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Chronic Rotavirus Infection in an Infant with Severe Combined Immunodeficiency: Successful Treatment by Hematopoietic Stem Cell Transplantation

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Kobrynski et al. [1] showed gastrointestinal complaints in children can be an early sign of primary immunodeficiency disease (PIDD). Rotavirus infection associated with PIDD can be life-threatening. Rotavirus is a leading cause of childhood gastrointestinal disease worldwide [2]. Most rotavirus disease is caused by 5 G types (G1-G4 and G9) and 3 P types (P1A[8], P1B[4], and P2A[6]) [2]. Two live oral rotavirus vaccines, RotaTeq® (5 different human-bovine reassortant rotavirus strains; Merck and Co, Whitehouse Station, NJ) and Rotarix® (1 human rotavirus strain; GlaxoSmithKline, Rixensart, Belgium) are recommended for routine immunization of US infants [2]. Disease caused by emerging worldwide rotavirus type, G9P[8] may be prevented by both vaccines although this strain is not included in either vaccine.

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Conflict of interest
All listed authors for this study have no conflicts of interest.

Severe combined immunodeficiency (SCID) is characterized by lack of T cells and life-threatening infections [3]. Treatment of viral infections prior to hematopoietic stem cell transplantation (HSCT) with intravenous immunoglobulin (IVIG) and antivirals has been attempted, but persistence of viral disease has been reported [3–8]. We report a 7 month-old male infant with SCID who had persistent, nonvaccine-associated rotavirus gastroenteritis and viremia despite oral and IVIG administration. T-cell engraftment following HSCT possibly helped by oral and IVIG was necessary to eliminate rotavirus infection.

The full-term, formula-fed infant received RotaTeq at 2 and 4 months of age. The patient developed chronic intermittent diarrhea at 2 months of age and was hospitalized at 7 months of age with respiratory distress, diarrhea, and failure to thrive. A peripheral white blood cell count was 16,140 cells/μl with 59% neutrophils, 17% lymphocytes (absolute lymphocyte count=2743cells/μl [normal range 3,900–9,000]), 7% monocytes, and 13% eosinophils. Bronchoscopy aspirate revealed *Pneumocystis jiroveci*. Stool for rotavirus was positive by electron microscopy (EM). Immunoglobulins were very low including IgG 77 mg/dL (normal range 184–974 mg/dL), IgA <6 mg/dL (normal range 9–107 mg/dL), and IgM 36 mg/dL (normal range 41–197 mg/dL). The $CD3^+$T cells were severely low (32 cells/mm^3, normal range 1919–5054 cells/mm^3), $CD19^+$B cells were elevated (2715 cells/mm^3, normal range 566–2535 cells/mm^3), and $CD3^-CD56^+CD16^+$NK cells were low (28 cells/mm^3, normal range 181–901 cells/mm^3). T-cell proliferation to mitogens was markedly depressed. A hemizygous mutation (nucleotide substitution A for G at position 1451 in the polyA tail region) was present in the common gamma chain of interleukin-2 receptor consistent with X-linked SCID. Multipe doses of IVIG (Gamunex®, Talecris) were given before and after transplantation, including two doses of 300 mg/kg administered orally at 8 months of age (Fig. 1). Molecular analysis of stool and serum specimens identified a non-vaccine associated human rotavirus strain G9P[8]. The patient received a 10/10 matched unrelated donor unfractionated HSCT with pretransplant myeloablative conditioning at 9.5 months of age. Rotavirus-positive diarrhea persisted until 2 months post transplant (age 11.5 months), coincident with T-cell engraftment (Fig. 1). The patient, last tested at 14.5 months of age, had no detectable rotavirus.

Reverse transcriptase polymerase chain reaction (RT-PCR) using rotavirus gene 9 and gene 4 primer sets resulted in cDNA products from stool and serum samples. Homology of gene 9 and gene 4 amplicon sequences to GenBank database sequences confirmed the patient's stools contained rotavirus strain G9P[8]. There was 98% nucleotide homology between the stool rotavirus gene 4 sequence, which comprised 51% of the 2328 nt ORF, and two fully-sequenced P[8] rotaviruses but no significant homology with a partial RotaTeq vaccine gene 4 sequence. There was 98% nucleotide homology between the stool rotavirus gene 9 sequence, which comprised 85% of the 978 nt ORF, and two fully-sequenced G9 rotaviruses. There was a single nucleotide change in gene 9 (residue 595 C→T, resulting in a silent mutation) between two stools obtained 74 days apart. There was no change in gene 4 sequence between stools obtained 54 days apart.

Neutralizing antibodies to rotavirus G9 were present in the orally administered immunoglobulin product at a concentration of 1:1600. Neutralizing antibodies to serotypes G1(WA, 1:800; K8, 1:1600) and G3 (SA11, 1:3200) were present at similar concentrations.

$CD3^+$T cells were very low (32 cells/ml, normal range 2500–6500 cells/ml) prior to transplantation (Fig. 1). Rotavirus became undetectable by EM two months post transplantation with $CD3^+$, $CD4^+$, and $CD8^+$T-cell engraftment as shown by return of lymphocytes by 65 days post transplantation ($CD3^+$T cells=138/mm^3 at 2 months post transplantation). T-cell proliferation, as assessed by response to mitogens, was <3% of normal range and became present at five months post transplantation (data not shown).

Chimerism analysis showed presence of donor T cells (100%) and absence of donor B cells (0%) at two and seven months post transplantation.

1. Discussion

We report a SCID infant with persistent rotavirus infection for whom HSCT resulted in T-cell engraftment and clearance of rotavirus despite absent donor B cells. Prior to transplantation, rotavirus infection persisted despite oral administration of immunoglobulin containing neutralizing antibodies to G9 serotype. The presence of neutralizing antibodies to G9 serotype in immunoglobulin preparations suggests exposure to G9 rotavirus serotype among the donor pool, or cross-reactivity among antibodies of rotavirus serotypes other than G9. Oral administration of immunoglobulin for treatment of rotavirus gastroenteritis has been reported with some success [9,10].

Lessons to be learned from this case are 1) gastrointestinal problems can be a presenting sign of PIDD as shown by Kobrynski et al. [1], 2) clearance of rotavirus was associated with T-cell engraftment and function, 3) oral IG despite containing neutralizing antibodies to G9, and IVIG prior to transplant did not eliminate infection, 4) rotavirus infection was associated with an emerging serotype, and 5) rotavirus infection did not arise from the vaccine possibly due to protection from maternal antibody.

In summary, this case highlights that T-cell engraftment and function appear to have been necessary for clearance of rotavirus and that oral IG, despite containing neutralizing antibodies to G9, and IVIG, did not eliminate the chronic infection prior to transplant. Secondly, rotavirus infection was associated with emerging serotype G9, so protective maternal antibody may not have been present, making this infant particularly vulnerable to this strain. Infection did not arise from the live rotavirus vaccine, however, possibly due to protection from maternal antibody.

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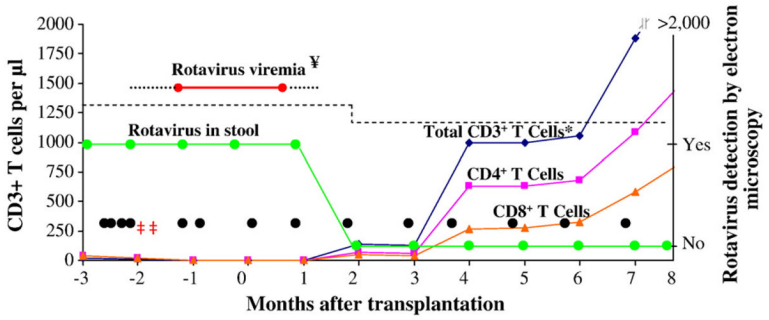

Figure 1.

The detection of rotavirus in relation to the presence of $CD3^+$,$CD4^+$, and $CD8^+$T-cell quantification before and after bone marrow transplantation. *=$CD3^+$T cells were 100% donor origin calculated by short tandem repeat studies; ¥=Several serum samples were positive for rotavirus by RT-PCR prior to transplantation; ‡‡=Oral IG administered in 2 separate doses; • =IVIG dose; (·····)=negative rotavirus viremia. The 10th percentile normal values for age for $CD3^+$T cells is represented by (– – – – – –) [11].