

# Primary myelofibrosis with concurrent paroxysmal nocturnal haemoglobinuria presenting with erectile dysfunction

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## Abstract

Primary myelofibrosis and paroxysmal nocturnal haemoglobinuria (PNH) are uncommon clonal blood disorders that are rarely found together. We report a case of primary myelofibrosis (PMF) with concomitant subtle PNH in a 42-year-old man who presented with a 4-week history of fatigue, unexplained chest pain, and new-onset erectile dysfunction. Bone marrow biopsy showed severe fibrosis consistent with PMF. However, smooth muscle dystonia symptoms in the form of new-onset erectile dysfunction and oesophageal spasm were not fully explained by PMF but were clues for PNH, confirmed by flow cytometric assays. Routine PNH testing for patients with new-onset PMF and clinical symptoms suggestive of PNH, as well as those with refractory anaemia despite effective therapy, is crucial since these two conditions can coexist. As a result, a lack of early testing may cause a delay in diagnosis, increasing the patient's transfusion load and the facility's costs.

## INTRODUCTION

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired clonal blood disorder due to somatic mutation of the phosphatidylinositol glycan class A (PIG-A). It is characterized by intravascular haemolysis, bone marrow failure and increased risk of thrombosis as well as smooth muscle dystonia. There is an intimate overlap between aplastic anaemia and PNH, with 40–60% of patients with aplastic anaemia having a PNH clone. However, there is an anecdotal report about a similar overlap between PNH and other marrow disorders [1, 2]. We report a case of primary myelofibrosis (PMF) with concomitant subtle PNH predicted by the presence of new-onset erectile dysfunction.

## CASE REPORT

This is a 42-year-old man who presented with a 4-week history of fatigue, tiredness and on-and-off central chest pain. These symptoms were associated with a new-onset 6-week history of erectile dysfunction and loss of morning erection even though he and his wife have

a good relationship. He had sought medical advice several times and received blood transfusions, with an insignificant transient response. His sister had been diagnosed with acute leukaemia at the age of 40, and she had passed away several months post-allogeneic stem cell transplantation. Clinical examination revealed pale conjunctiva along with non-tender palpable spleen approximately 4 cm below the left costal margin. However, the remainder of the physical examination was unremarkable.

At that moment, his total blood count showed haemoglobin of 6 g/dL, MCV of 85 fL, a reticulocyte count of 1.2% that was initially elevated but declined with time, a platelet count of  $35 \times 10^9/L$  and a white blood cell count of  $3.700 \times 10^9/L$ , with an absolute neutrophil count of  $1.22 \times 10^9/L$ . Both direct and indirect antiglobulin (Coombs) tests were negative (Table 1). A peripheral blood smear showed anisopoikilocytosis, teardrop cell and polychromasia. The other laboratory findings were as follows: serum lactic dehydrogenase (LDH) 600 units/L, total bilirubin  $14.9 \mu\text{mol/L}$ , iron serum  $43.55 \mu\text{mol/L}$ , iron-binding capacity total  $50.40 \mu\text{mol/L}$ ,

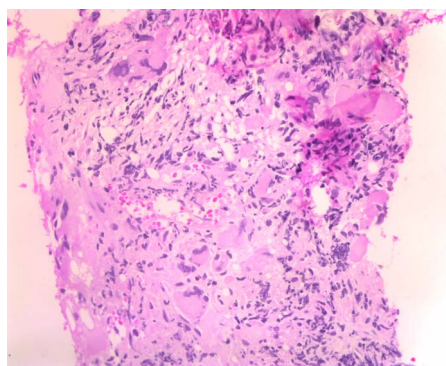
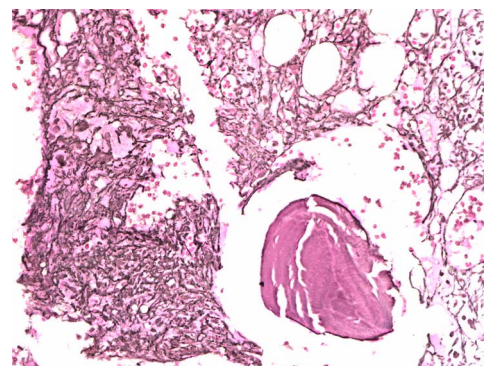
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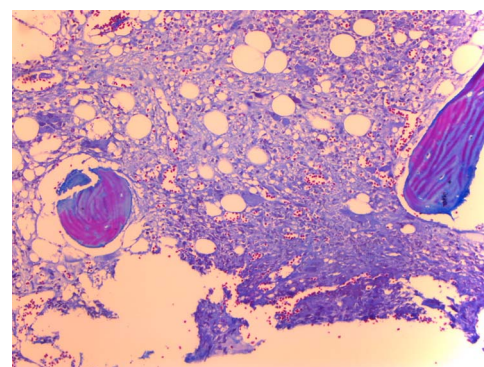
**Table 1.** Laboratory parameters on initial presentation

	On presentation	Reference range
Haemoglobin g/dL	6	13.5–16.5
WBC $\times 10^9/L$	3.7	4.0–10.5
Platelet $\times 10^9/L$	350	150–400
Iron serum $\mu\text{mol/L}$	43.55	6–27
Ferritin ng/mL	3239	50–200
Iron-binding capacity total $\mu\text{mol/L}$	50.40	47–80
Folate serum ng/mL	11.83	3–18
Total bilirubin $\mu\text{mol/L}$	14.9	0–17
Lactate dehydrogenase (LDH) units/L	600	135–225
Retic count (%)	1.2%	1–2%
Direct Coombs test (direct antiglobulin test)	Negative	Negative
Indirect Coombs test (indirect antiglobulin test)	Negative	Negative
Hepatitis B surface antigen	Negative	Negative
Hepatitis C antigen	Negative	Negative

**Figure 1.** Hematoxylin stain of bone marrow biopsy shows a hypocellular haemopoietic tissue with severe fibrosis along with an adequate number of dysmorphic megakaryocytes.**Figure 2.** Reticulin stain of bone marrow confirms the presence of severe fibrosis.

ferritin 3239 ng/mL and folate serum 11.83 ng/mL; hepatitis B surface antigen and hepatitis C antigen were both negative (Table 1).

Both the electrocardiogram and the chest x-ray were normal. Additionally, clinical and laboratory assessments for erectile dysfunction, including total testosterone level, lipid panel, fasting serum glucose level and thyroid-stimulating hormone, were done and found to be normal. Bone marrow biopsy revealed a hypocellular marrow with remarkable infiltration by dysmorphic megakaryocytes, some active myelopoiesis and erythropoiesis and severe fibrosis (mf 2.5) (Figs 1–3). A molecular study revealed positive CALR, whereas BCR-ABL, JAK2 and MPL were not detected. Further, the chromosomal analysis revealed t (12,13) and classified under a high-risk category of primary myelofibrosis based on both the Dynamic International Prognostic Scoring System (DIPSS) and Genetically Inspired Prognostic Scoring System (GIPSS) [3]. The presence of non-cardiac chest pain and new-onset erectile dysfunction in the context of bone marrow failure raised the possibility of PNH, where nitric oxide is expected to be depleted, resulting in vasoconstriction. Flow cytometric assays from peripheral blood revealed 83.3% CD59-negative granulocytes and 0.03% CD59-negative red blood cells consistent with a diagnosis of PNH.

**Figure 3.** Masson Trichrome stains of bone marrow confirm the presence of severe fibro-collagen deposits.

Following confirmation of diagnosis and risk stratification, the patient was transferred to another centre for allogeneic hematopoietic stem cell transplantation with the aim of prolonging survival and increasing the possibility of cure.

## DISCUSSION

Paroxysmal nocturnal haemoglobinuria (PNH) is a clonal hematopoietic stem cell disorder with heterogeneous clinical presentations. Therefore, the International PNH

Interest Group classifies it into three categories. The classical presentation is intravascular haemolysis accompanied by unusual site thrombosis or smooth muscle dystonia in the form of abdominal pain, oesophageal spasm, or erectile dysfunction. The other two categories are subclinical PNH and PNH in the context of marrow failure syndrome, including aplastic anaemia (AA) and myelodysplastic syndrome (MDS) [1, 4].

The International Clinical Cytometry Society (ICCS) guidelines state that all patients with thrombosis with unknown cytopenia or intravascular haemolysis should undergo PNH screening. Additionally, ICCS recommends screening all patients with AA and MDS, even in the absence of haemolysis [5].

Several case reports indicate the coexistence of PNH with PMF and other myeloproliferative neoplasms (MPN). Some of these cases were harbouring either JAK2<sup>V617F</sup> or CALR mutations in their PNH clone. However, most of these cases were diagnosed with PNH several years after being diagnosed with one of the MPNs. These findings support the hypothesis that clinically significant PNH results from a stepwise progression of multiple genetic mutations like MDS or MPN [6, 7].

To our knowledge, this is the third case where PNH is present simultaneously with PMF. Previously reported cases presented with overt PNH in the form of haemoglobinuria and thrombosis. Unlike previously reported cases, PNH diagnosis in our patient was easy to miss due to a lack of laboratory evidence of haemolysis. Moreover, flow cytometry findings in this patient were misleading. They showed a discrepancy between red and white blood cells' PNH clones, but this is likely attributed to prior blood transfusion and ongoing subtle haemolysis. On the other hand, smooth muscle dystonia symptoms in the form of oesophageal spasm and erectile dysfunction were clues for PNH diagnosis.

Routine PNH testing for patients with new-onset primary myelofibrosis and clinical symptoms suggestive of PNH, as well as those with refractory anaemia despite effective therapy, is crucial since these two conditions can coexist. As a result, a lack of early testing may cause a delay in diagnosis, increasing the patient's transfusion load and the facility's costs. Conversely, the process of thrombosis in an unusual site in PNH patients is not fully explained, and whether the coexistence of MPN causes this is an area for further research.

## CONCLUSION

PNH is a clonal hematopoietic stem cell disorder with subtle, heterogeneous presentation,

particularly if it coexists with other bone marrow disorders. PNH testing is recommended for patients with a previous diagnosis of AA, MDS, as well as those who have thrombosis with unknown cytopenia or intravascular haemolysis. Hence, additional studies are needed to better understand the association between PNH and MPN and whether all or only certain groups of patients need to be screened for PNH and vice versa.

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## CONFLICT OF INTEREST STATEMENT

No conflict of interest to disclose.

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## CONSENT

Written informed consent was obtained from the patient to publish this case report and images in this journal.

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