Paroxysmal Nocturnal Hemoglobinuria Associated With Infectious Mononucleosis

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A previously healthy 16-yr-old girl was found to have pancytopenia, low reticulocyte count, a cellular bone marrow, and a negative Coombs test, all coincident with clinical and laboratory evidence of infectious mononucleosis. Symptoms and signs of infectious mononucleosis subsided, but pancytopenia and hemolytic anemia persisted. Sucrose hemolysis and acid hemolysis tests supported a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH). After 18 mo, the platelet count is normal, but leukopenia and hemolytic anemia continue. The development of PNH in this patient suggests it may have resulted from an effect of infectious mononucleosis.

Paroxysmal nocturnal hemoglobinuria (PNH) is an uncommon syndrome of hemolytic anemia and pancytopenia that has been observed in association with several diverse hematologic disorders. We have recently seen a patient in whom infectious mononucleosis may have resulted in the development of PNH.

CASE REPORT

W. H. is a 16-yr-old girl who had been entirely well until the onset of fatigue and easy bruising in late January 1976. Two to three weeks later she developed a sore throat and was treated with antibiotics with no improvement of symptoms. In early March 1976, her physician noted cervical and axillary lymphadenopathy and splenomegaly. The hemoglobin was 5.6 g/dl, hematocrit 15.7%, and WBC 4500, with 19% neutrophils, 5% bands, 66% lymphocytes, 9% monocytes, and 1% basophils. The platelet count was 29,900/cu mm, and reticulocytes were 4.4%. The SGOT was 116 mU/ml (normal 10–40 mU/ml), LDH 3270 mU/ml (normal 110–200 mU/ml), bilirubin 1.7 mg/dl, and alkaline phosphatase 100 mU/ml (normal 25–200 mU/ml). The Coombs test was negative. Serum haptoglobin was less than 10 mg/dl. The heterophile titer was 1:1792, unchanged after guinea pig kidney cell absorption, and negative after beef red cell absorption. The platelet count was 29,900/cu mm, and reticulocytes were 4.4%. The SGOT was 116 mU/ml (normal 10–40 mU/ml), LDH 3270 mU/ml (normal 110–200 mU/ml), bilirubin 1.7 mg/dl, and alkaline phosphatase 100 mU/ml (normal 25–200 mU/ml). The Coombs test was negative. Serum haptoglobin was less than 10 mg/dl. The heterophile titer was 1:1792, unchanged after guinea pig kidney cell absorption, and negative after beef red cell absorption. Serum iron was 161 µg/dl, and total iron binding capacity was 355 µg/dl. Serum B₁₂ was 404 pg/ml, and serum folate was 6.7 ng/ml. Hemoglobin electrophoresis showed 91.7% HbA, 2.6% HbA₂, and 5.7% HbF. The urinalysis was normal. The antinuclear antigen test and the serologic test for syphilis (RPR) were negative. The serum calcium, phosphate, uric acid, creatinine, and BUN were normal. The bone marrow aspirate was hypercellular and showed erythroid hyperplasia and decreased stainable iron. She received 4 units of packed red blood cells.

By May 1976, the sore throat, lymphadenopathy, and splenomegaly had resolved. The hemoglobin was 7.7 g/dl, hematocrit 22.5%, platelets 75,000/cu mm, and WBC 3,200/cu mm, with 42% neutrophils, 51% lymphocytes, and 7% monocytes. The reticulocytes were 14%. The heterophile titer was 1:56. 1:14 after guinea pig kidney cell absorption, and negative after beef red cell absorption. She received 2 more units of packed red blood cells.

When we first saw the patient in June 1976, she was asymptomatic. There had been no fever, weight loss, abnormal bleeding, or discolored urine. Examination showed pallor, but no jaundice, purpura, lymphadenopathy, or organomegaly. The hemoglobin was 8.9 g/dl, hematocrit 25%, RBC 2,320,000/cu mm, platelets 78,000/cu mm, and WBC 5,500/cu mm, with 28% neutrophils, 2% bands, 1% eosinophils, 60% lymphocytes, and 9% monocytes. The reticulocytes were 9.6%. The red cell indices were MCV 108 cu µm, MCH 38 µg, and MCHC 36%. The SGOT was 145 mU/ml, LDH greater than 3000 mU/ml.
and bilirubin 1.6 mg/dl. The heterophile titer was 1:10. The direct Coombs and antinuclear antigen tests were negative. Cold agglutinin titer was 1:4. The serum iron was 109 µg/dl, and total iron binding capacity was 280 µg/dl. Hemoglobin electrophoresis revealed 92.7% HbA, 1.9% HbA₂, and 5.4% HbF. The serum contained free hemoglobin, and the urine contained hemosiderin. The leukocyte alkaline phosphatase score was 4 (normal 30–130). The sucrose hemolysis and acid hemolysis tests were both strongly positive. The bone marrow aspirate was hypercellular with erythroid hyperplasia, adequate megakaryocytes, diminished mature myeloid cells, and absent stainable iron.

Paroxysmal nocturnal hemoglobinuria was diagnosed, and she was treated with folic acid, oral iron, and transfusions of saline-washed packed red blood cells. In the 18 mo after diagnosis, she has felt well except for fatigue relieved by blood transfusions. There have been no infections or abnormal bleeding. The WBC has ranged from 2500 to 3700/cu mm, the reticulocytes have varied from 8.0% to 20.0%, and platelets gradually increased to 185,000/cu mm.

DISCUSSION

In PNH, portions of both the circulating red cells and granulocytes bind excess complement and have increased susceptibility to complement-induced lysis in vitro. These abnormal cells coexist in the circulation with red cells and granulocytes with normal in vitro complement sensitivity. Increased complement binding to platelets has also been reported. Laboratory evidence suggests that PNH results from the clonal proliferation of an altered bone marrow precursor stem cell. In a PNH patient heterozygous for two G-6-PD variants, the complement-sensitive red cells contained only one of the G-6-PD enzyme variants, whereas a mixture of the complement-sensitive and non-complement-sensitive red cells contained both variants.

PNH has been associated with acute nonlymphocytic leukemia, chronic granulocytic leukemia, myelofibrosis, and aplastic anemia, the last of which may be congenital, drug-induced, or idiopathic in origin. In Dacie and Lewis’s experience of 80 cases of PNH, 23 patients presented with aplastic anemia and later manifested typical PNH. These authors suggested that the frequency of the association of PNH and aplastic anemia may in fact be underestimated if the presumed marrow hypoplasia is relatively mild or brief and is thus overlooked. The link between PNH and these other disorders may be related to marrow stem cell injury.

In infectious mononucleosis, severe cytopenias are unusual and of brief duration. Severe anemia and thrombocytopenia are mediated by autoimmune mechanisms, and severe transient neutropenia may be associated with abnormal myeloid maturation in the bone marrow. Three patients with infectious mononucleosis complicated by transient pancytopenia have been described, but bone marrow examinations were not reported. We found reports of two cases of infectious mononucleosis complicated by aplastic anemia, one of which was fatal. We found no reports of PNH associated with infectious mononucleosis.

In our patient, the two illnesses could have occurred together by chance. Conceivably, infectious mononucleosis exacerbated antecedent subclinical PNH. Alternatively, the initial event may have been marrow stem cell injury induced by infectious mononucleosis resulting in the emergence of PNH. The lowest neutrophil, platelet, and reticulocyte counts occurred early in our patient’s illness, and all subsequently increased, compatible with a period of initial transient marrow suppression.
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REFERENCES

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