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CASE STUDY

PRIMARY EXTRA NODAL LYMPHOMA: A RARE CASE OF GNATHIC INVOLVEMENT

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ABSTRACT

Lymphomas are malignant neoplasm of lymphocytes and their cell precursors. The two main forms of lymphomas are: Hodgkin's lymphoma and Non-Hodgkin's lymphoma (NHL). The NHLs are a heterogeneous group of neoplasms with Diffuse large B-cell lymphoma (DLBCL) being the most common variant of NHL. It is an aggressive lesion that can either develop de novo or as a transformation from a less aggressive form of lymphoma. In the oro-pharyngeal region, DLBCL usually involves Waldeyer's ring (WR), paranasal sinuses, mandible and maxilla. Primary extra-nodal presentation of this entity within jawbones are rare and their initial manifestation is in the form of non-tender swelling. Other systemic symptoms may include night sweat, fever, and unexplained weight loss. Histopathologic evaluation together with immunophenotype and cytogenetic studies may reveal the histologic variant. Immunohistochemistry has an important role in distinguishing cell type and differential diagnosis. Treatment for primary extra-nodal lymphoma of the mandible typically consists of a combination of chemotherapy and radiotherapy. Proper evaluation and investigations are required for correct diagnosis so that patient may receive the treatment in early stage and attain good prognosis. Here we present a case of 48 year old male patient diagnosed with Diffuse B-cell lymphomaalong with its clinical, radiological, histopathological and immunohistochemical features.

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INTRODUCTION

Lymphomas are diseases of the haematopoietic system that occurs due to malignant proliferation of lymphocytes during various stages in their differentiation [(1)]. Lymphomas are mainly of two types: Hodgkin's lymphoma and Non-Hodgkin's lymphoma (NHL). According to latest statistics, the percentage of new cases of Non-Hodgkin Lymphoma are about 4.3% and the percentage of cancer death from NHL is 3.4%[(2)]. The NHLs are a heterogeneous group of neoplasms that areusually located in lymphoid tissues like lymph nodes, spleen, and bone marrow or extra-nodal sites like the gastro-intestinal tract, skin, oral cavity and pharynx, breast, kidney and central nervous system (CNS) [(3)]. Diffuse large B-cell lymphoma (DLBCL) is the most common variant of Non-Hodgkin's lymphoma accounting for 30%-40%of all cases of NHL. The median age of presentation is 70 years; however, it can occur at any age, with a slightly higher incidence in males. The neoplastic cells of DLBCL are of B-cell origin.

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Genetic mutations leads to changes in B-cells, thus modifying their gene expression and resulting in neoplastic transformation. The size of these neoplastic cells exceeds twice the size of normal lymphocytes. They may originate de novo or may develop from the transformation of other forms of B-cell neoplasms such as Chronic Lymphocytic Leukaemia, Lymphoplas macytic Lymphoma, Marginal Zone Lymphoma and Follicular Lymphoma [(4)]. The clinical manifestations of DLBCL is diverse and depends on the site of in volvement. The common intra-oral sites are the tonsils, palate, buccal mucosa, gingiva, tongue, floor of the mouth, salivary glands, and retromolarregion. Jaw bone involvement of the lesion shows a prevalence of maxilla over mandible. The most common intra-oral manifestations include swelling with or without ulceration, pain and par aesthesia. Alveolar bone loss with tooth mobility may also occur mimicking periodontal diseases [(5)]. Patients often presentB-symptoms like fever, night sweat and weight loss [(4)]. Radio graphically, intraosseous lesions appear as radiolucent areas eitherunilocular ormultilocular with diffuse edges. The FDG-PET (18F-fludeoxyglucose positron emission tomography) scan is now considered the choice of imaging for staging, restaging and

treatment modalities for most types of lymphomas [6]. Histopathologically, these lymphomas are characterized by a proliferation of lymphocyte like cells that may show varying degrees of differentiation. Low-gradelesions consist of well-differentiated small lymphocytes whereas the high-grade lesions are usually composed ofless differentiated cells. The neoplastic cells are present as infiltrative broad sheets with little or no evidence of necrosis. Immunohistochemical analysis revealed that these B-cell neoplasm has an array of biomarkers likeCD20, CD79a, BCL6, CD10, MYC, BCL2, Ki67, CD5 and CD45 [6]. Treatment strategies are based according to age, International Prognostic Index and feasibility of dose-intensified approaches. The treatment modality of DLBCL includes a combination of chemotherapy and radiotherapy. Six to eight cycles of chemotherapy with CHOP (cyclophosphamide, doxrubc In, vincristine prednisone) combined with eight doses of rituximab given every 21 days are most frequently applied. In cases, were radiotherapy is recommended, external beam radiotherapy is utilized [7]. The 5 year survival rate depends on the grading and staging of cancer, over all health and response to treatment. Usually 50% to 80% of patients survive 5 years or more[8]. Based on the above clinico-pathological, radiological, histological and immunohistochemical findings, a case of diffuse large B cell lymphoma involving the mandible was diagnosed and has been discussed herewith.

CASE REPORT

A 48 yr old male patient from a rural area reported to the Department of Oral and Maxillo facial Pathology, GNIDSR, Kolkata with the chief complaint of progressively increased swelling involving the left side of the lower jaw over a period of 2 years. Medical history revealed that the patient had episodes of low grade fever for past 2 years. He was also a chronic bidismoker. Extra-orallythere was presence of palpable, enlarged, non-tender, mobile, bilateral submandibular lymph nodes. Intra-orally there was presence of adiffuse, l obulated, firm to hard, nontender, non-pulsatile and non-compressible swelling measuring approximately 3cm×2.5cm×2cm in diameter without any surface ulceration involving the mandible extending from right mandibularcanine to left mandibular first molar region. Most of the mandibular teeth in this region got exfoliated. The panoramic radiograph revealed the presence of a large, multilocular, radiolucent lesion with irregular margins involving the parasymphyseal and left side of the body of the mandible. Aperiapicalradiolucency was also noted in relation to right mandibular first molar region.

All haematological parameters were within normal limits. Serological examination revealed that the patient was ELISA negative for hepatitis B and C, HIV and tuberculosis. For histopathological evaluation, an incisional biopsy was performed from the representative site of the lesion. The light microscopic features of the specimen revealed the presence of diffuse sheet like proliferation of neoplastic round cells showing pronounced cellular and nuclear pleomorphism with both hyper chromatic and or vesicular nuclei resembling neoplastic lymphocytes. The microscopic features led to a provisional diagnosis of “Non-Hodgkin’s Lymphoma”. For determination of the specific cell-type of origin, immunohistochemical analysis was performed, with cells exhibiting positivity for CD20, Bcl-2 and negativity for CD3, EMA. Based on the above histopathological, radiological and immunohistochemical findings, the lesion was finally diagnosed as “High-grade B-cell lymphoma”. The patient was then referred to IPGMER Hospital, Kolkata for further diagnostic evaluation and treatment. There, the patient underwent investigation of PET-CT scan of the whole body that revealedosteolytic lesion of the entire length of the mandible with multiple punched out lesions and soft tissue extensions into adjoining lower alveolus. According to Cotswolds modified Ann Arbor classification, this case pertained to Stage IE. Accordingly, a treatment plan consisting of 6 cycles of R-CHOP followed by radiotherapy was prepared. However, after receiving 4 cycles of chemotherapy, the patient succumbed due to medical co-morbidities.

Figure 1. (A) Extra-oral photograph of the patient,(B) Intraoral photograph showing the presence of diffuse,large,lobulated swelling involving mandibular alveolarridge extending from right lower canine to left first molar region

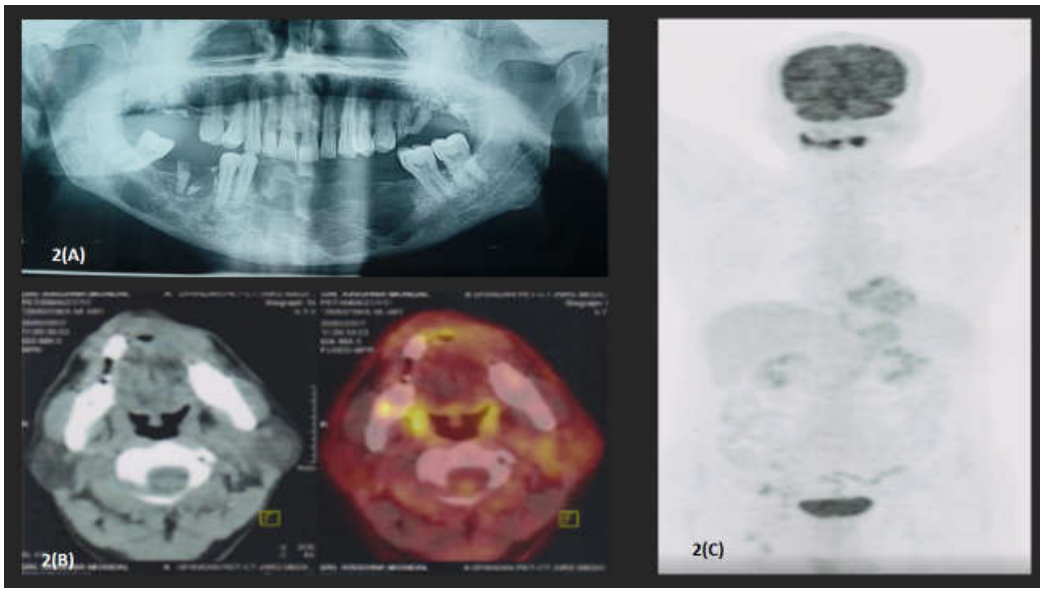

Figure 2. (A) Orthopantomogram showing multilocular, mixed radioluscent lesion involving the parasymphyseal and left side of the body of the mandible.(B),(C) PET-CT scan of the whole body revealed osteolytic lesion of entire length of the mandible with multiple punched out lesions and soft tissue extensions into adjoining lower alveolus

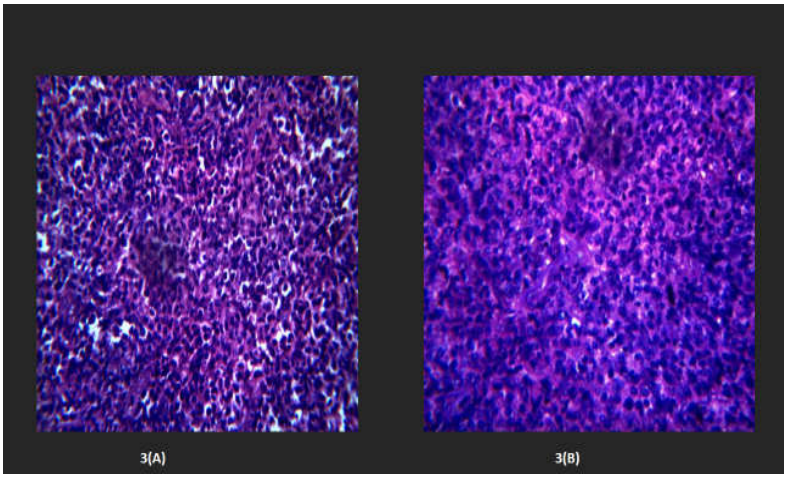

Figure 3. (A,B) High power photomicrographs showing diffuse sheet like proliferating neoplastic round cells with pronounced cellular and nuclear pleomorphism along with hyperchromatic and or vesicular nuclei resembling neoplastic lymphocytes (H&E X40)

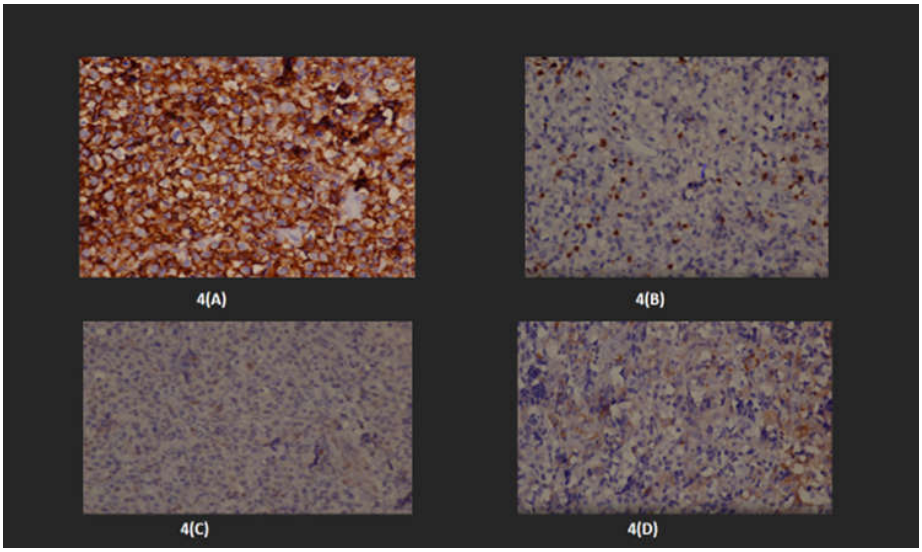

Figure 4. High power (40 x) photomicrograph showing (A): Intense immunoreactivity of lymphoid cells to CD 20. (B): Focal immunopositivity of lymphoid cells to Bcl-2. (C) & (D): Immunonegativity of lymphoid cells to CD 3 and EMA

DISCUSSION

Lymphomas are a hetero geneous group of neoplastic disorders due to genetic mutations within the progenitor cells of the lymphocytes and resulting in changes in their genetic expression. NHL has long been recognized as a distinct entity since 1950, and the spectrum of their behaviour ranges from the relatively indolent types to the highly aggressive variants [(8)]. Diffuse large B-cell lymphoma (DLBCL) is the most common of the aggressive NHLs. According to Hicks and Flaitz, 2001, diffuse large B-cell lymphoma (DLBCL) is the most common type noted in head and neck region [(10)]. Hashimoto, 1982 reviewed the pathological characteristics of NHL involving the oral cavity and concluded that Diffuse B-cell lymphoma is the most common variant [(11)]. Alexander *et al*, reported DLBCL as the most common histotype in jaw bones[(12)]. The etiology of diffuse large B-cell lymphoma is unknown. The predisposing factors include-immuno suppression (including AIDS, post transplantation or auto immune diseases), infections (EBV, HCV, H. Pylori), ultraviolet radiation, chemical exposures (pesticides, hair dyes), and diet. The patient under discussion was a 48 year old male patient who presented with a diffuse, lobulated, firm to hard, nontender, non-pulsatile swelling without any surface ulceration involving the mandible along with bilateral submandibular lymphadenopathy. These clinical features are consistent with the observations given by various authors [(8,9,10,11)]. This patient also revealed a systemic H/O fever which is in accordance with one of the B - symptoms of DLBCL. Radiological features of DLBCL involving bones are usually that of nonspecific osteolysis.

The panoramic radiograph of the present case revealed the presence of a large, multilocular, radiolucent lesion with irregular margins involving the mandible whereas the FDG-PET scan had revealed bony uptake only in the mandible. The clinical and radiographical features of this case may include a differential diagnosis of osteomyelitis as well as intra-osseous malignancy. Hence histological evaluation is important for proper diagnosis. Histologically, the stained sections showed presence of proliferating neoplastic round cells arranged in dense, monotonous diffuse sheet like pattern within the connective tissue stroma. The architectural pattern of the involved tissue and the neoplastic cells in the present case are strongly corroborative of DLBCL. IHC analysis revealed positivity of the neoplastic cells towards B-cell markers like CD20+, Bcl-2+, and negativity to CD3$^-$.CD20 was found to be strongly and diffusely positive. These immunohistochemical results are in conformity with the biomarkers of DLBCL. Hence, based on the IHC report, a confirmatory diagnosis of "High grade Diffuse B-cell lymphoma" is established. Various classifications and staging systems have been suggested that enables to make proper treatment plan and evaluate the prognosis of the disease [(14-17)].

These include: working formulation classification, REAL classification, WHO classification, IPI and Ann Arbor staging system. Ann Arbor staging system [(14)] has four stages. Most extra nodal head and neck NHL fall into stage IE if localized and additional suffix A which denotes-absence of systemic signs or B that denotes-unexplained weight loss or fever or night sweats. As per Ann Arbor staging this case relates to Stage IE. As primary mandibular NHL is extremely rare, proper treatment protocol has not been delineated. A case report by Parrington and Moorthy (BDJ, 1999) stated that the patient of primary mandibular NHL was treated by radiotherapy only [(18)].

Longo *et al*, 2003 reported a case of extra nodal NHL of mandible that provided a good response through a combination of chemotherapy (CHOP regime) and radiotherapy [(19)]. A treatment plan of chemotherapy (4 cycles of R-CHOP) followed by radiotherapy were recommended in the present case. However, after receiving 4 cycles of chemotherapy the patient died due to medical co-morbidities. Survival rates of DLBCL patients depends on the extent of the disease, presence of HIV , histopathology, and Ann Arbor staging[(9)]. According to Alexander *et al*, for extra nodal head and neck lymphoma 5-year survival rate is approximately 50%, whereas median survival rate for stage IE is 10 year [(12)]. A minority of patients with advanced stage disease and clinical risk factors may not be cured with R-CHOP based therapy [(9)].

Conclusion

Extra-nodal NHL involving the oral cavity is very rare. When lymphomas cannot be assessed properly, it may lead to multiple biopsies, diagnostic delays and inadvertent treatment failures. Hence the prognostic outcome of such diseases depends on early and effective diagnosis which can be achieved by proper histopathological evaluation backed by immunohistochemical analysis.

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