Case series of Cryptogenic Multifocal Ulcerating Stenosing Enteritis (CMUSE)

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Abstract

Background and study aims : **Small bowel ulceration poses a limited, but difficult differential diagnosis. The most common causes are Crohn's disease (CD), NSAID-associated enteritis, lymphoma, cytomegaly virus infection and tuberculosis. A less known and relatively novel differential diagnosis is cryptogenic multifocal ulcerative stenosing enteritis (CMUSE).**

Patients and methods : **Five patients referred for balloon-assisted enteroscopy for various reasons showed endoscopic features of CMUSE. These findings and, when available, medical imaging were reviewed in order to increase general knowledge on CMUSE.**

Results : **Five patients, 3 males and 2 females, with a mean age of 39±5 years, underwent balloon-assisted enteroscopy. Typical short, circular, ulcerative stenoses were detected in the jejunum in 2 and in the ileum in 3 patients. The number of stenoses ranged from 1 to 7 per patient. Histopathology revealed nonspecific granulocyte inflammation without specific CD findings. Stenoses were often missed on pre-enteroscopy CT or MRI enteroclysis due to their short length. Treatment consisted of endoscopic balloon dilation in 3, corticosteroids in 3, azathioprine in 1 and anti-TNFα biologicals in 3 patients. 3 patients needed additional surgery because of ongoing symptomatic small bowel stenosis or retained wireless videocapsule.**

Conclusion: **In patients with short, ulcerative small intestinal stenoses CMUSE is an important but often neglected differential diagnosis. The pathophysiology and relationship to CD are subject of ongoing debate, but specific endoscopic characteristics, different histopathological findings and lack of clear abnormalities on CT or MRI enterography suggest that CMUSE is a distinct albeit rare chronic inflammatory bowel disease.** (Acta gastroenterol., **2017**, 80, **361-364**).

Key words : CMUSE, short, ulcerative small intestinal stenosis

Introduction

Cryptogenic Multifocal Ulcerating Stenosing Enteritis (CMUSE) is a rare condition that affects the small bowel. CMUSE typically presents with short, ulcerative stenoses of the small bowel. It has a chronic and relapsing clinical course and patients present with episodes of small bowel (sub)obstruction, abdominal pain or anemia. Differential diagnosis of ulceration of the small bowel is limited but difficult. The most common causes are Crohn's disease (CD), NSAID-associated enteritis, lymphoma, cytomegaly virus infection and tuberculosis (1). CMUSE is a less known differential diagnosis that responds well to therapy with glucocorticoids, leading to corticosteroid dependence in many patients (1,2).

Case report

Case 1

A 54 year old male patient, with medical history of prostate adenocarcinoma treated with prostatectomy and adjuvant radiotherapy, celiac trunk stenosis and longstanding symptoms attributed to irritable bowel syndrome, was referred in 2006 for double-balloon enteroscopy because of obscure gastrointestinal bleeding. CT scan revealed some irregular intestinal wall thickening compatible with skip lesions. Antegrade double-balloon enteroscopy showed two short ulcerative stenoses in the small intestine at the jejunal-ileal transition, suggestive of CD. However, histopathology showed nonspecific inflammatory infiltrate composed of neutrophils and lymphocytes. MRI enteroclysis was considered normal. In 2010 he presented with oral aphtosis and skin lesions, presumably due to leucocytoclastic vasculitis. In 2011 he was admitted to the−intensive care unit because of idiopathic interstitial pneumonia and respiratory failure. Subsequently hemoglobin levels dropped to 6.7 g/dl. No bleeding cause was identified by upper, lower endoscopy and CT angiography. Because of persistent melena, a wireless video capsule examination was performed. The capsule was however retained at a small bowel ulcerative stenosis, needing surgical removal. Laparoscopy revealed the capsule being retained at the level of a short inflammatory stenosis. Pathology of the resection specimen showed nonspecific inflammation restricted to the mucosa and the submucosa, without specific CD characteristics. Treatment with temporary Budesonide and maintenance Mesalazine was initiated with good and lasting clinical response.

Case 2

A 29 year old male patient was diagnosed with irritable bowel syndrome because of longstanding abdominal complaints since 2002. However, ileocolonoscopy in 2008 revealed two aftous ulcerations in the ileum separated by normal small bowel mucosa, suggestive of CD. Histopathology was nonspecific. Corticosteroid and azathioprine treatment was started, but stopped because of lack of clinical response. Because of ongoing abdominal pain and weight loss the patient consulted our department in 2011. CT enteroclysis turned out normal

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and wireless video capsule examination showed multiple aftous ulcerations and erosions progressively increasing more distally in the small bowel separated by normal mucosa, suggestive of CD. A retrograde single-balloon enteroscopy showed characteristic short CMUSE-like ulcerative stenoses in the ileum. Histopathology was again nonspecific. Oral treatment with Budesonide and Prednisolone for several months and nasogastric tube feeding remained without clinical and endoscopic improvement. Conventional Infliximab induction treatment was initiated and a control enteroscopy was con-sequently performed because of rapid clinical improvement during the Infliximab induction phase. Complete endoscopic remission of all ulcerative lesions was seen, with only substenotic fibrotic remnants. Infliximab maintenance treatment was initiated with good clinical results.

Case 3

A 37 year old male patient was treated for small bowel CD and underwent multiple endoscopic balloon dilatations of strictures located in the proximal and distal small bowel resulting in temporary clinical improvement. Medical treatment based on Azathioprine and Infliximab was not well tolerated and the patient was switched to Adalimumab. He was referred to our center for endoscopic balloon dilatation of intestinal strictures because of postprandial pain and borborygmata suggestive of subobstruction. MR enteroclysis showed active stenosing CD located at the terminal ileum. Distal single-balloon enteroscopy showed multiple short, ulcerative stenoses and substenoses located in the ileum with prestenotic dilatation, suggestive for CMUSE (Fig. 1 and 2). No biopsies were taken because of oral anticoagulant treatment.

Case 4

A 47 year old female patient was referred for distal single-balloon enteroscopy because of suspicion of active CD of the terminal ileum. Multiple, superficial ulcerations were seen in the most distal 50 cm of the ileum with one short, ulcerative substenosis, suggestive of CMUSE. Histopathology showed non-specific ulcerating inflammation and was not diagnostic for CD. Treatment with oral Methyl-Prednisolone and intravenous Infliximab was started. There was no clinical response to treatment and 6 months later the patient complained of persistent abdominal pain despite biochemical improvement. Enteroclysis and enteroscopy confirmed a persisting short, ulcerative stenosis in the preterminal ileum. Persistent abdominal pain under treatment with Azathioprine and Infliximab led to surgical resection of an ileal segment at 60 cm proximal of the ileocaecal valve. Histopathology of the resected specimen revealed non-specific inflammation not suggestive of CD.

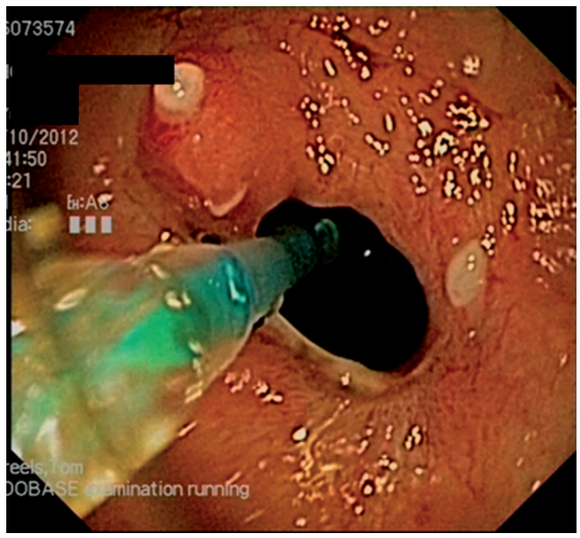

Fig. 1. — Endoscopic image of a short ulcerative stenosis in the terminal ileum in CMUSE. Treatment with endoscopic balloon dilatation.

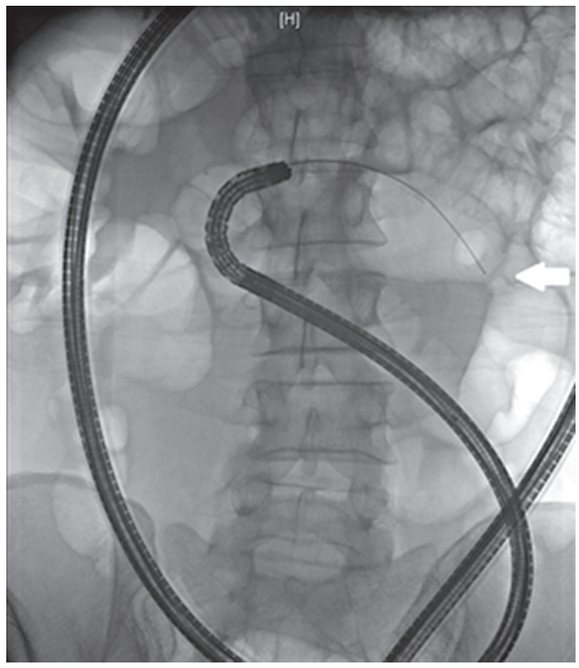

Fig. 2. — Fluoroscopic image of a short ulcerative stenosis in de terminal ileum in CMUSE. Treatment with endoscopic balloon dilatation.

Case 5

A 32 year old female patient, with a history of CD and jejunal resection, was referred for endoscopic balloon dilatation because of frequent vomiting. Proximal single-balloon enteroscopy showed multiple, circular ulcers separated by normal appearing mucosa and several fibrotic scars over a distance of 50 cm near the jejunal anastomosis. Short circular substenosis was successfully

Table 1. — Summery of the characteristics of 5 cases of CMUSE

Patient characteristics	- 5 patients: 3 males and 2 females - Mean age: 39±5 years (range 28-54) - No history of NSAID use
Endoscopic appearance	- Short circular ulcerative stenoses - Location: jejunum in 2 and ileum in 3 patients - No colonic abnormalities - Number of stenoses: 1 to 7 per patient
Histopathology	- Nonspecific granulocyte inflammation without specific Crohn's disease findings in all patients
Medical imaging	- Often missed on pre-enteroscopy CT or MRI enteroclysis, due to the short length (<1 cm) of the circular stenosis
Treatment	- Balloon dilation up to 15 mm in 3 patients - Corticosteroids in 3 patients - Azathioprine in 1 patient - Anti-TNFa biologicals in 3 patients - 5-ASA in 1 patient - Surgery in 2 patients

treated with endoscopic balloon dilatation. More distally the mucosa had normal appearance. Biopsies were not specific for CD.

Table 1 contains a summary of the characteristics of 5 cases of CMUSE.

Discussion

Cryptogenic Multifocal Ulcerating Stenosing Enteritis (CMUSE) is a rare condition that affects the small bowel with typical short, ulcerative, small intestinal stenoses. Other parts of the gastrointestinal tract, for example the colon are, to the contrary of CD, not affected. CMUSE presents a chronic and relapsing clinical course. Differential diagnosis of ulceration of the small bowel is limited but difficult. The most common causes are CD, NSAID-associated enteritis, lymphoma, cytomegaly virus infection and tuberculous enteritis. Other rare causes are oral potassium chloride toxicity, severe celiac disease (ulcerative jejunoileitis), systemic vasculitis, ischemia- or radiation-induced stenosis and CMUSE (3).

The pathophysiology and etiology of CMUSE is unclear and is subject to ongoing debate. The clinical resemblance to CD suggests a relationship between CMUSE and CD and differentiation between the two is usually difficult. However the endoscopic and histopathological appearance, when available, is clearly different from CD. Its immune-based pathogenesis is supported by the response to treatment with immuno-modulators (4). Also vasculitis seems to be involved (5). Our first case also presented with clinical signs of systemic vasculitis.

Recently, mutations in the PLA2G4A gene on chromosome 1 were identified as the underlying genetic deficit causing CMUSE (6). The 4 bp deletion in PLA2G4A gene leads to abrogation of the enzymatic function of its protein product cytosolic phospholipase A2-α (cPLA2 α) which catalyses the release of arachidonic acid (AA) from membrane phospholipids. AA is the substrate for a enzymes involved in the synthesis of eicosanoids, including COX-1, COX-2, lipoxygenases and cytochrome p450-epoxygenase. The rate limiting step in eicosanoid production is cPLA2 α – mediated AA release. Therefore cPLA2 α – mediated AA release is an important step in a large number of physiological and pathological processes affected by eicosanoids (7). 4 bp deletion in PLA2G4A gene thus leads to undetectable levels of cPLA2 α in the small intestine, leading to the inability to produce AA, prostaglandins and leukotrienes. Therefore it is suggested that the pathophysiology of CMUSE mirrors that of NSAID induced enteropathy (6).

CMUSE patients usually present with symptoms due to chronic or relapsing intestinal (sub)obstruction leading to abdominal pain and cramping, diarrhea, vomiting and weight loss. Some patients have also extraintestinal symptoms such as fever, joint aches, oral aphtae, Raynauds phenomenon, Sicca syndrome and pulmonary disease suggesting a systemic disorder (8). Chronic iron deficiency anemia due to small intestinal occult blood loss is also frequent (2). Perlemuter et al proposed diagnostic criteria for CMUSE: 1) unexplained small intestinal strictures found in adolescents and in middle-aged subjects, 2) superficial ulceration restricted to mucosa and submucosa, 3) a chronic or relapsing clinical course (even after surgery), 4) no biological signs of systemic inflammatory reaction and 5) a beneficial effect of treatment with steroids (1,5).

Small bowel endoscopy seems more specific as compared to CT or MRI enterography to identify CMUSE. The specific short circular ulcerations are easily detected during enteroscopy which also allows tissue sampling. Stenosis may develop, whereas progression to fistulae, fissures and cobblestone appearance is absent (2).

Histopathology of CMUSE reveals, in contrast to CD, an atypical mixed inflammatory infiltrate composed of plasma cells, monocytes, neutrophils and eosinophils and shallow ulcers usually restricted to the mucosa and the submucosa. The absence of granulomatous inflammatory changes and of transmural involvement also differentiates CMUSE from CD [2]. CT or MR enterography can be used in the diagnosis of CMUSE stenoses, however short stenoses are easily missed, as was described in case 1 reported above, where retention of a video capsule in a CMUSE stenosis occurred despite prior MR enterography. Wireless video capsule retention was also described by another author (9).

Treatment consists of immunosuppression. CMUSE may respond well to treatment with glucocorticoids, however recurrence after tapering is frequently leading to corticodependency. Experience with other immunosuppressive drugs, such as azathioprine and TNF alfa blokkers, is limited. Other treatment options are endoscopic balloon dilatations and surgery, however recurrence is frequent.

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