Lymphoreticular system pathology

lecture 2

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Neoplastic proliferations of white cells

- **The most important disorders of white cells are neoplasms.**
- **Virtually all of these tumors are considered malignant (lymphoma and leukemia).**
- **they demonstrate a wide range of behaviors, ranging from some of the most aggressive cancers of man to tumors that are so indolent that they were only recognized recently as true neoplasms.**

- According to origin and line of differentiation, tumors of white cells are classified into the following broad categories.

1. **lymphoid neoplasms** (include certain leukemias and the non-Hodgkin and Hodgkin lymphomas).

2. **myloid neoplasms** (which include certain leukemias like the chronic myloid leukemia).

3. **histiocytic neoplasms** (tumors of macrophages and dendritic cells).

Lymphoid Neoplasms

- The numerous lymphoid neoplasms vary widely in their clinical presentation and behavior, and thus present challenges to students and clinicians alike.

- Some characteristically manifest as ***leukemias,*** **with involvement of the bone marrow and the peripheral blood**.

- Others tend to present **as *lymphomas,* tumors that produce masses in lymph nodes or other tissues.**

- **Plasma cell tumors tend to form bone masses causing systemic symptoms related to the production of a complete or partial monoclonal immunoglobulin.**

- All lymphoid neoplasms have the potential to spread to lymph nodes and other tissues, especially the liver, spleen, bone marrow, and peripheral blood.
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- they have overlapping clinical course so that diagnosis depends on examination of the tumor cells characteristics.
- in other words diagnosis and prognosis depends on tumor cell type rather than on where the tumor reside within the patient.

Lymphomas

- Malignant lymphoma is the generic term given to tumors of the lymphoid system and specifically of lymphocytes and their precursor cells, whether of T, B, or NK phenotypes that accumulate in lymph nodes and other tissues.

- Lymphomas arise because of a series of mutations in a single lymphoid cell. So that all lymphomas are derived from a single transformed cell and thus are by definition monoclonal.

- Although having different characteristics from their normal counterparts, the neoplastic cells of many lymphomas have the features of lymphoid cells at a particular stage of differentiation.

- B- and T-cell tumors are composed of cells derived from specific stage of normal lymphocyte differentiation(for example early stages of B-lymphocyte differentiation like the pre-B-lymphocytes in bone marrow can give rise to precursor B lymphoblastic leukemia while Naïve B-lymphocytes give rise to chronic lymphocytic leukemia).

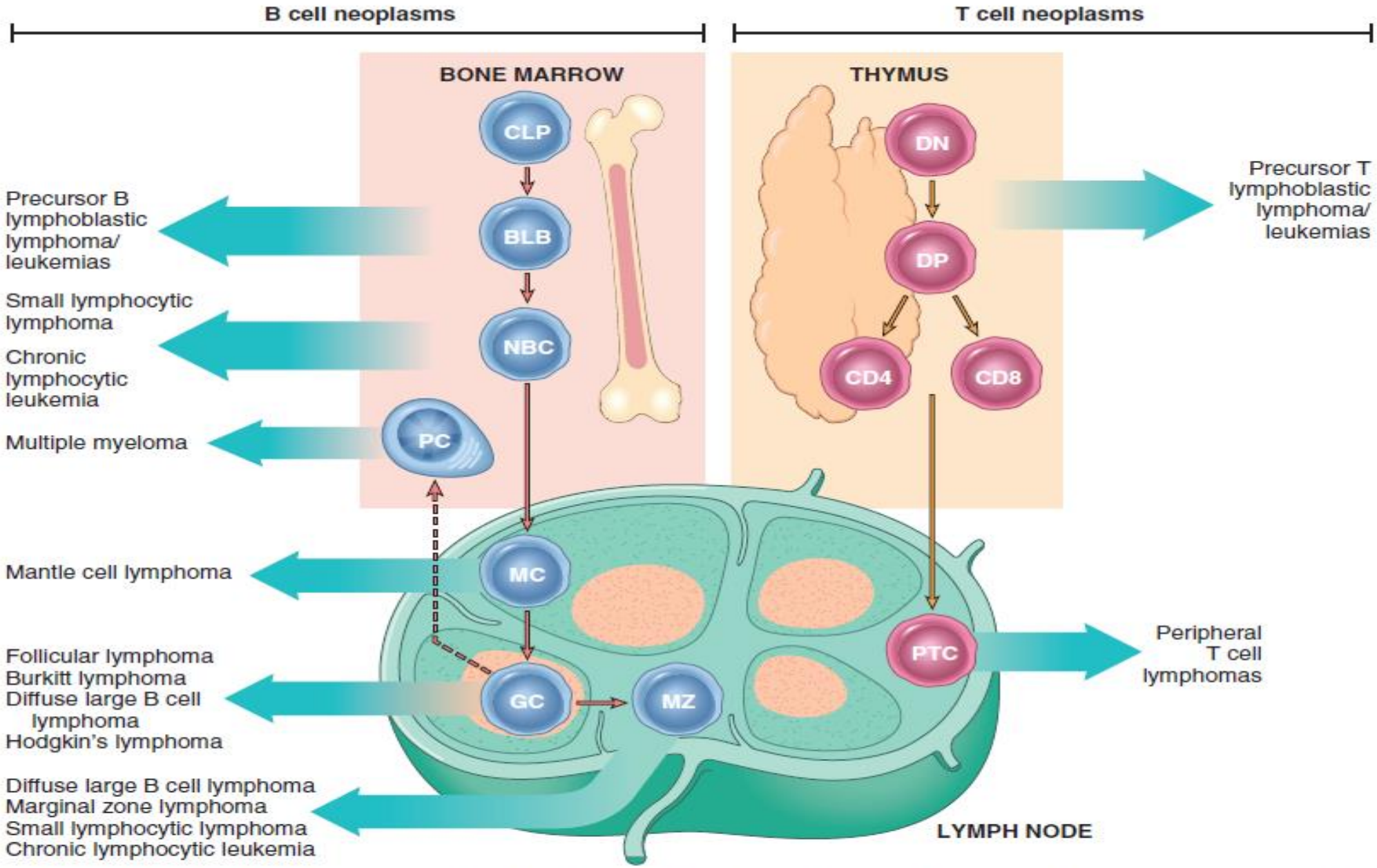


Fig. 12.13 Origin of lymphoid neoplasms. Stages of B and T cell differentiation from which specific lymphoid and tumors emerge are shown. *BLB*, Pre-B lymphoblast; *CLP*, common lymphoid progenitor; *DN*, CD4–/CD8– (double-negative) pro-T cell; *DP*, CD4+/CD8+ (double-positive) pre-T cell; *GC*, germinal center B cell; *MC*, mantle zone B cell; *MZ*, marginal zone B cell; *NBC*, naive B cell; *PC*, plasma cell; *PTC*, peripheral T cell.

Major classification of lymphoma

- The major subdivision of lymphomas is into **Hodgkin's lymphoma (HL)** and **non-Hodgkin's lymphoma(NHL)** is based on the histological presence of **Reed-Sternberg (RS) cells** in Hodgkin's lymphoma which is the neoplastic cell surrounded by plenty of non-tumor cells.

- The biologic behavior and treatment of Hodgkin lymphoma differ from those of most NHLs, thus making the distinction between the two is of practical importance.

Hodgkin's lymphoma

- Hodgkin lymphoma encompasses **a distinctive group of neoplasms that are characterized by the presence of a tumor giant cell, the RS cell**. Unlike most NHLs, Hodgkin lymphomas arise in a single lymph node or chain of lymph nodes and typically spread in a stepwise fashion to anatomically contiguous nodes.
- HL accounts for 30% of all lymphomas
- Molecular studies have shown that it is a tumor of B-cell origin
- It is characterized morphologically by the presence of distinctive neoplastic giant cells called Reed-Sternberg (RS) cells, and large mononuclear cells called Hodgkin’s cells in a reactive background composed of lymphocytes, histiocytes (macrophages), and granulocytes

- The neoplastic Reed-Sternberg cells typically make up **a minor fraction** (1 - 5%) of the total tumor cell mass, making HL more difficult to study than typical NHLs.
- The neoplastic RS-cells are derived from germinal center or post-germinal center B cells in the vast majority of cases.

- The **EBV genome** is present in the RS cells in up to 70% of cases of the mixed-cellularity type and a smaller fraction of the nodular sclerosis type. Thus, EBV infection is likely to be a contributing step to the development of Hodgkin lymphoma, particularly the mixed-cellularity type.

- The disease can present at any age but is rare in children and has a peak incidence in young adults. There is an almost 2 : 1 male predominance

- The usual clinical presentation is with painless asymmetrical lymphadenopathy–most commonly in the neck. Typically the disease is localized initially to a single peripheral lymph node region and its subsequent progression is by contiguity within the lymphatic system.

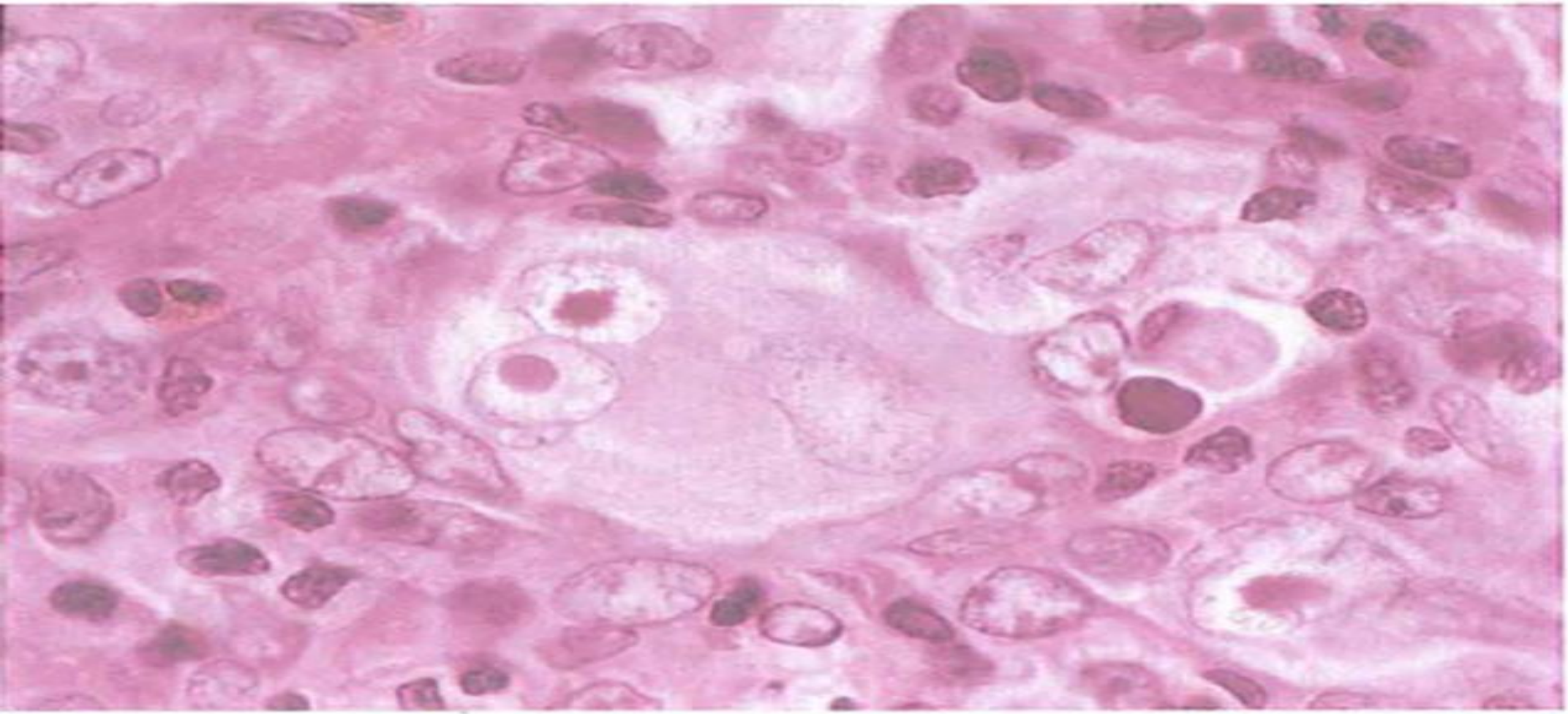
- Constitutional symptoms of fever, weight loss & sweating are prominent in patients with widespread disease.

Diagnosis and histological classification:

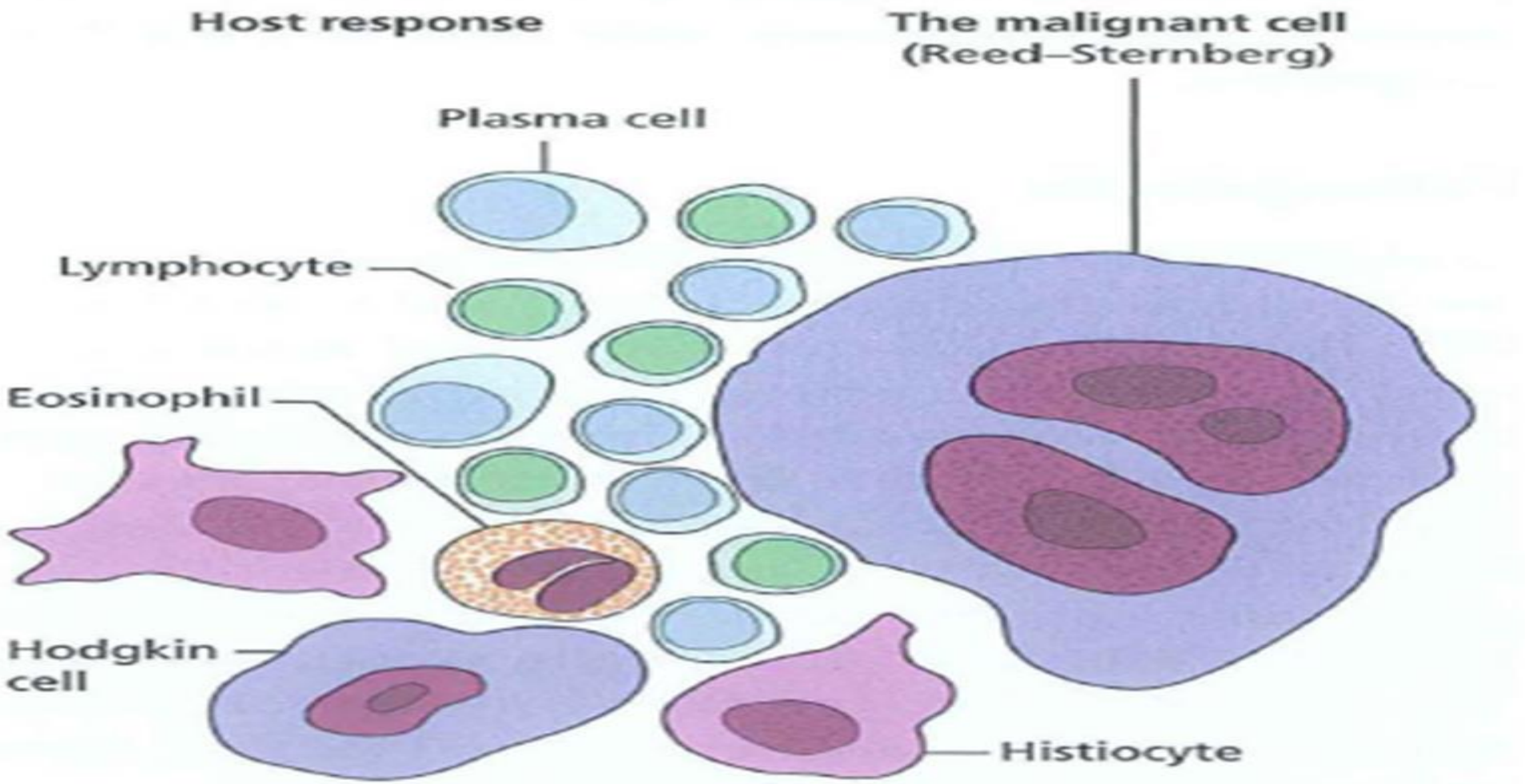
- The diagnosis is made by histological examination of an excised lymph node.
- **The histologic diagnosis of Hodgkin lymphoma rests on the definitive identification of Reed-Sternberg cells or their variants in the appropriate background of reactive cells.**

Morphology of Reed –Sternberg cells:

- The **Reed-Sternberg (RS) cell** is a large cell with an enlarged multilobated nucleus, prominent nucleoli, and abundant, usually slightly eosinophilic, cytoplasm. **Particularly characteristic are cells with two mirror-image nuclei or nuclear lobes, each containing a large (inclusion-like) acidophilic nucleolus surrounded by a distinctive clear zone; together they give an owl-eye appearance. The nuclear membrane is distinct.**
- Such "classic" RS cells are common in the mixed-cellularity subtype, uncommon in the nodular sclerosis subtype, and rare in the lymphocyte-predominance subtype.



Reed-Sternberg cell



Diagrammatic representation of the different cells seen histologically in Hodgkin's lymphoma.

- **Blood tests may show anaemia, neutrophilia, eosinophilia & raised erythrocyte sedimentation rate (ESR) or lactate dehydrogenase (LDH).**

- **<u>Five subtypes of Hodgkin lymphoma are recognized:</u>**

(1) Nodular sclerosis.

(2) Mixed cellularity.

(3) Lymphocyte rich.

(4) Lymphocyte depletion. (rare)

(5) Lymphocyte predominance (rare)

- The first four subtypes share common features and lumped together as **classical Hodgkin lymphoma**
- The fifth subtype is set apart as the **Nodular lymphocyte - predominant Hodgkin lymphoma**
- The "classic" RS cells are **common** in the **mixed-cellularity** subtype, uncommon in the nodular sclerosis subtype, and **rare** in the **lymphocyte-predominance** subtype.

Nodular sclerosis classical Hodgkin lymphoma

- The most common form.
- It is equally frequent in men and women.
- Most of the patients are adolescents or young adults.
- The overall prognosis is excellent.

- **Morphology :**
- **A variant of the RS cell, the lacunar cell** . This cell is large and has a single multilobate nucleus with multiple small nucleoli and an abundant, pale-staining cytoplasm.

- In formalin-fixed tissue, the cytoplasm often retracts, giving rise to the appearance of cells lying in empty spaces, or **lacunae**.
- There are varying proportions of lymphocytes, eosinophils, histiocytes .
- Classic RS cells are infrequent.
- There are fibrous(sclerotic) bands that divide the lymphoid tissue into circumscribed nodules hence the name as nodular sclerosis.

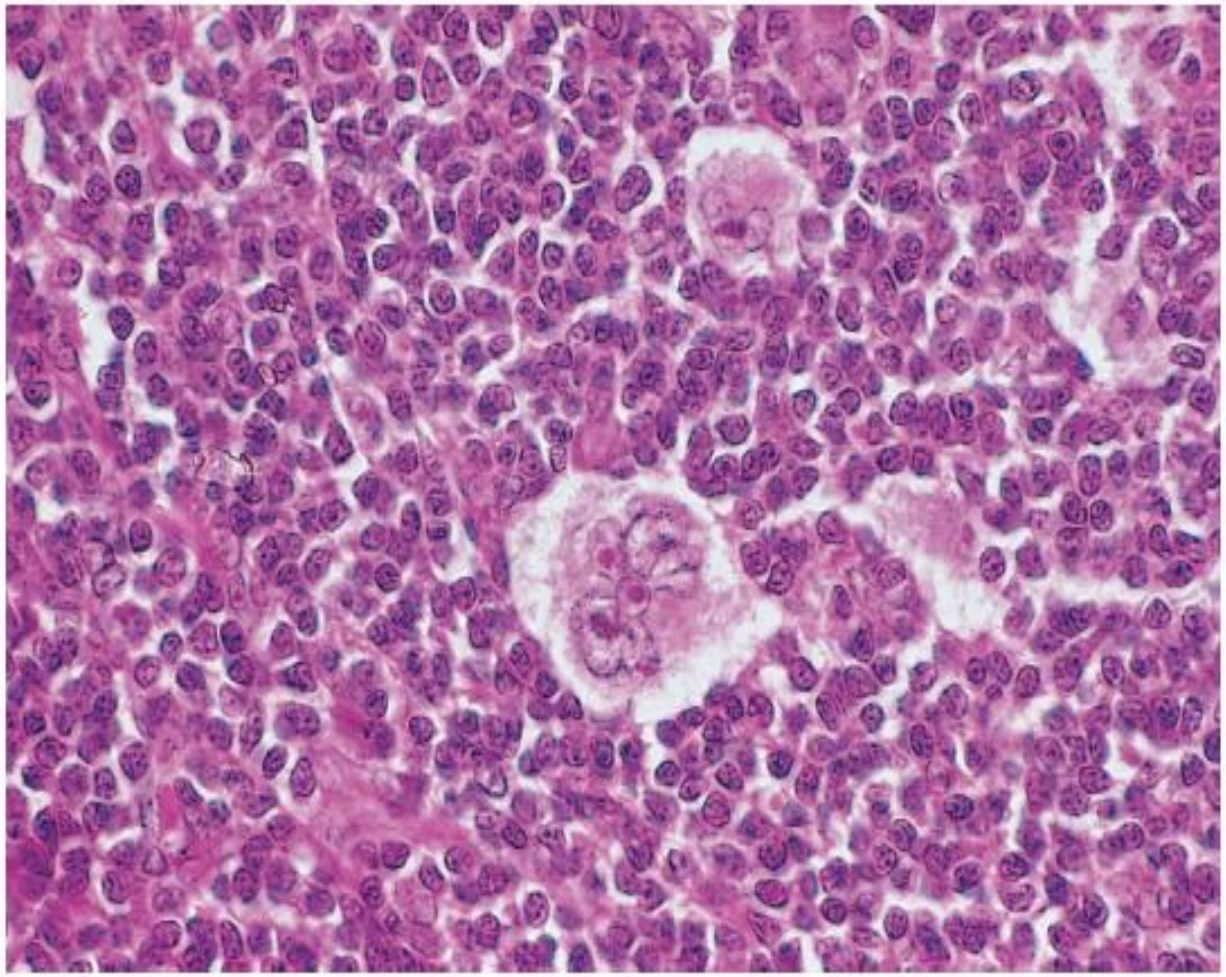


Fig. 12.21 Hodgkin lymphoma, nodular sclerosis type—lymph node. A distinctive "lacunar cell" with a multilobed nucleus containing many small nucleoli is seen lying within a clear space created by retraction of its cytoplasm. It is surrounded by lymphocytes. *(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)*

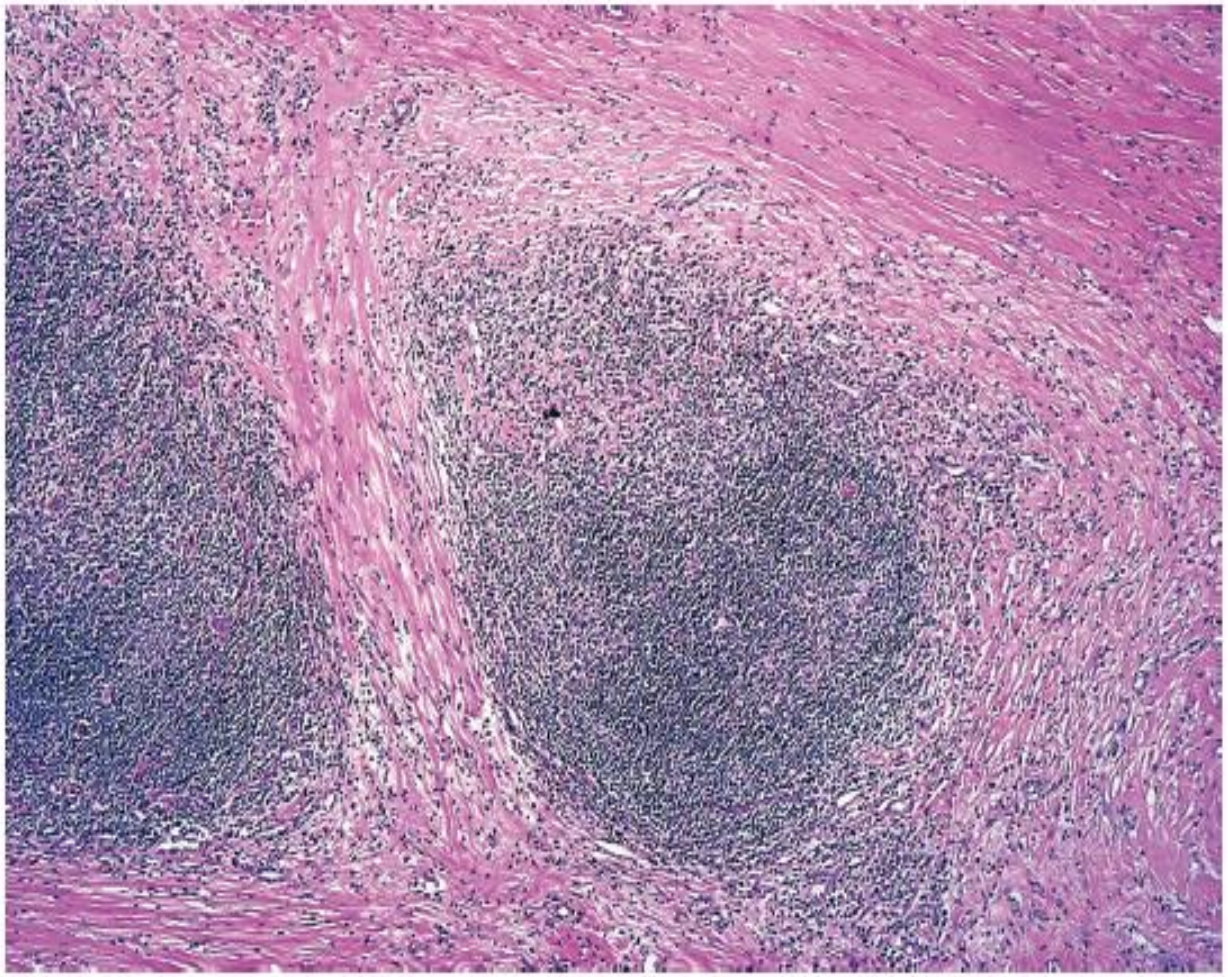


Fig. 12.22 Hodgkin lymphoma, nodular sclerosis type—lymph node. A low-power view shows well-defined bands of pink, acellular collagen that have subdivided the tumor cells into nodules. *(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)*

Mixed- cellularity classical Hodgkin lymphoma

- Patients older than the age of 50 year.
- Male predominance.
- **Classic RS cells are plentiful** within cellular infiltrate of small lymphocytes, eosinophils, plasma cells, and benign histiocytes.

- More patients with mixed cellularity have **disseminated disease and systemic manifestations**

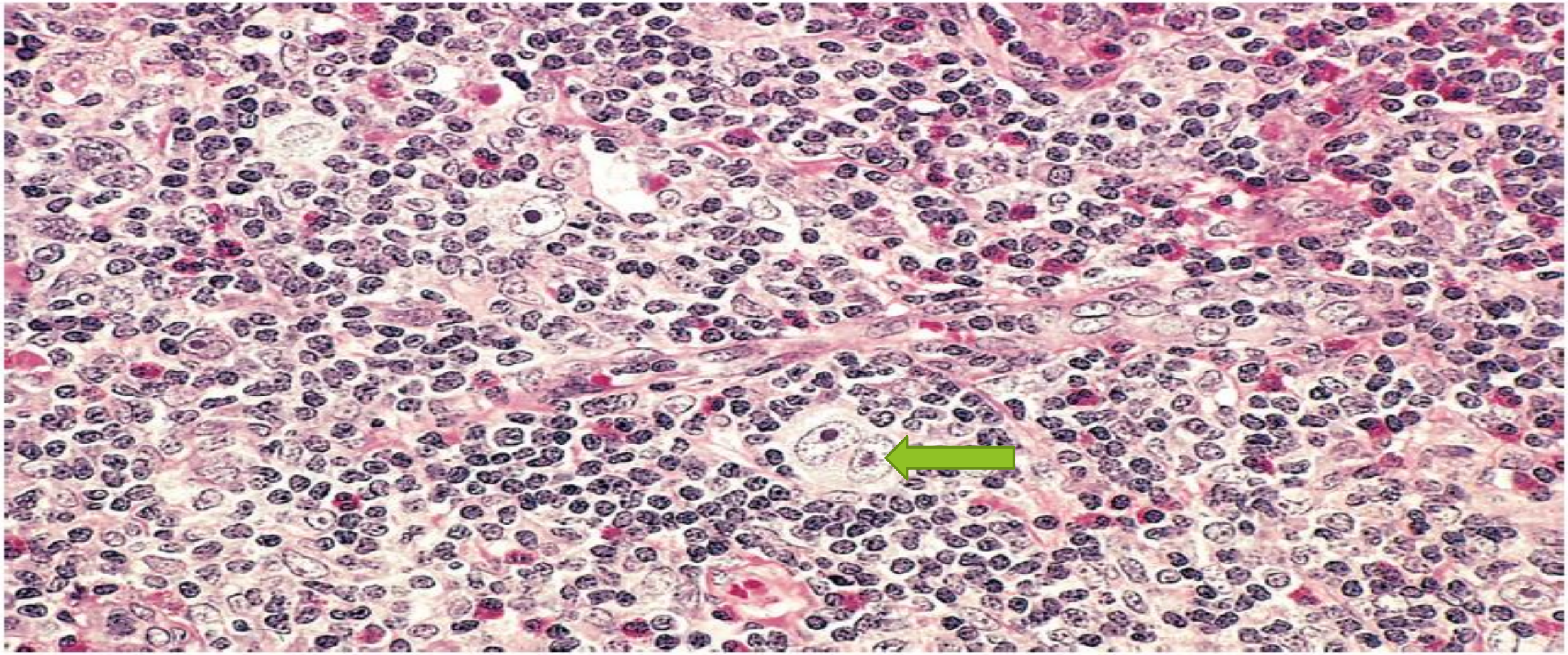
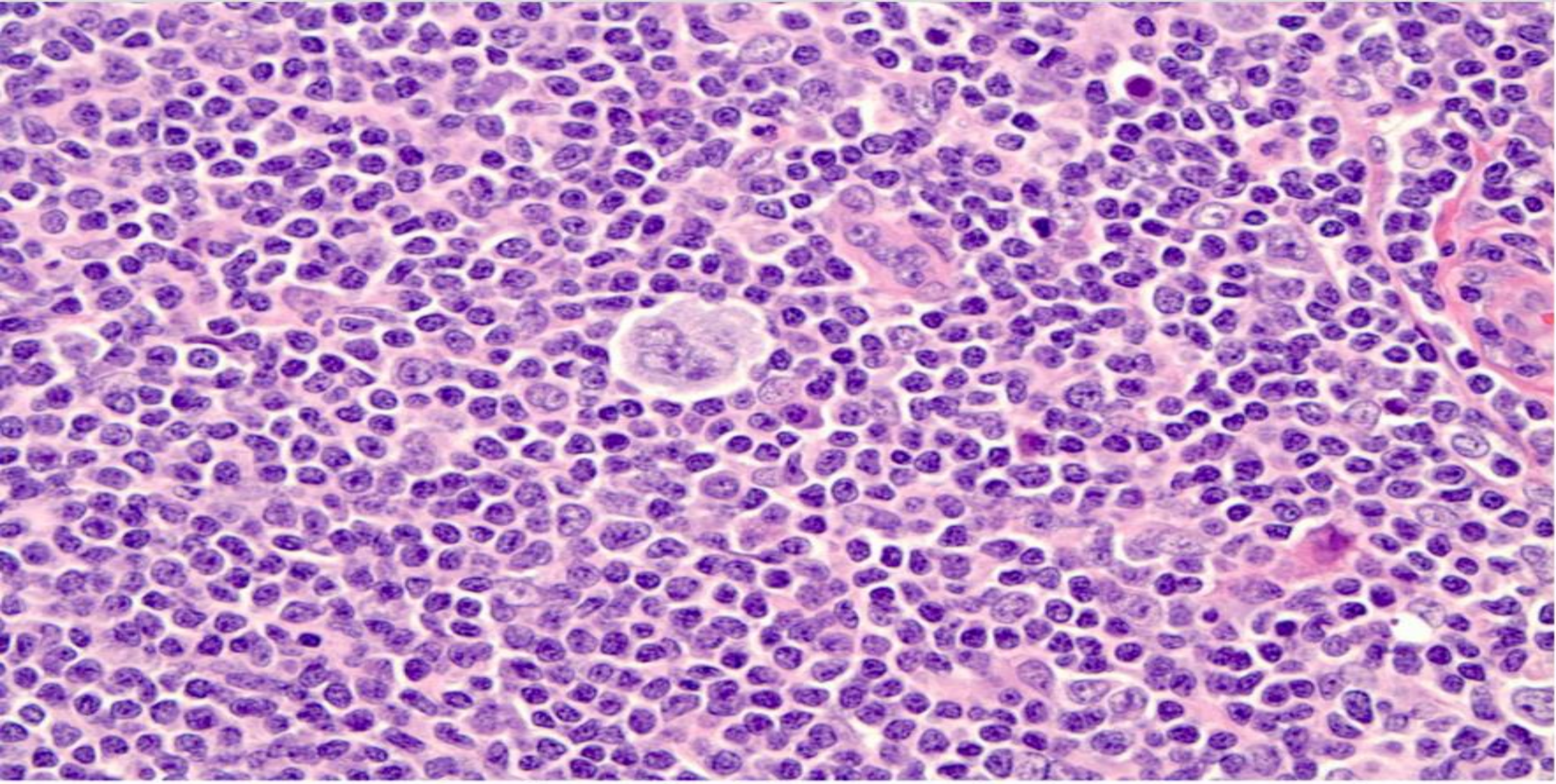


Fig. 12.23 Hodgkin lymphoma, mixed-cellularity type—lymph node. A diagnostic, binucleate Reed-Sternberg cell is surrounded by eosinophils, lymphocytes, and histiocytes. *(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)*

Nodular Lymphocyte-Predominance Hodgkin Lymphoma:

- This subgroup, comprising about 5% of Hodgkin lymphoma.
- It is characterized by a large number of background small resting lymphocytes admixed with a variable number of benign histiocytes.
- Eosinophils, neutrophils, and plasma cells, are scanty or absent, and classic RS cells are extremely difficult to find.
- **- Lymphohistiocytic (L&H) variant RS cells that have a delicate multilobed, puffy nucleus that has been likened in appearance to popcorn ("popcorn cell").**



Rare large neoplastic cell with irregularly contoured / folded nucleus

- **In all forms, involvement of the spleen, liver, bone marrow, and other organs may appear in the course of the disease.**

Non-Hodgkin's lymphomas

- These are a large group of clonal lymphoid tumors, about 85 % are of B cell origin and 15% of T or NK(natural killer) cell origin.

- They are characterized by an irregular pattern of spread and a significant proportion of patients develop extra nodal disease.

- The non-Hodgkin's lymphomas are a diverse group of diseases and vary from highly proliferative and rapidly fatal diseases to some of the most indolent and well-tolerated malignancies

Cell of origin for NHLs

- **B-cell lymphomas tend to mimic normal B cells at different stages of development .**
- **T-cell lymphomas resemble precursor T cells in bone marrow or thymus ,or peripheral mature T cells.**

Classification

- For many years, clinicians have subdivided lymphomas into **low and high-grade disease.**
- -In general terms, the low-grade disorders are relatively indolent, respond well to chemotherapy but are very difficult to cure whereas high-grade lymphomas are aggressive and need urgent treatment but are often curable.
- --Low grade lymphoma: e. g. Follicular lymphoma , mantle cell lymphoma.
- --High Grade Lymphoma: e. g. *Diffuse Large B-Cell Lymphoma ,Burkitt's lymphoma.*

Clinical Differences Between Hodgkin and Non-Hodgkin Lymphomas:

Hodgkin Lymphoma	**Non-Hodgkin Lymphoma**
1. More often localized to a single axial group of nodes (cervical, mediastinal, para-aortic	1.More frequent involvement of multiple peripheral nodes
2. Orderly spread by contiguity	2.Noncontiguous spread
3. Mesenteric nodes and Waldeyer ring rarely involved	3.Mesenteric nodes and Waldeyer ring commonly involved
4.Extranodal involvement uncommon	4.Extranodal involvement common