Non–Immune-Mediated Platelet Destruction

Disseminated Intravascular Coagulation

One of the most common and potentially life-threatening causes of nonimmune platelet destruction is DIC, which is associated with sepsis, malignancy, advanced liver disease, and other disorders that trigger endotoxin release or cause severe tissue damage (Table 51-4). In DIC caused by bacterial sepsis, circulating endotoxin induces expression of tissue factor on circulating monocytes and endothelial cells, a process leading to overwhelming thrombin and fibrin generation. Deposition of fibrin occurs throughout the vasculature, with relatively inadequate concurrent fibrinolysis leading to a thrombotic or microangiopathic vasculopathy and subsequent organ damage. Thrombin activation of platelets and circulating factors eventually overwhelms the bone marrow and liver synthetic capability, respectively, resulting in thrombocytopenia and prolongation of the PT and aPTT.

Although the primary lesion of DIC is thrombin and clot generation, the clinical end point is usually a consumptive coagulopathy with depletion of platelets and coagulation factors. Mucosal bleeding, especially in the GI tract, and oozing from intravenous puncture sites are early signs of DIC.

Fibrinogen levels are usually low but may be normal in DIC because the acute phase reaction to sepsis or the underlying disorder may increase fibrinogen secretion. DIC should not be ruled out because fibrinogen is in the normal range. Fibrinolysis in DIC is triggered by fibrin clot formation and the action of tissue-type plasminogen activator. Laboratory testing shows increased levels of fibrin split products to more than 40 μg/mL (i.e., cleavage of fibrin monomers) and D-dimer to more than 0.5 mg/mL (i.e., cleavage of fibrin-fibrin bonds). Although levels of fibrin split products are usually elevated in patients with DIC, this finding is nonspecific. An elevated D-dimer level is more specific for DIC and is often used to confirm or replace the fibrin split product screening assay. The blood smear may also help in the diagnosis of DIC by showing significant numbers of schistocytes, but this result is not specific for DIC and is found in other microangiopathies such as TTP (see Chapter 54).

Chronic DIC may be triggered by consumption of platelets and factors in large clots associated with aneurysms, hemangiomas, and mural thrombi. Another cause of chronic DIC is malignant disease, often adenocarcinoma or acute promyelocytic leukemia. Malignant cells in these disorders promote thrombin formation through secretion of tissue factor, elaboration of cysteine proteases that activate factor X, induction of platelet-ligand binding, and upregulation of endothelial cell plasminogen activator inhibitor-1 (PAI-1) or cyclooxygenase 2 (COX2). Chronic DIC associated with malignancy usually causes enough factor consumption that the PT and aPTT are prolonged. Clinically, patients exhibit migratory thrombophlebitis (i.e., Trousseau's syndrome) or nonbacterial thrombotic (marantic) endocarditis.

Therapy for DIC should be aimed at (1) treatment of the underlying disorder, such as antibiotics for sepsis or chemotherapy for malignant disease; (2) supportive hemostatic therapy, including platelets, cryoprecipitate (for fibrinogen), and FFP; and (3) disruption of the activation of coagulation factors and platelets. For the last approach, anticoagulation is usually not indicated unless the balance of procoagulant with anticoagulant activity actively favors clotting, such as arterial thromboemboli with mural thrombus or migratory thrombophlebitis with Trousseau's syndrome. These thrombotic complications of chronic DIC are often resistant to warfarin therapy and usually require more intensive anti-Xa therapy with unfractionated or low-molecular-weight heparin. In DIC precipitated by sepsis, use of pharmacologic activated protein C has significantly decreased mortality.

TABLE 51-4 CAUSES OF DISSEMINATED INTRAVASCULAR COAGULATION

SEPSIS OR ENDOTOXIN	**PRIMARY VASCULAR DISORDERS**
Gram-negative bacteremia	Vasculitis
TISSUE DAMAGE	Giant hemangioma (Kasabach-Merritt syndrome)
Trauma	Aortic aneurysm
Closed-head injury	Cardiac mural thrombus
Burns	**EXOGENOUS CAUSES**
Hypoperfusion or hypotension	Snake venom
MALIGNANT DISEASE	Activated-factor infusions (prothrombin-complex concentrate)
Adenocarcinoma	
Acute promyelocytic leukemia	

Thrombocytopenia with Pregnancy-Induced Hypertension

Mild thrombocytopenia in pregnant women is related to hemodilution, a normal physiologic response of pregnancy that can bring platelet counts into the range of 100,000 to 150,000/μL; these counts are not associated with maternal or fetal complications. However, pregnancy-induced hypertension can result in platelet counts of less than 100,000/μL, and these conditions can be associated with complications.

The spectrum of pregnancy-induced hypertension includes hypertension progressing to proteinuria and renal dysfunction (i.e., preeclampsia) and to cerebral edema and seizures (i.e., eclampsia). Thrombocytopenia may appear as a late finding accompanying pregnancy-induced hypertension, often occurring at the time of delivery or late in the third trimester. The HELLP syndrome in pregnancy (characterized by *h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet counts) is occasionally associated with hypertension. The thrombocytopenia associated with pregnancy-induced hypertension or HELLP may result from abnormal vascular prostaglandin metabolism or placental dysfunction that leads to platelet consumption, vasculopathy, and microvascular occlusions. Both disorders are usually reversed by delivery of the fetus and placenta. Occasionally, IVIG or plasmapheresis has been required when the disorder does not resolve after delivery.

Other conditions sometimes associated with pregnancy that mediate nonimmune platelet destruction include TTP, hemolytic-uremic syndrome (HUS), and antiphospholipid syndrome. However, these platelet-consumptive processes usually yield a thrombotic state rather than a bleeding tendency, despite the associated thrombocytopenia. These medical problems associated with thrombocytopenia are discussed in Chapter 54.