Chronic Enteropathy Associated with SLC02A1-Associated Primary Hypertrophic Osteoarthropathy in Female Patients: A Case Report and Literature Review

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Research

Keywords: Chronic enteropathy associated with the SLC02A1 gene (CEAS), Primary hypertrophic osteoarthropathy (PHO), Diagnose, Female, Diseases associated with SLC02A1

Posted Date: November 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1060971/v1>

Abstract

This paper reports a case of chronic enteropathy associated with the SLC02A1 gene (CEAS) combined with primary hypertrophic osteoarthropathy (PHO). The patient was a 25-year-old woman with a normal onset of puberty who was admitted to our hospital four times due to intractable oedema and anaemia. She had a history of hyperhidrosis since childhood, and her parents were close relatives (cousins). Enteroscopy revealed stenotic ulcers on the ileocecal valve and the terminal ileum. Computed tomography enterography (CTE) and magnetic resonance enterography (MRE) showed segmental thickening of the ileum and terminal intestinal wall and centripetal narrowing of some intestinal cavities. MRE also showed a marked "comb sign" in the adjacent mesentery, and X-rays of both lower limbs showed thickening of the tibiofibular cortex. The CEAS pathogenic genes were screened by whole exome sequencing, and a homozygous missense mutation of p. Gly222Asp (c.664G>A) was found in the fifth exon of the SLC02A1 gene, which was verified by Sanger sequencing. In conclusion, the patient was identified as CEAS with PHO associated with a SLC02A1 gene mutation, but the patient is a young woman, which has rarely been reported in previous studies. In addition to reporting her case, the relevant literature was reviewed to improve clinicians' understanding of diseases associated with the SLC02A1 gene.

Introduction

Chronic enteropathy associated with the SLC02A1 gene (CEAS) is a rare, autosomal recessive genetic disease caused by SLC02A1 gene mutation. It is a novel intestinal disease characterized by chronic persistent intestinal blood and protein loss due to nonspecific multiple small intestinal ulcers[1, 2]. SLC02A1 is also a pathogenic gene of primary hypertrophic osteoarthropathy (PHO)[3]. PHO, also known as pachydermoperiostosis (PDP), is a genetic disorder manifesting as abnormal hyperplasia of the skin and periosteum[4]. CEAS is seldom seen in clinical practice, and there are only a few scattered cases of the disease reported China[5–7]. Since the SLC02A1 gene is the common pathogenic gene of both CEAS and PHO[8], some patients with CEAS may develop clinical symptoms of PHO at the same time[1, 2]. Simultaneously, some patients with PHO also have gastrointestinal abnormalities[5, 9]. CEAS is more likely to occur in women, while PHO is more likely to occur in men[1–3, 5, 9, 10]. All CEAS patients who met the PHO diagnostic criteria so far were male[1, 2, 5].

In July 2020, our hospital admitted a female patient with end ileal ulcer and stenosis, anaemia, and hypoproteinemia. After a series of relevant examinations, combined with the patient's clinical symptoms, the final diagnosis was CEAS combined with PHO. The case report and a literature review are provided.

Materials And Methods

Basic information and diagnostic criteria of the patient

The patient, a 25-year-old woman, was admitted to the Department of Gastroenterology of the First People's Hospital of Yunnan Province (hereinafter referred to as our department) four times from July 2020 to November 2020. During hospitalization, she received relevant symptomatic treatment and follow-up every 3 months after discharge. This study was conducted with the approval of the Institutional Ethics Committee of the First People's Hospital of Yunnan Province. After the patient signed the relevant written informed consent form, various clinical data and genetic test results of the patient at the initial and previous follow-up visits were collected. All procedures were performed in accordance with the relevant guidelines and regulations. The CEAS diagnostic criteria adopted were the Japan Inflammatory bowel disease experts meeting diagnosis consensus[1] (Supplementary Table 1). The PHO diagnostic criteria are mainly based on clinical symptoms and imaging findings after excluding secondary factors such as cardiopulmonary disease, malignant tumours, osteoarthropathy, etc. The recommendations of Matucci-Cerinic et al.[11] include 3 major criteria and 9 minor criteria, and the disease is divided into complete type, incomplete type and atypical (light) type (Supplementary Table 2).

Laboratory and imaging related examinations

Samples of fasting blood samples were collected, and the complete blood count, CRP (C-reactive protein), and routine biochemical examination results were obtained. The imaging examination included CT, MRI, and upper and lower extremity bone and joint X-rays. Colonoscopy, oral and transanal enteroscopy were performed, and tissues were taken for pathological examination under endoscopy.

Mutation analysis

Before blood sampling and DNA analysis, informed consent was obtained from the patient. Five millilitres of peripheral venous blood was collected in an EDTA anticoagulant tube. Whole genomic DNA was extracted by a peripheral genomic DNA extraction kit (Beijing Genomics Institute, China). A sequencing chip (BGI, China) was used to capture exosomes with high-throughput sequencing (HTS) technology for whole-exome sequencing. Sanger sequencing was used to verify the screening results. SeqMan software was used to design forward and reverse primers encoding exon 5 of the *SLCO2A1* (NM_005630.2) gene, and an ABI 3730XL automatic sequencer (Applied Biosystems, USA) was used for forward and reverse DNA sequencing. Primer sequence (forward): ACAGGTGTGGGCTTATCAGG; primer sequence (reverse): GCACCCAGCCCATAGAAATA. The PCR mixture volume was 25 µL, including 10 pmol of each primer, 4 units of dNTPs, 0.25 units of La Taq enzyme, 5.25 µL double distilled H₂O (ddH₂O), 12.5 µL 2xGC Buffer, and 1 µL DNA template. The PCR conditions were as follows: 95°C for 5 min, 95°C for 30 s, 68°C for 30 s, and 72°C for 30 s. Each cycle dropped 1°C, for a total of 10 cycles, from 68°C to 58°C. Then, 94°C for 30 s, 58°C for 30 s, 72°C for 30 s, a total of 35 cycles, finally 72°C for 5 min, and hold at 4°C. Both the whole-exome sequencing and Sanger sequencing were completed by the Shenzhen BGI Clinical Laboratory Center.

Table 1
Diagnostic criteria of CNSU

1. Persistent and occult blood loss from the GI tract except during bowel rest or a postoperative period.
2. Confirmation of characteristic small intestinal lesions by microscopy, radiography, or enteroscopy.
2.1 Circular or oblique in alignment.
2.2 Sharply demarcated from the surrounding normal mucosa.
2.3 Geographic or linear in shape.
2.4 Multiplicity in number with a 4 cm distance from each other.
2.5 Ulcers not reaching the muscular layer.
2.6 Scarred ulcers are presumed to be the healing stage characterized by (a)-(e) ^a in cases treated by bowel rest
^a Depicted as symmetric and eccentric rigidity under small-bowel radiography and concentric or nonconcentric stricture under enteroscopy.

Table 2
Diagnostic criteria of primary hypertrophic osteoarthropathy

Major criteria	Minor criteria
1. Digital clubbing	1. Seborrhoea
	2. Folliculitis
	3. Hyperhidrosis
2. Pachydermia	4. Arthritis or arthralgia
	5. Acroosteolysis
	6. Gastric ulcer and/or gastritis
3. Periostosis	7. Neurovegetative syndrome
	8. Hypertrophic gastropathy
	9. Cutis verticis gyrata

Results

Case Presentation

A 25-year-old woman developed an onset of illness during adolescence. Her parents are close relatives (cousins). Since 2017, there has been no obvious cause of her intermittent diarrhoea, yellow watery stool 3–4 times/day, and she self-administered oral "norfloxacin 0.4 g/once"(once or twice a week treatment), and then her stool became dry, showing a "sheep dung" shape. Thereafter, diarrhoea and constipation alternately appeared, and she did not seek medical help for her symptoms. At the beginning of June 2020, the patient developed oedema, initially on her face and lower extremities, and then whole-body oedema. She went to the local hospital they found she had albumin at 17g/L, and she was given "albumin" symptomatic treatment (details unknown). She was discharged after the oedema improved. One week after discharge, the patient developed oedema of both lower limbs again. On July 9, 2020, she was admitted to our department with the chief complaint of "diarrhoea 4–7 times/day, anasarca". Physical examination showed that her general condition was slightly worse, BMI 18kg/m², an anaemic appearance, with facial oedema and pitting oedema of both lower limbs. The lungs, heart and abdomen were normal, myodynamic examination of the limbs was normal, and while there was a thumb valgus deformity of both lower limbs, there was no limitation of movement.

Laboratory, imaging and other related examinations

Laboratory examination: haemoglobin 104g/L, average red blood cell volume: 79.3fL, average haemoglobin content: 24.7 pg, average haemoglobin concentration: 312 g/L, albumin: 23.6 g/L (Supplementary Table 3). MRE showed that the ileum and its terminal intestinal wall segments were thickened, part of the intestinal cavity was narrowed concentrically, the adjacent mesentery showed an obvious "comb sign" (Fig. 1a-c). Transanal colonoscopy revealed ulceration and stenosis of the ileocecal valve and terminal ileum (Fig. 1f-h). Pathological examination: the mucosal tissue of the small intestine showed active chronic mucositis with erosion, inflammatory exudation, and granulomas were not detected (Fig. 1j-l), PAS (-), Masson (-), Congo red staining results (-), T-SPOT(-) and IGRA (-).

Initial diagnosis

After comprehensive consideration, the patient was diagnosed with "the cause of the terminal ileum ulcer is to be investigated, small cell hypochromic anaemia, hypoproteinemia, malnutrition". The patient was treated with anti-inflammatory therapy via oral mesalazine enteric-coated tablets (4.0 g/day) and oral Montolite powder (9 g/day) to protect the mucosa. At the same time, Ferralia and folic acid supplements were taken to improve her anaemia, and intravenous albumin supplementation and oral enteral nutrition treatment were initiated. After 2 weeks of treatment, the patient's diarrhoea symptoms were reduced to 1–2 times a day, and she was discharged after the oedema subsided. However, from August to November, the patient was admitted to our department repeatedly due to recurrences of diarrhoea and oedema of both lower limbs. Based on the patient's symptoms, examination results and poor treatment effect, we addressed the patient's concerns, careful follow-up revealed that the patient had concealed a family

history of consanguineous marriage between his parents. Based on this information, it was considered necessary to identify to test for a genetic disease, namely CEAS.

Genetic test results and final diagnosis and treatment

We performed genetic testing to confirm the diagnosis of CEAS, and the DNA sequencing results detected a homozygous mutation in exon 5 of the SLC02A1 gene (c.664G>A [missense mutations])(Fig. 1m). The patient had a history of hyperhidrosis since childhood. At the age of 15, there was no obvious cause of her hallux valgus deformity of both lower extremities with pain, but the pain was relieved spontaneously after 5 months. X-rays of both lower extremities showed proliferation of the tibia and fibula periosteum (Fig. 1n-p). In summary, the patient was diagnosed with CEAS associated with atypical PHO. During hospitalization, we administered symptomatic treatment to the patient (Supplement Fig. 2). Before discharge, she gained 2 kg of weight, her anaemia and lower extremity oedema improved, and the frequency of diarrhoea was reduced to 1–3 times per day.

Table 3
Results of laboratory examination (our hospital)

Check item	Specimen category	Test result	Reference range
HGB (g/L)	Blood	100 g/L	115–150 g/L
MCV (fL)	Blood	74.3 fL	82–100 fL
MCH (pg)	Blood	21.7 pg	27–34 pg
MCHC (g/L)	Blood	312 g/L	316–354 g/L
Prealbumin (mg/L)	Blood	156 mg/L	280–360 mg/L
Total protein (g/L)	Blood	38.4 g/L	65–85 g/L
Albumin (g/L)	Blood	23.6 g/L	35–55 g/L
Globulin (g/L)	Blood	14.8 g/L	20–30 g/L
Calcium (mmol/L)	Blood	1.91 mmol/L	2.11–2.52 mmol/L
hs-CRP (mg/L)	Blood	23.196 mg/L	0–8 mg/L
IgM (g/L)	Blood	0.18 g/L	7.51–15.60 g/L
IgG (g/L)	Blood	0.26 g/L	0.82–4.53 g/L
IgA (g/L)	Blood	0.26 g/L	0.46–3.04 g/L
FERR (ng/ml)	Blood	2.19 ng/mL	4.63–204 ng/mL
Folate (nmol/L)	Blood	6.40 nmol/L	7.0–46.4 nmol/L
Faecal occult blood test	Blood	Positive	Negative

Discussion

In this article, we reported a young woman patient with CEAS and PHO, a type of disease caused by a mutation in the SLCOA21 gene. The patient has gastrointestinal symptoms as the first symptom accompanied by skeletal symptoms.

CEAS

CEAS was initially referred to as chronic nonspecific multiple ulcers of the small intestine (CNSU)[12, 13], which is an intestinal disease characterized by ring-shaped ulcers and concentric stenosis. Its main clinical feature is chronic persistent gastrointestinal blood and protein loss caused by long-term recurring small intestinal ulcers. Most patients will have symptoms of anaemia and hypoalbuminemia[1, 2, 12–14]. In 2015, Umeno et al. identified seven candidate mutations in the SLCO2A1 gene through whole-exome sequencing of CNSU patients, which encodes a prostaglandin transporter. In contrast to the vague name of CNSU, a more suitable nomenclature of CEAS has been suggested and CEAS has been defined as a rare genetic disease characterized by multiple, circular, longitudinal or eccentric ulcers of the ileum[2]. CEAS principally occurs in women, with a male to female ratio of 1:2.5–4:14[1, 2]. It often presents in adolescence, and the median age of onset is 16.5 years; however, the age of onset ranges from 1 to 69 years old, and 28% of patients are the offspring of close relatives[1]. The main clinical manifestations of the patients are oedema, anaemia, hypoproteinemia or abdominal pain, and most patients have anaemia (98%), while diarrhoea, blood in the stool and fever are relatively rare[1, 2, 14]. This patient's parents were close relatives and she presented to the doctor with oedema of both lower limbs. She had severe anaemia and hypoproteinemia, which were consistent with the symptoms of CEAS previously reported. However, the faecal occult blood test in this case was positive, with severe diarrhoea and occasional bloody stool, which were slightly different from previous reports.

With the promotion and application of balloon-assisted enteroscopy (BAE), the diagnosis rate of intestinal ulcerative diseases has been greatly improved. However, because the endoscopic manifestations of ileal ulcers caused by CEAS are very similar to nonsteroidal anti-inflammatory drug-induced bowel disease (NSAID-bowel disease), Crohn's disease (CD), Behçet's disease (BD), cryptogenic multifocal ulcerative stenotic enteritis (CMUSE) and other intestinal ulcerative diseases, misdiagnoses and missed diagnoses often occur in the clinic. It has been reported that glucocorticoids and immunosuppressants are ineffective for CEAS[12–14]. Therefore, it is vital to identify and diagnose CEAS and select appropriate treatment. CEAS cases are easily misdiagnosed as Crohn's disease clinically, so they should be rigorously differentiated from CD initially. Both diseases share some common clinical features, such as a pubertal predisposition, persistent anaemia and hypoproteinaemia, ileal involvement and with or without stenosis. The patient in this case was considered to have Crohn's disease at the first

diagnosis. However, there are also differences. The morphological characteristics of small intestinal ulcers are different. Unlike Crohn's disease, there are multiple intestinal ulcers in CEAS (usually >20)[14]. The depth of CEAS ulcers is limited to the mucosa or submucosa and does not reach the muscle layer, so small intestinal lesions will not form transmural inflammation leading to fissures and fistulas or have a cobblestone appearance and granuloma manifestations. Furthermore, previous reports have confirmed that serum and urine prostaglandin E2 (PGE2) and prostaglandin E metabolite (PGE-M) levels in CEAS patients are increased[1, 2, 15]. Because PGE-M are more stable in urine, Matsuno et al.[16] confirmed that prostaglandin E-major urinary metabolite (PGE-MUM) measurement is a noninvasive and convenient detection method to distinguish CEAS from CD. In addition, in most CEAS patients, SLC02A1 gene mutations result in the loss of SLC02A1 protein expression in the vascular endothelial cells of the small intestinal mucosa and submucosa, whereas its expression is normal in healthy individuals and CD and BD patients[17, 18]. Moreover, CD patients are mainly male, while BD and CEAS patients are mainly female[14]. In Western countries and South Korea, a disease similar to CEAS called CMUSE has also been reported[19]. This enteropathy has been proven to be an autosomal recessive genetic disorder caused by a PLA2G4A gene mutation[20]. Patients with CEAS and CMUSE have similar clinical features, including anaemia and abdominal pain. Pathologically, they both show multiple mucosal and submucosal superficial ulcers and are prone to ulcerative stenosis of the small bowel[12–15, 19]. However, intestinal ulcers in CEAS patients mainly occur in the ileum, while CMUSE mainly occurs in the jejunum and can be accompanied by extraintestinal symptoms, including obstructive pulmonary disease, oral aphthae, arthralgia, Sjogren's syndrome, Raynaud's sign, and neuropathy[19, 21]. However, these comorbidities are rare in patients with CEAS[12, 13]. The symptoms can be improved by corticosteroid therapy, but this is not effective in CEAS[2, 12–14, 19, 21]. Combining these differences, CMUSE and CEAS can be distinguished, but the distinction between the two is mainly achieved through genetic testing.

NSAID enteropathy is also an important differential diagnosis of CEAS. Most patients with NSAID enteropathy have a history of a long-term history of using NSAIDs, and their symptoms are dramatically improved after drug withdrawal, while there is no significant improvement in the symptoms of CEAS patients. In short, gene analysis of SLC02A1 is the key to the diagnosis of CEAS. In this case, the female patient had an onset in adolescence of refractory oedema, hypoproteinemia, and anaemia. Colonoscopy revealed ileocecal valve and terminal ileum stenosis ulcers. Finally, a homozygous mutation c.664G>A in SLC02A1 exon 5 was found by gene sequencing and thus a conclusive diagnosis was reached.

PHO

Mutations in the SLC02A1 gene cause not only CEAS but also a subtype of PHO[3, 8–10, 22]. Hypertrophic osteoarthropathy (HO) can be divided into primary and secondary according to its aetiology. PHO is an autosomal genetic disease, accounting for only 3%-5% of HO[10]. Secondary hypertrophic bone arthropathy (SHO) is more common clinically, accounting for approximately 95%-97%, and is mainly secondary to cardiopulmonary diseases[23]. In addition to the typical clinical triad of digital clubbing, periostosis, and pachydermia, PHO can also manifest as symptoms such as hyperhidrosis, seborrhoea,

acroosteolysis, arthritis, joint pain and other symptoms[3, 9, 10]. In addition to the above clinical manifestations, PHO is often associated with some nonspecific complications: (1) Gastrointestinal diseases, including chronic gastritis, CNSU, peptic ulcer, gastric cancer, Crohn's disease, and CMUSE[4, 5, 24]; (2) anaemia, (3) hypoproteinemia, (4) and myelofibrosis [3, 9, 10, 22, 24, 25]. The clinical manifestations of primary hypertrophic osteoarthropathy are diverse. In 2013, Zhang et al.[3] reported that diarrhoea was a common symptom of PHO patients, and 6 out of 7 PHO patients had diarrhoea. In the report of Wang et al.[5], PHO patients with gastrointestinal involvement mainly showed diarrhoea (46.2%), gastric or duodenal ulcers (19.2%/11.5%) and chronic gastritis (7.7%). In a research report involving 43 Chinese PHO patients, more than half of the patients had watery diarrhoea[24]. Hou et al.[9] confirmed that diarrhoea is the most common complication among the digestive tract symptoms. Different patients have different causes of diarrhoea, such as eating spicy food or taking cold drinks, or even sexual intercourse[3]. Sethuraman et al.[25] reported for the first time that PHO was associated with protein-losing enteropathy, indicating that lymphatic infiltration into the abdominal cavity or intestinal cavity was caused by dilatation and rupture of the intestinal mucosa and submucosal lymphatic vessels, resulting in protein loss. Anaemia is also a common comorbidity in PHO associated with SLC02A1 mutations.

There are many factors that cause anaemia, including myelofibrosis and gastrointestinal bleeding [22, 24, 26]. Patients with SLC02A1 mutations have a high frequency of severe anaemia due to myelofibrosis[4, 26]. Previous studies have shown that PGE2 is necessary for the formation of haematopoietic stem cells (HSCs), but the dose of PGE2 is very important. High-dose PGE2 can inhibit the differentiation of stem cells, and anaemia in PHO patients may be caused by an increased level of PGE2[3, 24, 27]. Zhang et al. [3] reported 2 cases of female PHO patients with c.855delA homozygous mutations. Their clinical symptoms were severe anaemia and hypoalbuminemia, rather than skin and bone manifestations. Combining the patient symptoms and gene test results, we consider these two cases to be CEAS. A case of PHO associated with a SLC02A1 mutation in a postmenopausal elderly women was previously reported, but the patient did not present with the typical skin and bone manifestations[28]. Hou et al.[9] is by far the largest cohort study report of SLC02A1 mutations in China, in which all PHO patients with SLC02A1 mutations were male.

The patient in this paper with hyperhidrosis since childhood, when she was 15 years old, her lower limbs suddenly suffered from pain and formed hallux valgus. The X-ray of the lower limbs showed that the tibia and fibula periosteum was thickened, showing typical onion skin-like changes, and this was combined with severe diarrhoea, consistent with the clinical characteristics of PHO. A homozygous mutation of the SLC02A1 gene was detected by gene sequencing, which is consistent with the PHO diagnosis. The patient was mainly treated for oedema, accompanied by watery diarrhoea and severe anaemia. She liked spicy food; in severe cases, she had diarrhoea episodes 10 times per day, and the causes of her diarrhoea and protein loss are still worth exploring.

Diseases associated with SLC02A1

The SLC02A1 gene is located on chromosome 3q21.1-q22.2 and consists of 14 exons, encoding a prostaglandin transporter (PGT). When mutation of the SLC02A1 gene causes abnormal synthesis of PGT, abnormal prostaglandin metabolism leads to disease[10]. The degradation of prostaglandins in the human body is divided into two steps. First, PGT, including SLC02A1, actively transports extracellular prostaglandin into the cells, and the prostaglandins are degraded to 15-OXO-PGE2 by 15-hydroxyprostaglandin dehydrogenase encoded by HPGD and then by prostaglandin reductase to PGE-M[29]. In 2008, Uppal et al.[30] revealed an HPGD (MIM 606188) gene mutation in a PHO family. In 2012, Zhang et al.[10] demonstrated another pathogenic gene of PHO, SLC02A1 (MIM 601460). Previous molecular discoveries divided PHO into two types: PHOAR1 (MIM259100) with a HPGD gene mutation and PHOAR2 (MIM614441) with a SLC02A1 gene mutation[24]. The mutated HPGD and SLC02A1 genes inhibited the removal of prostaglandins, leading to local accumulation of prostaglandins, especially PGE2, a key factor in PHO pathogenesis[3, 10, 30]. The detection of PGE2 and PGE-M in urine can contribute to distinguishing between the two types: the levels of urine PGE2 and PGE-M in patients with PHOAR2 are increased. In PHOAR1 patients, urine PGE2 is increased and PGE-M is decreased[3, 9, 10, 24]. It has been previously reported that the level of PGE2 in PHOAR1 patients is significantly higher than that in PHOAR2 patients[24]. Since PGE2 levels in both PHO and CEAS are increased, we consider that PGE2 may be the main regulator of the clinical phenotype of the diseases associated with SLC02A1. Although PGE2 is an important component of the intestinal mucosal defence barrier and is considered to be a protective factor of gastrointestinal tissue via the prostaglandin receptor EP3/EP4[31], patients with CEAS still develop multiple intestinal ulcers, and the mechanism of how prostaglandins play a role in the pathogenesis of CEAS has not yet been clarified. Based on the results of previous studies, we speculate that PGE2 levels in an appropriate range may be a necessary factor to maintain intestinal mucosal homeostasis.

In 2015, Umeno found that the SLC02A1 gene is the cause of CEAS. Among the 7 different mutation sites detected, the splice site mutation c.940+1G>A is the most common in patients with CEAS[1, 2]. Mutation sites c.664G>A, c.940+1G>A, and c.1807C>T were also reported as pathogenic mutations of PHO[3, 9, 10, 26, 28]. PHOAR1 can have an onset within 1 year after birth, but the symptoms of PHOAR2 usually appear after puberty[10, 30]. In terms of complications, the incidence of anaemia, hypoproteinemia, and gastrointestinal lesions in the PHOAR2 type is higher than that for PHOAR1[3, 5, 9, 24]. In addition, there are also significant differences between males and females. In PHOAR1, the ratio of males to females is approximately 1:1; PHOAR2 patients are mainly male, and female patients are very rare[3, 9, 10, 24, 30]. Wang et al.[5] reviewed 158 PHO patients reported in China in the past 18 years (January 2000 to April 2018). That article reviewed and reported the first symptoms of 138 patients, and only a few patients (3.6%, 5/138) had gastrointestinal disease as their first symptom, but as the disease progressed, 17.2% (26/151) of patients had gastrointestinal complications. Among PHO patients with gastrointestinal involvement, peptic ulcers and chronic gastritis only occurred in patients with SLC02A1 gene deficiency[9], and gastrointestinal complications in PHO patients are more closely related to SLC02A1[5]. Previous studies have shown that CEAS and PHOAR2 share a common pathogenic gene[1, 2, 8, 14]. CEAS mainly occurs in women and it mainly manifests as anaemia and hypoproteinemia, without clubbing,

periostosis, or pachydermia[1, 2]. PHOAR2 mainly occurs in men, and all reported PHO patients with gastrointestinal involvement are men[5]. All CEAS patients who met the main diagnostic criteria of PHO were male, and no female CEAS patients have developed PHO[1, 2].

Our patient was female and was finally diagnosed with CEAS with light PHO. In retrospect, this is a rare case, and the patient was in her youth and could not be excluded from developing skeletal and skin tissue changes or other systemic symptoms in the future. The relationship between PHO and CEAS is very close, and some of their clinical symptoms overlap, and the relationship between the two is worth exploring. Sun et al.[32] believed that CEAS and PHO may be different manifestations of the same pathological process, and they are two sides of a coin. These findings indicate that the clinical characteristics of SLC02A1-related diseases are influenced by other factors. We consider that sex-related modifier genes or sex hormones may play a potential role in the occurrence and development of the disease, finally leading to differences in clinical symptoms.

After the patient was discharged from the hospital in November 2020, we followed her closely to seek a good treatment plan to control the progression of the disease. Currently, no effective drug treatment strategy has been reported for CEAS. This disease is characterized by chronic and refractory clinical characteristics, and its clinical course is characterized by postoperative recurrence and stenosis with small intestinal ulcers[2, 3, 12–14]. When small bowel stenosis occurs, the patient must undergo surgery. Balloon expansion under colonoscopy is the method used to treat this complication[14]. There is also currently no effective cure for PHO, and drugs are mainly used to relieve symptoms and plastic surgery is applied to improve the facial skin thickening for cosmetic purposes [22, 33]. Drug treatments mainly use nonsteroidal anti-inflammatory drugs (NSAIDs) that reduce prostaglandin synthesis. Previous studies have reported that NSAIDs are effective for both PHOAR1 and PHOAR2 patients and they can effectively alleviate the bone and skin symptoms of patients by inhibiting the production of PGE2[34]. Li SS et al. reported that etoricoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, has a significant effect on reducing urinary PGE2 levels and it can be used to improve symptoms of finger clubbing, joint pain and swelling, and pachydermia. However, NSAIDs are often ineffective in PHO patients with gastrointestinal involvement[4]. At present, the diagnosis and treatment of CEAS and PHO are still difficult problems for clinicians, and they require further study. We need to make more clinicians aware of CEAS and PHO, which are a class of diseases associated with SLC02A1 mutations that are characterized by multiple intestinal ulcers and abnormal bone and skin tissue. This case report is intended to provide valuable information for the diagnosis of CEAS and PHO and to shed new light on diseases associated with SLC02A1 mutations.

Conclusions

SLC02A1 is a common pathogenic gene of CEAS and PHOAR2, but the two diseases have different clinical manifestations. In addition, there are also differences by sex. CEAS tends to manifest in women while PHO is more likely to occur in men. Female patients with CEAS combined with PHO are very rare

and have rarely been reported. The clinical characteristics of SLC02A1-associated diseases may be influenced by sex or sex hormones, resulting in differences in clinical symptoms.

Abbreviations

CEAS: chronic enteropathy associated with the SLC02A1 gene; PHO: primary hypertrophic osteoarthropathy; PGE2: prostaglandin E2; CTE: computed tomography enterography; MRE: magnetic resonance enterography; CRP: C-reactive protein; CNSU: chronic nonspecific multiple ulcers of the small intestine; BAE: balloon-assisted enteroscopy; NSAID-bowel disease: nonsteroidal anti-inflammatory drug-induced bowel disease; CD: Crohn's disease; BD: Behçet's disease; CMUSE: cryptogenic multifocal ulcerative stenotic enteritis; PGE-M: prostaglandin E metabolite; PGE-MUM: prostaglandin E-major urinary metabolite; SHO: secondary hypertrophic bone arthropathy.

Declarations

Acknowledgements

We are very grateful to this patient for her participation and support in this study.

Authors' contribution

BL contributed to the article conception, data analysis and collation, literature collection, and wrote the original manuscript. PW participated in guiding the clinical diagnosis and treatment of the patient and providing financial support for the experiment. HT contributed to the review and revision of the original manuscript, and WZ participated in the conception of experimental ideas and guided the design of the experimental methods. RXZ, JC, and MT participated in the collection of clinical data and imaging and pathological pictures of the patient, respectively. CY and HT were responsible for the collection of endoscopic pictures. All authors read and agreed to the final manuscript.

Funding

Not applicable.

Conflict of interest

The authors declare that there are no conflicts of interest.

Availability of data and materials

All of the clinical and laboratory data, imaging, genetic test results, etc., are provided in the article.

Ethics approval and consent to participate

The Ethics Committee of the hospital reviewed and approved the use of clinical data and genetic test results for the patient.

Consent for publication

The patient in this manuscript signed written informed consent to publish her case.

Data availability statement

Not applicable.

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Supplementary

Figures

Figure 1

a-c MRE showed diffuse small bowel wall thickening in the ileum and its terminal intestinal wall. a Luminal narrowing concentric (bottom left arrow and top solid arrow), asymmetric mural hyperenhancement along the mesenteric border (bottom right arrow), multiple enlarged lymph nodes (dashed arrow). b Engorged and dilated vasa recta in the small bowel mesentery, showing a “comb sign” (solid arrow). c Mesenteric lymph node enlargement (solid arrow), bowel wall thickening with stratified (trilaminar) mural hyperenhancement (dashed arrow), b Severe wall thickening and the thickest part is about 13mm (dashed arrow). d-e CTE showed inflammation in the terminal ileum. d Moderate wall thickening of the bowel wall (arrows). e Stratified mural hyperenhancement and luminal narrowing, showing a “target sign” (arrows). f-g Colon enteroscopy (transanal) shows stenotic ulcerative lesion of ileocecal valve and terminal ileum, endoscopy could not pass, h Stenosis with scars, covered with purulent secretions. i Colonoscopy showed sigmoid colitis with erosion. j Pathology showed Inflammatory exudation (original magnification, ×200). k There are fibrin exudation (solid arrow) and haemorrhage (dashed arrow) (original magnification, ×200). l Small intestinal villi atrophy (arrows). m-o X-ray features of bilateral lower limbs, m Sanger sequencing of the SLC02A1 gene, a homozygous missense mutation of SLC02A1 p.Gly222Asp (c.664G>A) was found in exon 5 of the patient. The sequence was aligned with Reference sequence (NM_005630.3). n-o Anteroposterior and lateral

radiographs of bilateral tibial and fibular periosteum thickening, respectively (arrows). p Bilateral first metatarsal valgus (arrows).

Figure 2

Clinical treatment course and reactivity after admission. a-b Changes in hemoglobin and albumin over time in patients treated with Ferralia and mesalazinemesalazine enteric-coated tablets.