Platelets: Envoys at the Infection Frontline

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(See the major article by Metcalf Pate et al on pages 874–83.)

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Platelets play a central role in normal hemostasis, as well as in cardiovascular disease and inflammation, in the regulation of coagulation, and in tumor metastasis [1]. Thrombocytopenia is a known complication of human immunodeficiency virus type 1 (HIV-1) infection, primarily in patients with AIDS, low CD4 cell numbers, and advanced stages of disease. Thrombocytopenia (defined generally as a platelet count <100 × 10^9/L) [2] can occur in HIV-infected people, as well as in humans and nonhuman primates infected with other viruses [3, 4], through reduced production of platelets by infected megakaryocytes, through use of certain drugs used to treat infection that can also damage the bone marrow, and indirectly through certain AIDS-related conditions such as lymphoma [5]. Alternatively autoantibodies produced by the immune system can target healthy platelets in HIV-related immune thrombocytopenic purpura and trigger the spleen to remove circulating platelets. Furthermore, as part of frontline defensive duties in an innate immune response to acute HIV infection, platelets can bind to, and be sequestered by, specific inflammatory monocyte subsets. Thus the etiology of thrombocytopenia in this setting is complicated and likely to have multifactorial causes. In this issue of the Journal, Metcalf and colleagues [6] begin to examine this problem by presenting valuable analyses of the onset and progression of platelet depletion in the setting of HIV infection, using a simian immunodeficiency virus (SIV)/macaque model.

The authors analyzed blood from control and infected macaques during the acute phase of infection and monitored parameters of platelet production as well as platelet activation using flow cytometric approaches. Increasing levels of activated platelets coincidental with the acute phase of infection and the platelet count nadir were measured using surface P-selectin, CD40L, active integrin αIIbβ3, and major histocompatibility complex as activation indices. Levels of reticulated (newly produced) platelets and hepatic levels of thrombopoietin mRNA and levels of the thrombopoietin receptor on megakaryocytes isolated from macaque bone marrow were increased in line with the drop in platelet count and indicating no pronounced platelet production defect. Significantly, at the platelet count nadir, increased levels of platelet/monocyte, but not platelet/lymphocyte aggregates, were evident. Autoantibodies against platelet membrane receptors were below detectable limits at the day 10 time point, ruling out antibody-based depletion of platelets to explain the thrombocytopenia. Taken together, these studies indicate that the observed acute-phase thrombocytopenia in this macaque model of HIV infection was due to platelet activation and sequestration involving platelet/monocyte aggregates.

It is important to understand how platelets and monocytes interact at a molecular level because attenuation of platelet and immune cell hyperactivity (eg, through aspirin therapy) may limit disease progression [7]. The most commonly recognized mechanism involves platelet P-selectin binding to its counter-receptor, P-selectin glycoprotein ligand 1 (PSGL-1) on leukocytes. Importantly, if the interaction is P-selectin dependent, it must involve activated platelets, because P-selectin is not normally expressed on the surface of resting platelets, but it is expressed on α-granules and rapidly surface-expressed only on activated platelets. Once platelets bind, activated leukocytes express an active form of the integrin, Mac-1 (αMβ2), which can then bind the platelet receptor, glycoprotein Ibα (GPIbα) [8] (Figure 1). Monocyte–platelet interactions are proinflammatory, and monocyte–platelet aggregates may be elevated in disease states [9] or, interestingly, in the context of influenza immunization [10]. The requirement for activated rather than quiescent platelets in this process supports the viral-mediated activation of circulating platelets, and in their
model, Metcalf and colleagues [6] show increased platelet surface P-selectin and SIV-related monocyte–platelet aggregates, coincidental with acute thrombocytopenia. The rapid onset of thrombocytopenia (on/before day 10) may be consistent with an effect of infection on platelets systemically, rather than on platelet production from megakaryocytes in the bone marrow, and the authors address this point experimentally by showing a lack of pronounced abnormality of megakaryocyte number/density and signs of increased platelet production (increased size and reticulation).

With respect to diagnosis of thrombocytopenia, Althaus and Greinacher note that possibly the biggest risk for patients “are the adverse effects resulting from treatment based on the misdiagnosis of chronic autoimmune thrombocytopenia” [11]. Although not relating directly to viral-related thrombocytopenia, this statement highlights one of the major worldwide problems in clinical hematology—the lack of reliable platelet-based assays that reflect the quality of platelets, or, of particular significance in thrombocytopenia, that can be used at low platelet count, or that can distinguish between decreased platelet production (eg, bone marrow defects) or increased platelet clearance (eg, autoantibodies) (Figure 1). Platelet count is the most common clinical measurement, but it (1) does not predict bleeding risk and (2) does not discriminate production vs destruction defects. As a consequence, patients are subjected to unnecessary platelet transfusions (particularly for prophylaxis, such as in the event of surgery or childbirth) or, if autoimmune thrombocytopenia is misdiagnosed, treatment with steroids or immunosuppressants. This exposes the patient to risk from unnecessary and expensive transfusions or from side-effects of the drugs. Also, the clinical treatment of low platelet-related disorders may vary between centers, and this emphasizes the lack of uniform guidelines and appropriate platelet tests suitable for use at a low platelet count. The utility of the aspartate aminotransferase-to-platelet ratio index as a surrogate marker of hepatic fibrosis in hepatitis C [12] and as a mortality predictor in HIV infection [13] underscores the importance of increasing our ability to monitor platelet biology in diseases involving thrombocytopenia.

Interestingly, the findings from Metcalf et al [6] may also provide a clue to a second aspect of HIV pathogenesis and treatment. Antiretroviral therapy has significantly modified the course of HIV disease, with longer survival and improved quality of life, but it has also led to the appearance of previously unrecognized complications, such as ischemic cardiovascular events. In particular, myocardial infarction has been associated with recent use of the antiretroviral guanosine analogue abacavir [14]. This risk was not explained by underlying established cardiovascular risk factors, but it was reduced after 6 months cessation of the drug [14]. Such a rapid reversal of cardiovascular event risk is intriguing and could hint at a role for platelets—and platelet–monocyte aggregates—in the observed increased rate of myocardial infarction. Antiviral drugs such as abacavir may increase platelet reactivity [15, 16] and are likely to also affect monocytes and endothelium; however, the impact of antiretroviral therapy on platelets, platelet–monocyte aggregates, and thrombocytopenia in patients with HIV is unknown. In this regard, the SIV/macaque model
may represent a powerful tool to simultaneously monitor platelet and platelet-monocyte biology before and after therapy with abacavir or other agents in acute and chronic infection settings. More broadly, as envoys at the frontline of the response, detailed analyses of platelets may provide new approaches for diagnosis and monitoring of treatment in clinical thrombocytopenia due to infection or other causes and may help stratify bleeding risk.

Notes

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