CASE REPORT

Familial Hodgkin’s Lymphoma from the Perspective of HLA

Mehmet Sonmez 1, Nergiz Erkut 1, Fahri Ucar 2, Kurtulus Buruk 1, Umit Cobanoglu 4, Muhterem Bahce 5 and Ali Ugur Ural 6

Abstract

Although the incidence of Hodgkin lymphoma (HL) - a lymphoid tissue malignity - increases in the presence of several viruses, particularly EBV, as well as with autoimmune diseases and following transplantation, although to date, the exact etiopathogenesis is not known. The higher frequency of HL among family members suggests involvement of genetic factors in its etiology. Studies aiming to elucidate the etiopathogenesis of patients with familial HL (FHL) have reported that human leukocyte antigen (HLA) haplotypes might be involved. In this case presentation, the associations between HLs diagnosed in a father of consanguineous marriage and his two children and HLAs in other family members were investigated and the findings are discussed in view of the published literature; no direct association was found between HLA alleles and the development of the disease in the present case with familial HL.

Key words: familial hodgkin lymphoma, human leukocyte antigen


Introduction

Hodgkin lymphoma (HL) of the lymphoid tissue is histopathologically characterized by the presence of giant multinuclear Reed-Sternberg (RS) cells. The estimated annual incidence of HL is 2-3/100,000 and it is most commonly encountered in young adults (1). The presence of natural immune system cells of neutrophils, macrophages, eosinophils, basophils and mast cells and T and B lymphocytes in lymphoid structures together with RS cells suggests a potential involvement of the immune system in the pathogenesis of the disease (2). Higher incidences in the presence of Epstein-Barr virus (EBV) also suggest a possible infectious impact in the pathogenesis (3). Additionally, the high incidence of HL among immediate family members compared to other malignant diseases indicates that environmental and genetic factors might also be involved. The presence of HL in multiple family members was first reported by Razis et al (4). The etiologic and oncogenic mechanisms of the familial diseases have not currently been clearly understood. While HL may be seen in up to 4-5% of the family members, the risk increases by 3-9-fold in first degree relatives (5, 6). Studies to elucidate the etiopathogenesis of patients with familial HL (FHL) have reported individuals with certain human leukocyte antigen (HLA) haplotypes to be more susceptible. Although a weak correlation has been identified between FHL and HLA class I regions containing HLA A1, B5, B8 and B18 alleles, a recent correlation has been reported between familial nodular sclerosis type classical HL (NSHL) and HLA DRBI*1501, DQA1*0102, DQB1*0602 alleles and TAP gene (7, 8). In this case presentation, the relationship of HLAs between a HL father of consanguineous marriage with 2 HL children and his family members was examined and discussed in view of the published literature.

1Department of Haematology, Karadeniz Technical University, School of Medicine, Trabzon, Turkey, 2Department of Medical Biology and Genetics, Karadeniz Technical University, School of Medicine, Trabzon, Turkey, 3Department of Microbiology and Clinical Microbiology, Karadeniz Technical University, School of Medicine, Trabzon, Turkey, 4Department of Pathology, Karadeniz Technical University, School of Medicine, Trabzon, Turkey, 5Department of Medical Genetics, Gulhane Medical Academy and School of Medicine, Ankara, Turkey and 6Department of Haematology, Gulhane Medical Academy and School of Medicine, Ankara, Turkey

Received for publication September 8, 2009; Accepted for publication November 13, 2009

Correspondence to Dr. Mehmet Sonmez, mesonmez@yahoo.com
Figure 1. Nodular sclerosis type classical HL. Scattered classical RS cells set in a background of reactive inflammatory cells (Case 1).

Figure 2. Lymphocyte-rich type classical HL. RS cells in a background of mainly small lymphocytes (Case 2).

Figure 3. Lymphocyte-rich type classical HL. RS cells in a background of mainly small lymphocytes (Case 3).

Case Report

Case 1

A 44-year-old man presented to his local physician with a one-month history of swelling in the right axillary region, weakness, fever and night sweats. Excision biopsy from the right axillary lymphadenopathy (LAP) was done. Histopatologic examination revealed nodular sclerosing hodgkin lymphoma (NSHL) with RS cells surrounded by fibrotic collagen bands (Fig. 1). Computerized tomography (CT) of the patient revealed multiple LAPs in the right axillary and paraaortic regions, the largest of which were 40 × 20 mm and 20 × 15 mm, respectively. The liver size was 180 mm and the spleen size was 140 mm. There was no evidence of bone marrow infiltration and, the patient was staged as stage III B according to Ann Arbor Lymphoma Classification. A chemotherapy protocol of adriamycin-bleomycin-vinblastine and dacarbazine (ABVD) was started. Remission was achieved after 6 courses of ABVD treatment and the patient was asymptomatic in the 18-month follow-up. In the 20th month follow-up, the patient presented to hospital with back pain; a magnetic resonance image (MRI) revealed multiple masses in the paravertebral soft tissue at the T6-8 levels. Simultaneous CT also revealed multiple LAPs in the paraaortic region, the largest of which was 15 mm; 10 mm LAP in the cervical-submandibular region, and 20 × 10 mm mass in the left nasopharynx upper wall with bilateral pleural effusion. The patient received radiotherapy (RT) applied to the involved thoracolumbar region, and afterwards was referred to our hematolgy clinic for autologous stem cell transplantation. The patient was staged as relapsed HL and a therapy protocol including ifosfamide-etoposide-cisplatin (ICE) was started. After 2 courses of chemotherapy, remission was accomplished. Autologous stem cell transplantation could not be initiated due to inefficient stem cell mobilization possibly due to previous therapies. The patient is currently being followed up as asymptomatic on remission.

Case 2

A 22-year-old woman (daughter of the case 1) presented to the hospital with a past 1.5 month history of swelling in the right axillary region, weakness, fever and night sweats. Microscopic examination of the excision biopsy from the right axillary LAP revealed scattered RS cells in a lymphocyte rich background whereas other inflammatory cells, including eosinophils and plasma cells were generally sparse (Fig. 2). CT revealed multiple LAPs in the right hilus and right axillary region, with largest size of 30 × 20 mm. There was no infiltration in the bone marrow aspiration; the patient was staged as stage II B according to the Ann Arbor lymphoma classification. ABVD chemotherapy regimen was started and followed by involved field RT. Remission has been accomplished after the therapies, and the patient is still healthy on follow-up.

Case 3

A 13-year-old boy (son of the first case), presented to the hospital with a past 1 month history of swelling in the left axillary region, weakness, fever and night sweats. Microscopic examination of the excision biopsy from the left axillary LAP revealed scattered RS cells in a lymphocyte rich background along with other inflammatory cells, eosinophils and sparse plasma cells (Fig. 3). CT revealed multiple LAPs
in the left axillary region (largest 30 × 20 mm) and in cervi- 
cal, preauricular and submandibular regions (largest 25 × 10 
mm). There was no infiltration in the bone marrow aspira-
tion; the patient was staged as stage II B according to the 
Ann Arbor Lymphoma Classification. ABVD chemotherapy 
regimen was started and followed by involved field RT. Re-
mission was achieved following the therapies and the patient 
is healthy on follow-up.

The patient with relapsed HL was referred to our center 
for autologous stem cell transplantation following high-dose 
therapy, and an in-depth analysis of the patient’s family was 
initiated to rule out a possible familial HL link. Serological 
tests of all patients revealed evidence of past, but not recent 
EBV infection (specific IgG present, IgM absent). There-
fore, patients’ pathologic lymph nodes were analyzed with 
real time polymerase chain reaction (RT-PCR) method (Ro-
torgene 6,000) and EBV DNA was found to be negative. 
Conventional chromosome analyses of patients carried out 
with banding method determined 46 XY and 46 XX with no 
other accompanying abnormalities. Given that the patient 
had a consanguineous marriage, HLA tissue groups - a fac-
tor possibly responsible for the HL etiopathogenesis - were 
analyzed via the RT-PCR method (Thermocycler) (Table 1).

**Table 1. HLA Alleles of the Family**

Table 1. HLA Alleles of the Family

<table>
<thead>
<tr>
<th>HLA Allele</th>
<th>Presence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1<em>01, A1</em>02, A3<em>01, A3</em>02, B7<em>02, B8</em>01, B18*01</td>
<td>Present</td>
</tr>
<tr>
<td>A1<em>01, A1</em>02, A2<em>01, A3</em>01, B7<em>02, B8</em>01, B18*01</td>
<td>Present</td>
</tr>
<tr>
<td>A1<em>01, A1</em>02, A3<em>01, A3</em>02, B7<em>02, B8</em>01, B18*01</td>
<td>Present</td>
</tr>
<tr>
<td>A1<em>01, A1</em>02, A3<em>01, A3</em>02, B7<em>02, B8</em>01, B18*01</td>
<td>Present</td>
</tr>
<tr>
<td>A1<em>01, A1</em>02, A3<em>01, A3</em>02, B7<em>02, B8</em>01, B18*01</td>
<td>Present</td>
</tr>
<tr>
<td>A1<em>01, A1</em>02, A3<em>01, A3</em>02, B7<em>02, B8</em>01, B18*01</td>
<td>Present</td>
</tr>
<tr>
<td>A1<em>01, A1</em>02, A3<em>01, A3</em>02, B7<em>02, B8</em>01, B18*01</td>
<td>Present</td>
</tr>
<tr>
<td>A1<em>01, A1</em>02, A3<em>01, A3</em>02, B7<em>02, B8</em>01, B18*01</td>
<td>Present</td>
</tr>
<tr>
<td>A1<em>01, A1</em>02, A3<em>01, A3</em>02, B7<em>02, B8</em>01, B18*01</td>
<td>Present</td>
</tr>
</tbody>
</table>

**Discussion**

The exact etiopathogenesis of HL is not known. Seasonal 
features observed in HL diagnosis and higher frequencies in 
individuals with a history of EBV suggest the presence of 
environmental factors in the etiology of the disease (9). The 
presence of EBV DNA has been demonstrated in almost 
half of the patients with HL and high levels of EBV anti-
bodies were detected in the sera of patients (3). Although 
asymptomatic EBV infection is common in the normal 
population, the fact that HL does not develop in these pa-
tients suggests that various environmental factors and/or ge-
etic causes have a significant role in the etiopathogene-
sis (10). In addition to EBV, cytomegalovirus (CMV), hu-
man herpes virus type 6-7-8, polyomavirus JC and BK, ade-
ovirus and human T lymphotropic viruses have also been 
reported to be possibly responsible for HL development. In 
addition, an increased risk of HL was identified in autoim-
mune diseases such as rheumatoid arthritis, systemic lupus

erythematous, sarcoidosis and immune thrombocytopenic 
purpura and during the post-transplantation period, although 
no clear relationship could be established (3).

Risk of HL among family members is higher compared to 
other hematologic malignancies and the incidence of the dis-
ease is increased by 3-9 fold in relatives of patients with 
HL (6, 11). Mack et al demonstrated a higher risk of HL in 
monozygotic twins compared to dizygotic twins, suggesting 
a possible link of genetic risk factors in the etiology of the 
disease (12). The presence of similar HLA types among af-
fected family members also supports this opinion (5). Two 
types of FHL have been identified. In one of these FHL 
types, genetic factors such as HLA and EBV-like environ-
mental factors are involved in the etiopathogenesis and dif-
ferent histological types may be encountered. In the other 
type, environmental and genetic factors are ineffective and 
predominantly the nodular lymphocytic type HL is seen (6). 
The present cases suggest a possible link of environmental 
and genetic factors, since several coexisting histological 
types were observed.

HLA is a glycoprotein coded by the major histocompati-
bility complex (MHC) localized to the short arm of the 
chromosome 6. It is present in all tissues and cells and has 
an important role in regulating the immune response. HLA 
genes having a role in immune responses against viruses are 
believed to have a critical role in the etiology of 
HL (10, 13). It has been reported that the presence of some 
certain HLA haplotypes is correlated with impaired immune 
response that may contribute to development of HL. This 
point of view is supported by decreased cellular immunity 
oberved in patients with HL (6). Specific HLA haplotypes 
have been shown in patients with FHL. A weak correlation 
has been identified between FHL and HLA class I regions 
containing HLA A1, B5, B8 and B18 alleles (7). More re-
cent studies have shown epidemiologic and prognostic rela-
tionships between HL and HLA DP alleles contained in the 
HLA class II region (14). Harty et al reported a possible re-

doan between NSHL and HLA DRB1*1501, DQB1*0602, DQA1*0102 while Klitz et al demonstrated a positive 
relationship between NSHL and HLA DRB1*1501, DQB1*0602 and DRB1*1104 alleles and a negative relationship 
with DRB1*1601, DRB1*0404, DQB1*0303 alleles (8, 15). On the contrary to the families previously described, the

On the contrary to the families previously described, the
present cases of familial HL had quite similar types of HLA among the parents of consanguineous marriage and their children. This similarity even manifested as completely identical HLA types in the children. Determining the relationship between FHL and HLA in a HLA types with such close similarities and establishing a direct association was important in the etiopathogenesis of FHL. The most important finding of our investigation on the family was the presence of homozygote DRB1*11 HLA allele among the patients consistent with previous reports. A negative or positive relationship could not be identified between HLA alleles which were previously described to be possibly responsible. Although the detected homozygosis seems to be important in the etiopathogenesis, the fact that one of the siblings with the DRB1*11 HLA allele had completely identical HLA as the other sibling who was healthy. This feature indicates that the role of HLA in the etiopathogenesis is questionable. The high risk of future disease development is possible for this child with this allele HLA alone may not be the sole determination factor and environmental, genetic and currently unknown factors might be involved.

We can conclude that there is no direct association between HLA alleles alone despite a consanguineous marriage, history and the development of familial HL. Environmental, genetic and currently unknown factors might also be involved in this disease development and future studies of large series are warranted.

References