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CASE REPORT

Dramatic regression of mesenteric abnormalities demonstrated on angiography following prednisolone and cyclophosphamide combination therapy in a patient with polyarteritis nodosa associated with Sjögren's syndrome

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Abstract A 63-year-old woman, who had been followed for Sjögren's syndrome, was admitted due to cryoglobulinemia, leukocytoclastic vasculitis, and mononeuritis multiplexa. In spite of the administration of 60 mg prednisolone, fecal occult blood was strongly positive. The colonoscopy showed multiple colonic ulcers, and a diagnosis of polyarteritis nodosa (PAN) was made because abdominal angiography revealed markedly serpentine and narrowed superior and inferior mesenteric arteries. After steroid pulse therapy and daily oral administration of cyclophosphamide were initiated, her symptoms improved and abdominal angiographic findings were finally normalized. Although there are only three case reports on improvements in abdominal angiographic findings of PAN in the literature, our case and previously reported cases suggest that improvements in angiographic findings may reflect a good prognosis of PAN.

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Introduction

Sjögren's syndrome (SS) is an autoimmune disease characterized by chronic lymphocyte infiltration and reduced secretion from exocrine glands, such as the lacrimal and salivary glands [1, 2].

Vasculitis may accompany the primary disease or develop due to complications from cryoglobulinemia in primary SS [3–5]. However, complications from multiple colonic ulcers are very rare, and only one such case has been reported [6]. Generally, no abnormal finding is present on abdominal angiography.

Polyarteritis nodosa (PAN) is idiopathic full-thickness necrotizing vasculitis that mainly affects middle-to-small muscular arteries [7, 8]. Its prognosis has recently been markedly improved by the use of steroids and immunosuppressive therapy [9–13], but it is still sometimes intractable, with a high mortality. Multiple colonic ulcers often occur in PAN, and digestive organ lesions are important indicators of the prognosis. The diagnostic indicators of abnormal abdominal angiography findings due to PAN have been established [14, 15], and included in the ACR classification criteria [7], but their improvement has not been closely described.

We encountered an SS patient complicated by PAN who not only achieved clinical remission due to prednisolone (PSL) and cyclophosphamide (CY) combination therapy, but also yielded normalized findings on abdominal angiography.

Case report

The patient was a 63-year-old woman admitted for complaints of epigastralgia and diarrhea on 5 July 2001. There was no particular past or familial medical history.

The patient had been aware of dry mouth and visited our hospital in 1998. She had a mass in the right parotid gland. Lobectomy was performed, and the pathological diagnosis was a benign lymphoepithelial lesion. On blood testing, the antinuclear antibody titer was 1:1,280 (speckled), and the anti-SS-A antibody titer was 64 times, showing positivity. The gum test finding was 3 mm/10 min; Schirmer's test, 3 mm on the right and 2 mm on the left; and rose Bengal test, (++). Primary SS was diagnosed, and the patient was undergoing outpatient treatment when the present illness developed.

The patient had reported malaise and appetite loss since early May 2001. Urticarial rash with pruritus appeared on the bilateral legs on 23 May and spread to the arms. Numbness of the extremities developed during the same period. Serum IgG level was normal, cryoglobulin was positive. Biopsy from the left forearm skin lesion revealed leukocytoclastic vasculitis, and then epigastralgia and diarrhea developed around 27 June.

On admission, height was 157 cm; body weight, 58 kg (−5 kg/6 months); blood pressure, 116/70 mmHg; body temperature, 36.9 °C; pulse rate, 92/min; respiratory and cardiac sounds were clear, abdomen was flat and soft, peristalsis was slightly enhanced, and tenderness was absent. Edematous erythemas–purpuras were present over the bilateral lower limbs, and small erythemas were noted on the bilateral forearms. Deep tendon reflex was normal. Numbness and decreased sensation were noted in the bilateral fingers and toes, and the anterior tibial muscle showed slight weakness.

For test findings on admission, complete blood count (CBC) was normal, and erythrocyte sedimentation was 28 mm/h, showing a slight increase. Urinalysis was normal, and BJ protein was negative. On biochemical testing, TP was 5.1 g/dl and Alb was 2.6 g/dl, showing hypoproteinemia. On immunoserological testing, CRP was 3.2 mg/dl, RF was 785.1 U/ml, and RAPA was 1:320, showing a high value, and IgG-type RF was negative. Antinuclear antibody was higher than 1:1,280 (spe); anti-SS-A antibody, 1:16; anti-SS-B antibody, negative; and all other anti-DNA, RNP, cardiolipin β2GP1, and cardiolipin antibodies and lupus anticoagulant, MPO-ANCA, and RP-3 ANCA were negative. The immunoglobulin and complement levels were within the normal ranges, and immune complex (C1q solid phase), HBs antigen, and anti-HCV and HIV antibodies were negative. On immunoelectrophoresis, IgA-κ M protein was detected, and IgA-κ/IgG mixed-type cryoglobulin was positive. Bone marrow aspiration showed normal. Fecal occult blood (human hemoglobin method) was strongly positive.

Signs and symptoms were absent at the time of admission, but malaise, diarrhea, and abdominal pain aggravated on the second hospital day, and sensory disorder of the bilateral fingers and weakness rapidly progressed. On electromyography performed on the same day, features of mononeuropathy multiplex were present. Together with skin biopsy findings, vasculitis associated with cryoglobulinemia was suspected, and because of rapid progression of the symptoms, administration of 60 mg PSL was initiated. Abdominal pain and diarrhea improved, and malaise and skin eruptions also slightly improved.

Although the abdominal symptoms improved, fecal occult blood was strongly positive. Colonoscopy was performed on the eighth day, and erosion, flare, and ulcers were present throughout the large intestine (Fig. 1). CY was concomitantly administered at 50 mg/day in consideration of severe vasculitis. On biopsy of colonic ulcer, nonspecific mucosal inflammation was noted, but the presence or absence of vascular inflammation was unclear because the specimen did not contain the submucosal layer. To investigate the cause, abdominal angiography was performed on the 13th day, and widely serpentine narrowed superior and inferior mesenteric arteries (SMA and IMA, respectively) and aneurysm formation were present (Fig. 2).

Histopathologically, the gastrocnemius muscle with no pain was biopsied, but no necrotizing vasculitis was present. PAN was diagnosed because four items of the ACR

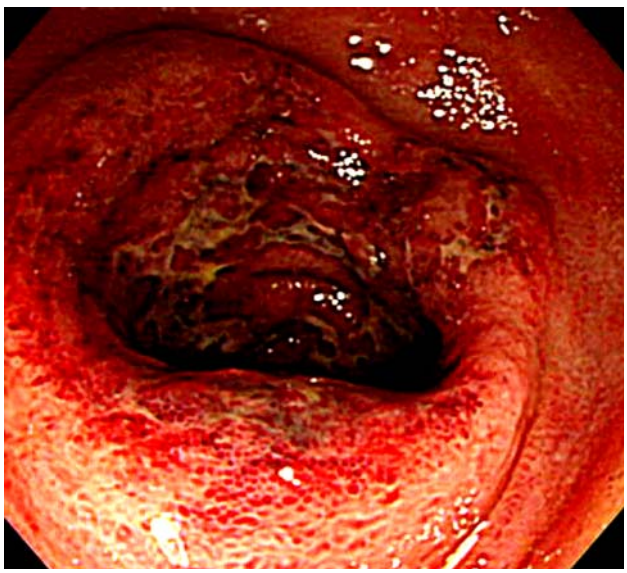

Fig. 1 Colonoscopy on the eighth hospital day. Map-like ulceration and erosion accompanied by severe flare were present in the ileocecal region. Similar ulceration was also seen in the splenic curvature of the transverse colon, and erosion and flare in the whole large intestine

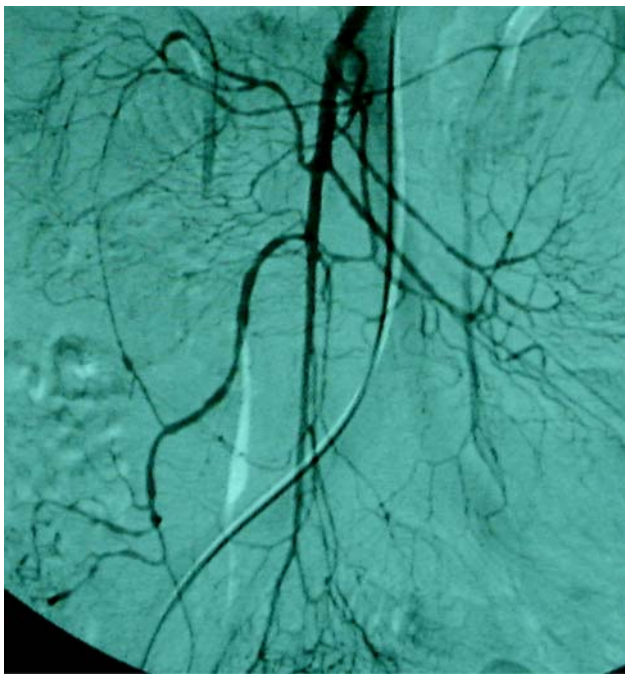

Fig. 2 Abdominal angiography on the 13th day. The superior mesenteric artery (SMA) was serpentine over a wide area, widened and narrowed, and accompanied by aneurysms. Similar changes were also noted in the inferior mesenteric artery (IMA)

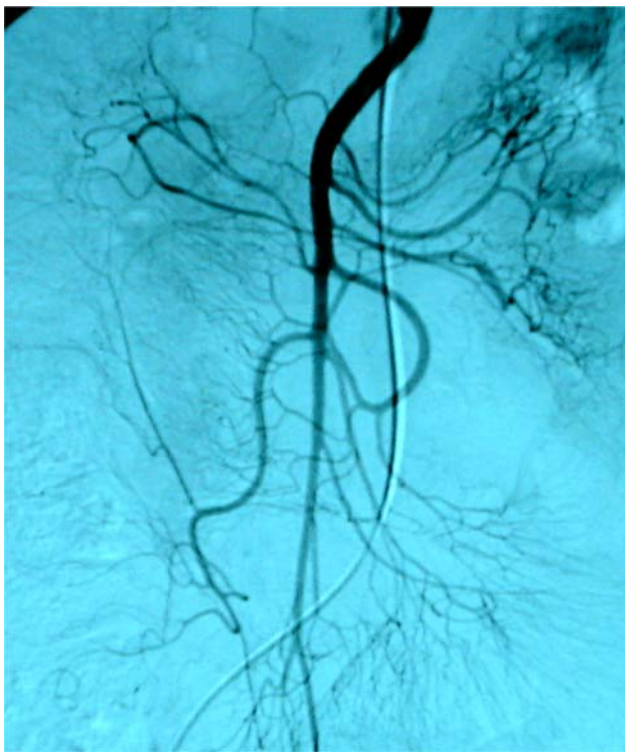

Fig. 3 Abdominal angiography on the 102nd day. The previous lesions had disappeared

classification criteria were met: body weight loss, weakness, mononeuropathy multiplex, and abnormal findings on abdominal angiography, with a five-factor score (FFS) [16] of 1, gastrointestinal (GI) tract involvement. The CY dose was increased to 100 mg on the 14th day, and steroid pulse therapy with 1 g/day methylprednisolone (MPSL) was performed on the 14–16th days, followed by 60 mg of PSL. Cryofiltration was performed for cryoglobulinemia on the 15th and 17th days, but it was discontinued after the second application because the IgG level decreased from 1,170 to 461.

The signs and symptoms markedly improved, excluding peripheral neuropathy, and CRP on the 19th day was <0.3 mg/dl. Fecal occult blood also became negative on the 29th day, and oral ingestion was initiated. The disease did not aggravate thereafter. Abdominal angiography was performed on the 34th day to assess the treatment, and both the SMA and the IMA had markedly improved. Colonoscopy was performed on the 42nd day, and the conditions had normalized, excluding the submucosal flare in the rectum. The final abdominal angiography was performed on the 102nd day, and the previous lesions had disappeared (Fig. 3). She was without recurrence thereafter. PSL was administered at 60 mg for eight weeks, and then the dose was reduced to 10 mg. The CY dose was also reduced to 75 mg/day on the 108th day. The symptoms remitted, excluding numbness of the hands and legs, and the patient was discharged on the 126th day. The course was stable on follow-up at the outpatient clinic, and CY treatment was discontinued on the 390th day (Fig. 4). There was no recurrence of the primary disease or complication by infection thereafter.

Discussion

Skin rash and mononeuropathy multiplex developed during the course of SS. We suspected vasculitis associated with cryoglobulinemia because cryoglobulin was positive, and features of leukocytoclastic vasculitis were noted on skin biopsy. However, multiple colonic ulcers were present, and abdominal angiography detected multiple aneurysms of the SMA and IMA and narrowed and serpentine arteries. Based on these findings, PAN was diagnosed. In SS, vasculitis may complicate directly due to SS or due to accompanying cryoglobulinemia [4, 5, 17]. In either case, skin rash and peripheral neuropathy generally develop, but multiple colonic ulcers are rare, and only one case has previously been reported in Japanese [6]. In a study of 70 SS cases reported by García-Bragado et al. [18], necrotizing vasculitis was noted on histopathology, but no abnormality was present on abdominal angiography. In vasculitis associated with cryoglobulinemia, immune

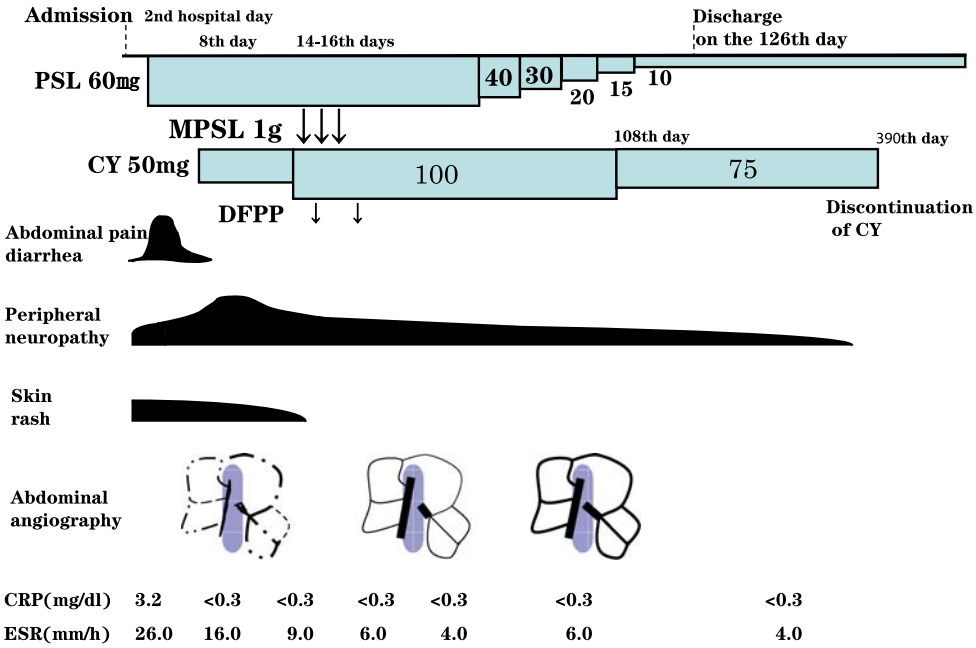

Fig. 4 Clinical course. *PSL* prednisolone, *MPSL* methylprednisolone, *CY* cyclophosphamide, *DFPP* double-filtration plasmapheresis

complexes are generally formed, causing hypocomplementemia and glomerular nephritis [19]. However, no immune complex was detected, the complement level was normal, and no clinical complication by glomerular nephritis developed in this patient. The incidence of multiple colonic ulcers is very rare in vasculitis associated with SS or cryoglobulinemia, but it often occurs in PAN. Based on the presence of lesions on the proximal SMA and IMA on abdominal angiography and the size of impaired blood vessels, it should not have occurred in vasculitis associated with conditions other than PAN. Therefore, the disease was diagnosed as PAN, although no histopathological findings of necrotizing vasculitis were obtained.

The findings on abdominal angiography improved and normalized with time. It has been suggested that the angiographic demonstration of aneurysms in PAN might identify a group of PAN patients with greater disease severity [20–22]. However, not all patients suffering from histologically verified PAN have angiographically demonstratable aneurysms [15]. Studies on angiographic changes in patients with PAN have been scarce, and controversy persists over what produces the regression of microaneurysms. While some authors consider regression to sclerosis or thrombosis to be without clinical significance [23, 24], others implicate a favorable prognosis induced by treatment [9, 25, 26].

To our knowledge, three cases with apparent improvement of abdominal angiographic findings on the proximal of middle size abdominal artery have been reported [27–29]. The primary disease rapidly remitted following concomitant steroid and CY treatment, and abdominal angiographic findings were improved in all patients (Table 1). The long-term prognosis of the three cases was unclear because it was not described in the reports, but it was possible to discontinue CY treatment in our patient, and the course was stable without recurrence of the primary disease or complication by infection.

The diagnostic criteria of PAN have been classified by the Amerian College of Rheumatology [7]. Three of the ten criteria must be present for a diagnosis of PAN. A positive angiography with typical findings is one of the ten criteria. The sensitivity and specificity of angiography in PAN have been reported to be 89 and 90%, respectively, with a positive predictive value of 55% and a negative predictive value of 98% [14]. New methods, such as multislice CT angiography or MRA of abdomen, may replace angiography in the future, but little experience of these imaging studies in relation to PAN exists [30].

The prognosis of untreated PAN is poor, with a five-year survival rate of 13% [31, 32]. Digestive organ lesions account for about 25% of deaths from the primary disease [33, 34], and so they show a marked influence on the prognosis, and this is one of the five factors in the prognostic score [16]. The five-factor score (FFS) considers the prognostic factors creatinemia (creatinine >1.58 mg/dl), proteinuria (>1 g/day), cardiomyopathy, GI tract involvement, central nervous system (CNS) involvement. When FFS = 0 (none of the five prognostic factors are present), mortality at 5 years is 11.9%; when FFS = 1, mortality is 25.9%; when FFS >2, mortality is 45.95% [16]. Steroid therapy and concomitant immunosuppressive therapy have markedly improved prognosis [9–13], but opportunistic infection due to long-term immunosuppressive therapy has become a serious issue [33, 34]. The prognosis of PAN is

Table 1 PAN cases with apparent improvements in angiographic findings

	Patient	Diagnosis	CRP (mg/dl)	ESR (mm/h)	Angiographic finding	Treatment
Yamada et al. [27]	16-year-old woman	CNS, HT, angiographic findings (muscular biopsy: no findings)	1.0	26	Narrowing of renal A, aneurysm •Improvement of abnormal findings 11 days after treatment •Improvement was maintained on 52 days after treatment	PSL60 mg, IVCY1 g × 3
Harada et al. [28]	51-year-old man	Body weight loss, mononeuropathy multiplex, angiographic finding (muscular biopsy: no finding)	0.1	70	Narrowing of IMA, multiple aneurysms •Aneurysms disappeared 37 days after treatment	PSL40 mg, IVCY1 g × 1
Raza et al. [29]	51-year-old man	Fever, body weight loss, angiographic findings, appendectomy, features of necrotizing vasculitis on autopsy	10	117	Irregular wall, linearity, aneurysm, and peripheral infarct of renal A •Improved, excluding infarction, after 6 doses of IVCY (after 4 months)	PSL40 mg, IVCY1 g × 6
This case	63-year-old woman	Body weight loss, mononeuropathy multiplex, skin rash, intestinal hemorrhage, angiographic findings (muscular biopsy: no finding)	3.2	26	Serpentine SMA and IMA, widening and narrowing, irregular wall, multiple aneurysms •Slightly improved 34 days after treatment •Improved at 102 days	MPSL pulse, PSL60 mg DFPP × 2, daily oral CY (discontinued after 390 days)

PSL prednisolone, *MPSL* methylprednisolone, *IVCY* intravenous cyclophosphamide, *CY* cyclophosphamide, *DFPP* double-filtration plasmapheresis, *SMA* superior mesenteric artery, *IMA* inferior mesenteric artery

dependent upon some clinical and biologic factors present at the time of diagnosis, independent of other clinical or biological events or side effects which can occur during follow-up [16]. In our report, improvement in angiographic findings served as a prognostic factor of PAN.

Conflict of interest All of the authors confirm that there is no conflict of interest with regard to this work.

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