Anti-cardiolipin-β2-GPI Complex Antibodies in Idiopathic Thrombocytopenic Purpura

To the Editor: We read with interest the article by Funauchi et al (1) indicating the clinical significance of anti-phospholipid antibodies in patients with idiopathic thrombocytopenic purpura (ITP). However, we have two major questions on this article. First, they defined anti-phospholipid syndrome (APS) by adopting thrombocytopenia as one of the clinical features. Therefore, “Group A” patients in this article should be diagnosed as having APS at the entry of their study. Their statement, “Three patients in Group A were diagnosed later to have APS because they had cerebral thrombosis or habitual abortion.” is confusing. Moreover, it is still controversial that thrombocytopenia can be suitable for one of the criteria items of APS (2). Second, they did not show any results of β2-GPI-dependent anti-cardiolipin antibodies which are generally referred to as anti-cardiolipin-β2-GPI complex antibodies or phospholipid-dependent anti-β2-GPI antibodies, although they state that they measured these antibodies by ELISA in the Methods.

Thus, we would like to present our data on the clinical significance of anti-cardiolipin-β2-GPI complex antibodies in patients with ITP. The subjects consisted of 83 patients with chronic ITP. Our patients had neither thrombosis nor intrauterine fetal death. IgG anti-cardiolipin-β2-GPI complex antibodies were examined by ELISA (3–5). Our patients were divided into 2 groups; (a) six patients with IgG anti-cardiolipin-β2-GPI complex antibodies and (b) seventy-seven patients who did not have IgG anti-cardiolipin-β2-GPI complex antibodies. Clinical characteristics such as fulfillment of three criteria items in the revised criteria of classification of systemic lupus erythematosus (SLE) (6), biologically false positive serologic tests for syphilis (BFP-STS) and antinuclear antibodies (ANA) were found in ITP patients with IgG anti-cardiolipin-β2-GPI complex antibodies, when the clinical features were compared between group (a) and group (b) patients (Table 1). These features in our group (a) patients can be included in the concept of lupus-like disease by Asherson and Cervera (7). Therefore, the diagnosis of ITP should be carefully made to exclude definite SLE and primary APS in those who do not have any underlying diseases. It is suggested that thrombocytopenia should not be listed in the criteria items of APS, and that both thrombosis and intrauterine fetal death are important in the clinical characteristics of APS. Also, these results are compatible with our previous reports indicating that anti-cardiolipin-β2-GPI complex antibodies are found in a unique form in patients with SLE and related disorders (3–5).

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Table 1. Clinical Characteristics of Idiopathic Thrombocytopenic Purpura (ITP) Patients with IgG Anti-cardiolipin-β2-GPI Complex Antibodies

<table>
<thead>
<tr>
<th>n</th>
<th>Fulfillment of Three Criteria Items</th>
<th>BFP-STS</th>
<th>ANA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group a</td>
<td>6</td>
<td>(50%)</td>
<td>(50%)</td>
</tr>
<tr>
<td>Group b</td>
<td>77</td>
<td>(5%)</td>
<td>(3%)</td>
</tr>
</tbody>
</table>

| P     | <0.005 | <0.005 | <0.05 |

Group a consisted of ITP patients with IgG anti-cardiolipin-β2-GPI complex antibodies. Group b included ITP patients who did not have IgG anti-cardiolipin-β2-GPI complex antibodies.

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Confusion in the Classification of Antiphospholipid Syndrome in Patients with Thrombocytopenia

To the Editor: Over a decade has passed since Hughes reported detailed clinical descriptions of antiphospholipid syndrome (APS). APS is now recognized to be one of the most common prothrombotic disorders (1). The main clinical features of APS are recurrent thrombosis, both venous and arterial and recurrent pregnancy loss associated with the presence of antiphospholipid antibodies (aPL).

Such patients sometimes have a thrombocytopenia. However, as Funauchi et al (2) described, severe thrombocytopenia and a bleeding tendency are rare in patients with APS who have a history of thrombosis or pregnancy loss. On the other hand, some patients with idiopathic thrombocytopenic purpura (ITP) are positive for antiphospholipid antibodies (3). According to Harris’ criteria of APS (4), thrombocytopenic patients with antiphospholipid antibodies can be diagnosed as APS, thus the ITP classification is erroneous since the thrombocytopenia in such patients is not ‘idiopathic’. Obviously many ITP patients have a life-threatening severe thrombocytopenia and a bleeding tendency.

The pathophysiology of thrombocytopenia associated with aPL is heterogeneous (5). aPL may function like antithrombocyte antibodies and immunological thrombocytopenia may ensue. Platelets may be constantly activated by aPL in the circulation and the turn-over of platelets may be shorter than unstimulated thrombocytes. Chronic thrombocytopenia may also occur. aPL can increase the consumption of platelets, which can also lead to secondary thrombocytopenia. In patients with SLE, a more heterogeneous origin of thrombocytopenia, such as bone marrow dysfunction or suppression, haemophagocytic syndrome, and thrombotic thrombocytopenic purpura, can be present. In some cases, thrombocytopenia is life-threatening while in other cases it is mild. Some of those mechanisms can co-exist. Heterogeneity must be taken account when treating patients with thrombocytopenia and aPL.

Regarding the diagnosis of APS, as Kaburaki et al (6) discuss in their letter in this issue of the journal, thrombocytopenia is too controversial to be included as one item of criteria and confusion in the definition of APS will follow.

Asherson defined APS patients without any underlying diseases as cases of primary APS (7), and when patients have some factors of SLE (less than 4 items of SLE criteria), he termed them as secondary APS to lupus-like disease. Here however, “lupus-like disease” should be clearly defined. Many individuals, including apparently healthy ones, carry one or two factors related to SLE criteria, but we usually do not classify them as patients with lupus-like disease. We suggest that use of “APS secondary to lupus-like disease” be avoided and that a new more appropriate criteria of APS and primary APS be designed.

This issue will be discussed in the APS criteria session at the 5th International Symposium on Antiphospholipid Antibody to be held October 6-9, 1998 in Sapporo, Japan.

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References

Thrombocytopenia in the Criteria for Anti-Phospholipid Antibody Syndrome

Dr. Funauchi’s reply:

To the Editor: Thrombocytopenia in the criteria of anti-phospholipid antibody syndrome (APS) poses problems of both diagnosis and differentiation (1, 2) as pointed out by Kaburaki et al (3). From the viewpoint of sensitivity, thrombocytopenia should be included in the criteria.

In our retrospective study (4), 7 out of 27 patients who had been once diagnosed as having idiopathic thrombocytopenic purpura (ITP) showed a prolonged activated partial thromboplastin time (aPTT) and positive anti-phospholipid antibodies (lupus anti-coagulant, β2-GPI-dependent anti-cardiolipin (aCL) or biologically false positivity for syphilis). However, only three of the above 7 patients later presented remarkable symptoms and signs of APS such as cerebral thrombosis or habitual abortion. During the clinical course, specific clinical findings of 2 of the rest of the patients were absent and those of another 2 patients (thromboplastiitis) were too mild to be suspective of APS unless they were positive for serum anti-phospholipid antibodies. There are two possible reasons for the difficulty of the diagnosis of APS: 1) the existence of subclinical APS, and 2) the influence of the treatment of ITP with adrenocorticosteroid hormones. Therefore, the detection of the serum anti-phospholipid antibodies was thought essential for the screening of the APS.

Thrombocytopenia is sometimes observed in APS (5) and it has been regarded as one of the criteria in the diagnosis of APS (1, 6). As Atsumi et al describes (7), there are several mechanisms which cause thrombocytopenia in APS; consumption of the platelets at the site of thrombosis and destruction of the platelets by hemophagocytic systems. Since there may be cases without typical symptoms or signs of APS regardless of a positive test for the serum anti-phospholipid antibodies, it is thought important that thrombocytopenia is included in the criteria as a clue to find APS.

In our previous study (4), 5 out of 7 patients (71.4%), who were positive for any of the serum anti-phospholipid antibodies or had symptoms and signs of APS, had a positive test for serum aCL as determined by enzyme-linked immunosorbent assay (ELISA). Among the 5 patients with a positive test for aCL, 3 patients (60%) were positive for antinuclear antibody. This is in accordance with the data presented by Kaburaki et al (3). These patients might belong to the group of patients with the lupus-like disease described by Asherson and Cervera (8). It is known that systemic lupus erythematosus (SLE) is frequently complicated by both ITP and APS, and that ITP is also complicated by SLE. Furthermore, thrombocytopenia can occur in any of these 3 disorders. Since thrombocytopenia in the criteria apparently lowers the specificity of APS, discrimination of APS and ITP by detection of anti-phospholipid antibodies and analysis of the epitopes of the anti-platelet antibodies (9–12) is important to diagnose APS and subsequently to prevent the irreversible lesions such as infarction of various organs. In any case, a new criteria for APS is needed for the discrimination of these borderline diseases.

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References