Further complexities in diagnosing acquired thrombocytopenia: unexpected parallels between antibody-mediated delayed thrombocytopenia with abciximab and heparin induced thrombocytopenia

Catherine P. M. Hayward
Departments of Pathology and Molecular Medicine, and Medicine, McMaster University, Hamilton, Ontario, Canada

Acute thrombocytopenias are common clinical problems of diverse etiologies and paradoxically, some of the most dramatic forms are iatrogenic in nature (1). For example, drugs that are given to patients to treat or prevent arterial or venous thrombosis (such as heparin, abciximab, and other agents that block the platelet integrin receptor \(\alpha_{IIb}\beta_3\)) can cause immune reactions that lead to life-threatening situations (1-8). The specific drug implicated as the cause of an individual patient’s thrombocytopenia is an important issue to sort out, and this is commonly done by evaluating the clinical scenario and excluding potential causes (1, 3). Laboratory tests have provided information about the causes and mechanisms of drug-induced thrombocytopenia (1, 3). However, the results of such tests, even if available, are typically reported long after clinical decisions are made about probable and potential causes and appropriate therapies.

Thrombocytopenia due to agents that block platelet \(\alpha_{IIb}\beta_3\) integrin-ligand interactions has increased, subsequent to an increased use of these drugs for arterial thrombotic states, including acute coronary syndromes and arterial revascularization procedures (2, 4-8). In some patients, anti-\(\alpha_{IIb}\beta_3\) therapy with abciximab is associated with acute thrombocytopenia, within hours of therapy, or pseudothrombocytopenia that does not need treatment (6-8). The more rapid thrombocytopenia after abciximab therapy has often been used to distinguish this entity from heparin-induced thrombocytopenia (HIT), which characteristically presents later, 5-10 days after heparin exposure (3, 6-8). However, there are now two reports, including the paper by Nurden and coworkers in this issue of Thrombosis and Haemostasis (see pages 820-828), illustrating that antibody-mediated thrombocytopenia complicating abciximab therapy can also present as a delayed, rather than an immediate fall in the platelet count (7, 8). The similar timing of delayed abciximab-related thrombocytopenia and HIT appears to represent emergence of antibodies from primary immunization in individuals exposed to these anticoagulants (3, 7, 8). The similarity in timing poses new and difficult challenges for clinicians relying on the clinical picture, and in particular the timing of the drop in the platelet count, to determine the most probable cause. This is an even greater problem when one considers that patients who receive anti-\(\alpha_{IIb}\beta_3\) therapy are also commonly exposed to heparin.

The study by Nurden and coworkers in this issue of Thrombosis and Haemostasis is important for several reasons. First, it reports a detailed analysis of the antibodies in a group of patients who developed delayed thrombocytopenia after therapy with abciximab, that demonstrates the characteristics of the antibodies generated, including their specificity for abciximab (7). It also illustrated that the association of these antibodies with delayed thrombocytopenia could not be attributed to HIT. Perhaps one of the most interesting and potentially important observations made by these investigators was the demonstration that three of their patients with delayed abciximab-associated thrombocytopenia had developed antibodies that induced platelet activation and aggregation in vitro, in a manner that required the an-
tibody against abciximab and abciximab bound to platelets (7). Although one might have postulated that blockade of \(\alpha_{\text{IIb}}\beta_3\) would prevent aggregation after platelet activation by abciximab antibodies, the authors observed that abciximab-coated platelets were incorporated into the aggregates generated by abciximab antibodies (7). Although there have been a number of reports of delayed thrombocytopenia associated with abciximab, the studies by Nurden et al (7), and by Curtis et al (8), have demonstrated that highly specific, abciximab-dependent antibodies are found in individuals with delayed thrombocytopenia after abciximab therapy, which has helped to define a new clinical syndrome. Nurden and coworkers (7) are the first to identify that these antibodies, at least in some individuals, have the ability to activate platelets.

Important questions remain about the mechanism, and the spectrum, of clinical problems associated with delayed thrombocytopenia related to the development of abciximab antibodies. First, it is likely, but not proven, that these antibodies activate platelets via the receptor FcγRIIa, as is the case for the antibodies that cause HIT (3). Second, the effects that some abciximab-dependent antibodies have on platelet activation in vitro (7) suggests it might be possible for these antibodies to activate platelets in vivo, with clinical consequences. For clinicians faced with a patient, exposed to both heparin and abciximab, who presents with delayed thrombocytopenia and thrombosis, this is an extremely important issue to resolve. One is tempted to speculate that the magnitude, and period, of risk for thrombosis associated with delayed abciximab thrombocytopenia might be lower, and shorter, than for heparin-induced thrombocytopenia, because the clearance of abciximab-coated platelets by antibody-mediated activation might hasten removal of the “fuel for the fire.” It is interesting that many of the cases described to date with antibody-mediated, abciximab-related, delayed thrombocytopenia have had more severe thrombocytopenia than is typical for HIT, and many had significant bleeding which is not a feature of HIT (3, 7, 8). The presentation with thrombocytopenia and bleeding problems could, in part, be due to continued therapy with other antiplatelet drugs, such as clopidogrel and aspirin, after abciximab is given. It is nonetheless possible that thrombotic events have already occurred due to abciximab thrombocytopenia but were not recognized, either because the diagnosis was not suspected, or because it was felt to be more typical of HIT. Further studies are needed to better define the proportion of patients that develop platelet-activating antibodies in abciximab-related delayed thrombocytopenia, which, based on data from Nurden et al (7), might be large. If there are thrombotic risks associated with delayed thrombocytopenia from abciximab antibodies, they may, like HIT, exhibit the “tip of the iceberg” phenomenon (3) as the clinical consequence could be influenced by antibody titre, other prothrombotic risk factors, and concurrent use of other anti-platelet therapies. As pointed out by Nurden et al (7), there is a need to determine the frequency of delayed thrombocytopenia associated with abciximab antibodies, and define the spectrum of its associated clinical problems, by larger prospective studies. The antibody assays developed to diagnose abciximab-related delayed thrombocytopenia (7, 8) represent a step forward in defining and characterizing a new clinical syndrome that clinicians need to be aware of in managing patients who receive abciximab.

**References**