ABO 일치 간 이식 후 발생한 Evans syndrome 증례보고

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Use of Splenectomy to Treat Evans Syndrome Following an ABO-Matched Liver Transplant

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INTRODUCTION

Evans syndrome is a rare complication that develops in adults after liver transplantation. The possible etiologies include ABO mismatch, viral infection, post-transplantation lymphoproliferative disease, graft-versus-host disease, and the use of certain immunosuppressive drugs (e.g., calcineurin inhibitors). Here, we present a case of Evans syndrome that developed after an ABO-matched liver transplant. Glucocorticosteroid, intravenous immunoglobulin, and alternative immunosuppressant therapies all failed. Weekly rituximab (375 mg/m²) was then administered for 4 weeks. The cytopenia improved transiently after the second dose of rituximab, but soon worsened again. However, the cytopenia normalized after a splenectomy. (Korean J Med 2015;88:464-468)

Keywords: Autoimmune hemolytic anemia; Idiopathic thrombocytopenic purpura; Liver transplantation; Splenectomy

Evans syndrome (ES) comprises the triad of autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), and a positive direct antiglobulin test in the absence of any known underlying etiology. ES is a chronic disease that presents with frequent exacerbations and remissions [1]. ES following solid organ transplantation is a rare complication, with only a few reported cases [2-7]. First-line ES therapy consists of corticosteroids and intravenous immunoglobulin (IVIG). Immunosuppressants, rituximab, splenectomy, and chemotherapy can also be administered when ES is refractory to first-line therapy [1].

Here, we report a case of ES that developed in an ABO-matched liver transplant patient who was treated successfully with a splenectomy after failing to respond to steroids, IVIG, changes in the immunosuppressant therapy, or rituximab.
CASE REPORT

A 51-year-old man visited our emergency room with a 3-day history of nausea, vomiting, general weakness, and dyspnea, but no abdominal pain. Six months prior, he had received a liver transplant from an ABO-matched donor because of hepatitis B and hepatocellular carcinoma, and he was receiving immunosuppressive therapy with mycophenolate mofetil 250 mg bid and tacrolimus 8 mg od. He had been diagnosed with diabetes mellitus 1 year earlier and treated with diet therapy. Tachycardia and pale conjunctivae were noted, but neither cardiac murmur nor abnormal breath sounds were observed. There was no abdominal tenderness, rebound tenderness, palpable masses, palpable lymph nodes, or hepatosplenomegaly. Laboratory testing revealed severe anemia, thrombocytopenia, and hyperbilirubinemia: white blood cells, 4,400/mm\(^3\); hemoglobin (Hb), 5.8 g/dL; hematocrit, 17.5%; platelets (PLT), 6,000/mm\(^3\); aspartate transaminase, 48 IU/L; alanine transaminase, 36 IU/L; alkaline phosphatase, 96 IU/L; total bilirubin, 8.5 mg/dL; direct bilirubin, 4.1 mg/dL; lactate dehydrogenase (LDH), 484 (normal 120-250) IU/L; blood urea nitrate, 29 mg/dL; and creatinine, 1.11 mg/dL. Serum levels of tacrolimus and mycophenolate mofetil were 4.5 ng/mL and 0.2 μg/mL, respectively. There were no significant findings upon chest or abdominal X-ray. Abdominal computed tomography revealed a small amount of ascites, but other findings were normal for the post-transplant state.

An anemia work-up revealed autoimmune hemolytic anemia with the following characteristics: reticulocyte count, 22.31%; reticulocyte product index, 2.58; iron, 251 μg/dL; total iron-binding capacity, 274 μg/dL; ferritin, 874 ng/mL; haptoglobin, < 7.6 mg/dL; and plasma hemoglobin, 16.6 mg/dL. A peripheral blood smear indicated pancytopenia and red blood cell (RBC) agglutination (Fig. 1). The Coombs’ test was IgG- and C3d-positive. A bone marrow biopsy revealed erythroid and megakaryocytic hyperplasia (Fig. 2). The serum Ebstein-Barr virus (EBV) polymerase chain reaction assay was positive with a measured titer of 1,746 copies/mL. The patient was PCR-negative for other viruses, including cytomegalovirus (CMV) and parvovirus.

Treatment began with 1 mg/kg methylprednisolone, but no cytopenic response was noted 4 days later. The Hb and PLT levels were 6.6 g/dL and 6,000/mm\(^3\), respectively. The reticulocyte count, haptoglobin, and LDH were 23.35%, < 7.6 mg/dL, and 490 IU/L, respectively. A dose of 0.5 g/kg/day IVIG was then given for 4 days, but the cytopenia remained. The EBV PCR titer turned negative 14 days later, but there was still no improvement in the cytopenia and the patient required transfusion of two units of RBCs and 16 units of PLTs daily. Hb and PLT levels were 5.7 g/dL and 2,000/mm\(^3\), respectively (Fig. 3A and 3B). The patient’s reticulocyte count and LDH levels were 24.12% and 676 IU/L, respectively (Fig. 3C and 3D). Beginning
16 days later, weekly rituximab (375 mg/m²) was administered for 4 weeks. Cytopenia improved without transfusion after the second dose of rituximab; Hb and PLT levels increased to 8.2 g/dL and 26,000/mm³, respectively, whereas the patient’s reticulocyte count, total bilirubin levels, and LDH levels simultaneously decreased to 4.99%, 0.8 mg/dL, and 307 IU/L, respectively. After the third dose of rituximab, however, the patient’s cytopenia worsened. Hb and PLT levels decreased to 7.6 g/dL and 2,000/mm³, respectively, while the patient’s reticulocyte count and LDH levels increased to 6.98% and 412 IU/L. Twenty-four days later, the immunosuppressant regimen was changed to sirolimus 1 mg, but no response was noted. Hb and PLT levels were 6.7 g/dL and 8,000/mm³, respectively. The patient’s reticulocyte count and LDH levels increased to 6.98% and 412 IU/L, respectively. The patient underwent a splenectomy 45 days later and his Hb and PLT levels increased without transfusion. Steroids were successfully tapered off.

DISCUSSION

ES is a rare disorder characterized by its association with AIHA and ITP, its occasional association with immune neutropenia, and the absence of a known underlying etiology. First-line ES therapy includes corticosteroids and IVIG. Immunosuppressive agents like cyclosporin, chemotherapies like vincristine and cyclophosphamide, danazol, and therapeutic antibodies such as rituximab, splenectomy, and plasmapheresis can be used as second-line therapies [1].

ES is a very rare complication of solid organ transplantation with only seven reported cases (Table 1): five following liver transplantation; one following a liver and small bowel transplantation; and one following heart transplantation. Five of these cases developed in children or infants, and two developed in adults. Four previous ES cases were associated with other medical problems, such as viral infection, post-transplantation
<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex</th>
<th>Primary diagnosis</th>
<th>Graft type</th>
<th>Blood group recipient/donor</th>
<th>Age at transplant</th>
<th>Immuno-suppressants</th>
<th>Time to presentation</th>
<th>Association</th>
<th>Hb (g/dL)/PLT (µL)</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacaille, et al. [5]</td>
<td>M</td>
<td>Hirschsprung’s disease</td>
<td>Liver + small bowel</td>
<td>AB+/B+</td>
<td>4 yr</td>
<td>Tacrolimus</td>
<td>4 yr</td>
<td>None</td>
<td>5/10,000</td>
<td>Steroid Rituximab</td>
<td>Remission in 3 wk, relapse after 1 yr</td>
</tr>
<tr>
<td>Tubman, et al. [6]</td>
<td>M</td>
<td>Congenital heart disease</td>
<td>Heart</td>
<td>Not available</td>
<td>7 mon</td>
<td>Cyclosporine</td>
<td>9 yr</td>
<td>None</td>
<td>6.1/36,000</td>
<td>Steroid Immunoglobulin Rituximab</td>
<td>Remission in 2 mon</td>
</tr>
<tr>
<td>Yokoyama, et al. [7]</td>
<td>M</td>
<td>Giant cell hepatitis</td>
<td>Liver</td>
<td>ABO-match</td>
<td>5 mon</td>
<td>Tacrolimus</td>
<td>3 mon</td>
<td>EBV</td>
<td>5.4/26,200</td>
<td>Steroid Immunoglobulin Acyclovir</td>
<td>Remission in 6 mon</td>
</tr>
<tr>
<td>Miloh, et al. [8]</td>
<td>F</td>
<td>Fulminant liver failure</td>
<td>Liver</td>
<td>ABO-match</td>
<td>4 yr</td>
<td>Tacrolimus</td>
<td>7 yr</td>
<td>None</td>
<td>6.7/1,000</td>
<td>Steroid Immunoglobulin Rituximab</td>
<td>Remission in 1 mo, relapse after 18 mo</td>
</tr>
<tr>
<td>Domenech, et al. [3]</td>
<td>M</td>
<td>Idiopathic sclerosing cholangitis</td>
<td>Liver</td>
<td>Not available</td>
<td>5 yr</td>
<td>Tacrolimus, Mycophenolate mofetil</td>
<td>20 mon</td>
<td>Parvovirus B19 PTLD</td>
<td>5.2/36,000</td>
<td>Immunoglobulin Steroid Rituximab Cyclophosphamide Fludarabine Splenectomy Cyclosporine</td>
<td>Remission in 40 mon</td>
</tr>
<tr>
<td>Au, et al. [2]</td>
<td>M</td>
<td>Polycystic liver disease</td>
<td>Liver</td>
<td>O+/O+</td>
<td>38 yr</td>
<td>Tacrolimus</td>
<td>7 mon</td>
<td>chronic GVHD</td>
<td>8/3,000</td>
<td>Steroid Rituximab</td>
<td>Died of sepsis</td>
</tr>
</tbody>
</table>

Hb, hemoglobin; PLT, platelets; M, male; EBV, Ebstein-Barr virus; F, female; PTLD, post-transplantation lymphoproliferative disease; GVHD, graft-versus-host disease.
lymphoproliferative disease (PTLD), or graft-versus-host disease (GVHD). EBV and parvovirus B19 were confirmed in two of these cases in which cytopenia improved after the viral titer turned negative. GVHD developed in two cases. Most of the previous cases of ES achieved remission, but one patient died from sepsis [2-7].

The etiology of ES following solid organ transplantation remains unknown. However, ABO mismatch, viral infection, PTLD, GVHD, and complications from immunosuppressive drugs are possible causes. ABO mismatch can also cause alloimmunity [4,5]. Viral infections such as EBV, CMV, and parvovirus B19 are other possible causes. Molecular mimicry and cross-reactivity with viral antibodies might influence the RBC or PLT antigens [3,7,8]. Immunosuppressants like calcineurin inhibitors (CNIs) can also induce ES. CNIs like cyclosporine and tacrolimus are commonly used as immunosuppressants to prevent graft rejection and are associated with some cases of AIHA that develop following solid organ transplantation. AIHA has been cured after changing the immunosuppressive agent to an mTOR inhibitor such as sirolimus [9]. This mechanism might also lead to the development of ES following solid organ transplantation. In our case, the donor was ABO-matched and there was no evidence of PTLD or GVHD. The EBV PCR titer was positive, but cytopenia persisted after the EBV PCR titer turned negative. Tacrolimus was used for immunosuppression, but the change to sirolimus was ineffective.

In all seven reported cases of ES that developed after solid organ transplantation, corticosteroids and IVIG were administered as the first-line therapy. However, this disease was refractory to first-line therapy in all except one case that developed 8 months after liver transplantation. Rituximab was given as the second-line therapy in six cases, and remission was achieved in four cases. Fludarabine, splenectomy, and cyclosporine were used in the rituximab-refractory patients and a response was observed after a splenectomy and cyclosporine intervention [2-7]. This indicates that ES following solid organ transplantation is usually refractory to corticosteroids and IVIG and other treatment modalities should be considered, such as rituximab, splenectomy, or different immunosuppressants.

In summary, ES after solid organ transplantation is a rare hematological complication. Clinicians should remember that ES is one of the causes of anemia and thrombocytopenia in solid organ transplant patients. ES following solid organ transplantation is usually refractory to steroid therapy and IVIG. Therefore, additional treatment modalities need to be explored.

중심 단어: 자가면역 용혈; 특발성 혈소판감소성 자반증; 간이식; 비장절제술

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