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Oral Lymphoma: A Case Series

Abstract: Oral presentation of lymphoma is rare but highlights the need for dentists in primary care to consider it for inclusion when determining differential diagnoses for patients who present with oral lesions. Oral lymphoma manifests in both intra- and extra-osseous sites within the oral cavity with a variety of clinical appearances which may mimic benign or innocuous processes. There may be non-specific signs which may be misleading to the clinician or present mimicking other oral malignancies, such as a non-healing ulcer, rapidly growing swelling with sudden onset or dental pathological processes. This case series highlights the varied presentations of oral lymphoma and the role of general dental practitioners in the early diagnosis, timely referral and management of these patients.
CPD/Clinical Relevance: This article highlights the need for primary care clinicians to consider oral lymphoma in patients who present in the general dental setting with oral lesions.
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This case series highlights the important role general dental practitioners play in the general screening and management pathways for rare oral malignancies outside the routinely diagnosed common oral conditions, which may present as innocuous swellings, ulcers or bony lesions, without any systemic signs to raise suspicion. By far the most common oral malignancy is squamous cell carcinoma however, rarely, malignant salivary gland tumours and oral lymphoma may present in the oral cavity, and should raise clinical suspicion.[1] Lymphomas encompass a broad range of cancers derived from lymphocytes (immune cells). These can occur both within lymph nodes and also extra-nodally within soft tissue and bone, including the oral cavity. Lymphomas can be divided broadly into Hodgkin's and Non-Hodgkin's type based on cell morphology and the presence of Reed-Sternberg cells (large binucleated cells with a distinct histological appearance). Hodgkin's lymphoma develops in the lymphatics, within lymph nodes, whereas Non-Hodgkin's lymphoma (NHL) can present intra- or extra-nodally, including in the oral cavity.[2] Both Hodgkin's and Non-Hodgkin's lymphoma can be divided into further subtypes according to histological morphology and lineage. The majority of adult presentations of Non-Hodgkin's lymphomas are Diffuse Large B Cell Lymphoma (DLBCL),[3] where the cell population is dominated by large neoplastic B cells. Five cases of extra-nodal oral NHL are described, including DLBCL, Richter's transformation of Chronic Lymphocytic Leukaemia (CLL), where DLBCL develops in patients with a history of CLL, and Follicular Lymphoma (FL). These patients presented to the Oral Medicine Department between 2012 and 2016 with a variety of oral presentations, with varying degrees of systemic involvement and dissemination. All cases were ultimately managed by the Haematology Department.

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Case reports (Table 1)

From 2012 to 2016, five patients with oral lymphoma presented to the Oral Medicine Department at Charles Clifford Dental Hospital. The patients were of an elderly age group, in their seventh and eighth decades, four female and one male, and all had a variety of oral presentations of lymphoma *(*Figures 1–4*)*. Three patients presented with DLBCL, one Richter's transformation of CLL and one oral FL in various oral locations with varying clinical sign and symptoms. Three patients had gingival swellings, one a history of a painful palatal ulcer and one with an asymptomatic swelling of the upper lip. All five cases of oral lymphoma were

Case	Sex	Age	Site of lesion	Referrer	Presenting Symptoms	Type of Lymphoma	Outcome
1	F	70	Maxillary alveolus	Oral Medicine	3 month history of right-sided headaches and facial pain	DLBCL	Received chemotherapy Ongoing remission at 2 years
2	M	64	Palate	Rheumatology	4 week history of a painful palatal ulcer and a recently loose-fitting upper denture	DLBCL	Received chemotherapy Ongoing remission at 2½ years
3	F	68	Palate	Haematology	Extensive gingival swelling of four months' duration	Richter's transformation of CLL	Received palliative radiotherapy Progressed with CNS disease
4	M	65	Maxillary gingivae	Primary care	Gingival lesion on the left maxilla	DLBCL	Received chemotherapy
5	F	63	Upper lip	Primary care	Asymptomatic lesion in the upper lip of eight months' duration	Follicular lymphoma	Monitoring

Table 1. Five patients with oral lymphoma presented to the Oral Medicine Department at Charles Clifford Dental Hospital from 2012 to 2016.

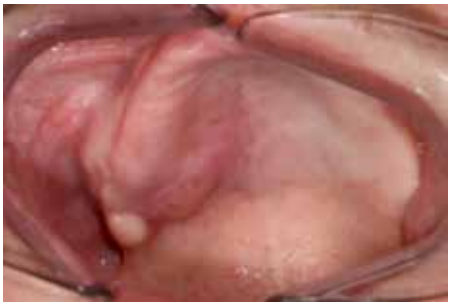

Figure 1. Case 1: Swelling right alveolus.

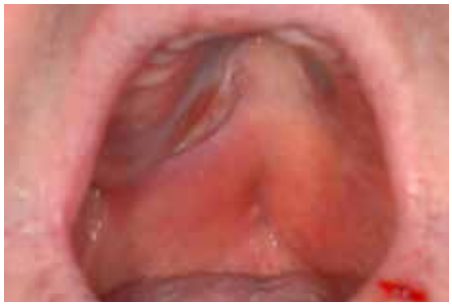

Figure 2. Case 2: Right palatal ulcer.

Figure 3. Case 3: Gingival swelling left palate.

initially diagnosed by oral histopathologists and confirmed by a specialist pathology lymphoma team using both morphological and immunohistochemical (IHC) analysis of the tissue samples. The histological features of lymphoma are highly variable.

Discussion

Lymphoma makes up a small but not insignficant proportion of oral malignancies. The oral cavity contains a large volume of lymphoid tissue which may undergo malignant transformation or manifest systemic signs of disseminated disease. NHL make up the majority of NHL oral cavity lymphomas which are mostly DLBCL,[2] as was the case for the patients in this case study. Studies have reported 58% of oral lymphomas are DLBCL, have a mean age at presentation of 62–71 years and have an aggressive phenotype with a poor long-term prognosis.[2,4] The most common oral site is Waldeyer's ring (an arch of lymphoid tissue at the posterior junction of the soft palate and oropharynx), the palate, maxilla and mandible.[5] The most important factors affecting prognosis of oral lymphoma are the histological classification subtype and clinical stage at presentation.[6] For oral lymphoma, intra- or extra-bony presentation does not appear to have an effect on the prognostic outcome.[7] Oral lymphoma may present as a solitary focus, but more commonly it may be a presenting manifestation of systemic and widespread disease, as was seen in some of the patients in this study,

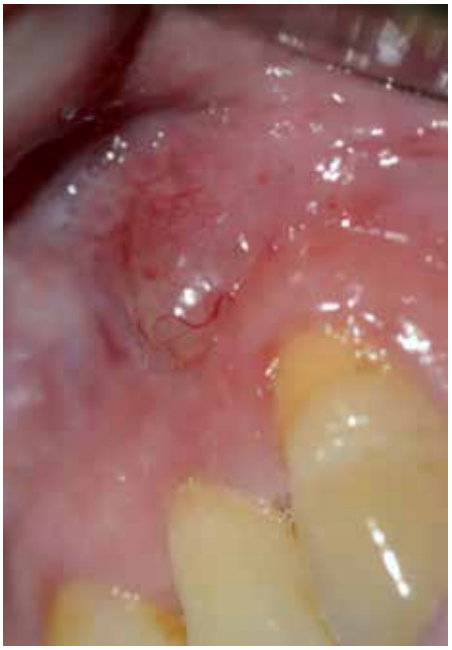

Figure 4. Case 4: Gingival lesion.

which would raise clinical suspicion for dentists treating these patients in primary care.[6] Lymphoma is often a relapsing remitting disease and many patients with a history of lymphoma may be treated in the primary care setting after discharge from tertiary care whilst in remission. These patients require ongoing regular screening and a low clinical threshold for clinical suspicion of unusual or fast-growing lesions or swellings with no obvious dental cause.

The patients in this case series have highlighted that oral lymphoma can manifest with varied clinical symptoms and sites within the oral cavity. Patients may at times appear well on initial consultation and not show any of the classical 'B' symptoms of fever, malaise and night sweats. Those presenting with jaw lesions may complain of symptoms of pain mimicking toothache or related osteomyelitis or infective processes.[8] Three of the patients in this case series had palatal swellings. To a dentally trained clinician, this may represent a myriad of dental-related pathologies, however, a careful history and adjunctive investigations will rule out any innocuous causes. Symptoms of atypical facial pain or numbness may be present in the absence of any organic signs, which will be useful in aiding clinicians to consider systemic disease or a malignant process.[9] Imaging is critical and may reveal bone lesions or oral presentation of metastatic disease, which should be included in the differential diagnoses.[9]

Treatment of DLBCL and FL includes chemotherapy or radiotherapy, with variable success; 70–80% of patients with DLBCL achieve complete remission.[7] In this case series the patients all presented in the seventh and eighth decades. The majority of cases were diagnosed as DLBCL, the most common oral presentation of lymphoma.[10] NHLs show varied and characteristic histopathological features with distinctive responses to treatment therapies.[11] DLBCL can be divided into two groups with varying prognosis. Those with germinal centre B cell-like formation (GCB) tend to show a better clinical outcome than those that do not form germinal centres. Studies have shown oral lymphomas tend to be non-germinal, centre-forming (non-GCB) and hence have a poorer prognosis.[12] The revised World Health Organization (WHO) classification of lymphoid neoplasms has further classified these types according to their prognostic outcome and is based on gene rearrangements diagnosed by gene expression profiling.[13]

Richter's syndrome can develop in patients with a previous CLL or small lymphocytic lymphoma (SLL). These patients undergo transformation of malignant CLL cells to a high-grade NHL or develop new disease because of already defective genetic anomalies related to their CLL.[14] Transformation has been reported to occur in up to 10% of patients with CLL.[15] Prognosis for patients with Richter's transformation of CLL is very poor.[16] Even when treated with chemotherapy, patients have a mean survival of less than 6 months.[15] PET/CT scanning may be of value in the continued monitoring of patients with CLL where there is a high suspicion for potential Richter's transformation.[17]

When managed in the primary care setting, dentists should be aware of the long-term poor prognosis for these patients and the high level of suspicion for any abnormalities in the oral cavity. Early diagnosis and management of oral lymphoma, whether *de novo* or as a part of disseminated systemic disease, is paramount for patients due to the poor overall survival rates and hence the need for prompt referral from primary care where these patients may first present. Even with continued monitoring, oral lymphoma is an aggressive disease process and many patients require extensive long-term follow-up from multiple specialties to allow for early diagnosis of disease progression.

Conclusion

Oral lymphoma may rarely present in the oral cavity either as a new diagnosis or on a background of lymphoma in other body sites. Any unusual lesions manifesting in the oral cavity warrant expedited investigation, as malignant processes do not always cause the typical clinical systemic signs or symptoms. These cases highlight the need for a cautionary approach and high level of suspicion from primary care practitioners for prompt referral for the diagnosis and management of rapidly growing lesions. Despite the aggressive nature of DLBCL, there is a good 5-year survival rate. This case series highlights to primary care clinicians the possible oral presentations of lymphoma, and the important role that dentists can play in identifying unusual presentations and referring patients to a tertiary care centre for prompt diagnosis and management of oral lymphoma.

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Book Review

Craig's Restorative Dental Materials 14th edn. Sakaguchi R, Ferracane J and Powers J. Oxford: Mosby Elsevier, 2019 (340pp; £84.99, p/b). ISBN: 978-0-323-47821-2.

First published in 1960, Sakaguchi *et al*'s textbook on restorative dental materials is now on its 14th edition, which is a measure of the success of previous editions. It is also a reflection of the need to keep abreast of developments in this ever and quickly changing subject.

The book is comprehensive, featuring sections on the full range of restorative dental materials, and begins by putting their role into context. Useful and helpful sections follow on the fundamentals of materials science, materials testing and biomechanics, which are very readable and easy to understand. There is a chapter which deals with biocompatibility and tissue reaction to biomaterials before the authors go systematically through all classes of restorative dental materials used in both the clinic and laboratory. In the last three chapters, more contemporary techniques and materials are discussed, such as digital impression taking, CAD/CAM and orofacial implants.

The text has been updated and revised to take account of the newer materials and technologies, in particular biomaterials and tissue engineering. It is a little surprising what subject matter has been included and omitted. The section on dental amalgam has rightly been reduced to reflect the phase down of this material in many countries across the globe. However, quartz-tungsten-halogen curing lights are discussed in depth, whereas more emphasis could have been placed on the now more commonplace LED units. There was also a lack of information on the tricalcium silicate cements such as MTA. These products have revolutionized endodontics since their introduction and their usage continues to increase apace. This may illustrate the point that textbooks are out of date before they are published!

It is fair to say that this tome is really a dental material's science textbook with its emphasis very much on the physics, chemistry and mechanics of materials. Unfortunately, there is very little in the way of clinical application of the materials themselves demonstrated by a paucity of clinical photographs, one of which features a resin composite core retained by four dentine pins!! Instead, images of products are presented but with a distinct and perhaps unconscious bias towards 3M products, which may be explained by the fact that one of the contributors has an association with that particular company. There is a lot of written prose and therefore information which is extensively referenced at the end of each chapter. The text is appropriately illustrated with many quality diagrams and photomicrographs.

In summary, *Craig's Restorative Dental Materials* would be a good addition to the library of any practising dental clinician, postgraduate student or keen undergraduate student who has an interest in dental materials or dental materials science.

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