Gastroenterology and Hepatology From Bed to Bench.
2023 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

CASE REPORT

p-ISSN: 2008-2258 e-ISSN: 2008-4234

Can eculizumab be an option in traditional treatment-resistant ulcerative colitis?

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ABSTRACT

Atypical/complement-mediated hemolytic uremic syndrome (A-HUS/CM-HUS) is a hereditary or sporadic disease with thrombotic microangiopathy (TMA). Diarrhea is a trigger that can cause attacks of CM-HUS. Although there are opinions that complement system activation plays a role in intestinal inflammation in patients with inflammatory bowel disease, the association of TMA with inflammatory bowel disease (IBD) has rarely been reported. In our case, a CM-HUS case that developed without an additional triggering factor in the course of ulcerative colitis (UC) was successfully treated with eculizumab, and then UC remission was also achieved. In this context, we would like to point out that the irregularities in the alternative pathway of the complement system may cause clinical findings in extra-renal organs, and the complement system may also play a role in the pathogenesis of inflammatory bowel disease. In addition, we think that our case may guide further studies on the usability of anti-complement therapies in treating patients with IBD who are resistant to conventional treatments.

Keywords: Gastric cavernous hemangioma, Endoscopy, Histopathology.

(Please cite as: **Ozer H, Baloglu I, Turkmen K, Tonbul HZ, Selcuk NY. Can eculizumab be an option in traditional treatment-resistant ulcerative colitis? Gastroenterol Hepatol Bed Bench 2023;16(4):445-450. https://doi.org/10.22037/ghfbb.v16i4.2689).**

Introduction

Thrombotic microangiopathies (TMA) are a group of diseases associated with microangiopathic hemolytic anemia, thrombocytopenia, and kidney dysfunction that can be fatal if not diagnosed and treated early. The most common TMAs are hemolytic uremic syndrome (HUS) following Shiga toxin-producing Escherichia coli infection, thrombotic thrombocytopenic purpura (TTP), and complement-mediated/atypical HUS (CM-HUS /A-HUS), which is caused by genetic or acquired dysregulation of the complement system (1).

Cases of CM-HUS can be inherited or sporadic and can occur at any age, but 40% are seen in adults. Irregularities of the alternative complement pathway, the most common factor H mutation, are responsible for the onset of the disease. In cases where CM-HUS is not diagnosed and treated early in the clinical course, mortality is 25%, while end-stage kidney disease may develop in 50% of survivors (2). Significant reductions in morbidity and mortality rates have been observed using eculizumab, a recombinant monoclonal antibody developed against human complement factor C5, in the treatment (3).

Although it is known that diarrhea is a trigger that can cause CM-HUS attacks, and some opinions complement system activation plays a role in intestinal inflammation in inflammatory bowel patients (IBD), the association of TMA with IBD has rarely been reported (4–10). Data on the development of CM-HUS in IBD patients are limited to case reports. A total of 7 cases, 5 of which were UC, have been reported in the literature so far. In a case with ulcerative colitis, eculizumab treatment was indicated due to CM-HUS that developed afterward, and UC was in remission after treatment. By presenting this rare case, we wanted to guide the planning of new studies on the effect of the complement pathway in the pathogenesis of IBD and its clinical utility.

Received: 01 May 2023 *Accepted*: 25 June 2023
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Case report

A 29-year-old female patient was followed for three years with the diagnosis of UC. Anti-TNF treatment was planned for the patient due to steroid resistance during her follow-ups, but the patient presented with diarrhea before the treatment could be started. The complaint of diarrhea has increased in the last three days and often contains blood. The patient described that her diarrhea complaint had increased for three days and often contained blood. Apart from diarrhea, she complained of fever and fatigue. The patient's Mayo Score / Disease Activity Index (DAI) was 8 at admission to the clinic. No parasites, parasite eggs, or amoeba were observed in the parasitological examination of the stool. The stool had no Helicobacter pylori antigen and Clostridium difficile toxin B (by PCR method). At her admission, hemoglobin (Hgb) was 4.5 gr/dl, platelet count (PLT) was 88000 10^3 U/L, serum creatinine was 6.75 mg/dl, and estimated glomerular filtration rate (e-GFR) was 7 ml/min. Direct-indirect coombs tests were negative, lactate dehydrogenase (LDH): 692 U/L, haptoglobulin<0.1 g/L, and the reticulocyte percentage was 11%.

The patient with diffuse schistocytes in her peripheral smear was considered to have TMA. Intermittent hemodialysis and five plasmapheresis sessions were performed. The patient was taking 32 mg/day methylprednisolone during her hospitalization, and her treatment was continued at 1 mg/kg/day after pulse steroid for the first three days during the treatment. The patient's ADAMTS-13 level was 61%. The genetic analysis detected deletion of complement Factor-H Receptor-1 (CFHR1) and Complement Factor-H Receptor-3 (CFHR3). Eculizumab was started, and the patient's kidney function tests regressed after the third dose of eculizumab treatment. After 45 days of treatment, the patient was weaned off hemodialysis, and the kidney function did not deteriorate again (Table 1). After two months of eculizumab, her UC-related complaints were wholly resolved. In the control endoscopy performed in the 4th month of the treatment, no pathological findings were observed, except for mild erythema (Figure 1). Mayo Score was determined as two. What makes this case interesting and valuable is the complete disappearance of gastrointestinal system symptoms and decreased disease activity score after eculizumab treatment in the patient who was scheduled for anti-TNF therapy for steroid-dependent UC.

Table 1. Change in laboratory results during the treatment process of the patient (e-GFR: estimated glomeruler filtration rate)

Day	e-GFR (ml/min)	Creatinine (mg/dl)	Hemoglobulin (g/dl)	Platelet Count (10^3/uL)	Haptoglobin (g/L)	Reticulocyte (%)	Proteinuria (mg/day)
0	7	7.1	4.5	88	0.1	11	2292
15	13	3.28	9.2	456	1.86	1.06	--
30	23	2.97	9.9	612	--	--	212
45	34	2.55	10.8	435	--	--	--
60	34	2.54	11	456	--	--	--
75	38	1.87	11.5	417	--	--	--
90	42	1.54	11.4	445	2	0.05	86

Day 0-8:Plasma Exchange

Day 18: Eculizumab was started

Day 45: No need for hemodialysis

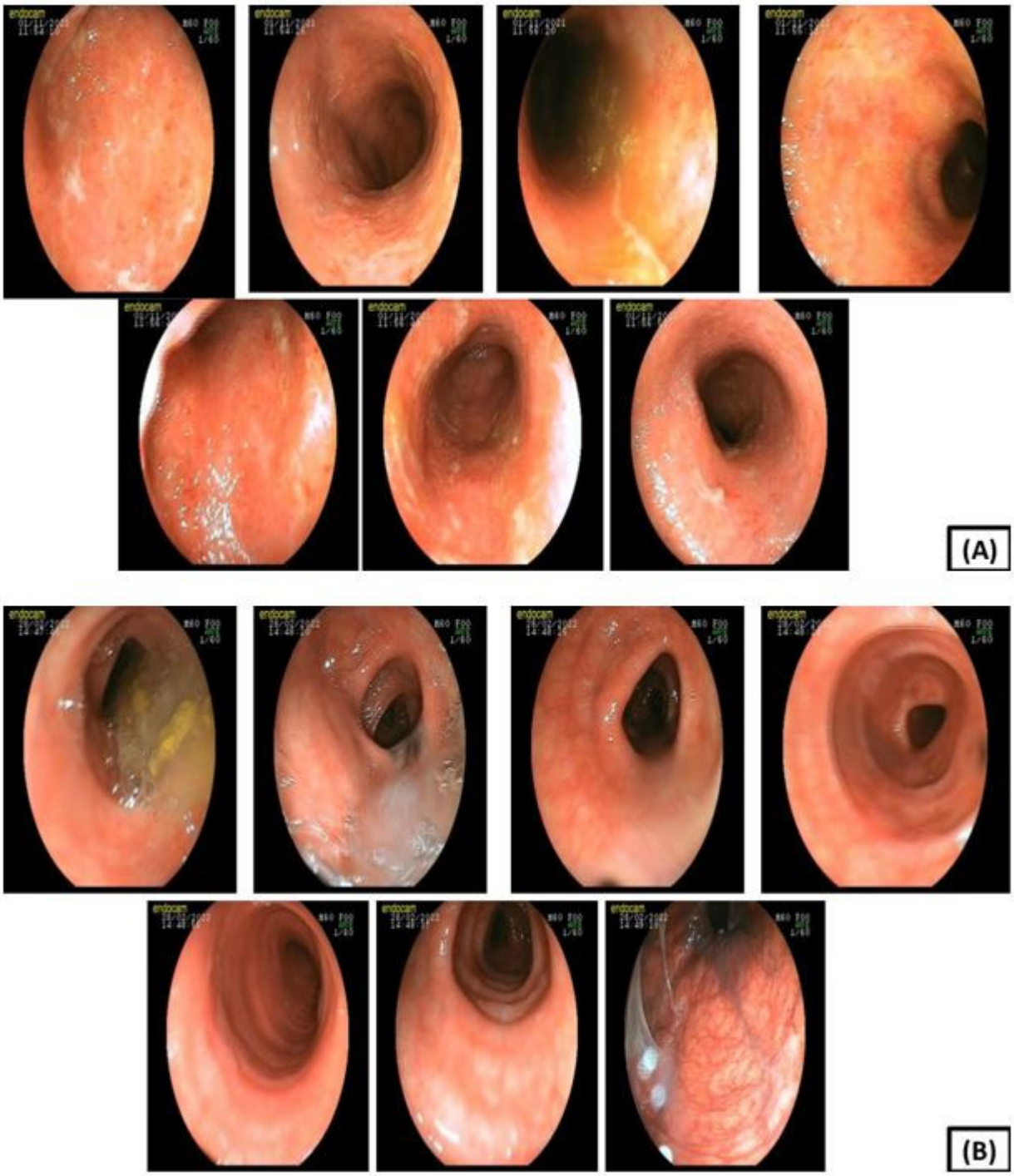

Figure 1. Images of the patient's lower gastrointestinal system endoscopy performed before (a) and after (b) eculizumab treatment.

Discussion

In our case, a CM-HUS case that developed without an additional triggering factor in the course of UC was successfully treated with eculizumab, and then UC remission was also achieved. In this context, we would like to point out that the irregularities in the alternative pathway of the complement system may cause clinical findings in extra-renal organs, and the complement system may also play a role in the pathogenesis of IBD. In addition, we think that our case may guide further studies on the usability of anti-complement therapies in treating patients with IBD who are resistant to conventional treatments.

Data on the development of TMA in IBD are still limited today (4–13). In the literature, there are 7 case reports, 5 of which are UC patients, examining the relationship between IBD and CM-HUS (8–13) (Table 2).

It is known that endothelial dysfunction has a role in the dysregulation of the complement system and microangiopathic hemolysis (14). Often, a specific trigger is not required for the onset of the disease, and complement activation in susceptible individuals may begin spontaneously due to chronic inflammation in IBDs (14). When studies on the role of activation of the complement system in the pathogenesis of IBD (15–17) are evaluated, it is emphasized that hyperactivity of the alternative complement cascade plays an essential role in the development of UC (8, 17). In addition, complement activation and accumulation of complement components on inflammatory mucosal surfaces contribute to the pathogenesis of IBD (18).

In the development of CM-HUS, various defects have been described, primarily genetic causes, which explain the pathophysiology of the complement system. CFH, membrane cofactor protein (MCF-CD46), and complement factor I (MFI) are cited as the leading genetic causes (1, 3, 19). We detected deletion in CFHR3/CFHR1 genes in our case. We know that there may be rearrangements in the CFH gene as a result of recombinations in existing gene regions, and existing deletions are observed in the vast majority of patients with anti-factor H antibody-positive CM-HUS. Still, we may also be associated with systemic lupus erythematosus (20, 21). When our case was evaluated regarding SLE, it did not meet the diagnostic criteria for SLE.

Despite these identified genetic events and therapeutic options for complement inhibition, the links between various immune-mediated diseases and CM-HUS are still not fully elucidated (22, 23). Recent studies have proven gastrointestinal complications and symptoms are more common in CM-HUS with anti-factor-H autoantibodies (24). It was also concluded that the irregularities in the alternative complement pathway might also occur in extra-renal organs, and the hyperactivity of the alternative complement cascade may play a role in the pathogenesis of IBD. Patients with gastrointestinal symptoms or who develop CM-HUS in the follow-up of IBD should be evaluated primarily for disease development due to anti-factor H antibodies (8).

In treating IBD, first-line therapy has always focused on suppressing the immune system to relieve inflammation and clinical symptoms. While studies have provided new therapeutic approaches, such as

Table 2. Cases in which IBD and CM-HUS cases were reported in the literature. (F: female, M: male, UC: ulcerative colitis, CD: Crohn's disease, CFH: complement mutation H, MCP: membrane co-factor protein, HZ-DKGE: heterozygous mutation in diacylglycerol kinase ε,)

	Published Date	Age	Sex	Disease	İmprovement in renal function	Genetic Result	Trigger Factor
Green	2014	27	F	UC	Yes	CFH Auto-Ab	Unknown
Webb	2015	16	M	UC	Yes	No Mutation	Unknown
Viada	2019	15	F	UC	No	HZ-CFH HZ-MCP	Unknown
Hanna	2019	19	M	CD	Yes	No Mutation	Unknown
Hanna	2019	49	F	UC	Yes	Unknown	Unknown
Ozbay	2019	26	F	UC	Yes	HZ-DKGE	Vedolizumab
Horvath	2021	13	F	CD	Yes	Factor-I Variant (R339l)	Unknown

anti-TNF-α antibodies, additional pharmacological treatment targets are required to improve IBD treatment, given the limited efficacy and broad side-effect limitations of immunosuppressive therapies such as corticosteroids, aminosalicylates, or biologic agents (25). Complement system regulators are among the drug groups whose importance in treating IBD has not been determined. Limiting the onset of the disease and improving clinical outcomes with C5aR-antagonists tested in IBD patients provides valuable information for the future (16, 17). Pre-clinical models show that C5a hyperactivation is detrimental in IBD. However, further research using complement inhibitors in the clinic is needed to test the applicability of these findings as a treatment goal (26). Considering the publications reporting that UC relapsed after monoclonal antibody therapy was discontinued in two UC patients treated with eculizumab for CM-HUS, it may be thought that complement system inhibition may have an essential role in treating UC (10, 12).

Conclusion

We described a severe CM-HUS case requiring HD in the course of UC. We observed that the gastrointestinal symptoms of the case were also entirely resolved after TMA treatment. Although current data suggest that these two diseases may have potential co-initiators, and dysregulation of the alternative complement pathway may be one of them, there are no detailed studies on using complement inhibitors in treating IBD yet. A common pathway may be associated with the complement system in the pathogenesis of HUS and IBD, and this issue is worth investigating. We think our case may form an additional basis for similar cases in the literature in studies to be conducted in this direction.

Acknowledgement

We thank Dr. Tacettin Akalın for his usefulness in obtaining endoscopic images.

Conflict of interests

Authors have no potential conflicts of interest to disclose.

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