JBACHS
Journal of Basic and Clinical Health Sciences

J Basic Clin Health Sci 2022; 6: 931-937
https://doi.org/10.30621/jbachs.1053749
CASE REPORT

A LIFE-SAVING EARLY DIAGNOSIS OF BURKITT LYMPHOMA INVOLVING BOTH JAWS, MISDIAGNOSED AS PERICORONITIS

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Received: 05.01.2022; **Accepted:** 23.04.2022; **Available Online Date:** 29.09.2022

Cite this article as: Ozdede M, Dere KA, Unver-Koluman B, Gormez A, Sen-Turk N, Hekimgil M. A Life-Saving Early Diagnosis of Burkitt Lymphoma Involving Both Jaws, Misdiagnosed as Pericoronitis. J Basic Clin Health Sci 2022; 6: 931-937.

ABSTRACT

Burkitt lymphoma (BL) is a highly aggressive and rare B-cell non-Hodgkin's lymphoma. In this paper, a rare case of BL, involving both jaws, was presented. A 24-year-old male patient was referred to our clinic with the complaint of mandibular and maxillary swelling for two months. He was previously misdiagnosed with pericoronitis and had a history of the right mandibular third molar tooth extraction, one-month prior. Intraoral examination showed swelling, ulceration, and spontaneous bleeding in both jaws. Radiographically, extensive osteolytic lesions, irregular periodontal space widening, loss of lamina dura, and peri-radicular radiolucencies were detected. Incisional biopsy was performed from both jaws and the final diagnosis was made as BL. It is crucial to be aware of the clinical and radiological features of this disease by dentists and to consult the attending physician without delay.

Keywords: burkitt's lymphoma, non-hodgkin's lymphoma, oral cavity, jaws, mandible

INTRODUCTION

Lymphoma is a neoplasm that originates in the lymphatic system and is classified as Hodgkin's and non-Hodgkin's lymphoma (NHL) (1). The incidence of NHLs increases over the years (2-4). Lymphomas are the second-most-common non-epithelial malignant tumors of the oral and maxillofacial areas. Less than 5% of oral malignancies are lymphomas (5). In perioral regions, lymphomas may occur in the maxillary sinus, bone, palatal, and tonsillar areas (6). NHL can affect patients in all age groups. The patients may have a fever, night sweats, and weight loss (6). The clinical features of oral NHLs may include swelling, pain, abscess, ulceration, gingival hyperplasia, paresthesia, teeth mobility, and rarely pathological fracture (2,7). The radiographic appearance is multilocular, ill-defined, invasive radioluceny with cortical destruction (6). These findings may cause misdiagnosis of dental infections, periodontal diseases, osteomyelitis, and pyogenic granuloma (2,7).

Burkitt lymphoma (BL) is a highly aggressive and rare B-cell, NHL (8). It is related to the Epstein Barr virus (EBV), human immunodeficiency virus (HIV), and

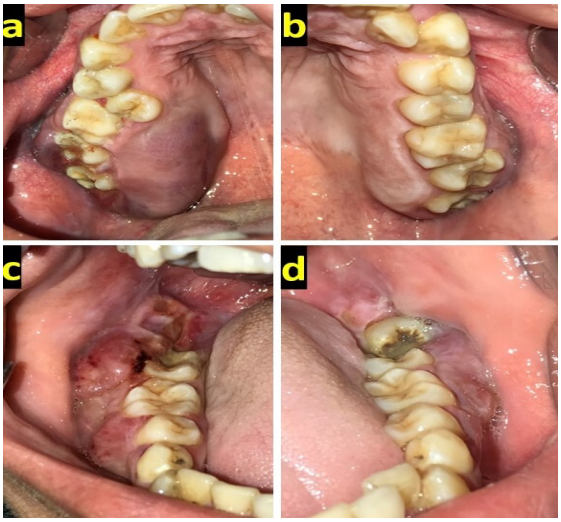

Figure 1. Clinical photographs of the right maxillary **(a)**, left maxillary **(b)**, right mandibular **(c)**, and left mandibular **(d)** posterior regions. Extensive swellings and ulceration effected molar regions of two jaws, more specifically on the right maxilla and mandible.

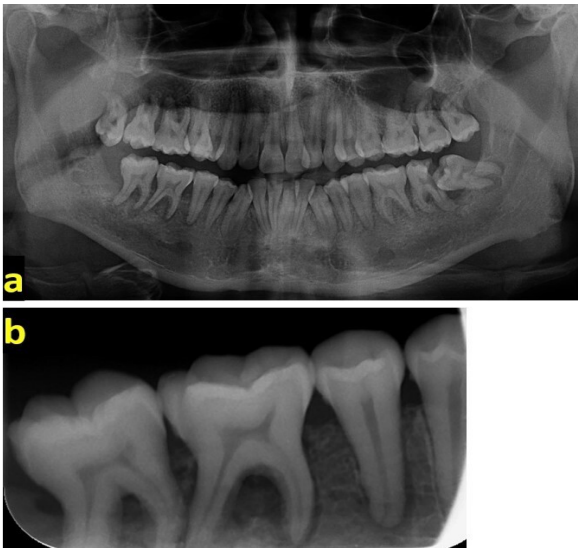

Figure 2. Panoramic **(a)**, and periapical radiographic image of right mandibular posterior teeth **(b)**. Osteolytic lesions, peri-radicular and periapical radiolucencies of the posterior teeth of both jaws. Note the irregular periodontal space widening and loss of lamina dura on the periapical image.

chromosomal translocations that cause the overexpression of oncogene C-MYC (9). As with most types of lymphoma, BL is more prevalent in males (3-4:1, male-to-female ratio) (10). The distribution of endemic cases of BL in some regions becomes prominent in areas where malaria and Epstein Barr virus are more prevalent (9). The sporadic form is more often in North America and Europe with a median age of diagnosis of 45. Sporadic BL has an annual estimated incidence of 2.5 per 1 million in adults, whereas the incidence is 4 per 1 million children younger than 16 years of age (9). BL has distinct clinical and pathologic features, characterized by rapidly progressive tumors with high rates of extra-nodal involvement (11).

In this report, we present a rare case of BL from Turkey, which affects both the mandible and maxilla, which was initially misdiagnosed as pericoronitis in a young male. Although this case has endemic type features such as jaw involvement, it also has sporadic type features and bone marrow involvement.

CASE REPORT

A 24-year-old male patient was referred to the Department of Oral Diagnosis and Radiology, with the complaint of mandibular and maxillary swelling for two months. He was previously misdiagnosed with pericoronitis and had a history of the right mandibular third molar tooth extraction, one-month prior. The patient stated pain only during chewing. He had no systemic disease, medication, or smoking history. No paresthesia, fever, weakness, night sweats, or weight loss was stated. An extraoral examination revealed facial asymmetry due to the swelling on the right mandible. A bilateral chronic submandibular lymphadenopathy was detected. Intraoral examination revealed swelling in all molar regions of both jaws (Figure 1). Ulceration and spontaneous bleeding were seen in the right mandible molars. Palpation of the swelling produced mild tenderness. Increased horizontal teeth mobility was detected in the right mandibular and maxillary molar teeth, while moderate mobility affected the right mandibular-maxillary premolar, left mandibular-maxillary molar teeth. Bleeding on probing was detected in all the posterior areas. All molar teeth had periodontal pocket depths, which measured higher than 10 mm on the right mandibular molars. The right maxillary third molar tooth impression was detected in the gingival swelling area of the right mandible third molar region.

On the panoramic and periapical radiographic im ages, extensive osteolytic lesions, irregular periodontal space widening, irregular loss of lamina dura, peri-radicular and periapical radiolucencies were detected on the posterior teeth of both jaws. Also, widening of the mandibular canal and mental foramen was seen on the panoramic image (Figure 2). Cone-beam computed tomography (CBCT)

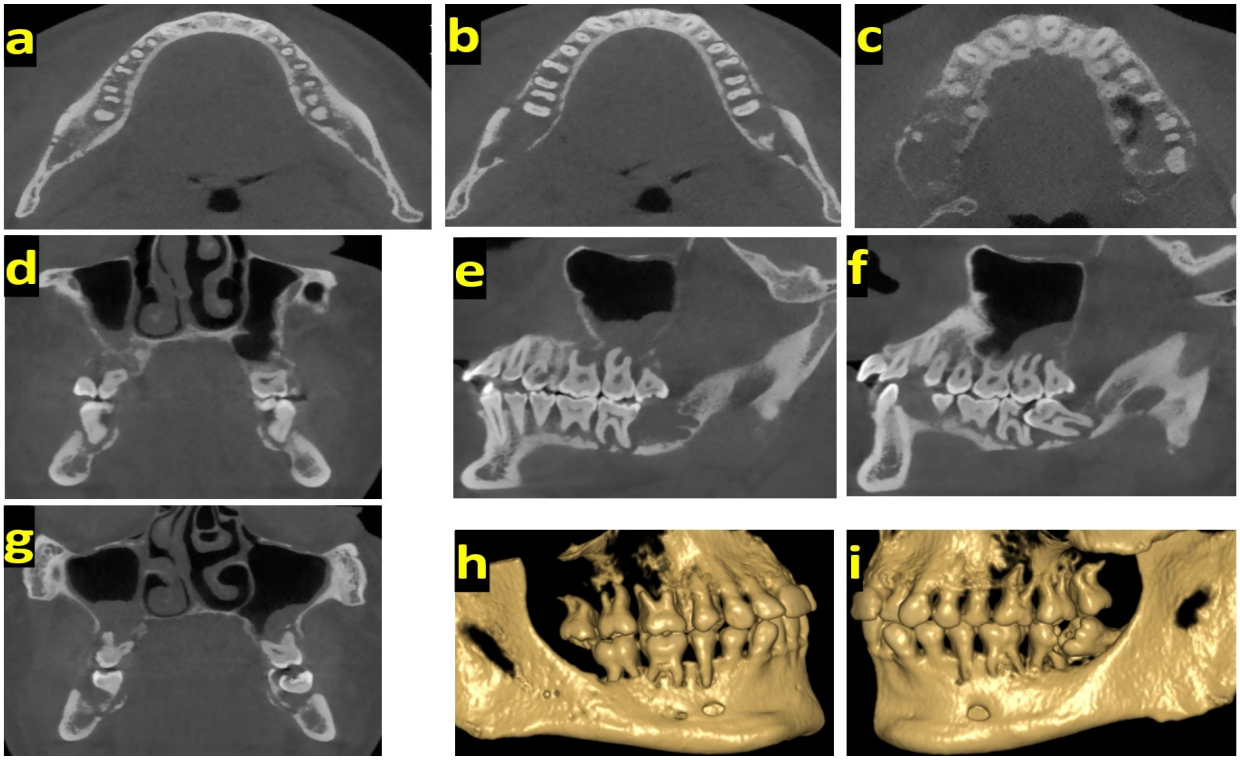

Figure 3. Axial **(a, b, c)**, coronal **(d, g)**, para-sagital (**e:** right, **f:** left) and three-dimensional reconstruction images (**h:** right, **i:** left) of cone-beam computed tomography images shows ill-defined destructive radiolucencies on mandibular and maxillary molar regions. Vestibule and oral cortex thinning-destruction, periodontal space widenings of the bilateral mandibular premolar and molar teeth are seen on the axial slices. Destruction of the bilateral maxillary sinus floor is shown on the coronal slices.

images revealed ill-defined destructive radiolucencies on mandibular and maxillary molar regions (Figure 3). Vestibule and oral cortical bone thinning, perforation and destruction were detected in four quadrants. There was cortical expansion in maxilla posteriors. Diffuse periodontal space widening was evident on the bilateral mandibular premolar and molar teeth. Destruction of the maxillary sinus floor and mucosal thickening were detected in both maxillary sinuses (Figure 3).

Considering the aggressive clinical and radiological signs, a hematopoietic system malignancy was suspected. The patient was referred to the Department of Oral and Maxillofacial Surgery, and incisional biopsy was performed under local anesthesia.

On microscopic examination of incisional biopsies from both mandibular and maxillary gum, under the atrophic squamous epithelium containing parakeratosis foci on the surface, infiltrating the epithelium in focal areas, dense infiltrate of round cells that appeared to be of lymphoid origin was observed. The tumor consisted of neoplastic lymphoid cells with medium-large-sized nuclei, prominent nucleoli, showing high mitotic activity, with scattered tangible-body macrophages resembling starry sky patterns. On immunohistochemical analysis, the tumor cells diffusely expressed pan-B-cell markers (CD20, PAX5, CD79a) and they were also positive for CD10, Bcl-6, c-MYC, CD38, TCL-1, and negative for CD3, CD5, CD15, CD23, CD30, CD44, Bcl-2, cyclinD1, MUM1, EMA, ALK. Ki-67 proliferation index of tumor cells was 100% (Figure 4). Neoplastic cells were negative for EBER by chromogenic in situ hybridization (CISH). Plasma cell neoplasia and any epithelial malignancies were ruled out based on CD138 and pan-cytokeratin negativity. Based on the morphological and immunohistochemical findings, a diagnosis of BL was made. Then, bone marrow trephine biopsy was performed, and bone marrow was also diffusely infiltrated by blastic cells with the same morphology and immunohistochemical profile as previous mandibular and maxillary gum biopsy (Figure 5).

After the diagnosis, the patient was consulted with the Department of Hematology. The patient was admitted to the hematology service. The patient with involvement in the neck, mandible, and maxilla, intra-

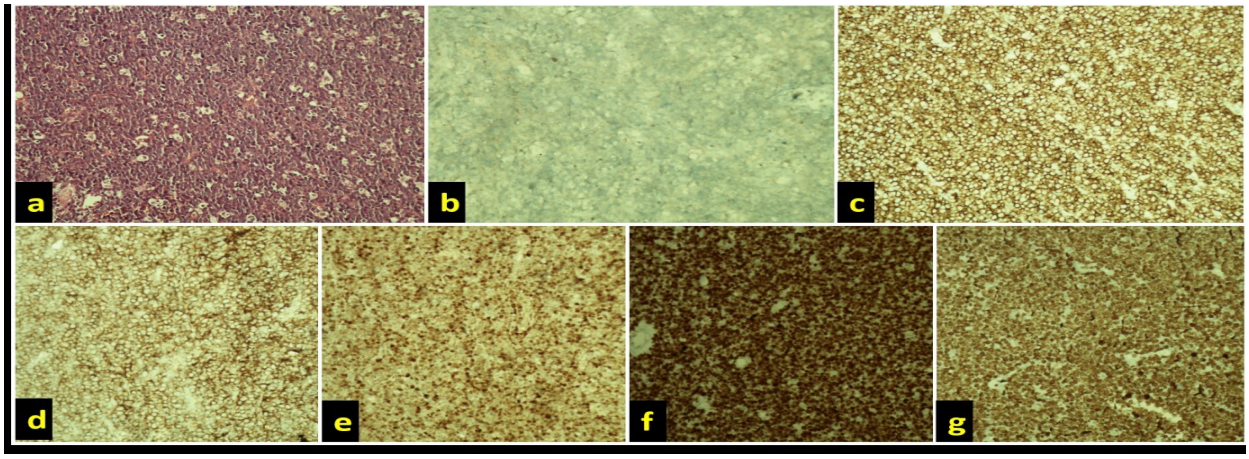

Figure 4. a) Incisional biopsies from both mandibular and maxillary gum demonstrating infiltrating solid sheets of medium-large sized neoplastic lymphoid cells, numerous mitoses, and tingible body macrophages resembling "starry sky pattern" (H&E stain, x200). The tumor cells were negative for CD3 **(b)** and positive for CD20 **(c)**. **d)** CD10 positivity, **e)** Bcl-6 positivity, **f)** c-MYC positivity were also shown. **g)** Ki-67 proliferation index was mostly 100%.

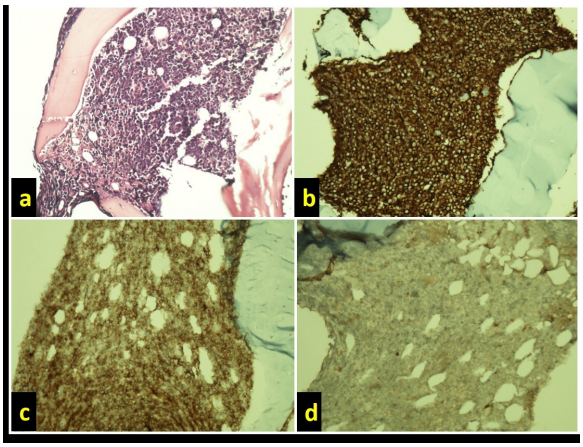

Figure 5. a) Bone marrow trephine biopsy showing diffuse infiltrate of neoplastic lymphoid cells replacing normal hematopoietic cells (H&E stain, x200). **b)** CD20 expression. The tumor cells were positive for CD10 **(c)** but negative for TdT **(d)**; ruling out lymphoblastic leukemic infiltration.

abdominal lymph nodes, and bone marrow was staged as Stage 4. EBV and HIV-related tests were requested, it was reported as negative. Hemodialysis was performed due to tumor lysis syndrome. An intensive chemotherapy protocol, R-HyperCVAD, was started. In the follow-up, the patient went into remission. A total of 4 cycles of R-HyperCVAD A and 4 cycles of R-HyperCVAD B were given to the patient. Afterward, the patient was started on chemotherapy maintenance treatment consisting of 6-mercaptopurine and methotrexate. The patient is still being followed up as in remission.

In the current clinical and radiological examination of the patient, it was observed that the lesions in the oral region had improved to a great extent (Figure 6).

DISCUSSION

BL is a rapidly progressing cancer that requires immediate imaging, biopsy, diagnosis, and aggressive chemotherapeutic treatment. BL is a type of aggressive B-cell lymphoma that can be endemic, sporadic, or immunodeficient. They have the same histology; however, they differ in epidemiology, clinical presentation, and genetic features. Although the histopathological findings of the three kinds are identical, they differ clinically in terms of age distribution and region of predominance. The endemic type, which is common in equatorial Africa, is generally documented to occur in early childhood, with a peak age of 6 years, and has a close relationship with the Epstein-Barr virus (EBV); in contrast, the sporadic variant has only a 20% relationship with EBV and is mostly found in Europe and North America and mostly affects children and adolescents. Several studies have strongly shown that EBV is involved in BL since EBV slows cell death and contributes to the formation and maintenance of BL. The endemic type often affects the jaw bones and belly, resulting in tooth movement, jaw growth, and an abdominal mass. The jaw involvement, on the other hand, is uncommon in the sporadic type. Patients with AIDS or other immune-compromising illnesses are more likely to have the immunodeficiency-related variations (12,13).

In more than half of the cases, the endemic form includes the jaw. It frequently appears as a painless face tumor that extends to extranodal sites. The sporadic variant is frequently accompanied by a large abdominal tumor. Oral lesions are observed in 9% of

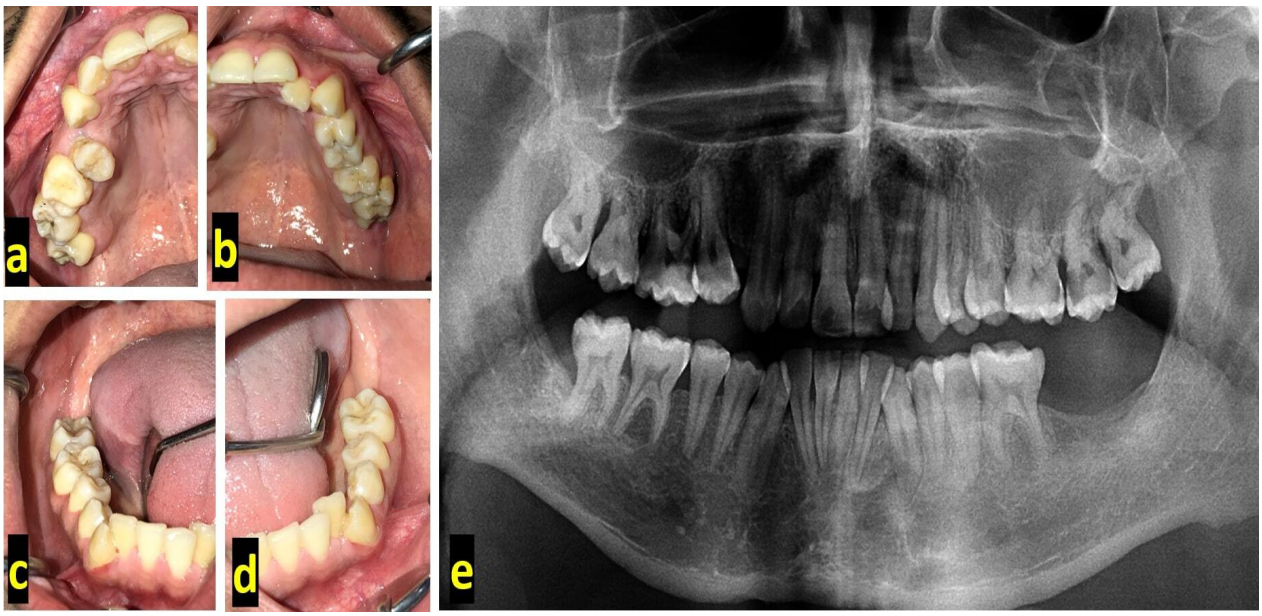

Figure 6. Current clinical photographs of the right maxillary (a), left maxillary (b), right mandibular (c), and left mandibular (d) posterior regions, and panoramic image of the patient shows the healing of the oral region (e).

sporadic cases. Adenopathies and bone marrow involvement are more common in the immunodeficiency-related variant, with clinical symptoms comparable to that seen in the sporadic form of BL. When it comes to oral presentations, the mandible is the most commonly used area. The most afflicted area is the posterior of the jaw. The most common symptoms of oral BL are swelling, discomfort, tooth displacements, and facial asymmetry. Other reported symptoms include increased tooth mobility and dental pain because of pulp invasion, particularly by growing teeth. It is typical to have paresthesia of the inferior alveolar nerve or other sensitive facial nerves (14).

Lymphoma can be seen anywhere in the mouth; however hard palate, gingiva, and tongue are the most common locations (15). The jaws are not a frequent site for NHLs (2,16). Because of the low rate of the lesion, lymphomas are often misdiagnosed (16,17). For the mandibular and maxillary involvement, soft tissue swelling is the most frequent clinical sign (17). Paresthesia, pain, ulceration, tooth mobility, and lymphadenopathy may also occur, but there are no specific clinical features (18). Pain-mimicking toothache is an important factor in the masking of lesions (19). In our case, the primary complaint of the patient was the swelling. Neural symptoms were absent because the lesions did not affect the mandibular canal.

On the radiographic images, ill-defined osteolytic radiolucencies are presented in the NHL (20). For the lesions in the maxillary sinuses, antral walls may be affected while the mandibular lesions destruct the mandibular canal cortex (6). The lesions may show finger-like destruction in the buccal or lingual sides (6). The periosteal reaction rarely occurs (17). Widening of the periodontal space is an important sign for NHL, as with other malignancies such as sarcoma, and carcinomas (19). Most of the radiolucent lesions around the periapical region are caused by dental inflammation. The imaging findings of NHL can mimic common dental originated lesions, such as periodontitis, chronic periapical periodontitis, pericoronitis, and osteomyelitis (2,19,21). Eosinophilic granuloma should also be included in the differential diagnosis (16). Periodontitis is a common disease, characterized by bone loss around the teeth roots and inflamed gingiva. However, periodontal diseases are slowly progressive lesions, and they cause horizontal alveolar bone loss, and usually occur in older age groups (16). Chronic periapical periodontitis is characterized by periapical radiolucencies which heals by root-canal treatment or tooth extraction (16). Eosinophilic granuloma of the alveolar region occurs in younger patients, and it has a clinical appearance of gingival inflammation with bleeding (16). Radiographically, eosinophilic granuloma starts in the epicenter of the roots, and destruction move to the superior border of the alveolar process (6,16). In our case, pericoronitis of the mandibular third molar tooth mimicked the NHL. Besides, there was no caries or periodontitis that

could cause destructive lesions in the peri-radicular region, and the lesions were affected all posterior teeth. Thus, a systemic malignancy was considered. The clinicians should notice the ill-defined borders and bone destruction of NHL (6).

Although BL is an aggressive tumor with a poor prognosis, the disease's cure rate depends on its stage. According to one study on oral BL, even stage III patients had a 97% survival rate (22). Dentists should be aware that mobile teeth and/or alveolar bone resorption may be the earliest clinical symptom of BL. The extent of the illness was determined following our early biopsy, and the patient received chemotherapy right away. As a result, the patient's prognosis was favorable, and he has been in remission for 20 months.

The stage of illness, lactate dehydrogenase (LDH) concentrations, leukemic bone marrow involvement, and central nervous system involvement, as well as treatment-related characteristics such as late or partial response, are all prognostic factors. The overall survival percentage for standard risk, early/moderate stage BL with chemotherapy alone is around 97%-98%, whereas the prognosis for more advanced, higher risk stages is 87.3%. A recent randomized, phase III trial discovered that adding six rounds of rituximab to conventional chemotherapy resulted in an overall survival rate of more than 95% for patients high-risk, high-stage BL. Clinical examinations, abdominal ultrasonography, and blood tests are conducted every 2–3 months during the first year after treatment. In future years, the frequency of follow-up diminishes. The majority of relapses occur within the first year of therapy (14).

Surface IgM, Bcl-6, CD10, CD19, CD20, CD22, and CD79a are all expressed in BL cells, but CD5, CD23, and TdT are not. Bcl-6 (B-cell lymphoma 6) and CD10 expression point to a germinal center origin for BL. The Ig variable heavy and light chain genes in BL were sequenced to confirm that the endemic, sporadic, and immunodeficiency-associated variants of BL all originated from a germinal center B cell, with evidence of somatic hypermutation. When the cytogenetic analysis is available, the WHO Classification of Lymphoid Diseases requires that BLL has a high growth fraction, with Ki67 staining exceeding 99%, and cytogenetic evidence of a c-myc rearrangement. At the molecular level, BL is distinguished by dysregulation of the myc protooncogene (23-25). On immunohistochemical analysis of the case, the tumor cells were diffusely expressed for pan-B-cell markers (CD20, PAX5, CD79a) and they were also positive for CD10, Bcl-6, c-myc, CD38, TCL-1, and negative for CD3, CD5, CD15, CD23, CD30, CD44, Bcl-2, cyclinD1, MUM1, EMA, ALK. Ki-67 proliferation index of tumor cells was 100%.

In terms of clinical and radiographic features of NHL, other malign lesions of the jaws should be considered in the differential diagnosis (6). Multiple myeloma, metastatic carcinoma, osteolytic osteosarcoma may be confused with NHL. Ewing sarcoma, leukemia, and Langerhans cell histiocytosis may have similar signs, but these lesions usually occur in younger patients. Maxillary sinus squamous cell carcinoma may not be distinguishable from maxillary sinus lymphomas (6). In our case, clinical-radiologic signs and multicenter location of the aggressive lesions highlighted the hematopoietic system malignancies and histopathological examination revealed a BL diagnosis.

All forms of BL are treated with brief, intense rounds of a mixture of several types of chemotherapy (cyclophosphamide, vincristine, prednisone, doxorubicin, alkylators and etoposide). In high-risk, high-grade, mature BL, the combination of immunotherapy (rituximab) with chemotherapy is a viable treatment strategy that dramatically improves overall survival. Because of the great sensitivity of BL cells to chemotherapy and the higher likelihood of local problems associated with early surgical therapies, there is no need for surgical resection or radiation. Anemia, thrombocytopenia, neutropenia, infection risk, weakness, nausea, vomiting, and hair loss are all possible side effects that vary depending on the type of chemotherapeutic drug used. Oral mucositis is another manifestation of the infection. Thrombocytopenia can cause gingival bleeding (14).

CONCLUSION

NHL, particularly BL, can mimic routine dental-originated infections. Although it is not very common in the oral cavity, it is crucial to be aware of the clinical and radiological features of this disease by dentists and to consult the attending physician without delay.

Acknowledgments: None.

Author contribution: Conceptualization: MO; Case follow-up: MO, KAD, BUK; Radiological evaluation: MO; Surgery: KAD; Pathology: BUK, AG, NST, MH; Writing: MO, BUK; Editing: MO, KAD, BUK, AG, NST, MH; Supervision: MO, MH.

Conflict of interests: The authors declare that they have no conflict of interest.

Ethical approval: None.

Funding: The authors declared that this study has received no financial support.
Peer-review: Externally peer-reviewed.

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