Chronic Enteropathy Associated with the *SLCO2A1* Gene: A Case Report

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ABSTRACT

Chronic enteropathy associated with the *SLCO2A1* gene (CEAS) is a condition characterised by multiple non-specific ulcers in the small intestine, which cause chronic blood loss and persistent hypoproteinaemia. CEAS is both rare and difficult to diagnose. This case report concerns a middle-aged male CEAS patient with recurrent black stools, anaemia, and joint enlargement. The patient was initially given a blood transfusion, albumin supplementation, and nutritional support. After being diagnosed with CEAS, the patient initially received hormone therapy; however, the response was suboptimal. Subsequently, nasogastric total enteral nutrition therapy successfully addressed the patient's black stools and anaemia. This case report aims to raise clinicians' awareness of CEAS and aid in improving the diagnosis and treatment of unexplained intestinal ulcers.

Key Words: *SLCO2A1 gene, Chronic enteropathy, Intestinal ulcers*.

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INTRODUCTION

Chronic enteropathy associated with the *SLCO2A1* gene (CEAS) is a clinically rare condition. In 1968, Japanese scholars first reported a case of persistent severe anaemia, hypoproteinaemia, and non-specific ulcers in the small intestine, which was termed as chronic non-specific multiple ulcers of the small intestine (CNSU). However, more than 40 years later, another Japanese scholar determined CNSU to be a single-gene disorder caused by *SLCO2A1* deficiency. Therefore, it is reasonable to refer to the condition as CEAS rather than CNSU.[1,2]

CEAS, Crohn's disease, and cryptogenic multifocal ulcerous stenosing enteritis are all rare diseases. The clinical manifestations of CEAS and cryptogenic multifocal ulcerous stenosing enteritis share many similarities, including recurrent intestinal obstruction, gastrointestinal bleeding, small intestinal ulcers, and signs of malnutrition, aspects that are easy to confuse during clinical diagnosis.[3] As the pathological changes in the intestinal ulcers of patients with CEAS are only non-specific inflammatory lesions without characteristic signs, it is impossible to provide a definite diagnosis based solely on pathology. Thus, it is necessary to comprehensively consider the clinical manifestations, pathology and imaging results, and findings of genetic testing when making a diagnosis.

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CASE REPORT

This case report presented a 42-year male patient from Sichuan Province in China, who was employed in the printer assembly industry. He was admitted to the hospital on May 9, 2023, due to a history of intermittent black stools for over a decade with an additional occurrence lasting three days. The patient had intermittent black stools for more than 10 years and had previously attended a local hospital in Sichuan for treatment, where no obvious abnormality was identified *via* gastroscopy (no report), and the patient was discharged after receiving a blood transfusion. Over the course of more than 10 years, the patient experienced episodes of intermittent melena accompanied by hypoproteinaemia. Routine blood examination showed that the minimum haemoglobin level was 20 g/L. In the past, the patient had received periodic blood transfusions and human albumin infusions every one to six months at a local hospital. His medical history included hyperuricaemia for four years and irregular use of oral febuxostat tablets for a long time. In addition, the patient had a history of anaemia that exceeded 30 years. The patient's father died of primary liver cancer, while his mother and two sisters were all healthy. The patient denied a family history of any genetic disease or consanguineous marriage.

The physical examination showed the patient to have clear consciousness, a soft spirit, an anaemic appearance, no enlargement of the superficial lymph nodes throughout his whole body, thick and rough skin on his face and skull, clear breath sounds in both lungs, and no dry or wet rales. His heart rhythm was normal, and no murmur was heard. His abdomen was soft, without tender rebound pain, and the spleen was palpable over the anterior midline. In terms of the joints of his extremities, the patient had clubbing at the tip of each finger of both hands,

swollen ankles without tenderness, and mild oedema of both lower limbs (Figure 1A, B). The neurological examinations, such as the Babinski sign, were all negative.

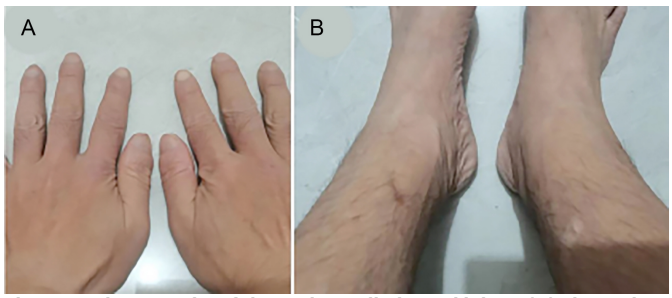

Figure 1: Photographs of the patient's limbs and joints. (A) The patient reported pain due to the clubbing of each finger of both hands (B) Ankle joint swelling without tenderness as well as mild oedema of his lower extremities.

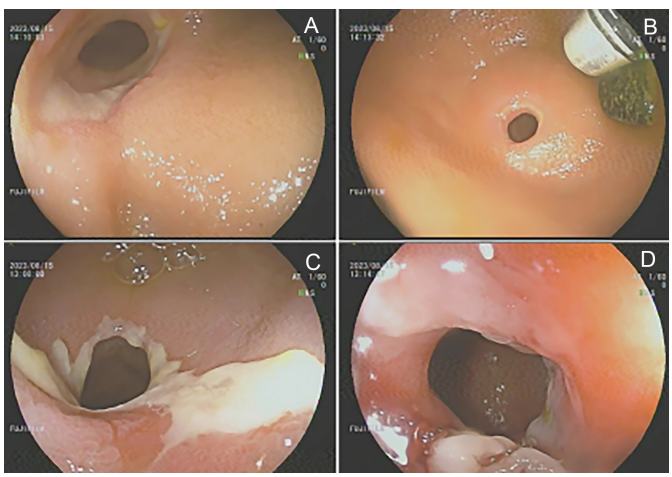

Figure 2: Double-balloon enteroscopy. (A, B) The oral side results showed jejunal stenosis with ulceration requiring pathological examination. (C, D) The results of the lateral anus showed ileal stenosis and ulceration, the nature of which required pathological examination.

Concerning the auxiliary examination, the patient's routine blood findings were as follows: Haemoglobin of 28 g/L, haematocrit of 0.093 L/L, and an erythrocyte sedimentation rate of 27 mm/1st hour. Moreover, his routine biochemical findings were as follows: Albumin of 22.3 g/L and B-type natriuretic peptide of 1166 pg/mL. The results of the other laboratory tests were all normal. Gastroscopy revealed superficial gastritis with erosion, while pathology revealed mild-to-moderate chronic superficial inflammation of the antrum. The *Helicobacter pylori* was negative. A colonoscopy demonstrated that there were no abnormalities in the colonic mucosa. A plain computed tomography scan of the whole abdomen revealed gallstones, splenomegaly, portal hypertension accompanied by tortuous and widened collateral arteries, and a small amount of peritoneal effusion. Capsule endoscopy revealed erosive gastritis and multiple ring ulcers in the small intestine, as well as intestinal stenosis.

After admission, the patient was infused with a white-suspended red blood cell suspension and human serum albumin. Afterwards, his melena improved, and he was discharged. However, during a telephone follow-up two weeks after discharge, the patient stated that the capsule had not been excreted, and his capsule endoscopy results indicated that it remained in the intestine. Therefore, the patient attended the Gastroenterology Department of Sir Run Run Shaw Hospital affiliated with the Zhejiang University School of Medicine in August 2023 and underwent computed tomography imaging of his small intestine, where a dense metal shadow was observed. The capsule endoscope was confirmed to be lodged in his small intestine. The patient subsequently underwent a double-balloon enteroscopy at the same facility, with separate procedures performed *via* the oral and anal approaches to remove the capsule endoscope (Figure 2A-D). The findings of the oral side histopathological examination were as follows: (Jejunal ulcer) widening and atrophy of the focal villi, focal distortion of the crypts, pyloric gland metaplasia, vasodilation, mild active inflammation, and small areas of inflammatory necrosis. Moreover, the results concerning the lateral anus were as follows: Distorted rectum focal crypts, ulcerated ileum, jejunum focal villous atrophy, distorted crypts, dilated vessels, and focal pyloric glandular metaplasia.

As detailed above, the patient reported anaemia as the initial symptom during childhood and intermittent melena as the prominent manifestation during adulthood. The latter was accompanied by severe anaemia, hypoalbuminaemia, megalosplenia, and multiple stenotic ulcers in the small intestine. The patient had coarse and thick skin on his face and skull, clubbing at the tips of the fingers of both hands, and ankle enlargement. In accordance with these clinical features, the doctors detected a heterozygous mutation (c.940 + 1G>A) in the patient's *SLCO2A1* gene. With regard to the diagnostic consensus of the Japanese expert meeting on inflammatory bowel disease, the patient had three relevant characteristics—namely, persistent occult blood loss in the gastrointestinal tract, characteristic intestinal lesions, and a *SLCO2A1* gene mutation.[4] Therefore, the patient was diagnosed with CEAS.

In terms of subsequent treatment, given the diagnosis of CEAS, total enteral nutrition was recommended as the primary treatment approach; however, the patient declined this regimen. Considering the reports that support the efficacy of hormone therapy for CEAS, in addition to oral polysaccharide iron complex capsules (one capsule /day) and febuxostat tablets (20 mg/day), the patient was prescribed oral prednisolone (40 mg/day).[5] Four days later, the patient reported the recurrence of black stools, occurring 2-3 times per day, with a volume of approximately 100-200 g each time, accompanied by fatigue. Consequently, the patient opted to receive total enteral nutrition therapy. After 8 weeks of nasogastric total enteral nutrition therapy, the patient reported the absence of black stools. Routine blood examinations showed a haemoglobin level of 122 g/L, normal serum albumin levels, and no other symptoms of discomfort. Furthermore, the patient reported no obvious discomfort during a telephone follow-up three months after he ceased nasal feeding.

DISCUSSION

Solute carrier organic anion transporter family member 2A1 (*SLCO2A1*) is a plasma membrane transporter composed of 12

transmembrane domains. It is ubiquitously expressed in tissues and mediates the membrane transport of prostaglandins, which are involved in the kidneys, neurons, respiratory system, female reproductive system, gastrointestinal tract, and liver.[6] *SLCO2A1* is also involved in important physiological processes in mammals. A recessive inheritance caused by mutations in *SLCO2A1* is associated with two rare and refractory conditions—namely, CEAS and primary hypertrophic osteoarthropathy (PHO). The *SLC02A1* gene is the second gene known to cause PHO after the *HPGD* gene. Therefore, CEAS and PHO are highly correlated. Five male patients with CEAS have been reported to exhibit skin and skeletal changes, such as facial skin thickening, finger acropsia, and large joint pain, which were preceded or followed by gastrointestinal symptoms.[7] In the present case, the patient was diagnosed with CEAS and exhibited the above-mentioned symptoms, so the possibility of comorbid PHO was considered.

It is important to note that not all CEAS cases are also diagnosed with PHO. For instance, women with the *SLCO2A1* gene mutation in the same PHO family often do not exhibit the typical clinical characteristics of PHO.[8] In this case, the sisters of the patient were healthy, while his mother was not found to have the condition, which indicates that the question of whether estrogen has a positive effect on the change in the *SLCO2A1* gene requires further study.

In summary, CEAS is a rare condition that differs from Crohn's disease, and a clear diagnosis is beneficial to subsequent treatment. There has been no statistical analysis of the regional characteristics of the distribution of reported CEAS cases in China, while the prevalence of CEAS cannot be reliably estimated due to speculation that the actual number of patients is greater than the number reported in the literature. An in-depth understanding of CEAS and the popularisation of genetic testing would reduce the prevalence of misdiagnosis or missed diagnosis and enhance the comprehension of CEAS.

PATIENT'S CONSENT:
Informed consent was obtained from the patient.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
LS: Manuscript writing.
ZY: Concept, design, and analysis.
YH: Interpretation of data and analysis.
LW: Analysis and literature review.
JL: Critical revision.
All authors approved the final version of the manuscript to be published.

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