Chula Med J Vol. 46 No. 6 June 2002

Severe combined immunodeficiency: a case report and review of literatures

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Chatchatee P, Vanichsetakul P, Tantibhaedhyangkul U, Sirivichayakul S, Kupatawintu P, Ngamphaiboon J. Severe combined immunodeficiency: a case report and review of literatures. Chula Med J 2002 Jun; 46(6): 495 - 500

Severe combined immunodeficiency (SCID) is a rare and fatal primary immunodeficiency syndrome with profoundly impaired cellular and humoral immune function. Without early diagnosis and immunoreconstitution, affected patients suffer from severe infections and generally die in infancy.

We report the clinical presentations, immunologic abnormalities and course of disease of a case of SCID. Since similar presentations may be found in pediatric HIV infection, physicians need high index of suspicion to detect SCID patients. Early recognition of SCID is a pediatric emergency since prompt diagnosis is critical to the treatment outcome which leads to a cure for this otherwise fatal disease.

Key words: *Severe combined immunodeficiency, SCID, Primary immunodeficiency, Manifestation.*

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Received for publication. March 15, 2002.

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Severe combined immunodeficiency (SCID) เป็นโรคภูมิคุ้มกันบกพร่องแต่กำเนิดที่รุนแรงถึงชีวิต ผู้ป่วยโรคนี้มีความบกพร่องอย่างมากของภูมิคุ้มกันทั้ง cellular และ humoral immune response ผู้ป่วยจะมีการติดเชื้อต่าง ๆ ได้ง่าย ถ้าไม่ได้รับการวินิจฉัยและการรักษาที่ถูกต้อง ผู้ป่วยเกือบทุกรายจะเสียชีวิตในวัยทารก

รายงานนี้นำเสนอผู้ป่วย SCID 1 ราย ในด้านของอาการแสดงทางคลินิก ผลการตรวจทางภูมิคุ้มกันวิทยา การดำเนินโรค พร้อมทั้งทบทวนวรรณกรรมที่เกี่ยวข้อง เนื่องจากอาการแสดงของผู้ป่วยโรคนี้คล้ายคลึงกับผู้ป่วยเด็กที่ติดเชื้อ HIV แพทย์ผู้ให้การดูแลรักษาจึงต้องนึกถึง SCID ไว้ในการวินิจฉัยแยกโรคด้วย การให้การวินิจฉัยที่ถูกต้องและทันท่วงที จำเป็นอย่างยิ่งเพราะทำให้การรักษาให้ผลดี ช่วยให้ผู้ป่วยโรคร้ายแรงนี้สามารถมีชีวิตรอดได้

Severe combined immunodeficiency (SCID) is a rare primary immunodeficiency with profound cellular and humoral immune defects. In this article, we report a case of 10 - month old male infant with recurrent pneumonia and mucocutaneous candidiasis. He was found to have severe combined immunodeficiency (SCID) with a phenotype that was compatible with the X-linked form of this disorder. Clinical presentations and current concepts on immunoreconstitution are reviewed.

Case report

A 10-month-old boy was referred to King Chulalongkorn Memorial Hospital for further evaluation of recurrent infections. He was born by normal delivery with the birth weight of 3400 grams. He received BCG immunization at birth and 2 doses of DTP and OPV at 2 and 4 months old respectively. His family history revealed that his maternal uncle died in early infancy due to infection.

At the age of 7 months, the patient developed oral candidiasis and since the age of 8 months, he had had recurrent pneumonia that required multiple hospitalizations. No causative organism could be identified. In the last admission prior to the referral, the pneumonia was treated with intravenous cefotaxime with slight improvement. He also developed mucocutaneous candidiasis that was treated with ketoconazole. Two weeks before the referral, the patient had mucous bloody diarrhea and high fever that persisted until the day he was referred to King Chulalongkorn Memorial Hospital.

On admission, the body temperature was 39.8 degree Celcius, heart rate 140/min, respiratory rate 60/min, blood pressure 85/50 mmHg. Physical examination revealed a cachectic child with mildly pale conjunctiva, no icteric sclera. There was no visible tonsillar tissue. Oral thrush was present. There was redness and induration on left shoulder at the site of BCG immunization (Figure 1) and palpable lymph nodes of 0.5-1 centimeter in diameter at left axillary region (Figure 2). Chest auscultation revealed occasional rhonchi at right upper lung field. Liver was palpable 2 centimeters below right costal margin with firm consistency. Spleen was not palpable.

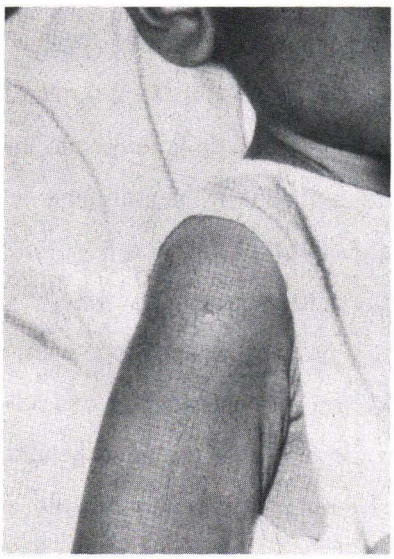

Figure 1. Suppuration of BCG inoculation site on left shoulder.

Figure 2. Enlarged lymph nodes at left axillary region.

Laboratory investigations yielded the following results: Hemoglobin 8.9 g%, hematocrit 28%, MCV 77 fl, MCH 24 pg, MCHC 31.7 g/dl, WBC 15,950/cu.mm. L 17%, Mo 6%, PMN 77% Platelet 388,000/cu.mm. Absolute lymphocyte count was 2,711/cu.mm. Total bilirubin 0.47mg/dl, direct bilirubin 0.14 mg/dl, alkaline phosphatase 80 u/l, SGOT 98 u/l, SGPT 32u/l, albumin 3.3 g/dl, globulin 1.9 g/dl. Anti HIV antibody was negative and chest X-ray showed atelectasis of right upper lung with air bronchogram.

Immunologic evaluations revealed low levels of IgG and IgA, and low normal IgM with IgG 8.9 mg/dl, IgA 5.6 mg/dl, IgM 29.8 mg/dl (normal values for this age are 310-800 mg/dl for IgG, 16-100 mg/dl for IgA, and 26-108 mg/dl for IgM). Lymphocyte phenotyping was performed and demonstrated very low T-cell with increase B-cell (CD3 =2%, CD4 =1%, CD8 =1%, CD16 =1%, CD19 =87%). T-cell response to mitogen using phytohemagglutinin (PHA) stimulation revealed very low response of the patient's T-cells (249 CPM compared to normal control 68,833 CPM) with stimulation index (SI) of 2.00 (control 11.21)

The patient was treated with intravenous cloxacillin and ceftazidime, intravenous immunoglobulin, isoniazid, rifampicin and ethambutol together with trimethoprim-sulfamethoxazole. On day 10thof the admission, right tension pneumothorax developed. He was transferred to intensive care unit and placed on high frequency ventilation. His condition deteriorated. He expired after 3 weeks of hospitaliza-tion. No organisms could be identified from lung and liver necropsy.

Discussion

SCID is a rare, fatal syndrome of a profoundly impaired cellular and humoral immune function.[1-3] Without immunoreconstitution, affected patients suffer severe and persistent infections, and generally die in infancy. Diagnosis of SCID is suggested when an affected infant has lymphopenia and severe hypogammaglobulinemia (IgG, <150 mg/dL).[4] Most SCID patients have peripheral $CD3^+$ T-cell counts of 500 cells/mm^3 or less (normal range, 3000-6500 cells/mm^3) and variable numbers of B and natural killer (NK) lymphocytes, depending on the underlying genetic defect. SCID can be classified according to the presence or absence of B and NK cells into $T^-B^+NK^+$, $T^-B^+NK^-$, $T^-B^-NK^+$, $T^-B^-NK^-$, and atypical T^+B^+ syndromes. Although both X-linked recessive and autosomal forms of SCID are recognized, the X-linked form is the most frequent. Patients with X-linked SCID generally have very low numbers of T cells and NK cells, whereas B cells are often found in relatively high numbers even though specific antibody responses are deficient (T^-, NK^-, B^+ phenotype).[4] X-linked SCID is caused by mutations of interleukin receptor gamma gene (IL2RG), [5,6] the gene encoding the common gamma (γ) chain, known as γc, found in the interleukin-2 (IL-2) receptor and multiple other cytokine receptors, including those for IL-4, IL-7, IL-9, and IL-15. The intracellular portion of γc is known to interact with Janus kinase 3 (Jak3), a signaling kinase that cooperates with other Jak and STAT proteins in a complex signal transduction pathway.[7,8]

Our patient presented with recurrent pneumonia and mucocutaneous candidiasis. Even though he did not have profound lymphopenia, he had a low lymphocyte count for his age. (ALC 2711, median value for age is 5990, range 3610-8840).[9] His low IgG level indicated B-cell defect while a low

lymphocyte proliferative response to PHA indicated T-cell defect. The lymphocyte phenotype in this patient was compatible with X-linked SCID ($T^-NK^-B^+$). This is supported by the family history of the maternal uncle who died of infection in early infancy. Molecular analysis for gene mutation in this family are underway. In a report by Buckley et al, reviewing 108 SCID cases, it was found that the mean age at diagnosis of SCID was 201 days, or 6.59 months. The common presentations were oral candidiasis, respiratory syncytial virus, parainfluenza 3 or *Pneumocystis carinii* pneumonia, adenovirus infection, gram- negative sepsis, persistent diarrhea, and failure to thrive.[4] In our patient, the causative organisms of recurrent pneumonia and diarrhea could not be identified.

Stem-cell transplantation is considered a life-saving treatment for patients with SCID. It is highly effective in reconstituting T-cell immunity in SCID patients.[10] The most optimal treatment is bone marrow transplantation or peripheral stem-cell transplantation from a histocompatible sibling. In cases where the patients do not have an HLA-identical family donor, T-cell-depleted haploidentical bone marrow transplantation from a parent can be performed and is successful in many patients with SCID.[11-13] If stem cells can be transplanted in the first 3.5 months of life, before infections develop, there is a high (95 percent) probability of success.[10]

Early recognition of SCID should be considered a pediatric emergency. Making a diagnosis before the onset of opportunistic infections is critical to successful outcome. If SCID is not detected until the infant is older, death can occur from infection before successful cellular therapy can be achieved. The absolute lymphocyte count is the most useful initial test, because lymphopenia is present in almost all patients with SCID from the time of birth.[14] Knowledge of the fact that normal ranges for lymphocyte counts are much higher in infancy than in older children is essential to the recognition of this syndrome; for example, the lower limit of normal for an absolute lymphocyte count at 4-8 months of age is 3,600/mm^3 and the median is 6,000/mm^3; in contrast the lower limit value is 1,600/mm^3 in adults.[9]

In our current situation where secondary immunodeficiency especially HIV infection is a much more common cause of immunodeficiency in infants, physicians need to have a high index of anopicion in order to detect patients with primary immuno-deficiency. Recurrent severe bacterial infections, prolonged suppuration of BCG vaccination site, persistent oral candidiasis (despite proper oral care) are the presentations that should prompt physicians to work up for immune defect. Low absolute lymphocyte count and low globulin levels especially with a relatively normal albumin level are strongly suggestive of T- and B-cell defects respectively.

Conclusion

We reported a case of infant with SCID who presented with recurrent pneumonia, mucocutaneous candidiasis and prolonged suppuration of BCG inoculation site. Early recognition of the disease will allow us to offer a cure to this otherwise fatal disease.

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