Case Report

Parvovirus B19-triggered Acute Hemolytic Anemia and Thrombocytopenia in a Child with Evans Syndrome

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Abstract. Background: Human parvovirus B19 (HPV-B19) is the etiologic agent of erythema infectiosum, of transient aplastic crises in individuals with underlying chronic hemolytic disorders, and of chronic pure red cell aplasia in immunocompromised individuals. Case report: We describe a 14-year-old girl with long-standing Evans syndrome, who presented with severe anemia, reticulocytopenia and thrombocytopenia. A bone marrow aspirate revealed severe erythroid hypoplasia along with the presence of giant pronormoblasts, while serological studies and real-time PCR of whole blood were positive for acute parvovirus B19 infection. The patient was initially managed with corticosteroids, but both cytopenias resolved only after administration of intravenous gamma globulin 0.8g/kg. Conclusion: Acute parvovirus B19 infection should be suspected in patients with immunologic diseases, who present reticulocytopenic hemolytic anemia and thrombocytopenia. In this setting, intravenous gamma globulin is effective for both cytopenias.

Keywords: Autoimmune hemolytic anemia, Evans syndrome, Parvovirus B19, Red cell aplasia, Thrombocytopenia.

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Introduction. Human parvovirus B19 (HPV-B19) is the etiologic agent of erythema infectiosum. In individuals with underlying chronic hemolytic disorders, HPV-B19 causes transient aplastic crises (TAC).1 In immunocompromised individuals, persistent HPV-B19 viremia presents as chronic pure red cell aplasia (PRCA).2 Finally, HPV-B19 rarely has been implicated as a cause of autoimmune hemolytic anemia (AIHA) in normal children.3-7 The cellular receptor of HPV-B19 is the blood group P antigen, which explains the viral tropism for erythroid precursors.8 We present a 14-year-old girl with long-standing Evans syndrome (ES), who developed severe anemia, reticulocytopenia and thrombocytopenia due to acute HPV-B19 infection, and briefly review the relevant literature.

Case Report. A known to us 14-year-old girl with long-standing ES was admitted because of fatigue that got progressively worse over three days and new-onset petechiae. The patient was diagnosed with ES at the age of 3 years, when she presented with symptomatic thrombocytopenia without...
hemolysis and was found to have a strongly positive direct antoglobulin test (DAT) for non-specific warm IgG that persists to nowadays. Over the years, she had required therapy with corticosteroids and intravenous globulin (IVIG) for symptomatic thrombocytopenia only, although she was treatment-free for almost four years. The patient’s last hemogram with reticulocyte count before this admission was three months ago and was normal.

On admission to us, she was pale, slightly tachypneic (heart rate of 108/min), had wet purpura, along with numerous petchiae and bruises on both lower extremities and a palpable spleen tip. Laboratory examinations on admission showed leukocytes 4,600/μL (53% neutrophils, 30% lymphocytes, 12% monocytes, 5% reactive lymphocytes), hemoglobin 8.4g/dL, hematocrit 24.4%, platelets 2,000/μL and reticulocytes 0.07%. DAT was 4+ positive for IgG alone. Biochemical studies revealed serum LDH 330U/L (reference range 120-246 U/L), total bilirubin 0.8mg/dL, direct bilirubin 0.2 mg/dL, alanine transaminase 14 U/L, aspartate transaminase 15 U/L, g-glutamyl transeptidase 9 U/L, ferritin 208 ng/ml, haptoglobin 5.8mg/dL (reference range 30-140), vitamin B12 460pg/ml, and serum folate 2.87ng/ml (reference range 3-14). An abdominal ultrasonogram showed borderline splenomegaly, without focal lesions or gallstones. Serological studies were positive for HPV-B19 IgM (210 U/ml, positive >24U/ml) by ELISA kit (RecomWell Mikrogen GmbH, Neuried, Germany), while real-time PCR of whole blood using the LightMix® Kit Parvovirus B19 (TIB MOLBIOL GmbH, Berlin, Germany) for the LightCycler 2.0 instrument (Roche GmbH, Mannheim, Germany) was positive for DNA of HPV-B19 (5.7x10⁶ copies/ml). Additional real-time PCR of whole blood was negative for CMV, EBV, HSV-1, and HSV-2.

Due to laboratory evidence of hemolysis (very low serum haptoglobin) in a child with ES, she was started on intravenous methylprednisolone 80mg/day. The next day, a repeated hemogram showed hemoglobin 6.9g/dL, hematocrit 20.1%, platelets 14,000/μL and reticulocytes 0.09%, while indirect bilirubin picked at 1.8mg/dL. Due to worsening anemia with severe reticulocytopenia, a bone marrow aspirate was performed and showed a regular maturation of the myeloid precursors and abundant megakaryocytes. The erythroid series demonstrated severe decrease of erythroid precursors that were almost exclusively represented by pronormoblasts, frequently of giant size. On the 3rd hospital day, due to persistent anemia and thrombocytopenia, a single dose of IVIG was administered (40g or 830mg/kg). Treatment was well-tolerated. The next morning, hemoglobin was 8.1g/dL, hematocrit 23.4%, platelets 136,000/μL and reticulocytes 0.23%. Two days later, the hemoglobin was further increased to 9.6g/dL, hematocrit 28.4%, platelets 517,000/μL, and reticulocytes 4.05%. The patient was discharged home to continue a 4-week tapering of oral prednisolone along with daily oral folic acid 5mg/day. At the end of therapy, she had a normal full blood count (hemoglobin 12.2g/dL, platelets 277,000/μL) and serum haptoglobin (122 mg/dL). Eight months after the described events, she remains asymptomatic, off-therapy, with normal hemogram, but continues to have 4+ positive DAT for IgG.

**Discussion.** It is well-known that HPV-B19 is associated with TAC in patients with shortened erythrocyte life-span and increased erythropoiesis.¹ Our patient, despite having a strongly positive DAT for years, she had never developed an episode of hemolysis in the past. We believe that the data linking HPV-B19 to the described episode of reticulocytopenic hemolytic anemia are strong since we found laboratory, cytological, serological and molecular evidence of acute HPV-B19 infection. First, in typical AIHA cases, with or without ES, the reticulocyte count is elevated, while our patient had profound reticulocytopenia, a well-known feature of acute HPV-B19 infection. Second, the observed bone marrow erythroid hypoplasia along with the presence of giant pronormoblasts are typical findings of HPV-B19 infection.³ Third, HPV-B19 infection was confirmed with appropriate molecular (real-time PCR) and serological studies (specific IgM). Finally, our patient had no clinical or laboratory evidence of chronic hemolysis (normal hemogram and reticulocyte count), when last seen as an outpatient three months ago. Thus, in all likelihood HPV-B19 triggered the hemolysis in our patient, who already harbored non-specific warm IgG anti-erythrocytic autoantibodies confirmed with several screening tests over the years.
Primary ES is defined by the concurrent or sequential occurrence of (auto) immune thrombocytopenia (ITP) and DAT positive AIHA in the absence of an underlying etiology. Active hemolysis is not always present, but erythrocyte involvement requires a positive DAT, like in our patient. Primary ES is a diagnosis of exclusion, and other causes of immune cytopenias such as autoimmune lymphoproliferative syndrome, systemic lupus erythematosus, IgA deficiency, common variable immune deficiency, and acquired immunodeficiency syndrome should be excluded. The natural history of ES is characterized by a chronic and relapsing course requiring immunosuppressive therapy. Almost all patients with ES are initially treated with corticosteroids, especially in cases with clinically significant autoimmune hemolysis. IVIG is preferred as first-line therapy in cases of symptomatic thrombocytopenia, but cannot be recommended as first-line therapy in AIHA, since only about 40% of patients will respond.10

Our patient had long-lasting primary ES, but without active hemolysis. Over the years, other causes of immune cytopenias were excluded by appropriate laboratory studies. The contemporary event of reticulocytopenic hemolytic anemia and relapse of thrombocytopenia leads us to suspect acute HPV B19 infection.

HPV-B19-associated aplastic crises in patients with sickle-cell anemia, thalassemia, spherocytosis, and glucose-6-phosphate dehydrogenase deficiency are usually managed with simple erythrocyte transfusions.2 However, in patients with ES, blood transfusions are generally not an option due to the difficulty in finding compatible blood.11,12

In immunocompromised individuals, IVIG therapy for PRCA related HPV-B19 infection appears to be effective. Kurtzman et al. were the first to report cure of enduring PRCA due to persistent parvovirus B19 infection with immunoglobulin therapy.13 Crabol et al. reviewed the efficacy of IVIG therapy in 133 patients with HPV-B19 PRCA. Hemoglobin was corrected after the first course of IVIG in 93% of the patients, while disease relapse occurred in 33.9% at a mean of 4.3 months.14 Our patient received a single dose of IVIG 0.8g/kg, lower than the typical dose described by Crabol et al., and had a quick response, as witnessed by the elevated reticulocyte count and rapid correction of anemia. Moreover, she demonstrated a dramatic rise of platelets number, and thrombocytopenia was fully corrected (platelets>150,000/μL) within two days after administration of IVIG.

Spontaneous recovery from HPV-B19 occurs in normal persons and typically correlates with the appearance of circulating specific antivirus antibodies.2 Our patient who suffered from ES despite having a high anti-HPV-B19 IgM titer had persistent reticulocytopenia that was corrected only after administration of IVIG. Hence, we believe that her recovery was not spontaneous, but rather the result of IVIG administration.

HPV-B19 not only causes TAC in patients with reduced red cell survival, but it also triggers AIHA. Five reported cases of AIHA due to acute HPV-B19 infection in healthy children are summarized in Table 1. As shown, three of the five patients were males, with a median age at presentation of 5 years.3-7

Few cases of HPV-B19 induced AIHA associated with the hemophagocytic syndrome have also been published,15-17 but our patient’s bone marrow showed no signs of hemophagocytosis or thrombophagocytosis. The presence of abundant megakaryocytes suggests that thrombocytopenia in our case was immune-mediated due to peripheral platelet

Table 1. Pediatric patients without underlying hematologic disease, who developed HPV-B19-associated AIHA.

| Author, reference | Age/Sex | Hemoglobin (g/dL) | BM erythroid series | Therapy given | Associated disease |
|-------------------|---------|------------------|---------------------|---------------|-------------------|
| Bertrand Y et al. [3] | 12 years/M | 6 | Hypoplasia | PRBC transfusion | None |
| Smith MA et al. [4] | 11 years/F | 6.5 | Hypoplasia | Corticosteroids | None |
| Chambers LA et al. [5] | 3 years/M | 5.5 | Hypoplasia | Corticosteroids, IVIG, PRBC transfusion | None |
| Nobili V et al. [6] | 1 month old/M | | Dysplasia (no further details) | Corticosteroids, cyclosporine A | Autoimmune hepatitis |
| Giovannetti G et al. [7] | 5 years/F | | Unknown (no BME performed) | Corticosteroids, PRBC transfusion | None |

BM: bone marrow, M: male, F: female, PRBC: packed red blood cells, BME: bone marrow examination.
HPV-B19 infection in the ITP group was significantly higher than that in the control group, confirming an association of HPV-B19 with ITP. 19

In conclusion, HPV- B19 infection should be suspected in patients with immunologic diseases, who present with anemia, reticulocytopenia, and thrombocytopenia. In this setting, IVIG therapy is indicated and can achieve rapid and long-standing correction of both cytopenias.

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