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Case Report
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Autoimmune Hemolytic Anemia Rare Complication in Ulcerative Colitis

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Abstract

Inflammatory Bowel Disease (IBD) is a chronic and recurring condition of unknown origin that affects the gastrointestinal tract. It presents in two distinct forms, Ulcerative Colitis (UC) and Crohn's Disease (CD). This case study focuses on a 28-year-old female patient who experienced symptoms such as diarrhea, abdominal pain, and rectal bleeding during her pregnancy. Subsequently, she was diagnosed with UC along with Autoimmune Hemolytic Anemia (AIHA). It is crucial to closely monitor patients with UC for potential complications like AIHA. Further research is necessary to enhance our understanding of this rare complication and develop more effective treatments for affected patients.

Introduction

Inflammatory Bowel Disease (IBD), is a chronic, incurable, relapsing disease of unknown etiology. IBD has two distinct forms; Ulcerative Colitis (UC) and Crohn's Disease (CD). In 2017 it was estimated that around 1.5 million people in the United States and 2.5 in Europe suffer from IBD. This chronic disease causes substantial costs for health care and substantial impact on different aspects of patient's life, including career aspirations, installing social stigma and impairing quality of life. Reports showed a lot of variation in incidence and prevalence of the disease between different geographic areas and different ethnic groups [1,2].

Some call for a systemic approach when dealing with this disease [3], as manifestation of this disease may be found in any organ system out of the GI tract, with a huge burden on the patient's quality of life. The disease manifestation commonly affects the joints, the skin, the hepatobiliary tract, less commonly the vascular system.

These manifestations are thought to be due to the same immunological process but outside the gastrointestinal system [4]. Although some of them may run parallel to the intestinal disease activity and some may not [5-7].

Anemia is common among patients with both types of IBD, with reports showing prevalence ranging from 6% to 74% [8-11].

There several causes of anemia in patient with IBS, with iron deficiency anemia as the most frequent, other causes include folate and vitamin B12 deficiency which appears significantly more prevalent in patient with IBD [12]. Another less frequent cause of anemia is the autoimmune hemolytic anemia.

Several reports investigated the prevalence of autoimmune hemolytic anemia in patient with ulcerative colitis, with some report's prevalence of 0.6% to 1.7 % which is higher than what is reported in Crohn's disease [5,13].

IBD may cause several complications, such as VTE, with a recent meta-analysis shows it carries 2-fold the risk of Venous Thromboembolism (VTE) than general population [14], with several possible contributing factors such as the effect of local and systemic inflammation with the resulting IL-6 medicated procoagulant state, dehydration and corticosteroid use [15,16]. Another contributing factor to the increased risk of VTE in patients with IBD is AIHA, which was investigated in a recent study and showed a 3-fold increase in the risk of VTE [17].

In this case report we report a female patient with acute severe ulcerative colitis, Coombs

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positive hemolytic anemia and splenic infarction.

Case Presentation

A 23-year-old female patient presented to the emergency room on February 15th, 2023 with abdominal pain and bloody diarrhea. She had a normal vaginal delivery three weeks prior and had been complaining of abdominal pain, perianal pain, fever, and non-bloody diarrhea two weeks prior which progressed to become bloody. She was admitted into a regional hospital and treated with metronidazole; however, her condition did not improve and her hemoglobin dropped, leading to referral as a suspected case of ulcerative colitis.

Upon presentation her vital signs were as follows: BP 100/62 mmHg, temperature 36.9°C, heart rate 85 bpm, respiratory rate 18 breaths per min, and oxygen saturation 95% on room air.

Laboratory tests revealed Leukocytosis (18.9×10^9/L) which were mainly neutrophils (neutrophils 78%), low Hemoglobin level (5 mg/dL), with a mean cell volume at the upper limit of normal (MCV 95 fL), thrombocytosis (769×10^9/L), low albumin level (1.8 g/dL), increased Lactate Dehydrogenase (LDH 512 U/L), low haptoglobin (10 mg/dL), high reticulocyte count (12%), ferritin was increased (11173 ng/mL), with increased inflammatory markers (CRP 25 mg/L, ESR 88 mm/h). Stool analysis revealed the presence of many red blood cells and white blood cells as well as *Entamoeba* spp. cysts and trophozoites; with significantly elevated fecal calprotectin (>1000 µg/mg). Stool was tested positive for Glutamate Dehydrogenase (GDH), and further testing revealed positive *Clostridium difficile* toxin A&B. Further laboratory workup revealed positive direct and indirect antiglobulin tests (Coombs), positive Antinuclear (ANA) autoantibodies in high titers (1/160, negative anti-double stranded DNA antibodies, normal levels of C3 and C4 complements.

Other tests including Alkaline Phosphatase (ALP), Gamma-Glutamyl Transferase (GGT), Aspartate Aminotransferase (AST), Alanine Transaminase (ALT) total serum bilirubin and direct serum bilirubin, International Normalized Ratio (INR), Blood Urea Nitrogen (BUN), Creatinine, Serum sodium, serum potassium, correct serum calcium, were all within the normal limit.

A peripheral blood smear showed nucleated red blood cells, with no schistocytes. The patient was seen by the hematology team and was diagnosed with Coombs Positive Autoimmune Hemolytic Anemia (AIHA) (Figure 1).

CT-scan of the abdomen was done and revealed diffuse colonic wall thickening with surrounding fat stranding. A hepatosplenomegaly was also noted with two wedges shaped hypodensities seen in the spleen suggestive of infarction (Figure 2, 3).

Upon admission flexible sigmoidoscopy was performed, which revealed hyperemic congested mucosa which bleeds with water irrigation, with diffuse small ulcerations. Biopsies were taken (Figure 4).

The patient was given methylprednisolone 100 mg/day for AIHA and suspected acute severe colitis. Antibiotics therapy were initiated for amebiasis (Metronidazole 500 mg three times daily) and *Clostridium difficile* infection (Vancomycin 125 mg orally four times daily). Low-Molecular-Weight Heparin (LMWH) was given for Venous Thromboembolism (VTE) prophylaxis (enoxaparin 40 mg subcutaneously once daily). And Intravenous (IV) fluid (normal saline 0.9%) was given at a rate of 70 cc/h.

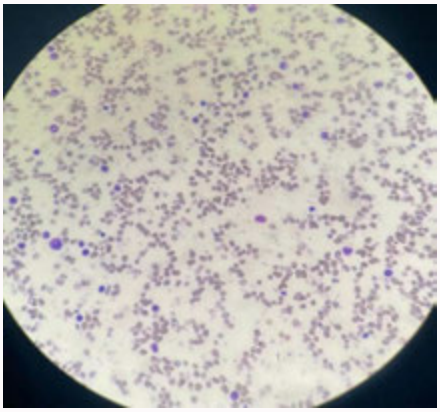

Figure 1: A peripheral blood smear showed nucleated red blood.

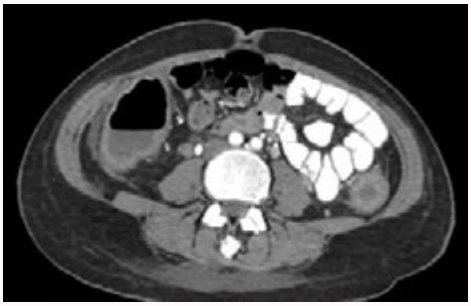

Figure 2: CT-scan of the abdomen was done and revealed diffuse colonic wall thickening with surrounding fat stranding.

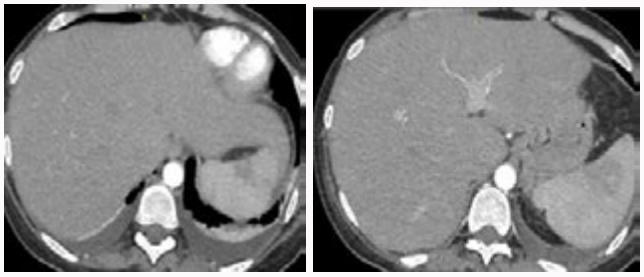

Figure 3: CT-scan of the abdomen revealed a hepatosplenomegaly with two wedge shaped hypodensities seen in the spleen suggestive of infarction.

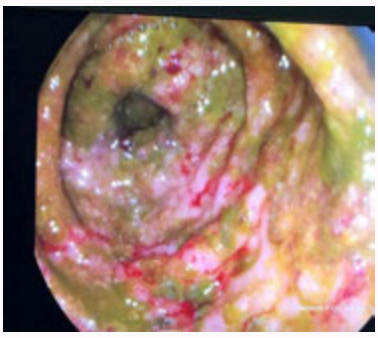

Figure 4: Flexible sigmoidoscopy revealed hyperemic congested mucosa with diffuse small ulcerations. Biopsies were taken.

Pretransfusion compatibility testing showed incompatible blood, for which the patient was given the least incompatible two units of packed RBCs. During hospitalization the patient was doing well, with

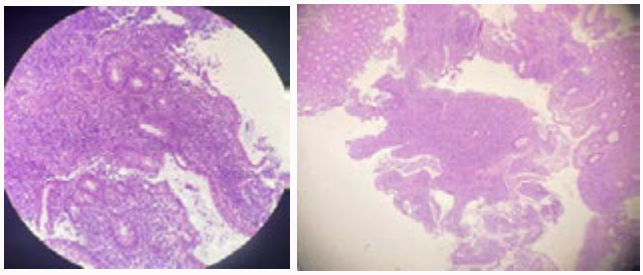

Figure 5: Pathology showing cryptitis, crypt abscess and crypt architecture distortion.

regular surgical follow up and three to five bowel motions per day, her vital signs were all normal, her CRP was going down and her hemoglobin level was stable, until the fifth day of admission, when the patient bowel motion increased up to 8 times, her CRP level increased to 50 mg/dl and her hemoglobin level dropped to 6.5 mg/dl (for which she was given two units of blood). At that time patient was still on methylprednisolone 100 mg/day, vancomycin and metronidazole. In the sixth day of admission the pathology report came out, showing cryptitis, crypt abscess and crypt architecture distortion, which was highly suggestive of Ulcerative Colitis (UC) (Figure 5).

Due to her deteriorating condition infliximab was given at a dose of 300 mg. in the next day the CMV stain came positive for CMV, so the patient was given ganciclovir.

On the 3rd day the infliximab patient was improving, her fever did not recur, her CRP dropped down, her bowel motion decreased to about 3 times a day with intermittent streaks of blood. Intravenous methylprednisolone was shifted to oral prednisolone 40 mg once daily and the patient was discharged home.

Discussion

Ulcerative Colitis (UC) is a chronic Inflammatory Bowel Disease (IBD) that affects the colon and rectum. It is characterized by inflammation, ulceration, and bleeding of the intestinal lining [2]. Autoimmune Hemolytic Anemia (AIHA) is a rare complication of UC that occurs when the immune system attacks and destroys red blood cells. This case study discusses a patient who was diagnosed with UC complicated b AIHA [18].

The first case of UC with AIHA was reported in 1955 by Lorber et al. who reported four cases of female patients with ulcerative colitis and AIHA. The four cases were diagnosed during flare up of the disease [19]. The exact mechanism behind the development of AIHA in patients with UC is not fully understood. However, it was believed that the development of AIHA in these patients may be attributed to autoimmunity and the cross-reactivity between antibodies produced against substances absorbed by the diseased colon and antigens present on the surface of red blood cells [20].

The patient in this case study was a 28-year-old female who developed symptoms of UC during her pregnancy. She experienced diarrhea, abdominal pain, and rectal bleeding, which are common symptoms of UC. After delivering her baby, her symptoms worsened, and she was diagnosed with AIHA. In a study on 8 patients with AIHA with UC done by Gumaste et al. autoimmune hemolytic anemia was diagnosed after a mean of 10 years after the diagnosis of colitis [18] although in our case AIHA was diagnosed at the time of the ulcerative colitis diagnosis.

There is no significant sex-based difference in the incidence of AIHA with UC [21]. The prevalence of AIHA in IBD is higher than non-IBD without difference between UC and Crohn's group [22]. There is evidence to suggest that AIHA may be related to flare-ups of IBD, as some patients experience remission of AIHA after treatment for IBD [23]. In Lorber et al. study all patients were having relapses at the time of diagnosis therefore AIHA considered as an extraintestinal manifestation of IBD [19].

It is widely accepted that corticosteroids are the primary treatment for warm antibody type AIHA, despite the lack of concrete evidence. Corticosteroids are expected to yield a response in 70% to 85% of patients, but only one-third of cases remain in long-term remission after discontinuing the drug. Half of the remaining patients require maintenance doses [24].

Infliximab is a type of monoclonal antibody that targets TNF-α, a protein involved in inflammation. It is made up of a combination of mouse and human proteins, with the mouse portion binding to TNF-α and the human portion providing stability. Infliximab can bind to both soluble and membrane-bound forms of TNF-α with high affinity, effectively blocking its activity. It has a long half-life in the bloodstream and is typically administered intravenously at doses of 5 mg/kg or 10 mg/kg [25].

In case of IBD flare, AIHA is thought to be a reactive type of Extraintestinal Manifestations (EMS). This particular group of EMS typically occurs concurrently with a flare-up of UC and can usually be treated by effectively managing the bowel disease. Infliximab has been found to be an effective therapeutic option for steroid-refractory UC, resulting in complete remission. Therefore, successful management of the bowel disease, as evidenced by mucosal healing, was the primary factor in resolving the clinical symptoms of AIHA [23]. Our patient was given intravenous corticosteroid for several days but showed no response, so we used infliximab as rescue therapy after which significant improvement was noted.

Other lines would have been considered in the treatment of AIHA if the IBD treatment did not resolve the AHIA, like Rituximab, which is considered the second line in isolated AIHA [26]. Such treatment was deferred as literature showed no benefit of such treatment on IBD flare [27].

Although several reports mentioned the association of IBD (especially ulcerative colitis) and the AIHA, Further research is needed to better understand their relationship and to develop more effective treatments for this rare complication. Additionally, studies exploring potential biomarkers for predicting the development of AIHA in patients with UC could help identify high-risk patients early on and improve outcomes.

Conclusion

This case study highlights the importance of monitoring patients with UC for potential complications such as AIHA. Further research is needed to better understand this rare complication and develop more effective treatments for affected patients.

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