

CASE REPORT

A Case of Probable MHC Class II Deficiency with Disseminated BCGitis

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ABSTRACT

Major histocompatibility complex (MHC) class II deficiency is a primary immunodeficiency disease characterized by abnormality of MHC class II molecules surface expression on peripheral blood lymphocytes and monocytes. Clinical manifestations include extreme susceptibility to viral, bacterial, and fungal infections but the immunodeficiency is not as severe as SCID (severe combined immunodeficiency), as evidenced by failure to develop disseminated infection after BCG vaccination. Therefore, MHC II deficiency with BCGosis, that is disseminated BCGitis, is not reported commonly. We report an interesting case of BCGosis after vaccination that was diagnosed to have probable MHC II deficiency.

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INTRODUCTION

Major histocompatibility complex (MHC) class II deficiency was described in 1979 for the first time (1). MHC class II deficiency is a primary immunodeficiency disease characterized by partial or total absence of constitutive and induced MHC class II molecules (HLA -DR,-DQ and -DP) surface expression on peripheral blood lymphocytes and monocytes leading to impaired immune responses in the patients (2). The Autosomal recessive type of MHC II deficiency diseases result from defects in one of four different MHC II-specific transcription factors: CIITA, RFX5, RFXAP, and RFXANK (3). Hypogamaglobulinemia and low CD4⁺ T cell count are found in most of these patients with normal or elevated number of CD8⁺ T cell (4). Bone marrow transplantation is the only known curative approach (5). The patients are prone to severe and recurrent respiratory, digestive tract and intestinal infections which lead to malabsorption and ultimately to failure to thrive. These patients have a poor prognosis and an average life expectancy of no more than 4 years (2). It is not usual to develop disseminated infection after BCG vaccination. A search through Pubmed revealed no report of MHC II deficiency with BCGosis. Herein, we report a probable case of MHC class II deficiency with disseminated BCGitis.

THE CASE

The case is an 18-month-old girl born from related healthy parents without any perinatal complication. She was exclusively breastfed and routine immunizations including *bacilli Calmette-Guérin* (BCG) on Rt deltoid muscle had been performed. She had no significant problem other than developmental delay until 8 months of age. She was admitted because of pneumonia and right lower extremity edema when 8 months old. The patient had another admission at 11 months of age due to prolonged fever, cough, and diarrhea. Many work-ups had been done for finding the cause of chronic diarrhea such as stool fat and stool PH but there was no evidence of malabsorption or other problems.

Table 1. Results of laboratory investigations.

First Admission	The Second Admission	The Last Admission
WBC=28400/mm ³ (lymph 37%)	WBC=6200/mm ³ (lymph:39%)	WBC=2400/mm ³ (lymph: 38%)
Hgb=9.4g/dl	Hgb=7.6 g/dL	Hgb=5.7g/dl
platelet=558×10 ³ /mm ³	platelet=84.5×10 ³ /mm ³	platelet=164×10 ³ /mm ³
Albumin=3.3mg/dl	blood culture: negative	Albumin=2.3 g/dl
ALT=4U/L	urine culture: E. coli>10 ⁵ /HPF	ALT=37 U/L
AST=18U/L	HIV antibody: negative	AST=73 U/L
total protein=4.4mg/dl	PPD test: negative	PT>60 sec
ESR=27mm/hr(<20mm/hr)		PTT>120 sec

Also, screening for celiac disease and sweet chloride test for cystic fibrosis has been done without any positive result. These problems continued until 18 months of age. The patient's laboratory findings are shown in Table 1.

Then, she was referred to our clinic for the first time and admitted in our hospital. On physical examination she was edematous, irritable and had poor growth and development with a weight of 5 kg (percentile for age<3th), length of 65 cm (percentile for age<3th), and head circumference of 40 cm (percentile for age<3th).

Other abnormalities found on physical examination included generalized papular rash, oral moniliasis, rales in lungs, right axillary lymphadenopathy, and hepatosplenomegaly. Response to light and sound was absent. Also the patient did not have red reflex on eye examination.

She had one elder sister that had repeated infections such as meningitis and hearing loss with normal immunologic examination.

Serum immunoglobulin profile of the patient showed low IgG level so she was given intravenous immunoglobulin (IVIg) in addition to antibiotic therapy (Table 2).

Table 2. Correlates of immune function in the case.

First Time	Second Time
WBC=6200/mm ³ (lymph,39%)	WBC=2800/mm ³ (lymph 33%)
CD3=36%(55-83)	CD ₃ =29.3%(55-83)
CD4=4%(28-57)	CD ₄ =2%(28-57)
CD8=28%(10-39)	CD8=27.3%(10-39)
CD4:CD8=0.14(1-3.6)	CD4:CD8=0.07(1-3.6)
CD19=49%(6-19)	CD ₁₉ =58.9%(6-19)
CD16=15%(10.1-20.9)	CD ₁₆ =57.3%(10.1-20.9)
IgG<1.98 g/l(3.49-11.39)	
IgM<0.25 g/l(0.4-2.29)	
IgA<0.16 g/l(0.04-0.75)	

She had the following paraclinical test results on the last admission:

Abdominal paracentesis: WBC=760 cells (neutrophil=10%, lymphocyte=87%), protein=3g /dl, LDH=585 IU/L glucose=74 mg/dl, culture=no growth, Polymerase chain reaction (PCR) examination for aspergillus and candida were negative. Bone marrow aspiration was done showing mild shift to the left in myeloid series with no evidence of mycobacterium tuberculosis.

However, in both Liver and axillary lymph node biopsy evidence of acid fast bacilli was seen. Polymerase chain reaction (PCR) for *Mycobacterium bovis* were positive and histopathological change with granulomatous inflammation were seen.

In brain MRI, a lesion at gray-white matter highly suggestive of abscess or tuberculoma was reported. Duodenal biopsy was normal and color Doppler sonography of both lower

extremities were normal. *Pneumocystis jiroveci* was not found by PCR in the bronchoalveolar lavage. Stool exam for *Giardia lamblia* was negative.

Expression of HLA-DR on surface blood lymphocytes were evaluated. The result was zero while proliferative responses to mitogens were normal and absent responses to Candida test were seen.

She received non-irradiated packed RBC two times during her admission without occurrence of graft versus host disease (GVHD). Four anti-tuberculosis agents including Isoniazid, Rifampin, Ethambutol and Streptomycin were started for her with respect to disseminated BCGitis.

DISCUSSION

Primary immunodeficiency diseases (PIDs) are a group of inherited disorders, characterized by failing of the immune system development presented with recurrent infections and occasionally with complication of vaccines like BCG (6).

Chemli and colleagues have reported a high frequency of severe adverse effects of BCG vaccination occurring in patients with immunodeficiency disorder (7). PIDs could show BCG complication with different severity, varying from a localized disease or BCGitis to a more severe and life threatening disseminated shape, so called BCGosis. PIDs which are susceptible to severe mycobacterial disease following vaccination with BCG, consist of severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD) and Mendelian susceptibility to mycobacterial diseases (MSMD) (8). Currently, MSMD is divided to other subtypes (IFN- γ R1, IFN- γ R2, IL12R β 1, IL12P40, STAT1, and IKBKG deficiencies). BCG complications may occur in X-linked Hyper IgM syndrome (XL-HIGM) and Hyper IgE syndrome (HIES) too but prevalence and severity are less than the above-mentioned PIDs (9,10).

Although disseminated BCGitis occur in a number of patients with T-cell deficiency, it had not been reported in MHC class II deficiency (9,11). MHC class II has been known to activate CD4 T helper immune cells. A deficiency in MHC-II is considered to be equivalent to the lack of CD4 T cells in developing host immune responses to pathogens (12). According to this, possibility of BCGosis must be considered in patients with MHC-II deficiency.

The diagnosis of BCGosis is made based on the following criteria (13):

Definitive

“A male or female patient with systemic symptoms, such as fever or sub-febrile states, weight loss, or stunted growth, and at least two areas of involvement beyond the site of a BCG vaccination, such as lymph nodes, skin, soft tissues, lungs, spleen, liver or bones.

Identification of *Mycobacterium bovis* BCG sub-strain from the patient’s organs by culture and/or standard PCR, as well as typical histopathological changes with granulomatous inflammation.”

Probable

“Systemic symptoms such as fever or sub-febrile states, weight loss or stunted growth, and at least two areas of involvement beyond the site of a BCG vaccination, such as lymph nodes, skin, soft tissues, lungs, spleen, liver or bones. Identification of *M.*

tuberculosis complex from the organs by PCR, without differentiation of *M. bovis* BCG sub-strain or other members of the *M. tuberculosis* complex and with negative mycobacterial cultures, with the presence of typical histopathological changes with granulomatous” inflammation.

Possible

“Systemic symptoms such as fever or sub-febrile condition, weight loss or stunted growth, and at least two areas of involvement beyond the site of a BCG vaccination, such as lymph nodes, skin, soft tissues, lungs, spleen, liver or bones. No identification of mycobacteria by PCR or culture, with the presence of typical histopathological changes with granulomatous inflammation.”

The diagnosis of MHC II deficiency diseases is made based on the following criteria (13):

Definitive

“Male or female patient with decreased intensity of expression (less than 5% of normal) of HLA-DR or DP on B cells or monocytes and a mutation in one of the following genes: CIITA, RFX-B, RFX-5 or RFX-AP”

Probable

“Male or female patient with decreased intensity of expression (less than 5% of normal) of HLA-DR or DP on B cells and monocytes and all of the following:

- 1) Failure to thrive, opportunistic infections or persistent viral infections
- 2) Normal numbers of T cells and B cells
- 3) Normal proliferative responses to mitogens”

Possible

“Male or female patient with decreased intensity of expression (less than 5% of normal) of HLA-DR or DP on B cells or monocytes, and normal numbers of T cells and B cells, who has at least one of the following:

- 1) Hypogammaglobulinemia
- 2) Normal mitogen responses but absent T cell proliferation to antigens
- 3) Reduced numbers of CD4+ cells
- 4) Failure of mononuclear cells to stimulate a mixed lymphocyte culture”

In our case all possible causes for secondary immune deficiency were excluded. Dihydrorodamint (DHR) test ruled out the possibility of CGD, which should be suspected in all cases of BCGosis (14). Other primary T cell immune deficiencies were excluded by the absence of lymphocytosis, normal CD8 T cell counts (ZAP-70) deficiency, eczema AND thrombocytopenia (Wiskott-Aldrich syndrome), complex cardiac and craniofacial defects (Di George Syndrome), and hepatitis, hemo phagocytic syndrome and aplastic anemia (X-linked lymphoproliferative syndrome) (15).

Although we did not have the result of genetic analysis in our patient, the history of recurrent pneumonia required admission in hospital and also chronic diarrhea, oral thrush, generalized papular rash, severe failure to thrive, hypogammaglobulinemia, reduced numbers of CD4+ cells, normal response to mitogen, absent responses to

Candida test and absence expression of HLA-DR on B cells surface are in favor of probable diagnosis of MHC class II deficiency diseases in this patient.

On the other hand, typical histopathological change with granulomatous inflammation, positive PCR for *M. bovis* and acid fast bacilli on smear in both liver biopsy and axillary lymph node aspiration were in favor of definitive BCGosis diagnosis.

In conclusion, MHC class II antigen presentation and CD4 T-cell activation are critical for acquired immunity to mycobacterium tuberculosis infections and susceptibility of mice deficient in MHC class II to infection with mycobacterium tuberculosis has been confirmed in previous study (16). Therefore, it is not impossible for disseminated BCG to occur in patients with MHC class II deficiency such as XL-HIGM and HIES, with relatively lower prevalence compared to SCID, CGD and MSMD disease.

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