THROMBOTIC MICROANGIOPATHY

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- In 1966, TTP or Moschcowitz' syndrome was redefined by Amorosi and Ultmann based on their review of 16 cases .They defined the diagnostic pentad for TTP as follows: (1) thrombocytopenia, (2) hemolytic anemia, (3) fever, (4) neurologic changes, and (5) kidney failure

- In 1977, Bukowski et al. described two patients with TTP who successfully responded to plasma exchange

- In 1982, Moake et al. reported the appearance of unusually large multimers of vWf in the plasma of patients with relapsing TTP before relapse

- In 1998, Tsai et al. and Furlan et al. identified an inhibitory antibody directed against vWf-cleaving metalloprotease ADAMTS13 .
- it was concluded that acquired or idiopathic TTP was an autoimmune disease
- The observation that ADAMTS13 levels were relatively normal in HUS

- Subsequently, there were attempts to etiologically define all nondiarrheal, non-DIC TMA cases as severe, antibodymediated ADAMTS13 activity deficiency. Most TPE-responsive patients with TTP, however, do not have severe ADAMTS13 deficiency .

- third of patients who present with a TMA for plasma exchange therapy have severe ADAMTS13 deficiency, with the vast majority of cases due to an inhibitor, and ,10% are attributable to a hereditary enzymatic deficiency of ADAMTS13

- HUS was originally described in 1955 by Gasser and colleagues in five children who presented with diarrheal illness and the triad of thrombocytopenia, hemolytic anemia, and renal failure

- This form of TMA was thought to be more common in children, but often occurs in adults
- The recent outbreak in Germany (E. coli O104:H4) affected women in 70% of cases,

- no compelling evidence that plasma exchange benefits patients with typical or dHUS, except possibly for those with severe neurologic or renal involvement.

- Less than 10% of HUS is not associated with diarrhea and is termed atypical HUS (aHUS). Most aHUS cases derive from genetic variants of complement regulatory factors

- Less than 10% of HUS is not associated withdiarrhea and is termed atypical HUS (aHUS). Most aHUS cases derive from genetic variants of complement regulatory factors, resulting in unrestrained complement activation

- A minority of these patients have depressed C3 levels. The most common forms of aHUS have loss-of-function abnormalities in factor H or I, or gain-of-function mutations in C3 convertase, C4-binding protein, complement factor B, thrombomodulin, and membrane cofactor protein.

- 50% of cases present in adulthood Approximately half of aHUS patients respond to plasma exchange, and nearly all will respond to eculizumab

- Given the considerable overlap of clinical manifestations of these disorders, the terms undifferentiatedTMA or TTP-HUS are suggested to initially describe individuals presenting with the clinical dyad of microangiopathic hemolytic anemia and thrombocytopenia

- Before the success of therapy (plasma, rituximab, and eculizumab), it was an academic exercise to differentiate between TTP, dHUS, aHUS, or secondary TMA

- In fact, when centers reviewed their cases of TTP that were treated successfully with plasma exchange, over half were thought to represent cases of secondary TTP with features of both TTP and HUS

- the adult presenting with the clinical dyad may have any form of TMA from idiopathic or acquired TTP to dHUS or atypical HUS; secondary TMA or hereditary TTP

- Survival in patients with TMA without treatment may be hours to days; therefore, diagnostic testing that requires weeks to months is of no immediate practical value,

- Treatment with plasma exchange appears to benefit the majority of adults with TMA,except in cases in which TMA is secondary to systemic sclerosis, malignancy, Shiga toxin positive bloody diarrhea in the absence of severe renal or neurologic involvement, malignant hypertension, stem cell transplantation, or mitomycin C

- Up to 90% of the primary forms of TTP, 50% of aHUS cases, and 70–80% of the secondary causes of TMA will respond to plasma exchange

- careful clinical evaluation directed toward identifying connective tissue disorders including the antiphospholipid antibody syndrome, underlyin gmalignancy or prior stem cell transplantation, malignant hypertension, drugs, sepsis (particularly Streptococcuspneumoniae), HIV infection, or pancreatitis. pregnancy testing.

- one third of patients will have a severe deficiency of ADAMTS13 activity and an inhibitory antibody characteristic of acquired TTP

- Only a minority of patients with aHUS will demonstrate low serum complement levels. Further evaluation requires testing for abnormalities of factor H or I, C3 convertase, C4-binding protein, complement factor B, thrombomodulin, and membrane cofactor protein. There will be no specific abnormality identified in approximately one third of patients with aHUS.

INITIAL MANAGMENT

- When plasma exchange is not immediately available, infusion of fresh frozen plasma after pretreatment with corticosteroids and antihistamines should be started,

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- Recommended clinical approach to thrombotic microangiopathies (TMAs).
- begins with initiation of daily plasma exchange
- Approximately 70–80%of patients with undifferentiated TMA respond to plasma exchange

- The volume or frequency of plasma exchange should be increased for patients who fail to show a rise in the platelet count, fall in the serum lactate dehydrogenase (LDH), or improvement in symptoms within 2 to 3 treatments.

- Patients who continue to fail to respond after 5 days of plasma exchange therapy should be treated with eculizumab for presumed aHUS, after excluding secondary forms of TMA.

- The majority of patients with acquired TTP respond to plasma exchange, but roughly 10%–20% of patients will be refractory, (within 30 days of successful response).

- moreAgressive plasma exchange, using either increased volumes of exchange or twice-daily exchanges with implementation of rituximab after achieving control of the disease. Rituximab is administered in 4 weekly doses of 375 mg/m once the platelet risen to $150,000/ml and the serum LDH level is ,25% of the upper limit of normal

- Immediate reinitiation of plasma exchange is indicated for recurrent symptoms, a decrease in the platelet count to ,50,000/ml, and/or when the serum LDH level is twice the upper normal limi

- Remission is defined as a decrease in the serum LDH level to within 25% of the upper limit of normal and normalization of the platelet count. One third of patients, however, are known to relapse frequently, as defined by disease recurrence on more than one occasion after 1 month of remission

- Plasma exchange appears induce remission in only approximately 50% of patients, whereas eculizumab induces remission in 80% of patients with atypical HUS

- Simple complement testing detects only a minority of cases at the outset, and the diagnosis should be suspected in those who fail to respond to 5 days of increasing frequency or high-volume plasma exchange

- Pretreatment meningococcal vaccination and prophylactic antibiotic coverage are mandatory. Even with appropriate prophylaxis, patients who have received eculizumab remain at risk for life-threatening meningococcemia.