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A Case of Hyalinizing Clear-cell Carcinoma With *EWSR1–ATF1* Fusion Gene Arising From the Minor Salivary Gland of the Tongue

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Abstract

Background/Aim: Hyalinizing clear-cell carcinoma (HCCC) is a rare malignant tumor of the minor salivary glands characterized by nests of clear cells within a hyalinized stroma. Its diagnosis remains challenging due to its histological similarity to other neoplasms, and the recent recognition of distinct molecular features, such as Ewing sarcoma breakpoint region 1 (*EWSR1)*–activating transcription factor 1 (*ATF1*) fusion. This report describes a rare case of HCCC arising from the tongue with confirmed *EWSR1–ATF1* fusion.

Case Report: A 54-year-old man presented with a painless mass on the right lateral border of the tongue. Clinical examination revealed an elastic hard tumor measuring 18×15×8 mm. Biopsy under local anesthesia revealed a malignant clear-cell neoplasm. The lesion was completely excised under general anesthesia 2 weeks later. Histopathology showed nests of clear cells with polygonal nuclei in a hyalinized stroma. Immunohistochemistry demonstrated positivity for cytokeratin AE1/AE3, p63 protein and cytokeratin 7, and negativity for cytokeratin 20, α-smooth muscle actin, S-100 protein, vimentin, and cluster of differentiation 10. Periodic acid–Schiff staining was positive, with no diastase sensitivity. Fluorescence *in situ* hybridization revealed *EWSR1* rearrangement, confirmed by reverse transcription-polymerase chain reaction as an *EWSR1–ATF1* fusion. Perifocal stroma showed marked hyalinization. These findings support a diagnosis of HCCC with hyalinization. The patient remained disease-free 5 years after surgery.

Conclusion: This case highlights the diagnostic importance of integrating histopathology, immunoprofiling, and molecular analysis in patients with rare salivary gland tumors and underscores the favorable outcomes of complete surgical resection for HCCC of the tongue.

Keywords: Hyalinizing clear-cell carcinoma, HCCC, tongue cancer, minor salivary glands, *EWSR1–ATF1* fusion gene.

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Introduction

Hyalinizing clear-cell carcinoma (HCCC) is a rare malignant epithelial tumor of the salivary gland that accounts for <1% of tumor arising from the minor salivary glands (1). Despite its rarity, HCCC shows a predilection for the minor salivary glands of the oral cavity, particularly the tongue and floor of the mouth. Clinically, HCCC is generally considered a low-grade malignancy characterized by an indolent course, low incidence of regional or distant metastasis, and favorable prognosis following complete surgical excision. To date, the effectiveness of radiotherapy and chemotherapy has not been clearly established, and wide surgical resection with adequate margins remains the mainstay of treatment (2). Owing to the limited number of reported cases, the clinicopathological and molecular features of HCCC have yet to be fully defined. Therefore, we report a case of CCC of the tongue with stromal hyalinization, histopathological findings, immunohistochemical profile, and molecular characteristics, to aid in the accurate diagnosis and improve awareness of this rare cancer. Informed consent was obtained from the patient included in the study, and permission was granted for the publication of clinical photographs.

Case Report

Patient consent. A 54-year-old man was admitted to our hospital in March 2019 with chief complaint of a mass on the right lateral border of the tongue. The patient's medical history included type 2 diabetes mellitus, hyperlipidemia, and bronchial asthma. He was a smoker with a Brinkman index of 640 but had no history of alcohol consumption. Clinical examination revealed an exophytic, pedunculated mass measuring approximately 18×15×8 mm at the base of the right side of the tongue, with partial surface ulceration. The lesion was elastic and firm, with no spontaneous pain or tenderness on contact (Figure 1). Incisional biopsy suggested moderately differentiated squamous cell carcinoma. Contrast-enhanced computed tomography demonstrated a well-defined lesion with high

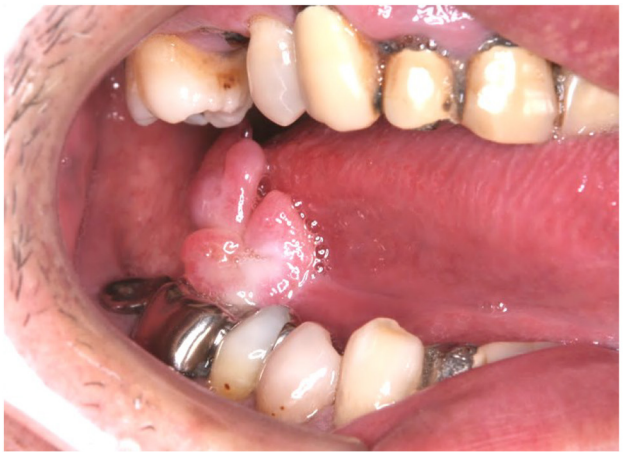

Figure 1. *Clinical findings of the tongue mass at initial examination. Clinical findings at the time of initial examination showing an indurated, ulcerative mass measuring approximately 18×15×8 mm at the base on the right of the tongue.*

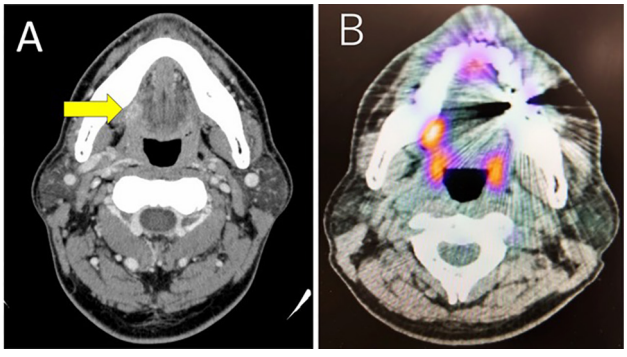

Figure 2. *Computed tomography and fluorodeoxyglucose (FDG) positron emission tomography findings of the tongue lesion. (A) An area of strong contrast (arrow) can be seen on the right edge of the tongue. (B) An area of high FDG accumulation was observed on the right edge of the tongue.*

contrast enhancement at the base of the right side of the tongue. Scattered cervical lymph nodes were observed bilaterally, with no radiological evidence of metastasis (Figure 2A). Positron-emission tomography–computed tomography showed increased ^{18}F-fluorodeoxyglucose uptake at the primary site (Figure 2B). Magnetic resonance imaging revealed a low signal intensity on T2-weighted imaging (Figure 3A), with high signal intensity on T1-weighted and short tau inversion recovery imaging (Figure 3B and C), and heterogeneous contrast

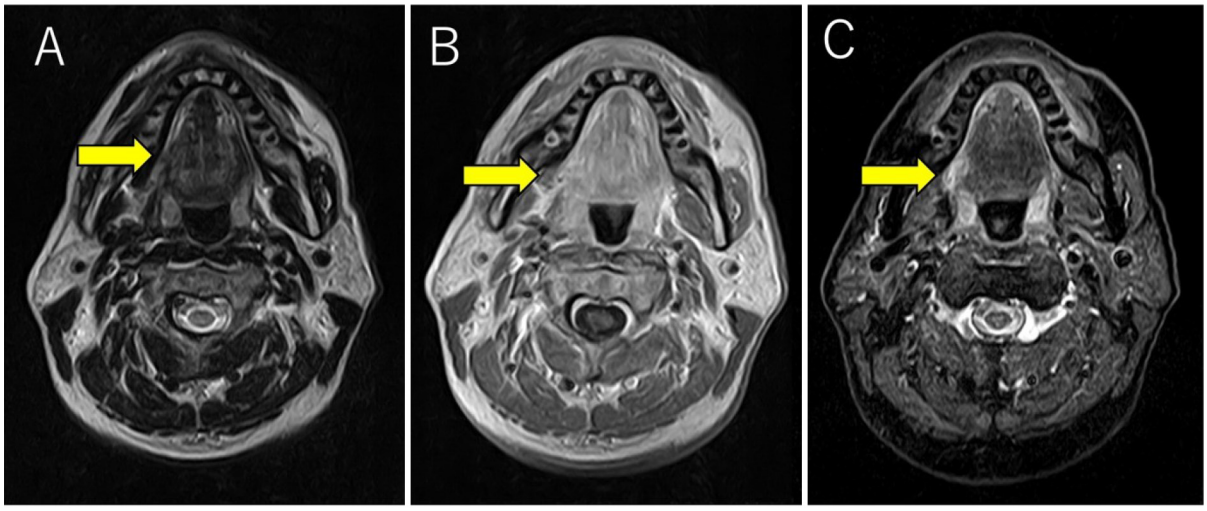

Figure 3. *Magnetic resonance imaging (MRI) characteristics of the tumor on the right side of the tongue. MRI showed low signal intensity on T2-weighted images (arrow) (A), high signal intensity on T1-weighted (arrow) (B) and short tau inversion recovery (arrow) (C) images, and an area of heterogeneous contrast in the right side of the base of the tongue.*

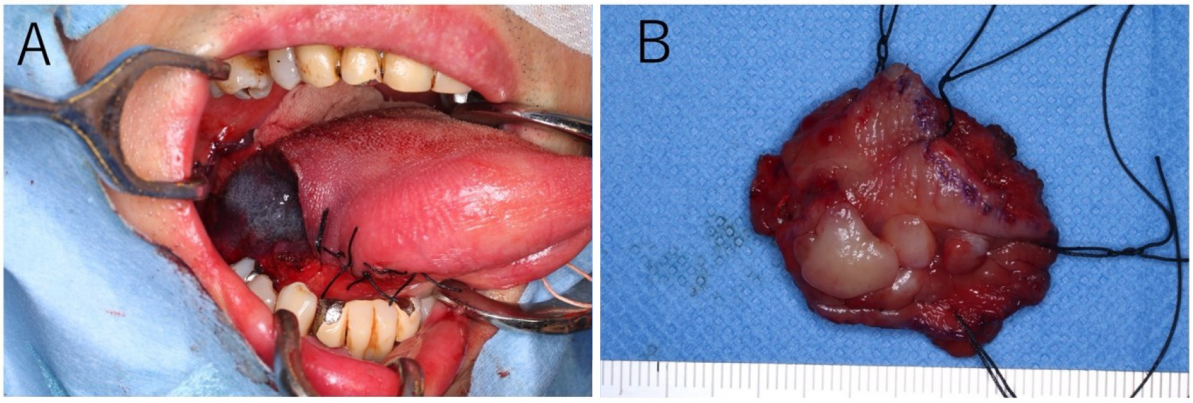

Figure 4. *Surgical procedure and resected specimen of the tongue lesion. (A) Surgical findings. Right partial glossectomy and polyglycolic acid sheet/fibrin glue covering were performed under general anesthesia. (B) Tissue measuring 34×33×20 mm was resected from the right of the tongue.*

enhancement at the tumor site. No distant metastases were detected.

Based on these findings, a clinical diagnosis of tongue cancer was established (T1N0M0: stage I). Right partial glossectomy was performed under general anesthesia, after which the surgical defect was covered using a polyglycolic acid sheet with fibrin glue (Figure 4).

Histopathological examination of the resected specimen revealed tumor cells arranged in alveolar and nested patterns. The tumor consisted predominantly of polygonal cells with eccentrically located nuclei, including areas composed of clear cells intermixed with pale eosinophilic cells. Marked stromal hyalinization was observed surrounding some of the tumor nests.

Immunohistochemical staining revealed positivity for cytokeratin AE1/AE3, cytokeratin 7 (CK7) and p63, and negativity for CK20, α-smooth muscle actin, S-100 protein, vimentin, and cluster of differentiation 10 (CD10).

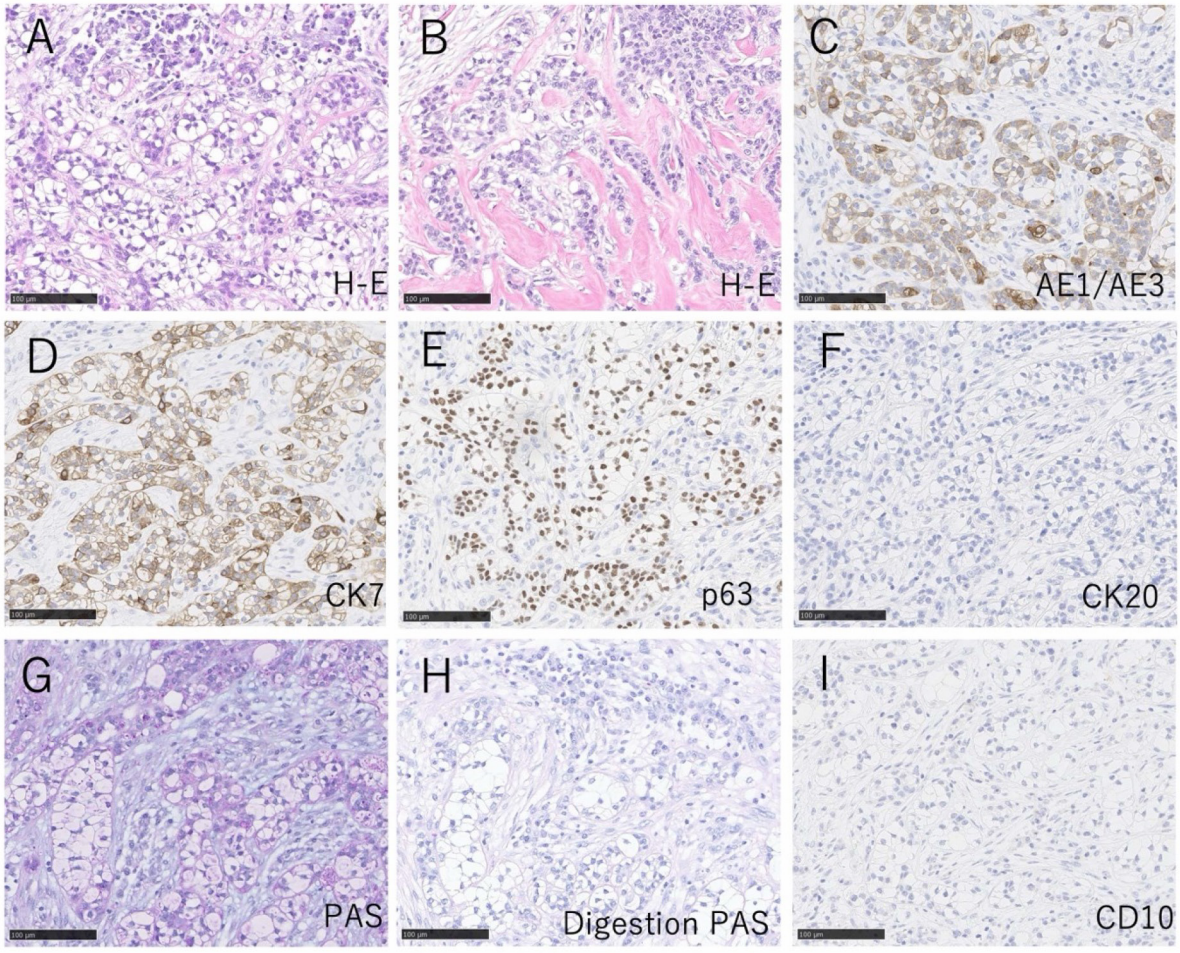

Figure 5. *Histological, immunohistochemical, and special staining findings of the tongue tumor. (A, B) Hematoxylin and eosin (H-E) staining showed tumor cells with uniform morphology and clear cytoplasm proliferated in sheets-like arrangements, separated by partially hyalinized stroma. Immunostaining showed positivity for cytokeratin AE1/AE3 (AE1/AE3) (C), cytokeratin 7 (CK7) (D) and p63 (E), as well as negativity for cytokeratin 20 (CK20) (F). (G, H) Special staining showed glycogen granule accumulation with periodic acid–Schiff and digest periodic acid–Schiff (no staining) within the cells. (I) CD10 immunostaining was negative, excluding metastatic renal cell carcinoma. Scale bar=100 μm.*

The CK7-positive CK20-negative profile supported tumor of salivary gland origin, whereas p63 positivity with the absence of other myoepithelial markers aided in differential diagnosis. Periodic acid–Schiff (PAS) staining demonstrated intracytoplasmic glycogen accumulation (PAS-positive and diastase-sensitive). The absence of CD10 expression excluded metastatic renal cell carcinoma (Figure 5). Furthermore, molecular analysis detected the presence of a Ewing sarcoma breakpoint region 1 (*EWSR1*)–activating transcription factor 1 (*ATF1*) fusion gene. Based on histopathological, immunohistochemical, and molecular findings, the tumor was diagnosed as HCCC of minor salivary gland origin arising from the tongue. The postoperative course was uneventful, and no evidence of local recurrence or metastasis had been observed during more than 5 years of follow-up (Figure 6).

Discussion

HCCC, previously referred to as CCC, is a rare malignancy of the salivary glands that is currently recognized as a distinct entity in the fifth edition of the World Health

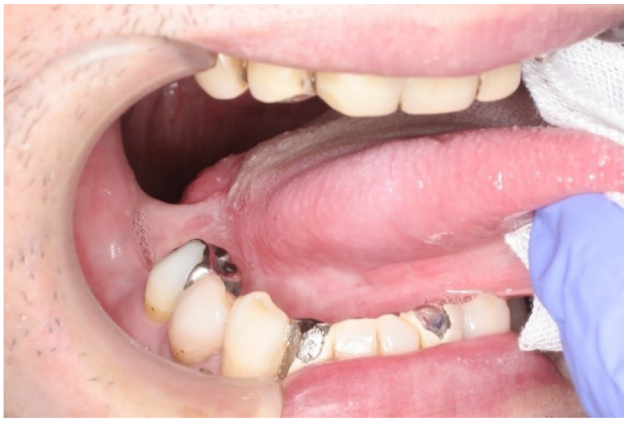

Figure 6. *Long-term postoperative outcome of the tongue lesion. A view of the right side of the tongue 5 years after surgery. No recurrence was observed.*

Organization Classification of Head and Neck Tumors (3). In 1996, Ellis and Auclair first described this tumor type as clear-cell adenocarcinoma in the Armed Forces Institute of Pathology classification (4). Earlier reports had described similar lesions under various terms, including HCCC and glycogen-rich CCC (5-8), reflecting historical uncertainty in nomenclature and classification.

HCCC is an extremely rare tumor, accounting for fewer than 1% of all salivary gland tumors and is said to be more common in the minor salivary glands (1, 9). A comprehensive literature review identified 254 cases reported between 1983 and 2020, with the palate being the most common site, followed by the tongue (10). Overall, HCCC represents approximately 0.2-1% of all salivary gland tumors, shows a slight female predominance, and predominantly affects the minor salivary glands (>80% of cases) (5). Consistent with this observation, the tumor in the present case originated from a minor salivary gland at the base of the tongue. Histopathologically, HCCC is characterized by nests comprising sheets of clear cells with polygonal nuclei embedded in a hyalinized stromal background. The tumor cells typically contain abundant intracytoplasmic glycogen (5), as demonstrated by PAS positivity that was abolished by diastase digestion, and lack mucin production on mucicarmine or Alcian blue staining. Immunohistochemically, the tumor cells expressed epithelial markers, such as cytokeratin (AE1/AE3) and epithelial membrane antigen but not myoepithelial markers, including S-100 protein, α-smooth muscle actin, vimentin, calponin, and p63 (9). The characteristic clear-cell morphology, diastase-sensitive PAS positivity, and expression of epithelial marker supported this diagnosis in the present case. Although p63 positivity was observed focally, the absence of other myoepithelial markers was consistent with the previously reported immunoprofile for HCCC.

Recent advances have highlighted the diagnostic importance of molecular alterations in salivary gland tumors. In 2012, fusion genes resulting from chromosomal rearrangements were identified in recurrent CCCs. Jin *et al.* reported *EWSR1* gene rearrangement in both primary and recurrent CCCs of the tongue, including high-grade recurrent lesions (11). Subsequently, Antonescu *et al.* demonstrated that the *EWSR1–ATF1* fusion gene, involving the rearrangement between *EWSR1* exon 11 and *ATF1* exon 3, observed this as a consistent molecular feature of HCCC in 18 out of 22 cases (12). Since then, multiple variants of EWSR1-related fusion gene have been reported in CCCs arising from the salivary glands. Hirose *et al*. identified a fusion variant in CCC arising from the salivary glands, *EWSR1* exon 15 – *ATF1* exon 5 and suggested it to be associated with an indolent clinical course (13). In contrast, certain *EWSR1–ATF1* fusion variants (*EWSR1* exon 8–*ATF1* exon 4) commonly observed in clear-cell sarcomas have been associated with aggressive behavior, including local recurrence and metastasis (14). These findings suggest that molecular characterization may contribute not only to accurate diagnosis but also to prognostic assessment. In the present case, detection of the *EWSR1–ATF1* fusion gene strongly supported the diagnosis of HCCC.

Furthermore, whole-body fluorodeoxyglucose positron emission tomography imaging revealed no evidence of malignancy in other organs, including the kidneys, which helped exclude metastatic clear-cell renal cell carcinoma.

HCCC is generally considered a low-grade tumor, with lymph node and distant metastasis reported infrequently (10, 15). However, cases of local recurrence after surgical resection (17), lymph node metastasis (16), and distant metastasis to the lungs and other organs (17, 18) have been described. Therefore, complete surgical resection with adequate safety margins remains the treatment of choice (10). Although Grenevicki *et al.* reported tumor shrinkage following combined chemotherapy with of 5-fluorouracil and cisplatin (1), evidence supporting the efficacy of chemotherapy or radiotherapy remains limited. In the current case, surgical resection was selected with an adequate safety margin and was performed alone, with no evidence of recurrence or metastasis at follow-up after more than 5 years. Nevertheless, given reports of aggressive behavior and poor outcomes in some cases (16, 17), long-term surveillance remains essential.

Conclusion

HCCC of the tongue is a rare malignancy originating from the minor salivary gland and may present diagnostic challenges due to its overlapping histological features with other clear-cell neoplasms. This case highlights the importance of integrating histopathological evaluation, immunohistochemical profiling, and molecular analysis, particularly the detection of the *EWSR1–ATF1* fusion gene, for accurate diagnosis. Complete surgical resection with adequate margins promoted a favorable outcome, with no evidence of recurrence or metastasis after long-term follow-up. Awareness of this entity and its characteristic molecular features is essential for appropriate diagnosis, management, and prognostic assessment.

Conflicts of Interest

All Authors declare that they have no conflicts of interest.

Authors' Contributions

KS, HT, DH, YK, ST and AT were involved in the treatment of the patient and made substantial contributions to the conception and design, acquisition of data, and analysis and interpretation of data. YO and JO made substantial contributions to the histopathological diagnosis.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine-learning software, were used in the preparation, analysis, or presentation of this manuscript

References

1 Grenevicki LF, Barker BF, Fiorella RM, Mosby EL: Clear cell carcinoma of the palate. Int J Oral Maxillofac Surg 30(5): 452-454, 2001. DOI: 10.1054/ijom.2001.0116
2 Oliver J, Wu P, Chang C, Roden D, Wang B, Liu C, Hu K, Schreiber D, Givi B: Patterns of care and outcome of clear cell carcinoma of the head and neck. Otolaryngol Head Neck Surg 161(1): 98-104, 2019. DOI: 10.1177/0194599819835779
3 Skálová A, Hyrcza MD, Mehrotra R, Leivo I: Hyalinizing clear-cell carcinoma. In: World Health Organization (WHO) Classification of Head and Neck Tumours, 5th Edition, Volume 9. Part A. WHO Classification of Tumours Editorial Board. International Agency for Research on Cancer; Lyon, p. 218, 2024.
4 Ellis GL, Auclair PL: Tumors of the salivary glands. In: Atlas of Tumor Pathology 3rd Series. Armed Forces Institute of Pathology; Washington, D.C, pp. 281-289, 1996.
5 Milchgrub S, Gnepp DR, Vuitch F, Delgado R, Albores-Saavedra J: Hyalinizing clear cell carcinoma of salivary gland. Am J Surg Pathol 18(1): 74-82, 1994. DOI: 10.1097/00000478-199401000-00007
6 Urban SD, Keith DA, Goodman M: Hyalinizing clear cell carcinoma: report of a case. J Oral Pathol Med 25(10): 562-564, 1996. DOI: 10.1111/j.1600-0714.1996.tb01732.x
7 Manoharan M, Othman NH, Samsudin AR: Hyalinizing clear-cell carcinoma of minor salivary gland: Case report. Braz Dent J 13(1): 66-69, 2002.
8 Balakrishnan R, Nayak DR, Pillai S, Rao L: Hyalinizing clear cell carcinoma of the base of the tongue. J Laryngl Otol 116(10): 851-853, 2002. DOI: 10.1258/00222150260293718
9 Suzuki H, Yamauchi G, Hashimoto K: Clear cell carcinoma of the mandibular gingiva 'minor salivary gland': a case report with immunohistochemical study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 103(3): e36-e40, 2007. DOI: 10.1016/j.tripleo.2005.11.027
10 Desai A, Faquin WC, Iafrate AJ, Rivera MN, Jaquinet A, Troulis MJ: Clear cell carcinoma: a comprehensive literature review of 254 cases. Int J Oral Maxillofac Surg 51(6): 705-712, 2022. DOI: 10.1016/j.ijom.2021.03.018

11 Jin R, Craddock KJ, Irish JC, Perez-Ordonez B, Weinreb I: Recurrent hyalinizing clear cell carcinoma of the base of tongue with high-grade transformation and EWSR1 gene rearrangement by FISH. Head Neck Pathol 6(3): 389-394, 2012. DOI: 10.1007/s12105-012-0338-7
12 Antonescu CR, Katabi N, Zhang L, Sung YS, Seethala RR, Jordan RC, Perez-Ordoñez B, Have C, Asa SL, Leong IT, Bradley G, Klieb H, Weinreb I: EWSR1-ATF1 fusion is a novel and consistent finding in hyalinizing clear-cell carcinoma of salivary gland. Genes Chromosomes Cancer 50(7): 559-570, 2011. DOI: 10.1002/gcc.20881
13 Hirose K, Usami Y, Kohara M, Sato S, Iwamoto Y, Murakami S, Uchihashi T, Oya K, Fukuda Y, Hori Y, Morii E, Toyosawa S: Clear cell carcinoma of palatal minor salivary gland harboring a novel EWSR1-ATF1 fusion gene: report of a case and review of the literature. Head Neck Pathol 15(2): 676-681, 2021. DOI: 10.1007/s12105-020-01211-6
14 Panagopoulos I, Mertens F, Dêbiec-Rychter M, Isaksson M, Limon J, Kardas I, Domanski HA, Sciot R, Perek D, Crnalic S, Larsson O, Mandahl N: Molecular genetic characterization of the EWS/ATF1 fusion gene in clear cell sarcoma of tendons and aponeuroses. Int J Cancer 99(4): 560-567, 2002. DOI: 10.1002/ijc.10404
15 Okada M, Kimizuka S, Kumamoto H, Endo T, Sugazaki M, Echigo S: A case of clear cell carcinoma, not otherwise specified, in the retromolar region. Jpn J Oral Maxillofac Surg 53(7): 449-453, 2007. DOI: 10.5794/jjoms.53.449
16 Milchgrub S, Vuitch F, Hossein Saboorian M, Hameed A, Wu H, Albores-Saavedra J: Hyalinizing clear-cell carcinoma of salivary glands in fine-needle aspiration. Diagn Cytopathol 23(5): 333-337, 2000. DOI: 10.1002/1097-0339(200011)23:5<333::aid-dc10>3.0.co;2-r
17 Wang B, Brandwein M, Gordon R, Robinson R, Urken M, Zarbo RJ: Primary salivary clear cell tumors – a diagnostic approach: a clinicopathologic and immunohistochemical study of 20 patients with clear cell carcinoma, clear cell myoepithelial carcinoma, and epithelial-myoepithelial carcinoma. Arch Pathol Lab Med 126(6): 676-685, 2002. DOI: 10.5858/2002-126-0676-PSCCTA
18 O'Regan E, Shandilya M, Gnepp DR, Timon C, Toner M: Hyalinizing clear cell carcinoma of salivary gland: an aggressive variant. Oral Oncol 40(3): 348-352, 2004. DOI: 10.1016/j.oraloncology.2003.08.023