Clinical Case Report

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Case report of a pair of siblings with cryptogenic multifocal ulcerating stenosing enteritis

A rare disease easily to be misdiagnosed as Crohn disease

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Abstract

Rationale: The rare disease cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) is characterized by multiple and recurring small intestinal ulcers with stenosis of unknown causes. In clinic, it is difficult to be differentiated from the inflammatory bowel disease, especially the Crohn disease.

Patient concerns: Here we report a pair of siblings who suffered from long-time anemia and abdominal pain and misdiagnosed with inflammatory bowel disease (IBD) for many years.

Diagnoses: They were finally diagnosed with CMUSE with intestinal obstruction.

Interventions and outcomes: They both accepted surgical treatment and recovered well. No abdominal symptom appeared in the two-year follow-up.

Lessons: This report underscores that CMUSE patients may have a long course of suffering from anemia and abdominal pain, normal inflammatory markers and normal colon, and sometimes have a family history of CMUSE. Surgery of segmental bowel resection is a good way to solve intractable intestinal obstruction in CMUSE.

Abbreviations: CMUSE = cryptogenic multifocal ulcerous stenosing enteritis, CNSU = chronic nonspecific multiple ulcer, CRP = C-reactive protein, CT = computed tomography, ESR = erythrocyte sedimentation rate, IBD = inflammatory bowel disease.

Keywords: case report, CMUSE, Crohn disease, siblings, small bowel ulcers

1. Introduction

Small bowel ulcers could be caused by multiple diseases, such as Crohn disease (CD), non-steroidal anti-inflammatory drug enteropathy, intestinal tuberculosis, T-cell enteropathy, and collagen vascular disease. As CD becoming more and more common in China recently, small bowel ulcers are catching more and more attention. Due to technical limitation, diagnosis of small bowel ulcer is not easy. Debray et al[1] first reported a case with intermittent small intestinal obstruction and ulcerative stenosis in the small intestine with unknown etiology in 1964. After that, about 60 cases have been reported.[2–12,13] As cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) is such a rare disease, the epidemiology, clinical characteristics, and the pathogenesis have not been clearly established. Perlemuter et al[11,14] proposed that CMUSE was a type of "atypical vasculitis," while Matsumoto et al[15] did not reveal any arteritis in their patients. In 2014, Brooke et al[16] reported a pair of CMUSE siblings with mutations in the *PLA2G4A* gene who had undetectable cPLA2α protein expression and reasoned that the mutations in the *PLA2G4A* gene as the cause of CMUSE.

Here, we describe a pair of siblings suffered from anemia and abdominal pain for tens of years. Both of them accepted capsule endoscopy examination and the capsules were stranded in the stenosis. Surgeries were performed and they were finally diagnosed with CMUSE. We also sequenced the *PLA2G4A* gene and measured cPLA2α protein expression in our CMUSE patients.

2. Case presentation

2.1. Case 1: the brother (41 years old)

A 41-year-old man has suffered from paroxysmal, lower abdominal pain, and anemia for more than 10 years with unknown cause. One year before admission, he felt weak, dizzy,

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Authors' contributions: YZ and QC designed the study and drafted the manuscript. YZ, LH, RL, and MW collected and interpreted the data. WZ performed the operation. ZJ performed the histopathological examination. All authors read and approved the final manuscript.

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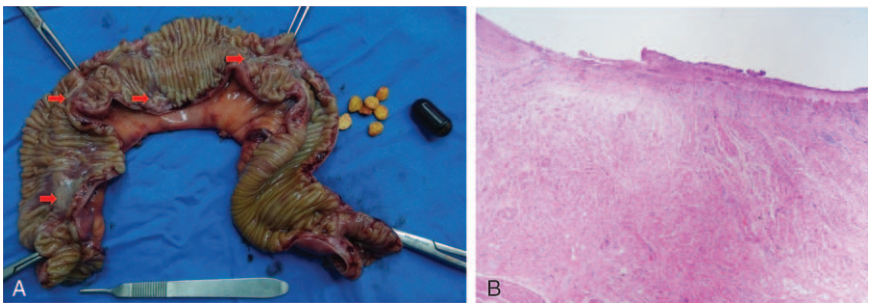

Figure 1. (A) The surgical specimens from the brother. It shows multiple longitudinal shallow ulcer in the mesenteric border with pus moss on the surface (red arrow), local stenosis and see a capsule endoscopy inside. (B) The histological findings of the brother shows dilated submucosal lymphatic vessels dilated, hyperplasia of inflammatory granulation tissue and fibrous tissue, local lymph follicles formation, with many chronic inflammatory cells infiltration (100×).

and nauseas. He went to local hospital and the laboratory examination reported a severe anemia (hemoglobin, 55 g/L), hypoalbuminema (30 g/L), an elevated platelet (536×10^9/L), a +++ stool occult blood, a normal C-reactive protein (CRP) (0.3 mg/L), and a normal erythrocyte sedimentation rate (ESR) (21 mm/h). Both colonoscopy and gastroscopy were normal. Abdominal small bowel computed tomography (CT) scan found that the ileum in the left lower abdomen segmentally thickened and inflammatory lesions was considered. His symptoms improved after blood transfusion. He also underwent the capsule endoscopy examination at the local hospital but the capsule was retained.

He was transferred to our hospital because of continuous dizzy, fatigue and nauseas 2 weeks before he went to our hospital. The small bowel CT scan reported segmental intestinal wall thickening, local stenosis, same as CD and could see a capsule stranded in the terminal ileum. He was transferred to the surgical department and a laparoscopic-assisted small bowel segment resection was performed. We saw a thickened intestinal wall, longitudinal shallow ulcers in the mesenteric border with pus moss on the surface, and local stenosis with a capsule endoscopy inside (Fig. 1A). Under the microscope, we saw several superficial ulcers, dilated submucosal lymphatic vessels, hyperplasia of inflammatory granulation tissue and fibrous tissue, formation of local lymph follicles, with many chronic inflammatory cells infiltration (Fig. 1B). His deoxyribonucleic acid was sent for sequencing and an immunohistochemistry for cPLA2α was required. No *PLA2G4A* mutation was found in the genetic analysis (Fig. 4A) and the cPLA2α was positive in the intestinal mucosa slides (Fig. 4C).

The patient recovered well after the surgery and his symptoms didn't recur during a 2-year follow-up.

2.2. Case 2: the sister (36 years old)

A 36-year-old female, suffered from repeated middle upper abdominal pain accompanied with weakness and dizziness for 20 years with no detectable cause. Gastroscopy and colonoscopy found nothing 20 years ago. She was treated with blood transfusion for her severe anemia. The capsule endoscopy examination 3 years ago revealed a 2.5×3.6 cm ileum mucosa ulcer. Enteroscope was not completed because of the grievous pain and bulge hyperplasia lesions were seen in the interminal ileum. She was diagnosed with CD in the local hospital and had been treated with mesalazine. The abdominal pain did not improve. She came to our hospital for help.

Physical examination had no other findings except mild abdominal tenderness. The lab examinations found a severe anemia (hemoglobin 6.6 g/L), an elevated platelet count (536×10^9/L), a mild hypoalbuminemia, a ++ occult blood in the stool, a normal CRP (0.4 mg/L), and a normal ESR (7 mm/h). Again, both gastroscopy and colonoscopy showed normal results. The enhanced CT scan of small intestinal was negative. The capsule endoscopy found multiple pleiomorphous ileum ulcers, leading to partial luminal narrowing (Fig. 2) with the capsule stranded. After twice of intestinal obstruction, she finally

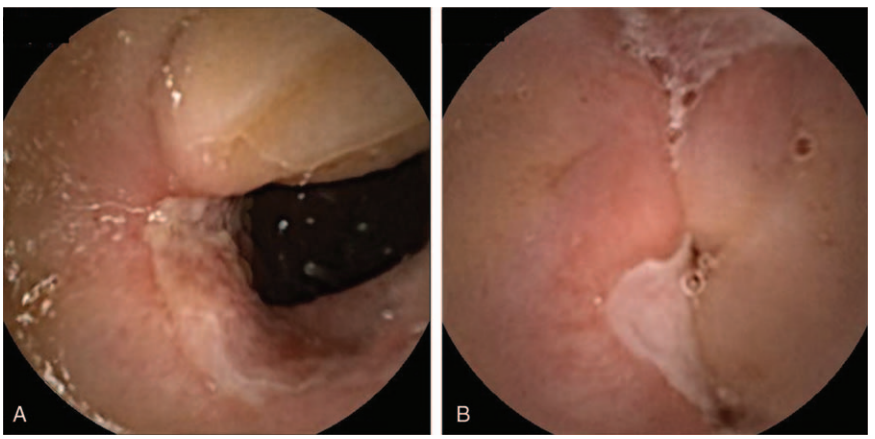

Figure 2. The capsule endoscopy image from small bowel of the brother. Ileum mucosa ulcer.

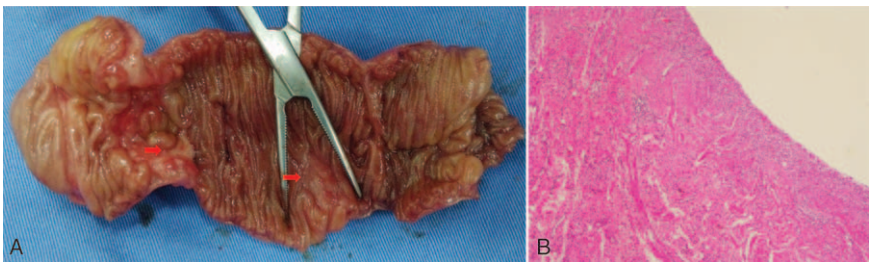

Figure 3. (A) The surgical specimen from the sister. Pitting ulcers ranging from 2.5 × 1 to 1.8 × 1 cm were located on the mesangial side (red arrow). (B) The histological findings of the sister. Superficial ulcers are confined to the submucosa, accompanied with focal pyloric gland metaplasia, nerve tissue hyperplasia, and lymphangiectasia around under the bottom of the ulcer infiltration (100×).

accepted laparoscopic-assisted small bowel segment resection surgery. We saw 4 strictures which could allow 1 finger through in the intestinal canal, 1 to 1.3 m back to ileocecal junction, with no edema or thickening of the intestinal wall. Pitting ulcers ranging from 2.5 × 1 to 1.8 × 1 cm were located on the mesenteric side (Fig. 3A). Under the microscope, the ulcers were superficial and confined to the submucosa, accompanied with focal pyloric gland metaplasia. In the submucosa under the bottom of the ulcer, we could see nerve tissue hyperplasia and lymphangiectasia (Fig. 3B). Like her brother, genetic analysis of *PLA2G4A* was negative (Fig. 4B) and the cPLA2α staining was positive (Fig. 4D). She was diagnosed as CMUSE and recovered well after the surgery. No symptoms recurred in the follow-up of almost 2 years.

The parents of the affected siblings are not consanguineous. Other family members have no similar symptoms.

3. Discussion

The clinical spectrum of symptomatic CMUSE is growing in China. After Debray et al[1] reported the first case of CMUSE, Okabe and Sakimura reported some cases of CMUSE in Japan in 1968, which they called chronic nonspecific multiple ulcers (CNSU) of the small intestine.[15] Different from inflammatory bowel disease (IBD) patients, the inflammation markers such as ESR and CRP in CMUSE patients are in normal ranges. Multiple shallow ulcers in the small intestine with discrete margins usually lead to segmentally luminal narrowing.[15] CMUSE patients

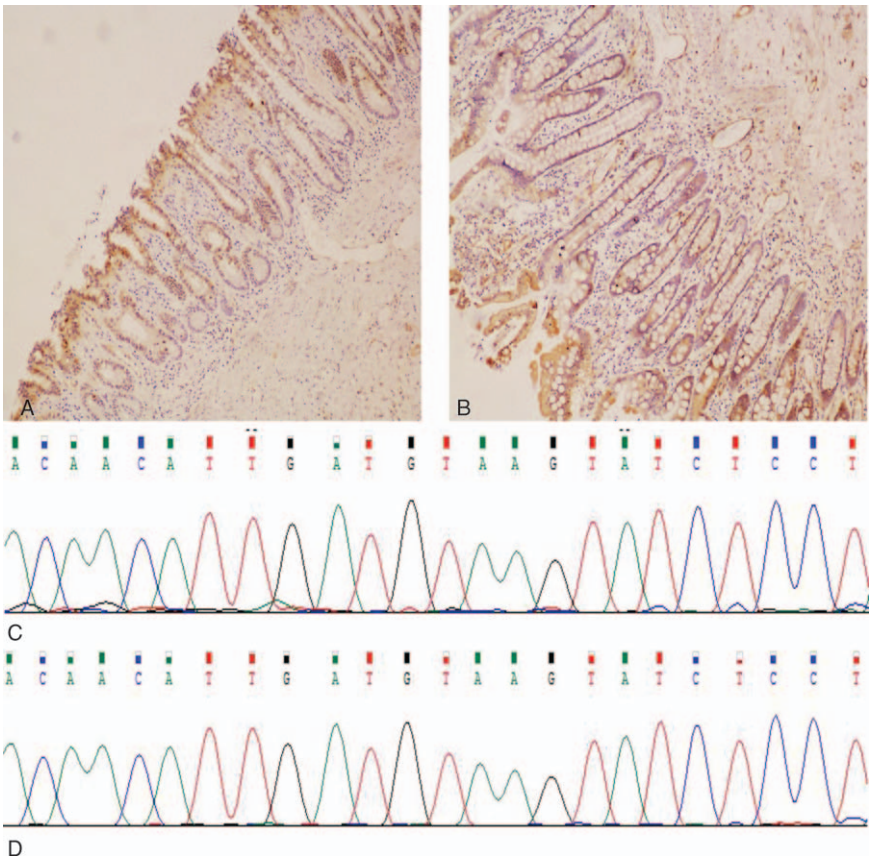

Figure 4. Representative immunohistochemical analysis of cPLA2α expression in small bowel biopsy specimens from the brother (A) and sister (B). Sanger sequence traces showing no mutation in *PLA2G4A* in the brother (C) and sister (D).

Table 1

Updated diagnostic criteria of CMUSE/CNSU.

(1) Medical history
(1.1) Long course, years to tens of years
(1.2) Persistent and occult blood loss from the gastrointestinal tract with severe anemia
(1.3) Some with a family history
(2) Clinical features
(2.1) Chronic and relapsing subileus episodes
(2.2) Chronic iron-deficiency anemia with fatigue, dizzy, edema, or growth retardation, rarely with diarrhea
(2.3) With normal inflammatory makers or other biological signs of systemic inflammation
(2.4) Normal colon and stomach
(2.5) No extrointestinal manifestations
(3) Imaging manifestation
(3.1) In enteroclysis: multiple persisting stenoses of the small intestine caused by brous strictures
(4) Endoscopic findings
(4.1) Multiple, pleiomorphous and superficial ulcers, and sharply demarcated from surrounding normal mucosa
(4.2) Cautious with capsule endoscopy examination for it may stranded in the strictures
(5) Histological findings
(5.1) Necrotic inflammatory ulcers not reaching proper muscular layer.
(5.2) Nonspecific inflammation, erosion with submucosal fibrosis

usually have an early onset beginning with abdominal pain and anemia, usually with normal shape of stool. According to Freeman, the absence of intestinal transmural and fistula formation, the absence of other parts of gastrointestinal tract and extraintestinal features make IBD less likely.[17] However, still many CMUSE patients are misdiagnosed with CD. We believe CMUSE should be regarded as a new additional cause of small bowel ulcers.

Diagnosis of CMUSE should based on medical history, clinical features, imaging manifestations, endoscopic findings, and histological findings. Matsumoto et al proposed diagnostic criteria of CMUSE/CNSU in 2004.[15,18] With our experience of CMUSE patients and literature reviews,[8,18,19] we think the diagnostic criteria should be updated to Table 1.

Gastroscopy and colonoscopy are quite common in China nowadays, while enteroscopy, difficult and expensive but more indispensable, is becoming more popular. Capsule endoscopy examination is the easier way, but only when the patient does not have a stenosis to strand the capsule. If stranded, the capsule will cause repetitive intestinal obstruction symptoms, and needs a surgery to remove it. Device-assisted enteroscopy is a good choice if a stenosis could not be rule out.

The etiology and pathogenesis of CMUSE is still poorly understood. With only about 60 CMUSE patients reported worldwide, the studies on CMUSE are limited and the opinions differing. Perlemuter et al[11,14] proposed that CMUSE was a type of "atypical vasculitis," while Matsumoto et al did not find any arteritis in his patients.[15] Perlemuter et al[14] also reported an association with C2 complement deficiency while this result could not be confirmed by Spencer et al.[20] Brooke et al[16] reported a pair of CMUSE siblings who have *PLA2G4A* gene mutations and undetectable cPLA2α protein expression. But we found the correct *PLA2G4A* gene sequences (Fig. 4C and D) and normal cPLA2α expression in our patients (Fig. 4A and B). So we conclude that mutations of the *PLA2G4A* gene should not be the only cause of the pathogenesis of CMUSE.

No standard therapy is available for CMUSE till now due to the lack of clinical experience. Corticosteroid treatment can improve the symptoms in most cases,[7,11,15] and most patients become corticosteroid dependent.[6] And in our case, the brother was treated with mesalazine and it was not helpful to relieve his symptoms. Blood transfusion, iron supplementation, and nutrition therapy are only effective to relieve the symptoms temporarily, so does in both siblings in our case. De Schepper et al[3] recently reported that infliximab was effective in CMUSE patients. However, most of the patients eventually underwent small bowel segment resection surgery for the recurring intestinal obstructions.[11,17] Both of our patients had capsule endoscopy stranded before the diagnosis was clarified. Surgical treatment of the involved bowel segment was effective in both of the siblings. They had no symptoms of anemia or abdominal pain during the 2-year follow-up after the surgery.

4. Conclusion

We reported the pair of siblings who both suffered from CMUSE. The present case suggests that a long disease course, severe anemia or iron deficiency, normal inflammation markers (ESR, CRP), and normal colon and multiple small intestinal shallow ulcers are distinguishing features of CMUSE. Segmental bowel resection is a good way to solve intractable intestinal obstruction in CMUSE. Also we should be cautious with the capsule endoscopy in patients with intestinal stenosis.

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