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Pathogenesis and prognosis of thrombotic microangiopathy

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Abstract

Thrombotic microangiopathy (TMA) is a clinicopathological syndrome characterized by thrombosis formation in the microvasculature of various organs. Included in the broad category of TMA are the hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). Typical HUS is caused by Escherichia coli O157:H7, which produces the Shiga-like toxins; Stx-1 and Stx-2. In addition to damaging endothelial cells via the inhibition of protein synthesis, Shiga-like toxins also activate endothelial cells to produce inflammatory mediators, amplifying the prothrombotic state. Although most patients with typical HUS recover renal functions, recent analysis has shown that typical HUS is not a benign disease in the long term. Genetic abnormalities of complement regulatory proteins predispose patients to atypical HUS. Mutations in factor H, membrane cofactor protein, and factor I are known to be associated with atypical HUS. Atypical HUS forms have a poor outcome and show recurrent and progressive courses. Autoimmune IgG inhibitors of a disintegrin and metalloprotease, with thrombospondin-1-like domains (ADAMTS) 13 and mutations of the ADAMTS13 gene lead to the development of TTP. Without treatment, TTP is associated with a very high mortality rate. As it is for atypical HUS, plasma exchange is currently the most feasible treatment for TTP. Etiological diagnosis at the bedside and the development of disease-specific therapeutic modalities will enable us to optimize the management of patients with TMA and improve their prognosis in the future.

Key words Thrombotic microangiopathy (TMA) · Hemolytic uremic syndrome (HUS) · Thrombotic thrombocytopenic purpura (TTP)

Introduction

The term “thrombotic microangiopathy (TMA)” defines a clinicopathological syndrome consisting of intraluminal platelet thrombosis in the microvasculature of various organs and the presence of fragmented red blood cells and thrombocytopenia in the peripheral blood.

The broad category of TMA includes the hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), which are clinically different but show similar morphologic pictures.1–3 When neurological abnormalities are dominant and renal function is normal, the disorder is considered to represent TTP. When acute renal failure is dominant and neurological abnormalities are minimal, the disorder is considered by some to represent HUS. Other disorders, such as complications with transplantations and lupus, may occasionally present with features of TMA. Based on new concepts of causation, a novel classification of TMA was recently proposed.4 The classification consists of two sections: part 1, in which concepts of etiology are reasonably advanced, and part 2, where clinical associations are used to describe patients for whom the cause remains unclear (Table 1).

Diagnosis of HUS and TTP

HUS is a disease characterized by nonimmune (Coombs negative) hemolytic anemia, low platelet count, and renal impairment. The anemia is microangiopathic in nature, with fragmented red blood cells. The level of serum lactate dehydrogenase, largely derived from ischemic or necrotic tissue cells rather than from lysed red cells, is elevated.

The most common form of HUS, typical HUS, develops in children and accounts for 90% of all cases. It usually occurs after a prodromal episode of diarrhea and is also referred to as D+ (diarrhea+) HUS. In D+HUS patients, abdominal cramps typically develop after an incubation period of 1–7 days, followed by nonbloody diarrhea.5
The diarrhea becomes bloody 1–3 days later. Complications of HUS appear 2–14 days after the onset of diarrhea. Fecal shedding of pathogenic Escherichia coli may persist for up to 2 months and person-to-person transmission can occur.

Atypical HUS is a heterogeneous disorder distinguished by the absence of diarrhea or Shiga toxin-producing E. coli infection. This disorder is also referred to as D-HUS. Other characteristic features of atypical HUS include an insidious onset and a relapsing or progressive course leading to severe renal dysfunction.

TTP is a more uncommon disorder that presents abruptly with the development of von Willebrand factor (VWF) and platelet-rich thrombi in the arterioles and capillaries of vital organs such as the brain. The pentad of signs and symptoms of TTP are thrombocytopenia, microangiopathic hemolytic anemia, neurological abnormalities, renal failure, and fever. Neurological abnormalities include confusion, focal neurological deficits, and seizures. In actual practice, however, the triad of thrombocytopenia, schistocytosis, and elevated lactate dehydrogenase levels is often sufficient to suggest the disorder.

As TTP overlaps with HUS in the severity of renal dysfunctions or neurological abnormalities, a disintegrin and metalloprotease, with thrombospondin-1-like domains (ADAMTS) 13 analysis may be needed to exclude the diagnosis of TTP in suspected cases. Details of ADAMTS13 are described below.

### Role of Shiga-like toxins (Stx) in HUS

In children, HUS is most commonly triggered by toxin-producing E. coli and manifests with bloody diarrhea (D+HUS). More than 20 years ago, Riley and co-workers described two clusters of patients with painful bloody diarrhea, linked by the common consumption of undercooked hamburgers; many of the patients in these clusters had E. coli with a rare serotype (O157:H7) in their stools. Subsequent studies of endemic and sporadic cases, including a massive outbreak of E. coli O157:H7 infections caused by the consumption of poorly cooked ground beef at outlets of a fast-food restaurant chain in the United States and several large outbreaks affecting more than 9000 people and causing 11 deaths in Japan, confirmed that most cases of Stx-HUS are secondary to infection with the E. coli serotype O157: H7.

Pathogenicity is conferred by bacteriophages encoding Stx that are cytotoxic to Vero cells. There are two main classes of Shiga-like toxins (Shiga-toxins or verotoxins); Stx-1 (STL1, VT1) and Stx-2 (STL2, VT2). Stx-1 is almost identical to Stx from Shigella dysenteriae type 1, differing...