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Varicella zoster-associated severe aplastic anemia in a child and its successful treatment with peripheral blood stem cell transplantation from HLA-5/6-identical donor

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Varicella zoster virus is very rarely associated with aplastic anemia. Bone marrow transplantation from an HLA-identical sibling is the treatment of choice.

Case Report: A seven-year-old boy presented with aplastic anemia (AA) following chicken pox infection. No clinical improvement was observed with pharmaceutical therapy and peripheral blood stem cell transplantation (PBSCT) was performed from his HLA 5/6 identical mother. Since the transplantation, the patient has had a durable, trilineage hematological response for 12 months.

Conclusions: The present case with varicella zoster-associated aplastic anemia was non-responsive to conventional therapies (ATG protocol, ALG protocol, oxymethalone, and cyclosporine A) and successfully treated with bone marrow transplantation from his 5/6 identical mother.

key words: varicella zoster • aplastic anemia • transplantation

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Background

Aplastic anemia (AA) is a disorder of diverse etiology, characterized by pancytopenia together with reduced bone marrow cellularity [1]. Viral infections may be associated with varying features, changing from cytopenia to dysplasia of the hematopoietic system [2–9]. Although the involvement of many viruses of different families has been suggested in the pathogenesis of AA, the exact mechanism has yet to be elucidated [10–12]. Only a few cases of varicella-associated pancytopenia and aplastic anemia have been reported in the literature [2,3,11]. Herein we report a child who developed AA following varicella infection and in whom complete recovery was achieved after peripheral blood stem cell transplantation (PBSCT) from his HLA 5/6 identical mother.

Case Report

A seven-year-old boy was referred to our hospital with the diagnosis of acquired aplastic anemia (AA). Ten months earlier he had been admitted to a different local hospital with complaints of petechiae, ecchymoses, and hematochezia after one month of chicken pox infection. While presenting to our hospital, he had none of the previous complaints and he had been healthy. There was no history of previous contact with toxic substances or drugs or parental exposure nor exposure to environmental pollution. His father was a police officer and his mother did not work. There was no family history of autoimmune disorders, leukemias, or lymphomas. During his follow-up at the local hospital, no immunosuppressive or other therapies were employed, except for erythrocyte and platelet transfusions. Physical examination revealed skin and conjuctival paleness, and multiple petechiae and ecchymoses on his trunk and extremities. No palpable lymph nodes, hepatosplenomegaly, or pharyngitis were observed. Laboratory results included hemoglobin 8.1 g/dl, white blood cell count 3.7×10^9/l, platelets 11×10^9/l, and reticulocyte count 0.2% (Table 1). The white blood cell differential count consisted of 2% neutrophils, 90% lymphocytes, and 8% monocytes. The peripheral smear showed an increased number of mature lymphocytes. The serum levels of LDH, bilirubin, and liver enzymes were normal. The bone marrow aspirate showed a very hypocellular, fatty marrow, without evidence of hemophagocytosis or myelodysplastic features. The tests for sucrose lysis and ascite-HAM were negative, and the level of CD55 and CD59, as determined by flow cytometry, were within normal limits. The serum levels of IgG, IgA, and IgM were within the normal range. Anti-varicella zoster-specific IgG antibody titer was positive and IgM was negative. However, varicella zoster IgM was reported to have been positive following chicken pox infection at the time of initial diagnosis of AA at the referring hospital. The serological tests for hepatitis A, B, and C, parvovirus, CMV, and EBV were negative or consistent with previous exposure (Table 1).

The patient was given antilymphocyte globuline (ALG) (10 mg/kg/day for 5 days), methylprednisolone (5 mg/kg/day, to be tapered in 1 month), and cyclosporine A (5 mg/kg/day for 6 months). A second course of therapy was administered with the substitution of antithymocyte globuline (ATG) (5 mg/kg/day for 5 days) for ALG due to a lack of response after initial therapy. Oxymethalon and cyclosporine therapy was then administered for six months as a third course of therapy, but again no response was noted. During a follow-up period of 15 months, the patient gradually needed more frequent red blood cell and platelet transfusions. He then underwent CD34-selected peripheral blood stem cell transplantation (PBSCT) from his HLA 5/6 identical mother. The conditioning regimen consisted of Fludarabine, cyclophosphamide, and total body irradiation (450 cGy). Low-dose methotrexate was given for graft-versus-host disease (GVHD) prophylaxis. The patient did not develop GVHD. Hematopoietic chimerism studies showed 62% donor origin five months after transplantation. Since PBSCT was employed, the patient has had a durable trilineage hematological response for 12 months (Hb: 14.1 g/dl, WBC: 6.8×10^9/l, ANC: 4×10^9/l, platelets: 286×10^9/l).

Discussion

Since the patient was healthy before infection, the occurrence of AA may probably have been related to varicella virus infection. AA is caused by several diverse factors, including absence or defect of hematopoetic stem cells, immune abnormalities, and disorders of the bone marrow microenvironment [1]. Several features and clinical associations of AA suggest an etiological role of viral infection. A number of specific viral agents have been linked to bone marrow failure or suppression, of which hepatitis B and Epstein-Barr viruses are the principle known agents [4,12]. Parvovirus B19 infection has occasionally been reported in patients with AA [4–6,10]. However, the causal relationship between viral infections and AA is not well documented. The role of viruses in the pathogenesis of AA has not been fully elucidated, but they are known to infect human bone marrow cells and may cause damage either by directly killing cells or by an indirect immune mechanism [1]. However, varicella has rarely been accused in the development of AA [2,3,11,13,14]. Varicella-associated hematological complications are unusual, albeit some cases of immune thrombocytopenia and disseminated intravascular coagulation have been reported [3]. Four cases of varicella-associated AA have been observed in which recovery occurred in four weeks and three months, respectively [2,3,11,13,14]. One of these patients had suffered from coexisting microfilaremia of *Wuchereria bancrofti* [2].

Despite great advances in clinical and experimental hematology, definitive assignment of an etiological agent for AA is usually difficult, and most cases are attributed to an idiopathic origin [1]. In our case, varicella infection may be considered as the triggering event of AA since serological tests for other viral infections known to be responsible for AA were negative or were consistent with previous exposure, and all other investigations failed to determine an underlying cause.

Conclusions

Currently, bone marrow transplantation is the treatment of choice for patients with severe AA who have HLA-matched donors [1]. Our case did not respond to conventional therapies, including ATG and ALG protocols, oxymethalon, and cyclosporine A. To the best of our knowledge, we report the first case of varicella-associated AA that underwent PBSCT. Fortunately, the patient experienced an uneventful transplant course and remains in full hematolog-

Table 1. Laboratory features of the patient.

WBC	3700/µl	EBV EBNA IgM	Negative
ANC	74/µl		
Hemoglobin*	8.1 g/dl	EBV EBNA IgG	Positive
Platelet	11,000/µl	EBV VCA IgM	Negative
Peripheral smear	Increased number of mature lymphocytes	EBV VCA IgG	Positive
The bone marrow aspirate	Very hypocellular, fatty marrow without evidence of hemophagocytosis or myelodysplastic feature	EBV EA	Negative
ALT	9 U/l (N: 5–40)	HSV I IgM	Negative
AST	10 U/l (N: 8–33)	HSV I IgG	Positive
Total bilirubin	0.35 mg/dl	HSV II IgM	Negative
Direct bilirubin	0.06 mg/dl	HSV II IgG	Negative
LDH	327	CMV IgM	Negative
Sucrose lysis	Negative	CMV IgG	Positive
Ascite-HAM	Negative	Parvovirus PCR	Negative
CD 55	Normal	Varicella IgM	Negative
CD 59	Normal	Varicella IgG	Positive
Vitamin B12	Normal	HBsAg	Negative
Folic acid	Normal	Anti-HBs	Positive
IgA	150	HBeAg	Negative
IgG	1160	Anti-HBe	Negative
IgM	101	Anti-HBc IgM	Negative
Chromosomal breakage studies	Normal	Anti-HbC total	Negative
		Anti HAV IgM	Negative
		Anti HAV IgG	Negative

* Following erythrocyte transfusion at another hospital.
WBC – white blood cells; ANC – absolute neutrophil count; ALT – alanine aminotransferase; AST – aspartate aminotransferase; LDH – lactate dehydrogenase; IgA – immunoglobulin A; IgG – immunoglobulin G; IgM – immunoglobulin M; EBV – Epstein-Barr virus; HSV I – herpes simplex virus type I; HSV II – herpes simplex virus type II; CMV – cytomegalovirus; HBs – hepatitis B virus surface antigen; HBe – hepatitis B early antigen; HBc – hepatitis B core antigen; HAV – hepatitis A virus.

ical response, in spite of the underlying risks consisting of mismatched transplant and a multiple transfusion history with allosensitization.

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