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Case Report

Cryptogenic Multifocal Ulcerous Stenosing Enteritis: An 18-Year History of Chronic Iron-Deficiency Anemia and Hypoalbuminemia

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Abstract

Cryptogenic Multifocal Ulcerous Stenosing Enteritis (CMUSE) is a rare condition which mimic Crohn's Disease, but differs from this by causing small-intestine inflammation and ulceration restricted to mucosa and submucosa. There are few cases described in the literature. This is the first case described in Brazil and the first in the America's treated with Adalimumab due to the development of autoantibodies against Infliximab.

Keywords: *Cryptogenic Multifocal Ulcerous Stenosing Enteritis; Small Bowel Ulceration; Inflammatory Bowel Disease*

Introduction

Cryptogenic Multifocal Ulcerous Stenosing Enteritis (CMUSE) is an extremely rare condition reported in some parts of the world since 1964, which causes benign small-bowel obstructions [1-3]. Strictures most commonly occur in the jejunum and proximal ileum, with superficial ulceration involving mucosa and submucosa [1,2,4].

The pathogenesis is poorly understood, symptoms are vague (such as chronic iron-deficiency anemia, abdominal pain and diarrhea) and as a result, the diagnosis is very difficult [5].

To contribute to the knowledge of the disease and to consider it as a differential diagnosis in cases where the cause of iron deficiency anemia and hypoalbuminemia is not detected, we describe the first case of CMUSE in Brazil.

Case Report

A 21-year-old female patient presented with an 18-year history of chronic iron-deficiency anemia and hypoalbuminemia.

She was a 3-year-old girl when complaint for the first time about weakness during physical exercises. Her pediatrician diagnosed iron deficiency anemia and began investigating the cause. Upper gastrointestinal endoscopy (UGE) showed duodenal lymphoid hyperplasia. Gastrointestinal scintigraphy ruled out Meckel's diverticulum and gastrointestinal bleeding. With no evident anemia's cause, the patient was managed with iron supplementation for 12 years. She did not have diarrhea, abdominal pain, fever, arthralgia and presented a normal child neurological development. There was no family history of digestive disease. She did not use nonsteroidal anti-inflammatory drug (NSAID).

With 14 years old, episodes of leg edema developed, but the patient only look for a doctor 4 years later when evaluated with anasarca. She was admitted to the hospital and received the diagnosis of hypoalbuminemia and microcytic anemia due to iron-deficiency. During

the hospitalization, she performed a new UGE with gastric and duodenum biopsies (for Celiac Sprue investigation), colonoscopy with terminal ileum and colon biopsies (for Inflammatory Bowel Disease investigation), laboratory evaluation for kidney disease, thyroid disease, HIV-infection, inflammatory markers (erythrocyte sedimentation rate and C reactive protein) and food allergies investigation, but all of them were normal or had negative results.

After hospital discharge, the patient performed an anterograde double-balloon enteroscopy (DBE), which did not achieve ileum, but showed jejunal angiectasias, that were managed with argon fulguration. Despite of endoscopic treatment, she did not improve the anemia (mean hemoglobin levels of 6.86 g/dL) and the ferropenia (mean ferritin levels of 28.79 ng/mL).

As the fecal blood test was positive and the DBE was incomplete, a fecal calprotectin was requested and reveals elevated levels (values varying from 587 to 1.132 µg/g). At this time, she initiated empirically corticosteroid treatment (deflazacort 12 mg per day for 3 months) associated with mesalazine doses (1,600 mg/day for 3 months) empirically for small intestine Inflammatory Bowel Disease (IBD), without improvement in iron-deficiency anemia, hypoalbuminemia or calprotectin levels.

With 20 years old, she presented to another clinician for a second opinion. At this occasion, the patient repeated DBE two times (anterograde and retrograde DBE; unfortunately, all incomplete) and biopsy samples were taken for Whipple disease, which were negative.

One year later, the patient consulted our department for another medical opinion. She had symptoms related to anemia and leg edema, but did not complaint about abdominal pain, diarrhea, vomiting, hematemesis or hematochezia. The use of NSAIDs was denied all these years and the unique medication received empirically was Nitazoxanide (500 mg tid for 3 days). Hemogram reveals hemoglobin levels varying between 5,2 d/dL to 7,8 g/dL and there was no leukocytosis. C-reactive protein tended to be normal. Antinuclear antibodies were negative.

At this time, her magnetic resonance enterography identified two small intestinal strictures (at jejune segment) and Crohn's disease was questioned. Based upon the clinical course and inconclusive DBE, capsule endoscopy (CE) was performed to evaluate the suspected small bowel lesions. Unfortunately, the CE was retained in a jejunal stricture and Coloproctology surgery team was consulted for capsule removal.

Initially we tried to reduce the inflammation and swelling with systemic corticosteroids (Prednisone 40 mg/day), expecting a CE expulsion. However, it did not occur during a 4 weeks-period of Prednisone use. Therefore, exploratory laparotomy was performed and dilatation of small bowel, proximal to the CE impacted area and others circumferential strictures areas nearby (Figure 1). Segmental distal jejunal resection (about 20 cm in length) with end-to-end anastomosis was executed.

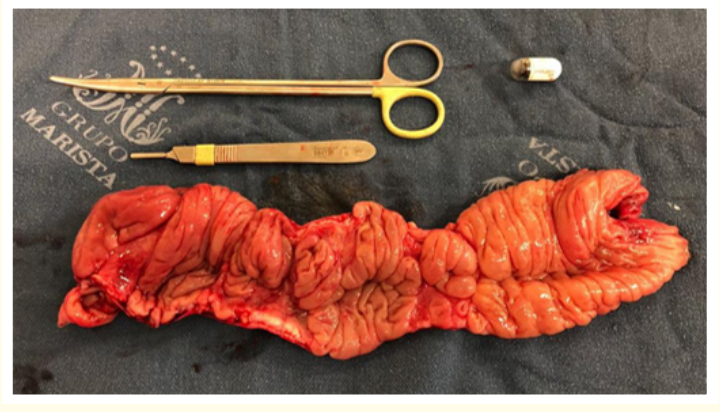

Figure 1: *Resected small bowel. Macroscopic appearance shows strictures associated with ulceration and normal mucosa surrounding the affected areas.*

Histopathology revealed acute and chronic ulcerative inflammation, associated with fibrosis, mainly at mucosal layer and in some area at submucosal too (Figure 2 and 3), without evidence of IBD or infection, compatible with Cryptogenic Multifocal Ulcerous Stenosing Enteritis (CMUSE). The pathological sample was sent for a second independent Pathologist review and the diagnosis of CMUSE was confirmed.

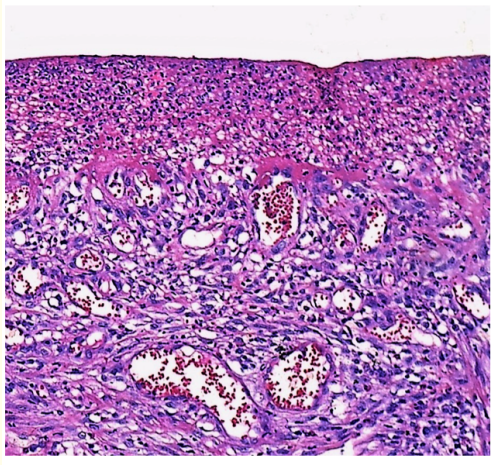

Figure 2: *Sample from the ulcerated and stenotic area in the jejunum. There is an exuberant granulation tissue, with fibrin deposit in the surface, congested capillaries, fibroblastis proliferation, collagen fibers deposition and chronic inflammatory cells, eosinophils and neutrophils. small bowel with stenose associated with ulcerated mucosa covered by fibrin and inflammatory infiltrate containing eosinophils, plasmocytes and neutrophils. Hematoxilin and Eosin, original magnification 200X.*

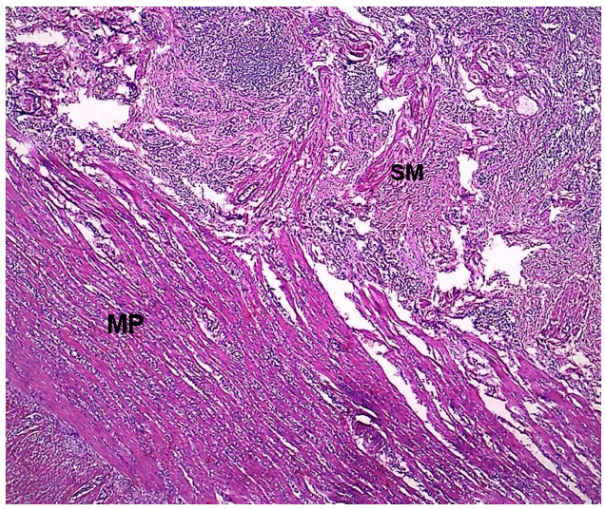

Figure 3: *Submucosa (SM) and muscularis propria (MP) in the stenotic area. The MP is almost normal with small amount of edema and rare eosinophils. In the SM, fibrosis, chronic inflammatory cell infiltration and lymphoid aggregates are seen. No epithelioid granulomas were observed. HE, original magnification 100X.*

After 5 total doses of Infliximab she got a 2 g/dL elevation in her hemoglobin level (8.9 to 9.3 g/dL). Despite this initial improvement, after the 5th Infliximab doses, she developed anti-bodies against the medication and hemoglobin level went down (5.9 to 7.3 g/dL). Adalimumab was started (week 0: 160 mg; week 2: 80 mg and 40 mg each 2 weeks) and her hemoglobin level returns to improve (8.3 g/dL). The patient signed the Informed Consent for this case report, and it is approved by the local Ethics Committee.

Discussion

CMUSE is an independent entity characterized by unexplained ulcerations and stenosis without systemic inflammation as found in inflammatory bowel disease [1,6]. The typical age of diagnosis varies from 2nd to 6th decades, but prevail in middle-aged or young patients [4,6]. Since 1964, about 65 cases were described (including siblings), most of them from Europe and Asia [3,6-8]. In 2010 the first case was reported in Chile by Nazal., *et al* [3]. Our case report is the first case described in Brazil and the second in South America.

The etiology and pathogenesis are unclear, but some authors describe CMUSE as a type of vasculitis (even representing a visceral variant of Polyarteritis Nodosa) or a genetic basis (related to an eicosanoid production defect in PLA2G4A gene mutation) [2,7,9]. Maybe the overstimulated production of fibrous tissue due to disturbance of proinflammatory cytokines, growth factors or collagen degradation may be responsible for some findings in gut of CMUSE's patients [10]. On the other hand, Singh., *et al.* published a case with angioectasia in the histological analysis of the small bowel, suggesting that vascular lesions (angioectasia) may play a role in disease pathogenesis [11].

A division of CMUSE in two subcategories was proposed: MUSE-I (idiopathic MUSE) and MUSE-V (vasculitis-related MUSE) [6,12]. For some authors, CMUSE could incorporate another disease called chronic nonspecific ulcers of the small intestine (CNSU), a disease reported in the Japanese population by Matsumoto., *et al* [1,11,13]. But, for Matsumoto., *et al.* CNSU, CMUSE and diaphragm disease of the small bowel without apparent NSAID use, belongs to a peculiar phenotype of Crohn's disease with less severe inflammation [13].

The big clinical picture may suggest an Inflammatory Bowel Disease. Patients complain about abdominal symptoms, such as chronic abdominal pain or discomfort, diarrhea or protein-losing enteropathy, vomiting (related to intestinal obstruction) and symptoms related to anemia due to obscure gastrointestinal bleeding [1-3,14]. Non-specific extraintestinal manifestations can occur in 70%: weight loss, malaise, fever and rarely join aches [1,2].

Blood analyses frequently show iron deficiency anemia and hypoalbuminemia (due to protein-losing enteropathy) [1]. Inflammatory markers (erythrocyte sedimentation rate and C reactive protein) have typically been described as normal or mildly elevated [15]. In a previous case report, CMUSE was associated with a C2 deficiency vasculitis [9]. There was not any strong correlation of CMUSE with specific autoantibodies [16]. In spite of, Chung., *et al.* found 3/20 patients with positive autoantibodies in their series [6]. A positive fecal occult blood test is detected in some cases.

The diagnosis is often delayed, because the small intestine is the most remote part of the alimentary tract to investigate. Nevertheless, new medical techniques, as double-balloon enteroscopy (DBE), capsule endoscopy (CE), computed tomography (CT) enterography and magnetic resonance (MR) enterography, allow more accurately diagnosis of small intestinal ulcers before surgery [12,15,17]. DBE has an advantage compared to others because allows biopsy under direct visualization [6]. In a cohort study with 20 CMUSE patients from South Korea, DBE and CE showed ulcerative lesions with linear, circular, geographic or irregular shapes [18]. In this paper, the radiological analysis found a total of 52 strictures (mean number per patient: 2.6), with a prevalence in the ileum, mean stricture length of 10.44 ± 3.95 mm and mean thickness of 5.56 ± 1.58 mm [18]. This authors documented that bowel wall strictures were short and thin with a layered enhancement pattern (< 2 cm long and < 1 cm thick), which may represent the superficial disease process [18].

Macroscopic examination from resected surgical specimens shows strictures that varies in number from 2 to 25 (mean 8.3) and can be separated by 2 to 10 cm of normal mucosa [16]. Histopathology of the small intestine shows an inflammatory response and ulcerative damage restricted to the mucosa and submucosa [1]. Ulcerations do not extend deeper into the underlying tissues [2]. Strictures are related to short segmental involvement and were often accompanied by ulcers [18]. There is no giant cell granulomas, aphthoid or fissural ulceration [16]. All stenosis were associated with a nonspecific inflammatory infiltrate only [2]. This infiltrate contains eosinophils and vessels wall degeneration with fibrous endarteritis in 55% of the cases [9].

CMUSE does not cause villous atrophy and duodenal biopsies are normal [16]. The absence of intestinal transmural and fistula formation distinguishes it from Crohn's disease [8].

Clinicopathological features and diagnostic criteria for CMUSE were proposed by Perlemuter., *et al.* unexplained small intestinal strictures; superficial ulceration restricted to the mucosa and submucosa; no biological signs of systemic inflammatory reaction; chronic or relapsing clinical course (even after surgery) and a typically (initially) positive beneficial effect produced by steroids [9,16]. On the other hand, to Matsumoto., *et al*. the diagnosis of CNSU is made on the basis of clinical manifestations (patients should have iron deficiency anemia and hypoproteinemia in their adolescence) and small-bowel lesions (multiple shallow ulcers in the ileum, with sharply demarcated margins and linear or oblique configuration) [13].

Differential diagnosis of multifocal small-bowel ulceration and stenosis should include Crohn's disease, nonsteroidal anti-inflammatory drug (NSAID) associated enteritis, infectious enteritis (e.g. tuberculous enteritis, *Cytomegalovirus*, *Campylobacter, Shigella*, *Yersinia* and *Salmonella*), lymphoma (T-cell enteropathy and α-chain disease), Zollinger-Ellison syndrome (gastrinoma), vasculitis (e.g. Behçet disease), ulcers due to heterotopic functioning gastric mucosa in a congenital Meckel's type diverticulum and ulcerative jejunoileitis (severe Celiac disease) [1-3,14]. Ulcerative jejunoileitis is a small-intestinal ulcerative disorder, which may represent a specific complication of celiac disease and need to be differentiated from focal lymphoma [2].

In spite of these extensive list of differential diagnosis, Crohn's disease and NSAID associated enteritis are the main ones [2]. Crohn's disease may occur in the jejunum without disease elsewhere, but seems to be uncommon, and as noted earlier, usually is associated with other clinical and pathological features [2]. Differentiation of CMUSE from Crohn's disease, as describe by Freeman, include: absence of clinical and laboratory of an inflammatory syndrome; absence of small-intestinal transmural inflammatory process or ulceration; absence of small-intestinal giant-cell granulomatous inflammatory process; absence of small-intestinal fistula formation despite recurrent chronic disease; absence of disease in other parts of gastrointestinal tract and absence of other extraintestinal features of Crohn's disease [2].

Since 1960, it was known that NSAID can cause small-intestinal frank ulcers, erosions, broad strictures and perforation [2,15,17]. The macroscopic lesions of NSAID associated enteritis are characterized by multifocal circumferential ulcers, with severe concentric stenosis, referred as "diaphragm disease" [17]. These lesions were located equally in the proximal and distal parts of small-bowel and capsule endoscopic studies reveal that significant lesions can occur even after short course of these drugs [15]. In our case, there is nor history of NSAID consumption, neither other pathological characteristics.

Medical therapy consists of corticosteroid induction and maintenance with slow tapering of daily dosage, although no randomized clinical trials or guidelines are available to defend this strategy [1]. On the other hand, some patients do not respond to corticosteroids (steroid-refractory CMUSE) [1,16]. The use of 5-aminosalicylic acid or other immune suppressive medication, such as oral azathioprine, failed to induce mucosal healing or prevent recurrence [1,10,18]. In contrast, monoclonal anti-TNF-α antibody (Infliximab) induced clinical remission in a 29-year-old male patient [1].

In one case, CMUSE associated with intestinal angioectasias was treated with medium chain triglycerides and high protein diet to improve hypoproteinemia and ethinyl estradiol and norethisterone for angioectasias' gastrointestinal bleeds [11]. Nevertheless, the literature emphasize that blood transfusion, iron supplementation and nutrition therapy are only effective to relieve the symptoms temporarily [8].

Surgery is the major therapeutic choice of treatment for CMUSE, but complete recovery occur in about 40% [1,2,4]. Recurrence may occur in 25 to 50% of patients and a second resection may be needed [1,2]. Another cause of surgical treatment was capsule endoscope retention due to a stricture in the small-intestine [18]. Endoscopic balloon dilatation can be used in order to prevent extensive resections of the small intestine [1,10]. Chung., *et al.* describe a median relapse-free survival of 67.1 months, with a longer relapse-free survival in female patients when compared with males (93 versus 9 months) [6].

Conclusion

In conclusion, the prognosis of CMUSE remains unclear. We emphasize that it is not easy to diagnose and manage CMUSE, since the disease is diagnosed after the exclusion of several other disorders and there is no defined treatment guideline.

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