Lymph Node Pathology

5

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Lymph nodes are small secondary lymphoid organs which play a key role in two important biological systems: the lymphatic system and the immune system. The normal lymph node is a small soft bean-shaped organ covered by a fibrous capsule. Approximately 500–600 lymph nodes can be found throughout the human body [1], with the exception of the central nervous system, and are concentrated at strategic sites which maximize the potential of identifying foreign antigens, such as at the proximal ends of extremities [2].

Lymph nodes have a highly specialized internal architecture, reflecting their dual functions. They are designed to allow for the passage of lymphatic fluid through the node while maximizing its exposure to a mixture of specialized immune cells [3]. Lymph nodes form as specialized nodules of fibrovascular tissue, which grow into and fill lymph sacs – areas of dilatation within lymphatic vessels [4, 5]. The architecture of the lymph node is maintained by a reticular meshwork of fibroblastic reticular cells (FRCs), immunologically specialized myofibroblasts of mesenchymal origin [6]. In addition to maintaining the structure of the node, FRCs play a key role in regulating the hematolymphoid population of the node, providing scaffolds along which lymphocytes and dendritic cells migrate, as well as forming conduits which allow for the transport of soluble antigens and signaling molecules deep into the lymph node [3, 7].

After lymph enters the lymph node via any of the afferent lymphatic vessels, it drains into the subcapsular sinus of the node, and from there filters through the sinuses of the node to leave in the efferent lymph vessel [2]. As the subcapsular sinus is the point of entry for lymph-borne materials, nodal metastases are frequently identified in the peripheral regions of the lymph node.

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Lymphocytes are the main hematopoietic cell present in lymph nodes, consisting of B cells and the various subclasses of T cells, which interact constantly with each other, with other hematopoietic cells in the lymph node, and with the stromal cells [8]. However, in spite of their relative dominance, lymphocytes are nomads in the lymph node, entering from the peripheral blood, homing to specially designated compartments following chemokine gradients, and then leaving in the absence of an appropriate stimulus to re-enter circulation [9]. This constant turnover of lymphocytes maximizes the supply of naïve lymphocytes to the node. In conditions of immunological stress, such as infection, the influx of lymphocytes is increased by dilation of the lymph node arteriole [10].

The compartmentalization of the lymph node by cell population results in three distinct regions, each with their own characteristic cellular population and function: the superficial cortex, the deep cortex (or "paracortex"), and the medulla [11, 12]. Anatomically, these regions can be grouped together into functional lobules, which vary in size and number per lymph node (Fig. 5.1) [2].

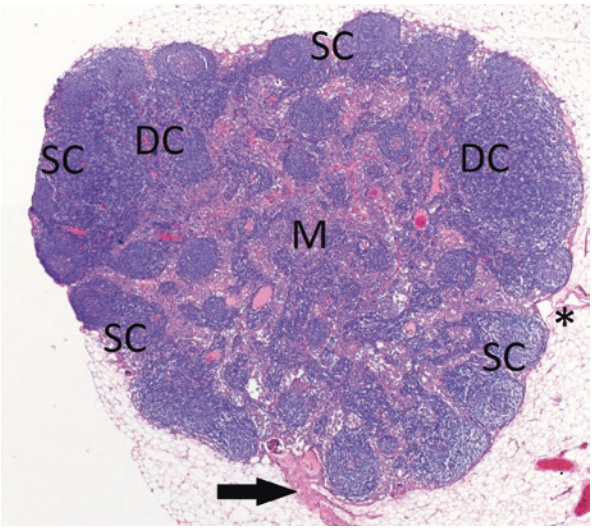

Fig. 5.1 A normal lymph node. SC superficial cortex, with follicular architecture, DC deep cortex (paracortex), M Medulla, Arrow Hilum of lymph node, with efferent lymphatic vessel and vascular supply. *: Thin-walled afferent lymphatic vessel

5.1 Superficial Cortex

The superficial cortex is the outermost part of the lymphoid lobule, and the first region through which lymph travels after entering the subcapsular sinus. In clinical practice, the superficial cortex is often referred to simply as the "cortex" of the lymph node, with the corresponding deep cortex referred to as the "paracortex." The lymphoid population of the superficial cortex consists predominantly of B cells, arranged in small primary follicles. The cortical tissue between the follicles is the interfollicular cortex, which contains T cells. After entering the lymph node, B cells home to primary follicles, following a chemokine gradient emitted by follicular dendritic cells (FDCs) [13]. FDCs are specialized antigen-presenting cells which capture and present antigen to B cells, and also serve to maintain the structure of the follicle [14].

When stimulated by antigens presented by FDCs, the B cells within primary follicles begin to proliferate rapidly. As the B cells proliferate, they create specialized structures termed germinal centers within primary follicles, leading to the formation of a secondary follicle [15, 16]. Germinal centers serve as transient, specialized compartments within which the T-cell-dependent immune response occurs [17]. Inside the germinal centers, antigen-stimulated B cells proliferate and undergo somatic hypermutation of their immunoglobulin genes, accompanied by switching of the produced immunoglobulin from IgM or IgD to either IgG, IgA, or IgE [18–21]. Following creation of a germinal center, non-proliferating B cells which were present in the primary follicle are pushed aside and form a ring of concentric layers of lymphocytes around the germinal center, referred to as the mantle zone.

Two main subtypes of proliferating B cell are present in the germinal center – centrocytes and centroblasts [22]. Centroblasts are rapidly proliferating B cells, with large, dark, round nuclei, whereas centrocytes have smaller, cleaved-appearing nuclei. A maturing germinal center displays polarization, with centroblasts and centrocytes clustered at opposite ends of the germinal center to form dark zones and light zones, respectively. Successful B-cell maturation leads to the expression of high-avidity antibodies on the B cell's surface [20]. These cells may subsequently serve as memory cells, or translocate to the medullary cords of the bone marrow to develop into plasma cells. Cells which fail to mature successfully undergo apoptosis and are ingested by so-called tingible-body macrophages, large macrophages containing apoptotic nuclear debris. A subclass of T cells, termed follicular helper T cells, play a critical role in supporting the germinal center reaction and plasmacytic differentiation of B cells (Fig. 5.2) [23].

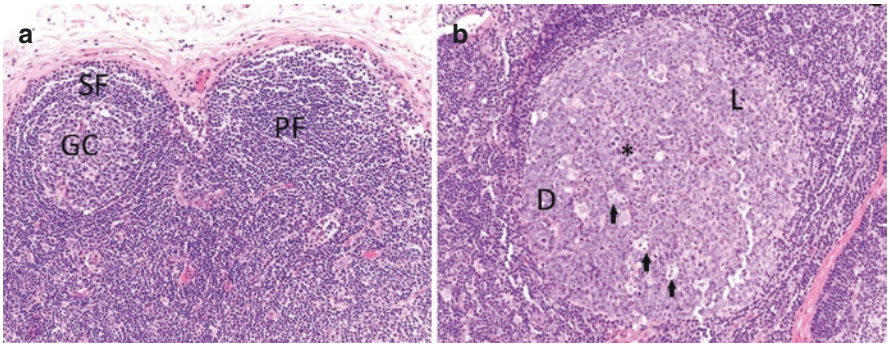

Fig. 5.2 Structures of the superficial cortex. (**a**) An inconspicuous primary follicle (PF) adjacent to a secondary follicle (SF) with a germinal center (GC). (**b**) A reactive germinal center, distinguishable by light microscopy into light (L) and dark (D) zones. Frequent mitoses (*) and tingible-body macrophages (arrows) testify to rapid proliferation within the germinal center, more prominent in the dark zone [22]

5.2 Deep Cortex (Paracortex)

More commonly referred to as the "paracortex" in clinical practice, the deep cortex of the lymph node is predominantly populated by T cells. Similar to the interaction between FDCs and B cells in the superficial cortex, antigens are presented to T cells in the paracortex by interdigitating-type dendritic cells (IDCs). The deep cortical structures of adjacent lobules may fuse and become functionally shared [2].

The deep cortex serves as an important branching point in the vascular supply of the lymph node. After entering the lymph node through the medullary arterioles, blood is carried throughout the deep and superficial cortex by progressively arborizing arterioles to capillary beds, before entering specialized vascular channels called high endothelial venules (HEVs). HEVs are a key component of the deep cortex, consisting of small blood vessels lined by plump specialized endothelial cells. HEVs are the main site at which lymphocytes enter the lymph node from the systemic circulation and control the type of cell, which may enter through the expression of adhesion molecules and chemokines in coordination with adjacent dendritic cells (Fig. 5.3) [24–26].

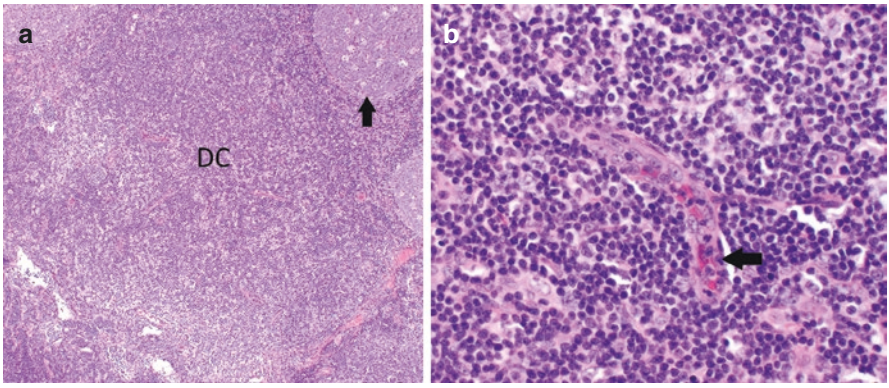

Fig. 5.3 The deep cortex (paracortex). (**a**) A low-power view of an expanded (reactive) deep cortex. Unlike the superficial cortex, distinct lymphoid structures are not typically seen in the deep cortex. Prominent germinal centers in the adjacent superficial cortex (arrow) demonstrate another reactive change in the lymph node. (**b**) A high-endothelial venule (HEV), with dark blue lymphoid cells visible crossing the endothelial lining to enter the lymph node from the peripheral blood (arrow)

5.3 Medulla

The medulla is the third main component of the lymph node and the final region through which lymph travels before exiting the node via the efferent lymphatic vessel at the hilus. The hilus also serves as the site of entry and exit of the lymph node's blood supply, and thus the effective anchoring point of the lymphoid lobules. The medulla can be divided into two main functional components: the medullary cords and medullary sinuses [2].

The medullary cords consist of lymphocytes and plasma cells arranged in cords and ribbons (see Fig. 5.4). Between the cords run the medullary sinuses, which are lined by fibroblastic reticular cells and histiocytes. The sinuses carry lymph draining from the smaller sinuses of the deep cortex toward the efferent lymphatic vessel. The sinuses are lined by fibroblastic reticular cells. The sinuses also contain histiocytes, which often cling to the lining, and remove cells, debris, and antigens from the lymph as it flows through the sinus system. After the lymph has traversed the various zones of the lobule, or circumvented the lobules through the transverse sinuses, it exits the lymph node through the efferent lymphatic vessel [27].

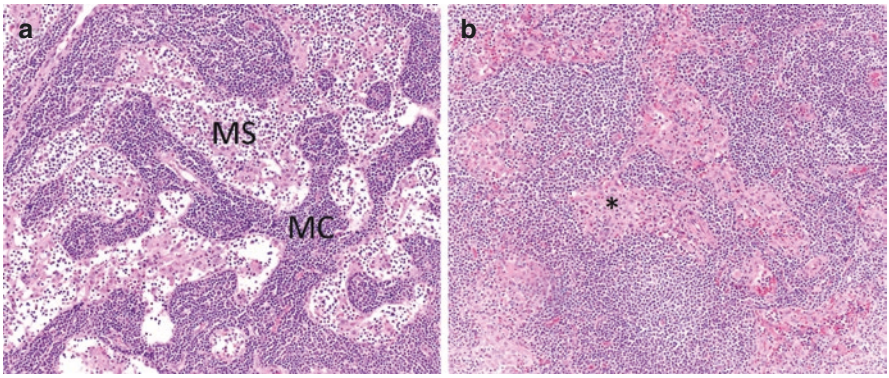

Fig. 5.4 The lymph node medulla. (**a**) The two main structures of the medulla are the medullary sinuses (MS) through which lymph flows, accompanied by histiocytes and lymphocytes exiting the node, and the medullary cords (MC), ribbon-like structures adjacent to the sinuses, containing lymphocytes and plasma cells. (**b**) In reactive conditions, the sinuses (*) may become filled and expanded by histiocytes, an appearance termed "sinus histiocytosis"

5.4 Lymph Node Pathology

As lymph nodes are at the crossroad of many different biological systems, they frequently demonstrate pathologic changes. The following section reviews a set of the most frequent changes observed in lymph nodes, divided into benign and malignant conditions.

5.4.1 Reactive/Benign Conditions

Reactive follicular hyperplasia is one of the most common changes observed in lymph nodes. It is characterized by an increase in the number of secondary follicles, typically accompanied by germinal centers of increased size and variably irregular shapes (Fig. 5.5). Follicular hyperplasia usually occurs in response to an unknown antigen and demonstrates evidence of proliferation in the germinal center, with tingible-body macrophages containing apoptotic cellular debris, well-defined polarization into dark and light zones, and an elevated proliferative index [22]. Follicular hyperplasia may be observed in conjunction with systemic disorders such as rheumatoid arthritis or other conditions which lead to long-standing immunologic stimulation [28].

In contrast to reactive follicular hyperplasia, in which the superficial cortex is expanded, paracortical hyperplasia is characterized by expansion of the deep cortex. This process is similarly etiologically non-specific and may be seen in reaction to viral infections, autoimmune processes, or nearby malignancies [29]. Prominent paracortical hyperplasia may also be seen in lymph nodes draining regions of chronically irritated skin, wherein the expanded T-cell population is accompanied by increased histiocytes, IDCs, and Langerhans cells, a pattern of findings termed "dermatopathic lymphadenitis" [30].

Sinus histiocytosis is a common and etiologically non-specific finding observed in lymph nodes, which is caused by the filling and expansion of sinuses by histiocytes. It may often be observed in chronically irritated lymph nodes, especially those of the mediastinum which are exposed to inhaled antigens, but may also be seen in other contexts, such as in nodes draining tumors [22]. An increased quantity of histiocytes may also be observed in lymph nodes draining prosthetic implants, or in conditions such as histiocytic storage disorders, Whipple's disease, or sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) [31–34].

Most non-reactive conditions do not limit themselves to a particular region of the lymph node. For example, granulomatous diseases of the lymph node typically do not display a zonal predilection. While a specific etiology or infectious agent is often not identifiable in these cases, granuloma formation may be seen in response to a wide variety of infections. Granulomatous disease is divided into non-necrotizing disease and necrotizing disease, depending on the presence of necrosis within granulomas. One of the best-known diseases causing a non-necrotizing granulomatous lymphadenitis is sarcoidosis, which is characterized by well-formed epithelioid granulomas, often surrounded by a small rim of fibrosis. Necrotizing granulomatous disease is typically associated with infection, with the most common causes being mycobacterial or fungal infection. Bacterial infections, such as cat-scratch disease, may also cause necrotizing granulomas (Fig. 5.6) [22].

Several diseases may lead to expansion of many compartments of the lymph node. For example, IgG4-related disease may yield a fibro-inflammatory pseudotumor, as at other anatomic locations, but may also present with a wide range of hyperplastic changes in different compartments of the node [35]. Finally, several disorders may display large areas of necrosis within the lymph node, such as Kikuchi's lymphadenitis, systemic lupus erythematosus, and viral lymphadenitis [36]. Viral lymphadenitis may also yield diffuse changes in the lymph node parenchyma and prominent reactive changes in lymphoid cells, which may be challenging to differentiate from lymphoma.

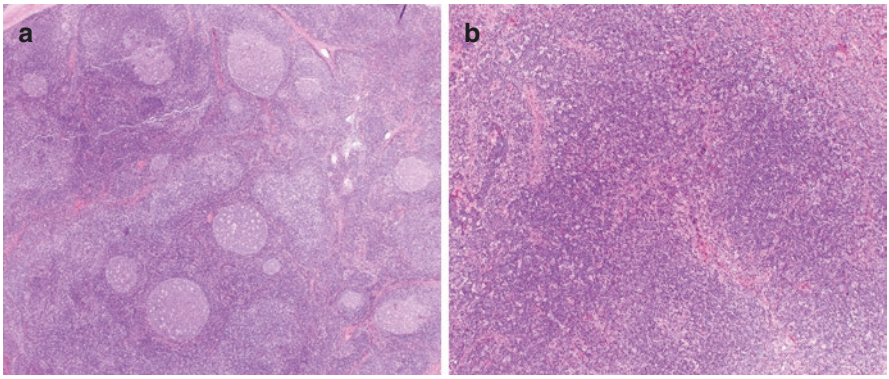

Fig. 5.5 Reactive changes in the lymph node. (**a**) Reactive follicular hyperplasia is characterized by an increased in number and size of follicles, often with irregular germinal center outlines. (**b**) Reactive paracortical hyperplasia does not generate distinct structures, and it appears as a relative increase in the prominence of the deep cortical (paracortical) compartment. The mottled appearance of the deep cortex is due to the mixed inflammatory cell population

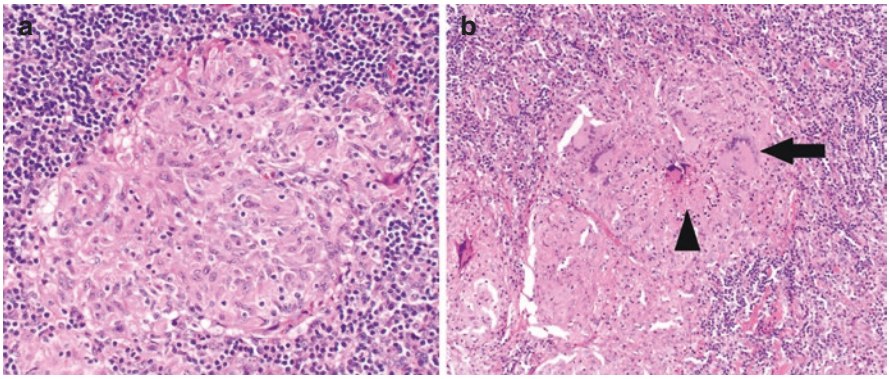

Fig. 5.6 Granulomatous lymphadenitis. Non-necrotizing, well-formed epithelioid granulomas are seen in sarcoidosis (**a**). With infectious etiologies (**b**), ill-defined foci of necrosis may be seen in the center of granulomas (arrowhead). In this patient with tuberculosis, horseshoe-shaped Langhans giant cells (arrow) are also present

5.4.2 Metastatic Disease

The presence of lymph node metastases is a key prognostic factor for many malignancies, and it is a key indicator of tumor aggressiveness [37]. As such, it is also a strong predictor of survival, and it is an important parameter used when determining disease stage and treatment options [38]. While lymphatic spread is observed relatively frequently in epithelial-derived malignancies (carcinomas), it is significantly less common in mesenchymal-derived malignancies (sarcomas) [39].

The presence of lymph node metastases is evidence of a fascinating interaction between the tumor and the lymphatic system. Tumor cells access small lymphatic vessels, which are simple endothelial-lined tubes without protective smooth muscle coats and only intermittent basement membranes [40], and from there travel through the subsequent lymphatic chain to arrive first in the nearest lymph node (the sentinel lymph node) [41], and then on through the subsequent nodes to re-enter the systemic circulation [42]. However, it has long been understood that metastases require an appropriate microenvironment to support them (the "seed and soil" theory, first proposed in the late nineteenth century) [43, 44]. Recent work has shown the extent to which the presence of an upstream tumor can modify downstream lymph nodes to prepare for metastases, such as by tumor-driven stimulation of lymphangiogenesis to significantly increase the flow of lymph through a node [45–47], tumor cells following chemokine signals to enter a lymph node [38, 48], and alteration of the mRNA profiles expressed in lymphatic endothelial cells [49].

When lymphatic involvement is present, the tumor will typically metastasize to a lymph node in a sequential fashion, first invading peritumoral lymphatics, and then spreading from node to node along the lymphatic channel. Metastases are often initially identified within or adjacent to the subcapsular sinus, the point of entry into the lymph node. Tumors may demonstrate characteristic morphologic features of

their primary tumors, such as the papillary growth pattern and intranuclear inclusions of papillary thyroid carcinoma (Fig. 5.7), or the prominent cherry-red nucleoli of melanoma. However, tumor metastases present within a lymph node may often be poorly differentiated and challenging to diagnose on morphologic features alone. In the absence of characteristic histologic features, immunohistochemistry is often helpful in confirming the primary site of the tumor (see Table 5.1 for a list of commonly-used immunostains in metastatic disease).

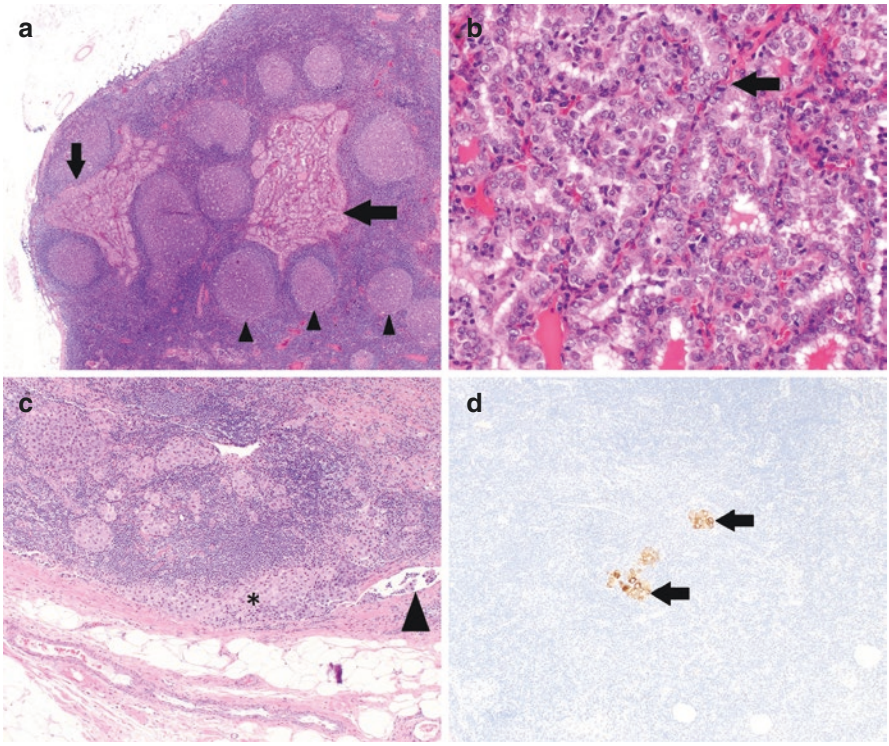

Fig. 5.7 Metastatic disease involving lymph nodes. Identification of the primary location of metastatic disease requires evaluation for characteristic histologic features. In this example (**a** and **b**), the cellular morphology and architecture is characteristic of papillary thyroid carcinoma, with a papillary growth pattern (arrow demonstrates a fibrovascular core within a papilla) and nuclear clearing, grooves, and pseudoinclusions. Note the reactive follicular hyperplasia (arrowheads) adjacent to the metastases (arrows) (**a**). Metastatic disease is often first identified in the subcapsular sinus, where the malignant cells first enter the lymph node. In this example (**c**), the subcapsular sinus (*) is distended by metastatic breast carcinoma, with malignant cells floating in less involved parts of the sinus (arrowhead). Immunohistochemistry may be helpful in identifying inconspicuous metastases (**d**), with a pankeratin stain highlighting scattered metastatic breast carcinoma cells (arrows)

Table 5.1 Common immunohistochemical markers examined in lymph node metastases

Stain	Significance if positive in metastatic tumor cells
Pankeratin	Epithelial origin (carcinoma)
Cytokeratin 7	Upper gastrointestinal tract, breast, lung
Cytokeratin 20	Lower gastrointestinal tract (colon)
TTF1	Thyroid, lung (adenocarcinoma)
PAX8	Müllerian tract, renal
CDX2	Gastrointestinal tract
P63	Urothelial, lung (squamous cell carcinoma)
NKX3.1	Prostate
PSA	Prostate
PSAP	Prostate
S100	Melanoma
MART-1/Melan-A	Melanoma
HMB45	Melanoma
MiTF	Melanoma

5.4.3 Hematolymphoid Neoplasia

As lymphoid organs, the lymph nodes may become also be involved by a wide range of hematolymphoid neoplasms, especially lymphomas. Lymphomas may be of B- or T-cell origin, with B-cell lymphomas further divided into Hodgkin lymphomas and non-Hodgkin lymphomas [50].

Hodgkin lymphomas are characterized by a combination of scattered malignant B cells in a background of a prominent reactive inflammatory response, leading to prominent lymphadenopathy. The two main categories of Hodgkin lymphoma are classic Hodgkin lymphoma, further subclassified by the background inflammatory component, and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). Although NLPHL displays the same overall features as classical Hodgkin lymphoma, the malignant cells of NLPHL (LP cells) have a distinct genetic and immunohistochemical profile from Reed-Sternberg cells – the malignant cells of classic Hodgkin lymphoma (Fig. 5.8) [51].

Non-Hodgkin lymphomas consist of a diffuse infiltrate of abnormal neoplastic B cells. Multiple distinct entities are defined based on cell morphology, genetic abnormalities, and immunophenotype (see Table 5.2 for a list of common immunostains used in evaluating hematolymphoid tissue).

Common examples of low-grade NHLs include chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), which leads to diffuse effacement of lymph node architecture by small, mature lymphoid cells and occasional larger cells (prolymphoblasts) with characteristic CD5 and CD23 positivity, or mantle cell lymphoma, whose small CD5-positive cells may mimic those are SLL, but are distinguished by MCL's characteristic t(11;14)(q13;q32) translocation, which forces

overexpression of cyclin D1 [52]. Overexpression of SOX11 is also observed in the majority of mantle cell lymphomas [53].

Follicular lymphoma (FL) is another common NHL, characterized by a proliferation of relatively uniform neoplastic follicles. In most cases of FL, the cells of the neoplastic germinal center contain a t(14;18) rearrangement which places the anti-apoptotic *BCL2* gene under the *IGH* promoter, protecting the neoplastic cells from apoptosis. Most cases of FL are low grade, but as the grade increases the absolute and relative quantity of centroblasts in the follicles increases, and the follicular architecture tends to give way to a diffuse growth pattern. The highest grade of FL overlaps with diffuse large B-cell lymphoma (Fig. 5.9).

More high-grade NHLs include Burkitt lymphoma (BL), which is a highly aggressive B-cell lymphoma with three distinct clinical variants: endemic BL, which occurs most commonly in equatorial Africa and is associated with Epstein-Barr virus infection [54, 55]; sporadic BL, which occurs in immunocompetent patients in developed countries; and immunodeficiency-associated BL, which is most commonly identified in patients with HIV. Histologically, the different clinical variants are indistinguishable, with a diffuse infiltrate of medium-sized lymphoid cells demonstrating extremely high proliferative activity, and frequent macrophages consuming apoptotic debris to yield a "starry sky" appearance [56]. Translocations involving *MYC* are characteristic of BL, most commonly yielding a t(8;14) rearrangement (Fig. 5.10) [57].

Diffuse large B-cell lymphoma (DLBCL) is a biologically heterogeneous group of aggressive B-cell lymphomas, and it is the most common NHL worldwide [58]. Histologically, DLBCL is defined by a diffuse infiltrate of neoplastic B cells with large nuclei, with a wide variety of mutations and translocations described. Gene expression profiling has traditionally allowed for subdivision of DLBCL into two groups based on the resemblance of tumor cell profiles to germinal center B cells or activated B cells [59], although recent work has led to the identification of at least four different subtypes based on shared genomic abnormalities [60].

Other B-cell neoplasms which may involve lymph nodes include lymphoplasmacytic lymphomas or plasma cell neoplasms. T-cell and natural killer (NK)-cell neoplasms may similarly involve lymph nodes, but they are significantly less frequent than those discussed above.

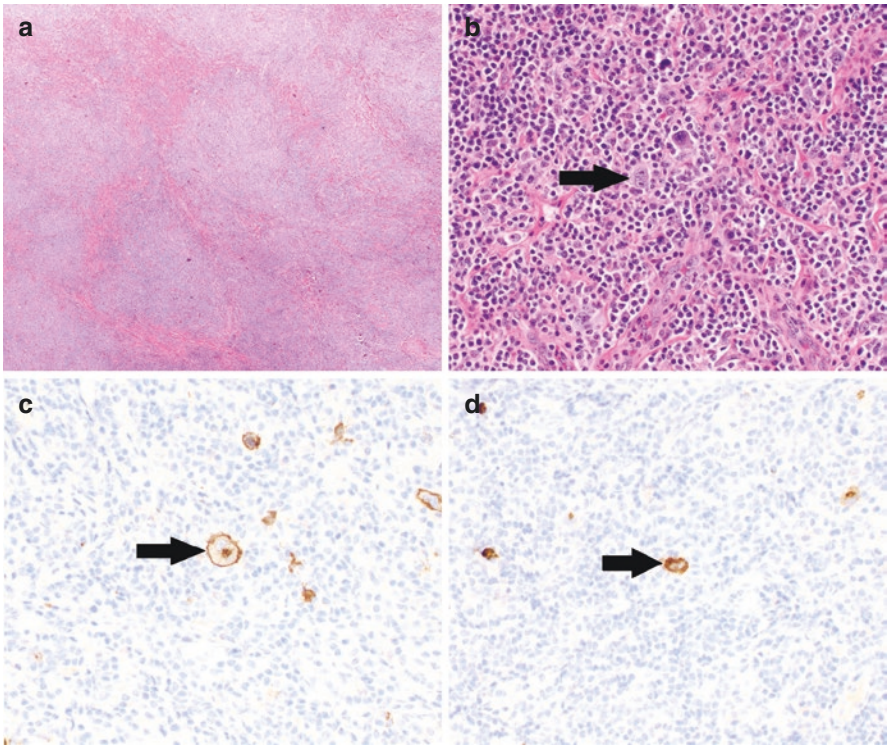

Fig. 5.8 Classical Hodgkin lymphoma, nodular sclerosis subtype. (**a**) This variant of Hodgkin lymphoma is characterized by nodules of inflammation surrounded by dense bands of fibrosis. (**b**) Like other subtypes of classical Hodgkin lymphoma, the malignant cell in the nodular sclerosis subtype is the Reed-Sternberg cell (arrow), with its characteristic binucleation and prominent nucleoli. The Reed-Sternberg cell is a crippled B cell, which aberrantly expresses CD30 (**c**) and CD15 (**d**)

Table 5.2 Common hematolymphoid immunohistochemical markers examined in lymph nodes (most common markers indicated by *)

Stain	Indication
CD1a	Langerhans cell
CD2	T cell
CD3	T cell*
CD4	T cell (helper)
CD5	T cell
CD7	T cell
CD8	T cell (cytotoxic/suppressor)
CD10	B cell (germinal center)
CD15	Granulocytic cells, Reed-Sternberg cells
CD20	B cell*
CD21	B cell
CD30	Immunoblasts, Reed-Sternberg cells
CD45	All hematolymphoid cells (except plasma cells)

Table 5.2 (continued)

Stain	Indication
CD68	Histiocytes
CD117	Mast cells
CD138	Plasma cells
PAX5	B cell[a]
BCL1 (Cyclin D1)	Mantle cell lymphoma
BCL2	Follicular lymphoma
BCL6	B cell (germinal center)
Kappa light chain	Assessing B- and plasma-cell clonality
Lambda light chain	Assessing B- and plasma-cell clonality

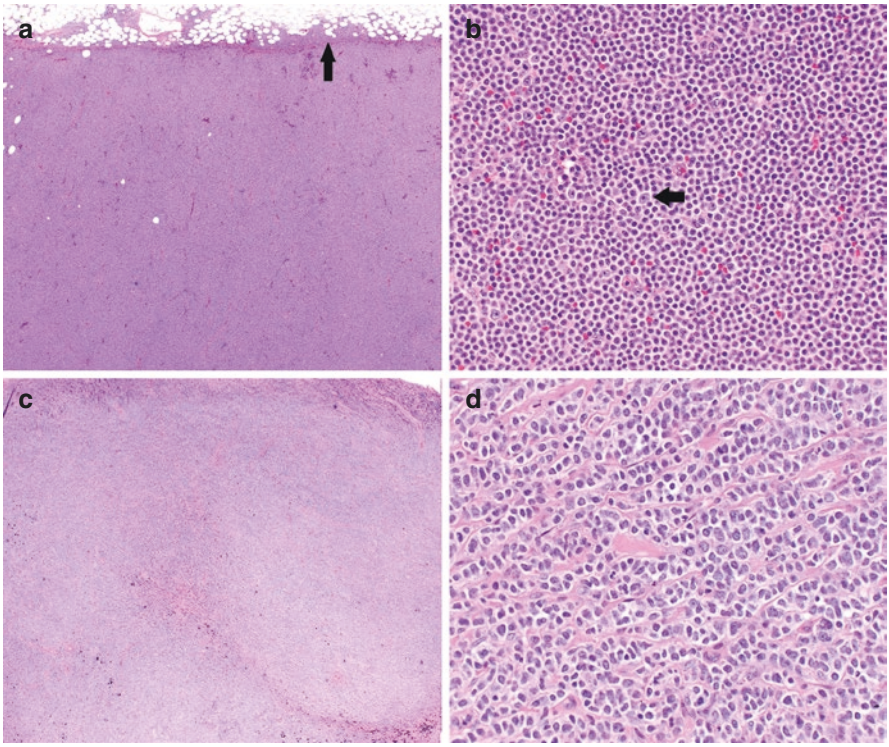

Fig. 5.9 Non-Hodgkin lymphoma. In this lymph node involved by small lymphocytic lymphoma (**a**), the lymph node architecture is completely effaced by a monotonous infiltrate of small lymphoid cells, extending into the adjacent fibroadipose tissue (arrow). On high power (**b**), the cells are small and bland, with occasional large cells (arrow). In diffuse large B-cell lymphoma, the lymph node is similarly effaced (**c**), but the infiltrate consists of large pleomorphic lymphoid cells (**d**)

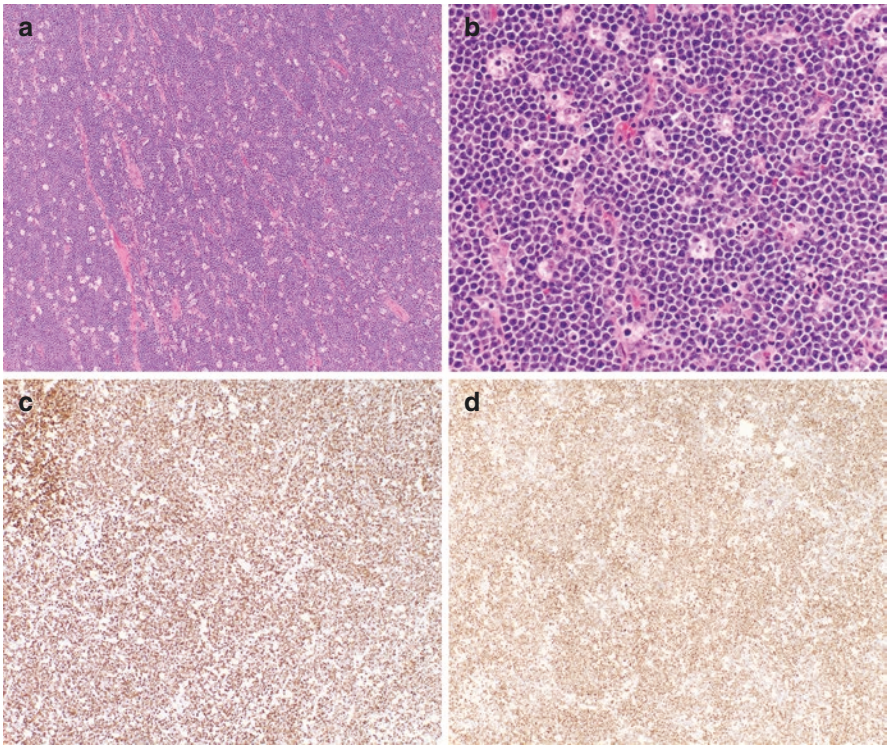

Fig. 5.10 Burkitt lymphoma, endemic subtype. From low power (**a**), Burkitt lymphoma forms a dense sheet of cells. The monotonous infiltrate is broken up by tingible-body macrophages to generate the characteristic "starry-sky" histologic picture. The tumor cells have an extremely high proliferation index, accounting for the extensive tingible-body macrophages (**b**). Burkitt lymphoma is typically driven by rearrangements in c-MYC, overexpressed by IHC in this case (**c**). In situ hybridization for Epstein-Barr virus is strongly positive (**d**), consistent with endemic Burkitt lymphoma

5.5 Note on Immunohistochemistry

Immunohistochemical staining is a simple yet indispensable tool, which allows the pathologist to evaluate expression of specific proteins in a cellular population of interest. Immunohistochemistry (IHC) involves antibodies targeted at proteins present in formalin-fixed paraffin-embedded tissue. After the primary antibody binds its target antigen, a detection system is introduced to highlight the bound primary antibody. Various systems have been developed, but they all share the end goal of bringing a chromogenic substrate into proximity of the primary antibody, followed by activation of the substrate by an enzyme. The chromogen is then detectable by light microscopy, demonstrating expression of the antigen of interest.

By evaluating the immunohistochemical expression profile of a cell, it is possible to subclassify the nature of the cell in far greater detail than by light microscopy alone. This is especially important in lymphoid populations, where the histology of the various subtypes of hematolymphoid cells overlaps to the extent that they are histologically indistinguishable. B and T cells, for example, are identical by light microscopy, but these may be quickly and confidently distinguished by their expression of B-cell markers, such as CD20, or T-cell markers, such as CD3. Table 5.1 includes a list of common immunohistochemical markers used in hematolymphoid populations. Table 5.2 reviews commonly used stains when evaluating metastases.

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