COVID19 infection in a patient with paroxysmal nocturnal hemoglobinuria
A case report

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Abstract

Introduction: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired, life-threatening hemopoietic stem cell disorder characterized by the triad of hemolytic anemia, thrombosis, and impaired bone marrow function. Evidence suggests that severe outcomes in COVID19 infection are attributed to the excessive activation of the complement cascade leading to acute lung injury and associated is with an increased prothrombotic state.

Patient concerns: A 27-year-old Caucasian man with PNH presented to the Emergency Department of our hospital with acute onset shortness of breath, cough and blood in urine.

Diagnosis: The patient was diagnosed with acute hemolytic exacerbation of PNH complicated with moderate COVID19 pneumonia.

Outcomes: The patient was initiated with an anticoagulant unfractionated heparin, dexamethasone, and cefuroxime injection. His symptoms quickly resolved, and he was discharged after 5 days.

Conclusion: The complement system activation is a critical component in the sequelae of COVID19 infection. Evidence suggests that severe outcomes in COVID19 infection are attributed to the excessive activation of the complement cascade leading to acute lung injury and associated is with an increased prothrombotic state. Notably, C5a concentration was noted to be higher in patients with COVID19 infection. The use of complement inhibitors to attenuate immune mediated damage in COVID19 nevertheless represents a very interesting theoretical approach. However, careful consideration as to which patients may benefit will be required and the outcome of clinical trials needed.

Abbreviation: PNH = paroxysmal nocturnal hemoglobinuria.

Keywords: case report, complement, COVID19, paroxysmal nocturnal hemoglobinuria, treatment, thrombosis

1. Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired, life-threatening hemopoietic stem cell disorder characterized by

the triad of hemolytic anemia, thrombosis, and impaired bone marrow function. PNH arises due to an acquired mutation in the synthesis of glycoprophosphatidylinositol (GPI) anchor protein, which leads to a deficiency of complement regulatory proteins and unregulated complement-mediated hemolysis.\textsuperscript{[1]} The world incidence of PNH is still unknown, but it is estimated to be 1 to 5 cases per million inhabitants in the USA, a much lower incidence than that of bone marrow aplasia, whose prevalence is 5 to 10 times higher. Still about statistics in the USA, prevalence does not vary by sex or race/ethnicity. The same occurs in some Asian countries, such as Thailand, Japan, and the Far East, where PNH has lower incidence than bone marrow aplasia. As regards sex, in Europe, PNH is more common in women, whereas in Asia it is more common in men. PNH can occur at any age, but it is generally diagnosed between third and fifth decades.\textsuperscript{[2–3]} Patients experience intravascular hemolysis, smooth muscle dystonia, renal failure, arterial and pulmonary hypertension, recurrent infectious diseases, and an increased risk of notably dreadful thrombotic complications.\textsuperscript{[4]}

The diagnosis of PNH is made by means of clinical findings and laboratory tests to confirm the degree of hemolysis (haptoglobin, lactate dehydrogenase, direct Coombs test, reticulocyte count and total bilirubin and bilirubin fraction) and deficiency of anchored proteins of the complement system (CD55, CD59, and FLAER) in granulocytes (CD15, CD33, and CD24) and
monocytes (CD14 and CD64) by flow cytometry, the gold standard method.[6-8] Management of PNH has been dramatically revolutionized by the development of eculizumab, which brings benefits in terms of hemolysis, quality of life, renal function, thrombotic risk, and life expectancy. Eculizumab is a humanized monoclonal antibody. It acts as a complement inhibitor, binding specifically to complement protein C5 with high affinity, thereby inhibiting cleavage to C5a, a prothrombotic and proinflammatory molecule and C5b, preventing the generation of the terminal complement complex C5b-9. Prophylaxis and treatment of arterial and venous thrombosis currently remain a challenge in PNH.[6] The objective of this study was to report the rare case of a PNH patient with COVID-19 pneumonia, strategies to diagnose, and therapeutic challenges.

2. Case report

A 27-year-old Caucasian man presented to the Emergency Department of our hospital with acute onset shortness of breath, cough, and blood in urine. Rapid antigen tests were positive for SARS-CoV-2 infection. He did not have any fever, chills, wheezing, sputum production, chest pain, palpitations, pressure, abdominal pain, abdominal distension, nausea, vomiting, and diarrhea.

Breathing problems had begun approximately 2 days before admission and had progressively worsened with no associated, aggravating, or relieving factors noted. He also complained of a paroxysmal productive cough of indeterminate origin that he had paroxysmally throughout the night. He had otherwise previously healthy. Since the urine problem developed, he had not had any fever, chills, pharyngalgia, paroxysmal productive cough, and no other symptoms. He presented to the Emergency Department with dark urine.

The past medical history was significant in that at the age of 26 years he presented to the Emergency Department with dark urine. He was otherwise previously healthy. Since the urine problem developed, he had not had any fever, chills, pharyngalgia, paroxysmal productive cough, and no other symptoms. He presented to the Emergency Department with dark urine.

The patient was diagnosed with acute hemolytic exacerbation of PNH complicated with moderate COVID19 pneumonia. The patient was initiated with an anticoagulant prophylactic subcutaneous Low Molecular Weight Heparin (enoxaparin 4000 UI anti-Xa, daily). Dexamethasone (6 mg intravenously every 24 hours) were added to the treatment. The chest radiograph displayed bronchopneumonia at the right lower lobe in the lower and middle segments (Fig. 1), and the ECG showed sinus tachycardia.

The patient was diagnosed with acute hemolytic exacerbation of PNH complicated with moderate COVID19 pneumonia. The patient was initiated with an anticoagulant prophylactic subcutaneous Low Molecular Weight Heparin (enoxaparin 4000 UI anti-Xa, daily). Dexamethasone (6 mg intravenously every 24 hours) and cefuroxime injection (1.5 g intravenously every 8 hours) were added to the treatment.

His symptoms quickly resolved, and he was discharged after 5 days. Hemolytic activity persists as before SARS-CoV-2 infection (see Table 1 & Fig. 2). Of note, COVID19 RT-polymerase chain reaction testing remained positive for the next 3 months. Although the patient was discharged without anticoagulant or antiplatelet therapy, he had not yet experienced with a thrombotic event.
3. Discussion

PNH is a clonal disorder of hematopoietic progenitor cells caused by an acquired mutation of the X-linked phosphatidylinositol glycan class A gene. The absence of glycosylphosphatidylinositol anchored complement regulatory proteins CD55 and CD59 from the membrane of circulatory cells is responsible for activation of the complement system on the surface of the red cell membrane. This leads to complement mediated intravascular hemolysis, activation of platelets, and the coagulation cascade resulting in a hypercoagulable state. PNH, although rare, can be fatal and includes an increased risk of thromboembolism and severe end-organ damage. Approximately, 35% of patients die within 5 years if untreated due to thrombosis and related complications.

The complement system activation is a critical component in the sequelae of COVID19 infection. Evidence suggests that severe outcomes in COVID19 infection are attributed to the excessive activation of the complement cascade leading to acute lung injury and associated is with an increased prothrombotic state. Notably, C5a concentration was noted to be higher in patients with COVID19 infection. Complement blockers can be used as potential therapeutic targets in COVID19 patients. In addition, there is no evidence of increased susceptibility to SARS-CoV-2 in patients on anticompement therapy. On the other hand, there is also evidence that eculizumab administered in a classical schedule for PNH did not contribute to control a severe course of COVID-19.

The use of complement inhibitors to attenuate immune mediated damage in COVID-19 nevertheless represents a very interesting theoretical approach. However, careful consideration as to which patients may benefit will be required and the outcome of clinical trials needed.

It is also important to note, that both diseases are known to cause hypercoagulability-related morbidity and mortality separately. Further research should also focus on anticoagulant therapy. Due to the mild course of COVID19, our patient received a prophylactic dose of Low Molecular Weight Heparin.

4. Conclusion

Here we report 1 case of COVID19 infection requiring hospitalization. As mentioned above, there is evidence of increased activation of coagulation pathways and susceptibility to thromboembolic disease in patients with COVID19, though we did not detect any thrombotic complications in this case. Infections increase risk of breakthrough hemolysis in PNH due to increased activation of the complement system. COVID19 induced breakthrough hemolysis was seen in our case report.

Author contributions

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