

Oral lymphoma: a report of two contrasting cases

Précis

We highlight the varying manifestations of lymphoma in the oral cavity by presenting two contrasting cases. The journey from referral to diagnosis and management is discussed.

Abstract

Introduction: Non-Hodgkin's lymphoma (NHL) is a broad term for malignancies of the lymphoreticular system. NHL of the oral cavity is relatively rare and can manifest in a variety of ways, which can make initial diagnosis difficult.

Objectives: We discuss two contrasting cases of patients who initially presented with oral lesions to highlight the heterogeneity of lymphoma in the oral cavity and the importance of a thorough history and examination.

Methods: Case note review was undertaken for Case 1 and Case 2.

Results: Case 1 involves a 56-year-old male who was referred from his general practitioner to the oral and maxillofacial surgery (OMFS) emergency clinic with a three-week history of painful, intra-oral, ulcerated swellings in all four quadrants. He had recently developed fever, drenching night sweats and unexplained weight loss. The patient was admitted under OMFS until biopsy confirmed NK-T cell NHL. Case 2 involves a 68-year-old male who was urgently referred by his dentist, who had noticed a red patch on the left hard/soft palate junction at routine check-up. On examination, there was a 15mm erythematous, fixed submucosal lump on the left hard/soft palate junction. He was otherwise asymptomatic. Biopsy confirmed follicular B-cell NHL. Both patients were referred to haematology for ongoing care.

Conclusions: For intra-oral lesions, lymphoma should be considered as a differential diagnosis until ruled out by biopsy. Biopsies should be performed promptly in order to prevent delays in treatment. A thorough history may help to identify the presence of 'B symptoms'.

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Introduction

Lymphoma represents a broad range of malignancies involving the lymphocytic cells. The World Health Organisation classification currently includes over 60 different types of non-Hodgkin's lymphoma, subdivided based on their histology and cell lineage. The most common presentation of lymphoma is swelling of the lymph nodes, often cervical or mediastinal, and the presence of 'B-symptoms', which include weight loss, fatigue, fever and night sweats. Lymphoma presenting in extra-nodal sites is less common and its presentation in the oral cavity can often be an indicator of widespread disease elsewhere in the body.

We present two cases of non-Hodgkin's lymphoma of differing subtypes,

presentation, severity and prognosis to indicate the heterogeneity of the condition. These cases illustrate the role of primary care clinicians, including general dental practitioners (GDPs), in the diagnosis of lymphoma affecting the oral cavity.

Case 1

A 55-year-old male initially presented to the oral and maxillofacial surgery (OMFS) emergency clinic with multiple, painful intra-oral gingival swellings in the upper left, upper right and lower left quadrants following an urgent referral from his general medical practitioner (GMP). The patient had initially been examined by his GDP, who had excluded dental aetiology.



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FIGURES 1a and 1b: Case 1: On intra-oral examination, multiple soft tissue gingival swellings were observed in the upper left quadrant buccally and palatally, the upper right quadrant buccally and palatally, and adjacent to the LL7.

History

The patient complained of a three- to four-week history of intra-oral swellings, severe intra-oral pain, fever, malaise, weight loss and night sweats. He had no previous medical history of note and was a non-smoker with a past history of moderate alcohol consumption.

Exam

Extra-oral examination revealed a high fever, with no palpable cervical/axial/inguinal lymph nodes or facial swelling. A two-finger-width mouth opening was noted secondary to pain. Intra-orally, multiple soft tissue gingival swellings were observed in the upper left quadrant buccally and palatally, the upper right quadrant buccally and palatally, and adjacent to the LL7 (**Figures 1a and 1b**). The swellings were most extensive in the upper left quadrant, measuring approximately 3.0 x 1.5cm buccally and 4.0 x 1.5cm palatally. In the upper right quadrant the swellings were 2.5 x 1.0cm buccally and 2.5 x 1.5cm palatally, and adjacent to the LL7 the swelling measured approximately 2.0 x 1.5cm. The swellings were irregularly shaped with obvious margins, soft, red/purple in colour with patches of white, showed friable surface ulceration, and were very painful to touch. There was no obvious suppuration and the teeth were not tender to percussion. The differential diagnoses included: infection or sepsis; neoplasia; metastatic neoplasia; haematological malignancy; or, chronic inflammatory conditions such as IgG4-related disease. The patient was admitted under OMFS with input from the medical team. Initial management included intravenous fluids, analgesia and broad-spectrum antibiotics.

Additional tests

Haematological investigations showed raised C-reactive protein (CRP), alkaline phosphatase and gamma-GT. A panoramic radiograph and chest x-ray showed no relevant findings. A computerised tomography (CT) scan of the thorax, abdomen and pelvis showed extensive malignant disease with masses in the liver, adrenals, pancreas and mesentery, with widespread lymphadenopathy and left portal vein infiltration. An urgent intra-oral incisional biopsy yielded three samples for which histopathology revealed extensive surface ulceration with an infiltration of medium/large-sized lymphocytes. The lymphocytes showed a high nucleus to cytoplasm (N:C) ratio, with small, moderately polymorphic nuclei. Immunohistochemistry analysis demonstrated that the cells expressed CD56, CD3 and CD2, indicating that the lymphocytes were NK-cells and T-cells. Additionally, viral markers were positive for Epstein Barr virus (EBV), which is associated with T-cell lymphomas. This confirmed the diagnosis of non-Hodgkin's NK/T-cell lymphoma stage 4B.



FIGURE 2: Case 2: A photograph accompanied the description of the lesion to aid triage.

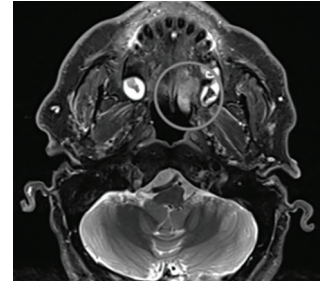


FIGURE 3: Case 2: Magnetic resonance imaging of the neck with contrast demonstrated the known lesion at the posterior hard palate.

The patient was subsequently referred to the haematology team and promptly commenced on chemotherapy; initially a cycle of cyclophosphamide, doxorubicin hydrochloride, vincristine sulphate and prednisone (CHOP) was prescribed, followed by PegAsparaginase, dexamethasone, cisplatin and gemcitabine (P-DGP). Unfortunately, the patient developed complications associated with his second round of chemotherapy and died three months following his initial presentation.

Case 2

A 68-year-old male was referred via a standard, electronic referral to the OMFS department. His GDP had noticed an erythematous lesion on the left side of the junction of the hard and soft palate at a routine dental check-up. This was described as a "red lesion, slightly raised, soft, no pain, no irritation, patient not aware, approximately 1cm". The GDP reviewed this lesion at two weeks and, due to lack of resolution, decided to refer the patient. A photograph accompanied the description of the lesion to aid triage (**Figure 2**). The referral was triaged and the patient was given an urgent telephone appointment 20 days after initial referral, where he was listed for biopsy.

Medical history

The patient's medical history consisted of hypertension and hypercholesterolaemia, for which he took amlodipine and a statin. The patient was being monitored for an enlarged prostate and there was a family history of cancer on his mother's side. The patient was a non-smoker. The patient was asymptomatic and had not experienced any 'B-symptoms'.

Exam

On examination, there was a 15mm soft, fixed, submucosal lump with overlying erythema at the left, posterior hard palate. There was no cervical lymphadenopathy.

Additional tests

An urgent incisional biopsy demonstrated a diffuse lymphocytic infiltrate and the sample was sent for expert histopathological review where a conclusive diagnosis of low grade, follicular B-cell lymphoma was made.

CT thorax, abdomen and pelvis revealed indeterminate, scattered, small mesenteric nodules. Magnetic resonance imaging (MRI) of the neck with contrast demonstrated the known lesion at the posterior hard palate: "There is a well-demarcated, subtle lesion seen along the posterior aspect of the hard palate on the left measuring about 18 x 11 x 7mm in size (TR x AP x SI). It appears mildly

Table 1: Risk factors associated with lymphoma.⁶

Age
Family history/genetics
Gender
Certain infections – viral (e.g., Epstein-Barr virus) and bacterial (e.g., <i>H. pylori</i>)
Immunodeficiency, e.g., HIV, post organ transplant
Autoimmune disorders, e.g., Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, coeliac disease, psoriasis
Chemicals/radiation
Smoking
Alcohol

T2 hyperintense and shows mild postcontrast enhancement, although there is no obvious marrow oedema seen at the edges" (**Figure 3**). A solid mass lesion involving the posterior aspect of the left submandibular gland, which was probably of the same aetiology, was also noted and was described as "a lobulated lesion seen along the posterior aspect of the left submandibular gland measuring 25 x 26 x 32mm in size. It appears intermediate signal on T2W images, hypointense on the T1W images and shows diffuse mild contrast enhancement. There is also intense diffusion restriction seen within this lesion". Blood investigations included slightly raised IgA. The patient was referred to haematology for discussion at their multidisciplinary team meeting and the decision was made to begin active monitoring.

Discussion

Lymphoma is a malignant disease characterised by neoplastic proliferation of lymphocytes or their precursor cells.¹ It can be broadly subdivided into Hodgkin's and Non-Hodgkin's, based on the presence or absence, respectively, of histologically distinct Reed-Sternberg cells.² Non-Hodgkin's Lymphoma (NHL) comprises 86% of lymphomas and 20-30% of cases show extra-nodal presentations.³ NHL can be further subdivided according to the types of lymphocytic precursors involved such as B-cell or T-cell. Oral cavity involvement is rare and seen in approximately 2% of cases; this explains why clinicians may not initially consider lymphoma as part of the differential diagnosis.⁴ However, lymphomas are the second most common malignancy to occur in the head and neck region (after squamous cell carcinomas), making up 3.5% of intra-oral malignancies.^{2,5} **Table 1** describes the risk factors associated with lymphoma.⁶ A review of the literature took place using PubMed and the search terms 'lymphoma' and 'oral cavity'. Our case comparison and the literature review demonstrate the varying clinical manifestations of lymphoma, which can mimic more common malignant, benign or dental pathologies. In particular, oral lymphoma has been known to mimic apical periodontitis, acute periapical abscesses, osteomyelitis, odontogenic tumours (e.g., ameloblastomas), and malignancies such as squamous cell carcinomas.² Common sites include the gingivae, palate, maxilla, mandible and tongue.⁷ One study reported that 40% of cases are initially misdiagnosed, which can delay the ultimate diagnosis and treatment.⁷ Since involvement of the oral cavity is often secondary to a more widespread malignant process, any delay in diagnosis can significantly reduce the prognosis.⁸ **Table 2** describes the common systemic and oral presentations of lymphoma.

In general, NHLs are highly sensitive to radiotherapy and chemotherapy, but

Table 2: Systemic and intra-oral presentations of lymphoma.⁷

Systemic	Intra-oral
Fever	Swellings of palate, gingivae, buccal mucosa
Drenching night sweats	Non-healing ulcers
Unexplained weight loss	Bony expansion
Painless enlarged lymph nodes	Osteolytic radiolucencies
Fatigue	Paraesthesia/anaesthesia
Cutaneous symptoms, e.g., rash/itching	Unexplained tooth mobility or pain
Frequent infections	

Table 3: Information to include when describing an intra-oral lesion.

Description of an intra-oral lesion should include the following:

Anatomical site/location
Size
Shape
Colour
Lesion type, e.g., plaque, nodule, papule, vesicle, ulcer, etc.
Distribution (if more than one lesion)
Margins
Texture, e.g., soft, indurated
History

high-grade, widely disseminated disease has a poorer prognosis.⁹ Prognostic factors for lymphoma include the patient's age, presence of 'B symptoms', stage and type of lymphoma, and lactate dehydrogenase levels (indicative of tumour metabolism). Five-year survival rates can vary greatly depending on the type of lymphoma; the survival rate of NK/T-cell lymphoma has been shown to be 20-35%, and given the poor prognostic factors presented in Case 1 this survival rate falls to approximately 6-7%.¹⁰ Follicular B-cell NHL, on the other hand, as presented in Case 2, has a five-year survival rate ranging between 80% and 95%, which reduces to approximately 50-60% in the presence of poor prognostic factors.¹¹

Routine oral examinations by healthcare professionals at check-ups provide an opportunity to screen for potentially malignant lesions and the importance of a thorough and confident extra- and intra-oral examination can never be underestimated. This consists of an examination of the head and neck region for swelling, asymmetry and discolouration, palpation of lymph nodes, identification of any sensory deficiency, and assessment of the temporomandibular joint bilaterally. Intra-oral examination should include the assessment of the mucosa of the oral cavity for swellings, ulcerations and red/white patches, and should include hard tissue charting with a basic periodontal examination. While there is no expectation to diagnose lesions, differentiating between normal anatomy and pathology, and understanding when to seek a second opinion, can be critical. An accurate description of intra-oral lesions, as shown in **Table 3**, can aid the referral process as triaging clinicians will gain a better understanding of each case.

Photographic records to aid triage are exemplary, such as those provided in Case 2, and potentially lead to more appropriate triaging.¹² In the current technological climate and with the regular use of photography within dentistry, this raises the question of whether all referrals for soft and hard tissue lesions should be accompanied with not only a thorough description of the lesion, but

also a clear photograph. For electronic referrals this would be similar to referrals for dental extractions requiring radiographs attached for acceptance. This photograph can also be used as a way of monitoring the progression/regression of the lesion over time.

The emergence of the Covid-19 pandemic has resulted in unprecedented challenges in the provision and continuity of care in dentistry and medicine. With this came the rise of teledentistry, which involves performing consultations via telephone or video-based platforms in order to reduce the risk of Covid-19 infection both to the clinicians and the patients. The additional advantages include reduced appointment time, less travel and waiting time for the patient, and increased scheduling flexibility. This was particularly relevant in Case 2, who was initially offered a telephone consultation during the height of the pandemic. This arrangement offered the patient a more specialised consultation and allowed the prioritisation of this case for a clinical biopsy appointment. This approach has been found to be well received by patients and supports an efficient use of resources.¹³ Of course, teledentistry represents a very real risk, as no photograph and verbal description from the patient/referrer will ever substitute for a face-to-face history and examination by a specialised clinician. Therefore, remote consultations need to be used with caution, and the risks and benefits balanced on a case-by-case basis.

Conclusion

A thorough history and examination followed by basic investigations is the initial responsibility of the primary care practitioner. Clinicians should be aware that radiolucencies associated with lymphoma may mimic peri-apical or periodontal pathology, odontogenic cysts, or tumours and infection. After excluding obvious odontogenic pathologies, the clinician must adopt a high degree of suspicion and refer onwards in a timely fashion. Clinicians should be familiar with the accurate description of intra-oral lesions and provide clinical photographs where possible to streamline the continuity of care and appropriate prioritisation of cases. Haematological and radiographic investigations are useful in staging, but in such cases the gold standard diagnostic technique is an urgent intra-oral biopsy. As presented in our cases, the histological and immunohistochemical evaluation was key to diagnosing and characterising the pathology.

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CPD questions

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CPD

1. Lymphoma involves malignant proliferation of:

- ☐ A: Erythrocytes
- ☐ B: Plasma cells
- ☐ C: Lymphocytes
- ☐ D: Nerve cells

2. The most common presentation of lymphoma is:

- ☐ A: Headaches
- ☐ B: Loss of appetite
- ☐ C: Dry mouth
- ☐ D: Enlarged lymph nodes

3. Which blood test can indicate the prognosis of lymphoma:

- ☐ A: Alkaline phosphatase
- ☐ B: Lactate dehydrogenase
- ☐ C: C-reactive protein
- ☐ D: IgA