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POSTER ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

Ahemolytic PNH: Clinical Features of a Distinct Phenotype of Paroxysmal Nocturnal Hemoglobinuria

Zehra Tombul[1], Waled Bahaj, MD[2], Merve Ozturk[1], Bhavisha A. Patel, MD[3], Alina Dulau-Florea, MD[4], Ahmet Celal Toprak, B.S.[5], Ibrahim F. Ibrahim, MD[6], Weina Chen[7], Franklin Fuda[8], Olisaemeka Ogbue[9], Carmelo Gurnari, MD[10,11], Charles Parker[12], Neal S. Young, MD[3], Jaroslaw P. Maciejewski, MD, PhD, FACP[10], Munevver Duran, BA[1], Taha Bat, MD[13]

[1] UT Southwestern Medical Center, Dallas, TX
[2] Translational Hematology and Oncology Research, Cleveland Clinic, Cleveland, OH
[3] Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD
[4] Hematology Service, Department of Laboratory Medicine, National Institutes of Health, Bethesda, MD
[5] University of Texas Southwestern Medical Center, Dallas, TX
[6] Department of Hematology and Oncology, UT Southwestern Medical Center, Dallas, TX
[7] Department of Pathology, The University of Texas Southwestern Medical Center, Dallas, TX
[8] Department of Pathology, UT Southwestern Medical Center, Dallas, TX
[9] Cleveland Clinic Foundation, Rocky River, OH
[10] Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH
[11] Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy
[12] Division of Hematology and Hematologic Malignancies, University of Utah School of Medicine, Salt Lake City, UT
[13] Department of Hematology and Oncology, University of Texas Southwestern Medical Center, Dallas, TX

Introduction: Paroxysmal nocturnal hemoglobinuria (PNH) is a hematopoietic stem/progenitor cell disorder caused by *PIGA* mutations. All hematopoietic lineages derived from the affected clone exhibit the PNH phenotype [deficiency of glycosyl phosphatidylinositol linked membrane proteins (GPI-APs)]. Diagnosis is made by flow cytometric analysis of red blood cells (RBC), granulocytes, and monocytes. The percentage of granulocytes and monocytes with absent expression of GPI-APs is a measure of the size of the PNH clone. Typically, the percentage of GPI-AP deficient RBCs is somewhat less than that of granulocytes and monocytes due to selective destruction by complement-mediated intravascular hemolysis, manifested by high LDH, bilirubin, reticulocyte count and low haptoglobin. Herein, we report five patients with large PNH clones based on percentage of GPI-AP deficient neutrophils and monocytes, but with absent or near absent PNH RBCs and no biochemical evidence of hemolysis. We call this unique disease subtype, ahemolytic PNH.
Methods: The medical records of PNH patients (174 patients with PNH granulocytes >20%) at the University of Texas Southwestern, Cleveland Clinic Foundation, and National Institutes of Health from 2000 to 2022 were examined. Information pertaining to their clinical, laboratory, and molecular attributes (NGS sequencing) was collected. Five patients with granulocyte clones >50% and RBC clones <5% were identified (Table).
Results: Patient 1 is a 63-year-old male with a remote history of non-severe aplastic anemia (AA) diagnosed at 11 years old. The first PNH flow cytometry, obtained at age 61 years, showed 0.02% type II PNH RBC, 0.5% type III PNH RBC, 96% PNH monocyte and 97% PNH granulocytes (Table). There was no biochemical evidence of hemolysis at the time of diagnosis or in the preceding 5 years. Patient 2 is a 50-year-old male who presented with pancytopenia and was diagnosed with acute myeloid leukemia with myelodysplastic-related mutations. Flow cytometry showed 85% PNH monocytes and 59% PNH with no detectable PNH RBCs and no biochemical evidence of hemolysis at diagnosis or in 3 years of follow-up (Table). Patient 3 is a 73-year-old female who presented with pancytopenia and marrow aplasia with unremarkable morphology, and a PNH granulocyte clone of 93.6% with 1.3% type III PNH RBCs and 1.3% and 0.5% type II PNH RBCs, with no evidence of hemolysis (Table). Patient 4 is a 21-year-old female who presented with Budd-Chiari syndrome. Flow cytometry showed 73% PNH granulocytes with 3.6% type III PNH RBCs and 1.8% type II PNH RBCs. There was no biochemical evidence of hemolysis, but because of thrombosis, she was treated complement inhibitor therapy (Table). Patient 5 is a 61-year-old female with history of severe aplastic anemia

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treated with immunosuppression (IST) and eltrombopag. PNH flow cytometry showed PNH granulocytes of 92.4% and 2.1% PNH type II RBCs 2.1% post IST treatment with no biochemical evidence of hemolysis (Table).

Conclusion:

Herein, we present five patients with a distinct PNH phenotype that we call ahemolytic PNH. Except for the absence or near absence of PNH erythrocytes, this entity shares clinical and pathophysiological features with classic PNH, including thrombophilia (Budd-Chiari Syndrome, Table). The basis of this phenotype is speculative but may be determined by the genotype of the affected HSPC in which the somatic mutation of *PIGA* first occurred. According to this hypothesis, somatic mutations other than *PIGA* skew differentiation toward granulocyte/monocyte lineages.

The International PNH Interest Group recognizes the following three categories of PNH: classic PNH, PNH in the setting of another define bone marrow abnormality, and subclinical PNH. Like ahemolytic PNH, subclinical PNH has no biochemical evidence of hemolysis. In this case, however, the absence of hemolysis is due to the small size of the PNH clone (median clone size <1%) as determined by flow cytometry analysis of peripheral blood granulocytes and monocytes. We propose that ahemolytic PNH, defined as patients having less than <5% PNH red cells and >50% PNH granulocytes/monocytes, be recognized as a distinct category of PNH.

Disclosures Maciejewski: *Alexion:* Membership on an entity's Board of Directors or advisory committees; *Regeneron:* Consultancy, Honoraria; *Novartis:* Honoraria, Speakers Bureau; *Omeros:* Consultancy. **Bat:** *Alexion pharma:* Membership on an entity's Board of Directors or advisory committees.

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Variable		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)		63	50	73	21	61
Sex		M	M	F	F	F
Race		Caucasian	Hispanic	Caucasian	Caucasian	Caucasian
Symptoms at Presentation		Asymptomatic	Fatigue	Fatigue	Abdominal pain	None
Remote history of Aplastic anemia/treatment		Exist/not needed	Exist/treated with IST	Exist/treated with IST	No	Exist/treated with IST
PNH Clone	Type II RBC	0.02%	0%	0.54%	1.80%	2.1
	Type III RBC	0.50%	0%	1.31%	3.60%	N/A
	Granulocyte	97%	59%	93.59%	73%	92.4%
	Monocyte	96%	85%	NA	NA	N/A
WBC, x10^9/L		3.51	2.28	2.89	4.17	2.19
RBC, x10^9/L		3.64	2.81	2.65	4.47	2.66
Hemoglobin, g/dl		13.7	9.1	8.4	12.2	10
MCV (fL)		105.5	98.2	90.6	87.2	111.3
Platelet counts, x10^9/L		61	270	8	133	14
Hemolytic markers	LDH (125 - 220 U/L)	184	218	205	158	196
	Haptoglobin (14 - 258 mg/dL)	51	123	35	56	N/A
	Reticulocytes count (0.2 - 2.5 %)	1.3	1.8	0.9	1	69.7
	T.bilirubin (0.2 - 1.3 mg/dL)	0.8	0.5	0.7	2.6	0.3
	D-dimer (<=0.59 mg/L FEU)	0.34	0.44	NA	220	0.27
Bone Marrow Biopsy at the time of PNH flow cytometry		Hypocellular (20% cellularity)	Hypercellular marrow (70%) with 34% blasts; consistent with AML	Markedly hypocellular (<5%)	N/A	Hypocellular (20% cellularity); markedly decreased megakaryocytes
Cytogenetics		Normal karyotype	N/A	Normal karyotype	N/A	Normal karyotype
PIG-A Mutation		PIGA (NM_002641.3), p.V231del (p.Val231del), c.690_692del, ChrX(GRCh37): g.15349360	N/A	Wild Type	p.H126Y, NM_002641.3, c.376C>T,VAF: 28.2%	N/A
Thrombosis type/Age at thrombosis		Coronary artery disease/58	N/A	N/A	Budd-Chiari syndrome/21	N/A
Treatment for PNH (after flow cytometry)		Not undergoing treatment, under close monitoring	In remission from AML, not undergoing treatment for PNH	Currently on Eculizumab	Started on eculizumab and switched to Ravulizumab	Not undergoing treatment
Most recent follow up (time since diagnosis)		31 months	2 months	57 months	3 months	22 months

Figure 1

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