Weekly long-term intravenous immunoglobulin for refractory parvovirus B19 and Epstein-Barr virus-induced immune thrombocytopenic purpura

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In pediatric acute immune thrombocytopenic purpura (ITP) cases, it is usually possible to determine an underlying pathology; among them, viral infections are the leading causative agents. In this report, we describe two cases of acute ITP complicated secondary to parvovirus B19 or Epstein-Barr virus (EBV) infections who were unresponsive to initial therapeutic measures, but who responded to long-term intravenous immunoglobulin (IVIG) treatment, given weekly for five to eight weeks.

Key words: acute immune thrombocytopenic purpura, intracranial hemorrhage, parvovirus B19, Epstein-Barr virus, long-term IVIG treatment.

Childhood acute immune thrombocytopenic purpura (ITP) is a typically benign, self-limiting illness usually occurring after an infectious disease. More than 80% of the children with acute ITP recover within six months. However, a minority of cases are complicated by intracranial hemorrhage (ICH), which is a devastating complication occurring in 0.1-1% of all children with acute ITP. When ICH complicates ITP, there is an approximately 50% mortality rate. Prevention of ICH is a principal goal of treating children with ITP[1-3]. Although parvovirus B19 is an erythrogenic virus, it may be a causative agent of various hematological diseases including aplastic and hypoplastic anemia, hemolytic anemia, and ITP, and associated with acute lymphoblastic leukemia. It was very recently reported that Ku80 autoantigen on the cell surface of B cells with CD20, T cells with CD3, and human bone marrow erythroid cells with glycophorin A or CD36 functions as a novel receptor for parvovirus B19 infection[4-8]. Epstein-Barr virus (EBV) infection is also a well-known offender of childhood ITP cases[9,10].

Standard first-line treatments for ITP include prednisone[11-15], intravenous immunoglobulin (IVIG)[14] and intravenous anti-D[16-18]. The mechanism of action of IVIG treatment is the blockage of the Fc receptors of macrophages in the spleen and inhibition of the platelet destruction. In this report, we describe two ITP patients with documented either parvovirus B19 or EBV infections who failed to respond to the first-line treatments but responded to long-term IVIG treatment, given weekly for five to eight weeks.

Case Reports

Case 1

A seven-year-old boy was admitted to our hospital with the complaints of abundant nose bleeding and blood in the urine for two days. His past medical history and family history were unremarkable. Physical examination revealed multiple petechia, purpura, and ecchymoses all over the body. He also had wet purpura in the oral mucosa. He had no organomegaly or lymphadenopathy and neurological examination was completely normal. Initial laboratory studies were as follows: hemoglobin (Hb) 9.6 g/dl, white blood cell count (WBC) $8.2x10^9$/L, platelet count $7x10^9$/L, mean corpuscular volume (MCV) 78 fl, and red cell distribution width (RDW) 12.5%. The biochemical parameters, prothrombin time (PT)

and partial thromboplastin time (PTT) were normal. Immunoglobulin levels, complement 3 (C3) and complement 4 (C4), Coombs tests, antinuclear antibody (ANA), antiDNA levels, and anticardiolipin-antiphospholipid antibodies were within normal reference range. The serology of cytomegalovirus (CMV), EBV, herpes virus, and hepatitis viruses were all negative. However, the serology of parvovirus B19 and parvovirus polymerase chain reaction (PCR) were positive. Examination of bone marrow (BM) aspiration smears showed normal cellularity with increased megakaryocytes and giant normoblasts. The diagnosis of acute ITP secondary to parvovirus B19 infection was established.

He was given 1 g/kg IVIG immediately because of the active epistaxis and wet purpura in the oral mucosa. However, he vomited twice and experienced lethargy and somnolence after the vomiting. Cranial computerized tomography revealed mild hydrocephaly and multiple hemorrhages, millimetric in size, with the largest 2x1 cm in diameter. No mid-line shift was evident. He was then transferred to the pediatric intensive care unit for further management. He was given platelet and erythrocyte transfusions. He also received mega-dose methylprednisolone (20 mg/kg/day for 4 days, followed by 10 mg/kg/day for 3 days and later tapering off the dosage). He remained stuporous approximately one week in the pediatric intensive care unit. His platelet count had only a minimal response to the IVIG and methylprednisolone therapies and only elevated from $7x10^9$/L to $26x10^9$/L within a week and decreased to a dangerous level within a very short time. Vincristine (1.5 mg/m^2/weekly) and cyclosporine (3 mg/kg/day) treatments were also tried, but his platelet counts remained low ($<10x10^9$/L). In addition to these therapies, IVIG treatment was continued for parvovirus B19 infection at a dosage of 0.5 g/kg/week for eight weeks. By the fourth week of the treatment, his platelet count reached $228x10^9$/L; his multiple petechia, purpura, ecchymoses, and the bleeding symptoms disappeared. After two months, his neurological examination was totally normal. However, the platelet count gradually decreased to $24x10^9$/L. Six months after discharge, his parvovirus PCR was negative; he remains neurologically intact and has platelet counts range between $20x10^9$/L and $119x10^9$/L. He was accepted as chronic ITP and splenectomy was suggested.

Case 2

A five-year-old boy with a chief complaint of multiple ecchymoses was admitted to our hospital. The past and family histories were unremarkable except an upper respiratory tract infection one week before that resolved without any medications. The physical examination revealed no organomegaly or lymphadenopathy; however, there were abundant petechia, purpura and ecchymoses all over the body and also a lingual hematoma. The complete blood count analysis was as follows: Hb 12.5 g/dl, WBC 8.2 $x10^9$/L, platelet count $5x10^9$/L, MCV 73 fl, and RDW 16.5%. The peripheral blood smear showed 62% neutrophils, 26% lymphocytes, and 12% monocytes and Downey cells were noticeable. The liver and renal function tests and PT, PTT were normal. Immunoglobulin levels, C3 and C4, Coombs tests, ANA, antiDNA levels, and anticardiolipin-antiphospholipid antibodies were within normal reference range. The viral serology was as follows: CMV IgM negative, CMV IgG positive; AntiHAV IgM negative, AntiHAV IgG negative; HBsAg negative, AntiHBs positive, AntiHBc total negative; and parvovirus B19 PCR negative. However, EBV EA IgG was 26.2 RU/ml, EBV VCA IgG was 70.6 RU/ml and EBV EBNA IgG was negative. Because of the very low platelet count and widespread petechia, ecchymoses and lingual hematoma, we initially applied IVIG (1 g/kg/day, for 2 days), but the platelet count showed no change on the fifth day of treatment, and BM aspiration was obtained. BM smears showed normal cellularity with increased megakaryocytes. After a diagnosis of leukemia was excluded and ITP diagnosis confirmed, we initiated mega-dose methylprednisolone (30 mg/kg/day for 3 days, followed by 20 mg/kg/day for 4 days). No significant improvement in the platelet count was observed and one week after the completion of the steroid therapy, platelet count was still $13x10^9$/L. We initiated 0.5 g/kg/week IVIG for five weeks. The initial improvement was observed by the third week and platelet count increased to $37x10^9$/L; weekly IVIG application was stopped by the fifth week when the platelet count was $95x10^9$/L. At the first month following the cessation of weekly IVIG administration, the asymptomatic patient's platelet count was $80x10^9$/L.

Discussion

Herein we report two ITP cases associated with viral infections resistant to conventional therapy who later responded to long-term weekly administered IVIG. ITP in children usually follows an acute viral illness and is thought to have an immunological basis[19,20]. Heegaard et al.[5] examined the role of parvovirus B19 in 47 children with newly diagnosed ITP, and it was demonstrated in 6 of 47 patients (13%) with PCR technique. They concluded that this virus should be considered as a possible etiologic agent in some children with ITP[5]. In a report from our center, parvovirus B19 DNA was also detected by PCR in 9 of the 19 (47%) patients with ITP[7].

The varicella virus and EBV are the most frequent pathogens among the identifiable viruses, but some studies have found them responsible for less than 10% of ITP cases[18], while Hsiao[10] reported that 35 (32.4%) of 108 children had ITP associated with acute EBV infection.

Although ICH is a rare complication, it continues to be the most important cause of morbidity and mortality in childhood ITP. In a review conducted by Butros et al.[1], the authors found 75 published cases of ICH with ITP from 1954 to 1998. Of these reported cases with ICH, 72% occurred within six months of the diagnosis, only 10% occurred within three days of the diagnosis, and most of the patients (71.4%) had platelet count less than $10x10^9$/L. The mortality rate was 55% in the report[1]. Recently, Tourneux et al.[21] reported a case of ITP and parvovirus B19 infection complicated by ICH, which was lethal seven days after the initial diagnosis. Our patient had a platelet count less than $10x10^9$/L and ICH occurred on the third day of the onset of the symptoms.

For those children with ITP and active bleeding there are a variety of treatment options, including corticosteroids, IVIG, and anti-D antibody. However, although these treatments offer a transient increase in the platelet count, none have been shown to change the course of the disease or to prevent morbidity or mortality of ITP. The goal of the treatment is to increase the platelet level to greater than $20x10^9$/L, as most ICHs occur in patients with platelets below this level[1,19,20,22].

In the present report, Case 1 initially received IVIG treatment based on the fact that he had a low platelet count and mucosal bleeding. However, when the ICH was detected, he was also treated with massive platelet transfusion and corticosteroid; vincristine and cyclosporine treatments were also added. None of those therapeutic agents was effective in increasing the platelet count up to a stable level for a reasonable period. After we extended the duration of the IVIG treatment, the platelet count had increased to $228x10^9$/L by the fourth week. Splenectomy was not recommended in the acute phase of the disease because of the risks of intraoperative bleeding, and also because the patient's ITP was in the acute phase and presented with parvovirus B19 DNA positivity. Parvovirus B19 should be routinely investigated as an etiological agent in ITP and other hematological diseases.

Case 2 was also refractory to the first-line treatments including 1 g/kg/day IVIG for two days and mega-dose methylprednisolone for one week. We achieved an increase in the platelet count with 0.5 g/kg/week IVIG for five weeks. The underlying pathology for acute ITP was found as EBV infection.

In virus-associated acute ITP cases, IVIG preference may be more rational than corticosteroids, since IVIG has an effect of blocking the virus.

The superiority of weekly IVIG application to conventional dose IVIG includes the application as outpatient and decrease in the hospitalization costs; however, the total IVIG amount is more in the weekly-applied group. The mechanism of the better outcome in the weekly-applied group may be related to a continuous blockage of the splenic Fc receptors of macrophages. However, a spontaneous recovery cannot be excluded. Based on this experience, we suggest that long-term IVIG treatment may be used routinely in ITP associated with any active viral illnesses, including parvovirus B19 and EBV, especially in the refractory cases. However, further studies are required to draw a clearer conclusion.

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