CASE REPORT

Diffuse Large B-Cell Lymphoma in the Oral Cavity - A Case Report

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Abstract

Introduction: Diffuse large B-cell lymphoma (DLBCL) is a type of Non-Hodgkin lymphoma that may clinically manifest in the oral cavity. Not many cases of Non-Hodgkin's lymphomas (NHL) have been reported till date. This case report describes a significantly rare presentation of diffuse large B-cell lymphoma in the oral cavity.

Case Presentation: A 79 years' old male patient reported to the clinic with the complaint of a rapidly growing mass in the right upper back tooth region since 2 months. Surgical excision of the lesion was done. Histologic and immunohistochemical (IHC) examination confirmed a diffuse B-cell lymphoma. Following which patient underwent chemotherapy.

Management and Prognosis: A complete remission of the disease was noted after the treatment and patient has been kept on follow up.

Conclusion: The report describes how care must be taken to consider lymphoma in the differential diagnosis of similar oral lesions, because this uncommon lesion can alter significant diagnostic approaches and can be frequently misdiagnosed.

Keywords: B-cell lymphoma, Non-Hodgkin's lymphoma, Diffuse Large B-cell lymphoma of Oral Cavity

Introduction

B-cell lymphomas result from malignant proliferation of B-cells in their various stages of development. Diffuse Large B cell Lymphoma is the most common type of NonHodgkin's lymphoma. Studies report incidence of 4 cases of NHL per 100000 people, out of which 34-60% cases are DLBCL. B-cells are known to have functional diversity and property to transform into multiple pathways. They can be indolent or aggressive.[1] Depending on the morphology, genetics and immunophenotype of the neoplastic cells, a cell of origin is proposed (coo- the cell that receives cancer causing mutation).1 B-cell lymphomas are categorized based on the stage of the B-cell development that has caused the malignancy. The cell of origin can be from any stage of development of the B-cell.[1] Only 15% of oral lymphomas are located in locations other than the palate or Waldeyer's ring, and less than 5% of mouth malignancies are primary lymphomas. The majority of DLBCL patients do not have underlying risk factors. The exact cause of DLBCL is unknown. Less frequently, instances may develop in the context of an immunodeficiency or from a high-grade transformation of a less aggressive lymphoma.[2] While it can infrequently afflict younger children, DLBCL primarily affects older males. Pain, numbness, loosening of the teeth, nasal discharge and blockage, painful throat and foreign body sensation in the throat, dysphagia, and odynophagia are the most often reported symptoms. When immunodeficient conditions are present, such as AIDS, the likelihood of acquiring DLBCL is elevated. Pathologists can shed light on the probable behavior and prognosis of DLBCL subtypes by classifying them, with germinal center b-cell-like subtypes showing

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better results than non-germinal center B-cell like subtypes.[2]

Case Presentation

A 79 years old male patient reported with the complaint of a rapidly growing mass in the right upper back tooth region since 2 months. Patient was apparently alright 2 months back since when he noticed a mild non-painful swelling in the right upper back tooth region which has grown to its present size over the past few days. Patient had no significant medical history. On clinical examination, No significant abnormalities were found extra-orally. Intraoral examinations revealed a solitary, purplish red, sessile mass measuring 38mm*19.5mm in its greatest dimension extending from the buccal vestibule to the palatal attached gingiva in relation to 15, 16(apparently missing), and 17 region. The surface of the mass had a few areas covered with slough (Figure 1). On palpation, the mass was soft to firm in consistency, non-tender and with normal surface temperature and no sign of bleeding on provocation. Patient was observed to have poor oral hygiene. A provisional diagnosis of Reactive gingival lesion was made. Peripheral giant cell granuloma, Vascular malformation and Kaposi's sarcoma were considered as the differential diagnoses. Patient was advised to produce an Orthopantomogram (OPG) and a cone beam computed tomography which revealed a radiopaque shadow in the lesioned area with mild breach in the lining of the maxillary sinus of the affected side (Figure 2). Patient was advised to have an incisional biopsy followed by histopathology for confirmation. Blood investigations prescribed were complete blood count (CBC) with Erythrocyte sedimentation rate (ESR), random blood glucose (RBG), activated partial thromboplastin time (aPTT), prothrombin time/International Normalized Ratio (PT/INR). The blood reports revealed lymphocytopenia with an absolute lymphocyte count = 874/microliter of blood. Incisional biopsy was performed under local anesthesia (Figure 3). The Histopathological findings revealed sheets of intermediate to large sized lymphoid cells having regular nuclear margins, opened up nuclear chromatin and some cells with distinct nucleoli. A fair number of mitotic numbers were seen. The surface had hyperplastic, ulcerated stratified squamous epithelium. Sulfur granules of Actinomyces were seen. Fibro-collagenous tissue with bundles of muscle fibers were also noted. (Figure 4 and 5) It could be concluded that the lesion was the result of lymphoproliferative disorder. But immunohistochemistry was needed for confirmatory diagnosis. Immunohistochemistry revealed lesioned cells expressed CD_{10}, CD_{20}, BCL_2, BCL_6, positive CD_5, MUM_1, Cyclin D_1 was negative. 15% of the lesional cells expressed c-myc. CD_3, CD_5 marked background t lymphoid cells. Mib1(ki67) was positive. Labelling index was 95-98%. Hence, all these markers confirmed diffuse large b-cell lymphoma (GCB type). After 5 cycles of Rituximab (dose- 375 mg/m2), Cyclophosphamide, AntiCD20 monoclonal antibody (dose- 750 mg/m^2), Doxorubicin (Dose- 50 mg/m^2), Vincristine [Dose- 1.4 mg/m^2 (up to a maximal dose of 2 mg)], Prednisone (tapering dose starting with 40 mg/m^2 for 5 days) (RCHOP) given every 21 days, a positron emission tomography scan revealed complete remission. Consolidative radiation was conducted successfully.

Discussion

DLBCL is the most common type of NHL worldwide. Up to 40% of the cases present with only extra-nodal involvement, and isolated bone marrow involvement is extremely rare. Oral manifestations are uncommon findings accounting for 3–5% of the cases. DLBCL rarely presents as a primary malignancy in the head and neck region (<1%). The presence of DLBCL in the head and neck may be associated with undiagnosed HIV infection since they account for 2% of oral neoplasms in patients with AIDS. DLBCL has been reported in the oral cavity in the buccal mucosa, hard palate and gingiva. Many of the cases in our study arose in intra-bony locations and the maxillary vestibule was a common site for the occurrence of soft tissue tumors.

The clinical manifestations commonly include enlarged lymph nodes or rapidly growing mass. 30% patients may complain of fever, night sweats, and weight loss. 50% patients have extranodal involvement - brain, spinal cord, bones, kidney (14%, ureteral obstruction), adrenal glands, testes etc. The most common extranodal (extralymphatic-disease spreads beyond lymphatics) sites involve the stomach and gastrointestinal tract, skin. DLBCL can also present with symptoms, suggestive of superior venacava syndrome, compression of the airways. Bone marrow involvement is seen in indolent disease (50% cases)

The oral manifestations include the presence of a bland, painful or painless nodular mass. Generalised numbness and tooth mobility may be seen in the affected area.

Nasal obstruction and(/or) discharge may be seen. Mostly, there is a Foreign body sensation in throat, along with symptoms of sore throat, Dysphagia, and Odynophagia can be seen.

A whole-body lymphoid survey including head, neck, cervical, supraclavicular, axillary, mesenteric, femoral, inguinal is needed. Abdominal examination should be done to check for enlarged liver or spleen

Laboratory investigations should be done, like CBC (reveals cellular atypia; cytopenia), Comprehensive metabolic profile, Lactate dehydrogenase (elevated in more than 50% cases; predictor of survival), HIV, Hepatitis B, C serology, Serum protein electrophoresis, excisional biopsy of the lymph node (no Fine Needle Aspiration Cytology) to look for entire architecture of lymph node along with histopathology and immunohistochemistry studies. Morphology and immunophenotyping along with staining for B-cell markers is needed for confirmatory diagnosis. Positron emission tomography (PET) and computed tomography (CT) scans are used for staging- sites with high standardized uptake value indicate aggressive disease. PET scan also indicates least invasive sites (aid in diagnostic biopsy). In absence of significant lymphadenopathy - tissue sampling from organs can be performed.

Although the hematological and biochemical profile of patients with DLBCL is generally normal, they may have a reduced number of peripheral B lymphocytes or a decrease in serum albumin and elevated levels of LDH, IL-6, IL-10 and IL-2 receptors, which have been associated with poor prognosis. Most of the time, DLBCL undergoes somatic mutation in the polymorphic regions of their IL-HHC genes, so it is thought that the B-cells that cause the disease are derived from either GC (genetic group) or post-glucose (glucose) B-cells (post-glucose B-cells). CDNA microarray technology has been used to evaluate gene expression profiles for DLBCL and identified two different molecular forms, GCB (Glucose-like) and non-glucose-like (non-glucose)-like DLBCL. Glucose-like DLBCL lesions express genes that are normally expressed by germ-centre B cells, while non-glucoside DLBCL expresses genes that are normally induced during peripheral blood B cell activation in vitro.[2]

Histopathologically, the normal architecture of lymph nodes is distorted and is replaced by sheets of atypical lymphoid cells with large nuclei, basophilic cytoplasm, and high proliferation rate.[1]

Immunohistochemistry markers -

- BCL2: Anti-apoptotic protein protecting cells from programmed cell death. Found in 30–60% of cases. Studies suggest its associated with a significantly worse overall survival rate.
- BCL6: Expressed by GC B cells in normal lymphoid tissues and a subset of CD4+ T cells. Found in a majority of the cases ranging from 57 to 100%. Reported in about 40% of DLBCL. Biological significance of this expression is not clear.
- MUM1: Lymphoid-specific member of the interferon regulatory factor family of transcription factors. Expressed in 50–75% of cases, with and without BCL-6 expression. It is associated with a poor overall survival rate. Marker of the non-GCB phenotype especially when used in conjunction with CD10 and BCL-6.
- CD10: Limited to the germinal center of secondary follicle. CD10 (Methyloproteinase-CD10) CD10 expression is Follicular lymphomas (CD10 positive)
- CD19: Marker for B-cell lineage
- CD20 (pan B cell antigen): A very specific marker for the B-cell lineage. Most DLBCL have homogeneously bright CD20 staining.
- CD22: Expressed early in the development of B cells in the bone marrow and spleen

Fig. 1: Clinical image of the lesion

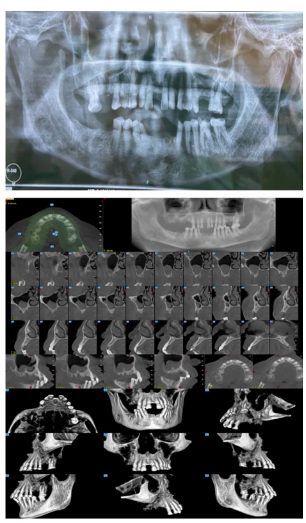

Fig. 2: OPG (top) and CBCT (bottom) images if the concerned lesion.

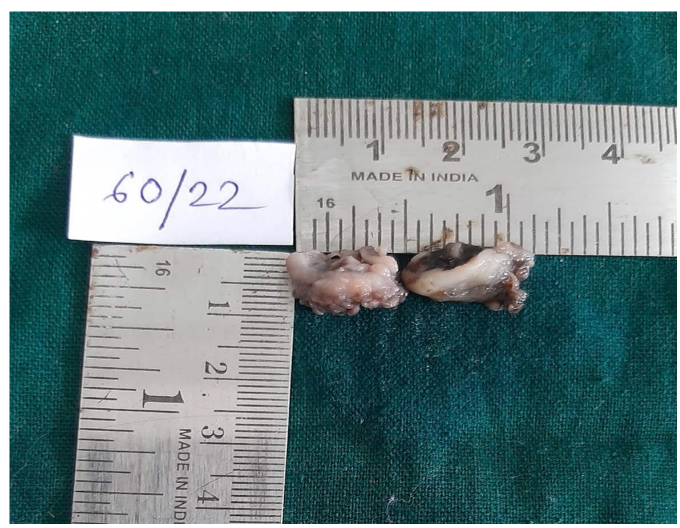

Fig. 3: Excised lesion

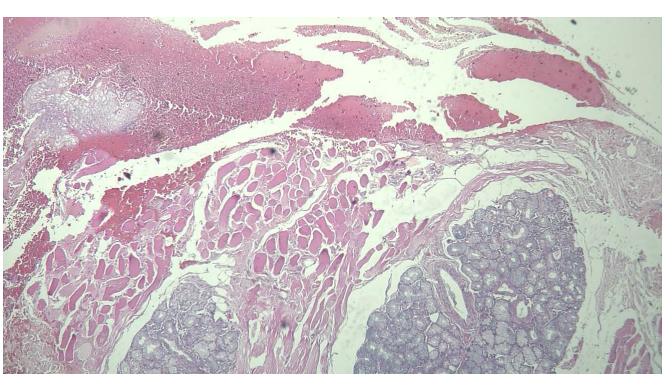

Fig. 4: Histopathological image of the lesion (10x view)

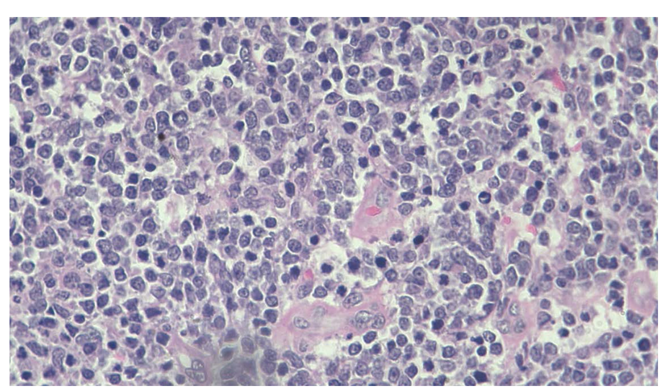

Fig. 5: Histopathological image of the lesion (40x view)

- CD 45: Leukocytes common antigen.
- CD79A: Expressed in some cases
- CD30: Expressed in 25% cases- favorable prognosis
- CD5: Expression is rare, poor prognosis
- Ki67(cell cycle marker) - Proliferative marker. It determines the growth fraction of the actively cycling cells. The expression of Ki67 in DLBCL ranges from 30 to 100%, but is generally high. High proliferative indices are generally considered negative prognostic factors. Tumors expressing >80% Ki67 are classified as highly proliferative or aggressive tumors.

The cell-of-origin (COO) (the classification subdivides DLBCL into the transcriptionally defined activated B-cell (ABC) and germinal center B-cell (GCB) subtypes.[3] A normal B cells go through the pre-germinal center, GC and post GC stages of differentiation. Pre GC-B-cells are virgin B cells. Cells comprising the GC consist of blast cells, centroblasts, centrocytes and occasionally plasma cells. The B cells that leave the GC and enter the post GC phase, differentiate either towards the memory cells or plasma cells. Normal GC B cells express CD10 and BCL-6. BCL-6 may be lost by late GC B cells, which in turn acquire MUM-1 expression. MUM-1, and CD138 are expressed by post GC B cells while MUM-1 may be acquired late in the GC reaction, CD138 expression is usually restricted to cells exhibiting plasmoblastic differentiation and to plasma cells.

It has been accepted that the distinct gene expression profiling subtypes, the GCB and non-GCB of DLBCL can be predicted using a panel of antibodies by immunohistochemistry that include CD10, Bcl-6 and MUM1. If both CD10 and BCL-6 are positive or if CD10 alone is positive the tumor can be assigned in the GCB subgroup. If CD10 is negative and Bcl-6 is positive, the expression of MUM-1 determines the subgroup. If MUM-1 is negative the tumor represents a GCB subgroup whereas if MUM-1 is positive, a non-GCB designation is given.[2]

Current treatment of DLBCL usually begins with multi-agent chemotherapy- RCHOP (Rituximab, Cyclophosphamide, Hydroxydoxorubicin, Oncovin and Prednisone). Though initial response to therapy is noted, more than half the patients succumb to the disease. Early-stage disease care involves either chemotherapy alone or a combination of chemotherapy and radiotherapy. The chemotherapy usually involves 6-8 cycles of RCHOP.[1] Patients are considered for bone marrow transplant if remission is not maintained. The role of surgery is severely limited in treatment of DLBCL. Other drugs used in multiagent chemotherapy for advanced stage disease usually involve various combinations of Methotrexate, Bleomycin, Doxorubicin, Vincristine, Dexamethasone and Leukcovorin, Etoposide, Mechlorethamine, Procarbazine, Cytarabine.[2] Chimeric antigen receptor (CAR) T-cell therapies that target CD19 have advanced the treatment of multiply relapsed large B-cell lymphoma and showed promising results.[5]

Conclusion

Very few cases have been reported on Diffuse Large B-cell Lymphoma in the Oral cavity. This report has been created keeping in mind that it helps all of the dental fraternity to think of all possible diagnoses that can result from a simple non-aggressive appearing oral lesion.

Clinical Significance

Being aware of all possible differential diagnoses for any oral pathology may save lives. Developing the clinical eye is very important while dealing with oral cavities on a regular basis. Early detection and hence biopsy can reveal the nature of lesions that appear to be benign. Hence identifying and sampling oral lesions, especially malignancies at the earliest can improve patient outcomes.

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