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

Mimi Nguyen, BS,a Samantha Ellis, MD,b Thomas H. Konia, MD,b Alain Brassard, MD FRCPC,b and Danielle Tartar, MD, PhDa

Sacramento, California

Key words: parvovirus B19; paroxysmal nocturnal hemoglobinuria; purpura.

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/mm3; reference range, 4500-11000/mm3; platelets, 32000/mm3; reference range, 130000-400000/mm3). 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).

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 range, 130000-400000/mm3). 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).

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

Abbreviation used:
PNH: paroxysmal nocturnal hemoglobinuria
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

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.)
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.

REFERENCES
1. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013;121(25):4985-4996. quiz 5105.
2. Patir P, Isik Y, Turk Y, et al. Necrotizing fasciitis in paroxysmal nocturnal hemoglobinuria. Case Rep Hematol. 2015;2015:908087.
3. Levi M, van der Poll T, Schultz M. New insights into pathways that determine the link between infection and thrombosis. Neth J Med. 2012;70(3):114-120.
4. Kelly R, Arnold L, Richards S, et al. Modification of the eculizumab dose to successfully manage intravascular breakthrough hemolysis in patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008;112(11):3441.
5. Cholez C, Schmutz JL, Hulin C, Hesse JY, Barbaud A. Cutaneous necrosis during paroxysmal nocturnal haemoglobinuria: role of parvovirus. B19? J Eur Acad Dermatol Venereol 2005;19(3):381-382.
6. Prasad B, St Onge J. Parvovirus leading to thrombotic microangiopathy in a healthy adult. BMJ Case Rep. 2016:2016.
7. Hsieh F-N, Chen T-Y, Lee JY-Y. Severe cutaneous thrombosis with hemorrhagic necrosis in a patient with paroxysmal nocturnal hemoglobinuria: A case report and review of literature. Dermatologica Sinica. 2017;35(3):138-141.
8. Nara T, Kimori S, Nakamichi H, et al. Extensive purpura in a patient with paroxysmal nocturnal hemoglobinuria. J Am Acad Dermatol. 2005;53(6):1090-1092.
9. Rietschel RL, Lewis CW, Simmons RA, Phyllyk RL. Skin lesions in paroxysmal nocturnal hemoglobinuria. Arch Dermatol. 1978;114(4):560-563.