Platelet Antibody Testing in Idiopathic Thrombocytopenic Purpura

To the Editor:

Although it has been accepted for decades that most cases of idiopathic thrombocytopenic purpura (ITP) are caused by autoantibodies against platelets, the clinical utility of serologic testing in ITP has never been established. A recent report by Brighton et al analyzed predictive characteristics of direct and indirect tests for platelet-associated IgG (PAIgG) and an antigen capture test (MAIPA) designed to detect autoantibodies specific for platelet glycoproteins Ib/IIa or Ib/IX. It was concluded that the MAIPA was better than tests for PAIgG in discriminating immune from nonimmune thrombocytopenia.

We recently analyzed the clinical utility in ITP of a commercially available serologic test for PAIgG, the Capture-P (Immucor, Inc, Norcross, GA). This is a solid-phase red blood cell adherence assay that is used to detect alloantibodies for platelet crossmatching and has also been reported to have high sensitivity and specificity in ITP. In this test, microwell plates are coated with an agent that binds platelets from autologous (direct method) or allogeneic (indirect method) platelet-rich plasma. Adherent platelets create a substrate for capture of antiplatelet IgG from test plasma. Platelet-bound IgG is detected by subsequent adherence of indicator red blood cells coated with anti-human IgG.

A search of the University of Iowa Hospitals’ medical record department computer data base retrieved 359 records that contained results of Capture-P tests performed between August 1989 and July 1994. Of these, 94 records that contained ICD-9 coded primary diagnoses of primary thrombocytopenia (287.3) or thrombocytopenia, unspecified (287.5), were reviewed. Patients were retrospectively classified into three groups: (1) ITP (platelet count <150,000/μL, normal or increased numbers of bone marrow megakaryocytes, and no other known cause of thrombocytopenia) (n = 46); (2) thrombocytopenia of other established cause (n = 15); or (3) thrombocytopenia of undetermined cause (incomplete data or criteria for ITP not met, and no other cause of thrombocytopenia established) (n = 33). Group 3 was excluded from analysis.

The sensitivity and specificity of the Capture-P for the clinical diagnosis of ITP were 37% and 67% for the direct method, and 43% and 67% for the indirect method.

Table 1. Predictive Characteristics of Serologic Tests for Platelet Autoantibodies

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Likelihood Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capture-P</td>
<td>Direct</td>
<td>17/46 (37%)</td>
<td>10/15 (67%)</td>
<td>1.1</td>
</tr>
<tr>
<td>Capture-P</td>
<td>Indirect</td>
<td>20/46 (43%)</td>
<td>9/15 (60%)</td>
<td>1.1</td>
</tr>
<tr>
<td>CELIAA</td>
<td>Direct</td>
<td>60/81 (74%)</td>
<td>12/46 (26%)</td>
<td>1.0</td>
</tr>
<tr>
<td>ELISA</td>
<td>Indirect</td>
<td>30/88 (34%)</td>
<td>41/53 (77%)</td>
<td>1.5</td>
</tr>
<tr>
<td>MAIPA</td>
<td>Modified</td>
<td>33/71 (47%)</td>
<td>34/40 (85%)</td>
<td>3.1</td>
</tr>
</tbody>
</table>

* Likelihood ratio = sensitivity/(1 − specificity).
† Competitive enzyme-linked immunoassay for PAIgG (data from Brighton et al).
‡ Enzyme-linked immunosorbent assay for PAIgG (data from Brighton et al).
§ Modified monoclonal antibody immobilization of platelet antigens (data from Brighton et al).
Fig 1. Dependence of positive predictive value (PPV) and negative predictive value (NPV) on prevalence of ITP in the population to be tested. (---), Direct capture-P; (-----), modified MAIPA from Brighton et al. 3

and 60% for the indirect method (Table 1). The likelihood ratio (LR) was 1.1 for both the direct and indirect Capture-P (Table 1), which indicates that a positive test result does not meaningfully increase the a priori odds ratio for the clinical diagnosis of ITP. The predictive characteristics of the Capture-P were very similar to those of the direct and indirect tests for PAIgG reported by Brighton et al, which produced LR values of 1.0 and 1.5, respectively (Table 1). The performance of the MAIPA in the Brighton study was better, with an LR value of 3.1 (Table 1).

An instructive way to assess clinical utility of serological tests is to calculate positive and negative predictive values, which are dependent on the prevalence of a disease in the population to be tested. For the Capture-P, the positive and negative predictive values differed little from prevalence of ITP at any range (Fig 1), which indicates that the Capture-P has essentially no diagnostic predictive value in ITP. In the study of Brighton et al, the negative predictive values of the MAIPA differed only slightly from prevalence (Fig 1). The positive predictive values of the MAIPA differed more distinctly from prevalence, especially when the prevalence of ITP was between 20% and 60% (Fig 1).

This analysis suggests that the Capture-P, like other serologic tests for PAIgG, 2 is not useful for establishing or excluding the diagnosis of ITP. Although tests for PAIgG differ in sensitivity and specificity, they all have low LR values and weak positive and negative predictive values, possibly because they detect IgG in platelet granules rather than true platelet autoantibodies. 3 These findings are in keeping with the recent American Society of Hematology practice guideline, which concludes that tests for PAIgG are neither necessary nor appropriate in the evaluation of childhood or adult ITP. 4

That better laboratory tests for the diagnosis of ITP are needed is evidenced by the large number of records excluded from our retrospective analysis because of ambiguous clinical findings. In the Brighton study, the MAIPA had a higher LR and better positive predictive values than tests for PAIgG, but almost equally low negative predictive values. Thus, the MAIPA appears to have modest clinical utility in supporting the diagnosis of ITP, but has little utility in excluding it. For example, based on the data of Brighton et al, if the true prevalence of ITP in the test population was 50%, then 76% of patients with a positive MAIPA result would have ITP. Clearly, the diagnosis of ITP in most patients must be based on clinical criteria.

The study by Brighton et al is exemplary for its prospective design and use of rigorous clinical criteria for classification of thrombocytopenic patients. As newer antigen-specific tests for antiplatelet antibodies become available, it will be important to subject them to rigorous clinical validation to avoid inappropriate widespread use of uninformative tests.

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REFERENCES
Response

Dr Raife and colleagues have recently analyzed the clinical usefulness of a commercially available test for platelet-associated IgG (PAIgG), the Capture-P assay (Immucor, Norcross, GA) in the diagnosis of idiopathic thrombocytopenic purpura (ITP). In agreement with our previously published results, they found that the test for PAIgG to have poor positive and negative predictive values and conclude that the Capture-P, like other PAIgG tests, is not useful for the diagnosis of ITP. They further emphasize that it is important that evaluation of tests for ITP be carried out prospectively as we did in our study. We fully agree with Dr Raife and colleagues on those two points.

In addition, we would strongly endorse their view that any new tests for platelet antibodies should be subjected to vigorous clinical evaluation prospectively to avoid widespread use of tests that have little or no clinical utility.

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Microsatellite Instability in Natural Killer Cell–Like T-Cell Lymphomas in Immunocompromised and Immunocompetent Individuals

To the Editor:

Cells that have altered or absent DNA repair mechanisms may be more susceptible to genetic alteration and, thus, neoplastic transformation. Alteration in the integrity of the DNA mismatch repair mechanism can be measured by documenting microsatellite instability (MSI). Microsatellite alterations may not affect the phenotype of the cell, but are a sensitive measure of defective DNA mismatch repair which in some cells is a precursor event to neoplastic transformation. Accordingly, patients with Lynch syndrome, a hereditary disorder of DNA mismatch repair, have an increased frequency of carcinomas.1 In addition, MSI has been implicated in the oncogenesis of at least 16 different types of sporadic carcinomas.2

In contrast to carcinomas, we and others have documented MSI in a cohort of B- and T-cell lymphomas arising in immunosuppressed hosts.3–5 We have also shown that microsatellite analysis is an effective means of determining the recipient/donor origin of the tumor when it arises in allograft recipients. We have extended our previous studies by analyzing a group of six natural killer cell–like T-cell lymphomas (NK-TCL) of which three arose in allograft recipients and three arose in immunocompetent hosts.6

We examined six microsatellite loci in each case as previously described7 (Table 1). Microsatellite instability was detected in five of the six microsatellite loci in one NK-TCL arising in an allograft recipient. In contrast, MSI was not detected at any of the six loci in three NK-TCL arising in immunocompetent hosts. Furthermore, one of the three NK-TCL arising in allograft recipients was of donor origin and did not have MSI. Loss of heterozygosity was not observed in any case.

Table 1. Summary of Analysis on NK-TCL and PTLD

<table>
<thead>
<tr>
<th>Lymphoma</th>
<th>No. of Cases</th>
<th>MSI</th>
<th>Donor Origin</th>
<th>Host Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK-TCL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allograft recipient</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Immunocompetent</td>
<td>3</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>All PTLD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases studied for</td>
<td>9</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MSI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases studied for</td>
<td>39</td>
<td>NA</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>donor/host origin</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: NK-TCL, Natural killer–like T-cell lymphoma; PTLD, posttransplant lymphoproliferative disorder; MSI, microsatellite instability; NA, not applicable.

Thirty-nine cases of posttransplant lymphoproliferative disorders (PTLD), including those reported here, have been studied for the host/donor origin in allograft recipients8–9 (Table 1). Seven tumors (18%) have been reported as donor origin and 32 were of recipient origin (82%). Interestingly, one case of NK-TCL arising in an allograft recipient was donor in origin, and represents the first reported case with these findings.

Nine cases of PTLD, including the cases in this report, have now been analyzed; of which two cases have MSI. Both cases were T-cell cases of recipient origin. This limited series of NK-TCL is consistent with the concept that microsatellite instability plays a role in the pathogenesis of a minority of cases of lymphomas arising in immunocompromised hosts.

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REFERENCES

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