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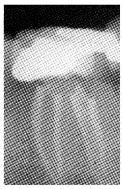

CASE REPORT

Non-resolving periapical inflammation: a malignant deception

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Abstract

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Aim To report a case of oral non-Hodgkin's lymphoma with a delayed diagnosis.

Summary Non-Hodgkin's lymphoma of the oral cavity is an uncommon but important condition. Early diagnosis is complicated when the presenting signs and symptoms are similar to those of odontogenic infections. This report describes the case of a 38-year-old female patient who presented to her dentist complaining of pain in her upper jaw. Subsequent dental treatment, including extraction, root canal treatment and apicectomy including biopsy were carried out by the patient's dentist and local dental hospital. Nine months elapsed before a more extensive surgical exploration established a diagnosis of lymphoma.

Key learning points

- To appreciate the importance of recognizing discrepancies between the clinical scenario and histopathological findings.
- To appreciate subtle radiographic changes that may accompany malignant disease of the jaw bones.
- To appreciate the need for early referral when a patient's symptoms do not satisfactorily respond to conventional dental therapies.
- To appreciate lymphoma should be considered in the differential diagnosis of non-healing periapical inflammation and non-healing socket.

Keywords: lymphoma, non-healing socket, periapical infection.

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Introduction

The incidence of non-Hodgkin's lymphoma (NHL) has increased by over 50% in the 20-year period between 1986 and 2005 (Cancer Research UK 2008a). NHL now accounts for 4% of all malignant neoplasms in the UK (Cancer Research UK 2008b). It is the third most common malignancy to affect the head and neck region, after squamous cell

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carcinoma and salivary gland tumours (Barker 1984). NHL can be classified according to the cell of origin into T-cell or B-cell lymphoma; the latter being more common in the oral cavity (Neville et al. 2009). The incidence of NHL is rare in patients under the age of 40, with approximately 70% of all cases being diagnosed in people over 60 years. It predominately occurs in lymph nodes but 20–40% arise in extra-nodal sites (Neville et al. 2009). The gut is the commonest site for extra-nodal lymphoma, but bone and the mouth are other frequently affected sites.

Non-Hodgkin's lymphoma can present in a number of different forms within the oral cavity, the more frequent being palatal (Tomich and Shafer 1975) and gingival swellings (Spatafore et al. 1989, Payne and al-Damouk 1993). It is reported that 36–45% of oral NHL can affect the jaw bones (Keyes et al. 1988). The initial diagnosis of oral lymphomas can be challenging as they may resemble pyogenic granulomas, ulcers, sinusitis (Spatafore et al. 1989), a non-healing socket (Thomas et al. 1991) or mimic an acute dental abscess (Spatafore et al. 1989, Rog 1991, Payne & al-Damouk 1993). Patients may complain of non-specific pain, which may be misdiagnosed as periapical inflammatory disease.

This report presents a case of malignant NHL which was originally diagnosed and treated as an odontogenic infection.

Case report

A 38 year-old Afro-Caribbean female referred herself to the Birmingham Dental Hospital, UK primary care unit in November 1998. She described a 6-month history of a spontaneous intermittent dull ache in the upper left canine region. There was no disturbance to her sleep pattern. She had visited her GDP on several occasions over the preceding 6 months without resolution of her discomfort, despite extraction of tooth 22 and root canal treatment to teeth 23 and 24. Her medical history was unremarkable. She was a non-smoker and drank 2 units of alcohol per week.

On clinical examination, there was no lymphadenopathy of the head and neck region. An intra oral inspection revealed a non-healing socket where the 22 had been removed 4 months previously. The buccal sulcus was tender to palpation over the apex of the 23, but no swelling or ulceration was apparent. The 23 and 24 were not mobile and were non-tender to percussion. She had a good standard of oral hygiene and there was no evidence of periodontal disease.

A periapical radiograph revealed a radiolucency and a dense radiopaque foreign body, probably amalgam, at the base of the 22 socket (Fig. 1). The 23 and 24 (Fig. 2) had satisfactory root canal fillings with no associated apical radiolucencies and good periodontal support. She was prescribed a course of amoxicillin and reviewed a week later. As her symptoms had not improved the 22 socket was surgically investigated. During this procedure, granulation tissue was removed but not submitted for histopathology.

Curettage of the 22 socket and a further two courses of amoxicillin failed to resolve her symptoms so the 23 and 24 region was investigated and an apicectomy performed on both teeth. Soft tissue was curetted from around the apices of 23 and 24 resulting in an oro-antral communication due to loss of bone. The histology revealed chronically inflamed granulation tissue.

Three months after her presentation to the dental hospital and 9 months following onset of her symptoms, radiographic follow-up revealed destructive bony changes (Fig. 3). The 23 and 24 apical radiolucency had increased in size, showed perforation of the cortical bone and loss of the bony antral floor (Fig. 3).

As a consequence, a further biopsy was performed, which revealed extensive soft tissue replacement of the left maxillary alveolar process extending from close to the

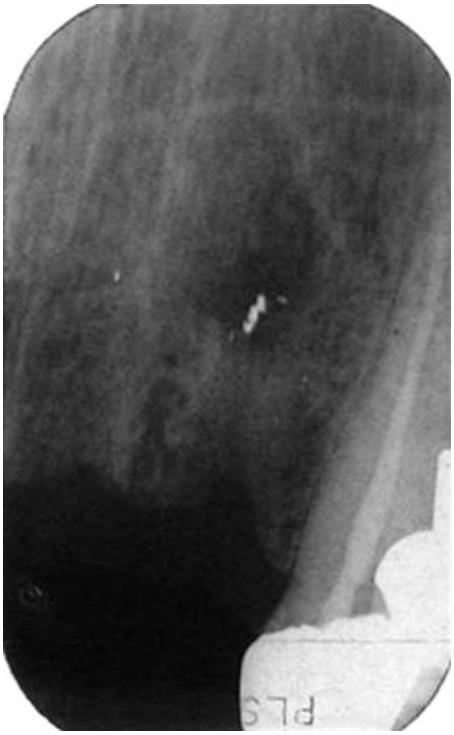

Figure 1 Periapical radiograph taken at presentation of UL2 socket demonstrating foreign body.

palatal midline, posteriorly to the left maxillary buttress and superiorly towards the floor of the nose. Extraction of the 23 led to the simultaneous removal of the 24 encased in a loose segment of surrounding maxillary alveolus.

The histology of the soft tissue component again showed a granulomatous foreign body reaction consistent with a periapical granuloma, whereas examination of the tissue block containing bone and teeth revealed a dense infiltrate of cells that had the appearance of malignant lymphoid cells. A preliminary diagnosis of lymphoma was made and the patient referred for further assessment and management. A computerized tomography (CT) scan showed destruction of the left maxillary alveolus (Fig. 4). Further biopsy confirmed a diagnosis of non-Hodgkin's lymphoma of the left maxilla. Additional investigations showed that there were no other lesions elsewhere in the body and thus the disease was classified stage 1AE (single extranodal site without systemic signs of disease). She was treated with radiotherapy to the left maxilla and chemotherapy. Seven years later the patient has no signs of recurrence and remains under annual review.

Discussion

Inflammatory processes of the jaws may present in an indolent manner or show a more aggressive behaviour. Typically odontogenic inflammation results in pain, widening of the periodontal ligament space, and the development of a periapical radiolucency that is usually well defined. Occasionally developmental anomalies, metabolic diseases and malignancies can resemble dental inflammatory disease but do not respond to root canal treatment or tooth extraction. In this situation the clinician should review the accuracy of the diagnosis so that the appropriate treatment is not delayed.

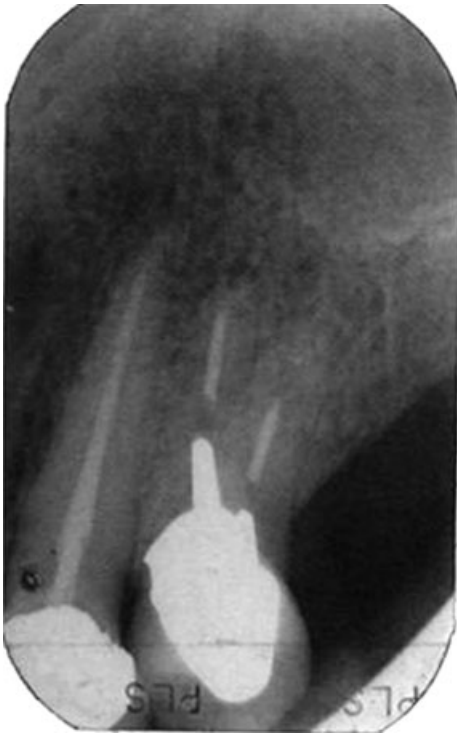

Figure 2 Periapical radiograph taken at presentation showing root fillings UL34 and periradicular bone.

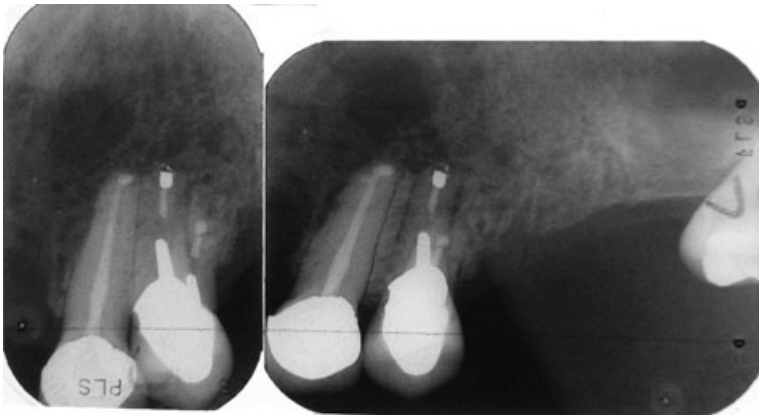

Figure 3 Periapical radiograph taken 3 months after presentation showing destructive features with cortical bony destruction above UL3.

The presented case and several others in the literature have demonstrated that extranodal lymphoma of the jaws may initially present, particularly in the early stages, with unspecific signs and symptoms mimicking periapical disease (Slootweg et al. 1985, Macintyre 1986). Lymphomas can become secondarily infected and present with swelling mimicking a dental abscess (Rog 1991, Bavitz et al. 1992, Ardekian et al. 1996). The initial clinical impression of inflammatory disease was supported when antibiotic therapy appeared to reduce symptoms (Keyes et al. 1988). Whilst many malignant lesions are easily recognized there are situations when they resemble other conditions. Although

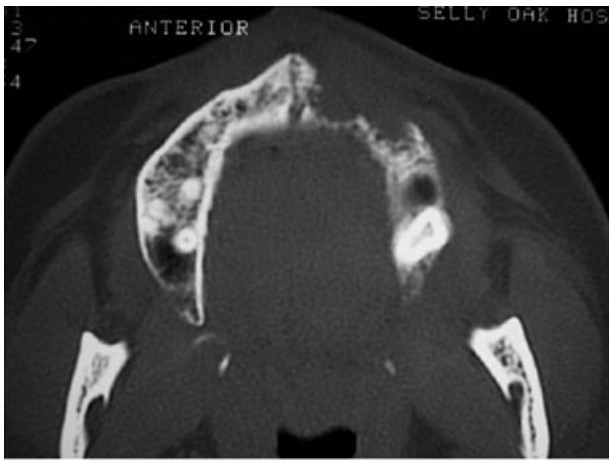

Figure 4 Axial CT image showing erosion of left maxillary alveolus following diagnosis of lymphoma.

certain clinical features such as increased tooth mobility in the absence of advanced periodontal disease and neurosensory disturbances may point towards non-odontogenic disease, they may not be present initially (Gusenbauer et al. 1990). Similarly, radiographs used to investigate dental disease may demonstrate findings such as poorly defined or 'moth-eaten' osteolytic lesions (Macintyre 1986), root resorption and erosion of crestal bone, which are not typical for odontogenic lesions. However, destructive radiographic changes may not be evident in slow growing lymphomatous lesions of the jaws (Keyes et al. 1988, Rog 1991).

Malignant disease involving bone can resemble periapical inflammatory disease particularly when the latter is infected changing its margin so it is less well defined. Periapical inflammation is common whilst lymphoma in the jaws is not thus one tends not to consider it in the diagnosis. It is important to review the clinical features and radiological findings, and when these are unusual the diagnosis needs to be reconsidered rather than persisting with inappropriate treatment. In addition, early referral to a secondary setting for specialist opinion must always be considered. However, cases such as the one presented here have to be cautiously interpreted with respect to missed clinical and radiographic signs, as *post-hoc* interpretation may be misleading because primary manifestation of lymphoma or other malignancies as periapical pathology is uncommon. Therefore, a significant proportion of cases presenting with one or more of the 'atypical' signs and symptoms discussed above may still represent odontogenic pathologies.

Whilst the authors cannot comment on the indications for, and the sequence of treatment undertaken by the general practitioner during the 6-month period prior to the patient's attendance in the hospital, it is quite clear that several therapeutic attempts aimed at what was thought to be an odontogenic problem had failed. When initially seen at our clinic, the non-healing extraction socket was attributed to the foreign body visible on the radiograph and surgically revised without obtaining any material for histopathological examination. Although an unlikely cause for the patient's symptoms, it is not unreasonable to remove a foreign body from a non-healing socket. However, the long history and failure to respond to previous treatment should have raised the suspicion that the condition was not infective and a tissue sample for histopathological examination should have been retrieved (Rog 1991). In the present case it is however unclear if this would have resulted in an earlier diagnosis, particularly when the

subsequent histology suggested an inflammatory process and the age of the patient was younger than one expects for lymphoma.

Histologically, the distinction between lymphoma and periapical inflammation is often challenging, and as in this and other cases, lymphoma has been interpreted as being inflammatory in nature (Keyes et al. 1988, Richards et al. 2000). These difficulties have been attributed to inadequate biopsy specimens and poor handling of the tissue by the clinician leading to 'crush artefact' which obscures the fine cytological detail needed to distinguish between benign and malignant lymphocytes. It is often difficult to obtain an adequate tissue sample because of the close location to roots (Wannfors and Hammarstrom 1990). To increase the chances of accurate diagnosis large specimens representative of the tumour are required (Rog 1991). One biopsy may be insufficient to make a diagnosis and re-biopsy of non-healing lesions including bone within the sample may be required. The diagnostic difficulty increases when lymphomas become inflamed, obscuring the neoplastic nature of the infiltrate (Wright and Radman 1995). Indeed, the soft tissue samples retrieved during the course of treatment were found to be consistent with a chronic inflammatory lesion. The histopathological diagnosis of lymphoma was made from the hard tissue block accidentally retrieved during the extraction of the associated teeth. This illustrates that, in order to obtain a correct diagnosis earlier, a block biopsy of the affected bone may have been required to yield the true nature of the disease process.. However, this constitutes a rather invasive, if not destructive procedure, and given that lymphoma is extremely rare, adoption of a practice of 'early block biopsy' would result in unnecessary morbidity in many cases. However, in light of diagnostic difficulties with histopathological examination and plain film radiography earlier referral for more advanced imaging techniques such as computed tomography or magnetic resonance imaging should have been considered.

Over the course of her treatment, the patient received three courses of antibiotics without resolution of her symptoms. Antibiotics have no role in the treatment of persistent non-healing sockets. Lymphomas and other non-odontogenic diseases may become secondarily infected. In this situation a reduction of symptoms with antibiotic treatment may delay proper diagnosis (Keyes et al. 1988).

Although extranodal lymphoma of the jaws is uncommon, perhaps with the increasing incidence of HIV infection (UNAIDS 2008), a continued increase in the incidence of lymphoma will be observed. As demonstrated, lymphoma may masquerade as common dental inflammatory disease and clinicians should be alert to the possibility of sinister pathology. In the study by Maxymiw et al. 2001 a high percentage of patients with NHL had dental symptoms. These cases often demonstrate recurrent or protracted disease patterns, as seen in this case with a delay of 9 months before making the correct diagnosis. This is longer than the average 2.5 months between presentation and treatment reported in other cases (Gusenbauer et al. 1990). NHL of the head and neck has a good prognosis with a median survival rate of 10–15 years but the prognosis is improved with early diagnosis (Payne & al-Damouk 1993).

Conclusion

Despite its rare occurance, dentists must consider lymphoma in the differential diagnosis of pain, swelling, ulceration and non-healing periapical inflammation. In general, dentists should have a high index of suspicion for lesions (including periapical lesions) that do not respond to conventional therapy or appear unusual in other ways and as such have a role in early diagnosis and prompt referral of patients for specialist secondary care. Finally, the possibility of false negative biopsy results must be considered and referral to specialist care may be warranted even in a case of a negative initial biopsy result.

Disclaimer

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