Classical Hodgkin lymphoma – differential diagnosis and tumour microenvironment

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Introduction

Hodgkin lymphoma (HL) accounts for approximately 15% to 30% of all malignant lymphomas. According to current diagnostic criteria, approximately 90% to 95% of HLs fall into the Classical Hodgkin lymphoma (CHL) category; the remaining cases are nodular lymphocyte-predominant subtype of Hodgkin's lymphoma (NLPHL) which is recognized as a separate entity in the World Health Organization (WHO) classification[1]. WHO classification is based on the fact that there are clear and consistent histologic, epidemiologic, immunologic, and genetic differences between NLPHL and CHL. NLPHL is an indolent germinal center (GC) B-cell malignancy, that represents a nodular proliferation comprised of a minority of large neoplastic centroblasts with multilobated nuclei, the so-called popcorn or lymphocyte-predominant (LP) cells. Immunohistochemically LP cells are CD20+, PAX5+, BCL6+, EBV-LMP1-, CD30- and CD15-. Background inflammatory infiltrate represent mixture of small B and T lymphocytes[1]. This type of tumour is characterised clinically by a relatively indolent course and a very good response to standard therapy in cases with low stage disease. Unfortunately, the prognosis is unfavourable for advanced stages[2].

CHL is also a clonal, malignant lymphoproliferation originating from germinal center B cells[3]. CHL has a bimodal age curve in western countries, showing a peak at 15-35 years of age and a second peak later in life at 45-60 years[1]. A histopathologic diagnosis of CHL is based on the identification of diagnostic Reed-Sternberg (RS) cells in an appropriate inflammatory background of mixed infiltrate by histiocytes, small lymphocytes, eosinophils, neutrophils, plasma cells, fibroblasts and colagen. Based on characteristics of the reactive infiltrate and the specific features of neoplastic cells, cases may be subclassified into one of four subtypes: nodular sclerosis (NSCHL), lymphocyte-rich (LRCHL), mixed cellularity (MCCHL) and lymphocyte-depleted classical Hodgkin lymphoma (LDCHL)[1,4]. Although most cases can be diagnosed on the basis of morphology alone, diagnostic criteria include the characteristic immunophenotype of the neoplastic population. RS cells and variants express the CD30 and CD15 antigens in the majority of cases and lack the common leukocyte antigen CD45[5,6]. The LMP-1 protein of EBV is expressed in approximately 25% to 50% of CHLs depending on the histologic subtype and patient age[7]. The staining is membranous and cytoplasmic, and usually most neoplastic cells are positive. Etiology of CHL is still questionable, but due to the unique epidemiologic and clinical features of the disease, an infectious cause has long been suspected. Currently, immunohistochemistry for the EBV latent membrane protein-1 (LMP-1) and nonradioactive *in situ* hybridization for EBV-encoded early RNAs (EBERs) are the methods of choice for the detection of EBV in routinely fixed, paraffin-embedded tissues[8]. Recent data suggest that the EBV status of tumour cells in classical HL could have prognostic significance for patients with this heterogenous disease[9].

Differential diagnosis of Hodgkin lymphoma

Although most cases of CHL can now be safely classified on the basis of morphology and immunohistochemical features, distinction from some subtypes of NHL, reactive disorders, or even nonhematopoietic neoplasms can in some cases be difficult. Furthermore, the differential diagnosis between NLPHL and LRCHL can be particularly challenging. The morphology of the neoplastic cells is of limited value because LP cells can occur in both entities, so immunophenotyping and architecture are of paramount importance for the differential diagnosis (CD20, CD30, CD15, CD45, CD3, PD-1, CD57, EBV-LMP, EMA)[10,11].

There are some subtypes of DLBCL that exhibit morphologic and phenotypic overlap with CHL. Those include primary mediastinal large B-cell lymphoma, THRLBCL, and EBV+ DLBCL of the elderly. There is also „grey zone“ lymphoma group, the new category of B-cell unclassifiable lymphoma, with features intermediate between DLBCL and CHL that sometimes has to be included in the differential diagnosis[1,11].

Anaplastic large cell lymphoma (ALCL) shows some morphologic and phenotypic similarities with CHL. ALCL tumour cells may resemble RS cells or mononuclear variants, but they are usually smaller than the neoplastic cells of CHL and often show bean-shaped or horseshoe-shaped nuclei (“hallmark” cells) rather than the round nuclei of Hodgkin cells. Peripheral T-cell lymphomas frequently show a polymorphic inflammatory background with eosinophils, neutrophils, plasma cells, and histiocytes and may contain RS-like giant cells. For this reasons ALCL as well as the peripheral T-cell lymphoma not otherwise specified (NOS) or angioimmunoblastic T-cell lymphoma (AITL) should sometimes be included in differental diagnosis.

Microenvironment of Hodgkin lymphoma

CHL is the example of a formerly lethal lymphoma that became curable mainly due to the considerable advances in therapeutic regimens[12,13]. These therapeutic improvements have transformed CHL into a curable disease in more than 85% of cases. However, a considerable percentage of patients still fail to respond to current standard therapies requiring more intensive treatments[14]. Identifying subgroups of patients with poor prognostic parameters has become the main objective of clinical and biological research. Studies on Hodgkin and Reed-Sternberg cells- related prognostic biomarkers have been unsuccessful but the microenvironmental composition seems to be of prognostic importance. Using immunohistochemical analysis some authors found that an increased number of tumour-associated macrophages was strongly associated with shortened survival in patients with classical Hodgkin lymphoma and provided a new biomarker for risk stratification[15]. Some other reports also now support the value of enumerating tumor-associated macrophages in pretreatment biopsies for outcome prediction in classical HL[16,17,18]. Their abundant signals could explain the deregulation of a critical apoptotic pathway in Reed-Sternberg cells that inhibits death in response to cytotoxic agents[19].

In HL several biomarkers other than CD68 have been reported to be associated with treatment outcome, in particular markers expressed by certain T-cell subsets[20]. A subset of regulatory T-cells (Treg) in the tumour microenvironment characterized by a CD4+CD25+ phenotype, is also in focus of interest, given the critical role of these cells in the modification of immune responses. FOXP3 is a master regulator of Treg cells. According to some autors FOXP3 density can contribute to the prediction of oucome in classical Hodgkin lymphoma.

The important question is whether these findings will have a notable impact on general practice in the management of HL patients. As some authors point out, it is of pivotal importance that a personalized treatment strategy is developed in the future treatment of patients with HL, identifying at the time of a diagnosis those individuals with increased resistance to chemotherapy and radiotherapy[21].

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