

CASE REPORT

Successful Treatment of Disseminated BCG Infection in a SCID Patient with Granulocyte Colony Stimulating Factor

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SUMMARY Severe combined immunodeficiencies (SCID) are disorders with impairment of humoral and cellular immune functions. The prognosis of disseminated bacillus Calmette-Guérin (BCG) infection in immunocompromised host is unfavorable since response to standard therapy is poor. We report a successful treatment of disseminated BCG infection with granulocyte colony stimulating factor (G-CSF) in a patient with severe combined immunodeficiency. The patient failed to respond to intensive anti-tuberculous (anti-TB) therapy. After 2 months of G-CSF, in addition to anti-TB treatment, the clinical signs of disseminated BCG infection were improved. Since serious BCG infections in SCID are not uncommon in developing countries, where BCG vaccination is mandatory to all newborns, the combination of G-CSF and anti-TB drugs should be considered in immunocompromised patients with protracted mycobacterial infection.

Bacillus Calmette-Guérin (BCG) vaccination is recommended by the World Health Organization for all infants living in endemic areas with high prevalence of tuberculosis (TB). BCG vaccine is a live-attenuated bacterial vaccine derived from wild-type *Mycobacterium bovis*. This vaccine is aimed to prevent severe TB infection particularly in children. Complications of vaccination are uncommon. However, abscesses at the site of inoculation, localized skin lesions and disseminated disease have been reported.¹

Patients with immunodeficiency are at greatest risk for developing disseminated infection following BCG vaccination and they respond poorly to standard therapies.²⁻⁴ Although, live-attenuated vac-

ination is contraindicated in persons with immunologic deficiency, BCG vaccine is usually inoculated prior to diagnosis.⁵ The prognosis of disseminated BCG infection in severe combined immunodeficiency (SCID) is unfavorable. There is limited information about suitable therapy for disseminated BCG disease in the immunocompromised patient.

We report a successful treatment of dissemi-

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nated BCG infection with the combination of granulocyte colony stimulating factor (G-CSF) and anti-TB drugs in a patient with SCID.

CASE REPORT

A 6-month-old female was referred to Siriraj hospital, Bangkok, Thailand due to chronic diarrhea, failure to thrive and generalized candidiasis. The patient experienced multiple infections, including infectious diarrhea and recurrent pneumonia since the age of 4 weeks. She was the second child of healthy first degree consanguineous parents. Her sister died at 3 months of age due to sepsis. She received BCG on the right deltoid muscle on the first day of life, without any local or systemic reaction.

Physical examination revealed a wasted female (weight 4 kg, <3rd percentile) with hepatomegaly. There was no palpable spleen or lymphadenopathy. Erythematous patch with satellite lesions were noted on her neck and chest.

Laboratory studies at the time of admission revealed a hemoglobin of 11.8 gm/dl, hematocrit 36.6%, WBC 17,830/mm³ (neutrophil 66% and lymphocyte 21%), and platelet count 568,000/mm³. Her chest X-ray showed perihilar infiltration and an absence of a thymic shadow. The antibody of human immunodeficiency virus of the patient and her

mother were non-reactive. Immunologic studies revealed: IgG 44 mg/dl, IgM 26 mg/dl, IgA <5.7 mg/dl, IgE <4.5 IU/ml, CD3 7 cells/mm³, CD4 1 cells/mm³, CD8 8 cells/mm³, CD19 2,082 cells/mm³, and CD16/CD56 663 cells/mm³. Lymphocyte proliferation in response to phytohaemagglutinin and purified protein derivative were absent. These findings are compatible with T^B⁺NK⁺ severe combined immunodeficiency (SCID). The diagnosis of IL-7R α deficiency SCID was confirmed by a mutation analysis.

The patient was treated with intravenous immunoglobulin (IVIG) and prophylactic cotrimoxazole. Bone marrow transplantation (BMT) was attempted at the age of 8 months. She underwent conditioning therapy with fludarabine (30 mg/m²/day), busulfan (4 mg/kg/day) and anti-thymocyte globulin (5 mg/kg/day). The purified CD34 haploidentical bone marrow from the father was infused to the patient. Graft versus host disease soon developed and there was no evidence of engraftment.

At 15 months of age, she developed abscesses at the site of BCG inoculation on the right shoulder (Fig. 1a). Numerous acid-fast bacilli (AFB) were demonstrated from abscesses. *Mycobacterium tuberculosis* complex was identified by polymerase chain reaction and culture. She was initially treated with isoniazid (10 mg/kg/day), rifampicin (10 mg/

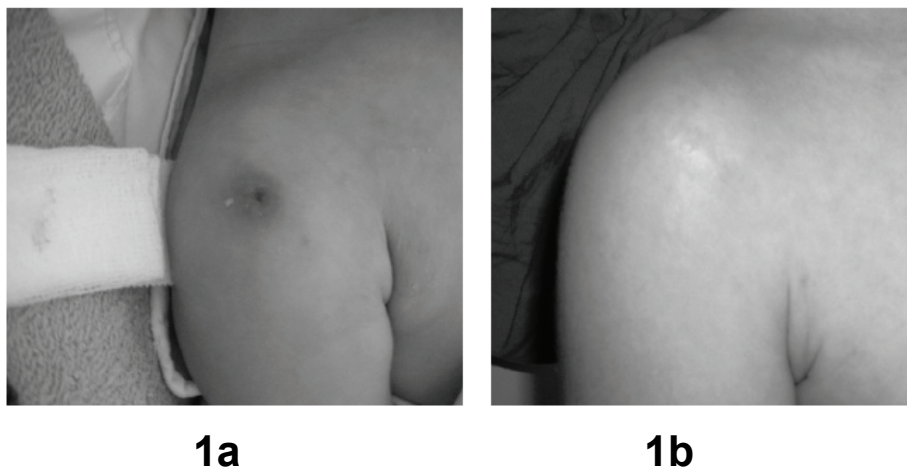


Fig. 1 Abscesses on right shoulder at the site of BCG inoculation prior to anti-TB and G-CSF treatment (a). Healed ulcer of right shoulder after 2 months of G-CSF treatment (b).

kg/day), pyrazinamide (20 mg/kg/day), and amikacin (15 mg/kg/day). In spite of 4 anti-TB therapies, she progressively developed multiple subcutaneous nodules, ranged from 1-2 cm in diameter, on anterior chest, left upper thigh and knee. The nodule biopsy showed granuloma and numerous AFB. Ethambutol (10 mg/kg/day) and levofloxacin (10 mg/kg/day) were added to previous anti-TB medications. According to in-vitro antimicrobial sensitivities of the culture, *M. tuberculosis* complex was resistant to pyrazinamide and this medication was discontinued.

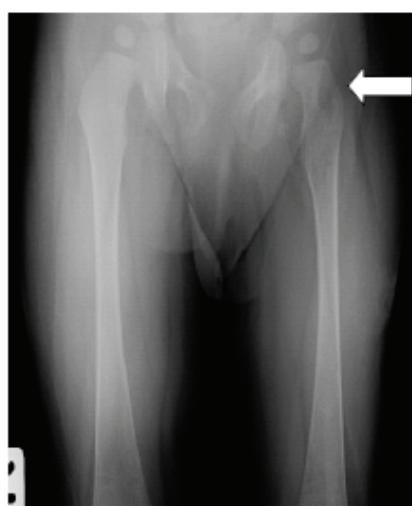
Despite of the anti-TB treatment for 2 months, she continued to develop hepatosplenomegaly and osteomyelitis of the left femur. A diagnosis of disseminated BCG infection was made. Radiological study revealed the cystic lesions in the proximal left femur (Fig. 2a). Whole body bone scan showed slightly increased blood flow and soft tissue uptake at the same area of the femur. There was no other abnormality in the rest of the skeleton. Computed tomography scan of the abdomen revealed hepatosplenomegaly without space taking lesion and no intra-abdominal lymphadenopathy.

Granulocyte colony stimulating factor (5 µg/kg/day) was added to the treatment at 18 months

of age. The dose of G-CSF was titrated to keep absolute neutrophil count $<15,000/\text{mm}^3$. After 2 months of G-CSF therapy, the abscess and multiple subcutaneous nodules were healed (Fig 1b). Hepatosplenomegaly and bone lesions of the left femur were improved (Fig 2b). Ethambutol and amikacin were stopped after 3 months of G-CSF treatment. During G-CSF therapy, there was no serious complication, except mild leukocytosis and neutrophilia. G-CSF was given for 4.5 months while triple anti-TB drugs and monthly IVIG were planned to be given until the proceeding 2nd BMT. There was no relapsing sign of active TB infection after discontinuation of G-CSF.

DISCUSSION

Disseminated BCG infection in the severely immunocompromised host was uniformly fatal.^{2,6} The Incidence of disseminated BCG disease ranged from 0.06 to 3.4 cases per million vaccination, and the mortality rates remained high in immunocompromised patients (60-83%).^{1,7,8} The immunodeficiency conditions such as SCID, cellular immune defect, chronic granulomatous disease, impaired IL-12 and IFN- γ mediated immunity and human immunodeficiency virus, have been identified as major pre-



2a



2b

Fig. 2 Anteroposterior roentgenogram of both femurs. Cystic lesion was found at left proximal femur (a, arrow). Improved cystic lesion after 18 months of G-CSF treatment (b).

disposing diseases to developing disseminated BCG infection.^{4,8-10}

The disseminated BCG infection may be the first presentation prior to the diagnosis of immunodeficiency.^{5,11} The most common symptoms of disseminated BCG disease were fever, lymphadenopathy, and weight loss.^{1,4} The preliminary prominent symptoms of our patient were abscess at the site of BCG vaccination and multiple subcutaneous nodules all over the body. Gonzalez *et al.*⁸ suggested that the clinical presentation and course of the infection varied considerably depending on the underlying immunodeficiency syndrome. He reported disseminated BCG infection in two SCID patients, presenting with cutaneous nodules. Furthermore, several studies also reported the localized adverse events of disseminated BCG infection at the site of inoculation in SCID patients.^{7,12,13} The diagnosis of disseminated BCG disease should be considered in SCID presenting with skin lesions despite of lacking common systemic symptoms.

The prognosis of disseminated BCG infection in immunocompromised host is unfavorable since response to standard therapy is poor. Our patient progressively developed hepatosplenomegaly and BCG-osteomyelitis of left femur despite of intensive anti-TB drugs. BCG-osteomyelitis usually involves the hand, foot, long bone, spine, rib, sternum, and clavicle.¹⁴ The bone lesion generally occurs in the metaphysis or epiphysis of the long bone.¹⁴⁻¹⁶ In our case, BCG-osteomyelitis involved epiphysis of left femur. Our finding was similar to a previous report of Hugosson *et al.*¹⁵ who demonstrated typical multiple small rounded osteolytic lesions without reactive sclerosis in a SCID patient with BCG-osteomyelitis.

There is little information about appropriate treatment of disseminated BCG infection in a SCID patient. Tabot *et al.*¹ reported that >70% of patients with disseminated BCG infection died even when they were aggressively managed. Possible explanations for poor prognosis of this serious infection include delay in diagnosis or treatment, initial treatment with pyrazinamide to which BCG is uniformly resistant, and developing of resistance to therapy. Previous studies suggested that early BMT and appropriate antimicrobial therapy were effective.^{2, 6, 17}

Jaing *et al.*¹⁸ suggested that disseminated BCG disease could not be cured with anti-TB agents unless immune reconstitution occurred.

Growth factor such as granulocyte-monocyte colony stimulating factor (GM-CSF) was used to treat disseminated BCG infection according to previous reports. Sanal *et al.*¹⁹ demonstrated the cutaneous response of disseminated BCG infection to GM-CSF treatment in an immunocompetent patient, even though there was no benefit to the other organ systems. In another study, GM-CSF treatment was shown to improve phagocytosis of *Mycobacterium avium* complex by peripheral blood monocytes in a patient with human immunodeficiency virus infection.²⁰

To our knowledge, this is the first case of SCID with disseminated BCG infection, which was successfully treated with anti-TB agents in conjunction with G-CSF, in the absence of immune reconstitution. The mechanisms of G-CSF to improve mycobacterial killing were supported by Santiago *et al.*,²¹ who showed that recombinant human G-CSF induced the production of macrophage colony stimulating factor by granulocytes. Moreover, G-CSF augmented endogenous leukotriene synthesis which enhanced killing of mycobacteria.²²

In conclusion, we suggest that the addition of G-CSF to anti-TB drugs should be considered in immunocompromised patients with protracted mycobacterial infection.

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