Chapter 9
Lymph Node

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Introduction

Non-neoplastic lymph nodes are often sampled to rule out lymphoproliferative disorders or metastatic malignancy in cases of persistently enlarged lymph nodes and concerning imaging findings. Non-neoplastic lymph nodes are often characterized by an overall intact nodal architecture including intact follicles, preserved capsule, and patent sinuses, as well as preserved normal compartmentalization of T-lymphocytes and B-lymphocytes at different maturing stage that can be demonstrated by immunostains (Fig. 9.1). Benign lymphadenopathy may be due to infectious causes or non-infectious inflammatory/autoimmune causes. Some entities show mainly follicular pattern while others present as interfollicular/parafollicular expansion. Some inflammatory cells may be more prominent in certain entities versus others, for example, eosinophils in Kimura disease and plasma cells in IgG4-related disease. Granulomas raise a wide range of differential diagnosis including infection, foreign body reaction, sarcoidosis, and even lymphoma. Necrosis is a key feature in Kikuchi-Fujimoto disease but also raise the concern of a high-grade malignancy. Solely, these morphological features are insufficient for a final diagnosis and need to be correlated with the clinical features and specific ancillary test results.

Cytopathologic evaluation of an enlarged lymph node, although has its limitation (see Table 9.1), has been accepted as an initial diagnostic method in distinguishing between benign and malignant lymph nodes, particularly when combined with ancillary testing, such as flow cytometry and molecular studies to exclude clonality,

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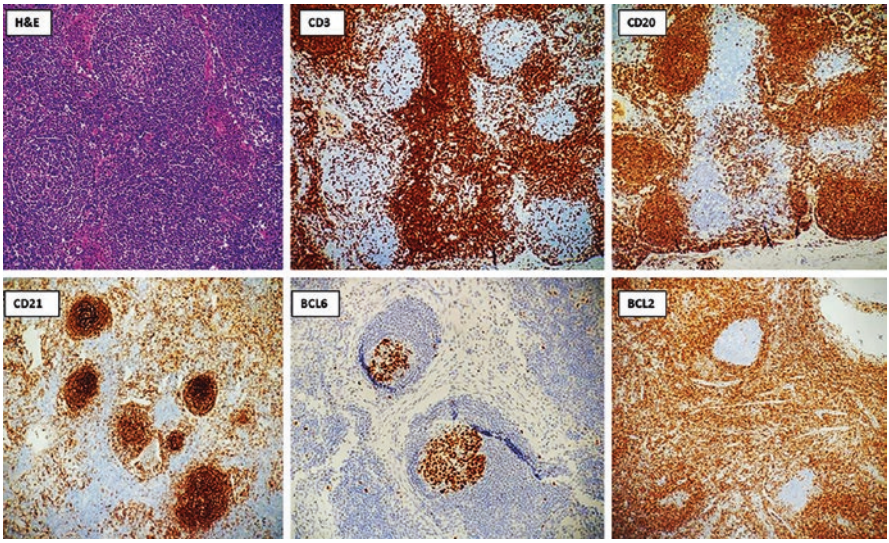

Fig. 9.1 Benign lymph node with intact architecture (40X). H&E section shows reactive germinal centers with well-defined mantle zone and normal distributed B- and T-lymphocytes. CD20 highlights B-cells arranged within CD21-positive follicular dendritic meshwork. CD3 stains properly highlight interfollicular T-cells. Germinal centers are appropriately BCL6 positive and BCL2 negative. BCL2 is also expressed by T-cells and mantle zone B-cells

Table 9.1 Limitation of fine needle aspiration in lymph node evaluation

• Lack key architectural features that distinguish certain benign lymphoid entities particularly Castleman disease, progressive transformation of lymphadenopathy (PTGC) and dermatopathic lymphadenopathy
• Limited sample with a potential risk of missing focal/partial lymphoid lesions, in-situ lymphoid neoplasm, and lymphomas that typically present with low neoplastic cells and a rich inflammatory background such as classic Hodgkin lymphoma
• Potential low cellular yield in fibrotic and necrotic lesions leading to false-negative result

and microbiology culture/staining when infection is suspected. However, further classification of benign lymph nodes is often precluded due to the lack of architecture evaluation. Additionally, one should keep in mind that ancillary testing also has limitations and may be misleading in certain instances, for example, flow cytometry usually shows negative findings in Hodgkin lymphoma, while on the other hand it may detect small clonal B-cells in reactive lymph nodes (see Table 9.2).

In this chapter, we will discuss key cytomorphological features of certain benign lymphoid lesions, the role and choice of ancillary testing to further characterize these lesions, differential diagnosis, and pitfalls. We think it useful to separate the topics that will be covered in this chapter by cause, topography, and key morphologic features (see Table 9.3).

Table 9.2 Limitation and pitfalls of flow cytometry

• A negative flow cytometry result does not exclude lymphoma particularly those with rich inflammatory background and limited neoplastic lymphoid cells
• A negative flow cytometry result may be due to sampling error of focal and partial lesions
• Identification of a monotypic B-cell population does not serve as definitive evidence of B-cell lymphoma, particularly if it is small and identified in tandem with polytypic B-cells. Small monotypic CD5 positive B-cells can be seen in chronic reactive lymph nodes and in situ mantle cell neoplasm, and small monotypic CD10 positive B-cells can be seen in lymph nodes with reactive follicular hyperplasia and in situ follicular neoplasm
• Fibrotic and necrotic samples may result in low yield cellularity leading to a non-diagnostic flow cytometry result

Table. 9.3 Classification of non-neoplastic lymphoid lesions

Infectious	Non-infectious/ reactive disorders
• Ebstein-Barr virus (EBV) (IM or IM-like hyperplasia) • Cytomegalovirus (CMV) • Human immunodeficiency virus (HIV) • Herpes simplex virus (HSV) • Cat-scratch disease • Toxoplasmosis • Mycobacterial infections	***Follicular:*** • Non-specific follicular hyperplasia • Progressive transformation of germinal center (PTGC) • Castleman disease • Kimura disease • SLE lymphadenopathy ***Parafollicular/interfollicular:*** • Dermatopathic lymphadenopathy ***Sinus:*** • Rosai-Dorfman disease ***Necrotic:*** • Kikuchi-Fujimoto disease ***Fibrotic:*** • IgG4-related lymphadenopathy ***Granulomatous:*** • Sarcoidosis

EBV Lymphadenitis (Infectious Mononucleosis)

The classic cases of infectious mononucleosis (IM) are associated with EBV, a member of the *Herpesviridae* family (HHV-4). Patients with IM will often present with typical symptoms, such as sore throat, fever, splenomegaly, and cervical or generalized lymphadenopathy [1]. To reach a proper diagnosis, clinicians will often correlate with cardinal laboratory findings, including leukocytosis, circulating atypical/reactive lymphocytes (Downey cells), a positive Monospot test and/or the presence of circulating antibodies by serology [2, 3]. Therefore, a lymph node biopsy is generally not needed. In fact, it is often discouraged as the histomorphologic features can easily mimic a neoplastic process. It is only when the patient presents with atypical signs and symptoms do healthcare professionals elect to perform a biopsy [4, 5].

Histological Findings:

Microscopically, the disease typically shows subtotal effacement of normal lymph node architecture, reactive follicular hyperplasia, and paracortical expansion mostly by a "polymorphous" B-cell infiltrate composed of immunoblasts, plasma cells, plasmacytoid B-cells, and small to medium sized B-cells [6, 7]. Focal necrosis is not an uncommon finding. Some of these features might be notably more prominent or exaggerated in immunocompromised individuals.

Cytological Findings

Lymph node aspirates will often contain small to medium sized lymphocytes mixed with a variable number of immunoblasts. Early in the disease course, immunoblasts might be scarce and difficult to detect. With more advanced stages of the disease, the immunoblast population becomes more visible and larger Reed-Sternberg like immunoblasts may start to appear (Fig. 9.2a). Although it is exceedingly rare to find multi/binucleated immunoblasts that would mimic the characteristic Reed-Sternberg cells seen in Classic Hodgkin Lymphoma (Fig. 9.2b) [8].

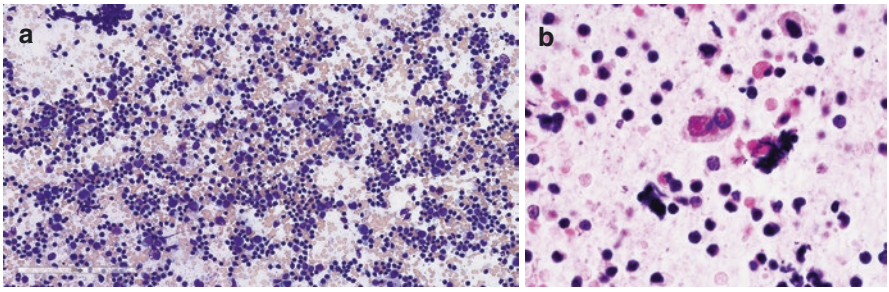

Fig. 9.2 EBV infection with immunoblasts: (**a**) Cytology smear (diff-quick stain 60X) demonstrating a mixture of variably sized cells including small lymphocytes, plasma cells, and large immunoblasts. (**b**) Cytology cell block section (H&E, 100X) showing typical Reed-Sternberg Hodgkin cells (binucleated with prominent red cherry nucleoli)

Differential Diagnosis:

Classic Hodgkin Lymphoma (CHL)

As mentioned above, IM can mimic CHL, especially when there are large Hodgkin-like immunoblasts. In such cases, the following features might help in supporting one versus the other. Nevertheless, definitive diagnosis can only be made on adequate histological sections.

- In contrast to CHL, reactive immunoblasts are CD45 positive and often retain B-cell markers expression including CD20 and strong PAX5. Reactive immunoblasts are negative for CD15 and may show variable staining with CD30. In contrast, Hodgkin cells show strong staining with CD30, partially or completely loss of B-cell markers expression and may or may not show CD15 co-expression.
- EBV (Epstein-Barr Virus) status can be determined by immunohistochemistry or in situ hybridization and could be positive in both CHL and EBV lymphadenitis. However, it is worth noting that EBV positivity tends to be in the small and large cells in IM (as opposed to only Hodgkin cells in CHL).

Other Viral-Induced Lymphadenitis

Alternative causes of viral lymphadenitis, HSV, CMV, and early HIV infections, share a lot of histologic and cytomorphologic features with IM; including having a mixed population of variably sized lymphocytes, immunoblasts, and histiocytes. In these situations, serological testing becomes necessary to make the diagnosis.

CMV Lymphadenitis

Like EBV, CMV is a member of the *Herpesviridae* family (HHV-5) and can cause infections in both immunocompetent and immunocompromised patients [9]. Healthy adult hosts are usually either asymptomatic or have an IM-like disease, whereas immunosuppressed hosts can experience a broad spectrum of disease manifestations, ranging from generalized constitutional symptoms to severe and potentially life-threatening infections [10]. In the vast majority of cases, performing a lymph node biopsy is deemed unnecessary and often avoided [11].

Histological Findings

The histomorphologic features of CMV lymphadenitis have been well documented [12, 13] and microscopic examination typically shows follicular hyperplasia, monocytoid B-cell proliferation, prominent vasculature, and paracortical expansion. These changes are parallel to those seen in other viral infections. Immunoblasts are also readily visible with some even resembling Reed-Sternberg cells.

Cytological Findings

Lymph node and fluid aspirate smears can show a mixture of small lymphocytes and proliferating immunoblasts as well as the distinctive viral cytopathic change seen in some of the infected cells; the so-called owl-eye eosinophilic inclusion body surrounded by a clear halo [14]. A CMV immunohistochemical stain or in situ hybridization may be used to highlight those intranuclear inclusions when necessary [15].

Differential Diagnosis

Infectious Mononucleosis (IM)

As mentioned above CMV lymphadenitis can resemble IM both clinically and microscopically, but IM is different in that:

- Laboratory testing will yield positive results for serum EBV IgM and heterophilic antibodies, especially in the acute phase.
- In situ hybridization for EBV-encoded RNA (EBER) will be positive.
- Will be negative for CMV (by in situ hybridization or immunohistochemistry).
- Will not have the characteristic “owl-eye” inclusion bodies.

HSV Lymphadenitis

Follicular hyperplasia is often present in HSV, and lymph nodes can show prominent monocytoid B-cell hyperplasia as well as extensive necrosis (similar to CMV lymphadenitis). Although the following features of HSV lymphadenitis will be helpful in making the distinction:

- Large multinucleated cells and chromatin margination.
- Nuclear molding (best appreciated by cytology).

- Ground-glass eosinophilic intranuclear inclusion bodies (Cowdry A).
- Positive serological testing for HSV.
- No "owl-eye" inclusion bodies.

Cat-Scratch Disease

Cat-scratch disease is a self-limited infection caused by facultative-intracellular, Gram-negative bacteria, *Bartonella henselae.* As the name implies, the disease is transmitted via asymptomatic feline carriers (primarily cats), usually after a scratch or a bite. In most instances, patients are younger than 18 years of age and typically present with tender lymphadenopathy localized to axillary, neck, or inguinal regions, which may be associated with mild constitutional symptoms, such as fever, fatigue, or generalized joint pains [16, 17]. The infection usually spontaneously resolves within 2 months in immunocompetent hosts. Although treatment may be indicated in more persistent cases or in patients with suppressed immune response [16].

Histological Findings

Initially, lymph nodes show proliferation of monocytoid cells and neutrophils as well as the characteristic amorphous eosinophilic deposits within germinal centers. As the inflammation progresses, small foci of necrosis start to appear, which eventually enlarge and coalesce to form necrotizing granulomas "*Stellate granulomas*" [18]. An immmunohistochemical stain or a modified silver stain (Warthin-Starry) is often used to detect *B. henselae*, with some studies suggesting combining the two methods for a higher sensitivity [19].

Cytological Findings

Smears show aggregates of epithelioid histiocytes with many interspersed neutrophils, and a varying number of medium sized monocytoid lymphocytes (Fig. 9.3). The number of neutrophils can be so high that it obscures the smaller granulomas [20]. These findings can be seen in other causes of granulomatous lymphadenitis (e.g., tuberculosis), which is why cytologic diagnosis must be suggestive at best, or confirmatory in cases with tangible clinical suspicion.

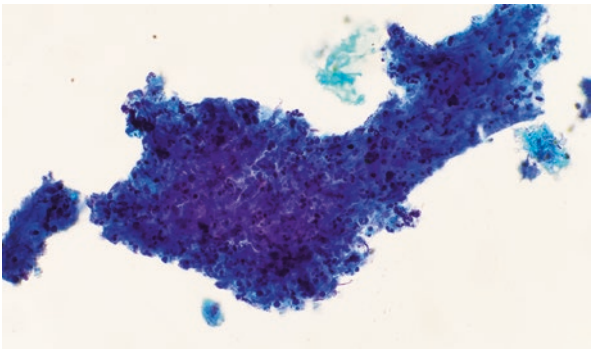

Fig. 9.3 Suppurative granuloma in cat-scratch infection: Cytology smear (Papanicolaou (PAP) stain 60X) showing granuloma with necrosis and numerous neutrophils

Differential Diagnosis

Mycobacterial Lymphadenitis

Some of the features that would support the diagnosis of mycobacterial lymphadenitis over cat-scratch disease are the following:

- Clinically, patients will often present with bilateral hilar lymphadenopathy, respiratory symptoms, and might have cavitary pulmonary lesions.
- Mycobacterial infections will cause caseating (not stellate) granulomas.
- Acid-fast staining may highlight the causative microorganism.
- Tuberculin skin testing, interferon gamma release assays (IGRA), and PCR molecular testing can be used for identification.

Fungal Lymphadenitis

The following are some helpful key features:

- Fungal elements, such as hyphae and yeast forms, may be appreciated on routine H&E stains.
- Definitive identification with culture study is necessary.
- GMS or PAS stains can be used to highlight the causative agent.

Classic Hodgkin Lymphoma (CHL)

Granulomas can occasionally be seen in CHL, particularly the mixed cellularity subtype. The granulomatous inflammation might be so exuberant that it may mask the neoplastic process and be misinterpreted as an infectious one [21]. In such cases, the following features help distinguish it from cat-scratch disease:

- The presence of Hodgkin/Reed-Sternberg cells with the classic immunophenotype.
- Mixed inflammatory background, including eosinophils and plasma cells.

Follicular Hyperplasia (FH) with Progressive Transformation of Germinal Center (PTGC)

PTGC is a benign reactive lymphoid lesion of unclear etiology commonly identified in the head and neck region. PTGC is usually self-resolved but may last more than 6 months.

Histological Findings

PTGC is characterized by large germinal centers with ill-defined mantle zone and dense small mantle B-cells occupying and disrupting the germinal centers. Florid reactive follicular hyperplasia is often present. Such morphology may resemble follicular lymphoma (FL) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL); therefore, both should be excluded. Of note, a small percentage PTGC are proceeded by or concomitantly associated with NLPHL.

Cytological Findings

The diagnosis of PTGC cannot be made in fine needle aspiration samples as it requires the identification of key architectural features described above. The cytology smear of a lymph node with florid follicular hyperplasia with or without PTGC is usually cellular with dense lymphoid population thus often triaged for flow cytometry when evaluated on site. The lymphocytes are heterogenous and include small mature lymphocytes with scant cytoplasm and dense nuclear chromatin, large centroblasts with vesicular nuclear chromatin and multiple membrane bound nucleoli, and immunoblasts with prominent central nucleoli. Tingible-body macrophages and fragments of follicular dendritic meshwork are frequently present (Fig. 9.4). Follicular dendritic cells (FDCs) show delicate nuclear membranes, vesicular nuclear chromatin, and ill-defined cytoplasmic membranes.

Differential Diagnosis

Mainly includes B-cell lymphoma. Features that distinguish FH/PTGC from B-cell lymphoma include the following:

- Heterogenous lymphoid population supports FH/PTGC, while a monomorphic lymphoid population, particularly if it constitutes of large B-cells, is concerning for large B-cell lymphoma. It is important to keep in mind that FL may not present as a monomorphic smear, and it usually shows a mixture of small centrocytes

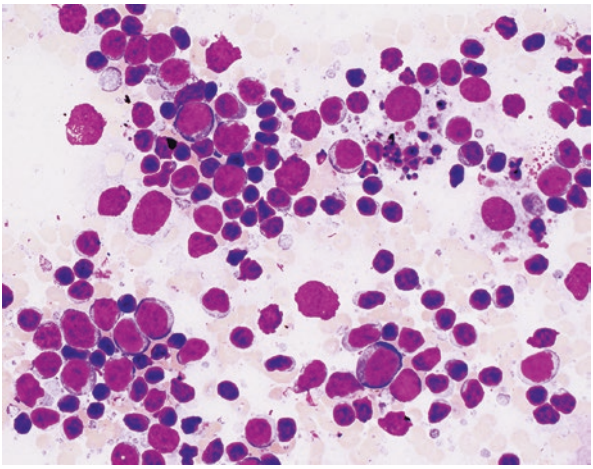

Fig. 9.4 Florid follicular hyperplasia with frequent centroblasts: Cytology smear (diff-quick stain 60X) showing mixture of large centroblasts and small centrocytes and tingible body macrophages

and large centroblasts in variable ratios depending on the cytological grade. Tingible body macrophages although less frequent, can be seen in FL.

- Flow cytometry in FH/PTGC show polytypic B-cells. However, one should always consider the limitations and pitfalls of flow cytometry (see Table 9.2).

Castleman Disease

Castleman Disease (CD) is a lymphoproliferative disorder that usually affects adults in the third decade of life. The etiology is still largely unknown, but is believed to be related to immune dysregulation, genetic factors, or infections in some cases. CD is divided into two types: unicentric (UCD) and multicentric (MCD). The extent of disease manifestation varies depending on the type. Patients with UCD are mostly asymptomatic or have localized lymphadenopathy found incidentally by imaging. Whereas the MCD type will often be found in immunocompromised (IC)/HIV-infected patients driven by HHV8 infection. MCD also can be HHV8 negative classified as "idiopathic" or associated with rare multisystemic diseases (i.e., POEMS syndrome, TAFRO syndrome) [22]. Patients with MCD present with generalized lymphadenopathy, and severe systemic features caused by high cytokine levels notably IL6. Fever, night sweats, pleural effusions, leukocytosis, and weight loss are common clinical features [23].

Histological Findings

CD is histologically divided into the "hyaline vascular" and the "mixed/plasmacytic" variants. The hyaline vascular CD variant is more frequent in UCD and shows many atrophic follicles with concentric layering of the mantle zones, commonly referred to as the "onion skin" appearance. The germinal center in these regressed

follicles will often be penetrated by a hyalinized blood vessel that if tangentially cut, will demonstrate the characteristic "lollipop" sign. Some follicles will also have two germinal centers, a feature commonly described as "twinning" [24]. Moreover, the interfollicular area will be expanded with high endothelial venules that may obliterate the sinuses. The mixed/plasmacytic variant is more common in MCD and shows a mixture of atrophic and hyperplastic follicles with interfollicular polytypic plasmacytosis. In some cases, particularly those associated with HIV and HHV8 infection, small clusters of HHV8-positive plasmablasts located primarily in the mantle zone can be seen. These plasmablasts are lambda restricted.

Cytological Findings

Findings on aspirate smears are non-specific and may reveal branching or fragmented blood vessels with a variable number of plasma cells in a background of a polymorphous cell population. Low frequency of plasmablasts and immunoblasts can also be seen (Fig. 9.5). The plasmablast are large in sized with abundant

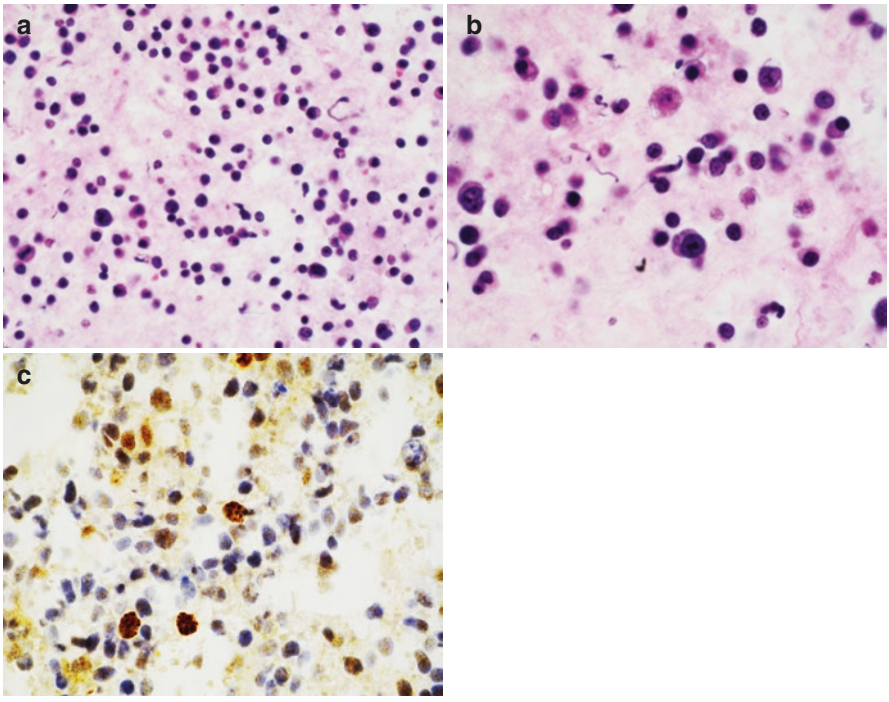

Fig. 9.5 Multicentric Castleman disease in HIV-infected patient: (**a**) Cytology smear (Papanicolaou (PAP) stain 60X) showing a mixture of small lymphocytes, plasma cells, and plasmablasts. (**b**) A large plasmablast with prominent nucleoli. (**c**) Few scattered plasma blasts are positive for HHV8 immunostain with typical nuclear dot-like pattern

basophilic cytoplasm and eccentric nucleus with prominent nucleoli (Fig. 9.5b). The immunoblasts are intermediate to large lymphoid cells with prominent nucleoli. Nonetheless, a lymph node excision is imperative for a certain diagnosis [25, 26].

Differential Diagnosis

HHV8-Positive Plasmablastic Malignancy, Primarily Include Primary Effusion Lymphoma (PEL) and HHV8-Positive Diffuse Large B-Cell Lymphoma (DLBCL)

Clinical features (HIV/IC patient, LAD, systemic disease), inflammatory blood tests (high IL6), and cytological findings (HHV8-positive plasmablasts) are found in PEL, HHV8-DLBCL, and MCD; therefore, the distinction between these entities is often challenging. Features that are in favor of a malignancy are the following:

- HHV8-positive plasmablasts are the prominent population in PEL and HHV8-DLBCL, while they are usually not frequent in multicentric CD specimen (Fig. 9.5c).
- While plasmablasts are lambda restricted in HHV8-DLBCL and MCD; PEL usually lacks surface/cytoplasmic light chain expression (small subset might be kappa restricted). Also, clonality by *IGH* gene rearrangement PCR test is only observed in PEL and HHV8-DLBCL.

Marginal Zone Lymphoma

Low-grade B-cell lymphomas, especially marginal zone lymphoma, can show marked plasmacytic differentiation but will also exhibit the following:

- Evidence of a monotypic and monoclonal B-cell population by flow cytometry, immunohistochemical stains for kappa and lambda light chain, and *IGH* gene rearrangement PCR test.

Systemic Lupus Erythematosis (SLE) lymphadenopathy

SLE as well as other autoimmune-related lymphadenopathies (e.g., rheumatoid arthritis, IgG4-related disease) are often considered in the differential diagnosis of CD, as they can also show prominent plasmacytosis [27]. Performing appropriate serological testing and knowing the patient's clinical presentation is crucial in such cases.

Kimura Disease

Kimura disease (KD) is a rare chronic inflammatory disorder of unknown etiology that involves the subcutaneous tissue and lymph nodes of the head and neck region. The pathogenesis is still poorly understood but is thought to be related to infectious causes although a definite correlation with a pathogen has yet to be identified. Other proposed causes include allergic conditions and various other immune-related phenomena [28]. It predominately occurs in young adult Asian males and presents as subcutaneous nodules in the head and neck area associated with regional lymphadenopathy. Patients may also have renal manifestations [29]. Peripheral blood eosinophilia and elevated serum immunoglobulin E (IgE) levels are essentially always detected [30], but systemic symptoms are not common.

Histological Findings

Microscopic examination often reveals a preserved, although somewhat distorted, lymph node architecture that is characterized by reactive follicular hyperplasia with marked eosinophilia, focally forming eosinophilic microabscesses [31]. The eosinophils can be seen trickling into the germinal centers, which in many cases, can have proteinaceous IgE deposits as well as Warthin-Finkeldey type prokaryocytes [31].

Cytological Findings

When carried out, fine needle aspirations yield a polymorphous cell population including many eosinophils and occasional interspersed Warthin-Finkeldey cells, the giant cells with multiple grape-like clustering of nuclei. Endothelial fragments and fibrinous strands can also be identified [32, 33]. However, establishing a diagnosis solely based on these cytomorphologic features is difficult and a biopsy is always strongly recommended to make a definite diagnosis [34].

Differential Diagnosis

Angiolymphoid Hyperplasia with Eosinophilia (ALHE)

The main differential diagnosis of KD is ALHE, also known as epithelioid hemangioma. Histologically similar although it has distinctive clinical and laboratory findings:

- No racial predilection and patients are predominantly female (as opposed to Asian males in KD).
- Typically presents with superficial skin nodules or papules without lymphadenopathy.

Peripheral eosinophilia and elevated serum IgE levels are not usually detected [35].

Drug Related or Non-Specific Follicular Hyperplasia

Knowing the patient's medication history and correlating it with the onset of lymphadenopathy is always important whenever there is obvious eosinophilia. The possibility of parasitic infections should also be investigated.

Systemic Lupus Erythematosus (SLE) Lymphadenopathy

SLE is a multisystemic autoimmune connective tissue disorder that predominantly affects young females. The etiology of this disease remains unknown, although numerous studies have set forth multiple potential mechanisms; namely those of dysregulation of the innate and/or adaptive immune system [36]. A specific constellation of symptoms, signs, and laboratory findings are required for fulfilling the criteria to diagnose SLE. Patients will have many clinical presentations with varying degrees of severity, ranging from mild fever and joint pains to possibly lethal multi-organ failure. Localized (e.g., cervical) or generalized lymphadenopathy is common in SLE, especially in the setting of high antibody titers [37].

Histological Findings

Histologically, lymph nodes will show abundant polytypic plasma cells and paracortical hyperplasia with varying degrees of coagulative necrosis, especially in the acute phase of the disease. The most specific finding is the presence of Hematoxylin bodies; amorphous basophilic material formed from necrotic nuclei [38]. Another classically identified feature, is when this basophilic material is deposited within the walls of the small blood vessels in the necrotic areas, which is termed the "Azzopardi phenomenon" [39]. It is important to note that some of these histopathologic features might be concealed by the effects of immunosuppressive therapy. Immunophenotypically, plasma cells and B-cells will be polytypic and a predominantly CD8-positive T-cells population will be present. Although not common, EBV has been detected using in situ hybridization in some cases of SLE lymphadenopathy [40].

Cytological Findings

The cytomorphologic appearance of SLE lymphadenopathy is mostly that of non-specific reactive hyperplasia with plasmacytosis, with some plasma cells having cytoplasmic inclusion bodies (Russell bodies). Acellular necrotic debris can also be identified.

Differential Diagnosis

Kikuchi-Fujimoto Disease

The major differential diagnostic consideration is Kikuchi-Fujimoto disease, which can be histologically and immunophenotypically indistinguishable from SLE lymphadenopathy, particularly in the absence of Hematoxylin bodies [41]. Moreover, patient demographics are similar between these two entities and generalized lymphadenopathy can be the first presenting symptom in SLE.

- A well-demarcated wedge-shaped pattern of necrosis is seen more in Kikuchi-Fujimoto disease.
- If present, Hematoxylin bodies and vascular fibrinoid necrosis can help favor SLE lymphadenopathy.
- Fulfilling the diagnostic criteria for SLE, such as detecting anti-dsDNA antibodies and other autoantibodies is necessary to make the distinction.

Other entities that can be considered in the differential diagnosis are IM, cat-scratch disease, and mycobacterial lymphadenitis.

Dermatopathic Lymphadenopathy

This is a distinctive type of lymph node reaction commonly involving inguinal and axillary lymph nodes and associated with chronic skin disorders such as eczema, psoriasis, mycosis fungoides among others. Occasionally, it has been reported in cases with no discernable skin diseases and in unusual sites [42].

Histological Findings

Dermatopathic LAD is mainly characterized by nodal paracortical expansion comprising a mixture of inflammatory cells with variable densities including dendritic cells, macrophages, melanophages, hemosiderin laden macrophages, and

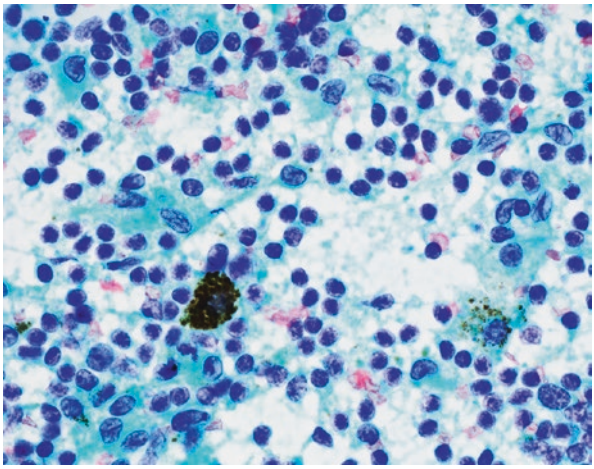

Fig. 9.6 Dermatopathic lymphadenopathy: Cytology smear (Papanicolaou (PAP) stain 60X) showing Langerhans cells with coffee-bean-like nuclei and melanopahges with coarse brown cytoplasmic granules. Eosinophils are not seen

variably-sized lymphocytes. The dendritic cells include mainly Langerhans cells (LCs), interdigitating dendritic cells (IDCs), and plasmacytoid dendritic cells (PDCs). LCs are characterized by moderate amount of vacuolated eosinophilic cytoplasm, ill-defined borders, and vesicular nuclei with twisted/grooved contour (Fig. 9.6). The lymphocytes are mainly small with mature condensed nuclear chromatin and scant cytoplasm. Scattered non-sheeting immunoblasts (large lymphocytes with prominent nucleoli) and atypical intermediate lymphocytes with twisted nuclear contours are also present in limited numbers. Plasma cells and eosinophils are present but usually not prominent.

Cytological Findings

Cytological smears demonstrate non-cohesive and polymorphous inflammatory cell population with similar constituents [43].

The evaluation of nodal architecture (precluded in cytology specimen) is essential to exclude other diagnostic mimickers. Ancillary studies including flow cytometry, immunohistochemical stains, and molecular testing that can be carried out on cytological specimens may help in certain instances.

Differential Diagnosis

Main diagnostic possibilities that come to mind with somewhat similar cytological findings include the following:

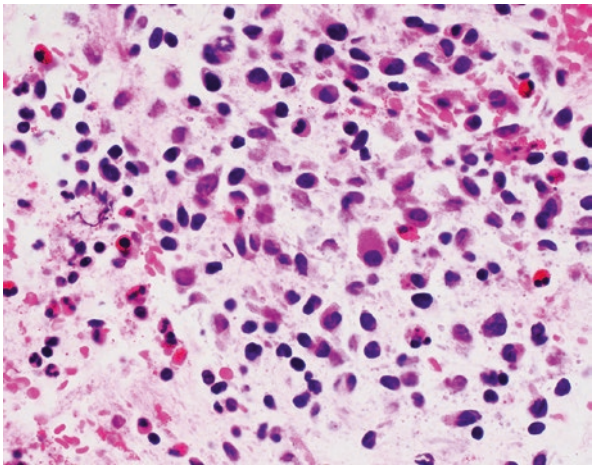

Fig. 9.7 Langerhans cell histiocytosis: Cytology cell block section (H&E, 60X) showing Langerhans cells with coffee-bean-like nuclei and frequent eosinophils

Langerhans Cell Histiocytosis (LCH)

Both dermatopathic LAD and LCH show a prominent population of Langerhans cell histocytes with characteristic coffee bean nuclei expressing S100, CD1a, and langerin immunostains [42]. Features that distinguish LCH from dermatopathic LAD are the following:

- Eosinophils are more prominent in LCH (Fig. 9.7).
- LCH show sinusoidal expansion as opposed to paracortical expansion in dermatopathic LAD (a feature evaluated only in excisional biopsies).
- LCH may harbor BRAF V600E gene mutation (50%) or genes involving mitogen-activated protein (MAP) kinase pathway (35%) [44]. These mutations can be detected by mutational analysis testing (e.g., NGS, pyrosequencing) or immunostain for BRAF V600E mutation. Additionally, strong and diffuse expression of cyclin D1 immunostain supports LCH. Cyclin D1 is a downstream transcription factor of MAPK pathway thus upregulated and overexpressed in LCH [45].

Mycosis Fungoides (MF)

It can be very challenging to distinguish dermatopathic lymphadenopathy from a lymph node that is partially involved by mycosis fungoides/sezary syndrome as both may show atypical intermediate size lymphocytes with irregular/grooved nuclear contours. Ancillary testing including flow cytometry and molecular test for TCR gamma gene rearrangement PCR test is vital in this situation; results that supports mycosis fungoides over dermatopathic LAD are the following:

- Flow cytometry shows distinct T-cell population with phenotypic features characteristic of MF (typically CD4 T-helper cells with major loss of CD7 and CD26). Other less frequent atypical immunoprofile have been reported [46].
- TCR gamma gene rearrangement PCR test show a clonal T-cell peak particularly if identical to peaks previously identified in other samples (e.g., skin and/or blood).

Classic Hodgkin lymphoma

Dermatopathic LAD can harbor frequent large immunoblasts with prominent nucleoli that may raise the concern for Hodgkin lymphoma. The constellation of clinical features, morphology, and the immunoprofile of these large cells may distinguish between these two entities. Features that support classic Hodgkin lymphoma:

- The identification of multi-nucleated large Reed-Sternberg cells is more concerning for CHL.
- CD30 is positive in both immunoblasts and Hodgkin cells; however, aberrant immunostains that support CHL include loss of B-cell markers (CD20, CD79a, OCT2, BOB1), dim PAX5 staining, co-expression of CD15, and lack of CD45.
- Dendritic cells are typically not present in CHL.

Rosai-Dorfman Disease

Rosai-Dorfman disease (RDD), formerly known as sinus histiocytosis with massive lymphadenopathy, is a rare benign histiocytic disorder that has a wide age range but primarily affects children and young adolescents. Patients often present with bilateral cervical lymphadenopathy although other lymph nodes can also be involved. Extranodal disease is common and has been documented in up to 40% of patients [47]. Frequently involved sites include the skin, bone, kidney, and upper respiratory tract. Despite being idiopathic in many cases, the etiology of RDD is thought to be multifactorial, with mutually exclusive *MAP2K1* and *KRAS* mutations found in approximately one third of cases [48].

Histological Findings

In RDD, lymph nodes will have a distorted architecture and markedly distended sinusoids containing large histiocytes with pale eosinophilic cytoplasm. Plasma cells will also be abundant between the sinuses, while eosinophils are scarce if present. Most importantly, histiocytes often exhibit “emperipolesis”; the presence of

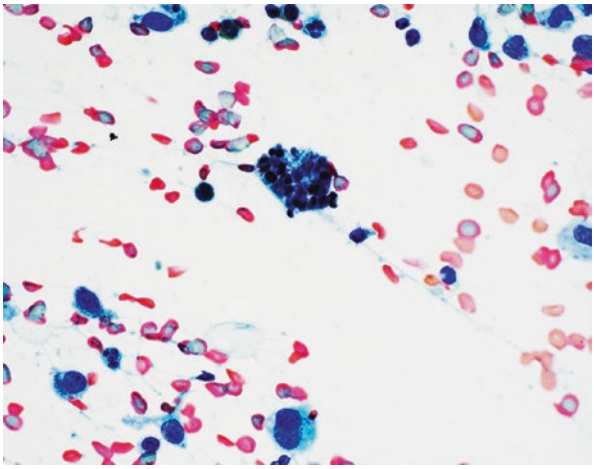

Fig. 9.8 Rosai-Dorfman disease (RDD). Cytology smear (Papanicolaou (PAP) stain 60X) showing a large histiocyte in the middle of the image with emperipolesis (lymphocytes and plasma cells within the cytoplasm borders)

intact small lymphocytes and plasma cells within the cytoplasm [47]. This feature might be inconspicuous in extranodal disease, where prominent stromal fibrosis may also be seen. S100 immunohistochemical stain is positive in the RDD histiocytes and will often demonstrate the emperipolesis phenomenon. In more challenging cases, OCT2 and Cyclin-D1 stains can also be used to highlight the cells.

Cytological Findings

Histiocytes with emperipolesis can also be identified by cytologic examination of RDD cases as the cells will have round nuclei, ample cytoplasm, and contain small viable inflammatory cells (Fig. 9.8). A mixed population composed of small lymphocytes, plasma cells, and immunoblasts can also be seen in the background, typically with no eosinophils [49].

Differential Diagnosis

Langerhans Cell Histiocytosis (LCH)

The main differential diagnosis of RDD is LCH, a neoplastic histiocytic disorder that typically occurs in the bone, skin, and to a much lesser extent, lymph nodes of younger children. In LCH,

- Smears will show a higher cellularity than in RDD and eosinophils are commonly increased in the background (Fig. 9.7) [50].

- The histiocytes have folded nuclei with linear nuclear grooving, and they will be positive for CD1a and Langerin (CD207) stains, which will immunophenotypically distinguish them from RDD histiocytes [51].
- Birbeck granules, which are tennis racket-shaped cytoplasmic organelles, can be observed by electron microscopy. These granules are not seen in RDD.

Erdheim-Chester Disease (ECD)

A rare histiocytic neoplasm that is often multisystemic, ECD can be considered in the differential diagnosis of RDD. Additionally, the two may potentially overlap morphologically and coexist [52]. The following are some of ECD's distinguishing features:

- The presence of touton-type giant cells and prominent fibrosis.
- Classic RDD histiocytes and emperipolesis are not seen.
- Immunophenotypically, the cells will be positive for CD68, CD163, and Factor XIII. While negative for S100 and OCT2.
- The histiocytes will also be negative for CD1a and Langerin (CD207), which will distinguish it from LCH.

Kikuchi-Fujimoto Disease (Histiocytic Necrotizing Lymphadenitis)

Kikuchi-Fujimoto disease (KFD) is a rare and benign self-limiting condition that typically occurs in young women; commonly in those of Asian descent. It often presents with tender cervical lymphadenopathy accompanied by mild fever and night sweats. The etiology is still unknown but it has been suggested to be related to viral or autoimmune-related causes [53] and the pathogenesis is driven by an exaggerated cytotoxic (CD8-positive) T-cell response.

Histological Findings

There are three histologic phases (or patterns) described in KFD that may overlap based on the timing of the lymph node biopsy. In early stages, a mixed population of histiocytes, plasmacytoid dendritic cells (PDCs), and immunoblasts start to proliferate with little to no necrosis. This phase is aptly named the "proliferating" phase. In the "necrotic" phase, a well-demarcated area of necrosis, containing numerous apoptotic bodies, karyorrhectic debris, and scattered fibrin thrombi are

seen. This distinct area of necrosis is arguably the most classic feature of the disease and what most diagnoses rely on. Eventually, it progresses into the "Xanthomatous/foamy cell" phase, where the histiocytes phagocytize the debris and start to align around the periphery of the necrotic areas forming a rim [54, 55]. Immunohistochemical stains, such as CD123 and TCL-1, highlight the PDCs well, and flow cytometry can also be helpful by identifying the CD123-positive PDC population.

Cytological Findings

Fine needle aspiration samples obtained from patients with KFD will have distinctive cytomorphologic features that can be diagnostic in the proper clinical context. Smears often show a gritty background full of necrotic matter and histiocytes with eccentric and crescentic nuclei, with some having phagocytized karyorrhectic debris [56]. Tingle-body macrophages are larger and have round nuclei, which can help distinguish them from the characteristic histiocytes seen in KFD. Other cell populations are also seen, including plasmacytoid monocytes and immunoblasts [57]. Although there will be hardly any neutrophils or plasma cells present.

Differential Diagnosis

As previously mentioned, SLE lymphadenopathy is the main entity to be excluded when considering the diagnosis of KFD (see section "SLE Lymphadenopathy"). Other causes of necrotizing lymphadenopathy can also be considered in the differential diagnosis, including herpes simplex lymphadenitis, IM, cat-scratch disease, mycobacterial or fungal infections.

IgG4-Related Lymphadenopathy

IgG4-related disease is an immune-mediated inflammation associated with various degrees of fibrosis and IGG4-positive plasmacytosis clinically presenting as an insidious tumor [58]. Clinical symptoms are mostly related to the obliterative effect of fibrosis, the organ involved, and the extent of organ damage. Commonly, it is asymptomatic and identified incidentally. Sites typically affected are the salivary glands, orbits, pancreas, retroperitoneum, lacrimal glands, kidneys, lungs, aorta, and meninges. IgG4-related lymphadenopathy usually occurs along with the extranodal disease and infrequently by itself.

Histological Findings

Histologically, lymph nodes involved by IgG4-related disease show variable histological patterns that mimic other entities such as CD, PTGC, non-specific follicular hyperplasia, inflammatory pseudotumor, and RDD [59, 60]. A common finding among these histological variants is the expansion of IgG4-positive plasma cells with an IgG4/IgG ratio exceeding 40%. Eosinophils are also commonly found in IgG4-related LAD and may further support this entity over its mimickers. Nevertheless, the diagnosis of IgG4-related disease cannot be rendered based on morphology alone.

Cytological Findings

Cytologically, the fine needle aspiration smears may show an expanded plasma cell population with a variable cellular yield depending on the density of fibrosis in the sampled lesion. This finding is non-specific at all; however, it may raise some diagnostic consideration and trigger further work up such as flow cytometry to rule out clonal B-cells and plasma cells, immunohistochemical stains, for example, IgG4, Treponemal, HHV8, and kappa and lambda light chain immunostains or in situ hybridization (ISH).

Differential Diagnosis

Elevated IgG4-positive plasma cells in a cytological and surgical lymph node specimen is a non-specific finding and has been reported in many other entities, such as marginal zone lymphoma, RDD, MCD, infections, among others [61]. Features that support IgG4-related disease are as follows:

- The presence of typical extranodal manifestation of IgG4-related disease.
- The exclusion of other entities associated with elevated IgG4-positive plasma cells as mentioned above.
- The rapid and sustained response to glucocorticoid therapy.

Features that support marginal zone lymphoma is the identification of monotypic B-cell and plasma cell populations by flow cytometry, or kappa and lambda light chain immunostains or in situ hybridization, or evidence of clonality by *IGH* gene rearrangement PCR testing. Features that support MCD is the identification of positive HHV8-positive plasmablasts in HIV and immunosuppressed patients, elevated IL6 and C-reactive protein (CRP) in serum, and severe systemic inflammatory

symptoms that are typically not seen in IgG4-related disease. Features that support RDD is the identification of histiocytes with emperipolesis with expression of S100, OCT2, and Cyclin-D1 immunostains [62].

Sarcoidosis

Sarcoidosis is a multisystemic granulomatous disease that more commonly affects African-American females. It is primarily immune mediated, but the exact etiology is unknown. Patients present with bilateral hilar lymphadenopathy and will frequently have pulmonary manifestations, often as interstitial lung disease. However, some patients may be asymptomatic with the enlarged lymph nodes being incidentally found on routine imaging (e.g., chest X-ray) [63]. Hypercalcemia, elevated angiotensin-converting enzyme (ACE) serum levels, and increased CD4+/CD8+ T-cell ratio in bronchoalveolar lavage specimens (can be assessed by flow cytometric immunophenotyping), might be helpful in making the diagnosis of sarcoidosis, although it is still a diagnosis of exclusion in most cases, as other causes of a granulomatous inflammatory response must be ruled out.

Histological Findings

The lymph node architecture will be predominantly effaced and densely occupied by well-formed granulomas, which will sometimes be referred to as "naked" granulomas; meaning devoid of any lymphocytes. The granulomas in sarcoidosis will mostly be non-caseating but can be necrotic in some cases [64]. Other findings that can be observed include asteroid bodies (stellate structures within granulomas, mostly containing calcium), Schaumann bodies (laminated concentric inclusions, composed of calcium and iron), and Hamazaki-Wesenberg bodies (large yellow-brown lysosomes) [64]. All of which are non-specific for sarcoidosis and can be seen in other diseases (e.g., berylliosis).

Cytological Findings

Smears usually show multinucleated giant cells and small aggregates of epithelioid histiocytes with elongated, spindle-shaped nuclei, and inconspicuous nucleoli [65]. The background will have a mixed population of lymphocytes and necrotic debris should be minimal if present.

Differential Diagnosis

As stated above, other causes of granulomatous inflammation must be thoroughly investigated before rendering a diagnosis of sarcoidosis. Fungal and mycobacterial infectious are among the most common entities to be excluded, which will have key defining characteristics (see the differential diagnosis in section "Cat Scratch Disease").

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