Hodgkin Lymphomas

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1. What are the major subtypes of Hodgkin lymphoma?

Hodgkin lymphomas (HLs) are mature B-cell malignancies characterized by a minor population of large neoplastic cells in a background of reactive inflammatory cells. Based on the cytomorphology and immunophenotypic profile of the neoplastic cells and the background reactive inflammatory cells, HLs are categorized as nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and classic Hodgkin lymphoma (cHL). Classic Hodgkin lymphomas (cHLs) are further divided into four subtypes: nodular sclerosis (NSCHL), lymphocyte-rich (LRCHL), mixed cellularity (MCCHL), and lymphocyte-depleted classic Hodgkin lymphoma (LDCHL). cHLs comprise approximately 90% of all HL cases with nodular sclerosis classic Hodgkin lymphoma being the most common subtype (about 70% of cHLs), while nodular lymphocyte-predominant Hodgkin lymphoma accounts for the remaining cases [1–5].

- Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)
- Classic Hodgkin lymphoma (cHL)
  - Nodular sclerosis classic Hodgkin lymphoma (NSCHL)
  - Lymphocyte-rich classic Hodgkin lymphoma (LRCHL)
  - Mixed cellularity classic Hodgkin lymphoma (MCCHL)
  - Lymphocyte-depleted classic Hodgkin lymphoma (LDCHL)

2. What are the major clinicopathological features of Hodgkin lymphoma?

- Hodgkin lymphomas are lymphoid neoplasms that usually affect lymph nodes and cause lymphadenopathy or masses.
- Classic Hodgkin lymphomas (cHLs) preferentially involve cervical lymph nodes and mediastinum (especially NSCHL), while NLPHL preferentially involves peripheral lymph nodes.
- Splenic involvement is more common in MCCHL. Bone marrow involvement is much less common.
- The patients can present with B symptoms, including fever, drenching night sweats, and weight loss [1]. Most of the Hodgkin lymphomas have male predominance except for NSCHL.
- *EBV* infection is more likely to be associated with classic Hodgkin lymphoma, especially MCCHL and LDCHL, but rarely with NLPHL [1, 6–10].
- In some patients, LDCHL is associated with HIV infection [11] and has more adverse risk factors than other subtypes of cHLs [12].

The clinicopathological features of Hodgkin lymphomas are summarized in Table 9.1 [1].

3. What are the typical morphological findings in Hodgkin lymphoma?

The typical morphological findings of Hodgkin lymphoma are summarized in Table 9.2 [1]. Morphological assessment for HLs involves the identification of the large neoplastic cells and the background inflammatory cells.

- Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)
  - The neoplastic cells in NLPHL are derived from germinal center B cells with intact clonal immunoglobulin gene rearrangements.
  - They are characterized by a nodular or at least partial nodular pattern. The nodules contain a minor population of individual large neoplastic cells surrounded by a predominant small B lymphocytic proliferation with background follicular dendritic meshworks (Table 9.2).
  - The large neoplastic cells show a lobulated nucleus and prominent but not inclusion-like nucleoli (popcorn, lymphocytic-histiocytic, or lymphocyte-predominant (LP) cells). Mononuclear variant resembling Hodgkin cells may occasionally be seen.

Table 9.1 Clinicopathological features of Hodgkin lymphomas

	NLPHL	NSCHL	LRCHL	MCCHL	LDCHL
Socioeconomic status	No association	High	Unknown	Low	Low
Gender predominance	Male	Female	Male	Male	Male
Age	Young adults	Young adults	Young adults	Children or elderly	Children or elderly
HIV infection	Rare	Rare	Unknown	Common	Common
EBV infection	Rare	Rare	Unknown	Common	Common
Anatomic sites	Peripheral and mesenteric lymph nodes	Mediastinal, cervical, and axial lymph nodes	Variable	Systemic with frequent bone marrow involvement	Systemic with frequent bone marrow involvement

Table 9.2 Histomorphologic features of Hodgkin lymphoma [1]

		NLPHL	NSCHL	LRCHL	MCCHL	LDCHL
Neoplastic cell	Classical LP cell	Frequent	Rare	Rare	Rare	Rare
	Classical RS/H cell	Rare	Rare	Frequent	Frequent	Frequent
	Lacunar cell variant	Rare	Frequent	Rare	Rare	Rare
	Mummified cell variant	Rare	Frequent	Rare	Variable	Variable
Histological pattern	Thickened capsule	Rare	Frequent	Rare	Rare	Rare
	Collagen fibrosis	Rare	Frequent	Rare	Rare	Rare
	Nodular pattern	Frequent	Frequent	Frequent	Rare	Rare
	Diffuse pattern	Rare	Rare	Rare	Frequent	Frequent
Background inflammatory cell	Small lymphocytes	Frequent	Frequent	Frequent	Variable	Rare
	Neutrophils/eosinophils	Rare	Frequent	Rare	Variable	Variable
	Histiocytes	Rare	Rare	Rare	Variable	Frequent
	Plasma cells	Rare	Variable	Rare	Variable	Frequent

  - The LP cells are ringed by PD1+/CD57+ T follicular helper cells in almost all the cases, while the reactive small lymphocytes in the nodules are mainly B cells.
  - Progression of NLPHL to diffuse large B-cell lymphoma is reported in approximately 3–5% of the cases [1, 13–15]. NLPHL can occur with diffuse large B-cell lymphoma concurrently or sequentially.
- Classic Hodgkin lymphoma (cHL)
  - The neoplastic cells in cHLs are also derived from germinal center B cells with crippled but clonal immunoglobulin gene rearrangements that somehow escaped the normal apoptotic process.
  - cHLs typically show scattered large atypical cells in the background of reactive inflammatory cells, including small lymphocytes, eosinophils, neutrophils, histiocytes, and plasma cells. The neoplastic cells are characterized by large cell size, abundant slightly basophilic cytoplasm, and a single nucleus (Hodgkin or H cell) or multiple nuclei (Reed-Sternberg or RS cell) with inclusion-like eosinophilic nucleoli.
  - Variants of RS/H cells include lacunar cells and mummified cells. Lacunar cells have smaller nuclei, less prominent nucleoli, and more abundant cytoplasm due to cytoplasmic membrane retraction. They are typically seen in NSCHL subtype.
  - Mummified cells have condensed cytoplasm and pyknotic hyperchromatic nuclei that can be seen in any of the subtypes. The neoplastic cells in cHLs account for less than 10% of the cellular infiltrate and generally do not form cohesive sheets or large aggregates except in the syncytial variant of NSCHL.
  - RS cells are not required for patients with cHLs diagnosed at another site [16].

4. What are the most typical immunophenotypes of classic Hodgkin lymphoma?

- cHL cells are transformed B cells that have lost the expression of B-cell markers.
- CD30 is positive in nearly all the cases, while CD15 is positive in subset of the cases or a minority of the cells [1, 17–19].
- CD20 is positive in 30–40% of the cases and is usually weak and in a minority of the cells [20, 21]. PAX5 is usually weaker than background reactive B cells [22]. Either OCT2 or BOB1 might be expressed in cHL but not both positive at the same time. CD79a is usually negative [23].
- Rare cases of cHL, especially NSCHL, can show aberrant expression of T-cell antigens, especially CD2 or CD4 [24, 25], and are reported to be associated with poorer prognosis [26]. Therefore, the most typical immunophenotype of cHL is as follows: CD45−, CD30+, CD15+/−, CD20 negative or weak+, PAX5 weak+, MUM1 strong +, EBER in situ hybridization for *EBV*+, CD79a−, OCT2−/+, BOB1−/+, EMA−.
- Diagnosis of classic Hodgkin lymphoma needs both positive and negative markers for a definitive diagnosis.

5. How to distinguish CD30 and CD15 staining in classic Hodgkin cells from those in non-Hodgkin cells?

- CD30 is the most sensitive marker for classic Hodgkin lymphoma. CD30 should be included in the initial workup of any lymphoma to detect potential or rare H or RS cells. However, CD30 is a non-specific marker and can also be

positive in reactive immunoblasts of the lymph nodes, in other B-cell lymphomas, as well as in T-cell lymphomas.
- CD15 positivity will help to confirm the diagnosis of cHL when positive with CD30. However, CD15 can also stain granulocytes or neutrophils in the background.
- It is important to tell the difference between real Hodgkin cell staining from non-Hodgkin cell staining. The typical Hodgkin CD30 and CD15 stains should be membrane staining of mostly large atypical cells with Golgi zone accentuation, while the staining of non-Hodgkin cells might show a spectrum of size and most cells do not show Golgi zone staining. CD15 staining of neutrophils usually shows small cells.

6. How to further classify classic Hodgkin lymphoma into subtypes?

- cHL is further subclassified into nodular sclerosis classic Hodgkin lymphoma (NSCHL), lymphocyte-rich classic Hodgkin lymphoma (LRCHL), mixed cellularity classic Hodgkin lymphoma (MCCHL), and lymphocyte-depleted classic Hodgkin lymphoma (LDCHL), depending on the degree of fibrosis and the number of background reactive lymphocytes.
- The histological pattern and composition of background inflammatory cells vary among the different subtypes of cHLs. For example, band-like collagen fibrosis is characteristic of NSCHL, but is absent in other subtypes. Eosinophilic microabscesses and necrosis are also frequently seen within the nodules of NSCHL, but are uncommon in other subtypes. In contrast, histiocytes are more common in LDCHL than in other subtypes of classic Hodgkin lymphomas (Table 9.2).
- If there is at least one broad band-like fibrosis surrounding the atypical lymphoid nodules, it is most likely to be NSCHL. The cytoplasm of H/RS cells frequently shows retraction of the cell membranes, and H/RS cells are called lacunar cells. When H/RS cells form prominent aggregates, the term syncytial variant can be used.
- If the fibrosis is minor and the background lymphocytes are rich and forming nodules, it is most likely LRCHL [27].
- If there are no lymphocyte nodules and the background consists of mixture of eosinophils, neutrophils, histiocytes, and plasma cells, it is likely to be MCCHL.
- If there are few lymphocytes and no band-like fibrosis but numerous H/RS cells, it should be called LDCHL [28].
- In some needle core biopsies with limited tissue, precise subclassification is not always feasible.

7. How to distinguish nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) from classic Hodgkin lymphoma (cHL)?

- Both NLPHL and classic Hodgkin lymphoma, especially lymphocyte-rich classic Hodgkin lymphoma (LRCHL), can show nodules of lymphocytes with scattered large atypical cells, making it necessary to keep them in the differentials of each other. NLPHL usually shows popcorn cells in B-cell nodules, while cHL shows H or RS cells in an inflammatory background including lymphocytes, eosinophils, neutrophils, and plasma cells.
- NLPHL and cHL also differ in that the neoplastic cells in NLPHL are positive for most of the B-cell markers, while H or RS cells lose most of the B-cell markers. NLPHL shows scattered popcorn cells that are usually CD20 strong +, CD30−, CD45+, CD79a+, CD15−, OCT2+, Bob1+ [29–34], while LRCHL shows H or RS cells that are usually CD20− or weak+, CD30+ with mostly Golgi zone staining, CD45−, CD15 subset+, CD79a−, OCT2−, and Bob.1− or positive but not both at the same time.
- CD21 can also show follicular dendritic meshwork and CD3/CD57/PD1 [35] rosette formation around popcorn cells in NLPHL, but not in cHLs. CD4/CD8 double positive T cell in the background is frequent in NLPHL [36, 37].
- EBER in situ hybridization for *EBV* might be positive in cHLs, but is usually negative in NLPHL.

8. What are the mimics of Hodgkin lymphoma and what are the clinical consequences of misinterpretation between Hodgkin lymphomas and their mimics?

- Hodgkin lymphomas have an excellent prognosis with 80–95% cure rate. Standard treatment for cHLs is chemotherapy with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and involved field radiation. Replacement of bleomycin with anti-CD30 antibody (brentuximab vedotin) has become the new frontline therapy for cHL with less pulmonary toxicity [38].
- Patients with low-stage or non-bulky NLPHL require no treatment or only require site radiation therapy. Those with high-stage or bulky disease are treated with ABVD or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus rituximab. Care should be taken to differentiate HLs from non-Hodgkin lymphoma mimics that usually have a poor prognosis and require a different or more aggressive therapy.
- The main mimics of Hodgkin lymphomas are listed in Table 9.3.

Table 9.3 Hodgkin lymphomas and their main morphologic mimics

Hodgkin lymphomas	Morphologic mimics
NLPHL	Progressive transformation of germinal center (PTGC) LRCHL T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) Follicular lymphoma (FL)
NSCHL	Primary mediastinal large B-cell lymphoma (PMLBCL) B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classic Hodgkin lymphoma (gray zone lymphoma, GZL) Anaplastic large cell lymphoma (ALCL) T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)
LRCHL	NLPHL Mantle cell lymphoma (MCL) Marginal zone B-cell lymphoma (MZL) Follicular lymphoma (FL)
MCCHL	T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) Peripheral T-cell lymphoma, not otherwise specified (PTCL NOS) Angioimmunoblastic T-cell lymphoma (AITCL)
LDCHL	NSCHL syncytial variant Anaplastic large cell lymphoma (ALCL) Diffuse large B-cell lymphoma (DLBCL) *EBV*+ diffuse large B-cell lymphoma NOS (*EBV*+ DLBCL) Histiocytic sarcoma Carcinoma Melanoma

9. How to distinguish nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) from progressive transformation of germinal centers (PTGC)?

- Both NLPHL and PTGC, a benign process, can show nodular structures. PTGC can occur prior to or co-occur with NLPHL. However, NLPHL shows large atypical popcorn cells in B-cell nodules that were ringed by rosette of PD1+ or CD57+ T follicular helper cells, while PTGC shows germinal centers with no popcorn cells and only occasional centroblasts.

10. How to distinguish nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) from T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)?

- Both NLPHL and THRLBCL show numerous lymphocytes with scattered large atypical B cells, which are positive for CD20, CD45, OCT2, and BOB1, so can be confused with each other in some cases.
- NLPHL usually presents as a local disease, while THRLBCL usually presents as a more aggressive or systemic disease.
- NLPHL shows popcorn cells in B-cell nodules that are ringed by CD3/CD57/PD1+ T cells, while THRLBCL shows large atypical lymphocytes in mostly T cell and histiocyte background without obvious nodular formation.
- Demonstration of at least one follicular dendritic meshwork by CD21 is sufficient to exclude THRLBCL.
- Predominance of CD8+ and TIA+ T cells favors THRLBCL.
- There is close relationship between NLPHL and THRLBCL in that NLPHL may progress into or contain areas indistinguishable from THRLBCL. In some small biopsies, differentiation between them may be impossible.

11. How to distinguish nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) from follicular lymphoma (FL)?

- In rare cases, NLPHL might be confused with FL when nodules of lymphocytes are seen with scattered large atypical cells in the centers. Both show lack of normal germinal center architecture (polarization and tingible body macrophages). The large atypical lymphocytes in both entities are positive for CD45, CD20, and other B-cell markers.
- The germinal centers in FL are usually more recognizable than those in NLPHL. The large cells in FL are centroblasts, while the large cells in NLPHL are popcorn cells. The germinal centers of FL also show clefted small atypical lymphocytes (centrocytes) that are positive for CD10, BCL6, and BCL2, while the B-cell nodules in NLPHL will be negative for CD10.
- FISH study might show diagnostic t(14;18) (*IGH/BCL2*) translocation in FL.

12. How to distinguish classic Hodgkin lymphoma (cHL) from T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)?

- Classic Hodgkin lymphoma, especially mixed cellularity classic Hodgkin lymphoma (MCCHL), can show scattered large atypical cells in the background of numerous inflammatory cells (small reactive lymphocytes, eosinophils, and plasma cells) and should be distinguished from THRLBCL [39, 40].
- Unsurprisingly, the H or RS cells in cHL should be CD30+ with Golgi zone staining, CD15+/−, CD45−,

CD20−/weak+, PAX5 weak+, Mum-1+, OCT2−, and BOB1− or not positive at the same time, while the large atypical lymphocytes in THRLBCL should be CD30− or small subset + without Golgi zone staining, CD15−, CD45+, CD20 strong +, PAX5 strong +, OCT2+, and BOB1+.

- cHL could be *EBV*+, while THRLBCL is usually *EBV*−. According to the WHO classification, large B-cell lymphoma with *EBV*+ and T-cell-rich background should be classified as *EBV*+ DLBCL instead of THRLBCL.

13. How to distinguish nodular sclerosis classic Hodgkin lymphoma (NSCHL) from primary mediastinal (thymic) large B-cell lymphoma (PMLBCL)?

- Both of these two entities commonly present as mediastinal masses and have a female preference [41–43]. Both entities can show large CD30+ atypical cells or Hodgkin/Reed-Sternberg-like cells in the background of fibrosis [44, 45]; therefore, they deserve to be differentiated from each other.
- The atypical cells in PMLBCL are usually medium-sized to large with abundant pale cytoplasm and relatively round or ovoid nuclei, while NSCHL will show typical Hodgkin or Reed-Sternberg cells. PMLBCL usually shows compartmentalization alveolar fibrosis [41, 46–49], while NSCHL usually shows broad band-like fibrosis.
- The Hodgkin or Reed-Sternberg cells in cHL are usually CD30+ with Golgi zone staining, CD15+/−, CD20−/weak+, PAX5 weak+, BOB1−, and OCT2− or not positive at the same time, CD45−, and CD23−, while the large atypical cells in PMLBCL are usually weak and homogenous CD30+ [49, 50], CD15− or + in minority of the cells, CD20 strong+, PAX5 strong+, OCT2+, and BOB1+, CD23+ [51–54], and CD45+ [41, 54–56].
- NSCHL could be positive for EBER ISH (*EBV*), while PMLBCL is usually negative for *EBV* [41].

14. How to distinguish classic Hodgkin lymphoma (cHL) from B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classic Hodgkin lymphoma (gray zone lymphoma, GZL)?

- Both cHL (especially NSCHL) and diffuse large B-cell lymphoma (DLBCL) especially PMLBCL can present with mediastinal mass [1, 45, 57]. Sometimes, the lymphoma cells exhibit atypical morphology or immunophenotype that is difficult to distinguish between cHL and DLBCL/PMLBCL [45] and is therefore called gray zone lymphoma. GZL generally has more aggressive clinical course and poorer outcome than either cHL or PMLBCL [1, 58]; therefore, it is important to distinguish them in diagnosis.
- cHL typically shows scattered Hodgkin or Reed-Sternberg cells that are CD30+ with frequent Golgi zone staining, CD15+ with Golgi zone staining or −, CD20− or weak+, PAX5 weak+, Bob.1−, and Oct.2− or not both positive at the same time, CD45−, while PMLBCL typically shows large atypical lymphocytes that are CD20+, PAX5 strong +, OCT2+, and BOB1+, CD15−, and CD45+.
- In GZL, the morphology might appear like cHL, but the large atypical cells are CD20 strong+, PAX5 not weak, CD79a+, or show Bob.1 and Oct.2 staining at the same time. CD45 usually shows diffuse staining of all the cells and most of the time is hard to unambiguously define.
- In other cases of GZL, the morphology might appear like PMLBCL, but the large atypical cells show weaker than typical CD20 and PAX5 staining and ambiguous BOB1 and OCT2 staining. CD30 is usually positive and CD15 may be expressed. In these cases, it is very difficult to unequivocally call it cHL or PMLBCL/DLBCL. A diagnosis of B-cell lymphoma, unclassifiable, with features intermediate between Hodgkin lymphoma and diffuse large B-cell lymphoma (gray zone lymphoma) is justified.
- Composite cHL and DLBCL/PMLBL in the same specimen are not strictly called GZL [1, 59, 60].

15. How to distinguish cHL from *EBV*+ diffuse large B-cell lymphoma NOS (*EBV*+ DLBCL)?

- Both cHL and *EBV*+ DLBCL can show *EBV*+ and CD30+ large atypical lymphocytes, including Hodgkin or RS-like cells. CD15 sometimes might be positive in *EBV*+ DLBCL too [61–63]. They should therefore be distinguished from each other.
- CD30 stain of cHL usually shows more typical Golgi zone staining in scattered large cells, while *EBV*+ DLBCL usually shows less typical Golgi zone staining.
- cHLs are usually CD45−, CD20 negative or weak+, PAX5 weak+, CD79a−, OCT2−, and BOB1− or not positive at the same time, while *EBV*+ DLBCL is usually CD45+, CD20+, PAX5+, CD79a+, OCT2+, and BOB1+.
- Cases that show sparse CD45+, CD20+, *EBV*+, large neoplastic cells, even though with Hodgkin-like morphology, should be considered *EBV*+ DLBCL, instead of classic Hodgkin lymphoma or THRLBCL [63, 64].

16. How to distinguish classic Hodgkin lymphoma (cHL) from peripheral T-cell lymphoma (PTCL)?

- cHL can show diffuse (MCCHL) lymphocyte infiltrate as PTCL NOS. PTCL NOS can also have large atypical *EBV*+ Hodgkin or Reed-Sternberg-like cells that are CD30+ [65, 66], and rarely CD15+, which is associated with adverse prognosis [67, 68]. PTCL can rarely be *EBV*-positive in standby B-cell immunoblasts [69–71]. Therefore, these two entities should be distinguished from each other in some situations.
- Typically, the Hodgkin or Reed-Sternberg cells in cHL should be CD30+ with Golgi zone staining, CD15+/−, CD45−, PAX5 weak+, and negative for CD3 and other T-cell markers, while PTCL NOS should be CD30+ without less typical Golgi zone staining or CD30−, CD15−, CD45+, and positive for one or more of the T-cell markers (CD2, CD3, CD4 or CD8, CD5, CD7).
- Rare cases of cHL, especially NSCHL, can show aberrant expression of T-cell antigens, especially CD2 or CD4. So a combination of positive and negative markers should be considered during the differentials.
- Abnormal T cells with pan T-cell antigen loss or alteration could be detected by flow cytometry in majority of PTCL, while reactive T cells in microenvironment of cHL often show no aberrant changes.

17. How to distinguish classic Hodgkin lymphoma from anaplastic large cell lymphoma (ALCL)?

- cHL, especially LDCHL or NSCHL syncytial variants, can show clusters or sheets of large atypical cells without many lymphocytes, morphologically similar to ALCL [72–74]. The large atypical cells in both entities are also positive for CD30 with potentially Golgi zone staining [1, 18, 74] and occasional CD15 expression [75], making it necessary to keep them in the differentials of each other. Rare cases of cHL can show aberrant expression of CD2 or CD4 [24], which are positive in ALCL.
- Typically, the large atypical cells in ALCL have abundant cytoplasm and eccentric pleomorphic horseshoe-shaped or kidney-shaped nuclei, often with an eosinophilic region near the nucleus (hallmark cells) [75].
- The Hodgkin or Reed-Sternberg cells in cHL should be CD15+/−, CD20− or weak+, PAX5 weak+, Mum-1+, and negative for the T-cell markers (CD3, CD2, CD4, CD5, CD7) and EMA, while the ALCL cells should be CD15− and positive for one or more of the T-cell markers (usually CD4, CD2, CD5), EMA, and/or ALK1.
- ALK+ ALCL will also show t(2;5)(*NPM1/ALK*) or variant translocations by FISH study. The small T cells in ALCL are also neoplastic and might have irregular nuclei [75].
- cHL could be *EBV*+, while ALCL is usually negative.

18. How to distinguish lymphocyte-rich classic Hodgkin lymphoma (LRCHL) from mantle cell lymphoma (MCL)?

- Both LRCHL and MCL can present as nodules of small mature lymphocytes. MCL with blastoid transformation could also show some large atypical lymphocytes. Therefore, it might be necessary to distinguish these two entities in rare instances.
- cHL should show Hodgkin or RS cells in clusters in expanded mantle zone. These clusters of Hodgkin cells are highlighted by pertinent immunohistochemical stains.
- cHLs are CD30+ with Golgi zone staining, CD15+/−, CD45−, CD20−/weak+, PAX5 weak+, BCL1−, MUM1+, OCT2−, and BOB1−, and SOX11−, while the mantle lymphoma cells should be CD30−, CD15−, CD45+, CD20 strong +, PAX5 strong +, BCL1+, SOX11+, OCT2+, and BOB1+.
- FISH study will show t(11;14) (*CCND1/IGH*) translocation in MCL.

19. How to distinguish lymphocyte-rich classic Hodgkin lymphoma (LRCHL) from follicular lymphoma?

- Both LRCHL and FL can present as nodules of small mature lymphocytes. High-grade FL could also show some large atypical lymphocytes. Therefore, it might be necessary to distinguish these two entities in rare instances.
- Typically, FL should show lymphoid follicles with germinal centers that can be demonstrated by CD21 immunostain. The lymphoma cells in FL should be CD30−, CD15−, CD45+, CD20+, PAX5 strong +, CD10+, BCL2+, BCL6+, OCT2+, and BOB1+, while the Hodgkin or Reed-Sternberg cells in cHL should be CD30+ with Golgi zone staining, CD15+/−, CD45−, CD20−/weak+, PAX5 weak+, CD10−, BCL2−, BCL6−, MUM1+, OCT2−, and BOB1− or not both positive at the same time.
- FISH study will likely show t(14;18) (*BCL2/IGH*) translocation in FL.

20. How to distinguish lymphocyte-depleted classic Hodgkin lymphoma (LDCHL) from histiocytic sarcoma?

- LDCHL usually shows clusters or sheets of large atypical cells without many lymphocytes, morphologically could resemble histiocytic sarcoma. Histiocytic sarcoma can rarely show weak expression of CD15 too [76].
- The Hodgkin or RS cells in LDCHL should be CD30+ with Golgi zone staining, PAX5 weak+, Mum-1+, and negative for histiocytic markers (lysozyme, CD4, CD64, CD68, CD163), while histiocytic sarcoma cells should be CD30−, CD45+, and positive for one or more of the above histiocytic markers.
- cHL could be *EBV*+, while histiocytic sarcoma will be negative.

21. For peripheral blood and bone marrow biopsies, what morphological findings are diagnostic and what findings are suspicious for classic Hodgkin lymphoma?

- Peripheral blood may show mild leukocytosis with left shift at the time of HL diagnosis. Mild eosinophilia may also be present. Circulating neoplastic cells are never seen in the peripheral blood. These findings are non-specific.
- Bone marrow involvement by cHLs occurs in less than 5% of the cases. Bone marrow aspirate smear usually shows left-shifted myelopoiesis. Neoplastic cells are rarely seen unless there is an extensive bone marrow involvement, particularly in LDCHL. These cells, if present, should be distinguished from the immature megakaryocytes that do not display inclusion-like nucleoli. Immunostain for CD61 will confirm the megakaryocytes, while CD30 positivity will favor cHL.
- The core biopsy of involved bone marrow usually shows lymphohistiocytic aggregates that contain scattered large atypical cells with monolobated or multilobated nuclei and prominent nucleoli. Classic RS/H cells are difficult to find, and immunohistochemical stains are essential to confirm the diagnosis and distinguish cHL from its morphologic mimics involving bone marrow. In the absence of typical H or RS cells, the presence of lymphohistiocytic aggregates is highly suspicious for cHL. Deeper sections sometimes might be helpful to reveal H or RS cells.

22. What is the minimal and optimal ancillary workup for the diagnosis of Hodgkin lymphomas?

- Immunohistochemistry with a panel of antibodies is the main ancillary tool for the diagnosis and classification/subclassification of HLs. A minimal panel of antibodies should include CD45, CD30, CD15, CD3, PAX5, CD20, CD45, and EBER ISH. CD57, CD79a, BOB1, OCT2, MUM1, BCL6, and PD1 should be added to the minimal panel in difficult cases for differential diagnosis.
- Flow cytometry is not helpful in the follow-up of classic Hodgkin lymphomas, but should be included in the initial workup for NLPHL or cHL, to exclude non-Hodgkin lymphomas or a composite HL. The increased CD4:CD8 ratio in the sample may be suggestive of, but is unreliable for, diagnosis or to exclude the diagnosis of classic HLs. An increase in CD4/CD8-double negative cells may suggest the diagnosis of NLPHL, but again is non-diagnostic.
- B-cell gene rearrangement and cytogenetic studies are usually not helpful to the diagnosis of Hodgkin lymphoma due to small number and the fragility of the large atypical lymphocytes. Molecular testing for immunoglobulin heavy/K (IgH/IgK) light chain and T-cell receptor gamma (*TCR*) gene rearrangements is of very limited utility in establishing or excluding the diagnosis of HLs. Monoclonal *IGH/IGK* gene rearrangements may be seen in a small subset of HLs. However, it may occasionally be needed to distinguish HL from its morphologic mimics.

23. What information provides prognostic and therapeutic target information for Hodgkin lymphomas?

- Strong CD30 expression provides an ideal target for anti-CD30 (brentuximab vedotin or Adcetris) treatment in patients with cHLs [77, 78]. More recently, it has reported to be useful when used in combination with chemotherapy adriamycin or doxorubicin, vinblastine, and dacarbazine (AVD) as a frontline treatment for adult patients with stage III or IV cHL [79, 80].
- Expression of CD20 is known to be associated with a worse prognosis in cHLs [81].
- *EBV* positivity is also associated with worse prognosis in cHL patients older than 60 years, but not in patients younger than 15 years [82].

- Immunostains for PD1/PDL1 are also helpful for immune check point inhibitor/immunomodulatory therapy with anti-PD1/PDL1 antibodies in cHLs [83, 84]. Anti-PD1 nivolumab (Opdivo) was approved by FDA in 2016 to treat relapsed/refractory HLs.
- In advanced cHL, increased expression of CD163 and c-Met is reported to have significant association with adverse prognostic parameters and poor response to treatment [85].

24. What are adequate specimens for the diagnosis of Hodgkin lymphomas?

- Excisional biopsy is the recommended specimen for the diagnosis of HLs. Core needle biopsy may contain too few large neoplastic cells to be diagnostic. Fine needle aspiration alone is insufficient for diagnosis of HL except when in combination with immunohistochemistry on cell block that happens to have typical H or RS cells.

25. What information can be conveyed to the clinician during each stage of the workup?

- Frozen section is not recommended for the workup of HLs. If performed for other reasons, such as staging for metastatic melanoma or carcinoma, and an HL is suspected on frozen section, the pathologist should inform the surgeon whether sufficient tissue is obtained for further morphological examination and ancillary studies. A touch imprint may be prepared at the time of frozen section. Fresh tissue can be triaged for ancillary studies, such as flow cytometric immunophenotyping, to differentiate HL from its morphological mimics of non-Hodgkin lymphomas, and to exclude a composite lymphoma.
- When hematoxylin-eosin-stained slides become available, the pathologist may discuss the preliminary diagnostic impression with the clinician and inform the clinician that additional studies are needed to confirm or exclude the diagnosis of HLs.
- The final diagnosis of HLs requires integration of histomorphology and other ancillary study results, particularly immunohistochemistry.

26. When are comments necessary and what should be discussed in the comments for Hodgkin lymphoma?

- With a definitive diagnosis, a diagnostic comment may just include the immunohistochemical profile of the neoplastic cells to support the diagnosis. When the diagnosis is inconclusive due to various limitations, such as small sample size or ambiguous immunohistochemical results, it is imperative to comment on the limitation of the biopsy, the degree of confidence, the atypical findings, the potential differential diagnoses, and the recommendation for additional tissue or external expert consultation.

27. When is it appropriate to seek external consultation for Hodgkin lymphomas?

- In academic centers with more than one hematopathologist, intradepartmental consultation should be obtained first. When a consensus diagnosis cannot be reached, the primary hematopathologists should seek an external consultation, especially when low confidence in diagnosis is encountered.

Case Presentations

Case 1 (Fig. 9.1)

Learning Objectives

1. To become familiar with the histologic morphologic features of NLPHL
2. To become familiar with the immunohistochemical features of the NLPHL
3. To become familiar with the differential diagnosis of NLPHL

Case History

A 40-year-old male presented with cervical lymphadenopathy.

Histologic Findings

- Nodular atypical lymphoid infiltrate with scattered popcorn cells

Differential Diagnosis

- NLPHL
- Progressive transformation of germinal center (PTGC)
- Lymphocyte-rich classic Hodgkin lymphoma (LRCHL)
- T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)
- Follicular lymphoma (FL)
- Diffuse large B-cell lymphoma (DLBCL)

IHC Studies

- CD20+, Oct2+, popcorn cells surrounded by PD1 T-cell rosettes.
- CD21 demonstrate expanded follicular dendritic meshworks.

Additional IHC Studies

- PAX5+ (strong), CD79a+, BOB1+, CD30−, CD15−, EBER for *EBV*−

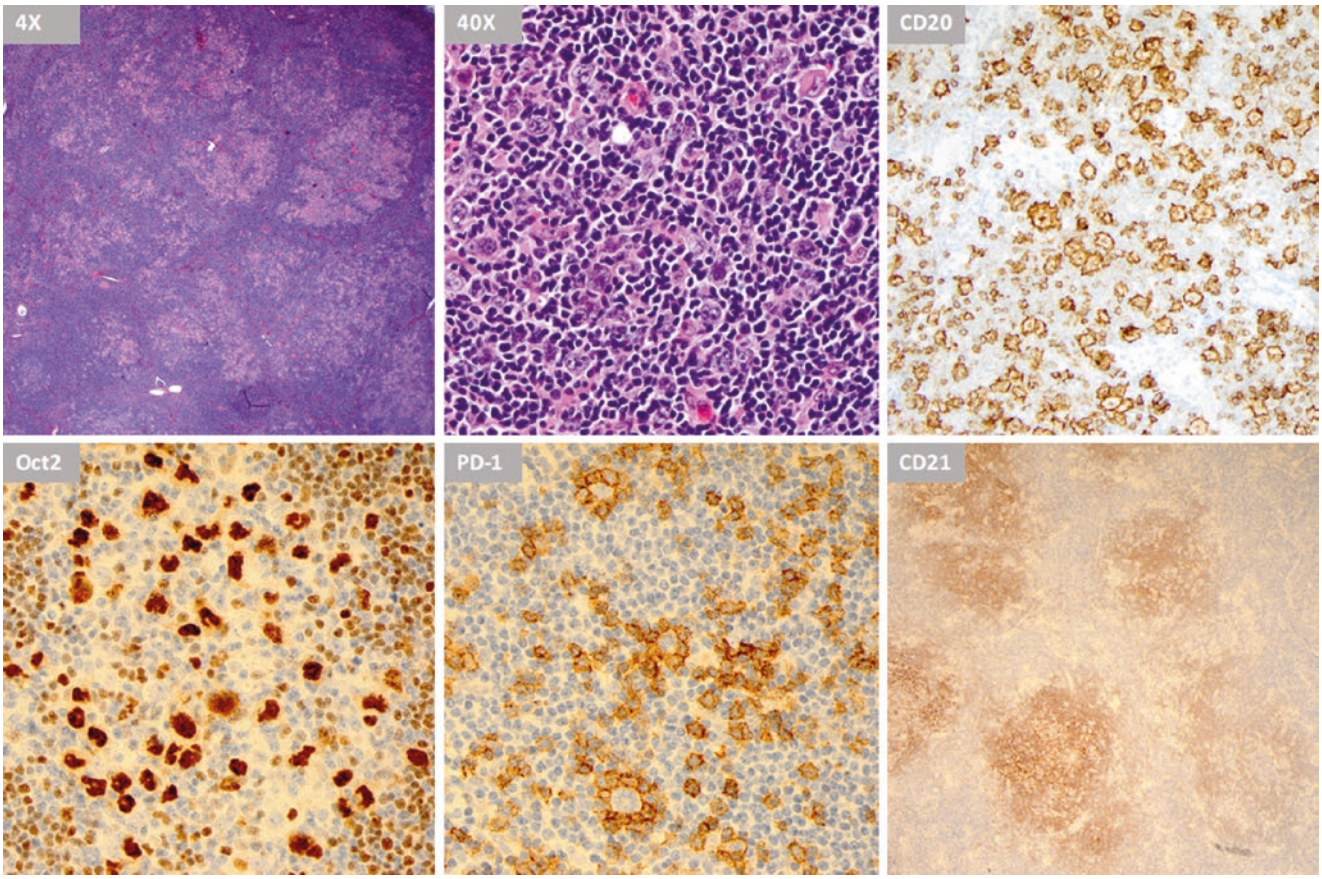

Fig. 9.1 Case 1, nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Nodular lymphoid infiltrate (40×) with a minor population of large neoplastic cells (40×) with popcorn cells or lymphocyte-predominant (LP) cells, which are positive for CD20 and Oct2 and ringed by PD1 positive T-helper cells. CD21 shows the presence of follicular dendritic meshworks

Final Diagnosis

Nodular lymphocyte-predominant classic Hodgkin lymphoma (NLPHL)

Take-Home Messages

1. NLPHL shows CD20+ popcorn cells in expanded follicular nodules and surrounded by CD57+/PD1 follicular helper T cells.
2. Popcorn cells often retain B-cell antigens, including CD19, CD20, CD79a, and leukocyte common antigen CD45.
3. Popcorn cells are usually negative for CD30 and CD15, which is in contrast to cHL.

Case 2 (Fig. 9.2)

Learning Objectives

1. To become familiar with the histologic morphologic features of NSCHL
2. To become familiar with the immunohistochemical features of the NSCHL
3. To become familiar with the differential diagnosis of NSCHL

Case History

A 30-year-old female presented with a mediastinal mass.

Histologic Findings

- Nodular atypical lymphoid infiltrate surrounded by broad band fibrosis
- Hodgkin, RS, or lacunar cells in the background of small reactive lymphocytes, histiocytes, plasma cells, and rare plasma cells

Differential Diagnosis

- NSCHL
- PMLBCL
- ALCL
- Gray zone lymphoma

IHC Studies

- CD30+, CD15+, CD20−, PAX5 weak+

Additional IHC Studies

- CD45−, Mum-1+, Oct2−, BOB1−, EBER for *EBV*−

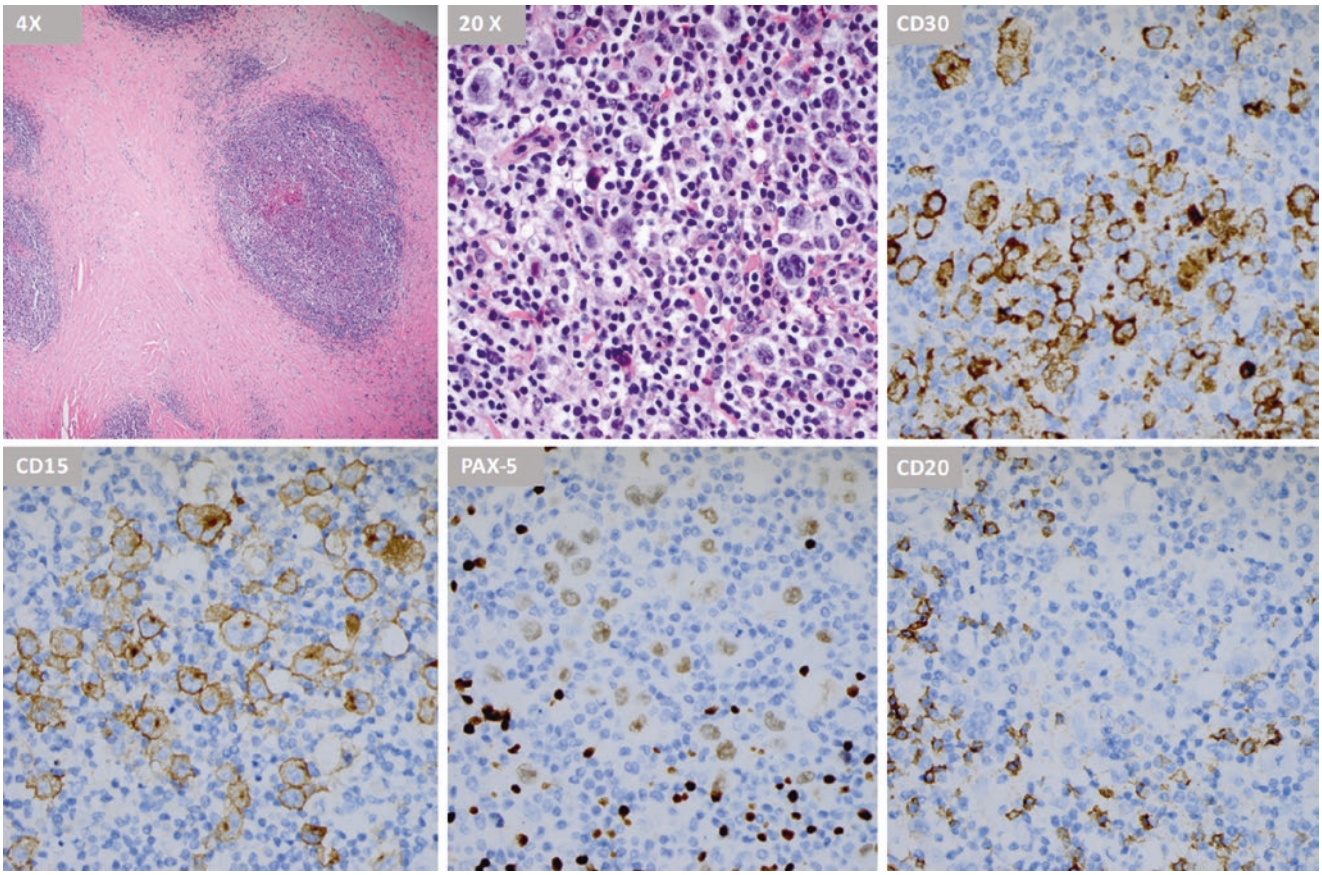

Fig. 9.2 Case 2, nodular sclerosis classic Hodgkin lymphoma (NSCHL). Nodular lymphoid infiltrate (40×) with broad band fibrosis. The nodular infiltrate consists of Hodgkin, Reed-Sternberg, or Lacunar RS cells. The background of reactive inflammatory cells includes eosinophils, small lymphocytes, neutrophils, histiocytes, and plasma cells (40×). The H or RS cells are positive for CD30, CD15, weak positive for PAX5 and negative for CD20

Final Diagnosis
Nodular sclerosis classic Hodgkin lymphoma (NSCHL)

Take-Home Messages
1. NSCHL show broad band fibrosis.
2. RS cells or variants in cHL have their B-cell program down-regulated, thus demonstrating negative staining for majority of B-cell antigens.
3. Typical cHLs are CD30+, CD15+, PAX5 weak+, CD20−, CD45−, Mum-1+, *EBV*+/−, OCT2−, BOB1−.

Case 3 (Fig. 9.3)

Learning Objectives
1. To become familiar with the histologic morphologic features of LRCHL
2. To become familiar with the immunohistochemical features of the LRCHL
3. To become familiar with the differential diagnosis of LRCHL

Case History
A 37-year-old male presented with left axillary lymphadenopathy.

Histologic Findings
- Nodular lymphoid proliferation with apparently reactive follicles and expanded perifollicular or interfollicular areas; no significant fibrosis is identified around the lymphoid nodules.
- Hodgkin or RS cells in the background of small lymphocytes and histiocytes.

Differential Diagnosis
- LRCHL
- NLPHL
- FL
- Castleman lymphadenopathy

IHC Studies
- CD30+, CD20−, PAX5 weak+, *EBV*-LMP1+

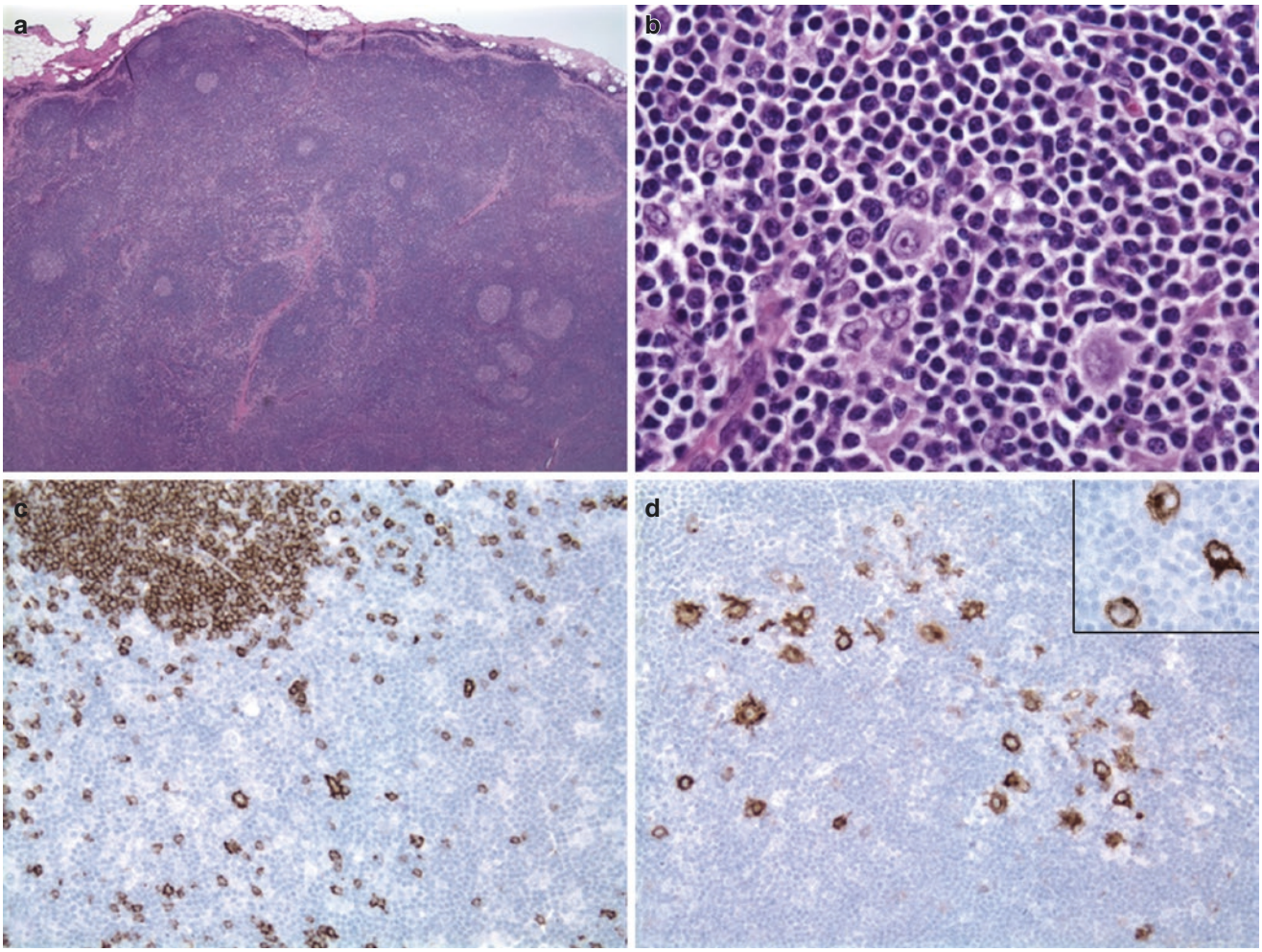

Fig. 9.3 Case 3, lymphocyte-rich classic Hodgkin lymphoma (LRCHL). (**a**) Section of lymph node biopsy shows largely preserved nodal architecture with apparently reactive lymphoid follicles and slight expansion of perifollicular/interfollicular areas. H&E stain, ×40. (**b**) High magnification shows scattered large atypical cells with prominent nucleoli in the background of many small lymphocytes in interfollicular area. H&E stain, 40×. (**c**) CD20 stain highlights aggregates of B cells, but the large atypical cells are negative for the stain. 20×. (**d**) The large atypical cells are positive for CD30, 20×. Inset shows three large cells positive for *EBV* latent membrane protein, 40×

Additional IHC Studies

- CD45−, CD15+, Mum-1+, OCT2−, BOB1−

Final Diagnosis

Lymphocyte-rich classic Hodgkin lymphoma (LRCHL)

Take-Home Messages

1. LRCHL show nodular lymphoid proliferation with RS or Hodgkin cells in expanded mantle zone, which could be highlighted by immunohistochemistry.
2. RS cells or variants in cHL have their B-cell program down-regulated, thus demonstrating negative staining for majority of B-cell antigens.
3. Typical cHLs are CD30+, CD15+, PAX5 weak+, CD20−, CD45−, Mum-1+, *EBV*+/−, OCT2−,BOB1−.

Case 4 (Fig. 9.4)

Learning Objectives

1. To become familiar with the histologic morphologic features of MCCHL
2. To become familiar with the immunohistochemical features of the MCCHL
3. To become familiar with the differential diagnosis of MCCHL

Case History

A 38-year-old male presented with right axillary lymphadenopathy.

Histologic Findings

- Diffuse atypical lymphoid infiltrate with mixed inflammatory background and scattered Hodgkin and RS cells

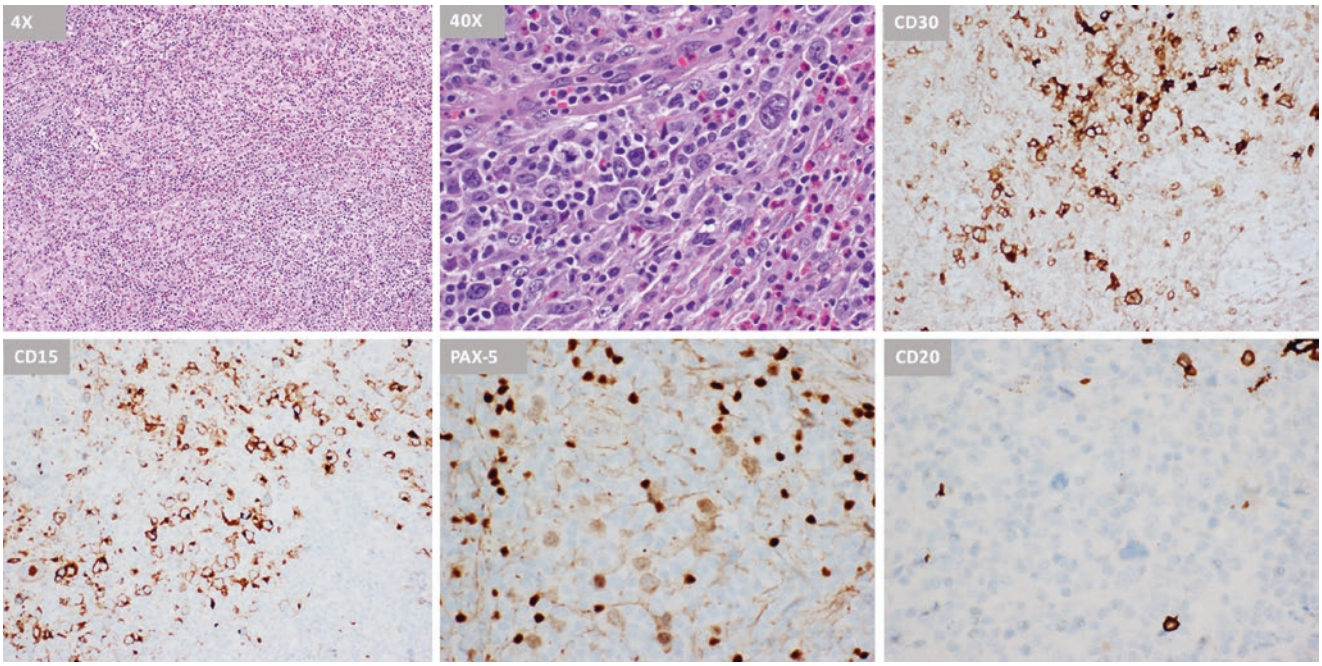

Fig. 9.4 Case 4, mixed cellularity classic Hodgkin lymphoma (MCCHL). The background shows mixed inflammatory cells without obvious nodular formation (40×). Large H or RS cells are seen (40×) and are positive for CD30, CD15, weak positive for PAX5, and negative for CD20

Differential Diagnosis
- T-cell/histiocyte-rich large B-cell lymphoma (T/HRLBCL)
- Peripheral T-cell lymphoma (PTCL), not otherwise specified

IHC Studies
- CD30+, CD15+, PAX5 weak+, CD20−

Additional IHC Studies
- Mum-1+, CD45−, OCT2−, BOB1−, EBER for *EBV*+

Final Diagnosis
Mixed cellularity classic Hodgkin lymphoma (MCCHL)

Take-Home Message
1. MCCHL shows CD30+, CD15+/−, PAX5 weak+, Mum-1+, CD20−, CD45−, Hodgkin or RS cells in the background of mixed inflammatory background, including significant eosinophils.

Case 5 (Fig. 9.5)

Learning Objectives
1. To become familiar with the histologic morphologic features of LDCHL
2. To become familiar with the immunohistochemical features of the LDCHL
3. To become familiar with the differential diagnosis of LDCHL

Case History
A 51-year-old male presented with a retroperitoneal mass.

Histologic Findings
- Enlarged lymph node with nodal architecture effaced by diffuse proliferation of large atypical cells with pleomorphic nuclei in a background of fibrosis and devoid of lymphoid cells.
- Hodgkin and RS are abundant with sarcomatoid morphology.

Differential Diagnosis
- LDCHL
- ALCL
- Sarcoma, including histiocytic sarcoma or other dendritic cell sarcoma

IHC Studies
- CD30+, CD15+, CD20−, PAX5 weak+

Additional IHC Studies
- CD45−, Mum-1+, Oct2−, Bob1−, CD163−, lysozyme−, CD21−, EBER for *EBV*+

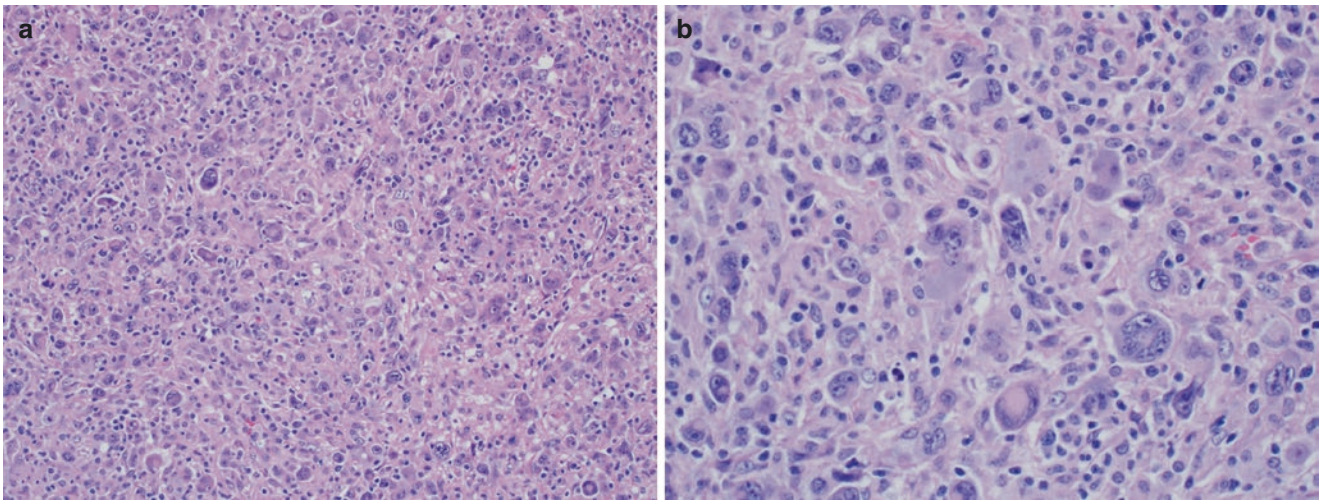

Fig. 9.5 Case 5, lymphocyte-depleted classic Hodgkin lymphoma (LDCHL). (**a**) Section of lymph node biopsy shows nodal architecture effaced by proliferation of large cells with pleomorphic nuclei admixed with other inflammatory cells. H&E stain, 10×. (**b**) A high magnification demonstrates many large cells with pleomorphic nuclei including a few with multinucleation and wreath-like nuclei. The background cells consist of small lymphocytes and histiocytes, though lymphocytes are apparently fewer than other subtypes of cHL. H&E stain, 40×

Final Diagnosis
Lymphocyte-depleted classic Hodgkin lymphoma (LDCHL)

Take-Home Messages
1. LDCHL shows pleomorphic morphology resembling sarcoma.
2. RS cells or variants in cHL have their B-cell program down-regulated, thus demonstrating negative staining for majority of B-cell antigens.
3. Typical cHLs are CD30+, CD15+, PAX5 weak+, CD20−, CD45−, Mum-1+, *EBV*+/−, OCT2−, BOB1−.

Case 6 (Fig. 9.6)

Learning Objectives
1. To become familiar with the histologic morphologic features of PTGC
2. To become familiar with the immunohistochemical features of the PTGC
3. To become familiar with its differentiation from NLPHL

Case History
A 32-year-old male presented with cervical lymphadenopathy.

Histologic Findings
- Mostly maintained lymph node architecture
- Occasional expanded lymphoid follicles with mantle cell invasion but without obvious large atypical cells

Differential Diagnosis
- Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)
- T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)
- Follicular lymphoma (FL)

IHC Studies
- CD20+ and OCT2 show no obvious large atypical lymphocytes.

Additional IHC Studies
- CD30 and CD15 show no large atypical cells.

Final Diagnosis
Progressive transformation of germinal centers (PTGC)

Take-Home Messages
1. PTGC shows overall maintained lymph node architecture, expanded lymphoid follicles with mantle cell invagination into germinal centers, but no obvious large atypical B cells by morphology or by IHC, in comparison to NLPHL.
2. Often demonstrates coexisting reactive hyperplasic follicles.
3. Often demonstrates patent sinuses.

Case 7 (Fig. 9.7)

Learning Objectives
1. To become familiar with the histologic morphologic features of THRLBCL

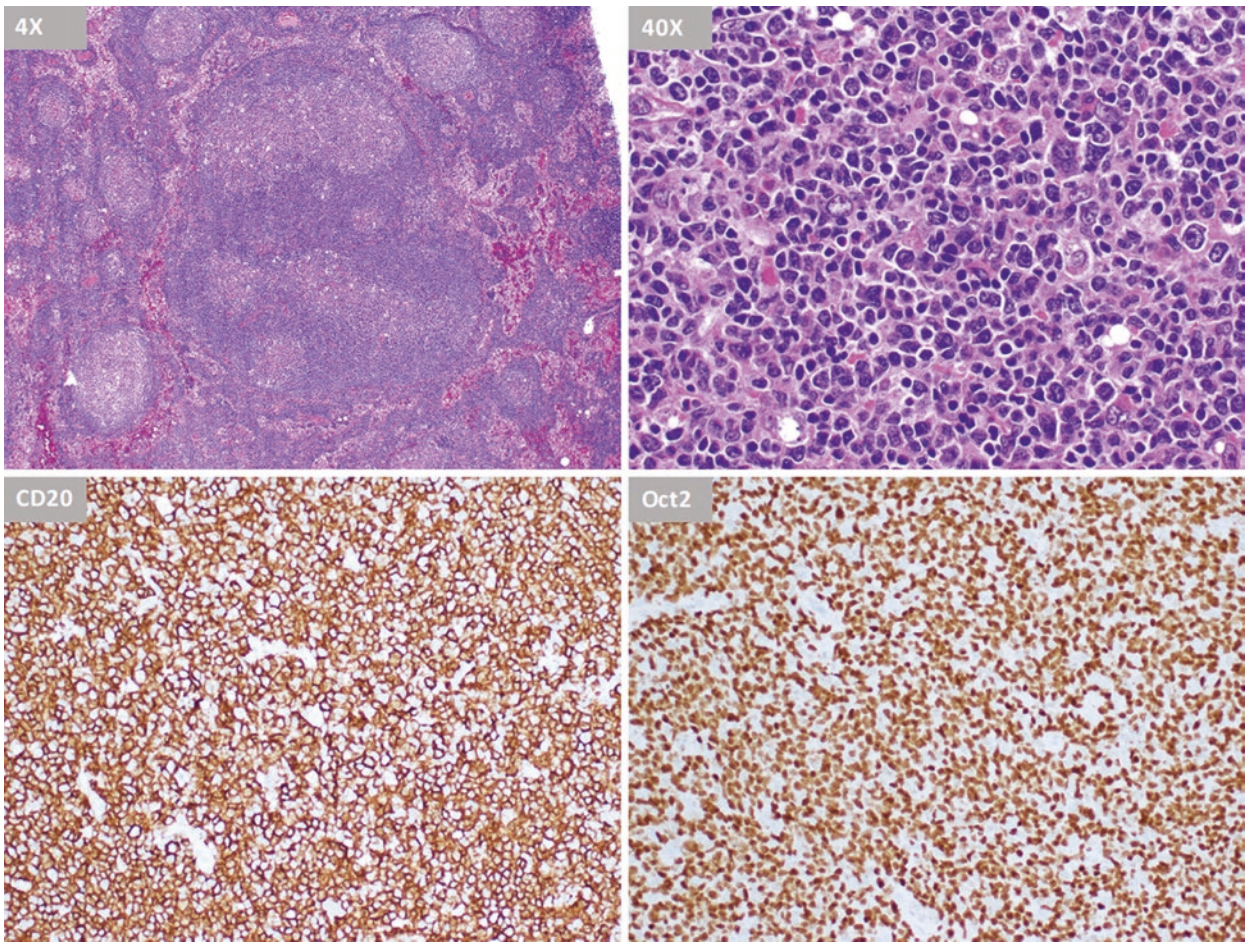

Fig. 9.6 Case 6, progressive transformation of germinal centers (PTGC). Large expanded lymphoid follicles are seen in the background of follicular hyperplasia (40×). No large atypical lymphocytes are present except for occasional immunoblasts (40×). CD20 and OCT2 only show small reactive B cells and no large atypical B cells, as seen in NLPHL

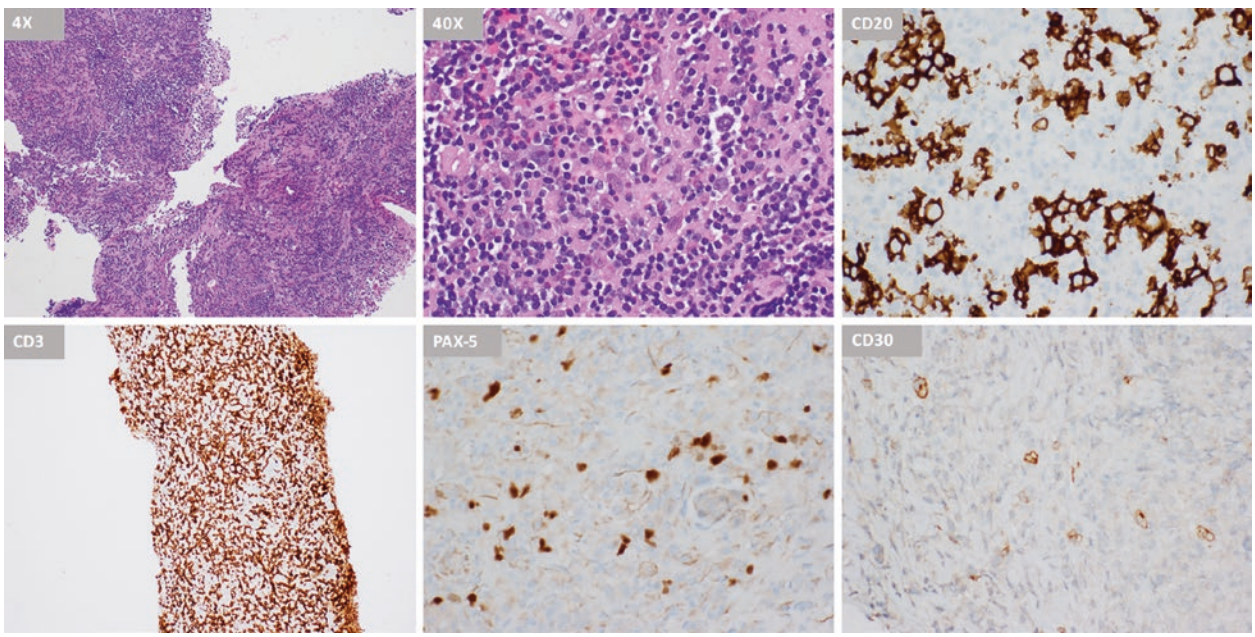

Fig. 9.7 Case 7, T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL). Diffuse lymphoid infiltrate (4×) with scattered large atypical cells including some Hodgkin-like cells (40×) that are strong positive for CD20, PAX5 occasionally positive for CD30. CD3 shows numerous T cells in the background

2. To become familiar with the immunohistochemical features of the THRLBCL
3. To become familiar with its differentiation from Hodgkin lymphoma

Case History
A 50-year-old male presented with fever, malaise, splenomegaly, hepatomegaly, and right inguinal lymphadenopathy.

Histologic Findings
- Diffuse atypical lymphoid infiltrate with scattered large atypical cells

Differential Diagnosis
- MCCHL
- LRCHL
- PTGC
- PTCL

IHC Studies
- CD20 strong +, PAX5 strong+, occasional CD30+ large typical lymphocytes.
- CD3 shows mostly T cell in the background.

Additional IHC Studies
- OCT2+, BOB1+, CD30−, CD15−, CD45+, EBER for *EBV*−.
- CD21 demonstrate no obvious follicular dendritic meshworks.

Final Diagnosis
T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)

Take-Home Messages
1. THRLBCL shows a few CD20+, PAX5+, OCT2+, BOB1+ large atypical B cells in the background of diffuse T-cell or histiocytic infiltrate without follicular dendritic meshworks.
2. NLPHL, particularly diffuse T-cell-rich variant, show similar large atypical B cells ringed by CD57+/PD1 T cells in the background of B-cell nodules with at least one follicular dendritic meshwork.
3. MCCHL or LRCHL shows CD30+, CD15+/−, PAX5 weak+, CD20−, CD45−, OCT2−, BOB1− H or RS cells in the background of lymphocytes.
4. Those cases with similar morphologic features but *EBV* infection in large cells are best classified as *EBV*-positive DLBCL per the recent WHO classification, rather than THRLBCL.

Case 8 (Fig. 9.8)

Learning Objectives
1. To become familiar with the histologic morphologic features of PMLBCL
2. To become familiar with the immunohistochemical features of the PMLBCL
3. To become familiar with its differentiation from classic Hodgkin lymphoma

Case History
A 35-year-old female presented with large mediastinal mass.

Histologic Findings
- Diffuse large atypical lymphocytes in the background of fine fibrosis

Differential Diagnosis
- cHL
- GZL
- Mediastinal involvement by conventional DLBCL

IHC Studies
- CD20+ (strong), CD30 occasionally +
- CD79a+, CD45+, CD15−

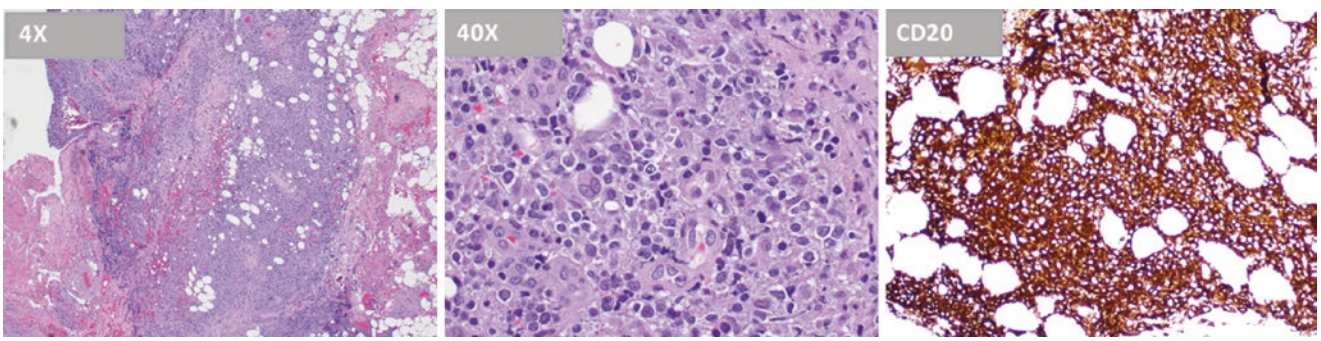

Fig. 9.8 Case 8, primary mediastinal (thymic) large B-cell lymphoma (PMLBCL). Sheets of large atypical lymphocytes in the background of compartmentalization alveolar fine fibrosis (4× and 40×). The large atypical lymphocytes are positive for CD20, and PAX5 (strong), Oct2, and CD23, and occasionally positive for CD30 (not shown)

Additional IHC Studies
- PAX5 strong +, CD30 occasionally+, CD23 subset+, EBER for *EBV*−

Final Diagnosis
Primary mediastinal (thymic) large B-cell lymphoma (PMLBCL)

Take-Home Messages
1. PMLBCL shows medium-sized to large atypical cells that are partially CD30+, but also strongly positive for CD20, CD45, PAX5, OCT2, and BOB1, which are usually negative or only weak positive in cHL.
2. The diagnosis of primary mediastinal (thymic) large B-cell lymphoma can be established only after ruling extrathoracic involvement of the disease.

Case 9 (Fig. 9.9)

Learning Objectives
1. To become familiar with the histologic morphologic features of gray zone lymphoma
2. To become familiar with the immunohistochemical features of gray zone lymphoma
3. To become familiar with its differentiation from classic Hodgkin lymphoma

Case History
A 30-year-old male presented with a large anterior mediastinal mass.

Histologic Findings
- Diffuse infiltrate of Hodgkin or RS cells or like cells (40×)

Differential Diagnosis
- Nodular sclerosis classic Hodgkin lymphoma (NSCHL)
- Primary mediastinal large B-cell lymphoma (PMLBCL)
- Anaplastic large cell lymphoma (ALCL)
- T-cell/histiocyte-rich large B-cell lymphoma (T/HRLBCL)

IHC Studies
- CD30+, CD20 strong+, OCT2 strong+, CD45 strong+

Additional IHC Studies
- CD15−, PAX5 weak+, EBER for *EBV*−

Final Diagnosis
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classic Hodgkin lymphoma (gray zone lymphoma)

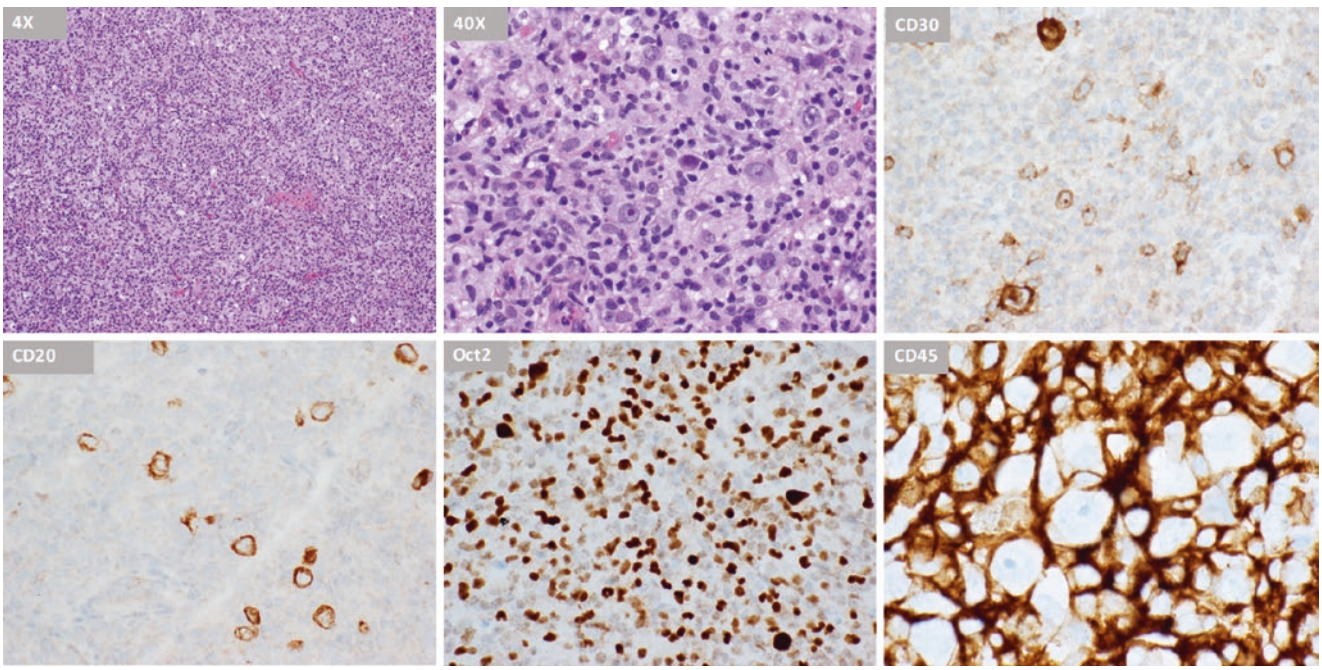

Fig. 9.9 Case 9, gray zone lymphoma (GZL). Numerous large atypical lymphocytes, including some Hodgkin or Hodgkin-like cells in an inflammatory background (4× and 40×). The large atypical cells are positive for CD30, but also show strong positivity for CD20, OCT2, CD45, as well as Bob1 (not shown)

Take-Home Messages

1. Gray zone lymphoma shows classic Hodgkin lymphoma-like morphology but with strong CD20 or OCT2/CD79a/BOB1 or CD45 expression (DLBCL phenotype) or, otherwise, demonstrates diffuse large B-cell lymphoma-like morphology but with weak CD20 and other B-cell markers (phenotype resembling cHL).
2. While most cases of gray zone lymphoma occur in anterior mediastinum, rare cases are reported in other anatomic sites.

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