

## AUTOIMMUNE THROMBOCYTOPENIA

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Autoimmune thrombocytopenia is due to accelerated destruction of auto-antibody sensitized platelets by reticular-endothelial system. It can be generally divided into 3 broad groups: 1) Idiopathic thrombocytopenic purpura (ITP), 2) Drug – induced immune thrombocytopenia, and 3) Thrombocytopenia associated with viral infection. As other causes may also be involved besides platelet autoantibodies in viral infection–induced thrombocytopenia, this will not be discussed in this review.

### **Idiopathic thrombocytopenic purpura, ITP**

Pathophysiology. Autoimmune thrombocytopenia may have no underlying cause (ITP) or may be associated with an underlying connective tissue disorder (e.g. systemic lupus erythematosus) or a lymphoproliferative disorder (e.g. Lymphoma). Harrington et al was the first to show that infusion of plasma from patients with ITP into healthy volunteers induced a rapid destructive thrombocytopenia. Shulman et al repeated these experiments with plasma fractions and located the thrombocytopenic factor in the gammaglobulin fraction, suggesting that it was an IgG antibody. In 50-70% of patients with ITP, the antibodies are directed against GP IIb/IIIa and GP Ib-IX complexes. Very occasionally, the antibodies may have specificity for other platelet membrane glycoproteins such as GP IV, GP V and GP Ia/IIa. Recently, epitopes of the antibodies have been mapped to various sites on these glycoproteins including 65kDa GPIb $\alpha$  fragment, a 50kD cysteine-rich region of GP IIIa and a cytoplasmic C-terminal domain of GP IIIa.

Clinical Features and Diagnosis. Acute ITP which occurs commonly in children,

frequently resolves spontaneously after 3 –6 months; whereas chronic ITP, which mainly affects adults, persists for many years unless remission is induced by treatment. The diagnosis is made clinically by exclusion of other causes of thrombocytopenia. Apart from signs of bleeding (purpura and bruises), the patients have no signs of an underlying disease. The presence of splenomegaly would strongly suggest an underlying cause such as bone marrow dyscrasia, connective tissue disorder and infection. Detection of an anti-platelet antibody (on the platelet surface – direct test) is not essential for the diagnosis of ITP. Platelet associated IgG assay is now considered to be nonspecific. Antigen-capture assays or platelet glycoprotein antibody tests (e.g. MAIPA & immunobead assay) are highly specific (80-100%) but not sufficiently sensitive (50-70%) because in about 50% of ITP patients, the identity of the autoantigen is still unknown. For secondary ITP, tests for the underlying autoimmune or lymphoproliferative disorder (e.g. antinuclear antibody, bone marrow, lymph-node biopsy, etc) will be helpful.

Management of ITP. The initial treatment of ITP includes glucocorticosteroid, anabolic steroid (danazol), high dose IgG and anti-D infusion. With steroid therapy, the aim is to maintain the patient on the lowest dose of the drug that will keep the platelet counts in a safe range ( $>30 \times 10^9/L$ ) and to avoid side-effects. IgG infusion is useful to induce a rapid rise of the platelet transiently, usually when the platelet count is very low ( $<10 \times 10^9/L$ ) and the risk of bleeding high. Splenectomy is recommended if ITP has yet not spontaneously remitted after 3 – 6 months and if the blood platelet count is not at a safe level. Second line drugs for ITP treatment include azathioprine,

cyclophosphamide, vincristine, combination chemotherapy (e.g. CVP), cyclosporin and recently rituximab.

#### **Drug-induced immune thrombocytopenia.**

Pathophysiology. Drug hypersensitivity may result in the formation of antibodies that bind drug-dependently to platelets leading to premature platelet clearance by the reticulo-endothelial system and consequently thrombocytopenia. Drugs commonly implicated include quinine, heparin, co-trimoxazole, ampicillin, cephalosporin, ranitidine, rifampicin, gold, sodium valproate and carbamazepine. Historically, two mechanisms have been postulated. Shulman proposed that the antibody reacted with the drug and the drug-antibody complex then bound nonspecifically to platelets resulting in their destruction by “an innocent bystander” mechanism. On the other hand, Ackroyd postulated that the antibody reacted directly with a drug-platelet complex. It is now clear that in most drug-induced thrombocytopenias, the antibody is directed against a platelet membrane glycoprotein-drug complex consistent with Ackroyd’s hypothesis. In quinine- and quinidine-induced thrombocytopenia, for example, the predominant antibody reacts with a drug-dependent epitope on GPIX. In some patients, antibodies with specificity against GPIIb $\alpha$ , GPIIb/IIIa and GP V have been reported. We recently showed that the anti- GPIIb $\alpha$  antibody is directed at a specific 11 amino acid region (residues 283-293) of the glycoprotein (Burgess JK et al, 1998) and the anti-GPIX antibody recognizes an epitope located in the region spanning residues R110 to Q115 of GPIX (Asvadi et al, 2003). Interestingly the epitope of three other drug-induced antibodies, namely quinidine-, ranitidine- and rifampicin-induced antibodies, have been mapped to the same region on GPIX as that of quinine-induced antibody indicating this region of GP IX is highly immunogenic when it complexes with a drug. Further analysis of this region of GP IX may provide useful insights into the pathogenesis of drug-induced immune thrombocytopenia. In carbimazole-induced thrombocytopenia, the

drug-related platelet autoantigen is PECAM-1. In some drug-induced thrombocytopenias, for example those due to methyldopa and gold, the platelet antibody binds drug-independently to platelets, like that in ITP, and thrombocytopenia may persist even after drug withdrawal.

#### Clinical features and Diagnosis.

Quinine-induced purpura is associated with a severe thrombocytopenia of an abrupt onset. The patients frequently present with extensive petechiae and bruises, and less commonly mucosal bleeding. The platelet count usually drops below  $10 \times 10^9/L$ . The thrombocytopenia due to other drugs is not usually as severe.

#### Thrombocytopenia due to GP IIB/IIIa inhibitors.

Pathophysiology and clinical picture. Platelet fibrinogen receptor antagonists (GP IIB/IIIa inhibitors) have been used in the treatment of patients with coronary artery disease. Currently, three GPIIb/IIIa antagonists are widely used in clinical practice – abciximab, tirofiban and eptifibatide. In the clinical trials, thrombocytopenia with an incidence of about 1% has been noted. In contrast to other drug-induced immune thrombocytopenia, severe thrombocytopenia can develop at the first exposure to the drug, sometimes even within a few hours, suggesting the presence of a pre-existing antibody. The incidence of thrombocytopenia is increased on re-exposure. Several studies have demonstrated a drug dependent antibody as the underlying cause. Anti-abciximab antibodies have been detected in the patients as well as healthy human subjects who have not been previously exposed to the drug. The antibody in the affected patients appears to recognize the murine component of the human-mouse chimeric Fab in abciximab. In contrast, the antibody in the healthy subjects recognizes an epitope on the human part of the Fab molecule. In tirofiban and eptifibatide-induced thrombocytopenia, the antibody appears to bind to an epitope that emerges only after drug binding to GPIIb/IIIa, a ligand induced binding site (LIBS).

#### Heparin-induced thrombocytopenia (HIT)

Pathophysiology and clinical features.

HIT is another drug-induced autoimmune thrombocytopenic disorder. In contrast to other thrombocytopenic states, it is frequently complicated by thrombosis which is life- or limb-threatening. The mild-moderate thrombocytopenia (platelet count 40-100 x10<sup>9</sup>/L) usually occurs 5-14 days after the commencement of heparin therapy. Bleeding is usually not a problem. In HIT, the IgG antibody is usually directed against an epitope on PF4/heparin complex but very rarely on IL-8/heparin or NAP2/heparin complex. The antigen-antibody complex then binds to platelets via platelet FcγRIIA receptors causing intense platelet activation. This leads to release of platelet procoagulant materials and platelet aggregation. In addition, the antibody binds to PF4/heparin complex on the endothelial cell surface. Concomitant platelet activation and endothelial cell immuno-injury are the most likely cause of the thromboembolic complications.

Diagnosis of Drug-induced Thrombocytopenia (including HIT and GPIIb/IIIa inhibitor):

Diagnosis is made clinically based on the characteristic clinical features, described above. Importantly, thrombocytopenia must occur during administration of the offending drug, and resolves after drug withdrawal, except for drugs such as methyl dopa and gold. Every attempt must be made to exclude other causes of thrombocytopenia. Whenever possible the diagnosis should be confirmed by a laboratory test that detects the drug-dependent antibody. Unlike ITP, the antibody is present in reasonably high titers in the patient's serum and can usually be detected by an 'indirect test' using assays such as ELISA, flow cytometry and antigen-capture assays (e.g. MAIPA). In HIT, the commonly used tests are ELISA, platelet aggregation test, <sup>14</sup>C-serotonin release assay and HIPA test.

Management of Drug-induced Thrombocytopenias. It is essential to stop the offending drug and the thrombocytopenia usually resolves in 5 – 7 days. In some patients( but NOT patients with HIT) who have bleeding or high risk of bleeding, additional measures such as glucocorticoid, high dose IgG infusion

and platelet transfusion may be given but the efficacy of these is uncertain. In HIT, in the presence or absence of overt thrombosis, an alternative anticoagulant (danaparoid (Orgaran), recombinant hirudin Lepirudin), or argatroban) should be administered after heparin withdrawal. A vitamin K antagonist (warfarin) is commenced after the thrombosis is under control and/or the platelet counts have normalized.

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