Classical Hodgkin lymphoma and its differential diagnoses

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Abstract

Classical Hodgkin lymphoma (CHL) is a unique type of B-cell lymphoma defined by the presence of characteristic neoplastic cells, termed Hodgkin- and Reed-Sternberg cells, in an exuberant inflammatory background. CHL constitutes 15–20% of malignant lymphomas. Modern treatment modalities are able to cure the majority of patients. Despite the presence of clonal immunoglobulin gene rearrangements, the tumour cells lack a B-cell-specific expression program and show a phenotype devoid of most B-cell antigens, with CD30 and CD15 as characteristic markers. Although most cases of CHL can be diagnosed readily by morphology and a limited panel of immunohistochemical markers, a variety of malignant lymphomas and reactive conditions can imitate CHL, and true borderline cases with features intermediate between CHL and large B-cell lymphoma exist. This review summarizes the diagnostic criteria and relevant biological features of CHL and describes the most important differential diagnoses, including lymphocyte predominant Hodgkin lymphoma.

Keywords classical Hodgkin lymphoma; immunohistochemistry; lymphoma classification; nodular lymphocyte predominant Hodgkin lymphoma

Definition and classification

Hodgkin lymphoma is a germinal center-derived B-cell neoplasm characterized by a small minority of neoplastic Hodgkin and Reed-Sternberg cells (usually 0.1–2%) with characteristic morphology and immunophenotype embedded in a reactive inflammatory infiltrate. In the current WHO classification, two main groups of HL are differentiated, namely classical HL (CHL), accounting for approximately 95% of cases, and (nodular) lymphocyte-predominant HL (NLPHL), also called nodular paragranuloma (Table 1).[1] The neoplastic cell of CHL is genotypically a B-cell with rearranged immunoglobulin genes, which has downregulated or lost virtually all B-cell markers.[2–5] The subtyping of CHL is mainly based on tissue architecture and the composition of the background infiltrate. In contrast, the tumour cells of NLPHL in general lack the expression of the hallmark CHL antigens CD30 and CD15 and have retained the expression of a variety of B-cell markers.[1,6] Despite the recognition of the B-cell origin, Hodgkin lymphoma remains classified separately from other B-cell neoplasms, based on clinical, morphological and biological features. This review focuses on CHL, but also summarizes the seminal findings and features of NLPHL.

Epidemiology

CHL accounts for 15–20% of all malignant lymphomas. The age-adjusted annual incidence rate in Western countries is approximately 2–4 per 100,000 population. CHL shows a typical bimodal age distribution, with a larger peak of incidence in early adulthood (15–35 years) and a second peak in elderly patients above age 55. The overall male-to-female ratio is approximately 1.5:1. Developing countries overall have lower incidence rates, but higher rates of childhood CHL and Epstein–Barr virus (EBV) positive cases.[7] Some types of immunodeficiency increase the risk for developing CHL, including HIV infection and status after solid organ or allogeneic bone marrow transplantation. These cases are virtually always EBV+ and predominantly of mixed cellularity subtype.

WHO classification of Hodgkin lymphoma

- Nodular lymphocyte-predominant Hodgkin's lymphoma
- Classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Lymphocyte-depleted classical Hodgkin lymphoma

Table 1

Clinical features

CHL manifests first in lymph nodes in >90% of cases, with cervical (75%), axillary, and inguinal nodes as the most frequently involved sites. Mediastinal disease is typical in nodular sclerosis (NS) subtype, and may be asymptomatic, with detection on a routine chest radiograph, but approximately 50% of cases present bulky mediastinal involvement (greater than one third of the intrathoracic diameter). Retroperitoneal lymphadenopathy and splenic involvement, occurring in 10% of patients are more commonly associated with mixed cellularity subtype. Bone marrow involvement is relatively rare in CHL, occurring in approximately 3–5% of non-immunosuppressed patients according to recent large series.

As CHL is almost always a node-based disease, a primary diagnosis of CHL in extranodal sites such as the gastrointestinal tract or the skin should be made with great caution. Most cases from older series of primary extranodal CHL probably represent different entities with morphological and immunophenotypical overlap with CHL as outlined below. Exceptions to this are the isolated involvement of the thymus by NS subtype, and CHL arising in the Waldeyer's ring.[8]

Approximately 30%–40% of patients with CHL presents with B symptoms. Although B symptoms are more frequent in advanced stages of disease, they can also occur in early stages, due to the inflammatory cytokines produced by the tumour. Other symptoms including the cyclic Pel-Ebstein type of fever, generalized pruritus and pain in involved nodes upon alcohol ingestion are rare.

Diagnosis of CHL

Morphology

The morphological diagnosis of CHL is based on the presence of diagnostic **Reed-Sternberg** (RS) and **Hodgkin cells** in the appropriate inflammatory background. The classic RS cell is large

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(up to 100 μm) and contains two to multiple nuclei or a large lobated nucleus, rendering the impression of multinucleation on sectioning (Figure 1a). The nuclei show an accentuated membrane, pale chromatin, and a single large, eosinophilic, viral inclusion—like nucleolus. The cytoplasm is ample and amphophilic. The mononuclear Hodgkin cells can be discerned from immunoblasts by virtue of their larger size, their huge, eosinophilic nucleolus, frequently surrounded by a clear halo, and their more eosinophilic cytoplasm. The typical cell of the nodular sclerosis subtype is the **lacunar cell** with abundant clear to slightly eosinophilic cytoplasm and sharply defined, round cellular borders and frequently lobated nuclei with coarse chromatin and less prominent nucleoli (Figure 1b). The cytoplasm is frequently condensed in the perinuclear area, with spider web-like extensions to the cell membrane. The lymphocyte-predominant (LP) cell or "popcorn" cell is the characteristic cell type of NLPHL, but a certain cytological overlap between the neoplastic cells of NLPHL and CHL can be encountered. Based on the morphology of the neoplastic cells, the tissue architecture, and the characteristics of the reactive infiltrate, four subtypes of CHL are currently recognized (Table 1).[1]

Nodular sclerosis (NS) CHL accounts for 50—80% of cases. Microscopically, cellular nodules surrounded by concentrically arranged collagen bands dominate in typical cases, but the amount of fibrosis can be extremely variable (Figure 2). Cases with incipient fibrosis have been designated "cellular phase" of NS. On the other extreme, lymph nodes can show almost complete obliterative fibrosis with a paucity of both tumour cells and reactive inflammatory cells. These cases can present significant diagnostic difficulties, especially in needle biopsies with crush artifacts due to the high fibre content. Lacunar cells occur sprinkled throughout the nodules or in clusters or compact sheets of cells. The reactive background population shows significant variation, usually containing a mixed population of lymphocytes, neutrophils, and frequent eosinophils, as well as plasma cells, macrophages and fibroblasts. Necrosis and eosinophilic or neutrophilic microabscesses rimmed by histiocytes and tumour cells are common, sometimes mimicking a necrotizing granulomatous process. The sub-classification of nodular sclerosis CHL into grades I and II as proposed by the British National Lymphoma Investigation (BNLI) which is primarily based on the amount and cytological features of neoplastic cells has lost its previous prognostic impact with modern therapies.[9]

Mixed cellularity CHL accounts for 20%—30% of cases in Western countries and usually shows diffuse obliteration of nodal architecture by a proliferation of classic HRS cells and variants in a heterogeneous background of small lymphocytes, eosinophils, plasma cells, and histiocytes (Figure 3). Rare cases show abundant clusters of epithelioid histiocytes, which can almost completely obscure both lymphocytes and the neoplastic cells.

Most cases of **lymphocyte-rich** CHL, which comprise approximately 5% of CHL and are not to be confused with nodular lymphocyte predominant HL (NLPHL), show a nodular architecture with a B-cell rich background composed of enlarged follicles with broad IgD+ mantle zones and regressed germinal centers. Single HRS cells with classical immunophenotype are distributed in the expanded mantles and in the interfollicular area (Figure 4). Other inflammatory cells such as eosinophils are usually rare. The diffuse subtype of lymphocyte-rich CHL with a T-cell dominated background is rare.[6]

Lymphocyte depleted CHL is a virtually vanishing diagnosis, since most cases previously diagnosed as such probably represent aggressive NHL or NS CHL with advanced obliterative fibrosis. Recurrent disease may present with depletion of the reactive background infiltrate, but this should not lead to a reclassification of the disease, which is always based on the presentation at primary diagnosis. If reliable subtyping is not possible, e.g. in small needle biopsies, the case should best be designated CHL unclassified, indicating the most likely subtype.

Immunophenotype

Although most cases of CHL can be identified correctly by morphology alone, confirmatory immunohistochemical examinations are usually performed in all cases especially at primary diagnosis and can help to exclude other lymphoid neoplasms simulating CHL. Owing to the unique features of CHL, both the

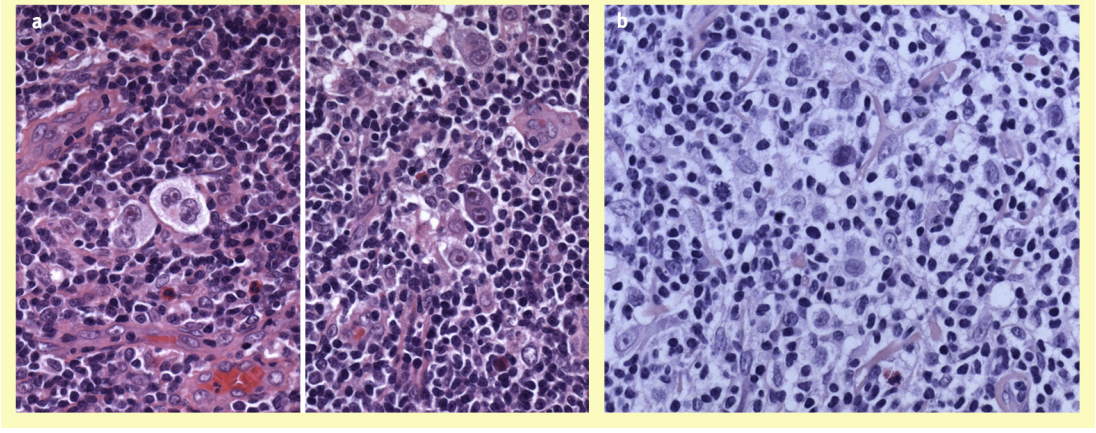

Figure 1 The spectrum of cytology of classical Hodgkin lymphoma. (**a**). Classical Reed-Sternberg cells of usual type with large nuclei with prominent eosinophilic nucleoli and variably stained cytoplasm. (**b**). Lacunar cells of nodular sclerosis subtype have less prominent nucleoli and light-staining cytoplasm with spider web-like extensions.