



Lymphoid Malignancies: Oral Manifestation and Considerations

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Abstract

Lymphoid tissues are distinguished anatomic structure in body responsible for host immune response. Malignancy of the lymphocyte cell line takes up about 14% of all head-neck malignancies. Due its manifestations resembling several non-malignant lesions of oral cavity oral malignant lymphomas are often misdiagnosed. The misdiagnosis may also result in diffusion of tumour when treated with invasive dental procedures. Hence this review was under taken to report the oral manifestations of lymphoid malignancies.

Introduction

Lymphoid tissues in the body are distinguished because of their complex anatomic arrangement and functionality in hosting an immune response. More than 40 malignancies involving the system has been classified indicating the diversity of this cell line [1,2]. Based on their cell lineage the Revised European-American Lymphoma classification, REAL/WHO system, describes them as B-cell malignancy, T-cell/natural killer malignancy, and Hodgkin's lymphoma (Table 1).

Commonly, the oral manifestations of lymphomas are secondary to a more widespread involvement. They account for 2.2% of all head and neck malignancies, 5% of salivary gland tumors, 3.5% of intraoral malignancies and 2.5% of all cases of lymphomas making it the second most common oropharyngeal malignancy [3]. Velez et al. [4] reported this incidence to be 5% of all lymphomas. This is a very rare condition and often mistaken for an odontogenic tumor, cyst, or infection. Radiographically also it appears as a radiolucent area that may mimic endodontic lesion, periodontal pathology, or odontogenic cyst or tumour, commonly resulting in multiple unnecessary extractions and/or root canal treatments [4]. Silva TD et al. [5] in his systematic review reported 40.52% were initially misdiagnosed as a different pathology leading to diagnostic delay as well as improper treatment. Hence the goal of this Review is to concisely review the oral manifestations of most common lymphoid malignancies.

General manifestations of lymphoid malignancies

Lymphomas mainly include Non-Hodgkin's Lymphoma (NHL), Mature T and NK neoplasms, Hodgkins Lymphoma (HL) and Post Transplant Lymphoproliferative Disorders (PTLD).

NHL

Predominantly of B-lineage, previously NHL comprised of B-cell, T-cell or natural killer/T-cell types also forming 86% of all lymphomas. Diffuse Large B-cell non-Hodgkin's Lymphoma (DLBCL) was the most common histological type of lymphoma in the head and neck region [3]. NHL was most common among male patients between 50 to 70 years of age [4]. A 100 to 200 times higher risk of developing NHL was reported in patients with Acquired Immunodeficiency Syndrome (AIDS) making it the second most malignancy next kaposi's sarcoma in AIDS patients [5]. NHL presents as extranodal disease in approximately 23% to 30% of cases commonly involving gastrointestinal tract, Waldeyer's ring, skin, bones and others [3].

Natural killer/T-cell lymphomas

Lymphoma of the putative Natural Killer (NK) cell lineage is strongly associated with Epstein-Barr Virus (EBV). The preferential site of NK/T-cell lymphomas in certain extranodal areas is the nasal cavity, but they also occur in the central nervous system, gastrointestinal tract, skin, salivary gland and testis. Characteristically has a poor prognosis. Due to local diffuse infiltration, necrosis, metastasis at an early stage, and the high resistance to treatment [6]. Oral cavity involvement is seen in only 2% of cases of T cell lymphoma which has slowly grown from a rare cancer to the fifth-most common cancer in the world over a period of 30 years [7].

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Table 1: 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms.

Mature B-cell neoplasms	Chronic lymphocytic leukemia/small lymphocytic lymphoma
	Monoclonal B-cell lymphocytosis*
	B-cell prolymphocytic leukemia
	Splenic marginal zone lymphoma
	Hairy cell leukemia
	Splenic B-cell lymphoma/leukemia, unclassifiable
	Splenic diffuse red pulp small B-cell lymphoma
	Hairy cell leukemia-variant
	Lymphoplasmacytic lymphoma
	Waldenström macroglobulinemia
	Monoclonal gammopathy of undetermined significance (MGUS), IgM*
	m heavy-chain disease
	g heavy-chain disease
	a heavy-chain disease
	Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
	Plasma cell myeloma
	Solitary plasmacytoma of bone
	Extrasosseous plasmacytoma
	Monoclonal immunoglobulin deposition diseases*
	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
	Nodal marginal zone lymphoma
	Pediatric nodal marginal zone lymphoma
	Follicular lymphoma
	In situ follicular neoplasia*
	Duodenal-type follicular lymphoma*
	Pediatric-type follicular lymphoma*
	Large B-cell lymphoma with IRF4 rearrangement*
	Primary cutaneous follicle center lymphoma
	Mantle cell lymphoma
	In situ mantle cell neoplasia*
	Diffuse large B-cell lymphoma (DLBCL), NOS
	Germinal center B-cell type*
	Activated B-cell type*
	T-cell/histiocyte-rich large B-cell lymphoma
	Primary DLBCL of the central nervous system (CNS)
	Primary cutaneous DLBCL, leg type EBV
	DLBCL, NOS*EBV
	mucocutaneous ulcer*
	DLBCL associated with chronic inflammation
	Lymphomatoid granulomatosis
	Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma	
ALK	
large B-cell lymphoma	
Plasmablastic lymphoma	
Primary effusion lymphoma	
HHV8	

	DLBCL, NOS*
	Burkitt lymphoma
	Burkitt-like lymphoma with 11q aberration*
	High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
	High-grade B-cell lymphoma, NOS*
	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
Mature T and NK neoplasms	T-cell prolymphocytic leukemia
	T-cell large granular lymphocytic leukemia
	Chronic lymphoproliferative disorder of NK cells
	Aggressive NK-cell leukemia
	Systemic EBV
	T-cell lymphoma of childhood*
	Hydroavacciniforme-like lymphoproliferative disorder*
	Adult T-cell leukemia/lymphoma
	Extranodal NK-/T-cell lymphoma, nasal type
	Enteropathy-associated T-cell lymphoma
	Monomorphic epitheliotropic intestinal T-cell lymphoma*
	Indolent T-cell lymphoproliferative disorder of the GI tract*
	Hepatosplenic T-cell lymphoma
	Subcutaneous panniculitis-like T-cell lymphoma
	Mycosis fungoides
	Sézary syndrome
	Primary cutaneous CD30
	T-cell lymphoproliferative disorders
	Lymphomatoid papulosis
	Primary cutaneous anaplastic large cell lymphoma
	Primary cutaneous gd T-cell lymphoma
	Primary cutaneous CD8
	aggressive epidermotropic cytotoxic T-cell lymphoma
	Primary cutaneous acral CD8
	T-cell lymphoma*
	Primary cutaneous CD4
	small/medium T-cell lymphoproliferative disorder*
	Peripheral T-cell lymphoma, NOS
	Angioimmunoblastic T-cell lymphoma
	Follicular T-cell lymphoma*
	Nodal peripheral T-cell lymphoma with TFH phenotype*
	Anaplastic large-cell lymphoma, ALK
	Anaplastic large-cell lymphoma, ALK
Breast implant-associated anaplastic large-cell lymphoma*	
Hodgkin lymphoma	Nodular lymphocyte predominant Hodgkin lymphoma
	Classical Hodgkin lymphoma
	Nodular sclerosis classical Hodgkin lymphoma
	Lymphocyte-rich classical Hodgkin lymphoma
	Mixed cellularity classical Hodgkin lymphoma
	Lymphocyte-depleted classical Hodgkin lymphoma
Posttransplant lymphoproliferative disorders (PTLD)	Plasmacytic hyperplasia PTLD
	Infectious mononucleosis PTLD

	Florid follicular hyperplasia PTLD*
	Polymorphic PTLD
	Monomorphic PTLD (B- and T-/NK-cell types)
	Classical Hodgkin lymphoma PTLD
	Histiocytic and dendritic cell neoplasms
	Histiocytic sarcoma
	Langerhans cell histiocytosis
	Langerhans cell sarcoma
	Indeterminate dendritic cell tumor
	Interdigitating dendritic cell sarcoma
	Follicular dendritic cell sarcoma
	Fibroblastic reticular cell tumor
	Disseminated juvenile xanthogranuloma
	Erdheim-Chester disease*

Hodgkin's lymphoma

A unique hematopoietic neoplasm occurs mainly in the lymph nodes (>90%). The nodal disease when involves the extranodal areas (1% to 4%) have predilection for neck and mediastinal nodes [8]. It can be further classified as classic HL or lymphocyte-predominant HL with respective incidences of 95% and 5% [3,5]. It had a bimodal age distribution with an early peak in young age group (ages 20 to 24) and second peak in elderly patients aged 80 to 84. Lymphocyte predominant HL latter can occur at any age, but most often occurs in individuals between 30 and 50 years of age [5]. HL is reported to be associated with EBV, immune suppression related to HAART therapy, (rate ratio 14.7 in USA) solid organ transplantation and in patients with a history of autoimmune conditions, such as rheumatoid arthritis (odds ratio [OR], 2.7), systemic lupus erythematosus (OR, 5.8), and sarcoidosis [9].

Post-transplant lymphoproliferative disorder (PTLD)

PTLD is a solid organ or bone marrow transplant complication characterized by uncontrolled lymphocyte proliferation [10].

85% PTLT is caused by B-cell proliferations, 14% are T-cell proliferations, and the remaining 1% is NK-cell or plasmocyte proliferations. The main risk factors being EBV infection, transplant type, age, and administered immunosuppressants.

Lymphomas generally present as fever of an unknown origin (>38°C), inexplicable weight loss (>10% of the body weight in the last 6 months before admission), night sweats [1,18], visceral pain and malaise ("B" symptoms), identified in 40% of the new cases [5]. HL also present with supradiaphragmatic lymphadenopathy and histologically typically characterized by cancerous Reed-Sternberg cells in an inflammatory background [9].

Oral manifestations

NHL form third most common group of malignant lesions in the oral cavity and maxillofacial region. 2% to 3% of the extranodal non-Hodgkin lymphomas appeared in the oral cavity. 41% of NHL extranodal involvement was reported in salivary glands followed by another 41% in the mandible and the maxilla and remaining around the paranasal sinus and Waldeyer ring [11]. Most head-neck NHLs are B-cell lineage, with Diffuse Large B-Cell Lymphoma (DLBCL) being the most commonly seen subtype, followed by small cell NHLs and Burkitt lymphoma [12]. Both primary and relapsed HL is rare

in the oral soft tissues and jaws. Darling et al in their review could trace only 12 reports of primary Hodgkin lymphoma occurring in the oral mucosa, 5 reports of disseminated Hodgkin lymphoma involving the oral mucosa. Tongue, palate and tonsil, Waldeyer's ring (nasopharynx, tonsil, base of tongue and posterior pharyngeal wall) [13].

Clinical features

Hard tissue lesions: Jaw bones: Appear as expansive lesions of jaws causing facial asymmetry. Bone changes in lymphoma may be because of the release of osteoclast-activating factors from the lymphoid cells. Endemic type (African) Burkitt's lymphoma involves the jaws in over 50% of cases [5].

Tooth and alveolar bone: When an osteolytic lesion of jaw involves the tooth they were reported to be mobile. Alveolar bone loss with oedema and pain may also occur which often mimics periodontal diseases [4].

Temporo Mandibular Joint: There was only one case of jaw pain and trismus reported Alexiev et al. [14]. In 2007 due to destruction of condyle by histiocytic sarcoma.

Soft tissue lesions

Soft tissue mass: Asymptomatic soft swelling with or without ulceration that primarily affect the tonsils, palate, buccal mucosa, gums, tongue, floor of the mouth, salivary glands, and retro molar region [5].

Large B cell lymphoma cases have also been reported to present as Gingival and palatal mass. The palatal mass was also associated with ulcerated tissue with destruction of the bone and exposed dental roots, extending to the vestibular area of maxilla [4] PTLT manifested as exophytic/ hyperplastic masses of tongue or buccal mucosa [10].

Ulcers: Unlike myeloid malignancies lymphomas are not commonly presented as ulcers. If present they may be present as ulceration of surface of swellings. A case of T cell lymphoma and few cases of PTLT was reported to be presented as ulcer of oral cavity [10,15]. Mycosis fungoides can also appear as depressed ulcer [16].

Mucosal lesions: Mycosis fungoides can appear as erythematous patches or plaques involving palate and tongue [16]. Oral hairy leukoplakia an asymptomatic, corrugated white patch like lesion on the lateral borders of tongue was reported by Davis et al secondary

Table 2: Oral Manifestations of Common Lymphoid neoplasms.

Neoplasm	Oral Manifestation
NON HODGKINS Lymphoma	- Red or purple extranodal rubbery masses, most commonly occurring on the palatal mucosa, buccal vestibule or gingiva
	- Middle-aged and older patients
	- Jaw bones, producing a ragged radiolucency with vague pain or paresthesia and eventual cortical expansion or perforation (or both)
	- Enlarged lymphnodes.
Primary Large B-Cell Lymphoma	- Painless swelling of the neck, non healing ulcer fever, sweats, and weight loss.
	- Osteolytic jaw lesion with floating tooth appearance.
AIDS-related NHL	- A large mass with bone destruction of the maxilla and sinuses.
	- Mass involving the gums and hard palate presents as ulcerative lesions
Burkitts lymphoma	- Swelling, pain, dental displacements, and facial asymmetry.
	- Radiographically resorptive lesions with diffuse boundaries.
Hairy cell leukemia	- Oral hairy leukoplakia
	- Fatigue and infection
	- Mature b lymphocytes with hairy projections on the cell surface in the blood, bone marrow and spleen
	- Enlarged spleen (90%)
Plasma cell myeloma	- Mandible is commonly involved
	- Soft tissue epulides and swelling.
	- Pain and numbness of mandible
	- Pathologic fractures
	- Lytic lesions of entire skeleton
- Bony hard swelling	
Mantle cell lymphoma	- Salivary gland tumours
Hodgkins Lymphoma	- Extremely rare
	- Presents as mass in oral cavity
	- Commonly involves waldeyer's ring
NK cell/T cell lymphoma	- Associated with EBV in a high proportion of cases
	- Male predominance
	- Originate more frequently in the palate and maxillary gingiva
	- Pursue a more aggressive course than T-cell or B-cell lymphomas
T cell lymphoma	- Uvular mass
	- Labial swelling
	- Mouth ulcers
	- Buccal mucosa and upper gingiva mass
Posttransplant lymphoproliferative disorders (PTLD)	- Oral mucosal hyperplasia
	- Gingival ulcers or erosions resulting from inflammations and transformed into hyperplasia
	- Tongue ulcers and tongue erosion,
	- Oral submucous exophytic fibroids
Langerhans cell histiocytosis	- Involves flat bones of the skull
	- Gingival hyperplasia due to destruction of underlying bone.
	- Multiple punched out lesions in the skull
	- Radiolucency mainly occurring in the central aspect of the mandible or maxilla.
	- Floating teeth appearance.
Histiocytic sarcoma	- Only one reported case involving condylar lesion
	- Paraesthesia of trigeminal nerve along the distribution of Maxillary branch

to hairy cell leukoplakia. The lesion was reported to be due EBV infection and the location of the lesion was due to constant contact of resting tongue by EBV infected saliva [17].

Lymph nodes: Non pain full enlargement of waldeyer's ring, tonsil and salivary gland lymph nodes has been reported.

Salivary glands: Among tumors of the parotid lymphomas present 1% to 4% of cases. They are either extra nodal in origin or due to secondary replacement of parotid parenchyma by nodal lymphomas. The morbidity rate of lymphoma is reported to be as high as 44% when parotid mass is associated with Sjogren Syndrome [18]. Mantle cell lymphoma accounts for 3% of salivary gland tumours [19]. Plasma cell myeloma of submandibular salivary gland was reported to be presented as non-tender upper neck swelling without any mass [20].

Neurologic manifestations: Numbness and paraesthesia has been reported in NHL, HL plasma cell myeloma and Histiocytic sarcoma [13,14,21,22].

Radiographic features

Radiographically, Burkitts lymphoma appears as radiolucent lesion with diffuse edges [5]. Exophytic mass or a facial swelling involving the jaws of Burkitt's lymphoma was noted to appear as noise traces with radiolucent edges, while cortical bone is expanded, eroded, or perforated by infiltration of soft tissues.

Five cases of primary Large B cell lymphoma cases have been reported to be presented as osteolytic, well-circumscribed multilocular lesion, when involving tooth they appeared to be floating in air [4]. Floating tooth appearance was also reported in Langerhans cell histiocytosis Martinelli Klay et al. [23]. Reported in rare cases, NHL may appear as a moth eaten or honeycomb pattern, pathological fracture or osteolysis with or without associated condensation of neighboring soft tissue or periosteal thickening, Tumour extension beyond the bony wall without bone destruction and widening of the mandibular canal and mental foramen in Computed Tomography (CT) were also reported in NHL [24]. Plasma cell myeloma is also known to cause radiolucencies and amyloid deposition in oral cavity [21].

Silva TD reported bone erosion, thickening of the periodontal ligament space and loss of the lamina dura as radiographic findings [5]. George et al had reported a case of pulpal infiltration by plasma cell myeloma appearing as periapical radiolucent lesion [21].

Discussion

Colmenero et al. [25] reported intraoral lymphomas' first signs may appear as infection in 50% of the cases and oral manifestations as the first and only sign of disease. Due its rare presentation and ability to mimic periodontal or common local oral infection and lesion may lead to incorrect and delayed treatment [25].

Common differential diagnosis of inflammatory lesion of dental origin that is misdiagnosed as lymphoma are odontogenic keratocystic tumor, ameloblastoma, other odontogenic lesions, and central giant cell tumor, squamous cell carcinoma versus other malignancy. Colmenero et al. also reviewed various studies where in either patients were subjected to scaling or extraction leading to delayed prognosis and worsening of disease prognosis [25].

Due to the vague presentation of the lymphomas is head and neck dentists must be trained regarding the signs and symptoms of the disease to avoid misdiagnosis. In the region of the head and the neck lymphoma must be considered as a differential diagnosis when there is an inexplicable toothache, insensitivity, and tooth mobility, increase of volume, ulceration, and mass in an extraction alveolus or ill-defined lytic bone alteration in association with lymph node

enlargement [26]. Also non painful lymph node enlargement and a submucosal lesion in the junction between hard and soft palate should be considered highly suspicious [5]. The elevation of serum Lactate Dehydrogenase (LDH) is also frequently seen in lymphoma patients, which is not only a clue of lymphoma but also an indicator of a worse prognosis [27].

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