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Pathobiology of Secondary Immune Thrombocytopenia

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Primary immune thrombocytopenic purpura (ITP) remains a diagnosis of exclusion both from nonimmune causes of thrombocytopenia and immune thrombocytopenia that develops in the context of other disorders (secondary immune thrombocytopenia). The pathobiology, natural history, and response to therapy of the diverse causes of secondary ITP differ from each other and from primary ITP, so accurate diagnosis is essential. Immune thrombocytopenia can be secondary to medications or to a concurrent disease, such as an autoimmune condition (eg, systemic lupus erythematosus [SLE], antiphospholipid antibody syndrome [APS], immune thyroid disease, or Evans syndrome), a lymphoproliferative disease (eg, chronic lymphocytic leukemia or large granular T-lymphocyte lymphocytic leukemia), or chronic infection, eg, with Helicobacter pylori, human immunodeficiency virus (HIV), or hepatitis C virus (HCV). Response to infection may generate antibodies that cross-react with platelet antigens (HIV, H pylori) or immune complexes that bind to platelet Fcγ receptors (HCV), and platelet production may be impaired by infection of megakaryocyte (MK) bone marrow–dependent progenitor cells (HCV and HIV), decreased production of thrombopoietin (TPO), and splenic sequestration of platelets secondary to portal hypertension (HCV). Sudden and severe onset of thrombocytopenia has been observed in children after vaccination for measles, mumps, and rubella or natural viral infections, including Epstein-Barr virus, cytomegalovirus, and varicella zoster virus. This thrombocytopenia may be caused by cross-reacting antibodies and closely mimics acute ITP of childhood. Proper diagnosis and treatment of the underlying disorder, where necessary, play an important role in patient management.

NORMAL PLATELET PRODUCTION

Platelet production starts with the complex bone marrow hematopoietic differentiation pathway known as megakaryopoiesis. Pluripotent hematopoietic stem cells commit to differentiation as either a common lymphoid progenitor or common myeloid progenitor (CMP). The CMP then commits to another level of differentiation into either the granulocyte-macrophage progenitor or the megakaryocyte-erythroid progenitor (MEP). The signals that cue the stages of commitment are as yet only beginning to be understood. GATA-1, a 50-kd zinc finger DNA-binding protein encoded by an X-linked gene, acts in concert with another protein, friend of GATA (FOG), which affects transcription
without binding to DNA. \textsuperscript{5,6} Cells committed to the megakaryocytic lineage and thrombopoiesis, rather than erythropoiesis, begin to express CD41 and CD61 (integrin \(\alphaIIb\beta3\) or \(\alphaIIb\beta1a\)), CD42 (glycoprotein [GP]Ib), and GPV.\textsuperscript{7,8} Once committed, each primitive megakaryocyte (MK) progenitor or burst-forming unit (BFU-MK), a large complex with satellite collections of MKs, is capable, under the influence of thrombopoietin (TPO) and interleukin (IL)-3 and Steel factor, of producing up to several hundred mature MKs. Another form of mature progenitor, the colony-forming unit (CFU-MK) produces colonies that consist of 3 to 50 MKs responsive to TPO, although approximately 25% require both TPO and IL-3 to generate platelets.\textsuperscript{9,10} Each MK produces up to about 4,000 platelets before undergoing apoptosis. A normal adult human produces about 10\(^{11}\) platelets daily, and this rate can be increased 20-fold with exogenous TPO.\textsuperscript{4}

TPO and its receptor, c-Mpl, are the major identified regulators of MK and platelet production and also have key roles in the differentiation of hematopoietic stem cells. TPO signals via c-Mpl through the Jak-STAT,\textsuperscript{11-14} Ras-Raf-MAPK,\textsuperscript{15} and PI3K pathways,\textsuperscript{16} which promote survival, proliferation, and polyploidy in MKs. In vitro TPO induces expression of \(c-MYC\), a proto-oncogene active in various physiologic processes and in the dysregulation of MK production.\textsuperscript{57} The implications of this finding have yet to be addressed in vivo. The stages of thrombopoiesis include regulation of transcription, MK development, endomitotic spindling of the MK nucleus, cytoplasmic maturation, formation of active projections (protoplatelets) from the MK cytoplasm, extrusion of these proplatelets from the bone marrow stroma into the circulation, and, finally, separation and maturation into individual platelets.\textsuperscript{18}

**PRIMARY ITP**

**Increased Platelet Destruction**

There is extensive evidence that patients with ITP develop autoantibodies, generally IgG, that bind to platelets, which leads to their phagocytosis via Fc\(\gamma\) receptors expressed on tissue macrophages located predominantly in the spleen and liver.\textsuperscript{1,19,25} What provokes autoantibody production is unknown, but most ITP patients have antibodies against integrin \(\alphaIIb\beta3\) (GPIIa/IIIb), GP Ib/IX, or multiple platelet proteins by the time clinical disease, characterized by thrombocytopenia and mucocutaneous bleeding, is evident.\textsuperscript{25} Platelet destruction within macrophages or dendritic cells degrades platelet antigens to peptides. Peptides are expressed on the cell surface in the context of MHCI and costimulatory help for presentation to T cells, amplifying the initial immune response and possibly generating cryptic epitopes from other platelet glycoproteins, which spreads the immune response to involve multiple platelet antigens.\textsuperscript{24} ITP is characterized by reducing T-regulatory cells (reviewed in Stasi et al.\textsuperscript{25}) and Thy-2 cytokines,\textsuperscript{26} leading to a Thyl/Thy0 profile (reviewed in Ho-Yen et al.\textsuperscript{27}) and upregulation of costimulatory molecules\textsuperscript{26,29} that facilitates proliferation of antigen-derived CD4-positive T cells and T-cell/B-cell cooperation to generate isotype-switched, high-affinity antibodies.\textsuperscript{30} There is emerging evidence that cytotoxic T cells are increased in the bone marrow\textsuperscript{31} and may contribute to platelet destruction\textsuperscript{32,33} or impaired production (see below). The importance of platelet destruction in the periphery is affirmed by the fact that two thirds of patients develop and maintain remission after splenectomy, which curtails phagocytosis, but may also reduce antibody production over time. Likewise, most first- and second-line medical therapies for ITP are believed to work by impeding platelet destruction.\textsuperscript{2,3}

**Decreased Platelet Production**

For many years, it was assumed that platelet production increased dramatically in patients with ITP as a compensatory response to thrombocytopenia mediated by peripheral destruction. However, it has become apparent, based on studies of in vivo kinetics, that platelet production varies from mildly increased to mildly impaired in most patients with ITP.\textsuperscript{34-36} Synthesis of TPO in the liver is not regulated at the level of transcription.\textsuperscript{37} Plasma TPO levels in patients with ITP are normal to minimally increased\textsuperscript{38} as a result of increased clearance of the hormone bound to antibody-coated platelets and binding to an expanded MK mass.\textsuperscript{39} ITP antibodies, and possibly T cells,\textsuperscript{24} inhibit MK development in vitro \textsuperscript{55,56,40} and may cause apoptosis and intramedullary destruction of platelets in vivo,\textsuperscript{41} contributing to failure of splenectomy and other treatments that act by inhibiting clearance. These findings also provide additional rationale for the effectiveness of TPO-receptor agonists.

**MECHANISMS OF IMMUNE THROMBOCYTOPENIA IN SECONDARY ITP**

**Autoimmune Disorders**

**Systemic Lupus Erythematosus**

Antinuclear antibodies are common in patients with ITP, but few develop systemic lupus erythematosus (SLE). However, approximately 20% to 25% of patients with SLE develop moderate-severe thrombocytopenia, which can be readily managed if immune-mediated or can be a marker of severe systemic disease.\textsuperscript{42} The pathogenesis of thrombocytopenia is multifactorial and includes: (1) antiplatelet glycoprotein antibodies as found in ITP; (2) immune complexes of diverse composition; (3) antiphospholipid antibodies (APLA) (see below); (4) vasculitis; (5) thrombotic microangiopathy;
(6) hemophagocytosis; (7) autoantibodies to the c-Mpl receptor and MK; and (8) bone marrow stromal alterations not characteristic of ITP. Therefore, a thorough clinical and laboratory assessment is often required before a diagnosis of secondary immune thrombocytopenia should be entertained. It is also important to limit the use of corticosteroids and cytotoxic agents in these often heavily treated patients. Splenectomy may provide only transient benefit and is reserved for patients in whom severe thrombocytopenia is the predominant reason for treatment.

Antiphospholipid Syndrome

APLA (lupus inhibitors and those that bind anionic phospholipids, beta-2-glycoprotein I [β2GPI], and prothrombin, among other specificities) are found in 20% to 70% of patients with ITP, depending on the thoroughness of the search, but their significance is debated and few patients develop antiphospholipid syndrome (APS). The presence of APLA per se does not influence the effectiveness of ITP therapy in terms of inducing a platelet response. However, some, but not all, studies suggest such patients may be at risk for thrombosis once they do respond. The diagnosis is complicated by the fact that approximately 25% of patients with APS develop mild-moderate thrombocytopenia. Severe thrombocytopenia in APS correlates more closely with the presence of antiplatelet glycoprotein antibodies than either APLA or clinical manifestations. However, platelets do express receptors for β2GPI, which in theory could lead to APLA-mediated platelet activation alone or in association with other agonists, and there are anecdotal reports of response to aspirin, perhaps by inhibiting coagulation-mediated platelet consumption.

Thyroid Disease

Mild-moderate thrombocytopenia is found commonly in patients with hyperthyroidism. Platelet survival is reduced, but returns to normal with restoration of the euthyroid state. Similarly, mild thrombocytopenia responsive to hormone replacement also occurs in some patients with hypothyroidism, possibly due to impaired production. However, patients with immune thyroid disease develop immune thrombocytopenia requiring ITP-directed therapy more commonly than can be attributed to chance. Moreover, antithyroid antibodies occur commonly in adults and children with ITP, leading some to recommend testing thyroid function in nonresponsive patients and prior to splenectomy.

Evans Syndrome

Patients with Evans syndrome (ES) develop immune hemolytic anemia, immune thrombocytopenia, and occasionally immune neutropenia. The remarkable coincidence of two or three seemingly unrelated hematopoietic cell antibodies has now been associated with an underlying complex immunodeficiency in some patients (see below). Hemolysis may precede or follow the onset of thrombocytopenia and is typically more refractory to intervention, and the two cytopneas are often dysynchronous in their manifestations. The response rates to ITP-directed therapy, including splenectomy, are less than in primary disease. More than 50% of children and some adults with ES have a clinical and pathological presentation that overlaps with the autoimmune lymphoproliferative syndrome (ALPS). ALPS is characterized by the chronic accumulation of nonmalignant lymphocytes leading to lymphadenopathy and (hepato)splenomegaly, >1% CD3+, CD4−, CD8− (double-negative) T cells, impaired Fas-receptor/ligand mediated apoptosis in vitro due to mutations in Fas (CD95/Apo-1), or less commonly Fas ligand (Fas-L), caspase-8 or -10. Immune thrombocytopenia develops in about 20% of patients and may respond relatively poorly to ITP therapies, although recent experience with rituximab and mycophenolate have been encouraging. Immune thrombocytopenia and ES also occur in approximately 10% to 15% of patients with common variable immune deficiency (CVID) and hypogammaglobulinemia. The onset of immune thrombocytopenia is typically in the third decade, although onsets from childhood to old age have been reported and typically precede the diagnosis of CVID by several years. The diagnosis should be sought in any patient with recurrent infection, as immunosuppressive therapy poses some risk and replacement with immune globulin is indicated.

Lymphoproliferative Disorders

There is an increased incidence of immune thrombocytopenia in patients with chronic lymphocytic leukemia (CLL), CD8 T-lymphocyte large granular lymphocytic leukemia (LGL), and possibly Hodgkin’s disease. In CLL, it may be difficult to distinguish immune thrombocytopenia from marrow infiltration and splenomegaly or in the setting of treatment with fludarabine. Severe thrombocytopenia, which occurs in about 1% of patients with LGL, has been associated with clonal suppression of megakaryopoiesis.

Infectious Agents

Human Immunodeficiency Virus

The association between immune thrombocytopenia and the acquired immunodeficiency syndrome and subsequently as a presenting feature of HIV infection has been recognized since the early to mid 1980s. Thrombocytopenia is characterized by an immune component similar in presentation and response to ITP, most evident in the early stages of disease, and...
Pathobiology of secondary immune thrombocytopenia

progressive ineffective hematopoiesis with a decrease in platelet production as a result of MK infection or marrow infiltration as the disease progresses. HIV binds the CD4 receptor and coreceptors expressed on MKs, which is internalized, leading to dysplasia, blebbing of the surface membrane, and vacuolization of peripheral cytoplasm. The immune component is mediated through molecular mimicry involving anti-HIV antibodies that cross-react with platelet-membrane glycoproteins, immune complexes, and anti-GPIIIa antibodies that induce platelet lysis, at least in vitro, through a peroxidase-mediated pathway. Secondary causes of thrombocytopenia during HIV infection are generally the result of underlying opportunistic infections, malignancy, medications (eg, chemotherapeutic agents, interferon, and antiviral agents), or, less frequently, thrombotic microangiopathy.

HIV should be excluded in at-risk patients who present with ITP. Patients who present with immune thrombocytopenia early in the course of HIV infection respond to medical therapy (corticosteroids, intravenous anti-D, and intravenous immunoglobulin [IVIG]) and splenectomy as well as patients with ITP without proliferation of HIV infection or untoward incidence of opportunistic infection. Thrombocytopenia in patients with more advanced disease generally responds to highly active antiretroviral therapy.

Hepatitis C Virus

In some parts of the world, hepatitis C virus (HCV) infection has been detected in up to 30% of patients presenting with immune thrombocytopenia, even in the absence of overt hepatitis. The diagnosis of immune thrombocytopenia is confounded in patients with advanced liver disease because of hypersplenism and decreased production of TPO. Antiplatelet antibodies are so common as to lack diagnostic utility. Possible mechanisms leading to immune destruction include binding of HCV followed by anti-HCV antibody to the platelet membrane, circulating anti-viral immune complexes, and direct infection of MKs with expression of HCV RNA in platelets. Bone marrow production may be suppressed by HCV or interferon antiviral treatment. Patients typically present with significant bleeding in the presence of moderate thrombocytopenia. Optimal management involves suppression of viral replication. Use of TPO-receptor agonist may raise platelet counts sufficiently to permit sustained treatment with interferon-based therapy in a high proportion of patients.

Helicobacter pylori

The success of eradicating infection with Helicobacter pylori among patients presenting with otherwise typical ITP varies from less than 1% to 5% in the United States to over 60% in Italy and Japan, with intermediate values reported from other countries. Several hypotheses relating H pylori to thrombocytopenia and to explain this variation have been proposed, including (1) regional differences in the expression of CagA-related genes, to which antibodies that cross-react with ITP platelets are generated through the process of molecular mimicry; (2) cross-reactivity between H pylori cytotoxin-A protein and platelet antigens; (3) adsorption to platelets of Lewis antigens, which are induced by H pylori in a strain-specific manner, where they are targets for anti-Lewis antibodies in patients with appropriate genetic backgrounds; (4) platelet activation and clearance through an interaction with H pylori–bound von Willebrand factor via platelet GPIIb receptor IIB and enhanced platelet phagocytosis, both of which are reversed after successful eradication; and (7) genetic variation, eg, the frequency of HLA-DRB*11,14, and HLA-DQB1*03 is higher in patients with immune thrombocytopenia positive for H pylori than in those who are H pylori–negative, and those expressing HLA-DQB1*03 have a higher probability of a platelet response to eradication therapy. Of interest, titers of autoantibodies fall 12 to 24 weeks after successful eradication, suggesting additional mechanisms are operative.

Many, but not all studies indicate that H pylori is found more commonly in patients with disease that is milder in severity and of more recent onset. H pylori should be sought in all patients who come from regions where there is a strong association, but no consensus has emerged in the United States as to whether all ITP patients should be tested and/or treated.

Vaccination and Other Infections

Transient but severe thrombocytopenia occurs with an incidence of 1 in 25,000-40,000 vaccinations for measles, mumps, and rubella, and less commonly after vaccination against pneumococcus, Haemophilus influenzae B, varicella zoster virus (VZV), and hepatitis B. More than 80% of patients recover within 2 months, typically within 2 to 3 weeks, with less than 10% evolving into chronic ITP responsive to ITP-directed therapy. Thrombocytopenia occurs occasionally after naturally occurring infection with cytomegalovirus, rubella, Epstein-Barr virus, VZV, the severe acute respiratory syndrome coronavirus, and many others. Thrombocytopenia may be immune, due to infection of MKs or progenitors, or result from
Post-transfusion Purpura

Post-transfusion purpura (PTP) is a rare but dramatic cause of immune thrombocytopenia. The typical patient is a multiparous or multitransfused female who presents with hemorrhage and the sudden onset of profound thrombocytopenia a mean of 7 days after transfusion of a blood product containing platelet antigens. The disease occurs primarily among the approximately 1% of Caucasians who are homozygous for HPA1b allele on GPIIa, although other specificities have been reported. Patients not only develop anti-HPA1a antibodies, but also self-reactive antibodies of undetermined specificity, presumably as a result of epitope spread. Remarkably, PTP is not seen in women with neonatal alloimmune thrombocytopenia due to anti-HPA1a antibodies. Patients are at a high risk of bleeding and the clinical course is often protracted without therapy. IVIG is the standard of care. The utility of preventing subsequent exposure to the inciting antigen using washed HPA1b blood products is logical but unproven.

Drug-Induced Thrombocytopenia

The first case of drug-induced thrombocytopenia (DITP) was identified with quinine 140 years ago.155 DITP can result from bone marrow toxicity or immune-mediated destruction of platelets. Several hundred therapeutic agents have been implicated,156 but few reports are compelling.157 The diagnosis of DITP is generally based on this clinical scenario: (1) therapy with a candidate drug precedes thrombocytopenia by sufficient time to develop antibody; (2) there is no such temporal relationship with another drug; (3) all other reasonable causes have been excluded; (4) recovery occurs upon the discontinuation of the drug; and (5) re-exposure to the drug, if attempted, leads to recurrent thrombocytopenia. However, these criteria are rarely met, as underlying clinical circumstances are often complex and introduction and withdrawal of multiple drugs within a short time frame is common. Moreover, testing for drug-dependent antibodies is fraught with difficulty (solubility, concentration, effect on platelet activation, in vivo metabolism, lack of control patients on drug but without thrombocytopenia, etc), and few patients require rechallenge.

DITP typically affects only a small percentage of exposed patients, with the exception of heparin-induced thrombocytopenia (see below), and no known genetic predispositions or environmental criteria have been identified. Diverse mechanisms have been postulated to cause DITP, including immune complexes (heparin); induction of autoantibody (gold salts); anti-drug-specific antibodies (abciximab); drugs that induce conformational changes in platelet antigens that are recognized by antibody (fiban drugs); drug-induced antibodies that bind to platelet membranes in the presence of soluble drug (quinine); and hapten-dependent antibodies (some beta-lactam antibiotics)158,157 (Table 1). Immune or nonimmune marrow suppression or nonimmune destruction (typified when ristocetin was introduced as an antibiotic), or thrombotic microangiopathy (eg, ticlopidine and possibly clopidogrel) occur less commonly.

Not surprisingly, most drug-dependent antibodies appear to recognize antigens involving prevalent platelet glycoprotein complexes such as αIIbβ3 or Ib/V/IX.159,160 It has been hypothesized that drugs become immunogenic when they bind to a larger molecule, such as a protein generating antibodies to the drug itself or a drug-protein complex or a drug-induced alteration of a binding protein to induce neoepitopes.161 These hypotheses have been based primarily on the kinetics of drug-dependent inhibition of antibody binding to platelets or other cells rather than isolation of drug-protein, drug-antibody, or drug-protein-antibody complexes. Bougie and colleagues have proposed a model to reconcile existing hypotheses using quinidine-dependent antibodies as a model.162 They posit that the drugs enhance the affinity of preexisting antiplatelet glycoprotein antibodies by providing a bridge between the complement determining region on the antiplatelet antibody with a drug-binding epitope on the platelet membrane. Whether the drug binds first to the antibody or to the platelet membrane protein depends on its relative affinity.

Thrombocytopenia Induced by Platelet Inhibitors

Tirofiban and epifibatide used to prevent restenosis after coronary angioplasty can cause severe thrombocytopenia within hours of the first or subsequent doses. These ligand-mimetic drugs (fibs) competitively inhibit fibrinogen from binding to the platelet αIIbβ3 integrin receptor.163 These drugs may act as mixed agonists/antagonists. It is presumed that binding induces novel epitopes on αIIbβ3 that are recognized by preexisting (possibly preactivated) or drug-induced antibodies.

Abciximab is a chimeric human Fab fragment linked to specificity-determining sequences from a murine antibody to αIIbβ3 integrin that blocks fibrinogen binding. Sudden and often profound thrombocytopenia163-165 develops within hours in about 0.5% to 1% of patients treated with abciximab for the first time, and in approximately 10% of those treated a second time. Delayed onsets after first exposure occur less commonly. Most healthy individuals have naturally occurring antibodies to the C-terminus on human Fab (the papain cleavage site), which is
present in the chimeric antibody. In contrast, patients who develop severe thrombocytopenia within a few hours of starting an infusion have preexisting antibodies that recognize the region that imparts GPIIIa specificity, although an effect of the drug on the conformation of GPIIbIIIa cannot be excluded. Abciximab-coated platelets may be detected for 10 to 14 days after treatment in some individuals, presumably due to coating of MKs or shuttling between destroyed and circulating platelets. IVIG and platelet transfusions have been used successfully to treat patients with profound abciximab- and fiban-induced thrombocytopenia.

Table 1. Mechanisms Underlying Drug-Induced Thrombocytopenia

| Classification (drugs) | Mechanism | Incidence |
|------------------------|-----------|-----------|
| Hapten-dependent antibody (penicillin, some cephalosporin antibiotics) | Hapten links covalently to membrane protein and induces drug-specific immune response | Very rare |
| Quinine-type drug (quinine, sulfonamide antibiotics, nonsteroidal anti-inflammatory drugs) | Drug induces antibody that binds to membrane protein in presence of soluble drug | 26 cases per 1 million users of quinine per week, probably fewer cases with other drugs |
| Fiban-type drug (tirofiban, eptifibatide) | Drug reacts with glycoprotein IIb/IIIa to induce a conformational change recognized by antibody (not yet confirmed) | 0.2%-0.5% |
| Drug-specific antibody (abciximab) | Antibody recognizes murine component of chimeric Fab fragment specific for platelet β3 | 0.5%-1.0% after first exposure, 10%-14% after second exposure |
| Autoantibody (gold salts, procainamide) | Drug induces antibody that reacts with autologous platelets in absence of drug | 1.0% with gold, very rare with procainamide and other drugs |
| Immune complex (heparins) | Drug binds to platelet factor 4, producing immune complex for which antibody is specific; immune complex activates platelets through Fc receptors | 1%-3% among patients treated with unfractionated heparin for 7 days, rare with low-molecular-weight heparin |

Table adapted from Aster and Bougie with permission from the Massachusetts Medical Society.

Thrombocytopenia From Drug-Induced Autoantibodies

Rarely, drugs stimulate the formation of autoantibodies that target platelets in the absence of the inciting drug. Autoantibodies with an affinity for platelet GPV have developed in a few patients with rheumatoid arthritis treated with gold salts. Drug-independent autoantibodies have also been reported in occasional patients treated with quinine, procainamide, sulfonamide antibiotics, and interferons alpha and beta. Thrombocytopenia is often protracted and may require ITP-directed therapy.

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) develops in 1% to 3% of patients who receive unfractionated heparin (UFH) intravenously in therapeutic doses for a minimum of 5 days. The prevalence is lower in patients treated exclusively with low-molecular-weight heparin or when UFH is given as thromboprophylaxis. The incidence is highest in patients undergoing cardiopulmonary bypass and orthopedic surgery, which is associated with intense platelet activation, inflammation, and underlying vascular disease, and lowest in children, during pregnancy, and patients receiving heparin during dialysis. Approximately 25% of patients develop arterial and/or venous thrombi, a number that may exceed 50% if the disease is not recognized and managed promptly. In treatment-naive subjects, an unexplained fall in the platelet count of greater than 40% begins 5 to 10 days after exposure; thrombosis typically follows soon after but can occur concomitantly or on occasion precede the fall in platelet count. Thrombocytopenia may occur within hours after exposure to heparin in patients who had been treated within the preceding 100 days in whom circulating antibodies may persist. Rarely, thrombocytopenia may be discovered or develop 1 to 2 weeks after the last known exposure (delayed HIT).
HIT antibodies recognize oligomeric complexes formed between platelet factor 4 (PF4) released from activated platelets and heparin or glycosaminoglycans expressed on endothelium, monocytes, and platelets.176-178 Heparin/PF4-IgG complexes bind to FcγRIIa (CD32) on platelets, targeting them for clearance, but also stimulating cell activation with release of additional PF4. Binding of these PF4 followed by antibody to glycosaminoglycans on endothelial cells179 and monocytes180,181 stimulates the expression of tissue factor, accelerating coagulation and reinforcing platelet activation. Heparin-independent anti-PF4 antibodies have been postulated to account for delayed HIT.175

Diagnosis rests on clinical recognition of the temporal relationship between heparin exposure and the signature clinical manifestation. Enzyme-linked immunosorbent assay (ELISA)-based assays that detect IgG, IgA, and IgM antibodies have a high sensitivity and negative predictive value but a false positive rate that can exceed 50% in patients post-bypass surgery,182 with unacceptably high false positive rates in other settings as well. The performance characteristics may be improved using newer assays that measure only IgG antibodies and using higher diagnostic cut-off optical density measurements, with little loss of negative predictive value.183 Assays based on platelet activation are more specific but less sensitive and the results are not routinely available in real time. Once the diagnosis is strongly suspected (moderate–high pretest probability), exposure to all forms of heparin (including flushes, heparin-bonded catheters, etc) must be discontinued and anticoagulation begun with either a direct thrombin inhibitor, such as hirudin or argatroban or an anti-Xa agent such as danaparoid, where available.184 Therapy reduces new thromboembolic events by approximately two thirds, but mortality rates and amputations due to preexisting clots are not affected. Therapy is continued until thrombocytopenia resolves and is overlapped with coumadin at a therapeutic international normalized ratio (INR) for 3 to 5 days. Anticoagulation is generally continued for 3 months, but may be extended depending on the underlying reason for the initial use of heparin and the sequelae of HIT-induced thrombosis.

CONCLUSION

There is compelling reason why the diagnosis of ITP requires the exclusion of other causes of thrombocytopenia, including conditions classified as secondary immune thrombocytopenia.185 The pathobiology of the various causes of secondary immune thrombocytopenia is often more complex than ITP (eg, marrow suppression or intravascular consumption due to clotted or vascular damage), they differ in natural history and responsiveness to ITP-directed therapy (eg, ES), and optimal therapy requires treatment of the underlying condition, eg, chronic infection, lymphoproliferative disease (CLL, LGL), and autoimmune conditions (eg, SLE, APS). Treatment of H pylori, HIV, or HCV may suffice to increase the platelet count and avoid protracted and sometimes ineffective and toxic treatments required to manage ITP. Drug-induced thrombocytopenias require recognition and withdrawal of the inciting agent. Posttransfusion purpura requires immediate recognition and treatment with IVIG. Patients with APS may be at risk for thrombosis. Treatment strategies for these forms of immune thrombocytopenia are discussed in greater detail elsewhere in this issue.

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