



# Retroperitoneal Abscess in Severe Combined Immunodeficiency Probably Due to BCG Vaccine

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## ABSTRACT

Severe combined immunodeficiency (SCID) is characterized by the impairment of T cells with or without B and Natural Killer (NK) cells, leading to recurrent bacterial and viral infections. Although hematopoietic stem cell transplantation (HSCT) is the curative treatment of SCID, many complications and especially infections can develop afterwards. Herein, we report a seven-month-old girl who was diagnosed with SCID and underwent HSCT from HLA-full-matched related donor. However, the patient was complicated with retroperitoneal abscess and chest wall granuloma following HSCT, probably due to the Bacillus Calmette Guerin (BCG) vaccine. The symptoms of the patient were controlled with anti-tuberculosis therapy and intravenous antibiotics.

**Keywords:** Hematopoietic stem cell transplantation, mycobacterium tuberculosis, primary immunodeficiency, retroperitoneal abscess, severe combined immunodeficiency

## INTRODUCTION

Severe combined immunodeficiency (SCID) is a primary immunodeficiency (PID) characterized by defective T cell development together with B and/or Natural Killer (NK) cell impairment. Patients present with recurrent oral moniliasis, diarrhea, life threatening bacterial and viral infections, or live vaccine associated complications (1). Bacillus Calmette Guerin (BCG) is a live vaccine applied routinely at the age of two months in many countries and may cause serious fatal complications in immunocompromised patients (2). Retroperitoneal abscess is a rare complication seen in patients with PID (2-4). In this report, a seven-month-old infant diagnosed with SCID complicated with retroperitoneal abscess and chest wall granuloma is presented. We attributed the findings to prior BCG vaccination, where symptoms occurred following hematopoietic stem cell transplantation (HSCT) from her HLA-full-matched related donor. The symptoms were successfully controlled with anti-tuberculous therapy and intravenous antibiotics.

## CASE REPORT

A seven-month girl born to second-degree consanguineous parents was referred to our department with the complaint of a widespread rash that had developed between the age of 40 days and six months. She had been hospitalized and given treatment for two pneumonia episodes when she was four and six months old, respectively. The patient also suffered from recurrent oral moniliasis since five months of age. She was born to a mother as the second live child of fourth gestation. The first child of the family had died of recurrent pulmonary infections when he was four months old, and the second gestation resulted in miscarriage in the eighth month of pregnancy. On physical examination, the height, weight and head circumference of the patient were less than the 3<sup>rd</sup> percentile. She had dry skin and seborrheic dermatitis. The vaccines in the first six months of life had been administered to the patient in accordance with vaccination program of the Ministry of Health. The patient received prophylaxis, including rifampicin and isoniazid due to BCG vaccination as soon as she was diagnosed as

SCID. The lymphopenia and hypogammaglobulinemia, and the low CD3, CD4, CD8, CD19 and high CD16/56 levels were compatible with T-B-NK+ SCID (Table I). Molecular analysis of the patient for Interleukin 7 Receptor (*IL7R*), Janus Kinase 3 (*JAK3*), CD3 T-cell receptor components  $\delta$  (*CD3\delta*),  $\epsilon$  (*CD3\epsilon*),  $\zeta$  (*CD3\zeta*), and recombination activation gene 1 and 2 (*RAG1* and *RAG2*) were all negative.

Her grandmother had HLA that was full-matched. Hematopoietic stem cell transplantation (HSCT) was performed at the age of 10 months from the grandmother. At the third day of HSCT, the patient presented with a maculopapular rash on her trunk, extremities, and especially the palms and soles. Acute graft versus host disease (GVHD) was confirmed by the skin biopsy taken

from her leg, and oral steroids and cyclosporine were initiated for GVHD. The skin rashes disappeared after treatment.

During the hospitalization, a 1.5 cm diameter lymphadenopathy in the left axilla and granuloma at the sixth rib level on left side of the chest were detected on her physical examination on the 42<sup>nd</sup> and 44<sup>th</sup> days of HSCT, respectively. Lymphadenitis and granuloma on the chest wall were attributed to the BCG vaccination, and rifampicin, isoniazid, ethambutol, clarithromycin, and ciprofloxacin were initiated. There was no history of contact with tuberculosis, and screening of the family was negative. Bone scintigraphy did not reveal any other involvement.

**Table I. Clinical and laboratory features of the patient.**

Age at onset of the symptoms (days)	40		
Age on admission (months)	7		
Infections	Oral moniliasis, pneumonia		
Complete Blood Count	Before HSCT (before regular IVIG treatment)	at the 15 <sup>th</sup> day of HSCT (on regular IVIG treatment)	at the 6 <sup>th</sup> month of HSCT (on regular IVIG treatment)
Hemoglobin (g/dl)	7.8	9.8	9.9
Leukocyte (/mm <sup>3</sup> )	7500	3200	15200
Thrombocyte (/mm <sup>3</sup> )	640000	320000	540000
Absolute lymphocyte count (/mm <sup>3</sup> )	<b>400</b> (3800-9900)	1500 (2600-10400)	1200 (2700-11900)
Absolute neutrophil count (/mm <sup>3</sup> )	7100	<b>200</b>	12900
Serum immunoglobulins	Before HSCT	at the 3 <sup>rd</sup> month of HSCT	at the 6 <sup>th</sup> month of HSCT
IgA (mg/dl)	<7.0 (7-123)	23 (17-69)	87.5 (30-107)
IgG (mg/dl)	190 (304-1231)	870 (463-1006)	354 (605-1430)
IgM (mg/dl)	<17 (32-203)	28 (46-159)	55.6 (66-228)
Total IgE (IU/ml)	<1,00		
Lymphocyte subsets (% / count) (/ $\mu$ l)	Before HSCT	at the 15 <sup>th</sup> day of HSCT	at the 6 <sup>th</sup> month of HSCT
CD3	<b>1</b> (50-77) (%) 4 (2400-6900)	80 (54-76) (%) <b>1200</b> (1600-6700)	49 (39-73) (%) <b>588</b> (1400-8000)
CD4	<b>24</b> (33-58) (%) <b>96</b> (1400-5100)	<b>15</b> (31-54) (%) <b>225</b> (1000-4600)	<b>17</b> (25-50) (%) <b>204</b> (900-5500)
CD8	16 (13-26) (%) <b>84</b> (600-2200)	70 (12-28) (%) 1050 (400-2100)	37 (11-32) (%) 444 (400-2100)
CD16-56	77 (2-13) (%) 308 (100-1000)	9 (3-17) (%) <b>135</b> (200-1200)	14 (3-16) (%) 168 (100-1400)
CD19	<b>6</b> (13-55) (%) <b>34</b> (700-2500)	<b>4</b> (15-39) (%) <b>60</b> (600-2700)	33 (17-41) (%) <b>396</b> (600-3100)
Lymphocyte transformation	Impaired		
Mutation	Not defined		

IVIG: Intravenous immunoglobulin

She was admitted with fever of two-weeks duration, left axillary lymph node and a fluctuating mass on the suprasternal notch at the sixth month of anti-tuberculosis therapy. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were 34 mm/hour and 5.04 g/dl, respectively. White blood cell, absolute lymphocyte, and absolute neutrophil counts were 11,800/mm<sup>3</sup>, 1,800/mm<sup>3</sup>, and 10,000/mm<sup>3</sup>, respectively. Purulent material was obtained by lymph node aspiration. The culture was negative for mycobacterium but the *Mycobacterium tuberculosis complex* polymerase chain reaction (PCR) analysis was positive. Abdominal ultrasonography and magnetic resonance imaging (MRI) studies were performed. A hypoechoic lesion of about 28x12 mm in size was determined in the left adrenal gland. It was consistent with retroperitoneal abscess extending from the right diaphragmatic crus and left renal hilus to bilateral paravertebral psoas muscles. Abscess drainage material from this lesion also revealed acid-fast bacilli and *Mycobacterium tuberculosis complex* PCR positivity. The culture was again negative. As the tuberculosis screening was negative, *Mycobacterium bovis/BCG strain* due to BCG vaccination was thought to be responsible. Molecular typing (genotyping) from the mycobacterial strain could not be performed. Following abscess drainage, anti-tuberculosis treatment (isoniazid, moxifloxacin, rifampicin, ethambutol, streptomycin) was started and antibiotherapy (vancomycin, ornidazole, meropenem, amikacin) was administered for three weeks. The abscess of the patient disappeared, and the symptoms were taken under control with this treatment.

## DISCUSSION

Severe combined immunodeficiency (SCID) is characterized by the susceptibility to opportunistic infections as well as complications with live vaccines. The present patient, who had undergone successful HSCT from an HLA-full-matched donor, was admitted with fever at the fourth month of HSCT. Although live vaccines are contraindicated in SCID, a live-attenuated BCG vaccine was administered to the patient because the BCG vaccine is routinely administered to infants at two months of age according to the Turkish national vaccination schedule (5). Disseminated BCG disease occurred in the left axillary lymph node, chest wall, and retroperitoneal region. Samples taken from the abscess revealed *Mycobacterium tuberculosis complex* ARB and PCR positivity, and she was successfully treated with abscess drainage, anti-tuberculosis

therapy and intravenous antibiotics. The patient was admitted with left axillary lymph node and granuloma on the chest wall. An additional lesion was present at the left adrenal gland as a psoas abscess. All these complications were thought to be due to BCG vaccine that contains the attenuated live *Mycobacterium bovis* strain. Complications due to BCG vaccination are classified as regional disease, extra-regional localized disease, and disseminated disease (6). These side effects are generally seen after 6 to 9 months following BCG vaccination (7). The most common form is regional lymphadenitis and subcutaneous abscess at the site of the injection (8). Although localized BCG complications are frequently seen in immunocompetent individuals, the disseminated form, which is defined as two or more infectious foci related to BCG vaccination excluding the injection site, is mostly observed in the patients with immunodeficiency (8, 9).

Almost half of the patients with SCID experience BCG-related complications, and there is a substantially high risk of mortality in disseminated disease (2). BCG vaccine-related complications mostly occur after HSCT, but are rarely seen in pre-transplant patients (10). This may be due to the immunosuppressive treatment given for GVHD as in our patient or failure to achieve full reconstitution following the HSCT. In the medical literature, disseminated BCG disease in patients with PID after HSCT has been reported and attributed to immune reconstitution syndrome (IRS) in which the immune system begins to recover and strongly responds to a previously acquired opportunistic infection (2, 3). IRS may present with disseminated BCG infection as seen in our patient (2). As there is a lag period before the development of T cell reconstitution after HSCT, and the patients are given immunosuppressive treatments such as corticosteroids in this period, the patients are susceptible to infections and live vaccine-associated diseases (11). Although naive T cell reconstitution is observed early after HSCT when a conditioning regimen is not given, B cell reconstitution is late after transplantation, usually at 6 months to 2 years (11). In our patient, disseminated mycobacterial disease probably due to BCG developed in the seventh month of HSCT. Bernatowska et al. reported guidelines for BCG disease in PID (12). Accordingly, if there is localized disease/BCGitis, anti-tuberculosis treatment with at least three drugs is recommended, to be followed by long-term prophylactic treatment with isoniazid and rifampicin. In the case of disseminated BCG disease/BCGosis, therapy is recommended with at least four anti-tuberculosis drugs until the patient

is fully recovered, again followed by the isoniazid/rifampicin combination. Furthermore, the prophylactic anti-tuberculosis combination should be ceased when reconstitution is achieved after HSCT. Unsuccessful outcomes may be seen in the patients under isoniazid and rifampicin prophylaxis. In these subjects, anti-tuberculosis combination therapy excluding pyrazinamide should be given to the patients as BCG strains have pyrazinamide resistance. Second line drugs such as fluoroquinolones, clofazimine, and aminoglycosides may be used, as we did in our case (13).

In the literature, disseminated BCG disease was evaluated in 177 patients with SCID who developed BCG vaccine complications (2). The most common localizations were extra-regional lymph nodes, skin, and lungs; however, the liver, spleen, and bones were the least reported sites of infection in these patients (2). On the other hand, chest wall granuloma and psoas abscess have been defined only in a few cases (14). Kim DH et al. also presented a 17 month-old female with chest wall abscess approximately 17 months following BCG vaccination (15). Although complications after BCG vaccine occur in patients with immunodeficiency, retroperitoneal abscess is an extremely rare side effect even in immunocompromised patients.

Chest wall granuloma and retroperitoneal abscess due to BCG vaccine are very rare complications, and very rarely reported. Although molecular typing (genotyping) was not made for *Mycobacterium tuberculosis complex*, the chest wall granuloma and retroperitoneal abscess in the present patient with SCID probably occurred due to BCG vaccination as there was no pulmonary focus and no contact with tuberculosis patients, and the lesions developed within the first year of the BCG vaccination. In patients with SCID, BCGitis and BCGosis may occur before and after HSCT. Therefore, a BCG-vaccinated patient with SCID should be evaluated for BCG vaccine-related complications in case of persistent fever and high acute phase reactants even if under anti-tuberculosis prophylaxis.

## REFERENCES

1. Le Deist F, Moshous D, Howe SJ, Nahum A, Kavadas FD, Lavine E, et al. Combined T-and B-Cell immunodeficiencies. In: Rezaei N, Aghamohammadi A, Notarangelo LD (eds). Primary Immunodeficiency Disorders. 1st ed. Heidelberg: Springer-Verlag, Berlin, 2008: 39-95.
2. Marciano BE, Huang C-Y, Joshi G, Rezaei N, Carvalho BC, Allwood Z, et al. BCG vaccination in patients with severe combined immunodeficiency: Complications, risks, and vaccination policies. *J Allergy Clin Immunol* 2014;133:1134-41.
3. Aytekin C, Yuksek M, Dogu F, Yagmurlu A, Yildiran A, Fitoz S, et al. An unconditioned bone marrow transplantation in a child with purine nucleoside phosphorylase deficiency and its unique complication. *Pediatr Transplant* 2008;12:479-82.
4. Alborzi A, Mostafavi N. Retroperitoneal abscess due to disseminated Bacille Calmette-Guerin infection. *Jpn J Infect Dis* 2007;60:392-3.
5. Kroger AT, Atkinson WL, Marcuse EK, Pickering LK. General recommendations on immunization; recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep* 2006;55:1-48.
6. Lotte A. Second IUATLD study on complications induced by intradermal BCG-vaccination. *Bulletin of the International Union Against Tuberculosis and Lung Disease* 1988;63:47-59.
7. Hengster P, Sölder B, Fille M, Menardi G. Surgical treatment of bacillus Calmette Guerin lymphadenitis. *World J Surg* 1997;21:520-3.
8. Hesseling A, Rabie H, Marais B, Manders M, Lips M, Schaaf H, et al. Bacille Calmette-Guérin vaccine—induced disease in HIV-infected and HIV-uninfected children. *Clin Infect Dis* 2006;42:548-58.
9. Norouzi S, Aghamohammadi A, Mamishi S, Rosenzweig SD, Rezaei N. Bacillus Calmette-Guérin (BCG) complications associated with primary immunodeficiency diseases. *J Infection* 2012;64:543-54.
10. İkinçioğulları A, Doğu F, Ciftci E, Ünal E, Ertem M, Reisli I, et al. An intensive approach to the treatment of disseminated BCG infection in a SCID patient. *Bone Marrow Transplant* 2002;30:45-7.
11. Seggewiss R, Einsele H. Immune reconstitution after allogeneic transplantation and expanding options for immunomodulation: An update. *Blood* 2010;115:3861-8.
12. Bernatowska E, Wolska-Kuśnierz B, Pac M, Kurenko-Deptuch M, Pietrucha B, Zwolska Z, et al. Clinical guidelines risk of BCG infection in primary immunodeficiency children. Proposal of diagnostic, prophylactic and therapeutic guidelines for disseminated BCG based on experience in the Department of Immunology, Children's Memorial Health Institute in Warsaw between 1980-2006. *Cent Eur J Immunol* 2007;32:221-5.
13. Nacheha JB, Chaisson RE. Tuberculosis drug resistance: A global threat. *Clin Infect Dis* 2003;36(Supplement 1):S24-S30.
14. Tasdan Y, Alikasifoglu M, Midilli K, Ilter Ö. Chest wall abscess as an unusual presentation of childhood tuberculosis. *Pediatr Infect Dis J* 1998;17:85-6.
15. Kim D, Choi C. Chest wall abscess likely due to BCG vaccination in a child. *Infection* 2009;37:286-8.