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Oral squamous cell carcinoma with synchronous follicular lymphoma: A rare case report

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Abstract

The occurrence of oral squamous cell carcinoma synchronously with lymphoma arising primarily in cervical lymph nodes is rare. Here, we report a case representing an infrequent finding. A 66-year-old male who was diagnosed with right mandibular squamous cell carcinoma and was subsequently found to have a nodal follicular lymphoma as a second malignancy. The patient underwent surgical resection for the oral squamous cell carcinoma with right selective neck dissection. The multidisciplinary team's postoperative treatment strategy involved adjuvant radiotherapy for the oral squamous cell carcinoma, while adopting a close follow-up approach for the follicular lymphoma. After an 18-month follow-up, there were no evidence of disease progression. This case report highlights the diagnostic challenges of synchronous primary malignancies occurring in the head and neck region. It also underscores the importance to conduct a comprehensive clinical and histopathological examination to rule out the possibility of synchronous neoplasms.

Keywords

Oral squamous cell carcinoma, follicular lymphoma, synchronous neoplasms

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Introduction

Oral squamous cell carcinoma (OSCC) represents 90% of head and neck cancers and is one of the most common cancers facing humanity.[1] Tobacco (whether smoked or smokeless) and alcohol abuse are major risk factors for OSCC development. OSCC develops because of an accumulation of genetic abnormalities that result in the transformation of normal cells into malignant cells. Mutations in tumor suppressor genes (e.g., TP53, CDKN2A) and oncogenes (e.g., EGFR, PIK3CA) have been found in OSCCs.[2] Several premalignant conditions can present and become transformed eventually into OSCCs, and, thus, early detection and awareness are recommended.[3] Although OSCCs frequently appear as ulcerative lesions with indurated borders, they may have other various clinical presentations, including pain, swelling, mobile teeth, and exophytic masses. Moreover, they can manifest as unhealed extraction sockets, a form that poses diagnostic difficulties.[4]

Follicular lymphoma is the second most common non-Hodgkin lymphoma, with the most common being diffuse large B-cell lymphoma. It originates from centrocytes and centroblast cells that form a germinal center; therefore, it expresses germinal center markers on immunohistochemical testing.[5] The main etiology of follicular lymphoma remains unknown; although the tumor acquires *t*(14;18) (q32; q21) *IGH/BCL2* translocation, this condition alone is

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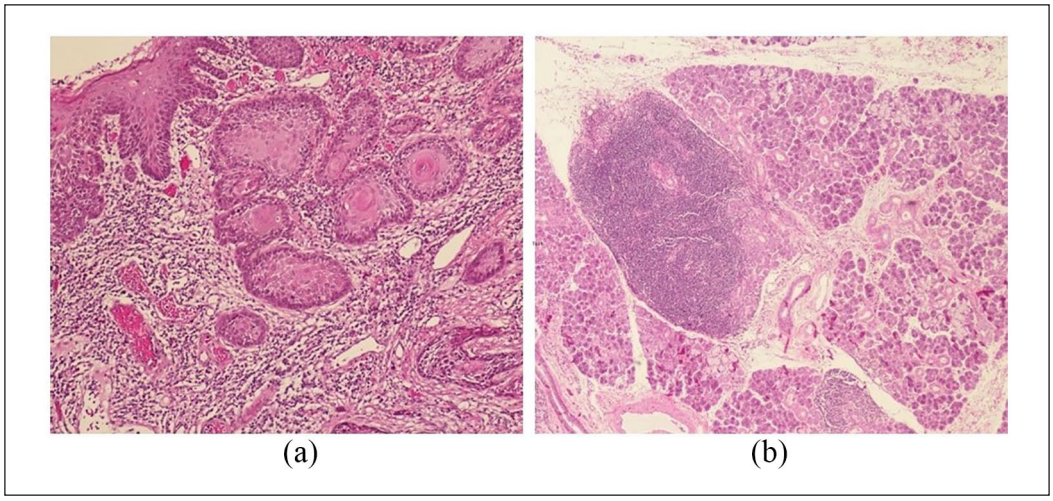

Figure 1. (a) An incisional biopsy of mandibular alveolar ridge showed well-differentiated squamous cell carcinoma (magnification 10× H&E). (b) Lateral tongue biopsy showed multiple lymphocytic aggregates within salivary gland parenchyma (magnification 10× H&E).

not sufficient to explain the development of follicular lymphoma. A family history, genetic susceptibility, and environmental factors may play roles.[6] Follicular lymphoma is considered an indolent lymphoma that mainly affects an older population. Despite the fact that 80% of follicular lymphomas affect nodal sites, tumors also can present in extranodal sites such as the bone marrow, liver, and spleen. Follicular lymphoma typically presents with broad lymph node involvement and is asymptomatic or oligosymptomatic at the time of diagnosis. Patients may also exhibit nonspecific symptoms such as fever, night sweats and unintended weight loss, and autoimmune cytopenia. Rarely, circulating neoplastic lymphocytes are observed in follicular lymphoma. The occurrence of the leukemic phase of lymphoma indicates the presence of atypical malignant lymphocytes in the peripheral blood.[7,8]

The chance of developing a second primary malignancy in patients with upper aerodigestive tract tumors has been estimated to be 3%–7% every year.[9,10] Unfortunately, in synchronous neoplasms of the head and neck area, a diagnosis can be challenging. This is especially true when patients suffer from metastatic deposits from OSCC in the lymph nodes with the coexistence of follicular lymphoma that is undetected.[11] To the best of our knowledge, we present the first reported case of a primary OSCC, manifesting as a non-healing extraction socket, diagnosed concomitantly with nodal follicular lymphoma, with emphasis on the diagnostic challenges associated with synchronous primary malignancies (SPMs).

Case presentation

A 66-year-old male was referred to the maxillofacial surgery department at the Faculty of Dentistry, King Abdulaziz University, Jeddah, Saudi Arabia, due to a persistent 3-month history of pain and numbness associated with a nonhealing extraction socket along his right alveolar ridge. The patient denied having any medical illnesses, shortness of breath, or dysphagia. He reported minimal weight loss over the past few months. He was a former smoker who had quit 40 years earlier, and he did not use any smokeless tobacco products or consume alcoholic beverages. Upon clinical examination, mild right facial swelling with a normal overlying skin color was noted, and no palpable cervical lymph nodes were detected. The intraoral findings were an ulcerative lesion with exposed bone on the right posterior alveolar ridge at the site of a recently extracted tooth. The patient had fair oral hygiene and a normal mouth opening and normal tongue mobility, with no uvular deviation or visible masses in the oropharynx.

Investigation

Histopathology. An incisional biopsy of the mandibular alveolar ridge revealed well-differentiated OSCC invading to the underlying bone. Another biopsy was taken from a suspicious area on the right lateral tongue, and it showed a nonspecific ulcer plus multiple lymphocytic aggregates in the salivary gland parenchyma (Figure 1). A diagnosis of lymphoproliferative disorder was reported, and further investigation was needed to rule out lymphoma.

Imaging examination. The preoperative head and neck computed tomography (CT) scan revealed a lytic lesion in the right mandibular body that extended from the right cuspid anteriorly to the remaining molar posteriorly. The lesion was noted to have eroded both the lingual and buccal plates of the mandible, indicating an aggressive tumor. The extraosseous soft tissue extension also suggested that the tumor had invaded the surrounding tissues (Figure 2(a)). Moreover, the neck CT scan with contrast showed a left level IV/supraclavicular lymphadenopathy with a matted appearance (see

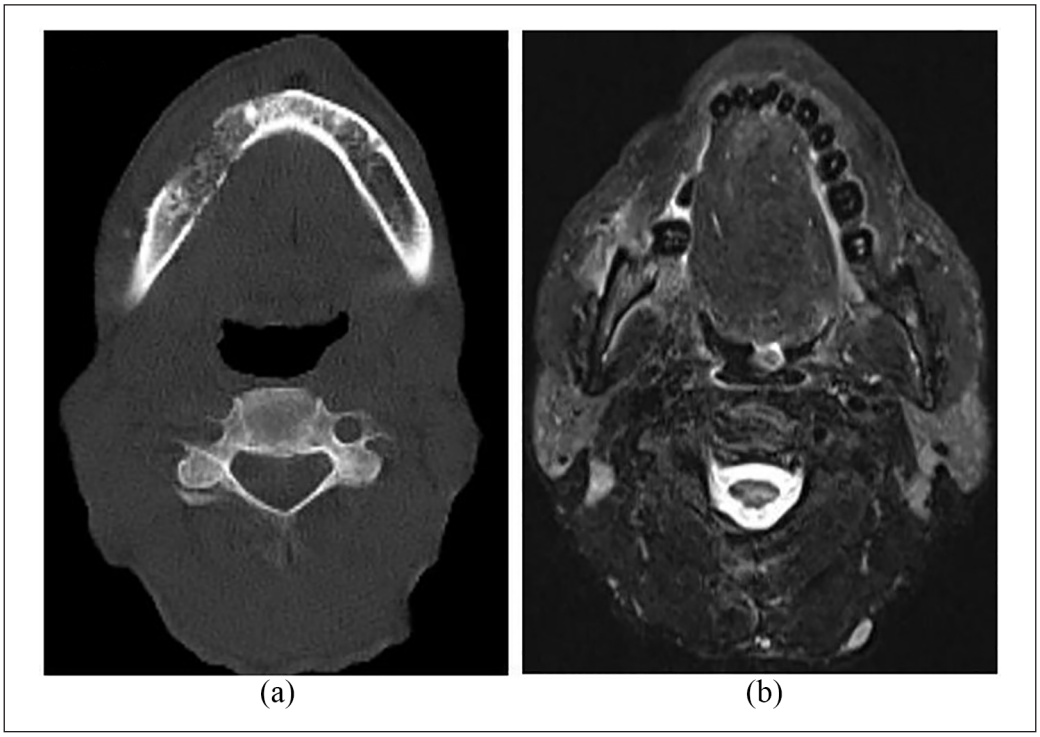

Figure 2. (a) Computed tomography (CT) scan axial section with right mandibular body lytic lesion. (b) Neck CT scan with contrast showed left level IV/supraclavicular lymphadenopathy.

Figure 2(b)). The largest node measured approximately 2.0×2.0 cm in maximum diameter on the axial plane. Abdominal and pelvic CT scans demonstrated radiographic features of extensive, discrete, matted retroperitoneal lymph nodes suggestive for lymphoma. Finally, single-photon emission computed tomography imaging showed no signs of bone metastasis.

Laboratory examination. A laboratory workup was done to prepare the patient for surgical intervention, including a complete blood count with differential. The laboratory results showed a low hemoglobin level (9.8 g/dL); normal platelet count (366×10^9/L); elevated white blood cell count ($160.43\ 10^9$/L); and automated lymphocyte (138.93 K/μL), eosinophil (1.89 K/μL), basophil (0.24 K/μL), monocyte (2.58 K/μL), and immature granulocyte (0.51 K/μL) counts, whereas the automated neutrophil count was normal (6.30 K/μL). Additionally, the atypical lymphocytes were elevated at 37%. The serum iron level was decreased (5.7 μmol/L), whereas the liver function test showed an increase in the alkaline phosphatase enzyme level (129 U/L) and the coagulation profile showed an increase in both the prothrombin time (15.7 s) and activated partial thrombin time (37.3 s), with an international normalized ratio equal to 1.09.

Flow cytometry was done after the unexpected results of the white blood cell count and interpreted as follows: the percentage of nucleated cells in the peripheral blood sample was 84.2%, of which 13.8% were normal cells and 70.4% were abnormal B cells that were positive for CD79a, CD19, CD10 (dim), CD45, CD20, HLA-DR, CD22, and positive to anti-kappa antibodies, but negative for CD3, FMC7, CD30, CD23, CD123, CD5, and CD2. These findings were consistent with a CD5– /CD10+ B-cell lymphoid neoplasm, which was most likely of an indolent nature. The patient was referred to the hematology/oncology department for further evaluation and treatment. The surgical removal of the OSCC with lymph node dissection was prioritized in the treatment of the patient.

Treatment

The surgical treatment consisted of a composite resection of the right mandible with right selective neck dissection. The surgical defect was reconstructed using a fibula free flap and split-thickness skin graft. The final pathology report confirmed the diagnosis of a well-differentiated squamous cell carcinoma (SCC) (PT4) with clear margins. The cervical lymph node examination showed no microscopic overt evidence of metastatic SCC. However, features suggestive of follicular lymphoma with back-to-back follicular proliferation and an absence of the mantle zone were observed. Immunohistochemical staining showed the positivity of CD10, BCL6, and BCL2 in the areas corresponding to the follicular pattern, whereas CD5 was negative, confirming the diagnosis of grade 1 or 2 follicular lymphoma of the cervical lymph nodes (Figure 3). Based on the AJCC (Americal Joint Committee on Cancer) criteria (8th edition), the OSCC was staged as PT4aN0M0.[12]

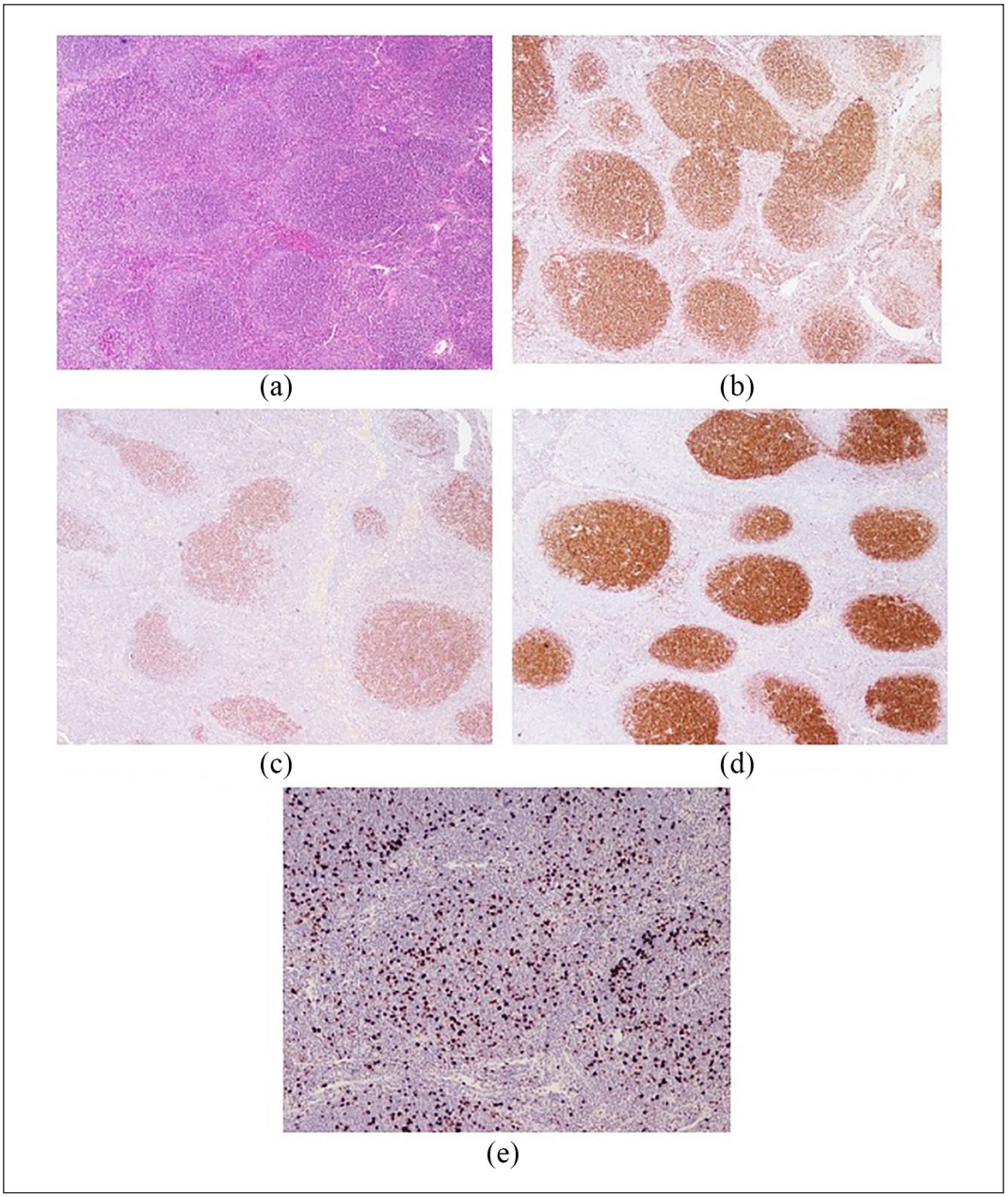

Figure 3. (a) Cervical lymph node (level 1B) showing back-to-back follicular proliferation and an absent mental zone. (b) CD10, (c) Bcl2, and (d) Bcl6 immunohistochemical results showing strong cytoplasmic positivity in germinal centers (a–d: magnification 4×). (e) Low Ki67 proliferative index area (magnification 20×).

The multidisciplinary consensus recommendation for postsurgery treatment was to proceed with adjuvant radiotherapy for OSCC and implement a watch-and-wait approach with close monitoring in the hematology clinic for follicular lymphoma.

Outcome and follow-up

The patient's white cell count decreased to the 20s, whereas his hemoglobin and platelet levels remained normal. He started to gain weight slowly after recovering from surgery and radiotherapy. Eighteen months after the primary diagnosis, there were no signs of disease progression, and there was no indication that further therapy was needed for follicular lymphoma. The patient had minor functional sequelae of the mouth, dysphagia, and xerostomia, but he did not experience any weight loss.

Discussion

The presence of multiple primary malignancies was initially described by Billroth in 1889, and since then, many cases

have been reported documenting the simultaneous occurrence of two or more primary independent malignant neoplasms. This phenomenon can be classified chronologically into (1) SPMs, which are tumors that present either concurrently with or within a 6-month period of identification of the primary tumor, or (2) metachronous primary malignancies (MPMs), which are tumors that are diagnosed more than 6 months after the diagnosis of the primary tumor.[13] The incidence of SPMs and MPMs, especially in patients with head and neck squamous cell carcinoma (HNSCC), is not uncommon.[14] The majority of cases are SCCs that frequently occur locally at different sites in the head and neck region followed by distant sites such as the lung and esophagus.[15] However, the simultaneous presence of a primary lymphoid malignancy and OSCC is extremely rare, with only a few cases reported in the literature.[16–18]

Herein, we reported a case of synchronous OSCC and an incidental finding of follicular lymphoma in the cervical lymph nodes during the initial staging of the primary tumor. The diagnosis of such cases poses a challenge. To achieve an accurate diagnosis of such synchronous tumors, Warren and Gates suggested using the following histopathological parameters: (1) each tumor must exhibit the defining features of malignancy; (2) all tumors have to be separated by normal tissue with no epithelial or submucosal connections; and (3) the possibility of metastasis from any of the tumors present should be excluded.[10] Our case fulfilled all of these criteria and, therefore, warranted the diagnosis of two SPMs occurring in the head and neck region.

In a systematic review by Parra-Medina et al. of the clinicopathological characterization of more than 300 synchronous solid neoplasms and lymphomas, 98% of lymphomas were incidental findings and most commonly found in the locoregional lymph nodes; follicular lymphoma was one of the most prevalent types of synchronous lymphomas, as was the case with our patient.[19] In the head and neck area, the concept of cancerization after exposure to chronic carcinogens is widely accepted as a possible explanation for multiple HNSCCs; this is due to the fact that these anatomic locations are subject to similar contributing risk factors and a common clonal origin that is subject to identical genetic alterations.[20] Other contributing factors are smoking, genetic susceptibility, a deleterious lifestyle in an aging patient, and a cumulative amount of cytotoxic chemotherapy and radiation.[21] Since our patient had not received prior chemotherapy or radiotherapy, we identified smoking and aging as risk factors that may have caused his tumors; they were known to be associated with OSCC. The pathogenesis of the synchronous nodal follicular lymphoma remains unknown. For all non-Hodgkin lymphomas, immunosuppression is considered a potential risk factor,[22] but blood studies for our patient did not show any signs of immunodeficiency. However, follicular lymphoma, in particular, has been linked to heavy cigarette smoking, as was the case with our patient, who was a heavy smoker before quitting.[23] Therefore, this finding raised several questions about the definitive pathophysiology of this synchrony. Did it occur independently or was it associated with exposure to similar risk factors? Was there a synergistic influence between the two malignancies? In the literature, studies have proposed possible theories that may explain the relationship of this rare combination of lymphoma and other neoplasms, such as the migration of mutated embryonic somatic cells to different anatomic locations at which these cells later become malignant during exposure to carcinogenic factors, a family history, or a mismatch of repair systems due to genetic defects.[24–28]

Management of synchronous carcinomas requires multidisciplinary team collaborations. The management strategy reported in the literature was limited for such cases and varied according to the type, location, and extension of the two malignancies. Overall, the evaluation and staging of each malignancy should be done independently. It was recommended that the management guidelines be followed, when possible, for each type of tumor. When modifications are necessary, minimal potential complications should be considered.[28] However, treatment should be prioritized for the malignancy that has the lower survival rate and worse prognosis.[26] In terms of multiple HNSCCs, studies have reported significantly reduced survival rates in patients with synchronous tumors, with an estimated 5-year overall survival rate of 25%.[29] Follicular lymphoma behaves in a more indolent fashion, with an estimated overall 10-year survival rate ranging from 60% to 90%. Even with the risk of progression, the observation of asymptomatic patients continues to be adequate.[30] Given the reduced survival rate of synchronous malignancies, the locally aggressive nature of OSCC, and the propensity for metastasis and the incidental finding of asymptomatic follicular lymphoma, we proceeded to treat the OSCC with adjunctive radiotherapy and followed a "watchful waiting strategy" to monitor the clinical course of the follicular lymphoma.

Conclusion

We reported a rare case of synchronous OSCC and follicular lymphoma. This finding is not common, and the presence of lymphoma may go unnoticed during a histopathological evaluation of a neck dissection because the pathologist's attention is usually directed toward ruling out a solid tumor metastasis. Patients presenting with OSCC are at an increased risk of a synchronous primary malignancy. Therefore, the information in our case report should alert clinicians to the importance of a thorough investigation of the patient and a careful histopathological evaluation of the lymph nodes, especially in cases of head and neck malignancy, to rule out the possibility of synchronous neoplasms. Further studies to understand the interactions and relationships between a synchronous lymphoid malignancy and HNSCC may improve patient management and prognoses.

Authors contributions

N.B., M.A., Y.D., B.J., and A.S.B. contributed to conception; N.B., M.A., Y.D., and A.S.B. contributed to data analysis and interpretation; M.A, G.S., H.S., and B.J. contributed to data collection; N.B., M.A., G.S., H.S., Y.D., and B.J. contributed to drafting the article; N.B., M.A., Y.D., B.J., and A.S.B. contributed to critical revision of the article. All authors approved the final version for publication.

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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References

1. Tandon P, Dadhich A, Saluja H, et al. The prevalence of squamous cell carcinoma in different sites of oral cavity at our Rural Health Care Centre in Loni, Maharashtra–a retrospective 10-year study. *Contemp Oncol/Współczesna Onkologia* 2017; 21(2): 178–183.
2. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol* 2009; 45(4–5): 309–316.
3. Bugshan A and Farooq I. Oral squamous cell carcinoma: metastasis, potentially associated malignant disorders, etiology and recent advancements in diagnosis. *F1000Research* 2020; 9: 229.
4. Singh T and Schenberg M. Delayed diagnosis of oral squamous cell carcinoma following dental treatment. *Ann Royal College Surg Engl* 2013; 95(5): 369–373.
5. Campo E, Harris NL, Jaffe ES, et al. Follicular lymphoma. In: Swerdlow SH (4th ed.) *WHO classification of tumours of haematopoietic and lymphoid tissues*. Lyon, France: International Agency for Research on Cancer, 2008.
6. Mamessier E, Broussais-Guillaumot F, Chetaille B, et al. Nature and importance of follicular lymphoma precursors. *Haematologica* 2014; 99(5): 802.
7. Al-Nawakil C, Kosmider O, Stern MH, et al. Leukemic phase of follicular lymphomas: an atypical presentation. *Leukemia Lymphoma* 2011; 52(8): 1504–1508.
8. Beltran BE, Quiñones P, Morales D, et al. Follicular lymphoma with leukemic phase at diagnosis: a series of seven cases and review of the literature. *Leukemia Res* 2013; 37(9): 1116–1119.
9. Shikhani AH, Matanoski GM, Jones MM, et al. Multiple primary malignancies in head and neck cancer. *Arch Otolaryngol–Head Neck Surg* 1986; 112(11): 1172–1179.
10. Warren S and Gates O. Multiple primary malignant tumors: a survey of the literature and statistical study. *Am J Cancer* 1932; 16: 1358–1414.
11. Schmidt C, Fingerle-Rowson G, Boehme A, et al. Changes in the diagnosis and treatment of patients with low grade lymphoma in Germany: years 2006–2009. *Leukemia Lymphoma* 2015; 56(3): 694–702.
12. Amin MB, Greene FL, Edge SB, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA: A Cancer J Clin* 2017; 67(2): 93–99.
13. Gluckman JL, Crissman JD and Donegan JO. Multicentric squamous-cell carcinoma of the upper aerodigestive tract. *Head Neck Surg* 1980; 3(2): 90–96.
14. Licciardello JT, Spitz MR and Hong WK. Multiple primary cancer in patients with cancer of the head and neck: second cancer of the head and neck, esophagus, and lung. *Int J Radiat Oncol* Biol* Phys* 1989; 17(3): 467.
15. Luciani A and Balducci L. Multiple primary malignancies. *Semin Oncol* 2004; 31(2): 264–273.
16. Millwaters M, Khan N and Halfpenny W. Simultaneous lymphoma and squamous cell carcinoma presenting as a neck lump. *Brit J Oral Maxillofac Surg* 2008; 46(2): 144–145.
17. Stack Jr BC, Ridley MB and Endicott JN. Simultaneous squamous cell carcinoma of the head and neck and reticuloendothelial malignancies. *Am J Otolaryngol* 1996; 17(3): 178–183.
18. Watanabe N, Inohara H, Akahani S, et al. Synchronous squamous cell carcinoma and malignant lymphoma in the head and neck region. *Auris Nasus Larynx* 2007; 34(2): 273–276.
19. Parra-Medina R, Rocha F, Castañeda-González JP, et al. Synchronous or collision solid neoplasms and lymphomas: a systematic review of 308 case reports. *Medicine* 2022; 101(28): e28988.
20. Mohan M and Jagannathan N. Oral field cancerization: an update on current concepts. *Oncol Rev* 2014; 8(1): 244.
21. Alexandrov LB, Ju YS, Haase K, et al. Mutational signatures associated with tobacco smoking in human cancer. *Science* 2016; 354(6312): 618–622.
22. Hartge P, Wang SS, Bracci PM, et al. Non-Hodgkin Lymphoma. In: Schottenfeld D and Fraumeni Jr JF (eds.) *Cancer epidemiology | prevention*. New York: Oxford University Press, 2006.
23. Talamini R, Polesel J, Montella M, et al. Smoking and non-Hodgkin lymphoma: case-control study in Italy. *Int J Cancer* 2005; 115(4): 606–610.
24. Bedi GC, Westra WH, Gabrielson E, et al. Multiple head and neck tumors: evidence for a common clonal origin. *Cancer Res* 1996; 56(11): 2484–2487.
25. Horii A, Han HJ, Shimada M, et al. Frequent replication errors at microsatellite loci in tumors of patients with multiple primary cancers. *Cancer Res* 1994; 54(13): 3373–3375.

26. Liao CT, Kang CJ, Chang JT, et al. Survival of second and multiple primary tumors in patients with oral cavity squamous cell carcinoma in the betel quid chewing area. *Oral Oncol* 2007; 43(8): 811–819.
27. Schwartz LH, Ozsahin M, Zhang GN, et al. Synchronous and metachronous head and neck carcinomas. *Cancer* 1994; 74(7): 1933–1938.
28. Van der Groen T, Shupak RP and Kim RY. Synchronous oral squamous cell carcinoma and a lymphoproliferative disorder in an adult: a challenge in diagnosis and management. *BMJ Case Rep* 2022; 15(2): e246641.
29. Bugter O, van Iwaarden DL, Dronkers EA, et al. Survival of patients with head and neck cancer with metachronous multiple primary tumors is surprisingly favorable. *Head Neck* 2019; 41(6): 1648–1655.
30. Freedman A. Follicular lymphoma: 2018 update on diagnosis and management. *Am J Hematol* 2018; 93(2): 296–305.