

## Can Burkitt's Lymphoma and Hodgkin's Lymphoma occur in siblings simultaneously?

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Familial clustering of Hodgkin lymphoma (HL) and increased risk of developing disease among the siblings has been reported earlier. Usually familial lymphoma in sibling pairs occurs in the pairs of either non-Hodgkin lymphoma or HL. In the familial HL, same type of human leukocyte antigens (HLA) is responsible in the affected family members. There are also some studies stating "Killer cell immunoglobulin like receptor (KIR)" genotypes can be important in the etiology of familial HL. Here we report two siblings; one with Non-Hodgkin and the other with Hodgkin lymphoma which showed Epstein-Barr virus encoded small RNAs positivity in the tumor tissues. We have also found that their HLA genotypes are same with each other. In addition, we have discussed familial lymphoma pathogenesis and HLA haplotypes.

**Key words:** familial lymphoma, EBV, HLA haplotypes, KIR genotypes.

The concordance of Hodgkin lymphoma (HL) in first degree relatives especially monozygotic twins, but also siblings, and parent-child pairs have been reported in several studies.<sup>1-3</sup> Clustering of cases of HL, within families or races may suggest a genetic predisposition to this disease or a common exposure to an etiologic agent. Epstein Barr virus (EBV) is the most well known environmental factor contributing to oncogenesis in HL<sup>4</sup>. Studies of affected families have suggested an increased association of HL with specific human leukocyte antigens (HLA-A1, B5, B8 and B18).<sup>5</sup> Also, there are some studies stating "Killer cell immunoglobulin like receptor (KIR)" genotypes can be important in the etiology of familial Hodgkin lymphoma (FHL).<sup>6</sup> The presence of KIR3DS1, KIR2DL5, KIR2DS5, and KIR2DS1 is protective for HL and contrary KIR2DS4(del) is associated with increased risk for HL.<sup>6</sup> Here we report siblings, one with HL and the other with Non Hodgkin lymphoma (NHL).

### Case Reports

#### Case 1

A 27/12 year-old girl presented with swelling at right side of her jaw. There was no history of frequent infection suggesting the immunodeficiency. There was consanguinity between her parents. On the magnetic resonance imaging of jaw a malignant mass, which was destructing the right side of the mandible with the size of 6x4x4 cm in diameter, was seen. There was intestinal mass at the pelvic grim in the abdominal computed tomography (CT) and increased 2-deoxy-2-(fluorine-18) fluoro-D-glucose activity at jaw and anterior side of the pelvic grim in the positron emission computed tomography (PET). The biopsy of the mass from jaw was reported as Burkitt lymphoma (BL) (Epstein Barr virus-encoded small RNAs [EBER] positive) (Fig. 1 A-B). There was no bone marrow or central nervous system involvement. Her EBV serological tests showed past infection. According to stage 3 BL, the chemotherapy protocol of BFM-95 NHL (R3) was started. She achieved complete remission

at the end of the third course of chemotherapy. We gave her five courses of chemotherapy and during the follow-up she is still in remission.

### Case 2

Within six months of the diagnosis of Case 1, her 72<sup>12</sup> year-old sister who has been living in the same household, presented with right cervical lymphadenopathy. Biopsy from lymph node revealed mixed cellular HL (MCHL) (EBER positive) (Fig. 1C-D). She did not have B symptoms or frequent infection suggesting immunodeficiency syndromes. The screening with neck and abdominal ultrasonography, CT and PET showed involvement of lymph nodes at the two side of her neck. Her EBV serological tests were congruent with past infection. She was stage 2 HL and we started adriamycin, bleomycin, vinblastine and dacarbazine protocol. At the end of the third course of chemotherapy she achieved complete remission. The involved field radiation therapy was given to her after 6 course of chemotherapy. She is still under follow-up and in remission.

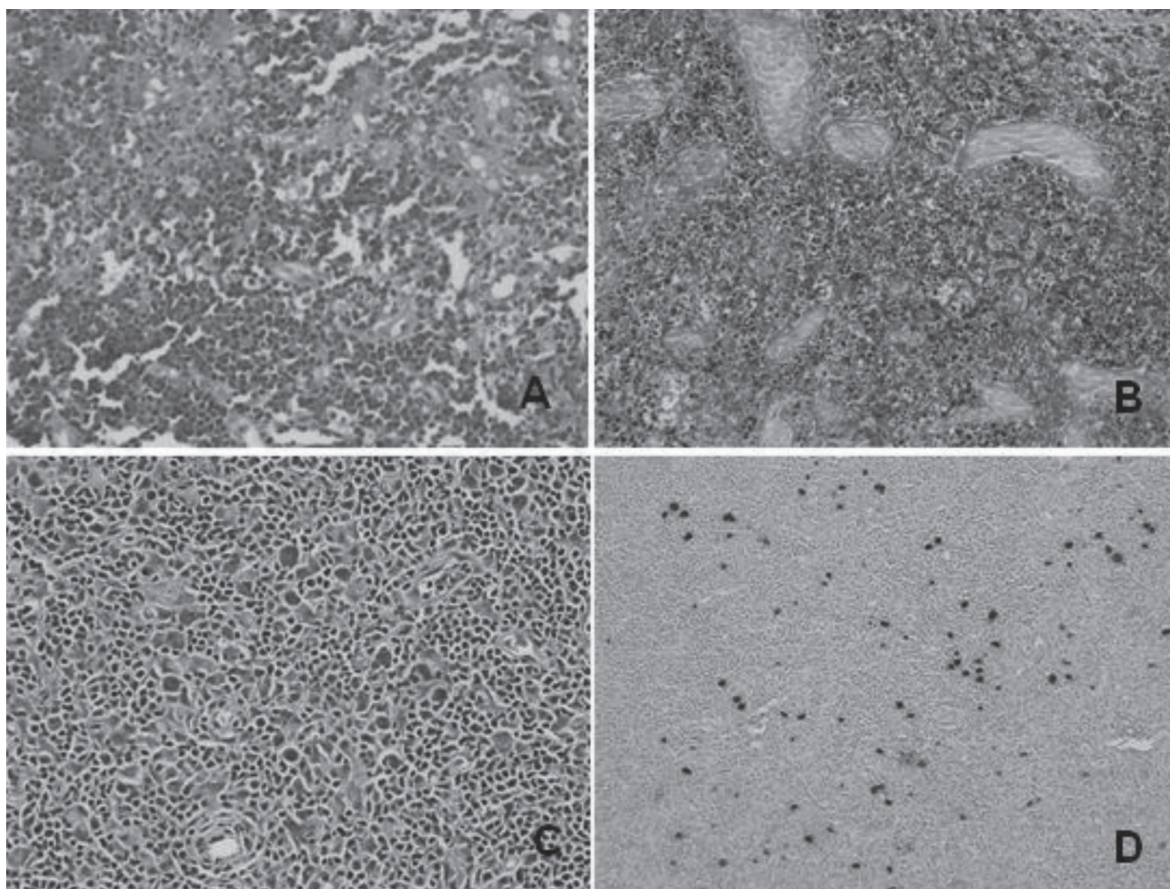
We thought that these are EBV positive familial lymphoma cases (Fig. 2). We investigated HLA of the siblings. Two sisters had same type of class 1 and class 2 HLA haplotypes (Fig. 2). The sister with BL was negative for p53 mutation and deletion. However her sister with HL was negative for p53 mutation but positive for p53 deletion. Because there are some studies about the role of KIR genotypes in the etiology of familial HL in literature<sup>6</sup>, we investigated KIR genotypes of the siblings (Fig. 2). They had protective KIRs and the sibling with BL had risky KIR genotype at the same time (Fig. 2). The immunoglobulin A, G, and M levels of siblings were normal in range.

### Discussion

In the families with HL cases there is 99-fold increased HL risk for monozygotic twins and 7-fold increased risk for siblings.<sup>4</sup> Also there is significant increased risk for lymphoma in the first degree relatives of HL and NHL.<sup>7,8</sup> Here we reported two sisters, one with HL and the other with NHL. A careful search of the literature revealed that this is a very rare co-occurrence in the same family. In the literature there are only two case reports with the pairs of siblings with HL and NHL.<sup>9,10</sup> One report is about the sister with latent membrane protein-1

(LMP-1) positive BL and her brother with EBV negative MCHL. The other report is about a woman with anaplastic large cell lymphoma and her brother with nodular sclerosing HL (NSHL). They are positive for LMP-1 in the tumor tissues and they have concordance of both HLA class 1 and 2.

Our patients had concordance for the positivity of EBV (EBER) in the tumor tissues and HLA haplotypes. In the pathogenesis of HL and BL, EBV plays a significant role. It is positive for >97% of cases of the endemic BL and 15-20% of the sporadic ones.<sup>11</sup> Mechanism of the EBV oncogenesis is not clearly understood. Type 1 latency of EBV leads to BL where Epstein-Barr nuclear antigen and EBERs play critical roles for oncogenesis. Epstein-Barr virus-infected B-lymphocytes carry the viral genome in the latent form. When the reactivation occurs, expressions of viral genes which encode series of products stimulate anti-apoptotic molecules, cytokines and signal transducers which can lead to neoplastic transformation.<sup>12</sup> Type 2 latency of EBV (LMP-1) resembles tumor necrosis factor receptor superfamily that effects a variety of signaling apoptotic and growth pathways and it is also associated with up regulation of bcl-2, interleukin-10 and major histocompatibility complex class 1 proteins which eventually causes HL.<sup>4</sup> Several authors have demonstrated EBV related proteins in HL biopsy materials.<sup>13,14</sup> Also in FHL EBV may play imported role for oncogenesis.<sup>15,17</sup> But some genetic factors like same HLA haplotypes are also important for the development of FHL. Hors and Dausset<sup>5</sup> found that HLA haplotype of A1, B5, and B18 are risky for the development of FHL. Alexander et al.<sup>18</sup>, stated that infectious mononucleosis history and EBV positive (tumor tissue) HL cases have 17-fold increased possibility of having HLA-DPB1\*0301. In the study of Harty et al.<sup>19</sup> in particular, familial NSHL has the DRB1\*1501-DQA1\*0102-DQB1\*0602 haplotype, and the DRB5-0101 allele. The effect of the same HLA in the FHL is not clearly understood. But they may affect the immunologic response of the host to the viruses and thus latency of the virus. Capability of the host for killing the virus may be influenced by these HLA types. Because both siblings revealed expression of EBV EBER in addition to the same HLA class 1 and 2 haplotypes, we hypothesized viral and genetic factors interacted with each other.



**Fig.1.** A, B. Photomicrographs of tumor tissue (Burkitt Lymphoma). A: The neoplastic infiltrate with small blue round cells are readily seen. Further, immunohistochemical investment revealed the CD20 positivity, bcl-2 negativity and very high Ki67 proliferative activity. (Hematoxylin-Eosin; 200 x). B: Diffuse Epstein Barr virus-encoded small RNAs (EBER) positivity of tumor tissue by using chromogenic in situ hybridization (EBER; 200 x). C, D. Photomicrographs of lymph node biopsy (Hodgkin Lymphoma with mixed cellularity). C: There are numerous Reed Sternberg cells with a background of mixed cellularity (Hematoxylin-Eosin; 400 x). D: EBER positivity in Reed Sternberg cells (EBER; 200 x).

Therefore we suggested that; both EBV and host related genetic factors (HLA class 1 and 2) played an important role in the pathogenesis of these familial lymphoma cases.

Natural killer (NK) cells are key actors of the innate immune response against viruses and also tumor cells. Function of NK cells are regulated by KIRs. They are inhibitory or activating transmembrane receptors, present on the surface of NK cells.<sup>20</sup> Besson et al.<sup>6</sup> conducted a study with 84 families with 84 index HL cases and their first degree relatives. They found that presence of KIR3DS1, KIR2DS1, KIR2DL5 and KIR2DS5, were protective for HL and contrarily KIR2DS4(del) was associated with increased risk for HL. Due to these results we searched KIR genotypes of the patients. They were positive for protective

KIRs genotype but also the patient with BL was positive for risky genotype for developing lymphoma (Fig. 2). So we could not suggest that KIRs are the key factor for the development of HL and the NHL in these siblings.

Our cases are rare because of the simultaneous occurrence of HL and NHL in two siblings. We think that EBV and some genetic factors (same HLA haplotypes in two sisters) contributed to pathogenesis of lymphoma in our cases. However we could not explain how HLA affected the oncogenesis, but we hypothesized that some individuals in the population are under the risk of EBV oncogenesis due to their innate immunity against to EBV and this may be influenced by HLA haplotypes and KIRs genotypes. It is obvious that to understand the role of HLA haplotypes, NK cells and

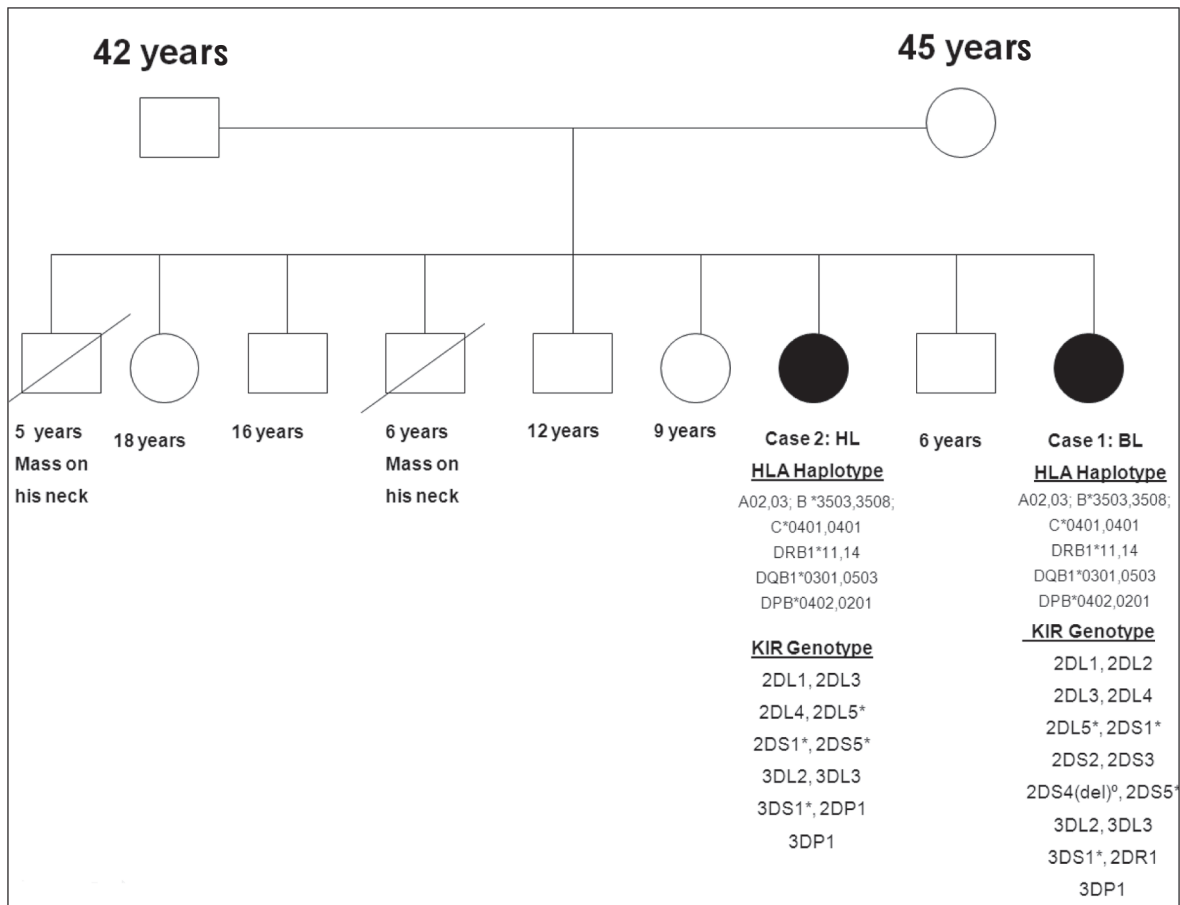


Fig. 2. Pedigree of family with patients HLA-types and KIRs genotypes.  
 \*KIRs which are protective for HL  
 °KIR which is risky for HL

KIRs genotypes in the pathogenesis of FHL or familial lymphoma cases, further studies with much larger series should be done.

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