

Chronic Enteropathy Associated with *SLCO2A1* in a Patient with Anemia Detected on Incidental Screening

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Abstract

A 74-year-old woman with a history of non-steroidal anti-inflammatory drug (NSAID) use for knee osteoarthritis was diagnosed with anemia during a Japanese comprehensive health check-up. Anemia was detected for 3 consecutive years but was left untreated as she was asymptomatic. She was referred to our hospital for workup of chronic anemia and pedal edema. A gastric ulcer and multiple intestinal ulcers were identified on upper gastrointestinal and capsule endoscopies. She was initially diagnosed with NSAID-induced gastric and intestinal ulcers and we discontinued NSAID therapy. This resulted in an improvement in the gastric ulcer but not the small intestinal ulcers. On further questioning, she reported a family history of consanguineous marriage. The patient underwent further investigations including genetic testing and a transanal double-balloon enteroscopy and was finally diagnosed with chronic enteropathy associated with *SLCO2A1* (CEAS). In this study, we report a case of CEAS diagnosed in a patient with anemia detected incidentally during routine screening which was differentiated from drug-induced small intestinal mucosal injury after additional investigations.

Keywords chronic enteropathy associated with *SLCO2A1* (CEAS), non-steroidal anti-inflammatory drugs (NSAIDs), capsule endoscopy, balloon enteroscopy

Chronic nonspecific multiple ulcers of the small intestine (CNSU) were first described by Okabe *et al.*¹ and Shimazaki *et al.*² and are characterized by chronic and intractable nonspecific ulceration of the small intestine. Following the recent identification of the causative gene *SLCO2A1*, chronic enteropathy associated with *SLCO2A1* (CEAS) was suggested as a more appropriate nomenclature. The increasing use of double-balloon enteroscopy and capsule endoscopy in routine clinical practice has led to improved awareness of the endoscopic features of diseases of the small intestine, including CEAS. Herein, we report a case of CEAS in a patient with a history of non-steroidal anti-inflammatory drug (NSAID) use that was initially diagnosed with drug-induced small intestinal mucosal injury.

Case Report

A 74-year-old woman visited our hospital for workup of asymptomatic anemia (Hemoglobin [Hb], approximately 10 g/dL) that was detected by opportunistic screening but left untreated for 3 years. The patient had a history of knee osteoarthritis for which she was

taking diclofenac (three 25 mg-tablets/day), without gastric protection, for approximately 3 years prior. She was born to consanguineous parents (first cousins). There was no personal or family history of enteropathy. General examination revealed conjunctival pallor and bilateral pedal pitting edema, with no abnormalities on abdominal and musculoskeletal examination.

Investigation Findings

Blood test results showed normocytic normochromic anemia, undernutrition, and mild elevation of inflammatory markers (Table 1). A single ulcer (stage A2) in the antral zone of the lesser curvature was seen on upper gastrointestinal endoscopy (Fig. 1a, b), with no evidence of atrophic changes or no signs of gastritis in the gastric mucosa surrounding the ulcer. Tests for *Helicobacter pylori* were negative. There was no evidence of pathology in the colon, rectum, or anus identified on lower gastrointestinal endoscopy. Capsule endoscopy identified more than 40 ulcers in the ileum. Ulcers were deeply penetrating, and some were annular (Fig. 2a, b).

Treatment

The patient was initially diagnosed with NSAID-

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Table 1. Blood Test Results at the Initial Hospital Visit

Full blood count			Biochemical tests	
WBC	7000	/ μ L	D.Bil/T.Bil	0.1/0.2 mg/dL
RBC	298×10^4	/ μ L	T.P.	6.5 g/dL
Hb	8.6	g/dL	Alb	3.1 g/dL
Ht	28.9	%	AST	23 IU/L
MCV	97	fL	ALT	19 IU/L
MCHC	39.8	Pg	LDH	235 IU/L
Plt	43.5×10^4	/ μ L	ALP	233 IU/L
Immunological test			γ -GTP	15 IU/L
CRP	0.41	mg/dL	Amy	80 IU/L
			BUN	10 mg/dL
			Cr	0.7 mg/dL
			Na/K/Cl	141/4.5/106 mEq/dL
			Fe	148 μ g/dL
			UIBC	307 μ g/dL
			Ferritin	9.8 ng/dL
			TBINF- γ	(-)

TBINF- γ : QuantiFERON-Plus TB IFN γ

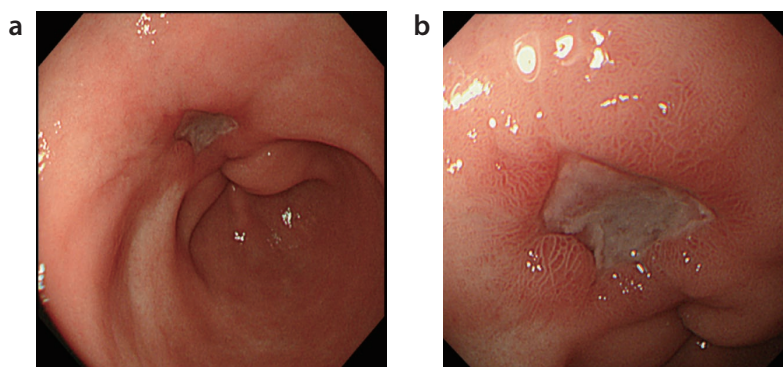


Fig. 1. Upper Gastrointestinal Endoscopy Findings at the Initial Visit Showing a Stage A2 Ulcer in the Antral Zone

(a): Low magnification. (b): High magnification.

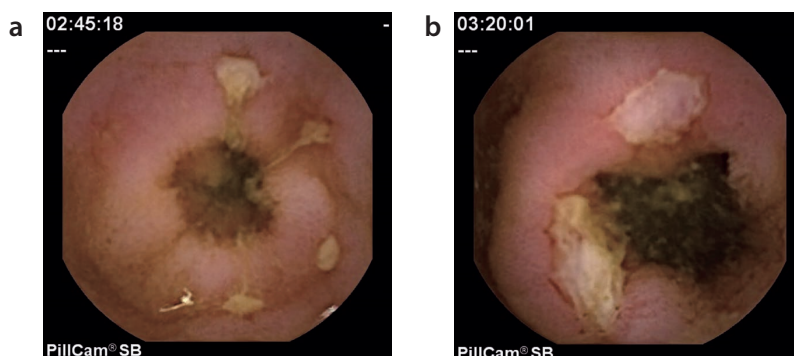


Fig. 2. Capsule Endoscopy Findings Showing Multiple Ulcers Detected Mainly in the Ileum (a). Annular Strictures Can Be Observed in Some Parts (b)

induced gastric and small intestinal ulceration. She was started on a proton pump inhibitor and NSAID treatment was discontinued; however, chronic anemia persisted. Repeat upper gastrointestinal endoscopy and capsule endoscopy performed 6 months after the initial examination showed a stage H1 gastric ulcer, suggesting healing (**Fig. 3**). However, as no changes

were observed in the small intestinal ulcers (**Fig. 4a, b**), transanal double-balloon enteroscopy was performed for further evaluation. No lesions were detected in the terminal aspect of the ileum, colon, rectum, and anus; however, multiple geographic ulcers, some of which were longitudinal or diagonal, were found in the ileum (**Fig. 5a, b**). A repeat enteroscopy performed 6 months

later detected greater changes in the lumen shape with cavitating ulcers and worsening of the annular strictures (**Fig. 6a, b**). Histopathology of a biopsy specimen taken during balloon enteroscopy indicated nonspecific inflammation only (**Fig. 7**). The results of polymerase chain reaction and stool culture test for tubercle bacilli

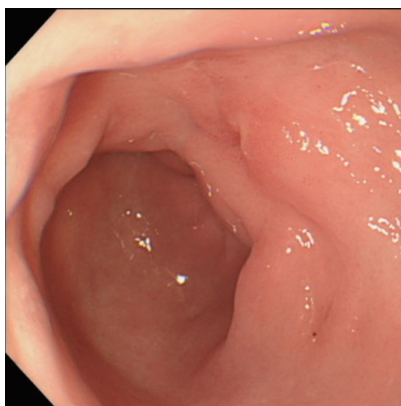


Fig. 3. Upper Gastrointestinal Endoscopy Findings 6 Months After Withdrawal of Medication Showing a Stage H1 Gastric Ulcer, Suggesting Healing

were negative.

Based on the above, and given the history of parental consanguinity, the initial diagnosis of drug-induced small intestinal ulceration was revised and the patient was diagnosed with CEAS. At the time of writing, the patient has been under follow-up for 3 years and 8 months. During this period, she has had two hospital admissions for intestinal obstruction which were treated conservatively. As there was no history of abdominal surgery to cause adhesions or strictures, the intestinal obstruction was attributed to ileal strictures associated with CEAS. Bilateral pedal edema, seen at the first hospital visit, resolved after withdrawal of the causative drug. The patient is currently undergoing outpatient treatment for symptomatic anemia.

Discussion

CNSU is a chronic intractable disease characterized by nonspecific ulceration of the small intestine that is often intractable and recurrent³⁻⁵. Clinical characteristics include chronic anemia and hypoproteinemia due to occult hemorrhage, and multiple nonspecific ulcers,

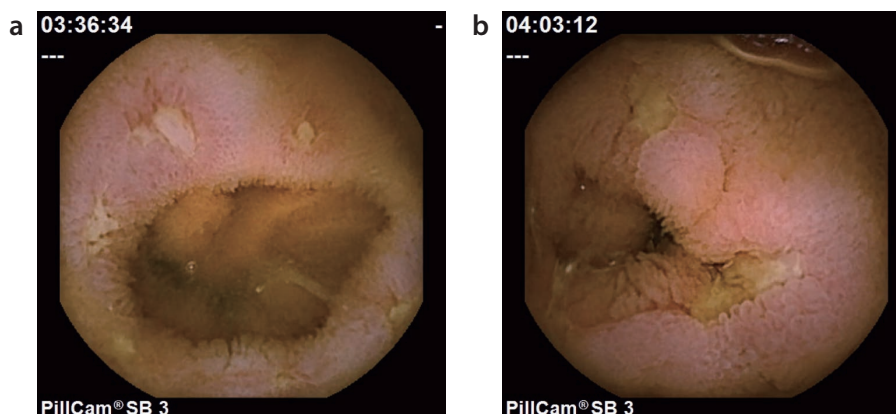


Fig. 4. Capsule Endoscopy Findings 6 Months After Withdrawal of Medication Show No Changes at Lesion Sites. The Number of Lesions (Approximately 40) Is Also Unchanged

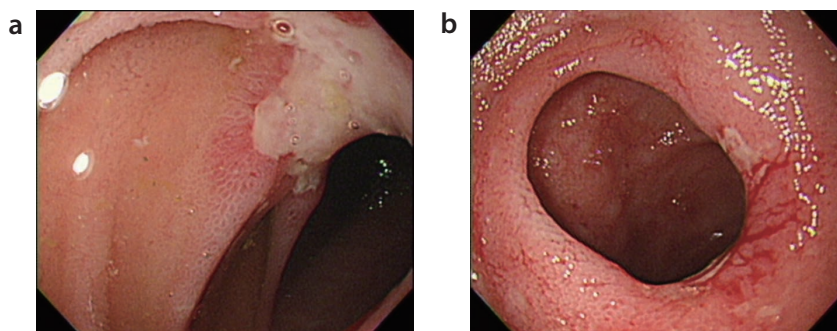


Fig. 5. Transanal Double-balloon Enteroscopy Findings

Multiple geographic ulcers with clear borders are observed in the ileum (a), some of which are annular ulcers (b).

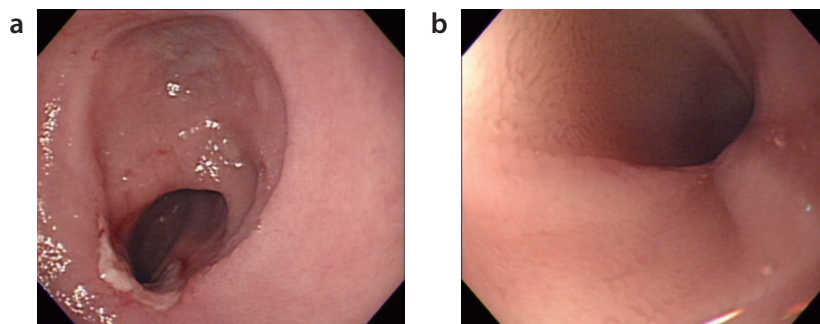


Fig. 6. Transanal Double-balloon Enteroscopy Findings 6 Months After Withdrawal of Medication

Ulcers are cavitating (a), with worsening of annular strictures (b).

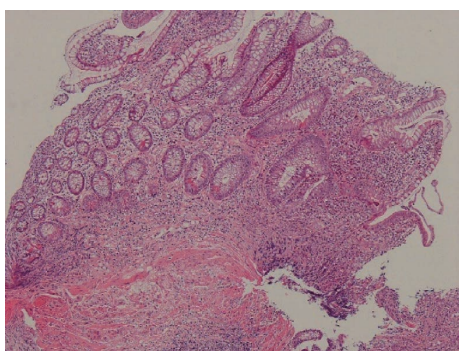


Fig. 7. Histopathology Findings of a Biopsy Specimen Showing Non-specific Inflammation

mainly in the ileum, which are unresponsive to treatment⁶. Systemic inflammation is rare.

Although the precise etiology of this disease has not been fully elucidated, the recent discovery of the *SLCO2A1* gene that encodes a prostaglandin transporter led to a change in nomenclature to CEAS. The average age at diagnosis ranges from adolescence to middle age, but one pediatric case has been reported⁷. CEAS diagnosed in elderly individuals, as in our case, is rare⁸. To the best of our knowledge, this is the first report of CEAS diagnosed based on the results of a Japanese comprehensive health check-up.

The main endoscopic findings in our patient were multiple ulcers with various morphologies (e.g., diagonal, geographic, latitudinal, and annular) accompanied by a deformity in the lumen in a spiral pattern. Small bowel contrast radiography can identify ulcers, strictures, and deformation of the intestinal tract. CEAS most commonly affects the lower ileum, excluding the terminal ileum. Severe narrowing of the tract occurs with treatment, but the ulcers themselves are intractable and strictures sometimes accompany open ulcers⁶. In our case, the borders between the ulcers and the normal mucosa were clear. There is no clear pattern in ulcer distribution, and ulcers develop irrespective of the sites of

mesenteric attachment. Such mucosal lesions can occur in the stomach, duodenum, and large intestine⁹. Histopathological features include ulcers penetrating into the submucosa, with mild infiltration of lymphocytes and plasma cells. The patient in this study also presented with multiple ulcers in the ileum. Because the patient declined to undergo small bowel contrast radiography, a less invasive capsule endoscopy was performed and the patient is currently under regular follow-up. As she continues to be at risk of developing of strictures with ulcer healing, small bowel contrast radiography may be required in the future.

CEAS is an autosomal recessive disorder caused by mutations in *SLCO2A1*, with an estimated prevalence of 150 and 200 patients in Japan^{10,11}. There is usually a positive family history and parental consanguinity, as with the current case. Interestingly, our patient was also found to harbor *SLCO2A1* mutations. Causative genes can be identified by using exome sequencing of genomic specimens, however our patient did not consent to a detailed family history and to undergo further genetic tests.

CEAS is usually diagnosed in patients with chronic anemia and hypoproteinemia that have a positive occult blood test further supported by characteristic imaging results and genetic tests. The differential diagnoses of CEAS include ischemic enteritis, intestinal tuberculosis, Crohn's disease, simple ulcers, intestinal Behcet's disease, and NSAID-induced small intestinal mucosal injury. The patient in this case did not have skin lesions or lesions at sites other than the intestinal tract to suggest Crohn's disease and Behcet's disease. Alternative diagnoses were also not supported by two biopsies, intestinal culture, or PCR tests. NSAID-induced ulceration of the small intestine was initially suspected because of the history of long-term NSAID use, but this was reconsidered after there was no improvement after stopping NSAID therapy. The patient's clinical course, genetic test results, endoscopic findings, and family history collectively led to the diagnosis of CEAS. However,

reaching this diagnosis was complicated due to the old age at onset and the use of NSAIDs.

CEAS is usually treated using central venous hyperalimentation and symptomatic treatment. Balloon dilation is an effective treatment for strictures. Mesalazine, steroids, immunosuppressive agents, and sulfa drugs, commonly used in the treatment of other inflammatory diseases, are usually ineffective^{8,9,11}. Careful consideration is given to surgical resection because of the risk of rapid recurrence of ulceration in the remnant small intestine.

CEAS usually has a favorable prognosis, but cases of CEAS complicated by hematologic diseases¹² or pachydermoperiostosis¹³ have been reported. However, these were absent in our patient. Nevertheless, given the contribution of abnormal expression and/or function of prostaglandins in CEAS etiology, patients should undergo comprehensive workup to confirm the diagnosis and rule out systemic manifestations.

This case also highlights the importance of adequately investigating incidental findings identified during a Japanese comprehensive health check-up. The patient described in this case underwent a comprehensive check-up every year, and anemia was detected for 3 consecutive years; however, she was not referred for further investigations. Medical professionals should be aware that incidental results may be identified during a Japanese comprehensive health check-up and refer patients for further investigations where appropriate.

Conclusion

CEAS is a rare autosomal recessive enteropathy with few reported cases worldwide. As a result, the nomenclature and clinical characteristics of this disease are still being elucidated. We reported a case of CEAS diagnosed in a patient with anemia detected during a Japanese comprehensive health check-up, which was difficult to distinguish from small intestinal mucosal injury induced by NSAIDs. This study demonstrates that CEAS should be suspected in cases of intractable ulcers of the small intestine, and highlights the need for more research including case reports to further elucidate the pathophysiology of this disease.

Conflicts of Interest

All authors declare that they have no conflict of interest.

Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed Consent

The patient provided informed consent.

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