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Aplastic Crisis Induced by Human Parvovirus B19 as an Initial Presentation of Hereditary Spherocytosis

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ABSTRACT

The association between aplastic crisis and human parvovirus (HPV) B19 infection has been described in patients with hereditary spherocytosis (HS). Most cases of aplastic crisis in patients with HS induced by HPV B19 have been reported in children and adolescents. In this paper, we describe an aplastic crisis induced by HPV B19 in the 34 year old female as an initial presentation of HS. Although other viral illnesses cause some decompensation in HS, the anemia is rarely as profound as seen in acute HPV B19 infections¹⁵.

Key words: hereditary spherocytosis, human parvovirus, aplastic crisis, giant pronormoblasts

Introduction

Human parvovirus (HPV) B19 is a small, non-enveloped single-stranded DNA virus, which belongs to the Parvovirus genus within the Parvoviridae family. It was first discovered in 1975 while screening units of blood for hepatitis B virus in asymptomatic donors¹. HPV B19 infection is common worldwide, and majority of individuals who contract the virus are infected by the age of fifteen². The most common means of transmission is exposure to infected respiratory droplets. Viremia occurs 7 to 10 days after exposure to B19 and usually lasts approximately five days³. HPV B19 infection can lead to a variety of clinical manifestations dependent on the underlying host. In children, parvovirus B19 can cause erythema infectiosum, a mild febrile illness with rash while patients with underlying hemolytic disorders (such as sickle cell disease, erythrocyte enzyme deficiencies, hereditary spherocytosis, thalassemias, paroxysmal nocturnal hemoglobinuria, and autoimmune hemolysis) can develop transient aplastic crisis and infection during pregnancy can lead to fetal death³. Severe manifestations of HPV B19 viremia relate mostly to the propensity of virus to infect and lyse erythroid progenitor cells of the bone marrow⁴. HPV B19 infection in most instances causes transient aplastic crisis, developing suddenly in patients with chronic hemolytic disease. Infected patients have severe reti-

culocytopenia lasting seven to ten days, and their bone marrow contains no erythroid precursor cells despite a normal myeloid series⁴. Giant pronormoblasts, hallmark of cytopathic effects of parvovirus B 19, often appear in the marrow⁵.

Virally induced aplastic crisis brings many patients to medical attention, particularly asymptomatic hereditary spherocytosis (HS) patients with normally compensated hemolysis⁶. Because aplastic crises usually last 10 to 14 days (about half the life span of HS red cells), the hemoglobin value typically falls to about half its usual level before recovery occurs. In patients with severe HS, the anemia may be profound, requiring hospitalization and transfusion⁵. However, most cases of aplastic crisis in patients with HS induced by parvovirus B19 have been reported in children and adolescents. In this paper, we describe an aplastic crisis induced by parvovirus B19 in the 34 year old female as an initial presentation of hereditary spherocytosis.

Case Report

Thirty four years old female was admitted to the hospital because of severe normocytic anemia and febrile

condition. From previous medical history it was found she had tonsillectomy at the age of two, and at the age twenty-one abdominal ultrasound revealed discreet spleen enlargement. She was not married and had no children. Five days before admission to hospital she had nausea, headache, chills and fever up to 39.6°C. Next few days she felt better but was still febrile up to 38°C. Day before hospitalization she was observed in Clinic for infective diseases where anemia was detected: white blood count (WBC) $4.1 \times 10^9/L$; red blood count (RBC) $2.79 \times 10^9/L$; hemoglobin (Hb) 99 g/L; hematocrit (Hct) 0.25 L/L; mean corpuscular volume (MCV) 90.2 fL; mean corpuscular hemoglobin (MCH) 35.3 pg; mean corpuscular hemoglobin concentration – MCHC 391 g/L (normal ranges 315–360 g/L); red cell distribution width (RDW) 14.8%; platelet count (Plt) $143 \times 10^9/L$ with high serum lactate dehydrogenase – LDH concentration (647 U/L), bilirubin (49.2 $\mu\text{mol/L}$), aspartate aminotransferase – AST (190 U/L), alanine aminotransferase – ALT (133 U/L) and almost normal C-reactive protein – CRP (13.1 mg/L). On the next day complete blood count worsened [WBC $2.7 \times 10^9/L$; RBC $2.02 \times 10^9/L$; Hb 66 g/L; Hct 0.18 L/L; MCV 89 pg; MCHC 369 g/L (normal ranges 320–345 g/L); Plt $123 \times 10^9/L$], hemolytic anemia was suspected and patient was sent to our Clinic for hospitalization. Prominent features at admission were pallor and palpable liver and spleen four cm from the costal margin. She was subfebrile (37°C), without peripheral lymph node enlargement. The day after admission her hemoglobin and Hct had fallen to 52 g/L and 0.14 L/L and platelets to $122 \times 10^9/L$. Absolute reticulocyte count (Rtc) was $39.8 \times 10^9/L$ (normal ranges $22\text{--}97 \times 10^9/L$) and relative 2.33% (normal ranges 0.5–2.16%). Liver function tests worsened; AST 230 U/L, ALT 232 U/L, bilirubin 45.3 $\mu\text{mol/L}$, and LDH 626 U/L. Serum iron (40.2 $\mu\text{mol/L}$), iron saturation (78%) and ferritin (>1500 ng/mL) were increased, and haptoglobin had been decreased to <0.07 g/L (normal ranges 0.30–2.0 g/L). The direct antiglobulin test was negative, and osmotic fragility of patient's red cells was increased. The peripheral blood smear revealed anisocytosis and poikilocytosis with some spherocytes (Figure 1). Bone marrow aspirate smears in accordance with aplasia of red line showed extremely reduced erythropoiesis without

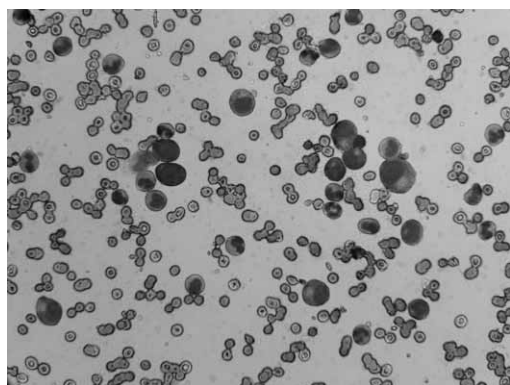


Fig. 1. Peripheral blood smear in HS patient reveal anisocytosis and poikilocytosis with some spherocytes.

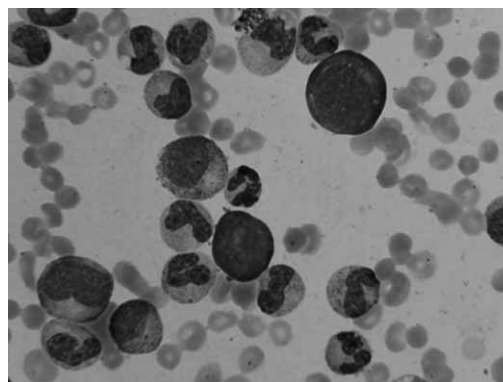


Fig. 2. Bone marrow aspirate smears show extremely reduce erythropoiesis without signs of maturation and giant pronormoblasts.

signs of maturation (Figure 2). HPV B19 IgM and IgG were both positive. Abdominal ultrasound revealed multiple gallstones and spleen enlargement (139 mm). Immunophenotypisation of peripheral blood for CD55 and CD59 were normal, excluding paroxysmal nocturnal hemoglobinuria as a potential cause of anemia. At second day of hospitalization patient received two units of packed red blood cells (560 mL), with marked clinical improvement. The hemoglobin was stable for the next seven days (Hb:74 g/L). On eight day rise in reticulocytes to 19.7% and platelet count to $596 \times 10^9/L$ was noticed, and on tenth day hemoglobin level was 86 g/L. She was discharged ten days latter when her hemoglobin reached 100 g/L and Hct 0.28 g/L, with Rtc of 11.6%. Level of aminotransferases and LDH normalized, but bilirubin was without change.

Discussion and Conclusion

Human Parvovirus B19 typically infects erythroid progenitor cells and inhibits erythropoiesis, leading to acute cessation of erythrocyte production⁷. In addition to reticulocytopenia, both neutropenia and thrombocytopenia associated with or without hemolytic disorders have been observed during HPV B19 infection^{8,9}, and were also seen in our patient. When infected with the virus, immunocompetent subjects may develop some degree of anemia, but normal erythrocyte life span prevents them from becoming significantly anemic¹⁰. In conditions such as hereditary spherocytosis, the shortened life span of the erythrocytes can lead to severe and abrupt development of anemia if erythropoiesis is interrupted. Giant pronormoblasts on peripheral blood smear or in the bone marrow aspirate are suggestive of parvovirus B19 infection but are not diagnostic¹¹. During the spontaneous recovery marrow may display cohorts of early erythroid cells. Occasionally, there are large, intensely basophilic cells termed giant pronormoblasts⁵. In our patient we did not find giant pronormoblasts because bone marrow aspirate was done during early phase of illness, when marrow is depleted of all erythroid elements. There are two types of diagnostic tests to confirm par-

vovirus B19 infection: B19-specific antibody testing and viral DNA testing. Parvovirus B19-specific IgM antibodies are detected at day 10 through 12 and can persist for up to five months. Specific IgG antibodies are detectable about 15 days post-infection and persist long-term³. Serologic test is incapable of detecting acute infection at the onset of symptoms, before the appearance of immunologic response¹². In the case of our patient, infection with HPV B19 was confirmed by detection of anti-HPV IgM antibodies on a serologic test requested on the 14th day of hospitalization. Hereditary spherocytosis (HS) is the most common hereditary hemolytic anemia among people of northern European descent. It is caused by membrane protein defects resulting in cytoskeleton instability. The classic laboratory features of HS include anemia (which is of variable degree), reticulocytosis, an increased MCHC, spherocytes on the peripheral blood smear, hyperbilirubinemia and abnormal results of the osmotic fragility test¹³. All of these were found in our patient. She also had gallstones, a very common finding during young age of these patients, and discreet splenomegaly. The length of time between infection and onset of aplastic crisis is known to be eight to ten days. The

interval between the onset of symptoms and reappearance of reticulocytes in peripheral blood ranges from five to twenty days¹⁴. The classical clinical picture was seen in our patient. Such crises may be clinically severe and require prompt red cell transfusion. This happened with our patient who was transfused with two packs of red blood cells.

Adults who remain undiagnosed for HS usually have a very mild form, and they live with the HS remaining undetected until challenged by an environmental stressor. Anemia is generally not present because the bone marrow is able to fully compensate for the persistent destruction of red cells. They are often not diagnosed until latter in life, usually due to hemolytic or aplastic episodes triggered by infection¹³. It is perhaps surprising that the diagnosis of HS is not always considered in a setting of gallstones and splenomegaly in adult life¹⁵.

In this report we described a woman with previously undiagnosed hereditary spherocytosis presenting with aplastic crisis induced by HPV B19 infection. Although other viral illnesses cause some degree of decompensation in HS, the anemia is very rarely as profound as seen in acute parvovirus infections¹⁵.

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APLASTIČNA KRIZA INDUCIRANA HUMANIM PARVOVIRUSOM B19 KAO INICIJALNA PREZENTACIJA HEREDITARNE SFEROcitoze

SAŽETAK

Povezanost između aplastične krize i infekcije humanim parvovirusom (HPV) opisana je u bolesnika s hereditarnom sferocitozom (HS). Većina slučajeva aplastične krize u takvih bolesnika opisana je u djece i adolescenata. U članku opisujemo aplastičnu krizu induciranu s HPV B19 u 34-godišnje žene kao inicijalnu prezentaciju HS. Orijaški pronormoblasti, obilježje su citopatskog efekta HPV B19 i često se nalaze u koštanoj srži. Iako i druge virusne infekcije uzrokuju dekompenzaciju u HS, anemija je rijetko tako izražena kao u akutnim HPV B19 infekcijama.