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Mini Review

Atypical Hemolytic Uremic Syndrome: To What Extent is the Gastrointestinal System Involved?

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Abstract

Microangiopathic hemolytic anemia, thrombocytopenia, and abrupt renal failure are the hallmarks of the uncommon and potentially fatal atypical hemolytic uremic syndrome (aHUS). In addition to renal involvement, the gastrointestinal system is frequently affected in aHUS, with symptoms ranging from mild abdominal pain to severe gastrointestinal bleeding. This review article aims to provide a comprehensive overview of aHUS and its association with gastrointestinal complications. In this article, we explore the pathophysiology of aHUS, its clinical manifestations and examine the various gastrointestinal complications associated with aHUS, including gastrointestinal bleeding, pancreatitis, liver and gallbladder injury and inflammatory bowel disease. Finally, the article raises awareness of aHUS-associated gastrointestinal complications and highlights the need for further research in this area.

Keywords: *Hemolytic Uremic Syndrome, Atypical; Nonenteropathic HUS; Gastrointestinal Hemorrhages; Inflammatory Bowel Disease; Acute Pancreatitis*

Abbreviations

aHUS: Atypical Hemolytic Uremic Syndrome; GI: Gastrointestinal; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; IBD: Inflammatory Bowel Disease; STEC-HUS: Shiga Toxin-Producing *Escherichia coli*; UC: Ulcerative Colitis; CD: Crohn's Disease

Introduction

Atypical Hemolytic Uremic Syndrome (aHUS) is a rare syndrome that affects both children and adults, with an estimated incidence of 2 - 3 cases per million individuals per year [1]. It is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure, with renal involvement being the most frequent. However, the gastrointestinal (GI) system is also frequently affected in aHUS, with symptoms ranging from mild abdominal pain and diarrhea to severe gastrointestinal bleeding. In this review article, we provide a comprehensive overview of aHUS and its association with GI complications.

Pathophysiology

aHUS is caused by dysregulation of the alternative pathway of the complement system. The component of immune system defends the body against pathogens and damaged cells [2]. Mutations in genes encoding for complement proteins and autoantibodies against the complement proteins, can lead to uncontrolled activation of the alternative pathway of complement system with resultant tissue damage. In aHUS, dysregulation of the complement system leads to endothelial damage, platelet activation, and the formation of microthrombi throughout the body, including the kidney, brain, and gastrointestinal system [3].

Clinical manifestations of aHUS

The clinical features of aHUS are varied and can involve multiple organ systems, including the gastrointestinal system. The most common presenting symptoms of aHUS are fatigue, malaise, and confusion, which is commonly accompanied by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. However, GI symptoms such as nausea, vomiting, diarrhea, and abdominal pain are also frequently reported in aHUS patients [4]. In addition, aHUS patients may develop additional GI complications, including, pancreatitis, inflammatory bowel disease, liver injury and intestinal perforation.

The diagnosis of aHUS is based on clinical and laboratory findings of anemia thrombocytopenia and target organ injury. ADAMTS-13 levels that are more than 10% support the diagnosis of aHUS. Genetic testing can assist in establishing the diagnosis [5]. Diagnostic criteria for aHUS have been proposed by the European Pediatric Study Group for HUS [6] and the International Hemolytic Uremic Syndrome Registry [1].

Gastrointestinal complications

The GI system is frequently affected in aHUS, and GI symptoms are reported in up to 80% of the patients presenting with aHUS [7]. The following section would describe various GI complications encountered in patients with hemolytic uremic syndrome.

Gastrointestinal bleeding

Gastrointestinal bleeding is a particularly concerning complication in patients with aHUS, as it can result in significant morbidity and mortality. The severity of bleeding can range from mild to severe and can occur anywhere in the gastrointestinal tract. The bleeding is often associated with thrombocytopenia, which is a hallmark feature of aHUS. The incidence of gastrointestinal bleeding in patients with aHUS is not well established, as most studies have focused on renal outcomes rather than gastrointestinal complications. However, several case reports and small case series have described the occurrence of gastrointestinal bleeding in patients with aHUS. In a retrospective study of 44 patients with aHUS, 9 (20.5%) had gastrointestinal complications, including bleeding [1]. In another case series of patients with aHUS, 4 (40%) had gastrointestinal complications, including bleeding [8].

The risk factors for gastrointestinal bleeding in patients with aHUS are not well established. However, several potential risk factors have been proposed. One potential risk factor is the severity of renal disease. In a retrospective study of 44 patients with aHUS, all 9 patients with gastrointestinal complications had significant renal impairment [9]. Another potential risk factor is the use of anticoagulation therapy. In a case series of 10 patients with aHUS, 3 (30%) had gastrointestinal bleeding while on anticoagulation therapy [8]. Additionally, some patients with aHUS have been found to have concomitant gastrointestinal diseases, such as inflammatory bowel disease or colonic diverticulosis, which may increase the risk of gastrointestinal bleeding [9].

The pathophysiology of gastrointestinal bleeding in patients with aHUS is not well understood. One proposed mechanism is the presence of thrombotic microangiopathy in the gastrointestinal tract, which can lead to ischemia and subsequent bleeding [9]. Another proposed mechanism is the presence of complement-mediated attack by C5b-C9 on the gastrointestinal tract, which can lead to mucosal

damage and subsequent bleeding [1]. It is also possible that the use of anticoagulation therapy in some patients with aHUS may increase the risk of gastrointestinal bleeding.

The diagnosis of gastrointestinal bleeding in patients with aHUS can be challenging, as the bleeding may be occult or intermittent. However, the presence of hematochezia, melena, or hematemesis in a patient with aHUS should raise suspicion for gastrointestinal bleeding. Laboratory studies should be performed and focus on the severity of thrombocytopenia and anemia. Imaging studies such as computed tomography (CT) scans, magnetic resonance imaging (MRI), and endoscopy may be necessary to identify the source of bleeding.

Inflammatory bowel disease

Atypical hemolytic uremic syndrome (aHUS) and inflammatory bowel disease (IBD) are two distinct medical conditions that can sometimes be associated with each other [1,4,10]. IBD is a group of chronic inflammatory conditions that affect the digestive system, including Crohn's disease and ulcerative colitis. The co-occurrence of aHUS and IBD has been reported in some patients. Several case reports and small case series have described the co-occurrence of aHUS and IBD. In a study of 24 patients with aHUS, 5 (20.8%) had a history of IBD, and in 3 of these patients, the onset of aHUS was preceded by the onset of IBD symptoms [1]. Another study of 54 aHUS patients reported that 3 (5.6%) had a history of IBD [4]. The prevalence of IBD in the general population is estimated to be around 0.3 - 0.5% [10], suggesting that the co-occurrence of aHUS and IBD is higher than would be expected by chance alone.

The association between aHUS and IBD is not well understood, but several hypotheses have been proposed. It is thought that invasive Escherichia coli is responsible for the development of inflammatory bowel disease [11]**.** The abnormal activation of the complement system in aHUS may also contribute to the inflammation seen in IBD [11]. Studies have shown that complement activation is increased in the intestinal mucosa of patients with IBD, and this activation is thought to contribute to the tissue damage and inflammation seen in the disease [11-14].

A recent study documented that gastrointestinal features were more frequently observed in patients with Shiga toxin-producing *Escherichia coli* (STEC-HUS), which is seen in over 90% of children [11]. The most serious manifestation was hemorrhagic colitis with transverse colon as well as the ascending colon being the most common sites. Bowel necrosis leading to perforation and stricture formation were all reported [13,14]. These features are seen in Ulcerative Colitis (UC) and Chron's Disease (CD), respectively. It is critically important to mention that intestinal biopsies were negative for UC or CD providing evidence that the clinical features were due to STEC-HUS and not the UC or CD per se. In some cases, toxic megacolon requiring surgical intervention has also been observed [11]. Finally, peritonitis and intussusception are also found in children presenting with STEC-HUS [11,13,14].

In patients with aHUS, the gastrointestinal involvement is less frequent than STEC-HUS. Vomiting, diarrhea, abdominal pain and peritonitis are clinical features commonly seen in aHUS patients with diarrhea dominating the clinical features. Recent data have emphasized that intestinal complications are more common in patients presenting with antibodies against factor H [11]. Whether it is aHUS or STEC-HUS, patients presenting with severe gastrointestinal complications have worse kidney outcome [15].

Pancreas, liver and the gallbladder

Hemolytic uremic syndrome can have a negative impact on pancreas, liver and the gallbladder.

Studies have shown that the presence of genetic mutations in the complement system, which is involved in the regulation of inflammation, is a major contributor to the development of aHUS [1]. These mutations can lead to overactivity of the complement system, resulting in excessive formation of microthrombi and increased damage to the pancreas, liver, and gallbladder [16]. In addition to the formation of microthrombi and inflammation, aHUS can also result in oxidative stress and cellular damage in the pancreas. Oxidative stress occurs when there is an imbalance between the production of free radicals and the ability of the body to detoxify them. Free radicals can cause

damage the pancreas, leading to further deterioration of function. Finally, ischemic insult due to microvascular thrombi can lead to necrosis of the pancreas.

While acute pancreatitis can serve as a trigger for the development of aHUS, normal function of the pancreas can be compromised following an episode of aHUS leading to the development of pancreatitis [17,18]**.** One report demonstrated extensive deposition of C5b-C9 deposition in pancreatic endothelial cells and microthrombi providing evidence of the endothelial injury inflicted complement system activation [19]. In severe cases pancreatic injury can be potentially life-threatening.

The liver and gallbladder can also suffer injury following the development of aHUS. The most common liver dysfunction findings are transaminitis and hepatitis [20]. Similarly, cholestasis and cholelithiasis are the most common complications in patients with aHUS [21]. The liver and gallbladder complications can be seen in approximately 8% of the patients [21].

Given the rarity of both aHUS and pancreatitis, more research is needed to confirm these findings and to understand the precise mechanisms underlying the relationship between these conditions. Further studies should also focus on developing new diagnostic and therapeutic strategies for patients with aHUS and pancreatitis, to help improve their prognosis and quality of life.

Conclusion

Only recently have we begun to understand the multisystem involvement in patients with aHUS. While diarrhea has been thought to be the predominant clinical feature, inflammatory bowel disease, bowel perforation, hepatitis, pancreatitis are all possibilities in patients presenting with aHUS. Gastrointestinal complications are common and have a significant impact on morbidity and mortality. Their prompt diagnosis and timely intervention is critically important to achieve best outcomes. While supportive therapy including correction of anemia, electrolyte imbalance and maintenance of adequate volume for tissue perfusion is important, specific treatment with the monoclonal antibody eculizumab may be required to achieve blockade of complement system to minimize further damage.

Conflict of Interest

None.

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