Clinical Case Report

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Successful azathioprine treatment in an adolescent with chronic enteropathy associated with *SLCO2A1* gene

A case report

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Abstract

Introduction: Chronic nonspecific multiple ulcers of the small intestine (CNSU), an entity with female preponderance and manifestations including anemia and hypoproteinemia reflecting persistent gastrointestinal bleeding and intestinal protein loss, has been considered idiopathic. Umeno et al recently reported that CNSU is caused by loss-of-function mutations in the solute carrier organic anion transporter family member 2A1 gene (*SLCO2A1*) encoding a prostaglandin transporter, renaming the disorder "chronic enteropathy associated with *SLCO2A1* gene mutation" (CEAS). Treatments for chronic enteropathies such as inflammatory bowel disease, including 5-aminosalicylic acid, corticosteroids, azathioprine, and anti-tumor necrosis factor-α antibody, often are ineffective in CEAS, which frequently requires surgery.

Case presentation: A 14-year-old girl had refractory anemia and hypoproteinemia for more than 2 years. Video capsule endoscopy showed nonspecific jejunal and ileal ulcers with varied sizes and shapes. She was diagnosed with CEAS resulting from compound heterozygous mutation of the *SLCO2A1* gene. After corticosteroid treatment without improvement, azathioprine treatment improved her anemia and edema as hemoglobin and serum protein increased. Video capsule endoscopy 1 year after initiation of azathioprine showed improvement of small intestinal ulcers.

Conclusion: Physicians should consider CEAS in patients with refractory anemia, hypoproteinemia, and multiple small intestinal ulcers. Why our patient responded to azathioprine but not to corticosteroids is unclear, but azathioprine might benefit some other patients with CEAS.

Abbreviations: CEAS = chronic enteropathy associated with *SLCO2A1* gene, CMUSE = cryptogenic multifocal ulcerous stenosing enteritis, CNSU = chronic nonspecific multiple ulcers of the small intestine, PHO = primary hypertrophic osteoarthropathy, *SLCO2A1* = solute carrier organic anion transporter family member 2A1 gene.

Keywords: azathioprine, chronic enteropathy associated with *SLCO2A1* gene, chronic nonspecific multiple ulcers of the small intestine

1. Introduction

Chronic nonspecific multiple ulcers of the small intestine (CNSU) denotes a disorder of unknown etiology with female preponderance and manifestations including anemia and hypoproteinemia reflecting persistent gastrointestinal bleeding and intestinal protein loss.[1] Umeno et al[2] recently reported that CNSU is caused by loss-of-function mutations in the solute carrier organic anion transporter family member 2A1 gene (*SLCO2A1*) encoding a prostaglandin transporter—suggesting an updated name, "chronic enteropathy associated with *SLCO2A1* gene" (CEAS). Subsequent reports stress distinction between CEAS and Crohn disease.[3,4] Agents used in chronic enteropathies such as inflammatory bowel disease, including 5-aminosalicylic acid, corticosteroids, azathioprine, and antitumor necrosis factor-α antibody, often are ineffective in CEAS, which frequently requires surgery.[1–4]

We report an adolescent with CEAS whose anemia, hypoproteinemia, and small intestinal ulcers improved with azathioprine.

2. Case presentation

A 14-year-old girl was referred to our hospital with refractory anemia and hypoproteinemia over 2 years. At 11 years, she had undergone distal gastrectomy with Billroth II reconstruction for a hemorrhagic gastroduodenal ulcer. Her height and weight were 150.7 cm (−1.1 standard deviation) and 46.7 kg (−0.5 standard deviation). Her parents were not consanguineous, and no chronic gastrointestinal disease was evident among first- or second-degree relatives. Neither abdominal pain nor diarrhea was present. Her

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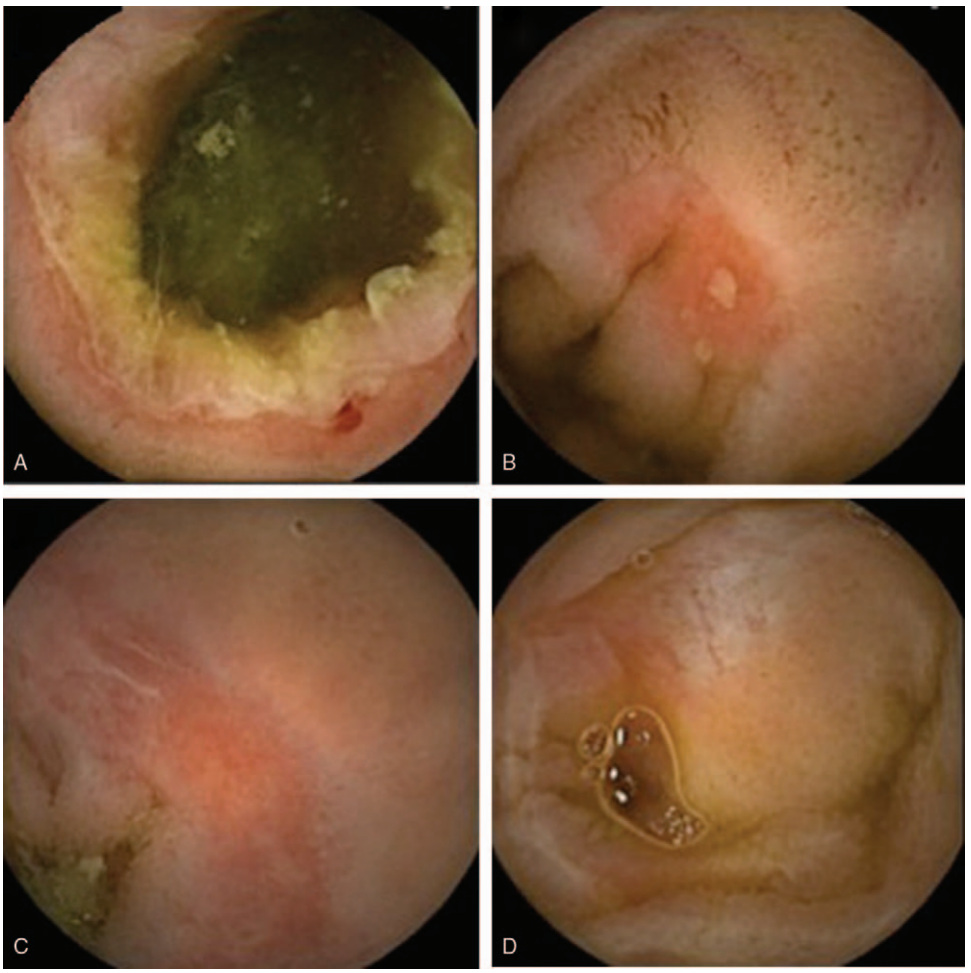

Figure 1. Video capsule endoscopic findings before and after initiation of azathioprine. Video capsule endoscopy showed multiple annular (A) and small, round (B) ulcers in the small intestine. On subsequent re-examination 1 year after initiation of azathioprine, the ulcers showed scarring (C and D).

conjunctivae and lips were pale. Mild upper eyelid and leg edema was noted bilaterally. Vital signs were normal, as were abdominal and neurologic findings.

Laboratory assessment disclosed anemia (hemoglobin, 10.9 g/dL; normal range, 11.6–14.8) and hypoproteinemia (total protein/albumin, 4.7/2.6 g/dL; 6.6–8.1/4.1–5.1). The white blood cell count (6000/μL; 3300–8600), C-reactive protein (0.04 mg/dL; <0.14), and erythrocyte sedimentation rate (12.0 mm/h; 3.0–15.0) were normal. Liver and renal function tests yielded normal results, as did urinalysis. A stool occult blood test was positive, whereas stool culture detected no pathogens. Breath urea screening for *Helicobacter pylori* was negative. We diagnosed the patient with protein-losing enteropathy based on a technetium-99m-labeled human serum albumin scintigraphic finding of abnormal albumin accumulation in the ileocecal region at 5 hours after injection, together with increased fecal α1-antitrypsin clearance (164 mL/day; <13). Lower gastrointestinal endoscopy showed small round ulcers involving the terminal ileum and ileocecal valve, while the colonic mucosa was normal. Biopsy specimens from the terminal ileum disclosed nonspecific, non-granulomatous inflammation. Video capsule endoscopy showed nonspecific ulcers with varied sizes and shapes in the jejunum and ileum (Fig. 1 A and B). *Mycobacterium tuberculosis* infection was ruled out by an interferon-γ release assay.

Prednisolone therapy (40 mg/day) failed to improve anemia or hypoproteinemia and was complicated by hemorrhagic gastritis. When azathioprine at a dose of 50 to 100 mg/day was substituted, anemia and edema improved as hemoglobin and serum protein increased (Table 1). Video capsule endoscopy 1 year after initiation of azathioprine showed improvement of small intestinal ulcers (Fig. 1 C and D). Because the clinical course and endoscopic findings suggested CEAS, we performed direct sequence analysis of the *SLCO2A1* gene using genomic DNA isolated from peripheral blood mononuclear cells following patient and parental informed consent. We identified 2

Table 1

Laboratory findings before and after initiation of azathioprine.

	Pre	3 mo	13 mo	28 mo
TP, g/dL	4.7	5.0	5.6	5.5
Alb, g/dL	2.6	3.0	3.5	3.4
Hb, g/dL	10.9	12.0	11.1	13.1
AZA, mg/day	–	50	75	100
Iron, mg/day	50	50	50	50

Alb = serum albumin, AZA = azathioprine, Hb = hemoglobin, Iron = oral iron supplementation with sodium ferrous citrate, mo = month(s) after initiation of azathioprine, Pre = pretreatment, TP = serum total protein.

heterozygous mutations in the patient (c.830dupT/c.940 + 1G>A) and a heterozygous mutation in each parent (mother, c.830dupT; father, c.940 + 1G>A). Based on clinical, endoscopic, and genetic findings, we diagnosed the patient with CEAS resulting from compound heterozygous mutation of the *SLCO2A1* gene.

Currently, 3 years after initiation of azathioprine, the patient is in sustained clinical remission without anemia or edema while receiving azathioprine (100 mg/day) and oral iron supplementation with sodium ferrous citrate (50 mg/day).

3. Discussion

We describe an adolescent with CEAS whose anemia, hypoproteinemia, and small intestinal ulcers improved with azathioprine.

CEAS, a hereditary disease typically presenting in adolescent girls, is caused by *SLCO2A1* gene mutations affecting a prostaglandin transporter protein. Onset at other ages ranged from 1 to 69 years.[2–4] The clinical course is chronic and intractable. No specific laboratory test for CEAS exists. Laboratory results reflect anemia and hypoproteinemia from persistent gastrointestinal bleeding and intestinal protein loss. Inflammatory markers like C-reactive protein usually are normal or slightly increased.[1–4] The patient had refractory anemia and hypoproteinemia, with normal C-reactive protein. Ulcers in CEAS can cause ileal deformity or stenosis.[1–4] In the patient, video capsule endoscopy displayed varied ulcer morphologies at sites ranging from the jejunum to the terminal ileum, leading us to suspect CEAS.

Umeno et al[3] described 11 *SLCO2A1* mutations among CEAS patients including a splice-site mutation at intron 7 (c.940 + 1G>A; rs765249238), the most frequent (present in 54%). The patient was heterozygous for this mutation and another. Homozygous or compound heterozygous mutations in *SLCO2A1* can cause not only CEAS but also a subtype of primary hypertrophic osteoarthropathy (PHO),[2] which occurs in males as an autosomal recessive disease affecting skin and bones. PHO shows digital clubbing, periostosis, acroosteolysis, painful joint enlargement, and thickened skin. Clinical features of *SLCO2A1* expression likely are influenced by modifiers such as sex-influenced genes or related hormones, considering that CEAS occurs predominantly in females and PHO in males.[2,3] The patient had 2 heterozygous *SLCO2A1* mutations, both previously reported among Japanese CEAS patients.[2–4] Findings suggesting PHO were absent in the patient, whom we diagnosed with CEAS caused by compound heterozygous *SLCO2A1* mutations.

CEAS typically follows a chronic or recurrent course. In previous reports, most CEAS patients showed little response to prednisolone, 5-aminosalicylic acid, azathioprine, or anti-tumor necrosis factor-α antibody. Indeed, some required urgent surgery before a medical option such as azathioprine could be tried.[1–4] Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE), showing features resembling CEAS, has been reported from Europe and Korea.[5,6] Notably, CMUSE shows ulcerative stricture of the small intestine, which may recur after surgical resection. However, CMUSE differs from CEAS in being likelier to respond to steroids.[5,6] In CEAS, on the contrary, Uchida et al[7] reported that early immunomodulatory and/or antitumor necrosis factor-α antibody therapies sometimes succeeded, avoiding surgery.

Limitations of this study include its focus on only 1 patient with CEAS. A large-population, prospective, multicenter study is needed to establish the extent to which azathioprine is effective in CEAS.

In conclusion, we report a girl with CEAS responding to azathioprine. Physicians should consider CEAS in patients with refractory anemia, hypoproteinemia, and multiple small intestinal ulcers. The mechanism underlying our patient's response to azathioprine is unclear, but this drug might benefit some other patients with CEAS.

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Author contributions

TM contributed to the concept and design of the study. KE, TM, YT, KU, and YY carried out analysis and interpretation of data. JU performed genetic analysis. KE and TM wrote the manuscript, which was edited by JU. YY supervised the study and reviewed the manuscript. Thus, all authors contributed to the manuscript.

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