Paroxysmal Nocturnal Hemoglobinuria in Myelofibrosis

By Niels Ebbé Hansen and S.-Aa. Killmann

Ten consecutive patients with myelo- fibrosis were examined for the following signs of PNH: Ham's test, the sucrose hemolysis test, low red cell acetylcholinesterase (ACHE) activity and intravascular hemolysis. Two of the patients displayed all these signs and also had clinical symptoms of PNH. Two patients had positive sucrose hemolysis tests, low red cell ACHE and intravascular hemolysis. One patient had a positive sucrose hemolysis test and low red cell ACHE. The remaining patients had no signs of PNH. In two of the patients, the PNH signs disappeared after splenectomy. The concurrence of myelofibrosis and PNH supports the hypothesis that PNH is a disease of the common hemopoietic stem cell.

It is established that some patients with aplastic anemia develop paroxysmal nocturnal hemoglobinuria (PNH).1 In contrast, the development of PNH in other blood diseases has been infrequently reported.2-6 Dacie suggested that PNH may develop as a somatic mutation of the hemopoietic stem cell in the regenerative phase of aplastic anemia.7 Extrapolating from this hypothesis, PNH may be expected to develop also in other conditions with impaired bone marrow function. Thus far, one case of simultaneous PNH and myelofibrosis has been recorded.8 In the present report, 10 consecutive cases of myelofibrosis have been studied with respect to the occurrence of PNH. Overt PNH was found in two cases, and laboratory signs of PNH were observed in several additional patients.

Material and Methods

Ten patients with a clinical diagnosis of the myelofibrosis syndrome (agnogenic myeloid metaplasia) were studied. The relevant clinical findings are summarized in Table 1. Patients 1, 2, 3, 4, 5, 7, and 9 were severely anemic, with hemolysis as a major factor. In the remaining patients, anemia was slight or moderate (hemoglobin above 10 Gm. per 100 ml.).

The following PNH tests were carried out: Ham's test,9 the sucrose hemolysis test,10,11 and acetylcholine esterase activity (ACHE) in the red cells.12 In all cases, the sucrose hemolysis test was done (at 37°C) on 3 consecutive days; the results were reproducible. From visual appraisal, the following gradation was used: + + + strong hemolysis, + + hemolysis definitely present, + slight hemolysis, 0 no hemolysis. As evidence for intravascular hemolysis was taken: raised plasma hemoglobin,13 hemoglobinuria (Hemastix), and
Table 1.—Clinical Features of Patients Studied

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Patient Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatosplenomegaly</td>
<td>+ + + + + + + +</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>+ + + + + + + +</td>
</tr>
<tr>
<td>Proven extramedullary hemopoiesis</td>
<td>+ – + + 0 0 + +</td>
</tr>
<tr>
<td>Proven marrow sclerosis/fibrosis</td>
<td>0 0 + + 0 + + 0</td>
</tr>
<tr>
<td>Dry tap</td>
<td>0 0 0 0 + + + 0</td>
</tr>
<tr>
<td>Increased marrow reticulum cells</td>
<td>+ 0 + + + + 0 +</td>
</tr>
<tr>
<td>Bone changes on X ray</td>
<td>0 0 + + 0 + + 0</td>
</tr>
<tr>
<td>Raised serum uric acid</td>
<td>+ 0 + + + + + +</td>
</tr>
<tr>
<td>Raised basal metabolic rate</td>
<td>+ – + + + + + –</td>
</tr>
</tbody>
</table>

Signs: +, positive finding; 0, negative finding.

Table 2.—PNH Signs in Patients with Myelofibrosis

<table>
<thead>
<tr>
<th>PNH Signs</th>
<th>Patient Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ham’s test</td>
<td>+ + 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Sucrose hemolysis test</td>
<td>+++ + + + + + + 0 0 0</td>
</tr>
<tr>
<td>Low red cell ACHE</td>
<td>(µM/min./Gm. Hb)</td>
</tr>
<tr>
<td>Normal range: 16.0–23.2</td>
<td>13 13.8 15.5 14.0 13.6 21.2 36.7 25.6 17.7 16.8</td>
</tr>
<tr>
<td>Intravascular hemolysis</td>
<td>(mg./100 mL)</td>
</tr>
<tr>
<td>(Normal value: 0)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobinuria</td>
<td>+ + + 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Hemosiderinuria</td>
<td>+ + 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Raised serum LDH</td>
<td>(µM/hr./µL)</td>
</tr>
<tr>
<td>(Normal range: 7–23)</td>
<td></td>
</tr>
</tbody>
</table>

Signs: +, positive finding; 0, negative finding.

* Anodic isoenzyme pattern.
Discussion

Fundamental to the interpretation of the findings reported here is a consideration of the basis for the diagnosis of PNH, or more precisely, what is the minimum requirement for the diagnosis of the PNH defect? Ham's test is universally accepted as diagnostic of the PNH defect (except in hereditary erythroblastic multinuclearity, of which there were no signs in our patients), and as this test, as well as the other tests listed, were positive in patients 1 and 2, the diagnosis in these two patients appears well established. The sucrose hemolysis test as described by Hartmann and Jenkins appears specific for PNH, although the specificity has been challenged by others. In our experience, the test seems to be specific for PNH, the only patients with positive sucrose hemolysis tests and negative Ham's tests we have encountered are the three patients reported here. It should be noted that, in these cases also, other features were present that are compatible with the diagnosis of PNH, i.e., reduced concentration of red cell ACHE, signs of intravascular hemolysis, or both. The combination of a positive sucrose hemolysis test and a negative Ham's test could be interpreted in two ways: either the sucrose hemolysis test is not specific, or it is more sensitive that Ham's test. The presence of other signs compatible with PNH favors the latter interpretations; this is also supported by other evidence. This view implies that there are gradations of the PNH defect, and that a positive Ham's test reflects a rather severe defect.

The fact that two patients in a series of 10 with myelofibrosis had overt PNH, and the probability that three additional patients had the PNH defect to a milder degree is definitely more than could be expected by chance, although admittedly the series is somewhat biased in that sense that the study was prompted by the clinical observation of patient 1. As to the question of which of the two diseases came first, the clinical course in patient 1, described elsewhere, suggests that myelofibrosis became manifest first. The data on the remaining patients of this series do not elucidate this problem.

More intriguing is the problem: what is the connection between these conditions? Myelofibrosis, as well as aplastic anemia, may well be diseases of the common hemopoietic stem cell. It is well established that both conditions may lead to acute leukemia. PNH may occur both in aplastic anemia and in myelofibrosis; moreover, PNH may terminate in acute myeloid leukemia. In this context it is of interest to note that recent evidence suggests that acute myeloid leukemia is a disease of the common hemopoietic stem cell. On this background it appears likely that the PNH defect is linked to disease(s) of the common hemopoietic stem cell.

The significance of the postoperative disappearance of the PNH-defect in the two patients who were splenectomized is not clear. Among several possible explanations it may be considered that the PNH-cells were primarily formed in the spleen.

References


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