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An overview of hodgkin lymphoma

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Abstract
Hodgkin lymphoma (HL) represents about 10% of all lymphomas and distinct from other non- Hodgkin lymphomas, clinically by the contiguous spread of tumour along the lymphoid system, and morphologically by the presence of a spectrum of neoplastic cells. Factors associated with an increased risk for Hodgkin lymphoma include exposure to viral infections, familial factors, and immunosuppression. Most patients with Hodgkin lymphoma present with supradiaphragmatic lymphadenopathy. An accurate determination of disease stage in patients with Hodgkin lymphoma is vital to selection of the appropriate initial treatment. Positron emission tomography (PET) has recently emerged as an important tool for optimizing the staging of Hodgkin lymphoma. The factors determining the optimal treatment for patients with Hodgkin lymphoma that play a major role include the histologic features, the stage of the disease, the presence of clinical factors that suggest a poor prognosis, the presence of systemic symptoms, and the presence or absence of a bulky mass.

Keywords: hodgkin lymphoma, reed sternberg cells, prognosis, ebstein bar virus, positron emission tomography

Introduction

The designation lymphoma represents a large group of malignant neoplasms arising from components of the immune system, namely T and B cells. Hodgkin lymphoma has a bimodal disease distribution, with an increased incidence in patients in their teenage years or early 20s and a similar increased incidence in patients older than 55 years [1]. The first lymphoma type recognized was by Dr Thomas Hodgkin in 1832. In 1865 Dr Samuel Wilks recognized additional cases, rediscovered the report by Hodgkin, and designated this neoplasm as 'Hodgkin disease', a name used for over 100 years. This disease is now known as Hodgkin lymphoma (HL) and represents about 10% of all lymphomas. HL is distinct from other non- Hodgkin lymphomas, clinically by the contiguous spread of tumour along the lymphoid system, and morphologically by the presence of a spectrum of neoplastic cells, including mononuclear Hodgkin (H) cells, classic multinucleated Reed–Sternberg (RS) cells, and mummified (degenerating) cells against an inflammatory background [2, 3]. The first histologic classification of HD was described by Jackson and Parker in 1944. They divided HD into 3 types, paragranuloma, granuloma, and sarcoma, which are equivalent to nodular lymphocyte predominant, nodular sclerosis, and lymphocyte depleted types, respectively, as recognized in the current classification system [4]. Modern terminology related to the histopathology of HD was coined in 1966 by Lukes and Butler, who introduced 6 types, including (1) lymphocytic and/or histiocytic (L & H) nodular, (2) L & H diffuse, (3) nodular sclerosis, (4) mixed, (5) diffuse fibrosis, and (6) reticular [5].

Pathogenesis

The exact cause of Hodgkin lymphoma remains unknown, but factors associated with an increased risk for Hodgkin lymphoma include exposure to viral infections, familial factors, and immunosuppression. Siblings of patients with Hodgkin lymphoma have an increased risk for this disease [6, 7]. HL is one of the most common non-AIDS defining neoplasms in the HIV+ population and is increasing in prevalence in patients treated with Highly Active Antiretroviral Therapy (HAART) whereas the incidence of non- Hodgkin's lymphoma has fallen in such patients [8]. EBV-positive HL is observed more frequently in childhood (<10 years) and in older adults (>60 years), and is highest in MC type and lowest in NLPHL type [9, 10]. This biphasic pattern possibly represents two distinct phenomena, one related to age of EBV acquisition and the other to the decline in immune function, each of which would likely predominate in different populations. With improvements in public health status, it appears that EBV positivity in HL is becoming associated with older age. These findings support the hypothesis that HL may have different etiologies in different age groups and indicate that the association of EBV with HL likely becomes more common in older patients as age of primary EBV infection rises in any given country [10]. Most patients with Hodgkin lymphoma present with supradiaphragmatic lymphadenopathy. Retroperitoneal and inguinal lymphadenopathy occur less frequently. Approximately one-third of patients present with constitutional symptoms. These symptoms include high fevers, drenching night sweats, and profound weight loss. Patients may also present with chronic pruritus. Although it is more common for the disease to involve regional lymph nodes, Hodgkin lymphoma may also involve extranodal sites either by direct invasion or hematogenously. Common sites that may be involved include the spleen, liver, lungs, and bone marrow [11].

Classification

Based on the morphology and immunophenotype of the neoplastic cells and the background cellular infiltrate, HL is subdivided into nodular lymphocyte predominant (NLPHL) type and classic type. These diseases should be clearly distinguished because, in spite of some common morphological features, they differ in their molecular pathogenesis, immunophenotype, prognosis and therapy. Classic HL is further subdivided into nodular sclerosis (NS), mixed cellularity (MC), lymphocyte rich classic (LRC), and lymphocyte depleted (LD). Worldwide, about 90% of HLs are one of the classic types and 10% or less are NLPHL [12].

The pathologic hallmark of classical Hodgkin lymphoma is the presence of large malignant multinucleated Reed-Sternberg cells, which are present within a characteristic reactive cellular background [13]. CD30 is a universal marker for classic HL cases; all cases are positive without exception. Additionally, almost all HL cases exhibit weak PAX5 staining of HRS cells, thus reflecting the B-cell origin of the neoplastic cells. CD15 is present in about 75% classic HL cases, but again this is not an entirely specific marker, since CD15 expression can be found in other B- and T-cell lymphomas [14].

Nodular sclerosis subtype tends to affect adolescents and young adults. Most commonly, this subtype presents with localized disease often involving the mediastinum and supraclavicular or cervical lymph nodes [15]. Diagnosis is based on the presence of nodules surrounded by collagen bands (nodular sclerosis) and HRS cells, together with the polymorphic inflammatory infiltrate characteristic for HL cases. Most cases also show fibrosis, geographic necrosis and lacunar cells (large pleomorphic CD30+ cells with abundant clear cytoplasm) [13].

Mixed cellularity Hodgkin lymphoma is more prevalent either in children or elderly persons, commonly presents with advanced-stage disease, and sometimes has a poorer prognosis. They contain classic HRS cells in an inflammatory background environment [13, 15].

Lymphocyte depletion Hodgkin lymphoma is reported less frequently than it was previously because many of the previously reported cases are now reclassified as non- Hodgkin lymphomas. This subtype often occurs in elderly patients and is commonly associated with AIDS. These patients often present with extensive extranodal disease without substantial lymphadenopathy [15]. Lymphocyte-rich classical Hodgkin lymphoma has an appearance similar to nodular lymphocyte-predominant Hodgkin lymphoma, but Reed-Sternberg cells are identified with a more classical immunophenotype consistent with classical Hodgkin lymphoma rather than nodular lymphocyte-predominant Hodgkin lymphoma [15].

Nodular lymphocyte-predominant Hodgkin lymphoma is a unique pathologic entity that is distinct from classical Hodgkin lymphoma. This entity lacks typical Reed-Sternberg cells but instead has a neoplastic population of large cells known as lymphocytic and histiocytic (L&H) cells. These cells typically express CD20 and are usually negative for CD30, in contrast with classical Hodgkin lymphoma [16]. Nodular lymphocyte-predominant Hodgkin lymphoma is more frequent in males and may present with limited nodal disease often involving the neck but often sparing the mediastinum. The clinical course of nodular lymphocyte predominant Hodgkin lymphoma differs from that of classical Hodgkin lymphoma in that the disease has a more indolent course but displays a propensity for late relapses [17].

Staging and treatment

An accurate determination of disease stage in patients with Hodgkin lymphoma is vital to selection of the appropriate initial treatment. The staging system for Hodgkin lymphoma is based on the location of lymphadenopathy, the number and size of lymph node sites, and whether the extranodal lymph node involvement is contiguous or due to dissemination of the disease systemically. Constitutional symptoms (also called B symptoms) are also incorporated into the standard staging classification. Positron emission tomography (PET) has recently emerged as an important tool for optimizing the staging of Hodgkin lymphoma [18].

In determining the optimal treatment for patients with Hodgkin lymphoma, the factors that play a major role include the histologic features of the disease (classical Hodgkin lymphoma compared with nodular lymphocyte-predominant Hodgkin lymphoma), the stage of the disease (particularly whether the patient has early- or advanced-stage disease), the presence of clinical factors that suggest a poor prognosis, the presence of systemic symptoms, and the presence or absence of a bulky mass, defined as a single site of disease greater than 10 cm in diameter. [18F]-Fludeoxyglucose (FDG) ePso plays a key role in defining the initial treatment. It is *Et al* particularly important in confirming the stage of the disease and is also used to determine treatment success [19].

Prognostic Factors in Hodgkin Lymphoma

Many prognostic factors, used in standard clinical practice, have been known for a long time. These factors often reflect disease burden and disease activity that is related to the inflammatory microenvironment [20].

Tumor Burden: stage and bulk

Extension of disease and tumor burden is indubitable the most important disease characteristic, that is used to stratify treatment strategies [21]. In limited stage disease, the presence of bulky disease detected on chest radiography or CT at staging is considered a negative predictor of outcome. By contrast, in advanced stage disease, the presence of a bulky tumor is not a risk factor in the international prognostic score (IPS) for HL [22, 23].

Age

Age is the most important and independent factor to analyze the overall survival. In the International Prognostic Score for patients with advanced stage disease the cut-point is age of 45 years, the EORTC lists age more than 50 years as a risk factor for patients with limited stage disease. Older age associates with a higher frequency of the mixed cellularity histotype and presence of EBV in the neoplastic cells, when compared to younger patients [24].

Gender

Males with HL have a poorer outcome than females. A preponderance of male gender is observed in elderly patients, and as a consequence male have more often unfavorable disease characteristics. Another mechanism for the gender effect in lymphoma may be due to differences in pharmacokinetics [25].

B-Symptoms

Constitutional symptoms defined by unexplained fever >38°C, drenching night sweats and weight loss >10% of the weight are a presenting sign in about 10–25% of patients with limited stage disease, and up to 70% of patients with advanced stage disease [26].

Anemia

Anemia is a frequent finding at HL diagnosis and is present in about 40% of patients. It is usually a mild to moderate normocytic anemia, with the characteristics of anemia of inflammation. Cut-off point for prognosis in the IPS is a hemoglobin level of 10.5 g/dl, and this is independent of gender. Elevated IL-6 levels correlate with hemoglobin levels and that IL-6 levels correlate with levels of hepcidin, an acute phase reactant and a major regulator of iron metabolism [27].

Albumin

Low levels of serum albumin are associated with a worse prognosis in many hematological neoplasia, including HL. The IPS score defines albumin levels of 4.0 g/dl as cut-point. Albumin levels inversely correlate to IL-6, TNF alpha and IL1-RA.[20] Raised levels of erythrocyte sedimentation rate (ESR), beta2 microglobulin and biohumoral factors (IL-10, IL-6, sCD30, TNF) are associated with poor prognosis in Hodgkin lymphoma [28].

Conclusion

Hodgkin lymphoma represents about 10% of all lymphomas lymphoma and has a bimodal disease distribution. It is distinct from other non- Hodgkin lymphomas, clinically by the contiguous spread of tumour along the lymphoid system. Prognostic factors are often used in standard clinical practice and reflect disease burden and disease activity. An accurate determination of disease stage in patients with Hodgkin lymphoma is vital to selection of the appropriate initial treatment. Positron emission tomography (PET) has recently emerged as an important tool for optimizing the staging of Hodgkin lymphoma and to determine treatment success.

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