Multisite Thrombosis in a Patient with Paroxysmal Nocturnal Hemoglobinuria

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Hamostaseologie

Case

Paroxysmal nocturnal hemoglobinuria (PNH) is an extremely rare bone marrow disorder caused by acquired mutations in the phosphatidylinositol glycan class A gene, which lead to a partial or total loss of the cellular complement regulators CD55 and CD59.[1] In addition to complement-mediated hemolysis and cytopenia, venous and arterial thromboses at multiple and/or unusual sites are a common complication and occur in up to 44% of patients in historic PNH cohorts.[1,2]

A 58-year-old woman was admitted to our emergency department with a 2-day history of rapidly progressive muscle weakness of all extremities and altered behavior (►Fig. 1). The patient reported severe headache and abdominal pain for about a week. Imaging diagnostics revealed extensive thromboses of cerebral sinus and bridging veins with congestive brain infarctions and hemorrhages (►Fig. 2A–C). In addition, multilocular hepatic vein thrombosis (►Fig. 2E–G) and splenic infarction were identified. In patients with multisite thrombosis, antiphospholipid syndrome, thrombotic microangiopathy, disseminated intravascular or paraneoplastic coagulopathy, antithrombin deficiency, JAK2^{V617F}-positive myeloproliferative neoplasm, or PNH should be considered. Blood count showed mild anemia and thrombocytopenia (►Table 1). While global coagulation tests were normal, plasma D-dimers were markedly elevated. Deficiencies in antithrombin or protein C, activated protein C resistance, dysfibrinogenemia, antiphospholipid syndrome, and JAK2^{V617F} mutation were excluded (►Table 1). Three days after admission (►Fig. 1), flow cytometric analysis of peripheral blood revealed glycosylphosphatidylinositol (GPI) anchor protein deficiency in up to 65% of leukocytes and erythrocytes confirming diagnosis of PNH (►Fig. 3). Despite immediate initiation of anticoagulation with unfractionated heparin and endovascular mechanical thrombectomy (►Fig. 2D), the patient died few days later (►Fig. 1). At the time of PNH diagnosis, complement inhibitory therapy was not initiated due to the patient's unfavorable clinical prognosis.

Although thrombosis was fatal in our case, it can be successfully treated with therapeutic anticoagulation in combination with complement inhibitors in less severely affected PNH patients.[3,4] Long-term complement inhibitory therapy offers the opportunity of disease control. In such patients, the risk of recurrent thrombosis is low, and thus termination of anticoagulation might even be considered.[3,4] In addition, allogenic hematopoietic stem cell transplantation remains a curative option for some patients.[1]

In summary, although PNH is an orphan disease, it has promising treatment options. PNH should be considered in patients with newly diagnosed thromboses, especially if located at multiple and/or unusual sites.

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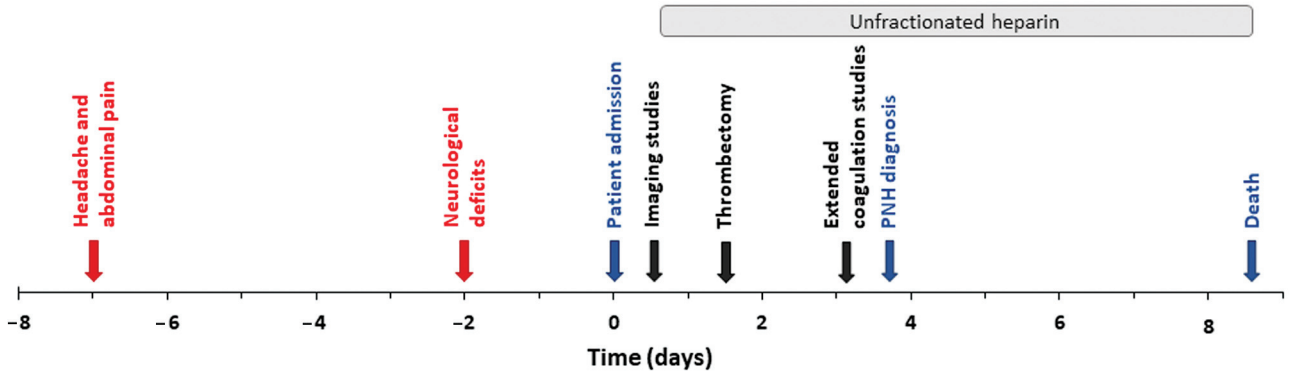

Fig. 1 Clinical course of the patient. PNH, paroxysmal nocturnal hemoglobinuria.

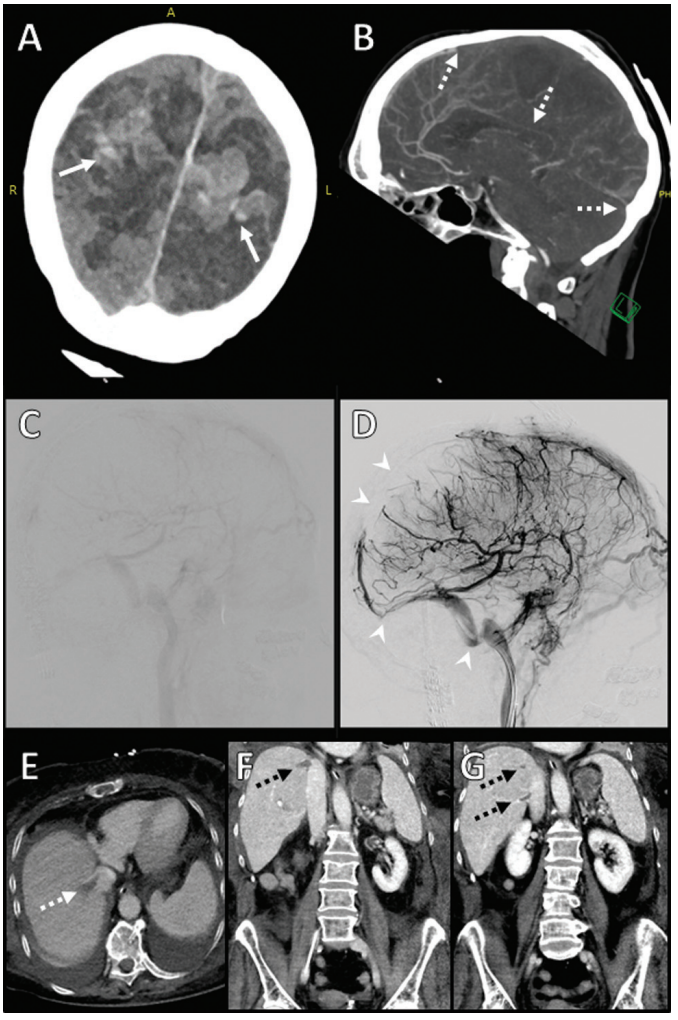

Fig. 2 Radiological imaging studies. (**A**) Noncontrast head computed tomography (CT) in axial orientation of the cerebral vertex showed severe bilateral intraparenchymal bleeding with associated perifocal edema (*white arrows*) suspicious of a vascular cause. (**B**) Additional CT angiography (sagittal orientation) revealed longitudinal filling defects within the superior and inferior sagittal sinus, the rectal sinus (*dotted white arrows*), and the transverse and sigmoid sinus (the latter of which are not displayed) indicating a massive multifocal thrombosis. Decision for consecutive endovascular treatment was made. (**C**,**D**) Sagittal digital subtraction angiography images from the catheterization laboratory. Severe delay or absence of contrast opacification and thus barely any venous egress could be seen within the above-mentioned major draining cerebral veins (**C**). Improved venous egress was observed after intervention with endovascular thrombectomy within the superior sagittal sinus and the transverse sinus (**D**). However, significant amounts of thrombus remained in the posterior part of the sagittal sinus, the left transverse and sigmoid sinus, and the straight sinus (*arrow heads*), which could not be removed by endovascular measures. (**E–G**) Abdominal contrast-enhanced CT in axial and coronary orientation revealed multilocular hepatic vein thrombosis with thrombus extension up to the vena cava inferior (*dotted white* and *black arrows*).

Table 1 Laboratory workup of the patient

	Value	Reference range
Blood count		
Hemoglobin (g/dL)	12.1	12.4–16.1
Leukocytes ($\times 10^9$/L)	11.9	3.8–11.0
Platelets ($\times 10^9$/L)	71	150–350
Schistocytes (%)	0.8	<0.1
Clinical chemistry		
Total bilirubin (mg/dL)	1.3	0.3–1.2
Conjugated bilirubin (mg/dL)	0.8	<0.3
Haptoglobin (g/L)	0.28	0.4–2.8
AST (U/L)	36	<35
ALT (U/L)	47	<35
Creatinine (mg/dL)	0.72	0.6–1.3
LDH (U/L)	578	87–241
Coagulation parameters		
Prothrombin time (%)	123	80–130
INR	0.9	0.85–1.15
aPTT (s)	36	25–38
Thrombin time (s)	15.5	16–22
Fibrinogen (g/L)	3.39	1.8–4.0
D-dimer (mg/L)	12.5	<0.5
Antithrombin (%)	87	83–118
PC activity (%)	83.5	70–140
Free PS antigen (%)	47.8	60–114
Ratio APC resistance	7.41	>0.7
FVIII:C (%)	>450	70–150
ADMATS13 activity (U/mL)	0.39	0.40–1.30
ADAMTS13 antigen (U/mL)	0.27	0.41–1.41
Autoantibodies		
IgM-aCL (U/mL)	<0.9	<10
IgG-aCL (U/mL)	1.1	<10
IgM-anti-β_2GPI (U/mL)	<2.4	<7
IgG-anti-β_2GPI (U/mL)	1.1	<7
LA	Negative	Negative
Anti-ADAMTS13 (U/mL)	1.4	<12.0
Genetic analysis		
JAK2, pV617F	Negative	Negative

Abbreviations: aCL, anticardiolipin antibody; anti-β2GPI, anti-β2-glycoprotein-I antibody; ALT, alanine aminotransferase; APC, activated protein C; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; FVIII:C coagulation factor VIII clotting activity; INR, international normalized ratio; JAK2, Janus kinase 2; LA, lupus anticoagulant; LDH, lactate dehydrogenase; PC, protein C; PS, protein S.

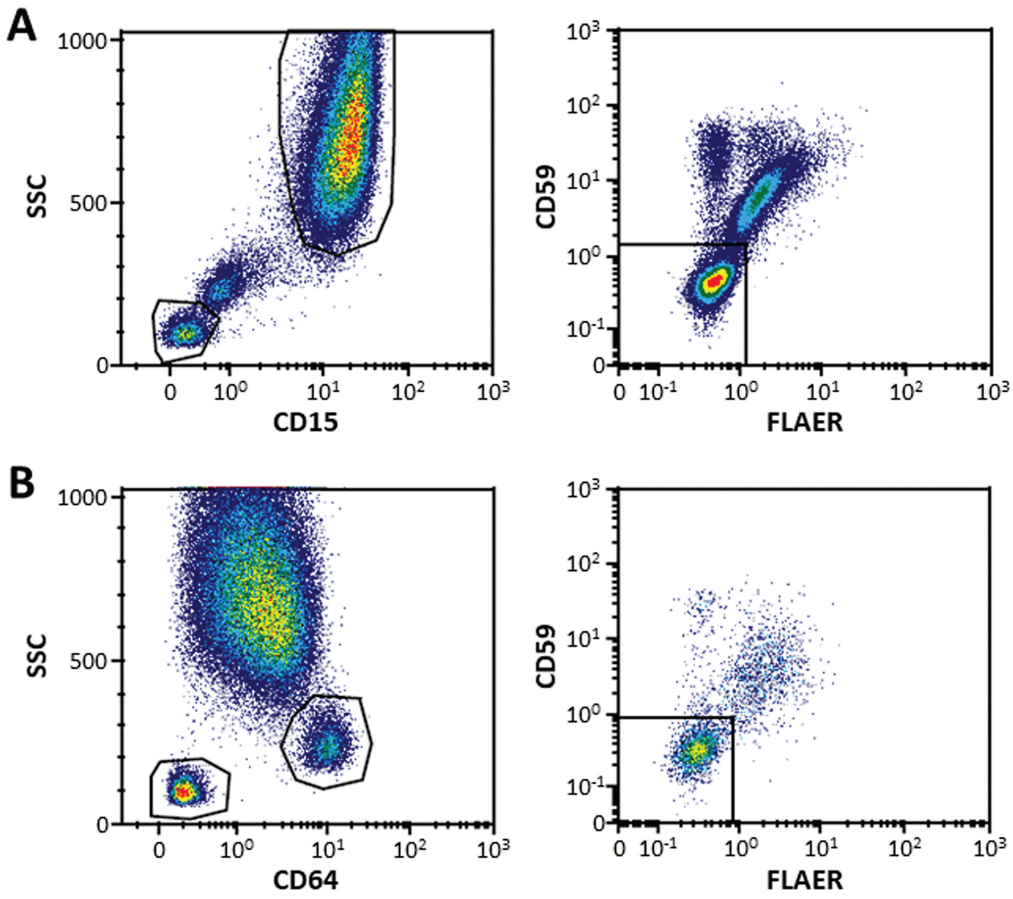

Fig. 3 Diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) using flow cytometry. Peripheral blood neutrophil granulocytes and monocytes were identified by flow cytometry using positive staining for CD15 or CD64, respectively. Lymphocytes were excluded by negative staining for both markers. Subsequently, (**A**) CD15-positive neutrophils or (**B**) CD64-positive monocytes were analyzed for the loss of glycophosphatidylinositol (GPI) linked proteins, as indicated by negative staining for the complement regulatory protein CD59 and by the absence of FLAER (fluorescent-labeled inactive variant of aerolysin) binding. Upon quantitative analysis, 65% of neutrophils and 64% of monocytes were GPI deficient. Red blood cell analysis was limited due to several recent blood transfusions, but findings were still consistent with PNH diagnosis (data not shown).

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Conflict of Interest

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