**CORRESPONDENCE**

**Proposal for a Classification of the Clinical Stages of Paroxysmal Nocturnal Hemoglobinuria**

To the Editor:

Recently, the molecular mechanism of the membrane abnormality that leads to an increased susceptibility of affected erythrocytes to complement, resulting in intravascular hemolysis, has been clarified in paroxysmal nocturnal hemoglobinuria (PNH). The next concerns are the mechanisms of thrombosis and bone marrow (BM) hypoplasia that are the major causes of death. Progress in research on the hemolysis has led to the development of new methods for diagnosis: flow cytometric identification of affected cells lacking glycosylphosphatidylinositol (GPI)-anchored proteins, biochemical detection of the GPI-anchor defect, and detection of the PIG-A mutation in PNH clone.

Clinical application of these methods has shown the presence of subclinical PNH, which lacks the hemolytic features characteristics to PNH and which therefore does not meet the conventional criteria for diagnosis. In subclinical PNH, affected erythrocytes are undetectable despite the existence of affected progenitors in the BM and affected leukocytes in the peripheral blood. Such subclinical PNH eventually progresses to apparent PNH. For example, subclinical PNH has been shown in PNH-predisposing disorders such as aplastic anemia (AA) and pancytopenia of unknown origin. In AA, the frequency of detection of PNH leukocytes, ie, the incidence of subclinical PNH, has been reported as 3/16, 3/7, and 11/29 (total, 17/52 = 33%). Subclinical PNH is further noted in patients who once experienced apparent PNH and have been in a long-term clinical remission for more than 10 years. Although these patients remain free of any symptoms of hemolysis and negative for Ham's acidified serum test, affected lymphocytes have been detectable in their peripheral blood. Taken together with occasional relapse of hemolytic manifestation, these findings support that the remission is a subclinical PNH.

For appropriate diagnosis and a better understanding of the entire course of PNH, we propose a classification of the clinical stages of PNH (Table 1): stage I, latent PNH with affected cells in BM alone; stage II, smoldering PNH with affected cells in BM and in circulating leukocytes; stage III, classical PNH, which satisfies the conventional criteria; and stage IV, dormant PNH with clinical remission. In patients with PNH-predisposing disorders, attention should be paid to subclinical PNH (stages I and II), because the existence of PNH clone may alter the prognosis of these disorders.

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**REFERENCES**


**Table 1. A Classification of Clinical Stages (PNH)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Designation</th>
<th>Detection of PNH Cells</th>
<th>by Flow Cytometry in BM Cells</th>
<th>Leukocytes</th>
<th>Erythrocytes</th>
<th>by Ham's Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Latent PNH</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Smoldering PNH</td>
<td></td>
<td></td>
<td>+</td>
<td>+†</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Overt PNH (classical PNH)</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>- ~ +†</td>
</tr>
<tr>
<td>IV</td>
<td>Dormant PNH (clinical remission)</td>
<td></td>
<td></td>
<td>- ~ +</td>
<td>- ~ +†</td>
<td>-</td>
</tr>
</tbody>
</table>

* Affected cells are preferentially detected among peripheral granulocytes and monocytes.
† For the detection of affected erythrocytes, flow cytometry is usually less sensitive than Ham's test.
‡ Predominant persistence of affected T-lymphocytes is often noted.

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