



# Familial Hodgkin Lymphoma: A Case Report and Sort Review

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## Abstract

**Introduction:** Mixed cellularity Hodgkin's Lymphoma (HL) is a subtype of classic HL (c-LH), constituting the second most common subtype and 15% to 30% of all cases of HL. It is mostly observed in patients with either Epstein-Barr Virus (EBV) or Human Immunodeficiency Virus (HIV) infection, having less inheritance rate comparing to other subtypes. Familial HL is very rare.

**Aim:** The aim of this paper is to present a case of familial HL and to review the literature about the incidence and the relationship by histology, age at diagnosis, and gender.

**Materials and Methods:** Two siblings, a girl 15-year old and a boy 25-year old, presented with HL, stage IIIs, with the same affected sites of lymph nodes. The open node biopsy revealed the histological type of mixed cellularity c-HL, in both cases. At the biopsy specimen, both cases were negative for EBV.

**Results:** The girl achieved remission with chemotherapy, only. The boy received also initially chemotherapy but due to relapse during chemotherapy, radiotherapy was added. Unfortunately, he succumbed from refractory disease. The girl, up to date remains in first remission, 10 years after the diagnosis. By contrast, her older brother had a poor outcome.

**Conclusion:** It is a report of familial HL in two siblings. The only apparent difference between the two cases was the presenting age and gender. The girl was diagnosed at the age of 15 years old and the boy at the age of 25 years old. Considering that both patients were similar on their disease characteristics and both were negative for EBV infection, it seems that the age of onset and maybe the gender in this subtype of HL, has a crucial role on the outcome in familial cases of the disease.

**Keywords:** Familial hodgkin's lymphoma; Mixed cellularity classical hodgkin lymphoma; Familial hodgkin's lymphoma-EBV negative

## Abbreviations

HL: Hodgkin's Lymphoma; EBV: Epstein-Barr Virus; HIV: Human Immunodeficiency Virus; HL (NLPHL): Hodgkin's Lymphoma Nodular Lymphocyte Predominant; c-HL: Classical HL; 5y-OS: Five Year Over all Survivor; NLPHL: Nodular Lymphocyte-Predominant Hodgkin Lymphoma; NSHL: Non-Sclerosing Hodgkin Lymphoma; HLA: Human Leukocyte Antigen; CR: Cumulative Risk

## Introduction

Lymphomas are the most common malignancy among adolescents, accounting for more than 25% of newly diagnosed cancers in the age group of fifteen to nineteen years old, while HL accounts approximately two-thirds of cases [1]. The worldwide incidence of HL is approximately two to four new cases per 100,000 population/year [1]. The incidence of HL has increased among adolescents and young adults in recent decades, but the relevant risk factors in early life are still unknown. In most developed nations, the age-specific incidence HL has a bimodal pattern, with an initial peak occurring among young adults ages fifteen to thirty-nine years old, followed by a second peak among older adults over fifty years old. In developing nations, the first peak occurs earlier, among children under the age of fifteen years old [2]. Bleyer et al. [3] reported in 2006, that although HL represents only approximately 4% to 5% of all malignancies in children younger than fifteen years of

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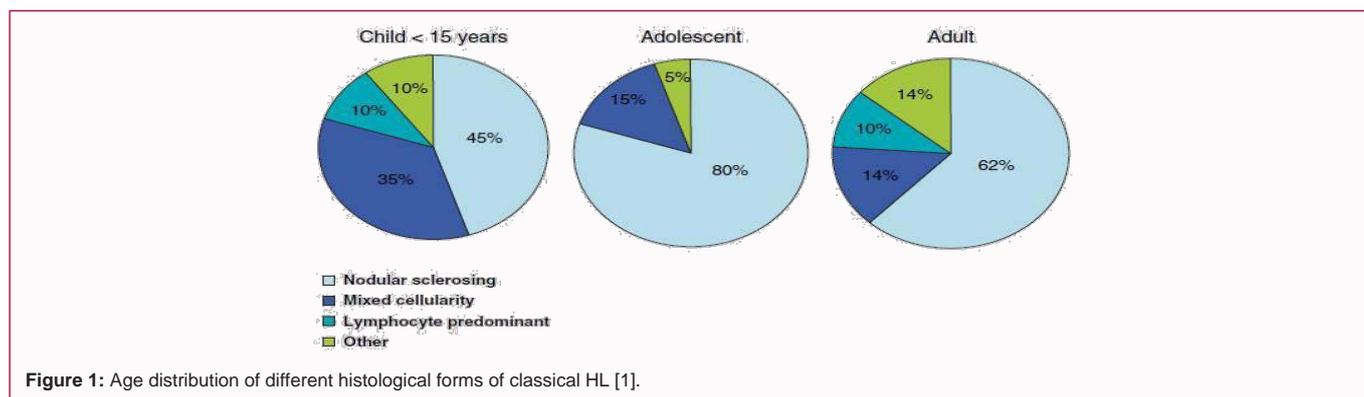


Figure 1: Age distribution of different histological forms of classical HL [1].

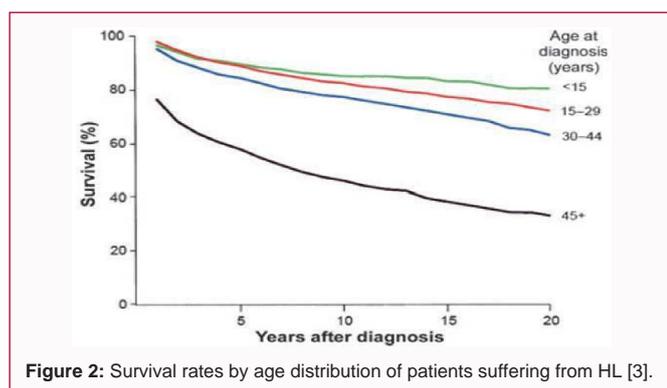


Figure 2: Survival rates by age distribution of patients suffering from HL [3].

age, this percentage increases to approximately 16% in the adolescent, making HL the most common malignancy within this age group. There is also a slight overall male predominance with a male to female ratio of 1.7:1 to 2:1 in childhood. However, there is no significant difference in gender within the adolescent population. Infection with Epstein-Barr Virus (EBV) confers a fourfold risk, often preceding the diagnosis of HL by many years. However, whereas EBV-positive HL is often identified in younger patients with naive immune systems as well as older patients that have decreased immune surveillance, there is a less striking association in the adolescent population despite a higher rate of infectious mononucleosis in this age group. This may represent differences in immune status among the different age groups [2,4]. Depending on the study, data show that up to 30% of cases of classical Hodgkin lymphoma may be positive for EBV proteins. In addition, a case control study supports an increased risk of c-HL after EBV infection, with a risk of approximately 1 in 1,000 cases [5]. The incidence of EBV positivity varies with subtype. Nodular Lymphocyte-Predominant HL (NLPHL) rarely expresses EBV proteins. In c-HL, EBV positivity is most common in the mixed-cellularity variant. However, the exact mechanism by which EBV can lead to HL is not known [6]. HIV-positive patients also have a higher incidence of HL compared with HIV-negative patients. However, HL is not considered an AIDS-defining neoplasm. The Revised European American Lymphoma (REAL)/WHO lymphoma classification now recognizes two major types of HL: Nodular Lymphocyte Predominant HL (NLPHL) and classical HL or c-HL. NLPHL is rare in the adolescent/young adult age group as it typically presents with a peak age distribution in the 4<sup>th</sup> decade in males. Among c-HL, there are four histological subtypes: nodular sclerosing, mixed cellularity, lymphocyte rich and lymphocyte depleted. There are significant differences in the distribution of subtypes by age that are summarized in (Figure 1). Five year Over all Survival (OS) depends on risk group.

The low-risk group is associated with a 5-year OS of 95% and the high risk with a 5-year OS of 85%. This is influenced in part using field radiotherapy in combination with multiagent chemotherapy in high-risk groups and its omission in lower risk groups [7]. Although, there are not many studies published with directly comparison of adolescent outcomes, overall prognosis seems to be related to age at diagnosis as summarized in (Figure 2). The achieved good prognostic rate seems to have a secondary cost in observed cardiovascular toxicity and second malignancies, mostly seen in combined and prolonged chemo and radiotherapy [8]. Family history for HL is a risk factor for which advice and management is a need. Few studies have provided familial risks by gender of the patient and the relative, suggesting gender concordance among sibling pairs with HL.

### Case Report

Two siblings, the younger sister, aged fifteen when presenting the disease (2008) and her brother aged 25 year old, presented with six years (2014) difference from each other the same type of classical HL. Both had the mixed cellularity c-HL, both had stage (III) of disease, with the same affected sites. Specifically, the location of the disease was common in both cases. The presenting symptoms were a persisting over a month, painless swelling of the left cervical lymph nodes that initially explained as a reaction to an upper respiratory infection. Later, the chest x-rays showed enlargement of the hilar nodes of the left lung. Excisional lymph node biopsies in both cases proved that the histological form was classified using the WHO classification system for Lymphomas as classical HL with mixed cellularity and negative LMP-1, protein of the EBV infection. The CT scan of the chest and the abdomen, and the PET/CT scan showed involvement of lymph nodes in left cervical area, hilar nodes of the left lung and mediastinal lymph nodes, left axillary area, abdominal paraaortic nodes, nodes of the hilum of the liver, and infiltration of the spleen. Bone marrow biopsy was negative for the disease.

The imaging investigation revealed that the stage of the disease in both cases was III<sub>s</sub>.

The female patient due to her age at diagnosis fifteen years old was treated in our Department of Pediatric Hematology-Oncology. She received chemotherapy with the authorized protocol of the International Society of Pediatric Oncology. She received two cycles of OEPA (Vincristine, Etoposide, Prednisone, Doxorubicin) followed by four cycles of COPP (Cyclophosphamide, Vincristine, Prednisone, Procarbazine). An interim PET-CT scan after the second cycle of chemotherapy was negative for the disease, and the PET-CT scan at the end of therapy was also negative. She achieved remission and during her treatment, she didn't present with any serious

complications. Since the end of her treatment in 2009 and throughout her follow-ups, she is free of HL without adverse side effects.

Her older brother then aged 25 years old affected as mentioned above by the same anatomical located sites, stage III, and the same histological subtype c-HL disease. As a young adult he was treated in an adult Department of Oncology and received initially chemotherapy with a BEACOPP protocol (Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisone). He received eight cycles of chemotherapy. Initially showed signs of remission but under treatment he suffered a recurrence of his disease, in the mediastinal lymph nodes. Radiotherapy was added to his treatment but unfortunately, he succumbed from refractory disease.

## Discussion

Although, HL is a very common malignancy in many age groups its etiology is unknown [1,2].

Genetic predisposition plays a role in the pathogenesis of Hodgkin lymphoma. Approximately 1% of patients with HL have a family history of the disease [9-12], and siblings of an affected individual have a 3-7 fold increased risk of developing the disease [13]. Most evidence for a genetic etiology has been established in the distinct subtype of Non-Sclerosing HL (NSHL). NSHL has been shown to be one of the most heritable types of neoplasm, with a 100-fold increased risk in identical twins [14]. There is evidence that NSHL may result from an atypical immune response to a virus or other trigger, in an individual with a genetic predisposition to such a response [15]. For decades, specific Human Leukocyte Antigen (HLA) class II genotypes, including HLA-DRB1 and HLA-DQB1, have been known to be associated with NSHL, and this has been confirmed by genome-wide association studies [16]. Several single-nucleotide polymorphisms in the 6p21.32 region, which is rich in genes associated with immune function, have also been associated with NSHL risk [17].

The national Swedish cohort study, involving 3,571,574 individuals born in Sweden in 1973-2008 and followed up for HL incidence through 2009, aimed to examine perinatal and family risk factors for HL in childhood through young adulthood (ages 0-37 years) [12]. The study concluded that Family history of HL in a sibling or parent was strongly associated with an increased risk. No association was found between gestational age at birth, birth order, twinning, parental age, or parental education and Hodgkin lymphoma. These findings did not vary by age at HL diagnosis. Similar associations were found for nodular sclerosis and mixed cellularity subtypes. The study concluded suggesting that: perinatal factors including possible growth factor pathways may contribute to the risk of HL in childhood through young adulthood [12].

Most of the data on familial HL derive from the large Nordic study, published in 2015. The cohort of the study included 57,475 first-degree relatives of 13,922 HL patients diagnosed between 1955 and 2009 from Denmark, Finland, Iceland, Norway, and Sweden [10]. The aim of the study was to provide the familial risk of classical HL by relationship, histology, age at diagnosis, and sex. The study showed that the overall lifetime Cumulative Risk (CR) of HL in first-degree relatives of a patient with HL was 0.6%, which represents a threefold increased risk over the general population risk. The risk in siblings was significantly higher than in parents. Very high lifetime risk of HL was found for those with multiple affected first-degree relatives and for same-sex twins. The authors found that high familial risks between some concordant histologic subtypes of HL such as

lymphocyte-rich and that nodular sclerosis and also between some discordant subtypes. The familial risk in sisters was higher than in brothers or unlike-sex siblings, as in our case. The lifetime risk of HL was higher when first-degree relatives were diagnosed at early ages under the age of thirty years old [10].

In our familial case reported, despite the negative EBV and HIV infection in both siblings, both affected from HL. The sister was younger and affected first at age fifteen years old. Although, had different gender that correlates to a low risk as discussed above in the Nordic study, the brother also affected at the age of 25 years old. Also, this family members, having already two of them, affected from HL have an additional higher risk for suffering in future as they are now multiple cases in the same family as well as both existing cases of HL presented in early age, under the age of 30 years. The grave outcome of the older to suffer in young adulthood-brother correlates to the worse prognosis reported in literature for this age group and summarized in (Figure 2).

## Conclusion

Considering that both patients were similar on their disease characteristics and both were negative for EBV infection, it seems that the age of onset and maybe the gender in this specific subtype of HL, plays a crucial role on the outcome in familial cases of HL. These findings must alert physicians taking care of these patients to stress the need for long time surveillance among members of families with a history of HL.

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## Authorship

M.M and A.C.P. conceived and designed the paper; M.M. N.T. and A.L., provided patient data. A.C.P and M.M assembled, analyzed the data, interpreted the results and wrote the manuscript; all authors reviewed and commented on manuscript and approved the final version.

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