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【 CASE REPORT 】

Characteristic Facial Appearance Was the Key to Diagnosing Chronic Enteropathy Associated with *SLCO2A1*-associated Primary Hypertrophic Osteoarthropathy

Akira Sonoda[1], Yasuhiro Wada[1,2], Kazumi Togo[1], Kazuhiro Mizukami[1], Yuta Fuyuno[3], Junji Umeno[3], Shin Fujioka[3], Kensuke Fukuda[1], Kazuhisa Okamoto[1], Ryo Ogawa[1], Tadayoshi Okimoto[1] and Kazunari Murakami[1]

Abstract:
Patients with chronic enteropathy associated with *SLCO2A1* (CEAS) develop multiple circular, longitudinal, or eccentric ulcers in the ileum. It is sometimes difficult to distinguish CEAS from Crohn's disease. CEAS and primary hypertrophic osteoarthropathy (PHO) are together known to be caused by a mutation of *SLCO2A1* gene. The case of a 65-year-old man whose characteristic appearance due to pachydermia of the forehead folds led to the diagnosis of CEAS with PHO is presented.

Key words: chronic enteropathy associated with *SLCO2A1*, primary hypertrophic osteoarthropathy, pachydermia of the forehead folds

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Introduction

Chronic enteropathy associated with *SLCO2A1* (CEAS) is a rare disease in which multiple circular, longitudinal, or eccentric ulcers develop in the ileum. Most CEAS patients present with anemia and hypoalbuminemia (1). However, some patients with advanced disease develop abdominal pain with intestinal stenosis and require repeated surgeries (2). Because the appearance of ileal ulcers in patients with CEAS sometimes resembles that of Crohn's disease (CD) or intestinal tuberculosis, it is sometimes difficult to distinguish CEAS from them (3-6). Umeno et al. reported that CEAS is a hereditary disease caused by mutations in the *SLCO2A1* gene (1, 7). The *SLCO2A1* gene is also a causal gene of primary hypertrophic osteoarthropathy (PHO), which is an extremely rare disease in which patients present digital clubbing, periostosis, and pachydermia (8). In particular, cutis verticis gyrata (CVG) and thickening and furrowing of the skin on the forehead due to pachydermia are highly characteristic signs of this condition. We herein present the case of a patient whose characteristic facial appearance led to a diagnosis of CEAS associated with PHO.

Case Report

The patient was a man who had repeated presented with anemia and positive fecal occult blood since his 30s. At 65 years of age, severe anemia was seen on a laboratory examination, and multiple gastric ulcers (Fig. 1) and a longitudinal ileal ulcer were seen on esophagogastroduodenoscopy (EGD) and ileo-colonoscopy. The patient was therefore referred to our hospital due to suspected Crohn's disease.

Gitelman syndrome was suspected based on the presence of hypokalemia, hypomagnesemia, and a low urine potassium level when he was 58 years of age (details unknown).

[1]Department of Gastroenterology, Oita University, Japan, [2]Division of Diagnostic Pathology, Department of Clinical Laboratory Medicine, Shiga University of Medical Science, Japan and [3]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Japan
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Correspondence to Dr. Akira Sonoda, load2akr@oita-u.ac.jp

His other past history included appendectomy and uveitis, but not tuberculosis. He was treated with oral famotidine, potassium, magnesium oxide, and iron, but he was not taking any non-steroidal anti-inflammatory drugs (NSAIDs). He had no family history of enteritis or tuberculosis, and his parents were non-consanguineous. Vital signs were normal, and his palpebral conjunctivae looked anemic. The patient' s laboratory data were as follows: WBC count, 10,520/μL; Hb, 8.5 mg/dL; ALB, 3.07 g/dL; K, 3.86 mEq/L; and C-reactive protein (CRP), 0.71 mg/dL. Video capsule endoscopy (VCE) was performed with a Pillcam® SB3 (Covidien Japan Inc., Tokyo, Japan) after assessing the patency of the small intestinal tract with a Pillcam® patency capsule (Covidien Japan Inc.). VCE showed multiple circular and longitudinal ulcers throughout the entire small intestine, especially in the lower ileum (except for the terminal ileum) (Fig. 2). Gastric involvement showed scarring on EGD. Double-balloon endoscopy (DBE) was performed via the anal route and showed a longitudinal shallow ulcer in the lower ileum (Fig. 3). Granulomas were not detected, and non-specific enteritis was found on a pathological analysis of biopsy specimens from the edge of the ulcer. Biopsy specimens from the ileum were subjected to culture, and polymerase chain reaction (PCR) in order to identify tubercu-

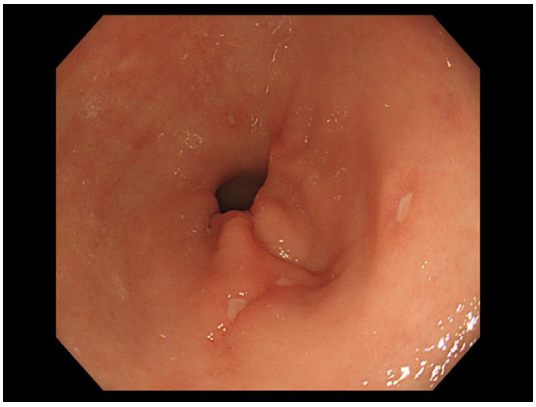

Figure 1. Esophagogastroduodenoscopy shows multiple ulcers in the antrum of the stomach.

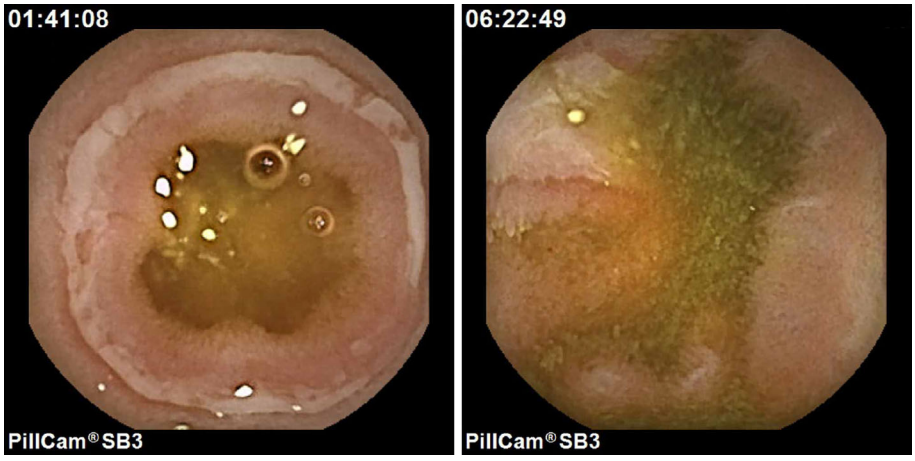

Figure 2. Video capsule endoscopy on admission shows multiple circular and longitudinal ulcers throughout the entire small intestine.

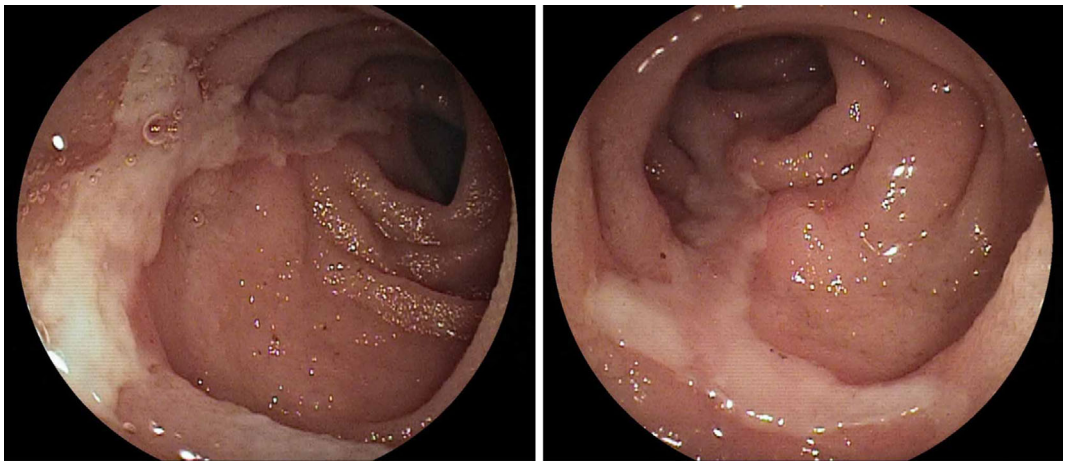

Figure 3. Double balloon endoscopy on admission shows a longitudinal shallow ulcer in the lower ileum.

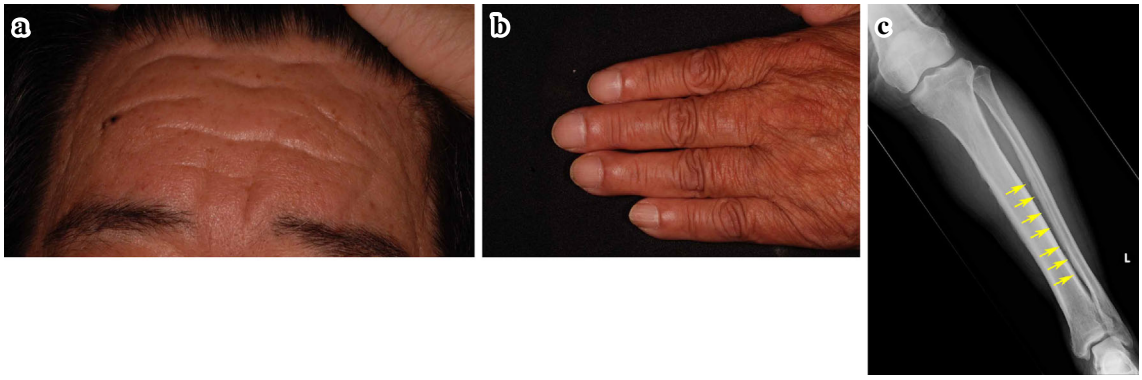

Figure 4. **a: Characteristic facial appearance due to pachydermia of the forehead folds. b: Digital clubbing. c: Periostosis of the tibia and fibula.**

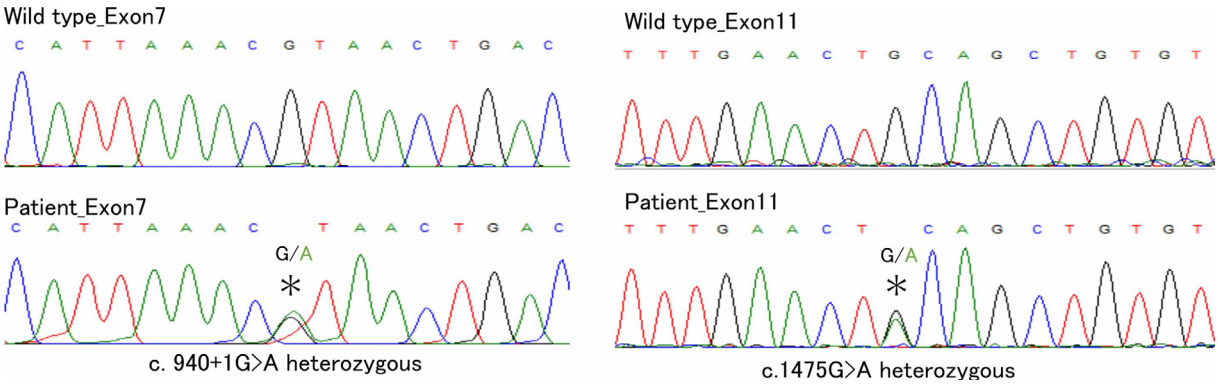

Figure 5. **Sequencing the *SLCO2A1* mutations. Compound heterozygous mutations of *SLCO2A1* gene, c.940+1G>A (splice site variant) and c.1475G>A (p.Cys792Tyr), were detected. Upper: Wild-type. Lower: The present patient. Left: Exon7. Right: Exon11.**

losis, however, all results were negative. In addition, the findings of interferon gamma release assays were also negative. The patient was diagnosed with Crohn's disease and was treated with oral mesalazine. However, it was ineffective and was discontinued after 22 months. A trial of antituberculosis agents as a diagnostic therapy was considered, but the patient refused.

Symptomatic treatment was then continued, and 46 months after his first visit to our hospital, we noticed his characteristic facial appearance due to pachydermia of the forehead folds (Fig. 4a). The patient had been aware of thickening and furrowing of the skin on the forehead and CVG since his 30s. Digital clubbing was also present (Fig. 4b), and an X-ray examination revealed periostosis of the long bones (Fig. 4c). A diagnosis of PHO was made, and CEAS was strongly suspected. A genetic analysis was performed, and compound heterozygous mutations of the *SLCO2A1* gene [c.940+1 G>A (splice site variant) and c.1475 G>A (p.Cys792Tyr)] were detected (Fig. 5). CEAS was definitely diagnosed, and symptomatic treatment was continued.

Discussion

CEAS, which was previously called chronic nonspecific multiple ulcers of the small intestine (CNSU), is rare in the Japanese population (2). CEAS is a hereditary disease and it has been reported that approximately one-quarter of patients have consanguinity or siblings with enteropathy (1, 9). Recently, mutations in the *SLCO2A1* gene were identified in patients with CNSU, and a more appropriate name, CEAS, was suggested (1, 7). Among *SLCO2A1* mutations, a splice-site mutation at intron 7 (c.940+1 G>A; rs765249238), which was detected in the present patient, was the most frequently observed in CEAS patients (1). This mutant allele frequency is 0.091% in the Japanese population (1), but it is rarely found in Caucasian populations (1, 7). *SLCO2A1* gene encodes OATP2A1, which is a prostaglandin (PG) transporter that may be involved in mediating both the influx and efflux of prostaglandins in numerous tissues (10). It is interesting that the circular ulcers in the small intestine observed by VCE in the present patient are very unique and resemble those of NSAID-induced enteropathy. NSAIDs are known to block cyclooxygenase-derived PG synthesis (11). Nakanishi et al. hypothesized that the local PGE_2 concentration is also decreased in patients with CEAS due to impairment of the PG efflux function, but not the influx function, of OATP2A 1 (10). Umeno et al. proposed a new entity of gastrointestinal disorders together with NSAID-induced enteropathy called "prostaglandin-associated enteropathy" due to im-

paired prostaglandin use (1).

CEAS is characterized by multiple small intestinal ulcers of nonspecific histology and chronic persistent gastrointestinal bleeding. However, most patients do not experience hematochezia (1). The hematochezia in the present patient confused us when CEAS was diagnosed. Some patients with advanced disease develop intestinal stenosis and require repeated surgeries. Although total parenteral nutrition (TPN) is the only effective therapy (9), it was not tried because it had the potential to worsen the patient' s intestinal stenosis. We consider symptomatic treatment to be necessary and sufficient for patients with mild symptoms.

The endoscopic findings of CEAS are characterized by multiple circular, longitudinal, or oblique shallow ulcers with discrete margins in the ileum (except for the terminal ileum), which resemble Crohn's disease or intestinal tuberculosis (3, 6).

We think that it is difficult to diagnose this rare disease, especially in a patient without consanguinity or a family history. The key to the diagnosis in the present case was the characteristic facial appearance of patients with PHO. PHO is an extremely rare disease that causes digital clubbing, periostosis, and pachydermia (8). In particular, increased furrowing of the forehead folds due to pachydermia is a highly characteristic sign of the condition. PHO is also known to be caused by *SLCO2A1* gene mutation (12). Umeno et al. reported that digital clubbing or periostosis was found in 28% of patients with CEAS, with 10.8% fulfilling the major diagnostic criteria of PHO. It is interesting that all of these patients were male, like the present patient, even though CEAS predominantly affects females (1). The symptoms of PHO are especially important for the diagnosis of CEAS in males. Some patients with CD and PHO have been previously reported (13, 14); they seem to have had CEAS rather than CD. The present patient had a history of suspected Gitelman's syndrome. Jiang et al. also reported a case of PHO with Bartter's-like syndrome (15). An association between PHO and hypokalemia has been suggested.

Although no effective treatment other than TPN has been established, the diagnosis of CEAS and the exclusion of other diseases are important to avoid unnecessary treatment. The number of patients diagnosed with CEAS will increase with progress in modalities for examining the small intestine and improved recognition of the disease. The characteristic facial appearance that is seen in some patients can be very helpful for making the diagnosis.

Conclusion

The characteristic facial appearance of pachydermia of the forehead was useful for diagnosing CEAS.

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

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