Clinics and Research in Hepatology and Gastroenterology (2019) 43, e68—e72

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CASE REPORT

Chronic enteropathy associated with SLCO2A1 gene: A case report and literature review

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Available online 10 June 2019

KEYWORDS
Chronic enteropathy associated with *SLCO2A1* gene;
Computed tomography enterography;
Magnetic resonance enterography

Summary A case of chronic enteropathy associated with SLCO2A1 gene (CEAS) is presented. The female patient was readmitted four times during a three-year follow-up period for intractable dropsy and anemia. Multiple ulcers of small bowel wall were revealed by endoscopic examination. Computed tomography enterography (CTE) and magnetic resonance enterography (MRE) showed the segmental wall thickening of the small bowel. Hepatosplenomegaly and increased bone density of spine and pelvis suggested the diagnosis of myelofibrosis. X-ray films showed the cortical thickening of tibiofibula. The mutations of SLCO2A1 gene were revealed by gene test and the diagnosis of CEAS was confirmed. According to our case report, imaging examinations, including CTE, MRE and X-ray films provide additional valuable information during the diagnostic procedure of CEAS.

Introduction

Chronic enteropathy associated with solute carrier organic anion transporter family member 2A1 (SLCO2A1) gene (CEAS) was a new term of enteropathy which caused by mutations of the SLCO2A1 gene and characterized by chronic loss of blood and protein due to nonspecific small intestinal ulcers. To date, the diagnosis of CEAS is still a challenge for clinicians with the clinical symptoms and endoscopic findings. However, CEAS should be considered in the differential diagnosis despite of its rarity to avoid inappropriate therapies. We report a case of CEAS and review the literatures.

Case presentation

A 29-year-old woman had recurrent general dropsy for 7 years, which got worse for 3 months and a history of

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https://doi.org/10.1016/j.clinre.2019.05.003
2210-7401/

iron-deficiency anemia for 10 years. Blood tests of another hospital showed: red blood cell count was 2.93×10^{12}/l, a haemoglobin level was 6.6 g/dl, the serum albumin level was 15.5 g/dl. The pathologic finding of outside endoscopic examination was focal lymphangiectasia of the base of terminal ileum mucosa. She was referred to our hospital and diagnosed as anemia, hypoproteinemia and intestinal lymphangiectasia. A stool occult blood test was positive. Magnetic resonance enterography (MRE) found the thickened wall of small bowel, enlargement of mesenteric lymph nodes and small amount of ascites (Fig. 1b). Barium meal radiography displayed the thickened intestinal mucosal folds and stenosis of ileum (Fig. 1a). Capsule endoscopy revealed multiple ulcers of small bowel wall, which needed to be differentiated with Crohn's disease. Capsule retention was noted during this examination and the patient was treated with mosapride citrate tablets and lactulose oral solution. Then the capsule was excreted. Chronic non-atrophic gastritis was revealed by gastroscope. This patient's symptoms relieved after being provided with symptomatic treatment. She was readmitted three times during the following three years for intractable dropsy and anemia. Following colonoscopies showed irregular ulcers of terminal ileum (Fig. 2a) and edematous colonic mucosa and the pathologic finding was nonspecific chronic inflammation. Following computed tomography enterography (CTE) and MRE showed that segmental wall thickening of the small bowel (Fig. 1c—f). Furthermore, hepatosplenomegaly and increased bone density of spine and pelvis were revealed and the diagnosis of myelofibrosis was suspected (Fig. 3a—c). The recent capsule endoscopy found multiple ulcers of small bowel with luminal stenosis. Finally, CEAS was considered in the differential diagnosis during her last hospitalization. Then the X-ray films showed the cortical thickening of tibiofibula (Fig. 3d and e) and the whole exome sequencing showed two mutations in the SLCO2A1 gene, including a heterozygous frameshift mutation, c.1633A[2 > 1] (std: c.1633A[1] alt: c.1634delA) in exon 12 and a heterozygous splice-site mutation, c.724 + 1G > A in intron 5.

Discussion

With the widespread use of genetic testing, the etiology of some diseases was illustrated at the genetic level. Solute carrier organic anion transporter family member 2A1 (SLCO2A1) gene was identified as the causative gene of the chronic non-specific multiple ulcers of the small intestine (CNSU), which was a relatively new term of an autosomal recessive inherited disease. Then chronic enteropathy associated with SLCO2A1 (CEAS) was proposed to replace previous inaccurate terminology. To date, most cases of CEAS were reported by Japanese. However, Sun et al. had reported a male Korean patient with CEAS and they believed that some CEAS cases of other Asian countries may be misdiagnosed as other disorders due to their lack of awareness of the disease [1]. Umeno et al. had reported eleven SLCO2A1 gene mutations identified in 46 patients with CEAS [2]. We presented two new mutations in a Chinese woman with CEAS.

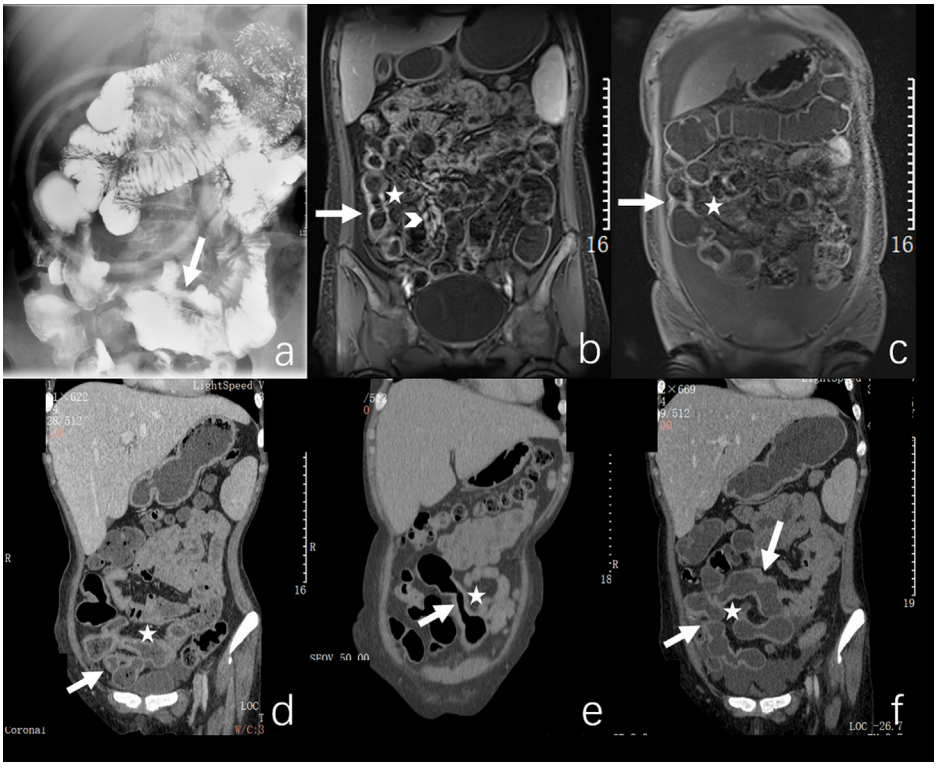

Figure 1 Colonoscopy examination (a) showed showing multiple irregular shallow ulcers of terminal ileum. Coronal post-contrast T1 weight imaging (b and c) and axial post-contrast imaging (d—f) at five different time points showing the normal terminal ileum (arrow).

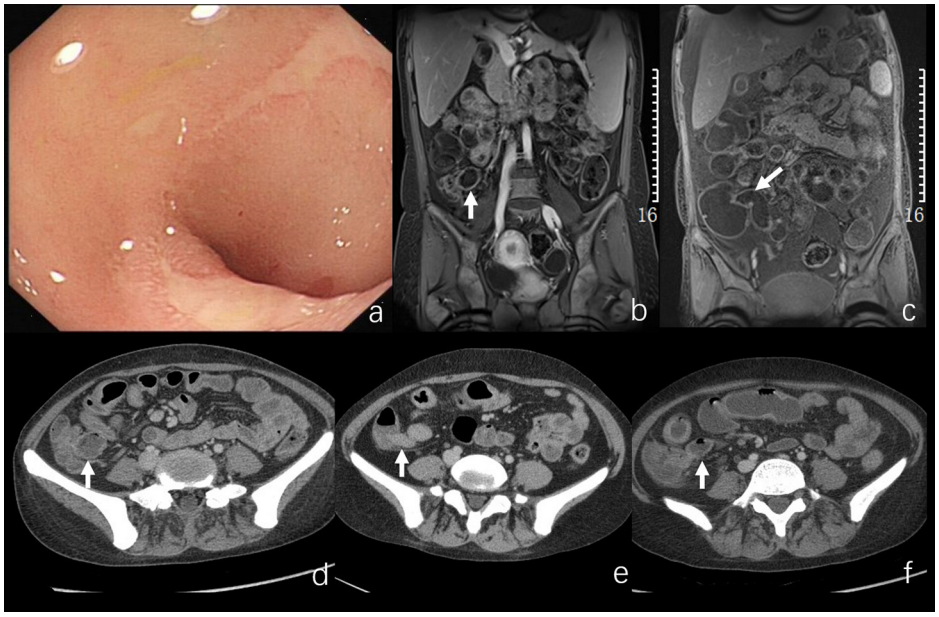

Figure 2 Barium meal radiography (a) showing the thickened intestinal mucosal folds and stenosis of the ileum. Coronal post-contrast T1 weight imaging (b and c) and axial post-contrast imaging (d-f) at five different time points showing the uniform thickening of small bowel wall (arrow), ''clear'' mesentery (star) and enlarged nodes (arrow head). The imaging findings at different time points are similar.

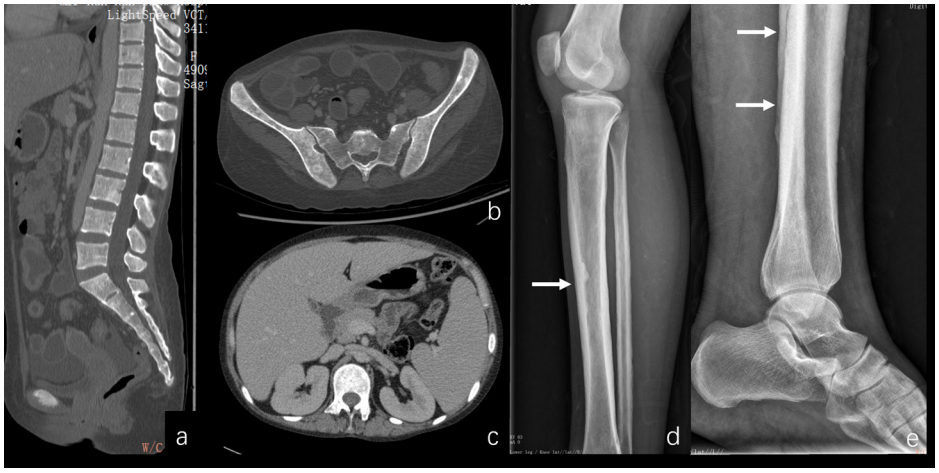

Figure 3 Sagittal and axial CT imaging (a and b) showing the increased bone density of spine and pelvis. Axial CT imaging showing (c) the hepatosplenomegaly. X-ray films (d and e) showing the cortical thickening of tibiofibular(arrow).

CEAS predominantly occurs in woman and the male: female ratio was 1:2.5-4:14 [2,3]. CEAS tends to affect the adolescents, however, it can be found in people aged 1 to 69 years. The characteristic clinical manifestations of CEAS include abdominal pain, chronic anemia, hypoproteinaemia and oedema caused by persistent, intractable nonspecific ulcers [4]. Endoscopic features of CEAS are characterized by multiple sharply demarcated shallow ulcers with or without luminal narrowing [4,5]. Perhaps for this reason, capsule retention was noted in our patient and Sun et al. case [1]. Ulcers of CEAS could be found in stomach and small bowel. However, the ileum is the most commonly involved site, regardless of mesenteric or anti-mesenteric side [4,6,7]. It's worth mentioning that no involvement of the terminal ileum was revealed in Umeno et al. reports and they speculated that the sparing of the terminal ileum in CEAS may be a differential point of CEAS and Crohn's disease (CD). However, Eda et al. presented a CEAS patient with small round ulcers involving the terminal ileum and ileocecal valve[8]. Irregular ulcers of terminal ileum could also be found in our patient (Fig. 2a). Therefore, intact terminal ileum may not be useful enough to differentiate these two entities. No colonic involvement was found in previous reports and our patient.

Surgical pathology findings of CEAS were shallow ulcers (depth within the submucosal layer) with mild inflammation and fibrosis [4]. The initial pathologic finding of our patient was focal lymphangiectasia of the base of terminal ileum mucosa, which may be a secondary change and

used to explain the hypoproteinemia in CEAS patient. However, these pathologic changes are nonspecific. Fortunately, SLCO2A1 protein could be found in the cellular membrane of vascular endothelial cells within the small intestinal mucosa and submucosa in healthy people, CD and intestinal Behçet's disease (BD) patients while loss of SLCO2A1 protein expression was noted in most CEAS cases [5,9], This difference may be useful tool in differentiating between a diagnosis of CEAS or other inflammatory bowel diseases.

Hydroxyprostaglandin dehydrogenase 15-(NAD) (HPGD) gene and SLCO2A1 gene are identified as the two causative genes of primary hypertrophic osteoarthropathy (PHO). Correspondingly, PHO was subdivided into two types (PHOAR1 and PHOAR2). There are several characteristic differences between these two types of PHO, such as time of symptom onset, sex ration and clinical spectrum. Prostaglandin (PG) transporter is encoded by SLCO2A1 gene which could mediates the active transepithelial uptake of PG against a concentration gradient and mutations of SLCO2A1 gene might lead to elevated level of prostaglandin E2 (PGE2) and prostaglandin E metabolite (PGE-M) in serum and urine [9,10]. Persistently high PGE2 could result in the clinical characteristics of PHO, such as digital clubbing, pachydermia and periosteal reaction [11,12]. However, It's not a necessary factor for CEAS, because CEAS were not found in PHOAR1 patients. Male predominance of PHO could be explained by higher level of PGE2 in males than females. However, elevated level of PGE2 cannot explain female predominance in CEAS. The exact mechanism still remains unknown, especially the high level of PGE2 were known to protect gastrointestinal mucosa [3]. According to previous literature, PG transporter can also function as an organic anion exchanger, and play a role in the release of newly synthesized prostaglandins from cells. Nakanishi et al. suggested that this function could be a potential explanation of CEAS [13].

The imaging features of CEAS were often ignored and they were not described in details in previous reports. Our patient had undergone barium meal radiography, two MRE and three CTE examinations over a three-year period. Based on these image data, we found that segmental small intestinal wall thickening could be found in CEAS patient. However, the imaging findings were different from these of CD in some ways. The differences including (Figs. 1 and 2): (a) intestinal wall thickening of CEAS was uniform, while the mesenteric plane of the bowel of CD patient was more involved; (b) the small intestinal mucosa of CEAS was more intact in CT and MRI imaging which could be explained by shallow ulcers. Mucosal ulceration and transmural ulcer formation of CD were common findings in CT and MRI examinations [14,15]; (c) mesentery of affected bowel wall segments of this case was more ''clear''. No obvious ''comb sign'', inflammatory adhesions, sinus tracts and fistulas were revealed; (e) although multiple ulcers of terminal ileum of this CEAS patient were displayed by colonoscopy, the wall of the terminal ileum remained normal in CT and MR imaging; (d) the imaging manifestations of the affected intestinal segment and mesentery of this patient remained basically unchanged with symptomatic treatment for over three years, while mural enhancement degree of CD could be changeable depending on the inflammation activity.

As mentioned above, some clinical features of PHO could be found in the patients with CEAS, because these two diseases share the same causative gene mutation. However, PHO associated clinical manifestations mainly occurred in male CEAS patients due to sex-related hormones [2,3]. X-ray film of our patient showed the cortical thickening of tibiofibula (Fig. 3d and e) while no pachyderma and digital clubbing was revealed by physical examination. Diggle et al. found that SLCO2A1-deficient PHO patients have a high frequency of severe anemia due to myelofibrosis [16]. In this case, whole abdominal CT imaging showed hepatosplenomegaly and extensive increased bone density of spine and pelvis which suggested the diagnosis of myelofibrosis (Fig. 3).

The treatment of CEAS was often frustrating for corticosteroids and immunosuppressive therapies were usually not effective. However, Eda et al. reported a successful treatment in a CEAS patient with azathioprine [8]. Guda et al. reported that disordered prostaglandin catabolism caused by HPGD and SLCO2A1 mutations could increase the risk of colorectal neoplasia in man and colon neoplasia screening at a young age was suggested [17].

In conclusion, CEAS is a chronic inflammation of gastrointestinal tract different from Crohn disease. In clinical work, if the patient has abdominal pain, stool occult blood, chronic anemia, hypoproteinaemia, dropsy and multiple ulcers on endoscopy with sparing of terminal ileum and colon in CTE or MRE, we should consider the possibility of CEAS, especially the imaging findings are inconsistent with those of Crohn's disease. The gene examination is suggested to get the definite diagnosis. Tests for PGE2 and PGE-M in serum and urine, immunohistochemical analysis of SLCO2A1 protein and X-ray examinations of the extremities may provide additional valuable information.

Disclosure of interest

The authors declare that they have no competing interest.

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