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Single Case

A Case Report: Cryptogenic Multifocal Ulcerative Stenosing Enteritis – A Diagnostic Challenge Mimicking Crohn's Disease

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Abstract
Introduction: Cryptogenic multifocal ulcerative stenosing enteritis (CMUSE) is a rare and underrecognized small bowel disorder that often mimics Crohn's disease, leading to delays in diagnosis and misdirected treatment. Given its relapsing nature and resistance to conventional inflammatory bowel disease (IBD) therapies, CMUSE presents significant diagnostic and therapeutic challenges. ***Case Presentation:*** We present the case of a 41-year-old male with chronic anemia, fatigue, weight loss, and intermittent abdominal pain with melena, who remained undiagnosed for 9 years despite extensive evaluations. Imaging and endoscopy failed to identify a definitive cause, and management with TNF inhibitors and IL-12/IL-23 blockade provided only temporary relief. The patient required multiple surgical resections due to recurrent strictures. Pathological examination consistently revealed multifocal jejunal ulceration with stenosis but lacked granulomas, vasculitis, or systemic inflammatory markers, ultimately confirming CMUSE. Given its distinct pathology and treatment resistance, differentiating CMUSE from Crohn's disease is essential. The patient's ongoing management includes upadacitinib, a JAK1 inhibitor, which may help modulate immune pathways contributing to ulcer formation and stricture development. ***Conclusion:*** This case underscores the need for heightened clinical recognition of CMUSE, particularly in patients with unexplained small bowel strictures and ulceration unresponsive to standard IBD therapies. Genetic testing may aid in distinguishing CMUSE from Crohn's disease, preventing unnecessary immunosuppressive treatments. Further research is necessary to establish effective, targeted therapies and improve outcomes for patients with this rare condition.

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Introduction

Cryptogenic multifocal ulcerative stenosing enteritis (CMUSE) is a rare, underrecognized small bowel disorder characterized by recurrent superficial ulcers and multifocal strictures, leading to chronic anemia, intermittent abdominal pain, and small bowel obstruction. Unlike Crohn's disease, CMUSE typically lacks systemic inflammation, granulomas, or penetrating complications such as fistulas or abscesses [1–3]. Histopathologically, CMUSE is defined by discrete, shallow ulcers with intervening normal mucosa, predominantly affecting the jejunum and ileum [1, 3, 4]. The condition remains poorly understood, with proposed etiologies including immune-mediated mechanisms, atypical vasculitis, and genetic mutations affecting prostaglandin metabolism [2, 5, 6]. Given its rarity and overlapping features with more common conditions like Crohn's disease and nonsteroidal anti-inflammatory drug (NSAID) enteropathy, CMUSE presents a significant diagnostic challenge. In this report, we describe a case of CMUSE initially misdiagnosed as Crohn's disease, underscoring the complexities of its clinical presentation, diagnostic pitfalls, and therapeutic challenges. This highlights the importance of considering CMUSE in differential diagnoses when encountering patients with recurrent small bowel strictures and ulcers, especially in the absence of systemic inflammatory markers and granulomas.

Case Report

This is a 41-year-old male with a history of chronic anemia, fatigue, weight loss, and intermittent abdominal pain associated with melena over several years. He was initially diagnosed with anemia around the age of 10 and required iron replacement therapy and multiple transfusions since early childhood.

After immigrating to the USA as an adult, he continued to present to the hospital with exertional dyspnea, fatigue, and severe anemia, with hemoglobin levels persistently below 7 g/dL. He did not smoke, drank alcohol infrequently, and rarely used NSAIDs. Platelet count and coagulation factors remained within normal limits, while iron (17 μg/dL), iron saturation (4%), and ferritin (8 ng/mL) were low. Vitamin B12, folate, and thyroid hormone levels, Coombs test, and antinuclear antibody were normal. Inflammatory markers, including C-reactive protein, erythrocyte sedimentation rate, and calprotectin, remained largely within normal limits.

Extensive imaging, including computed tomography of the abdomen and pelvis with intravenous contrast, magnetic resonance imaging of the abdomen with and without contrast, and magnetic resonance angiography of the abdomen with and without contrast was unremarkable and did not successfully identify the cause of his symptoms. Initial endoscopic evaluations were also unremarkable. In 2013, capsule endoscopy was attempted but unable to progress beyond a stenotic area in the jejunum, prompting a laparoscopic procedure that was converted to an open small bowel resection. A total of 45 cm of small bowel was removed, revealing six sequential strictured segments with ulceration. Pathological examination of the resected bowel demonstrated focal transmural inflammation with ulcerating and stenosing features. The differential diagnosis at that time included an atypical variant of Crohn's disease versus chronic multiple ulcerative stenosing enteritis (CMUSE).

In 2014, he was started on infliximab; however, treatment was complicated by the development of obstructive symptoms, leading to a transition to adalimumab with continued intravenous iron therapy. Despite this, he experienced recurrent obstructive symptoms and persistent anemia, prompting a switch to ustekinumab. Antegrade double-

balloon enteroscopy and mesenteric angiography failed to identify the source of his occult bleeding. Repeat capsule endoscopy was deferred due to a significant risk of capsule retention given his multiple surgical interventions. By 2019, due to ongoing abdominal pain and the need for frequent packed red blood cell and intravenous iron transfusions, the patient underwent laparoscopic-assisted enteroscopy with adhesiolysis. Multifocal jejunal disease with strictures and ulceration was identified and resected. Pathology once again demonstrated transmural inflammation with strictures and ulcers, but no granulomas were found. Ustekinumab was eventually discontinued due to recurrent symptoms.

In 2023, the patient was again hospitalized for symptomatic anemia. Computed tomography enterography and magnetic resonance imaging remained inconclusive. An exploratory laparotomy with intraoperative enteroscopy was performed, revealing a cratered jejunal ulcer and a stricture at a prior anastomotic site, along with an additional proximal ulcer. The prior anastomosis was resected, and pathology confirmed two distinct ulcers with intervening normal-appearing mucosa (shown in Fig. 1). Microscopically, the villous architecture was preserved without evidence of active or chronic enteritis, granulomas, or vascular abnormalities (shown in Fig. 1). The ulcers extended to the muscularis propria, consistent with a diagnosis of CMUSE. The patient has reported only temporary symptomatic relief following surgery. His current management consists of ongoing intermittent intravenous iron infusions and upadacitinib, a selective Janus kinase 1 (JAK1) inhibitor. By modulating pathways beyond TNF and IL-12/IL-23, upadacitinib may help regulate aberrant immune activation in CMUSE, potentially reducing inflammation and mitigating ulcer formation and stricture development [7, 8]. As of December 2024, the patient has managed to maintain their weight and employment but has required more frequent iron infusions. They are scheduled for prompt reinvestigation with long tube enteroscopy, with the potential for laser therapy of lesions.

Discussion

CMUSE is characterized by its distinct pathology, featuring superficial, discrete ulcers, and strictures in the small intestine that are not commonly observed in other inflammatory bowel diseases (IBDs). Other characteristic features of CMUSE include relapsing or chronic ulcerative stenosis after surgical resection, absence of systemic inflammation, and superficial ulceration of the mucosa and submucosa with a lack of penetrating disease, such as fistulas or abscesses [6, 9–13]. Steroids are the initial treatment option for CMUSE, although their efficacy is mixed [14, 15]. Limited cases suggest that azathioprine and infliximab, used either separately or in combination, may improve clinical outcomes [4, 14, 15]. Surgery is often required for patients with obstructive symptoms or complications such as perforation. Segmental bowel resection can be effective in resolving intractable intestinal obstruction, although recurrence of symptoms is common [1–4].

The pathogenesis of CMUSE remains poorly understood, though immune-mediated processes have been proposed (shown in Table 1). Perlemuter et al. suggested that atypical vasculitis associated with complement C2 deficiency may contribute to small bowel ulceration and stenosis in CMUSE [15]. This theory implies an immune dysfunction leading to vascular injury, which in turn may cause ischemia and ulcer formation. In contrast, Kohoutová et al. [16] proposed a structural rather than an immune-mediated explanation, hypothesizing that fibroblast overstimulation or defective collagen fiber degradation could drive the formation of stenosis in idiopathic small bowel enteropathies. This model suggests that abnormal tissue remodeling or impaired extracellular matrix turnover leads to progressive luminal narrowing. However, neither theory adequately

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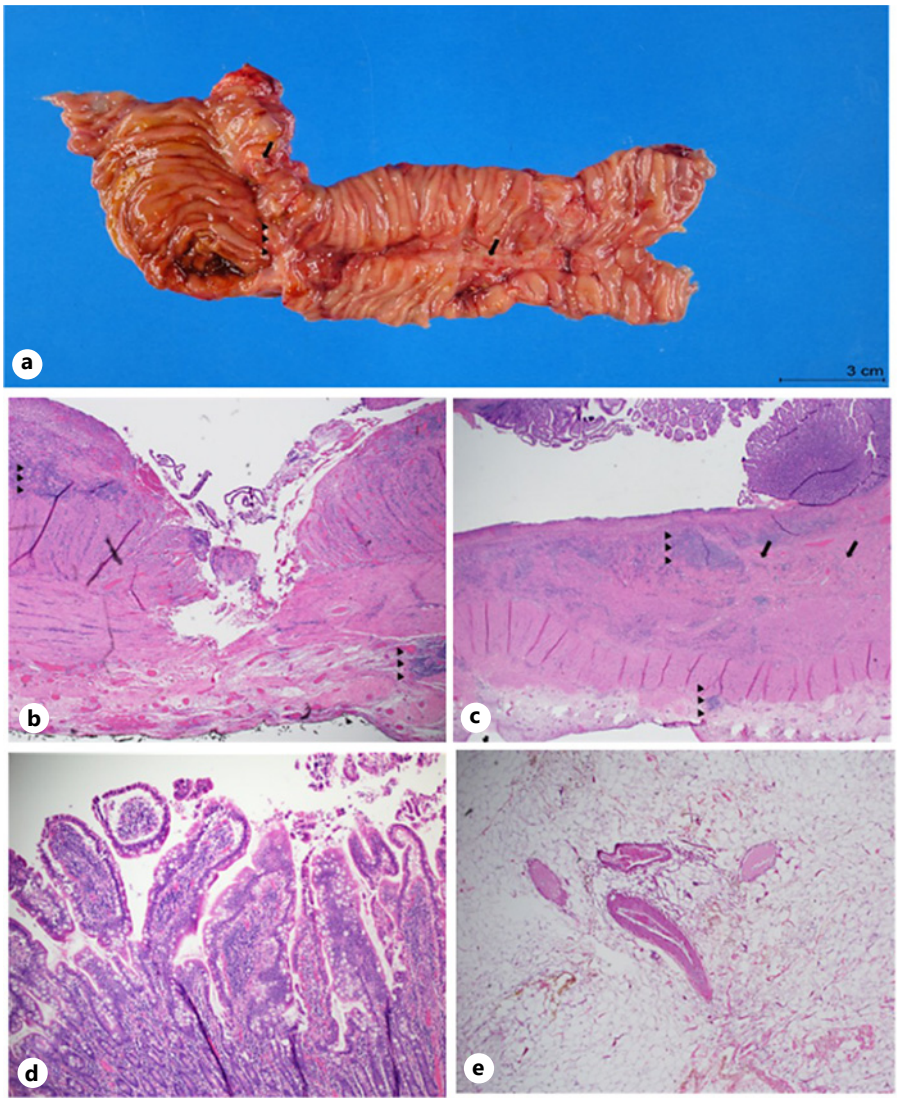

Fig. 1. **a** Segmental resection of small intestine with two ulcers (arrow). Note the end-to-side anastomotic line (arrowhead) between two segments of small intestine consistent with patient's prior surgical history of resection. The ulcer was characterized by a wide, clean base, and adjacent grossly unremarkable enteric mucosa. **b** An ulcer involving deep muscularis propria (×40). Note the nonspecific transmural inflammation (arrowhead). **c** Abrupt transition from ulcer to adjacent enteric tissue (×20). There were submucosal fibrosis (arrow) and mild nonspecific transmural inflammation (arrowhead). **d** Patchy mild increase in intraepithelial lymphocytes was noted. However, the villous architecture was preserved (×100). **e** Patent mesenteric vasculature without thrombosis or vasculitis (×40).

explains CMUSE's non-inflammatory nature [6]. Unlike classical IBDs, CMUSE lacks the typical inflammatory infiltrates seen in Crohn's disease or vasculitic disorders, raising questions about whether its pathogenesis is primarily immune-mediated, vascular, or due to an intrinsic defect in tissue repair and fibrosis. More recent research suggests that autosomal recessive genetic mutations may be another plausible cause of CMUSE. Brooke et al. identified a Phospholipase A2 group IVA (PLA2G4A) gene deletion in two English siblings with CMUSE [2], while Umeno et al. [17] noted solute carrier organic anion transporter family member 2A1 (SLCO2A1) gene mutations in 5 Japanese patients with chronic nonspecific multiple ulcers of the small intestine, a term used exclusively in Japan

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Table 1. Summary of key studies on CMUSE: genetics and treatment outcomes

First author [ref.] (year)	Study type	Sample size	Key findings	Genetic links	Treatment outcomes
Perlemuter et al. [15] (2001)	Retrospective	12 patients	Defined CMUSE as a distinct entity with superficial mucosal-submucosal ulcers, no granulomas, and absent systemic inflammation, suggesting atypical vasculitis linked to complement C2 deficiency as a potential cause	Type I C2 deficiency	Steroids provided symptomatic relief but with mixed long-term outcomes
Kohoutová et al. [19] (2013)	Literature review	N/A	Suggested that defective collagen fiber degradation or fibroblast overstimulation may contribute to stenosis formation	N/A	Highlighting the importance of alternative therapies to immunosuppressives, deep enteroscopy enables accurate diagnosis and treatment of stenoses, potentially reducing surgery and bowel resection
Brooke et al. [2] (2014)	Case report	2 siblings	Identified PLA2G4A gene deletion as a possible cause of CMUSE in English siblings	PLA2G4A gene mutations	Patients had recurrent symptoms despite surgery; no definitive cure
Umeno et al. [17] (2015)	Genetic study	5 Japanese patients	Found SLCO2A1 mutations in patients diagnosed with CNSU (chronic nonspecific multiple ulcers of the small intestine), which closely resembles CMUSE.	SLCO2A1 mutation	Patients required multiple surgical resections due to relapsing ulcerative stenosis
Singh [6] (2019)	Literature review	N/A	Defines CMUSE, CNSU, and NGUJI as distinct yet overlapping small bowel disorders, distinguishing CMUSE by superficial ulcers, strictures, and absence of granulomas or systemic inflammation	Prostaglandin pathway mutations, specifically SLCO2A1 and PLA2G4A	TNF antagonists and azathioprine show some efficacy, while corticosteroids induce remission, though surgery is often needed for obstruction or steroid-refractory disease
Chen et al. [9] (2020)	Retrospective study	14 cases CMUSE 61 cases SBCD	Compared to small bowel Crohn's, CMUSE featured circumferential mucosal-submucosal ulcers without systemic inflammation	N/A	Steroids induced remission in many patients but had a high relapse rate, while surgery was required for obstructive or steroid-refractory cases

NUJI, non-granulomatous ulcerating jejunoileitis.

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for a condition with symptoms similar to CMUSE [18]. PLA2G4A and SLCO2A1 play a key role in prostaglandin metabolism and have been implicated in CMUSE pathogenesis [2, 6, 17, 18]. These mutations may impair gut mucosal integrity, making patients more susceptible to ulceration and stenosis [2, 5]. While our patient has not undergone genetic testing, this may be an avenue to explore in future cases to confirm the diagnosis and guide treatment.

Given its rarity, CMUSE should be differentiated from other pathologies with Crohn's disease being the primary differential diagnosis. CMUSE often presents with nonspecific gastrointestinal symptoms, such as recurrent melena, chronic anemia, and intermittent abdominal pain, making diagnosis challenging and often delayed. Unlike Crohn's disease, CMUSE does not show signs of systemic inflammation, often correlating with a negative erythrocyte sedimentation rate and C-reactive protein, as was seen in our patient. Multiple endoscopic evaluations are typically required to rule out other causes of small bowel disease. The presence of superficial ulcers, short-segment strictures, and a thorough medication history can help differentiate CMUSE from NSAID enteropathy, while malabsorption is more commonly associated with non-granulomatous ulcerating jejunoileitis and chronic nonspecific multiple ulcers of the small intestine [6].

With the recent discovery of genetic associations in CMUSE, genetic testing should be strongly considered to distinguish CMUSE conclusively from Crohn's disease, particularly as both conditions can present similarly but may require different therapeutic approaches. Identifying mutations in genes such as PLA2G4A and SLCO2A1 could aid and inform treatment strategies.

In this patient's case, symptoms began during childhood with chronic symptomatic anemia as the most prominent feature. Initial diagnostic evaluations, including capsule endoscopy, suggested possible small bowel Crohn's disease, leading to treatment with various biologics such as infliximab, adalimumab, and ustekinumab. Despite these therapies, the patient experienced recurrent obstructive symptoms and anemia which ultimately led to surgical intervention. The diagnosis of CMUSE was confirmed by the absence of systemic inflammation, granulomas, or penetrating disease on histopathology. Instead, this patient's pathology was marked by discrete, superficial ulcers extending to the muscularis propria, with intervening normal mucosa, characteristic of CMUSE.

The patient's need for repeated surgical resections also reflects the chronic and relapsing nature of CMUSE. While surgical intervention can provide temporary symptom relief, it does not prevent recurrence, as seen in this patient who required multiple resections. This is consistent with the literature indicating a high rate of recurrence following surgery, with many patients eventually developing short bowel syndrome due to repeated resections. This patient's transient postoperative improvement followed by recurrence of symptoms underscores the progressive course of CMUSE and its resistance to conventional treatments.

A notable aspect of this case is the patient's lack of response to biologic therapies typically used for Crohn's disease. Due to the rarity and poorly understood etiology of CMUSE, there are no specific, targeted treatments available. The failure of infliximab and adalimumab, both TNF inhibitors, followed by the inadequate response to ustekinumab, a monoclonal antibody targeting IL-12/IL-23, suggests that CMUSE does not share the same inflammatory pathways as Crohn's disease, despite some clinical overlap. Management is largely empirical, with therapeutic approaches focused on symptom relief and palliative interventions. The lack of well-defined diagnostic criteria and the incomplete understanding of its pathogenesis underscore the imperative for case documentation, further research, and increased awareness among clinicians to better recognize and manage this rare disease.

Conclusion

CMUSE remains a rare and poorly understood condition, often mimicking Crohn's disease but lacking systemic inflammation and penetrating complications. This case highlights the diagnostic challenges associated with CMUSE, emphasizing the importance of considering this entity in patients with recurrent small bowel strictures, chronic anemia, and failure to respond to conventional IBD therapies. Our patient experienced a prolonged disease course with multiple surgical interventions, reflecting the relapsing nature of CMUSE and the limited efficacy of current treatment options.

The failure of TNF inhibitors and IL-12/IL-23 blockade in this case underscores the distinct pathophysiology of CMUSE, which may involve prostaglandin metabolism and genetic predisposition rather than classic inflammatory pathways. Given recent insights into the genetic basis of CMUSE, genetic testing should be strongly considered in suspected cases to differentiate it from Crohn's disease and guide more tailored therapeutic strategies.

With limited established treatment options, JAK inhibition with upadacitinib represents a potential novel therapeutic avenue, given its efficacy in refractory Crohn's disease. Further research is needed to elucidate the disease mechanisms, optimize management strategies, and evaluate emerging therapies that may alter the progressive course of CMUSE and improve patient outcomes.

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary Figure 1 (for all online suppl. material, see https://doi.org/10.1159/000544941).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Naveena Luke, MD, Shayan Azizi, MD, and Inna Carmela De Leon, MD: substantial contributions to the design of the work, drafting the work and reviewing it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Seymour Katz, MD MACG: substantial contributions to the conception and design of the work and the acquisition of data for the work; drafting the work and reviewing it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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