Invited Review

Lymph nodes in health and disease – A pathologist's perspective

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Abstract

A lymph node (LN) being a unique immunological organ has the ability to adapt when exposed to emigrants. The structural and architectural components are tampered, and it acts as an efficient immune checker in the presence of an antigen and also exhibits a morphological drift when neoplastic cells evade the organ. So, understanding the basics of histology of a lymph node is essential for the better identification and interpretation of pathological events occurring in a lymph node. A phenomenon pertaining to LNs, interpretation of reactive and neoplastic lymph nodes at morphological levels and pathological diversity of LNs in selected disease processes are emphasised.

Keywords: Lymph node, lymphadenopathy, lymphatic metastasis

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INTRODUCTION

A lymph node (LN) is an immunologically effective organ, which is strategically located and scattered throughout the body in large numbers. It is a dynamic, remarkably organised structure and unique in the sense that

- LN has a concept of compartmentalisation or zonation, and its architecture includes capsule, cortex, medulla and para cortex.
- Cellular diversity within the LN creates a unique microenvironment.
- There is an adipose tissue (perinodal fat – PAT) around the LN: It is specialised to provide fatty acids, adipokines and dendritic cells that may influence local immune response.[1]
- Functional adaptation leads to reconstruction or remodeling within the LN.

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ANATOMICAL COMPARTMENTS IN NORMAL LN

Cortex

It is a B cell area composed of lymphoid follicles. Primary follicle is round in shape with 1 mm diameter, composed of inactive B lymphocytes. The long axis is oriented at right angle to the capsule. Secondary follicle is formed when an antigen enters the lymph node. Size varies and is composed of heterogeneous population of lymphoid cells of various stages of maturation.[2]

Mantle zone

It is a distinctly appearing corono, which surrounds the germinal centre. It is thicker in the subcapsular aspect of the lymphoid follicle and thinner in the opposite site.[2]

Germinal centre (GC)

It exhibits polarisation where one pole is dark zone facing towards medulla, composed of small and large noncleaved

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cells (centroblasts), and another pole is light zone facing towards capsule, composed of cleaved cells (centrocytes).[2]

TBM (tingible body macrophage)

They are large histiocytes, which reside in a germinal centre of secondary follicles. They have irregular morphology and abundant cytoplasm with phagocytised apoptotic bodies (referred to as tingible – stainable bodies) in various states of degradation.[3]

Medulla

It is the main site of plasma cell proliferation, differentiation and production of antibodies and is composed of large tortuous sinuses called medullary sinuses, surrounded by lymphoid clusters called medullary cords.[2]

Para cortex (PC)

It is a densely cellular T cell area, which is also called interfollicular cortex. It is anatomically and functionally divided into central and peripheral deep cortical units.[2]

HEV (high endothelial venules)

High endothelial venules are highly distinct vessels seen in PC, which are lined by plump cuboidal endothelial cells with vesiculated nuclei. It has thick basement membrane and seldom, lumen of vessels is obliterated by endothelium. They play a crucial role in recirculation and distribution of lymphocytes.[2]

Lymphatic sinuses

Three sinuses (subcapsular/trabecular/medullary sinuses) carry lymph from afferent lymphatics on the convex surface of LN into the efferent lymphatics in the hilum. They vary in size and composition according to functional demands.[2]

ESSENTIAL PHENOMENON IN LN

Folliculolysis

It is the process where the eosinophilic infiltration into GC causes lysis and disruption of the follicles.[4] It gives a moth-eaten appearance to the follicle. Eosinophilic folliculolysis is a helpful feature in diagnosing Kimura's disease [Figure 1].[5]

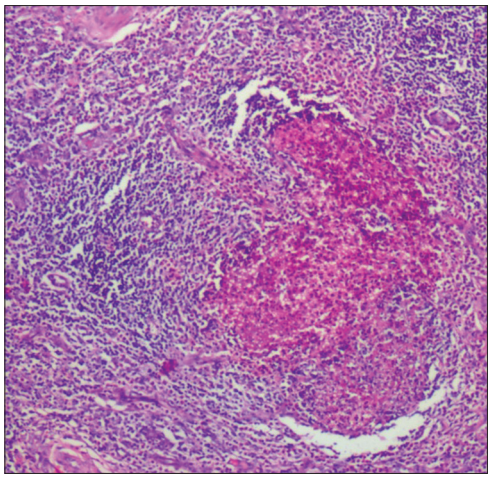

Figure 1: Folliculolysis in Kimura disease

Lipomatosis

LN lipomatosis is a common phenomenon, which occurs in an aging human lymph node and is caused by transdifferentiation of fibroblasts into adipocytes in the medulla [Figure 2]. Adipocytes are associated with down regulation of lymphotoxin beta expression. Lipomatosis also induce extensive vascular remodeling with loss of medullary lymphatic vessels and dysfunctional, highly dilated HEVs with lower density of naïve T-cells and trapped plasma cells. Thus, LN lipomatosis is considered as a major factor for decreased immune functions in the elderly.[6]

Desmoplasia

Fibrosis in LN can be evident in the form of capsular fibrosis or stromal fibrosis [Figure 3]. The presence of fibrosis in general is a valuable feature in distinguishing Kimura disease from angiolymphoid hyperplasia with eosinophilia (ALHE).[5] Fibrosis is characterised by the accumulation of a pronounced number of fibroblasts, deposition of collagen and distortion of normal tissue architecture. It is considered to correlate with multiple immune-mediated mechanisms and cytokine networks and is evident in both benign and malignant LN pathologies. It seems morphologically to be a host induced reaction. It can be a constant feature of some types of lymphomas.[7]

Necrosis

The presence of necrosis in LN may be challenging to pathologists as it is evident in both benign inflammatory lesions as well as in metastatic malignancies. Necrosis can be focal, diffuse or extensive. Nature of necrosis can vary from fibrinoid to caseation necrosis. Necrotic area is characterised by eosinophilic granular area infiltrated with neutrophils, lymphocytes and macrophages [Figure 4]. Caseation necrosis is the hall mark of tuberculosis and is related to delayed hypersensitivity reaction.[8]

A. Morphological patterns in Reactive Lymph nodes:

Reactive is the term used when there is host response due to inflammation in the absence of neoplasia. Reactive lymphadenopathy is the most common cause of lymph node enlargement, which is a non-neoplastic and reversible enlargement of the lymphoid tissue secondary to antigen

stimulus. There are three major basic morphological patterns, which are distinctly seen[9] [Table 1, Figure 5].

B. Morphological patterns in Neoplastic Lymph node: LN with a size of more than 1 cm and round shape is considered malignant on ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI). This criterion may demonstrate low specificity, and histopathological analysis accurately determines the presence of malignancy within the LN.[10]

The lymph node expedition in the assembly of oral squamous cell carcinoma (OSCC) is exhaustive and complex. Complementary chemokine expression by tumour cells and the lymphatic endothelial cells lining the subcapsular sinus may facilitate tumour migration into the cortex. Then, tumor cells proliferate within the cortex and later can migrate and invade and break out of the capsule.[11]

The involved LN in OSCC may exhibit keratinising or non-keratinising tumor islands occupying various compartments of a LN [Figure 6].

1. Extra nodal extension (ENE): It is the extension of metastatic carcinoma within the lymph node, through the capsule, and into the surrounding connective tissue, regardless of associated stromal reaction.[12] It is categorised as follows:

1. ENEn: absence of ENE
2. ENEmi: presence of ENE ≤2 mm
3. ENEma: presence of ENE ≥2 mm

C. Morphology of lymph node pathologies:

1. **Kimura disease:** Kimura disease is a rare chronic inflammatory disorder of unknown etiology. The exact pathogenesis is still unclear, although it might be a self-limited allergic or autoimmune response triggered by an unknown persistent antigenic stimulus [Table 2].[13]
2. **Kikuchi Disease:** It is an enigmatic, self-limiting nongranulomatous lymphadenitis, which is diagnosed

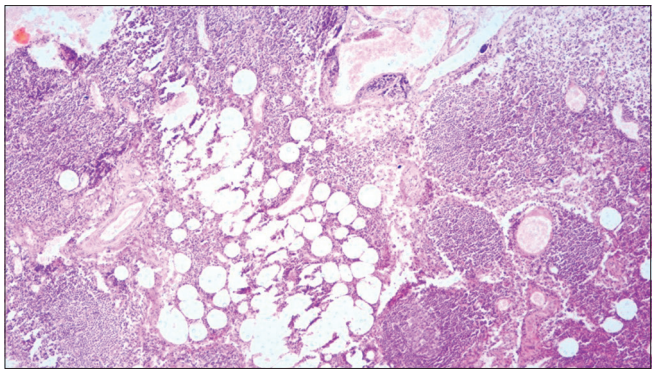

Figure 2: Lipomatosis

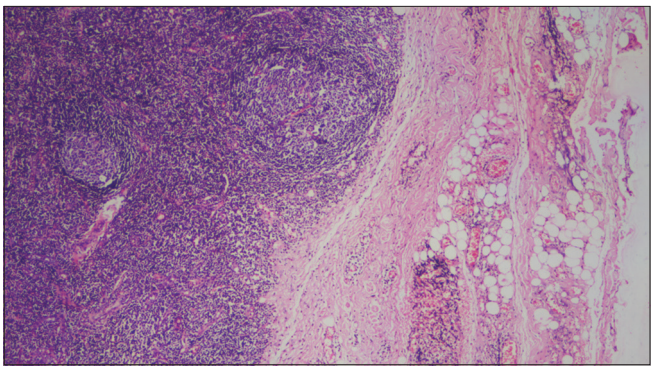

Figure 3: Capsular fibrosis

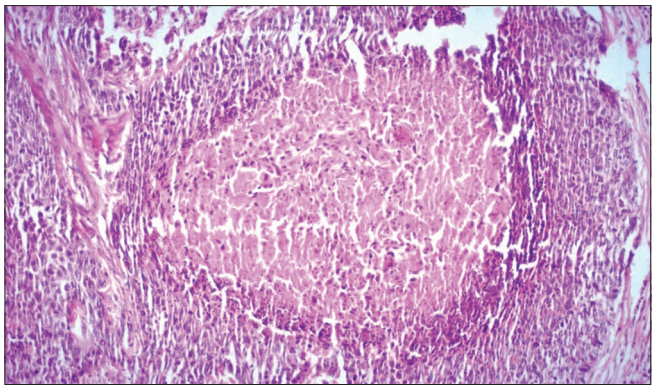

Figure 4: Necrosis

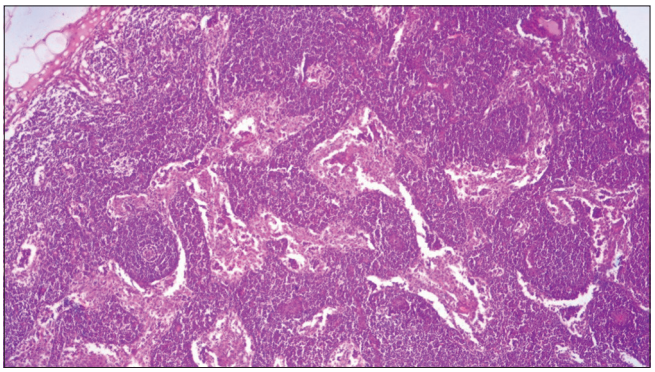

Figure 5: Sinus hyperplasia

Table 1: Morphological patterns in a reactive lymph node

Follicular hyperplasia	Sinus Hyperplasia	Para cortex Hyperplasia
Nodal architecture is preserved. Size and shape of the secondary follicles are altered. Seen in infections and autoimmune disorders.	Most common pattern, but least significant Medullary sinuses are distended and enlarged and contain histiocytes Seen in viral lymphadenitis/Rosai Dorfman disease	Loss of nodal architecture PC expansion can be active or passive. Seen in viral infections, skin diseases and drug reactions.

with confidence if careful attention is given to the architectural features [Table 3]. Kuo proposed classification of the histopathologic features of KFD into three evolving histologic stages: proliferative, necrotising and xanthomatous.

3. **Tuberculous Lymphadenitis:** It presents with characteristic histopathological features of well-formed granulomas as a primary component [Table 4]. Ramanathan *et al.* (1999) have proposed a system for the granulomatous lesions localised only in the LN for a better assessment of the TB. The system includes four types of granulomas: G1 – hyperplastic granuloma, G2 – hyper reactive granuloma, G3 – hypo reactive granuloma and G4 – non-reactive granuloma.[15]

D. Morphological patterns in the metastatic lymph node:

1. **Metastatic lymph nodes in ameloblastoma:** The frequency and occurrence of metastasis in odontogenic tumors are a rare event. Lung is the commonest site of metastasis, and cervical lymph nodes are the second most frequent site for metastasis in ameloblsatoma.[17] The histopathological features will be identical to a primary tumor. Metastatic LNs show a distorted architecture due to the proliferation of odontogenic epithelium in the follicular or plexiform pattern with basal cells showing reversal of polarity and central stellate reticulum like cells [Figure 7]. Predominant cystic areas are also evident.
2. **Metastatic lymph nodes in Ca-ex-PA:** Carcinoma ex pleomorphic adenoma is a malignant tumor of salivary gland having proportion of adenoma and carcinoma components. The malignant component of Ca ex PA is most often adenocarcinoma not otherwise specified. Sometimes, the component may be adenoid cystic carcinoma, muco-epidermoid carcinoma or salivary duct carcinoma.[18]

Lymph node metastasis is a rare phenomenon in salivary gland tumors. When there is LN involvement, there can be invasion into the capsule. Infiltrating tumor islands with abundant areas of necrosis can alter the LN architecture [Figure 8].

Table 2: Morphological descriptors in Kimura disease[5]

Features	Description
Architecture	Preserved nodal architecture with follicular lymphoid hyperplasia and prominent germinal centres Expanded inter follicular areas are seen. Germinal centres may show progressive transformation along with the proteinaceous deposits. Folliculolysis: The eosinophilic infiltrate may partially disrupt reactive follicles to give a moth-eaten appearance.
Cellular component	Eosinophilic microabscesses are evident. Polykaryocytes are evident.
Fibrous component:	Dense stromal fibrosis along with capsular fibrosis
Vascular component	HEV and vascular hyperplasia with flat or low cuboidal endothelial cells Perivascular sclerosis

Table 3: Morphological descriptors in Kikuchi disease[14]

Features	Description
Architecture	Distorted nodal architecture due to irregular para cortical hyperplasia.
Cellular component	Predominantly histiocytes and plasmacytoid monocytes, immunoblasts are seen. Three types of histiocytes: Crescent histiocytes, foamy histiocytes and signet ring histiocytes.
Necrosis	Neutrophil free necrosis with abundant Karyorrhectic debris and fibrin deposits Thrombosed vessels usually are seen around the areas of necrosis

Table 4: Morphological descriptors in tuberculous lymphadenitis[16]

Features	Description
Architecture	Partial/total effacement of architecture Multiple, confluent epithelioid granulomas
Necrosis	Caseation necrosis
Cellular component	Macrophages, epithelioid cells and lymphocytes Langhans giant cell (nucleus is arranged in horse shoe pattern)

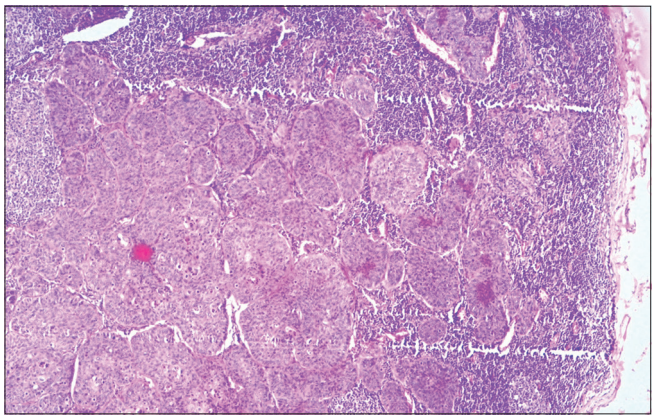

Figure 6: Tumor islands in level 1 LN - OSCC

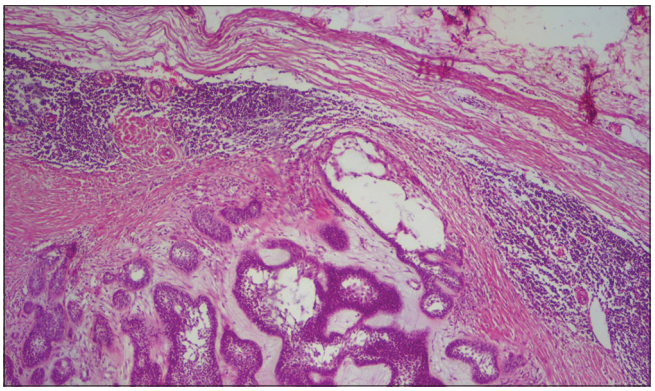

Figure 7: Metastatic submandibular LN - ameloblastoma

Note on gross appearance of lymph node

The following data should be recorded while grossing the LN.[19]

- Total no of LN: Some systemic diseases can cause an increase/decrease in the number of LN.
- Size: Previous radiation/chemotherapy can reduce the size and number of LN.
- Shape: Ovoid/round/bean-shaped/kidney shaped/matted LN [Figure 9]
- Consistency: Normal LN is not palpable. LNs are soft in acute inflammation, firm in chronic inflammation and hard in malignancy. Rubbery LN is a characteristic of lymphomas and matted LN seen in TB.
- Description of the cut surface: Grey–white homogeneous areas, haemorrhagic areas and the presence of necrosis [Figure 10].

Grossing

A small LN should be processed in toto, and a large LN should be bisected/trisected. If the size of the lymph node exceeds 2 cm, it should be sectioned like a bread loaf. The section thickness should be 3–4 mm for a LN.[19]

Lymph node yield (LNY): It is defined as the number of lymph nodes retrieved after neck dissection.

Lymph node ratio (LNR): It is defined as the ratio of pathologically positive lymph nodes out of the total number of retrieved lymph nodes after neck dissection.

LNY and LNR are measurable factors with potential prognostic implication. Higher LNY suggests removal of more potential occult pathological tissue. And lower LNR signifies higher the survival rate.[20]

CONCLUSION

Lymph nodes are easily accessible as diagnostic tools, and the pathologists keep a vigilant eye at morphological levels to arrive at the diagnosis. However, lymph node pathologies are enigmatic and at times challenging in diagnostic pathology.

This narrative emphasises on the journey of a lymph node from infection to neoplasm in selective pathologies and its functional adaptability to an antigen or a neoplastic cell, where it proves itself as a reliable source of fragment for diagnosis.

There are many areas where research needs to be addressed in the field of LN. One amongst them is age-related changes to LN stroma and is emerging as an important area of research, and possible molecular targets to rejuvenate the aging LN should be addressed upon as a future perspective.

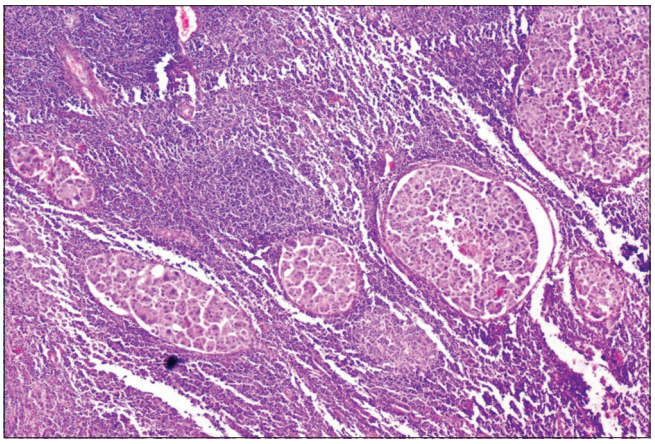

Figure 8: Metastatic level 1 LN – Ca-ex-PA

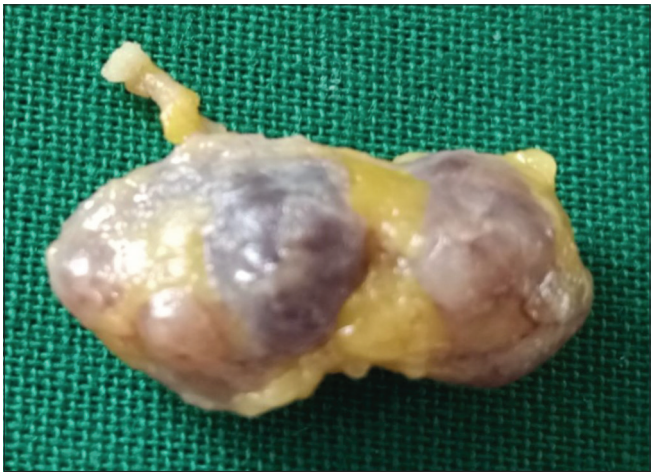

Figure 9: Gross appearance of matted LN

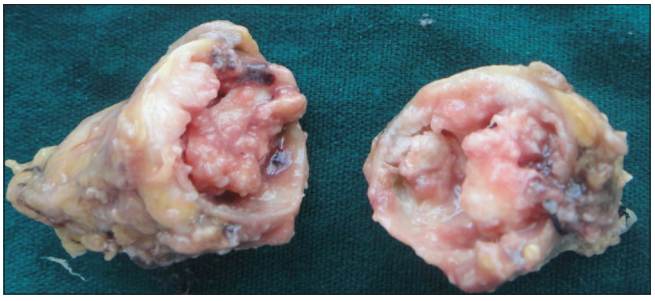

Figure 10: Gross appearance of necrotic LN

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Conflicts of interest
There are no conflicts of interest.

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