



Primary Non-Hodgkin Lymphoma of the Maxilla

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Abstract

Lymphomas, or malignant lymphatic tissue neoplasms, can be classified as Hodgkin (HL) or Non-Hodgkin (NHL). Although head and neck lymphomas more frequently involve NHL, indicating extranodal proliferation, these cancers are relatively rare in the oral cavity. We report a case of a 56-year-old Caucasian woman who visited a dentist because of gradual buccal-side swelling near the upper left canine. The initial diagnosis was periapical abscess. She was later admitted to the department of Oral and Maxillofacial Surgery, Thessaloniki, Greece because of persistent swelling, where a diagnosis of primary NHL of the oral cavity was established following radiographic, histological and immunochemical studies. The patient was referred to the Department of Hematology, where she received R-CHOP therapy, concurrent intrathecal chemotherapy and subsequent involved field radiation therapy. After treatment completion, the findings of scheduled PET-CT restaging were consistent with a complete metabolic response. The patient continues to undergo regular follow-up CT scans and physical examinations. Our case experience suggests that each aggressive oral lesion should be screened to detect possible malignancy. An excisional biopsy and extensive histopathology evaluation should be performed prior to treatment initiation, and cooperation between hematologists and oral and maxillofacial surgeons is essential to early detection, diagnosis, and treatment and follow-up.

Introduction

Lymphomas, or malignant neoplasms of lymphatic tissue, are characterized by lymphocytic proliferation. These cancers can be divided into two main types: Hodgkin (HL) and Non-Hodgkin (NHL). The former type arises primarily within the lymph nodes, with extranodal involvement in only 5% of cases. By contrast, the latter type exhibits extranodal involvement in approximately 24% to 40% of cases [1,2]. Extranodally, NHL most frequently involves Waldeyer's ring, the gastrointestinal tract, skin, bones, retroperitoneum, lung and central nervous system; by contrast, NHL of the oral cavity is relatively rare [2].

Reported locations of NHL in the oral cavity include the tonsils, soft tissue, gingiva, bone, palate, paranasal sinuses, floor of the mouth and salivary glands [2,3]. The oral manifestation of NHL is usually secondary due to the dissemination of the disease. Primary oral manifestations are relatively rare, with only a few recorded cases. NHL may be associated with swelling, pain, paresthesia of the lip or osteonecrosis [4]. However, these nonspecific manifestations of NHL may mimic other pathologic lesions, such as gingival swelling, periodontal disease, pericoronitis, apical radiolucency or dental abscesses, and a definitive diagnosis may therefore be challenging [1,2,4,5].

Patients who are infected with the human immunodeficiency [6], have undergone solid organ and hematopoietic stem-cell transplantation, have primary immunodeficiency syndromes, are receiving immunosuppressive therapy and have experienced increased exposure to ultraviolet radiation are reported to have a higher risk of developing NHL [7]. Moreover, various NHL subtypes have been attributed to infection with microbial or viral pathogens such as the Epstein-Barr virus (Burkitt's lymphoma, extranodal NK-cell or T-cell lymphoma nasal type), *Helicobacter pylori*, *Chlamydia psittaci* (mucosa-associated lymphoid tissue lymphoma) [8], human herpesvirus-8, human T-cell lymphotropic virus-1, hepatitis C virus and simian virus 40. Currently, Diffuse Large B-Cell Lymphoma (DLBCL), an aggressive lymphoid neoplasm with nodal or extranodal involvement, is the most common subtype of NHL, accounting for approximately 80% of all lymphomas [2,4].

We report here a case of an extranodal DLBCL of the maxilla that presented as an odontogenic radiolucent lesion, as well as the diagnosis and treatment of this rare involvement.

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Figure 1: Axial computed tomography scan completed at the initial visit, showing a large area of bony destruction within the anterior maxilla and infiltrating the left sinus.

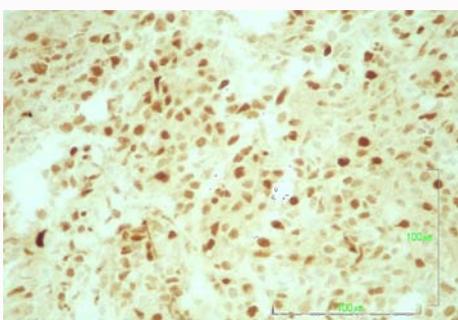


Figure 2: Bcl-6 (HE, magnification x400).

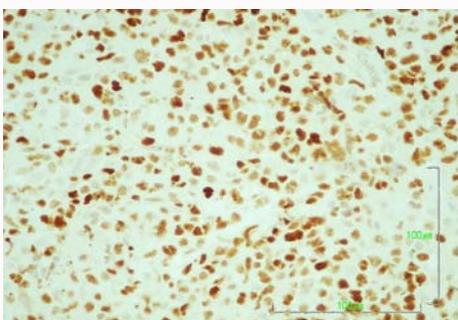


Figure 3: MUM-1 (HE, magnification x400).

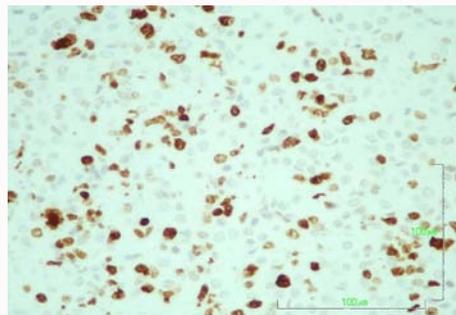


Figure 4: Ki-67 (proliferation marker) analysis (HE, magnification x400).

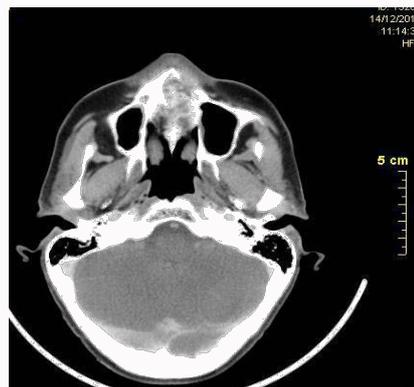


Figure 5: Axial computed tomography scan after 3 cycles of chemotherapy, showing a reduction of the lytic lesion.

Case Presentation

A 56-year-old Caucasian woman presented with buccal-side swelling near the upper left canine (tooth #23) that had evolved gradually. She additionally complained of a sense of swelling in the region beneath the nose and above the upper left canine. She had no relevant medical history and no history of tobacco or alcohol use. The patient had been referred to a dentist who administered antibiotics and performed a root canal of the suspected tooth. The initial diagnosis was a periapical abscess of the canine.

However, swelling persisted after the initial and shifted to the palatal site of the suspected tooth. The patient was subsequently admitted to the Department of Oral and Maxillofacial Surgery at our institution, where an ordered Computed Tomography (CT) scan revealed a large area of bone destruction (45 mm × 27 mm × 20 mm). The lesion extended from the anterior medial and left aspect of the maxilla relative to the roots of the left central and medial incisor and

canine and to the nasal cavity and inferior internal wall of the sinus (Figure 1).

The maxillary lesion was biopsied and subjected to a pathologic evaluation. Hematoxylin and Eosin (H&E) staining revealed a diffuse infiltration of large lymphoid cells with irregular and gigantic nuclei, multiple nucleoli and nuclear divisions (Figure 2). The neoplastic cells exhibited the following staining characteristics: CD20+, CD79a+, CD3-, CD5-, CD10+/-, MUM1+ and cyclin D1- (Figure 3 and 4). The cells were also positive for both Bcl-2 and Bcl-6; however, c-myc and EBER staining was unavailable (Figure 5 and 6). Among the neoplastic cells, the positive Ki67 rate was 55%, and a significant reactive T cell population was detected (Figure 7). These morphologic and immunohistochemical findings led to a diagnosis of DLBCL-Not Otherwise Specified (NOS). The patient was subsequently referred to the Department of Hematology.

The patient's serum immunoglobulin (Ig)G, IgA and IgM; beta 2 microglobulin and lactic dehydrogenase levels were within normal ranges, and her International Prognostic Index was 0 (low). Additionally, she tested negative for HIV-1 and -2 and EBV. Disease staging included CT scans of the head and neck, lung, abdomen and pelvis; lumbar puncture for Cerebrospinal Fluid (CSF) evaluation and bone marrow aspiration with trephine biopsy. Neither the imaging scans nor bone marrow assessment indicated disease involvement. The CSF examination also indicated no Central Nervous System (CNS) involvement. The disease was classified as stage IE according to the Ann Arbor staging system with extranodal involvement (E, bone involvement of the maxilla).

The patient initially received three 21-day cycles of the R-CHOP-21 regimen [rituximab, 375 mg/m² intravenously (iv) on

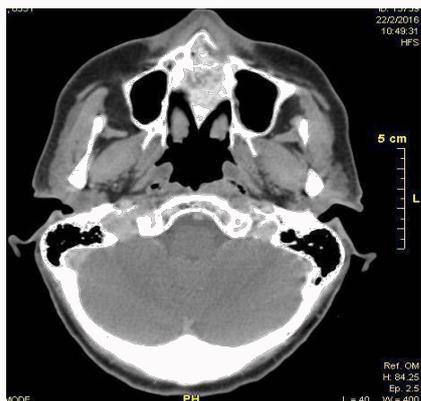


Figure 6: Axial recall CT scans showing reduction of the lytic lesion after 8 cycles of chemotherapy.

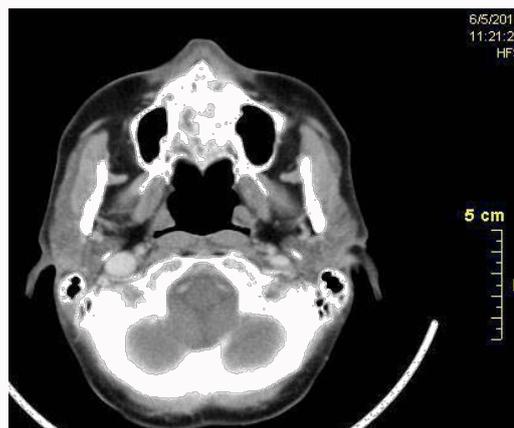


Figure 9: Axial recall CT scans showing reduction of the lytic lesion after 8 cycles of chemotherapy.

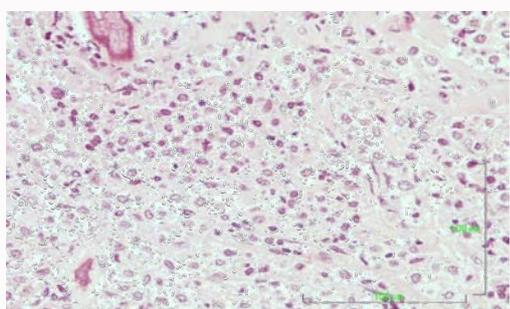


Figure 7: High-power view of the lesion biopsy reveals scattered large, atypical lymphoid cells (hematoxylin and eosin (HE), magnification x400).

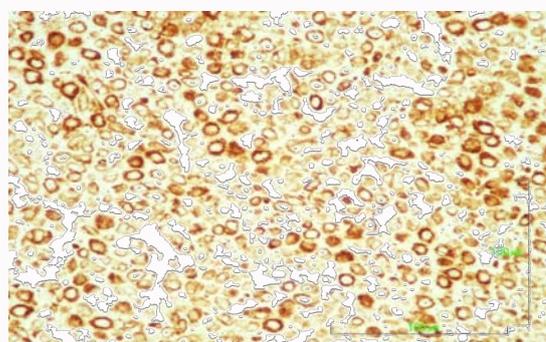


Figure 10: Bcl-2 (HE, magnification x400).

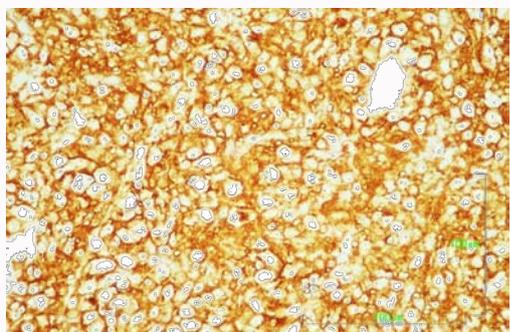


Figure 8: Diffuse CD20 (B-lymphocyte marker) staining in the lesion (HE, magnification x400).

day 1; cyclophosphamide, 750 mg/m² iv on day 1; doxorubicin, 50 mg/m²; vincristine, 1.4 mg/m² iv on day 1 and methylprednisolone, 100 mg orally on days 1-5]. Primary CNS prophylaxis comprising intrathecal methotrexate 15 mg, cytarabine 50 mg and hydrocortisone 100 mg were administered on day 1 of each cycle. The patient developed alopecia and grade 4 neutropenia after the first cycle, and pegfilgrastim 6 µg was administered subcutaneously as a secondary prophylaxis in each subsequent cycle to maintain grade 2 neutropenia.

The initial restaging CT scan showed a partial response of 60% in the SPD of the lesion, and three more R-CHOP cycles were administered without a further mass decrease. As per local protocol, a PET-CT scan was performed and yielded findings consistent with a complete metabolic remission. Accordingly, two additional R-CHOP cycles were administered to complete a 6-month treatment regimen as per local protocol, and involved site radiation therapy (total dose:

3,600 cGy) was administered to consolidate extranodal disease. Repeated CT scans every 4 months revealed a pattern of reduction of the lytic lesion (Figures 8-10), and a second biopsy of the affected area (buccal site, #23) showed no signs of NHL recurrence.

The patient remains in complete remission at 27 months after the initial diagnosis and 15 months after treatment completion. Her performance status is excellent, and she has not exhibited evidence of late toxicity.

Discussion

Lymphoma is the second most frequent malignant lesion of the head and neck region, after squamous cell carcinoma [2]. Although the usual clinical manifestation is nodal disease, lymphoma may also affect extranodal sites, as noted in the introduction. Waldeyer's ring is the extranodal site most commonly affected by NHL [9,10], whereas the paranasal sinuses are rarely targeted (0.2% to 5% of cases) [11]. Regarding oral sites, the maxillary sinus is most commonly affected, although lymphomas have also been reported in the soft tissues, gingiva, bone, palate, floor of the mouth and salivary glands [3,4]. The differential diagnosis includes similarly appearing conditions such as dental abscesses or osteonecrosis [4], as well as infectious processes such as systemic or deep mycosis and Wegener's granuloma, as well as squamous cell carcinoma, metastatic tumors or neoplastic process; notably, very rapid growth is a feature of both sarcomas and lymphoproliferative disorders [12].

To our knowledge, fewer than 20 cases of NHL with a primary oral manifestation have been reported worldwide, thus underscoring the

rarity of this disease. NHL of the jaws accounts for <5% and in case of the mandible is 0, 6% of NHL of the bones. Paresthesia of the inferior alveolar nerve may be a common finding of NHL of the mandible, whereas pain and swelling are the most common manifestations of NHL of the maxilla [13]. Overall, the most frequently reported subtype of NHL is DLBCL, and the reported incidence of this subtype is even higher among cases affecting the oral cavity (58% to 68%) [14,15]. The median ages at diagnosis range between 67 and 71 years, although a few cases have been described in younger individuals [1,14]. These reports are consistent with the characteristics of our case. Given the importance of early identification to the timely initiation of treatment and a favorable outcome, these findings suggest that dental health providers must have a high index of suspicion regarding this rare clinical manifestation of NHL.

Currently, CT is considered to be the most useful preoperative study for defining the initial dimensions of the mass. Radiographically, NHL most commonly appears on CT images as an area of poorly defined radiolucency (lytic pattern), as seen in our case, whereas only a small percentage (~2%) of reported cases have exhibited a radio-opaque (sclerotic) appearance. These radiolucent lesions may resemble common odontogenic pathologies such as chronic apical periodontitis and chronic periodontitis [9]. However, typical generalized sclerosis of the affected bone has also been described [16]. As these radiologic findings are not specific to lymphoma, the clinicians consider that almost 80% of bone lesions exhibit an osteolytic pattern, whereas the remaining 20% exhibit a sclerotic pattern [2]. Accordingly, a diagnosis of NHL cannot be established from radiographic criteria alone, and a histopathological evaluation is required to establish early oncologic treatment [16]. Malignancy should be considered for oral lesions with aggressive growth patterns and poor responses to antibiotics and dental treatment, and excisional biopsies should be performed for suspected lymphomas because a differential diagnosis cannot be safely established via aspiration or punch biopsy [17].

Currently, chemotherapy followed by radiation therapy is the treatment of choice for DLBCL-NOS, and R-CHOP-21 is the most commonly administered regimen. Histologic subtypes predictive of inferior outcomes should be identified through extensive immunohistochemistry and/or FISH and molecular studies; as such cases require the use of more intensified protocols as R-CHOP or Burkitt-like regimens [15]. Additionally, as patients with paranasal sinus involvement have a high risk of CNS involvement, a lumbar puncture and CSF examination should be included in the initial staging. For cases with negative CSF findings, CNS prophylaxis comprising intrathecal treatment or the addition of systemic methotrexate for 6 cycles to 8 cycles is indicated. Reports of such cases have described systematic consolidation with complementary craniofacial radiotherapy, and this is always included in treatment regimens [11]. Early diagnosis is required, and continuous monitoring and close follow-up are strongly recommended for the early detection of relapse.

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