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Manifestation of paroxysmal nocturnal hemoglobinuria after COVID-19 mRNA vaccination

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To the Editor:

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare acquired hematological disorder caused by a genetic mutation of the X-linked gene phosphatidylinositol glycan class A (*PIGA*) [1,2]. This mutation leads to a reduction or even absence of the glycosylphosphatidylinositol (GPI)-anchored proteins such as complement inhibitors CD55 and CD59, on the cell surface of the affected hematopoietic stem cells and their cellular progeny. Subsequently, patients with PNH are at an increased risk of intravascular hemolysis, thrombosis, cytopenia, organ dysfunction, and a hypocellular or dysplastic bone marrow [2,3]. The risk of complications becomes even higher when the patient is under a stressful event because of the increased complement amplification [3]. The gold standard test for diagnosis is flow cytometry, which provides the advantage of determining the type and size of the PNH clone [1,4]. The management of this disease is defined by each PNH category. As such, the hemolytic PNH is best managed with C5 complement inhibitor like eculizumab or ravulizumab, the subclinical PNH by close watchful waiting, and finally, allogenic HSCT is offered to patients with bone marrow failure [5,6].

Lately, with the emerging COVID-19 pandemic, new vaccines have been developed against the causative coronavirus 2 (SARS Cov-2). Two of these vaccines are mRNA based and previously published case series in 6 patients have shown that mRNA based COVID-19 vaccines seem to exacerbate PNH. This is thought to be due to the transient expression of the SARS-CoV-2 spike protein that leads to amplification of the alternative pathway of complement on cell surfaces through competition with complement factor H (CFH) for binding heparan sulfate. We hereby report a case of a patient whose PNH diagnosis was established after she received mRNA COVID-19 vaccine which uncovered her underlying blood disorder.

The patient is a 29-year-old female, previously healthy except for an abnormal complete blood count, namely mild thrombocytopenia that was not investigated several years ago. She presented to our clinic for evaluation of fatigue and shortness of breath in the setting of a new onset of pancytopenia. Six months earlier, she acquired COVID-19 infection that was mild in nature and she was treated at home with supportive therapy. However, she started complaining of recurrent episodes of headaches and palpitations afterwards. Four months after the recovery from COVID-19 infection, she received her first mRNA COVID-19 vaccine (Pfizer BioNTech). One week later, she reported worsening of her headache that failed to resolve on paracetamol. Otherwise, she denied any neurologic or visual deficit. New blood studies showed leukopenia, macrocytic anemia, and thrombocytopenia. Blood chemistry, kidney and liver function were all within normal. Haptoglobin Comb's test, lactate dehydrogenase (LDH), and blood smear were in favor of non-immune mediated intravascular hemolysis (Table 1). A bone marrow aspirate was done and revealed erythroid hyperplasia without any evidence of malignancy. PNH was suspected and a flow cytometry confirmed the diagnosis as it showed loss of Anchor proteins in granulocytes (60%) and monocytes (50%), and RBCs (3%). A whole-body CT scan with IV contrast was then performed and showed no abnormalities.

The clinical presentation of PNH is variable. Patients can present with a range of symptoms related to hemolytic anemia such as: dyspnea, fatigue, and tachycardia, in addition to pain, organ dysfunction, and thrombosis [2,5]. The prognosis of this disease has significantly improved after the introduction of novel therapeutic agents such as the C5 complement inhibitor. Patients with the hemolytic type tend to have a better outcome than patients with a remarkable bone marrow failure component, as the earlier responds to eculizumab [1,5]. Data from the International PNH Registry revealed that almost 75% of patients with PNH are being treated with eculizumab.

Few case reports on hemolysis after COVID-19 infection or vaccination in patients known to have PNH have been reported since the emergence of the pandemic [7,8]. Here, we report a case where the diagnosis of PNH was established after an exacerbation of hemolysis, with PNH signs and symptoms post the administration of the first dose of mRNA COVID-19 vaccine. The underlying pathophysiology of PNH is thought to be the absence of the negative complement regulatory proteins CD55 and CD59 on the surface of erythrocytes, and processes that activate the complement pathway, thus making these erythrocytes vulnerable to complement-mediated hemolysis [2,3]. The lack of GPI-linked complement regulators, CD55 and CD59, make PNH erythrocytes exquisitely sensitive to complement activation, which can lead to uncontrolled intravascular hemolysis [6]. The hemolysis, in turn, can be

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Table 1
Laboratory blood tests. NA, not available; WBC, white blood count; ANC, absolute neutrophil count; RBC, red blood cell; MCV, mean corpuscular volume; LDH, lactate dehydrogenase.

Test (unit)	2021	2015	Normal range
WBC (cu·mm)	3200	4100	4000–11,000
Neutrophils (%)	36.8	29	40–65%
Lymphocytes %	53.9	58	25–40%
Absolute neutrophil count (ANC)	1177	NA	1600–7200
RBC count (mil/cu·mm)	1.99	3.42	4–6.5
Hemoglobin (g/dl)	7.2	12.1	12–18
Hematocrit (%)	22	34.9	37–54
MCV(fl)	113	102	80–94
Platelet count (cu·mm)	27,000	134,000	150,000-400,000
LDH (U/L)	426	NA	10–250
Haptoglobin (g/l)	0	NA	
D-dimer (ng/ml)	303	NA	<500
Direct Comb's test	Negative	NA	
Blood smear	Anisocytosis, poikilocytes, schictocystes, intracellular and extracellular inclusins, rouleux formation.	NA	

precipitated in untreated and treated patients with anti-complement therapy by any complement activating events such as infection, trauma, surgery, and pregnancy [9]. In our patient, we suspect that the trigger might be the initial SARS Cov2 infection, that was later on exacerbated after receiving the mRNA COVID19 vaccine; however, our patient was worked up only after worsening of her symptom of headache which was a week post the administration of the first dose of vaccine. It is unclear if the acute COVID-19 infection amplified a pre-existing PIG-A mutation that was exacerbated post vaccination.

As for the exact mechanism behind the flare of hemolysis post vaccination, studies have shown that post vaccination hemolysis is mediated through the strong complement amplification as a byproduct of the inflammatory response which is responsible for the clinically observed hemolysis [7]. Other studies demonstrated that in patients who acquire the SARS CoV-2 spike proteins may activate the alternative complement pathway. Moreover, disruption of the interaction between the spike proteins and factor D or C5 inhibited this immunopathology [10].

As the infection itself leads to a severe inflammatory state, the benefits of vaccinating patients with PNH likely outweigh the risks despite the fact that the vaccine itself could exacerbate hemolysis in PNH. For this reason, clinicians and patients should be aware of this serious adverse effect, and patients should be educated to report any symptoms post-vaccination. Adverse reactions appear to be time-limited and can be managed with supportive care and transfusions as needed [7]. Current guidelines in the United Kingdom recommend that COVID-19 vaccines are not contraindicated and should be encouraged for patients with PNH including those who have had COVID-19 infection [11]. PNH is a thrombo-inflammatory disorder and this pathophysiology overlaps with the cytokine storm environment which characterizes severe COVID-19, and thus raising the concern that patients with PNH are at a higher risk for COVID-19 regardless of the treatment status for their disease [12]. However, it is worth noting that data pertaining to the safety and efficacy of the Pfizer-BioNTech and Moderna, COVID-19 vaccines for people with PNH is currently limited [11]. Patients who are on C5 complement inhibitor should time their vaccination as close as possible to their treatment (within days before or days after the dose) because of the theoretical possibility that this may reduce their chance of having exacerbation of their disease related to vaccine administration [11].

In summary, we report here a case of 29 year-old female with undiagnosed PNH who became symptomatic a week after receiving the first dose of COVID-19 vaccine and later diagnosed with PNH on flow cytometry. Clinicians and patients must be aware of the possible serious adverse events of mRNA COVID-19 vaccines which are in general manageable with supportive care and transfusions as needed. In patients who are not diagnosed with PNH, COVID-19 vaccination may be the trigger for a PNH flare and subsequently the emergence of PNH manifestations. Clinicians should, therefore, be vigilant of this rare but significant entity in order to promptly diagnose and treat such cases efficiently.

Author contributions

All authors contributed to manuscript drafting or critical review and final approval for submission.

Informed consent

The patient gave informed consent.

Data availability statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

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Declaration of competing interest

The authors declare no competing financial interests.

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