Extensive purpura as presenting sign of parvovirus B19 infection in a patient with paroxysmal nocturnal hemoglobinuria

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INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired mutation that makes all hematopoietic cells more susceptible to lysis by complement. This mutation can result in intravascular hemolysis, pancytopenia, and thrombosis, which can be exacerbated by infection. We present a case of PNH-associated dermal thrombosis, presenting as widespread purpura, in the setting of parvovirus B19 infection.

CASE REPORT

A 54-year-old woman with a 20-year history of paroxysmal nocturnal hemoglobinuria presented for evaluation of extensive purpura that had been rapidly evolving over the last 24 hours, with concurrent joint pain and fatigue. Her arthralgia was in her hands, wrists, and ankles, and was so severe that she was no longer able to ambulate. She otherwise reported a 1-week history of nausea, vomiting, and diarrhea. Her PNH was previously well controlled for more than 10 years with eculizumab (a monoclonal antibody inhibitor of C5), 900 mg biweekly.

On examination, she had diffuse purpuric patches, some with a retiform pattern scattered over the scalp, face, upper back, abdomen, extensor arms, thighs, and lower legs, sparing the hands, feet, and mucous membranes (Fig 1). She was otherwise afebrile and hemodynamically stable. Her blood count was notable for anemia (hemoglobin, 5 g/dL; reference range, 12.0-16.0 g/dL) and pancytopenia (white blood cell count, 1000/mm^3; reference range, 4500-11000/mm3; platelets, 32000/mm^3; reference range, 130000-400000/mm^3). Additional studies found low haptoglobin (5 mg/dL; reference range, 10-210 mg/dL) and elevated lactate dehydrogenase (859 U/L; reference range, 90-200 U/L), consistent with hemolysis. Her reticulocyte count was 6.9% (reference range, 0.4%-2.4%), indicating compensation. The direct Coombs test was positive, consistent with a PNH flare. Complement levels were accordingly low (C3, 91 mg/dL; reference range, 92-210 mg/dL; C4, 16 mg/dL; reference range, 18-56 mg/dL).

Abbreviation used:
PNH: paroxysmal nocturnal hemoglobinuria

Although she was otherwise well appearing, a disseminated intravascular coagulation panel was ordered given the rapidly progressive purpura, which found an elevated d-dimer (5646 ng/mL; reference range, 0-230 ng/mL), but international normalized ratio (1.05; reference range, 0.87-1.18) and fibrinogen (279 mg/dL; reference range, 179-395 mg/dL) were within normal limits. The peripheral smear was remarkable only for pancytopenia.

A bone marrow biopsy was performed because of the pancytopenia and found mildly hypocellular marrow (60%-70%) with erythroid hyperplasia but no evidence of excess blasts or any dysplastic process.

A punch biopsy of a retiform patch in the left axilla found organizing thrombin within the lumens of superficial and deep small vessels, with minimal

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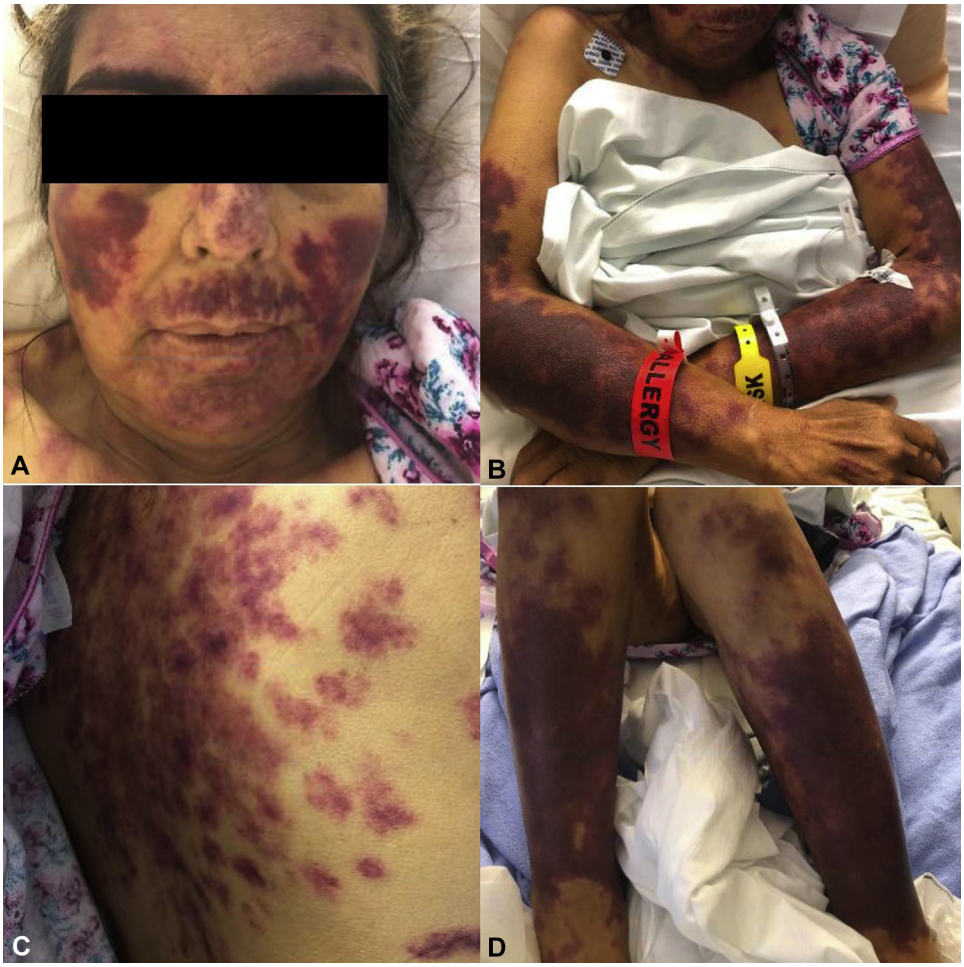

Fig 1. Diffuse purpuric patches, some with a retiform pattern scattered over the (**A**) face, (**B**) extensor arms, (**C**) upper back, and (**D**) lower legs.

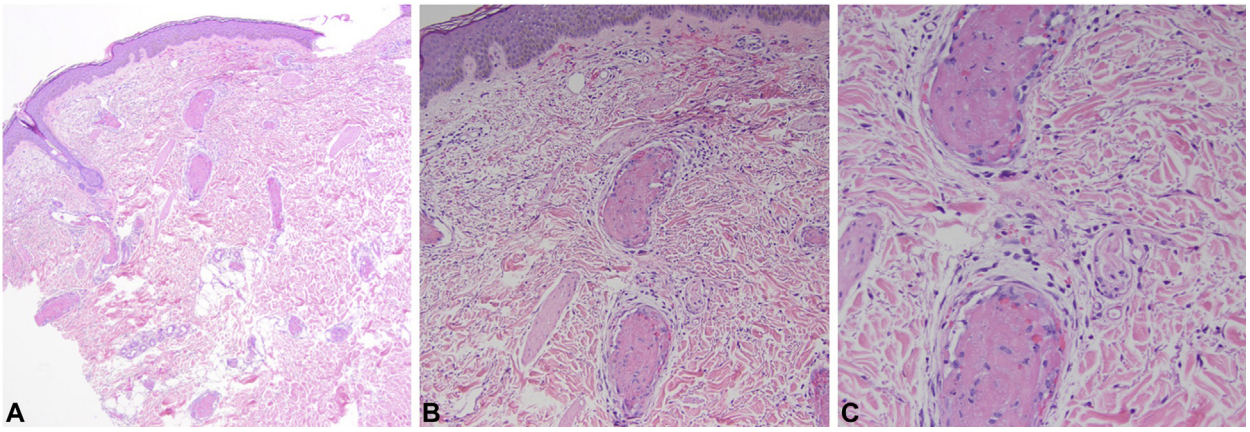

Fig 2. Punch biopsy of a retiform patch in the left axilla found organizing thrombin within the lumens of superficial and deep small vessels, with minimal inflammation, consistent with a thrombotic coagulopathy. (Original magnifications: **A**, ×5; **B**, ×10; and **C**, ×20.)

inflammation, consistent with a thrombotic coagulopathy (Fig 2). Special stains for infectious agents and tissue cultures were negative. Given her systemic symptoms (joint pain, fatigue), laboratory findings revealed the parvovirus serologies to be elevated (parvovirus B19 IgM, 19.25 IV; reference

range, <0.89 IV; IgG, 5.88 IV; reference range, <0.89 IV). Other viral etiologies including cytomegalovirus, human immunodeficiency virus, hepatitis A, hepatitis B, hepatitis C, and Epstein-Barr virus were negative. A diagnosis of PNH-associated cutaneous thrombosis in the setting of infection with parvovirus B19 was made.

She was treated with supportive care, including red blood cell transfusions and an increased frequency of dosing of eculizumab. She is now well maintained on 900 mg weekly.

DISCUSSION

PNH is caused by an acquired mutation of the *PIGA* gene in a clone of hematopoietic stem cell, resulting in a deficiency of glycosylphosphatidylinositol in bone marrow stem cells. Glycosylphosphatidylinositol anchors complement regulatory proteins CD55 and CD59 on bone marrow stem cells, and these proteins are necessary to protect against complement-mediated activation and hemolysis of all hematopoietic cells.

Thrombosis is a feared complication of PNH and accounts for approximately half of the mortality in this disease.[1] Activation of platelets is thought to be the primary reason for thrombosis in PNH. Multiple mechanisms play a role in platelet activation in PNH, including nitric oxide depletion, release of free hemoglobin, and endothelial dysfunction.[1] One direct cause is the absence of CD59 in patients with PNH. CD59 is a protein responsible for inhibiting the formation of the membrane attack complex, and its absence leaves platelets vulnerable to complement-mediated lysis and activation.[1] This finding contributes to the thrombocytopenia in patients with PNH as well as excessive platelet activation and aggregation. In our patient, excess platelet activation was likely triggered in the setting of infection, in part because of systemic activation of the coagulation system and release of prothrombotic cytokines.[2,3]

Eculizumab is a humanized monoclonal antibody that binds to complement protein C5, preventing C3b from cleaving C5 into C5a and C5b, and ultimately inhibiting downstream formation of the membrane attack complex.[4] Eculizumab is the treatment of choice in PNH, as it provides the molecular defense that is absent in PNH. Breakthrough hemolysis on the standard dosing of eculizumab was believed to have contributed to our patient's clinical picture, which has been seen in a small percentage of patients with PNH.[4] At our patient's 2-month follow-up, her pancytopenia had stabilized and her laboratory values did not show signs of hemolysis on the increased, weekly dosing of eculizumab.

Our patient initially presented with acute-onset arthralgia and pancytopenia, which can be seen in adults infected with parvovirus. However, unlike in our patient, cutaneous purpura in parvovirus classically presents in a "gloves and stocking" distribution.[5,6] PNH can also present with purpura, although it is extremely rare and typically appears on the lower extremities and ears.[7] Although there have been multiple reported cases of purpura in the setting of PNH,[1,5,7-9] only a single case of PNH-associated cutaneous thrombosis, triggered by parvovirus infection has been described in the literature.[5] However, our patient presented with appreciably more extensive skin involvement. The extensive purpura seen in our patient is likely a manifestation of PNH-associated cutaneous thrombosis, exacerbated by parvovirus infection.

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