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Research Article

Paroxysmal Nocturnal Hemoglobinuria Associated Myelodysplastic Syndrome and Aplastic Anemia: A Single Center Experience

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Abstract

Objectives: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease that could accompany aplastic anemia (AA) and myelodysplastic syndrome (MDS). In this study, we wanted to share our experiences about PNH clone positivity rates and the clinical effects in patients who were being followed up with diagnoses of AA and MDS.
Methods: We investigated 30 people in our study, 22 of whom had MDS and 8 of whom had AA. The PNH scan was carried out using the FLAER method, which is considered the gold standard today.
Results: PNH clone positivity rates were 4.5% in MDS and 62.5% in AA. Two of the patients initiated eculizumab treatment.
Conclusion: It is important to detect a PNH clone because of its effect on the course of other bone marrow diseases, especially AA and MDS.
Keywords: Complement system, Paroxysmal nocturnal hemoglobinuria, Thrombosis

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PNH is a rare disorder with different clinical manifestations.[1] It is caused by a somatic mutation in a hematopoietic stem cell that inactivates the PIG-A gene (phosphotidylinositol glycan anchor biosynthesis, class A). This mutation is concluded with a deficiency of the glycosylphosphatidylinositol (GPI) molecule.[2] GPI-linked proteins, CD55 (decay accelerating factor, DAF) and CD59 (membrane inhibitor of reactive lysis, MIRL), are involved in the regulation of the complement system.[3] Deficiency of these proteins results in increased complement sensitivity of PNH cells.[4] The International PNH Interest Group (I-PIG) has proposed a working diagnostic classification with the

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following three categories: classical PNH, PNH accompanying other bone marrow failure conditions (aplastic anemia, myelodysplastic syndrome), and subclinical PNH.[1,5,6]

Myelodysplastic syndrome (MDS) is a group of bone marrow disorders that arise from a defective stem cell. It results in peripheral blood cytopenias.[7,8] In patients with MDS, PNH clone positivity has been reported as 1.1%–8%, and in the MDS-refractory anemia subtype, it has been reported as 17.6%–53.3%. The underlying cause of erythrocyte transfusion dependence in patients with MDS could be PNH clone positivity.[7]

Aplastic anemia is derived from a decrease or absence of hematopoietic precursors in bone marrow and is also characterized by peripheral blood cytopenias.[8,9] PNH clones could be detected in AA; however, most patients express only a small PNH clone size (<10%).[10] It was observed that PNH-associated AA had a better response to immunosuppressive treatment.[10–12] Also, it was shown that 10%–25% of PNH clone-positive AA patients undergo clonal expansion and develop clinical PNH in the future.[12]

In this study, we wanted to share our experiences about PNH clone positivity rates and the clinical effects in our patients who were being followed up with diagnoses of AA and MDS.

Methods

Patients who were admitted to the Department of Hematology of Manisa Celal Bayar University Hospital between May 15, 2015, and January 31, 2018, were included in our work. The PNH test is routinely performed for patients who are followed up in our clinic and diagnosed with MDS and AA. We scanned these patients retrospectively. All patients with aplastic anemia and MDS with hypoplastic or refractory cytopenia or no blast increase were included.

Blood samples were collected from selected patients into two ethylenediaminetetraacetic acid (EDTA) tubes, 2 ml per tube, and were studied within 48 hours. A PNH clone search was performed on a FacsCanto II flow cytometry instrument. Evaluation was performed using CD56, CD24, CD16, and fluorescent aerolizine (FLAER) antibodies that bind to the binding site of GPI, CD45, CD15, and CD64 gating antibodies. CD59 was used to detect type II and type III PNH cells in erythrocytes. For confirmation, CD24 was used in granulocytes, and CD14 was used in monocytes. Complete blood count, LDH, and indirect bilirubin values of the patients included in the study were recorded.

The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed with SPSS Statistics v18.0 software (Armonk, New York: IBM Corp.). In the study, descriptive statistics were performed by determining the mean, median, and ratios of the variables related to the results. A p-value of <0.05 was considered statistically significant.

Ethics Approval and Consent to Participate

Manisa Celal Bayar University Ethics approval was received for this study on 13.05.2015 with number 20478486.220.

Results

A total of 30 people were included in our study, 22 of whom had MDS and 8 of whom had AA. Fifteen of the participants

Table 1. Age-sex-hemogram and biochemical parameters and the first positive clone percentages of patients with PNH clone positivity

Patient	1	2	3	4	5	6
Age	62	65	50	76	55	31
Gender	Female	Female	Female	Female	Female	Female
Diagnosis	PNH, MDS	PNH, AA	AA	AA	AA	AA
PNH clone size, granulocytes (%)	93.75	2.42	0.53	0.13	0.34	0.23
PNH clone size, monocytes (%)	96.9	6.73	1.93	1.55	0.87	0.47
Hb (g/dL)	8.4	6.5	13.3	9.8	11.7	9.6
WBC (/mm^3)	3400	3200	3700	4700	3200	4000
Neu (/mm^3)	2400	2600	1100	1900	1500	2300
Plt (x10^3/ mm^3)	85	16	60	48	155	43
LDH (IU/L)	845	407	237	231	202	190
Indirect Bilirubin (mg/dL)	0.7	0.3	0.36	0.5	0.4	0.4
Time of PNH clone positivity (year)	2016	2016	2017	2017	2015	2016

PNH: Paroxysmal Nocturnal Hemoglobinuria; MDS: Myelodysplastic Syndrome; AA: Aplastic anemia; Wbc: White blood cell; Hb: Hemoglobin; Plt: Platelet; LDH: Lactic dehydrogenase.

were female, and 15 were male. A PNH clone was detected positive in 6 patients, and all of them were female (Table 1). When the PNH clone was diagnosed as positive, none of the patients had PNH-related complications, such as infections, thrombosis, and renal insufficiency.

Fourteen of the patients included with the diagnosis of MDS were male, and 8 were female. In 1 (4.5%) of 22 patients diagnosed with MDS, the PNH clone was positive. The PNH clone-positive patient was female, and her clone size was over 10% (Patient 1, Table 1). This patient received transfusion support, methylpredinizolone, and intravenous immunoglobulin (IVIG) therapy before the PNH clone was detected positive. Because of continued transfusion requirement and increased lactic dehydrogenase (LDH) levels, PNH was tested, and high clone levels were detected (Table 1). Anti-C5 monoclonal antibody treatment had initiated.

One of the patients included with the diagnosis of AA was male, and 7 were female. In 5 (62.5%) of 8 patients with aplastic anemia, the PNH clone was positive. All of these 5 patients were female. Patient 2 was treated with methylprednisolone and cyclosporine, and transfusion support was provided before the PNH clone was detected positive. The first PNH clone-detected positive patient was followed up. Anti-C5 monoclonal antibody treatment had initiated due to the patient's non-response to immunosuppressive treatment, transfusion dependence, and clone progression (11.2% in granulocytes and 8.17% in monocytes). The patient's transfusion dependence disappeared. Other patients had minor PNH clones (Patients 3, 4, 5, and 6, Table 1), and they were also followed up for clone progression, and no clone progression had occurred yet. Also, all patients were alive.

Discussion

In many non-PNH situations, such as AA and MDS, testing for PNH can be informative. Patients with AA or MDS with unexplained cytopenia should be tested for PNH at the time of diagnosis for differential diagnosis.[1] Depending on the case selection criteria among MDS patients, the rate of PNH-positive cases varies in the literature, ranging between 1.8% and 41%. GPI-deficient cells are found more commonly in low-grade MDS patients with hypoplastic bone marrow characteristics than in other MDS subtypes.[11]

In our study, we found PNH clone positivity in 4.5% of patients who were diagnosed with MDS. In patients with MDS, the PNH clone positivity rate was reported as 9.8% by Morado et al.[11] and 5% by Mercier et al.[13]. Our rates were similar to those in these studies. Raza et al. found that when all MDS subgroups were included, the detection rate of a PNH clone size above 1% was 1.1% in their prospective multicenter study. Also, there were differences between MDS subtypes: refractory anemia, 1.3%; unclassified, 1.5%; refractory anemia with excess blasts type 1 and type 2, 0.3%; 5q- syndrome, 0%; and refractory cytopenia with multilineage dysplasia, 1%.[14] We found higher rates compared with this study. Consequently, because of the differences in the literature and between MDS subtypes, we need well-designed studies according to the guidelines.

Although the rate of PNH-positive AA cases varies significantly in the literature, ranging from 22% to 89%, it is currently estimated to be about 40% of cases. According to their data, Morado et al.[11] emphasized the importance of testing for PNH in patients diagnosed with AA at any age. In aplastic anemia, we found a clone positivity rate of 62.5%. According to their research, PNH clone positivity rates in patients with AA were described as 45% by Morado et al.[11] and 47% by Mercier et al.[13]. Compared with these studies, we found a higher rate of clone positivity. However, according to the literature, in acquired AA, small-sized PNH clone positivity rates are about 70% at the time of diagnosis.[1] Compared with the literature, our results were similar. We found that a PNH clone size ≥1% was prevalent in 12.5% of patients with AA, which was reported as 18.5% by Raza et al.[14] and 21% by Dunn et al.[15]. Our results were compatible with these studies. As a result, considering these rates, it is worth testing the PNH clone in patients diagnosed with AA.

All of our patients in whom PNH clone positivity was detected were alive. One of our patients received anti-C5 monoclonal treatment because of transfusion dependence, while the other patients were followed up for clone progression. Wang et al. showed that patients who had minor populations of PNH-positive cells had a better response to immunosuppressive treatment than PNH cell-negative patients. Also, none of the PNH-positive patients progressed to acute myeloid leukemia. Furthermore, some patients' pancytopenia remained stable or improved spontaneously without any treatment.[16] Maciejewski et al.[17] studied the relationship between bone marrow failure syndromes, GPI-A protein deficiency, and response rates to immunosuppressive treatment, which were higher in patients who had PNH clones. Considering all these studies and the fact that our patients who had minor clones of PNH are still alive without disease progression, the presence of minor PNH clones increases survival in MDS and AA.

Our study has some limitations. PNH is such a rare disease that its prevalence is estimated to be approximately 16 per million.[18] Our center is small, so the number of patients tested for PNH has been low for this rare disease. In addition, since this study is single-centered, PNH clone positiv-

ity and its effect on MDS and AA were evaluated only in terms of patients in a specific region.

Conclusion

In conclusion, we shared our data about a rare disease that could accompany AA or MDS. Our knowledge of MDS and AA has also improved since we started using the FLAER test. It is important to detect a PNH clone because of its effect on the course of other bone marrow diseases, especially AA and MDS. Since PNH is a rare disease, more studies are needed to determine the frequency of PNH accompanying MDS and AA.

Disclosures

Ethical Committe Approval: Manisa Celal Bayar University Ethics approval was received for this study on 13.05.2015 with number 20478486.220.

Author Contributions: Concept – İA, FA, SED; Design – İA, İB, SED; Supervision – AT, TB, SED; Fundings – İA, AT, SED; Materials – MM, TB, AT; Data collection &/or processing – AT, TB, SED; Analysis and/or interpretation – TB, İA, MM; Literature search – İB, FA, MM; Writing – İA, İB, SED; Critical review – FA, TB, SED.

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