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Reshma Poothakulath Krishnan, Deepak Pandiar, Pratibha Ramani

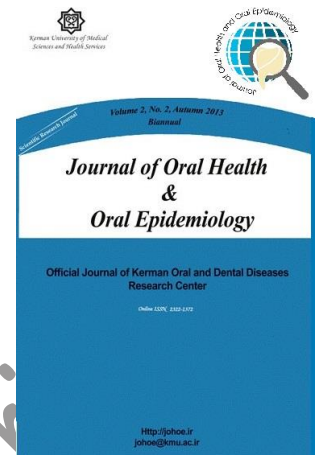
DOI: <https://doi.org/10.34172/johoe.2302.1533>

### Article History:

Received Date: May 6, 2023

Accepted Date: August 17, 2023

epublished Author Accepted Version: March 27, 2024



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**Please cite this article as:** Krishnan RP., Pandiar D., Ramani P. Differential diagnosis of hematopoietic malignancies of head and neck: Report of six cases. *Journal of Oral Health and Oral Epidemiology*, 2024; 13(1). [doi.org/10.34172/johoe.2302.1533](https://doi.org/10.34172/johoe.2302.1533).

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Manuscript Type: Case Report(s)

## **Differential diagnosis of hematopoietic malignancies of head and neck: Report of six cases**

Reshma Poothakulath Krishnan<sup>\*1</sup>, Deepak Pandiar<sup>2</sup>, Pratibha Ramani<sup>3</sup>

1. Senior lecturer, Oral Pathology and Microbiology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India.
2. Associate Professor, Oral Pathology and Microbiology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India
3. Professor and Head, Oral Pathology and Microbiology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India.

**Correspondence to:** Ala Alwan; [aalwan1@outlook.com](mailto:aalwan1@outlook.com)

### **Abstract**

**Background:** Lymphoma and multiple myeloma account for a small but significant proportion of all oral malignancies. Oral manifestations of hematopoietic malignancies are sometimes diagnosed with delay as most of them mimic various other diseases like osteomyelitis and periodontal diseases. We present five unusual, challenging cases of head and neck lymphomas and one case of oral myeloma.

**Methods:** In this article, we report six cases, five cases of oral lymphomas, and one oral multiple myeloma case. All cases were initially diagnosed by oral histopathologists and then referred to specialists for further treatment.

**Results:** We report these cases to understand these lesions better, as we saw some worrisome delays in their diagnoses. We aim to raise awareness about these hematopathological diseases among general dentists.

**Conclusion:** It is crucial for the multidisciplinary team members to thoroughly examine the oral cavity for any worrisome lesions like these, as they might be an initial sign of a systemic disease. Pathologists must also be aware of the pitfalls in the interpretation of immunohistochemical sections and the immune profile of a tumor.

### **Keywords**

lymphoma, multiple myeloma, oral malignancies, Hodgkins' lymphoma, neoplasm

## **Introduction**

Several systemic diseases, like Crohn's disease, myelomas, and lymphomas, show oral manifestations; however, these symptoms are not pathognomonic and might be the initial signs of the disease. Lymphoma, a malignant hematopathological disease, shows clonal proliferation of lymphoid cells or their precursors 1. The lymphoid tissue in the oral cavity can potentially undergo malignant transformation and cause systemic diseases, such as lymphoma 2. They account for 14% of head and neck cancers, and 97% of these are reported to be non-Hodgkin's lymphomas 3. Multiple myeloma shows monoclonal proliferation of plasma cells and is rarely reported in the oral cavity 4. These account for only 10% of hematological cancers 5. Multiple myeloma exhibits varied clinical presentations; therefore, awareness of suspicious lesions of the oral cavity is critical for proper diagnosis and treatment.

In this article, we report six cases: five cases of lymphomas and one multiple myeloma case that presented initially in the oral cavity. This article also highlights the various clinical symptoms of these hematopathological diseases, the diagnostic challenges faced, and the role of general dentists in diagnosing these diseases.

## **Methods**

From 2008 to 2021, five patients with oral lymphoma and one with multiple myeloma presented to the Department of Oral Pathology of a private dental college and hospital in Chennai, Tamil Nadu. Four patients presented with diffuse B cell lymphoma and one patient with Hodgkin's lymphoma. Oral pathologists diagnosed all the above cases and then referred them to the specialists for further treatment. Clinical presentation (Figure 1), histopathological features (Figure 2), and immunohistochemical findings are provided in Table 1.

## **Results**

We report these cases to improve practitioners' understanding of these lesions, as we saw some worrisome diagnosis delays. Various diagnostic procedures were performed due to the wide variety of differential diagnoses. Biopsy procedure was also found to be delayed in a few cases.

## **Discussion**

Hematological malignancies like lymphomas and myelomas present as the proliferation of lymphoid and plasma cells, respectively. Lymphoma and multiple myeloma comprise a small but significant proportion of oral cancers, and these lesions have various presentations in the oral cavity 6. The data for the above malignancies in India is limited. In this case series, we report six cases of lymphoma and myeloma for a better understanding of these lesions.

Hematological malignancies like lymphomas and myelomas show varied clinical presentations, which mimic diseases like osteomyelitis, sarcomas, and common conditions such as periodontitis. In our case series, all the patients, including those with Hodgkin's and non-Hodgkin's lymphoma, complained of swelling, and two patients reported pain. The patient with Hodgkin's lymphoma showed multiple swellings along the course of lymph nodes. None of the clinical features mentioned above are specific to lymphoma. Moreover, the patient with Hodgkin's lymphoma had been treated with antibiotics, suspecting a bacterial infection, and there was a delay in performing a biopsy. Differentiating these malignancies from infectious diseases like cytomegalovirus and Epstein-Barr virus infections is also important. Multiple myeloma is less common in the oral cavity and might present as swelling in the jaw with tooth mobility, paresthesia, and cortical destruction of bone 7. Our case also had swelling and a mobile tooth in the upper front tooth region. None of these symptoms are particularly specific to multiple myeloma and can lead to a misdiagnosis in their initial stages. The clinical symptoms of oral lymphoma (both Hodgkin's and non-Hodgkin's lymphoma) and multiple myeloma were heterogeneous in our case series. A wide range of differentials can be given for these lesions.

Lymphoma and myeloma diagnosis is one of the most complicated tasks in histopathology, and the exact classification greatly affects the patient's treatment and overall prognosis. An invasive diagnostic procedure like a biopsy should be taken if the clinical or radiographic findings are doubtful and do not match the patient's history and symptoms. Adequate tissue sampling and auxiliary pathologic tests are necessary for an accurate diagnosis. In our case series, an incisional biopsy was done in five cases, and a true-cut biopsy was done for the Hodgkin's lymphoma case. As it was a true cut biopsy specimen, further subtyping of Hodgkin's lymphoma was impossible. Improper biopsy techniques with insufficient tissue will further hinder the diagnosis and delay the treatment 8. We recommend an incisional biopsy to ensure sufficient tissue for further diagnostic procedures, such as immunohistochemistry and molecular diagnostic tests. This prevents delays in diagnosis and treatment. Oral pathologists should communicate with the surgeons in case of doubts regarding the symptoms and inform them about the adequate tissue requirement.

Pathologists must be aware of the pitfalls in the interpretation of immunohistochemical sections and the immune profile of a tumor. Immunohistochemistry must be used with knowledge of the sensitivity and specificity of each marker. In our case of multiple myeloma, CD45 was positive. CD45, a common leukocyte antigen, is a transmembrane protein found on all nucleated hematopoietic cells. Most myeloma cases are not positive for CD45. However, it has been reported that immature proliferating myeloma cells are positive for CD45 9. According to Kumar S et al., myeloma patients with CD45 positivity have an increased overall survival 10. Knowledge of the immunohistochemical markers and their staining patterns is critical in diagnosing a disease. As CD45 was positive in our case, other than lymphoma, we had a differential diagnosis of multiple myeloma, and the patient was sent for flow cytometry. Flow cytometry can be used when immunohistochemical techniques

fail to identify the antibodies in FFPE (formalin-fixed paraffin-embedded sections). These diagnostic methods should be implemented in the routine diagnosis of hematopathological diseases.

This article describes various clinical presentations of patients with hematopathological diseases affecting the oral cavity and raises awareness among general dentists. The main cause of misdiagnosis or delay in these types of lesions could be lack of access to specialists, poor compliance, and similarity of pathological manifestations. In our experience, if a patient presents with an unusual swelling and is not responding to the primary treatment modality, other rare lesions should be considered, and a biopsy should be performed.

### **Strengths and Limitations**

This case series provides the demographic data, clinical symptoms, and diagnostic procedures performed on six patients with lymphoma and myeloma referred to our department. Furthermore, the article also explains the importance of the judicious use of diagnostic techniques like immunohistochemistry and flow cytometry in diagnosing these lesions.

### **Conclusion**

General dentists must be aware of these rare conditions as they play an important role in diagnosing and treating these hematological lesions. The entire oral cavity should be thoroughly examined, and the pitfalls in interpreting immunohistochemical sections should also be considered before the final typing of these lesions.

### **Acknowledgments**

**NIL**

### **Authors' Contribution**

Conceptualization: Reshma Poothakulath Krishnan and Deepak Pandiar

Data Curation: Reshma Poothakulath Krishnan and Deepak Pandiar

Investigation: Reshma Poothakulath Krishnan and Deepak Pandiar

Formal Analysis: Reshma Poothakulath Krishnan and Deepak Pandiar

Methodology: Reshma Poothakulath Krishnan

Project Administration: Reshma Poothakulath Krishnan

Supervision: Deepak Pandiar and Pratibha Ramani

Software: Reshma Poothakulath Krishnan

Resource: Pratibha Ramani

Validation: Reshma Poothakulath Krishnan and Deepak Pandiar

Visualization: Reshma Poothakulath Krishnan

Writing – Original Draft: Reshma Poothakulath Krishnan

Writing – Review & Editing: Deepak Pandiar and Pratibha Ramani

**Competing Interests: NIL**

**Data Availability Statement: NIL**

**Ethical Approval: Institutional Ethics Committee number was obtained (IHEC number: SRB/SDC/FACULTY/22/OPATH/053).**

**Funding: NIL**

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Table 1: Clinical presentation, histopathological features, and IHC findings of the lymphoma and myeloma cases

No.	Age	Sex	Site	Duration	Clinical features	Differential diagnosis	Diagnostic methods	Histopathological finding	IHC	Diagnosis	Additional findings
1	29	F	Right and left side neck  (Figure 1A)	3 months	Multiple swellings on both sides of the neck  Dull aching pain  H/O pruritis (past 3 months)  H/O treatment with antibiotics expecting an infectious cause.	Infection  Granulomatous lesions  Lymphoma	True cut biopsy	Small lymphocytes showing irregular nuclei  Few large binucleated cells resembling Reed-Sternberg cells and lacunar cells	CD15 <sup>+</sup> +ve for Reed-Sternberg cells	Lymphoproliferative disorder  Hodgkin's lymphoma.  The patient was advised to have a CT scan.	CT scan: Multiple enlarged submandibular, bilateral axillary, paraaortic, upper and lower paratracheal and prevascular nodes  Multiple enlarged inguinal and femoral nodes were noted on either side.  The spleen was mildly enlarged.  Diagnosis of Hodgkin's lymphoma was confirmed.

2	37	F	Swelling in the left maxillary back tooth region	20 days	Swelling expanded buccopalatally from the 24–27 region  The swelling was a reddish, soft, raised lesion with a smooth surface.	Squamous cell carcinoma  Soft tissue sarcomas  Hematological malignancy	Incisional biopsy	Large tumor cells exhibiting round to oval-shaped vesicular nuclei with prominent nucleoli  Few large cleaved cells and numerous mitotic figures were evident.	CD 45, CD 20+ve for tumor cells.	Lymphoproliferative disorder  Diffuse Large B-cell lymphoma.
3	60	F	Growth in the maxillary anterior tooth region  (Figure 1B)	2 months	The swelling was 2×3 cm in size with a reddish-white color and firm consistency (Figure 2).  An area of necrosis was seen on the swelling.	Squamous cell carcinoma  Metastasis  Odontogenic cyst/tumor  Soft tissue sarcomas	Incisional biopsy	Numerous monomorphic round cells, seemingly of lymphoid origin, arranged in sheets with large round nuclei, showing vesicular chromatin patterns with prominent nucleoli along with pale scanty cytoplasm, were seen (Figure 3).  Numerous mitotic figures	CD 45 (Figure 4) and CD 20 showed strong positivity for tumor cells.	Lymphoproliferative disorder  Large Non-cleaved diffuse B-cell lymphoma.
4	44	M	Swelling in the left mandible	2 months	Diffuse swelling was evident, extending from the 34–48 region.  Soft in consistency with mild	Odontogenic tumor  Intraosseous malignancy  Metastasis  Soft tissue sarcoma	Incisional biopsy	Atypical lymphoid cells arranged in sheets and scattered cells (Figure 5).  Their cells were monotonous and round, with	CD 45 and CD 20+ve among tumor cells	B cell lymphoma, possibly diffuse large B-cell lymphoma.



					tenderne ss on palpatio n.  On radiogra phic examina tion, multiloc ular radioluc ency was evident in the left body of the mandibl e.			scanty cytoplasm, vesicular nuclei, and prominent nucleoli.  Numerous mitotic figures (4- 5/10 hpf) were also evident.			
5	40	F	Swelli ng in the left maxill ary back tooth region	2 mont hs	Swellin g was evident in relation to the 25, 26, and 27 regions showing buccal and palatal expansi on.  CT scan revealed an expandi ng lesion in the sinus.	Odontoge nic tumor  Sinus pathology  Intraosseo us malignanc y  Soft tissue sarcoma	Incisio nal biopsy	Few small round cells with round to ovoid nuclei, irregular or cleaved nuclear contours, and scanty cytoplasm suggestive of centrocytes intermixed with numerous large round cells with round to ovoid nuclei, open nuclear chromatin, several nucleoli and a modest amount of cytoplasm suggestive of centroblasts .	CD 20, BCL2 - showe d strong positi vity amon g the tumor cells. CD 45 showe d diffus e focal positi vity for tumor cells.	Lymphoprolif erative disorder  Diffuse large B-cell lymphoma.	

6	54	M	Swelling and mobile tooth in the upper front tooth region  History of exfoliation of tooth 20 days back.  (Figure 1C).	15 days	A growth was seen in the upper front teeth region, reddish-white in color and firm in consistency.	Metastasis  Oral squamous cell carcinoma  Hematopoietic lesion	Incisional biopsy	Monotonous sheets of variably differentiated pleomorphic round cells with many cells showing eccentrically placed hyperchromatic vesicular nuclei, increased nuclear-cytoplasmic ratio, and few mitotic figures were evident.  Numerous oval-shaped cells with eccentrically placed nuclei resembling plasma cells	CD 45-+ve	Malignancy of hematopoietic origin.  The patient was advised to have a CT scan and flow cytometry.	CT scan: A well-defined heterogeneously enhancing lesion in the anterior maxilla and upper lip with extension and erosion of adjacent bones. A few small lytic lesions in the D1 vertebral body and frontal bone were evident. Correlating radiographically and comparing the flow cytometric results, a final diagnosis of multiple myeloma was made.
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## Figures

Figure 1: Photomicrograph shows clinical presentation of (A) Hodgkin's lymphoma, (B) non-Hodgkin's lymphoma, (C) multiple myeloma

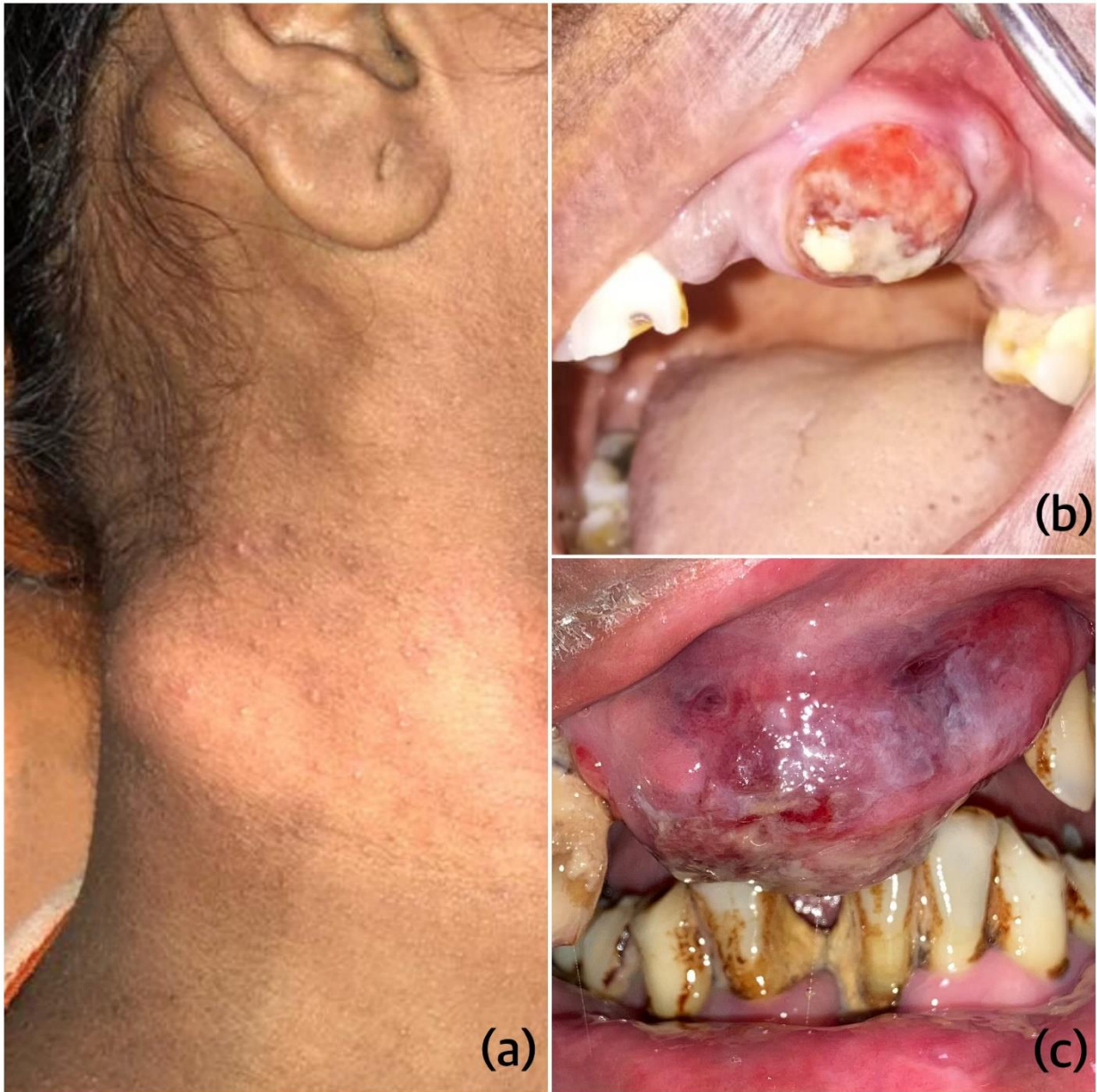


Figure 2: Photomicrograph shows histopathological features of lymphomas and myeloma (a, b, c, e, f: 400× and d: 40×)

