Severe Acute Ulcerative Colitis Disease with Severe Celiac Disease Associated with *Clostridium difficile* Colitis Infection Complicated with Refeeding Syndrome, Challenging Case Report

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Crohn's disease, ulcerative colitis, and celiac disease are disorders mediated by the immune system. The coincidence of celiac disease with inflammatory bowel disease is an infrequent occurrence, particularly in pediatric populations, though it is acknowledged in adult cases. This paper presents a unique case involving a 24-year-old male patient who experienced persistent vomiting, significant weight loss, and bloody diarrhea accompanied by abdominal pain and urgency. During his medical evaluation, we detected the presence of celiac antibodies, elevated inflammatory markers, and anemia. Endoscopic examination revealed pancolitis, pseudomembranous colitis, and atrophy of the duodenal villi. The patient concurrently had celiac disease, ulcerative colitis, Clostridium difficile colitis, and active Helicobacter pylori-associated chronic gastritis. Clostridium difficile colitis is a serious yet common complication in patients with IBD, necessitating simultaneous management of both disorders. His dual autoimmune conditions deteriorated, necessitating immunosuppressive therapy. However, the initiation of immunosuppression led to refeeding syndrome, adding complexity to the management of his condition.

Introduction

Celiac disease is an enteropathy of the small intestine triggered by gluten in susceptible individuals. Currently, the sole long-term treatment for this chronic ailment is strict, lifelong avoidance of gluten. Genetic factors primarily determine this susceptibility [1,2,3]. The prevalence of celiac disease among individuals with IBD remains uncertain, although there are numerous reports of concurrent occurrence of both conditions within the same family or individual [4–9]. Some researchers argue that the incidence of celiac disease in IBD patients is merely coincidental and aligns with its prevalence in the general population [10.[

Clostridium difficile colitis is a serious yet common complication in patients with IBD, necessitating simultaneous management of both disorders. In cases where IBD patients show no improvement after three to four days of appropriate antibiotic therapy, there may be a requirement to intensify immunosuppressive treatment. However, therapeutic approaches must be tailored to each patient's unique circumstances [11.[

Refeeding syndrome encompasses a range of clinical and metabolic disturbances that arise from the reintroduction of nutrition to those who are chronically malnourished [12]. Awareness of undernutrition risks is critical since inappropriate nutritional rehabilitation, although

infrequent, can precipitate multi-organ dysfunction [13]. This paper discusses a case involving a patient with severe manifestations of acute ulcerative colitis and celiac disease, compounded by Clostridium difficile colitis, occurring against a backdrop of severe malnutrition, which subsequently led to refeeding syndrome.

Case Details

A 24-year-old male presented at the ER for the fifth time due to persistent vomiting associated with food intake. The patient's symptoms initiated two months prior to his ER visit, including nocturnal episodes of bloody and watery diarrhea occurring six to seven times, anorexia, a profound weight loss of 14 kilograms over eight weeks, and epigastric and abdominal pain with urgent sensations. Despite testing positive for Entamoeba histolytica in stool samples and subsequent treatment with metronidazole, the patient's condition remained unchanged, leading to recurrent ER visits for the same symptoms. The patient reported no familial history of gastrointestinal malignancies or inflammatory bowel disease nor any recent travel or consumption of food outside his usual diet.

The physical examination showed the following vital signs: a temperature of 36.7°C, blood pressure at 133/93 mmHg, respiratory rate of 20 breaths per minute, heart rate at 114 beats per minute, and an oxygen saturation of 97% on room air .

Cardiac and pulmonary assessments were unremarkable. Abdominal examination revealed a soft and non-distended abdomen with mild epigastric tenderness. The patient had an old eczematous rash on his lower limbs. The musculoskeletal evaluation was normal, and mucous membranes appeared hydrated without evidence of ulceration.

Laboratory investigations

The patient's laboratory tests revealed several diagnostic values: hemoglobin at 10.8 g/dL, an elevated white blood cell count at 21 x10^3/µL, mean corpuscular volume at 68 fL, C-reactive protein significantly raised at 139 mg/L, and erythrocyte sedimentation rate at an accelerated 73 mm/hr. Procalcitonin was marginally elevated at 0.11 ng/mL, with plasma lactate levels at 7.4 mg/dL. Immunological assays showed Anti-Saccharomyces Cerevisiae Antibodies (ASCA) IgA at 32.1 U and IgG at 29.22 U. Tests for Anti-Neutrophil Cytoplasmic Antibodies (ANCA) returned negative results. In contrast, Anti-tissue Transglutaminase Antibody IgA was positive at 34.9 U/mL, with the IgG isotype returning a negative result. Immunoglobulin A levels were 636.0 mg/dL. Thyroid-stimulating hormone (TSH) was measured at 2.20 uIU/mL. Helicobacter Pylori antigen was detected in stool analysis, which also identified Entamoeba histolytica cysts and a positive result for Clostridium difficile toxin. No microbial growth was observed in blood and stool cultures. The patient tested non-reactive for HIV, and the hepatitis profile was negative. Vitamin D (25-OH) levels were deficient at 5.1 ng/mL, whereas vitamin B12 levels were at 961 pg/mL. Liver function tests, pancreatic enzymes, kidney function, and electrolytes all returned results within normal ranges.

Imaging and endoscopic investigations

Imaging via a computed tomography (CT) scan of the abdomen revealed widespread edematous thickening of the large bowel wall, consistent with global colitis. However, the rectum and sigmoid colon exhibited decreased haustration and displayed the characteristic "lead pipe" sign. Additionally, the CT scan identified widespread mesenteric lymphadenopathy, including enlargement of mesorectal lymph nodes on the right side.

Endoscopic investigation yielded the following findings: Upper gastrointestinal endoscopy elucidated diffuse edema of the gastric mucosa, ranging from moderate to severe gastritis, an edematous pylorus, severe duodenitis in the D1 segment, and mucosal edema with atrophy in the D2 segment. Histological examination of the acquired biopsy samples indicated total atrophy of the duodenal mucosa corresponding to MARSH grade B2 type 3, which aligns with a diagnosis of Celiac disease. Concurrently, mild active chronic gastritis was present, and the test was positive for Helicobacter pylori.

Furthermore, a proctoscopy conducted without preparatory measures or air insufflation revealed diffuse rectal mucosal erythema and edema, accompanied by exudate and superficial ulcerations. The excessive exudate suggested the features of pseudomembranous colitis. Histopathology of rectal biopsies confirmed the presence of continuous ulcerative lesions of the rectum, aligning with active and severe ulcerative colitis.

Final diagnosis:

Severe Acute ulcerative Colitis disease with severe celiac disease MARSH grade B2 type 3 associated with Clostridium difficile colitis infection and Active H. pylori chronic gastritis .

Management, outcome and Follow UP:

During the initial hospitalization, the patient was administered treatments targeting distinct aspects of his condition. For the Clostridium difficile infection, a regimen of oral vancomycin and intravenous metronidazole was prescribed for 10 days. Mesalamine suppositories, at a dosage of 1 gram and an oral intake of 4 grams, were given in addition to 9 mg of budesonide MMR daily.

For H- pylori-associated chronic gastritis, the patient received a combination therapy involving metronidazole, clarithromycin, and proton pump inhibitors. The patient was also put on a strict gluten-free diet and referred to a dietitian for further management.

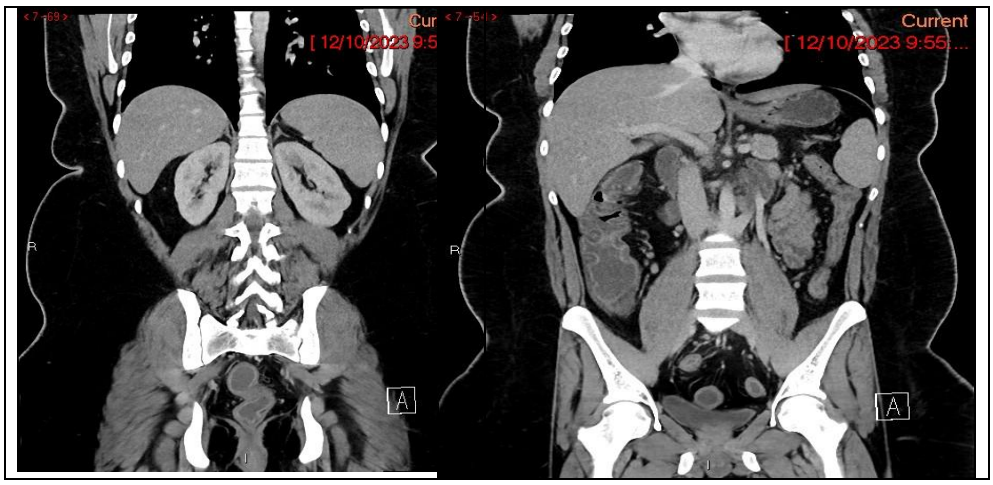
Despite these interventions, after ten days, while the abdominal pain and vomiting had resolved, the patient continued to experience bloody diarrhea. He was readmitted due to a flare of IBD shortly after being discharged from the emergency room. Preventive screenings for latent tuberculosis and viral hepatitis were conducted, and he underwent a biologics assessment, which included an intravenous steroid induction for remission. The initiation of Adalimumab therapy followed, starting at 160 mg, then 80 mg after two weeks, and subsequently 40 mg bi-weekly.

in Table 1.

Two months after that, the patient reported the persistence of his symptoms, which was confirmed by a colonoscopy and proctoscopy, indicating mild endoscopic improvement. Despite his diligent adherence to the gluten-free diet and regular Adalimumab injections, the patient frequented the ER due to continued abdominal pains, bloody diarrhea, anorexia, significant weight loss, and malnutrition, necessitating repeated corticosteroid interventions.

Subsequently, the patient transitioned from Adalimumab to Infliximab therapy, following the 0-2-6-week induction protocol and sustaining a maintenance dose of 5 mg/kg every eight weeks. This amendment to his treatment plan led to appreciable improvements in oral intake, appetite-reduced ER visits, and hospitalizations due to IBD flares, alongside better clinical symptoms and inflammatory markers, as detailed in Table 1.

However, after the initial doses of Infliximab and noting an improved oral intake with enhanced appetite, the patient developed muscle weakness, diplopia, fatigue, delirium, headaches, and significant electrolyte disturbances, including hypokalemia, hypophosphatemia, hypomagnesemia, and hypocalcemia. He was managed in the ICU for three days for refeeding syndrome. Following his ICU management, the patient continued with Infliximab and demonstrated clinical and laboratory improvement, as summarized



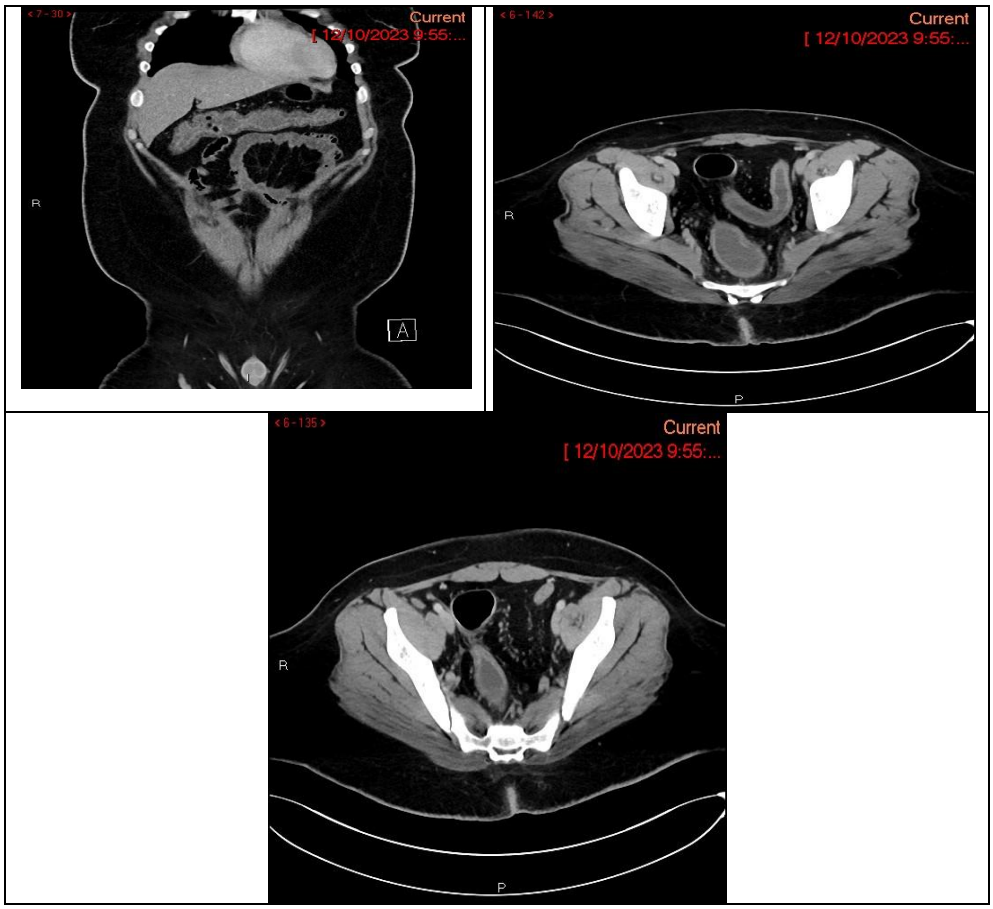


Fig 1: Coronal and axal CT scan with IV contrast revealed

- Diffuse Increased mucosal wall thickness from the rectum to the caecum
- Submucosal fat deposition seen in the rectum (fat halo sign)
- Loss of colonic haustration mainly seen at the sigmoid colon
- There is associated mild engorgement of the pericolic vasa recta
- Multiple small mesenteric lymph nodes.

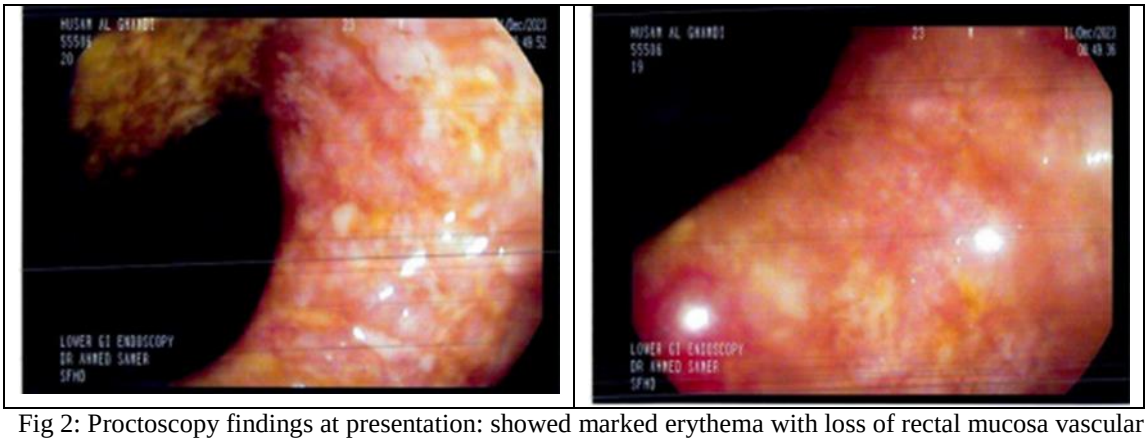


Fig 2: Proctoscopy findings at presentation: showed marked erythema with loss of rectal mucosa vascular pattern with pseudomembranous mucosa.

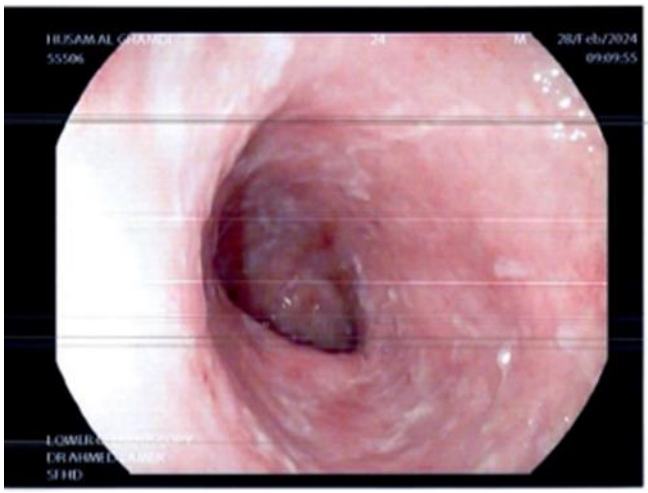


Fig 2: colonoscopy findings after remission: showed marked improvement mild erythema with decrease of colonic mucosa vascular pattern.

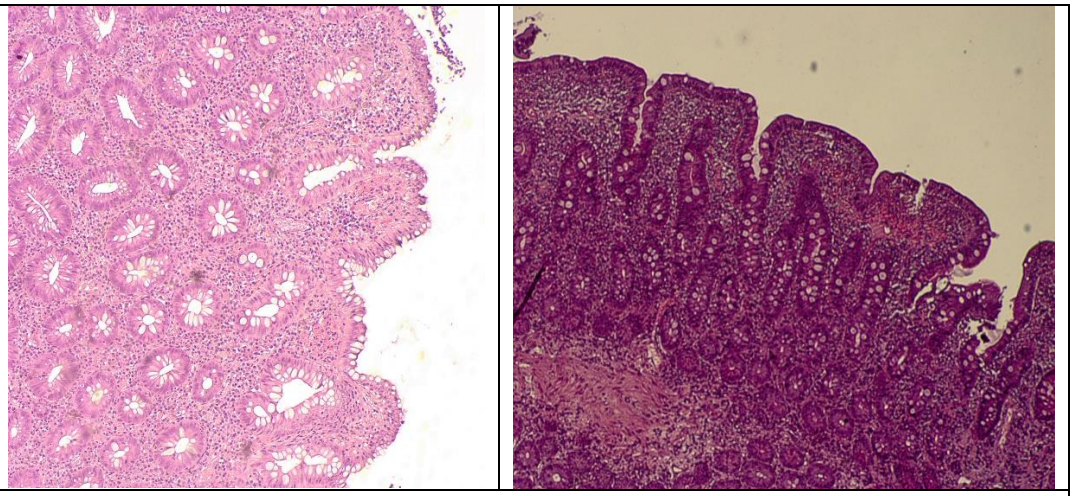


Fig 4: Duodenum, Atrophic duodenal mucosa
Marsh type 3c: increased intraepithelial lymphocytes (intraepithelial lymphocytosis), complete (total) villous atrophy, crypt hyperplasia.

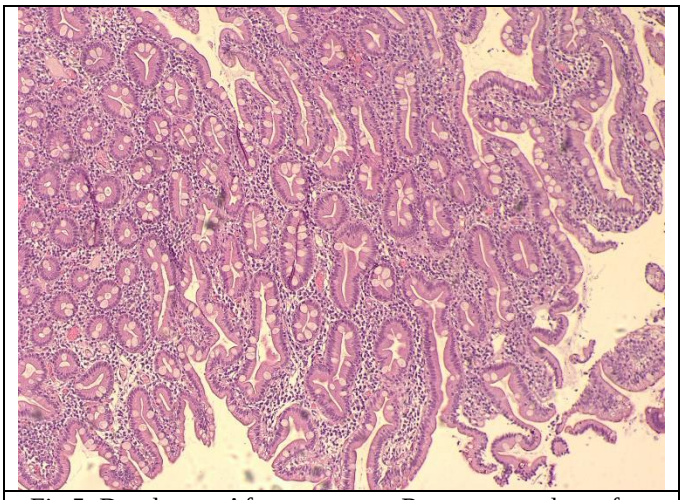


Fig 5: Duodenum After treatment, Response to gluten free diet with resolving of villous atrophy.

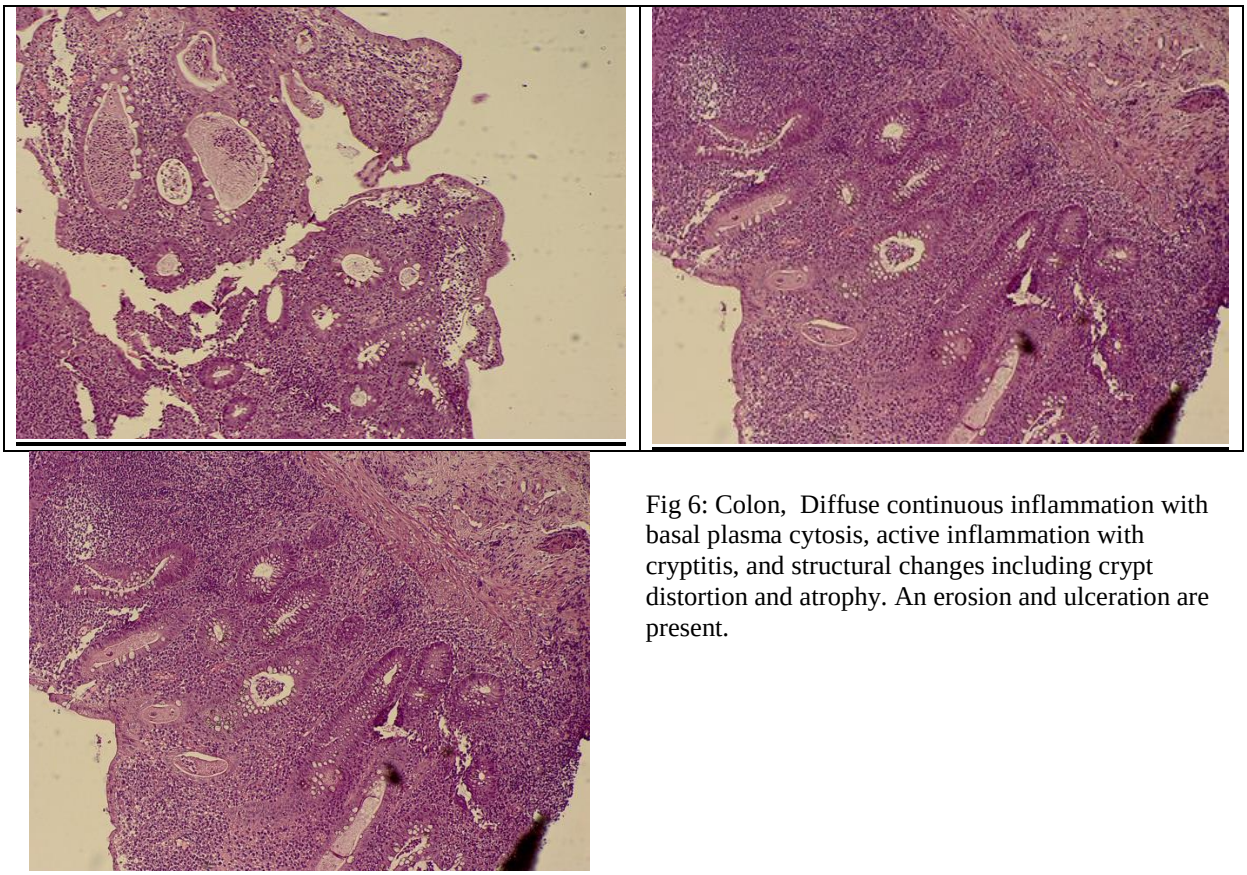


Fig 6: Colon, Diffuse continuous inflammation with basal plasma cytosis, active inflammation with cryptitis, and structural changes including crypt distortion and atrophy. An erosion and ulceration are present.

Table (1): American College of Gastroenterology ulcerative colitis activity index [39].

	1ST Admission	2nd Admission Start adalimumab	3 Months after adalimumab	Shift to infliximab After 4 months	2 weeks after infliximab	One month after infliximab	6 months after infliximab
Stools/d (n)	>6	>6	>6	>6	<4	Formed stools	Formed stools
Blood in Stools	Continuous	Frequent	Frequent	Intermittent	None	None	None
Urgency	<75% of normal	<75% of normal	Mild, occasional	Mild, occasional	None	None	None
Hemoglobin	Transfusion required	Transfusion required	<75% of normal	<75% of normal	Normal	Normal	Normal
ESR	140	110	85	55	34	11	10
CRP (mg/L)	240	218	116	63	33	10	4
FC (µg/g)	479	NOT DONE	NOT DONE	NOT DONE	NOT DONE	NOT DONE	45
Endoscopy (Mayo Sub score)	3	NOT DONE	NOT DONE	2	NOT DONE	NOT DONE	0
UCEIS	8	NOT DONE	NOT DONE	6	NOT DONE	NOT DONE	0
Physician's global assessment*	Sever UC	Moderate UC	Moderate UC	Moderate UC	Moderate UC	Mild UC	Remission

*The physician's global assessment acknowledged other criteria including the patient's daily abdominal discomfort, general sense of well-being, performance status, and physical findings.

Discussion :

Genetic factors have been recognized as one of the numerous commonalities shared by Inflammatory Bowel Disease (IBD) and Celiac Disease. Certain genetic loci, such as PUS10, protein tyrosine phosphatase non-receptor type 2 (PTPN2), T-cell activation RhoGTPase-activating protein, and the interleukin 18 receptor accessory protein, have been identified as predisposing elements for both conditions [14[

Studies focusing on Egyptian pediatric populations have established a higher prevalence of Celiac Disease amongst individuals with IBD compared to the general populace [14]. Detailed research, including a meta-analysis conducted by Pinto-Sanchez et al., scrutinized the association between Celiac Disease and IBD. Their findings indicated that patients with Celiac Disease have an elevated risk of developing IBD. Similarly, IBD patients are at increased risk for Celiac Disease when contrasted with control groups [15]. Further research highlighted an increased incidence rate of IBD in patients with Celiac Disease compared to the broader population [16]. The case detailed here illuminates the manifestation of concurrent IBD and Celiac Disease, reaffirming the interrelation between the two disorders.

When the two diseases occur together, the disease may worsen. The rising use of immunomodulators among celiac-UC patients by Oxford et al. found that IBD and celiac disease patients are more prone to have pancolitis [17]. Combining celiac diseases and IBD may worsen the clinical picture, requiring colectomy as a last resort [16]. Our present celiac disease –IBD patient has a more severe condition, as shown by numerous medication changes and lack of progress after routine management. Because celiac disease and IBD symptoms are similar, diagnosing one takes longer, and one may go undiagnosed. Yang et al. [16] found that the time between diagnosis of CD-celiac diseases and

UC-celiac diseases ranged from 1 to 12 years in the former and a month to 46 years in the latter. Fortunately, our patient had celiac disease and IBD simultaneously .

Infection with Clostridium difficile (CDI) may not necessarily exacerbate relapses of IBD, but its presence is associated with heightened morbidity and mortality rates. Analyzing a collective data set of 124,570 hospital admissions revealed that the presence of CDI in combination with IBD was found in 2.3% of the cases involving comorbid conditions. The study indicated that patients with either IBD (OR: 4.7) or CDI alone (OR: 2.2) experienced shorter hospitalizations and had quadruple mortality risk compared to individuals battling both CDI and IBD concurrently. Additionally, it was observed that patients with Crohn's disease, a specific type of IBD, encountered fewer emergency surgical complications than those diagnosed with Ulcerative Colitis [18 .[

For patients with IBD who have previously experienced CDI, initiating biological therapies early is crucial to mitigate the risk of grave complications. A cohort analysis involving 654 individuals revealed that 57% of IBD patients with a history of CDI required the early introduction of biological treatments to subdue the intensity of their aggressive disease course, as opposed to the 37% of those without a prior CDI [19]. Consequently, we commenced treatment with Infliximab for our patients grappling with severe IBD and concurrent CDI.

Prompt recognition of suspected CDI, followed by microbiological verification, is critical. When CDI is confirmed, the administration of vancomycin is indicated [20, 21]. With the growing resistance of CDI to metronidazole, vancomycin has been promoted to the position of first-line treatment [22]. Recent studies have pointed out an increase in the failure rate of metronidazole from 10% in the 1990s to a range of 22%–26% [22]. Fidaxomicin, a potent and narrow-spectrum antibiotic introduced in 2011, has shown effectiveness in managing both initial appearances and recurrences of CDI [23]. Current expert recommendations for treating severe CDI episodes have shifted from metronidazole to a preference for vancomycin or fidaxomicin [24], though the higher cost of fidaxomicin may limit its accessibility [23]. Patients with IBD and CDI, particularly those who do not respond to conventional therapies, are at heightened risk of clinical deteriorations that necessitate intensive care [25, 26–27]. Markers such as acute kidney injury, hypoalbuminemia, and elevated white blood cell counts serve as indicators of severe CDI, and an aggressive treatment approach is suggested to minimize adverse outcomes [26, 28]. Considering these factors, accounting for CDI severity within IBD treatment plans is prudent.

Therapeutic strategies for CDI in IBD usually encompass a combination of antibiotic treatment and the use of immunosuppressive or immunomodulatory drugs. Currently, there are no standardized guidelines for managing CDI in IBD patients, and the research presents mixed results [20]. An investigation encompassing 155 patients evaluated the effectiveness of antibiotics in combination with multiple immunomodulatory drugs—including prednisone, thiopurines, methotrexate, cyclosporine, and tacrolimus—in managing CDI within this patient demographic .

The management of CDI in patients with IBD was assessed through comparison with antibiotic treatments. To gauge treatment efficacy, we considered major clinical outcomes such as colonic perforation, toxic megacolon, cardiogenic shock that required the use of vasopressors, the necessity of intubation and ventilation, mortality, or the need for a colectomy within three months following hospital admission. The combination of antibiotics with immunomodulators succeeded in achieving all predetermined primary outcomes. This success was observed in 8% of the patients (12 out of 104) or 12% (12 out of a total of 155) in the overall study group. However, the use of multiple immunomodulators was linked to an increased incidence of adverse effects. Notably, in contrast, antibiotic monotherapy did not result in any detrimental effects [29.[

Further research indicated that the use of immunomodulators, corticosteroids, and tumor necrosis factor inhibitors was not associated with increased harm in IBD patients who also had CDI. Instead, the presence of low serum albumin levels, anemia, and acute renal failure was more reliable in predicting the outcomes of mortality and colectomy [28]. Given the lack of prospective data, we advise against the sole use of antibiotic therapy for treating CDI during severe episodes of IBD recurrence without concurrent immunosuppression. In cases where symptoms are not adequately managed by

vancomycin, metronidazole, and/or fidaxomicin, it seems wise to initiate corticosteroids and consider additional immunosuppressive treatments. Hence, there is merit in beginning immunosuppressive therapy while vigilantly monitoring patients for any signs of clinical worsening [20.[

In the treatment of UC, Infliximab was the pioneering anti-TNF medication to gain approval, with adalimumab entering the market several years subsequently. Both medications have proven efficacy in managing UC ranging from mild to severe intensity, yet the superior choice between the two remains undetermined. Our inquiry into this issue involved a network meta-analysis comparing critical studies relevant to each medication [30.[

Lee and colleagues conducted research with a cohort of 113 biologic-naïve patients suffering from moderate to severe UC to assess the long-term outcomes and the effectiveness of treatments using Infliximab and adalimumab. During the median follow-up duration of 26 months, the infliximab cohort exhibited a marginally higher incidence of UC-related hospital admissions compared to the adalimumab cohort ($p = 0.051$); however, no significant discrepancy was noted in adverse clinical outcomes such as overall hospitalization rates cessation of drug therapy, initiation of corticosteroid treatment, or the need to switch medications [31.[

Efforts have been made to gauge the real-world effectiveness of Infliximab and adalimumab in treating biologic-naïve patients with UC. Findings from a Danish nationwide cohort study indicated a higher frequency of hospitalizations and serious infections among patients treated with adalimumab as opposed to those treated with infliximab [32]. Conversely, an analysis of a U.S. cohort using an administrative claims database revealed comparable rates of hospitalization and serious infections between both treatment groups. Still, it highlighted that patients treated with Infliximab had a reduced requirement for corticosteroids compared to those treated with adalimumab [33]. Meanwhile, a single-centre investigation in France determined similar adherence rates for both medications. Still, a separate study in the U.S. suggested that the adherence to adalimumab surpassed that of Infliximab after one year of treatment [34–35.[

Although preliminary data may suggest that adalimumab and Infliximab are comparably effective in treating UC from mild to severe cases, conclusive evidence is lacking, warranting a dedicated head-to-head clinical trial. Therefore, when it comes to selecting a treatment, healthcare providers might consider individual patient preferences and socioeconomic factors .

Refeeding syndrome is a complex and potentially fatal condition characterized by significant hormonal and metabolic alterations. This syndrome can pose risks to individuals with pre-existing low levels of phosphate, potassium, and magnesium, particularly those with a history of malnutrition due to conditions such as inflammatory bowel disease, celiac disease, cancer, dysphagia, anorexia nervosa, depression, alcoholism, among others. Patients exhibiting a significantly decreased BMI are particularly susceptible. For these patients, energy replacement through nutritional intake should be implemented gradually. The cases we encountered included patients with celiac disease who experienced hypophosphatemia, hypocalcemia, hypokalemia, and severe malnutrition. Conditions associated with RFS, such as dehydration, electrolyte disturbances, and mineral deficits, have been linked to the process of renutrition. The prognosis may have been improved if a multidisciplinary approach involving a psychologist, an internist, and a nutritionist had been employed collaboratively to enhance adherence to dietary recommendations and acceptance of the condition. Enteral feeding was initiated promptly after hospital admission.

In the context of a celiac crisis, corticosteroids may be employed as a treatment strategy. However, they can increase the risk and further deplete electrolyte levels, pointing towards a necessity for supplementation with vitamins, selenium, magnesium, and necessary cofactors [36]. It is important to evaluate the risk of RFS in the setting of cardiac crises. Current literature suggests the proactive supplementation of vitamins, selenium, magnesium, and thiamine right at admission, even in the absence of biological abnormalities, with an emphasis on the prevention of hypophosphatemia [37.[

When reintroducing oral feeding to patients, both statistical and subjective evaluations of the protein and caloric intake are warranted. For individuals identified as high-risk, continuous monitoring of clinical and biochemical

parameters is imperative. Modifications to nutritional support must consider both clinical outcomes and electrolyte imbalances, specifically targeting hypophosphatemia, hypokalemia, and hypomagnesemia [38.[

Conclusion: Celiac disease and IBD are both rooted in immune system dysfunction, representing chronic inflammatory disorders. Recent studies suggest an association between IBD and an increased prevalence of CDI. The presence of CDI in patients with IBD may reflect a more complicated clinical scenario. It is vital for healthcare practitioners to have a high index of suspicion and to diagnose CDI promptly to avert challenging or potentially life-threatening exacerbations of IBD.

In instances where antibiotic therapy is ineffective, a relapse may necessitate the initiation or escalation of immunosuppressive and biological therapies. It is important to frequently evaluate patients undergoing such treatments for any signs of clinical deterioration.

Implementing a gluten-free diet and vigilant monitoring of clinical and biochemical parameters are critical measures in the prevention and management of refeeding syndrome during a celiac crisis. Regrettably, awareness of this approach remains limited. The role of multidisciplinary teams is pivotal in educating both patients and healthcare providers on how to prevent RFS effectively.

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Conflict of interest disclosure:

No conflicts of interest

Ethics approval statement:

The study is approved by the ethics committee of Security forces hospital Dammam and conducted in accordance with Helsinki standards.

Research Highlights

- The etiology of ulcerative colitis and celiac disease is yet unknown; however, both diseases have a complicated origin with complex genetic and environmental components.
- Clostridium difficile infection is the most common complication in IBD patients. Management of both disease in the setting of Clostridium difficile infection is challenging .
- Refeeding syndrome is an uncommon pathology with poly visceral manifestations occurring in severely malnourished patients receiving either enteral or parenteral artificial refeeding and may cause serious complications.

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