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Received 28 July 1992.
Accepted 22 December 1992.

#1628

0041-1337/93/5604-0835$03.00/0
TRANSPLANTATION

Vol. 56, 835–838, No. 4, October 1993
Printed in U.S.A.

PARVOVIRUS B19 INFECTION IN PEDIATRIC TRANSPLANT PATIENTS

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Evidence of recent parvovirus virus infection (as determined by the presence of a positive IgM antibody titer) without other identified causes of anemia was found in 5 of 26 pediatric solid-organ transplant recipients evaluated for moderate-to-severe anemia between June 1990 and July 1991. Anemia tended to be chronic (median duration of anemia at the time of diagnosis was 12 weeks) and was associated with normal red blood cell indices in the absence of reticulocytes. The median age of the children at the time of presentation with anemia due to parvovirus was 1.8 years at a median time of 8 months after transplantation. Four of the 5 children were treated with i.v. immunoglobulin because of persistance of anemia requiring blood transfusions. A response characterized by an increase in reticulocyte count and normalization of hemoglobin was seen in each of these patients 2–4 weeks after treatment. The remaining patient experienced a spontaneous recovery from her anemia. Parvovirus infection should be included in the differential diagnosis of solid-organ transplant recipients presenting with severe anemia associated with low or absent reticulocytes.

Human parvovirus B19 has been identified as the cause of erythema infectiosum (Fifth's Disease) in children (*1–3*). Infection with this virus has resulted in the development of red cell aplasia in patients with underlying hemolytic anemias (including sickle cell disease, hemoglobin SC disease, hereditary spherocytosis, thalassemia, pyruvate kinase deficiency, and acquired hemolytic anaemia) (*4–10*). Persistent anemia associated with chronic parvovirus B19 infection has been reported in the absence of pre-existing hemolytic tendencies in immunocompromised patients including those with acute leukemia, congenital immunodeficiencies, and HIV infection and in recipients of bone marrow transplantation (*11–20*). This report documents our experience in 5 pediatric solid-organ transplant recipients with severe anemia associated with active parvovirus B19 infection.

MATERIALS AND METHODS

Between June 1990 and July 1991, 26 children who had received solid organ transplants at the Children's Hospital of Pittsburgh were investigated for the etiology of moderate-to-severe anemia. The evaluation included a complete blood count, reticulocyte count, haptoglobin and free hemoglobin level, iron studies (serum iron, total iron binding capacity, and saturation), serum folate and B12 levels, stool hematest, and measurement of blood urea nitrogen and serum creatinine. Additionally, all patients had serologic studies performed for the presence of antibody against CMV, EBV, and parvovirus B19. Some of the patients also underwent bone marrow aspiration.

All patients were immunosuppressed in a standardized fashion with either a combination of CsA, steroids, and AZA (*21*) or FK-506 (*21*).

IgG and IgM antibodies against parvovirus B19 were determined by a commercial laboratory (Specialty Laboratories, Inc., Santa Monica, CA) utilizing Western blot analysis in all but 2 of the patients who were evaluated by enzyme immune assay (Nichols Institute Reference Laboratory, San Juan Capistrano, CA). A positive IgG titer was considered to be additional support for this diagnosis. Patients who had a positive IgG titer in the absence of IgM were considered to have past infection and were not included.

RESULTS

Five of 26 patients (23 liver and 3 heart transplant recipients) evaluated for anemia were found to have serologic evidence of recent parvovirus B19 infection without other identified causes of anemia. IgM antibody studies were negative in the remaining

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21 children undergoing evaluation. Four of the 5 patients were positive for both IgM and IgG at the time of evaluation. Patient 4 was initially positive for IgM only but on follow-up testing 2 months later was found to be seropositive for IgG and negative for IgM. Table 1 outlines the clinical course and outcome of these children. The median age of the children at the time of presentation with anemia due to parvovirus was 1.8 years (range of 1.4 to 4.7 years). The median time that anemia was first noted after transplantation was 8 months (range of 2 to 34 months). The median duration of anemia at the time of diagnosis was 12 weeks (range of 4 to 14 weeks).

The clinical presentation of parvovirus B19 was limited to severe anemia associated with reticulocytopenia in 4 of the 5 patients. Patient 1 presented with a typical rash of erythema infectiosum.

None of the 5 patients had any history of an underlying hemolytic anemia. All had normal RBC indices with slight hypochromia and anisocytosis without hemolysis on evaluation of peripheral blood smears. Reticulocytes were absent despite severe anemia in 4 of the 5 children; the remaining child had a reticulocyte count of less than 1%. White blood cell counts were decreased in 2 of the patients; patient 4 had an absolute neutrophil count of 520 cells/mm^3 during his admission with fever and croup. Platelet counts, as well as serum levels of erythropoietin, haptoglobin, iron, TIBC, folate, and B12, were normal in all cases. Bone marrow biopsies performed on 3 children revealed erythroid hypoplasia. One of the 3 biopsies was available for retrospective review and revealed the presence of pronormoblasts.

All of the children were initially treated unsuccessfully with iron. Four children required one or more blood transfusions; patient 1 received a total of 11 transfusions during her illness. Patient 3 was unique in that anemia and areticulocytosis appeared to be self-limited. Both her hemoglobin and reticulocyte count were recovering by the time the results of her serologies became available. All of the remaining children were treated with i.v. immunoglobulin (IVIG)* (see Table 1). A response characterized by an increase in reticulocyte counts and normalization of hemoglobin and hematocrit levels was seen in each of the treated patients between 2 and 4 weeks after treatment. Long-term recovery from anemia has been sustained in these patients (follow-up greater than 1 year).

DISCUSSION

Human parvovirus B19 was initially discovered in 1975 and was recognized as the primary etiologic agent of erythema infectiosum (Fifth disease) in 1980 (*1*). The recent availability of serologic tests for and the ability to detect DNA of parvovirus B19 has led to the recognition of an expanding spectrum of clinical disease associated with infection by this virus. The clinical manifestations of parvovirus B19 infection appear to vary according to underlying host factors. Its propensity to infect and lyse red cell progenitors explains the development of red cell aplasia in patients with shortened red cell life spans. Chronic parvovirus B19 infection has led to red cell aplasia in immunocompromised patients in the absence of underlying hemolytic anemia (*11–20*). This has been reported in a child

* Abbreviations: IVIG, i.v. immunoglobin.

TABLE 1. General description of pediatric transplant recipients with parvovirus B-19 infection

Patient	Age (yr)	Sex	Type TX	Immune suppression	Onset of anemia after TX (mo)	Lowest Hgb (gm/dl)	Reticulocyte count	Signs & symptoms	Duration of anemia prior to treatment (wk)	Treatment	Outcome
1	1.8	F	Liver	FK-506	2	4.6	0	Erythema infectiosum	14	Iron & folic acid IVIG 1 gm/kg × 3 days	Hb normalized with good retic count 4 wk after IVIG
2	4.7	F	Liver	CyA	34	7.3	0.4	None	12	IVIG 400 mg/kg × 10 days; repeat every 2 wk for 6 mo	Hb normalized with good retic count 2 wk after IVIG
3	1.8	F	Heart	FK-506	8	5.4	0	None	N/A	Iron, erythropoetin	Hb improved with good retic count within 4 wk of diagnosis without treatment
4	1.4	M	Liver	FK-506	6	6.9	0	Fever, stridor	10	Iron IVIG 400 mg/kg × 5 days, GCSF	Hb improved with good retic count 4 wk after IVIG
5	1.4	M	Liver	FK-506	8	7.0	0.8	None	12	Iron IVIG 400 mg/kg × 5 days	Hb improved with good retic count within 2 wk of IVIG

with Nezelof's syndrome (*11*), in patients with leukemia or cancer receiving maintenance chemotherapy (*13–16*), bone-marrow transplant recipients (*17*), and in patients infected with HIV (*18–19*). Children undergoing solid-organ transplantation are also at risk of red cell aplasia due to parvovirus B19 infection.

The observation that a parvovirus induced red cell aplasia crisis can occur in pediatric solid-organ transplant recipients has important implications. Seroprevalence studies have estimated that 30–70% of all adults show serologic evidence of past infection. Antibody is most commonly acquired between 5 and 15 years of age (*2*). Therefore, young children who have undergone solid-organ transplantation seem likely to experience infection with parvovirus B19 while receiving chronic immunosuppressive therapy. Since the reports to date suggest that red-cell aplasia is seen in patients experiencing primary infection, these young (and presumably seronegative) transplant recipients may be at a relatively high risk of developing this complication.

The actual incidence of parvovirus B19–associated anemia in pediatric solid-organ transplant recipients is unknown. Anemia is a relatively common occurrence in these patients, and the systematic work-up for this problem may vary from one transplant center to another. Recognition of parvovirus B19 as a potential etiology in patients with chronic anemia prompted our evaluation of these children. Several reports have documented the presence of parvovirus DNA in serum of patients in the absence of detectable antibody (*14, 16, 19, 20*). This suggests that the diagnosis may be missed (especially in an immunosuppressed population) if only antibody levels are measured. Therefore, several investigators have suggested the use of polymerase chain reaction, dot-blot hybridization, or other assays to look for direct evidence of the virus rather than relying on host immune response for diagnosis (*18, 19*).

Some authors have suggested that the diagnosis of parvovirus B19 can has also be made by evaluation of bone marrow specimens. Infection is suggested by the presence of giant pronormoblasts on bone marrow smears (*12*) or electron micrographs (*22*). The finding of a readily identifiable intranuclear inclusion limited to erythroid line cells on air-dried, formalin-fixed bone marrow smears stained with hematoxylin-eosin or Wright-Giemsa has been suggested as a rapid and sensitive method of identifying parvovirus B19 infection (*23*). This finding was found retrospectively in the only bone marrow biopsy available for review from these patients. The utility of this finding as a screen for parvovirus infection in organ-transplant recipients remains to be validated.

Infection in immunologically normal individuals results in a relatively short period of viremia followed by the production of specific neutralizing antibodies resulting in protection of erythroid progenitor cells and clearance of infection (*24*). Persistence of infection has been noted in the absence of an adequate antibody response (*18*), placing immunosuppressed patients (including transplant recipients) at risk for chronic infection. The chronicity and severity of anemia in immunodeficient patients may in part be due to the presence of chronic infection with persistent lysis of erythrocyte progenitors in the bone marrow in combination with the normal destruction of peripheral red blood cells with aging (*16*).

All of our patients presented with severe anemia. IVIG (0.4 g/kg for 5 days) has been suggested for immunosuppressed patients with chronic anemia caused by parvovirus based upon laboratory and anecdotal clinical experience (*12–14, 18–20, 25*). Four patients were treated with varying regimens of IVIG; all had an apparent clinical response shortly after completion of their therapy. Although the lack of a controlled study evaluating the use of IVIG for these patients raises doubt as to whether the observed clinical response might have occurred spontaneously, the coincidental timing of the clinical response to IVIG treatment in our patients (and in the literature) suggests the likely efficacy of this treatment.

Patient 3 was unique in that she did not require blood transfusion and she experienced a spontaneous recovery of her bone marrow beginning 4 weeks after initial presentation. Her clinical course illustrates the potential variability in the effects of parvovirus infections in transplant recipients with recognized anemia. IVIG therapy may only be necessary in those patients with evidence of chronic infection requiring one or more blood transfusions.

Parvovirus infection should be included in the differential diagnosis of solid-organ transplant recipients presenting with severe anemia and low or absent reticulocytes. While specific antiviral therapy is not currently available and some patients may spontaneously recover, IVIG does appear to be efficacious and safe. Further studies on parvovirus prevalence, spectrum of disease, and role of treatment with IVIG in this population of children are warranted.

Acknowledgments. We thank Dr. Ellen Wald for her thoughtful review of the manuscript.

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Received 13 October 1992.
Accepted 5 January 1993.

0041-1337/93/5604-0838$03.00/0
TRANSPLANTATION

Vol. 56, 838–842, No. 4, October 1993
Printed in U.S.A.

FATE OF RENAL ALLOGRAFTS TRANSPLANTED IN PATIENTS WITH URINARY DIVERSION

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Fifty-five kidneys were transplanted into 50 patients with supravesical urinary diversion at 16 transplant centers between 1970 and 1991. Of the 32 males and 18 females, 40 were adults (≥18 years) and 10 were less than 18 years old at the time of first transplant. Mean follow-up was 7.8 years. At last follow-up, 94% of recipients were alive and 73% of the kidneys were functioning. Fifteen kidneys were lost: 9 to rejection, 3 to noncompliance, and 3 patients died with a functioning kidney. Ten (18%) transplants were followed by surgical complications. Twenty-four (44%) were followed by medical complications of which urinary tract infection was most common. Recipients age 18 or younger had more urinary tract infections than older patients. No patient had urinary stones and no patient required medical treatment for metabolic abnormalities. We conclude that drainage of kidney transplants into a supravesical urinary diversion is an effective treatment for end-stage renal disease patients without adequate urinary bladders.

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In 1966 Kelly, Merkel, and Markland (*1*) first reported the use of intestinal conduits for drainage of transplant kidneys. In their pioneering series of 8 kidneys transplanted into 7 patients, half were functioning at up to 10 months follow-up. Three of 7 patients died of sepsis in the perioperative period and 1 patient had a small bowel obstruction. In the 1970s, reports of long-term follow-up of patients with ileal conduit urinary diversion documented an increased risk of stomal stenosis, acute and chronic pyelonephritis, renal scarring, renal failure, calculi, and metabolic alterations in patients with urinary diversion (*2*). Despite concerns about complications,