Drug-Induced Immune Cytopenias (13-Nov-2004)

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Abstract

Drugs can induce thrombocytopenia by several mechanisms, including marrow suppression and destruction of platelets in the peripheral blood by non-immune and immune mechanisms. We will review here current understanding of the immune mechanisms by which drugs promote immune-mediated platelet destruction resulting in thrombocytopenia.

Introduction

Immune cytopenia is a relatively common and poorly understood side effect of many drugs. Affected target cells include erythrocytes, leukocytes, platelets and, probably, hematopoietic precursor cells in the marrow. For unknown reasons, platelets are affected much more often than the other cell types. We will here consider drug-induced immune thrombocytopenia (DITP) as a model for drug-induced blood dyscrasias having an immunologic pathogenesis. Drug-induced antibodies cause platelet destruction by a number of different mechanisms (Table 1), each of which will be discussed in turn.

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Hapten-induced Antibodies

It is well known that low molecular weight compounds are generally not immunogenic but can stimulate antibodies when they are coupled covalently to a carrier protein used for immunization. Antibodies raised after immunization of animals with drug-protein conjugates can usually be shown to be specific for drug alone, drug plus peptide residues adjacent to the site of conjugation and, occasionally, adjacent peptide residues alone. It is thought that these antibodies are produced in response to
peptides generated from the intact protein by intracellular processing that appear to be "foreign" by virtue of possessing a
drug molecule ligated to a critical amino acid residue (Weltzien 1996). Penicillin and a few other drugs become linked
spontaneously to plasma proteins and cell membrane proteins (Levine 1967). Hapten-dependent antibodies specific for these
adducts appear to provide an explanation for immune hemolytic anemia sometimes experienced by patients given massive
doses of penicillin and penicillin derivatives for several weeks (Garratty 1993). A few case reports suggest that rare instances
of thrombocytopenia in patients given penicillin and structurally related drugs are caused by a similar mechanism (Murphy
1983, Salamon 1984). In patients with immune cytopenia induced by hapten-specific antibodies, it is sometimes possible to
establish a diagnosis by coating the target cells in vitro with the suspect drug and, after washing, showing that the treated
cells bind antibody. This is rarely possible in patients with drug-induced thrombocytopenia.

"Quinine-type" Immune Thrombocytopenia
Acute, sometimes severe and life-threatening thrombocytopenia is a recognized complication of treatment with quinine,
quinidine, sulfonamide antibiotics and many other medications. Although platelets are affected most often, immune
hemolytic anemia and/or neutropenia can be caused by the same underlying mechanism (Aster 1999). Because quinine (Qn),
usually taken to ameliorate nocturnal leg cramps, has been implicated more often than any other medication, we will refer to
this type of immune thrombocytopenia as "Qn-type DITP." Qn-type DITP usually develops after 5 - 8 days of exposure to the
sensitizing medication or, after a single exposure in a patient exposed previously to the same drug. Patients with this
condition often present with widespread petechial hemorrhages in the skin and buccal mucosa sometimes accompanied by
urinary tract or gastrointestinal bleeding. Intracranial hemorrhage is rare, but numerous examples have been reported
(Freiman 1990). After discontinuation of the provocative medication, platelet counts usually return to normal within three to
days.

Qn-type DITP is caused by a remarkable class of IgG and/or IgM immunoglobulins that react with selected epitopes on
platelet membrane glycoproteins, usually GPIIb/IIa (fibrinogen receptor) or GPIb/IX (von Willebrand factor receptor) only
when drug is present in soluble form (Aster 1999). The antibodies are clearly not hapten-specific because they do not react
demonstrably with platelets pre-treated with the drug and then washed or with platelets isolated from the peripheral blood of
a person taking the medication. Moreover, antibody binding is strongest at the highest concentration of drug that can be
achieved in vitro rather than being inhibited as would be expected of a classic "hapten-dependent" antibody. How soluble
drug promotes binding of an otherwise innocuous antibody to a membrane glycoprotein to cause platelet destruction is not
understood. Nor is it clear how certain drugs interact with the immune system to trigger antibody production.

It is often not possible to detect drug-dependent antibodies in patients with acute thrombocytopenia induced by drugs other
than quinine, quinidine or sulfonamide antibiotics. One reason for this is that a drug metabolite can be the sensitizing agent
(Kiefel 1987, Bougie 2001). In such cases, it is sometimes possible to demonstrate a metabolite-dependent, platelet-reactive
antibody provided the appropriate metabolite is available for testing.

Thrombocytopenia Associated with Sensitivity to Ligand-mimetic GPIIb/IIa Inhibitors
Ligand-mimetic (LM) GPIIb/IIa inhibitors bind to the RGD recognition site on the platelet membrane glycoprotein IIb/IIa
complex (αIIb/βIII integrin), thereby inhibiting the reaction of activated GPIIb/IIa with fibrinogen, a necessary step in the
formation of a platelet aggregate and a critical part of the normal hemostatic process (Coller 1997). Two such agents, the
intravenous drugs tirofiban and eptifibatide, have been shown to be effective in preventing secondary complications
following coronary angioplasty and are now widely used for this purpose. Other agents, including oral drugs, are in various
stages of development.

In every clinical trial of ligand-mimetic GPIIb/IIa inhibitors, a subset of patients has developed acute, often severe
thrombocytopenia (Coller 1997, Curtis 2002, Bougie 2002). Because this complication usually develops after the first
exposure to a ligand-mimetic drug, the possibility that non-immune mechanisms were responsible was considered but this
could not be confirmed in various studies (aster 2004). Recent findings indicate that LM-induced thrombocytopenia is caused
by drug-dependent antibodies that recognize GPIIb/IIa complexed with drug and are "naturally occurring" (or at least
preexisting) (Bougie 2002). It is known that mice immunized with GPIIb/IIa sometime produce antibodies specific for
conformational changes (ligand-induced binding sites or LIBS) induced in the integrin by the binding of fibrinogen, RGD
peptide or a ligand-mimetic drug (Frelinger 1988, Kouns 1992). It seems possible that antibodies causing thrombocytopenia
in patients given an LM drug are specific for LIBS and represent human analogues of these murine monoclonals but this has
not been proved experimentally. Why a subset of normal individuals should have high titer, naturally occurring antibodies
that recognize ligand-occupied GPIIb/IIa and can cause severe thrombocytopenia when an LM drug is administered is an
interesting and unresolved question.
Drug-specific Antibodies
Abciximab, a chimeric (human/mouse) Fab fragment specific for GPIIb/IIIa that inhibits the reaction of the activated integrin with fibrinogen by steric hindrance (Coller 1997). Like the LM inhibitors, abciximab has been proved effective in preventing serious complications following coronary angioplasty and is widely used for this purpose. About 1% of patients given abciximab for the first time develop acute thrombocytopenia within a few hours of their first exposure and 5 - 10% experience this complication when given the drug a second time (Dery 2004). Patients with abciximab-induced thrombocytopenia usually have IgG and/or IgM antibodies that recognize abciximab-coated platelets (Curtis 2002). However, similar but weaker antibodies are present in about 50% of the general population (Curtis 2002, 2004). Recent studies show that these "normal" (naturally occurring?) antibodies are specific for a neoepitope created at the C terminus of the abciximab Fab fragment when it is cleaved from the intact chimeric IgG molecule with papain (Curtis 2002, 2004). Accordingly, binding of these antibodies to abciximab-coated platelets can be inhibited by normal Fab fragments. In contrast, "dangerous" antibodies capable of causing thrombocytopenia in a patient given abciximab are resistant to this treatment. Antibodies from patients with abciximab-induced thrombocytopenia may be specific for murine peptide sequences that confer specificity for GPIIb/IIIa on the abciximab molecule (Curtis 2004). However, the possibility that they recognize abciximab-induced conformational changes in the integrin has not been ruled out. Why the naturally antibodies commonly found in normal persons appear not to cause thrombocytopenia, whereas those found in patients do is still unresolved. Nor is it clear why high titer antibodies capable of causing platelet destruction following abciximab administration are present in a significant minority of normal individuals.

Drug-induced Autoantibodies
Patients who make "quinine-type" antibodies sometimes produce non-drug-dependent, platelet-reactive antibodies simultaneously (Lerner 1985, Aster 2000). Usually these presumptive autoantibodies are transient. Occasionally, however, a patient with Qn-type thrombocytopenia remains thrombocytopenic for a long period of time and behaves like an individual with chronic autoimmune thrombocytopenic purpura (AITP) (Fig 1). In such cases, it appears likely that the drug somehow induces a true platelet-specific autoantibody that persists and causes AITP.

Figure 1. Chronic autoimmune thrombocytopenia in a patient who presented initially with sulfamethoxazole (SMX)-dependent, platelet-reactive antibodies. SMX-dependent antibodies were identified in acute phase serum together with GPIIb/IIIa-specific non-drug-dependent autoantibodies. Persistent non-drug-dependent antibodies reactive with autologous platelets were identified during Weeks 1, 5, and 9. SMX, sulfamethoxazole; ICH, intracranial hemorrhage; IVIgG, intravenous gamma globulin. From Aster 2000 with permission from WB Saunders Company. - To view this image in full size go to the IVIS website at www.ivis.org.

The mechanism by which this might take place is unknown. It is well established that autoimmune hemolytic anemia can be induced by certain medications such as alpha methylldopa and procaine amide (aster 1999). The only drug known to induce chronic autoimmune thrombocytopenia with some regularity is gold (gold salts) given in the form of a depot injection for treatment of refractory rheumatoid arthritis (von dem Borne 1986). Heavy metals are known to induce autoimmune phenomena in animals (Greim 1998), possibly by perturbing the processing of autologous proteins in such a way that cryptic peptides are presented to T cells (Greim 1998) Whether this explains development of AITP in about 1% of patients given gold salts is uncertain. Procaine amide and a few other drugs may on rare occasions induce chronic AITP. In such cases, the disease behaves clinically like "idiiosyncratic" AITP.

Thrombocytopenia Caused by Immune Complexes
Platelets contain low affinity (FcgammaRII) Fc receptors that are capable of binding immune complexes, leading to platelet activation. The only well-documented example of a drug-induced immune complex that causes thrombocytopenia is heparin-induced thrombocytopenia/thrombosis (HIT) (Visentin 1999, Warkentin 2003). Heparin is a high molecular weight, sulfated, linear polysaccharide that inhibits blood coagulation by activating regulatory proteins such as anti-thrombin III. About 50% of patients anticoagulated with heparin for at least seven days produce antibodies that recognize complexes consisting of heparin and platelet factor 4 (PF4), a CXC chemokine normally stored in platelet alpha granules (Visentin 1999). When a patient with such an antibody is given heparin, heparin/PF4 complexes are formed that react with antibody to form immune complexes. These, in turn, can bind to the platelet FcgammaRIIa receptors, leading to platelet activation, additional PF4 release and eventually, platelet destruction. Thrombocytopenia occurs in about 5% of patients given heparin and is rarely severe enough to cause bleeding. However, about 10% of the affected patients experience paradoxical thrombosis which can be life-threatening (Warkentin 2003).
References


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