Delayed diagnosis of oral lymphoma: a case series

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Key points

- Oral lymphomas are the second most common neoplasm in the head and neck after squamous cell carcinoma.
- Clinical presentation of non-Hodgkin lymphoma is variable and difficult to differentiate from odontogenic infections.
- Delayed diagnosis of oral lymphoma can adversely affect patients' prognosis.
- Clinicians should maintain a high level of suspicion for malignancy when inflammatory lesions fail to respond to normal modes of treatment.

Abstract

Lymphomas are the second most common neoplasm in the head and neck. The clinical and radiographic presentation of non-Hodgkin lymphoma in the oral cavity is non-specific and can be hard to differentiate from other common infectious or inflammatory conditions. We report four cases of lymphoma of the head and neck, which presented as odontogenic infection, osteomyelitis, or cutaneous infection, and subsequently led to a delay in provision of appropriate treatment. Correlation between clinical, radiographic and histological findings is essential in reaching an accurate diagnosis. It is important for clinicians to consider malignant lesions, such as lymphoma, in the differential diagnosis of pain, swelling, tooth mobility or radiographic radiolucencies. Clinicians should maintain a high level of suspicion for malignancy when inflammatory lesions fail to respond to normal modes of treatment.

Introduction

Lymphoma is a malignant disease of the lymphatic system, characterised by proliferation of lymphocytes or their precursors.[1] Lymphomas are broadly divided into two categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), of which NHL has a significantly higher incidence.[2] In comparison with HL, extranodal NHL is common. The most frequent site is the gastrointestinal tract, followed by the head and neck, which has an incidence varying from 11–33%.[3] Oral lymphomas comprise 3.5% of all intraoral malignancies[4] and are the second most common neoplasm in the head and neck after squamous cell carcinomas.[5] The most common intraoral sites are the maxilla, mandible, palate and gingivae.[6]

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Refereed Paper.
Submitted 26 May 2022
Revised 3 September 2022
Accepted 16 September 2022
https://doi.org/10.1038/s41415-023-5462-0

The clinical presentation of NHL in the oral cavity is variable and leads to difficulty in diagnosis. Common symptoms include pain, swelling, paraesthesia, or tooth mobility, which are hard to differentiate from diagnoses of odontogenic infection, periodontal disease, osteomyelitis, or other malignancies.[7]

Case 1

A 39-year-old woman with no comorbidities presented to the emergency department with swelling of the right mandible and sudden onset trismus. She described a nine-month history of altered sensation to the right side of her lower lip, which led to extraction of the lower right third molar by her general dental practitioner.

On presentation at the hospital, examination revealed that the lower right second molar was tender to palpation and slightly mobile. An orthopantomogram (OPG) radiograph (Fig. 1) demonstrated diffuse apical radiolucency and periodontal ligament widening around the lower right second molar, which resulted in a differential diagnosis of chronic dental infection associated with the lower right second molar.

The patient underwent a general anaesthesia for exploration of the submasseteric space,

Fig. 1 An OPG radiograph showing diffuse radiolucency around the roots of the lower right second molar with loss of the lamina dura and widening of the periodontal ligament space. The extraction socket is visible following removal of the lower right third molar, initially thought to be the cause of the symptoms.

drainage of any potential infection and extraction of the lower right second molar. Samples of the mandibular alveolar bone and adjacent soft tissues were taken for both microbiological and histological evaluation.

The histology reported features of high-grade B-cell lymphoma and the patient was referred onward to the haematology multidisciplinary team (MDT) and for a staging positron emission tomography (PET) computed tomography (CT) scan. The patient underwent R-CHOP chemotherapy (immunochemotherapy regimen consisting of rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride, oncovin and prednisone) and experienced complete remission.

Fig. 2 Extraoral clinical photograph of initial presentation of lymphoma of the right mandible

Fig. 3 Intraoral clinical photograph of diffuse large B-cell lymphoma in the right mandible, with speckling of the buccal mucosa and bleeding of the lesion

Fig. 4 An OPG radiograph demonstrating initial presentation of the patient, with pathological fracture of the left body of the mandible and patchy diffuse radiolucency of the alveolar bone

Case 2

An 81-year-old woman initially presented to her dentist with mobility of teeth in the lower right quadrant, which the dentist had managed unsuccessfully with periodontal treatment and then extracted two teeth. Her medical history included Waldenström's macroglobulinaemia, which was treated with chemotherapy eight years prior and she was in remission, and a history of malignant melanoma. In the following three months, she presented to a local emergency department twice after swelling began to develop and was discharged on both occasions with a course of oral antibiotics and no follow-up.

On her third presentation, she was referred urgently to the oral and maxillofacial surgery department with a firm right-sided submandibular and buccal swelling, suspected to be of odontogenic origin (Fig. 2). Intraoral examination revealed a firm, indurated speckled lesion of the right alveolar ridge and buccal mucosa which bled on contact (Fig. 3). On investigation, there were no raised inflammatory markers and the OPG radiograph showed a diffuse area of radiolucency, highly suspicious for malignancy. A CT scan of the neck and thorax revealed a large soft tissue mass in the body of the right mandible, with local bony destruction, mediastinal lymphadenopathy and subcutaneous masses, likely to be metastatic in nature. A further CT scan of the abdomen and thorax confirmed no lymphadenopathy or metastases.

Incisional biopsies of the right buccal and alveolar mucosa were taken and histopathological analysis confirmed a diagnosis of diffuse large B-cell lymphoma. The patient was subsequently referred to haematology for palliative management.

Case 3

A 53-year-old man attended the emergency department regarding pain of the mandible following a loud cracking noise while eating a few days prior. He had no co-morbidities but was a smoker. He had experienced a 12-month history of numbness of the lip and chin and loss of sound teeth. An OPG radiograph was performed which revealed patchy radiolucency and a pathological fracture of the mandibular body (Fig. 4). CT imaging of the facial bones suggested severe

osteomyelitis with bony destruction of almost 50% of the mandible (Fig. 5).

The patient underwent elective examination under anaesthesia, where the bone was debrided, multiple teeth were extracted and biopsies of the bone and soft tissue were taken. The histopathology report confirmed a diagnosis of osteomyelitis, for which the patient underwent six months of intravenous antibiotic therapy as advised by microbiology.

The patient developed swelling of the mandible which prompted a further CT scan that revealed progression of the bony destruction and prompted a re-exploration of the area for further tissue sampling. The results of the repeat biopsy revealed a diagnosis of diffuse large B-cell lymphoma. The patient had a staging PET scan and was treated with six cycles of R-CHOP chemotherapy; following chemotherapy, the residual lymphoma was treated with radiotherapy and is under ongoing review.

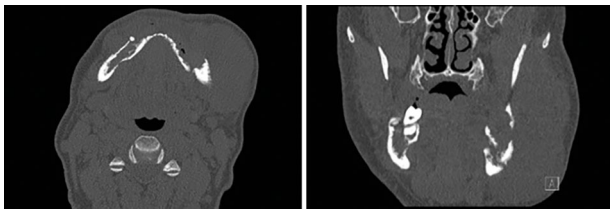

Fig. 5 Coronal and axial CT views demonstrating the extent of swelling and bony destruction of the left mandible

Fig. 6 Extraoral clinical photograph of cutaneous lymphoma affecting the upper left lip extending onto the vermillion border but not crossing into the oral cavity

Case 4

A 44-year-old man was referred urgently on a two-week wait pathway to the oral and maxillofacial surgery department by his general practitioner for a lesion on the upper left lip. The general practitioner had suspected infection and unsuccessfully attempted treatment with flucloxacillin, phenoxymethylpenicillin, clarithromycin and 2% fucidic acid cream. The patient's medical history comprised myocardial infarction, percutaneous balloon angioplasty, coronary stent, diverticulosis, nasal septoplasty and hypertension. He was on no regular medications and was not a smoker.

On examination, there was a superficial skin lesion of the upper left lip crossing the vermillion border, but not breaching into the oral cavity (Fig. 6). The lesion was approximately 4 cm in diameter and had a thick yellow scab superior to exudate. The patient had experienced no change in sensation to the lip and no other symptoms.

Wound care was performed with saline and the scab was removed under local anaesthetic. Microbiological and histological samples were sent. Blood tests and microbiology tests were inconclusive. Serology was negative for *Treponema pallidum*, hepatitis B, hepatitis C and human immunodeficiency virus. The mesial aspect of the lesion appeared to improve initially; however, the lateral portion of the lesion worsened and developed similar infiltration and crusting. The histopathology report concluded primary cutaneous anaplastic large cell lymphoma.

The patient was referred to the haematology MDT for a PET scan. He underwent biopsies of the left submandibular node, a colonoscopy and biopsies of suspicious nodules. No additional lymphoma was identified. Over a period of observation, a spontaneous resolution of the lip lesion occurred; therefore, the decision was made not to proceed with radiotherapy. Patient remains under haematology review and has a further PET scan planned.

Discussion

In a 2016 systematic review, 40.5% of cases were initially misdiagnosed and managed as alternative conditions – most commonly, extractions for odontogenic infections – which delayed appropriate therapy and allowed progression of lymphoma. Most common initial management included extractions and treatment of periodontal disease or dental abscesses.[8] According to Colmenero *et al.*, 50% of intraoral lymphomas cases first manifest with the appearance of infection.[9]

Clinical and radiographic presentations are not specific to lymphoma and they most commonly present with clinical features which mimic an odontogenic inflammatory process. Hard tissue lesions present as painful expansile lesions of the jaws causing asymmetry. When they involve the dentition, tooth mobility is commonly observed. Soft tissue lesions will often present as soft swellings with or without ulceration. Numbness, paraesthesia and lymphadenopathy have also been reported.[6,8,10,11,12,13]

The most frequent radiological finding is radiolucency representative of bone resorption.[8] Other signs include widening of the periodontal ligament space and loss of the lamina dura. Diffuse large B-cell lymphoma has been described as well-circumscribed multilocular lesions, moth-eaten diffuse pattern, or pathological fracture.[14,15] Radiographic manifestations could be interpreted as periodontal diseases, bony diseases, or dental abscesses.

Oral manifestations may present as the first and only sign of disease, so accurate diagnosis is essential.[16] Misdiagnosis can lead to ineffective treatment with oral antibiotics or periodontal or endodontic treatment. The first and second case reports highlight the importance of considering all differential diagnoses, even those of malignant aetiology, when evaluating symptoms of jaw pain and swelling. As with many cases in the literature, patients often undergo unnecessary dental extractions following misdiagnosis and effective treatment is only delivered when symptoms persist, or atypical findings are highlighted.

Because of the broad range of radiographic appearances associated with lymphoma of the mandible and maxilla, it can be easily misinterpreted as the diffuse radiographic appearance of osteomyelitis. In the third case report above, pathological fracture should be a sign that maintains high suspicion, as should paraesthesia of the lip or chin.

There are multiple reports in the literature of patients undergoing unsuccessful treatments for dermatitis, psoriasis, exanthema, erysipelas, or borreliosis before diagnosis of cutaneous lymphoma.[17,18,19] The final case report highlights the importance of considering cutaneous lymphomas in the differential diagnoses of chronic skin lesions which do not respond to conventional therapy.

As with any history and examination, presence of systemic symptoms, such as pyrexia, weight loss, night sweats, or fatigue, should alert clinicians to the need to rule out more sinister diagnoses. Persistent jaw pain and tooth mobility can also be early signs of malignancy.[20]

Treatment of lymphoma in the head and neck is complex and prognosis will depend on the patient's age, as well as the type and stage of lymphoma.[21] Chemotherapy is the most common treatment modality. Lymphomas generally respond well to chemotherapy; however, there have been cases reported in the literature where patients have died following misdiagnosis of lymphoma as odontogenic infections. The most common type of NHL in the head and neck is diffuse large B-cell lymphoma,[22] which is normally managed with multiagent chemotherapy combined with rituximab.[23] Other therapies include radiotherapy, growth factors, bone marrow transplant and monoclonal antibodies.[8]

Appropriate investigations, such as imaging with CT, cone beam computed tomography or magnetic resonance imaging, are crucial in the process of diagnosis, as are immunohistochemistry and histopathological analysis. Correlation between clinical findings and pathological findings are essential in accurate diagnosis of suspicious clinical lesions, especially in the case of those which have not responded to initial treatment.

Conclusion

Oral lymphoma has diverse signs and symptoms and can be easily misdiagnosed as dental abscesses, periodontal disease, osteomyelitis, skin infections, or other diseases. Misdiagnosis will delay treatment and worsen the prognosis for the patient. It is important for clinicians and pathologists to consider malignant lesions, such as lymphoma, in the differential diagnosis of pain, swelling, tooth mobility or radiographic radiolucencies. Features such as numbness or loosening of teeth in periodontal health demands thorough investigation without exception. Clinicians should maintain a high level of suspicion for malignancy when inflammatory lesions fail to respond to normal modes of treatment. Early biopsy and scrupulous follow-up are advised.

Author contributions

Sophie Mills, Evaldas Lukosevicius, Richard Sisson and Sharon Prince contributed equally to the manuscript, with Sophie Mills writing the first draft and all authors participating in the editing process and approving the final version.

Acknowledgements

To the Oral and Maxillofacial Surgery Departments of Norfolk and Norwich University Hospital and James Paget University Hospital.

Ethics declaration

The authors declare no conflicts of interest.

Written consent to publish was obtained from all four participants for inclusion of their radiographic/clinical images and personal information.

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