Case report

PRIMARY EXTRANODAL NON-HODGKIN'S LYMPHOMA INVOLVING RIGHT MAXILLA

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ABSTRACT

Background: Lymphoma in a single bone without any nodal or visceral involvement is known as primary intra-osseous lymphoma, which is a very uncommon malignancy. It constitutes 3.1% of malignant bone tumours and 5% of extranodal lymphomas, and the incidence is only 0.6% in the jaws. These tumours can be primary or secondary (in the disseminated forms). The primary intra-osseous lymphoma of the jaws is a challenge to diagnose, because of their various clinical presentation, which can mimic an odontogenic tumour, cyst or a fibro-osseous lesion.

Purpose: This case report discusses a rare malignancy of jaw bones, including clinical presentation, histopathologic features, immunologic profile, PET scan, management and prognosis.

Material and methods: We present a case of a primary intraosseous lymphoma in a 45-year-old female who presented with a swelling in the right maxilla. It highlights the importance of recognizing rare entities that may present in the jaws, the impact of the disease and its management.

Results: Jaw localization of Non-Hodgkin's lymphoma is rare. Clinical symptomatology and radiological signs are poorly contributive. The diagnosis relies on the histopathological analysis.

Conclusion: One of the diagnostic problems with regard to NHL is the variable nature of clinical symptoms. A biopsy allowed diagnosing an intra-oral bone lymphoma, and the patient was referred to the hematooncology unit for treatment.

Keywords: non Hodgkin's lymphoma, extranodal, jaws,

INTRODUCTION

The malignant lymphomas are neoplastic transformations of cells that reside predominantly in lymphoid tissues. The two main variants of malignant lymphoma are Hodgkin's disease and Non-Hodgkin's lymphoma (NHL) [1, 2]. Unlike Hodgkin's disease, Non-Hodgkin's lymphoma has a firmly established cellular origin with morphologic subtypes corresponding to various stages of lymphocyte differentiation. The appropriate treatment depends on the histology and extent of the disease [3]. Approximately 70% of the cases of NHL arise from lymph nodes while the remaining 30%,

comprising the extranodal lymphomas arise from lymphoid tissue in other organs and from sites normally lacking organized lymphoid tissue such as the stomach, skin, brain and testis [1, 4]. The most common site of extranodal NHL in the head and neck region is Waldeyer's ring [5].

Lymphoma arising from a single bone without any nodal or visceral involvement is known as primary intra-osseous lymphoma. It is a very uncommon malignancy and constitutes 3.1% of malignant bone tumours and 5% of extranodal lymphomas. [1] Extranodal non-Hodgkin lymphoma (NHL) represent 20% to 30% of all the NHL. [6] Among the NHL that occurs in the maxillofacial area, 15-45% arise in the oral cavity [7] engaging the upper jaw (11%), the lower jaw (8%), the palatal soft tissue (8%) and gum (7%). The incidence in jaw bones is only 0.6%. [8]

Extranodal lymphoma of the head and neck comprise a heterogeneous group of tumours with different histological types, modes of presentation and prognosis. The unique jaw bone and soft localization are very rare for the NHL, and in some cases, differential diagnosis with the most common dental lesions and other soft tissue pathologies and tumours may be difficult.

One of the diagnostic problems with regard to NHL is the variable nature of clinical symptoms. Although the lymph nodes are the principal location for these proliferations, all other organs, in particular, those containing normal lymphoid tissues can also develop lymphoma [9]. These tumours can be primary or secondary (in the disseminated forms) [9, 10]

Patients may be of any age group, but there is a tendency to involve adults, especially older adults. The Epstein Barr virus (EBV) is specifically associated with Burkitt's lymphoma. Lymphomas can be associated with other viruses such as that of hepatitis C (HCV) and herpes virus type 8 (HHV-8). The stages of passage between infection by a virus and the appearance of lymphoma are not known. Patients with immunodeficiencies, such as transplant patients or those with Human immunodeficiency virus (HIV), would be prone to the development of NHL [10, 11]

In 1994, the International Lymphoma Study Group [11] proposed a classification of various uniform groups of lymphoma, taking into consideration different morphological, histopathological, phenotypic, anatomic and clinical data. Depending on the criteria of malignancy and the

prognosis index, a treatment strategy is defined and then assessed [10].

Most of the lymphomas are of B cell lineage (85% of NHL in adults). The following can be discerned:

- Follicular lymphoma: the proliferation phenotypes are CD10+, CD5 and CD23. These lymphomas are rarely localized and generally appear as deep peripheral adenopathies, with damage to the spleen and invasion of bone marrow.

- Mantle cell lymphomas: phenotypes CD5+, CD10, CD23 and CD43+.

- Extranodalmarginalzonelymphomasoflymphoid tissue associated with mucous membranes (MALT): phenotypes CD5, CD10 and CD23.

- Other small-cell lymphomas.

- Diffuse, large-B-cell lymphoma: phenotypes CD20+, (CD79a+. They account for 40% of NHL and are considered to be "aggressive."

- Burkitt's lymphoma: initially described in Africa, this is associated with the EBV and observed particularly in children and patients with HIV. [10]

(Phenotype T lymphoma, counts only for 15% of NHL in adults. Diagnosis of NHL is based principally on morphological, histological and cytological investigations, and is confirmed immunohistochemically. The biopsy specimen should be large enough to enable standard morphological and pathological examinations, culture and histochemical analyses (as well as, sometimes, the freezing of tissue for future additional tests). It needs to be emphasized that a superficial biopsy may lead to an error in diagnosis. Once the diagnosis is confirmed, the staging is clinical and radiological [10]

- Estimation of the tumour mass.

- Examination of lymph node regions.

- Standard X-rays (panoramic jaw, chest) and abdominal and chest scans.

- Bone marrow sampling.

Chemotherapy must be adapted to the staging and histological classification of the lymphoma associated with local radiation treatment of the region (35-40 Gy). This combination is recommended in particular for high grade localized lymphomas [11, 12]. As a general rule, this means 3-4 courses of CHOP chemotherapy (Cyclophosphamide, Adriamycin, Vincristine and Prednisolone); or other protocol such as ACVBP chemotherapy (Adriamycin, Cyclophosphamide, Vindesine, Bleomycin and Prednisolone) [11, 12]. Once remission has been obtained, the aim of clinical monitoring is to detect early signs of recurrence. The follow up must be at least 10 years, an examination every 3 months is appropriate during the first 5 years. Patient information and the role of the general practitioner are important. [10]

The prognosis of NHL does not depend on the multiplicity of clinical aspects, but mainly on the histology and the stage of the tumour (whether it is localized or not, stage of evolution, number of extra-nodal localizations, etc.). Age is also an important factor [10, 12]

Tumour localization (e.g.in jaws) is not found to be a significant prognosis factor. Although rare in the jaws [12], it is most often found in Waldeyer's ring and then in

the air filled cavities of the face (one third of extra-nodal NHL), the salivary glands and exceptionally in the mouth [13, 14] Primary NHL's make up 8% of mandibular tumours and 0.6% of all NHL's [15]

The bone lesions of Burkitt's disease are characterized by a high incidence of mandibular tumours (more than 50% of cases). This localization is also present in 15% of non-epidemic Burkitt's disease [9, 10]. Tumours of the jaw are generally seen in adults (between the ages of 40 and 50) with a male to female ratio - 0.5 [10, 15].

CASE REPORT

A 58- years- old female presented with an intraoral swelling in the right molar and palatal area noticed around three weeks ago. There was not any extraoral swelling causing facial asymmetry, nor any history of trauma to the site or toothache in the region. She gave no history of nasal congestion or watering of the eyes or any changes in the surface sensations. The intraoral swelling was not associated with pain. At the time of presentation, the patient did not report any systemic symptoms and had no fever or history of weight loss or sweating. She was not on any medication, was a non-smoker and non-alcoholic. The patient's previous medical, family and past dental histories were non-contributory. The patient had a history of Lime disease and allergy to doxycycline and sulfonamides. On local examination, a diffuse intraoral swelling involving the upper molar and palatal area was detected, which several days after the incisional biopsy reduced its size (fig.1). No palpable lymph nodes were present. None of the teeth in the quadrant were decayed, no periodontal pockets were present in relation to teeth # 13, 14, 15 but the grade I mobility was noted and upper molar teeth were tender on percussion. No other abnormalities were detected on hard or soft tissue examination. The clinical differential diagnosis included the plasmocytoma, fibro-osseous lesions such as ossifying fibroma, fibrous dysplasia, nonodontogenic and odontogenic bone tumours involving the maxilla. The panoramic radiograph showed obliteration of the right maxillary sinus with loss of continuity in the floor of the maxillary sinus and the alveolar bone in the region of teeth # 14, 15 appeared dense and granular. Obliteration of maxillary sinus with the destruction of the posterior and anterior walls was noted on axial sections. (fig. 2, 3) On computed tomography (CT), the coronal section of paranasal sinus region revealed a soft tissue lesion causing local destruction of the floor of the right maxillary antrum and encroaching onto the alveolar process. (fig. 4) An incisional biopsy of the swelling was performed, and the histopathology showed sheets of round and spindle shaped cells with vesiculated nuclei in a fibrous connective tissue stroma. Poorly differentiated tumour cells with increased mitotic figures and vascularity with multinucleated giant cells were seen. The features were suggestive of malignant tumour of mesenchymal origin. Immunohistochemistry played an important role in distinguishing the cell type and differential diagnosis (# 181478/18.09. 2018). In the present case the tumour cells were positive for Leucocyte common antigen (LCA/CD45), CD20+ a marker that recognizes the surface antigen which is ex-

pressed on B-cells); CD5+; CD10+; BCL6+;MUM1+; BCL2+, TdT-; C- MYC+ in15% of all cells, Ki67+ in 80% of cells. PET scan reveals tumour mass in right maxillary sinus 22x26x29mm. (fig. 3.) Cytokeratin AE1-AE3- negative. The above findings of the histochemical study indicate that the tumour cells were of large B-cell origin. Thus based on the immunologic profile, a diagnosis of diffuse large B-cell lymphoma was given IV stage, NCCN-IPI-2, R-IPI 1, CNS-IPI 1. The patient was referred to medical oncology for chemotherapy and was managed with cyclophosphamide, doxorubicin (hydro doxorubicin), vincristine (oncovin) and prednisone (CHOP) regimen and 3 courses R-CHOP. The patient was on periodic follow-up; PET scan (fig. 5) on 20.02.2019 reveal fully regression of the disease and after restaging again CHOP and R- CHOP(8 courses from the beginning). The decision was two more courses with the same scheme and two more courses after that with R- CHOP. 05.2019 dated CT scan after 6 courses of chemotherapy revealed no tumour lesion or any changes of the maxillary sinus, lymph nodes and liver.

Fig. 1. Intraoral photograph showing clinical features of a patient: the appearance of a mass and buccal expansion in the right maxillary premolar and molar sector with low mobility of related teeth 7 days after the incisional biopsy.

Fig. 2. Axial CT scan of the patient: tumour mass in the right maxillary sinus and osteolytic image concerning lateral wall of the maxillary sinus

Fig. 3. Axial CT scan of the patient: tumour mass in the right maxillary sinus invading jaw and nasal cavity.

Fig. 4. Coronal CT image(soft tissue window)showing space occupying lesion in the right maxillary sinus with destructive margins

Fig. 5. PET scan of the NHL

DISCUSSION

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) lymphocytes. Primary non-Hodgkin's lymphoma (NHL) is found outside nodal tissues in 24–45% of cases. Common extranodal sites include the GI tract, skin, and less often, bones. In the head and neck region, Waldeyer's ring, oral mucosa, salivary glands, paranasal sinuses, laryngeal tissue, and osseous structures have been found to exhibit primary NHL. The incidence of NHL has increased dramatically in the last 3 decades, which has been attributed partly to the human immunodeficiency virus (HIV) epidemic and the development of AIDS-related NHL [1]

We present a case of primary intraosseous lymphoma in a 58-year-old female who presented with a swelling in the right maxilla. It highlights the importance of recognizing rare entities that may present in the jaws, the impact of the disease and its management.

The most common presentation of the intrabony lymphomas would be a painless local mass that gradually increases in size. This can be associated with tooth mobility and alveolar bone loss. The other clinical features include pain, paraesthesia of the lip, cervical lymphadenopathy [1]. Due to the varied clinical presentation of lymphoma, this has often led to misdiagnosis and a delay in the treatment until proven by biopsy. [1]

The radiological features of intraosseous lymphomas reveal the lowering of the alveolar margin and diffuse bone destruction or solitary bone defect, and these findings resemble those of periodontal inflammation, osteomyelitis, and other malignant tumours. Almost all NHLs involving the jaw bone tend to have ill-defined margins [5]

The histopathological study of the tumour cells,

along with immunohistochemical evaluation is instrumental in arriving at the diagnosis of lymphoma. The immunologic markers will help in detecting the cell lineage and various subtypes of lymphomas. Diffuse large B cell lymphoma is one of the most common lymphoid malignancies in adults, representing about 30–40% of adult NHL diagnosed de novo on the basis of morphology and immunophenotype. Diffuse large B-cells typically express the B-cell markers CD19, CD20 and CD22 and the surface immunoglobulin. The tumour cells are larger and more irregular than immunoblasts, and the cytoplasm is less basophilic [19].

When tissue diagnosis of NHL is given, whole body survey using CT or MRI to evaluate the extent of the disease involvement is necessary for accurate staging and appropriate management of the disease. Positron emission tomography (PET) scanning is reported to be comparable to CT and provides no additional information than the typical work-up [18]

Bone involvement in itself, however, does not appear to be a poor prognostic sign; rather, the extensive disease is a more important determinant of treatment outcome [10]

The patient presented here was treated with chemotherapy - on CHOP (cyclophosphamide, doxorubicin (hydro doxorubicin), vincristine (oncovin) and prednisone regimen and is on regular follow-up.

The international prognostic index (IPI) was developed to predict outcome in patients with aggressive NHL, based on patients' clinical characteristics before treatment. The predictors which signify worst prognosis include advancing age, advanced disease, more extranodal sites of disease, elevated serum lactate dehydrogenase levels, and delayed response to chemotherapy. Based on these predictors patients are grouped under low risk; low-intermediate risk; high-intermediate risk; and high risk with predicted 5-year survivals of 75%, 51%, 43%, and 26%, respectively [20]. The patients with NHL involving the Waldeyer's ring had a low-risk international prognostic index (IPI) [21]. The 5-year survival rate for stage I NHL of maxillo-mandibular region is reported to be approximately 50%. The patients with primary intra bony lymphoma have an excellent prognosis, with a 5-year survival rate of 95% with combined chemo radiation therapy [22].

In the cohort described by Pazoki et al. [13], the mean age of patients was around 40 years at time of biopsy. The diagnosis may be difficult because there is frequently a low index of clinical suspicion. The following unexplained symptoms should urge the referring physician or dentist to request a Computerized Axial Tomography (CAT) scan, as well as a bone and/or gum biopsy [10, 13]:

- Persistence of pain.
- Persistent ulceration of mouth mucosa.
- Neurological disorders.
- Tumour mass of gums.
- Unexplained mobility of a tooth (or teeth).
- A mass in an extraction socket.

- Ill defined osteolytic changes.

According to Edeiken-Monroe et al. [16], the radiological aspect of these lesions showed lyses in 80% of cases. The process is poorly delimited with a wide area of transition to normal bone. Differential diagnosis includes odontogenic inflammatory or periodontal disease and squamous cell carcinoma.

There was approximately 10 weeks delay between initial presentation and the diagnosis [15], and in our case, it was at about 5 weeks. Surgical contribution is limited to obtaining a specimen representative of the lesion and sufficient for complete histological examination [15]. Where lymphoma is suspected the specimen is placed in saline not formalin solution to facilitate flow cytometry. A long-term retrospective study showed a 5-year survival rate around 50%. [10, 13, 23, 24, 25]

We have reported a rare case of primary intraosseous lymphoma in a 58-year-old female patient who presented to us with a swelling in the right maxilla. Primary intra-osseous lymphomas are relatively rare and are often difficult to diagnose as the clinical features may mimic other pathological entities like odontogenic cyst, odontogenic tumour, fibro-osseous lesion or other malignancies. A careful clinical evaluation that is supported by radiologic, histopathologic and immunohistochemical

studies can help for early diagnosis. Early and accurate diagnosis followed by aggressive chemotherapy is crucial, and any delay in management warrants a poor prognosis. This case report also emphasizes the importance of including a rare entity like primary intraosseous lymphoma in the differential diagnosis of unilateral jaw swellings. Our case is a rare presentation of Non-Hodgkin's lymphoma confined to the maxilla, seen in a 58-year-old immunocompetent individual with impeccable medical history and yet immunohistochemically very aggressive. Very few such cases are reported in the literature. It has broadened our horizon of differential diagnosis and persuade us not to accept any swellings involving the orofacial structures at its face value.

CONCLUSION

Jaw localization of non Hodgkin's lymphoma is rare. Clinical symptoms and radiological signs are poorly contributive. The diagnosis relies on a histopathological analysis.

One of the diagnostic problems with regard to NHL is the variable nature of clinical symptoms. A biopsy allowed diagnosing an intra-oral bone lymphoma, and the patient should be referred to the hematooncology unit for treatment.

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