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Review Article **Oral Pathology and Microbiology**

Lymph Node Responses in Oral and Maxillofacial Pathology: A Review

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Abstract

Introduction: Lymph nodes in the oral and maxillofacial region serve as critical indicators of immune activity. They reflect a wide range of pathological processes. Various types of lesions, including infectious, autoimmune, neoplastic, or idiopathic, trigger a specific pattern of lymph node response, characterized by distinct structural and cellular changes. These patterns may resemble malignant conditions complicating diagnosis. Recognition of these patterns supports effective disease characterization and informed clinical decision-making. Accurate assessment requires integration of morphological features with clinical findings and the usage of appropriate ancillary studies. This review highlights the diverse spectrum of lymph node responses encountered in oral pathology and emphasizes their diagnostic and clinical relevance. ***Objectives:*** The key objectives of this review are to elucidate the anatomical, histological, and molecular basis of lymph nodes in the oral and maxillofacial region, to analyze the physiological and immunological functions of lymph nodes in health and disease, to explore the influence of local microenvironmental factors on lymph node responses in inflammatory, infectious, and neoplastic oral conditions, and to assess the diagnostic, prognostic, and therapeutic significance of lymph node involvement in oral and maxillofacial pathology. ***Materials and Methods:*** The present review synthesizes data from reputable sources on lymph node responses in oral and maxillofacial pathology. Electronic databases including PubMed, ScienceDirect, Google Scholar, and SAGE Journals were systematically searched for original research articles, reviews, and clinicopathological studies published between 1926 and 2025. ***Conclusion:*** Standard textbooks and classical literature on lymphatic system anatomy, histology, immunology, and oral pathology were also consulted for foundational context. The selected studies addressed normal lymph node architecture, lymphatic drainage patterns, immunological and pathological lymph node responses, and their role in oral inflammatory, infectious, and neoplastic conditions, particularly oral squamous cell carcinoma. Approximately 30–35 peer-reviewed articles were analysed to provide an integrated overview of the diagnostic, prognostic, and therapeutic significance of lymph node involvement in oral and maxillofacial pathology.

Keywords: Lymphadenopathy, Oral Pathology, Lymph Nodes, Oral Squamous Cell Carcinoma, Immune Response, Diagnostic Histopathology.

INTRODUCTION

Lymph nodes (LNs) serve as integral components of the immune system. They function as highly organized secondary lymphoid organs that mediate both local and systemic immune responses. Their architecture is characterized by compartmentalized regions, such as the cortex, paracortex, and medulla.[1] The lymph node microenvironment is highly dynamic. It plays a crucial role in antigen recognition and the priming of immune cells. This environment also orchestrates adaptive immune responses. Its structural organization supports the efficient trafficking, activation, and interaction of lymphocytes, antigen-presenting cells, and stromal components.[2]

Within the head and neck region, lymph nodes, particularly those in the oral and maxillofacial areas, are strategically positioned to encounter a wide range of antigenic stimuli. These include microbial pathogens, environmental antigens, neoplastic cells, and autoimmune triggers. The lymph node response in these settings may range from benign hyperplasia to malignant infiltration, offering valuable diagnostic and prognostic insights. Despite their clinical importance, the full spectrum of lymph node responses in oral pathology remains underrepresented in current literature. There is a lack of integration between morphological patterns, immunological mechanisms, and clinical relevance. This review aims to comprehensively summarize lymph node responses associated with diseases of the oral and maxillofacial region.

Anatomy and Physiology of Lymph Nodes in Oral Regions

Lymph Nodes are highly organized secondary lymphoid organs, structurally specialized to support immune surveillance. [4] Each node is enclosed by a capsule and divided into distinct compartments: the cortex, paracortex, and medulla. The cortex contains B-cell zones with lymphoid follicles and germinal centers. The paracortex houses T-cell zones and high endothelial venules, which facilitate lymphocyte entry. The medulla consists of plasma cells and medullary sinuses.

Lymph enters the node through afferent vessels, passes into the subcapsular sinus, and then flows through the cortical and medullary sinuses. It exits via efferent lymphatics at the hilum.[5]

In the head and neck region, oral lymphatic drainage primarily targets the submental, submandibular, cervical, and retropharyngeal lymph nodes. [6]

Surrounding each lymph node is perinodal adipose tissue (PAT), which contributes to immune regulation. PAT releases cytokines and adipokines and supports dendritic cell function. It also plays a role in lymph node remodeling, especially during aging or disease [7] (Figure 1).

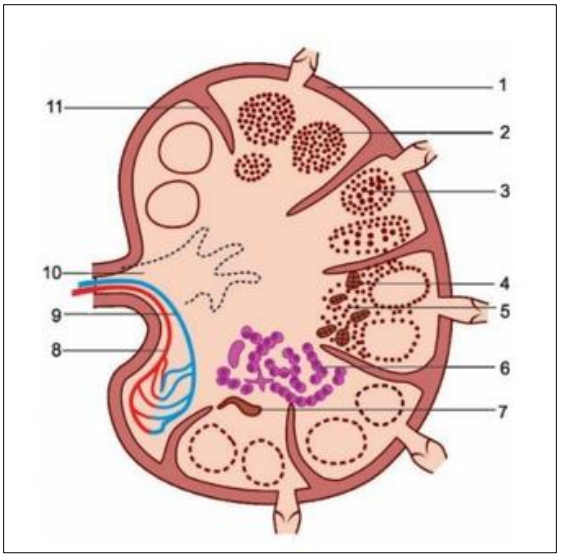

Figure 1: Diagrammatic representation of zones and structures in a lymph node 1. Capsule, 2. Primary follicle in cortical area (B cell areas), 3. Secondary follicle in the cortical area with reactive center (B cell areas), 4. High end venules (HEV), 5. Paracortical area (T cell areas)

Mechanisms and Morphological Patterns of Lymph Node Response

Lymph nodes are dynamic immune organs. They undergo structural and cellular changes in response to antigenic stimulation. [4] In the head and neck region, this adaptability is crucial for detecting and regulating immune reactions triggered by oral antigens. Their compartmentalized architecture enables specific immune functions that manifest as distinct histological patterns [3].

Antigenic Stimulation and Immune Cell Trafficking

The immune response begins when dendritic cells migrate from peripheral tissues and present

antigens. These are displayed to naïve lymphocytes within defined zones of the lymph node. High endothelial venules control lymphocyte entry. B cells are directed to follicles, while T cells migrate to the paracortex. This compartmentalization supports focused and efficient adaptive immune activation. [8,9]

B and T Cell Zone Dynamics

B-cell activation leads to germinal center formation and clonal expansion. This produces polarized follicles containing centroblasts and centrocytes. T-cell activation in the paracortex results in interfollicular expansion and increased cell turnover. These changes are histological indicators of active antigenic stimulation. [10,11]

Classical Morphological Patterns of Immune Activation

- Follicular hyperplasia shows enlarged, polarized germinal centers with increased mitosis. It reflects humoral immune activation.
- Paracortical hyperplasia involves expansion of the T-cell zone with prominent immunoblasts. This indicates strong cell-mediated immune responses.
- Sinus histiocytosis is characterized by dilated lymphatic sinuses filled with activated histiocytes. It reflects enhanced antigen clearance and tissue remodeling. [3,12]

Structural adaptations reflecting chronicity or dysregulation

- Folliculolysis refers to germinal center breakdown, often caused by cytotoxic or enzymatic activity. It suggests altered immune regulation.
- Lipomatosis is the replacement of medullary lymphoid tissue with adipocytes.

This reduces immune efficiency by disrupting stromal and vascular networks.

- Desmoplasia involves fibroblast proliferation and extracellular matrix deposition. It is associated with chronic immune activity and changes in nodal architecture. [3]

Granulomatous Inflammation

Granulomas are organized clusters of epithelioid histiocytes and giant cells. They form in response to persistent antigens and reflect a delayed-type hypersensitivity reaction. Granulomas often distort nodal structure and require careful evaluation to distinguish them from neoplastic lesions. [13]

Non-Lymphoid Cellular Contributions

- Macrophages support antigen presentation, phagocytosis, and cytokine release.
- They regulate local immunity and tissue remodeling.
- Eosinophils contribute to cytotoxic responses and matrix remodeling. Their presence may lead to tissue alteration.
- Plasma Cells represent sustained antigenic stimulation and drive antibody production.

They reshape interfollicular regions during prolonged immune activity. [14,15]

Angiogenesis

Angiogenesis is a key feature of reactive lymph nodes. Expansion of venules and capillaries enhances lymphocyte trafficking and supports metabolic demands. It also contributes to structural remodeling of nodal tissue. [12]

Necrosis and Tissue Damage

Necrosis, including karyorrhexis and coagulative patterns, signals strong cytotoxicity or vascular injury. These changes alter nodal morphology and require correlation with additional diagnostic data. [12]

Lymph Node Response in Oral Pathologies

In oral and maxillofacial pathology, reactive lymphadenopathy is a common finding of systemic or localized disease. Recognizing the full spectrum of lymph node responses is essential for accurate diagnosis. [16]

(i) Infectious Diseases

Infectious lymphadenitis is a common cause of cervical lymphadenopathy, especially in the oral and maxillofacial region. The oral cavity is continuously exposed to diverse microbial flora and is prone to mucosal injury. As a result, regional lymph nodes frequently respond to infections ranging from transient viral illnesses to chronic granulomatous diseases. In many cases, the histopathological features of lymphadenitis offer useful clues to the underlying cause. However, overlapping patterns may sometimes complicate the diagnostic process. [16,17]

Etiologic Diversity in the Oral Region

A wide range of infectious agents can affect lymph nodes in patients with oral or perioral involvement. Viral pathogens are among the most common, particularly Epstein– Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), and human immunodeficiency virus (HIV). These are especially prevalent in young individuals and immunocompromised patients.

Bacterial causes include treponema pallidum (syphilis), bartonella (cat-scratch disease), and various anaerobic organisms associated with odontogenic infections. Mycobacterial infections, both tuberculous and non-tuberculous, are important, particularly in endemic regions or among immunosuppressed individuals.

In addition, deep fungal infections such as, cryptococcus, and coccidioides may involve cervical lymph nodes. Protozoal infections like toxoplasmosis and leishmaniasis can also affect these nodes, either as localized findings or part of systemic disease. [18]

Histological Features and Immune Response Patterns

Microscopically, the lymph node is a well-encapsulated lymphoid organ composed of lymphoid tissue and an extensive system of lymphatic sinuses. The outer capsule consists of dense connective tissue rich in collagen and elastic fibers, from which trabeculae extend into the interior and provide structural support.

The lymph node is divided into three main regions: cortex, paracortex, and medulla. The cortex lies beneath the capsule and contains lymphoid follicles, which may be primary or secondary. These follicles are predominantly composed of B lymphocytes. Surrounding the follicles is the paracortical region, which is rich in T lymphocytes and contains prominent high endothelial venules that facilitate lymphocyte trafficking.

The medulla forms the inner region of the lymph node and is composed of medullary cords and medullary sinuses. The cords contain lymphocytes, plasma cells, and macrophages, while the sinuses allow the flow of lymph through the node.

The entire lymphoid tissue is supported by a fine reticular fiber network formed by reticular cells. Functionally, the lymph node shows distinct B-cell and T-cell compartments, and its microscopic appearance varies depending on the degree of antigenic stimulation. [19] (figure 2) (figure 3).

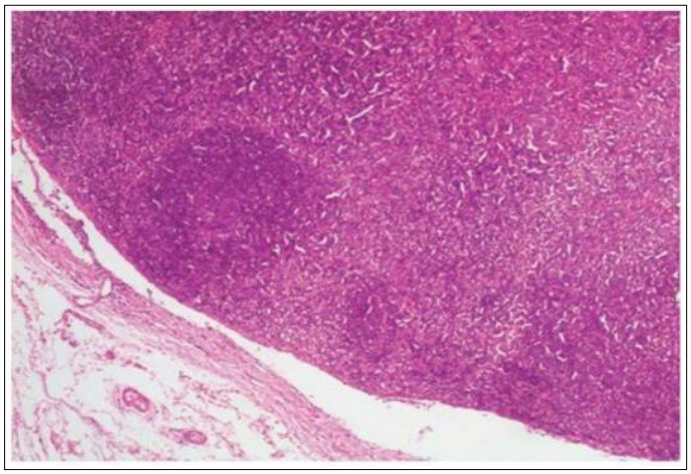

Figure 2: Capsule of a lymph node seen along with a primary follicle (H & E stain x40)
Source: Kumar GS, editor. Orban's oral histology, embryology, and physiology. 16thed. New Delhi: Elsevier; 2021

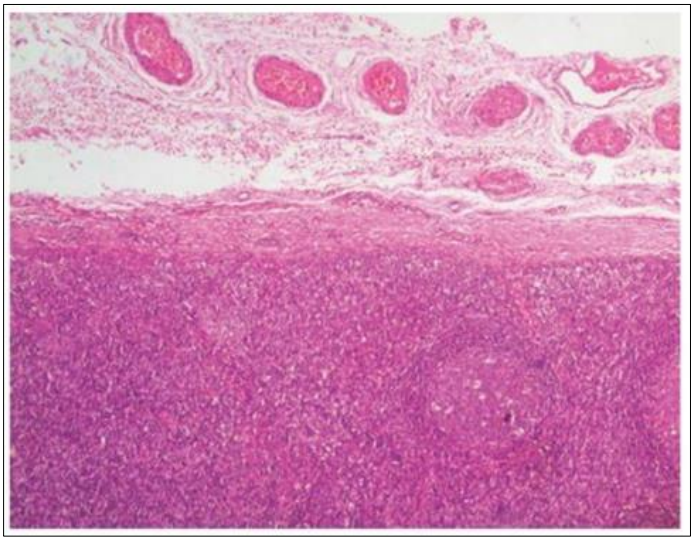

Figure 3: Capsule and trabeculae seen along with supra capsular arterioles. Lymph node shows reactive or secondary follicle. (H&E stain x40)
Source: Kumar GS, editor. Orban's oral histology, embryology, and physiology. 16thed. New Delhi: Elsevier; 2021

Each pathogen class tends to produce a characteristic lymph node reaction, though this may vary with disease stage and host immune status.

Viral lymphadenitis shows paracortical hyperplasia with numerous immunoblasts. Some cells may appear atypical. Proliferation of monocytoid B cells and preservation of nodal architecture help distinguish this from lymphoma. Bacterial infections often result in follicular hyperplasia or suppurative necrosis. In cat-scratch disease, stellate microabscesses surrounded by palisading histiocytes are characteristic. [20] Syphilitic lymphadenitis usually displays dense plasma cell infiltration, follicular hyperplasia, and vascular changes such as endarteritis. [19] Mycobacterial infections generally produce granulomatous inflammation. Tuberculous nodes show caseous necrosis and Langhans-type giant cells. Non-tuberculous forms may present similarly but often with less necrosis. Fungal infections typically result in necrotizing granulomas. Diagnosis often depends on the identification of fungal organisms using special stains such as Grocott methenamine silver (GMS) or periodic acid– Schiff (PAS). Toxoplasmosis commonly presents with reactive follicular hyperplasia. Clusters of epithelioid histiocytes and monocytoid B cells are often seen, sometimes forming ill-defined granulomas. [13]

(ii) Autoimmune Diseases

Autoimmune conditions affecting the oral cavity or salivary glands often lead to secondary lymph node changes, particularly in the cervical region. These lymph node responses are typically reactive but may mimic infectious, neoplastic, or metastatic processes. [21]

Systemic Lupus Erythematosus (SLE)

Cervical lymphadenopathy in SLE reflects systemic immune dysregulation. It frequently occurs during disease flares. Histologically, lymph nodes show areas of coagulative necrosis, hematoxylin bodies, and fibrinoid necrosis of blood vessels. A dense plasma cell infiltrate and disrupted germinal centers are common. These features may resemble viral or necrotizing lymphadenitis. However, the presence of autoantibodies (e.g., ANA, anti-dsDNA) and systemic signs support the diagnosis. In some cases, lymphadenopathy may be an early manifestation, preceding other organ involvement. [22,23]

Sjögren Syndrome

Sjögren syndrome causes chronic inflammation of salivary glands and is often associated with cervical lymphadenopathy. The affected lymph nodes typically show follicular hyperplasia, interfollicular plasma cells, and monocytoid B-cell proliferation. Prolonged antigenic stimulation can result in marginal zone hyperplasia, which may evolve into MALT lymphoma in a subset of patients. Parotid gland enlargement often reflects underlying ductal lymphoepithelial lesions with secondary nodal response. [2]

Sarcoidosis

In sarcoidosis, lymphadenopathy is due to a granulomatous immune reaction. Cervical nodes are frequently involved in cases with oral, salivary, or pharyngeal manifestations. Histologically, nodes show well-formed non-caseating granulomas composed of epithelioid histiocytes and multinucleated giant cells. Necrosis is absent, which helps distinguish sarcoidosis from infectious granulomatous diseases. In active disease, follicular effacement and sinus distortion may also be observed.

Granulomatosis with Polyangiitis (GPA)

GPA, formerly known as Wegener' s granulomatosis, is a vasculitic disorder with prominent involvement of the upper aerodigestive tract. Clinical features include oral ulceration, palatal perforation, and gingival hypertrophy. Lymphadenopathy results from adjacent granulomatous inflammation. Histologically, lymph nodes show necrotizing granulomas, vasculitis, and a mixed inflammatory infiltrate. These changes may resemble infectious processes or lymphoma. Testing for ANCA is crucial for diagnosis. [27,28]

IgG4-Related Disease

IgG4-related disease is a chronic fibroinflammatory condition that may involve the salivary glands and regional lymph nodes. Cervical nodes often show follicular hyperplasia, germinal center enlargement, and sometimes storiform fibrosis. The interfollicular areas are rich in IgG4-positive plasma cells, which are key to diagnosis. The lymphadenopathy may be pronounced and mimic lymphoma, but the polyclonal plasma cell population and steroid responsiveness help differentiate it from lymphoma. [29]

(iii)Neoplastic Lesions

Lymph node involvement plays a pivotal role in the progression, staging, and prognosis of oral squamous cell carcinoma (OSCC), the most common malignancy of the oral cavity. As OSCC advances, regional lymph nodes often lose their immune-regulatory function. This occurs due to metastatic infiltration, which overwhelms or bypasses local immune mechanisms. Such invasion results in distinct histopathological and immunophenotypic changes. Timely recognition of these alterations is essential for accurate diagnosis, risk stratification, and therapeutic planning. [30]

Lymphatic Spread of OSCC: Path of Metastasis

The metastatic spread of OSCC to cervical lymph nodes typically follows an orderly and anatomically defined pattern. Tumor cells first colonize the subcapsular sinus. Here, they lodge within thin-walled lymphatic channels beneath the nodal capsule. Subsequently, they infiltrate the cortical parenchyma, disrupting normal follicular architecture.

With further progression, tumor cells may penetrate the nodal capsule. This leads to invasion of the adjacent perinodal soft tissue, a process termed Extranodal extension (ENE). ENE reflects increased tumor burden and immune evasion. Its identification carries significant clinical implications, especially in staging and treatment planning.[31]

Extra nodal Extension and Its Prognostic Significance

ENE is a well-established adverse prognostic factor in head and neck squamous cell carcinomas, including OSCC. The 8th edition of the AJCC Cancer Staging Manual incorporates ENE into the nodal(N)classification [32]. This inclusion is based on its strong association with local recurrence, distant metastasis, and reduced overall survival. ENE may be classified as microscopic or macroscopic.

Microscopic ENE is detectable only through histopathological examination. Macroscopic ENE is visible on gross inspection or imaging. Histologically, ENE is characterized by tumor infiltration beyond the nodal capsule. This invasion often involves surrounding adipose, muscle, or fibrous tissue. It is frequently accompanied by stromal desmoplasia and an associated inflammatory response.

Even when ENE is microscopic, it may warrant the use of more aggressive adjuvant therapies. [3,31]

(iv) Idiopathic and Inflammatory Disorders Presenting with Cervical Lymphadenopathy

Several non-neoplastic, non-infectious, and often idiopathic disorders can cause prominent cervical lymphadenopathy. This is particularly evident in the context of head and neck pathology. Although these disorders are benign, they often mimic malignancy both clinically and histologically. Therefore, recognizing these entities is essential in the differential diagnosis of lymph node responses in oral and maxillofacial disease.

Kimura Disease

Kimura disease is a chronic inflammatory disorder. It is characterized by painless cervical lymphadenopathy and subcutaneous swellings. These features are most often seen in young Asian males. Eosinophilia and elevated serum IgE levels are hallmark laboratory findings.

Histologically, lymph nodes typically show florid follicular hyperplasia. Eosinophilic microabscesses and folliculolysis (disruption of germinal centers by eosinophils) are also present. A perinodal infiltrate and vascular proliferation may be noted.

Though the disease is self-limiting, it may persist or recur. It must be distinguished from eosinophilic granulomas and Hodgkin lymphoma. [3]

Kikuchi-Fujimoto Disease (KFD)

KFD, also known as histiocytic necrotizing lymphadenitis, is most common in young women.

It presents with tender unilateral cervical lymphadenopathy and low-grade fever. Histologically, it is defined by paracortical necrosis, karyorrhectic debris, and abundant crescentic histiocytes. Neutrophils and plasma cells are notably absent.

These features may resemble systemic lupus erythematosus (SLE) or lymphoma. However, KFD is self-limiting. Rarely, it may precede or coexist with autoimmune conditions like SLE, which warrants clinical surveillance. [3]

Castleman Disease

Castleman disease is a heterogeneous lymphoproliferative disorder. It presents as either unicentric or multicentric lymphadenopathy.

The hyaline vascular variant shows small, atrophic germinal centers with onion-skin mantle zones. It also features prominent vascular proliferation.

The plasma cell variant shows interfollicular plasmacytosis and hyperplastic follicles.

Cervical nodes may be involved in either form.

Multicentric Castleman disease is often associated with HHV-8. It presents with systemic symptoms such as fever and weight loss. It may also overlap with autoimmune or neoplastic syndromes. [33]

(v) Odontogenic Tumors

Most odontogenic tumors, such as ameloblastoma, are benign but locally invasive. Lymph node involvement is extremely rare. When present, it typically suggests malignant transformation—such as metastasizing ameloblastoma or ameloblastic carcinoma. In these cases, cervical lymphadenopathy may result from true metastasis or secondary inflammation. Histological confirmation is essential. Reactive nodal changes can mimic early neoplastic spread, particularly in recurrent or ulcerated lesions. [34,35]

(vi) Periodontal Disease

Chronic periodontal disease is a common inflammatory condition. It induces reactive lymphadenopathy in draining nodes—primarily the submandibular and deep cervical chains. Histologically, affected nodes show follicular hyperplasia, plasma cell infiltration, and occasionally sinus histiocytosis. These findings reflect sustained immune stimulation by bacterial antigens and tissue breakdown products.

While usually clinically insignificant, this reactive enlargement can mimic more serious conditions.

Therefore, it should be interpreted in the context of active periodontal inflammation. [36]

Lymphomas with Oral Manifestations

Primary or secondary non-Hodgkin lymphomas can involve the oral cavity. MALT lymphoma and diffuse large B-cell lymphoma (DLBCL) are particularly notable. They may present as mucosal swellings, ulcerations, or bone lesions—especially in the palate, gingiva, or salivary glands. Cervical lymphadenopathy is common, particularly in disseminated disease.

Histologic examination of affected nodes typically shows architectural effacement and monomorphic lymphoid populations. Immunophenotypic markers such as CD20, BCL2, or Ki-67 aid in distinguishing lymphoma from reactive processes.

Unlike benign lymphadenopathy, lymphoma-related nodes are usually firm, non-tender, and persistent. [37]

Table 1: Classification of Lymphadenopathy [18]

Criteria	Type	Description	Possible Cause
Swelling	Localized	Involvement of a single node or group in one area	Local infection, trauma, dental abscess
	Generalized	Multiple regions affected	Viral infection, HIV, Tuberculosis, malignancy
Consistency	Soft	Compressible, elastic	Acute inflammation, Reactive node
	Firm/ Rubbery	Resilient, less compressible	Chronic infection (e.g. Tuberculosis), Lymphoma
	Hard	Rigid, immobile	Metastatic cancer, scirrhous carcinoma
Pain/Tenderness	Tender, mobile	Painful, freely movable	Acute infection, viral or bacterial
	Tender, fixed	Painful, adhered to tissue	Abscess, cellulitis, severe infection
	Non tender, mobile	Non painful, moves freely	Early malignancy, chronic reactive enlargement
	Non tender, fixed	Not painful, adherent to deeper tissue	Cancer, tuberculosis, fibrosis

Clinical Relevance

Lymph node evaluation is a critical adjunct in diagnosing, staging, and managing oral and maxillofacial diseases. Morphological patterns such as follicular and paracortical hyperplasia, sinus histiocytosis, granulomatous inflammation, and desmoplastic remodeling offer clues to the underlying etiology. These may range from infectious and autoimmune processes to malignant transformation. In oral squamous cell carcinoma, nodal metastasis and extranodal extension significantly impact TNM staging. They also guide adjuvant therapy decisions. [3,32]

Integrating lymph node histology with clinical, serological, and immunophenotypic data enhances diagnostic precision. It supports prognostic stratification in both benign and malignant oral pathologies.

Table 2: Lymph Node Response Patterns and Associated Oral Pathologies [18]

Lymph Node Response Pattern	Associated Diseases/Conditions
Follicular Hyperplasia	EBV, HIV, Syphilis, Sjögren syndrome, Castleman disease (hyaline vascular), Toxoplasmosis, Periodontal disease
Paracortical Hyperplasia	CMV, Drug reactions, EBV (later stages)
Sinus Histiocytosis	Oral squamous cell carcinoma (draining nodes), Rosai-Dorfman disease
Desmoplasia	Oral squamous cell carcinoma (with extra nodal extension), chronic immune stimulation
Lipomatosis	Age-related involution, chronic immune inactivity, immune senescence
Folliculolysis	Kimura disease
Paracortical Necrosis	Kikuchi-Fujimoto disease
Necrosis	Systemic Lupus Erythematosus (SLE), Kikuchi disease, Granulomatosis with Polyangiitis (GPA)
Granulomas	Sarcoidosis (non-caseating), Tuberculosis (caseating), GPA (necrotizing), Cat-scratch disease, Fungal infections
Follicular Disruption	SLE, Kimura disease
Eosinophilia	Kimura disease, Drug-induced hypersensitivity
Plasmacytosis	Castleman disease (plasma cell variant), Sjögren syndrome, SLE
Metastatic Deposits	Oral squamous cell carcinoma, Ameloblastic carcinoma

Future Directions

Future research should focus on characterizing the lymph node microenvironment. This includes immune cell subsets, cytokine profiles, and stromal interactions. These factors may help predict disease progression and therapeutic response. Techniques like multiplex immunohistochemistry, spatial transcriptomics, and single-cell RNA sequencing may identify novel biomarkers. These can help distinguish reactive from neoplastic changes. They may also reveal immune signatures linked to prognosis [38]. In oral cancers, identifying predictive markers in sentinel or regional nodes could enhance risk stratification.

CONCLUSION

This review highlights the diverse morphological and immunological patterns of lymph node responses in oral and maxillofacial pathologies. By synthesizing knowledge across reactive, infectious, autoimmune, and neoplastic conditions, it underscores the diagnostic, prognostic, and clinical relevance of lymph node evaluation. Understanding these patterns aids in accurately distinguishing between benign and malignant processes. It also informs treatment planning and supports future research directions.

Author Contributions

1. **Dr. Bhagyeshree TK-** Conceptualization of the topic, literature review, manuscript drafting, figure design, and overall coordination of the manuscript preparation.
2. **Dr. Sahana N S**- Critical revision of the manuscript, supervision, and final approval of the version to be published
3. **Dr. Chandrakala J** - Contributed to the conceptual development, literature validation, and critical review of immunological and oncopathological mechanisms.
4. **Dr. Gopika G Menon**- Assisted in literature collection, organization of references and preparation of figures
5. **D. Lakshmi B**- Contributed to literature review, helped in manuscript formatting.
6. **Dr Akhila S-** Assisted in literature collection, final proofreading and referencing.

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