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Primary diffuse large B-cell lymphoma in the maxilla

A case report

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Abstract

Rationale: Lymphomas are the second most common non-epithelial malignant tumors in the oral and maxillofacial region. Non-Hodgkin's lymphoma (NHL) develops at extranodal sites, and cases involving the maxilla account for less than 1% of all NHLs. We describe a case of diffuse large B-cell lymphoma (DLBCL) in the maxilla, and highlight the clinical signs, symptoms, differential diagnosis, and appropriate treatment of DLBCL in the oral cavity and maxillofacial region.

Patient concerns: A 67-year-old woman was admitted to our surgical department with pain and swelling in her right upper posterior teeth for about six months. She was previously misdiagnosed with periodontal disease and had a history of tooth extraction.

Diagnoses: Computed tomography (CT) scan revealed extensive osteolysis in the right posterior part of the maxilla with enhanced neoplasm. A solid mass was found upon incisional biopsy, and immunohistochemistry confirmed the diagnosis of DLBCL.

Interventions: The patient was treated with six courses of rituximab, cyclophosphamide, pirarubicin, vincristine, and prednisolone (R-CHOP), followed by external irradiation treatment.

Outcomes: The treatment was well tolerated, and the patient is presently alive after two years of follow-up.

Lessons: Non-specific symptoms, such as unclear primary dental pain and unresolved periapical swelling, can make an accurate diagnosis of DLBCL difficult, which frequently lead to delayed diagnosis. A CT or cone beam computed tomography (CBCT) scan of the maxilla and immunohistochemical staining of the biopsy specimen is recommended. Combination therapy including radiotherapy and chemotherapy is the optimal treatment for NHL.

Abbreviations: CBCT = cone beam computed tomography, CHOP = cyclophosphamide, pirarubicin, vincristine, and prednisolone, CT = computed tomography, DLBCL = diffuse large B cell lymphoma, NHL = non-Hodgkin's lymphoma, R-CHOP = rituximab, cyclophosphamide, pirarubicin, vincristine, and prednisolone.

Keywords: DLBCL, lymphoma, malignant tumors, maxilla, NHL

1. Introduction

Lymphomas are a diverse group of neoplasms that originate in the lymphatic system and are traditionally classified into 2 major categories: Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL).[1] Lymphomas are the second-most common non-epithelial malignant tumors in the oral cavity and maxillofacial region, accounting for 3% to 5% of the reported cases and fewer than 5% of all oral malignancies.[2]

Nearly 25% of NHL cases occur at extranodal sites, with the skin, gastrointestinal tract, and central nervous system being the most commonly affected sites.[3] In the oral cavity, the majority of cases occur in the Waldeyer's ring, followed by the buccal mucosa, tongue, floor of the mouth, and retromolar area.[4,5] Involvement of the maxillary bones is very rare and represents <1% of all NHLs and 8% of all tumors in the skeletal system.[6]

Diffuse large B cell lymphoma (DLBCL) is the most frequently reported NHL subtype. It is an aggressive, rapidly growing neoplasm of large lymphoid cells, and commonly occurs in men older than 50 years. The representative symptoms in the mouth cavity include nonspecific swelling, dental extraction wounds that do not heal, ulceration, and aposteme, and DLBCL may be misdiagnosed as osteomyelitis, periodontosis, and pyogenic granuloma, as well as malignant tumors such as squamous cell carcinoma.[7] A delay of about 10 weeks is common between initial presentation and final diagnosis, which is confirmed by immunohistochemical staining.[8]

Few publications have focused on DLBCL in the mouth cavity, leading to difficulties in diagnosing and comprehending biological characteristics, choosing rational treatment, and providing an accurate prognosis for this disease. The present study describes a case of DLBCL in the maxilla to highlight the clinical signs, symptoms, differential diagnosis, and appropriate treatment of DLBCL in the oral cavity and maxillofacial region.

2. Case presentation

A 67-year-old woman was admitted to the Stomatology Department at the Second Affiliated Hospital of Nanchang University with pain and swelling that had gradually increased
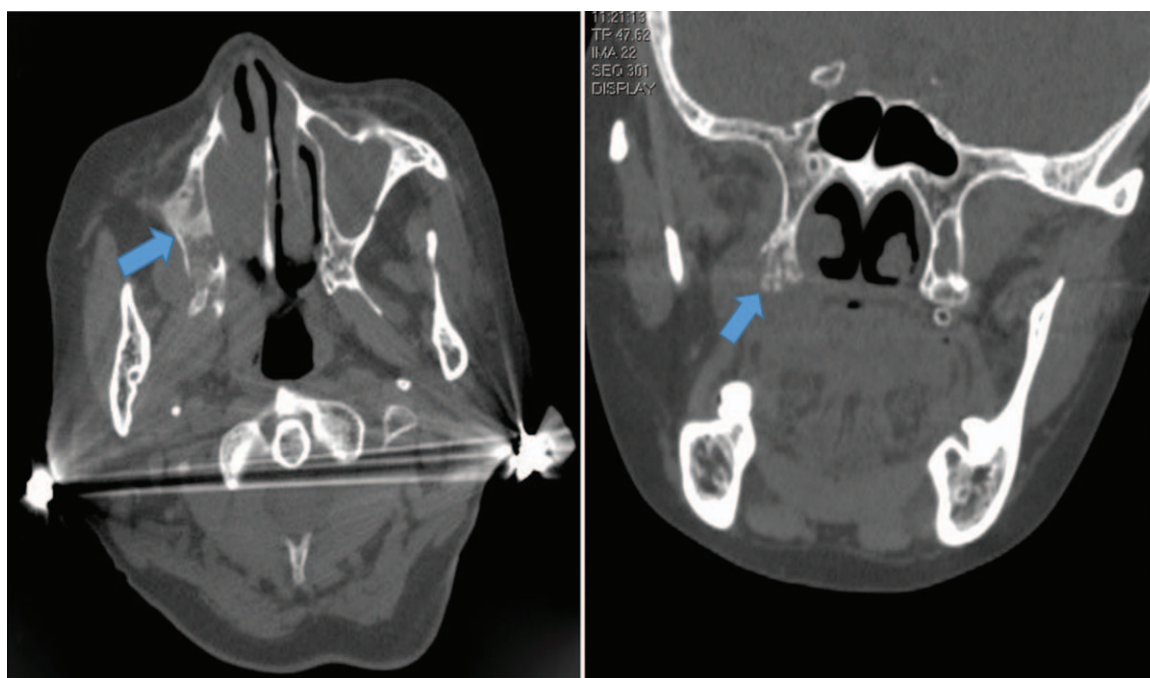
Figure 1. CT scan demonstrating the osteolytic focus in the right maxilla. CT = computed tomography.

over the previous month. For approximately six months, she had experienced ambiguous pain and discomfort in the teeth in the right upper posterior region. Her upper right third molar had been extracted 3 months earlier. Nearly one month later, the second molar was also luxated and extracted. Following antibiotic therapy, her symptoms did not improve, and an aching elastic and nontender mass was noticed in the palatal aspect of the posterior right maxilla. She had no history of any systemic disease.

The cervical lymph node was not detectable by palpation. Upon oral examination, a swelling measuring 2.5×2 cm was evident in the palatal aspect of the posterior left maxilla adjacent to the apical region of 36. The overlaying mucosa was smooth and normal in color. The swelling was palpated and considered as not tender but solid with homogeneity. Laboratory evaluation showed no abnormal findings.

Contrast-enhanced computed tomography (CT) scan revealed extensive osteolysis in the right posterior part of the maxilla (Fig. 1); no lesion was found in the lateral cervical lympho-glandula.

The patient was locally anesthetized for an incisional biopsy. The solid mass responsible for the palatal cortical plate perforation was found, and the diagnosis of diffuse, high-grade, large B-cell NHL was confirmed by immunohistochemistry and microscopy examinations (Fig. 2).

There were neither extramaxillary signs of the disease nor were there abnormalities found by chest radiography, abdominal ultrasound, or bone scan and bone marrow biopsy, which confirmed it to be a focal lesion.

The patient's oncologists ordered sequential courses of chemotherapy. The patient was considered to be at IE stage and treated with the CHOP regimen, consisting of cyclophos-phamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 2.0 mg given intravenously on day one, and prednisone 100 mg/m^2 daily, administered orally on days 1 to 5; this regimen was combined with rituximab (375 mg/m^2 given 1 day before the CHOP course). The current prescription of rituximab plus CHOP (R-CHOP) was given every 21 days for 6 cycles, followed by external beam radiation therapy (30 Gy in 3 weeks). She exhibited a desirable tolerance to this therapy without any negative side effects, and has remained alive over 2 years of follow-up.

3. Discussion

NHL consists of a group of abnormal proliferation of 2 distinct lymphocyte types, B or T lymphocytes, and their precursor cells. The etiology of this disease is still uncertain, and the main risk factors include immunodeficiency, autoimmune diseases, infections, exposure to noxious chemical agents, chemotherapy, and radiation.[9]

Although only a few extranodal NHL cases have been reported that occurred in the head and neck region, it is the second most common nonepithelial tumor in this area, arising relatively frequently in the Waldeyer's ring. However, maxillary involvement is rare, and the published literature indicates that the posterior portion of the maxilla is the most frequent site when NHL is found in the maxilla.[10] The average age of maxillary lymphoma patients at diagnosis is 50 to 55 years, with a male predominance and a male to female ratio of 3:2.[11]

In general, primary NHL in the bone is categorized as stage IE. The 5-year survival rate for stage IE NHL of the maxillo-mandibular region is around 50%.[12] Ostrowski et al[13] found that maxillary NHL has a higher rate of local relapse than does NHL at other sites; nevertheless, overall survival is not affected. The prognosis and treatment outcome depend on many factors, such as the histologic type, type of treatment, presentation of B symptomatology, tumor size, and patient age.

DLBCL is the most common type of NHL. Based on cytomorphology, it is subdivided into centroblastic, anaplastic,
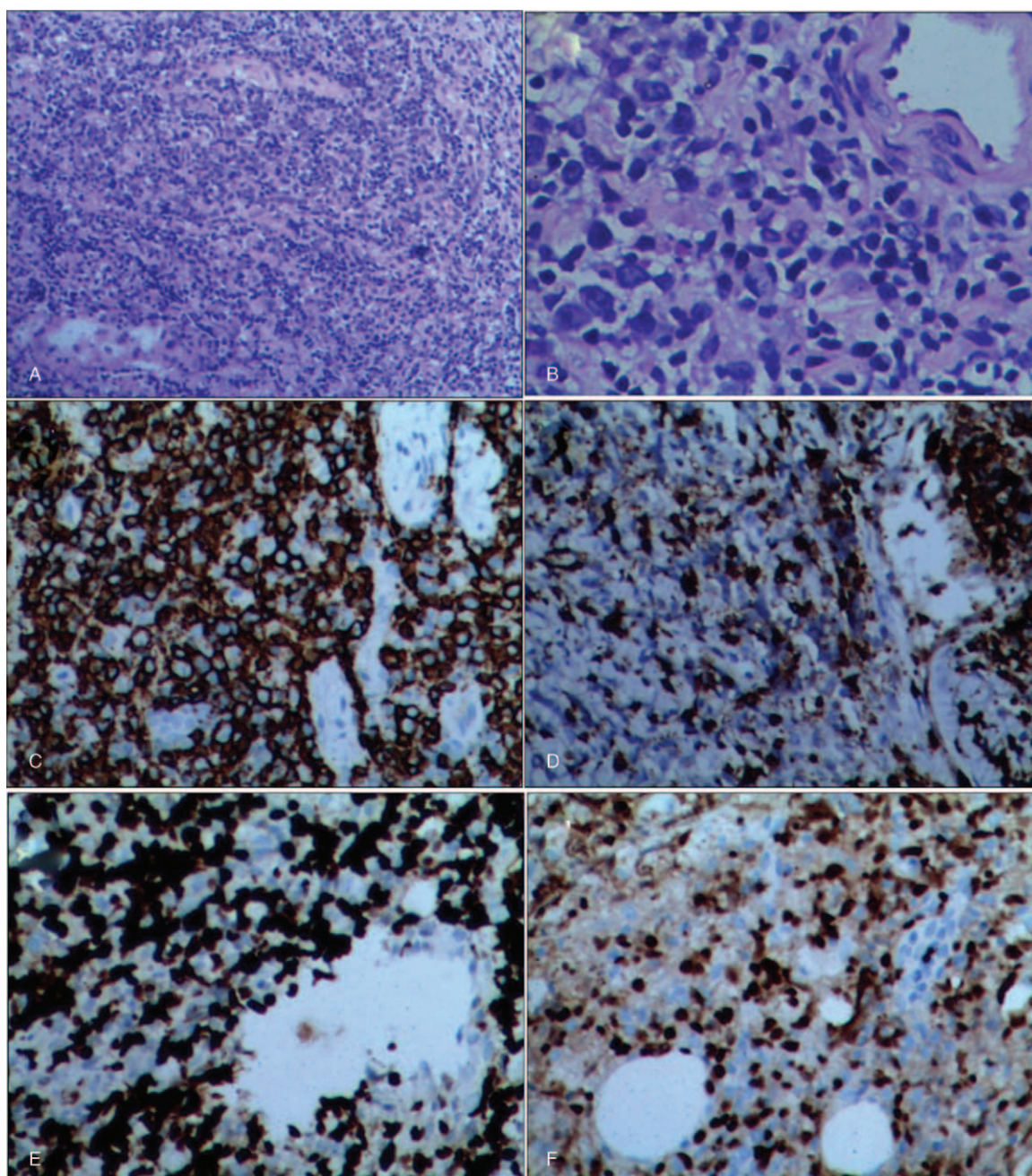
Figure 2. Hematoxylin-eosin staining showing consistent with diffuse large B-cell lymphoma (original magnification [A] ×100 and [B] ×400). Immunohistochemistry staining showing positivity for (C) CD20 and (D) CD79a, (E) PAX5, and (F) Ki67 (immunohistochemical staining, original magnification ×200).

and immunoblastic types. DLBCL can also be further subdivided by gene expression profiles, being center B cell-like, activated B cell-like, or type 3 gene expressing profile.[14] Each type has a different clinical outcome, genetic alterations, and underlying oncogenic mechanisms. Most maxillary lymph gland tumors are highly malignant diffuse large cell lymph gland tumors.[15] However, due to the limited number of cases, they are currently not classified.

The chief common complaints of DLBCL in the maxilla are pain (55%) and swelling accompanied by paresthesia or numbness (20%); symptoms of lower frequency include poor dentition, tooth mobility, continuous pain and swelling after exelcymosis, and even pathologic fracture.[15] Discomfort,

painful viscera, night sweats, weight loss, and fever rarely occur in these patients. Because of these atypical symptoms, patients are often misdiagnosed as having inflammatory odontogenic or periodontal diseases, or potentially other cystic and osteolytic lesions, resulting in untimely processing and unnecessary or inappropriate treatment (e.g., root canal therapy, extraction, and antimicrobial chemotherapy).[16] It is worth noting that the overwhelming majority of published cases reported significantly delayed diagnosis due to symptoms similar to those of dental diseases. In the current study, the patient first sought help from an alveolar surgeon. Her condition was misdiagnosed as periodontal disease with tooth extraction history, but the symptoms did not improve significantly in the initial stage. There was a delay of

about 3 months until the lesion was confirmed by immunohistochemical staining, which is consistent with a previous report.

Conventional radiography for these lesions shows the lowering of the alveolar margin, loss of cortical definition, widening of the periodontal space, irregular radiolucent lesions, and ill-defined borders.[16] In addition, conventional radiography may reveal that the tooth roots are substantially or completely denuded of bone.

The best method for managing lymphoma is accurate diagnosis. Ideally, an excisional or incisional biopsy to obtain adequate tissue for morphologic and molecular analysis should be performed. Core needle biopsy with lower invasion is considered appropriate for establishing diagnoses under many circumstances, and tiny or atypical samples collected by fine-needle aspiration generally result in unacceptable misdiagnoses.[17] Differential diagnoses of odontogenic inflammatory process, periodontal disease, squamous cell carcinoma, multiple myeloma, Ewing sarcoma, Langerhans cell histiocytosis, leukemia, osteosarcoma, bone metastasis, and osteomyelitis have been made by doctors who examined the oral and maxillofacial region of patients with maxillary DLBCL.[18–21]

Classifying cases simply by hematoxylin and eosin stains usually results in inaccuracy. The World Health Organization recommends using a panel with a battery of monoclonal antibodies accompanied with molecular techniques with the aim of improving the accuracy and precision of the systematization. Studies on genetic rearrangements, immunophenotypes, fluorescence in-situ hybridization, and cell genetics are utilized to characterize and diagnose NHL with increasing frequency.[22] Histologically, DLBCL is composed of large lymphoid cells showing abundant cytoplasm and nuclei, comparable in size or larger than reactive histiocytes. At least 1 pan-B cell marker, including PAX5, CD79, CD22, CD20, or CD19 accompanied with CD45, is expressed distinctively in DLBCL.[23] The positive expression of IRF4/MUM-1, CD5, BCL2, cyclin D2, cyclin D3, survivin, XIAP, and CD95 seem to be factors predicting unfavorable therapy response and shorter survival.[18–21,23]

The R-CHOP regimen is the most widely used for stage IE NHL and yields favorable results.[24] A combination of radiation and chemotherapy is used to treat patients with high-grade local lymphoma.[25] The pharmaceutical effect of rituximab is also promisingly improved by the addition of vitamin D, the insufficiency of which reduces the activity of natural killer cells and the cytotoxic effect dependent of rituximab in a lymphoma cell line composed of CD20+ B cells.[26] Several new 'small molecules', such as ibrutinib, the BCL-2 inhibitor ABT199, and idelalisib, which is an inhibitor of phosphoinositol-3 kinase-δ, also show desirable efficacy in early-stage DLBCL clinical trials.[27–29] The potency of the above-mentioned innovative medicines in treating DLBCL should further be confirmed by appropriately designed trials in the future. Patients with recurrent progressive disease could be treated by autologous stem cell transplantation or salvage chemotherapy.[30] Further, individualizing treatments based on personal genetic information has increasingly been emphasized. The methodology of surgeries is confined to the acquisition of samples sufficient for a complete histologic examination.

4. Conclusion

When patients are seen for gingivitis, uncured periapical bump, unclearly originated odontalgia, or abnormal sensation or numbness related to the infraorbital nerve region, doctors should consider the possibility of lymphoma. These nonspecific symptoms make accurate diagnosis relatively difficult and may explain the frequent delay in the initial stages of treatment. CT or CBCT scan of the maxilla and immunohistochemical staining of the biopsy specimen with lymphoid markers are recommended. The treatment of maxillary NHL with combined chemotherapy and radiotherapy is usually favorable.

5. Ethical review

Approval was provided by Medical Research Ethics Committee of the Second Affiliated Hospital of Nanchang University. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Author contributions

HZ drafted this manuscript. HY and YZ analyzed and interpreted the patient data. LL evaluated the histopathological images and prepared the figures. LS reviewed the clinical notes and edited the document. All authors read and approved the final manuscript.

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Supervision: Li Song.
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Writing – review & editing: Li Song.

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