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Hodgkin lymphoma: Pathology and biology

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ABSTRACT

The Hodgkin and Reed-Sternberg (HRS) tumor cells of classical Hodgkin lymphoma (HL), as well as the lymphocyte predominant (LP) cells of nodular lymphocyte predominant HL (NLPHL), are derived from mature B cells. However, HRS cells have largely lost their B-cell phenotype and show a very unusual expression of many markers of other hematopoietic cell lineages, which aids in the differential diagnosis between classical HL (cHL) and NLPHL and distinguishes cHL from all other hematopoietic malignancies. The bi- or multinucleated Reed-Sternberg cells most likely derive from the mononuclear Hodgkin cells through a process of incomplete cytokinesis. HRS cells show a deregulated activation of numerous signaling pathways, which is partly mediated by cellular interactions in the lymphoma microenvironment and partly by genetic lesions. In a fraction of cases, Epstein-Barr virus contributes to the pathogenesis of cHL. Recurrent genetic lesions in HRS cells identified so far often involve members of the nuclear factor-κB (NF-κB) and JAK/STAT pathways and genes involved in major histocompatibility complex expression. However, further lead transforming events likely remain to be identified. We here discuss the current knowledge on HL pathology and biology.

1. Introduction

More than 170 years ago, Thomas Hodgkin first described the disease named after him [1]. For several reasons, Hodgkin lymphoma (HL) is, despite recent progress, still one of the most fascinating hematopoietic malignancies. First, the unique histopathological appearance with rare lymphoma cells embedded in an inflammatory background represents also today a technical challenge and impedes rapid advances with respect to its pathogenesis. For a long time, these technical challenges also prevented the identification of the cellular origin of the HL tumor cells. Furthermore, the HL phenotype at the crossroads of inflammation and malignancy is unique among malignancies. Finally, a key driver genomic alteration in HL is not known. Despite these obstacles, the cellular origin of HL tumor cells has been clarified, and various molecular and genomic defects were identified which allowed the development of a concept for HL pathogenesis. In this article, we discuss current concepts on pathology, the cellular origin, known molecular and genomic defects, and the interaction between tumor and infiltrating surrounding cells in HL.

2. Pathology

The main histological feature of HL is the abundance of reactive bystander cells and the paucity of tumor cells in affected lymph nodes. Four classical HL (cHL) subtypes and nodular lymphocyte-predominant HL (NLPHL) can be distinguished. The malignant Hodgkin and Reed/Sternberg (HRS) cells in classical subtypes show expression of CD30 (Fig. 1a), MUM1, variable expression of CD15 (Fig. 1b), and a typically weak expression of PAX5 (Fig. 1c). HRS cells have usually downregulated B-cell markers (Fig. 1d). In contrast, tumor cells of NLPHL—the lymphocyte-predominant (LP) cells—resemble germinal center (GC) B cells in their immunophenotype. Whereas the immunophenotype of HRS cells in classical subtypes is comparable, the microenvironment presents striking differences.

2.1. Nodular sclerosing HL (NSHL)

This is the most frequent subtype in Western countries (around 80% of cases) mainly occurring in adolescents [2]. NSHL frequently presents with large mediastinal tumors. Histologically, fibrotic

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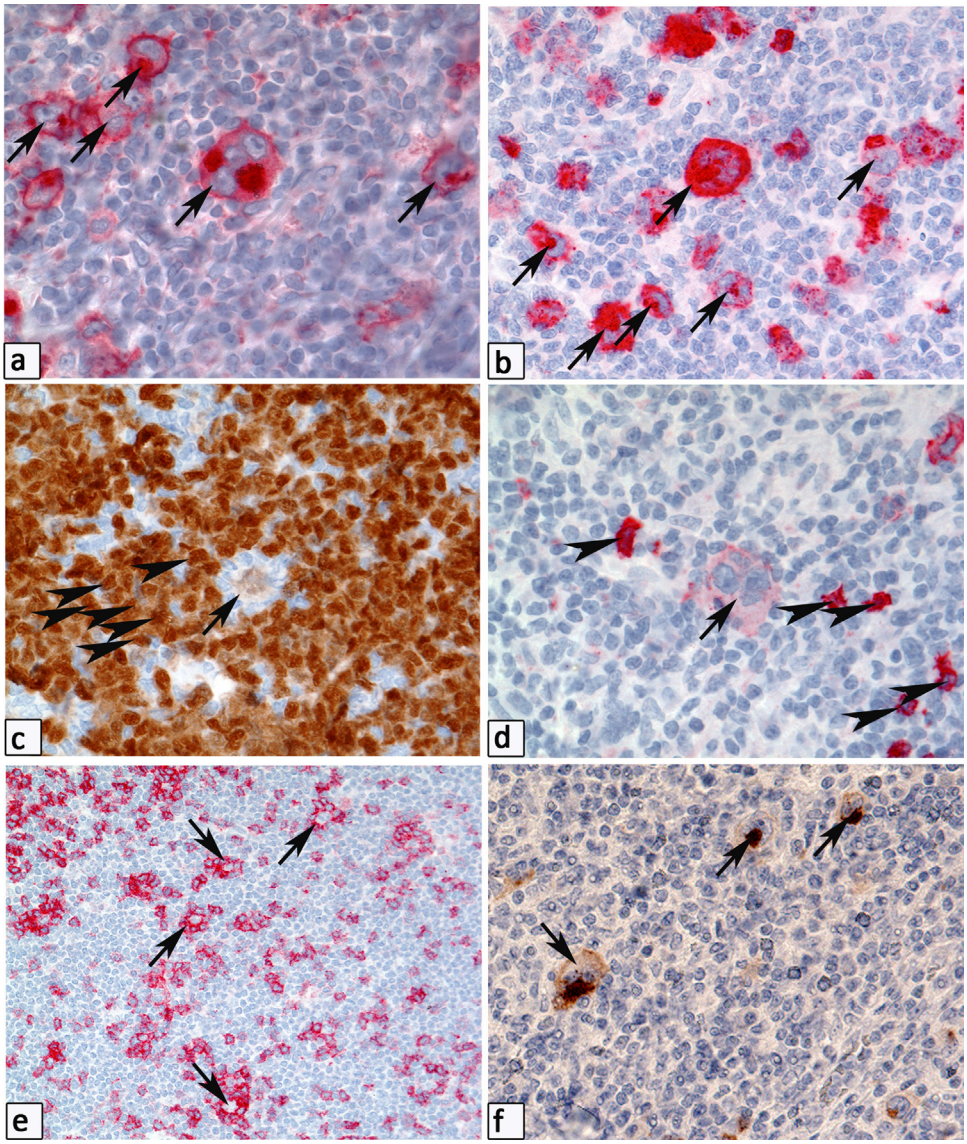

Fig. 1. Typical immunohistochemical features of HL. (a) Expression of CD30 in HRS cells (arrows, membrane bound and golgi field, NSHL, CD30-immunostaining, 400x). (b) Strong cytoplasmic CD15 expression in HRS cells (arrows, NSHL, CD15-immunostaining, 400x). (c) Typical weak PAX5 expression in a HRS cell in LRCHL (arrow). Surrounding mantle zone B cells show a more prominent PAX5 expression (arrow heads, PAX5-immunostaining, 400x). (d) Weak CD20 expression in an HRS cell, as it is observed in some cases (arrow). The few B cells in the reactive infiltrate present a strong CD20 expression (arrow heads, CD20-immunostaining, 400x). (e) PD1-positive T-cell rosettes surrounding LP cells in NLPHL (arrows, PD1-immunostaining, 200x). (f) CD83 expression in HRS cells (arrows, MCHL, CD83-immunostaining, 400x).

bands confine nodular compartments containing the typical infiltrate consisting of HRS cells, epithelioid cells, T cells, and variable numbers of neutrophils and eosinophils (Fig. 2a). Due to shrinking artifacts the HRS cells can be located in lacunar-like spaces and are then called lacunar cells (Fig. 2b). In NSHL, HRS cells are usually Epstein-Barr virus (EBV)-negative.

2.2. Mixed cellularity HL (MCHL)

This subtype usually occurs in children or elderly people, as well as in immunocompromised patients. HRS cells tend to be frequently EBV-infected [2]. The affected lymph node presents a completely effaced architecture with diffuse infiltrates containing histiocytes and eosinophils. In EBV-negative cases, the histiocytes rather present as epithelioid cells (Fig. 2c), whereas in immunocompromised patients they rather appear as spindle shaped macrophages (Fig. 2d) [3,4].

2.3. Lymphocyte-depleted HL (LDHL)

This subtype has become exceedingly rare, since with better reagents for PAX5 staining, PAX5-positive LDHL can now be better distinguished from PAX5-negative (and ALK-negative) anaplastic large cell lymphoma. In LDHL, HRS cells can be relatively abundant (reticular variant). Other cases of LDHL represent a diffuse fibrosis in which scattered HRS cells are embedded. LDHL is more likely to be encountered in immunocompromised patients (human immunodeficiency virus (HIV)-positive), and HRS cells are frequently EBV-infected.

2.4. Lymphocyte-rich cHL (LRCHL)

This is another rare subtype of HL that usually occurs in adults and shows a prevalence for cervical lymph nodes and the Waldeyer lymphatic tissue. LRCHL frequently presents with early