# Recurrent Infections and Bilateral Uveitis in a Patient with CD8 Deficiency

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## ABSTRACT

CD8 deficiency is a rare primary immunodeficiency with low or absent peripheral CD8 cells which results from TAP deficiency, Zap 70 deficiency and CD8 α gene mutation.

We report a 14 year old female who presented with a history of recurrent pneumonia, bronchiectasis, otitis, severe varicella, herpetic lesions of mouth, bilateral uveitis, and cataract formation since the age of 8 years.

She had growth failure, a huge spleen and moderate clubbing. In immunologic workup, humoral and phagocytic systems were normal. DTH response to candida, PPD and DT were negative but LTT response to PHA mitogen was normal. HLA typing showed normal class I expression. Flowcytometry of peripheral blood showed CD8: 0 to 2% (absolute count, 0-60 cells/$mm^3$) with increased CD4/CD8 ratio on several occasions.

Diagnosis of this patient cannot be HLA class I deficiency (TAP1 or TAP2), because class I expression had been normal. It is possible to be Zap -70 deficiency or CD8 α gene mutation. Bilateral uveitis in our patient was a unique presentation which might have resulted because of immune dysregulation in CID.

**Keywords:** CD8-Positive T-Lymphocytes; Immunologic Deficiency Syndromes; Uveitis; Zap 70 Protein



## INTRODUCTION

CD8 deficiency is a rare primary immuno-deficiency characterized by the absence of peripheral CD8 cells and normal or elevated CD4 cells which has been first reported by Roifman et al in 1988.[1]

Monafo et al reported additional cases with a similar clinical phenotype in 1992.[2] In 1994, several studies demonstrated that CD8 deficiency in these patients was due to mutations of Zap -70 tyrosine kinase gene which transduced the signals from T cell receptor.[3-5]

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During the same year and in 1995, Dela salle et al and Donato et al reported two patients who had a selective decrease of CD8 cell due to HLA class I deficiency secondary to TAP peptide transporter mutation.[6,7]

Recently, a Spanish group reported familial CD8 deficiency due to a mutation in the CD8 alpha gene.[8] The prevalence of these particular CD8 defect with such a dramatic effect on lymphocyte phenotype should be extremely low, since CD8 expression has been widely determined without any report of a CD8 deficient case. We describe a patient with recurrent infection who had CD8 deficiency due to zap -70 deficiency or CD8α gene mutation.

## CASE REPORT

A 14 year old female from a consanguineous family was referred to immunologic clinic of our hospital with a past history of recurrent pneumonia, bronchiectasis, otitis media, persistent oral candidiasis, herpetic lesion around the mouth, severe chickenpox from the age of 7 and bilateral uveitis which had resulted in cataract formation of the eyes from the age of 11.

In physical examination, growth failure, a huge spleen, moderate clubbing, and cataract of eyes were detected. Although bacterial infection and bronchiectasis suggested an antibody deficiency, immunoglobulin levels and IgG subclasses were normal. Natural antibodies were in the low normal range and antibody response to different antigens such as rubella and measles was present.

Complement levels and oxidative capacity of neutrophils were also normal. Lymphocyte phenotyping detected near total absence of $CD8^+$ cells, both $CD3^+$ and $CD4^+$ T cell, B cell and natural killer cell percentages and absolute numbers were normal whereas CD4/CD8 ratio had increased (table 1).

DTH responses to candida, PPD and DT were negative but proliferative responses to PHA mitogen were normal. A differential diagnosis of immunodeficiency with low CD8 cells such as Zap 70 deficiency, TAP deficiency and CD8 α gene mutation was made. HLA class 1 molecule expression was normal in the CD8 deficient patient and TAP deficiency was ruled out. Further investigation for definite diagnosis including Zap70 protein expression assessment and mutation analysis for CD8 α gene was not done in our clinic. The results of workup for bilateral uveitis and huge splenomegaly included: negative auto antibodies; serology for HIV infection, Brucella infection, and tuberculosis were also negative. Bone marrow examination was normal. ACE level (Angiotensin converting Enzyme), which is increased in sarcoidosis, was normal. Although bone marrow transplantation (BMT) was recommended for our patient HLA match donor has not been found until now.

**Table 1. Laboratory data of the case with CD8 deficiency.**

| Test | Results |
|---|---|
| ***CBC*** | |
| White Blood Cell (cell//mm³) | 4600 |
| Polymorphonuclear (%) | 28% |
| Lymphocyte (%) | 70% |
| Monocyte (%) | 2% |
| Hemoglobulin (gr/dl) | 10 |
| Platelete (cell//mm³) | 126000 |
| ESR | 50 |
| ***Flowcytometry (%)*** | |
| CD3 | 81% |
| CD4 | 71% |
| CD8 | 2% |
| CD19 | 12% |
| CD16-56 | 7% |
| CD8 Absoulute Count (cell//mm³) | 60 |
| ***Immunoglobulins (mg/dl)*** | |
| IgG | 2400 |
| IgM | 320 |
| IgA | 70 |
| IgE (IU/ml) | 17 |
| Lymphocyte Transformation Test with PHA | Normal |
| C3, C4, CH50 | Normal |
| NBT | 93% |
| ANA, Anti ds DNA | Negative |
| HIV PCR | Negative |

## DISCUSSION

A patient with repeated bacterial infection, persistent thrush, severe varicella and bilateral uveitis from late childhood is bring described in whom CD8 cells were shown to be absent and other known immunodeficiencies were ruled out.

A differential diagnosis of immunodeficiencies with low CD8 cells such as Zap70 deficiency[4,5] TAP deficiency[7] CD8 α gene mutation which has been described recently[8] was made.

TAP deficiency was ruled out for the patient because HIA class I molecule expression was normal. Further workup for definite diagnosis between Zap70 deficiency and CD8 α gene mutation was not done in our clinic. Different presentations of CD8 deficiency have been reported in other studies. Katamura et al reported a 2 month old boy with Zap70 deficiency, who had infiltrative erythematous skin lesions on his face and extremities from birth and immunohistological examination of his skin lesion revealed dense infiltration of CD4 T cell, which had characteristics of memory and activated $CD4^+$ T cells.[9] Elder et al reported a 10 month caucasian male with Zap 70 deficiency who presented with *Pneumocystis carinii* pneumonia at the age of 7 months and LTT responses were absent to PHA, PWM and con A.[10] Barata et al presented child with recurrent infections since the age of 4 months including bilateral pneumonia due to *Pneumocystis carinii* and protracted varicella which Zap 70 cDNA sequencing showed to be mutation and moreover no Zap-70 protein was detected in T cells.[11]

De La calle - martin et al,[8] reported a 25 year male from a consanguineous Spanish family with recurrent bacterial infections including repeated bouts of bronchitis and otitis media since the age of five years. PBMC proliferative responses to different stimuli were normal. For patient TAP and Zap-70 defects were ruled out and a missense mutation (gly 90→ ser) in both alleles of the immunoglobulin domain of the CD8 α gene was shown to correlate with the absence of CD8 expression found in the patient and two sisters. These studies showed that Zap 70 deficiency usually presented with SCID form of immuno-deficiency and had negative response to LTT with PHA. Diagnosis of our patient may be most compatible with CD8 α gene mutation because the onset of disease was from late childhood and LTT response to PHA was normal.

Bilateral uveitis and cataract in our patient have not been reported in other studies and in spite of negative workup for important causes of anterior uveitis such as JRA, sarcoidosis and TB it may be due to infiltration of autoreactive Tcell to uveal tract similar to the skin infiltration reported by katamura et al.[9]

BMT is the treatment of choice for these patients and recently, Fagioli et al,[13] reported successful unrelated cord blood transplantation in one patient with Zap -70 deficiency. Although BMT was recommended for our patient, the HIA match donor has not been found until now.

We emphasize the importance of performing tests such as Zap 70 protein expression detection and mutation analysis for CD8 α gene for diagnosis of these patients.

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