Epidemiology and Pathologic Features of Hodgkin Lymphoma

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Abstract

Hodgkin lymphoma (HL) has unique epidemiologic characteristics. The variation in incidence according to age, sex, race, socioeconomic status, and histologic subtype suggests an etiologic heterogeneity for this tumor. Epidemiologic studies have shown that both genetic and environmental factors play a role in the pathogenesis of HL. HL is one of the Epstein-Barr virus–associated lymphomas, but the oncogenetic mechanism of HL remains to be elucidated. Recent advances in molecular biology have revealed the peculiar nature of the nodular lymphocyte predominant subtype, and as a result this disease is separated from classic types of HL in the new World Health Organization classification. Reed-Sternberg (RS) cells and lymphocytic and/or histiocytic (L&H) cells originate from germinal center B-cells. Loss of the B-cell phenotype due to down-regulation of several B-cell–specific transcription factors is characteristic of RS cells in classic HL.

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Key words: Hodgkin lymphoma; Nodular lymphocyte predominant; Reed-Sternberg cells; Germinal center; B-cells

1. Introduction

Hodgkin lymphoma (HL) is an uncommon lymphoid malignancy comprising fewer than 10% of all malignant lymphomas in Japan, whereas HL is relatively common in Western countries. HL usually arises from lymph nodes and is histologically characterized by a small number of scattered large multinucleated or mononucleated tumor cells, so-called Reed-Sternberg (RS) and Hodgkin cells, that reside in a heterogeneous nonneoplastic background consisting of an admixture of various kinds of inflammatory cells. The first histologic classification for HL proposed by Jackson and Parker in 1944 was followed by the classification of Lukes and Butler, which was revised at the 1966 Rye conference. It is noteworthy that in the Revised European-American Lymphoma classification (1994) and the newly edited World Health Organization (WHO) classification (2001) the nodular lymphocyte predominant (NLP) type of HL was separated from the “classic” HL types on the basis of the different biological and clinical features established for the NLP type during the last 2 decades [1]. The nodular sclerosis (NS), mixed cellularity (MC), lymphocyte-depleted (LD), and lymphocyte-rich (LR) types of classic HL are based on the characteristics of the reactive infiltrates and the morphology of RS cells. The clinical and pathologic findings of each HL subtype are summarized according to the new WHO classification.

2. Epidemiology of HL

HL has been attracting a great deal of scientific and clinical interest because this tumor has unique epidemiologic features, such as an unusual age-related pattern of incidence and geographic/racial differences in disease susceptibility. The variation in incidence by age, sex, race, socioeconomic status, and histologic subtype suggests that HL comprises etiologically heterogeneous diseases. The annual incidence of HL in Europe and North America has been estimated to be 1.3 to 4.0 per 100,000 in males and 0.9 to 3.1 per 100,000 in females, whereas the incidence in Asian countries is significantly lower: 0.1 to 1.3 in males and less than 0.7 in females (Figure 1; data from Cancer Incidence in Five Continents 1993-1997, http://www-dep.iarc.fr/). HL comprises approximately 30% of all malignant lymphomas in Western countries, whereas the incidence is 9% among the more than 2000 cases of malignant lymphoma in Japan (Osaka Lymphoma Study Group, unpublished data). A study of cancer incidence in California, USA, showed that whites are the most susceptible to HL, followed by blacks and Hispanic individuals; the lowest incidence was observed among people of Asian origin [2].
The association between the risk of HL and socioeconomic status has been well documented. Correa and O’Conor found a significant inverse relationship between the incidence of HL in children and that in young adults on the basis of the international data [9]. In developing countries, incidence peaks are found in childhood and in older individuals with a predominance of the MC and LD subtypes, whereas the incidence is highest with a predominance of the NS subtype in young adults in industrial countries. However, a recent study has shown that this tendency has become weaker over the past 20 years [7]. It is well known that the risk of HL among young adults in industrial countries is associated with socioeconomic factors in childhood, which include small family size, early position in the birth order, single-family housing, and high maternal education. All of these factors can diminish and delay exposure to common infectious agents. The speculation based on these findings is that HL among young adults may result from aberrant host response to a delay in first infection by common infectious agents (Gutensohn and Cole’s “delayed exposure” model [10]).

HL may affect members of the same family: familial HL represents 4.5% of all newly diagnosed cases [11]. A 3- to 17-fold excess of disease risk in close relatives of HL patients has been reported. Mack et al reported that monozygotic twins had a 99-fold increased risk for HL, whereas dizygotic twins had no increased risk [12]. A population-based analysis of the results of HLA typing showed that 3 antigens were clearly associated with HL: HLA class I alleles A1, B5, and B18 [13]. HLA class II allele DRB1*0301 in female patients and a combination of DRBI*1501, DQA1*0102, and DQB1*0602 in the NS subtype have also been implicated [14]. Furthermore, a recent study showed that the microsatellite markers within the HLA class I region are specifically associated with Epstein-Barr virus (EBV)-associated HL (see below), suggesting that presentation of EBV antigens is involved in the pathogenesis of EBV-associated HL [15]. Aberration and polymorphism of genes within or near the HLA region may be involved in HL oncogenesis, but it is noteworthy that environmental and familial factors also affect excess risk among siblings of HL patients. These findings indicate that both genetic and environmental factors play a role in the development of HL.

No consistent association has been established in the literature between HL risk and any occupational exposures, chemical exposures, cigarette smoking, other lifestyle issues, or ionizing irradiation.

3. Viruses and HL

An excess risk for HL was observed among patients with a history of infectious mononucleosis [10]. Patients with HL show higher antibody titers to EBV viral capsid antigen than control subjects, and preceding EBV infection increases the risk of HL by 3- to 4-fold [16]. In situ hybridization and immunohistochemistry analyses have demonstrated that EBV is localized to RS cells, which express EBV latent genes. Southern blot analysis of the