Case Report

Transplantation of Related Histocompatible Marrow and Peripheral Blood Stem Cells in a Patient with Severe Combined Immunodeficiency and Disseminated BCG Infection

We report the results of allogeneic bone marrow transplantation (BMT) in a 15-month-old boy with severe combined immunodeficiency (SCID) complicated by disseminated *Bacillus Calmette-Guerin* (BCG) infection. Slow immunological recovery after BMT is considered to be associated with prolonged BCG infection. After one booster dose of allogeneic peripheral blood stem cell transplantation (PBSCT), there was still little improvement in immune reconstitution. The patient finally expired because of failure to achieve a functioning immune system after BMT and septic shock.

**CASE REPORT**

A 9-month-old male infant born at term was admitted because of prolonged fever for 3 months. He had healthy sister and parents with no history of consanguineous marriages. Refractory oral thrush and loose stool were found since the age of 3 months. Generalized macular papular skin rash was also noted. Local induration at the left thigh over the DPT vaccination site, as well as intermittent fever, had developed since the age of 6 months. *Candida albicans* had been cultured from skin, blood, and urine. *Staphylococcus aureus* had also been cultured from blood. After a few weeks of aggressive antifungal/antibacterial treatment, it was noticed that the

Vaccination with live *Bacillus Calmette-Guerin* (BCG) is contraindicated in persons with immune deficiency. Severe opportunistic BCG infection can occur when BCG vaccination is performed at birth, before the presence of congenital immune deficiency. Therefore, the prognosis of BCG infection in a SCID patient is usually highly unfavorable. Stem cell transplantation to restore a patient’s immune status and control disseminated disease has been reported. We here report a case with severe combined immune deficiency who had distinct clinical presentation of persistent and disseminated BCG infection after neonatal BCG vaccination. The patient finally died of disseminated disease after allogeneic BMT and PBSCT.
patient’s skin rash seemed to be totally unresponsive. Skin cancer or other malignancy, HIV infection were suspected. Physical examination revealed pale conjunctiva, hepatosplenomegaly and generalized maculopapular skin rash, oral thrush with ulceration, se vere di a per rash with perianal candidiasis, and local swelling with tender ness over the left thigh.

The patient had received BCG immunization over the left upper arm the day after birth, according to the national BCG vaccination program, with no local or systemic responses. After admission, skin biopsy was done to reveal acid-fast bac te ria-loaded histiocytes in the absence of infiltrating lym pho cytes. The BCG strain My co bacterium bovis (M. bovis) was identified later from skin, gastric juice, and cerebrospinal fluid. Antimycobacterial therapy with rifampin, isoniazid, and streptomycin was ini ti ated.

Initial investigation showed hemoglobin 8.6 g/dL, leuko cyte count of 13940 cells/mm³ with 20% lym phocyte. Peripher al lym pho cyte sub sets re vealed that CD3, CD4, CD8, and CD19 cells were 0.3%, 1.3%, 0.5%, and 81%, respectively. Serum immunoglobulin concentrations were very low (IgG 33 mg/dL, IgA 3 mg/dL, IgM 24 mg/dL). The diag no sis of SCID was made on the ba sis of nu mer i cal de fi ciency of T lym pho cytes, the ab sence of in vitro trans for ma tion re sponses to PHA, PPD skin tests and se vere hypogammaglobulinemia.

Non-T cell-depleted BMT from the patient’s HLA-compatible sis ter was per formed at the age of 15 months. The in fused nu cleated cell dose was 3.70 × 10⁸ per kilogram of body weight (/kg) (CD34+ cells 4.74 × 10⁶/kg). No preparatory conditioning regimen was used during BMT.⁴ Cyclosporine prophylaxis of graft-versus-host disease (GVHD) was discontinued 6 weeks after BMT when there was no ap parent ev i dence of GVHD. Ex ac er ba tion of the dis sem i nated my co bac te ria with fe ver and gen er al ized erythematous maculopapular skin nodules on day 4 was treated intensively with multiple anti tuberculosis drugs, including streptomycin, ciprofloxacin, ethambutol, isoniazid and rifampin without clin ic al re sponse. Mixed chimerism was de tected in the patient’s pe riph eral blood on day 28 by us ing poly morphic short tandem repeats (DNA-STR).⁵ However, the following DNA-STR as say re vealed a grad ual di min ish ing of the donor com ponent. Persis tent py rexia oc cur ring with fungus infection was found in bone marrow. Cytomegalovirus (CMV) se rol ogy and urine PCR were checked be fore and after BMT, and the patient was neg a tive in CMV in fec tion by serological test and PCR as say through out the course. Al though im prove ment of the patient’s oral thrush and perianal candidiasis was ob served, the blood lym pho cyte count did not in crease; and nu mer ous acid-fast ba cilli per sisted in skin biopsy smears.

Due to persis tence of the in fec tion and progres sively di min ished do nor chimerism, the pa tient re ceived allo geneic PBSCT with nu cleated cells 2.34 × 10⁸/kg from the same donor 3 months post BMT to boost engra ftment. How ever, the pa tient died of sep tic shock on day 130. The clinical course and recovery of white blood cells and plate lets are shown in Fig. 1 and Table 1.

DISCUSSION

Serious complications due to BCG vaccination are very rare in new borns and are as so ciated with the presence of underlying congenital immunodeficiency. The risk of persistent and disseminated BCG infection has
been estimated to range from 0.5 to 9 cases/million world-wide.6 The observed incidence may closely reflect the incidence of severe congenital immunodeficiencies.

Our patient developed severe disseminated BCG infection after BCG vaccination prior to the diagnosis of SCID. His skin lesions appeared before other manifestations of disseminated BCG infection. According to the family’s statement, the patient’s skin lesions were not obvious until the age of 4 months. Romanus et al. reported on 4 BCG-vaccinated infants with SCID, whose underlying immunodeficiency was diagnosed at an average age of 5.3 months (range 4–7 months), as compared with 8 months for our case.7 Delay in diagnosis resulted in prolonged and widespread BCG infection, which is implicated as a possible reason for slow immunologic reconstitution after BMT in infants with SCID.8,9

As reported by Buckley et al., "The cause of the BCG skin test reaction may be due to the patient’s concomitant BCG vaccination. The patient’s skin test reaction was not obvious until the age of 4 months. Romanus et al. reported on 4 BCG-vaccinated infants with SCID, whose underlying immunodeficiency was diagnosed at an average age of 5.3 months (range 4–7 months), as compared with 8 months for our case.7 Delay in diagnosis resulted in prolonged and widespread BCG infection, which is implicated as a possible reason for slow immunologic reconstitution after BMT in infants with SCID.8,9

As reported by Buckley et al., "Be cause the de fect in in fants with se vere com bined im mu no de fi ciency is im munologic rather than hae matologic, and because these in fants can not re ject allo grafts, suc cess ful mar row trans plan ta tion for the treat ment of this dis ease does not re quire che motherapeutic con di tion ing be fore trans plan ta tion." We also used non-conditioning reg i men for the patient’s ini tial BMT and sub se quent PBSCT with rapid tapers of cyclosporin A.4

M. bovis is re sis tant to pyrazinamide. The com bined ther apy com posed of isoniazid (INH), rifampicin (RFP) and ethambutol (EMB) was sug gested for the treat ment of sys temic BCG (de rived from M. bovis) in fec tion by The San ford Guide to Antimicrobial Ther apy 2002. Most au thors use INH, RFP, and strep to mycin (SM) or EMB for the initial treat ment with var i ous clin i cal out comes.1,2,8,9

In our case, tri nit ry com bined ther apy was used with INH, RFP and SM ini tially, and the ther apy was then ad justed to the appear ance of side effects and/or the number of acid fast bacilli seen in the patient’s skin biopsy. However, the BCG in fec tion could still not be erad i cated.

Disseminated BCG infection might be missed in chil dren who fail to de velop a lo cal re ac tion. In coun tries where BCG revaccination of in fants im mu nized at birth is rec om mended if a BCG scar is ab sent, it may be im por tant to rec og nize that lo cal BCG re ac tions may not oc cur in chil dren with se vere con gen i tal or ac quired de fi ciencies in cellar im munity.1

One of the cases re ported by Romanus et al. died of severe pancytopenia suspected to be drug-induced (RFP). Our case also had pancytopenia ob served dur ing RFP treat ment. How ever, the con di tion was re versed af ter dos age ad just ment.7

BCG vac cina tion is in cluded in na tional tu ber cu lo sis con trol pro grams world wide for mass vac cina tion or for the se lec tive vac cina tion of groups at risk. The global BCG coverage in 1989 was es ti mated to be ap prox i mately 71% of chil dren un der the age of 12 months. Since the fre quency of tu ber cu lo sis has di min ished mark edly, some au thors re com mend postponing BCG vaccina tion to 3–9 months of age to avoid vac cini ng im munode fi cient per sons. Our ex per i ence in this patient also sug gests this.1,7,10

**REFERENCES**


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**Table 1. Hematological investigation at presentation and post-BMT**

<table>
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<tr>
<th>Days post-BMT</th>
<th>0</th>
<th>+7</th>
<th>+9</th>
<th>+14</th>
<th>+21</th>
<th>+28</th>
<th>+43</th>
<th>+57</th>
<th>+94</th>
<th>+118</th>
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<tbody>
<tr>
<td>TLC (µL)</td>
<td>3981</td>
<td>1176</td>
<td>2347</td>
<td>4181</td>
<td>1728</td>
<td>1273</td>
<td>1872</td>
<td>1587</td>
<td>960</td>
<td>940</td>
</tr>
<tr>
<td>(21%)</td>
<td>(14%)</td>
<td>(16%)</td>
<td>(31%)</td>
<td>(18%)</td>
<td>(19%)</td>
<td>(16%)</td>
<td>(18%)</td>
<td>(20%)</td>
<td>(20%)</td>
<td></td>
</tr>
<tr>
<td>WBC (µL)</td>
<td>18960</td>
<td>8400</td>
<td>14670</td>
<td>13490</td>
<td>9600</td>
<td>6700</td>
<td>11700</td>
<td>6900</td>
<td>4800</td>
<td>4700</td>
</tr>
<tr>
<td>Plt (×10^9/L)</td>
<td>483</td>
<td>121</td>
<td>46</td>
<td>157</td>
<td>344</td>
<td>264</td>
<td>306</td>
<td>162</td>
<td>152</td>
<td>146</td>
</tr>
</tbody>
</table>

BMT = bone marrow transplantation; Plt = platelets; TLC = total lymphocyte count; WBC = white blood cells.


