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Review

What is the evidence for the role of therapeutic apheresis in the management of complement-associated thrombotic microangiopathies?

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ABSTRACT

Thrombotic microangiopathies (TMAs) are disorders characterized by endothelial cell activation, microangiopathic hemolytic anemia, thrombocytopenia and organ failure of variable intensity. The pathophysiology of various types of TMAs have become an interesting field of study. Alternative complement system activation plays an important role in several pathophysiological conditions. Complement activation is also described in an increasing number of TMAs. Inherited defects in complement regulatory genes and acquired autoantibodies against complement regulatory proteins have been described. Atypical hemolytic uremic synrome (HUS) is caused by uncontrolled activation of the alternative complement system, now called complement-mediated TMAs. Recently, application of a monoclonal antibody that specifically binds to C5 became available to treat patients with complement-mediated TMAs. Eculizumab is a humanized monoclonal antibody that blocks complement C5 activation. Empiric therapeutic apheresis is also recommended in all forms of complement-mediated TMAs. The justification for therapeutic apheresis use in all forms of complement-mediated TMAs is that it can effectively remove the autoantibodies or mutated circulating complement regulators while replacing absent or defective complement regulators. Currently, therapeutic apheresis and eculizumab are the available treatment options for complement-mediated TMAs. In this paper, we review the evidence for the role of therapeutic apheresis in the management of complement-associated TMAs.

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1. Introduction

Thrombotic microangiopathies (often abbreviated as TMAs) are rare but potentially life-threatening conditions. TMAs comprise a heterogeneous set of conditions and can be presented in a wide clinical spectrum. They may be hereditary or acquired [1]. They may occur in pediatric age group or in adults [2].

TMAs are pathological processes characterized by endothelial injury and platelet-rich thrombi formation in microvasculature, leading to microangiopathic hemolytic anemia, consumptive thrombocytopenia, and end-organ ischemic damages [3]. Endothelial damage and thrombosis within the microvasculature create

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abnormally high shear stress, leading to thrombocyte aggregation and red blood cell destruction.

The presence of schistocytes (fragmented red blood cells) on the peripheral blood smear suggests red blood cell injury from damaged endothelium and is a characteristic feature of TMAs [4]. Elevated serum lactate dehydrogenase (LDH), hyperbilirubinaemia (unconjugated), elevated reticulocyte count and low serum haptoglobin level reflect haemolysis and/or tissue ischaemia and are useful both diagnostically and in monitoring disease activity [5].

Our knowledge of the pathogenesis of TMAs has greatly advanced in recent years, improving the diagnosis and treatment. Prognosis and treatment depend on the nature of the underlying disease. The immediate recognition and categorization of TMAs by both clinical presentation and pathophysiologic mechanisms should become uniform as they are very important to an ideal treatment plan. The differential diagnosis of TMAs is complex and uneasy, the patients tend to be very sick, and effective treatment requires providing therapy directed at the underlying pathology as quickly as possible.

TMAs are multisystem disorders and often present with prominent renal and neurologic involvement [6]. Endothelial injury is likely the encouraging factor leading to thrombosis in the kidney and in many other organs. The histopathologic features are similar in all the causes of TMAs. Kidney biopsy reveals thrombi in the glomeruli and arterioles [7]. The causes or precipitating factors of TMAs include [8]:

- Shiga toxin
- Abnormal complement activation (genetic or acquired)
- ADAMTS13 deficiency (genetic or acquired)
- Drugs
- Coagulopathies (cobalamin C deficiency, diacylglycerol kinase epsilon, plasminogen and thrombomodulin mutations)
- Infections (human immunodeficiency virus, *streptococcus pneumoniae*)
- Malignancies
- Kidney and stem cell transplantation
- Rheumatologic diseases (scleroderma, systemic lupus erythematosus, vasculitis and antiphospholipid syndrome)
- Malignant hypertension
- Pregnancy

As mentioned above, there are many conditions that can be related with TMAs. The most frequent causes of TMAs are thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) and atypical hemolytic uremic syndrome (atypical HUS) [9].

1.1. Thrombotic thrombocytopenic purpura

TTP was initially described by Elie Moschcowitz in 1924 in a young woman with hyaline thrombi and a rapidly progressive febrile illness [10]. TTP is characterized by clinical symptoms with fever, thrombocytopenia and microangiopathic hemolytic anemia accompanied by multi-organ failure. TTP often manifests as acute kidney injury (AKI) and mental status changes which results from a severe defect in ADAMTS13 [11].

ADAMTS13 is a plasma enzyme specifically involved in the cleavage of highly hemostatic unusually large von Willebrand factor (VWF) multimers into smaller and less adhesive VWF forms [12]. Failure to degrade these unusually large VWF multimers leads to excessive thrombocyte aggregates and microvasculature occlusion.

ADAMTS13 deficiency results from mutations in hereditary TTP, whereas in acquired forms it results from autoantibodies that alter the protein function [13]. The most common form of TTP is an acquired disorder that is seen in adulthood associated with autoantibodies directed against ADAMTS13. Pathogenic antibodies that have been identified are typically directed against the cysteine-rich/spacer domain of ADAMTS13 [14]. The hereditary deficiency of ADAMTS13, known as the Upshaw-Shulman syndrome, often presents in infancy or childhood and may recur as chronic relapsing TTP. Over 70 genetic mutations of the ADAMTS13 gene on chromosome 9q34 have been identified [15].

Although the ADAMTS13 analysis is important for diagnosing TTP, in suspected cases therapeutic plasma exchange should be started urgently until the laboratory test results return. Therapeutic apheresis removes autoantibodies to ADAMTS13 from the blood, removes circulating large VWF multimers and replaces the missing ADAMTS13. Untreated, TTP is progressive with irreversible AKI, neurologic deterioration and high mortality rate. Therapeutic apheresis has been shown in clinical trials to be superior to plasma infusion in normalizing thrombocyte counts and reducing mortality [16].

Patients who have a relapse and whose disease is refractory to therapeutic apheresis have been treated with corticosteroids, splenectomy or immunosuppressive agents (cyclophosphamide, cyclosporine or azathioprine) [17]. Rituximab (a monoclonal antibody directed to CD20 molecules expressed on the surfaces of pre-B and mature B lymphocytes) has recently been used as second-line therapy in refractory or relapsing immune-mediated TTP or idiopathic TTP [18]. Other potential treatment modalities including recombinant active ADAMTS13 are under investigation [19].

1.2. Hemolytic uremic syndrome

HUS (also called typical HUS or STEC-HUS) is characterized prominently by a AKI. In most cases, HUS is caused by enterohemorrhagic *Escherichia coli* strains that produce Shiga toxin leading to endothelial and glomerular damage [20]. HUS is associated with a gastrointestinal infection (diarrhea) with Shiga toxin-producing *Escherichia coli* (STEC) infection [21].

The process of pathogenesis in HUS is apparently initiated when the Shiga toxin, a known potent cytotoxin, binds to cell membrane glycolipid Gb3 [22]. It is internalized and subsequently halts protein synthesis and induces apoptosis of the affected cell. The Shiga toxin has several additional effects on endothelial cells, one of which is enhanced expression of functional tissue factor that could contribute to microvascular thrombosis. The toxin causes damage to or activation of endothelium, red blood cells and thrombocytes. The main reason why gastrointestinal infection particularly affects kidneys is thought to be the tissue tropism of Shiga toxin on the basis of the strong expression of Gb3 on the glomerular endothelium [23].

The impact of complement in the pathogenesis of HUS is still uncertain. Complement activation may also contribute to pathogenesis in some patients with HUS either by regulation defects or by triggers that lead to enhanced complement activation.

Treatment of HUS is usually supportive (volume resuscitation, parenteral nutrition) with renal replacement therapy (dialysis) and red blood cell transfusions as needed. Unlike TTP, therapeutic apheresis is not indicated and the prognosis is usually favorable [24]. In addition to basic supportive care, multiple treatment modalities ranging from anti-thrombotic agents, tissue-type plasminogen activators, Shiga toxin binding agents and eculizumab (humanized monoclonal antibody that blocks complement C5 activation) have been studied in the management of HUS [25]. These therapies are not shown to be effective in HUS and there is a dire need to continue research and randomized controlled trials to find better treatment options [26].

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