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Case Report

Extra-nodal non-Hodgkin's lymphoma (ENHL) affecting oral cavity misinterpreted as painful dental infection, delaying diagnosis – case report

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Abstract – An 83-year-old woman was referred with a painful, broad-based right facial swelling. It was firm to palpation, with mucosa intact. Symptoms had been present for about six months, during which time she was treated with multiple antibiotics, endodontic therapies, and extraction of all right maxillary molars. Her medical history included hypertension, arthritis, depression, and colon carcinoma treated four years previously. Orthopantomography revealed a poorly demarcated area of low bone density affecting the entire molar region, with diffuse opacification of the maxillary sinus and with destruction/perforation of alveolar cortical bone. A CT scan showed a soft tissue mass filling the sinus and destroying the sinus floor and underlying alveolus, also the right facial alveolar cortex, with broad proliferation outside that cortex. Incisional biopsy revealed a proliferation of large lymphoid cells (kappa B-cells), consistent with follicular lymphoma. Tissue was strongly immunoreactive to CD20, CD10 and BCL2, with partial reactivity to Ki67 and with a CD21 reactive dendritic meshwork around neoplastic cells. With this diagnosis, a PET scan was performed, showing involvement of the right submandibular, bilateral axillary and hilar lymph nodes, as well as scattered retroperitoneal nodes. The patient was referred to the regional cancer center, where surgery and chemotherapy were scheduled.

Introduction

Lymphomas are the most common non-epithelial tumors of the head and neck area, accounting for approximately 14% of all malignant neoplasms of that region. Both subtypes, Hodgkin's lymphomas (HL) and non-Hodgkin's lymphomas (NHL) are seen in the maxillofacial region, but extra-nodal disease is more common among NHL patients [1–4]. The oral cavity constitutes 2% of the extra-nodal localization of NHLs. When they occur, they are typically the first sign of disease, presenting with local pain, diffuse swelling and destruction of alveolar bone. These signs can be misinterpreted as a dental problem, thereby delaying proper diagnosis and treatment [3–6]. We present a case of NHL located on the maxillary buccal vestibule, which initial symptoms were toothache and facial swelling, and were interpreted as an odontogenic disease, thereby delaying an appropriate diagnosis and treatment for significant time. We emphasize the importance of rigorous examination in diagnosing orofacial pain and recognizing the distinctive pattern of lymphoma bone destruction, the use of suitable oral and maxillofacial imaging and early biopsy of such lesions.

Patient information

An 83-year-old woman was referred to the oral medicine clinic of the West Virginia University, School of Dentistry with a constantly painful, broad-based facial enlargement of the right maxillary alveolus. It was firm to palpation, but not bony hard, and with no mucosal alterations. Symptoms had been present for more than six months, during which time she was treated with multiple antibiotics, endodontic therapies of upper right premolars and canine, and extraction of all right maxillary molars. Her medical history included hypertension, arthritis and depression, and colon carcinoma treated surgically four years previously. She was taking medications for the medical

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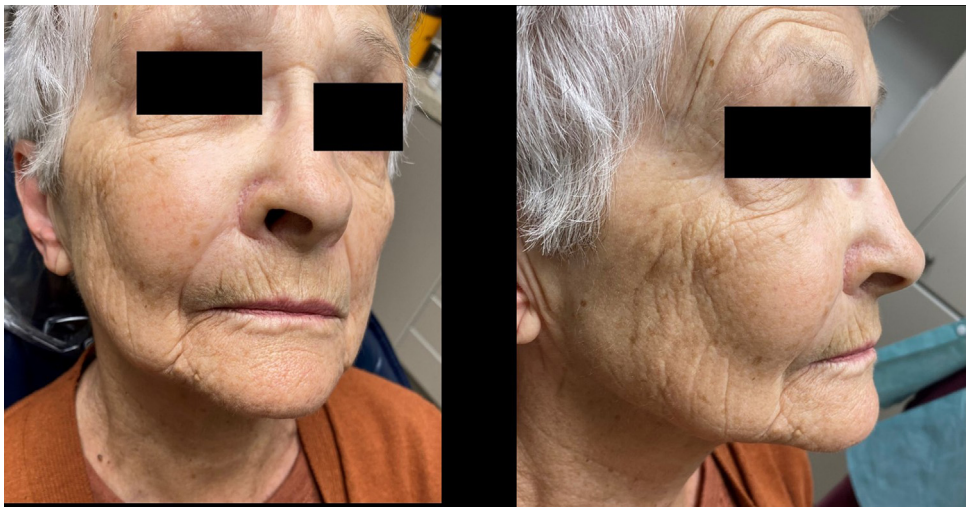

Fig. 1. Facial swelling on the R side of the face.

conditions mentioned above. She denied alcohol and drug use. Complete blood count with differential, complete metabolic panel, liver function and coagulation studies were normal.

Clinical findings

Extraoral examination revealed a well-nourished woman in moderate distress, facial asymmetry with a right swelling, poorly-defined limits, slightly firm and tender to palpation. Gross cranial nerve examination was normal and no lymphadenopathy (Fig. 1). Intraoral exam showed right upper buccal vestibule with localized swelling, firm to palpation, and intact mucosa (Fig. 2).

Diagnostic assessment

Orthopantomography revealed a poorly demarcated area of low bone density affecting the entire molar region, with diffuse opacification of the maxillary sinus and with destruction/perforation of alveolar cortical bone (Fig. 3). A CT scan showed a large right buccal lesion with underlying bony erosive changes in the maxilla and invasion into the right maxillary sinus and orbital floor, compatible with malignant neoplasm. There was associated obstructive chronic right maxillary sinusitis. Asymmetric enlargement of the right infraorbital foramen was concerning for perineural tumor spread (Fig. 4). Differential diagnosis included benign and malignant neoplasia such as odontogenic cyst and squamous cell carcinoma. Incisional biopsy revealed a proliferation of large lymphoid cells (kappa B-cells), consistent with follicular lymphoma (Figs. 5 and 6). Tissue was strongly immunoreactive to CD20, CD10 and BCL2, with partial reactivity to Ki67 and with a CD21 reactive dendritic meshwork around neoplastic cells (Fig. 7). With this diagnosis, a PET/CT was performed, showing involvement of the right submandibular, bilateral axillary and hilar lymph nodes, as well as scattered retroperitoneal nodes.

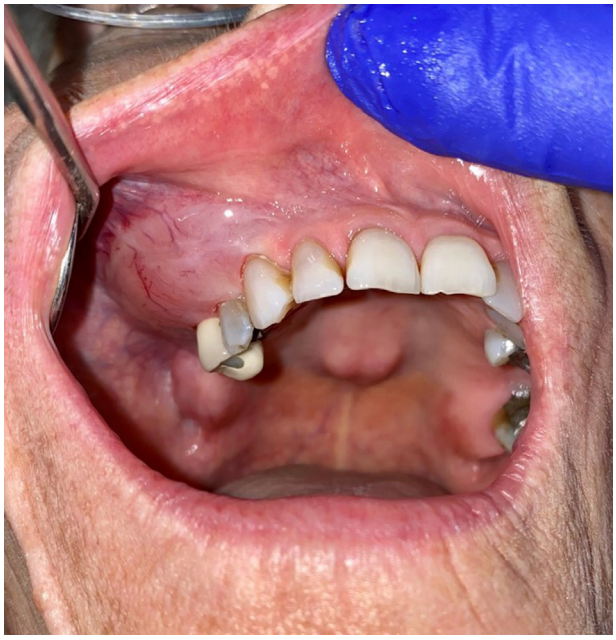

Fig. 2. Localized swelling in upper right buccal vestibule.

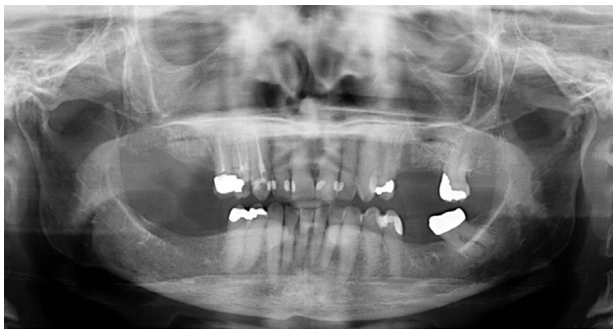

Fig. 3. Panoramic radiography shows low bone density affecting the entire molar region, with diffuse opacification of the maxillary sinus.

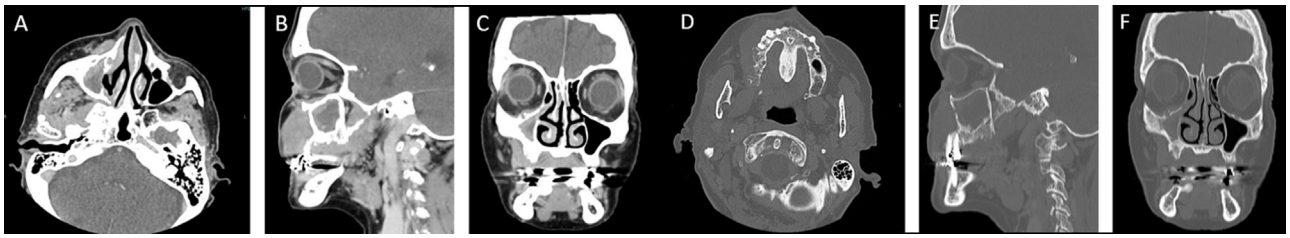

Fig. 4. Contrast enhanced CT facial bones: (A) Axial, (B) Sagittal and (C) Coronal soft tissue windows demonstrate an enhancing soft tissue mass extending from the right gingivobuccal sulcus along the anterior maxillary wall, with invasion into the right orbit and maxillary sinus (D) Axial, (E) Sagittal and (F) Coronal bone windows demonstrate osseous involvement of the maxillary alveolus and anterior maxillary sinus wall. Enlargement of the infraorbital foramen indicating perineural spread is also well visualized on coronal bone window (F) with abnormal soft tissue in the pterygopalatine fossa (A).

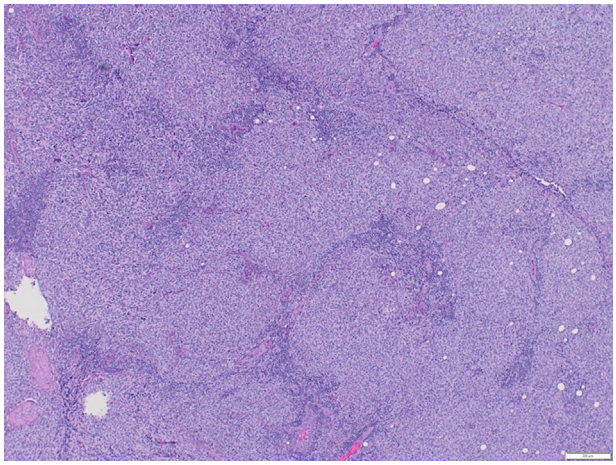

Fig. 5. H&E 4X grade 3B — Low power image demonstrating the follicular/nodular growth pattern of the neoplastic cells in the grade 3B component.

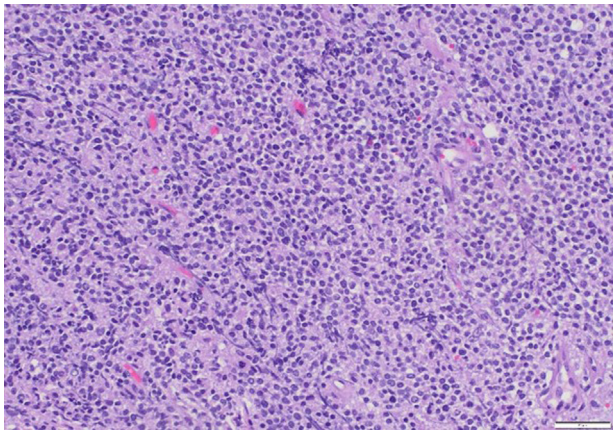

Fig. 6. H&E 20X grade 3B — Detailed image of the nodular region demonstrating numerous centroblasts without admixed centrocytes in the grade 3B component. Mitotic figures are readily apparent.

Therapeutic intervention

The patient was referred to the regional cancer center, where surgery and chemotherapy were scheduled. The patient underwent 6 cycles of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. A PET/CT taken 1.5 months after the infusions showed interval resolution of previous intense fluorodeoxyglucose (FDG) avid right-sided buccal lesion and FDG avid lymph nodes. At the time of submission of this report, she reported continuous improvement.

Discussion

While the differential diagnosis should include several benign odontogenic tumors (ameloblastoma, adenomatoid odontogenic tumor, keratocystic odontogenic tumor, odontogenic myxoma), the clinical and radiological features of this case—including rapid growth, bony destruction, and ill-defined margins—strongly suggested a more aggressive, potentially malignant condition. Odontogenic carcinoma or primary intraosseous carcinoma were the most probable malignant causes to consider in this case.

Lymphomas are a diverse collection of hematological system malignant neoplasms, and can differ greatly in their immunophenotypes, histological characteristics, clinical symptoms, and genetic anomalies [1,4,6]. Clonal proliferation of lymphoid cells that correlate to distinct stages of maturity of normal B-cells, T-cells, or natural cytotoxic cells is a characteristic of tumor transformation. When left untreated, aggressive lymphomas can cause deaths in a matter of weeks and have particular B symptoms such weight loss, fever, and night sweats. In contrast, indolent lymphomas typically appear with waxing and waning lymphadenopathy over many years [4,6].

HLs frequently express as localized disease in lymph nodes of the mediastinum and neck, while extra-nodal variants are rare accounting for only 5% of HL, for instance in the tonsils [4,7]. NHL refers to a broad category of immune system tumors. Based on the kind of cell involved, the NHL are divided into more than 60 different types of lymphomas, and there is a great variation in their clinical features, histology, phenotypes, and genetic anomalies [8]. 85–90% of NHLs derive from B lymphocytes and the remaining ones arise from T lymphocytes or Natural Killer (NK) lymphocytes. HL and NHL can have nodal and extra-nodal localization [2,9].

Nodal NHLs are characterized by a large number of painless lymph nodes in different locations, including the head and neck region, many of which can be unintentionally found. Despite the rarity of oral involvement, NHL is believed to be the second most common oropharyngeal malignancy after squamous cell carcinoma. In clinical practice, a dentist can observe it when it happens

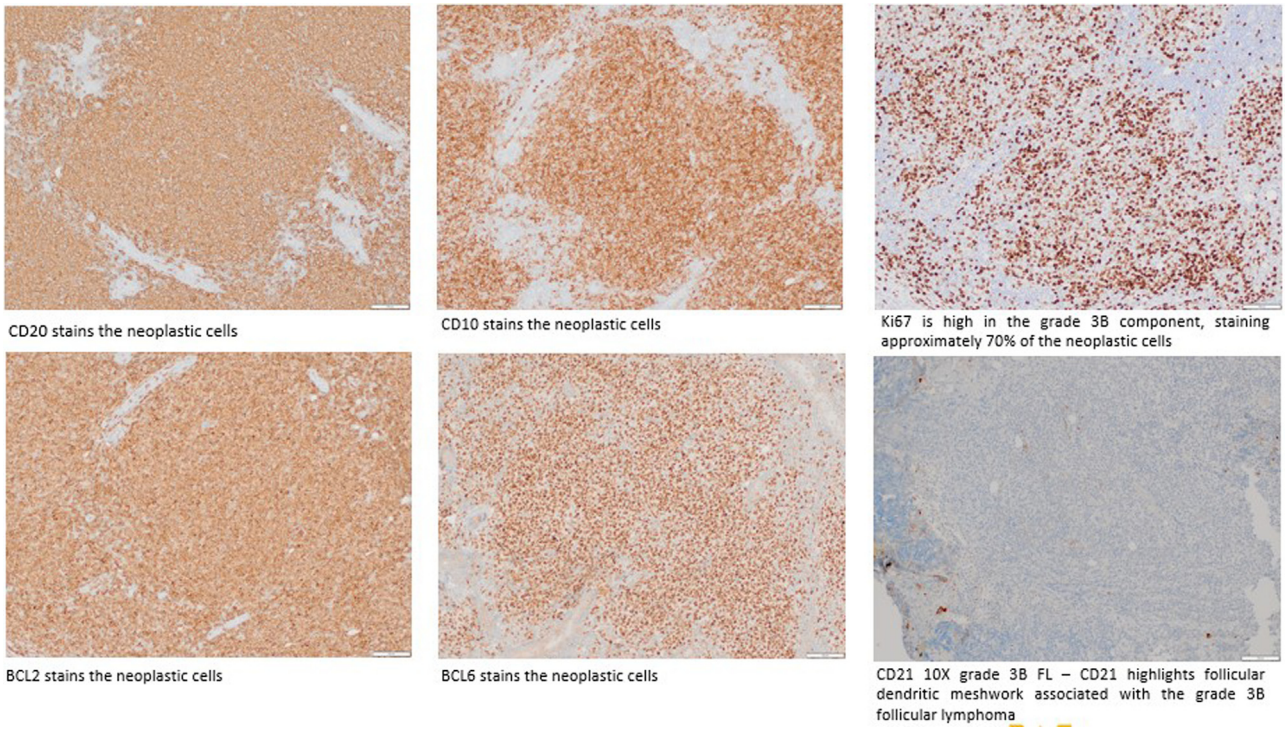

Fig. 7. Immunohistochemistry.

in the oral cavity [2,5,9,10]. NHL occurs quite frequently in extra-nodal regions, and the most common localization is the gastrointestinal tract, followed by the head and neck area. Half of those are located in Waldeyer's ring. Oral involvement is rare, about 2%, and sometimes it presents as ulceration with bone destruction [3,9,11]. In 1983, it was Wright and Isaacson who were the first to characterize specific extra-nodal lymphomas linked with mucosa-associated lymphoid tissue (MALT) as a distinct entity apart from peripheral lymph nodes. Later on, more extra-nodal low-grade B-cell lymphomas were added to these data, notably those of the thyroid, lung, and salivary glands [12].

Diffuse Large B-cell lymphoma (DLBCL) is the most prevalent histological subtype of NHLs in the head and neck region, whereas B-cell NHLs are the most common NHLs overall. Subtype follicular lymphoma is the second most common. About 30% of NHL cases are follicular lymphomas, which are made up of a combination of centrocytic and centroblastic cells [3,5,10].

NHL oral lesions can arise in the soft tissues, most commonly the gingiva, palate, or buccal vestibule, or they might appear centrally within the bone. Signs and symptoms including tooth movement, localized swelling with ulcers, inexplicable dental discomfort, or ill-defined lytic osseous alterations are frequently seen in patients. Oral lesions might mimic the symptoms of benign reactive hyperplasia, periodontal disease, or tooth abscess. NHL that originate in the mouth tend to be more aggressive [2–4,10].

Congenital or induced immunodeficiency, such as HIV infection or severe combined immunodeficiency disease, is the most widely recognized risk factor for the development of ENHLs. In some cases, Epstein-Barr virus (EBV) infection appeared to be substantially related with B-cell lymphomas. Genetics (*e.g.*, a family history of hematologic malignancies), immune disorders (*e.g*, Sjogren's syndrome, rheumatoid arthritis), infections (e.g., Helicobacter pylori and HCV), modifiable risk factors (*e.g.*, body mass index, alcohol consumption, and cigarette smoking), toxins and drugs (*e.g.*, phenytoin, digoxin, pesticides), chromosomal translocations, and employment (*e.g.*, agricultural or health workers) are additional factors implicated in the genesis of NHL [1–3,11].

Chemotherapy, radiotherapy, or both are used for treating head and neck NHL. The standard chemotherapeutic regimen is a combination of cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP therapy) [2] For head and neck lymphomas, the 5-year survival rate typically falls between 35.1% and 92%. The clinical stage and the patient's response to chemotherapy are undoubtedly the most prevalent prognostic variables for head and neck lymphoma patients. Additional factors could include the patient's age, the immunophenotype, the size of the tumor, the histological grade, and the existence of viral infections [2,3,13].

Because symptoms of an intraoral extra-nodal lymphoma are uncommon, there may be a chance for a delayed diagnosis, particularly in cases where the lymphomas are in the gingiva or alveolar crest. Depending on the location, the clinical appearance may change, although it typically manifests as a bulging or swollen mass that may or may not have an abscess visible. Usually, the growth happens rather quickly. Lesions on the gingiva/alveolar crest or palate are most likely to cause subjective symptoms like pain or discomfort, however many

lymphomas do not cause significant symptoms. Clinical observations that indicate a non-odontogenic lesion should be taken seriously, such as poor healing following tooth extraction or no response to antimicrobial therapy. Additional clinical examination and images might be warranted for paresthesia, numbness, or pain symptoms that do not clearly have an odontogenic etiology [4,5]. Compared to intraoral or panoramic X-rays, computer tomography might offer more useful information. When there is even the least doubt as to the true nature of a mucosal lesion, we strongly recommend biopsy.

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Conflicts of interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoria; edicational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Data availability statement

The research data are available on request from the corresponding author. No new data were created or analyzed in this study.

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