A Case with Iron Deficiency Anemia Developed Aplastic Crisis

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   A toddler with an unbalanced diet and gastrointestinal bleeding by juvenile polyp developed an aplastic crisis due to the human parvovirus B19 (HPVB19). Although he exhibited microcytic anemia without iron deficiency in the acute phase of HPVB19 infection, he presented with iron deficiency anemia (IDA) in the chronic phase. IDA results in erythroblast hyperplasia and shortened red blood cell lifespan as like congenital hemolytic diseases, which may lead to an aplastic crisis during HPVB19 infection. It should be noted that iron deficiency is often masked, and microcytic anemia may be a clue for IDA.

   The human parvovirus B19 (HPVB19), a single-stranded DNA virus that was discovered in the blood for transfusion, is a common cause of infection in children(1). Infection with HPVB19 can present as infectious erythema; pruritus; arthritis; and influenza-like symptoms, such as fever, malaise, and muscle aches. HPVB19 is also known to cause aplastic crisis in patients with congenital hemolytic diseases, such as hereditary spherocytosis, sickle cell disease, and glucose-6-phosphate dehydrogenase deficiency(2, 3, 4). However, there are few reports about aplastic crises associated with HPVB19 in patients without hemolytic diseases(5, 6). We report a pediatric case of a male with iron deficiency anemia (IDA) who had an aplastic crisis due to HPVB19 infection. The understanding of aplastic crisis associated with IDA is still poor. As such, we reviewed the literature on similar patients and considered their pathology.

CLINICAL CASE

   A 5-year-old boy presented with fever, anemia and leukopenia for 2 days, which prompted his referral and admission to our hospital. Six months before the consultation, he was accidentally pointed out to have mild anemia (hemoglobin, 10.0 g/dL; mean corpuscular volume, 73 fL; mean corpuscular hemoglobin, 22.8 pg; mean corpuscular hemoglobin concentration, 31.1%), and he had an unbalanced diet. He avoided both meat and fish and ate only vegetables. Physical examination revealed conjunctival pallor. Laboratory tests at admission revealed microcytic hypochromic anemia (hemoglobin, 5.1 g/dL; mean corpuscular volume, 61.2 fL; mean corpuscular hemoglobin, 16.3 pg; mean corpuscular hemoglobin concentration, 26.7%) with reduced reticulocyte count (0.2%), leukopenia (3200/μL; Seg 43.9%, Eosino 2.2%, Mono 8.1%, Lympho 45.8%) and normal platelet count (18.7×10^4/μL). However, the serum levels of iron, ferritin, and total iron-binding capacity were normal (Fe, 89 μg/dL; ferritin, 68.2 ng/dL; total iron-binding capacity, 219 μg/dL). In addition, the serum levels of lactate dehydrogenase, soluble interleukin-2 receptor, total bilirubin, direct bilirubin, haptoglobin, vitamin B12, and folic acid were 230 U/L, 1210 U/mL, 0.30 mg/dL, 0.07 mg/dL, 144 mg/dL, 315 pg/mL, and 6.8 ng/mL, respectively. Spherical or target red blood cells were not detected, and the red blood cells had varying sizes in the peripheral blood smear. The fecal occult blood test result was positive, but he exhibited no gross blood in his stools. Abdominal ultrasound and computed tomography showed an asymptomatic intussusception accompanied by a tumor (Figure 1A, B), which was treated with a high-pressure enema. These imaging studies showed no splenomegaly or gallstones. As for the viral serologic tests, the test for the HPVB19-specific IgM antibody was positive. Therefore, we diagnosed the patient with an aplastic crisis due to HPVB19 infection. One week after the onset of infection, the anemia continued to progress (hemoglobin, 4.7 g/dL) despite the mild recovery in the reticulocytes (0.62%). As such, we performed red blood cell transfusion, bone marrow examination, and tumor resection using a lower gastrointestinal endoscope (Figure 1C, D). Bone marrow examination revealed erythroblastic hyperplasia without leukemic blast cells (Figure 1E), with polychromatic erythroblasts accounting for 69% of all the cells. Furthermore, there was a high proportion of erythroblasts in the bone marrow findings, indicating the aplastic crisis was in the recovery phase. The tumor was pathologically diagnosed as a juvenile polyp. Thereafter, the serum iron and ferritin levels decreased to 37 μg/dL and 13.1 ng/dL, respectively, as the hemoglobin and reticulocyte count improved. The patient was diagnosed with IDA and was discharged with iron

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medication. Thereafter, no erythema or arthralgia appeared. Although iron medication was discontinued 3 months after discharge, anemia did not progress and there were no abnormalities in serum markers indicating hemolytic anemia at 6 months post-discharge (hemoglobin 13.2 g/dL, aspartate aminotransferase 24 IU/L, total bilirubin 0.50 mg/dL, lactate dehydrogenase 221 U/mL, Fe 63 μg/dL, ferritin 27 ng/dL).
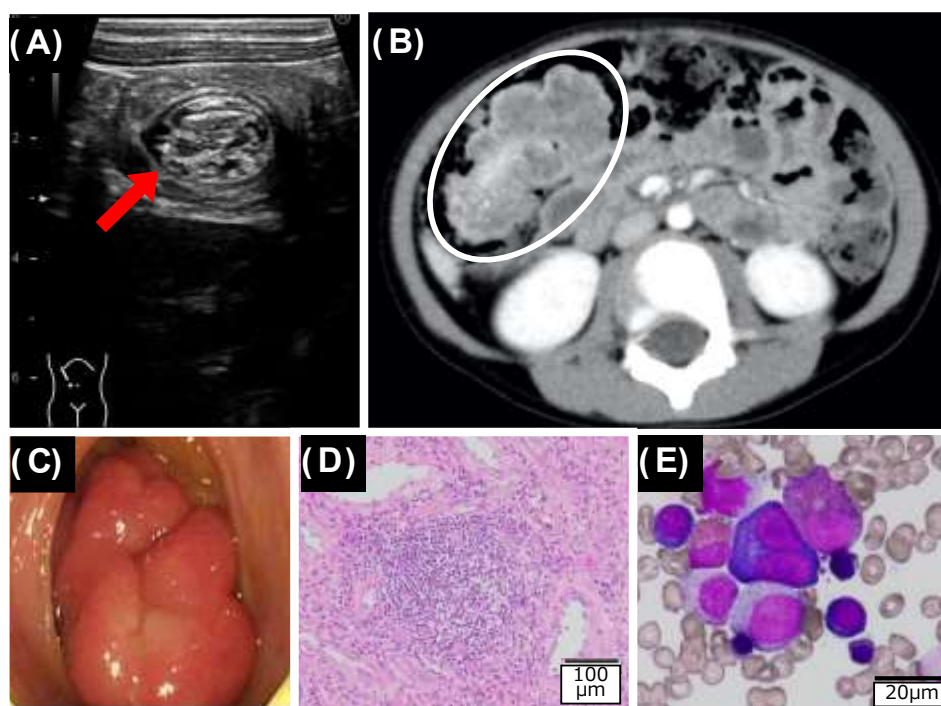

Figure 1. The results of image inspection, lower gastrointestinal endoscope, and bone marrow examination.
(A) Abdominal ultrasound findings: target sign (red arrow).
(B) Abdominal computed tomography findings: intussusception in the ascending colon (circle).
(C) Lower endoscope findings; pedunculated polypoid lesion.
(D) Pathological findings reveal a juvenile polyp. There is an expansion of the stroma with infiltration of prominent inflammatory cells but with no obvious malignant findings.
(E) Bone marrow examination: erythroblastic hyperplasia without morphological abnormalities and malignant findings.

Table I. Characteristics of HPVB19-induced aplastic crisis with iron deficiency anemia

	Case 1	Case 2	Case 3	Case 4	Our case
Age (year) / Sex	13 / M	13 / F	14 / F	14 / F	5 / M
Laboratory Tests on admission					
Hb (g/dL)	6.8	4.9	5.3	8.2	5.1
MCV (fL)	52.5	60.5	62.4	83.0	61.2
MCH (pg)	15.1	15.8	N/A	N/A	16.3
Reticulocyte (%)	0.0	0.1	0.2	1.4	0.2
Fe (μg/dL)	179.0	149.0	10.0	13.0	89.0
Ferritin (ng/ml)	88.6	14.0	17.0	38.0	68.2
TIBC (μg/dL)	355.0	350.0	357.0	354.0	219.0
Erythroblasts in bone marrow (%)	0.8	N/A	1.5	N/A	71.8
HPVB19 IgM	+	+	+	+	+
Laboratory Tests in Remission					
Fe (μg/dL)	10.0	29	N/A	N/A	37.0
Ferritin (ng/ml)	<10	<7.8	N/A	N/A	13.1
Treatment	No treatment	Iron	Transfusion Iron	Iron	Transfusion Iron
Reference	16	17	18	18	

M: male, F: female, NA: Not Available, MCV: mean corpuscular volume, MCH: mean, TIBC: total iron binding capacity

DISCUSSION

We reported that the patient had IDA due to an unbalanced diet, chronic bleeding of polyps, and hematopoietic disorders caused by infection with HPVB19. HPVB19 targets the erythroid progenitor cells in the bone marrow during infection via the erythrocyte P antigen. While the virus propagates in the infected cells, progenitor cells are killed by cell lysis, releasing the virus(7). For this reason, hematopoiesis of red blood cells is temporarily ceased for approximately 1 to 2 weeks during HPVB19 infection(8). However, healthy people do not show severe anemia because their red blood cells have a lifespan of about 120 days(8).

The following two mechanisms have been identified as the cause of the aplastic crisis that occurs in patients with hemolytic anemia. First, the red blood cells in patients with hemolytic anemia have a much shorter survival time compared to those in healthy controls. To illustrate, the lifespan of erythrocytes in patients with chronic hemolytic anemia patients is only 5–15 days. This difference in the lifespan of red blood cells causes severe anemia during HPVB19 infection(9). Second, patients with hemolytic diseases compensate for the anemia through erythroblast hyperplasia, which facilitates HPVB19 replication and increases the concentration of HPVB19 DNA in the acute phase(10).

IDA is the most common anemia in daily pediatric practice. In this case, he has also had microcytic hypochromic anemia for at least six months. Its major causes include decreased iron intake due to inappropriate weaning and diet, increased iron demand with growth, gastrointestinal bleeding, menstruation, etc(11). In various types of anemia, including IDA, the lack of oxygen supply in arterial blood promotes the production of erythropoietin in the kidney, which increases the plasma levels of erythropoietin depending on the degree of anemia. Erythropoietin binds to receptors expressed on erythroid progenitor cells, leading to the differentiation and proliferation of erythroid precursors in the bone marrow(12).

In addition, some reports have shown that the red blood cells have a shorter life span in patients with IDA. Rodvien et al. suggested that the activation of the glutathione peroxidase in the red blood cells was decreased in rabbits with IDA, leading to increased oxidative damage and shortened survival of the red blood cells(13). Daniela et al. also reported that mice with iron deficiency readily undergo erythrocyte apoptosis due to the enhanced activity of the Ca^{2+} permeable cation channel, resulting in a reduced red blood cell lifespan at 60% compared to controls(14). In addition, Vayá et al. reported decreased erythrocyte deformability in human IDA patients leading to shortened erythrocyte lifespan(15). Based on these, it may be assumed that IDA patients are characterized by erythroblast hyperplasia and a shortened erythrocyte life span. Therefore, HPVB19 infection may cause an aplastic crisis in patients with IDA, similar to those with hemolytic anemia. On the other hand, there are very few reports of IDA-associated aplastic crisis relative to the high prevalence of IDA, which may suggest the involvement of other mechanisms.

To date, there have only been five pediatric IDA cases with aplastic crisis due to HPVB19, including our case (Table I)(16, 17, 18). Interestingly, the serum iron and ferritin levels were within the normal range for aplastic crisis in three of the five cases, including our patient. It was believed that the transient elevation in the serum iron and ferritin levels during the aplastic crises was caused by a temporary decrease in iron demand. In addition, obvious microcytic anemia was observed in three cases, except in case 4, the sibling of case 3, who exhibited extremely mild symptoms. This finding suggests that the patients had IDA as an underlying disorder. On the other hand, it has also been reported that patients with hereditary spherocytosis may also present with microcytic anemia(19). Therefore, a differential diagnosis of the underlying diseases is required. Based on peripheral blood smear findings, blood tests, family history, and imaging studies, we considered congenital hemolytic diseases such as hereditary spherocytosis, thalassemia, sickle cell disease, and glucose-6-phosphate dehydrogenase deficiency to be negative. In fact, blood tests 6 months after discharge from the hospital showed no findings of hemolytic anemia. It is also necessary to note that iron deficiency may become apparent again after the acute phase of HPVB19 infection. In our case, IDA was caused by an extremely unbalanced diet and chronic gastrointestinal bleeding caused by juvenile polyps. There have been no reports on the association between juvenile polyps and aplastic crisis, and we believe that the juvenile polyps in the present patient were incidental findings.

In conclusion, we report a case of aplastic crisis associated with IDA. IDA results in erythroblast hyperplasia and shortened red blood cell lifespan, which may lead to an aplastic crisis during HPVB19 infection. It should be noted that iron deficiency is often masked, and microcytic anemia may be a clue for IDA.

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