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9. Drug Induced Thrombocytopenia

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I. INTRODUCTION

Drug-induced thrombocytopenia (DIT) is a relatively common clinical disorder. It is imperative to provide rapid identification and removal of the offending agent before clinically significant bleeding or, in the case of heparin, thrombosis occurs. DIT can be distinguished from idiopathic thrombocytopenic purpura (ITP), a bleeding disorder caused by thrombocytopenia not associated with a systemic disease, based on the history of drug ingestion or injection and laboratory findings. DIT disorders can be a consequence of decreased platelet production (bone marrow suppression) or accelerated platelet destruction (especially immune-mediated destruction).

II. CLINICAL FEATURES

Clinically, these patients present with moderate to severe thrombocytopenia (defined as a platelet count of less than $50x10^9$/L), and spontaneous bleeding varying from simple ecchymoses, petechiae and mucosal bleeding to life-threatening spontaneous intracranial hemorrhage. Exclusion of other causes of thrombocytopenia (such as congenital disorders and inflammatory processes), anamnestic analysis (such as a temporal relationship between the administration of the putative drug and the development of thrombocytopenia), recurrence of thrombocytopenia following reexposure to the drug and laboratory investigation (such as total blood count and platelet serology tests) are all important factors for the differential diagnosis [1;2]. Moreover, pseudothrombocytopenia, an artifactual clumping of platelets *in vitro* without clinical significance, should also be ruled out [3–6].

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The frequency of DIT in acutely ill patients has been reported to be approximately 19–25% [7;8]. Generally, platelet count falls rapidly within 2–3 days of taking a drug which has been taken previously, or 7 or more days after starting a new drug. When the drug is stopped, the platelet count rises rapidly within 1–10 days of withdrawal.

Thus, the primary treatment for drug-induced thrombocytopenia is to discontinue the suspected causative agent. Patients experiencing life-threatening bleeding may benefit from intravenous immunoglobulin (IVIG) therapy, plasmapheresis, or platelet transfusions [9;10]. Corticosteroids seem inefficient in the treatment of DIT [11].

III. ETIOLOGY

Hundreds of drugs have been implicated in the pathogenesis of DIT. As noted, DIT disorders can be a consequence of decreased platelet production or accelerated platelet destruction.

A **decrease in platelet production** is usually attributable to a generalized myelosuppression, a common and anticipated adverse effect of cytotoxic chemotherapy [12]. In addition, it has been reported that some chemotherapeutic agents can induce thrombocytopenia secondary to an immune-mediated mechanism [13–17].

Selective suppression of megakaryocyte production, mediated by thiazide diuretics, ethanol and tolbutamide, could lead to isolated thrombocytopenia [1;18;19]. However, thiazides can also induce severe thrombocytopenia secondary to an immune-mediated mechanism [20].

An accelerated platelet destruction in the presence of the offending drug is most often of immune origin. Non-immune platelet destruction, associated to a small number of antineoplastic agents such as bleomycin, can occur in thrombotic microangiopathy (TMA) and its variant form, hemolytic uremic syndrome (HUS)[19], Immune-mediated platelet consumption is associated with a large number of drugs leading to drug-induced immunologic thrombocytopenia (DITP) by a number of different mechanisms.

IV. MECHANISMS OF DRUG-INDUCED IMMUNOLOGIC THROMBOCYTOPENIA (DITP)

DITP is a relatively common and sometimes serious clinical disorder characterized by drug-dependent antibodies (DDAbs) that bind to platelets and cause their destruction. Antibodies associated with DITP are unusual in that they typically bind to glycoproteins (GPs) on the cell membrane of the platelets only in the presence of the provocative drug [21;22]. Hundreds of drugs have been implicated in its pathogenesis, among those, drugs most often associated with DITP are: heparin, cinchona alkaloid derivatives (quinine and quinidine), penicillin, sulfonamides, non-steroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, antirheumatic and oral antidiabetic drugs, gold salts, diuretics, rifampicin and ranitidine [23–27]; several other drugs are occasionally described in case reports of thrombocytopenia [28; 29]. Quinidine and quinine appear to cause this condition more often than other medications, with the exception of heparin [22;30;31].

In the past twenty years, much has been learned about the pathogenesis of DITP. However, knowledge of the molecular nature of the immune-response is far from complete. It is also unknown how drugs induce the development of such antibodies. Following the observation that drug-dependent antibodies bind to platelets via their Fab regions [32], subsequent studies have documented the mechanisms of drug-dependent antibody formation (Table 1) [21;22].

Hapten-Induced Antibody

Karl Landsteiner's pioneering studies in the in the field of immunochemistry in the 1930's, showed that small molecules, such as drugs, organic compounds, peptides and oligosaccharides with a molecular weight of less than 2–5 kDa are not capable of inducing an immune response. Conversely, these small molecules, called haptens, could induce an immune response when covalently attached to a carrier protein. Penicillin and penicillin derivatives are an example of this category. Penicillins constitute a large family of compounds whose common structural basis is a beta-lactam ring condensed to a thiazolidine ring. In the presence of free amino groups of proteins the beta-lactam ring opens up and the penicilloyl group covalently links to epsilon-amino groups of lysine residues of proteins [33;34]. Covalent linkage of the drug to the protein can perturb in different ways the antigen processing of proteins, therefore eliciting an immune response [34;35].

Hapten-dependent immune hemolytic anemia is a well documented occurrence during therapy with penicillin [36]. However thrombocytopenia induced by the "hapten" mechanism is a rare event [21;37;38].

Drug-Dependent Antibody ("Compoud" or "Conformational-Dependent" Antibody)

Antibody binding to the platelets is the causative mechanism. These antibodies are heterogeneous and directed toward different epitopes on major platelet membranes glycoproteins (GPs), most often GPIb/IX, GPV and GPIIb/IIIa [23;39–42] and platelet-endothelial cell adhesion molecule-1 (PECAM-1) [43] only when drug is present in soluble form [22]. Remarkably, antibodies in an individual patient are often highly specific for a single GP. Quinine and quinidine are the most common causative drugs, but many other medications, including sulfonamide antibiotics and drug metabolites are implicated in the pathogenesis [21;44].

The target of these antibodies appears to be either a "compound" epitope, made of the drug bound noncovalently (drugs are easily dissociated from platelets by in vitro washing procedures; demonstration of drug-dependent antibodies requires the continual presence of the suspected drug during the reaction) to one or multiple site of the platelet GPs, or a conformational change elsewhere on the GP molecule that is created in the presence of the offending drug in soluble form [45;46]. An alternative, but perhaps less likely possibility, is that the drug may react first with an existing antibody to induce a conformational change in the antibody binding site itself [47]. Finally, the existence of a drug-specific antibody has been recently reported that directly recognizes quinine itself in a subset of patients experiencing quinine-induced immune thrombocytopenia [47].

The epitopes recognized by antibodies from patients with quinine- and sulfonamide-induced thrombocytopenia have been characterized for selected target molecules. Precise localization, however, has been achieved only for a limited number of quinine-dependent antibodies shown to bind to a restricted 70 amino acid domain of GPIIIa located just N-terminal from a well-defined disulfide-bonded region that is resistant to protease digestion [46] and further restricted to a 17-amino acid sequence (AA residues 50–66) [48]. The binding site of a quinine-dependent antibody specific for GPIb (alpha subunit) has been mapped to an 11 amino acid sequence (AA residues 283–293) of the glycoprotein [45]. Furthermore, it has been reported that Arg110 and Gln115 of GPIX are important in the formation of the quinine-dependent anti-GPIX antibody binding site [49]. There is also evidence that within GPIX there exists a site that is favored not only by quinine but also by rifampicin- and ranitidine-induced antibodies [25;26]. Platelet-reactive antibodies induced by sulfonamide antibiotics were reported to react almost exclusively with epitopes displayed only on the intact GPIIb-IIIa complex [24]. Overall, the

immunologic specificity appears not to be important in the explanation and/or prediction of the pathogenesis and gravity of DITP.

GPIIb-IIIa Inhibitors

Thrombocyotopenia associated with GPIIb/IIIa inhibitors, such as tirofiban (Aggrastat®; Merck Sharp & Dohme; Whitehouse Station, NJ), eptifibatide (Integrilin®, Millennium Pharmaceuticals; Cambridge, MA) and abciximab (ReoPro®; Eli Lilly; Indianapolis, IN), is a well-recognized entity [50;51]. Thrombocytopenia is even more common with the oral GPIIb/IIIa inhibitors [52].

Tirofiban and eptifibatide are synthetic compounds that mimic or contain the Ang-Gly-Asp (RGD) motif and bind tightly to the RGD recognition site in GPIIb/IIIa (ligand-mimetic GPIIb/IIIa inhibitors); abciximab is a Fab fragment, of the chimeric human-murine monoclonal antibody 7E3 [53], specific for an epitope on GPIIIa [50;54].

The onset of acute thrombocytopenia within hours of the first exposure to a GPIIb-IIIa inhibitor suggested that nonimmune factors might be responsible. However, it has been shown that tirofiban- and eptifibatide-induced thrombocytopenia is due to antibodies specific to ligand-induced binding sites (LIBS) exposed after conformational changes in the GPIIb/IIIa molecule following binding of these ligand-mimetics [55]. Such DDAbs may develop following previous tirofiban (or eptifibatide) exposure or may indeed be naturally occurring and thus be associated with acute thrombocytopenia on first exposure to the drug [52;55;56]. Similarly, severe immune-mediated thrombocytopenia can be observed within hours of a patient's first exposure to abciximab [50]. Delayed onset of thrombocytopenia can be ascribed to the persistence of platelet-bound abciximab for several weeks after treatment, rendering platelets susceptible to destruction by newly formed antibody [56;57]. It has been proposed that antibodies from patients with abciximab-induced thrombocytopenia recognize either murine sequences incorporated into abciximab or conformational changes induced by abciximab in GPIIb/IIIa when abciximab binds [50]. Conversely, antibodies found in healthy individuals, that recognize enzymatic cleavage sites in human immunoglobulins, appear not capable of causing thrombocytopenia in patients who have received the drug [58].

Drug-Induced Autoantibody

During the exposure to a medication, some patients make drug-dependent antibody and drug-independent antibodies (autoantibodies) simultaneously [59;60]. Usually these autoantibodies are transient. On rare occasions, these autoantibodies can persist for a long period of time leading to a chronic autoimmune thrombocytopenic purpura (AITP) as it could be the case during the exposure to gold salts [21;61]. The underlying mechanism of this immune-response is unknown. A possibility, is that the drug might alter the processing of platelet GPs in such a way that one or more peptides not ordinarily seen by the immune system, "neoantigens", are generated, thus "conventional" and "cryptic" GP-derived peptides could be presented to T cells in the context of Class II HLA. Generation of such "cryptic" peptides through various mechanisms is an important theme in autoimmunity [62;63]. In murine models, heavy metal ions such as Hg^{++} and Au^{+++} have been shown to alter processing of proteins, leading to presentation of cryptic (and immunogenic) peptides [64;65]. It has been speculated that sensitivity reactions (including thrombocytopenia) seen in patients with rheumatoid arthritis who are treated with gold salts may be related to this mechanism [66], although other possibilities have been suggested.[67] In several human models, protein-specific antibodies [68] and other ligands [69] perturb protein processing, leading to the generation of cryptic peptides recognized by T cells.

Immune Complex

It was hypothesized that antibodies causing DITP recognize circulating drug directly to form immune complexes somehow reacting with platelets as "innocent bystanders" to cause their destruction [21;70;71]. However, the putative immune complexes were never demonstrated experimentally and it was later shown that DDAbs bind to platelets via their Fab rather than Fc receptors [32;72].

Indeed, a peculiar immune complex mechanism is responsible for the thrombocytopenia occurring in heparin-induced thrombocytopenia (HIT). HIT differs from most other forms of drug-induced immune thrombocytopenia in that the responsible antibodies bind to complexes resulting from non-covalent interaction of a platelet alpha granules releasate, the CXC chemokine platelet factor 4 (PF4; CXCL4), and heparin [73–75] to produce immune complexes that engage with the Fc gamma RIIA receptor on platelets and induce platelet activation [74–77], rather than merely binding to platelets to promote their destruction in the reticuloendothelial system. Paradoxically, about 10% of patients with HIT also experience life-threatening thrombosis [78;79].

V. LABORATORY DIAGNOSIS

The diagnosis of drug-induced thrombocytopenia is often empirical. In patients exposed only to a single drug, recovery after its discontinuation provides circumstantial evidence that the thrombocytopenia was caused by drug sensitivity [28;44]. *In vitro* documentation of platelet-bound immunoglobulins, in the presence of the putative drug, provides direct evidence for the involvement of the tested drug in causing *in vivo* platelet destruction.

Many different methods have been used to detect the presence of DDAbs. These include the use of radiolabeled or fluorescein-labeled (platelet immunofluorescence test; PIFT) anti-IgG to detect platelet-bound immunoglobulin, enzyme-linked immunospecific assay (ELISA), flow cytometry and immunoprecipitation-Western blotting (IP-WB) [46;80;81]. ELISA and IP-WB allow assessing both the presence and specificity of DDAbs. Because the formation of the target for DDAb occurs when the drug noncovalently associates with a specific protein, the drug must be constantly present in every step of the assay, including washing buffer. The specificity of the reaction is assessed by comparing the reactivity of the serum or plasma sample in the presence and in the absence of drug.

Flow cytometry is a rapid and highly sensitive technique for the detection of platelet-reactive antibodies induced by several drugs, including, but not limited to, quinine, quinidine and sulfamethoxazole [24;80]. As noted, the ELISA techniques, while not as sensitive, facilitates identification of the target molecules with which DDAb react; these include the antigen capture ELISA assay, in which a monoclonal antibody specific for a platelet membrane glycoprotein is plated onto microtiter wells and used to capture the specific membrane glycoproteins from a platelet lysate (ACE, MAIPA) [80;82] and a modified antigen capture ELISA in which the drug-dependent antibodies are first incubated in the presence or absence of drug with intact platelets, the cells containing bound antibodies then lysed in Triton X-100, and the lysate applied to a monoclonal antibody coded ELISA well [46].

Factors that should be considered for the failure to demonstrate DDAbs include poor solubility in an aqueous medium of some drugs; the possibility that the sensitizing agent can be a structurally modified form of the sensitizing drug resulting from *in vivo* metabolism [44;83–85]; and a possible requirement that autologous cells be used for testing [86].

VI. SUMMARY

DIT disorders can be a consequence of decreased platelet production (bone marrow suppression) or accelerated platelet destruction (especially immune-mediated destruction). Immune-mediated platelet consumption is associated with a large number of drugs leading to drug-induced immunologic thrombocytopenia (DITP) in which platelet destruction is caused by immunoglobulins that recognize specific platelet membrane glycoproteins (GPs) only in the presence of the sensitizing drug noncovalently associated with a specific GP. In some instances, not only the drug itself but also its metabolites are responsible for the immune response in the patient. DDAbs bind to “neoantigens” on platelets via their Fab fragments and most frequently recognize epitopes on the GP complexes Ib/IX/V and/or IIb/IIIa and PECAM-1. The drug must be present for the drug-dependent antibody to bind to the surface of the platelets and cause their destruction. However, it is controversial whether the binding sites of DDAbs are compound epitopes consisting of elements of the cell membrane protein and the drug or if the drug induces conformational changes of the target molecule, thereby creating “neoepitopes” on other parts of the molecule.

DITP is a relatively common side effect of GPIIb/IIIa inhibitors, but the mechanism responsible for GPIIb/IIIa inhibitors-induced thrombocytopenia differs from those implicated in quinine-, quinidine- and sulfonamide-induced thrombocytopenia. It is imperative to provide rapid identification and removal of the offending agent before clinically significant bleeding or, in the case of heparin, thrombosis occurs. Many different methods can be used for detecting drug-dependent antibodies. Flow cytometry appears to be one of the most rapid and sensitive technique for the identification of drug-dependent antibodies in patient sera or plasma.

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Abbreviations

DIT
drug-induced thrombocytopenia

DITP
drug-induced immune thrombocytopenia

DDAb
drug-dependent antibody

GP
glycoprotein

RGD
Arg-Gly-Asp

Table 1

Drug-induced immunologic thrombocytopenia (DITP): pathogenetic mechanisms

Type	Mechanisms	Examples
Hapten-induced antibody	Drug forms covalent linkage to membrane glycoprotein and acts as a hapten to induce a drug-dependent antibody response	Penicillin and penicillin derivatives?
Drug-dependent antibody	Drug binds to site on membrane glycoprotein and forms a “compound” epitope or induces a conformational change elsewhere in the molecule for which the antibody is specific. The immunogen can be a drug metabolite	Quinidine, quinine, NSAIDs, various antibiotics, sedatives, anticonvulsants, many others
GPIIb/IIIa inhibitors		
Ligand mimetic	Drug reacts with the RGD recognition sequence on (GPIIb/IIIa) and induces a conformational change elsewhere in the integrin complex that is recognized by antibody?	Tirofiban, eptifibatide, roxifiban, others
Drug-specific antibody	Drug (chimeric Fab fragment) induces antibody-specific for murine sequences that control specificity for GPIIb/IIIa	Abciximab
Drug-induced autoantibody	Drug perturbs the immune response in such a way that drug-independent antibodies specific for a cell membrane GP are produced	Gold salts, procaine amide
Immune complex	Drug reacts with a normal protein (PF4) and reconfigures it to form an immunogenic complex; antibody binds to thiscomplex and forms an immune complex; the immune complex activates platelets via Fc receptors	Heparin

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