INSTRUCTIVE CASE

An infant with disseminated bacillus Calmette-Guerin infection (BCGitis)

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Abstract The bacillus Calmette Guerin (BCG) vaccine contains live attenuated Mycobacterium bovis bacteria. There is a long-standing controversy surrounding the efficacy of BCG against TB and whether it should be used. BCG is associated with significant adverse effects, including life-threatening disseminated BCG infection in children with primary immunodeficiency (PID). Here, we present a case report of an infant diagnosed with severe combined immunodeficiency disease and disseminated BCGitis. There are no clear guidelines for the most suitable treatment for disseminated BCG disease. Hematopoietic stem cell transplantation (HSCT) is needed in urgent cases. BCGitis is known to exacerbate clinically after HSCT while immune reconstitution occurs. During this time, rapidly expanding peripheral T cells of the graft result in a severe inflammatory response, lymphadenitis, multiple abscesses, and sepsis, and fatal multiple organ failure is possible. Modification of the transplant procedure and the use of immunosuppressive medications and prednisolone to treat cytokine reactions at the time of overwhelming immune reconstitution are usually necessary.

1. Introduction

An eight-month-old Saudi girl was referred to King Faisal Specialist Hospital & Research Centre (KFSH&RC) to rule out primary immunodeficiency disease.

The patient was born via normal spontaneous vaginal delivery with a birth weight of 2.8 kg. At the age of 4 weeks, she began to have recurrent chest infections, chronic diarrhea and poor weight gain, which necessitated two hospital admissions. At the age of five months, she
Presented to the local hospital with persistent fever, swelling, tenderness and discharge from the BCG vaccine site associated with generalized lymphadenopathy, hepatosplenomegaly and a scattered macular rash. A lymph node aspiration, bronchoalveolar lavage and skin biopsy revealed acid fast bacilli; as a result, she was started on isoniazid, rifampicin, ethambutol and clarithromycin. In addition, bronchoalveolar lavage identified a Pneumocystis jiroveci pneumonia infection, which was treated with trimethoprim-sulfamethoxazole therapy. The parents of the patient were cousins with a family history of a sibling dying at ten months of age due to suspected meningitis.

Based on the family history and clinical findings, the patient was referred to KFSH&RC to rule out primary immunodeficiency disease. On examination, she was chronically ill and emaciated, with a weight of 4.8 kg. She had generalized lymphadenopathy involving both axilla with lymph node sizes of 3 × 3 cm with small subclavicular and inguinal lymph node enlargement. There was swelling at the BCG site of 0.5 × 0.5 cm and a scattered macular rash over her entire body. She was afebrile with a respiratory rate of 32 breaths per minute and good air entry with scattered crepitation. Abdominal examination revealed a palpable spleen 2 cm below the costal margin.

Laboratory investigation as shown in Table 1 showed severe lymphopenia, an absence of T & B cells via lymphocyte phenotyping and a poor lymphocytic response to mitogen stimulation; these signs are suggestive of severe combined immunodeficiency. Lymph node and skin biopsy confirmed the presence of acid fast bacilli, and mycobacterium bovis was isolated. The isolate was susceptible to isoniazid, rifampicin, ciprofloxacin, amikacin and clarithromycin. CT scan of the chest and abdomen showed multiple cold abscesses and necrotic lymph nodes of the chest and abdomen. Skeletal survey revealed multiple small lytic lesions distributed in the upper and lower extremities, including both hands and feet, associated with a periosteal reaction of the proximal tibia, fibula, proximal humeri and both femurs; there were also pathological fractures (Fig. 1).

Based on the family history, clinical findings, and immunological work-up, the patient was diagnosed with severe combined immunodeficiency with disseminated BCGitis. She was started on anti-TB therapy including, isoniazid, rifampicin, ethambutol, ciprofloxacin and clarithromycin. Patient underwent hematopoetic Stem Cell Transplantation (HSCT) using her father as a donor, who was HLA matched for risk of graft vs host disease (GVHD) and haploidentical for risk of rejection.

On the second week post HSCT, the patient started to develop a persistent fever associated with a flare up of the swelling at the BCG site. She also had an enlarged Lt axillary lymph node with abscesses requiring lymph node excision and drainage; this was associated with generalized papulonodular skin lesions over the entire body (Fig. 2). Lymph node and skin biopsy also confirmed the presence of acid fast bacilli. The severe inflammatory response post HSCT dictated the initiation of steroid treatment to control the post engraftment inflammatory response to disseminated BCGitis. The patient’s symptoms of fever, skin lesions and persistent lymphadenopathy lasted for one year post HSCT, at which time her immune system controlled the disseminated BCG infection. She completed a 2-year course of anti-TB therapy. Currently, she is 30 months post HSCT, she is no longer taking anti-TB therapy, and she is on regular intravenous immunoglobulin because she had no B-cell engraftment. A chimerism study showed evidence of 100% lymphocytes and 3.9% myeloid cell engraftment. The detailed immune reconstitution post HSCT is shown in Table 1.

2. Discussion

The bacillus Calmette Guerin (BCG) vaccine contains live attenuated Mycobacterium bovis and is the only available vaccine for TB disease [1–3]. There is a long-standing controversy surrounding its efficacy against TB and whether it should be used [4]. In addition to its low efficacy, BCG is associated with significant adverse effects, including local

<table>
<thead>
<tr>
<th>Table 1 Laboratory data.</th>
<th>At diagnosis (8 months of age)</th>
<th>2 years post HSCT</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count/mm³</td>
<td>2750</td>
<td>2770</td>
<td>6000–18000</td>
</tr>
<tr>
<td>Lymphocytes/mm³</td>
<td>50</td>
<td>1110</td>
<td>4000–12000</td>
</tr>
<tr>
<td>Neutrophils/mm³</td>
<td>2200</td>
<td>860</td>
<td>1000–6000</td>
</tr>
<tr>
<td>Monocytes/mm³</td>
<td>300</td>
<td>690</td>
<td>200–1200</td>
</tr>
<tr>
<td>IgG (g/L)</td>
<td>13.3</td>
<td>7.5</td>
<td>3.5–12.4</td>
</tr>
<tr>
<td>IgA (g/L)</td>
<td>0.82</td>
<td>0.32</td>
<td>0.4–1.2</td>
</tr>
<tr>
<td>IgM (g/L)</td>
<td>0.66</td>
<td>&lt;0.18</td>
<td>0.43–1.7</td>
</tr>
<tr>
<td>CD3/mm³</td>
<td>3</td>
<td>1082</td>
<td>3100–4800</td>
</tr>
<tr>
<td>CD4/mm³</td>
<td>2</td>
<td>667</td>
<td>2200–3300</td>
</tr>
<tr>
<td>CD8/mm³</td>
<td>1</td>
<td>404</td>
<td>1100–1700</td>
</tr>
<tr>
<td>CD19/mm³</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>1100–1900</td>
</tr>
<tr>
<td>CD56/16/mm³</td>
<td>59</td>
<td>205</td>
<td>300–700</td>
</tr>
<tr>
<td>Lymphocytes chimerism (%)</td>
<td>–</td>
<td>100</td>
<td>–</td>
</tr>
<tr>
<td>Myeloid chimerism (%)</td>
<td>–</td>
<td>3.9</td>
<td>–</td>
</tr>
<tr>
<td>PHA (C.P.M. × 10³)</td>
<td>28,512</td>
<td>78,417</td>
<td>94935–171149</td>
</tr>
<tr>
<td>Con A (C.P.M. × 10³)</td>
<td>17,332</td>
<td>59,117</td>
<td>78011–133442</td>
</tr>
</tbody>
</table>
ulceration at the vaccine site, lymphadenitis and osteomyelitis. Another important complication of BCG is a life-threatening disseminated BCG infection. This complication has been noted in children with primary immunodeficiency (PID), including severe combined immunodeficiency (SCID), chronic granulomatous diseases (CGD), complete DiGeorge syndrome (cDGS), acquired immune deficiency syndrome (AIDS) and the Mendelian susceptibility to mycobacterial disease (MSMD) (e.g., IFN-γ receptor 1/2 deficiencies, IL-12/23 receptor β1 chain deficiency, IL-12p40 deficiency, STAT1 deficiency and NEMO deficiency) [5-13].

Severe combined immunodeficiency (SCID) is the most severe form of primary immunodeficiency diseases and is characterized by a block in T lymphocyte differentiation that is variably associated with the abnormal development of other lymphocyte lineages, i.e., B and NK lymphocytes and, more rarely, myeloid lineages [14,15]. The clinical presentation of SCID is fairly uniform and is characterized by early onset and diverse infections. Oral candidiasis, persistent diarrhea with growth impairment and/or interstitial pneumonitis are the most frequent infectious manifestations leading to the diagnosis of SCID [16]. Persistent infections with opportunistic organisms lead to death in the first two years of life, unless immune reconstitution can be accomplished by hematopoietic stem cell transplantation (HSCT) or gene therapy.

There are no clear guidelines on the most suitable treatment for disseminated BCG disease [17,18]. Aggressive therapy involving at least four anti-TB drugs is usually needed. Furthermore, BCG vaccine strains differ in their susceptibility pattern to antituberculous drugs, and this should be considered when administering empirical therapy. SCID should be considered a pediatric emergency, and hematopoietic stem cell transplantation (HSCT) should be performed on an urgent basis. BCGitis is known to exacerbate clinically after HSCT, while immune reconstitution occurs. During this time, rapidly expanding peripheral T cells of the graft result in a severe inflammatory response, lymphadenitis, multiple abscesses, and sepsis, and fatal multiple organ failure is possible. Modification of the transplant procedure and the use of immunosuppressive medications and prednisolone to treat cytokine reactions at the time of overwhelming immune reconstitution are usually necessary.

The frequency of SCID throughout the world is estimated to be 1 in 75,000—100,000 live births [19,20]. The high rate of consanguinity in the Saudi population (56%) [21] predisposes Saudi individuals to a high incidence of primary immunodeficiency disorders. The estimated SCID incidence in Saudi Arabia is 1 in 5000 live births, making this population more vulnerable to BCG complications. The BCG vaccine is part of the routine vaccination program for all newborns in the country. Based on available data that indicate that the BCG vaccine has low efficacy with serious complications and the high incidence of primary immunodeficiency disorders among Saudi children, the need for BCG vaccination in our community and the possible benefit of postponing BCG vaccination until 12 months of age should be evaluated. By 12 months of age, most congenital
immunodeficiency disorders are apparent, which would allow BCG vaccination to be avoided in patients with such disorders.

Conflict of Interest

The author declares that he has no competing interests.

References