



Deception in Crohn's Disease: A Case of Cryptogenic Multifocal Ulcerous Stenosing Enteritis

Huafeng Shen¹, David R Cave² and Seymour Katz^{3,4,5*}

¹Division of Gastroenterology and Hepatology, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA

²Division of Gastroenterology, UMass Memorial Medical Center, Worcester, Massachusetts, USA

³Division of Gastroenterology, New York University School of Medicine, New York, USA

⁴North Shore University Hospital-Long Island Jewish Health System, Manhasset, New York, USA

⁵St. Francis Hospital, Roslyn, New York, USA

*Corresponding author: Seymour Katz, MD, Division of Gastroenterology, New York University School of Medicine; North Shore University Hospital-Long Island Jewish Health System; St. Francis Hospital, Roslyn, New York, 1000 Northern Blvd, Great Neck, NY 11020, USA, E-mail: Seymourkatz.md@gmail.com

Abstract

Cryptogenic multifocal ulcerous stenosing enteritis is a rare idiopathic condition, characterized by multiple small intestinal fibrous strictures with superficial ulcerations. It typically has a chronic or relapsing clinical course and has been mainly reported from Asia and Europe. We report a case of cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) in a patient with chronic anemia with melena and intermittent abdominal pain. The clinicopathological features of CMUSE are different from other small bowel disease. Our patient had a remarkable response to adalimumab. The area of gene mutations in CMUSE is promising but need further investigation.

Keywords

Cryptogenic multifocal ulcerous stenosing enteritis, CMUSE

Abbreviations

CMUSE: Cryptogenic Multifocal Ulcerous Stenosing Enteritis; EGD: Esophagogastroduodenoscopy; CT: Computed Tomography; CNSU: Chronic Nonspecific Multiple Ulcers of the Small Intestine; CRP: C-reactive protein; CD: Crohn's Disease; CUJI: Chronic Ulcerative Jejunoileitis; NSAID: Nonsteroidal Anti-inflammatory drug; anti-TNF: Anti-tumor Necrosis Factor.

Introduction

Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) is a rare idiopathic disease characterized by multiple small intestinal fibrous strictures with superficial ulcerations with a chronic or relapsing clinical course responding favorably to glucocorticosteroids. It has been mainly reported from Asia and Europe. We report a patient with chronic anemia with melena and intermittent abdominal pain who was diagnosed with CMUSE by small bowel resection.

Case Report

A 30-year-old man of Indian origin presented to the gastroenterology clinic in April 2013, with a history of anemia

since age 15 and with a 4-month history of intermittent abdominal pain. Esophagogastroduodenoscopy (EGDS) and colonoscopy in 2010 were unremarkable. In February 2013, he was found to have a hemoglobin of 2.8. He received 4 units of packed red blood cell transfusion and IV iron infusion. For the preceding 4 months, the patient had intermittent abdominal pain with a decrease appetite. The pain was described as sharp and wave-like. He had black stools, lasting for several days which resolved spontaneously. He was otherwise completely asymptomatic between episodes. He denied diarrhea, blood in the stool or NSAID use and lost 20 pounds over the last year. He had past medical history of lactose intolerance and was found to be clubbed. He came from India about 6 years ago and worked in computer science. On physical exam, his body mass index (BMI) was 19.9, but it was otherwise normal. He had an extensive work up for his iron deficiency anemia at a Boston hospital in 2012. This included 2 bone marrow biopsies which were non diagnostic. No explanation was found for the anemia.

Computed tomography (CT) of the abdomen and pelvis in February 2013 showed mild splenomegaly, mesenteric lymphadenopathy, diffuse sclerosis of the bones, and with mild thickening of the distal colon. Colonoscopy was normal to the terminal ileum. Video capsule endoscopy in April 2013 showed mid-jejunal ulcerations and stenosis. The capsule did not pass into the cecum. His most recent X-ray showed that the capsule was retained. CT enterography on May 7, 2013 showed less than optimal distention of the small bowel proximally, but with an apparent wall thickening of the jejunum in the left mid abdomen with areas of mucosal hyperemia in the ileum and the retained video capsule. Ten days later, a laparotomy with intraoperative enteroscopy (Figure 1 and Figure 2) revealed six tight ulcerated stenoses within a 45cm segment at approximately 120-140 cm from the ileocecal valve. The capsule was stuck at the second stricture. Intra-operative endoscopy was unsuccessful due to the tight and firm strictures. Approximately 45 cm of small bowel was resected.

Post-operatively, he tolerated a full diet without abdominal



Figure 1: Intra-operative enteroscopy findings. It showed a tight ulcerated stenosis of the mid-jejunum.



Figure 2: The gross finding of the resected specimen. It showed multiple fibrous stenoses and ulcers.

bloating. At follow-up, iron was 25 but his ferritin was normal. Pathology revealed multifocal ulcerous stenosing enteritis as reviewed by 3 pathologists. Post-operative infliximab was started as an attempt to preclude recurrent inflammation. However, due to the poor response, it was switched to adalimumab. He was also treated with rifaximin for small intestinal bacterial overgrowth. He has improved remarkably with lessened iron infusion requirement and is now having 1-2 bowel movements a day.

Discussion

CMUSE was first described by Debray *et al.* in 1964 [1]. There have been about sixty cases of CMUSE published [2]. Matsumoto *et al.* [3] reported 15 cases from Japan between 1964 and 2006, in which the illness was named chronic nonspecific multiple ulcers of the small intestine (CNSU). All of them presented with anemia and 10/15 patients underwent multiple small bowel resections due to recurrent strictures. Oral 5-aminosalicylic acid, prednisolone, or azathioprine failed to induce mucosal healing or prevent the recurrence of small intestinal ulcers. A French study [4] published 12 cases of CMUSE between 1965 and 1993. Despite surgery, symptoms recurred in seven of ten patients with strictures in four. Glucocorticosteroid therapy was effective but led to dependency. Kohoutová *et al.* [5] reported 3 cases diagnosed between 1994 and 2009 in Czech Republic, with colicky abdominal pain, recurrent ileus and weight loss, responding to glucocorticosteroid therapy. Double balloon enteroscopy were used to dilate the tandem tight jejunal stenosis. Two cases diagnosed by means of double balloon enteroscopy in Korea in 2007 were

Table 1: Different clinicopathological features among CD, CUJI and CMUSE*.

	CD	CMUSE	CUJI
Clinical presentation:			
Abdominal pain	+	+	+
Diarrhea	+	-	+
Malabsorption	+	-	+
Fever	+	-	+
Weight loss	+	+	+
Anemia	+	+	+
Melena	+	+	+
Hematochezia	+	-	+
Obstruction	+	+	+
Perforation	+	-	+
Extraintestinal manifestations	+	-	-
Histopathology:			
Intestinal transmural inflammatory process	+	-	+
Intestinal giant-cell granulomas	+	-	-
Fistula	+	-	+
Involvement of other parts of gastrointestinal tract (i.e. stomach or colon)	+	-	-
Infiltration of eosinophils	-	+	-
Villous atrophy	-	-	+
Laboratory tests:			
Elevated CRP or ESR**	+	-	+

*CD: Crohn's disease, CUJI: Chronic ulcerative jejunoileitis, CMUSE: Cryptogenic multifocal ulcerous stenosing enteritis;

**CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

presented with chronic recurrent abdominal pain and melena [6]. One patient underwent surgery because of retention of a capsule endoscope at the stenotic site.

The etiology and pathogenesis of CMUSE remains poorly understood. One hypothesis claims overstimulated production of fibrous tissue due to disturbance of proinflammatory cytokines, growth factors or collagen degradation [2,5]. Perlemuter *et al.* [4,7] reported a case of CMUSE associated with heterozygous type I C2 deficiency and 5 cases related to either arterial stenosis or aneurysm, proposing that CMUSE may be an atypical type of vasculitis or a disease mimicking vasculitis. However, these findings were not confirmed [3,6]. A recent study identified homozygous deletion mutations in PLA2G4A as a cause of CMUSE in two affected siblings [8]. This could be a potential diagnostic and/or therapeutic target in the future.

The clinicopathological features of CMUSE have been summarized as follows: (1) chronic iron-deficiency anemia due to small intestinal occult blood loss, (2) rarely diarrhea, malabsorption, hematochezia or fever, (3) unexplained small intestinal strictures found in adolescent and middle-aged subjects, often requiring multiple resections of the small bowel, (4) multiple superficial ulceration of the mucosa and submucosa, predominantly in the ileum (the terminal ileum is usually spared) with infiltration of plasma cells, lymphocytes, and eosinophils, (5) a chronic or relapsing clinical course, even after surgery, (6) no biological signs of systemic inflammatory reaction, C-reactive protein (CRP) and other acute inflammatory reactants remain within normal limits or slightly increased, and (7) beneficial effect of systemic glucocorticosteroids [3,4,7]. Our patient was presented with chronic anemia with melena and recurrent abdominal pain. No diarrhea, malabsorption, hematochezia or fever was documented. His small bowel resection for the strictures with intraoperative enteroscopy revealed six tight ulcerated stenoses. The capsule endoscopy was found to be retained at the second stricture.

The other entities causing multifocal small bowel ulcerations mainly include Crohn's disease (CD), chronic ulcerative jejunoileitis (CUJI), nonsteroidal anti-inflammatory drug (NSAID) or potassium tablets induced enteropathy, lymphoma, Behçet's disease, infections (e.g. tuberculosis), trauma and ischemia. A comparison of different clinicopathological features among CD, CUJI and CMUSE is listed in table 1 [9-12]. Our patients did not have CUJI or celiac disease in the

absence of villous atrophy and malabsorption. The absence of small intestinal transmural and granulomatous inflammatory process ruled out CD.

The treatment of CMUSE is usually symptomatic with iron replacement either oral or by infusion. Systemic glucocorticosteroid therapy is still the mainstay of treatment, but results in steroid dependence [2-5]. A case of steroid-refractory CMUSE was reported by Kim *et al.* [13]. Oral 5-aminosalicylic acid or azathioprine were reported to be ineffective to induce mucosal healing or to prevent small intestinal strictures [3]. Recently, de Schepper *et al.* [14] reported an anti-tumor necrosis factor (TNF)-alpha therapy (infliximab) induced remission for 6 months in a 29-year-old male patient with CMUSE. However, a recent meta-analysis cannot exclude that anti-TNF-alpha therapy may increase the long term risk of lymphoma in patients with inflammatory bowel disease [15]. Anti-TNF-alpha therapy should be used with caution in patients with CMUSE. The intestinal strictures can be treated by either surgical resection or double balloon enteroscopy [5,16].

The prognosis of CMUSE remains unclear. Due to the relapsing clinical course (even after surgery) of CMUSE, our patient was started on infliximab post-operatively and then switched to adalimumab. Although he failed to respond to infliximab initially, he has improved remarkably while on adalimumab and treatment of bacterial overgrowth. To date, the optimal treatment strategy for CMUSE is still open to discussion, anti-TNF may be considered in some cases.

References

1. Debray C, Besancon F, Hardouin Jp, Martin E, Marche C, et al. (1964) [cryptogenetic plurifocal ulcerative stenosing enteritis]. *Arch Mal Appar Dig Mal Nutr* 53: 193-206.
2. Kohoutová D, Bártová J, Tachecí I, Rejchrt S, Repák R, et al. (2013) Cryptogenic multifocal ulcerous stenosing enteritis: a review of the literature. *Gastroenterol Res Pract* 2013: 918031.
3. Matsumoto T, Iida M, Matsui T, Yao T (2007) Chronic nonspecific multiple ulcers of the small intestine: a proposal of the entity from Japanese gastroenterologists to Western enteroscopists. *Gastrointest Endosc* 66: S99-107.
4. Perlemuter G, Guillevin L, Legman P, Weiss L, Couturier D, et al. (2001) Cryptogenetic multifocal ulcerous stenosing enteritis: an atypical type of vasculitis or a disease mimicking vasculitis. *Gut* 48: 333-338.
5. Kohoutová D, Bures J, Tycová V, Bártová J, Tachecí I, et al. (2010) Severe cryptogenic multifocal ulcerous stenosing enteritis. A report of three cases and review of the literature. *Acta Medica (Hradec Kralove)* 53: 25-29.
6. Chang DK, Kim JJ, Choi H, Eun CS, Han DS, et al. (2007) Double balloon endoscopy in small intestinal Crohn's disease and other inflammatory diseases such as cryptogenic multifocal ulcerous stenosing enteritis (CMUSE). *Gastrointest Endosc* 66: S96-98.
7. Perlemuter G, Chaussade S, Soubrane O, Degoy A, Louvel A, et al. (1996) Multifocal stenosing ulcerations of the small intestine revealing vasculitis associated with C2 deficiency. *Gastroenterology* 110: 1628-1632.
8. Brooke MA, Longhurst HJ, Plagnol V, Kirkby NS, Mitchell JA, et al. (2014) Cryptogenic multifocal ulcerating stenosing enteritis associated with homozygous deletion mutations in cytosolic phospholipase A2-a. *Gut* 63: 96-104.
9. Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of American College of Gastroenterology (2009) Management of Crohn's disease in adults. *Am J Gastroenterol* 104: 465-483.
10. Van Assche G, Dignass A, Panes J, Beaugerie L, Karagiannis J, et al. (2010) European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. *J Crohns Colitis* 4: 7-27.
11. Freeman HJ (2009) Multifocal stenosing ulceration of the small intestine. *World J Gastroenterol* 15: 4883-4885.
12. Biagi F, Lorenzini P, Corazza GR (2000) Literature review on the clinical relationship between ulcerative jejunoileitis, coeliac disease, and enteropathy-associated T-cell. *Scand J Gastroenterol* 35: 785-790.
13. Kim CW, Yu CS, Yoon YS, Yoon SN, Lim SB, et al. (2011) Steroid-refractory cryptogenic multifocal ulcerous stenosing enteritis. *Am J Surg* 202: e48-51.
14. De Schepper H, Macken E, Van Marck V, Spinhoven M, Pelckmans P, et al. (2013) Infliximab induces remission in cryptogenic multifocal ulcerous stenosing enteritis: first case. *World J Gastroenterol* 19: 1661-1664.
15. Williams CJ, Peyrin-Biroulet L, Ford AC (2014) Systematic review with meta-analysis: malignancies with anti-tumour necrosis factor-a therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 39: 447-458.
16. Rejchrt S, Kopácová M, Tachecí I, Bureš J (2008) Interventional double balloon endoscopy for Crohn's, gastrointestinal bleeding, and foreign body extraction. *Tech Gastrointest Endosc* 10: 101-106.