

[CASE REPORT]

Chronic Enteropathy Associated with *SLCO2A1* with Pachydermoperiostosis

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Abstract:

A 49-year-old man complained of chronic palpitation and shortness of breath, which had recently become exacerbated. A blood examination indicated severe refractory anemia and hypoproteinemia. Physical examinations revealed anemia, a systolic murmur, and spoon nails. Multiple nonspecific ileal ulcers were observed. A pathological examination indicated a small granuloma with CD68-positive histiocytes. He had a deeply wrinkled forehead, chiseled face, and clubbed fingers. Radiography revealed periostosis of the fingers and long bones in the limb. He was diagnosed with pachydermoperiostosis. *SLCO2A1* demonstrated a c.1807C>T homo-mutation. He was also diagnosed with *SLCO2A1*-associated chronic enteropathy and thus was treated with 5-aminosalicylic acid, which temporarily improved the ileal ulcers, anemia, and hypoalbuminemia.

Key words: CEAS, *SLCO2A1*, pachydermoperiostosis

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Introduction

The classification of small intestinal ulcer subgroups has recently been revised. Diseases associated with multiple ulcers in the small intestine include chronic nonspecific multiple ulcers of the small intestine (CNSU), Crohn's disease (CD), Behçet's disease (BD), non-steroidal anti-inflammatory drug (NSAID)-induced ulcers, tuberculosis, and other unknown etiologies.

A diagnosis of CNSU, as proposed by Matsumoto et al., is based on the clinical manifestations, endoscopic appearance, and pathological features (1). Thereafter, CNSU, an inherited autosomal recessive disease, has been analyzed for genetic mutations (2). The CNSU subgroup is characterized by pachydermoperiostosis, which includes specific features

such as hypertrophy of the skin and bones, finger clubbing, and periostosis (3). Mutation of the solute carrier organic anion transporter family member 2A1 (*SLCO2A1*) has been reported in patients with CNSU by Umeno et al. (4), who proposed that the disease entity be termed chronic enteropathy associated with *SLCO2A1* (CEAS). This disease entity was previously considered to be Japanese ethnicity-specific. However, CEAS has also been reported in Korea and China (5). To date, 11 mutations of *SLCO2A1* have been reported in CEAS patients (6). *SLCO2A1*, known as the prostaglandin transporter, is a protein encoded by *SLCO2A1*. In CEAS, multiple ulcers of the small intestine, accompanied by anemia and hypoproteinemia, result in chronic gastrointestinal bleeding and protein loss. This ulceration, attributed to the dysfunction or deficiency of prostaglandins in cells affected by *SLCO2A1* mutation, leads to the patho-

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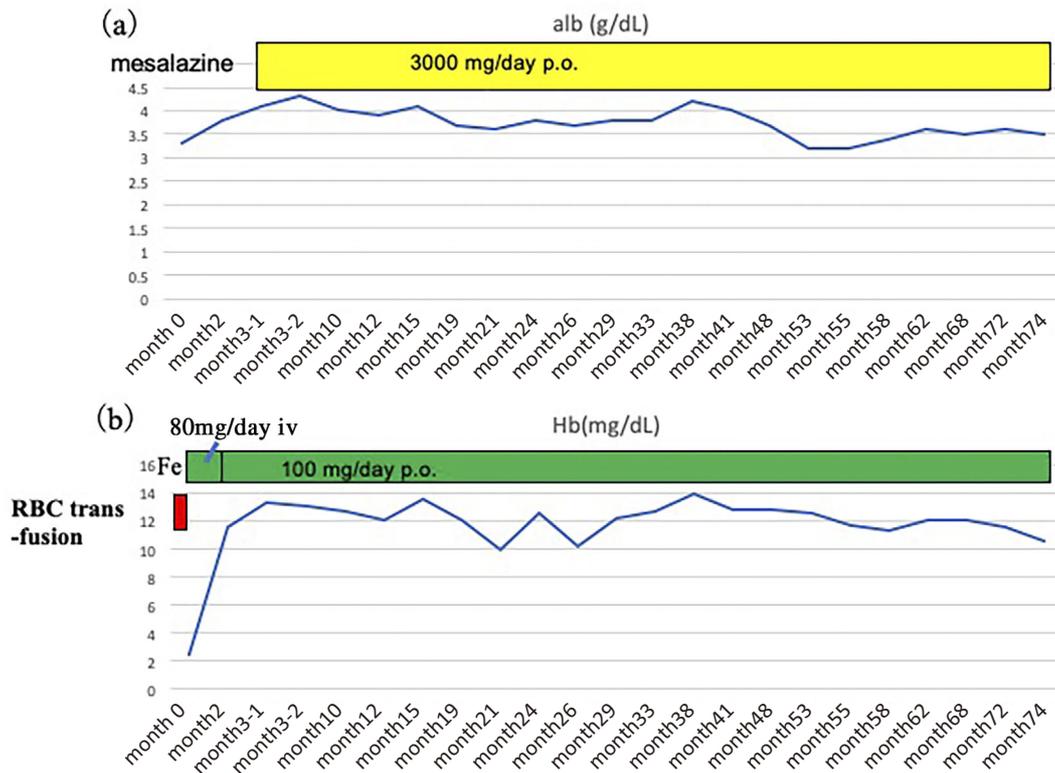


Figure 1. Clinical course of treatment and responsiveness. Time course changes of albumin (a) and hemoglobin (b) showing responsiveness to mesalazine and iron agent.

physiology of small intestinal ulcers and pachydermoperiostosis. Notably, 28% of CEAS patients are offspring from consanguineous marriages (6). CEAS has been described as female dominant, with a susceptible age of onset at approximately 40 years of age and a 98% incidence of anemia.

We herein report a man diagnosed with CEAS with pachydermoperiostosis.

Case Report

The patient gave his written informed consent for the use of his data and images.

Chief complaints

A 49-year-old man presented at our hospital complaining of palpitation and shortness of breath upon exertion.

History of present and past illness

Palpitation and shortness of breath had begun approximately 3 years prior to presentation, but had become exacerbated over the past several weeks. The patient did not experience either palpitation or shortness of breath prior to the onset of CEAS 3 years previously.

Esophagogastroduodenoscopy (EGD) and colonoscopy showed no abnormality, whereas intestinal capsule endoscopy demonstrated scattered round ulcers throughout the entire ileum. He had undergone treatment for the eradication of *Helicobacter pylori* infection because of a gastric ulcer. No disease-related family history was reported.

Physical examination

Physical examination revealed anemia, tachycardia, functional systolic murmur, and spoon nails.

Laboratory examination

A blood examination showed severe refractory anemia (hemoglobin: Hb, 2.5 g/dL), hypoproteinemia (total protein: TP, 5.8 g/dL), hypoalbuminemia (albumin: alb, 3.3 g/dL), and normal C-reactive protein (CRP: 0.2 mg/dL) before treatment. The fecal occult blood test was positive. Laboratory parameters improved approximately one month after treatment with iron tablets and mesalazine (Hb, 13.9 g/dL; TP, 7.6 g/dL, alb 4.1 g/dL, CRP, 0.48 mg/dL). Data at the most-effective time point with treatment were Hb, 13.6 g/dL; TP, 7.4 g/dL, alb 4.1 g/dL, CRP, 0.26 mg/dL, and at the time of relapse were Hb, 9.9 g/dL; TP, 6.5 g/dL, alb 3.6 g/dL, CRP, 2.3 mg/dL. The time-course changes of hemoglobin and albumin are demonstrated in Fig. 1.

Imaging examinations and further diagnostic work-up

EGD showed atrophic gastritis, whereas colonoscopy showed no abnormal findings. Video capsule endoscopy (VCE) revealed multiple nonspecific ileal ulcers of various sizes and shapes (Fig. 2). Double balloon enteroscopy (DBE) and VCE showed multiple longitudinal and spiral ulcers in the ileum except in the terminal ileum (Fig. 3a, b). NSAID use was excluded. However, cryptogenic multifocal

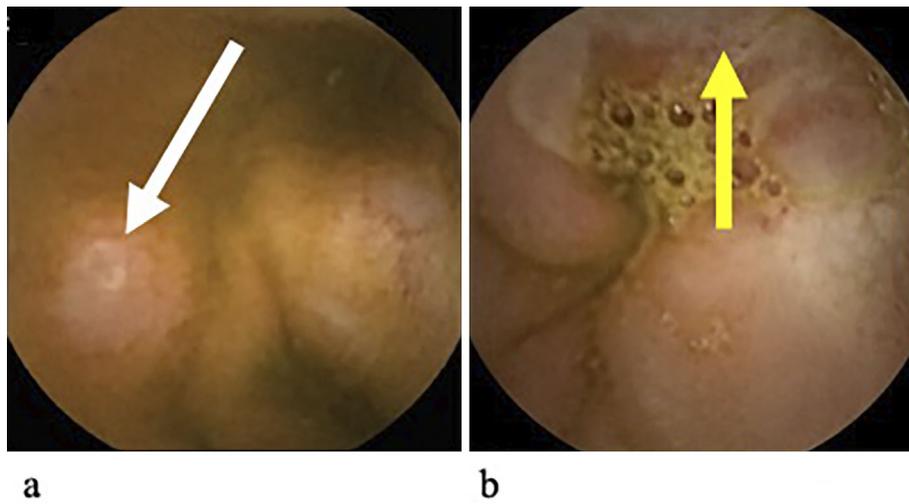


Figure 2. a: Erosion of the small intestine was revealed by video capsule endoscopy (VCE) (white arrow). b: Small intestinal ulcers surrounded by erythematous mucosal changes were revealed by VCE (yellow arrow).

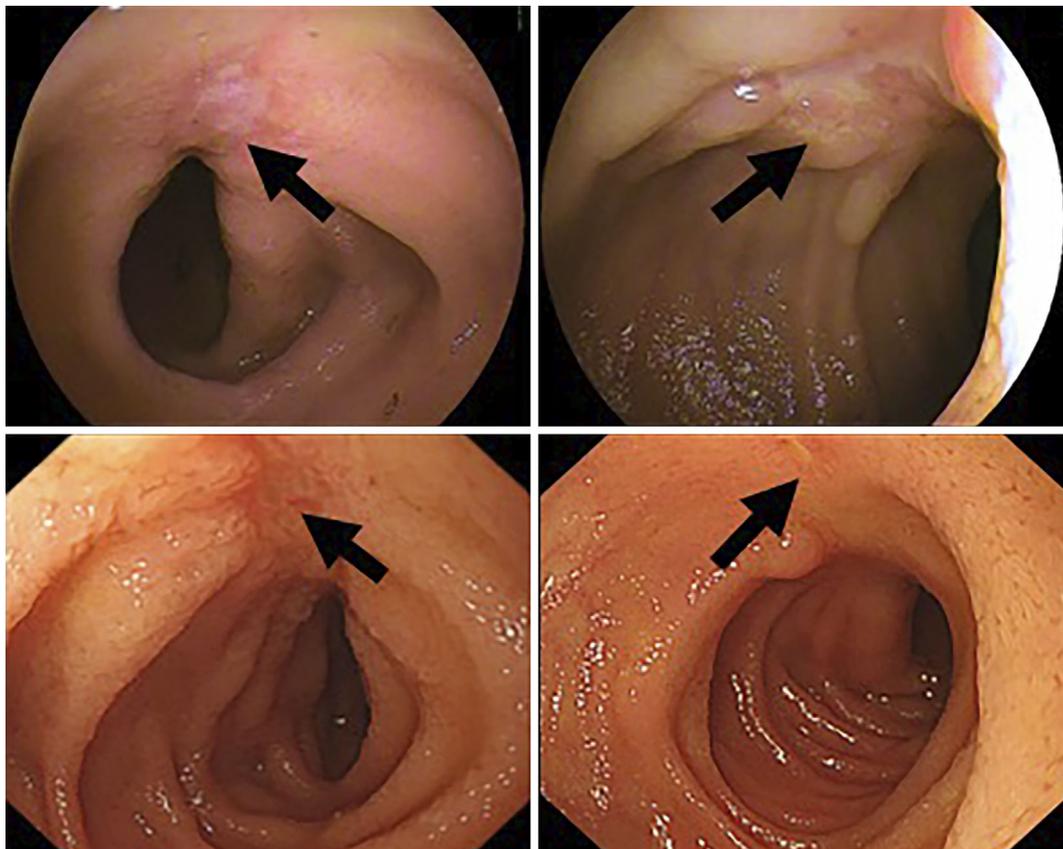


Figure 3. a, b: Double balloon enteroscopy (DBE) demonstrated oblong or longitudinal ulcers in the mid-ileum. c, d: DBE demonstrated an amelioration following mesalazine treatment (201X+2/2), showing residual small ulceration in the ileum after mesalazine treatment, but a marked improvement compared to that before mesalazine treatment.



Figure 4. a: Long bones of the limb demonstrated primary hypertrophic osteoarthropathy (PHO). b: Brain-CT showed skin hypertrophy.

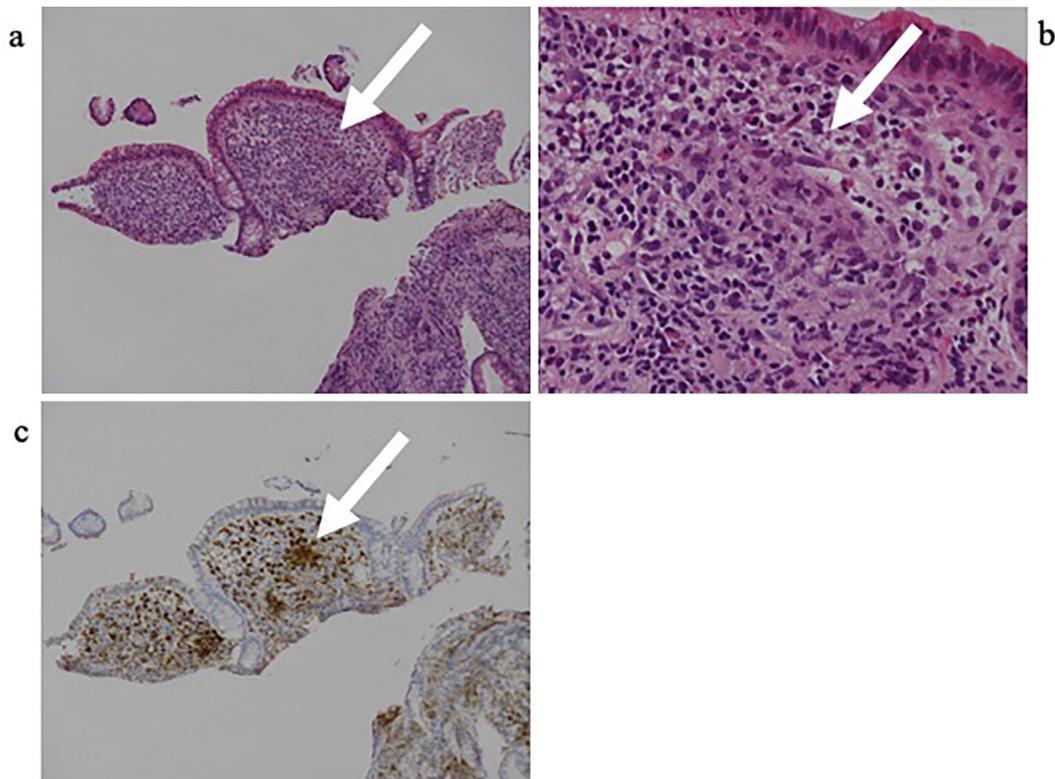


Figure 5. a, b: Hematoxylin and Eosin staining of tissue specimens from ileal ulcers showed a small granuloma (a: $\times 20$, b: $\times 100$) (white arrow). c: Immunohistochemistry demonstrated that this small granuloma had CD68-positive histiocytes ($\times 20$) (white arrow).

ulcerous stenosing enteritis (CMUSE) or CD could not be excluded based only on the features of ileal ulcers. Although the multiple longitudinal and spiral ulcers in the ileum remained, those ulcers showed improvement, with evidence of granulation, after treatment with mesalazine 3,000 mg/day per oral (p.o.) (Fig. 3c, d). Bone radiography indicated periostosis of the fingers and long bones in the limb (Fig. 4a).

Brain-CT revealed skin hypertrophy (Fig. 4b).

Pathological examination

A pathological examination of the ileal ulcers showed non-specific inflammation (Fig. 5a, b). Follow-up DBE showed longitudinal or irregular-shaped ulcers and erosions. Immunohistochemistry demonstrated CD68-positive histo-

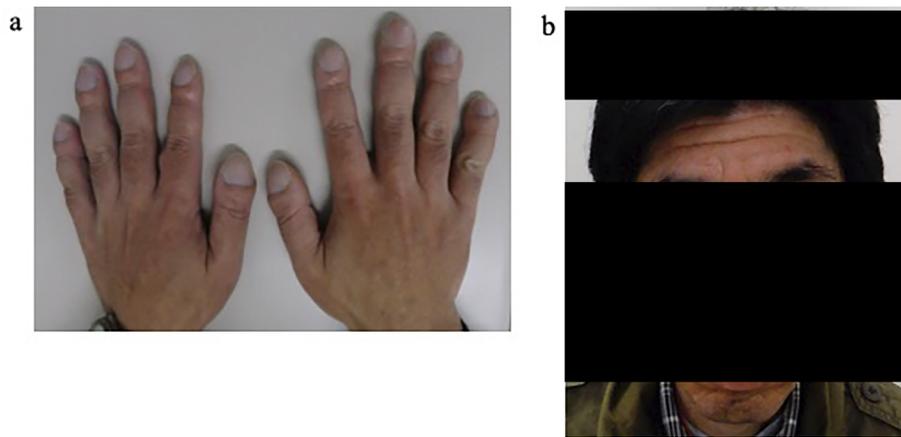


Figure 6. a: The patient had digital clubbing. b: The patient had a deeply wrinkled forehead and a chiseled face.

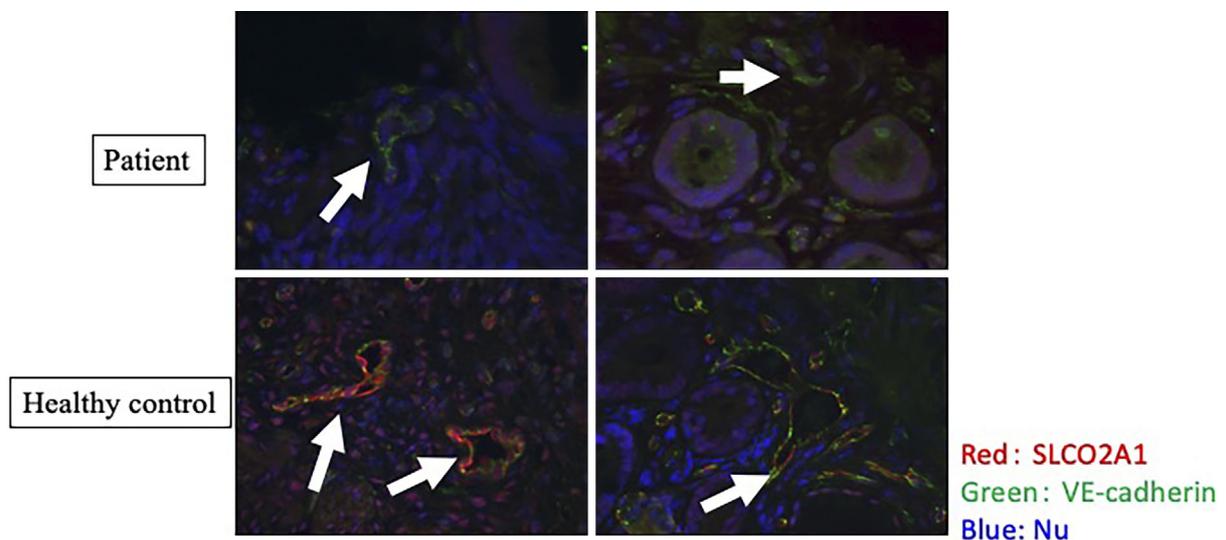


Figure 7. Immunohistochemistry for *SLCO2A1* protein in the vascular endothelium of the ileal mucosa. The patient did not express normal *SLCO2A1* protein (upper: white arrow). Normal *SLCO2A1* protein was expressed in the vascular endothelium of healthy control tissue (lower: white arrow).

cytes of a small granuloma (Fig. 5c). The patient was suspected to have CD. However, the terminal ileum lacked longitudinal ulcers or a cobblestone appearance, which are typical findings in CD (7). The patient exhibited digital clubbing (Fig. 6a), a deeply wrinkled forehead, and a chiseled face (Fig. 6b). Immunohistochemical studies of *SLCO2A1* expression in the vascular endothelial cells of ileal ulcers showed that the patient did not express normal *SLCO2A1* protein (Fig. 7). In addition, next-generation sequencing revealed a point mutation of the 1807C>T homo-mutation in the 13 exon allele of *SLCO2A1* (Fig. 8) (4).

Differential diagnosis

CD, BD, NSAID-induced ulcers, and tuberculosis should be considered in the differential diagnosis.

Final diagnosis

The patient was diagnosed with pachydermoperiostosis, which is also known as primary hypertrophic osteoarthropathy (PHO). Since the *SLCO2A1* mutation has been reported in pachydermoperiostosis, the present patient was diagnosed with CEAS with ileal ulcers and pachydermoperiostosis.

Treatment

The patient was treated with an RBC transfusion for severe anemia at hospitalization in 201X/10. The administration of oral Fe tablets (100 mg/day) was commenced a few weeks later, which took 3 months to achieve an improvement in anemia, and he continues to take this medication at the time of writing this report. Additionally, oral mesalazine (3,000 mg/day) has been administered from 201X+1/1 until now. The TP and albumin were improved at 201X+1/2;

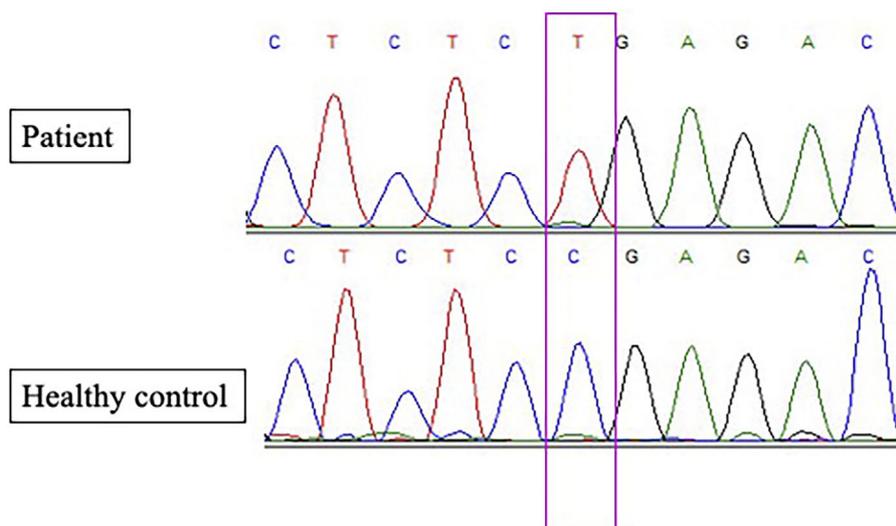


Figure 8. Next-generation sequencing (Sanger sequencing) for *SLCO2A1* gene mutation in the patient and a healthy control. The homozygous mutation c.1807C>T was detected in *SLCO2A1* in this case.

therefore, improvement in TP and albumin by mesalazine took approximately 4 weeks in the initial phase. However, as shown in Fig. 1, the effect of oral mesalazine for albumin and Hb fluctuated during the time course. The inflammation improved 2 years later after the commencement of mesalazine. The combination of Fe tablets and oral mesalazine was continued without other treatments even in the relapsing periods, because anemia and inflammation were within the acceptable range.

Outcome and follow-up

The albumin, Hb as shown in Fig. 1, and inflammation fluctuated during the time course, and the patient occasionally has diarrhea. We continue to follow this patient on an out-patient basis while continuing to administer Fe tablets and mesalazine.

Discussion

We herein report a man with CEAS and pachydermoperiostosis. This disease was previously described as “CNSU” (4). Umeno et al. proposed a CEAS diagnosis based on multiple intestinal ulcers accompanied by a *SLCO2A1* mutation (4). Thereafter, Umeno et al. reviewed and summarized the epidemiologic, endoscopic, and genetic aspects of CEAS in 65 Japanese patients (6).

The age of our patient at the time of diagnosis was 49 years, which is consistent with the average age of 40 years in their report (6). Although CEAS patients are predominantly female, our patient being male was consistent with cases of CEAS with pachydermoperiostosis, who are mainly male. CEAS with pachydermia and periostosis may be significantly more frequent in male patients (8 out of 13; 62%, and 7 out of 13; 54%, respectively) than in female patients (0% and 13%, respectively) (6). In contrast to PHO, the ra-

tios of intestinal ulcers between male and female patients are not significantly different. Moreover, in contrast to male patients, gastric symptoms and more severe hypoproteinemia are the features frequently found in female patients (6). The current patient’s parents were non-consanguineous, as opposed to a frequency of 28% in a published report (6). These data suggest that intestinal ulcers in CEAS might be associated with X chromosome-related dominant inheritance, while PHO might be associated with Y chromosome-related recessive inheritance. However, the causal relationship between sex-related genes and the absence or presence of intestinal ulcers or PHO remains unknown.

The patient was observed in an outpatient unit after an improvement in ileal ulcers. He was observed to have a deeply wrinkled forehead, a chiseled face, and clubbed fingers. Radiographic findings of periosteal thickening of the finger bones and long bones led to a diagnosis of pachydermoperiostosis.

VCE and DBE demonstrated oblong or irregular shaped ulcers in the mid ileum of our patient, in addition to circular or obliquely shaped ulcers with clear margins, suggesting that various shapes of ulcers could be formed in CEAS (6, 8, 9). Moreover, although the terminal ileum is the most frequent site of ulcers in CD, no involvement in the terminal ileum was noticed in our case. These findings supported that our patient had CEAS instead of CD or BD, however, CD or BD has to be ruled out because anti-tumor necrosis factor (TNF)- α antibody therapy or immunomodulators are ineffective for CEAS.

The *SLCO2A1* protein in the vascular endothelium of our patient was expressed at a lower level compared to that in CD or intestinal BD (IBD) (10). Additionally, pathological examination by immunohistochemistry demonstrated inflammatory cell infiltration in the epithelium, including CD68+ histiocytes (small granuloma), in our case. Although the

presence of a CD68+ granuloma supports the diagnosis of CD, this finding is not specific for CD. Therefore, a definitive diagnosis based on a gene analysis was needed.

CEAS is an autosomal recessive hereditary disease caused by *SLCO2A1* mutations (11). Reportedly, *SLCO2A1* mutations may also cause pachydermoperiostosis and sex differentiation (3, 12, 13). CNSU patients have the same homozygous mutations in *SLCO2A1* as those with pachydermoperiostosis. Therefore, this disease was called chronic enteropathy associated with *SLCO2A1* (CEAS) (4). Umeno et al. described 11 *SLCO2A1* mutations among CEAS patients, including a splice-site mutation in intron 7 (c.940+1G>A) (4) as the most frequent mutation (present in 54%) (6). *SLCO2A1* may contain multiple mutations, such as the c.1807C>T homozygous mutation in the exon 13 (c.1807 C>T) allele and in exon 7 (c.940+1G>A). Homozygous *SLCO2A1* mutations may induce CEAS and a subtype of PHO, which is an autosomal recessive disease causing pachydermoperiostosis. PHO shows digital clubbing, periostosis, acroosteolysis, painful joint enlargement, and thickened skin. Considering that CEAS occurs predominantly in female patients and PHO in male patients, the clinical features associated with *SLCO2A1* mutations might be influenced by modifiers such as sex-influenced genes or related hormones. Further, the absence of any significant difference between c.940+1G>A and non-c.940+1G>A homozygotes in the expression of pachydermia and periostosis suggests that other mutations such as c.1807 C>T might also contribute to these features (6).

SLCO2A1 protein reportedly transports prostaglandin E2 protein into intracellular spaces. Dysfunction caused by *SLCO2A1* mutations may inhibit this transport, resulting in high prostaglandin E2 protein concentration in both blood and urine. However, precise mechanisms that induce dysfunction or affect the clinical features, including skin hyperplasia, bone proliferation, and mucosal ulceration in the intestinal tract, caused by stored prostaglandin E2 protein, remain unclear.

Treatments for CEAS have not yet been established to date. CEAS treatments such as 5-aminosalicylic acid (5-ASA), corticosteroids, azathioprine, and anti-TNF- α antibodies are frequently ineffective (14). These medications have been proposed in the IBD guidelines, suggesting that CEAS and IBD may have different etiologies and should therefore be distinguished. CEAS frequently requires surgery unless early intervention by immunomodulatory and/or anti-TNF- α antibody therapies is found to be effective. 5-ASA was partially effective in our case, because mesalazine 3,000 mg was started in 201X+1/1, and TP was improved in 201X+1/2; therefore, the improvement in TP by mesalazine took approximately 4 weeks in the initial phase. We surmise that mesalazine is an anti-inflammatory agent that improved the enteric mucosal permeability, thus leading to a reduction of protein loss from the gut and an increase in blood TP. However, once relapse occurs, these medications may be added if they were once effective to control this disease.

The main limitation associated with this study are that we

only describe one case of CEAS with pachydermoperiostosis treated with 5-ASA. A similar case in Korea has been reported by Eda et al (14).

Conclusion

We herein described a male patient with CEAS and pachydermoperiostosis, who was treated with 5-ASA. CEAS should be listed in the differential diagnosis for small intestinal ulcers. Furthermore, a randomized, prospective, and large-population study is required to establish the diagnostic and treatment guidelines for CEAS depending upon the clinical features or gene mutations.

The authors state that they have no Conflict of Interest (COI).

References

1. Matsumoto T, Nakamura S, Esaki M, et al. Endoscopic features of chronic nonspecific multiple ulcers of the small intestine: comparison with nonsteroidal anti-inflammatory drug-induced enteropathy. *Dig Dis Sci* **51**: 1357-1363, 2006.
2. Matsumoto T, Kubokura N, Matsui T, Iida M, Yao T. Chronic nonspecific multiple ulcer of the small intestine segregates in offspring from consanguinity. *J Crohns Colitis* **5**: 559-565, 2011.
3. Zhang Z, Xia W, He J, et al. Exome sequencing identifies *SLCO2A1* mutations as a cause of primary hypertrophic osteoarthropathy. *Am J Hum Genet* **90**: 125-132, 2012.
4. Umeno J, Hisamatsu T, Esaki M, et al. A hereditary enteropathy caused by mutations in the *SLCO2A1* gene, encoding a prostaglandin transporter. *PLoS Genet* **11**: e1005581, 2015.
5. Sun X, Hosoe N, Miyanaga R, et al. A male Korean who was diagnosed with chronic enteropathy associated with *SLCO2A1* (CEAS): case report with literature review. *BMJ Open Gastroenterol* **5**: e000223-e000226, 2018.
6. Umeno J, Esaki M, Hirano A, et al.; The CEAS study group. Clinical features of chronic enteropathy associated with *SLCO2A1* gene: a new entity clinically distinct from Crohn's disease. *J Gastroenterol* **53**: 907-915, 2018.
7. Hosoe N, Ohmiya N, Hirai F, et al.; CEAS Atlas Group. Chronic enteropathy associated with *SLCO2A1* gene [CEAS]-characterization of an enteric disorder to be considered in the differential diagnosis of Crohn's disease. *J Crohns Colitis* **11**: 1277-1281, 2017.
8. Matsumoto T, Iida M, Matsui T, Yao T. Chronic nonspecific multiple ulcers of the small intestine: a proposal of the entity from Japanese gastroenterologists to Western enteroscopists. *Gastrointest Endosc* **66**: S99-S107, 2007.
9. Esaki M, Umeno J, Kitazono T, Matsumoto T. Clinicopathologic features of chronic nonspecific multiple ulcers of the small intestine. *Clin J Gastroenterol* **8**: 57-62, 2015.
10. Yanai S, Yamaguchi S, Nakamura S, et al. Distinction between chronic enteropathy associated with the *SLCO2A1* gene and Crohn's disease. *Gut Liver* **13**: 62-66, 2019.
11. Yuan L, Chen X, Liu Z, et al. Novel *SLCO2A1* mutations cause gender differentiated pachydermoperiostosis. *Endocr Connec* **7**: 1116-1128, 2018.
12. Yamaguchi S, Yanai S, Nakamura S, et al. Immunohistochemical differentiation between chronic enteropathy associated with *SLCO2A1* gene and other inflammatory bowel diseases. *Intest Res* **16**: 393-399, 2018.
13. Uchida K, Nakajima A, Ushijima K, et al. Pediatric-onset chronic nonspecific multiple ulcers of small intestine: a nationwide survey and genetic study in Japan. *J Pediatr Gastroenterol Nutr* **64**: 565-568, 2017.

14. Eda K, Mizuochi T, Takaki Y, Ushijima K, Umeno J, Yamashita Y. Successful azathioprine treatment in an adolescent with chronic enteropathy associated with *SLCO2A1* gene: a case report. *Medicine (Baltimore)* **97**: e12811-e12814, 2018.

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