Natural Killer Cell Deficiency Associated with Hodgkin's Lymphoma: A Case Report

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Abstract: Natural killer (NK) cells are large granular lymphocytes that play important roles in immunity against viral infection. NK cell deficiency is associated with recurrent episodes of severe herpes group virus reactivation. Few cases of NK cell deficiency have been reported. Here, we report the case of a Taiwanese girl who had suffered from severe atopic dermatitis since infancy, and recurrent episodes of herpes virus reactivation since the age of 3 years old. NK cell deficiency was diagnosed based on the finding of persistently low NK cell counts in peripheral blood. Hodgkin's lymphoma developed when she was 6 years old. The present case suggests that NK cell deficiency may be an important risk factor in the development of Hodgkin's lymphoma.

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Key words:
NK cells
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Natural killer (NK) cells are large granular lymphoid cells that can mediate cytotoxic activity and produce certain chemokines and cytokines. Without any major histocompatibility molecule restriction, they kill certain tumor cells and virus-infected cells by means of the release of perforin, granzyme, proteases, and tumor necrosis factor-α (TNF-α), and induction of apoptosis [1]. The killer function does not depend on prior sensitization, so these lymphocytes are called natural killers. The major physiologic roles of NK cells are in early host defense against microbial agents [2]. Few cases of NK cell deficiency have been reported in the literature [3, 4]. Poor immune defense against herpes group viruses was a common presentation in these cases.

We report a case of NK cell deficiency with severe atopic dermatitis in infancy, bronchial asthma and recurrent herpes zoster infection in early childhood, followed by development of Hodgkin's lymphoma.

Case Report

A 6-year-old Taiwanese girl was admitted to the pediatric ward of National Taiwan University Hospital because of fever, hepatosplenomegaly, and enlargement of multiple lymph nodes around the neck.

She had suffered severe atopic dermatitis since infancy, which involved the skin on her face, neck, trunk, and extremities. Topical steroid and antihistamine were used as maintenance therapy for the atopic dermatitis, with intermittent oral steroid during episodic deterioration. Antibiotics had been prescribed due to recurrent bacterial infection of the skin. She had been admitted three times because of pneumonia and bronchial asthma before she was 3 years old, when the painful recurrent herpes simplex and zoster infection became manifest and required treatment. She was referred to our hospital at the age of 4 years. Groups of vesicles over her face, neck, and trunk were noted on physical examination and disseminated herpes zoster was diagnosed. Immunodeficiency was suspected, so a series of immunologic studies were performed. Lymphocyte surface marker examination using a fluorescence activated cell sorter (FACS) scan showed scanty numbers of CD3-/CD16+/CD56+ cells (ie, NK cells), comprising only 1% of peripheral blood lymphocytes (normal, 5–15%). Mitogen responses of the lymphocytes to concanavalin A (ConA), phytohemagglutinin (PHA), and pokeweed mitogen (PWM) were within normal limits (Table 1). The results of complete blood cell counts, biochemistry, and serum immunoglobulins are shown in Table 2. Eosinophilia, reversed CD4/CD8 T-cell ratio, and few NK cells were noted. NK cell deficiency was, therefore, suspected in light of her recurrent herpes infection and low number of NK cells. A repeated examination 3 months later confirmed NK cell deficiency, when NK cells were 0% of her peripheral blood lymphocytes and 2% of her bone marrow

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Table 1. Results of mitogen response test

Age	Medium	Con A		PHA		PWM	
	Count	Count	SI	Count	SI	Count	SI
4y	2,812	12,312	4.38	187,449	66.7	25,639	9.12
4y3m	2,889	9675	3.45	93,239	32.3	35,379	12.2
4y9m	2,685	33,039	12.3	22,118	8.24	86,714	32.3

Con A = concanavalin A; PHA = phytohemagglutinin; PWM = pokeweed mitogen; SI = stimulation index; y = years; m = months.

lymphocytes. Over the following 2 years, she was re-admitted four times, twice due to herpes zoster flare-up and twice due to pneumonia and asthma.

At the age of 6 years, fever, enlarged lymph nodes, and hepatosplenomegaly were noted. Her spleen was enlarged to the umbilical level. She was admitted because a malignancy or an unusual infection was suspected. Widening of the mediastinum was noted on chest roentgenogram. Chest and abdominal computerized tomography (CT) scans were performed and revealed multiple soft tissue masses around the aorta (Figure) characteristic of lymphoma. Biopsy of the paraaortic lymph node and liver showed Hodgkin's lymphoma (HL) of the mixed cellular type at clinical stage IVB. It has been reported that HL may be related to Epstein-Barr virus (EBV) infection [5, 6]. Therefore, titers of antibodies against EBV were examined and the results were as follows: EBV-associated nuclear antigen 1:32 (+), EBV early antigen (EA) immunoglobulin A (IgA) 1:10 (+), EBV EA IgG 1:40 (+), EBV viral capsid antigen (VCA) IgM (-), EBV VCA IgG 1:5120 (+), and EBV VCA IgA 1:10 (+).

Chemotherapy using prednisolone, adriamycin, cyclophosphamide, vincristine, and procarbazine was administered. The spleen and lymph nodes shrank after chemotherapy. The treatment course was complicated with herpes zoster reactivation, six episodes of neutropenic fever, and one episode of retropharyngeal abscess. However, the lymphoma relapsed during the course of chemotherapy. The patient died at the age of 8 years due to respiratory failure secondary to peritonitis and pneumonia.

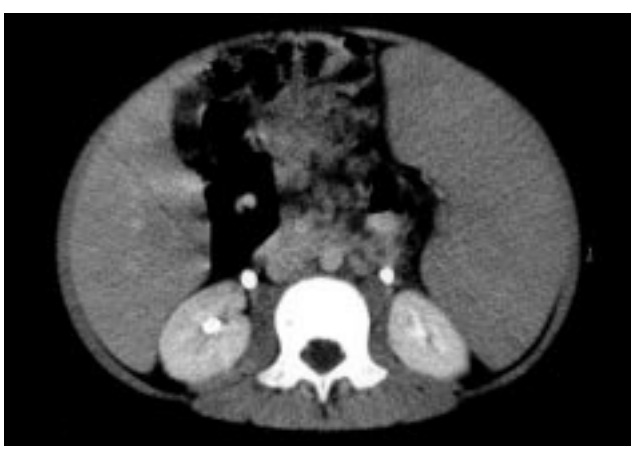

Figure. *Abdominal computerized tomography scan of the patient shows splenomegaly and multiple confluent enlarged lymph nodes.*

Discussion

NK cells are lymphoid cells that take part in immune responses such as defense against viral infection, malignancy, intracellular bacteria, and parasites, and in the production of cytokines and chemokines regulating T-cell function and hematopoiesis [1, 2]. In humans, NK cells express a unique pattern of surface molecules: CD16, which is a low-affinity Fc receptor (FcgRIII), and CD56, which is an isoform of the neural cell adhesion molecule [1, 2]. The number of NK cells can be accurately counted by the detection of cell surface marker (CD16 + CD56) via flow cytometry. Our patient had very few NK cells, only 1% at the age of 4 years, with a further reduction of NK cells to 0% of peripheral blood lymphocytes and 2% of bone marrow lymphocytes at a repeated examination 3 months later. Based on her clinical history of recurrent episodes of severe herpes group virus reactivation, NK cell defi-

Table 2. Hematologic and immunologic data

	Age (yr)		
	1	4	6
Red blood cell count (x 10^6/μL)	4.62	4.17	3.25
Hemoglobin (g/dL)	12.5	11.2	8.2
Mean corpuscular volume (fL)	84.8	76.3	75.7
Platelet count (x 10^3/μL)	533	213	136
White blood cell count (/μL)	20,300	12,030	6,500
Band (%)	1	1	2
Segment (%)	23	14	46
Monocyte (%)	8	7	16
Eosinophil (%)	10	30	18
Lymphocyte (%)	54	48	18
Atypical lymphocyte (%)	4	0	0
IgG (mg/dL)	435	1,250	1,800
IgA (mg/dL)	82	70	56
IgM (mg/dL)	244	218	345
IgE (kU/L)	546	148	ND
C3 (mg/dL)	176	66.8	ND
C4 (mg/dL)	32	30	ND
T cells (%)	ND	88	91
B cells (%)	ND	7	7
Natural killer cells (%)	ND	1	1
CD4+ T cells (%)	ND	32	35
CD8+ T cells (%)	ND	47	46
CD45RO+ CD4+T cells (%)	ND	13	14
CD45RA+ CD4+T cells (%)	ND	19	21

Ig = immunoglobulin; ND = not done.

ciency was diagnosed. A test to determine the cytolytic function of NK cells was not available at that time.

NK cells play roles in the defense against malignant cells. This is reflected in the higher likelihood of melanoma growth and metastasis in mice with NK cell deficiency [7]. Whether a causal relationship between NK cell deficiency and HL exists remains unclear. In the present case, NK cell deficiency developed 3 years before the diagnosis of HL. The interaction of NK cells, EBV, and HL is complex. EBV infection can suppress NK cell function, induce B-cell activation and proliferation, and then reactivate T-cell proliferation and activation [8]. These immunologic changes during EBV infection are usually transient. Chronic active EBV infection with NK cell defects has been reported [9]. HL is associated with immune dysfunction such as skin test anergy, poor T-cell response to mitogens and cytokines, failure to reject skin grafts, and decreased NK cell activity [8, 10]. However, a recent report by Ikinciogullari et al found no correlation between NK cell activity and the etiology, prognosis, and severity of HL in children with HL [11]. More studies are needed to clarify the relationship between NK cell deficiency and HL.

NK cells, in the presence of infection, can release interferon gamma (IFN-γ). In cases of NK cell deficiency, IFN-γ decreases and so does the ratio of IFN-γ to interleukin-4 [2]. It therefore seems reasonable that patients with NK cell deficiency would be at increased risk of developing Th2-predominant disorders such as atopic dermatitis and bronchial asthma.

Transient decrease in the number of function of NK cells may also occur secondary to infection, malignancy, or poor nutrition. NK cell function usually recovers if the underlying causes disappear. The persistence of NK cell deficiency in our patient suggests that it was primary in nature. However, there is no specific treatment at present for idiopathic NK cell deficiency. In our patient, episodic reactivation of herpes virus was treated with oral or intravenous acyclovir, and chemotherapy was given when HL developed.

In conclusion, NK cell deficiency is associated with recurrent episodes of severe herpes group virus reactivation. Physicians need to check NK cell numbers and function in suspected cases of NK cell deficiency. Lymphoma should be highly suspected when patients present with prolonged fever, lymphadenopathy, or hepatosplenomegaly.

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