

Hematolymphoid Tumors of the Oral and Oropharyngeal Region: A Retrospective Case Series from a Tertiary Care Centre

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ABSTRACT

Background: Head and neck malignancies constitute a significant oncological burden in India, with oral and oropharyngeal cancers ranking among the top five in males. Hematolymphoid tumors represent the second most common malignancy type in this region; however, their clinical and pathological characteristics remain underreported, particularly from tertiary Indian centers.

Objective: To analyze the clinical presentation, histopathological features, treatment modalities, and short-term outcomes of hematolymphoid tumors involving the oral and/or oropharyngeal regions at a tertiary care oncology center.

Methods: A retrospective review of patient digital records maintained from April 2021 to March 2024 was conducted. All cases histologically confirmed as oral oropharyngeal hematolymphoid malignancies were evaluated for demographics, clinical features, diagnostic workup, treatment, and follow-up outcomes.

Results: Six cases were identified (4% of 150 oral/oropharyngeal malignancies). The majority were elderly males (mean age 66.7 years; male-to-female ratio 5:1). Non-Hodgkin lymphoma (NHL) was the most common diagnosis (n=4, 67%), followed by multiple myeloma (n=1) and chronic myeloid leukemia in blast phase (n=1). The most frequently affected subsites were the hard palate and buccal mucosa. Treatment regimens were histology-specific: R-CHOP for NHL, imatinib for CML, and the VRD protocol for multiple myeloma. Complete remission was achieved in three patients (50%).

Conclusion: Hematolymphoid tumors are important diagnostic considerations for oral and oropharyngeal lesions. Incisional biopsy at early stage with immunohistochemical panel analysis is critical for accurate subtyping. Appropriately tailored systemic therapy can yield favorable outcomes even in elderly and comorbid patients.

Keywords: Oral cavity; non-Hodgkin lymphoma; hematolymphoid tumors; multiple myeloma; chronic myeloid leukemia; immunohistochemistry; R-CHOP.

INTRODUCTION

Cancer of the oral cavity and oropharynx constitute one of the most significant oncological burdens globally, with an estimated 377,713 new cases and 177,757 deaths recorded worldwide in 2020 according to GLOBOCAN data.^[1] In India, this burden is disproportionately heavy, with lip, oral cavity, and oropharyngeal cancers together accounting for approximately 11–12% of all incident cancers in males, which contributes to nearly one-third of all oral cancer deaths worldwide.^[2,3] This epidemiological evidence is linked to the high prevalence of tobacco use in South Asian populations, both in its smoked (cigarettes, bidis, hookah) and smokeless (khaini, gutkha, pan masala) forms, remaining the dominant etiological drivers of oral squamous cell carcinoma (SCC).^[4] SCC accounts for more than 90% of malignant neoplasms of the oral cavity and oropharynx worldwide.^[5] However, the head and neck region harbor a broad spectrum of non-epithelial malignancies. Among these, hematolymphoid tumors, a heterogeneous category encompassing non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, plasma cell neoplasms, and leukemic infiltrates (including myeloid sarcomas), represent the second most common malignant tumor type of this anatomical region, with a reported incidence ranging from 2% to 8% of all head and neck malignancies in population-based series.^[6,7] Despite this, they remain strikingly underrepresented in the published literature relative to their SCC counterparts, particularly in resource-limited and high-tobacco-burden settings such as India. Over 100 subtypes of hematological malignancies are provided in the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues (5th edition, 2022) along with providing the framework for pathological diagnosis.^[8] Primary Extra nodal NHL, with

diffuse large B-cell lymphoma (DLBCL) accounts for the majority of such presentations.^[6,9] Other entities encountered in this anatomical site include follicular lymphoma, mantle cell lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, Burkitt lymphoma, and natural killer/T-cell (NK/T-cell) lymphoma.^[10,11] Myeloid sarcoma may arise de novo or in the context of a known hematological malignancy such as acute myeloid leukemia or CML blast crisis, and their occurrence in the oral and jaw region, though rare, is documented in case reports.^[12] The clinical presentation of oral and oropharyngeal hematolymphoid tumors is frequently non-specific and overlaps substantially with SCC and other benign lesions. Patients may present with submucosal swelling, mucosal ulceration, bone destruction, or dysphonia, often accompanied by constitutional B-symptoms like fever, drenching night sweats, and unintentional weight loss exceeding 10% of body weight over six months).^[6,9] In India, where the background prevalence of tobacco use creates a strong clinical prior for SCC, this phenotypic overlap is particularly problematic. The consequent diagnostic delay - well documented in the international literature - is compounded in settings where fine-needle aspiration cytology (FNAC) is used as the sole initial investigation, given the established inadequacy of cytological preparations for lymphoid subtyping and the critical need for tissue architecture preservation.^[13,14] From an epidemiological standpoint, oral extra nodal NHL has been described with greater frequency in immunocompromised patients, including those with HIV infection, solid organ transplant recipients, and individuals receiving immunosuppressive therapy.^[9,15] Chronic antigenic stimulation from periodontal disease, dental infections, and oral mucosal inflammation has been proposed as a potential promoter of

localized lymphoproliferation, paralleling the well-established association between *Helicobacter pylori* gastritis and gastric MALT lymphoma.^[16] Accurate diagnosis mandates a structured, protocol-driven approach. In accordance with current guidelines from the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), incisional biopsy with a comprehensive immunohistochemical (IHC) panel is the gold standard for diagnosis and subtyping.^[17,18] Fluorescence in situ hybridization (FISH), molecular clonality studies, and next-generation sequencing (NGS) are increasingly incorporated in the workup of B-cell lymphomas to inform prognostication (e.g., double-hit or triple-hit DLBCL identification) and guide treatment selection.^[19] Staging investigations include 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET-CT), which has superseded conventional CT for initial staging and response assessment in FDG-avid lymphomas, as endorsed by the Lugano Classification.^[20]

Despite the clear clinical importance of these tumors, structured data from Indian tertiary oncology centers are sparse. Existing publications from the region are predominantly individual case reports or small institutional series, limiting the ability to characterize demographic patterns, diagnostic delays, treatment choices, and outcomes in a population with distinct risk factor profiles and healthcare access barriers.^[21] This gap is of direct clinical relevance: clinicians managing oral and/or oropharyngeal lesions in India must maintain an appropriately broad differential diagnosis even in the context of heavy tobacco exposure, since the presence of a recognized risk factor for SCC does not exclude a concurrent or independent hematolymphoid malignancy.

This case series presents six consecutive patients with histopathologically confirmed hematolymphoid tumors of the oral and oropharyngeal region managed at a single

tertiary care oncology center between April 2021 and March 2024. We describe the diagnostic workup, histopathological findings, treatment decisions, and short-term outcomes with the aim of contributing clinically meaningful observational data to the published literature on this underreported disease subset.

CASE PRESENTATIONS

All the 6 patients with diagnostic considerations are summarized in Table 1

Case 1: Stage II Diffuse Large B-Cell Lymphoma of the Hard Palate

Patient: A 55-year-old male, chronic betel quid and cigarette user (30 pack-years), presented with a two-month history of progressive pain and swelling over the hard palate. Constitutional enquiry revealed fatigue and weight loss of 3 kg over six weeks. ECOG performance status was 1. No prior hematological diagnosis.

Diagnostic Workup: Intraoral examination identified a 3 × 2.5 cm firm, non-ulcerated, erythematous submucosal mass over the right hard palate without cervical lymphadenopathy. Prior FNAC at a referring center was non-diagnostic. Incisional biopsy demonstrated sheets of large atypical lymphoid cells with vesicular nuclei and prominent nucleoli. IHC confirmed DLBCL: CD20+, CD79a+, BCL6+, MUM1+ (non-GCB subtype, Hans algorithm)^[22], Ki-67 approximately 80%. 18F-FDG PET-CT showed FDG-avid disease confined to the hard palate and ipsilateral level IB nodes (Ann Arbor Stage II, Lugano Classification; IPI score 1).

Treatment and Outcome: The patient received six cycles of R-CHOP (rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m², prednisolone 100 mg daily for 5 days) administered every 21 days. Treatment was well tolerated with grade 1 hematological toxicity managed with G-CSF prophylaxis. End-of-treatment PET-CT demonstrated a complete metabolic response (Deauville score 1). The patient remains in complete remission.

Case 2: Stage IV Non-Hodgkin Lymphoma of the Buccal Mucosa with Systemic Dissemination

Patient: A 68-year-old male, chronic smokeless tobacco (khaini) user of over 25 years, with a history of hypertension and currently on amlodipine, presented with a four-month history of a rapidly enlarging painful mass over the right buccal mucosa. The patient also gave history of symptoms including drenching night sweats, fever, and weight loss of 6 kg (B-symptoms) on Examination the ECOG performance status was 2.

Examination and Investigations: A 4 × 3 cm indurated, partially ulcerated mass was identified on the right buccal mucosa, abutting the gingiva. Multiple enlarged cervical lymph nodes were palpable bilaterally. Incisional biopsy and IHC confirmed NHL (DLBCL, germinal center B-cell [GCB] subtype): CD20+, CD10+, BCL2+, Ki-67 approximately 90%. Bone marrow trephine biopsy revealed lymphomatous infiltration. 18F-FDG PET-CT demonstrated nodal and extra nodal disease with hepatic and splenic involvement, consistent with Ann Arbor Stage IV disease and IPI score 4 (denoting high-risk).

Treatment and Outcome: Six cycles of R-CHOP were administered. The patient achieved a partial metabolic response on interim PET-CT after cycle 3 and ongoing restaging is in progress. Due to persistent residual disease, consolidative therapy options, including autologous stem cell transplantation, are under multidisciplinary team discussion.

Case 3: Stage IV Non-Hodgkin Lymphoma of the Hard Palate - Complete Remission

Patient: A 72-year-old male, ex-smoker with a 30 pack-year history and known hypertension on antihypertensive therapy, presented with a three-month history of progressive palatal pain, decreased oral intake, and weight loss of 4 kg. ECOG performance status was 2.

Examination and Investigations:

Examination revealed a 4.5 × 3 cm erythematous, firm mass over the hard palate, crossing the midline. Biopsy and IHC confirmed DLBCL: CD20+, CD79a+, MUM1+, BCL6+, Ki-67 approximately 85% (non-GCB subtype). 18F-FDG PET-CT demonstrated involvement of the hard palate, bilateral cervical nodes, and retroperitoneal nodal involvement (Ann Arbor Stage IV; IPI score 3, interpreted as high-intermediate risk).

Treatment and Outcome: Six cycles of R-CHOP were completed with dose reductions in cycles 5–6 for grade 2 mucositis and transient leucopenia requiring G-CSF support. End-of-treatment 18F-FDG PET-CT demonstrated a complete metabolic response with Deauville score 2. The patient is alive and in complete remission during the last follow-up.

Case 4: Stage IV Non-Hodgkin Lymphoma of the Buccal Mucosa in an Octogenarian - Refractory Disease

Patient: An 84-year-old male, with a long history of pipe tobacco use and a concurrent psychiatric illness (managed schizophrenia on antipsychotics), presented with a six-month history of a painless, slowly growing mass over the left buccal mucosa. He reported fatigue and mild appetite loss. ECOG performance status was 2. His age and comorbidity profile mandated a modified treatment approach.

Examination and Investigations: A 3 × 2 cm firm, non-tender, submucosal swelling was identified over the left buccal mucosa. Incisional biopsy with IHC confirmed DLBCL: CD20+, CD79a+, BCL6+, Ki-67 approximately 75%. 18F-FDG PET-CT revealed multifocal nodal and extra nodal disease (Ann Arbor Stage IV). Cardiology clearance was obtained (mildly reduced ejection fraction (EF 48%), given age-related cardiac risk assessment prior to anthracycline use.

Treatment and Outcome: In view of the patient's advanced age (>75 years), the first two cycles were administered as R-CVP

(rituximab, cyclophosphamide, vincristine, prednisolone) to assess tolerability, as per geriatric oncology principles. Cycle 3 was escalated to R-CHOP. Unfortunately, restaging after cycle 4 demonstrated progressive disease. The patient was transitioned to oral metronomic chemotherapy (chlorambucil and prednisolone) and best supportive care, given his frailty and primary refractory status. At the last follow up patient remains under active symptom management.

Case 5: Tonsillar Plasmacytoma with Soft Palate Extension - Multiple Myeloma (RISS Stage II)

Patient: A 60-year-old female, a non-tobacco user, presented with a three-month history of progressive dysphagia, muffled voice, and right-sided throat pain. On examination ECOG performance status was 1. This was the only case in the cohort with a non-lymphomatous diagnosis presenting as a primary oropharyngeal lesion.

Examination and Investigations: Oropharyngeal examination revealed a 4 × 3 cm fleshy, pale, polypoid mass arising from the right tonsil and extending to the soft palate. Biopsy and IHC revealed plasmacytoma: CD138+, CD38+, MUM1+, monoclonal kappa light chain restriction. Systemic evaluation, including serum protein electrophoresis (IgG monoclonal paraprotein), 24-hour urine Bence Jones protein, serum free light chain ratio. Bilateral iliac crest bone marrow trephine biopsy revealed >20% clonal plasma cells, confirming a diagnosis of multiple myeloma. Staging by RISS placed her at Stage II (intermediate serum albumin, elevated beta-2-microglobulin, favorable cytogenetics).^[23] Whole-body MRI and PET-CT identified a solitary lytic lesion in the right iliac wing.

Treatment and Outcome: The patient was started on the VRD protocol (bortezomib 1.3 mg/m² subcutaneously on Days 1, 4, 8, 11; lenalidomide 25 mg orally Days 1–14; dexamethasone 40 mg weekly) in 21-day cycles. The therapy was tolerated well, with

the patient experiencing only grade 1 peripheral neuropathy managed with dose adjustment of bortezomib. A very good partial response (VGPR) was achieved based on serum immunofixation and free light chain normalization after four cycles. She is currently being evaluated for high dose melphalan and autologous stem cell transplant consolidation.

Case 6: Chronic Myeloid Leukemia in Blast Crisis Presenting as a Mandibular Chloroma with Pathological Fracture

Patient: A 63-year-old male, occasional alcohol consumer and non-tobacco user, presented acutely with a six-week history of progressive jaw pain, facial swelling, and an inability to chew, culminating in an acute pathological fracture of the right mandibular body. There was no prior hematological diagnosis. ECOG performance status was 2.

Examination and Investigations: Radiological examination revealed a pathological fracture of the right mandibular body with associated soft tissue swelling and right submandibular lymphadenopathy. Peripheral blood count showed leukocytosis (WBC 85,000/μL) with 32% circulating blasts. LDH was markedly elevated (1,840 U/L). Mandibular mass biopsy and IHC confirmed myeloid sarcoma: MPO+, CD33+, CD34+, CD117+, TdT+, CD19+ (indicating lymphoid blast crisis). BCR-ABL1 quantitative PCR (peripheral blood) detected p210 BCR-ABL1 transcript (IS 48%). Bone marrow examination confirmed CML in lymphoid blast crisis (>30% TdT+/CD19+ lymphoblasts). Conventional cytogenetics: t (9;22) (q34; q11.2). 18F-FDG PET-CT confirmed disease localized to the mandible without evidence of additional extramedullary sites beyond the bone marrow.

Treatment and Outcome: Maxillofacial stabilization with intermaxillary fixation was performed prior to systemic therapy. The patient was initiated on imatinib mesylate 400 mg orally once daily (European LeukemiaNet, (ELN)2020 guideline-concordant) ^[24], with concurrent

hematological supportive care. After three months of therapy, BCR-ABL1 transcripts decreased by 1.5 log (IS: 1.5%), signifying a hematological and early cytogenetic response. The patient indicated edema as the primary adverse effect, which was

addressed with dose adjustment and dietary sodium limitation. Further consolidation with allogeneic stem cell transplantation is being investigated due to the blast crisis presentation, with the response assessment now in progress.

Table 1. Summary of patient demographics, histopathological diagnoses, treatment regimens, and outcomes.

Case	Age (yrs)	Sex / Tobacco	Site	Histopathology	Stage	Treatment	Outcome
1	55	Male / Yes	Hard palate	DLBCL (NHL)	Ann Arbor II	R-CHOP ×6	Complete remission
2	68	Male / Yes	Buccal mucosa	DLBCL (NHL)	Ann Arbor IV	R-CHOP ×6	Ongoing / Partial response
3	72	Male / Yes (ex)	Hard palate	DLBCL (NHL)	Ann Arbor IV	R-CHOP ×6	Complete remission
4	84	Male / Yes	Buccal mucosa	DLBCL (NHL)	Ann Arbor IV	R-CVP → R-CHOP	Refractory → Metronomic
5	60	Female / No	Tonsil / Soft palate	Multiple myeloma	RISS II	VRD protocol	VGPR / Ongoing
6	63	Male / No	Mandible / Submandibular	CML blast crisis (chloroma)	Blast crisis	Imatinib 400 mg	Partial molecular response

DLBCL: Diffuse Large B-Cell Lymphoma; NHL: Non-Hodgkin Lymphoma; CML: Chronic Myeloid Leukemia; RISS: Revised International Staging System; VGPR: Very Good Partial Response.

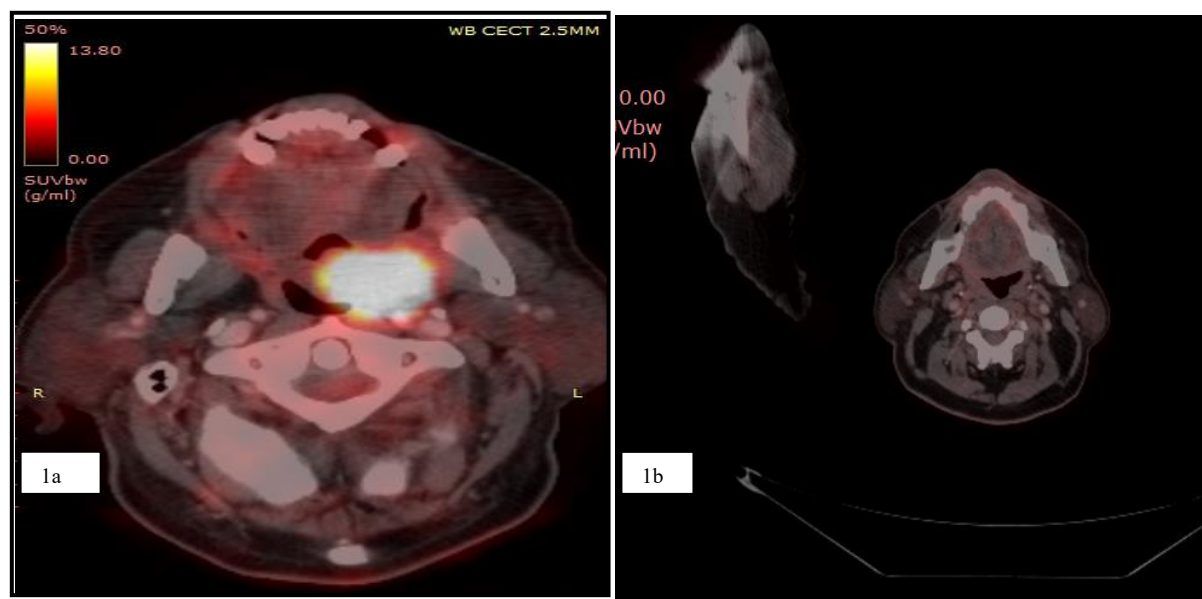


Figure 1. Showing PET-Based Evaluation of pretreatment and post-treatment images for a patient of Oropharyngeal NHL. Figure 1a: Disease in Left Tonsillar Region involving soft palate; Figure 1b: Imaging Done After 6 cycles of RCHOP-Based chemotherapy showing complete Metabolic Response

DISCUSSION

Incidence, demographics, and epidemiological Context

In our cohort, hematolymphoid tumors accounted for 4% of all oral and oropharyngeal malignancies, consistent with

published estimates of less than 10% among head and neck cancers.^[6,7] DLBCL was the commonest subtype (67%), mirroring global trends in which NHL is the most frequent hematolymphoid neoplasm of the oral cavity and oropharynx.^[8-11] The strong male

predominance (5:1) and older mean age at presentation (66.7 years) also align with international data.^[6,7,9] Three of four NHL cases presented at Ann Arbor Stage IV, reflecting the diagnostic delays typical of these lesions in the oral cavity. Clinically, they may resemble SCC, but unlike SCC, which often shows keratinization, surface induration, and a strong association with tobacco and alcohol, hematolymphoid tumors usually present as submucosal swelling without keratinization and may grow rapidly.^[6]

Tobacco Use and Lymphomagenesis

Chronic tobacco use was documented in four of six patients (67%). Although tobacco is a well-established risk factor for oral SCC^[4], its role in hematolymphoid malignancies is less certain. Morton et al. reported a significant association between cigarette smoking and some NHL subtypes, particularly follicular lymphoma, mediated through immunosuppressive effects.^[25] In our cohort, the high tobacco exposure may partly reflect background population habits in India rather than a direct causal role, though this warrants further study.

Diagnostic Imperative: Biopsy and Immunohistochemistry Over FNAC

A major lesson from this series is the inadequacy of FNAC for definitive diagnosis. In several cases, FNAC performed at referring centers was indeterminate or non-diagnostic. This reflects the limitations of cytology in lymphoid neoplasms, where preservation of tissue architecture is essential and reactive lymphoid hyperplasia cannot be reliably distinguished from lymphoma on single-cell preparations.^[13,14] Incisional biopsy with a comprehensive IHC panel was diagnostic in all six cases. In non-Hodgkin lymphoma (NHL), the main markers that were evaluated included CD20, CD79a, CD3, BCL2, BCL6, CD10, MUM1, and Ki-67 to help identify the type of lymphoma and its biological behavior. In multiple myeloma, the most important markers were CD138

and CD38, along with kappa and lambda light chain restriction. For myeloid sarcoma, MPO, CD33, CD34, CD117, and TdT were informative, while BCR-ABL1 quantitative PCR confirmed the CML case.^[24] These findings support biopsy with IHC as the diagnostic gold standard for atypical oral lesions.^[17,18]

Site-Specific Diagnostic Challenges

The hard palate and buccal mucosa, commonly involved in our series, are also frequent sites for SCC and benign lesions such as palatal tori, salivary gland tumors, and necrotizing sialo metaplasia. Features suggesting a hematolymphoid lesion include rapid growth, absence of surface keratinization or leukoplakia, systemic symptoms, and bone erosion without the typical radiographic appearance of SCC.^[5,6] The pathological mandibular fracture in Case 6 due to myeloid sarcoma shows how unusual oral presentations may be the first sign of systemic hematological disease.

Treatment Rationale, outcomes, and limitations

R-CHOP remains the standard treatment for DLBCL.^[17,18] All four NHL patients received R-CHOP-based therapy, with complete remission in two cases. In an 84-year-old patient, initial treatment was modified to R-CVP, reflecting geriatric oncology practice of adjusting therapy to age, comorbidity, and fitness.^[26] The VRD regimen used in the myeloma case produced VGPR after four cycles and may allow transplant consolidation.^[27] The CML case treated with imatinib showed molecular response but retained a guarded prognosis because blast crisis has poor outcomes, with allogeneic transplantation being the only potentially curative option.^[24]

CONCLUSION

This case series demonstrates that hematolymphoid tumors, although constituting a small minority of oral and oropharyngeal malignancies, represent diagnostically important entities that must

be considered in the differential diagnosis of any unusual oral or oropharyngeal mass. Their clinical similarity to squamous cell carcinoma, combined with the high background prevalence of tobacco-associated oral SCC in India, creates conditions in which these tumors may be misdiagnosed or have their diagnosis delayed. Heightened clinical awareness, early biopsy, and multidisciplinary management are essential to improving outcomes for this rare but treatable subset of head and neck malignancies.

Declaration by Authors

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