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by Priyansh Faldu, Rania Abdelaziz, Muhammad Yousuf, Animesh Pardanani, Mrinal Patnaik, Ayalew Tefferi and Naseema Gangat

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Myeloproliferative neoplasms with clinically relevant paroxysmal nocturnal hemoglobinuria: clinical correlations and outcomes

Priyansh Faldu,[1] Rania Abdelaziz,[1] Muhammad Yousuf,[1] Animesh Pardanani,[1] Mrinal Patnaik,[1] Ayalew Tefferi,[1] Naseema Gangat.[1]

[1]*Divisions of Hematology and Hematopathology, Mayo Clinic, Rochester, Minnesota, USA*

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Corresponding Author: Naseema Gangat, MBBS, Division of Hematology, Department of Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905; E-mail: gangat.naseema@mayo.edu

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders driven by mutations in *JAK2*, *CALR*, or *MPL*, and include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF)(1). Clinical manifestations include thrombohemorrhagic complications and risk of leukemic or fibrotic progression (2). Paroxysmal nocturnal hemoglobinuria (PNH) is also an acquired hematopoietic stem cell disorder caused by *PIGA* mutations. Clinical manifestations include complement-mediated intravascular hemolysis and thrombosis (3). PNH is typically associated with aplastic anemia (AA) and myelodysplastic syndrome (MDS) (3, 4). Although the coexistence of MPN and PNH is rare (4-8), both entities are associated with anemia and increased thrombotic risk (2, 3). The main objectives of the current study were to characterize the clinical phenotype, and evaluate treatment outcomes, including response to complement inhibition in patients with MPN and PNH.

A Mayo Clinic enterprise-wide database search was conducted to identify patients with MPN and concomitant PNH following institutional review board approval. The requirement for informed consent was waived by the ethics committee. Between January 2000 and June 2025, 8 patients had a diagnosis of MPN per the International Consensus Classification, and treatment-requiring PNH. Evaluation for PNH was performed in MPN patients with intravascular hemolysis or splanchnic venous thrombosis. Clinical features, including hemolysis and thrombosis, and therapeutic interventions were recorded.

The study cohort included 8 patients (median age 65 years; 88% males) with MPN (5 with PMF, 2 ET, 1 post-ET MF) in whom PNH was diagnosed concomitantly (*n*=3), or at a median of 8 years (range: 2-14) after MPN diagnosis (*n*=5). In 7 of 8 patients (87%), workup for PNH was instigated by hemolytic anemia, while in 1 patient (13%), it was prompted by splanchnic vein thrombosis. MPN driver mutations were evaluated in 6 cases: *JAK2* (*n*=2) and *CALR* (Type 1, *n*=3; Type 2, *n*=1); an additional case was *JAK2* negative. Next-generation sequencing was performed in 5 patients and identified additional mutations in *ASXL1*, *ZRSR2*, and *SF3B1* in 1 case each. Cytogenetics data were available for all except 1 patient, and only 1 (14%) showed an abnormal but favorable karyotype. PNH clone size was evaluated in

7 cases; median (range) was 3.92% (0.02%–10.96%) in red blood cells (RBCs), 28.8% (6.1%–91.2%) in granulocytes, and 60.1% (6.6%–98.8%) in monocytes. Table 1 outlines presenting laboratory values; information on the clinical characteristics and course for each of these cases are summarized in Tables 2 and 3 and discussed below.

Patient #1, a 67-year-old male, was diagnosed with concomitant PNH and PMF following hemolytic anemia workup and was initiated on eculizumab; during follow-up of 5 years, hemoglobin was steady at 12 g/dl.

Patient #2, a 63-year-old female, presented with hemolytic anemia and was diagnosed with *CALR* and *ASXL1*-mutated PMF and concomitant PNH with a granulocyte clone size of 28.8%. She had a baseline hemoglobin of 10.5 g/dl and received ruxolitinib for symptomatic splenomegaly. However, a month later, eculizumab was initiated due to ongoing hemolysis requiring transfusions. During 8.5 years of follow-up, she remained transfusion dependent, despite switch in treatment from ruxolitinib to pacritinib.

Patient #3, a 70-year-old male with *CALR*-mutated ET, was diagnosed with PNH, ten years after MPN diagnosis, following workup for hemolysis. PNH clone in granulocytes was 63.9% and baseline hemoglobin at PNH diagnosis was 8.6 g/dL. He received eculizumab without improvement in anemia. Thereafter, due to concern for disease evolution to MDS, he underwent allogeneic stem cell transplantation (allo-SCT). Five months after transplant, he had recurrence of PNH and received two donor lymphocyte infusions (DLIs) and eculizumab was reinitiated which led to eradication of the PNH clone. At ten months post-transplant, he developed deep venous thrombosis (DVT), which was managed with anticoagulation. In addition, during the eight-year follow-up, he developed chronic graft-versus-host disease (GvHD) with ocular, skin, and hepatic involvement.

Patient #4, 68-year-old male with *CALR*-mutated MF, experienced multiple recurrent venous thrombotic events, involving portal and mesenteric veins, as well as pulmonary embolism, prompting PNH workup fourteen years after MPN diagnosis. PNH clone in granulocytes was 14.65%. A year prior to PNH

diagnosis, hemoglobin was 4 g/dL due to gastrointestinal bleed associated with massive splenomegaly, for which he underwent splenectomy. Over the next two years, despite use of eculizumab and low-molecular weight heparin (LMWH), he had recurrent thromboses, involving infrarenal inferior vena cava (IVC), bilateral common iliac veins, suprarenal and intrahepatic IVC, and middle hepatic vein, and remained transfusion dependent.

Patient #5, a 69-year-old male with *CALR*-mutated post-ET MF developed hemolytic anemia (baseline hemoglobin 9 g/dl), two years after MPN diagnosis. PNH clone was 22.58% in granulocytes. He received eculizumab without improvement in hemolysis and underwent allo-SCT one year post-diagnosis. While he achieved remission from the MF and PNH standpoint, post-transplant course was complicated by end-stage renal disease.

Patient #6, a 76-year-old male with *JAK2*-mutated ET, developed progressive anemia (hemoglobin 8 g/dl), eight years later. PNH clone in granulocytes was 91.19 %. Despite optimal eculizumab trough levels (>350 mcg/mL) and <10% activity on complement inhibition assay, hemolysis was uncontrolled requiring multiple therapies: ravulizumab, followed by iptacopan, and later transitioned to dual complement blockade with ravulizumab and danicopan.

Patient #7, 66-year-old male with *JAK2*-negative PMF presented with hemolysis three years after diagnosis, at which time a 6.1% PNH clone in granulocytes was noted. Over the next five years, he received erythropoiesis-stimulating agents (ESAs), danazol, thalidomide, and prednisone, which failed to alleviate transfusion dependent anemia. Thereafter, he received eculizumab for 2.5 years and ruxolitinib without improvement in hemoglobin. Unfortunately, he died due to sepsis.

Patient #8, a 67-year-old male was referred for transfusion-dependent anemia and was diagnosed with concomitant *JAK2*-mutated PMF and PNH, with a clone size of 90.6% in granulocytes. He was initially treated with eculizumab and later switched to ravulizumab due to treatment failure. He subsequently

underwent allo-SCT; over the next five years, post-transplant course was complicated by acute skin GvHD. At last follow-up, he remains in remission from PMF and PNH.

Overall, complement inhibition was the mainstay for PNH management with all patients receiving either eculizumab (*n*=7) or ravulizumab (*n*=2); 5 of these received eculizumab as monotherapy. Only 1 of 8 patients achieved disease control using complement inhibition alone. 3 patients underwent allo-SCT, of whom 2 achieved sustained remission with follow up exceeding five years, while the third patient experienced PNH recurrence five months post-transplant. Among patients treated with complement inhibition therapy but not transplanted, 4 of 5 (80%) remained transfusion dependent at last follow-up. Treatment for MPN included hydroxyurea (*n*=3), ruxolitinib (*n*=3), pacritinib (*n*=1), and ESAs (*n*=3). Additionally, 1 patient received anticoagulation alone and 2 were treated with a combination of antiplatelet and anticoagulation therapies.

During a median follow-up of 8.4 years (range, 5-19), 2 patients (25%) experienced venous thrombosis, and 1 patient (13%) had progression to MDS. 3 patients (38%) died, including 2 from sepsis. The incidence rate of thrombosis was 24 events per 100 person-years. Recurrent thrombosis was observed in a 68-year-old male with *CALR*-mutated MF and PNH clone size of 14.65% in granulocytes, with history of portal vein thrombosis. Despite treatment with eculizumab and LMWH, he developed thromboses involving the IVC, common iliac, and hepatic veins. The second thrombotic event occurred in a patient who developed DVT while in remission and not receiving anticoagulation.

A recent study showed presence of PNH clones in 3 of 119 (2.5%) MPN patients (9). The current study represents one of the largest series of patients with MPN and PNH. It reveals a predominance of MF patients, particularly with *CALR* mutations. Sutra del Galy et al (5) described 20 patients with PNH and myeloid neoplasms, including 8 with MPN (5 *JAK2*, 2 *CALR*). The study reported thrombosis in 50% and hemolysis in all patients. 80% of the patients were transfusion dependent, and despite treatment with eculizumab in 13 patients, none achieved transfusion independence. By contrast, 4 of 5 patients who underwent transplantation were alive in remission. Additionally, several case reports have described

coexistence of PNH and MPN including, *JAK2*-negative ET (4), *CALR*-mutated ET (6), PV (7), and *CALR*-mutated post-ET MF (8).

PNH should be suspected in MPN patients with active intravascular hemolysis or splanchnic venous thrombosis. However, the limitations of hemolysis evaluation in the context of MPN should be noted (10). Although complement inhibition was the first-line treatment for PNH, its efficacy was suboptimal, with only 20% achieving transfusion independence. By contrast, among 3 patients who underwent transplant, only 2 achieved durable remission, while the third patient experienced recurrence of PNH, which required DLIs and re-treatment with eculizumab before successful remission was achieved. Given the modest response to complement inhibition, allo-SCT should be considered sooner rather than later. Taken together, these findings highlight the therapeutic challenges in managing patients with concomitant MPN and PNH.

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Table 1. Baseline presenting features at diagnosis of myeloproliferative neoplasm and paroxysmal nocturnal hemoglobinuria

Variables, median (range)	**Diagnosis of MPN**	**Diagnosis of PNH**
Age, years, median (range)	65 (54-68)	68 (63-76)
Male gender, *n* (%)	7 (88%)	7 (88%)
Hemoglobin, g/dL, median (range)	10.8 (5.8-15.4)	8.3 (5.8-10.8)
Hematocrit %, median (range)	34 (21-46)	27 (21-33)
Leukocyte count, x 10^9/L, median (range)	7.8 (6.9-12.4)	6.9 (5.7-9.4)
Platelet count, x 10^9/L, median (range)	485 (174-1100)	350 (171-1027)
Absolute Reticulocyte count, x 10^9/L, median (range)	136.6 (77.4-210)	135.1 (71-210)
Relative Reticulocyte count %, median (range)	3.9 (1.6-9.1)	5.7 (2.2-9.1)
Haptoglobin, mg/dL, median (range)	13 (5-69)	13 (5-13)
Lactate Dehydrogenase, U/L, median (range)	955 (471-2694)	1124 (487-2694)
Ferritin, ng/mL, median (range)	62 (54-70)	443 (54-1815)
Iron, ug/dL, median (range)	70 (67-73)	73 (67-79)
Total Iron Binding Capacity, ug/dL, median (range)	310 (304-316)	304 (251-316)
% Saturation, median (range)	22.6 (22-23)	22 (23-31)
Total Bilirubin, mg/dL, median (range)	0.8 (0.5-1.7)	0.9 (0.5-1.7)
Aspartate Aminotransferase, U/L, median (range)	37 (25-145)	44 (13-145)
Alanine Aminotransferase, U/L, median (range)	23 (22-26)	23 (8-33)
Alkaline Phosphatase, U/L, median (range)	95 (68-112)	104 (75-156)

Abbreviations: MPN, myeloproliferative neoplasm; PNH, paroxysmal nocturnal hemoglobinuria.

Table 2. Clinical and molecular characteristics of patients with concomitant myeloproliferative neoplasm and paroxysmal nocturnal hemoglobinuria

Patient	Gender	Type of MPN	Age at Diagnosis of MPN/PNH	Temporal Order of Diagnosis	Mutations, other than *PIGA*	Karyotype	PNH Clone Size at Diagnosis
#1	M	PMF	67/67	Concomitant	Not available	Not available	Not available
#2	F	PMF	63/63	Concomitant	*ASXL1, CALR*	46,XX[20]	3.92% R, 28.8% G, 27.74% M
#3	M	ET	60/70	MPN first	*CALR, ZRSR2*	46,XY[20]	4.99% R, 63.94% G, 74.7% M
#4	M	PMF	54/68	MPN first	*CALR*	46,XY[20]	0.02% R, 14.65% G, 18.79% M
#5	M	ET, Post-ET MF	67/69	MPN first	*CALR, SF3B1*	46,XY,del(13)(q12q14)[1]/46,XY[19]	0.92% R, 22.58% G, 60.1% M
#6	M	ET	68/76	MPN first	*JAK2*	46,XY[20]	9.2% R, 91.19 % G, 98.78% M
#7	M	PMF	63/66	MPN first	Not available	46,XY[20]	0.23% R, 6.1% G, 6.6% M
#8	M	PMF	67/67	Concomitant	*JAK2*	46,XY[20]	10.96% R, 90.6% G, 92.1% M

Abbreviations: MPN, myeloproliferative neoplasm; PNH, paroxysmal nocturnal hemoglobinuria; PMF, primary myelofibrosis; ET, essential thrombocythemia; PV, polycythemia vera; R, red blood cell; G, granulocytes; M, monocytes.

Table 3. Clinical course and treatment approaches in patients with concomitant myeloproliferative neoplasm and paroxysmal nocturnal hemoglobinuria

Patient	History and Type of Thrombosis	History of Hemoglobinuria (Timing of the First Episode)	Transfusion-dependent Anemia	Management of MPN	Management of PNH	Allogeneic Stem Cell Transplant
#1	No	No	No	NA	Eculizumab	No
#2	No	Yes (3.5 years postdiagnosis)	Yes	Ruxolitinib, switched to Pacritinib	Eculizumab	No
#3	Yes, Venous (DVT, 1.25 years post-PNH diagnosis)	Yes (2 months post-PNH diagnosis)	No	Hydroxyurea, anticoagulation, antiplatelets	Eculizumab	Yes, 6 months post-PNH diagnosis
#4	Yes, Venous (multiple prior and post-PNH diagnosis including portal, mesenteric, infrarenal IVC, common iliac, suprarenal, intrahepatic IVC, and hepatic vein)	Yes (1.5 years post-PNH diagnosis)	Yes	Hydroxyurea, Epoetin alfa, anticoagulation	Eculizumab	No
#5	No	No	No		Eculizumab	Yes, 1 year post-PNH diagnosis
#6	No	Yes (1 year post-PNH diagnosis)	Yes	Hydroxyurea, antiplatelets, Ropeginterferon alfa-2b, Epoetin alfa, Ruxolitinib, anticoagulation	Ravulizumab, switched to Iptacopan, switched to Ravulizumab and Danicopan combination	No
#7	No	No	Yes	Epoetin alfa, Iron chelation, Ruxolitinib	Eculizumab, Danazol, Thalidomide, Prednisone	No
#8	No	Yes (at the time of the diagnosis)	Yes		Eculizumab, switched to Ravulizumab	Yes, 1 year and 9 months postdiagnosis)

Abbreviations: MPN, myeloproliferative neoplasm; PNH, paroxysmal nocturnal hemoglobinuria; DVT, deep vein thrombosis; IVC, inferior vena cava; pRBCs, packed red blood cells