



# Chronic nonspecific multiple ulcer of the small intestine segregates in offspring from consanguinity

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## Abstract

**Background and aims:** Chronic nonspecific multiple ulcer of the small intestine is a recently proposed enteropathy characterized by persistent blood and protein loss from the small-bowel. We examined possible segregation of the disease in family pedigrees.

**Methods:** All cases of the disease diagnosed at our institution were reviewed with respect to particular focuses on the presence of close consanguinity in the families, the enteroscopic findings and the long-term clinical course. The diagnosis was based on persistent occult gastrointestinal bleeding and hypoproteinemia for more than 5 years, and irregularly shaped shallow ulcers in the ileum.

**Results:** During a 45-year-period, 13 patients were diagnosed as having the disease. There were 11 females and 2 males, with ages ranging from 8 to 37 years at the time of the initial presentation and with those from 13 to 38 years at the diagnosis. Enteroscopy performed in 11 patients with a time duration ranging from 0.5 to 44 years after the diagnosis revealed active ileal ulcers in 10 patients. Parents' consanguineous marriage was verified in 6 patients, two of whom also had siblings with the enteropathy. Another patient without consanguinity had a sibling with protein-losing enteropathy.

**Conclusion:** Chronic nonspecific multiple ulcer of the small intestine seems to segregate in offspring from consanguineous marriage.

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## 1. Introduction

The use of capsule endoscopy and balloon endoscopy has led to an increase in the chance of encountering small-bowel ulcers, especially in patients with obscure gastrointestinal bleeding.<sup>1,2</sup> While Crohn's disease, intestinal tuberculosis,

radiation enteropathy, and nonsteroidal anti-inflammatory drug (NSAID) enteropathy are entities predisposing to chronic or recurrent small-bowel ulcers, there are cases of ulcers with obscure origin.

We recently reported on a peculiar form of enteropathy characterized by chronic blood and protein loss through persistent small-bowel ulcers.<sup>3</sup> Because the ulcers of the disease had nonspecific histology, we referred to the condition as "chronic nonspecific multiple ulcer of the small intestine (CNSU)".<sup>3,4</sup> CNSU does not seem to be a rare entity, because cases of exactly the same clinicopathologic features have subsequently been reported in the literature.<sup>5–7</sup> Furthermore, a similar enteropathy with different nomenclatures has been described in Caucasians and referred to as "diaphragm disease of the small bowel without apparent NSAID use"<sup>8</sup> or as "cryptogenic multifocal ulcerous stenosing enteritis".<sup>9</sup> More recently, Adler et al.<sup>10</sup> reported a novel enteropathy in a middle aged American male characterized by blood loss from recurrent small-bowel ulcers. Surprisingly, Adler's case had compound heterozygous mutations in the encoding regions of *cytosolic phospholipase A2 $\alpha$*  (*cPLA2 $\alpha$* ) gene. Based on the description, we hypothesized CNSU to be a hereditary condition with genetic alterations. We thus retrospectively investigated family histories of CNSU in patients with the disease identified at our institution.

## 2. Patients and methods

### 2.1. Survey for CNSU

We reviewed the diagnosis, the prevalence, and the management of inflammatory bowel diseases diagnosed during a period 1964–2009 at Kyushu University Hospital, Fukuoka University Chikushi Hospital, and their satellite hospitals, and collected data for clinicopathologic features of patients with CNSU. The two referral centers have been treating approximately 600 patients with Crohn's disease and 800 patients with ulcerative colitis.

### 2.2. Diagnosis of CNSU

The diagnosis of CNSU was made on the basis of clinical manifestations and small-bowel lesions.<sup>4</sup> As for clinical manifestations, patients with CNSU should have iron deficiency anemia and hypoproteinemia in their adolescence.<sup>4</sup> Small-bowel lesions should be multiple shallow ulcers in the ileum, with sharply demarcated margin and linear or oblique configuration (Fig. 1).<sup>11</sup> Furthermore, the repeated ascertainment of those clinical manifestations with time intervals for more than 5 years was inevitable for the diagnosis of CNSU.

### 2.3. Data collection

We focused on the demographic data regarding the initial clinical manifestation, which led to the identification of small-bowel ulcers, the age at the onset, and the laboratory values of serum protein, serum albumin, C-reactive protein (CRP), hemoglobin, and white blood cell count at the time of the initial diagnosis. We also reviewed histories and laboratory data presumably associated with other enteropathy. They



**Figure 1** Typical macroscopic findings of the resected ileum in a case of CNSU (Case 9). There are shallow and clear ulcers in circular or linear configuration in the ileum. The intervening mucosa is not affected.

included history of NSAID use, purified protein derivative (PPD) skin test, interferon- $\gamma$  assays (IGRA) for *Mycobacterium* infection, anti-tissue transglutaminase (tTGA) antibodies, findings obtained by esophagogastroduodenoscopy with forceps biopsy, and histologic findings of the resected small bowel. In addition, medical and surgical treatments, response to the medication as determined by changes in serum protein value, and prognosis were retrospectively investigated. We also collected data of the final enteroscopic findings. The procedures for enteroscopy included retrograde ileoscopy (RI), double balloon endoscopy (DBE) and intraoperative endoscopy (IOE). The enteroscopic findings were evaluated with regard to the stage (open or scarred), the depth (deep or shallow), and the configuration (circular, linear, or their combination) of the representative lesion.<sup>11</sup>

We directly contacted the patients and/or their relatives to obtain family histories. The items of special interest were consanguinity, anemia, malnutrition, abdominal surgery, and clinical diagnosis of enteropathy, if any, in the family pedigrees. Family history of enteropathy was regarded as positive in the case of surgical interventions for the small bowel, the established diagnosis of small-bowel ulcers or both. We examined the medical records of the relatives with enteropathy in the case that the records were available.

This retrospective study was approved by the ethical committee at Kyushu University Hospital, and it was undertaken in accordance with Helsinki Declaration.

## 3. Results

### 3.1. Clinical features and laboratory data

During a period from 1964 to 2009, 13 patients were diagnosed with CNSU. Table 1 summarizes the clinical features of the patients. There were 11 females and two males. All patients had anemia of obscure origin as the presenting symptom. In addition, three patients had edema and other two patients complained of abdominal pain. The age at the time of the onset ranged from 8 to 37 years. Eleven patients complained of the symptoms at the age of less than 20 years. The time interval

**Table 1** Cases of CNSU diagnosed at our institution during 1964–2009.

Case no.	Age (yrs)/gender		Presenting symptoms	Laboratory data		
	Onset	Diagnosis of CNSU		Hemoglobin (g/dl)	Serum protein (g/dl)	CRP (mg/dl)
1.	20/F	27	Anemia, edema	8.2	4.9	—*
2.	15/F	24	Anemia, edema	3.5	5.0	—*
3.	10/M	26	Anemia, growth retardation	4.4	4.5	—*
4.	15/F	28	Anemia, edema	4.7	5.3	—*
5.	12/F	27	Anemia, abdominal pain	9.7	5.8	0.3
6.	17/F	34	Anemia	9.6	4.6	0.5
7.	10/F	13	Anemia, abdominal pain	7.4	5.4	0.1
8.	37/F	38	Anemia	9.5	6.7	0.5
9.	15/M	30	Anemia, edema	7.4	8.2	0.1
10.	13/F	29	Anemia	5.9	4.6	0.2
11.	16/F	52	Anemia	5.3	6.3	0.1
12.	13/F	40	Anemia	9.4	4.1	1.1
13.	8/F	33	Anemia, edema	8.6	4.5	0.6

\* CRP was determined to be negative under semi-quantitative measurement.

from the onset until diagnosis of CNSU ranged from 1 to 27 years (median; 15 years). NSAID use was not verified in any patient at the time of the initial diagnosis. We further confirmed possible use of NSAID in seven patients who had been under observation. Those patients again clearly denied any continuous use of NSAID or other medications at the time of their first diagnosis of CNSU.

Laboratory data at the initial diagnosis showed hypochromic anemia and hypoproteinemia. The hemoglobin value ranged from 3.5 to 9.7 g/dl and serum protein value from 4.1

to 8.2 g/dl. In four patients (Cases 1–4) with the diagnosis of CNSU in 1970s, CRP value was not quantified. In the remaining nine patients, there were slight increases in CRP with values from 0.1 to 1.1 mg/dl.

Eleven patients were treated by surgery. The remaining two patients (Cases 11 and 13) were diagnosed with CNSU on the basis of the clinical and enteroscopic findings. Results of the diagnostic work-up are summarized in Table 2. PPD skin test and IGRA showed none of the patients to be positive for *Mycobacterium* infection. Anti-tTGA antibodies were measured

**Table 2** Results of diagnostic work up for patients with CNSU.

Case no.	PPD skin test	IGRA test	Anti-tTGA antibody	Gastroduodenal lesions			Surgically removed ileal lesions			Final enteroscopic findings			
				Endoscopy	Granuloma	Villous atrophy	Maximal depth of ulcer	Granuloma	Villous atrophy	Concentric stenosis	Non-stricturing ulcers		
										Number	Open ulcer at stenosis	Circular	Linear
1.	—	NE	NE	NS	—	—	Submucosa	—	—	NE	NE	NE	NE
2.	—	NE	NE	Gastric ulcer	—	—	Submucosa	—	—	Multiple	+	+	+
3.	—	NE	NE	NS	—	—	Submucosa	—	—	NE	NE	NE	NE
4.	—	NE	NE	NS	—	—	Submucosa	—	—	Single	+	—	—
5.	+	—	NE	Duodenal ulcer	—	—	Submucosa	—	—	NE	NE	NE	NE
6.	+	—	NE	NS	—	—	Submucosa	—	—	Multiple	+	+	+
7.	—	—	NE	NS	—	—	Submucosa	—	—	Single	+	+	—
8.	±	—	NE	Stomal ulcer	—	—	Submucosa	—	—	—	—	+	+
9.	—	NE	NE	Stomal ulcer	—	—	Submucosa	—	—	Single	+	+	—
10.	—	NE	NE	NS	—	—	Submucosa	—	—	Multiple	+	+	+
11.	—	NE	NE	NS	—	—	NE	NE	NE	Single	+	—	—
12.	—	NE	NE	NS	—	—	Submucosa	—	—	Multiple	+	—	+
13.	—	—	—	NS	—	—	NE	NE	NE	Single	+	—	+

PPD; purified protein derivative. IGRA; interferon- $\gamma$  release assays for tuberculosis. tTGA; tissue transglutaminase.

NS; no significant finding. NE; not examined.

in only one patient, who showed a negative result. Two patients had a prior history of gastrectomy for gastroduodenal ulcers. Both patients had stomal ulcers. Two patients had gastric or duodenal ulcer. However, duodenal biopsies performed in all the patients were negative for villous atrophy. Also, villous atrophy of the ileum was not evident in any patient treated by ileal resection. The depth of the ileal ulcer was restricted to the submucosa in those patients. There was not any patient who had caseating or non-caseating granuloma in the biopsy or surgical specimens.

Table 3 summarizes the treatments applied for the patients. During the follow-up periods, prednisolone, aminosalicylates, combined anti-*Mycobacterium* agents, azathioprine and infliximab were used for nine patients, seven patients, six patients, two patients and a patient, respectively. The serum protein did not respond to any of those medications. In nine patients, the malnutrition transiently improved after total parenteral nutrition. Eleven patients were treated by ileal resection because of small-bowel stricture. Ten of those 11 patients, however, required repeated surgery after the recurrence of strictures. As indicated in Table 3, two patients were lost to follow up, while other four patients died. The remaining seven patients have been under observation. They still have hypoproteinemia and anemia, which require iron supplementation and total parenteral or enteral nutrition.

### 3.2. Final enteroscopic findings

We attempted enteroscopy in 11 patients during the clinical course. The time interval from the initial diagnosis until the final enteroscopy ranged from 0.5 to 44 years. In a patient (Case 5), however, enteroscopy was unavailable because of a duodenal stenosis.

The enteroscopic findings are indicated in Table 2. Nine patients had single or multiple concentric strictures. In those patients, shallow and clearly demarcated ulcers were seen at the most severe stenosis (Figs. 2A and 3A). In addition, shallow ulcers accompanied by faint mucous exudates were seen in eight patients (Figs. 2B and 3B). A patient had a single stenosis without any accompanying mucosal defects.

### 3.3. Family history

Family histories of the patients are indicated in Table 4. The interviews to the patients and their relatives revealed that four patients were offspring of consanguineous marriage of 3 degrees, which means that their parents were cousins. In addition, other two patients were those of 5 degrees, indicating that their maternal and paternal grandparents were cousins. Four patients denied any such consanguinity in their family pedigrees. In the remaining three patients, we were not able to confirm their family pedigrees.

Information with regard to family histories of enteropathy was available in 11 patients. None of the patients commented on enteropathy in their parents or in their offspring. However, three patients commented on enteropathy in their siblings. The enteropathy included small intestinal stenoses of obscure origin (an elder sister of Case 4), CNSU (a younger sister of Case 10) verified in her medical record, and protein-losing enteropathy of obscure origin (an elder sister in Case 13). Two of the three family pedigrees were siblings of consanguineous marriage, while consanguinity was not evident in the remaining pedigree.

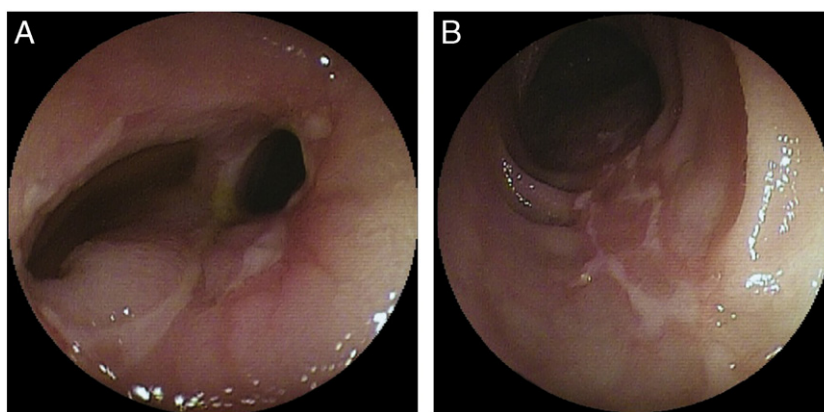
### 4. Discussion

We could confirm in this report that 1) CNSU is an enteropathy characterized by persistent anemia and hypoproteinemia occurring in childhood or in adolescence, 2) patients with CNSU had life-long illness, and 3) more than half of the patients had consanguinity and/or family history of enteropathy in their siblings even though vertical heredity was not obvious. These clinical observations suggest that CNSU is possibly a chronic enteropathy, which segregates in offspring from consanguinity. Even though most autosomal recessive disorders of the human bowel occur in infancy,<sup>12</sup> there have been recently reported two gastrointestinal disorders with such a hereditary trait, one being adenomatous polyposis with homozygous mutations of *MUTYH*<sup>13–15</sup> and the other chronic colitis with homozygous mutations of *IL10R*.<sup>16</sup>

**Table 3** Treatment and prognosis of patients with CNSU.

Case no.	Medication		Efficacy of total parenteral nutrition	Number of ileal resection	Prognosis
	Species	Efficacy			
1.	PSL, cAMA	Not effective	Effective	2	Lost to follow-up
2.	PSL, cAMA, SASP	Not effective	Effective	3	Died of liver cirrhosis at age of 49 years
3.	PSL, cAMA	Not effective	(Not performed)	6	Lost to follow-up
4.	PSL, cAMA, SASP	Not effective	Effective	3	Died of pancreas cancer at age of 73 years
5.	PSL	Not effective	Effective	2	Alive at age of 59 years
6.	PSL, 5ASA, AZA	Not effective	Effective	1	Alive at age of 58 years
7.	PSL, cAMA	Not effective	Effective	6	Died of thyroid cancer at age of 58 years
8.	PSL, 5ASA	Not effective	Effective	2	Alive at age of 75 years
9.	PSL, cAMA, SASP	Not effective	(Not performed)	2	Alive at age of 67 years
10.	5ASA	Not effective	Effective	2	Died of stroke at age of 46 years
11.	IFX	Not effective	(Not performed)	0	Alive at the age of 60 years
12.	(None)		Effective	3	Alive at the age of 50 years
13.	5ASA, AZA	Not effective	(Not performed)	0	Alive at the age of 35 years

PSL; prednisolone, cAMA; combined anti-*Mycobacterium* agents, SASP; sulfasalazine, 5ASA; 5-aminosalicylate, AZA; azathioprine, IFX; infliximab.



**Figure 2** Enteroscopic findings of Case 13. This case is a daughter of a consanguineous marriage of 3 degrees, who has an elderly sister with protein-losing enteropathy. A; DBE reveals a severe concentric stenosis in the middle ileum. The stenotic area is accompanied by circular and sharply demarcated ulcer. B; DBE also shows a shallow, linear mucosal defect with clear margin in the distal ileum.

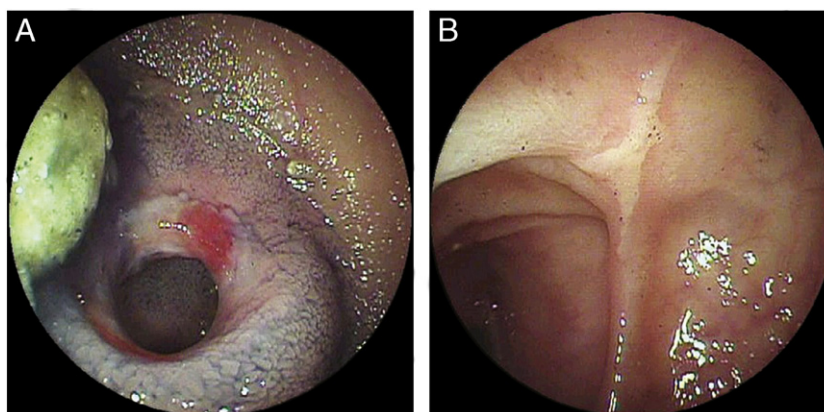
Small-bowel ulcers are known to occur in various types of chronic enteropathy of obscure etiology. These include Crohn's disease, chronic ulcerative duodenojejunoileitis,<sup>17–19</sup> cryptogenic multifocal ulcerous stenosing enteritis (CMUSE),<sup>9</sup> and diaphragm disease of the small bowel without apparent NSAID use.<sup>8</sup> CNSU shares common clinical manifestations with CMUSE and diaphragms unrelated to NSAID with respect to less severe inflammatory infiltrates and stenosing lesions of the ileum. We thus cannot conclusively distinguish CNSU from those two conditions. There also seems to be an argument that CNSU, together with CMUSE and diaphragms, belongs to a peculiar phenotype of Crohn's disease with less severe inflammation. The occurrence in adolescents with predominant involvement of the ileum in CNSU apparently mimics Crohn's disease, although the ileal phenotype is different between the two diseases.

In 1990s, data on the familial acquisition of Crohn's disease were accumulated. Analyses of those data from all over the world showed that the occurrence of Crohn's disease in the first-degree relatives of a proband ranged from 2.2% to 13.6%.<sup>20–26</sup> A common trend in those analyses was that the siblings of a proband were at the highest risk for the occurrence of the disease while parents have the lowest risk. Although a similar trend was also found in our patients with CNSU, the occurrence of enteropathy in the siblings was much higher,

with a value of 23%. In contrast, the consanguinity has rarely been described in Crohn's disease. It thus seems likely that CNSU is genetically different from Crohn's disease.

So far as we reviewed the literature, two types of enteropathy are described in association of consanguinity. The first one is an intractable ulcerating enterocolitis of infancy characterized by diarrhea in the first year of life with large and deep ulcers in the colon.<sup>27</sup> The other enteropathy, referred to as intestinal epithelial dysphasia, has also been characterized by severe diarrhea in infants with disorganization of enterocytes in the epithelium and basement membrane abnormalities of the small-bowel.<sup>28,29</sup> The clinicopathologic features of the infantile enteropathy are obviously different from those of CNSU with respect to the age of onset and the clinical course.

Glocker et al.<sup>16</sup> recently analyzed two unrelated consanguineous families with an early onset of colitis, and they identified homozygous mutations in *IL10RA* and *IL-10RB* genes in the families. Even though the predominant site of involvement and other phenotypes are different between the cases reported by Glocker et al.<sup>16</sup> and those of CNSU, *IL-10R* may be one of the candidate genes associated with CNSU. Adler et al.<sup>10</sup> reported on another peculiar form of enteropathy with a life-long history of occult gastrointestinal



**Figure 3** Enteroscopic findings of Case 6. This case is a daughter of a consanguineous marriage of 5 degrees. A; DBE shows a concentric stenosis with a clear ulcer in the ileum. B; in the distal ileum, sharply demarcated and linear mucosal defects are also seen.

**Table 4** Consanguinity and family history of patients with CNSU.

Case no.	Consanguinity (degrees)	Family history of enteropathy
1.	Present (3)	None
2.	Absent	None
3.	Unknown	Unknown
4.	Absent	None
5.	Absent	A sibling
6.	Present (5)	None
7.	Present (5)	None
8.	Present (3)	None
9.	Unknown	Unknown
10.	Present (3)	A sibling
11.	Unknown	None
12.	Absent	None
13.	Present (3)	A sibling

blood loss, iron deficiency anemia and relapsing abdominal pain. The male patient had multiple, sharply demarcated ulcers and stenoses in the jejunum and in the ileum during his middle-aged period. Histological examination of the resected small-bowel disclosed nonspecific ulcers with minimal inflammatory infiltrates. Furthermore, Adler et al.<sup>10</sup> confirmed that the patient had inherited compound heterozygosity in *cPLA2 $\alpha$*  gene, which resulted in a reduction in eicosanoid biosynthesis in platelets and leukocytes. Based on these observations, it was suggested that homozygous or compound heterozygous mutations of *cPLA2 $\alpha$*  gene and a consequent reduction in substrates for arachidonic acids result in an enteropathy with recurrent small-bowel ulcers. It thus seems possible that *cPLA2 $\alpha$*  is another candidate gene for CNSU. This hypothesis is under investigation.

The present case series has some limitations due to a retrospective analysis of historically accumulated patients. First, we cannot completely deny undisclosed use of NSAID, because we did not measure its metabolites in blood or urine samples.<sup>8,30</sup> However, we believe the enteroscopic findings and the extra-ordinary long-term clinical course of CNSU to be completely different from NSAID enteropathy.<sup>3</sup> Second, we could not serologically deny chronic jejunoileitis complicating celiac disease in 12 of 13 patients. However, we consider celiac disease to be unlikely, because the patients did not have any villous atrophy, and furthermore, the disease is extremely rare among Asians.

In conclusion, a retrospective analysis of patients with CNSU revealed that the disease is possibly an enteropathy segregating in offsprings from consanguineous marriage. This concept may explain the rarity of the disease, and suggests that CNSU is a disease distinct from Crohn's disease. Further accumulation of the patients together with genetic analyses will be needed to conclude that CNSU is an autosomal recessive disorder.

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TaM contributed to the analysis of the data and the writing of the manuscript. NK collected all the demographic and

endoscopic data. ToM, MI and TY contributed to the concept of the manuscript and the management of the study subjects.

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