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Hodgkin lymphoma: differences and differential diagnosis

Andrzej Gruchała

National Institute of Oncology, Institute of Research M. Sklodowska-Curie Memory, Krakow Branch, Poland

Abstract

Hodgkin lymphoma accounts for approximately 15% of all lymphomas. The World Health Organization 2017 classification lists two main types as separate entities: classic Hodgkin lymphoma and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL).

The morphology of neoplastic cells differs slightly in both types, while these cells in typical cases show a different immunophenotype. Overlapping histological images and immunophenotypes cause diagnostic difficulties and the need for detailed differential analysis. The classic form accounts for about 90% of cases and occurs in four histoclinical subtypes, requires differentiation from other lymphomas and immunoproliferation, and neoplasms with other differentiation. NLPHL occurs in six immunohistochemical patterns. An increase in the number of T lymphocytes and histiocytes, and a disappearance of the nodular structure, are associated with a more aggressive course and the possibility of transformation into diffuse large B-cell lymphoma, most often T-cell/histiocyte rich large B-cell lymphoma. Recent reports demonstrate the importance of stroma in maintaining tumor viability. Accurate histopathological diagnosis must be based on representative material that allows the assessment of the architecture of the tissue.

Key words: classic Hodgkin lymphoma, nodular lymphocyte predominant Hodgkin lymphoma, gray zone lymphoma

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Introduction

Thomas Hodgkin presented a lecture entitled 'On some morbid appearances of the absorbent glands and spleen' at a meeting of the Medical and Chirurgical Society of London in January 1832, and then published a paper in Medical-Chirurgical Society Transactions. It is noteworthy that in the era of numerous infectious lesions of lymph nodes, Hodgkin distinguished a clinical course and an autopsy picture of the disease, which was named after him, and he did it without the benefit of microscopic examination. The name of Hodgkin's disease was finally introduced by Samuel Wilks in 1865, when he published material extended to include his own cases with clinical and pathological details [1].

Understanding of the disease continued to grow after the use of microscopic examination of tumors and the description of the histology of Hodgkin's disease by Theodor Langhans (1872) and characteristic diagnostic cells by Carl Sternberg (1898), and Dorothy Reed (1902) [2]. It took another 100 years to elucidate the neoplastic nature of the disease, detailed microscopic and immunophenotypic description, histological subtypes, and combining them with etiological factors and the clinical course. For the last

Address for correspondence: Andrzej Gruchała, National Institute of Oncology, Institute of Research M. Sklodowska-Curie Memory, Garncarska 11, 31–115 Kraków, Poland, e-mail: gruchalaandrzej@poczta.onet.pl

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20 years, researchers have been interested in the relationship between cancer cells and a niche microenvironment that they can create themselves [3–5].

General information

The current World Health Organization (WHO) 2017 classification, based on the histological picture and immunohistochemical staining, distinguishes two types of Hodgkin lymphoma (HL), i.e. the classic form, classic Hodgkin lymphoma (cHL), which accounts for about 90%, and the non-classical form, nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) [6–8]. Distinguishing these types allows for proper correlation with clinical data as well as different treatments. In the histological picture of both types, neoplastic cells constitute a small percentage of tissue and occur in their niche microenvironment.

Diagnostic for cHL are large multi-lobated Reed-Sternberg cells (RS) and mononuclear Hodgkin (H) cells, hence sometimes the joint term Hodgkin/Reed-Sternberg (H/RS) is used. Diagnostic for NLPHL are smaller cells with polylobular nuclei (LP) with nucleoli, commonly called popcorn cells [6, 7].

Neoplastic cells

Neoplastic cells of both types of HL originate from the B-cell germinal center line [2, 3, 9], but they present other differentiation stop points, and thus differ in antigens used in histopathological diagnostics, and recently also in the treatment of patients. In cHL, cells typically show the transcription factor PAX5 (low expression), CD30 and CD15, but negative CD45 and B-cell antigens, in contrast to NLPHL CD45 positive with B-cell antigens (PAX5-high expression, CD19, CD20, CD79a, OCT2 , BOB.1, J-chain) but CD15 and CD30 negative [6]. In some cases, the immunophenotypes differ from the typical ones, which makes diagnosis difficult.

Neoplastic cells, as cells of origin from the immune system, retain the ability to produce many active cytokines and interleukins, influencing the cellular composition of the stroma they surround them with [3, 4, 6, 7]. This influence translates into histological images, and these also into the clinical course.

Cell survival is possible thanks to stimulation of multiplication, blocking apoptosis and creating a useful microenvironment to protect against the immune system. Genetic studies have shown activations of signaling pathways, especially JAK/STAT, NF-kappaB, P13K/AKT, which affect the cell cycle and block the apoptotic pathways. Changes in PDL1/PDL2 genes affect the regulation of the immune system through check point inhibition, in which T helper lymphocytes, NK cells and macrophages are involved [3, 4, 10–13]. H/RS cells can transfer important receptor proteins, PDL1 ligands, to other cells in the process of trogocytosis, blocking the aggressive action of the immune system [14]. Epstein-Bárr virus (EBV) is involved in the etiopathogenesis of cHL through the epigenetic action of the LMP1 and LMP2 proteins [15–17]. Contrary to the classical form in NLPHL, EBV is not detected in neoplastic tissue, but recent reports indicate the similarity of *Neisseria catarrhalis* and its possible involvement in the pathogenesis of NLPHL similar to *Helicobacter pylori* in gastric marginal lymphoma [18].

Classic Hodgkin lymphoma

The WHO classification distinguishes cHL in its classical form into four histo-clinical subtypes:

1) nodular sclerosis (NSCHL);
2) mixed cellularity (MCCHL);
3) lymphocyte-rich (LRCHL);
4) lymphocyte depleted (LDCHL).

Nodular sclerosis classic Hodgkin lymphoma (NSCHL) is characterized by intensive fibrosis of the stroma causing thickening of the lymph node capsule and division of the tissue into nodules. H/RS cells take the form of lacunar cells and are often found in diffuse areas with necrotic foci. There are numerous eosinophils and histiocytes in the background. In a longer-lasting disease, the stromal lesions may be so strong that the neoplastic tissue disappears and, with small sections, diagnostic material may not be obtained. The diagnosis becomes a challenge for the surgeon and pathologist. This is the most common type of cHL (70%) in countries with higher socioeconomic status. Young people (especially in II–III decade) suffer most often, men and women with similar frequency. The disease most often affects the mediastinum and is often diagnosed during X-ray screening. The prognosis is better than for the other subtypes [6, 7, 10].

Mixed cellularity (MCCHL) subtype accounts for about 25% of the cHL. In the histological picture, it is characterized by diffuse mixed-cell stroma with dispersed H/RS cells, most often with typical morphology. In this type, a bimodal peak in incidence is observed among children and adults aged over 60. Of all the subtypes, it is most often associated with EBV infection (about 75%); in developing countries it affects children and is EBV positive. It occurs more often in patients with HIV infection and immunodeficiency. The group of patients is dominated by men (c.70%). Peripheral lymph nodes are most often affected. The prognosis is intermediate between NSCHL and LDCHL [6, 7, 10].

Lymphocyte-rich (LRCHL) subtype accounts for approximately 5% of cHL cases, and is characterized by the presence of dispersed H/RS cells in nodular, less often diffuse, small lymphocyte-abundant stroma. The histological picture requires differentiation from NLPHL, especially that in immunohistochemical staining, antigens characteristic for NLPHL, such as transcription factors BOB.1, OCT2, bcl6, may be present atypically. EBV antigens are less common

than in MCCHL, but more often than in NSCHL. The disease affects peripheral lymph nodes in patients most commonly in their 30 s, with a 2:1 male predominance. The prognosis is better than for other cHL subtypes [6, 7, 10].

Lymphocyte-depleted (**LDCHL**) subtype is the rarest among cHL and accounts for less than 1%. It is associated with HIV infection and similarly to MCCHL with EBV latent infection. In the histological structure, numerous atypical forms of H/RS cells are present, the stroma is dominated by histiocytes and fibrosis, and lymphocytes are sparse. From the point of view of a pathologist, other neoplasms, including sarcomas, should be considered in everyday work. The age of patients varies widely, the disease occupies the retroperitoneal space, and bone marrow involvement is frequent. The prognosis is worse than in the other cHL subtypes [6, 7, 10].

Establishing a diagnosis of cHL subtype requires appropriate diagnostic material, preferably surgical biopsy. Core-needle biopsy and fine-needle aspiration biopsy can be used only at the initial stage of tumor diagnosis in order to direct further diagnosis [non-Hodgkin lymphoma (NHL), HL, melanoma, carcinoma, sarcoma]. Flow cytometric diagnosis is not efficient in the diagnosis of HL [10], but it is useful if there is a need to differentiate from selected NHL. WHO classification allows the diagnosis of cHL without specifying the subtype, but requires differentiation from NLPHL [6].

Differential diagnosis of cHL

In typical images and immunophenotypes, making an accurate diagnosis is quite simple. Overlapping histological images and the appearance of atypical antigenic constellations is a challenge for a pathologist. WHO 2017 has accepted a new entity: B-cell lymphoma unclassifiable, with features intermediate between diffuse large B-cell lymphoma and cHL also called gray-zone lymphoma (GZL), especially for mediastinal tumors that share common features for cHL and primary mediastinal large B-cell lymphoma, co-express CD20 and CD30, which can be used in the treatment of patients. Molecular studies indicate a closer association of the gray-zone lymphoma with cHL [6, 7, 10]. However, GZL does not release the pathologist from trying to diagnose both entities if possible.

Other diseases requiring differentiation from cHL are EBV-dependent lymphomas and lymphoproliferation, such as EBV-positive diffuse large B-cell lymphoma (DLBCL), muco-cutaneous ulcer, and polymorphic forms of lymphoproliferation associated with age-related or iatrogenic immunosuppression. Anaplastic large cell lymphoma, especially ALK negative, as well as peripheral T-cell lymphoma may be a diagnostic problem [9, 10].

Apart from neoplasms of the immune system, the initial diagnosis should take into account neoplasms with other differentiations, in particular melanoma metastases into lymph nodes. Thanks to immunohistochemical staining, diagnostics is possible. LDCHL may be more difficult in a few cases to differentiate sarcomas in which the CD30 antigen may be present.

Non classic Hodgkin lymphoma — nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)

NLPHL accounts for c. 5–10% of all HLs. It has a separate histological picture in relation to cHL, its own immunophenotype, it is EBV-independent, and it requires differentiation from other tumors. It typically presents as a long-lasting peripheral lymphadenopathy with no systemic symptoms. The mediastinal and mesenteric nodes may be involved in a few cases. Patients usually present first and second stage disease. Long-lasting disease is associated with a more aggressive course [6, 10].

In the histological picture, LP cells constitute a small percentage of cells with the immunophenotype mentioned above. Six immunohistochemical patterns have been distinguished, of which C-D-E are associated with the appearance of T lymphocytes in the background, in the E pattern resembling T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) [8, 19]. Differentiation of diffuse NLPHL with abundance of T lymphocytes and macrophages from THRLBCL is difficult and sometimes impossible in the absence of even one typical nodule. Transformation of NLPHL into DLBCL has been reported in recent actuarial studies in up to 30% of cases, especially into THRLBCL [8]. Transformation is now believed to be a continuum of changes depending on the environment in which lymphoma cells exist.

The WHO classification indicates that the presence of one common nodule is sufficient to diagnose the disease as NLPHL, and the presence of diffuse T-cell and histiocyte-rich tissue should be noted in the report as an E-pattern [6, 10]. A diagnosis of THRLBCL is possible when the histological picture shows the presence of dispersed single large B cells, CD20 positive, sometimes resembling H/RS cells in a background rich in T lymphocytes and/or histiocytes and without small B lymphocytes [6, 7]. Genetic and molecular studies do not differentiate tumors. Due to diagnostic difficulties, some clinicians believe that the stage of disease is a more important prognostic and predictive factor than the histological picture of NLPHL [10]. In advanced cases, patients require intensive treatment.

Conclusions

The development of diagnostic methods over the years has allowed for the expansion of information about HL and the separation of cHL from NLPHL. These diseases have different etiological factors, a different histological picture and immunophenotypic profile, and they require differentiation

from other neoplasms and lymphoproliferations. Diagnostics requires obtaining representative material, preferably the entire lymph node or a surgical biopsy sample. Current knowledge allows for the application of different therapeutic procedures. Contemporary treatment is based not only on the cytotoxicity of drugs, but also on interference in the microenvironment in which cancer cells live.

Author's contributions

AG — sole author.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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