Chapter 27
Thrombotic Microangiopathies

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27.1 Clinical Presentation

The basic problem in all thrombotic microangiopathies (TMs) is occlusion of the vasculature by platelet aggregates. This event restricts blood flow which leads to areas of high shear that damage red cells resulting in fragmentation. This is the origin of the "helmet cells" or "schistocytes" part of the diagnostic criteria (microangiopathic hemolytic anemia). This vascular occlusion leads to tissue ischemia and end-organ damage. In classic hemolytic uremic syndrome (HUS), this pathophysiology is restricted to the kidney leading to renal failure while in thrombotic thrombocytopenic purpura (TTP), it can occur in any organ. The high lactate dehydrogenase (LDH) that is seen in TMs is due to both red cell destruction and tissue ischemia. In transplant patients, the onset of the TM is often gradual with slowly rising LDH and deteriorating renal function. Often, hypertension develops and can be an early clue to the diagnosis. In TMs associated with agents such as calcineurin inhibitors (CNI), the onset can be more rapid. As the TM progresses, renal insufficiency and neurological symptoms are the most common findings, in many patients running a relentless course until the patient expires.

27.2 Risk Factors

Many risk factors for TM have been proposed. One difficulty with these risk factors is that any widespread disease process such as severe infection or graft-versus-host disease (GVHD) can lead to a clinical syndrome similar to TM. This lack of clarity

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R. T. Maziarz, S. S. Slater (eds.), *Blood and Marrow Transplant Handbook,*
DOI 10.1007/978-3-319-13832-9_27

in identification of etiologic events results in the extreme variations in reported incidence rates ranging from 0 to 93 % of patients!

Risk factors include:

1. Older age
2. Female gender
3. Advanced disease
4. Unrelated donor transplant
5. Radiation-containing conditioning regimens
6. Calcineurin inhibitors
7. Infection
8. GVHD

27.3 Classification

Pettitt and Clark (1994) proposed a classification which still provides a useful schema for thinking about transplant-related TM.

1. One group is the "multiorgan fulminant" which occurs early (day +20–60), has multiorgan system involvement, and is often fatal.
2. A second type of TTP/HUS is similar to CNI-associated HUS.
3. A third type described as "conditioning" TTP/HUS occurs 6 months or more after total body irradiation and is associated with primary renal involvement.
4. Finally, patients with systemic cytomegaloviral (CMV) infections may present with a TTP/HUS syndrome related to vascular endothelial cell CMV infection.

27.4 Etiology

In classic TTP, most patients have very low levels of ADAMTS-13 (< 5 %) which is thought to lead to spontaneous platelet aggregation via the failure to cleave the ultra-high molecular weight multimers of von Willebrand protein. In patients with transplant related TM, most reports show reduced but not extremely low levels of ADAMTS-13. The underlying factor in most transplant-associated TMs is endothelial damage, either by GVHD, medications, radiation, or infection. This endothelial damage leads to platelet aggregation, microangiopathic hemolytic anemia, and end-organ damage. Over-activation of complement has been reported, similar to genetic atypical HUS, suggesting inhibition of complement may be a future therapeutic target. This premise that endothelial injury is the main trigger for transplant TM would explain why vascular damage is a shared component of many of the risk factors for TM.

27.5 Diagnosis

Given that the diagnosis of any TM is a clinical one and that transplant patients are prone to have many complications that can mimic a TM, it is easy to appreciate and understand the great center-to-center variation in describing the incidence. Recently, two groups have proposed diagnostic consensus criteria that share the common features of evidence of a microangiopathic hemolytic anemia and elevated LDH. However, applying these criteria to an individual patient still requires clinical judgment.

1. Blood and Marrow Transplant Clinical Trial Network (BMT-CTN) Criteria
    a. RBC fragmentation and ≥ 2 schistocytes per high-powered field
    b. Concurrent increase in LDH from institutional baseline
    c. Concurrent renal and/or neurological dysfunction with no other explanation
    d. Negative Coombs test
2. International Working Group Criteria
    a. Increased percentage (> 4 %) of schistocytes in the blood
    b. New, prolonged or progressive thrombocytopenia (< 50,000/uL or > 50 % decrease from previous counts)
    c. Sudden and persistent increase in LDH
    d. Decreased hemoglobin or increased transfusion requirements
    e. Decrease in serum haptoglobin

27.6 Treatment

1. Calcineurin inhibitor TM: This disorder often occurs either days after the introduction of these medications or with an increase in blood levels of these agents. The renal and neurological manifestation can be rapid and severe including malignant hypertension, seizures, and cortical blindness. Therapy is discontinuation of the medications and to manage the closely associated hypertension. In patients with mild TM and high serum levels, one can lower the dose to see if the symptoms abate.
2. Conditioning TM: This subtype is rare and may be a manifestation of radiation damage to the vasculature. Usually, the course is progressive with no specific therapy available.
3. Systemic CMV TM: CMV is trophic to the endothelium and aggressive therapy of CMV is the cornerstone of therapy.
4. Multiorgan fulminant: Therapy remains unsatisfactory. The first step is to maximize treatment of any process that may be aggravating the TM (GVHD, infections, etc.).

a. Unlike classic TTP, the role of plasma exchange remains controversial.
    i. Most series report very poor response rates with poor outcomes and high rates of complications.
    ii. It is common that the patient may respond for a few days but then relapse.
    iii. A practical approach would be to use one plasma volume/day exchange daily in patients with TM until it is clear that they are not responding to therapy.
    iv. For patients who respond, the frequency of plasma exchange can be tapered once renal function and LDH returns to normal.

b. Based on the findings of over-activation of complement, there are anecdotes of successful use of eculizumab (Soliris®), the monoclonal inhibitor of C5a, in patients who have failed plasma exchange, but more research is needed before widespread use of this agent can be recommended.

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