Cytomegalovirus-associated Immune Thrombocytopenic Purpura After Liver Transplantation

Shu-Hao Wei, Ming-Chih Ho, Yen-Hsuan Ni, Dong-Tsamn Lin, Po-Huang Lee

Immune thrombocytopenic purpura (ITP) is a rare complication after liver transplantation. Infection with cytomegalovirus (CMV) is a frequent complication of organ transplantation and may induce autoimmune diseases, such as ITP. We report a case of ITP after primary CMV infection in a 3-year-old boy recipient of living-related orthotopic liver transplantation (OLT). The ITP developed 2 years after OLT in this patient who had received tacrolimus as an immunosuppressive agent, with nadir platelet counts of 5000/mm³ in 2 weeks. The patient was treated with two courses of intravenous gamma globulin (1 g/kg/day for 2 days) and subsequent oral prednisolone (1.3 mg/kg/day for 2 weeks). He recovered from thrombocytopenia 4 weeks later. An inadequate immunosuppression, as evident by the low serum tacrolimus level (5.8 ng/mL before the episode of ITP) in this patient, may allow the development of ITP after CMV infection. [J Formos Med Assoc 2007;106(4):327–329]

Key Words: cytomegalovirus infection, immune thrombocytopenic purpura, liver transplantation, tacrolimus

Immune thrombocytopenic purpura (ITP) was previously known as idiopathic thrombocytopenic purpura. The etiology of so-called “idiopathic” thrombocytopenic purpura is usually unknown. However, some viral infections are possible culprits. Viral infection can induce autoimmune diseases including ITP. Probably most acute and/or chronic ITP may be immunologically caused by molecular mimicry, and antibodies formed in response to viral infection may cross-react with antigens naturally present on platelets. Infection with cytomegalovirus (CMV) is a frequent complication of organ transplantation. CMV-related ITP is rarely reported in transplanted children, who are usually under immunosuppressive therapy and supposed to be free from such diseases.

In this report, the possible mechanism in a 3-year-old boy recipient of liver transplantation after primary CMV infection complicated with ITP was explored. This case may highlight that relatively immunosuppressed patients are still susceptible to immune-mediated diseases.

Case Report

This 3-year-old boy was diagnosed with biliary atresia 2 months after birth. He underwent Kasai operation at 67 days of age. However, liver function deteriorated progressively in subsequent follow-ups. He underwent living-related liver transplantation at the age of 11 months and the
donor was his mother. Serum CMV IgM and IgG antibodies of the donor were both negative while serum Epstein-Barr virus (EBV) IgM and IgG antibodies of the donor were negative and positive, respectively. CMV and EBV serologic tests of the recipient before transplantation were all negative. He had received blood transfusion during operation of liver transplantation, and serum CMV IgM antibody 2 weeks after liver transplantation was negative. One rejection episode was diagnosed 15 days after transplantation. Steroid pulse therapy was given and his condition was stable. He received long-term tacrolimus after liver transplantation. He was hospitalized due to suspicion of post-transplantation lymphoproliferative disorder 1.5 years after transplantation and the dosage of tacrolimus was adjusted later. Serum CMV IgM antibody turned positive at this admission. The serial CMV serology data are summarized in the Table. Before the episode of ITP, the dose of tacrolimus was 0.5 mg/day and the latest serum level of tacrolimus was 5.8 ng/mL.

He had multiple petechiae and ecchymosis 2 years after transplantation. Intermittent cough and rhinorrhea were only noted for 1 month before hospitalization. Thrombocytopenia (platelet count 5000/μL) was found. Blood smear showed giant platelets. Serum CMV IgM antibody was positive while EBV serologic test was negative. Intravenous immunoglobulin (IVIG) (1 g/kg/day) was given for 2 days. The platelet count was 277,000/μL after the second dose of IVIG. Unfortunately, petechiae recurred 20 days later after first ITP. Blood examination showed platelet count 7000/μL, and CMV and EBV serologic tests revealed the same results as previously. IVIG (1 g/kg/day) was given again plus prednisolone (1.3 mg/kg/day) for 2 weeks. The platelet count elevated to 72,000/μL. Regular follow-up for 6 months showed no more thrombocytopenia. The clinical course is summarized in the Figure.

**Discussion**

In general, childhood acute ITP is considered to be associated with a viral infection. Some viruses, such as HIV, CMV, EBV, varicella, herpes

<table>
<thead>
<tr>
<th>Days post-OLT</th>
<th>Before OLT*</th>
<th>15</th>
<th>550</th>
<th>820</th>
<th>845</th>
<th>900</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV IgM</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Equivocal</td>
</tr>
<tr>
<td>CMV IgG</td>
<td>1:64+</td>
<td>1:128+</td>
<td>1:128+</td>
<td>1:32+</td>
<td></td>
<td></td>
</tr>
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*Before OLT: CMV IgM antibody of both donor and recipient are negative. CMV = cytomegalovirus; OLT = orthotopic liver transplantation.*
simplex, rubella, measles, parvovirus, influenza A, and hepatitis C, have been identified as causes of immune-mediated thrombocytopenia. Two-thirds of children with acute ITP have a history of an infectious illness a few days to a few weeks before the onset of thrombocytopenia and 13.3% have documented acute viral infection.

Molecular mimicry between viral antigens and host proteins has been implicated in the pathogenesis of ITP. ITP is an immune-mediated syndrome with autoantibodies against platelets. Patients with liver transplantation are under immunosuppressive therapy and have relatively low immunoreactive level. How does ITP, an autoimmune disease, occur in a patient with liver transplantation under immunosuppressive therapy?

We found in the literature that some of these post-transplantation children with acute ITP had viral infection. One previous report showed that ITP developed in three patients 1 day, 3 months, and 13 months, respectively, after transplantation in 266 biliary atresia patients who received orthotopic liver transplantation (OLT); all were treated with IVIG with a transient recovery of thrombocytopenia in two cases and a sustained recovery in the other. Among the three ITP cases, one had CMV infection and positive CMV antibody, another was not checked, and the other was negative for CMV. Besides CMV, other viruses including human parvovirus B19 and herpes zoster virus might relate to ITP after transplantation. These viruses play some roles in stimulation of immunity that cross-reacts with platelets and cause ITP in these post-transplantation children.

A recent study reported eight cases of new-onset ITP among 1105 liver transplantation recipients (incidence of 0.7%) over a 15-year period at a single center. There were no positive studies of EBV- and CMV-associated ITP in these eight adult cases.

Patients with liver transplantation under immunosuppressive therapy have relatively low immunoreactivity. CMV infection is more frequent in children, with post-transplantation and long-term use of immunosuppressive agents, than a normal population. CMV is an immunostimulatory agent and has potential to induce autoimmune disease. Due to the low serum tacrolimus level, immunity in our patient was not suppressed. CMV infection in this patient triggered immune response to subsequent immune reactivity to platelet surface antigens, which then induced ITP. Hence, immunosuppressed patients can still develop an immune-mediated disease, albeit rarely.

We believe that this case should highlight the potential for CMV infection in children after OLT to induce immune-mediated disease, including ITP. Further study to elucidate the mechanisms of viral-mediated immunologic disease in recipients of transplantation with immunosuppressive agents is laudatory.

References