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BARE LYMPHOCYTE SYNDROME WITH LACK OF HLA CLASS I AND II ANTIGENS

Presentation of Two Cases*

*Fügen Ersoy MD***, Özden Sanal MD***, İlhan Tezcan MD****
*Leman Yel MD*****, Ayşe Metin MD******

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Bare lymphocyte syndrome (BLS) is a rare disorder characterized by deficient expression of human leukocyte antigens (HLA antigens) and combined immunodeficiency to various degrees. Recurrent severe infections especially due to opportunistic organisms are common. Here, we present two patients with BLS who lack both class I and II antigens (Type III). They had the typical clinical and immunologic findings of BLS. The first patient showed marked improvement in pulmonary symptoms resulting from cytomegalovirus infection by means of gancyclovir treatment. However, intramuscular injections of interferon-α (IFN-α) had no beneficial effect in either the expression of HLA antigens or the clinical status. The second patient died of septicemia while being prepared for bone marrow transplantation. *Key words: bare lymphocyte syndrome, HLA antigens, combined immunodeficiency, interferon-α.*

"Bare lymphocyte syndrome (BLS)" or "major histocompatibility complex (MHC) class I or II deficiency syndrome" is a rare disorder in which patients have a deficient expression of human leukocyte antigens (HLA antigens). The usual clinical manifestations consist of recurrent severe and opportunistic infections, persistent gastroenteritis and overwhelming septicemia[1-3]. The first patient with BLS in the literature was found to have a defect in the expression of HLA class I antigens (Type I)[4]. However, BLS may also involve only class II antigen expression (Type II), or both class I and class II antigen expression (Type III)[1,2]. In Type I, beta-2 microglobulin, a structural component of class I antigens, is not found on the surface of the cells either[1,3,5].

We present here two patients with defective expression of both class I and II antigens.

Case Reports

Case 1

ÖS, the fourth child of consanguineous parents (first cousins), was admitted to our hospital with the complaints of fever, tachypnea and diarrhea at the age of 5.5 months.

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* From the Immunology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

** Professor of Pediatrics and Pediatric Immunologist, Hacettepe University Faculty of Medicine.

*** Associate Professor of Pediatrics, Hacettepe University Faculty of Medicine.

**** Pediatrician and Fellow in Immunology, Hacettepe University Faculty of Medicine.

***** Pediatrician and PhD Student in Immunology, Hacettepe University Faculty of Medicine.

The past history revealed that she had been born with a body weight of 3800 g (90-95th percentile), and her clinical condition at birth and development during the first 3.5 months had been seemingly normal. Then, however, she had recurrent otitis media, urinary tract and pulmonary infections despite appropriate antibiotic therapy. BCG and two doses of DTP-OPV vaccinations had been administered without any complication. Her two female siblings were healthy, but a male sibling who had been diagnosed with combined immunodeficiency (CID) had died of intractable pneumonia at the age of eight months. Postmortem tissue specimens had revealed lymphoid depletion and absence of germinal center formation in the spleen, consistent with severe combined immunodeficiency (SCID), and pneumocystis carinii pneumonitis.

On admission, her weight was 6500 g (25th percentile), she had respiratory failure, oral candidiasis and hepatomegaly. The laboratory data are shown in Table I.

Table I: Laboratory Data of The Patients

	Case 1	Case2
Hemoglobin (g/dl)	11.8	9.8
White cell count (/mm^3)	5800	7200
Total lymph.count (/mm^3)	1450	1944
Serum immunoglobulins		
IgG (mg/dl)	< 52.4	59.2
IgM (mg/dl)	< 13.1	< 13.1
IgA (mg/dl)	< 21.0	< 21.0
DTH: PHA	(–)	(+)
Candida	(–)	(–)
Tetanus	(–)	(–)
PPD	(–)	(–)
Lymphocyte markers*		
CD3	10% (326)	32% (622)
CD4	11% (358)	8% (156)
CD8	5% (163)	28% (544)
CD20	4% (130)	38% (738)
CD56	6% (196)	ND
Lymphocyte stimulations		
PHA (cpm)	48499	63867
Con-A (cpm)	39787	49059
Media (cpm)	1673	3300
MLR	uninformative	ND
HLA Class I	(–)	(–)
Class II	(–)	(–)

DTH : delayed type hypersensitivity reaction.
MLR : mixed lymphocyte reaction.
ND : not determined.
* : absolute counts per mm^3 are shown in parenthesis.

There was radiologic evidence of interstitial pneumonia. HLA class I and II antigens were negative by microcytotoxicity assay. However, HLA A2, A3, B51, B50, BW4 and BW6 antigens could be detected on peripheral blood mononuclear cells after in vitro treatment with IFN-α. Oligotyping for DR loci was kindly performed by M. Oudshoorn (Blood Bank, Leiden, Netherlands) and found to be identical to one of her sisters (Table II).

Table II: HLA Antigens of The Cases and The Family Members

Case 1	: Negative
	: A2, A3, B50, B51, BW4, BW6 (After in vitro IFN-α treatment)
Father	: A2, A3, B51, CW-, DR4, DR11, DQ7, DQ8, BW4, DR52, DR53
Mother	: A1, A3, B7, B50, CW6, CW7, DR15, DR17, DQ2, DQ6, BW6, DR51, DR52
Sibling 1:	A1, A2, B7, B51, CW7, DR4, DR15, DQ6, DQ8, BW4, BW6, DR51, DR53
Sibling 2:	A2, A3, B50, B51, CW6, DR4, DR17, DQ2, DQ8, BW4, BW6, DR52, DR53
Oligotyping for the DR-loci:	
Case1	: DRB1*0402, DRB1*0301, DRB3*0202
Sibling 2:	DRB1*0402, DRB1*0301, DRB3*0202
Case 2	: Negative
Father	: A3, B44, BW4, DR4, DR53, DQ7
Mother	: A11, A23, B27, B49, BW4, DR1, DR11, DR52, DR53, DQ5, DQ7
Sibling 1:	A3, A23, B44, B49, BW4, DR4, DR11, DR52, DR53, DQ7
Sibling 1:	A3, A11, B44, B27, BW4, DR4, DR11, DR52, DR53, DQ7

Intravenous immunoglobulin (IVIG), antibiotic and antifungal therapy were initiated. As cytomegalovirus (CMV) inclusion bodies were identified in the urine, gancyclovir treatment was given for three weeks and resulted in marked improvement in pulmonary findings and a gradual decrease in the elevated transaminases and the hepatomegaly. She was discharged with intravenous immunoglobulin, prophylactic trimethoprim-sulfamethoxasole and ketoconazole. During follow-up at the outpatient clinic, she had chronic diarrhea which led to failure to thrive and finally to marasmus. Intramuscular injections of human interferon-α administered for seven weeks in the hope of ameliorating the symptoms was of no benefit to either the disease course or the expression of HLA antigens. At 22 months, she weighed 5100 g (< 5th percentile) and BCG lymphadenitis appeared in her left axillary region. She was referred to Prof. Dr. J.M.J.J. Vossen (Department of Pediatrics, University Hospital of Leiden) for bone marrow transplantation (BMT) from her HLA identical sibling.

Case 2

The second case, ÖF, was also a female infant referred to our hospital because of pneumonia at the age of four months. The part history revealed that she had

been born with a body weight of 2200 g (< 5th percentile) and had begun to suffer from persistent cough, recurrent fever and diarrhea during the neonatal period. BCG had been administered at birth with no complication. She was the fourth child of consanguineous parents (first cousins). A male sibling had died of persistent pneumonia and gastroenteritis at home at the age of six months. Two female siblings were healthy.

On referral, she weighed 5000 g (25th percentile) and the physical examination revealed palpable small cervical lymph nodes, oral candidiasis, intercostal retractions and bilateral rales. Atelectasis, hyperinflation and bronchial thickening were seen on the chest roentgenogram. The laboratory data are shown in Table I. HLA class I and II antigens were negative by microcytotoxicity method. In vitro treatment of lymphocytes by IFN-α had no effect on the expression of HLA antigens (Table II).

The patient was given IVIG, antibacterial and antifungal therapy. During follow-up, intractable diarrhea requiring hospital care persisted on two occasions. She succumbed to death at home, presumably because of septicemia three months after the diagnosis.

Discussion

BLS was first described by Touraine et al.[4] in 1978. Several additional cases have subsequently been reported[2, 3, 5-7]. Among these, two siblings born to a family of Turkish origin have been reported by Schuurman et al.[5] Having an autosomal recessive form of inheritance, relatively frequent occurrence of BLS can be expected in our country because of the high incidence of marriages among relatives.

The HLA antigens function as important recognition signals on the surface of lymphocytes and play a crucial role in modulating lymphocyte functions such as antigen presentation to immunoregulatory T cells (especially CD4 helper cells) and T cell development in the thymus. In BLS, as a result, both T and B cell functions are impaired to various degrees[1, 2, 5]. Apart from a few patients reported lacking HLA class I antigens without suffering from apparent immunodeficiencies, all others described in the literature have a combined type of immunodeficiency with slight variations in the degree of the defects and the severity of the disease[2, 3, 5-8]. Both of our cases presented with recurrent lower respiratory tract infections, gastroenteritis and oral candidiasis in early infancy, as did the vast majority of the patients in the review by Haas and Steihm[2]. Despite all the supportive therapy, IVIG, prophylactic antifungal and antibacterial agents, the inevitable, gradually developing marasmic state of our first patient was noteworthy.

Although both patients had hypogammaglobulinemia; while T and B cells were diminished in the first patient, diminished T cells and slightly increased B cells were discovered in the second patient. This finding supports the view that

defective T-cell function leads to deficient B-cell response to antigenic stimulation. Negative delayed hypersensitivity skin test (DTH) reactions of Case 1 were consistent with most of the cases in the literature[2]. However, in the second case, DTH response to one of the mitogens (PHA) was slightly positive, as in Tourain's case[4]. Normal or near-normal proliferative response to mitogens, a characteristic finding of BLS, was observed in both of our patients. Although absent proliferative response to specific antigens is another consistent finding in BLS, we could not demonstrate it as our tests failed.

It has been reported that both α and β human interferons could enhance the expression of HLA class I antigens in vitro[9]. We observed the same effect in Case 1. On the other hand, intramuscular injections of IFN-α were beneficial neither in alleviating clinical symptoms nor in expression of HLA antigens in the same patient.

BMT is now accepted as the treatment of choice when an HLA-matched sibling is available[10]. It is necessary to perform genotyping with DNA probes to determine the HLA antigens of the patient in order to choose the donor[11]. Successful BMT from a haploidentical parent or from an unrelated donor has also been reported[7, 12]. Furthermore, successful in utero transplantation of fetal liver stem cells in two patients with BLS diagnosed prenatally has already been mentioned as an alternative to therapeutic abortion[13]. However, the overall prognosis of BLS is still poor. Elucidation of the precise molecular pathogenesis of the illness and cloning of the regulatory genes for HLA antigen expression may contribute to the development of more promising therapeutic approaches, such as gene therapy.

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