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HODGKIN LYMPHOMA: AN UPDATE ON ITS BIOLOGY WITH NEWER INSIGHTS INTO CLASSIFICATION

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Abstract

In the last few years, there has been a greater understanding of the spectrum and biology of Hodgkin lymphoma. In standard texts, Hodgkin lymphoma is classified as two distinct entities, namely nodular lymphocyte predominant Hodgkin lymphoma and classical Hodgkin lymphoma. However, recent evidence suggests that classical Hodgkin lymphoma is not a single disease. While the mixed cellularity and lymphocyte depleted subtypes may be part of a biologic continuum, the nodular sclerosis subtype has a distinct epidemiology, clinical presentation and histology. Nodular sclerosis Hodgkin lymphoma may also be related to primary mediastinal B-cell lymphoma and mediastinal grey zone lymphomas. We present an update on the pathobiology of Hodgkin lymphoma and discuss these biologic and clinical differences in this review.

Keywords

Classical Hodgkin lymphoma; Nodular lymphocyte predominant Hodgkin lymphoma; Primary mediastinal large B-cell lymphoma; Grey zone lymphomas; Epstein Barr virus; Epidemiology; Biology; Immunophenotyping

The eponym ‘Hodgkin’s disease’ was conferred by Samuel Wilks in 1856 1, almost 25 years after the first description of ‘morbid appearances of the absorbent glands and spleen’ by Thomas Hodgkin. Interestingly, of the seven original cases described by Dr. Hodgkin at the Guy’s hospital, only three were later shown to be truly Hodgkin’s disease in 1926, by the diagnostic criteria in use at that time 2. Also of interest is the fact that Dr. Hodgkin’s contributions in other fields of medicine and social sciences were far greater and had much more impact in his lifetime. Hodgkin lymphoma, as it is now termed, has an incidence rate of 2.7 per 100,000 population and is estimated to account for 11.7% of all lymphomas diagnosed in 2006 [3]. The last decade has seen tremendous advances in the understanding of its biology and we present an update on the pathobiology of Hodgkin lymphoma [HL] along with newer insights into its classification.

HODGKIN LYMPHOMA – HOW MANY DISEASE ENTITIES?

Presently, HL is classified into two largely distinct entities, namely nodular lymphocyte predominance HL (NLPHL) and classical HL (CHL), the latter being further subtyped as nodular sclerosis (NSCHL), lymphocyte rich (LRCHL), mixed cellularity (MCCHL), and lymphocyte depletion (LDCHL) subtypes [4]. Salient clinical and histopathologic features of each subtype are shown in tables 1 and 2. While CHL tends to be regarded in the clinical and

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experimental literature as a single disease, consideration of all epidemiological, biological and clinical data suggests that CHL probably consists of more than one entity.

Nodular Sclerosis CHL

NSCHL stands apart from other forms of CHL and NLPHL. Young adults are more often affected than the elderly and this subtype is more frequently seen in developed countries, accounting for the early peak in Western populations [5]. It differs from all other forms of classical Hodgkin lymphoma as being more common in females than males, and less frequently associated with EBV. The epidemiologic risk patterns of NSCHL are distinct from those of MCCHL, suggesting that the two may not share a common etiology [6]. Over the last few decades, the incidence of NSCHL has continued to rise [7]. The incidence of NSCHL in HIV-positive individuals decreases with decreasing CD4 counts, suggesting that it needs an intact immune system for its development [8].

Clinically, mediastinal involvement is more common in NSCHL than in other types of CHL. Recent studies have indicated a close relationship to primary mediastinal large B-cell lymphoma (PMLBL), and a possible origin from a thymic B-cell [9–11]. Both NSCHL and PMLBL lack immunoglobulin expression and functional expression of HLA class I antigens, and share cytogenetic abnormalities. *MAL*, a gene involved in T-cell activation that is expressed in PMLBL, is only expressed by NSCHL and no other HL subtypes [12]. CD23, which is expressed on normal thymic B-cells and PMLBL, is also expressed in some cases of NSCHL. The existence of mediastinal grey zone lymphomas (MGZL) with transitional morphology and phenotype between NSCHL and PMLBL, further supports a relationship between these two entities [11].

Studies employing gene expression profiling as well as immunohistochemistry have provided evidence for underlying biological and clinical differences between NSCHL and other forms of CHL, in particular MCCHL [13–15]. A histological hallmark of NSCHL is the presence of broad bands of birefringent collagen (Fig. 1), suggesting differences in cytokine networks as compared to other subtypes, with increased production of IL-13 16. Residual B cells are often relatively abundant in NSCHL, with preservation of follicular structures. The lacunar and other HRS-cell variants may be associated with lymphoid follicles, and sometimes intimately associated with the follicular dendritic cell meshworks [17]. This preservation of the nodal structures contrasts with MCCHL and LDHL, which have a high ratio of T:B lymphocytes (with an increase of the CD4+ subset) [18].

In addition to the abundant lymphocytes in the background, there are variable numbers of neutropils and eosinophils, sometimes forming microabscesses within the nodules. Some cases may have a high proportion of HRS cells, resulting in a “lymphocyte-depleted” appearance [19]. A high content of HRS cells, extensive necrosis, and a prominent fibrohistiocytic stroma all are features associated with Grade 2 NSCHL [20]. While grading is optional in the WHO classification, in some studies Grade 2 NSCHL has been associated with a higher relapse rate and poorer response to therapy, particularly in patients with advanced stage disease.

Mixed Cellularity and Lymphocyte Depleted CHL

In contrast to NSCHL, MCCHL and LDCHL are associated with lower socio-economic status, greater prevalence in males, frequent EBV infection of the neoplastic cells, and a different pattern of spread within the immune system – typically sparing the mediastinum and thymus gland. MCCHL and LDCHL have overlapping clinical, epidemiological and biological features, differing largely in the extent of depletion of normal background lymphocytes and the degree of immunosuppression in the host. Just as NSCHL can be graded according the

proportion of tumor cells, MCCHL and LDCHL can be viewed as two grades of a single disease entity. Both occur often in the setting of HIV-infection.

Although histologic subtype has historically been known to impact prognosis [21, 22], current multimodality treatment protocols achieve cure in over 90% of patients with early-stage disease and have blunted the effect of histology on outcomes. Presently, disease stage, presence of B symptoms and risk factors such as coincidental AIDS are considered to be the most important prognostic factors [23–25]. However, even in the modern treatment era, morphologic groups continue to have prognostic significance, with LDCHL (Fig. 2) and MCCHL subtypes conferring a significantly worse prognosis [26].

MCCHL exhibits a bimodal age-incidence curve and represents most cases of CHL in the pediatric age group. It is relatively uncommon in young adults, but increases in incidence after the age of 50. These incidence patterns mirror that of EBV infection, which are seen in the very young and the elderly [27]. The epidemiological observations with respect to EBV and HL have provided support for a three disease hypothesis, first offered by MacMahon, prior to the modern classification of Hodgkin lymphoma [28].

Lymphocyte Rich CHL

The most recently identified subtype of HL is lymphocyte-rich CHL (LRCHL), a subtype that was often mistaken for NLPHL in older studies. First recognized as follicular Hodgkin lymphoma by Ashton-Key et al. [29], this form of CHL usually presents with Stage I or II disease. As the name implies, there is a rich background of normal lymphocytes, with the malignant cells found in a B-cell rich milieu in the mantle and marginal zones of reactive follicles 30. The neoplastic cells have the phenotype of classical HRS cells, but are smaller and, in H&E stained sections, may resemble LP cells. Thus, immunohistochemical studies are critical for correct diagnosis (Fig. 3).

It has been questioned whether LRCHL is just an early form of NSCHL, but in patients with sequential biopsies, the histological pattern is usually constant. Clinically, the cases differ from NSCHL in having infrequent mediastinal involvement, and an older age at presentation [31]. The prognosis is excellent, with event-free and overall survival of 97% at 30 months.

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma, and classical Hodgkin lymphoma

A new category was created in the WHO classification of 2008 to accommodate those cases in which the distinction between CHL and diffuse large B-cell lymphoma (DLBCL) is not possible [32] Cases with these features have been referred to in the literature as “grey zone lymphomas 11, 33. The majority of such patients present with mediastinal masses, and there is an increased male:female ratio, in contrast to both NSCHL and PMLBCL, which are more common in females 11, [34] In the past many of these lymphomas were diagnosed as Hodgkin’s-related anaplastic large cell lymphoma [35]. However, a biological relationship to anaplastic large cell lymphoma is lacking [36]. The optimal therapy has not been determined [37, 38]. However, use of both chemotherapy and radiation therapy appears required for prolonged relapse-free survival [39].

There are other instances in which the distinction between CHL and DLBCL is problemmatic. For exmaple, EBV-positive DLBCL of the elderly may display Hodgkin-like features with neoplastic cells resembling HRS cells [40]. In any given case the diagnosis is based on a combination of clinical, histological, immunophenotypic, and genotypic features. However, the borderline or grey zone cases usually demonstrate a discordance between the morphology and the expected immunophenotype. In most such cases the therapy is based on DLBCL-type

regimens, and as CD20 is usually strongly expressed, rituximab is included in the treatment protocol.

Nodular lymphocyte predominant HL

NLPHL was the first subtype to be recognized as a distinct biologic entity and to be distinguished from CHL [41]. It typically presents in peripheral lymph nodes, and is the only HL subtype to involve mesenteric lymph nodes; the mediastinum is nearly always spared. Other common sites of involvement are periparotid and inguinal lymph nodes. While the peak incidence is in the fourth decade, NLPHL is also seen in children, much more commonly in males. Patients lack B-symptoms and have a good prognosis, sometimes even without therapy [26, 42, 43].

At the cellular level, NLPHL lacks HRS cells. The neoplastic cell of NLPHL was originally termed the L&H cell, after the original description of this form of HL by Lukes and Butler as "lymphocytic and histiocytic predominance" [44]. These cells have also been referred to as "popcorn" cells, but the WHO classification of 2008 recommended the use of the term "LP cell" [32]. LP cells arise in the germinal center or follicular environment (Fig. 4), and NLPHL is sometimes seen in association with progressive transformation of germinal centers (PTGC) [45]. Overall, PTGC has a low incidence of progression to NLHPL, when diagnosed independently 46.

While NLPHL arises in a B-cell rich follicular environment, T-cells are recruited to the lesion and eventually become predominant over time 41, [47]. With time, there is also a loss of the nodular growth pattern, such that NLPHL may progress to a process that is almost indistinguishable from T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) [48, 49]. Features that are helpful in distinguishing NLPHL from THRLBCL include evidence of nodular pattern as manifested by CD21+ follicular dendritic cells and admixed small IgD+ positive B-cells. In addition, the nature of the T-cell component differs with CD8+ T-cells predominating in THRLBCL, as contrasted with CD4+ CD57+ T-cells in NLPHL 49. A recent study found that de novo THRLBCL lacks follicular T-helper cells (T_{FH}) identified by PD-1, yet PD-1-positive cells are abundant in NLPHL, as well as in cases showing borderline features between THRLBCL and NLPHL [50]. The clinical significance of a T-cell rich pattern, or diffuse areas is controversial. One study found that NLPHL patients with T-cell rich nodules often presented at high stage and with B symptoms, but still had a good prognosis, similar to NLPHL [49]. Fan et al. found that NLPHL patients with diffuse areas or T-cell rich nodules were more likely to have recurrent disease [47]. However, whether recurrence leads to long term survival differences is not clear.

NLPHL is generally associated with a good prognosis, but patients presenting with advanced stage disease do not respond well to CHL treatment regimens 42. Based on the biology of NLPHL, which is closer to that of other B-cell lymphomas than CHL, alternative treatment regimens, including the use of rituximab, have been employed more recently [51]. NLPHL progresses in approximately 5% of patients to diffuse large B-cell lymphoma (DLBCL), which may be composite with the NLPHL in the same anatomic site [52, 53]. As a rule NLPHL is not associated with EBV, but a recent report described three cases of EBV-positive NLPHL in Vietnamese children, suggesting that as B-cells, LP cells are at risk to become EBV-transformed 54.

The Neoplastic Cells in Hodgkin Lymphoma

Hodgkin lymphoma is unique in that the neoplastic cells constitute a minority population (less than 1%) in the affected lymph nodes. The classic binucleate Reed-Stenberg (RS) cell was independently described by Carl Sternberg in 1898 [Sternberg, 1898 #543] and Dorothy Reed

in 1902 [55] (Fig. 5A). The binucleation is an artifact seen as a result of deep indentations and folds in the nuclear membrane. Classical RS cells are seen relatively infrequently; cells exhibiting a similar phenotype but varied morphology are more common. These are collectively referred to as Hodgkin/RS (HRS) cells. Well-recognized variants include lacunar cells and mummified cells, but in actuality the morphological spectrum is very broad. The LP cells of NLPHL exhibit a similar broad range in morphological features, but, in general, lack prominent nucleoli (Fig. 5B). The immunophenotype of HRS and LP cells is summarized in Table 3.

HRS cells can be characterized by lineage specific markers, as well as those representing activation markers and transcription factors. In approximately 85% of cases, the HRS cells are positive for CD15 (the Lewis × blood group carbohydrate, 3-fucosyl N-acetyl lactosamine), whereas CD30 is expressed nearly universally. Most B-lineage associated markers are absent, but CD20 is expressed weakly in up to 50% of cases of CHL.

Analysis of B-cell-specific transcription factors is useful in understanding the differentiation-linked phenotype in HL. Oct-2, BOB.1, Pax-5, and PU.1 belong to a group of transcription factors whose expression correlates with cell lineage and/or the stage of B-cell differentiation 56. Oct-2 and BOB.1 are required for germinal center formation and immunoglobulin production [57]. PU.1 plays an essential role in the development of both lymphoid and myeloid lineages, by regulating the cytokine-dependent proliferation and differentiation of precursor cells. Pax-5, also known as B-cell specific activator protein (BSAP), is essential for B-cell commitment in early B cells and also the maintenance of B-cell identity in mature cells [58, 59], and is nearly always positive, albeit weak, in CHL 60. HRS cells are universally negative for B-cell transcription factor PU.1; transcription factors Oct-2 and BOB.1 are either negative or inconsistently expressed 61–63. On the other hand, transcription factors Pax-5, Oct-1, Oct-2, BOB.1, and PU.1 are universally expressed in all cases of NLPHL [62, 64, 65]..

Approximately 10% of cases of CHL have been reported to express surface T-cell markers on HRS cells [66, 67]. Lineage-inappropriate markers of dendritic cells, monocytes and plasma cells such as CD2, CD3, CD4, CD5, CD8, granzyme B, fascin, CD138 and MUM1 have also been detected on HRS cells [68–72]. Although most cases that show a T-cell immunophenotype are also of B-cell origin on molecular analysis [73], a T-cell origin was suggested in three reported cases, based on the presence of T cell receptor gene rearrangements [74, 75]. However, conclusive evidence for a T-cell form of CHL is lacking. For one, at the time the two reports were published, it was not appreciated that peripheral T-cell lymphomas could express both CD30 and CD15, and mimic CHL at both the phenotypic and morphological levels [76]. Additionally, cases of pleomorphic T-cell lymphomas following primary cutaneous anaplastic large cell lymphoma, mycosis fungoides and lymphomatoid papulosis may closely simulate CHL [77]. Much of the biology that we understand regarding CHL is related to its derivation from rescued germinal center B-cells [78]. Conceptually, suggesting that the same disease entity may be of T-cell derivation runs counter to the view that lineage is a primary factor in defining disease entities [79].

Histogenesis of the neoplastic cells of Hodgkin lymphoma—As suggested by immunophenotypic studies, both HRS cells and LP cells are derived from B-cells at the germinal center or post-germinal center stage of differentiation [80, 81]. Immunoglobulin gene rearrangement studies have established the clonal nature of HRS cells [82]. A high load of somatic mutations in the rearranged immunoglobulin genes supports a germinal center derivation, specifically preapoptotic germinal center B-cells 81, 83–85. HRS cells show evidence for a partial deletion of the IGH constant region by interphase cytogenetics, suggesting the presence of class switch recombination [86]. Further, chromosomal breakpoints affecting the immunoglobulin loci are recurrent in CHL. In a recent study of CHL with respect to B-cell

differentiation stage based on phenotypic markes (bcl6/CD10/MUM1/CD138), most cases of CHL were at a late germinal center or post-germinal center stage [87].

In spite of their B-cell origin, HRS cells have a global loss of B-cell gene expression [88] in that they neither produce immunoglobulin nor have a functional B-cell antigen receptor [89, 90]. Although HRS cells do harbor somatic mutations, these may be 'crippling mutations', meaning that these mutations lead to lack of *IGH@* gene function [91]. It also was speculated that HRS cells are unable to transcribe immunoglobulin genes due to a lack of key B-cell gene transcriptional regulators Oct-2, BOB.1 and PU.1 [61, 62, 65, 84] and/or aberrant expression of suppressors of B-cell genes [92]. However, in at least a proportion of cases the transcription apparatus is intact. An alternative hypothesis is epigenetic silencing of immunoglobulin gene transcription by promoter hypermethylation [93]. Genomic imbalances or rearrangements are not a cause of PU.1, BOB1, and OCT2 deficiency in CHL and argue for another mechanism underlying this phenomenon [94] Ordinarily, crippling mutations in a germinal center B-cell will arrest further differentiation and cause apoptosis of the cells. The fact that HRS cells continue to proliferate in spite of having these deleterious mutations suggests that they somehow acquire the capacity to escape apoptosis, survive and continue proliferating. Escape from apoptosis probably represents the major oncogenic event in CHL lymphomagenesis. Apoptosis appears to be inhibited by several means in HRS cells [78, 95–97]:

1. Constitutive activation of the transcription factor NFkB either autonomously, by rosetting T-cells, by EBV or by inactivation of its inhibitors such as IkB [98–103].
2. Inactivation of the CD95 death receptor pathway [104, 105]
3. Inhibition of executors of apoptosis by expressing X-linked inhibitor of apoptosis (XIAP) [106, 107].
4. Altered regulation of bcl-2 family proteins [108–110].
5. Protection from Fas-induced cell death by expression of FLICE-like inhibitory protein molecule, a potent inhibitor of Fas-induced death [111].

The transforming events that lead to the development of HL are largely unknown. Mutations in tumor suppressor genes *p53* and RB have only been inconsistently reported [112, 113]. While most HRS cells express proliferation associated molecules such as Ki-67 and PCNA 99, a considerable fraction of these undergo abortive mitoses with arrested metaphases, multinucleation and single cell death 114. In addition to multinucleation, which is not due to cellular fusion 115, HRS cells are near tetraploid, and almost all show rather random numerical chromosomal aberrations [116]. Comparative genomic hybridization (CGH) studies have identified a set of recurrent chromosomal abnormalities in CHL, with gain of 17q being the most frequent in one series [117]. These features suggest that HRS cells undergo nuclear division but may have defects in cell division and cytokinesis. Indeed, profound deregulation of cell cycle checkpoints with cyclin E persistency have been reported in HRS cells 118. Recently, COX-2 expression has been associated with cell proliferation and angiogenesis in HL 119. HRS cells also elaborate cytokines that act as paracrine or autocrine factors that assist cell survival and proliferation 120, [121], and produce the characteristic inflammatory background of CHL.

LP cells are also presumably derived from selected germinal center B-cells. However, unlike HRS cells that carry crippling immunoglobulin gene rearrangements, LP cells often show ongoing somatic hypermutation. Activation-induced cytidine deaminase (AID), a factor indispensable for class switch recombination and somatic hypermutation of immunoglobulin genes, is consistently expressed in LP cells but only infrequently in CHL [122]. Frequent occurrence of *BCL6* gene rearrangements also support the hypothesis of a germinal center B

cell origin of LP cells and indicate a significant role of *BCL6* in the pathogenesis of NLPHL [123].

The role of cytokines and infiltrating cells—Interactions between HRS cells and background inflammatory cells are important in the pathogenesis and progression of Hodgkin lymphoma 124. A variety of cytokines, chemokines, growth factors and their receptors including interleukins (IL1 to IL10), interferon, TNF-a, TGF-b, G-CSF, GM-CSF and others play a role in creating this microenvironment 120, 121. The clinical manifestations (such as B symptoms and immunosuppression) and pathologic features reflect imbalances in chemokines, cytokines and their receptors elaborated both by the neoplastic cells and surrounding tissues 18, 99, 125, 126. The T-cell infiltrate in CHL predominantly comprises Th2 and T-regulatory cells, and generally lacks Th1 cells, CD8 cytotoxic T cells and NK cells, thereby preventing cytotoxic anti-tumor immune responses. Cytokine production is driven by expression of T-cell transcription factors [127]. HRS cells secrete Th2 type chemokines and cytokines (such as TARC, MDC, MIG, and IP-10), and cytokines that inhibit Th1 responses (such as IL-10 and TGF-beta) which induce apoptosis of activated Th1 and CD8 T cells [93], 128, 129. The expression of Th2 cytokines and chemokines leads to the reactive infiltrate of eosinophils, Th2 cells, and fibroblasts characteristic of CHL. Cytokines such as IL1, IL6 and TNF have been shown to proffer an unfavorable prognosis including advanced stage, the presence of 'B' symptoms, decreased response to therapy and reduced survival 130, 131. The production and induction of various other cytokines may also explain the influx of eosinophils (IL-5, eotaxin, IL-9), mast cells (IL-9) and plasma cells (IL-6) 132, 133. Nodal fibrosis is mediated by cytokines such as IL-13, TGF-beta, matrix metalloproteases and their inhibitors (TIMP-1 and TIMP-2)16, 134, 135. Certain cytokines also function as autocrine growth factors (e.g. IL-13/IL-13R, IL-3/IL-3R, TIMP-1), perpetuating the proliferation of neoplastic cells 16, 126, 134. 136, 137. Cytokine signaling is probably mediated through aberrant activation of transcription factors of the signal transducer and activator of transcription (STAT) family 138–140. HRS cells also express a number of molecules that are important for T-cell and B-cell interactions (CD40, MHC class II, CD80, CD86). The presence of T-rosettes around HRS cells suggests that T-cells play an important role for HRS cell survival 78. CD30 and CD40 ligands found on HRS cells have pleiotropic biologic activities and their activation might be a critical element in the deregulated cytokine network and cell contact-dependent activation cascade typical for CHL 141.

The cytokine milieu in CHL may lead to the generation of regulatory T (Treg) cells, positive for CD4, CD25, and CCR4, which may be associated with immune escape 142, 143. Many of the cells resetting the HRS cells in CHL have the phenotype of Treg cells. Low numbers of infiltrating CD8, CD 56, CD 57+ cells and high numbers of granzyme B and TIA-1+ cells have been associated with an unfavorable clinical course (presence of leukocytosis, B symptoms, advanced clinical stage (III/IV) and non-response to therapy) 144, 145. Imbalances in T-cell subsets are not confined to the involved lymph nodes, but are also found in the peripheral blood 146, 147. A lack of MHC class I antigen expression on HRS cells also has been postulated to decrease the population of CD8+ T-cells and contribute to the altered CD4:CD8 ratio [130], [148]. Patients with CHL demonstrate impairment of cellular immunity, including a diminished delayed-type hypersensitivity reaction, reduced antigen-dependent proliferation of T and B lymphocytes and a decreased CD4:CD8 ratio [130], [132]. The background of NLPHL differs from that of CHL. LP cells are closely associated with T_{FH} cells, and these cells lead to a distinct cytokine mRNA profile [149], [151]. Patients with NLPHL do not demonstrate impaired immunity.

ETIOLOGIC CONSIDERATIONS

Genetic predisposition

Familial HL represents 4.5% of all newly diagnosed cases [151]. Anticipation (i.e. earlier onset and/or increasing severity in successive generations) occurs in families that exhibit both HL and NHL and it has been suggested that both neoplasms may have a common genetic basis [152]. The relative risk of the development of HL increases approximately 100-fold in monozygous twins 153, 154 and seven-fold in siblings of patients less than 45 years of age 155. However, the cumulative lifetime risks are very small for the development of HL de novo or in first-degree relatives of affected patients [154]. HLA associations have been described in familial HL including HLA A1, B5, B18, DPB1, DRB1, DQA1 and DQB1 [156, 157]. HLA phenotypes may determine the immune response to EBV and maybe implicated in the pathogenesis of HL [158]. Risk of HL is reported to be lower among young adults with multiple older siblings, at least to some extent explained by the fact that having older siblings is associated with earlier exposure to common childhood pathogens 159. Obviously, the interrelations between CHL and infectious agents are complex and are dependent, at least to some degree, on genetics 153, 154. Familial cases of NLPHL have also been reported but the genetics are less well studied [160]. Interestingly, both NLPHL and CHL have been reported with increased frequency in patients with the autoimmune lymphoproliferative syndrome (ALPS), which is associated with defective lymphocyte apoptosis [161].

EBV and Classical HL

20–100% of HL appear to be associated with EBV infection, the association varying with age (more frequent in children and older adults), gender(more frequent in males), geography (higher in Asia than in the US) and histology (more likely in MCCHL and LDCHL than in other subtypes) [54, 162–166]. EBV infection increases the risk of CHL by 3–4-fold 167. Importantly, EBV infection is localized to HRS cells and is clonal, suggesting a possible causal role [168]. HRS cells positive for EBV express a limited number of latency genes, exhibiting a type II latency phenotype [165]. LMP-1 expression is not a constitutive characteristic and may be induced by extracellular signals [169]. LMP-1 functions as a viral oncogene in that it can immortalize B cells [104, 113, 137, 170] and can constitutively activate TNF receptor/CD40 signaling pathways and induce NF- k B. It is also interesting to note that EBV-associated CHL occurs in patients without clinically manifest deficiencies in anti-viral immunity. In spite of expressing viral proteins, tumors are apparently able to escape EBV-specific immunity in vivo [171]. The expression of galectin-1 may play a role in blocking the T-cell cytotoxic response [172].

Nevertheless, most adults that carry EBV never develop CHL. A variety of mechanisms are proposed to determine lymphomagenesis in affected individuals including promotion of genetic instability and alteration of normal processes of apoptosis [173]. Loss of function of one or more tumor suppressor proteins (p16, p53, Rb) may be involved in defective cell regulation of H/RS cells. EBV may have a role in inhibiting P16(INK4A) expression, thus resulting in a perturbed p16(INK4A)-Rb cell cycle checkpoint [113]. Whether or not EBV-positivity has prognostic significance remains controversial, with data on both sides of the question 162, 174–178. In addition to an epidemiologic association and potential role in pathogenesis, viral antigens may pose theoretical targets for anti-cancer therapies, including vaccination [173, 179]. {Ambinder, 1996 #3920; Meyer, 2004 #3914}.

HIV infection and Hodgkin lymphoma

HIV-infected individuals (especially those with AIDS) have up to 10-fold increase in incidence of CHL 180–183. HIV-associated CHL (HIV-CHL) is usually MCCHL or LDCHL, is of advanced stage at diagnosis, and has a near-universal association with EBV infection. HIV-

HL patients are infected by multiple EBV variants and, with progression, LMP-1 deletion mutants may preferentially accumulate within neoplastic tissues. In HIV-HL, there is intratumoral loss of CD4+ T cells and a decrease in intratumoral activated cytotoxic T lymphocytes leading to a striking inversion in the CD4/CD8 ratio 184. The risk of Hodgkin lymphoma in persons with HIV/AIDS (PWHA) increased substantially over the 1990–2002 period at a time when highly active antiretroviral therapy (HAART) was introduced, and associated with HAART-related improvements in CD4 counts 8, 185. Interestingly, this increase was coincident with a decrease in immunoblastic lymphomas, usually seen in late stage AIDS associated with profound loss of T-cell function.

Hodgkin lymphoma and other immune disorders

An increased incidence of CHL is also reported in other immunodeficiencies including ataxia telangiectasia, Wiskott-Aldrich syndrome, Bloom's syndrome, autoimmune lymphoproliferative (Canale-Smith) syndrome [161] and following transplantation, as a post-transplantation lymphoproliferative disorder 186. An increased risk of CHL has also been reported in patients with a personal or family history of sarcoidosis 187 {Landgren, 2006 #3553} and multiple sclerosis 188. EBV-positive CHL is increased in incidence in patients receiving immunosuppression for a variety of immune conditions, including rheumatoid arthritis [189, 190]. Immunodeficiency-related Hodgkin lymphoma has been recently reviewed [191].

Association with non-Hodgkin lymphoma

Synchronous and/or metachronous occurrence of Hodgkin lymphoma and B-cell non-Hodgkin lymphoma is not unexpected given the B-cell origin of the neoplastic cells in NLPHL and CHL 192–196. In selected cases subjected to sequence analysis of the immunoglobulin genes in both lesions, a clonal relationship has been shown in most instances 11, [197]. CHL is also increased in patients with chronic lymphocytic leukemia (CLL). In patients with CLL, the secondary CHL are nearly always EBV-positive, and immunosuppressive therapy, in particular fludarabine, appears to increase this risk [198, 199]. A further discussion of the relationship between CHL and B-cell lymphoma is beyond the scope of this review.

Geographic and socioeconomic considerations

In the West, HL is most prevalent among whites, followed by blacks and Hispanics, with the lowest incidence in Asians. The age-incidence patterns of the subtypes vary, with MCCHL seen in the very young, followed by NSCHL in young adults, and MCCHL and LDCHL in the elderly. In contrast, in developing countries, , there is an expanded early peak in young children associated with MCCHL, probably related to the age of first EBV infection [27, 200, 201]. Incidence rates are low in Asian subgroups, but approximately double in US Asians as in native Asians. The consistently low rates of HL in Asians may be due to genetic resistance to disease development or environmental influences in its etiology [202].

The risk of CHL is inversely associated with socioeconomic status lending support to the hypothesis that CHL in young adults may occur as a result of aberrant host responses to a delay in first infection by common infections [203, 204]. Early exposure to other children at nursery school and day care seems to decrease the risk of Hodgkin lymphoma in young adults, most likely by facilitating childhood exposure to common infections and promoting maturation of cellular immunity [159].

SUMMARY

Hodgkin lymphoma is a biologically heterogeneous group of neoplasms brought together by morphologic and phenotypic similarities. Although NLPHL is clearly identified as a separate

entity, there is also a greater appreciation today for the differences between NSCHL and the other subtypes, mainly MCCHL/LDCHL and LRCHL. NSCHL affects young adults, is associated with mediastinal involvement and requires an intact immune system for its development. In addition to histological differences, its cytokine milieu and background lymphocyte population differ from other subtypes of CHL. The presence of an overlap with PMLBL suggests a thymic origin for mediastinal NSCHL. MCCHL and LDHL represent a spectrum, sharing many features related to incidence, pattern of spread, and association with immunodeficiency.

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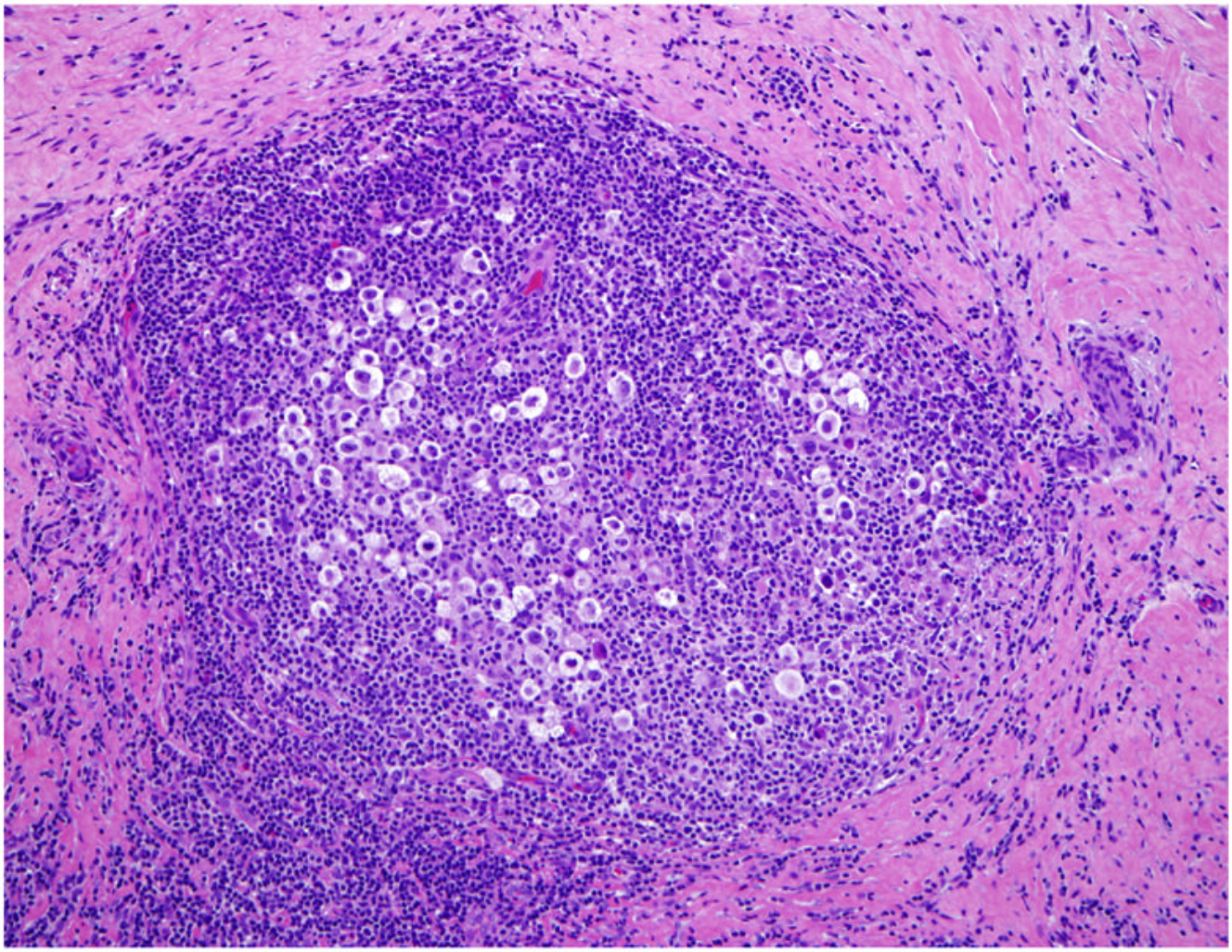

Figure 1.
Nodular sclerosis Hodgkin lymphoma is characterized by broad bands of birefringent collagen. Lacunar variants of HRS cells often cluster within the nodules (H&E).

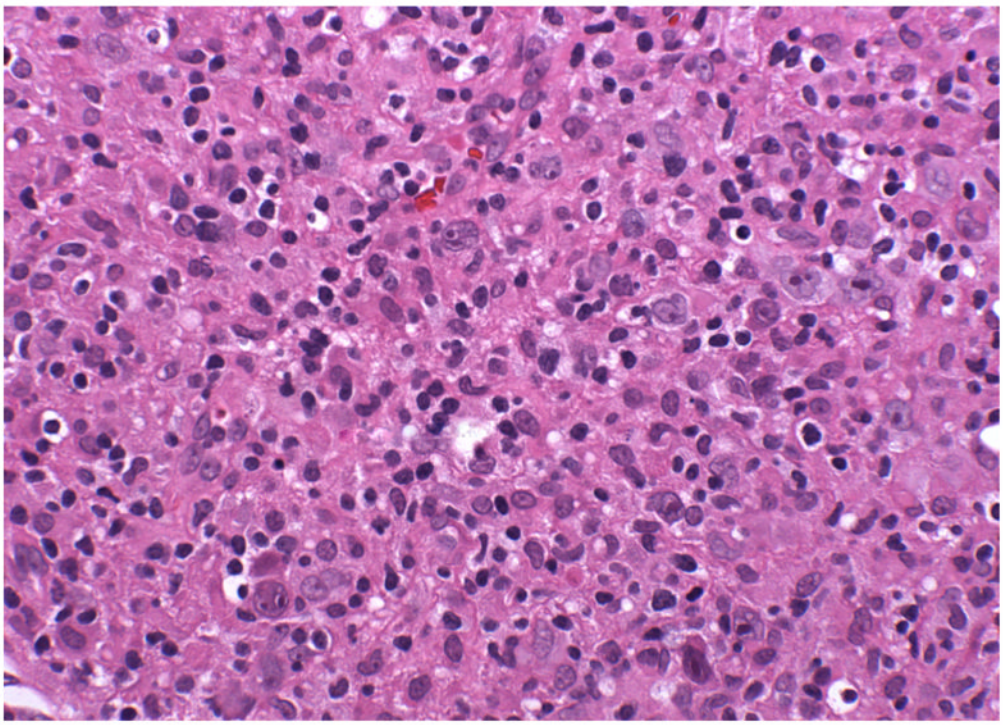

Figure 2.
Lymphocyte depleted CHL with abundant HRS-cells in a background rich in histiocytes, but with few lymphocytes (H&E).

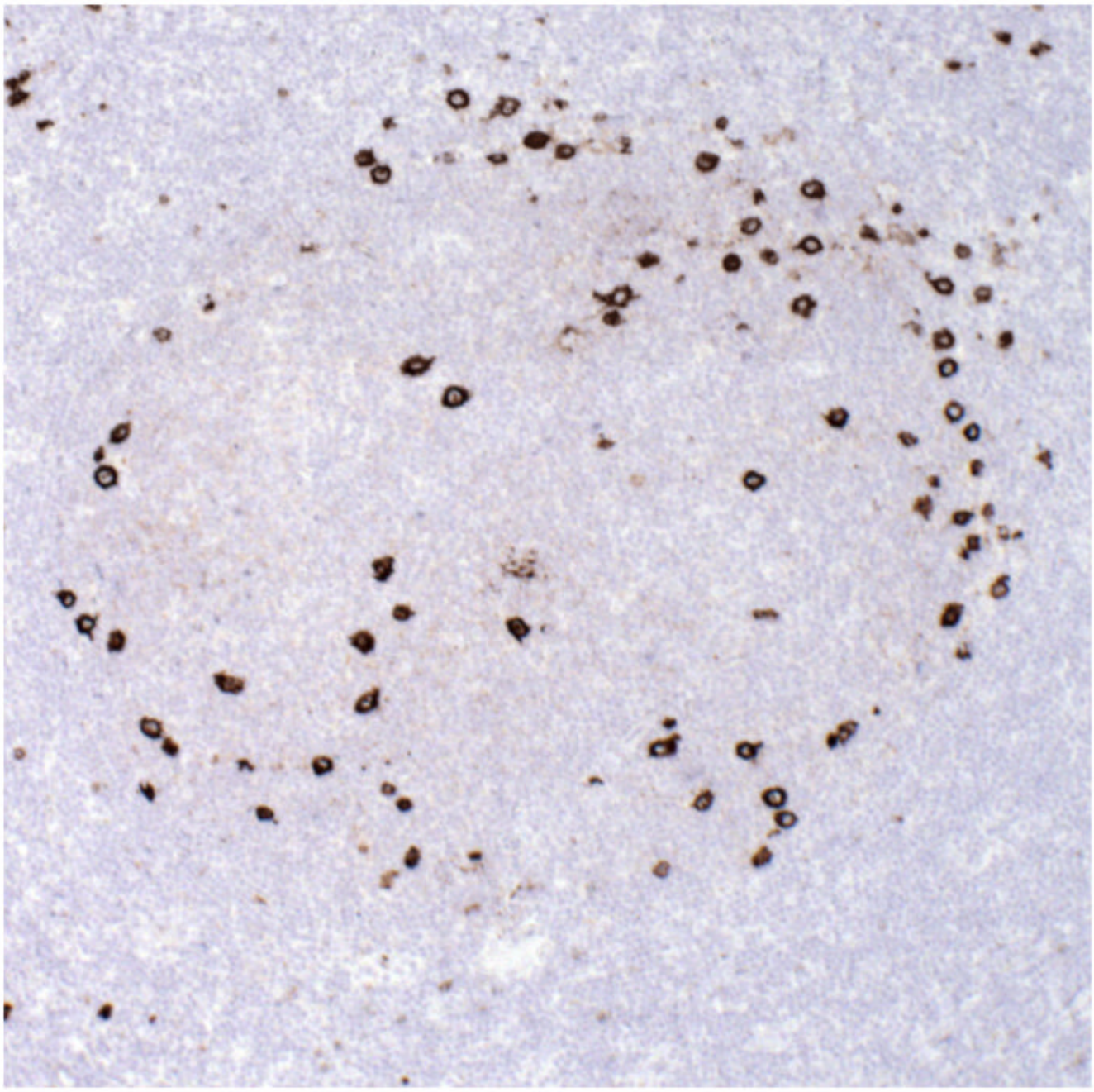

Figure 3.
Lymphocyte rich CHL with HRS cells within expanded follicles, mainly at the periphery in the mantle and marginal zone (CD15 immunostain).

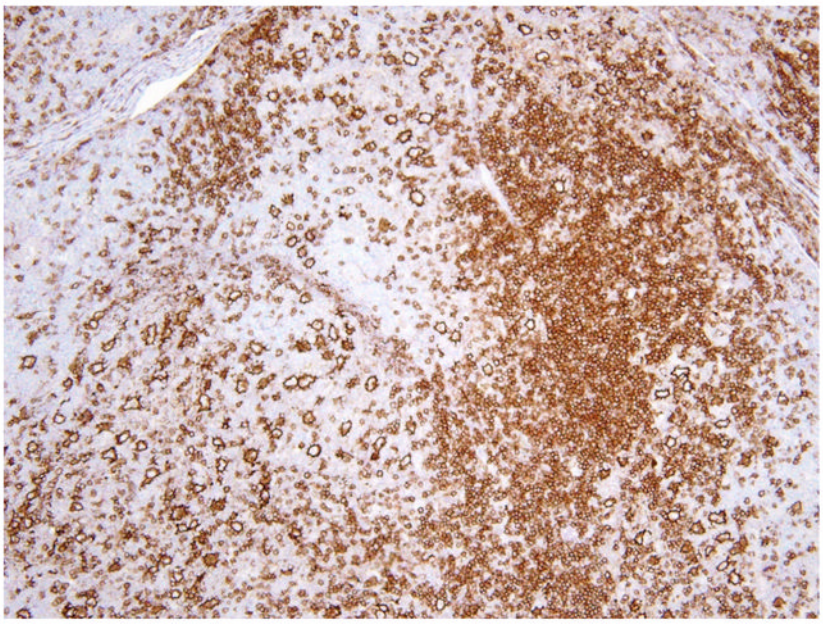

Figure 4.
In nodular lymphocyte predominant HL, LP cells are strongly positive for CD20 and are seen in the context of lymphoid follicles (CD20 immunostain).

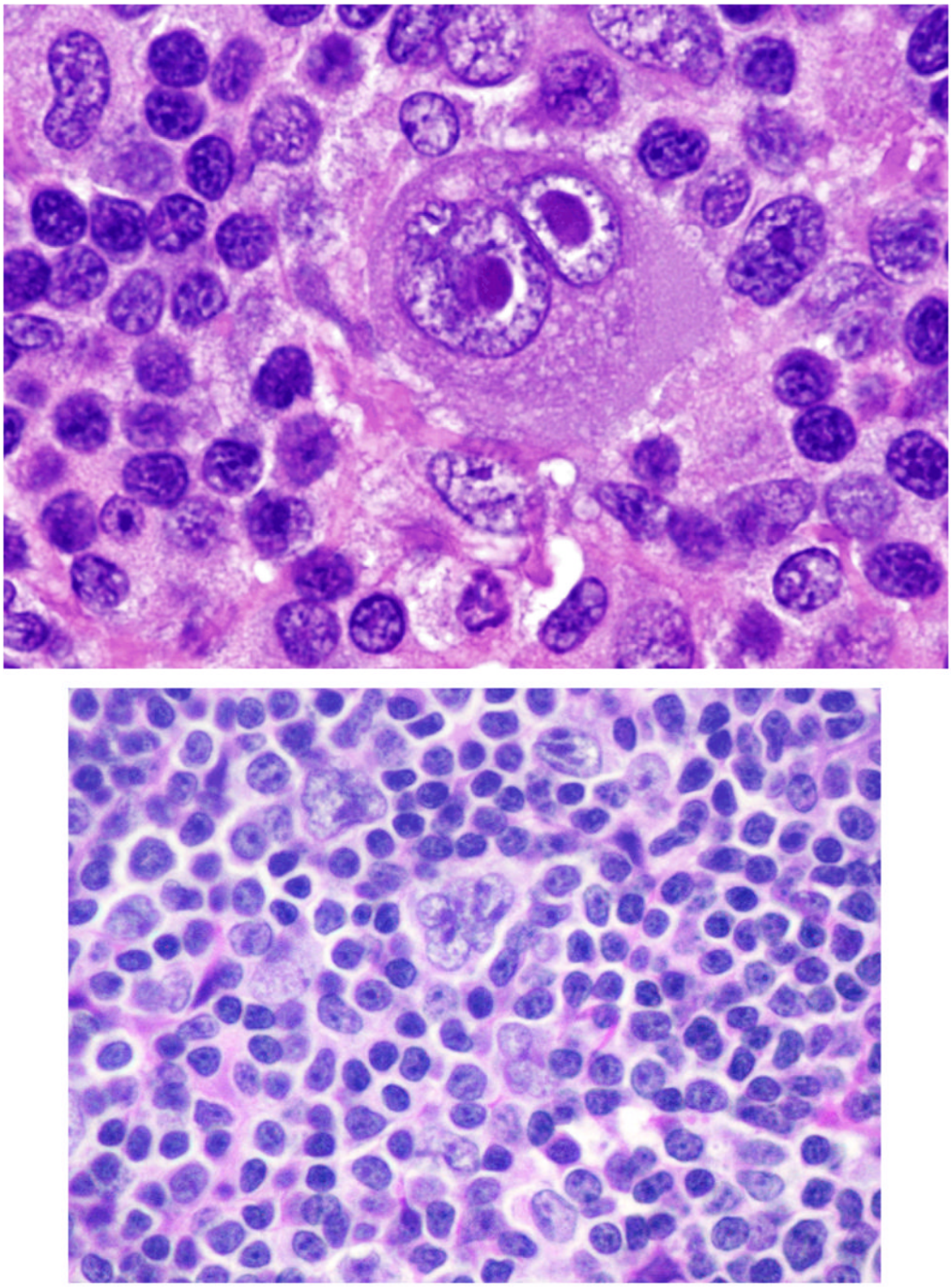

Figure 5.
A. The classical RS cell is binucleate, each nucleus contains a prominent eosinophilic nucleolus with perinucleolar halos giving the cell an “owl-eye” appearance (H&E). B. The LP cell, the neoplastic cell in NLPHL, has a multilobate/folded nucleus with smaller basophilic nucleoli giving the cell a “popcorn” appearance (H&E).

Table 1

Salient Clinical Features of Hodgkin lymphoma

Subtype	Incidence/Epidemiology	Sites	Prognosis
NLPHL	M:F (3:1), unimodal peak in 4th decade, also occurs in children	Peripheral LN; single node rather than group of nodes	Good response to Rx, slow progression, frequent relapses, may 'progress' to THRBCL or DLBCL
LRCHL	M:F (2:1)	Peripheral LN	Usually low stage, good prognosis, infrequent relapses
MCCHL	M:F (2:1), Developing countries, young children and older adults, HIV, B-symptoms	Peripheral LN, spleen, advanced stage	Prognosis intermediate between LRHL and LDHL
LDCHL	M:F (4:1), Rare, HIV, Developing countries, B- symptoms	Retroperitoneal and abdominal Advanced stage	Aggressive course
NSCHL	M:F (1:1), Most common subtype in West, adolescents and young adults, B-symptoms	Cervical,, axillary and mediastinal	Prognosis intermediate between LRHL and LDHL

Table 2

Salient Histopathologic Features of Hodgkin lymphoma

Subtype	Salient histopathologic features
NLPHL	LP cells Background of small lymphocytes in a nodular or nodular and diffuse pattern (nodular pattern must be present at least focally). Background small B-cells with mantle cell phenotype (IgD+, IgM−). Expanded meshworks of FDCs, as seen by CD21 immunostain Epithelioid histiocytes are present in varying numbers
LRCHL	Classical HRS cells few in number. Most often nodular. HRS cells found in marginal/mantle zone around regressed GCs with dense FDC networks). May show aggregates of epithelioid histiocytes, but eosinophils and neutrophils are rare.
MCCHL	Diffuse lymph node effacement with numerous HRS cells; mixed inflammatory background with lymphocytes, eosinophils, plasma cells, histiocytes. Granulomas may be present.
LDCHL	Diffuse fibrosis variant - Hypocellular background and abundant disordered non-birefringent fibrosis, abundant histiocytes but fewer lymphocytes. Reticular variant - Numerous HRS cells with bizarre cytological features.
NSCHL	Capsular fibrosis and broad collagen bands, often perivascular Lacunar cells and mummified cells Grades I and II differ in number of HRS cells and presence of necrosis in latter.

Table 3

Comparison of LP and HRS cells

	LP cell	HRS cells
Nucleus	Polylobated with finely dispersed chromatin	Single to multilobated with peripherally condensed chromatin
Nucleoli	Small, usually basophilic	Large, often eosinophilic
Cytoplasm	Relatively sparse	Abundant
CD15	Negative	Membrane and/or Golgi positivity
CD30	Negative; rare weak positive cells	Membrane and/or Golgi positivity
CD20	Positive	Variable (30–40% cases +)
CD79a	Positive	Negative to variably weak
CD45	Positive	Negative
J-chain	Positive	Negative
OCT 2	Positive	Often negative
BOB.1	Positive	Often negative
PU.1	Positive	Negative
PAX5	Positive	Positive (weak)
EBV	Negative	Variably positive