

Recognition of Non-Hodgkin Lymphoma of the Maxilla

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ABSTRACT Primary (extranodal) non-Hodgkin lymphoma (NHL) in the oral cavity is rare, but causes local morbidity and leads to mortality. Head, neck and oral involvement can be the first site of presentation or it may occur in previously diagnosed cases. A thorough history, clinical evaluation, imaging, interdisciplinary consultation, biopsy and laboratory testing are all necessary to lead to diagnosis. Dentists must be aware that early recognition of this aggressive disease can lead to improved outcomes.

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Conflict of Interest
Disclosure: None reported.

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Image above: CSF cytology of a diffuse large B-cell non-Hodgkin lymphoma. (Credit: Jensflorian/Wikimedia Commons)

Lymphoma is a cancer of the blood that affects the infection-fighting cells of the immune system, the B and T lymphocyte cells. The two main types of lymphoma, which involve abnormal and uncontrolled growth of the lymphocytes, are Hodgkin's lymphoma that arises from abnormal B cells and non-Hodgkin lymphoma (NHL) that may develop from either abnormal B or T cells. Primary (extranodal) NHL in the oral cavity is relatively rare, but can be locally destructive and lead to mortality. Early detection is critical. Head, neck and oral involvement can be the first site of presentation of NHL or it may occur in previously diagnosed cases.¹⁻⁶ A thorough history, clinical evaluation, imaging, interdisciplinary consultation, biopsy and laboratory testing are all necessary to achieve diagnosis. Dentists must be aware that early recognition of this aggressive disease can lead to earlier treatment and improved outcomes.

Case Report

A 51-year-old female presented to her general dentist with a nine-month history of worsening pain and swelling over the upper left lateral incisor (tooth No. 10) and with awareness of a "sharp pointy ridge" above the upper left second molar (tooth No. 15). Tooth No. 10 was root canal treated more than 20 years earlier. Due to the presenting symptoms and a diffuse radiolucency adjacent to the tooth, endodontic retreatment was completed by her dentist and a second canal was found and treated. Due to a penicillin allergy, the patient was put on azithromycin and clarithromycin on separate occasions to treat the presumed dental infection. Two weeks after endodontic retreatment, the patient reported that severe pressure sensitivity had returned in the area of tooth No. 10. She was then referred to an endodontist for evaluation and treatment.

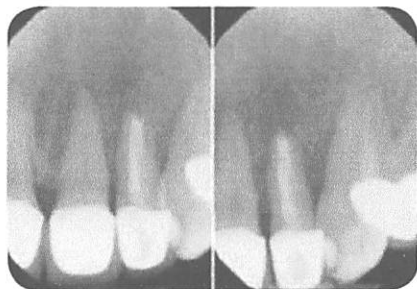


FIGURE 1. Diffuse radiolucency after endodontic retreatment and apicoectomy on tooth No. 10.



FIGURE 2. Intraoperative photo of excision of necrotic segment of maxillary bone, including the area of labial and palatal bony plate, as well as extraction of teeth Nos. 9 and 11.



During consultation with the endodontist, the patient related a history of an intermittent palatal swelling adjacent to tooth No. 10 along with a bump in the posterior hard palate. An incision and drainage and apicoectomy were performed and the patient was placed on clarithromycin and metronidazole (**FIGURE 1**). During the surgery, the endodontist noted that the periosteum seemed to be stuck to the cortical bone. The bone was described as noncohesive in the area of teeth Nos. 9–12 compared to normal bone over tooth No. 8. The clinician noted that the lesion seemed abnormal. Suspicious of a malignancy, the endodontist submitted a sample for biopsy. The initial report indicated malignancy, but an addendum report issued a final diagnosis of “chronic apical periodontitis” without evidence of malignancy.

On follow-up one week later with the endodontist, the soft tissue appeared to be healing and the swelling behind tooth No. 10 was reported as indurated. Tooth No. 9 tested nonvital, which had previously tested vital, and it was recommended the patient have a root canal on tooth No. 9. The endodontist recommended a referral to an oral and maxillofacial surgeon (OMS) for an examination and biopsy of the persistent palatal swelling, which measured 1 cm in diameter. The endodontist suspected the swelling was unrelated to the dentition.

Over the next few months, the patient saw multiple specialists for

recurrent swelling of her left nasolabial region and palate and eventually had tooth No. 10 extracted by her general dentist who noted pus expressed from the socket. She was treated intermittently with oral clindamycin, azithromycin and moxifloxacin by various dentists and specialists with no resolution of her symptoms. A diagnosis of advanced osteomyelitis in the anterior maxilla was made after a cone beam computed tomography (CT) was performed, which demonstrated extensive osteolysis of the anterior maxilla and a periapical lesion on tooth No. 9. She was then seen by an OMS who identified mild facial asymmetry, a firm, tender swelling in the left nasolabial region including the left anterior mucobuccal fold and labial and palatal cortical expansion with crepitus suggesting altered cortical bone.

The OMS ordered a CT with contrast, medical and laboratory testing and consultation with an infectious disease specialist. The new CT showed extensive osteolysis reported consistent with osteomyelitis. Laboratory results showed a normal hematologic panel. The infectious disease specialist planned daily intravenous antibiotics (vancomycin and ertapenem). Soon after antibiotics were initiated, the patient underwent a maxillary sequestrectomy.

Intraoperatively, extensive lysis of bone with gelatinous material completely replacing the interseptal bone between the maxillary teeth was noted (**FIGURE 2**). Excision of a

necrotic segment including the area of labial and palatal bony plate as well as extraction of teeth Nos. 9 and 11 were completed. Her pathology report described findings consistent with osteomyelitis, however due to a comment in the previous biopsy report indicating the inability to assess the inflammatory cells due to crush artifact, further evaluation and differential staining of original sections were requested by the OMS.

The specimen was then re-examined with immunohistochemistry staining that showed strong positivity for CD20, less intense CD3 and reverse expression of Ig Kappa and Ig Lambda consistent with B-cell lymphoma. However, due to the extensive crush artifact, it was difficult to specify the lymphoma type.

Upon further work up, an underlying low-grade lymphoma was identified in the bone marrow in addition to the apparent intermediate-grade lymphoma not otherwise specified in the head and neck causing bony destruction of the left maxillary bone and palate. The final diagnosis was stage IVA transformed non-Hodgkin B cell lymphoma. The ertapenem therapy was continued to address the potential infectious component of the process and the vancomycin was discontinued.

The patient was then referred to an oncologist and she underwent six cycles of R-CHOP chemotherapy. A PET/CT at the end of treatment showed resolution of all previously



FIGURE 3. Reconstruction of anterior maxilla with iliac crest bone graft.

identified lymphoma lesions. She reported no symptoms of recurrent disease or infection and was placed on maintenance rituximab (375 mg/m² q3mo for 8 cycles). Upon confirmation of full remission of her lymphoma, the patient had reconstructive surgery of her maxillary defect using an autogenous iliac crest bone graft (**FIGURE 3**). After a six-month consolidation of the graft, multiple dental implants were placed using CT-guided technology and a fixed implant-retained prosthesis in the maxilla (**FIGURE 4**).

Discussion

Non-Hodgkin lymphoma is the second most common neoplasm of the head and neck, even though overall it accounts for only 3.5 percent of oral malignancies.¹ The oral cavity might be the first and/or only site of presentation even with disseminated involvement. Most lymphomas are of B-cell origin followed by T-cell and the NK/T cell. The most common subtype is diffuse large B-cell lymphoma. It has an aggressive, fast-growing course but is curable, therefore early recognition and treatment is of paramount importance. Oral care providers must be aware that head, neck and oral involvement is common. The most prevalent site is the tonsils (32.7 percent) followed by the parotid gland (16.1 percent).¹ Clinical presentation of NHL often begins as an asymptomatic, slowly growing mass and this is usually the first complaint

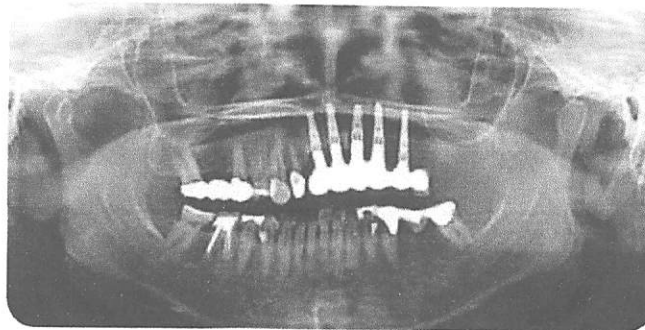


FIGURE 4. Panoramic radiograph showing CT-guided dental implants with fixed implant-retained prosthesis after maxillary resection and reconstruction.

of most patients.²⁻⁴ A review of 40 cases of NHL involving the oral cavity revealed 28 percent involved the maxilla or palatal bone.⁵ As the disease progresses, intraoral signs suggestive of NHL include unexplained dental pain, numbness, tooth mobility, swelling or ill-defined lytic osseous changes.⁶

The lymphoma in this case initially presented as a tender swelling of the labial tissue in the area of tooth No. 10. Radiographic evaluation showed a diffuse periapical radiolucency and the incisional biopsy revealed erosive osseous changes.

The 20-year-old root canal in tooth No. 10 appeared intact radiographically, despite diffuse bone loss seen in the anterior maxilla. The patient did not respond to multiple antibiotic courses directed toward a possible dental infection, yet multiple endodontic procedures were completed before lymphoma was considered in the differential diagnosis. The history, diffuse bone destruction and the palatal swelling, despite the radiographic appearance of the prior endodontic treatment, suggest a potential cause other than dental pathology. Differential diagnosis is critical at this stage of care. Further, this case highlights the challenges in histologic diagnosis and that definitive diagnosis requires laboratory and clinical evaluation.

Dental abscess, periodontal infection and benign reactive hyperplasia should all be considered in the differential

diagnosis. Differentiating between lymphoma and infectious disease may be difficult, but if a patient is not responding as expected to treatment it is essential to review the working diagnosis, repeat or complete new testing and refer to the appropriate specialists to determine diagnosis and appropriate treatment.⁶ Delayed diagnosis may have led to a more advanced stage of disease, as was seen in this case.

Testing for primary NHL requires immunohistochemistry and in situ hybridization staining. Routine hematoxylin and eosin is not sufficient for lymphoma diagnosis, and as seen with this case, hematologic and biochemical profiles of the patients are usually normal.^{7,8} Histological evaluation, including B and T cell markers, is important in differentiating the types of cells involved and differential diagnosis, and additional markers can help discern subtypes.⁵

In this case, A2 staining, CD20, CD3 and Ig Kappa and Ig Lambda were used to establish a diagnosis of B-cell lymphoma. Unfortunately, the initial biopsy sample was not ideal in that there were many crushed cells due to the tissue obtained by curettage and the type of B-cell lymphoma could not be identified. Clinical, laboratory studies, imaging to evaluate bony destruction and positron emission tomography (PET) scan with 18F-fluorodeoxyglucose (FDG) may be used for staging and evaluation of therapeutic response.⁸

Treatment for oral NHL involves primarily chemo-immunotherapy and may include radiation therapy with bone marrow/hematopoietic stem cell transplant reserved mainly for relapsed and refractory cases. The overall three-year survival rate is still only around 65 percent, and after salvage therapy, two-year survival is only about 55.3 percent.^{9,10} Our patient achieved a complete remission with six cycles of R-CHOP chemotherapy, which is a 21-day course of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone per cycle

and eight cycles of maintenance therapy of rituximab, a monoclonal antibody directed to the CD20 antigen.⁸ Reconstructive maxillary surgery was completed three months after negative PET scan.

Extranodal NHL should be included as a rare differential diagnosis when a patient presents with gingival swelling that cannot be explained by more common causes. It is important for dentists to be aware of this due to the aggressive nature of the malignancy so that diagnosis can be achieved and treatment initiated as early as possible. ■

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