Clear Cell Carcinoma of the Hard Palate in an Adolescent Patient: A Case Report

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Clear cell carcinoma is an extremely rare low-grade malignancies occurring in less than 1% of salivary gland tumors. We report a case of clear cell carcinoma of the hard palate in a 15-year-old adolescent patient. She first noticed a palatal tumor at age 9, but the tumor was left untreated for 6 years. We performed incisional biopsy, but no definitive diagnosis was obtained. Excisional biopsy was then performed, and the histopathological diagnosis was clear cell carcinoma of the salivary gland. However, the tumor was exposed at the margin of the surgical specimen; thus, additional excision was performed. Five years after the treatment, no local recurrence or metastasis has been observed.

Key words: Clear cell carcinoma, Salivary gland neoplasm, Hard palate, adolescent, Pathology

INTRODUCTION

Clear cell carcinoma (CCC) of the salivary gland is a malignant tumor characterized by clear cytoplasm caused by glycogen and frequent fibrosis/hyalinization of the tumor stroma. CCC was first reported in 1994 as a low-grade malignant tumor of minor salivary glands [1]. This tumor was described as CCC, not otherwise specified in the third edition of the World Health Organization (WHO) classification of head and neck tumors published in 2005 [2]. In 2011, Antonescu *et al*. reported that the specific fusion gene t (12:22) (q13:q12)/EWSR1-ATF1 was detected in this tumor [3]. As a result, the fourth edition of the WHO classification, which was published in 2017, described that definitive diagnosis of CCC of the salivary gland can be obtained by detecting this fusion gene [4]. This tumor often occurs in minor salivary glands such as the tongue and palate. Because CCC is a low-grade malignancy, it is mainly treated by surgery. CCC predominantly affects women aged 40–70 years, but it is extremely rare in adolescents. In our experience, we performed surgery for a CCC arising from the palatal gland that developed in a 15-year-old patient and obtained good results. Herein, we present this rare case of CCC.

CASE REPORT

A 15-year-old female adolescent patient with a painless palatal swelling was referred to our hospital. She first noticed a tumor on her palate at age 9, but it was left untreated for 6 years because it does not show significant changes.

The patient had no remarkable medical and familial history. Her facial appearance was symmetric, and there was no hypoesthesia. Lymphadenopathy suggesting metastasis was not found in her cervical region. Intraoral examinations revealed an elastic hard swelling with redness in the left side of the hard palate. The size of the swollen area was 16 × 14 mm (Fig. 1).

Computed tomography (CT) revealed a well-defined mass with heterogeneous weak enhancement in the left side of the hard palate. In the CT bone window, the left palate showed compressive bone resorption because of the tumor, but there were no findings suggestive of invasion into the nasal floor (Fig. 2A, B). Because a salivary gland tumor of the palate was suspected, an incisional biopsy was performed. Histopathological examinations revealed clear tumor cells and eosinophilic cytoplasm, surrounded by fibro-collagenous stroma under the mucosa.

In the immunohistochemical study, tumor cells were positive for cytokeratin (CK) AE1/AE3 and negative for CD68, HMB-45, and S-100. It was found to be an epithelial tumor, but no definitive diagnosis including malignant tumor was obtained. Therefore, an excisional biopsy of the tumor including the periosteum with bone preservation was performed (Fig. 3A, B).

In the excisional biopsy specimen, histologically, well-defined tumor without capsule was located in the submucosa, but invasive growth was shown. Although we observed some salivary interlobular glands were

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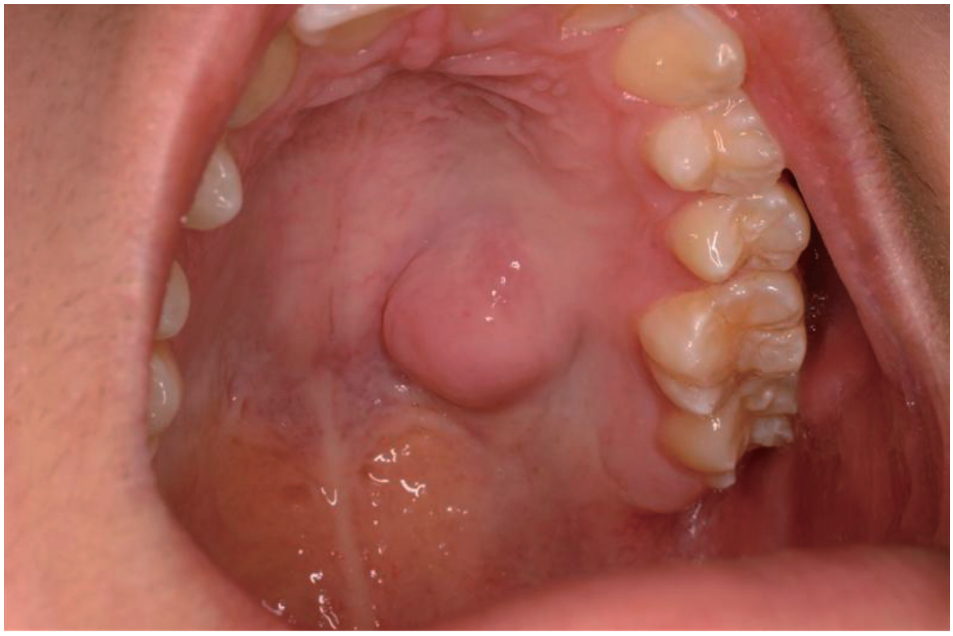

Fig. 1 Intraoral examinations revealed an elastic hard swelling with ulceration in the left side of the hard palate. The size of the swollen area was 16 × 14 mm.

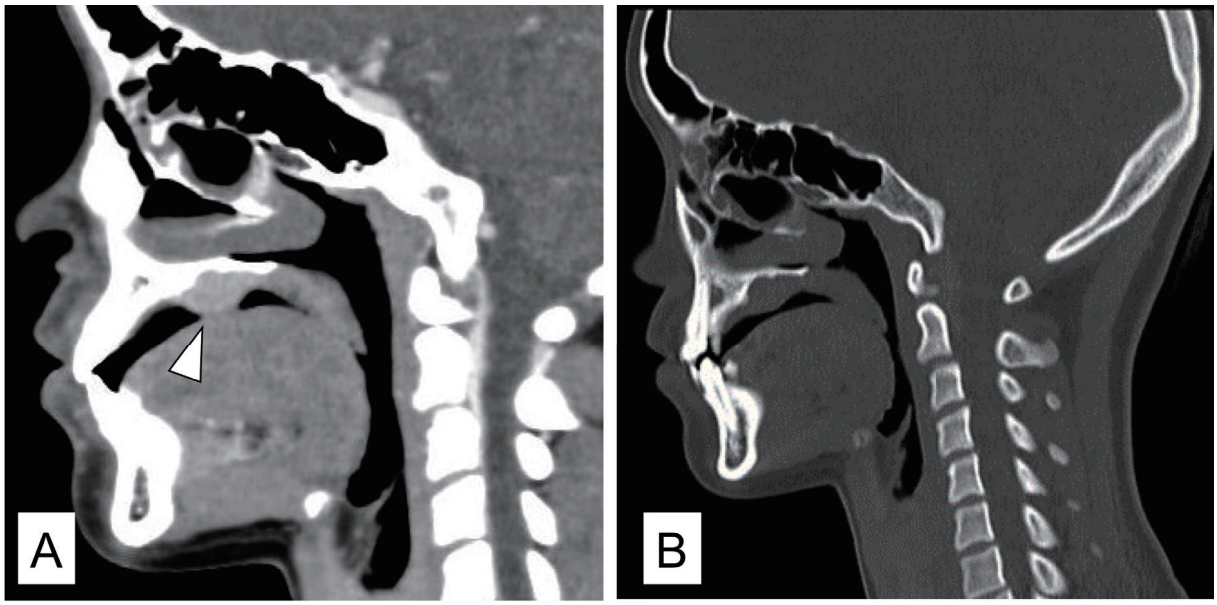

Fig. 2 A. Contrast-enhanced CT, sagittal view. A well-defined mass with heterogeneous weak enhancement in the left side of the hard palate (Arrow).
B. CT bone window, sagittal view. the left palate showed compressive bone resorption because of the tumor, but there were no findings suggestive of invasion into the nasal floor.

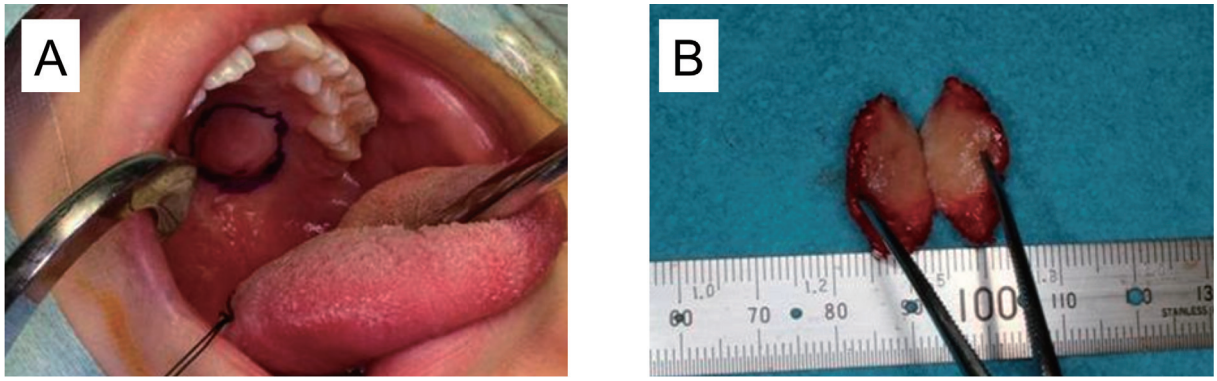

Fig. 3 A. An excisional biopsy of the tumor including the periosteum with bone preservation was performed.
B. The section showed a yellowish white and solid tumor with unclear boundaries.

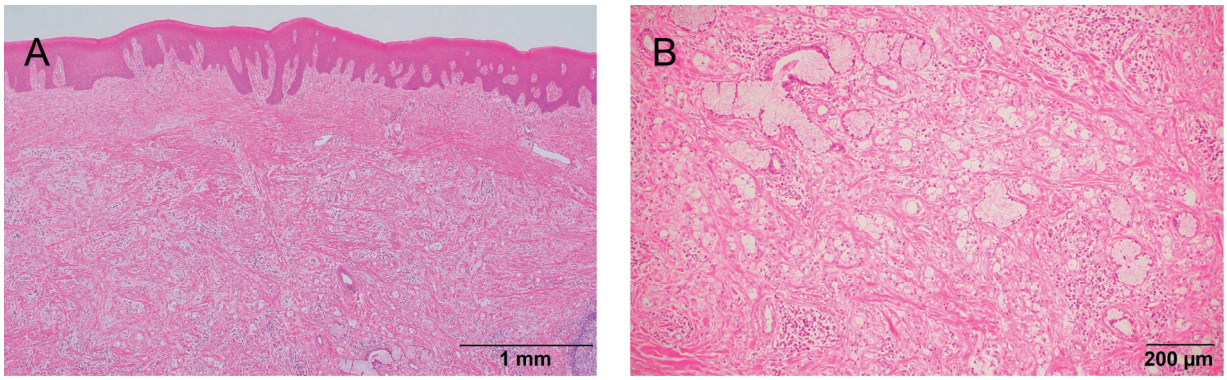

Fig. 4 A. He relatively well-defined tumor under the mucosa was unencapsulated and had grown infiltratively. The lobular structure of the salivary gland disappeared or was obscured by the invasive growth of the tumor.
B. Tumor cells were round/polygonal epithelial cells having clear or rich eosinophilic cytoplasm and arranged in trabecular, notochord, or solid nesting patterns.

replaced by the tumor, residual salivary ducts were holding in the tumor. Tumor cells tend to be small in size with clear or eosinophilic cytoplasm and grow nest or trabecular arrangement surrounded by hyalinized stroma. The nuclea atypia and mitosis was not remarkable (Fig. 4A, B).

Since the tumor cells expressed for PAS, and sensitive (negative) for Diastase-PAS, that revealed glycogen rich neoplasm without scant mucin production. The tumor was not continuously contact with the mucosal epithelium, but was accompanied by squamous metaplasia.

Immunohistochemically, the tumor cells expressed for keratin, AE1/AE3, CK19, p63, and were not expressed for S-100, smooth muscle actin (SMA), epithelial membrane antigen (EMA).

In addition, tumor counted by Mib-1 index (%) was approximately 1%.

Based on these findings, we concluded this neoplasm as glycogen rich clear cell tumor with low grade malignancy arising from minor salivary duct. However, we must exclude mucoepidermoid carcinoma, and metastatic clear cell carcinoma from other organ as the differential diagnosis. However, there was not so aggressive tumor with abundant mucin production such as mucoepidermoid carcinoma and there was no history of clear cell renal carcinoma in the present case, it was finally diagnosed as clear cell carcinoma arised from small salivary duct.

Since this tumor was malignant, systemic examinations were performed, but no metastases were found. However, the tumor was exposed at the margin of the surgical specimen; hence, additional excision including the maxilla was performed. An incision was made at the mucogingival junction, clearly showing the piriform aperture. Then, the mucosa of the nasal floor was peeled off and lofted up from the piriform. The maxilla in contact with the tumor was resected using ultrasonic bone cutting instrument (Piezosurgery®, Mectron s.p.a., Carasco, Italy) and the exposed mucosal surface was covered with the tie-over method. Thereafter, the surface of the wound formed epithelialization and healed without forming a fistula (Fig. 5A–C). Surgical specimens revealed no evidence of residual tumor, and no adjuvant treatment was performed. Five years after the treatment, no local recurrence or metastasis has been observed.

DISCUSSION

CCC (or previously called hyalinized CCC) was first reported in 1994 as a low-grade malignant tumor of minor salivary glands [1]. Initially, this tumor was diagnosed by excluding similar diseases. In the present case, most of the CCCs had hyalinization, but this was not always present. The incidence of CCC is extremely low, which accounts for 0.3%–1.5% of all salivary gland tumors [5–12]. CCC of the salivary glands is often recognized as a painless mass. It is often well-defined, localized, and grows slowly. In this case, the patient was aware of a palatal tumor since age 9, but the tumor was not treated for 6 years because it did not show significant changes.

CCC of the salivary glands rarely developed in young people, and minor cases have been reported so far, that is, in a 17-month-old boy with CCC of the tongue and a 15-year-old male adolescent with a CCC of the larynx [13, 14]. The presented case is the third.

Fang *et al.* analyzed salivary gland tumors of pediatric patients and reported that they often occur in major salivary glands such as the parotid and submandibular glands [15]. Most of these tumors were benign, such as pleomorphic adenoma, and thus far, only 17 cases of malignant tumors of major salivary glands were reported [15]. Furthermore, 47% of these malignant tumors were mucoepidermoid, and there was no CCC [15].

Histologically, CCC is unencapsulated and infiltrative with solid sheet, nesting, cord, trabecular, and single-cell growth patterns. Perineural and bone invasions are common. Ducts and gland-like spaces can be seen. Most of the cases are characterized by sclerotic or hyalinized stroma surrounding the tumor nests juxtaposed to variable fibrocellular myxoid stroma. The tumor cells are polygonal, with distinct cell borders and lightly eosinophilic to clear cytoplasm. CCC may also show overt squamous and even mucinous differentiation. Intracytoplasmic glycogen that gives a diastase-sensitive PAS reaction is present in CCC. The tumor may also show punctate or even overt intracytoplasmic mucicarmine staining patterns [1]. Immunohistochemically, CCCs are positive for epithelial markers such as CKs (CK5, CK7, CK8, CK14, and CK19), EMA, carcinoem-

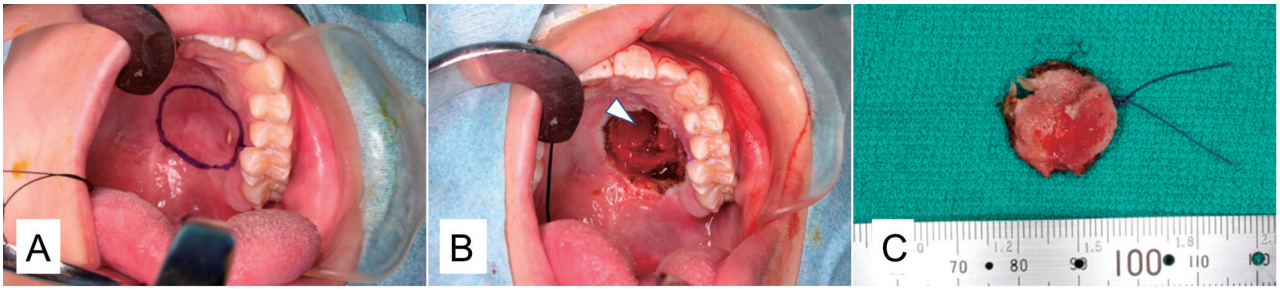

Fig. 5 A. Set up an incision line including Surgical safety margin.
B. Excised including maxilla, but nasal floor mucosa is intact (Arrow).
C. Deep side of tumor. Macroscopically, maxillary bone does not show tumor invasion.

bryonic antigen, and p63 [16, 17]. It was noted to be negative for other myoepithelial markers such as vimentin, S-100 protein, smooth-muscle actin, muscle-specific actin, calponin, and glial fibrillary acidic protein [18]. These features differentiate the carcinoma from oral and metastatic clear cell mimics, particularly myoepithelial carcinoma and metastatic renal cell carcinoma [16, 17]. Ki-67 proliferative index was low in most cases, reflecting the indolent nature of the tumor [18]. In the present case, these characteristics are also observed, prompting the diagnosis of CCC of the salivary gland. Salivary gland tumors that need to be differentiated from CCC include metastatic renal cell carcinoma, clear cell odontogenic carcinoma, mucoepidermoid carcinoma, epithelial-myoepithelial carcinoma, acinic cell carcinoma, calcifying epithelial odontogenic tumor, and clear cell variants of squamous cell carcinoma. CCC was reported to show consistent EWSR1-ATF1 gene fusion [3].

Although this case was a typical CCC of the salivary gland, the detection of this fusion gene may be useful for differential diagnosis of this disease. In the fourth edition of the WHO classification of head and neck tumors, the presence of EWSR1-ATF1 fusion in (hyalinizing) CCC along with the distinctive morphologic appearance was effectively removed from the previous suffix of "not otherwise specified" [2, 19, 20]. Therefore, we think that future histopathological diagnosis may be further reclassified based on key molecular alterations.

Because CCC is a low-grade malignancy, it is mainly treated by surgery. In some reports, CCC cases were treated by radiotherapy and chemotherapy, but the usefulness of these therapies has not been established [5–7]. There have been reports of CCC with recurrence or metastasis over the long term [21]. Therefore, careful and regular follow-up with attention focused on both the local recurrence as well as the cervical lymph node and distant metastases is essential for the management of CCC. Using necessary equipment, such as CT and ultrasonography, we intend to closely follow-up this case in the future.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest associated with this manuscript.

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REFERENCES

1) Milchgrub S, Gnepp DR, Vuitch F, Delgado R, Albores-Saavedra J. Hyalinizing clear cell carcinoma of salivary gland. Am J Surg Pathol 1994; 18: 74–82.
2) Barnes L, Eveson JW, Reichart P, Sidransky D. World Health Organization classification of tumours. Pathology and Genetics of Head and Neck Tumours. Lyon: IARC Press, 2005.
3) Antonescu CR, Zhang L, Chang NE, Pawel BR, Travis W, Katabi N, *et al.* EWSR1-POU5F1 fusion in soft tissue myoepithelial tumors. A molecular analysis of sixty-six cases, including soft tissue, bone, and visceral lesions, showing common involvement of the EWSR1 gene. Genes Chromosomes Cancer 2010; 49: 1114–24.
4) El-Naggar AK, Chan KKC, Grandis JR, Takata T, Slootweg PJ. WHO Classification of Head and Neck Tumours, 4th Edition. Geneva; IARC Press, 2017.
5) Daniele L, Nikolarakos D, Keenan J, Schaefer N, Lam AK. Clear cell carcinoma, not otherwise specified/hyalinising clear cell carcinoma of the salivary gland: the current nomenclature, clinical/pathological characteristics and management. Crit Rev Oncol Hematol 2016; 102: 55–64.
6) Yang S, Zhang J, Chen X, Wang L, Xie F. Clear cell carcinoma, not otherwise specified, of salivary glands: a clinicopathologic study of 4 cases and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008; 106: 712–20.
7) Weinreb I. Hyalinizing clear cell carcinoma of salivary gland: a review and update. Head Neck Pathol 2013; 7: S20–S9.
8) Buchner A, Merrell PW, Carpenter WM. Relative frequency of intra-oral minor salivary gland tumors: a study of 380 cases from northern California and comparison to reports from other parts of the world. J Oral Pathol Med 2007; 36: 207–14.
9) Lukšić I, Virag M, Manojlović S, Macan D. Salivary gland tumours: 25 years of experience from a single institution in Croatia. J Craniomaxillofac Surg 2012; 40: e75–e81.
10) Wang XD, Meng LJ, Hou TT, Huang SH. Tumours of the salivary glands in northeastern China: a retrospective study of 2508 patients. Br J Oral Maxillofac Surg 2015; 53: 132–7.
11) Gao M, Hao Y, Huang MX, Ma DQ, Chen Y, Luo HY, *et al.* Salivary gland tumours in a northern Chinese population: a 50-year retrospective study of 7190 cases. Int J Oral Maxillofac Surg 2017; 46: e343–e9.
12) da Silva LP, Serpa MS, Viveiros SK, Sena DAC, de Carvalho Pinho RF, de Abreu Guimarães LD, *et al.* Salivary gland tumors in a Brazilian population: a 20-year retrospective and multicentric study of 2292 cases. J Craniomaxillofac Surg 2018; 46: 2227–33.
13) Uri AK, Wetmore RF, Iozzo RV. Glycogen-rich clear cell carcinoma in the tongue. A cytochemical and ultrastructural study. Cancer 1986; 57: 1803–9.
14) Nayak DR, Balakrishnan R, Rao RV, Hazarika P. Clear cell carcinoma of the larynx--a case report. Int J Pediatr Otorhinolaryngol 2001; 57: 149–53.
15) Fang QG, Shi S, Li ZN, Zhang X, Liu FY, Sun CF. Epithelial salivary gland tumors in children: a twenty-five-year experience of 122 patients. Int J Pediatr Otorhinolaryngol 2013; 77: 1252–4.
16) Lai G1, Nemolato S, Lecca S, Parodo G, Medda C, Faa G. The role of immunohistochemistry in the diagnosis of hyalinizing

clear cell carcinoma of the minor salivary gland: a case report. Eur J Histochem. 2008; 52:251–4.
17) Weinreb I. Translocation-associated salivary gland tumors: a review and update. Adv Anat Pathol. 2013; 20: 367–77.
18) Brandwein-Gensler M, Wei S. Envisioning the next WHO head and neck classification. 2014 Head Neck Pathol. 2014; 8: 1–15.
19) Antonescu CR, Katabi N, Zhang L, Sung YS, Seethala RR, Jordan RC, *et al*. EWSR1-ATF1 fusion is a novel and consistent finding in hyalinizing clear-cell carcinoma of salivary gland. Genes Chromosomes Cancer 2011; 50: 559–70.
20) Seethala RR, Stenman G. Update from the 4th Edition of the World Health Organization Classification of Head and Neck Tumours: Tumors of the Salivary Gland. Head Neck Pathol 2017; 11: 55–67.
21) Yamashita K, Kawakami F, Nakashima Y, Murakami K. Clear cellcarcinoma of the minor salivary gland: an autopsy case with multiple metastases 29 years after the initial surgery and a review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009; 107; 819–25.