Blood, 15 June 2004, Vol. 103, No. 12, pp. 4380-4381.

HEMOSTASIS, THROMBOSIS, AND VASCULAR BIOLOGY

Antibodies redux

Platelet antibody testing in patients with idiopathic thrombocytopenic **purpura** (**ITP**) has acquired a somewhat tarnished reputation. Measurements of platelet-associated immunoglobulin, while sufficiently sensitive to have a high negative predictive value, also carry a rate of false-positive results so high as to be of no clinical use. Assays that detect platelet glycoprotein-specific antibodies, while more specific, are not sufficiently sensitive to exclude the diagnosis of **ITP**,[1] and the extent of interlaboratory reproducibility is appreciable and troubling.[2] As a result, platelet antibody testing was not included in the diagnostic criteria for **ITP** formulated by either the Practice Guideline Committee of the American Society of Hematology or the Task Force of the British Committee for Standards in Haematology.

Results of more recent studies have placed a slight wrinkle in this dismissive assessment. An acceptable level of discrimination between **ITP** and thrombocytopenic conditions in which an immune etiology is deemed unlikely has been achieved in several recent studies.[3,4] For example, once patients with "nonimmune" causes of thrombocytopenia (eg, chronic lymphocytic leukemia, myelodysplasia, and myeloproliferative disorders) who responded to **ITP**-directed therapy had been excluded from analysis, the specificity of a positive antibody assay for the diagnosis of **ITP** approached 95% in one large recently published study.[5]

Into this setting enters the provocative paper by Fabris and colleagues (page 4562) in the current issue of *Blood.* The authors report that the detection of platelet-specific autoantibodies is a useful prognostic marker in patients who fit the classic clinical definition of **ITP**. Specifically, the authors found that 72% of 25 patients with positive antibody tests developed severe thrombocytopenia or required treatment a median of 2.1 months after testing, compared with 25 test-negative patients, only 32% of whom showed clinical worsening, which occurred at a median of 27.7 months. Although the absolute difference in the numbers of patients in various subgroups was quite small, making the confidence intervals wide, the findings reinforce those of others who have found a correlation between the prevalence and/or titer of antibody and the severity of

thrombocytopenia.

The fact that the severity of the thrombocytopenia and the duration of disease were comparable in the 2 populations reported by Fabris et al raises several interesting questions concerning the antibody-negative **ITP** population. Is the threshold required to clear antibody-coated platelets below the detection limits of the assay employed? If so, what caused the increase in antibody production over time in some patients but not in others? Alternatively, does somatic mutation of the autoantibodies lead to the recognition of additional epitopes, including one or more of the more prevalent platelet glycoprotein complexes that are detected in these assays, thereby enhancing platelet opsonization or further impeding platelet production? Or might T-cell-mediated cytotoxicity,[6] alterations in Fcγ receptor-mediated platelet clearance, or additional, as yet unrecognized, processes make a greater contribution to the severity of the thrombocytopenia in this subpopulation?

Although platelet antibody testing cannot as yet be recommended in routine clinical practice to either make or exclude the diagnosis of **ITP**, the study by Fabris et al raises the possibility that measuring platelet-specific antibodies may be of use to prognosticate the clinical course in patients with an established diagnosis. Serial prospective studies in much larger patient populations showing that "seroconversion" precedes clinical deterioration in the antibody-negative group would be required to prove this point and to identify how much warning, if any, such data provide.

— Douglas B. Cines
University of Pennsylvania

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