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CASE REPORT

Cutaneous polyarteritis nodosa in a patient with Crohn's disease

Atsushi Komatsuda · Koji Kinoshita · Masaru Togashi · Nobuki Maki · Rie Masai · Hidetaka Niitsu · Setsuya Ohtani · Masato Sageshima · Ken-ichi Sawada · Hideki Wakui

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Abstract A 19-year-old Japanese woman with a 4-year history of Crohn's disease (CD) developed high fever, polyarthralgia, and painful subcutaneous nodules of the legs. A skin biopsy showed panarteritis with fibrinoid necrosis in the deep dermis. Endoscopic examination showed aphthous lesions in the entire colon. She was diagnosed with cutaneous polyarteritis nodosa (PAN) associated with CD. Steroid therapy improved her symptoms. To our knowledge, this is the first Japanese case of cutaneous PAN associated with CD.

Keywords Crohn's disease · Subcutaneous nodules · Inflammatory bowel disease · Polyarteritis nodosa

Introduction

Crohn's disease (CD, regional enteritis) is a chronic inflammatory bowel disease that commonly affects the ileum and cecum, small intestine, or colon [1]. CD is also associated with manifestations in other organ systems. Extraintestinal manifestations typically involve the musculoskeletal system, liver, skin, and eyes. Cutaneous lesions in patients with CD include granulomatous dermatitis, neutrophilic folliculitis, neutrophilic dermatoses including pyoderma gangrenosum, panniculitis, granulomatous vasculitis, leukocytoclastic vasculitis, psoriasis, and so-called metastatic CD [2].

On the other hand, cutaneous polyarteritis nodosa (PAN) involves the deep dermis, with pathological findings diagnostic for arteritis [3]. Moderate fever, arthritis, and painful skin nodules of the legs are frequently associated symptoms. Inflammatory active skin nodules show necrotizing arteritis with fibrinoid necrosis and leukocytoclasia.

In 1970, Dyer et al. [4] reported four cases of cutaneous PAN associated with CD as a hitherto unrecognized association. Since then, 11 similar cases have been described in the English literature [5–13]. Here, we report the first Japanese case of cutaneous PAN associated with CD.

Case report

A 19-year-old Japanese woman was admitted because of high fever, polyarthralgia, and painful subcutaneous nodules of the legs on 14 August 2007. In May 2003, she suffered from abdominal pain, diarrhea, and weight loss. Double-contrast barium enema revealed extensive ulceration of the wall of the descending colon and the sigmoid colon (Fig. 1a). Endoscopic examination showed multiple aphthous lesions and longitudinal ulcers in the sigmoid colon (Fig. 1b). Light microscopy of colon biopsy specimens showed chronic inflammation with lymphocyte infiltration and atrophic granuloma in the mucosa (Fig. 1c).

A. Komatsuda (✉) · K. Kinoshita · M. Togashi · N. Maki · R. Masai · K. Sawada · H. Wakui
Third Department of Internal Medicine,
Akita University School of Medicine,
1-1-1 Hondo, Akita 010-8543, Japan
e-mail: komatsud@med.akita-u.ac.jp

H. Niitsu
Department of Hematology,
Municipal Akita General Hospital, Akita, Japan

S. Ohtani
Department of Gastroenterology,
Municipal Akita General Hospital, Akita, Japan

M. Sageshima
Department of Pathology,
Municipal Akita General Hospital, Akita, Japan

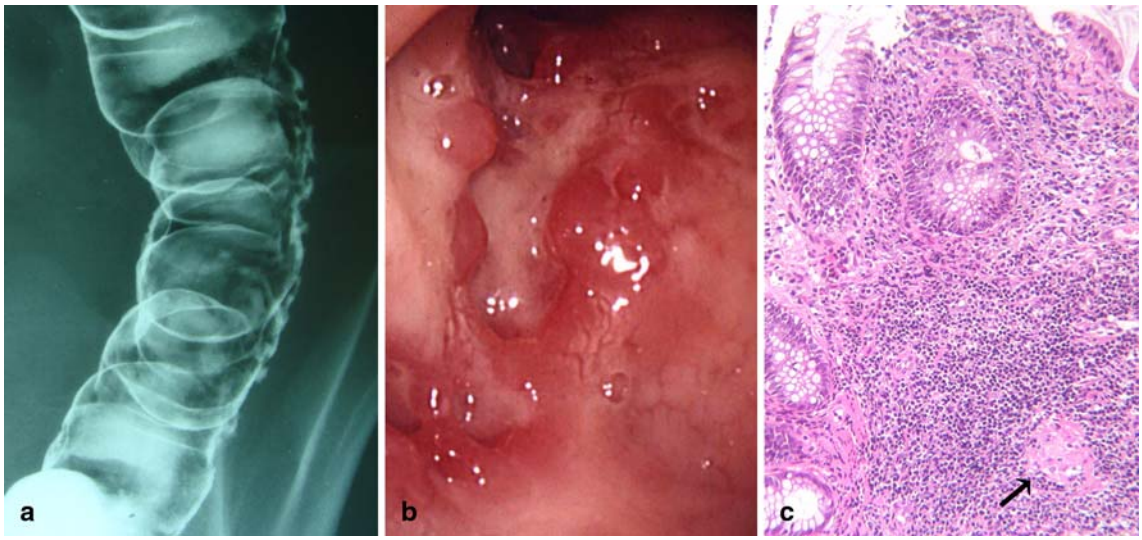

Fig. 1 **a** Double-contrast barium enema showing extensive ulceration of the wall of the descending colon. **b** Colonoscopy showing multiple aphthous lesions and longitudinal ulcers in the sigmoid colon. **c** Light microscopy of colon biopsy showing chronic inflammation with lymphocyte infiltration and atrophic granuloma (*arrow*) in the mucosa (H&E ×100)

From these findings, she was diagnosed with CD. Behçet's disease was excluded, because she had no symptoms such as oral and genital aphthous ulcers or uveitis. She was treated with mesalazine. Thereafter, her CD had been well controlled. From 2 August, she suffered from high fever, polyarthralgia, and painful subcutaneous nodules of the legs. Antibiotic therapy did not improve her symptoms.

On admission, the body temperature was 38.6°C, pulse rate 100 beats/min, and blood pressure 109/68 mmHg. A physical examination showed tender subcutaneous nodules of the legs. No abnormal signs were observed in the lungs, heart, or abdomen. There was no evidence of peripheral neuropathy.

Leukocyte count was 8,600 /μl (83% neutrophils, 1% eosinophils, 9% monocytes, 1% basophils, and 6% lymphocytes), hemoglobin 19.7 g/dl, and platelet count 48.0×10^4 /μl. Results of urine and sediments analyses were unremarkable. Serum total protein was 8.3 g/dl, blood urea nitrogen 11.1 mg/dl, creatinine 0.52 mg/dl, and uric acid 2.6 mg/dl. Liver function tests were normal. Serum C-reactive protein (CRP) was 8.92 mg/dl, IgG 1,610 mg/dl, IgA 138 mg/dl, IgM 81 mg/dl, CH50 45 U/ml (normal, 30–45 U/ml), C3 103 mg/dl (normal, 60–119 mg/dl), C4 24 mg/dl (normal, 16–43 mg/dl), and ferritin 2.0 ng/ml. Anti-nuclear antibodies and rheumatoid factor were negative. Circulating immune complexes were not detected by the C1q binding assay. Anti-neutrophil cytoplasmic antibodies (ANCA) were negative by the indirect immunofluorescence staining. Anti-myeloperoxidase ANCA and anti-proteinase 3 ANCA were not detected by enzyme-linked immunosorbent assays.

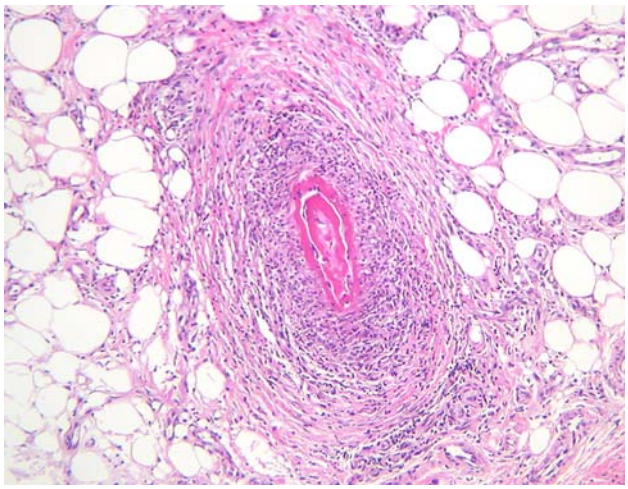

Fig. 2 Light microscopy of a skin biopsy specimen. Small subcutaneous artery in the deep dermis showing fibrinoid necrosis of wall, obliteration of lumen, and perivascular infiltration of lymphocytes (periodic acid-Shiff stain ×100)

A skin biopsy was performed on 17 August. Light microscopy showed panarteritis with fibrinoid necrosis and lymphocyte infiltration of a small artery in the deep dermis (Fig. 2) and septal panniculitis. There was no finding of granulomas. Endoscopic examination on 23 August demonstrated multiple aphthous lesions in the entire colon and terminal ileitis. From 3 September, she suffered from abdominal pain. A computed tomographic scan showed thickening of the bowel walls of the ascending colon.

From these findings, she was diagnosed with cutaneous PAN associated with active CD. She was treated with central

venous (CV) infusion and intravenous prednisolone (60 mg/day for 2 weeks). Intravenous prednisolone was then tapered gradually. Although cutaneous PAN improved, high fever persisted. From 3 October, methylprednisolone pulse therapy (500 mg/day) was performed for 3 days. On 12 October, CV catheter was removed, because catheter fever was considered. Thereafter, she turned afebrile, and oral prednisolone was tapered gradually from 15 October. She was discharged on 2 November. At that time, serum CRP was 0.13 mg/dl. At a follow-up on 26 March 2008, she was treated with 10 mg/day of prednisolone and 1.5 g/day of mesalazine. Her CD was well controlled.

Discussion

Our patient developed high fever, polyarthralgia, and painful subcutaneous nodules of the legs 4 years after the onset of CD. Clinical symptoms and histological findings were consistent with those of cutaneous PAN [3]. Steroid therapy improved the symptoms.

The two common cutaneous complications of CD are pyoderma gangrenosum and erythema nodosum [1]. Pyoderma gangrenosum almost always develops during a bout of acute colitis and generally resolves with control of the colitis by steroid therapy. The activity of erythema nodosum, which is seen particularly in children, follows the activity of CD. Other common cutaneous complications of CD are granulomatous dermatitis, neutrophilic folliculitis, and granulomatous vasculitis [2].

Cutaneous PAN is a rare cutaneous complication in patients with CD. To our knowledge, 15 cases of cutaneous PAN associated with CD were described in the English literature [4–13]. All reports were from Europe or the US. Tables 1 and 2 summarize clinicopathological features in the previously reported cases and our case (eight males and seven females). The median age was 31 years (range 13–57). Cutaneous manifestations included painful subcutaneous nodules, erythema, livedo reticularis, and ulcerations. Common pathological findings of skin biopsy specimens were necrotizing arteritis. Systemic manifestations, such as fever, arthralgia, and myalgia, were observed in some patients. Other manifestations were episcleritis and genital ulcers. There was no description of the occurrence of peripheral neuropathy. In the majority of patients, cutaneous PAN developed after the onset of CD. Pre-existing periods of CD were variable among the patients. Most patients had active CD and were treated with steroids with or without immunosuppressive agents. Aminosalicylates, such as sulfasalazine and mesalazine, were also used in nine patients. In eight patients, surgical therapy was required. Cutaneous PAN and CD improved in all patients after treatment, except for two unknown cases. To our knowledge, there is no case repot of systemic PAN complicating with CD.

Abnormal immune responses to some specific pathogen have been implicated in the pathogenesis of CD and cutaneous PAN [1, 3]. Graña Gil et al. [12] suggested that an association between CD and cutaneous PAN is not casual, and that they have a common etiopathogenic basis,

Table 1 Skin manifestations in published cases and our case of cutaneous PAN associated with CD

Patient no.	References	Age	Sex	Skin manifestation	Skin biopsy pathology
1	[4, 5]	25	M	Purplish erythema with nodulation	Necrotizing arteritis
2	[4, 5]	32	M	Indurated erythematous patches	Resolving vasculitis[a]
3	[4, 5]	41	M	Erythema	ND
4	[4, 5]	16	F	Painful nodules, reticulation	Necrotizing arteritis
5	[5]	24	M	Violaceous discoloration	Normal[a]
6	[5]	20	M	Erythematosus papules, purplish tender nodules	Granulomatous arteritis
7	[6]	NA	NA	NA	NA
8	[7]	20	F	Painful subcutaneous nodules, livedo reticularis	Panarteritis
9	[7]	46	F	Painful subcutaneous nodules, livedo reticularis, ulcers	Polyarteritis nodosa
10	[8]	24	M	Painful subcutaneous nodules	Panarteritis
11	[9]	13	F	Erythema, painful subcutaneous nodules	Granulomatous panarteritis
12	[10]	54	M	Painful subcutaneous nodules, ulcers	Panarteritis
13	[11]	31	F	Painful subcutaneous nodules	Necrotizing arteritis
14	[12]	57	F	Painful subcutaneous nodules	Necrotizing arteritis
15	[13]	45	F	Subcutaneous nodules, livedo reticularis, ulcers	Necrotizing arteritis
16	Present case	19	F	Painful subcutaneous nodules	Necrotizing panarteritis

NA not available, *ND* not done

[a] After treatment

Table 2 Clinical findings and outcomes in published cases and our case of cutaneous PAN associated with CD

Patient no.	Systemic manifestation				Pre-existing period of CD	CD activity	Treatment	Outcome
	Fever	Arthralgia	Myalgia	Others				
1	+	+			4 years	Active	Steroid	Improved
2	+			Episcleritis	18 months	Active	Steroid, OP	Improved
3		+			1 year	Active	OP	Improved
4					[a]	Active	OP	Improved
5	+				2 years	Active	Steroid	Improved
6					6 months	Active	Steroid, AZP	Improved
7					1 year	NA	NA	NA
8					1 year	Inactive	PSL, SS, OP	Improved
9		+		Episcleritis	Uncertain	Active	OP, steroid, SS	Improved
10					2 years	Active	SS, steroid, AZP	Improved
11					6 years	Inactive	SS, steroid	NA
12			+		30 years	Active	SS, steroid, AZP, CPA	Improved[b]
13		+	+		[a]	Active	Steroid, CPA, AZP, OP, SS	Improved
14		+			[c]	Active	OP, SS, PSL,	Improved
15	+	+	+	Genital ulcers	[a]	Active	CPA, steroid, OP, SS, AZP	Improved
16	+	+			4 years	Active	MS, steroid	Improved

AZP azathioprine, *CPA* cyclophosphamide, *MS* mesalazine, *NA* not available, *OP* operation, *PSL* prednisolone, *SS* sulfasalazine

[a] Symptoms of cutaneous PAN developed before the onset of CD

[b] Lymphoma developed 5 months after all therapy was stopped

[c] Cutaneous PAN and CD developed at the same time

because the two disorders have been described in association with various diseases with underlying immunological alterations. However, differences in immunological abnormalities between CD patients with and without cutaneous PAN are uncertain at present. The accumulation of cases will be needed to clarify this issue.

In summary, we report the first Japanese case of cutaneous PAN associated with CD. When patients with CD develop painful subcutaneous nodules, cutaneous PAN should be considered as a rare complication. Since the involved artery is always located in the deep dermis [3], superficial punch biopsies should be avoided and excision biopsies should be performed for correct diagnosis.

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