatinine 0.4 mg/dl. Immunological studies showed C-reactive protein (CRP) 1.6 mg/dl (normal less than 0.2 mg/dl), CH50 23.1 U/ml (normal 29–48 U/ml), C3 60.7 mg/dl (normal 55–120 mg/dl), and C4 24.7 mg/dl (normal 20–50 mg/dl). Immunoglobulin including IgG 136 mg/dl (normal 800–1800 mg/dl), IgA 0 mg/dl (normal 90–450 mg/dl) and IgM 2 mg/dl (normal 60–250 mg/dl) were severely suppressed due to high-dose corticosteroid treatment and intestinal bleeding. The patient's antinuclear antibody titer was 1:320 with a speckled pattern, antibody to DNA antigen 2 IU/ml (normal less than 6 IU/ml), antibody to scleroderma 70 antigen titer negative, antibody to U1-ribonucleoprotein antigen titer 1:1, antibody to Sm antigen titer negative, and perinuclear antineutrophil cytoplasmic antibody negative. Antiphospholipid antibodies, including lupus anticoagulant, IgG anticardiolipin antibody, and anti-$\beta_2$-glycoprotein-I antibody, were negative. The patient's coagulation profile was within the normal range. The cytomegalovirus antigenemia assay was negative, and the stool culture was negative.

After admission (Fig. 3), because of frequent generalized seizures and severe enteritis, plasma exchange (PE) with 60 mg prednisolone was performed, and the patient's seizures stopped immediately. However, her severe enteritis was not improved by three rounds of PE. A colonoscopy performed after PE revealed moderate mucosal edema and

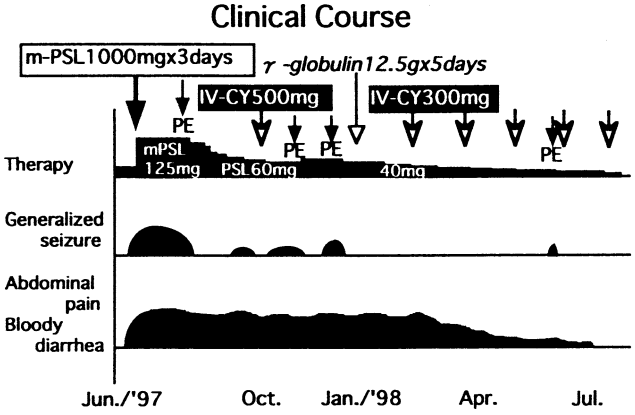


**Fig. 3.** Clinical course of the patient. *m-PSL*, methylprednisolone; *PSL*, prednisolone; *PE*, plasma exchange; *IV-CY*, intravenous pulse cyclophosphamide

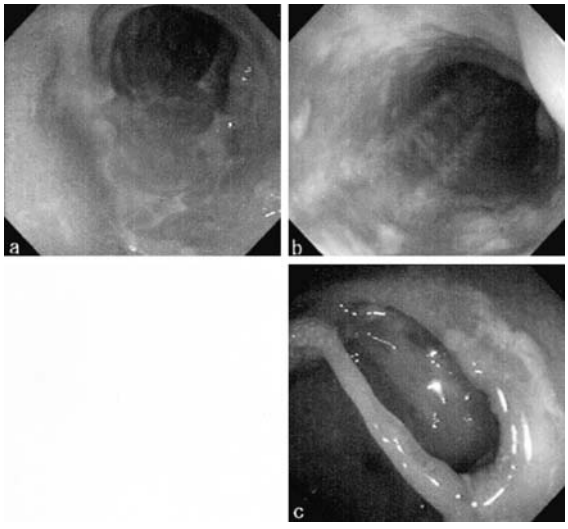


**Fig. 4.** Colonoscopy performed before the first IV-CY treatment showing multiple (**a**) irregular and (**b**) linear ulcers throughout the colon. Some deep ulcers forming a blind-ended false lumen (**c**) were also detected

multiple irregular, linear, and moderately deep ulcers, with frequent bleeding throughout the colon (Fig. 4). The histological findings of biopsy specimens of the colonic ulcers showed the early stages of ischemic changes, but failed to show vasculitis or thrombosis (Fig. 5). After the administration of intravenous cyclophosphamide pulse therapy (IV-CY) using 500 mg cyclophosphamide (417 mg/m$^2$), the patient's abdominal pain and bloody diarrhea decreased slightly. However, her bone marrow became severely suppressed (white blood cell count to 200/mm$^3$), and the patient became septic. The sepsis resolved after the administration of antibiotics and granulocyte colony stimulating factor. When generalized seizures recurred, two sets of three rounds of PE were administered and were effective. The patient was also treated with large amounts of γ-globulin (12.5 g for 5 days), but this was not effective in treating her enteritis. Finally, she was treated monthly with a relatively

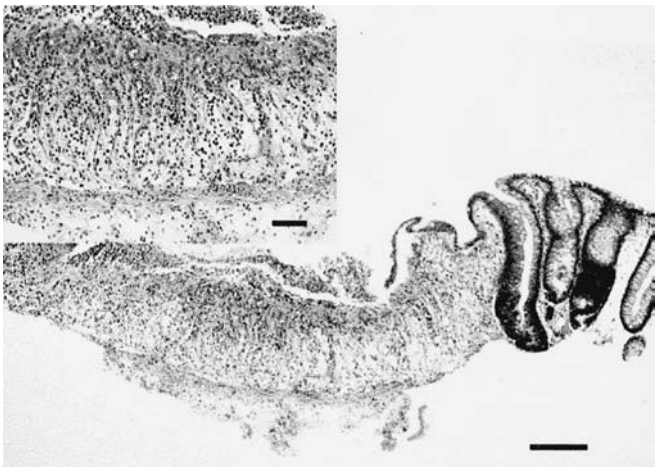

**Fig. 5.** Histological findings of biopsy specimens of the colonic ulcers showed the total disappearance of the surface and crypt epithelia from the mucosa, which was covered with surface deposits of fibrinopurulent exudates. The lamina propria and muscularis mucosae were well preserved, indicating the early stage of ischemic changes. Epithelial cell regeneration was visible at the margin of the lesion. No vasculitis or thrombosis was evident. Hematoxylin–eosin stain. *Bar* 200 μm

low dose of IV-CY using 300 mg (250 mg/m$^2$) cyclophosphamide. After five such treatments, her enteritis had clearly improved and her bone marrow was no longer suppressed. Her abdominal pain, bloody diarrhea, and seizures also disappeared, enabling us to taper her prednisolone gradually. No colonoscopy was performed after the patient's enteritis had resolved owing to the lack of patient consent.

## Discussion

Major intestinal manifestations of SLE include dysmotility, vasculopathy (vasculitis or thrombosis), and malabsorption.[2,3] Ulcer, bleeding, or perforation related to lupus is usually caused by vasculopathy, which is a life-threatening complication, requiring correct and prompt diagnosis. The differential diagnosis for multiple colonic ulcers in SLE includes mesenteric vasculitis, thrombosis, bacterial or viral infection such as cytomegalovirus, and tubercular colitis.[5] Moreover, ulcerative colitis or Crohn's disease may also occur in SLE patients.[7–11] In addition, our patient suffered from SSc, which may also cause ulcerative lesions of the gastrointestinal tract.[12–15] However, we were not able to find any reports of multiple colonic ulcers caused by mesenteric vasculitis in patients with SSc or overlap syndrome (SLE and SSc).

We decided that the multiple colonic ulcers in our case were due to mesenteric vasculitis related to overlap syndrome because of the accompanying CNS lupus, several laboratory tests, and biopsy specimens, even though they failed to show vasculitis. To prove vasculitis, a biopsy should be performed that includes submucosal tissue, thus limiting diagnosis by colonoscopy.

SLE or overlap syndrome complicated with both severe colonic ulcers and active CNS lupus has not previously been reported. The reason why both complications seldom occur together is not clear. One reason may be that colonic ulcers are a rare complication of connective tissue disease.

Therapeutically, the use of high-dose corticosteroids is the most common treatment for SLE with mesenteric vasculitis.[16,17] After diagnosis in our case, corticosteroid pulse therapy and subsequent PE were administered to treat both enteritis and CNS lupus. While PE was effective for treating CNS lupus, neither therapy improved the enteritis. Recently, IV-CY has been widely used in the management of severe connective tissue disease. Indeed, Laing[4] first reported the successful treatment of corticosteroid-resistant gastrointestinal vasculitis due to SLE with IV-CY (1000 mg/day). Grimbacher et al.[5] also reported a successfully treated case of gastrointestinal vasculitis with IV-CY (12.5 mg/kg). In our case, since the usual dose of 500 mg (417 mg/m$^2$) cyclophosphamide resulted in severe bone marrow suppression, we tried a relatively low dose of cyclophosphamide using 300 mg (250 mg/m$^2$) monthly. This treatment clearly improved the enteritis. Martin-Suarez et al.[18] reported a low-dose IV-CY treatment for severe connective tissue disease, in which they used cyclophosphamide not monthly but weekly for a median of 3 weeks (2–10 weeks). Although the reason why monthly treatment with relatively low doses of IV-CY is effective is unknown, a recent report[19] suggests that one possible mechanism may be a polymorphism in the enzymes that metabolize cyclophosphamide. Specifically, this polymorphism may be associated with the blood concentration of cyclophosphamide. If this is true, measurements of blood concentrations of cyclophosphamide may be needed in IV-CY treatment to determine the most suitable dose.

In conclusion, we have presented the case of a patient with overlap syndrome (SLE and SSc) who developed severe enteritis, probably caused by mesenteric vasculitis. Although several cases describing corticosteroid-resistant severe lupus enteritis have been reported, this case is rare for two reasons. First, to our knowledge, this is the first reported case of enteritis complicated with overlap syndrome (SLE and SSc), and second, this corticosteroid-resistant, severe enteritis was effectively treated with monthly, relatively low doses of IV-CY.

## References


1. Dubois EL, Tuffanelli DL. Clinical manifestations of systemic erythematosus: computer analysis of 520 cases. JAMA 1964;190: 104–11.
2. Hallegua DS, Wallace DJ. Gastrointestinal manifestations of systemic lupus erythematosus. Curr Opin Rheumatol 2000;12:379–85.
3. Sultan SM, Ioannou Y, Isenberg DA. A review of gastrointestinal manifestations of systemic lupus erythematosus. Rheumatology (Oxford) 1999;38:917–32.
4. Laing TJ. Gastrointestinal vasculitis and pneumatosis intestinalis due to systemic lupus erythematosus: successful treatment with pulse intravenous cyclophosphamide. Am J Med 1988;85:555–8.
5. Grimbacher B, Huber M, von Kempis J, Kalden P, Uhl M, Kohler G, et al. Successful treatment of gastrointestinal vasculitis due to systemic lupus erythematosus with intravenous pulse cyclophosphamide: a clinical case report and review of the literature. Br J Rheumatol 1998;37:1023–8.
6. Eberhard A, Shore A, Silverman E, Laxer R. Bowel perforation and interstitial cystitis in childhood systemic lupus erythematosus. J Rheumatol 1991;18:746–7.
7. Buchman AL, Wilcox CM. Crohn's disease masquerading as systemic lupus erythematosus. South Med J 1995;88:1081–3.
8. Stevens HP, Ostlere LS, Rustin MH. Systemic lupus erythematosus in association with ulcerative colitis: related autoimmune diseases. Br J Dermatol 1994;130:385–9.
9. Ishikawa O, Miyachi Y, Fujita K, Takenoshita S, Nagamachi Y, Hirato J. Ulcerative colitis associated with preceding systemic lupus erythematosus. J Dermatol 1995;22:289–91.
10. Koutroubakis IE, Kritikos H, Mouzas IA, Spanoudakis SM, Kapsoritakis AN, Petinaki E, et al. Association between ulcerative colitis and systemic lupus erythematosus: report of two cases. Eur J Gastroenterol Hepatol 1998;10:437–9.
11. Garcia-Porrua C, Gonzalez-Gay MA, Lancho A, Alvarez-Ferreira J. Systemic lupus erythematosus and ulcerative colitis: an uncommon association. Clin Exp Rheumatol 1998;16:511.
12. Rose S, Young MA, Reynolds JC. Gastrointestinal manifestations of scleroderma. Gastroenterol Clin North Am 1998;27:563–94.
13. Duchini A, Sessoms SL. Gastrointestinal hemorrhage in patients with systemic sclerosis and CREST syndrome. Am J Gastroenterol 1998;93:1453–6.
14. Lock G, Holstege A, Lang B, Scholmerich J. Gastrointestinal manifestations of progressive systemic sclerosis. Am J Gastroenterol 1997;92:763–71.
15. Sjogren RW. Gastrointestinal features of scleroderma. Curr Opin Rheumatol 1996;8:569–75.
16. Cabrera GE, Scopelitis E, Cuellar ML, Silveria LH, Mena H, Espinoza LR. Pneumatosis cystoides intestinalis in systemic lupus erythematosus with intestinal vasculitis: treatment with-high dose predonisone. Clin Rheumatol 1994;13:312–6.
17. Hiraishi H, Konishi T, Ota S, Shimada T, Terano A, Sugimoto T. Massive gastrointestinal hemorrhage in systemic lupus erythematosus: successful treatment with corticosteroid pulse therapy. Am J Gastroenterol 1999;94:3349–53.
18. Martin-Suarez I, D'Cruz D, Mansoor M, Fernandes AP, Khamashta MA, Hughes GR. Immunosuppressive treatment in severe connective tissue diseases: effects of low-dose intravenous cyclophosphamide. Ann Rheum Dis 1997;56:481–7.
19. Chang TK, Yu L, Goldstein JA, Waxman DJ. Identification of the polymorphically expressed CYP2C19 and the wild-type CYP2C9-ILE359 allele as low-Km catalysts of cyclophosphamide and ifosfamide activation. Pharmacogenetics 1997;7:211–21.