

CASE REPORT

Centroblastic variant of diffuse large B-cell lymphoma: Case report and review of literature

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ABSTRACT

Diffuse large B-cell lymphoma (DLBCL) is a subtype of non-Hodgkin's lymphoma (NHL) making up about approximately 30% of all NHL. Its occurrence in the mandible is very rare. Histopathologically, five variants of DLBCL have been recognized among which centroblastic variant is the one with better prognosis. We report a case of a 55 year-old patient who presented with a painless swelling in the lower right body of the mandible since 4 months. Incisional biopsy revealed NHL like features, confirmed by immunohistochemistry using CD45, CD20, and CD3 markers to be a DLBCL of centroblastic variant. Patient was treated with chemotherapy following which the lesion regressed completely with no further recurrences. Precise histological diagnosis is crucial for the clinical management and ultimately for the survival of the patient.

Key words: Centroblastic variant, diffuse large B-cell lymphoma, extranodal, immunohistochemistry, non-Hodgkin's lymphoma

INTRODUCTION

Lymphomas are a heterogeneous group of malignancies of the immune system. Non-Hodgkins lymphoma (NHL) are a group of neoplasms that originate from the cells of the lymphoreticular system.^[1] They constitute 5% of all head and neck cancers.^[2] A 25-30% of NHLs present in extranodal sites with the gastrointestinal tract being the most frequent site followed by the head and neck region constituting 11-33% of the cases.^[3]

Parker and Jackson in 1939 were the first to propose that extranodal lymphomas arising at a primary site in bone offered a favorable prognosis.^[4] Among the jaw lesions, maxilla is more commonly affected than the mandible with a predilection for the posterior sites.^[1]

Diffuse large B-cell lymphoma (DLBCL) is considered to be the most common subtype of NHL including primary mandibular NHL.^[5] According to the World Health Organization (WHO) classification of neoplastic diseases

of hematopoietic and lymphoid tissues, DLBCL accounts for 40% of the adult NHL's. This heterogeneous group of lymphoid neoplasm is characterized by diverse spectrum of clinical and morphological features, response to therapy and survival.^[6]

DLBCL is characterized by diffuse proliferation of large neoplastic B lymphoid cells with nuclear size equal to or exceeding normal macrophage nuclei, or more than twice the size of a normal lymphocyte.^[7] DLBCL may arise de novo, as a primary tumor or as a result of progression and transformation of a less aggressive lymphoma of a lower grade such as lymphocytic, follicular or marginal lymphoma.^[8] Classification systems as elicited by Kiel, subdivided DLBCL based on its morphology into centroblastic and immunoblastic lymphomas.^[9] Centroblastic lymphoma is the most common subtype with better prognosis (and overall survival) when compared with immunoblastic and anaplastic variants of DLBCL.^[10]

We present a case of primary diffuse centroblastic variant of large B-cell lymphoma in the mandible with added review of literature.

CASE REPORT

A 55 year old male patient reported to the dental hospital in the year 2007 with a complaint of painless swelling in the lower right body of the mandible for the last 4 months. The swelling was insidious in onset and gradually increased in size.

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Facial asymmetry was seen on the right side. Examination revealed a nontender, solitary diffuse swelling measuring 3.5 cm × 3.5 cm in the lower right body of the mandible. The swelling was fixed, firm to hard in consistency. Intraorally, the swelling extended from 44 to 48 regions obliterating the buccal vestibule, with buccal cortical plate expansion. Computed tomography (CT) of mandible showed an osteolytic lesion with soft tissue density in the right body of the mandible at the mental foramen region with break in the cortical plates both on buccal and lingual side [Figure 1]. Incisional biopsy showed the lesion to be composed of abnormal large lymphoid cells with high nuclear cytoplasmic ratio. These large lymphoid cells were arranged in diffuse pattern, with the large cells having coarse chromatin and inconspicuous nucleoli [Figure 2]. Mitotic figures were also evident. The above mentioned findings favored the diagnosis of DLBCL.

Investigations like chest X-ray, ultrasonography of abdomen and pelvis, and bone scan of whole body were done. Bone scan showed minimal increase in uptake in the right mandible anteriorly indicating slow bone destruction. There

was no evidence of distant bone involvement. Clinical examination and investigations classified the disease under stage IAE. Following this, immunohistochemical analysis was done for the expression of pan B-cell markers like CD45 (leukocyte common antigen), CD20 (selective marker that recognizes a subpopulation of B-cells), and CD3 (marker for T-cells and natural killer cells). CD45 [Figure 3] and CD20 [Figure 4] were positive and CD3 was negative. Based on immunohistochemistry report the lesion was diagnosed as DLBCL of the mandible. Centroblastic, immunoblastic, T-cell/histiocytic-rich, anaplastic, and plasmablastic variants are the five histopathological subtypes of DLBCL according to WHO classification.^[6] Histopathological examination of our case revealed centroblastic variant of DLBCL with few immunoblast like cells. Centroblasts are large noncleaved cells, with round to oval centrally placed nuclei and peripherally located nucleoli [Figure 5]. They have moderate to scanty cytoplasm with fragmentation of nucleoli being quite common among these cells. Based on histopathological examination and immunohistochemistry study, the following lesions under differential diagnosis were ruled out; Hodgkin's

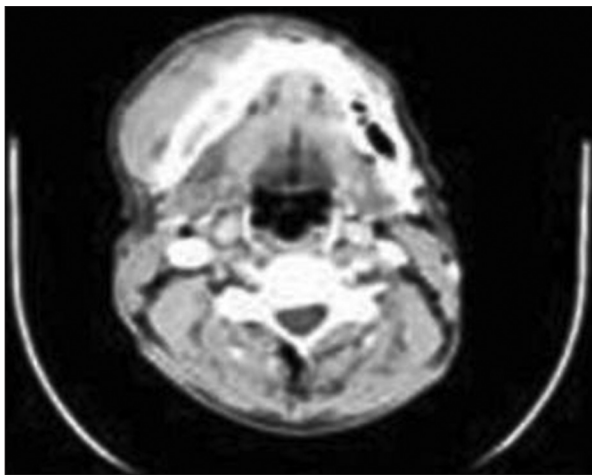


Figure 1: Computed Tomography of mandible showing an osteolytic lesion with soft tissue density in the body of the mandible

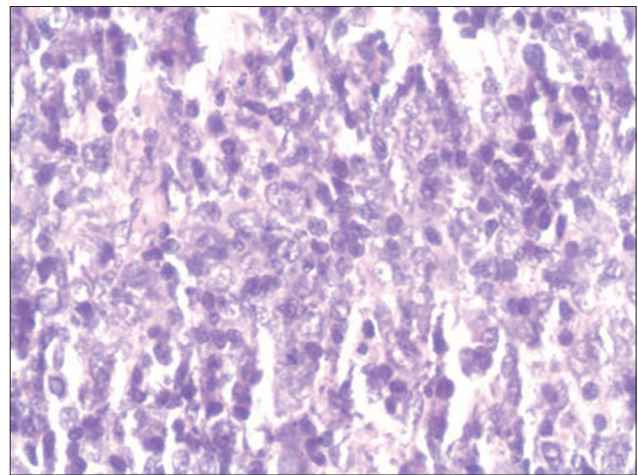


Figure 2: Photomicrograph shows diffuse large lymphoblasts arranged in sheets (H&E stain, ×400)

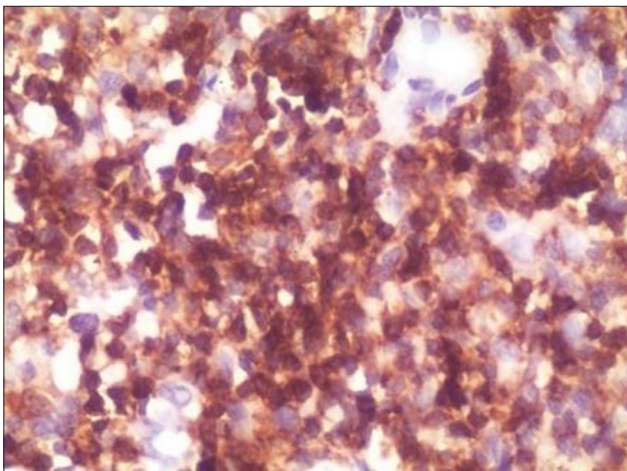


Figure 3: Immunohistochemistry shows positivity for CD45 (IHC stain, ×400)

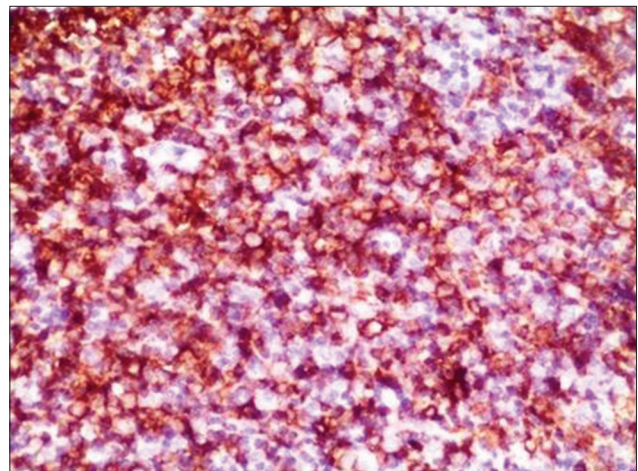


Figure 4: Immunohistochemistry shows positivity for CD20 (IHC stain, ×400)

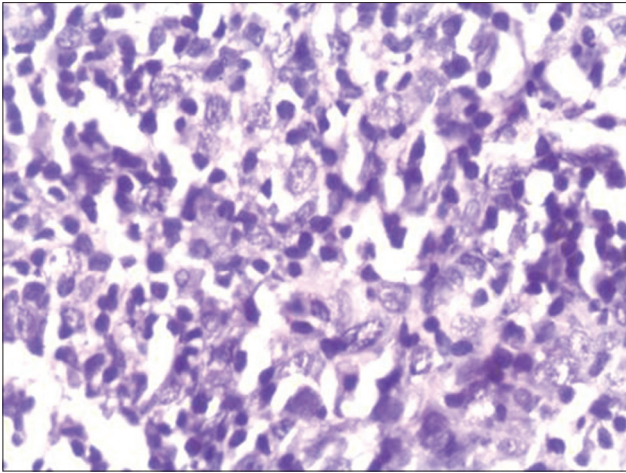


Figure 5: Photomicrograph showing centroblasts with vesicular nuclei, prominent nucleoli and basophilic cytoplasm (H&E stain, $\times 400$)

lymphoma, large cell lymphoma of T-Cell type, Burkitt's lymphoma, follicular lymphoma, undifferentiated carcinoma, and amelanotic melanomas.

Based on the final diagnosis, chemotherapy was advised by the oncologist and a total of six cycles were suggested at the gap of every 3 weeks. The treatment regimen followed was that of cyclophosphamide, hydroxydoxorubicin, oncovin, and prednisone (CHOP) therapy comprising of cyclophosphamide, doxorubicin, vincristine, and prednisolone. Patient is being examined periodically once in 2 months and he has had no recurrences from past 3 years and is disease free.

Review of literature

NHL arises primarily within the lymph nodes; however extranodal presentations are common in patients with NHL. Oral manifestations presented in only 3-5% of cases of NHL and are rarely the initial manifestation of the disease.^[1]

Of the NHLs that occur in the oral cavity, 15-45% occur in the maxilla and mandible.^[11] A review of oral NHL shows upper jaw maxilla (11%), mandible (8%), palatal soft tissue (8%), vestibule, and gingiva (7%) to be the most common locations.^[12] Isolated mandibular NHL accounts for only 0.6% of the cases reported. Such cases when occur commonly mimic odontogenic infections leading to delay in diagnosis and therapy for the patients. To be classified as a primary NHL of bone there must be no evidence of visceral or lymphatic involvement and no distant metastases for at least 6 months following diagnosis.^[5] The peak incidence for primary NHL of jaws is in the 4th-5th decade. Equal sex distribution is usually reported with few cases showing female predominance.^[13] Mandibular NHL may involve any site with Gusenbauer *et al.*'s series involving the body of the mandible followed by ramus, angle and symphysis region.^[14] In our case, the patient had undergone extraction, following which he developed a nontender swelling in the right mandibular body. Some authors reported paresthesia

(about 20-100% of cases) along the inferior alveolar nerve to be common in NHL involving the mandible.^[13]

There are no pathognomonic radiographic features for NHL involving the mandible. Features of osteolysis are usually suggestive with other radiological findings of destruction of the alveolar bone, diffuse trabecular pattern, mottling appearance, and resorption of roots of teeth. CT scan of our case showed an osteolytic lesion with soft tissue density in the right body of mandible at the mental foramen region with break in the cortical plates involving both buccal and lingual cortical sides. Histology coupled with immunophenotyping and cytogenetic evaluation can suggest the subtypes of NHL and thus help in rendering prompt treatment and aid in better survival rates of lymphoma patients.

The primary NHL involving the mandible for most of the times is of intermediate to high grade malignancy although it tends to remain localized at times of diagnosis with stage IAE presentation.^[13,15]

DLBCL constitutes a heterogeneous group of lymphoid neoplasm's that is characterised by diverse spectrum of clinical and morphological features, response to therapy and survival. Morphologically DLBCLs replace the normal architecture of lymph nodes in a diffuse pattern. Neoplastic cells are at least twice the size of normal lymphocytes with vesicular nuclei, prominent nucleoli, and basophilic cytoplasm.^[6] DLBCL may be arising de novo, or as a primary tumor or as a result of transformation of a less aggressive lymphoma of lower grade such as lymphocytic, follicular, or marginal lymphoma.^[8]

Twenty-eight percent of DLBCL's depict chromosomal translocations and molecular rearrangements such as translocation of t (14;8) (q32;q21) involving the Bcl-2 gene. Several classification systems have categorized DLBCL into its morphologic and phenotypic variants in the past.

WHO Revised European American Lymphoma (REAL) classification of NHL according to clinical aggressiveness; groups DLBCL under the aggressive lymphomas.^[1]

The 2001 WHO classification being an update of REAL classification is given below.^[16]

DLBCL subtypes according to 4th edition of the WHO classification of tumors of the hemopoietic and lymphoid tissues.

DLBCL, not otherwise specified (NOS)

Common morphologic variants

- Centroblastic
- Immunoblastic
- Anaplastic

Rare morphologic variants

Molecular subgroups

- Germinal center B-cell like (GCB)
- Activated B-cell like

Immunohistochemical subgroups

- CD5-positive DLBCL
- GCB
- Non-germinal center B-cell like (non-GCB)

DLBCL subtypes/entities

- Primary mediastinal (thymic) large B-cell lymphoma
- T cell/histiocyte rich large B-cell lymphoma
- Intravascular large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- Primary cutaneous DLBCL, leg type
- DLBCL associated with chronic inflammation
- Anaplastic lymphoma kinase (ALK) positive DLBCL
- Large B-cell arising in human herpes virus (HHV) 8-associated multicentric Castleman disease
- Plasmablastic lymphoma and primary effusion lymphoma

Borderline cases

B-cell lymphoma, unclassifiable with features intermediate between DLBCL and Burkitt's lymphoma.

B-cell lymphoma unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma.

Histopathologically, our case was diagnosed as centroblastic variant having medium to large sized lymphoid cells with oval to round vesicular nucleus with fine chromatin and 24 membrane bound nuclei, the cytoplasm being amphophilic to basophilic. The tumor represented a monomorphic pattern with more than 90% comprising of centroblastic cells. Centroblastic DLBCL being the most common variant is composed of cells that resemble their normal counterparts in the reactive germinal centers.^[8] Variable number of immunoblasts may be found admixed, but generally comprises less than 90% of the tumor cell population.^[7]

Histopathology, immunohistochemistry, immunophenotyping, and genetic studies help to categorize DLBCL further, in order to direct a specific regimen of therapy. DLBCL usually express pan B-cell markers such as CD19, CD20, CD75, CD79a, PAX5, and CD22; but may lack one or more of these. Surface and/or cytoplasmic immunoglobulins (IgM > IgG > IgA) can be demonstrated in 50-75% of cases.^[6,17] CD20 expression by B-cells from mature precursor B-cell until the preplasma cell stage of differentiation is highly specific for B-cell lineage and mostly DLBCL show homogeneously bright staining for this as seen in our case.^[18]

Bcl-6 is selectively expressed by germinal center B-cell like GCB cells in normal lymphoid tissues and in DLBCL at

about 57-100%, but with unclear biological significance with reports suggesting Bcl-6 expression related to oncogenesis.^[18,19]

Prognosis

Patients with DLBCL have variable clinical courses and prognosis depending on many clinical, morphological, phenotypic, and genetic parameters. International prognostic index (IPI) is widely used as a predictive model in DLBCL patients of all ages and clinical stages. The IPI combines patient's age with easily measured clinical parameters which can serve as surrogate markers of tumor burden. Performance status, extranodal involvement, serum lactate dehydrogenase levels, stage of disease, and Bsymptom status are significantly associated with survival.^[10]

A 5 year disease free survival was 53.2% for patients with centroblastic and 26.9% for patients with immunoblastic NHL.^[10] Patients with germinal center B-cell like lymphoma had the highest 5 year survival rate. DLBCLs of germinal center B type have a better prognosis than those derived from activated B-cell type.^[6]

Treatment

Early stage disease care in DLBCL patients involves either chemotherapy alone or a combination of chemotherapy and radiotherapy. The chemotherapy usually involves three cycles of CHOP. The role of surgery is severely limited in treatment of DLBCL. Current treatment of DLBCL usually begins with multiagent chemotherapy, typically CHOP as done in our present case with 6 cycles of CHOP.^[1,18] Recently, anti-CD20 monoclonal antibody (rituximab) has been added to this regimen and has been found to improve failure-free survival.^[18] With the well-accepted addition of rituximab to the typical large B-cell lymphoma chemotherapeutic regimen, a revalidation of any survival differences between large B-cell lymphoma subtypes is necessary. So far, only a few studies have been published and we need more investigations in this field.^[19]

Localized (stage I and stage II) low grade extranodal lymphomas in the head and neck are treated primarily with radiation therapy. Patients with localized intermediate grade lymphomas should be treated with combination chemotherapy as done in our case. There is evidence that CHOP regimen could be curative for this subset of patients. Radiation therapy alone was the mainstay of treatment for these disorders until curative combination chemotherapies were developed. High grade and advanced stage NHL should be treated with aggressive chemotherapy regimen.^[3]

Treatment options with combination chemotherapy alone CHOP had no recurrences seen in patients with NHL similar to our case.^[20]

CONCLUSION

In this brief case report and review of literature we describe a case of DLBCL, which is a subtype of NHL making up about approximately 30% of all NHLs. Its occurrence in the mandible is very rare. Centroblastic variant of DLBCL is known to have a better prognosis and overall survival in patients as observed in the previous literature reported and the same has been observed in the present case reported.

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