Mechanisms of Thrombocytopenia in Tick-Borne Diseases

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Abstract

Thrombocytopenia is a common manifestation of all tick-borne diseases. Low platelet numbers contribute significantly towards the morbidity and mortality of infection. However, the pathogenesis of thrombocytopenia in many of the tick-borne diseases is poorly understood. Quantitative changes in platelet counts associated with infection may result from decreased marrow production, hypersplenism, consumption due to widespread endothelial damage or disseminated intravascular coagulation, as well as immune-mediated platelet destruction. Infection-induced thrombocytopenia may infrequently be associated with serious thrombosis. Direct infection of platelets by selected tick-borne pathogens also facilitates their dissemination within the host. This article reviews the mechanisms of thrombocytopenia associated with tick-borne infections, and discusses the therapeutic options available for managing this potentially fatal complication.

INTRODUCTION

Ticks are hematophagous parasites that are worldwide in distribution. They are efficient transmitters of viral, bacterial, rickettsial and protozoal pathogens. Nearly all of the tick-borne infections in mammalian hosts may have, as a component of the clinical syndrome, thrombocytopenia. Quantitative changes in platelet counts may result from decreased platelet production, hypersplenism and non-immune as well as immune-mediated destruction or consumption of platelets. Thrombocytopenia usually presents with bleeding, characteristically mucosal and cutaneous. Bleeding into the skin is evident as petechiae or superficial ecchymoses. Most patients with Rocky Mountain Spotted Fever (RMSF), for example, develop a maculopapular rash on the third day of illness, which later evolves to become petechial. Heavy gastrointestinal bleeding and bleeding into the central nervous system may be life-threatening manifestations of thrombocytopenia. Profuse bleeding and ecchymoses with hypovolemic shock are features commonly found in Crimean-Congo Hemorrhagic Fever (CCHF) viral infections (Zaki and Peters 1997), and occasionally in babesiosis (Mintz et al 1991). The pathogenesis of thrombocytopenia in many of the tick-borne diseases is poorly understood. Therapy for this complication has been largely anecdotal and poorly addressed in the literature. This article reviews some of the mechanisms of thrombocytopenia associated with tick-borne infections, and explores the therapeutic options for this potentially fatal complication.

DECREASED PLATELET PRODUCTION

Morulae and granulomas may be found in the bone marrow of pancytopenic patients with ehrlichiosis (Dumler et al 1993; Marty et al 1995). In general, actual platelet production by the bone marrow may be impaired either due to decreased megakaryocyte numbers or ineffective formation of platelets. It is not known if abnormalities in regulatory mechanisms promoting stem cell growth, which usually give rise to multilineage cytopenias, may be involved in tick-borne diseases. Pancytopenia, usually with significant neutropenia and a mild anemia, occurs in some patients infected with the Colorado tick fever (CTF) virus. Bone marrow CD34-positive stem cells are directly invaded by CTF virus (Philipp et al 1993). CTF virus has also been shown to replicate in erythroblasts of infected mice (Oshiro et al 1978). Ehrlichia cause a similar trilineage hematological perturbation (Pierce et al 1977; Bakken et al 1996). Pancytopenia due to marrow hypoplasia (Woody and Hoskins 1991; Dumler et al 1993; Klein et al 1997) in patients with ehrlichiosis may cause fatal hemorrhage and secondary infections (Marty et al 1995). While suppression of platelet production in the marrow may provide one mechanism to account for low circulating platelet numbers in tick-borne infections, direct infection of megakaryocytes has not yet been shown.

HYPERSPLENISM

The spleen plays a pivotal role in host defense by clearing microorganisms and antibody-coated cells. It is also

important for antibody synthesis. Furthermore, it acts as a reservoir for platelets, containing a large exchangeable platelet pool. In some animals, like dogs and cats, the spleen provides an important reservoir for erythrocytes. Splenomegaly, which is associated with many of the tick-borne diseases, causes increased platelet sequestration and destruction by splenic macrophages. Whole-body scans of dogs infected with Ehrlichia canis showed that labeled platelets were destroyed primarily in the spleen (Smith et al 1975). The spleen is usually severely affected in cases of babesiosis, becoming congested and enlarging to several times its original size (Hildebrandt 1981). In chronic babesial infections extramedullary hematopoiesis also contributes to splenomegaly (Hildebrandt 1981). Enlargement of the spleen results in increased pooling of platelets. This lowers the circulating number of thrombocytes. Normally, the human spleen pools approximately one third of all circulating platelets. In patients with hypersplenism, as many as 90% of platelets can be sequestered by this organ.

NON-IMMUNE PLATELET CONSUMPTION

Thrombocytopenia may occur as a consequence of vascular damage, with widespread deposition of platelets on damaged endothelial surfaces (Silverman 1986; Elghetany and Walker 1999). Injured endothelium may become denuded, exposing thrombogenic subendothelium. The endothelial cell is the primary target in rickettsial infections. Platelet adhesion to injured endothelium is the major mechanism of thrombocytopenia in the spotted fever group of diseases (Rao et al 1988). In certain infections the coagulation system gets activated, which evokes a hypercoagulable state. This, in turn, results in consumption of coagulation factors and platelets, with subsequent thrombus formation throughout the microcirculation. This clinical condition is referred to as disseminated intravascular coagulation (DIC). Simultaneous with, and secondary to, the activation of the coagulation cascade, the fibrinolytic system gets activated. The clinical manifestation of DIC is thus diffuse hemorrhage and/or ischemic tissue damage. Such a consumptive coagulopathy explains some of the clinical features seen with the tick-transmitted viral hemorrhagic fevers. Thrombocytopenia as low as 14×10^9/L is characteristic of CCHF, and is usually accompanied by severe hemorrhage (Joubert et al 1985). Bleeding in CCHF infection, initially only petechial into the skin and mucous membranes, later develops into hypovolemic shock. As a result of an ensuing DIC, hemorrhage is accompanied by widespread focal, and sometimes massive, multiorgan ischemic necrosis. Patients

who develop CCHF-induced DIC usually succumb to fatal infection (Joubert et al 1985). Fatal cases of DIC following babesial infection have also been documented (Marcus et al 1982). Hemophagocytosis may also rarely account for thrombocytopenia. Severe, but reversible, hemophagocytosis has been reported in patients with babesiosis (Auerbach et al 1986) and ehrlichiosis (Abbott et al 1991).

THROMBOTIC THROMBOCYTOPENIA

Thrombotic thrombocytopenic purpura (TTP) is a potentially fatal disease characterized by widespread thrombi in the microcirculation. The hallmarks of TTP are thrombocytopenia, microangiopathic hemolytic anemia (with fragmented erythrocytes seen on a blood smear), fluctuating neurologic abnormalities, fever, and renal disease. The pathologic feature characteristic of TTP is microthrombi, composed of platelets and fibrin, which occlude arterioles and capillaries in multiple organs. Unlike DIC, however, localized fibrinolytic activity is absent in vessels occluded by these microthrombi, and the coagulation parameters are rarely affected. TTP is often associated with the excessive release of unusually large von Willebrand factor (vWF) multimers, from disturbed systemic endothelial cells. Patients with tick-borne diseases, such as RMSF (Turner et al 1986) and ehrlichiosis (Marty et al 1995; Modi et al 1999), may present with findings compatible with TTP. Associated with rickettsial injury to endothelial cells is an increased plasma concentration of vWF (Elghetany and Walker 1999). An etiologic relation between bartonella organisms and TTP has also been reported (Mettler 1969; Tarantolo et al 1997). If an underlying infection in patients presenting with TTP is not unveiled, such patients may be inappropriately treated. Turner and colleagues (1986) reported a case of a 25 year-old man suffering from RMSF who presented with headaches, fever, a low platelet count and renal failure, who initially received plasmapheresis after a diagnosis of TTP had been made. Only after RMSF had been diagnosed serologically was plasmapheresis discontinued and appropriate antibiotics administered, resulting in a favorable outcome. In two reported cases of ehrlichiosis clinically confused with TTP, the correct diagnosis was made only at post-mortem (Marty et al 1995; Modi et al 1999). In a study carried out in Massachusetts in the United States of America, where Human Granulocytic Ehrlichiosis is endemic, acute ehrlichia infection appeared not to be associated with adult TTP patients, even though some of these individuals did have tick bites (Pantanowitz et al., 2001).

DIRECT INFECTION OF PLATELETS

Direct infection of platelets, as occurs with Ehrlichia platys (Simpson and Gaunt 1991; Arraga-Alvarado et al 1999), has been observed. Infectious strains of Lyme disease spirochetes have been shown to bind to integrin IIb 3 (glycoprotein IIb-IIIa) on human platelets in vitro (Coburn et al 1994). Glycoprotein IIb-IIIa binds to a number of adhesion molecules (like fibrinogen and vWF) which play a critical role in hemostasis and thrombosis. Functional expression of this receptor, however, requires platelet activation. This probably explains why Borrelia burgdorferi spirochetes adhere only to activated platelets (Coburn et al 1993). Binding of borrelia to platelets might promote their hematogenous dissemination to diverse tissues (Coburn et al 1994). Alternatively, adhesion to platelets might provide a foothold for spirochetes after transmission. To what extent attachment onto or invasion into platelets contributes to thrombocytopenia, or qualitative platelet defects, is unknown.

IMMUNE-MEDIATED PLATELET DESTRUCTION

Autoimmunity is a phenomenon observed in many tick-borne diseases, and may contribute to thrombocytopenia in these cases. Autoreactive antibodies that bind to platelets shorten their life span, due to the clearance of antibody-coated platelets by the reticuloendothelial system. The incidence of autoimmune disorders in patients with Q fever (Levy et al 1989; Krutitskaya et al 1996), ehrlichia (Codner et al 1985; Wong and Thomas 1998) and babesiosis (Zuckerman 1964) is unexpectedly high. Antiplatelet antibodies have been detected in the sera of dogs with naturally occurring and experimentally induced Rickettsia rickettsii infection (Grindem et al 1999). The antibodies persisted for months, even when the platelet counts had normalized (Grindem et al 1999). Platelet antibodies have also been detected in thrombocytopenic patients with Mediterranean Spotted Fever (Raoult et al 1985). Autoantibodies to phosphatidyl-serine may contribute to the thrombocytopenia seen in Babesia bovis infections (Orinda et al 1994). Evidence also exists for the presence of antiplatelet antibodies in sera of dogs with Ehrlichia canis infection (Waner et al 1995; Lewis et al 1995; Harrus et al 1996; Waner et al 2000). Serum samples from patients with human granulocytic ehrlichiosis have likewise been shown to exhibit antiplatelet antibodies (Wong and Thomas 1998). In addition to causing thrombocytopenia, immune dysfunction also contributes to other aspects of infection, such as secondary fatal infections in ehrlichiosis (Walker

and Dumler 1997).

CONCLUSIONS

Thrombocytopenia due to tick-borne infection is likely to be of multifactorial etiology. In many of these infections, however, the actual mechanism of thrombocytopenia still remains unknown. Iatrogenic causes in some cases, such as drugs, should not be overlooked. Low platelet numbers in infected individuals may not only manifest with increased bleeding, but may herald more widespread life-threatening microthrombus formation. In addition to quantitative platelet disorders, qualitative defects may also be present. For example, inhibition of platelet migration has been induced by serum from E.canis-infected dogs, even before platelet numbers declined and before the appearance of specific humoral antibodies (Kakoma et al 1978). The release of platelet factor 3, a phospholipid released from activated platelets that is necessary for the intrinsic conversion of prothrombin to thrombin, is also markedly decreased as a result of ehrlichial infection (Pierce et al 1977). Furthermore, platelet aggregation in ehrlichiosis can be prevented by autoantibodies directed against their surface glycoproteins (Lovering et al 1980; Harrus et al 1996).

Therapy for thrombocytopenia requires treatment or removal of the underlying infection, in addition to maintenance of platelet counts and hemostatic function. However, identification and correction of a specific tick-borne infection is only possible if the infection is considered in the differential diagnosis of thrombocytopenia. Rapid treatment of the underlying infection should result in normalization of platelet counts. Ehrlichia, bartonella and RMSF should also be excluded in cases presenting with a clinical picture resembling TTP, particularly in those patients that prove difficult to manage, and in regions where the incidence of tick-borne illness is high. The efficacy of platelet transfusions in many of the tick-borne diseases is unclear and anecdotal (Van Eeden et al 1985). The value of prophylactic platelet transfusion may only be of transient benefit. Smith and coworkers (1975) showed that transfusing radiolabelled platelets into dogs infected with ehrlichia were destroyed in the spleen at an accelerated rate. Furthermore, exogenous platelet concentrates are probably best avoided in thrombotic-associated thrombocytopenia. In this condition, transfused platelets may become incorporated into platelet-fibrin thrombi and thus trigger a serious thrombotic event. The role of intravenous immunoglobulin, corticosteroids, plasmapheresis and even splenectomy in treating these patients has not been explored. Mild infections with babesia,

for example, can be exacerbated by corticosteroids and/or splenectomy (Rosner et al 1984). Since thrombocytopenia contributes significantly to both morbidity and mortality associated with tick-borne diseases, further research directed specifically towards improving our understanding and guiding treatment of these platelet irregularities is required.

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