FOCUS ON RESEARCH

Drug-Induced Immune-Mediated Thrombocytopenia — from Purpura to Thrombosis

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In 1949, Ackroyd reported the abrupt onset of severe thrombocytopenia and purpura in patients receiving the sedative allylisopropylacetylcarbamide (Sedormid).[1] All the patients had taken Sedormid previously and had become sensitized to it. Today, this classic picture of drug-induced, immune-mediated thrombocytopenia is most often caused by quinine in outpatients and by vancomycin in hospitalized patients, as discussed by Von Drygalski et al. in this issue of the *Journal* (pages 904–910).

In 1973, Rhodes, Dixon, and Silver described thrombocytopenia and thrombosis occurring a week after the initiation of heparin therapy and provided evidence of an immune pathogenesis for this complication of heparin therapy.[2] In clinical trials of glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, or tirofiban), the abrupt onset of severe thrombocytopenia occurred in about 0.5 to 1% of patients who were receiving the agent for the first time; this unusual pattern of drug-induced thrombocytopenia was also found to have an immune-mediated pathogenesis.[3] These three distinct drug-induced immune-mediated thrombocytopenic syndromes — quinine-induced immune thrombocytopenia, heparin-induced thrombocytopenia and thrombosis, and thrombocytopenia within hours after a first exposure to a glycoprotein IIb/IIIa antagonist — differ from one another considerably with respect to pathogenesis, severity of thrombocytopenia, clinical manifestations, diagnostic laboratory tests, and treatment.

Classic drug-induced immune-mediated thrombocytopenia (the quinine type) is caused by unusual antibodies that bind not to the drug alone but to complexes of drug (or drug metabolite) bound to platelet glycoproteins — typically, glycoprotein IIb/IIIa (fibrinogen receptor), glycoprotein Ib/IX (von Willebrand factor receptor), or both. The antibody-coated platelets are cleared from the circulation by macrophages of the mononuclear–phagocytic system, which recognize the Fc "tails" of the drug-dependent antibodies. Platelets bear thousands of copies of glycoproteins IIb/IIIa and Ib/IX, and consequently, the antibodies in these cases cause severe thrombocytopenia; in about 85 to 90% of patients, the nadir platelet count is less than 20,000 per cubic millimeter.
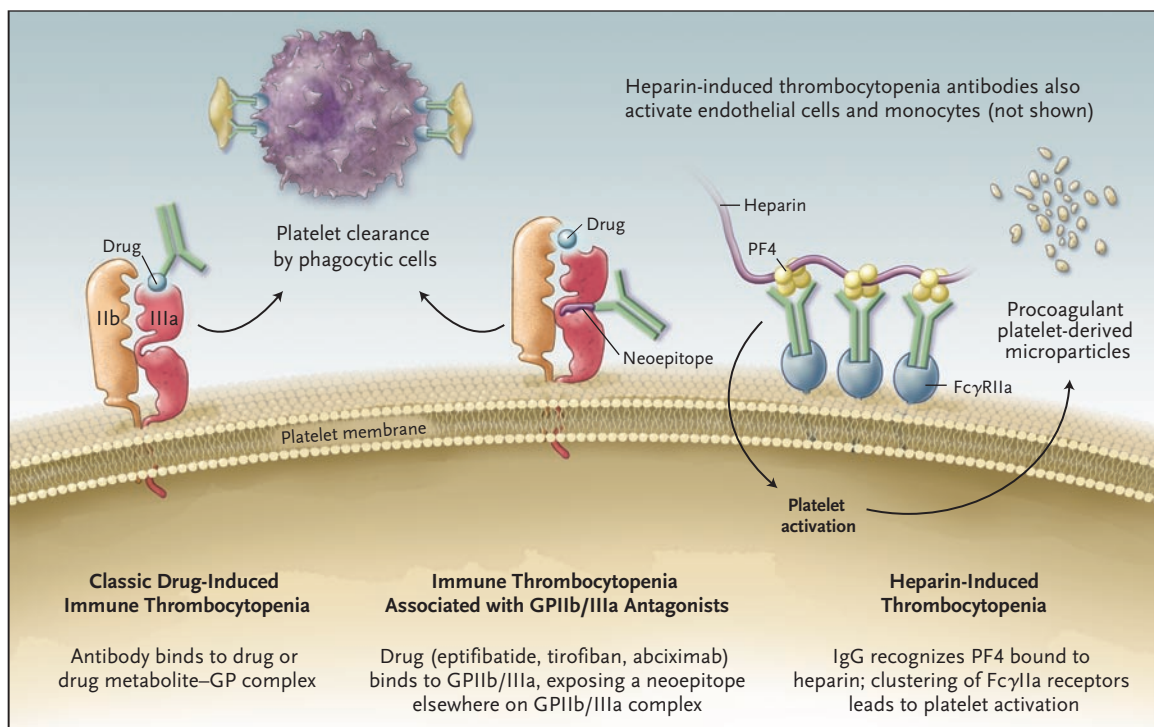
A useful clinical rule, in fact, is that immune-mediated thrombocytopenia is unlikely to be drug-induced unless it is this severe. One exception is the immune thrombocytopenia caused by carbimazole: in that instance, the moderate degree of thrombocytopenia (median platelet count at nadir, 60,000 per cubic millimeter) can be explained by the fact that the drug forms a complex with a less abundant glycoprotein, platelet–endothelial-cell adhesion molecule 1. Another, and a major, exception to this clinical rule is heparin-induced thrombocytopenia (see graph).

In classic drug-induced immune-mediated thrombocytopenia, isolated thrombocytopenia
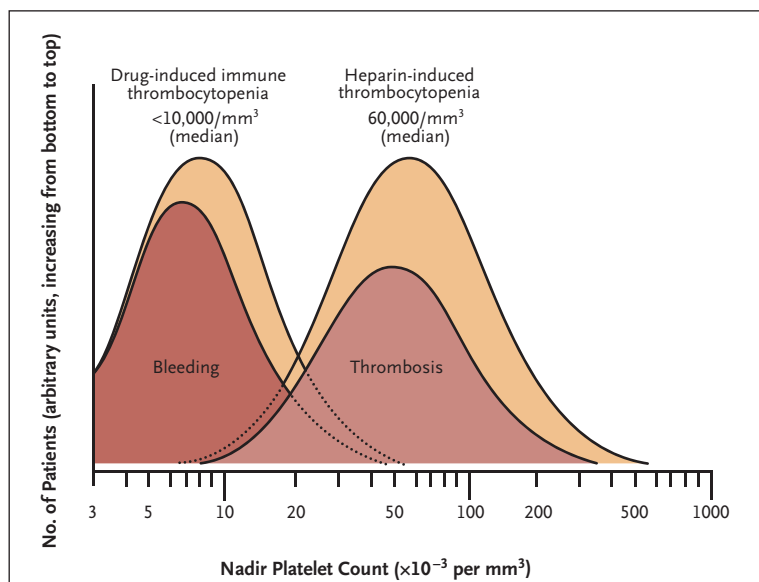
Nadir Platelet Counts Shown on a Log₁₀ Scale.

Heparin-induced thrombocytopenia is most common (not drawn to scale).

Heparin-induced thrombocytopenia antibodies also activate endothelial cells and monocytes (not shown)

Platelet clearance by phagocytic cells

Drug

IIb   IIIa

Platelet membrane

Drug

Neoepitope

Heparin

PF4

FcγRIIa

Procoagulant platelet-derived microparticles

Platelet activation

Classic Drug-Induced Immune Thrombocytopenia

Antibody binds to drug or drug metabolite–GP complex

Immune Thrombocytopenia Associated with GPIIb/IIIa Antagonists

Drug (eptifibatide, tirofiban, abciximab) binds to GPIIb/IIIa, exposing a neoepitope elsewhere on GPIIb/IIIa complex

Heparin-Induced Thrombocytopenia

IgG recognizes PF4 bound to heparin; clustering of FcγIIa receptors leads to platelet activation

Immune-Mediated Thrombocytopenia.

Naturally occurring antibodies can explain the rapid onset of thrombocytopenia with glycoprotein (GP) IIb/IIIa antagonists, even in the absence of previous drug exposure. In the case of abciximab-induced thrombocytopenia, naturally occurring antibodies against the mouse anti–GPIIb/IIIa domain are reported. FcγRIIa denotes Fcγ receptor IIa, and PF4 platelet factor 4.

and purpura (especially petechiae) are prominent. Especially with quinine, a minority of patients evince concomitant immune neutropenia, disseminated intravascular coagulation, or the hemolytic–uremic syndrome. Only about three dozen drugs have been convincingly implicated as causes of immune-mediated thrombocytopenia.[4,5] These drug reactions are rare, occurring in only a few exposed patients among many thousands. When the implicated drug (such as vancomycin) is given infrequently to a particular patient, onset of thrombocytopenia typically occurs about a week after therapy begins. When a person is exposed to a drug intermittently (as with quinine contained in tonic water or used to treat leg cramps), the onset is usually abrupt, reflecting re-exposure in a sensitized patient. Along with

the rapid drop in the platelet count, there may be an anaphylactoid reaction. This type of rapidly developing thrombocytopenia can occur in a patient who had previously received the drug many weeks or even years earlier. Treatment includes cessation of use of the drug and either simple support or measures to increase the platelet count (e.g., intravenous immune globulin), depending on the severity of the bleeding. Fatal hemorrhage, usually from intracranial bleeding, is rare.

Immune-mediated thrombocytopenia associated with glycoprotein IIb/IIIa antagonists resembles the classic syndrome with respect to the severity of thrombocytopenia, the risk of bleeding, and occasional anaphylactoid reactions. In these cases, however, the thrombocytopenia is usually evident within hours after drug adminis-

tration begins, even though most patients do not have a history of previous exposure to the glycoprotein IIb/IIIa antagonist. In the cases of eptifibatide and tirofiban, an explanation of this paradox is that naturally occurring antibodies against glycoprotein IIb/IIIa can bind to structures in the glycoprotein that are revealed by drug-induced conformational changes (a neoepitope) in the glycoprotein complex (see diagram). In the case of abciximab, which is a chimeric (human–mouse) Fab fragment, naturally occurring antibodies against the mouse anti–glycoprotein IIb/IIIa domain could explain an abrupt onset of thrombocytopenia.

With all three glycoprotein IIb/IIIa antagonists, antibodies induced by the first administration can lead to rapid-onset thrombocytopenia on re-exposure to the

drug. With abciximab, which binds irreversibly to platelets, thrombocytopenia can occur even a week after an initial brief exposure to the drug. Platelet transfusions can raise the platelet count in cases of thrombocytopenia caused by abciximab but are usually less helpful with thrombocytopenia caused by eptifibatide or tirofiban. In some patients who seem to have thrombocytopenia after the administration of a glycoprotein IIb/IIIa antagonist, there is platelet clumping in vitro, caused by naturally occurring EDTA-dependent antibodies; in such cases, no treatment is indicated, since the thrombocytopenia is spurious.

Heparin-induced thrombocytopenia is a distinctive antibody-mediated syndrome. The degree of thrombocytopenia is usually moderate (median platelet count at nadir, 60,000 per cubic millimeter); in 85 to 90% of patients, the platelet count is above 20,000 per cubic millimeter. The thrombocytopenia is caused by heparin-dependent IgG antibodies that bind to multimolecular complexes consisting of platelet factor 4 (PF4) bound to heparin. The antibodies activate platelets by means of their FcγIIa receptors, releasing platelet-derived procoagulant microparticles. These microparticles accelerate coagulation reactions and the generation of thrombin. Venous thromboembolism (the most common complication), arterial thrombosis (especially involving limb and cerebral arteries), adrenal hemorrhagic necrosis (due to adrenal-vein thrombosis), necrotizing skin lesions at heparin-injection sites, anaphylactoid reactions after an intravenous bolus of heparin, and overt disseminated intravascular coagulation can occur.

Stopping heparin therapy does not prevent further thrombosis, necessitating inhibition of thrombin or its generation by rapidly acting non-heparin anticoagulants. Anticoagulation with coumarin (warfarin) substantially increases the risk of microvascular thrombosis (causing venous limb gangrene and skin necrosis), and it is therefore contraindicated during the acute thrombocytopenic phase.

The pathogenic antibodies appear in the blood only transiently, which means that a rapid onset of thrombocytopenia on beginning heparin therapy occurs only in patients who have been exposed to heparin within the previous several weeks. Indeed, deliberate brief re-exposure to heparin, such as for cardiac surgery, is feasible after recovery from an episode of heparin-induced thrombocytopenia. Sometimes, thrombocytopenia and thrombosis begin a week or two after all heparin therapy has been stopped ("delayed-onset" heparin-induced thrombocytopenia). Unlike the purpura-inducing drug reactions discussed above, which only rarely have long-term effects, heparin-induced thrombocytopenia is often associated with long-term sequelae from thrombosis.

Laboratory detection of drug-dependent antibodies can be invaluable. For the classic syndrome, detection of drug-dependent (or drug-metabolite–dependent) binding of antibodies to platelet glycoproteins has high specificity but only moderate sensitivity, perhaps because relevant drug metabolites may not be present within the test system. In contrast, with thrombocytopenia associated with glycoprotein IIb/IIIa antagonists or heparin, the challenge is to distinguish nonpathogenic from pathogenic antibodies. Thus, for heparin-induced thrombocytopenia, test sensitivity is high, but specificity (especially with the use of enzyme immunoassays for antibodies against the PF4–heparin complexes) is only moderate. This is because heparin frequently induces formation of heparin-dependent antibodies, but only some of these have the biologic properties needed to activate platelets and thereby evince their pathogenic potential. Although commercial enzyme immunoassays permit many hospitals to offer standardized testing for antibodies against the PF4–heparin complexes, all the other tests for drug-dependent antibodies require referral to a handful of specialized reference laboratories.

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1. Ackroyd JF. The pathogenesis of thrombocytopenic purpura due to hypersensitivity to Sedormid (allyl-isopropyl-acetyl-carbamide). Clin Sci 1949;7:249-85.
2. Rhodes GR, Dixon RH, Silver D. Heparin induced thrombocytopenia with thrombotic and hemorrhagic manifestations. Surg Gynecol Obstet 1973;136:409-16.
3. Aster RH, Curtis BR, Bougie DW, et al. Thrombocytopenia associated with the use of GPIIb/IIIa inhibitors: position paper of the ISTH working group on thrombocytopenia and GPIIb/IIIa inhibitors. J Thromb Haemost 2006;4:678-9.
4. Warkentin TE, Kelton JG. Thrombocytopenia due to platelet destruction and hypersplenism. In: Hoffman R, Benz EJ Jr, Shattil SJ, et al., eds. Hematology: basic principles and practice. 4th ed. New York: Elsevier Churchill Livingstone, 2005:2305-25.
5. Tinmouth AT, Semple E, Shehata N, Branch DR. Platelet immunopathology and therapy: a Canadian Blood Services Research and Development symposium. Transfus Med Rev 2006;20:294-314.

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