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REVIEW

Diagnosis and management of complement mediated thrombotic microangiopathies

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ABSTRACT

Historically, attempts were made to differentiate acquired thrombotic thrombocytopenic purpura (TTP) from atypical hemolytic uremic syndrome (aHUS) based upon the age at presentation and the presence of neurologic or renal injury. Although these means of differentiating acquired TTP from aHUS have now been demonstrated to be inaccurate, there were no clinical consequences as the treatment for both disorders remained plasma exchange therapy (PEX). With the regulatory approval and remarkable efficacy of eculizumab (Soliris) for the treatment of aHUS, the accurate and timely differentiation of acquired TTP from aHUS now has real clinical consequences. In the following review we will address the emerging methods of clinically differentiating acquired TTP from aHUS using collectively their clinical presentation, laboratory data, and initial response to PEX therapy to differentiate patients more consistent with a diagnosis of aHUS, and therefore more likely to benefit from complement inhibition therapy.

1. Introduction

While the clinical dilemma regarding the accurate differentiation of thrombotic thrombocytopenic purpura (TTP) from atypical hemolytic uremic syndrome (aHUS) has been present for decades, it has only been recently that the answer to this question has real and significant clinical consequences. With the regulatory approval of eculizumab (Soliris) by the United States Food and Drug Administration and the European Medicines Agency for the treatment of aHUS and its remarkable efficacy [1], there are very real clinical consequences that depend on both the accurate and timely differentiation of aHUS from TTP.

The clinical differentiation of these disorders is challenging in part due to their overlapping clinical presentations. Both disorders share common clinical findings at presentation including thrombocytopenia, microangiopathic changes in the peripheral blood, and the potential for widespread end organ injury. This may be related to the fact that both disorders share common clinical endpoints, the development of microvascular thrombosis and end organ injury, despite their distinct underlying pathophysiologies. The pathophysiology of acquired TTP is based upon the development of severely deficient ADAMTS13 activity (<10%) due to an autoantibody inhibitor of the ADAMTS13 protease. The function of the ADAMTS13 protease is to cleave ultra-large von Willebrand factor (ULVWF) multimers under conditions of high shear stress to the more physiologic-sized multimers. In the context of severely deficient ADAMTS13 activity, these ULVWF multimers may spontaneously aggregate platelets resulting in the formation of microthrombotic disease and the characteristic clinical features of TTP. In contrast, aHUS is a disorder of complement dysregulation that can arise in patients with mutations of specific complement control proteins (*Factor H*, *Factor I*, *MCP*, and *THBD*), gain of function mutations that renders *C3* and *Factor B* less susceptible to inactivation, or auto antibodies that develop against specific complement components such as Factor H [2–4]. It is this resulting uncontrolled complement activation that can lead to the activation of platelets and leukocytes and microvascular endothelial injury that collectively may result in widespread microthrombotic disease and the clinical phenotype of aHUS.

2. Recent data and the importance of differentiating aHUS from acquired TTP

Historically the discussion regarding the clinical differentiation of aHUS from TTP had no clinical significance, as the treatment for both disorders was plasma exchange therapy (PEX). It must be emphasized that both aHUS and TTP are clinical diagnoses that rely on the collective clinical and laboratory findings and the exclusion of other potential diagnoses rather than one objective diagnostic test. The lack of objective diagnostic criteria with which to differentiate acquired TTP from aHUS has confounded efforts to accurately characterize the true response rates of aHUS patients to PEX [5–11]. This has resulted in differing efficacy rates and conflicting data regarding the use of plasma-based therapy for the treatment of aHUS. With the exception of aHUS patients

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with *MCP* mutations whose prognosis is quite good, the long-term outcome for aHUS patients treated with plasma-based therapy is poor, with up to 65% of patients progressing to end stage renal disease or death with the first year after diagnosis [12].

In the context of these historical data, the recently published data from Legendre et al. regarding the efficacy of eculizumab for the treatment of aHUS al have led to a renewed focus on the accurate and rapid differentiation of aHUS from TTP [1]. These data from Legendre et al. reported together the results of two prospective studies involving adults and adolescents (age 12 or older) with a clinical diagnosis of aHUS (microangiopathic hemolytic anemia and impaired renal function). The first trial (n = 17) enrolled patients with a progressive thrombotic microangiopathy (TMA) despite PEX, while the second trial (n = 20) enrolled patients who were responding to and being maintained on long-term PEX [1]. The primary endpoint of the first study was an improvement in the platelet count (surrogate for inhibition of the TMA) and the primary of the second study was TMA event-free status (platelet count increase >25%, no PEX or infusion, no new initiation of hemodialysis), and the normalization of hematologic parameters (platelet count and LDH) that were sustained for at least 4 weeks. In trial 1, all 13 patients with a low platelet count at baseline who were treated with eculizumab for at least 26 weeks had a normalization of the platelet count. More importantly, there was a time-dependent increase in the estimated GFR from baseline to week 26, with 4/5 (80%) of dialysis dependent patients at initiation of the study becoming independent of the need for hemodialysis. In trial 2, 80% of patients achieved TMA event-free status with 90% of patients normalizing their hematologic parameters.

Data was also reported regarding the relationship of the time to initiate therapy and the improvement in renal function. In both trials, there was a relationship between the time to initiate therapy with eculizumab and the improvement in the estimated GFR with the earlier initiation of therapy associated with a greater improvement in the estimated GFR. These data suggest that the timely diagnosis of aHUS and initiation of therapy with eculizumab is a clinically significant issue with real consequences in terms of clinical outcomes for patients. Similar to concerns regarding the failure to promptly initiate PEX in a patient with a clinical diagnosis of TTP, physicians should be equally concerned about the failure to initiate therapy with eculizumab in a patient with a diagnosis of aHUS. Again, the difficulty lies in the accurate clinical differentiation of aHUS from TTP, conditions that may present similarly despite being clinically distinct diseases with different approaches to therapy.

3. Historical approaches to the differentiation of aHUS from TTP

Historic approaches to the diagnosis and differentiation of aHUS from TTP have relied heavily on the age of presentation and the presence or absence of clinical findings at the time of the patient's initial clinical presentation. It was also commonly thought that aHUS was a pediatric disorder that only rarely if ever affected adults. This has been contradicted by case reports [13,14] and a series of adults diagnosed with aHUS [15] where the diagnoses were made clinically and confirmed in most cases with complement mutation studies. Additionally, in the two prospective studies of eculizumab for the treatment of aHUS the median age was 28 years across both studies for the 37 subjects enrolled. Along the same lines, it was incorrectly thought that neurologic involvement at presentation pointed to a diagnosis of acquired TTP as neurologic injury was not thought to be a feature of aHUS. It is now recognized that presenting clinical symptoms cannot be used to differentiated aHUS and TTP from other TMA [16,17].

While it is not possible to differentiate aHUS from acquired TTP on the basis of clinical symptoms alone, there are specific clinical scenarios that should raise suspicion for the diagnosis of aHUS. These clinical scenarios may be thought of as events that can lead to complement activation, but in the context of a patient with the inability to downregulate complement activation, these events may initiate an acute TMA episode. In patients with the development of an acute TMA post kidney transplantation in the absence of other potential etiologies (acute and chronic rejection, cyclosporine toxicity), the diagnosis of aHUS should be strongly considered given that 50% of patients with a diagnosis of aHUS may suffer a recurrence of their acute TMA after undergoing kidney transplantation [18,19]. The development of a post-partum TMA should also prompt consideration of aHUS as a diagnosis given that the post-partum state is associated with the development of aHUS [2,12]. Malignant hypertension is also a well-known potential cause of TMA findings in the peripheral blood and renal insufficiency, but it can also be a clinical feature of aHUS [20]. In cases where uncontrolled hypertension is felt to be the etiology of the microangiopathic findings, progressive end organ injury and persistent hematologic abnormalities despite the control of the blood pressure should raise the question of an underlying diagnosis of aHUS as the cause of both the hypertension and the TMA findings.

4. Clinical symptoms and the differentiation of aHUS and TTP

4.1. Neurologic injury and the differentiation of aHUS and TTP

Neurologic injury is a common finding at presentation in patients with TTP and has historically been used as a criterion in studies to differentiate acquired TTP from aHUS. In patients with a diagnosis of acquired TTP with severely deficient ADAMTS13 activity, neurologic injury has been reported in 25%–79% of patients at presentation [21–25]. While there may be some subjectivity in the specific definitions and study methodologies that could result in differing rates of neurologic injury, these data do support the hypothesis that neurologic injury is a common finding in patients with acquired TTP. However, Coppo et al. recently reported on behalf of the French TMA registry data that the rates of CNS injury in TMA patients were not significantly different between ADAMTS13 deficient and non-deficient patients. The finding of non-deficient ADAMTS13 activity in the context of microangiopathic findings in the peripheral blood is not diagnostic of aHUS, but it is reasonable to hypothesize that this cohort of patients would be enriched for the diagnosis of aHUS. With this assumption, these data would suggest that rates of neurologic injury are not significantly different in TTP patients versus TMAs caused by other etiologies including aHUS [26].

Renal injury is remains the most involved end organ in aHUS patients at presentation, but extrarenal involvement, including neurologic injury can been seen in 10–30% of patients [27,28]. A better understanding of aHUS as a disorder of complement dysregulation, coupled with the ability to more easily obtain complement mutation studies to provide confirmation of the clinical diagnosis of aHUS have provided support for the hypothesis that neurologic injury can be seen in patients with aHUS. Indeed, recent case reports have demonstrated that profound neurologic injury may be seen in patients with a clinical diagnosis of aHUS confirmed by documented mutations of complement regulatory proteins [14,29,30]. In one more striking case treated at our institution, Salem et al. described a 66 year-old female with a clinical diagnosis of aHUS based upon the finding of an acute TMA and non-deficient ADAMTS13 activity, in the context of renal failure progressive neurologic injury in the face of PEX therapy. The diagnosis of aHUS was supported by the documentation of a mutation of *C3* and the subsequent recovery after therapy with eculizumab [14]. Given these data, the presence of neurologic injury should not be viewed as a finding that can accurately differentiate aHUS from acquired TTP.

4.2. Renal injury and the differentiation of aHUS and TTP

Analogous to the to the use of neurologic injury to define acquired TTP, renal failure requiring hemodialysis has been considered a diagnostic criteria to differentiate aHUS. While renal failure requiring hemodialysis is a prominent finding in aHUS [2], renal injury severe enough to require hemodialysis may be seen in patients with a diagnosis of TTP and severely deficient ADAMTS13 activity. In the report by Hovinga