

Primary Diffuse Large B-Cell Lymphoma Involving the Maxilla: A Great Imitator

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ABSTRACT

Introduction: Intraoral lymphomas are rarely encountered, usually mimicking benign entities, such as odontogenic abscesses or reactive lesions.

Case presentation: A 35-year-old man was referred to our Hospital, complaining of a painless swelling on the buccal plate of the left maxilla over the past two months, which was previously radiologically diagnosed as a cystic lesion.

Management and prognosis: CT and MRI revealed a well-defined osteolytic lesion of the left maxilla. No abnormalities were noted on cervical lymph nodes. Clinically, the differential diagnosis included giant cell tumor, schwannoma, ameloblastoma and Langerhans cell histiocytosis. FNA and FNB established the diagnosis of diffuse large B-cell lymphoma. Supplementary investigation (blood tests, imaging, bone marrow biopsy), clinical examination and absence of B-symptoms were suggestive of focal disease, with the lesion being classified as stage IE, according to the Ann Arbor staging system. R-CHOP regime was the treatment of choice with complete remission and no signs of recurrence within two years of close follow-up.

Conclusion: Intraoral lymphomas may mimic inflammatory lesions or periodontal disease, hence it is important for the clinician to be aware of various manifestations of NHL in order to have a correct and timely diagnosis.

Key words: cytopathology, intraoral, maxilla, Non-Hodgkin's lymphoma

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INTRODUCTION

Lymphomas are malignant neoplasms that are divided in two distinct clinical entities: Hodgkin's (HLs) and non-Hodgkin's (NHLs). They account for 5% of head and neck malignancies, consisting the second most frequent malignant lesion of this region after squamous cell carcinoma.¹ HLs commonly affect lymph nodes of younger individuals, whereas NHLs are more common in older adults, over the fifth decade of life.² Extranodal involvement is less frequent in HLs (5%), while in NHLs it accounts for approximately 24 to 40 percent (%) of cases.³ Regarding the oral cavity, reported locations of NHLs include the tonsils, soft tissue, gingiva, jawbones, palate, paranasal sinuses, floor of the mouth and salivary glands. The maxilla is rarely being affected, representing less than 1% of all NHLs and 8% of all tumors in the skeletal system.⁴

Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL and is characterized by a diffuse proliferation of large neoplastic B cells. As far as the oral cavity is concerned, the representative symptoms are non-specific, including swelling, non-healing post-extraction wounds, ulceration and abscess.⁵ Thus, the uncommon localization of NHL in the maxilla can be frequently misdiagnosed as osteomyelitis, periodontal disease and pyogenic granuloma, or even as malignant tumors such as squamous cell carcinoma.⁶ Herein we present a case of primary diffuse large B-cell lymphoma of the maxilla in a young individual, which

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was initially clinically misdiagnosed as a dental abscess and later as a giant cell tumor. To the best of our knowledge, there are only few similar reports in the literature.⁴

CASE REPORT

A 35-year-old man was referred to the Oral and Maxillofacial Surgery outpatient clinics at Patras University Hospital, complaining of a painless swelling on the buccal plate of the left maxilla over the past two months. There was no history of trauma or inflammation, nor any signs of sinus involvement or periodontal disease. However, the lesion had initially been diagnosed as a dental abscess and oral antibiotics were prescribed by the patient's dentist, without any improvement. A previously obtained orthopantomogram

revealed slight attenuation of the bone density at the premolar area of the left maxilla, without a distinct lytic appearance referring to a cystic lesion. The patient sought for a second opinion and the referring ENT colleague advised for an excisional biopsy of a seemingly giant cell tumor by an Oral and Maxillofacial Surgeon.

On extraoral examination a remarkable protrusion of the left zygoma was evident (Figure 1), while intraoral examination revealed a circumscribed, sessile, tumor-like lesion of the left maxillary buccal plate, respectively to the upper left premolars and first molar, measuring approximately 25mm in greatest diameter (Figure 2). On palpation the lesion was elastic, non-tender, without fluctuance, and was covered by normal

oral mucosa. Examination of the neck did not reveal cervical lymphadenopathy, and the patient's past medical history was noncontributory.

Management and Prognosis: CT and MRI scans with IV contrast were ordered on initial presentation. The imaging studies showed a well-defined osteolytic lesion of the left maxilla, measuring 41x30x27mm, extending to the respective zygomatic buttress, and repelling the overlying facial muscles with no evidence of infiltrating them. Borderline expansion of the ipsilateral infraorbital foramen was also noticed. The magnetic signal of the lesion was higher than the muscles' on T2-weighted images and similar to them on T1-weighted images, while low ADC was shown (Figure 3). No abnormalities were noted on

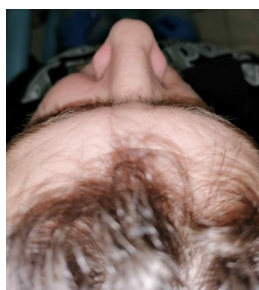


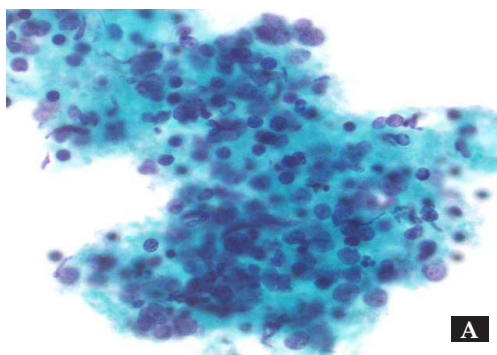
Fig. 1: Extraoral view of the affected area. Marked protrusion of the left zygomatic bone is obvious.



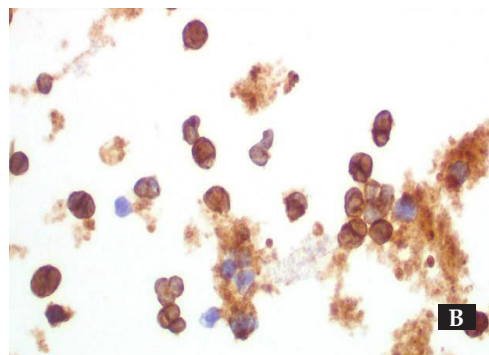
Fig. 2: Intraoral close view of the upper left buccal sulcus. The tumour is covered by normal oral mucosa.



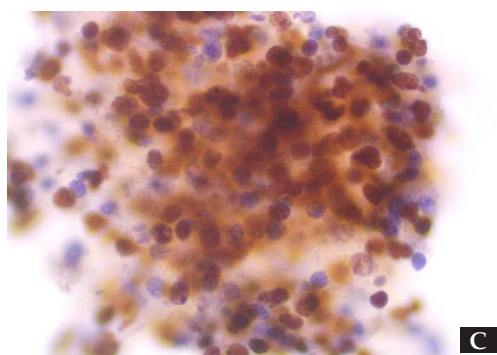
Fig. 3: T2-weighted images of the lesion on axial (A) and coronal (B) planes.



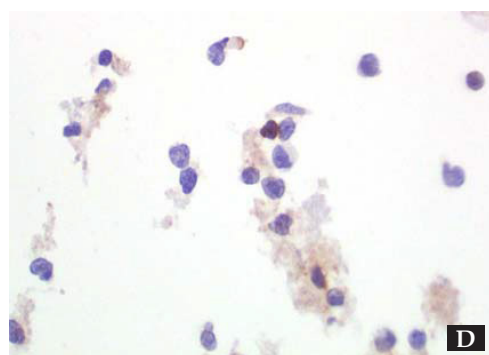
A



B



C



D

Fig. 4: FNA of NHL of maxilla. Liquid Based Cytology (LBC). **A.** Medium sized atypical lymphocytes, Papanicolaou stain x400. **B.** PAX-5 positive nuclear immunocytochemistry x400. **C.** CD79a positive membranous expression x400 **D.** CD3 negative membranous immunostaining x400.

cervical lymph nodes. Clinically, the differential diagnosis included giant cell tumor, schwannoma, ameloblastoma and Langerhans cell histiocytosis.

An FNA with a 25-gauge needle was performed. Conventional smears, as well as liquid-based cytology smears (Thin Prep, Hologic) were prepared and stained with Papanicolaou stain. The observation of the aspiration smears revealed a monomorphous population of medium size atypical lymphocytes with a cytoplasmic rim (Figure 4A). Positive immunocytochemistry for LCA, Vimentin, PAX-5 and CD79a was noticed, while CD3 negativity was detected. (Figure 4B, C, D). The cytological diagnosis was consistent with B- NHL.

An incisional biopsy was then decided. The specimen was fixed in neutral formalin, and haematoxylin/eosin stained sections revealed a diffuse proliferation of predominantly medium-to-large-size lymphoid cells, which presented irregular nuclei with prominent nucleoli and vesicular chromatin, as well as mitotic and apoptotic activity. Immunohistochemistry showed CD20, CD79a, PAX-5 and bcl-2 positivity, but was negative for CD3, CD5, CD43, CD10 and FOXP1 (Figure 5) The majority of the lymphoid cells were negative for LCA, while they revealed a heterogeneous immune expression for bcl-6. Moreover, some of them were positive for MUM1, c-myc, p53 and CD23. A diagnosis of DLBCL was thus established.

The patient was subsequently referred to the Department of Haematology for further investigation and treatment.

Supplementary investigation and clinical examination were suggestive of focal disease (stage IE - Ann Arbor).

Clinical Implications: Non- Hodgkin's lymphomas are malignant proliferation of the lymphoid tissue and are divided in B- and T-cell lymphomas. According to the International Agency for Research on Cancer (IASR)-GLOBOCAN 2020, they represent the twelfth most frequent type of cancer worldwide, with an annually increasing incident rate. Intraoral lesions are uncommon and the most common type is the DLBCL; it is usually diagnosed in the sixth decade of life and it has a male to female ratio of 3:2.7 The etiological factors have not been fully elucidated yet, but the main risk factors include immunodeficiency, autoimmune disease, infections, exposure to noxious chemical agents, chemotherapy and radiation.⁸ The most frequent sites of occurrence in the oral cavity are the hard palate, gingiva and tongue.⁹ The jaw bones are rarely involved, with the maxilla being more frequently affected.⁵

The most common clinical manifestations of DLBCL in the maxilla are pain, swelling and discomfort, accompanied by paresthesia or numbness. There are also some less frequent symptoms, such as tooth mobility, poor dentition, continuous pain and swelling after ecchymosis and pathologic fracture. However, these non-specific symptoms may mimic inflammatory odontogenic or periodontal disease, cystic lesions, dental abscess or gingival swelling, resulting in a false diagnosis and inappropriate management.¹⁰ The majority of

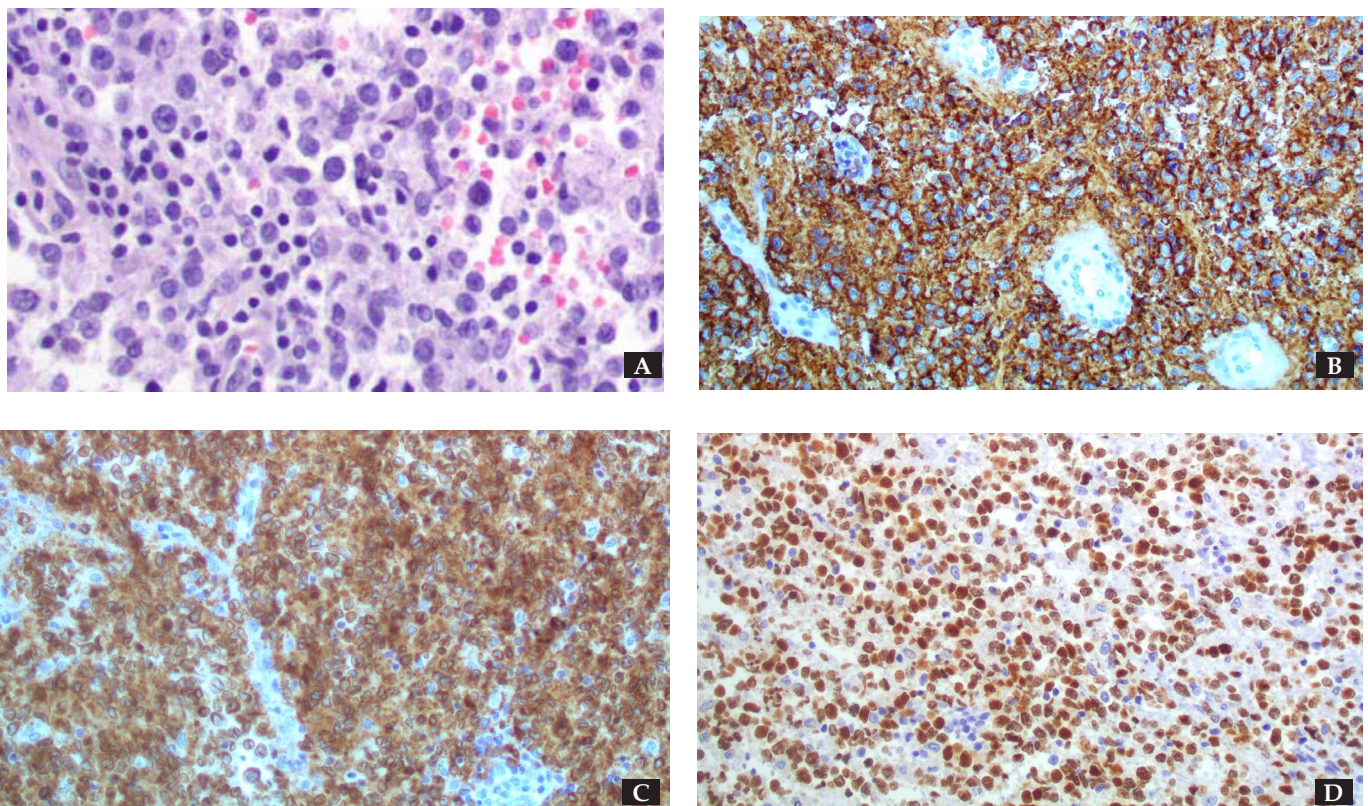


Fig. 5A: Medium to large sized atypical lymphoid cells, H&E X200. **B.** CD20 membranous immunohistochemistry X200. **C.** CD79a cytoplasmic expression. **D.** PAX-5 nuclear IHC X200.

published cases reported significantly delayed diagnosis due to these non-specific manifestations, and most patients were initially misdiagnosed as having an infection.

CT images usually reveal a soft-tissue-density lesion of poorly defined radiolucency which may resemble common odontogenic pathologies. In our case, MRI showed a lesion which did not infiltrate adjacent structures, misleading the diagnosis. However, it is reported in some cases that the lesion can cause destruction of the maxillary sinus walls and invasion to the adjacent structures (nasal cavity, orbit, hard palate), indicating the presence of a malignant neoplasm.¹¹ Accordingly, the diagnosis cannot be established on radiographic criteria alone; cytology and histopathology evaluations are required.

Diagnostic accuracy of cytology in FNA smears is intermediate in DLBCL (62%) and it can be made by morphological criteria combined with immunocytological features.¹² In our case, cytology revealed medium size neoplastic cells with a lymphoid phenotype (LCA and Vimentin positive) of B cell lineage (PAX-5 and CD79a positive). Histologically, DLBCL is composed of a diffuse proliferation of large lymphoid cells with irregular nuclei with prominent nucleoli, along with frequent mitoses.¹¹ At least one pan-B cell marker, including PAX-5, CD79a, CD22, CD20 and CD19 is expressed and the expression of IRF4/MUM-1, CD5, bcl-2, cyclin D2, cyclin D3, survivin, XIAP and CD95 seem to be unfavorable predicting factors.¹³ In the present case, the cells were of medium size with a morphology as described above and expressed CD20, CD79a, PAX-5 and bcl-2, but were negative for CD3, CD5, CD43, CD10 and FOXP1, leading to the diagnosis of DLBCL.

Clinical staging is important, in order to determine the prognosis. The Ann Arbor staging system classifies the disease in four stages, according to its spread. In stages I and II the disease is located in one or two and more lymph nodes on the same side of the diaphragm respectively, while in stages III and IV there is nodal involvement on both sides of the diaphragm or multiple involvement in one or more extranodal sites respectively.⁷ Patients with a single extranodal site involved, as in the present case, are classified as stage IE.

Regarding treatment, rituximab-cyclophosphamide, vincristine, doxorubicin and prednisone (R-CHOP) is the most commonly administered regimen for stage IE and yields favorable results.¹⁴ Radiotherapy is used secondarily, when there is incomplete response or, in combination with chemotherapy, for patients with high-grade local lymphoma.⁷ In our case, R-CHOP regime was the treatment of choice with complete remission and no signs of recurrence within two years of close follow-up.

CONCLUSION

In conclusion, patients with non-specific symptoms from the

oral cavity, such as swelling, pain, tooth mobility or numbness should be dealt with caution by health professionals. Intraoral lymphomas may mimic inflammatory lesions or periodontal disease; hence it is important for the clinician to be aware of the various manifestations of NHL. Collaboration of clinicians and laboratory doctors is crucial in order to establish a correct and timely diagnosis of such sinister lesions, so that patients will benefit from the appropriate treatment.

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