

Multifocal Primary Non- Hodgkin's Lymphoma of the Oral Cavity: Report of Three Cases and Review of the Literature

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Abstract

Objective: Oral non- Hodgkin's lymphoma (NHL) is a relatively rare neoplasm that may develop in the soft tissues or jaw bones, with or without node or marrow involvement. Oral lymphomas are often difficult to diagnose as there are no characteristic clinical features and usually appear as non-tender swellings.

Case: We describe clinical, radiographic, histopathological and immunohistochemical findings of three cases of multifocal NHLs presenting in the oral cavity.

Conclusion: If the oral lesion is multifocal, extra nodal lymphoma must be considered in the differential diagnosis.

Key words: Malignant, Multifocal, Neoplasm, Non-Hodgkin's lymphoma, Oral cavity.

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Introduction:

Non- Hodgkin's lymphoma (NHL) is a malignant lesion usually involving lymph nodes. The head and neck is the second most common area for extra-nodal lymphoma after the gastro-intestinal tract. Oral lymphomas are extremely rare accounting for 0.1 to 5% of disease cases. This tumor commonly affects the vestibule, gingiva, or posterior hard palate (1, 2). The malignant behavior of NHL ranges from relatively indolent to highly aggressive and potentially fatal (3, 4). It more commonly affects the middle-aged and the elderly with a slight male predilection (5). The etiology is unknown even though virus and immune suppression are associated. NHL may be an important clue for undiagnosed HIV infection (6) because these patients are 60 times more at risk than the general population(7).If multifocal oral lesions are seen in a patient, extra nodal lymphoma must

be considered in differential diagnoses. Knowledge of the clinical patterns may lead to early diagnosis and improved prognosis. The purpose of this paper was to report 3 multifocal primary non-Hodgkin's lymphomas of the oral cavity.

Cases:

Case1:

A 32 year old woman was referred to the Department of Oral Pathology of Shahid Beheshti University, with multiple painless maxillary and mandibular gingival masses. The patient had noticed their appearance after extraction of the molar tooth in these areas about 3 months prior to referral. There was no response to antibiotic treatment. On extra-oral examination, facial asymmetry was seen without palpable lymph nodes in the head and neck region; she mentioned recent weight loss of

about 7 Kg. She complained of chin numbness of 1 month duration. Intraoral examination revealed gingival growth extending from the mandibular left first premolar region to the ipsilateral retromolar trig one, from the maxillary first premolar region to tuberosity and in the area of right canine and premolar. The masses were soft to firm and the overlying mucosa was slightly edematous and purple in color (Figure 1).

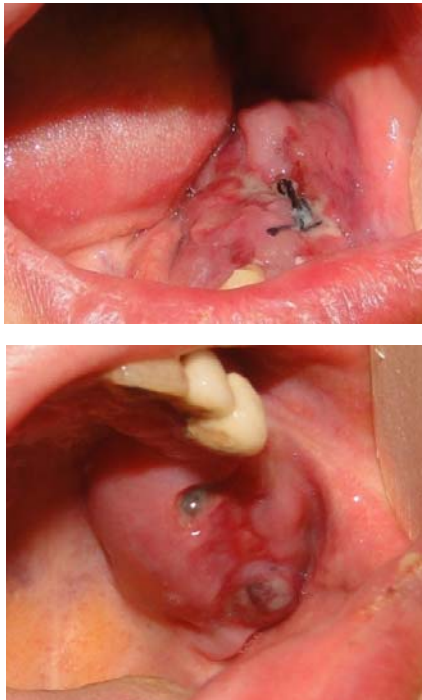


Figure 1- Gingival mass in the mandible and maxilla

A panoramic radiograph revealed bone resorption in these regions and the extraction sites did not show healing. On the CT scan, destruction of bone and swelling were seen. Her medical and family histories were not contributory. The patient underwent incisional biopsy from the left maxillary and mandibular lesions. (Figure 2) Histopathological exam revealed atypical large lymphoid cells with pleomorphism and hyperchromatism arranged in diffuse sheets in a delicate connective tissue. These findings were consistent with NHL and the immunohistochemical analysis was done to

confirm this diagnosis. (Figure 3)



Figure 2- Ill-defined bone destruction and unhealed extraction socket are evident in panoramic radiograph. An extensive, destructive mass and swelling are seen on CT scan.

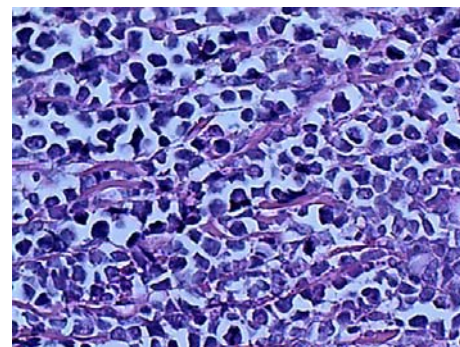


Figure 3- Microscopic view shows the proliferation of atypical lymphocytes (400X magnification).

This specimen was positive for LCA and CD20 and negative for bcl-2, bcl-6, CD10 and CD3. (Figure 4) The Ki67 marker was positive in over 90% of the tumoral cells. Serology for human immunodeficiency virus was negative. (Figure

5) With a diagnosis of diffuse large B cell lymphoma, the patient was examined to rule out the involvement of other sites which were tumor-free and she underwent chemotherapy. She is alive and responded well to chemotherapy.

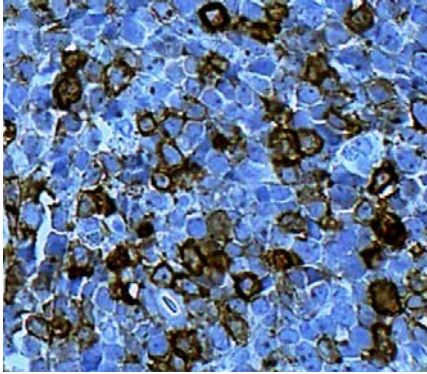


Figure 4- Membrane staining for CD20 marker (400X magnification)

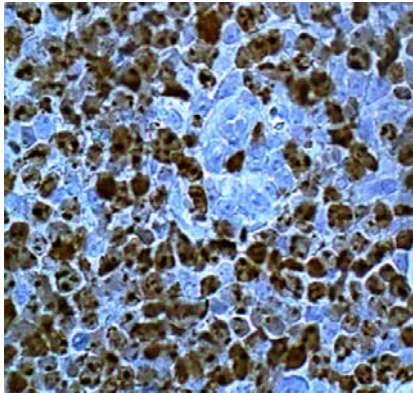


Figure 5- Nuclear staining for Ki67 (400X magnification)

Case2:

A 37 year old man was referred to the Department of Oral Pathology of Shahid Beheshti University, with multiple swellings of the maxillary gingiva and palatal area with 1-year duration. On extra-oral examination, mild facial asymmetry was seen that had pain of about one month duration. No palpable lymph nodes were found. On intraoral examination, the masses were soft to firm and the overlying mucosa was intact. His right canine tooth had been extracted six months ago due to clinical diagnosis of an abscess. These lesions did not respond to antibiotic therapy. His medical and

family histories were not contributory. (Figure6)



Figure 6- Multiple normal-colored masses on the gingiva, vestibule and hard palate

Serology for human immunodeficiency virus was negative. The patient underwent incisional biopsy from the vestibule of canine area and the microscopic findings were in accordance with NHL. (Figures 7, 8)

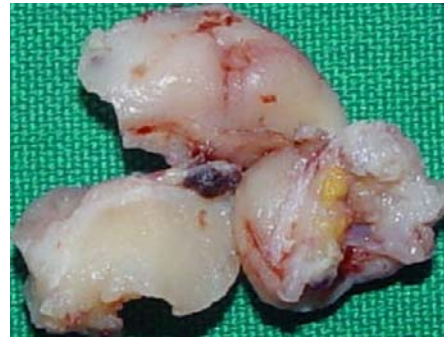


Figure 7- Gross pattern of the mass resembled fish flesh suggesting the diagnosis of lymphoma

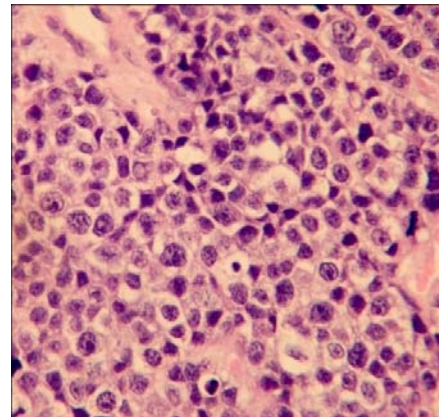


Figure 8- Microscopic view indicates the infiltration of large lymphocytes (400X magnification)

Immunohistochemical staining was positive for

LCA and CD20 and negative for CD3, CD10 and bcl-6. The diagnosis of diffuse large B cell lymphoma was confirmed. He did not have evidence of lymphoma in any other area of the body and the patient underwent chemotherapy and all lesions resolved completely after therapy. He is alive now without recurrence 4 years after treatment.

Case3:

A 70 year-old edentulous man was referred to the Department of Oral Pathology of Shahid Beheshti University, with bilateral painless swellings of the palate with no other clinical symptoms of 12 months duration. The masses were soft to firm and the overlying mucosa was intact and non-tender. An incisional biopsy was performed and the microscopic findings were positive for LCA and CD20 and negative for CD3 indicative of NHL. (Figures 9, 10, 11)



Figure 9- Note the bilateral palatal involvement. The patient also suffers inflammatory papillary hyperplasia of the palate due to denture use

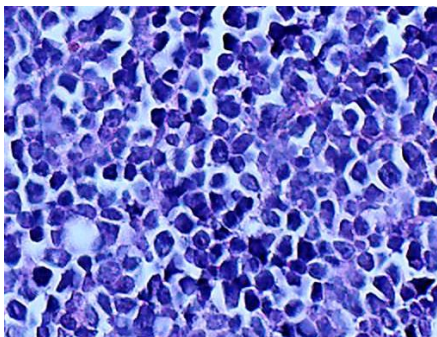


Figure 10- Microscopic view shows the proliferation of atypical lymphocytes (400X magnification)

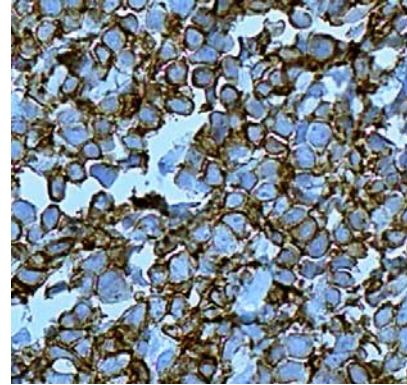


Figure 11- In IHC staining, cells were positive for CD20 marker.

The patient was referred to an oncologist for further evaluation and treatment.

Discussion:

Lymphomas are a diverse group of neoplasms affecting the lymphoreticular system; most of them originate from B lymphocytes (6). The most frequent type is diffuse large B-cell lymphoma (DLBL) (8).

Nonspecific clinical signs and symptoms like local swelling, pain or discomfort, and ulcer may be seen (9). The high incidence of dental abscesses and inflammation lead many dentists to associate a swelling or tumor formation of the jaw and palate with these usual clinical conditions (10). Most of the cases initially present as an odontogenic infection (11). The gingival and palatal regions are commonly affected (12). In our cases, the gingival and the palate were involved. The diagnosis of lymphoma in the jawbone is often delayed and biopsy is considered when there is a non-healing extraction site for a prolonged period (6). Parrington and Punnia-Moorthy (1997) discussed a case of primary lymphoma of the mandible presenting after tooth extraction (13). Djavanmardi, *et al.* (2008) found diagnosis of NHL difficult and often misleading and delayed before bone biopsy (14). Two of our cases of NHL initially diagnosed as dental abscess and inflammation received antibiotic therapy. This

incorrect diagnosis leads to patient complications and delayed treatment. There are no pathognomonic radiographic findings and usually mimic non-specific osteolysis (11). Lymphomas are usually submucosal, and on gross appearance, differ from squamous cell carcinoma, which is usually ulcerated. Bony lesion may be associated with pain, swelling, numbness of the lips, and pathologic fractures (15). In our series, one patient complained of a numb chin of 1 month duration. Metastatic breast cancer and lymphoma account for most cases of numb chin in adults and acute lymphoblastic leukemia accounts for a significant number of cases in children (16, 17). Thus numbness in the lower lip, the mental or gingival area must alert the clinician to the possibility of serious disease (17). The exact mechanisms underlying this disorder in malignant diseases are not well known and a number of hypotheses have been proposed such as direct compression of the nerve, perineural invasion, leptomeningeal seeding, paraneoplastic syndrome, and invasion of the dura mater, cavernous sinus, or skull base by the malignancy, involving the trigeminal ganglion (17).

DLBL demonstrated a diffuse proliferation of large neoplastic B cells with nuclear size equal to or exceeding normal macrophage nuclei, or more than twice the size of a normal lymphocyte (8). The microscopic diagnosis has to be confirmed by immunohistochemistry (11).

Palatal lymphoid lesions can be divided into three categories: Primary lymphoma of the palate, with no other lymphomatous lesion detected elsewhere in the body, palatal lymphoma occurring as one of the lesions in a case of disseminated lymphoma and benign lymphoid hyperplasia of the palate (18). Secondary organ involvement along with the primary lesion in the oral cavity is generally observed (12); but in our cases other sites were not involved. Some reported cases of NHL in the literature were bilateral or multifocal (17, 10).

Among all cases of NHL in our institute only three cases were multifocal.

DLBL is divided into two prognostically important subgroups, namely germinal center B-cell like (GCB) and non-germinal center B-cell like (non-GCB) lymphomas based on immunohistochemical expression of CD10, BCL6 and MUM-1. GCB lymphomas tend to exhibit a better prognosis than non-GCB lymphomas (8). In two cases of our series, bcl-6 and CD10 were negative; this may worsen its behavior. Cell variables that may be important in predicting outcome are anti-apoptotic bcl-2 expression, cell proliferation rate (Ki-67), p53 expression and mutation, and bcl-6 rearrangements (19). Early diagnosis will improve the prognosis. However, patients older than 60, stages 3 or 4 and multiple organ involvement will have an unfavorable prognosis. The initial response to treatment is good but this entity demonstrates a prolonged course with remissions and exacerbations. NHL may progress to leukemia (19). Chromosomal translocations play a critical role in the pathogenesis of NHL, determining oncogenic activation or the inactivation of tumor suppressor genes, with the consequent malfunction of the mechanism of genomic rearrangement in lymphoid cells (20).

Overall evaluation is necessary to rule out nodal and visceral involvement. Laboratory assessment is not specific, although elevated lactate dehydrogenase is observed as a poor diagnostic factor (11). Accurate staging is essential to start the treatment and management. Staging takes into account the involved site and degree of dissemination (11). Generally, a combination of chemotherapy and field radiation is recommended for treatment. Monoclonal antibodies directed against antigens and interferon injection has also been used. In localized disease, the prognosis is excellent; while in disseminated disease, it is less favorable (6).

Conclusion:

In multifocal oral lesions, extra-nodal lymphoma must be considered in the differential diagnosis. The knowledge of these clinical patterns can lead to early diagnosis to ensure appropriate treatment, and improve prognosis and quality of life. Biopsy is necessary to distinguish these

lesions from other inflammatory conditions or neoplasms and immunohistochemistry staining can confirm the diagnosis. Numbness of the chin, lower lip and gingiva must alert the clinician to the possibility of malignancy and NHL.

Conflict of Interest: “None Declared”

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