Paroxysmal Nocturnal Hemoglobinuria with Deletion of Chromosome 13q (q12q14): a Case Report and Review of the Literature

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Abstract. A normal karyotype is usually present in cases of classic paroxysmal nocturnal hemoglobinuria (PNH), whereas chromosomal abnormalities involving chromosome bands 13q12 to 13q14 (13q12q14) are frequently found in various hematologic malignancies, including chronic lymphoblastic leukemia (CLL) and myelodysplastic syndrome (MDS). Here, we present a case of a 55-year-old male patient with PNH who had a deletion of chromosome 13q [del(13q)]. He presented with cough, fever, and pancytopenia. Flow cytometry of the patient’s peripheral blood demonstrated that 21.7% and 21.5% of the erythrocytes were CD59 and CD55 deficient, respectively, and 63.5% of the granulocytes were FLAER and CD24 deficient. Examination of the bone marrow indicated that blasts were not increased but mild dyshematopoietic features were present. Conventional cytogenetic analysis and fluorescence in situ hybridization revealed a deletion of chromosome 13q (q12q14). The patient received an allogeneic hematopoietic stem cell transplantation. Whether this abnormality can be considered as an evidence of MDS in the setting of overt PNH requires an evaluation in the future.

Key words: PNH, chromosome 13, MDS

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal bone marrow disorder characterized by an increased number of cells deficient in glycosylphosphatidylinositol (GPI)-anchored membrane proteins, which is due to these cells being the progeny of hematopoietic progenitor cells that have a somatic mutation in the X-linked phosphatidylinositol glycan complementation group A (PIG-A) [1]. PNH frequently occurs alongside aplastic anemia, and there is a relationship between PNH and myelodysplastic syndrome (MDS) as well [2]. A concurrent diagnosis of MDS can be made in patients with PNH who have dyshematopoietic features and karyotypic abnormalities in their bone marrow [2-3]. In classic PNH, the karyotype is usually normal, yet the clinical and/or diagnostic significance of the cytogenetic abnormalities in PNH patients who have them is not clear [2, 4]. Some cytogenetic abnormalities, such as trisomy 8 and the loss of the Y chromosome, are not generally accepted as definitive evidence of MDS in the absence of morphological evidence. However, according to the WHO classification guidelines, some MDS-specific cytogenetic abnormalities are considered presumptive evidence of MDS even in the absence of definitive morphological features. Chromosomal abnormalities that involve chromosome bands 13q12 to 13q14 (13q12q14) are categorized as such MDS-specific cytogenetic abnormalities [5]. Here, we present a case of a patient with PNH and deletion of chromosome 13q. We also reviewed other reported cases of PNH with deletion of chromosome 13q in conjunction with this case in order to explore the clinical and diagnostic relevance of chromosome 13q deletion in PNH.

Case Report

A 55-year-old-male patient presented with a 3-day cough and fever in December 2010. His initial
blood cell counts at our hospital were the following: white blood cells, $3.84 \times 10^3 / \mu L$; hemoglobin, 5.5 g/dL; platelets, $60 \times 10^3 / \mu L$; MCV 114.8 fL; MCH 38.7 pg; and MCHC 33.7 g/dL. His peripheral blood smear showed a macrocytic normochromic anemia, mild leukopenia, moderate thrombocytopenia, and an increased reticulocyte count. An anemia work up was done, and the results were: iron, 18 mcg/dL; total iron-binding capacity, 222 mcg/dL; ferritin, 467.1 ng/mL; folate, 17.45 ng/mL; and vitamin B12, $> 2000 \text{ pg/mL}$. In regard to hemolysis, laboratory tests showed decreased haptoglobin levels (<10 mg/dL), increased plasma hemoglobin (33.8 mg/dL), and increased lactate dehydrogenase (896 IU/L), thus indicating intravascular hemolysis. Furthermore, the direct/indirect antiglobulin tests were negative. A bone marrow study revealed a lack of an increase in blasts (0.9% of all nucleated cells) but erythroid hyperplasia with mild dyserythropoietic features and

Figure 1. A. Immunophenotyping using CD55/CD59 in erythrocytes demonstrates that 21.7% and 21.5% of the erythrocytes were CD59 and CD55 deficient (Type II), respectively. B. Granulocytes show that 63.9% (Type III) were FLAER deficient and 63.5% (Type III) were CD24 deficient.
normal cellularity. Flow cytometric immunophenotyping was performed on the patient’s peripheral blood with a CYTOMICS FC 500 flow cytometer (Beckman Coulter, Miami, FL). CD59 and CD55 were used as RBC markers, and FLAER and CD24 as granulocyte markers. The results demonstrated that 21.7% and 21.5% of the erythrocytes were CD59 and CD55 deficient, respectively (Figure 1A), and 63.5% of the granulocytes were FLAER and CD24 deficient (Figure 1B). Conventional cytogenetic analysis showed an abnormal karyotype of 46, XY, del(13)(q12q14)[2]/46,XY[18]. In addition, interphase fluorescense in situ hybridization (FISH) analysis which used a probe targeting the RB1 gene (Vysis LSI 13 (RB1) 13q14 probe, Abbott Molecular) confirmed a RB1 gene deletion on the long arm of chromosome 13 in 4.5% of the cells (Figure 2). The patient was diagnosed as having PNH, but MDS could not be ruled out because of the mild dysplastic features and the cytogenetic abnormality. After one cycle of decitabine therapy, the percentage of PNH clones in the granulocyte population increased to 76.99%, and the patient’s blood cell counts were the following: white blood cells, 6.93 × 10³/uL; hemoglobin, 10.9 g/dL; and platelets, 187 × 10³/uL. Further, conventional cytogenetic analysis showed a normal karyotype of 46,XY[20], and the RB1 gene deletion was not observed on FISH analysis.

Discussion

PNH is frequently associated with bone marrow failure disorders, particularly aplastic anemia and MDS [6]. A significant proportion of patients progress from PNH to AA/MDS and vice versa [7], however there is confusion in the categorization and management of these patients. Even if a PNH clone is detected, it should be clinically corroborated with a hemolysis work up in order to make a definitive diagnosis of PNH.

Cases of PNH are subclassified as classic PNH, PNH in the setting of another specified bone marrow disorder, and subclinical PNH [6]. For a diagnosis of PNH in the setting of another specified bone marrow disorder, a patient should have clinical and laboratory evidence of hemolysis and concomitantly have, or have a history of, a defined underlying marrow abnormality such as MDS or AA.

Bone marrow morphology and the finding of a
non-random cytogenetic abnormality are important factors for the diagnosis of this subtype of PNH. The subclinical PNH category includes patients who have a small population of PNH clones, another bone marrow failure syndrome such as AA or MDS, and no clinical evidence of hemolysis [2].

Our case showed intravascular hemolysis and a large PNH clone population. Consequently, it was compatible with a diagnosis of classic PNH. However, mild dysmaturational features were observed in the bone marrow aspirate, and the deletion of 13q was observed by both conventional cytogenetics and FISH. The deletion of 13q is categorized as a MDS-related change and is presumptive evidence of MDS according to the WHO classification guidelines. Thus, we could not rule out MDS. However, it is questionable whether this cytogenetic abnormality is evidence of MDS in the setting of classic PNH. A literature review revealed that PNH with abnormal cytogenetics has been reported in a limited number of cases (three cases including the one presented here) [2, 4], but it still appears to occur more frequently than other MDS-specific changes such as the deletions of 7q and 5q in PNH cases. All three cases showed a relatively large percentage of PNH clones (range: 22-63.5%) and had a diagnosis of either AA/PNH or MDS/PNH. None of these patients developed high-grade MDS or leukemia, and one patient showed improvement as time elapsed (Table 1). With such a limited number of cases and insufficient information about the reported cases, the clinical significance of MDS-related cytogenetic abnormalities, including 13q deletion, in the setting of overt PNH is still unclear. This topic needs to be more thoroughly evaluated through the further accumulation of such cases.

In summary, we have presented a patient with overt PNH and a 13q deletion and reviewed the reported cases of PNH with cytogenetic abnormalities. Among the MDS-related abnormalities, the deletion of 13q seems to be the most frequently occurring in conjunction with overt PNH. Whether these abnormalities can be considered as evidence of MDS in the setting of overt PNH needs to be evaluated in the future. In cases such as these, a PNH clone study and cytogenetic studies are important tests to perform in order to obtain the baseline data needed for a diagnosis.

### Table 1. Summary of 3 cases with PNH with deletion of chromosome 13q

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex/Age</th>
<th>Karyotype</th>
<th>Diagnosis</th>
<th>PNH population</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/19</td>
<td>46.XX,del(13)(q12q14)[5/10]</td>
<td>AA, PNH</td>
<td>22% (erythrocytes) 60% (granulocytes)</td>
<td>ATG, Cyclo</td>
<td>Improved</td>
<td>[7] Araten D et al. (2001)</td>
</tr>
<tr>
<td>3</td>
<td>M/55</td>
<td>46.XY,del(13)(q12q14)[2]/46.XY[18]</td>
<td>PNH, r/o MDS</td>
<td>21.5% (erythrocytes) 63.5% (granulocytes)</td>
<td>decitabine</td>
<td>Clinically stable PNH clone increased</td>
<td>Present case (2011)</td>
</tr>
</tbody>
</table>

Abbreviations: AA, aplastic anemia; ATG, anti-thymocyte globulin; Cyclo, cyclosporine; F, female; M, male; r/o, rule out; NA, not available.
References


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