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Atypical Hemolytic Uremic Syndrome (aHUS): Making the Diagnosis

Plus: A Review of Case Studies

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Atypical Hemolytic Uremic Syndrome (aHUS): Making the Diagnosis

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Abstract: Atypical hemolytic uremic syndrome (aHUS) is a major thrombotic microangiopathy (TMA). A TMA is recognized by the laboratory signs of microangiopathic hemolysis, as indicated by schistocytes, elevated lactate dehydrogenase, low haptoglobin, and low hemoglobin, plus thrombocytopenia and accompanying signs and symptoms of organ system involvement. aHUS results from chronic, uncontrolled activity of the alternative complement pathway. In most patients, this defect is related to a genetic deficiency in one or more soluble and/or membrane-bound complement regulatory proteins. Complement factor H is most frequently implicated. Clinically, aHUS is often indistinguishable from the other TMAs: Shiga toxin–producing *Escherichia coli* (STEC) hemolytic uremic syndrome and thrombotic thrombocytopenic purpura (TTP). TTP and aHUS are associated with high morbidity and mortality. aHUS has a distinct pathology from TTP. In nearly all patients, aHUS can be distinguished from TTP on the basis of an ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) enzyme activity measurement. It is essential that aHUS and TTP be differentiated quickly, as they require markedly divergent treatments. The standard treatment for TTP is plasma exchange, a therapy that has no role for patients with a diagnosis of aHUS established by ADAMTS13 activity levels.

Introduction

Since the initial descriptions of the 2 principle categories of systemic microvascular clotting disorders—thrombotic thrombocytopenic purpura (TTP) by Moschcowitz[1] in 1924 and hemolytic uremic syndrome (HUS) by Gasser in 1955[2]—there have been but a handful of critical diagnostic and therapeutic breakthroughs. Each of these key discoveries, however, has dramatically altered the course of TTP and HUS. First, there was identification of the utility of plasma exchange (PE) in the treatment of TTP. This was followed by isolation of Shiga toxin–producing *Escherichia coli* (STEC) as the etiologic agent of many cases of diarrhea-associated [D+] HUS, now known as STEC-HUS. More recently, the means to distinguish between TTP and "atypical" (a)-HUS, using assays for a specific protease activity, was reported (the latter formerly grouped into a heterogeneous syndrome referred to as non–diarrhea-associated [D-] HUS). Finally, genetic defects in regulation of the alternative complement pathway have been uncovered in aHUS, leading to an effective treatment for that disorder. This review focuses on aHUS, a rare, chronic, life-threatening, systemic disease. Frequently unrecognized, it has a high

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degree of morbidity and mortality within the first year of presentation unless appropriately treated.

The three conditions noted above—TTP, STEC-HUS, and aHUS—are collectively referred to as the major thrombotic microangiopathies (TMAs). Clinically, they are often indistinguishable.[3] Indeed, the distinction between TTP and HUS had been vague from the outset: Gasser included a case of "Moschowitz's disease" in his HUS series, and HUS was originally referred to as "TTP of children."[4]

The fact that the TMAs are rare is a further impediment to an accurate diagnosis. Yet the high morbidity and mortality associated with TTP and aHUS, and the markedly divergent treatments they require, mandate swift recognition of a TMA, as well as the ability to distinguish the two conditions. This review highlights the differences in pathophysiologic and diagnostic criteria among TMA subtypes. An article appearing on pages 9–11 of this supplement examines case studies to elucidate important diagnostic issues in patients with aHUS.

Incidence of the Major Thrombotic Microangiopathies

The annual incidence of STEC-HUS is about 2 per 100,000 in adults and 6.1 per 100,000 in children younger than 5 years.[5] The incidence of aHUS is thought to be much lower, about 2 per million for adults and 3.3 per million in children younger than 18 years.[6] The latter aHUS figures are similar to those recorded for TTP in the general US population. But the reported frequency of the TMAs has varied greatly over the past 3 decades, and the number of adults diagnosed and treated for TTP has risen seven-fold during that period.[7] Why? According to one review, documentation of the efficacy of PE for TTP, leading to a decline in mortality from more than 90% to less than 10%,[8] "created an urgency for diagnosis which has resulted in decreased stringency of diagnostic criteria."[3] In turn, that led to the application of prolonged plasma-infusion based therapies for aHUS, and TMAs erroneously bundled as "TTP/HUS," despite the lack of any controlled trial indicating that such therapy was effective in influencing disease progression or mortality in aHUS.

Distinguishing Among the TMAs: Primary Considerations

Development of both TTP and aHUS appears to require two conditions: (1) pre-existing susceptibility factors, which may be familial (i.e., genetic) or acquired, and are capable of promoting endothelial cell activation, platelet aggregation, or both; and (2) modulating factors, encompassing a variety of conditions that can be infectious, inflammatory, or related to pregnancy, stress, or drugs, and are linked epidemiologically to both TTP and aHUS. The latter would account for the sporadic development of overt clinical signs and symptoms of disease. For example, the first clinical manifestation of familial TTP (Upshaw-Schulman syndrome) may not occur until late in life, and relapses are infrequent. Similarly, the first overt signs of aHUS may not be recognized until adulthood, despite the fact that the genetic predisposition is present at birth. In reality, however, in between the often dramatic episodes of clinically apparent aHUS which are often initiated by heightened activation of the alternative complement pathway by modulating factors, tissue damage continues to occur. This is evidenced by persistent platelet activation and renal injury, as discussed below.

The vast majority of cases of TTP are idiopathic, and disease susceptibility usually results from an autoantibody-mediated deficiency of the von Willebrand factor (vWF) cleaving protease ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). This leads to propagation of platelet aggregates, related to the inability to cleave long tethers of platelets bound to vWF in ultra-high molecular weight multimers, an activity which requires an intact enzyme. The subsequent uncontrolled microthrombus formation is clinically devastating.[9] This acquired condition parallels the susceptibility of individuals with loss of function mutations in ADAMTS13 to development of familial TTP.[10]

By contrast, in the vast majority of aHUS cases, susceptibility factors are familial, not acquired. They are genetic defects in complement and complement regulatory proteins or related factors which, as discussed below, permit uncontrolled amplification of the alternative complement pathway. This potentiates platelet activation, platelet aggregation, and complement-mediated endothelial cell injury throughout the microvasculature.[5,11,12] (These processes may also play a role in some cases of STEC-HUS[13] and in TMAs occurring in the setting of pregnancy, organ and tissue transplantation, autoimmune disease, and malignancy.[14] Those topics are outside the range of this review.)

Given these pathophysiologic differences between aHUS and TTP, one might think that diagnostic criteria for the TMAs would be relatively simple to apply. Often they are, and this is critical clinically, as it will guide treatment decisions. Just as the mortality from TTP declined from more than 90% to less than 10% with institution of appropriate treatment—plasma exchange[8]—outcome is highly unfavorable in aHUS treated with PE. Up to 50% of patients progress to end-stage renal failure within a year, and 25% die during the acute phase.[15]

Four standard initial steps can be used to reach a specific TMA diagnosis:

1. As outlined in Figure 1, a TMA must first be recognized. This involves examining the principle laboratory criteria for microangiopathic hemolysis: schistocytes on peripheral blood smear, low haptoglobin levels, and a

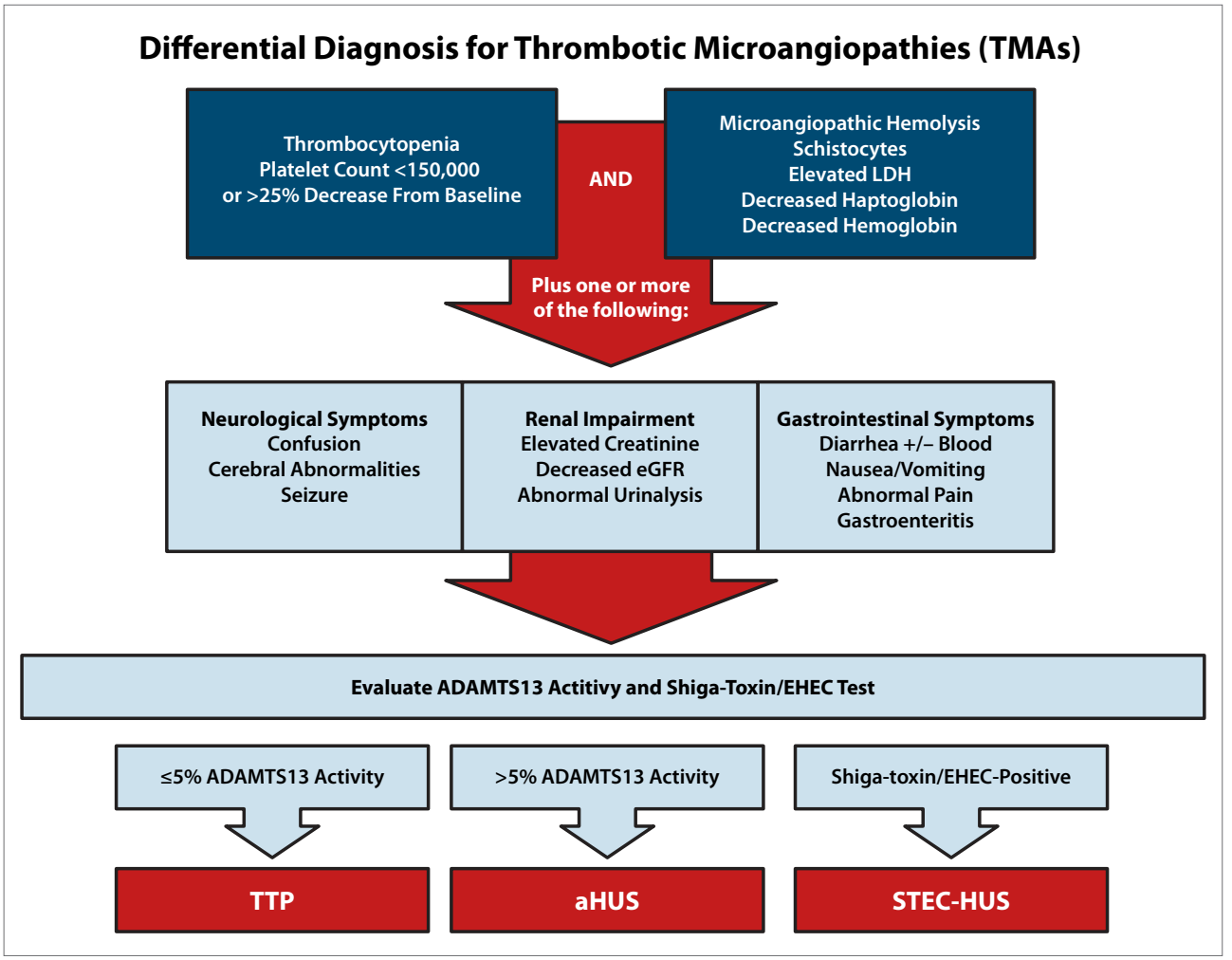

Figure 1. Diagnosis of a thrombotic microangiopathy requires certain laboratory signs coupled with evidence of involvement of at least one organ system. Three such organ systems are illustrated here, but all tissues can be injured, with development of clinical signs related to microthrombosis and ischemia. (The one potential exception is the lung, which is rarely involved in TTP.) In terms of hematologic parameters, thrombocytopenia is characteristically severe in TTP, while in atypical hemolytic uremic syndrome, platelet counts are higher and can be near normal at presentation. ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS=atypical hemolytic uremic syndrome; eGFR=estimated glomerular filtration rate; EHEC=*Escherichia coli*; LDH=lactate dehydrogenase; STEC-HUS=Shiga toxin–producing *Escherichia coli* (STEC) hemolytic uremic syndrome; TTP=thrombotic thrombocytopenic purpura.

decline in baseline hemoglobin. These changes are usually accompanied by thrombocytopenia, although it should be recognized that while severe decreases in platelet counts are typical of TTP, TMAs such as aHUS, characterized by ADAMTS13 levels >5–10% (depending upon the assay used), have significantly higher platelet counts,[16] which can be near normal at first presentation. Schistocytes are the *sine qua non* of a TMA, although they may be infrequent on initial presentation (fewer than 1 per high-power microscopic field). An elevated level of lactate dehydrogenase (LDH)—virtually always higher than 600 IU/L—is also characteristic of a TMA. But though an elevated LDH is often attributed to ongoing hemolysis, LDH levels may be far out of proportion to the degree of red cell destruction evinced by changes in indirect bilirubin and hemoglobin. LDH isoenzyme analysis has shown that a substantial portion of LDH elevation in a TMA is instead due to its release from tissues damaged as a result of microthrombosis-associated systemic ischemia.[17]

2. These laboratory changes must be accompanied by involvement of at least one organ system. Figure 1 lists the three most common sites: neurologic, renal, and gastrointestinal. But both aHUS and TTP can affect any tissue, as microvessel thromboses lead to tissue ischemia and infarction. In some 20% of initial aHUS presentations in children and adults,

renal function is preserved, despite the word "uremic" in the name of the disease.[18] These patients may have some proteinuria and hematuria, but their serum creatinine is in the normal range.[19] Arterial hypertension is also frequent and often severe in later stages of aHUS, due to volume overload in cases of oliguria and to hyperreninemia secondary to renal thrombotic microangiopathy.[18] Proteinuria and hematuria are also common in classic TTP, although acute renal failure at presentation is unusual, affecting less than 5% of patients (4 of 115 individuals with TMA and severe ADAMTS13 deficiency followed in four different studies).[20] The one possible exception to the universality of tissue involvement in the TMAs is the lung, which is virtually never directly involved in TTP, while pulmonary pathology is frequent in untreated aHUS.[21]

3. aHUS and TTP can be distinguished from STEC-HUS by PCR, or culture-based assays for the Shiga-toxin producing *E. coli*, using stool or a rectal swab. Gastrointestinal signs and symptoms cannot be relied upon to distinguish among the TMAs, however. Prodromic diarrhea, particularly bloody diarrhea, had been considered a classic sign of a STEC-HUS, but up to one-third of aHUS cases involve diarrhea, which can be bloody, and it is also not uncommon in TTP.[6] Because of this, the terms D (diarrhea)+ HUS and D- HUS should no longer be used. Indeed, diarrhea—and the infectious pathogens responsible for it—is one of the most potent activators of the alternative complement pathway. It may itself unmask overt clinical manifestations of aHUS, as breaching of intestinal epithelial barriers leads to microbial translocation and a positive feedback loop for complement activation.

4. Finally, in the majority of cases, TTP typically responsive to PE can be distinguished from aHUS, for which plasma therapy does not have a role, on the basis of ADAMTS13 activity levels. The utility of ADAMTS13 testing is detailed below. In most settings, it takes from 48 hours to 1 week to obtain results from the tests, which are generally performed by only specialty laboratories.

Distinguishing Between aHUS and TTP: Additional Considerations

A new patient presenting with laboratory and clinical signs of a TMA, as recognized by fulfilling the criteria in the first two rows of the algorithm of Figure 1, is usually begun on plasma therapy. Plasma exchange rather than plasma infusion is the initial standard of care for an undifferentiated TMA.[8] If an apheresis station is not immediately available, and renal function permits, fresh frozen plasma infusions may instead be initiated, awaiting eventual pheresis. In cases involving diarrhea, the possibility of STEC-HUS should be ruled out, which takes less than a day.

PE is continued pending ADAMTS13 activity results. Blood for such testing must be drawn prior to initiating plasma therapy. Based on those results, there are three possibilities; two are straight-forward and one is more complex:

1. If the ADAMTS13 activity is less than 5% of normal control levels by the most commonly available fluorescence resonance energy transfer (FRET)-based assays (or <10% in some gel-based assays), the diagnosis is TTP.[22] In this case, PE should be continued. In addition, acquired inhibitors of ADAMTS13, usually immunoglobulin G autoantibodies, are detectable in 80–90% of TTP patients with severe ADAMTS13 deficiency.[22] If, after 1–3 treatments, each representing replacement of 1–1.5 plasma volumes, there are only minor responses in laboratory and clinical parameters—the meaning of "response" is discussed below—other treatment modalities shown to be effective in recalcitrant TTP, and involving various immune suppressive protocols, should be considered.

2. If the ADAMTS13 activity is >5–10%, depending on the assay used, the diagnosis is aHUS.[22] PE should be stopped, and specific, complement-based treatment instituted. Complement-based assays have been used by some groups in an attempt to confirm the diagnosis of aHUS, but they have no relationship to treatment response and, as discussed below, are often of little utility.

3. But what if an ADAMTS13 assay was not initially drawn, and the patient has now had multiple cycles of PE, rendering suspect any subsequent ADAMTS13 determination? This is an important consideration, as the major effect of PE in TTP is thought to be restoration of a functional ADAMTS13 enzyme and, after several cycles of PE, the patient will have exogenous enzyme, which represents replenishment from donor plasma. Secondly, what if the treating physician believes that the diagnosis of TTP is firm, despite ADAMTS13 levels in the normal range, based on his or her interpretation of certain published studies? That is, in one large series, ADAMTS13 activity of less than 5% was seen in only 33% of patients with "idiopathic TTP."[9] A parallel study was a bit clearer, but it was not absolute: 29% of patients diagnosed as having idiopathic or secondary TTP, responsive to PE, did not have an ADAMTS13 deficiency.[23] This issue is confounded by the fact that it cannot always be established that ADAMTS13 levels were obtained prior to initiation of plasma therapy. In addition, misdiagnosis may be common amongst individuals labeled as having "TTP" but who have an ADAMTS13 activity >10%, as we have discovered searching for complement regulatory protein mutations in archived samples from such TMA cases only partially responsive to PE (unpublished observations). More problematic, and in apparent support of the contention, by some, that diagnosis dependent upon an ADAMTS13 level alone may not be definitive, are instances in which the patient appears to be responding to

PE, at least in terms of some laboratory and/or clinical parameters. Where does one go from here?

An additional source of delay in diagnosis may be failure to consider that a variety of other disorders, particularly autoimmune diseases such as systemic lupus erythematosus (SLE) and malignant hypertension, can present with signs and symptoms similar to aHUS or TTP. In turn, aHUS and TTP can co-exist with SLE and related conditions.[19] Unless a primary TMA is considered, and appropriate diagnostic procedures undertaken, accurate treatment decisions will not be made.

These are critical considerations. In the majority of cases, delays in confirming a diagnosis of aHUS and institution of effective therapy result in the need for renal dialysis or renal transplantation, or in death within a year.[15] Laboratory evidence for ongoing disease in aHUS despite intensive plasma therapy has been well documented, and includes progressive decline in the glomerular filtration rate and continued platelet activation.[24]

Defining a Response to Plasma Exchange in the Context of Distinguishing aHUS From TTP

As a general rule, response in the context of idiopathic TTP involves improvement or complete correction in the TMA parameters of Table 1.[25] If a plasma taper or 2 plasma exchanges are completed after normalization of these measures, and the patient remains off PE for at least 1 month, a "complete response" has been achieved. TMA recurrence beyond a month is considered a relapse in TTP. Recurrence within 1 month is evidence of inadequate treatment.

Response may also be defined in terms of the amount of plasma required. The first randomized study of PE versus plasma infusion in TTP, defined clinically and without the benefit of ADAMTS13 testing, demonstrated the superiority of PE over plasma infusion.[8] Forty-seven percent of those receiving PE had a complete response after the first cycle, which involved an average of 21.5 ± 7.8 liters of fresh frozen plasma exchanged over 9 days. In an additional 31% of patients, 1 or 2 further cycles of PE were required to effect a complete response.[8] This is similar to many later trials of PE, where remissions were obtained with a mean number of plasma exchanges of 19 ± 17 in one study,[26] and a median of 9 exchanges (mean cumulative infused plasma of 43 ± 77 liters) in another.[27]

Table 1. Defining a Response to Plasma Exchange in the Setting of TTP

Thrombotic Microangiopathy Parameter	Mean Time to Resolution With Daily Plasma Exchange (Days)[25]
Neurologic symptoms	3
Serum LDH	5
Thrombocytopenia	10
Renal function (serum creatinine)	15

By contrast, upwards of 80% of patients with classic aHUS have partial responses to short-term PE that are limited to increases in platelet count and hemoglobin and a decline, but usually not a normalization, in LDH.[5] Tissue damage persists, and maintenance of even those partial responses is dependent upon continued PE. Recall that aHUS is a chronic, genetic disease, leading to high morbidity and mortality despite plasma therapy. Therefore, if a TMA patient experiences such a limited response to PE, or is requiring quantities of plasma exceeding those outlined above for TTP, it is prudent to re-evaluate the diagnosis.

Rethinking the Diagnosis: TTP Versus aHUS

- ***Expanding upon the complement system in the setting of a TMA***

Components of the complement system are required to mount an appropriate innate immune response to pathogens. The classic complement pathway is primarily activated following formation of immunoglobulin-antigen immune complexes, while the alternative pathway is an amplifying system responsive to groups of molecules present on a virus or bacterium, such as polysaccharide and endotoxin. Both can activate C3, converting it to C5, which is then broken down into C5a (anaphylatoxin) and C5b-9 (membrane attack complex or MAC). The importance of the alternative pathway—and its relevance to aHUS—is that it is always "on," at low levels, ready to be amplified by certain stressors such as infection, trauma, pregnancy, or surgery. But C5a and MAC can help destroy the membranes of pathogens as well as of normal cells.

To prevent the panoply of activities related to unchecked activation of the alternative pathway—particularly endothelial cell activation and injury, platelet activation and aggregation, and inflammation—most mammalian cells have membrane-bound regulators that block complement activation. They function in concert with soluble complement regulators.[18,28] Soluble factors H and I, and the membrane-bound proteins MCP (CD46) and CD55, regulate conversion of C3 to C5. Membrane-bound CD59 regulates C5b-9.

In aHUS, identifiable mutations—usually heterozygous—in one or more of these proteins, along with related molecules (CFHR1, CFHR3, C3, complement factor B, and thrombomodulin, which can inactivate C3a and C5a) account for disease susceptibility in up to 60% of cases.[11,19] (Ten percent of aHUS cases may have an acquired component, linked to

development of anti-factor H autoantibodies leading to decreased factor H function.[29] Even in these instances, a C mutation is often present.[14]) In the absence of these functional regulators, aHUS may develop.[28] Reduction in expression of even 50% of normal levels in just one of these regulators appears to leave an individual vulnerable to overt clinical manifestations of aHUS at times of infection, injury, pregnancy, surgery, or other stressors. These details help explain why a complement-based strategy should be effective in treating aHUS. But this information is of far less help in the clinic in distinguishing aHUS from TTP.

Currently, complement and soluble complement regulatory protein levels in plasma or serum are unreliable in the diagnosis of aHUS. A low C3 level accompanied by a normal C4 level would be consistent with selective alternative pathway activation, but this pattern is only occasionally observed—serum C3 is normal in up to 80% of aHUS patients—and is too inconsistent for diagnostic purposes.[6,30] Complement pathways can also be transiently activated in classic TTP, leading to elevated plasma levels of C3a and C5b-9.[31]

Similarly, as noted above, genetic mutations of soluble and membrane-linked C regulatory proteins have been documented in only about half of classic aHUS cases, and thus are an unreliable means of excluding an aHUS diagnosis.[32] (It is hypothesized that more extensive, genome-wide sequencing will eventually reveal complement-related abnormalities in most aHUS cases. Such analyses will be complicated by the fact that non-synonymous mutations involving amino acid substitutions in factor H—the most frequently involved protein in aHUS—are present in 5% of healthy controls, with no family history of TMA.[33]) In addition, such testing takes months, and is not generally available, making genetic testing unnecessary for initial assessment and management of aHUS. (A center at the University of Iowa provides such services, but they are expensive. Genetic testing can be useful, however, in the counseling of family members of an affected proband, as carriers might be closely monitored during conditions triggering marked C activation, such as surgery, trauma, infection, malignancy, and pregnancy.[6]) Clearly there is room to improve diagnostic associations and testing for complement activation.

• ***Examining tissue***

Biopsies are rarely done in the TMAs, although they may serve as a guide in difficult diagnostic situations.[34] Gingival tissue, skin, or bone marrow are suggested sites to sample, regardless of whether there is an apparent lesion.[35] The thrombi of TTP are typically composed of platelets and vWF, with only small amounts of fibrin.[22] Vascular or perivascular inflammatory cell infiltrations are minimal or absent,[22] consistent with the fact that endothelial cell damage is apoptotic in nature, and such programmed cell death, as opposed to necrosis, typically lacks an inflammatory component.[21] In contrast, biopsy of similar sites in aHUS typically reveals microthrombi in which fibrin dominates, and an inflammatory infiltrate may be seen.[22,36] Deposits of terminal components of complement (C5a and C5b-9) may be seen in involved microvessels. It must be emphasized, however, that the sensitivity and specificity of such biopsy results in distinguishing TTP from aHUS, or from TMAs arising in the setting of other disorders such as SLE, particularly with reference to the potential for a response to plasma-based versus complement-based therapies, have not been authenticated in clinical trials. Kidney biopsy is rarely necessary in patients with renal manifestations of a TMA as little diagnostic or prognostic information is added to that derived from more basic laboratory tests.[37] (Post-renal transplant syndromes are an exception, where it may be otherwise difficult to distinguish antibody-mediated rejection from aHUS and other TMAs in the absence of tissue.[37]) The use of tissue-based testing should not be done routinely, but rather on a case-by-case basis. Larger scale studies are needed to define and standardize such an approach.

Summary

• aHUS is a chronic, rare, life-threatening, systemic disease. Its etiology is based upon unregulated activation of the alternative complement system. Unrecognized and inappropriately treated, it has a high degree of morbidity and mortality within the first year of presentation.

• aHUS is one form of thrombotic microangiopathy (TMA). A TMA is recognized by the laboratory signs of microangiopathic hemolysis (schistocytes, elevated LDH, low haptoglobin), accompanied by signs and symptoms of organ system involvement. Thrombocytopenia is common, although it is much less severe than in TTP, another major TMA, and may be near normal at presentation.

• The clinical presentation of the 3 major TMAs—aHUS, STEC-HUS, and TTP—can be identical. For example, despite the term "uremic" in the disease name, approximately 20% of aHUS cases have preserved renal function at diagnosis, defined by a serum creatinine in the normal range. All of the TMAs can occur at any age. The presence or absence of diarrhea or neurologic symptoms does not reliably distinguish among these TMAs. Any patient presenting with diarrhea, however, should be evaluated for STEC-HUS.

• aHUS is distinct pathologically from TTP. aHUS results from chronic, uncontrolled activity of the alternative complement pathway. In the majority of cases, this defect is related to a genetic deficiency in one or more soluble and/or membrane-bound complement regulatory proteins. Complement factor H is most frequently implicated.

• In the vast majority of cases, aHUS can be distinguished from TTP on the basis of an ADAMTS13 enzyme activity measurement. It is important to order this test, prior to initiating any plasma therapy, in a patient presenting with the laboratory and clinical signs of a TMA, even though the results may take several days to obtain.

• Assessment of complement levels or currently identifiable complement regulatory protein mutations cannot be used to rule out a diagnosis of aHUS.

• Unlike TTP, plasma therapy has no role in the treatment of aHUS. Short-term, partial responses in hematologic parameters (platelet count, hemoglobin, and LDH) have been seen in up to 80% of cases of aHUS treated with PE. This is thought to be related to replacement of soluble complement regulatory proteins by plasma infusion. However, ongoing tissue damage persists.

• A specific, FDA-approved, complement-based therapy for aHUS is now available. Once an ADAMTS13 activity of >5–10% (depending on the assay used) has been documented in the setting of a TMA, and thus the diagnosis of aHUS has been made, plasma therapy should be discontinued and appropriate treatment instituted.

• If a putative TTP or other TMA patient is not responding to plasma therapy, according to generally accepted measures of hematologic, clinical, and organ system changes, or requires prolonged plasma exchange to effect and/or maintain a partial remission, it is necessary to re-evaluate the diagnosis and consider aHUS. If an ADAMTS13 level had not been obtained prior to institution of PE, consideration should be given to stopping plasma infusions and ordering this test, so that a definitive treatment might be applied.

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Diagnosis of Atypical Hemolytic Uremic Syndrome: A Review of Case Studies

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Diagnosis of atypical hemolytic uremic syndrome (aHUS) can be difficult, but is of critical importance given the recent approval by the US Food and Drug Administration (FDA) of an effective therapy for this disorder. The following published case studies highlight important points regarding the distinction between the 2 principle thrombotic microangiopathies, aHUS and thrombotic thrombocytopenic purpura (TTP).

aHUS in an Infant

Ariceta and colleagues reported a case of a 28-day-old male infant who presented with the symptoms of a classic thrombotic microangiopathy (TMA).[1] Despite multiple blood and plasma infusions for a presumptive diagnosis of TTP, the infant experienced continued thrombocytopenia, hemolysis with schistocytes on peripheral blood smear, and rising creatinine. The infant also had other manifestations of systemic microvascular thrombosis, including multiple intestinal perforations and skin necrosis.

On day 10 of admission, with continued failure of plasma therapy and recognition of complement activation with a low C3 level, eculizumab was initiated. Within 4 days, hemodialysis could be discontinued, and C3 levels as well as platelet counts normalized within 2 weeks. However, signs and symptoms of persistent thrombotic microangiopathy were manifested 11 days after the first eculizumab dose, related to inadequate pharmacologic levels. An increase in dose led to TMA resolution, and therapy has continued. Levels of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), which is an enzyme with von Willebrand factor cleaving protease activity that characteristically is severely reduced in TTP (<5% of normal activity) but normal (>5–10% of normal activity, with cut-off values dependent on the assay method) in aHUS, was determined several weeks later and found to be normal (56%). The authors also performed several sophisticated tests for complement regulatory factors including search for mutations in soluble and membrane-bound complement regulatory proteins and autoantibodies against the principal such protein, complement factor H (CFH). No abnormalities were documented.

Key Points

This patient shows that TMAs can occur at any age, from very young infants, as in this case, to the elderly. Another important point is that measurement of complement abnormalities are not reliable indicators of an aHUS diagnosis, nor a reliable way to distinguish among the TMAs. In this patient, a low level of complement protein C3 was found, but this is not often present in aHUS. It is possible for a patient to have a severe complement problem leading to a TMA and to have normal, low, or high levels of complement proteins C3 and C4. In addition, approximately 50% of patients with aHUS responsive to appropriate therapy with eculizumab lack a documented genetic mutation in the complement regulatory system, as in this case. It is generally believed that more than 90% of aHUS cases have a genetic, complement-based abnormality, but that some 30–50% of these abnormalities are not identified when sought because the assays that are currently available are not global enough to detect the abnormalities. Finally, one clinical pearl: In general, it is not possible to distinguish clinically among the TMAs. Some 20% of individuals with aHUS have serum creatinine levels within the normal range at first presentation, and almost 50% have neurologic changes. Diarrhea, including bloody diarrhea, may be a feature of all of the TMAs. This infant, however, was noted to require mechanical ventilation. Although the authors do not explain why such support was required, the lungs are often involved in late stages of aHUS, but are virtually never involved in classic, ADAMTS13-deficient TTP.

aHUS in a Young Man

Durán and coworkers discussed the case of a 28-year-old man, a known cocaine user, who presented with renal failure and hemolytic anemia.[2]

Evidence for the latter included a high level of lactate dehydrogenase and a low level of haptoglobin. A microangiopathic process was documented on renal biopsy. The patient also had low levels of complement proteins C3 and C4, although, as I mentioned previously, these values are not reliable indicators of a systemic TMA. Levels of complement factor H protein were low-normal. The authors also tested for a mutation in this protein, which is the most common complement regulatory factor to be mutated in patients with aHUS. The mutation was found, and the patient was diagnosed with aHUS. The authors instituted plasma exchange, which was administered every other day for 1 month with no response.

Key Points

This patient represents a case of aHUS diagnosed not in the typical fashion, by recognition of classic laboratory and clinical signs of a TMA in the setting of a normal ADAMTS13 level, but via an involved tissue (kidney) biopsy together with identification of a complement factor H mutation. The first teaching point is that although the patient was diagnosed via genetic analysis, this is an unreliable method. The assays are not generally available, and require several months to complete, during which time, in the absence of appropriate anti-complement therapy, tissue damage continues. As noted in the prior case, levels of complement and/or complement regulatory factors can be normal, and complement mutations not identifiable, in aHUS.

The second teaching point is that although this patient was diagnosed with aHUS and not TTP, plasma exchange was instituted anyway. There are no clinical trials indicating a role for plasma infusion or plasma exchange in the treatment of aHUS, and in this patient, plasma exchange was continued for 1 month with no response. As a guide, plasma exchange is usually initiated upon first presentation of a TMA, before appropriate ADAMTS13 testing can be completed, and these results can take more than 1 week to return. In that period of time, upwards of 60–80% of classic aHUS patients may have a transient partial response to plasma therapy, typically limited to an increase in platelet counts and resolution of hemolysis, but the underlying process of unregulated complement activation persists. The latter may be evidenced by continued decline in renal function, persistent platelet activation, or failure to completely normalize the LDH. As a general guide, the majority of classic TTP patients, with ADAMTS13 activity less than 5–10% (the cut-off depending on the assay method used), will have resolution of thrombocytopenia within 7 days and of creatinine within 2 weeks, and will require an average of about 20 liters of plasma administered over 7–9 days, to get there.[3] Failure to reach these milestones, and certainly a requirement for continued plasma therapy for more than 2 weeks in the context of a normal ADAMTS13 activity, should lead one to rethink the diagnosis and consider aHUS. An educational point illustrated by this patient is that he presented with his first manifestation of a TMA at age 28, and yet was documented to have a genetic mutation in complement factor H. The question arises as to why this patient did not manifest a clinically apparent TMA much sooner in his lifetime. The answer is that the genetic mutation in and of itself was insufficient to lead to a clinically recognizable TMA, just as patients with familial TTP and mutations in the ADAMTS13 gene infrequently develop clinical TTP before the age of 6 years, and then may have only a few episodes of TTP over their lifetimes. It is now recognized that there are modulating factors in aHUS that act in concert with this chronic, genetic condition, and these modulating factors are complement-related. Potent activators of the alternative complement pathway include surgery, trauma, infection, and pregnancy. In this case, the authors suggested that cocaine use was the modulating factor. Cocaine has been shown in animal models to activate complement. It could also offer a "double-hit," as cocaine can directly injure small blood vessels, which may accentuate the microthrombotic characteristic of aHUS.[4]

Severe aHUS in a Woman

Ohanian and colleagues reported a case of a 50-year-old woman with a history of rheumatoid arthritis.[5] She presented with fatigue, abdominal pain, bloody diarrhea, sepsis, acute renal failure, and thrombocytopenia. Testing for Shiga toxin was negative. This patient had low complement protein C3 and C4 levels. ADAMTS13 activity was normal, and schistocytes were seen on the peripheral blood smear. Further evidence for microangiopathic hemolysis included a haptoglobin level of less than 6 mg/dL and a negative direct Coombs test, to rule out an autoimmune hemolytic anemia.

The patient underwent total abdominal colectomy and end ileostomy, with intestinal pathology showing evidence of microthrombotic angiopathy. During surgery, she received 2 units of packed red blood cells, 2 units of fresh frozen plasma, and 2 units of pooled platelets. Her platelets increased following this intervention, but she developed respiratory failure. Electroencephalography (EEG) showed evidence of a cerebral dysfunction, and magnetic resonance imaging (MRI) of the brain showed infarcts. Her renal failure progressed, and she required hemodialysis. aHUS was diagnosed based on her clinical features (severe renal failure, neurologic changes), evidence of TMA, including microangiopathic hemolysis, and normal ADAMTS13 activity. She also had low complement levels, which supports the diagnosis of aHUS, but was not required for it.

Key Points

There are 3 major types of TMAs: Shiga toxin–related STEC-HUS; TTP, which is related to an ADAMTS13 deficiency; and aHUS, which is related to abnormalities of the alternative pathway of complement. Before there were effective treatments for aHUS, patients who presented with bloody diarrhea were usually diagnosed with D(diarrhea)+ HUS—a term that should no longer be used—of which STEC-HUS is a subset. But bloody diarrhea can present in all 3 of the TMAs, so it is not a useful distinguishing point. Indeed, diarrhea is one of the most potent causes of activation of the alternate complement pathway. The bacteria and viruses that are typically associated with diarrhea injure the epithelium lining the intestine. This injury can result in relative transparency that allows microbial translocation—the movement of bacterial products directly from injured epithelium into the bloodstream. Microbial translocation is a very potent complement activator.

With her renal failure, mental status changes, and intestinal and respiratory conditions, this patient shows that aHUS is often a multisystem disease. As noted above, renal failure is not necessarily associated with aHUS—approximately 20% of patients with aHUS do not have manifestations of acute renal disease on their first presentation—while involvement of other organ systems can predominate. TMA-related perforations of the colon that can lead to sepsis have been reported. This patient also had small bilateral pleural effusions. As noted earlier, lung pathology is not uncommon in aHUS, while in classic TTP, the lung is virtually never involved. A key teaching point in terms of evaluating a "response" to therapy in aHUS is the fact that the patient's platelet count increased when she received 2 units of packed red blood cells, 2 units of fresh frozen plasma, and 2 units of pooled platelets during surgery. A complete hemolytic response with normalization of the platelet count, normalization of the hemoglobin, and disappearance of schistocytes on peripheral blood smear may be interpreted as evidence that the patient's disease is responsive to plasma therapy. However, in aHUS, there is no evidence that plasma alters the ultimate course of disease, with persistent decline in glomerular filtration rate, persistent platelet activation, and continuation of other systemic organ pathology.

Conclusion

All three of these cases illustrate the significant morbidity that accompanies aHUS, and consequences of the failure to recognize the condition, distinguish it from other TMAs, and treat it appropriately. Now that an effective therapy is available, the importance of quickly making the diagnosis of aHUS is clear.

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Editor's Note

Further citations for the information in this review can be found in the article "Atypical Hemolytic Uremic Syndrome (aHUS): Making the Diagnosis," which appears on pages 2–8 of this supplement.

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