

Epithelial-Myoepithelial Carcinoma of The Minor Salivary Glands: Report of Two Cases with Literature Review

Kohei Okuyama (✉ okuyamak.0429@gmail.com)

Tokyo Medical and Dental University <https://orcid.org/0000-0002-5616-902X>

Yasuyuki Michi

Tokyo Medical and Dental University

Yoshihisa Kashima

Tokyo Medical and Dental University: Tokyo Ika Shika Daigaku

Hirofumi Tomioka

Tokyo Medical and Dental University: Tokyo Ika Shika Daigaku

Hideaki Hirai

Tokyo Medical and Dental University: Tokyo Ika Shika Daigaku

Misaki Yokokawa

Tokyo Medical and Dental University: Tokyo Ika Shika Daigaku

Yuko Yamagata

Tokyo Medical and Dental University: Tokyo Ika Shika Daigaku

Takeshi Kuroshima

Tokyo Medical and Dental University: Tokyo Ika Shika Daigaku

Yuriko Sato

Tokyo Medical and Dental University: Tokyo Ika Shika Daigaku

Maiko Tsuchiya

Tokyo Medical and Dental University: Tokyo Ika Shika Daigaku

Kou Kayamori

Tokyo Medical and Dental University: Tokyo Ika Shika Daigaku

Tohru Ikeda

Tokyo Medical and Dental University: Tokyo Ika Shika Daigaku

Hiroyuki Harada

Tokyo Medical and Dental University: Tokyo Ika Shika Daigaku

Case report

Keywords: Epithelial-myoepithelial carcinoma, Minor salivary gland, Ki-67, Pleomorphic adenoma.

Posted Date: June 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-623888/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Epithelial-myoepithelial carcinoma (EMC) is a rare malignant salivary gland tumor, which is especially uncommon in the minor salivary glands (MSG). We report literature review of EMC of the MSGs with our experience of two cases. Case 1 is a 75-year-old woman with a hard elastic mass in the hard palate, sized 2.5×2 cm without ulceration. Incisional biopsy was suggestive of pleomorphic adenoma. Tumor resection was performed with adequate surgical margin. Case 2 is a 44-year-old woman with a mass in the hard palate, sized 1.8×1.6 cm without ulceration. Incisional biopsy was suggestive of pleomorphic adenoma or a low-grade salivary gland carcinoma and intraoral tumor resection was performed. Both have good postoperative courses and are alive with no evidence of local recurrence or metastasis at 25 and 10 months. The Ki-67 labeling index in Case 1 and 2 were 10.6 and 3.8 %. Considering that the anatomy, structure, and size of salivary glands are quite different from MSGs, EMCs of the MSG cannot be predicted similarly to EMCs of the major salivary glands. The present review with 18 cases revealed no consensus on treatment methods for MSG cases other than surgery.

Background

Epithelial-myoepithelial carcinoma (EMC) is a rare malignant salivary gland tumor that accounts for < 1% of all salivary gland epithelial neoplasms and approximately 2% of malignant salivary gland neoplasms [1, 2]. The mean age of patients with EMC at diagnosis is 60 years, and it shows a slight female predilection [3]. Most EMCs develop in the parotid gland, while some develop in the submandibular gland [1, 4]. In general, EMC is indicated by the recurrence rate of 30–50%, lymph node metastasis rate of 15–20%, and 5- and 10-year survival rates of 80–94% and 72–90%, respectively [1, 4–6]. However, these were evident in most of major salivary gland cases. The minor salivary glands (MSG) cases are an uncommon anatomic site for the origin of EMCs.

Histopathologically, it is characterized by a biphasic glandular arrangement of inner eosinophilic ductal epithelial cells and outer clear myoepithelial cells [1, 2]. However, several histologic variants of EMCs, such as sebaceous [5, 7], oncocytic/apocrine [8, 9], and double-clear [5, 10], have been described. In addition, some cases experienced high-grade malignancy, which is often associated with a poorer prognosis [1, 2, 5, 11–17]. Furthermore, other benign or malignant neoplasms can exhibit clear myoepithelial features, which render the differential diagnosis of EMCs further complicated [18].

Due to its rare occurrence, the clinicopathological features and optimal treatment strategies of EMCs of the MSGs have not been fully described, and the relevant literature mostly comprises case reports. Herein, we report two cases of EMC originating from the MSG, and review the relevant literature and assessed our cases.

Case Presentation

Case 1

A 75-year-old woman referred to our department with a complaint of an abnormal swelling on the hard palate for a few months. The patient did not have any history of specific underlying systemic disease or trauma. Intraoral examination revealed a hard, elastic mass in the right side of the hard palate, sized 2.5 × 2 cm and without ulceration. Histopathological analysis of the sample obtained from incisional biopsy was suggestive of pleomorphic adenoma (PA) of the hard palate. The patient refused excision; therefore, regular follow-up visits for monitoring the tumor had been performed. After a follow-up period of about 14 months, the tumor showed rapid growth. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed an internal non-uniformly enhanced tumor mass, which led to pressure absorption of the palatal bone but invasion of the sinus and nasal cavity was not evident. Although the imaging examinations could not indicate the significant findings of malignancy, it guided a presumptive diagnosis of malignancy, based on the intratumoral heterogeneity. The significant cervical adenopathy was not evident. After 1 year and 3 months from the first examination, tumor resection with adequate surgical margins through an intraoral approach was finally performed under general anesthesia. Intraoperatively, the tumor was resected including the surrounding gingiva and the periosteal, and a layer of the palatal bone was shaved off.

Case 2

A 44-year-old healthy woman presented at our department with a complaint of a swelling in the hard palate. It had been followed up by her regular dentist for 2 months, but the swelling was not improved. Intraoral examination revealed a hard, elastic mass in the right side of the hard palate, sized 1.8 × 1.6 cm and without ulceration. Histopathological analysis of the incisional biopsy sample was suggestive of PA or a low-grade salivary gland carcinoma of the hard palate. CT and MRI revealed an internal non-uniformly enhanced tumor mass, which led to pressure absorption of the palatal bone but invasion of the sinus and nasal cavity and significant cervical adenopathy were not evident. Thereafter, the treatment was restricted because of the SARS-CoV-2 infection pandemic in Japan. There was no evidence of rapid tumor growth or metastasis. After four months from the first examination, since the treatment restrictions were released, intraoral tumor resection was performed under general anesthesia. Similar to Case 1, the tumor was peeled off including the periosteal and a layer of the palatal bone was shaved off. Both patients have good clinical courses on surgical sites and are alive with no evidence of local recurrence or cervical lymph node / distant metastasis at 25 and 10 months after the surgery, respectively.

Microscopical findings

In our cases, a biphasic glandular structure consisting of glandular cavities with acidophilic vesicles and neoplastic myoepithelial cells with clear vesicles outside the cavities was observed under high magnification. IHC showed that the tumor was diffusely positive for AE1/AE3; neoplastic myoepithelial cells were positive for p63, S100, calponin, and α -smooth muscle actin (α -SMA), and glandular duct-forming cells were positive for epithelial membrane antigen (EMA). In Case 1, the tumor was diagnosed as EMC due to the active fission images and the high score of Ki-67 labeling index (10.6%) (Figure 1). In Case 2, although Ki-67 labeling index score was 3.8% and fission images were not frequent, as invasion

into the existing MSGs was evident (Figure 1), the tumor was diagnosed as EMC. Both cases were negative at the surgical margin.

Review of literature

We searched the PubMed database for English literature pertaining to EMCs of the MSGs using the keywords “epithelial-myoepithelial carcinoma” and “minor salivary gland” (www.ncbi.nlm.nih.gov/pubmed). Literature published between January 2000 and December 2020, with well-written description of disease condition, treatment, clinical course, histopathological analysis and findings including IHCs, and prognosis were considered eligible for inclusion. EMC cases in the floor of mouth were excluded because it was not clear if the primary site was the MSGs or the sublingual gland.

We identified 38 cases in 27 articles about EMCs in the MSGs. Of the 38 cases, 18 cases satisfied the above-mentioned inclusion eligibility. The details are summarized in Table 1 [3,19-29]. The cohort included 10 women and 8 men with a median age of 64 (range: 29–83) years. The distribution of the primary subsite was as follows: the hard or soft palate in 12 patients, buccal mucosa in 4, nasal cavity in 2, oropharynx and subglottis in 1 patient, respectively. Regarding the diagnosis, while only 3 cases (3/18 cases, 16.7%) were diagnosed as EMC by incisional biopsy, other cases were pathologically diagnosed by the whole tumor examination. The primary antibodies used to diagnose EMC were almost similar: cytokeratins (CK), EMA, S100 protein, p63, calponin, CD10, CD117, vimentin, SMA, glial fibrillar acid protein, and Ki-67, and appropriate positive and negative controls were employed. Ki-67 labeling index was calculated in 10 cases, and the median index value was 17.65% (range: 3.5-40) (Table 2). The tumor size ranged from 1 × 1 cm to 3.7 × 2.5 cm. The disease duration, from self-noticing the lesion for the first time to the first visit to the hospital, ranged from 1 month to 8 years. The median postoperative follow-up period was 18.0±21.2 months (range: 6–84). Adjuvant radiotherapy was performed in 5 cases (27.8%) with a positive surgical margin in 4 cases and a narrow margin in 1 case. One patient died due to local failure 48 months after tumor resection and postoperative radiotherapy.

Discussion And Conclusion

Some reports have highlighted the aggressive nature of EMCs. However, the prognosis indicated a low-grade malignancy of the tumor. Seethala et al. reported that 61 patients with EMC showed a local recurrence rate of 36.3%, distant metastasis rate of 5.2%, but 5-year survival rate of 93.5% is high [5]. Moreover, distant metastases to the lung, kidney, or brain were found in 8–10% of the cases [30]. Vazquez et al. reported that the 10-year survival rate of patients treated only by surgery was 93.2% and of those treated by surgery and adjuvant radiotherapy was 87.6% ($p = 0.4832$) [6]. They also reported that the > 4 cm lesion was one of the significant poor prognosticators [6]. However, above-mentioned reports included EMCs in the major salivary glands in a significant proportion, demonstrates the low credibility to apply directly for the MSG cases. Moreover, since the anatomy, structure, and the size of major salivary glands are different from MSGs [31], the size of the tumor also cannot be directly considered as a factor to

decide treatment for the MSG cases. In the present review, in fact, tumor size of MSG cases ranged from 1×1 to 3.7×2.5 cm: their sizes were all under 4 cm. Other, the disease duration (range: 1 month – 8 years) had a large width, means MSGs cases always cannot be found earlier than that in major salivary gland cases.

Regarding the treatment, the present review could not establish no consensus in the optimal treatment strategy of EMCs of the MSGs due to the limited number of the MSG cases. The role of radiotherapy in EMCs of the MSGs is not discussed adequately. Adjuvant radiotherapy is recommended in major salivary gland tumors where the primary tumor is > 4 cm in size or where the surgical margins are positive [33, 34, 35]. However, no significance in the survival has been reported in adjuvant radiotherapy [6]. The data from the present review cannot also validate radiotherapy ($n = 5$, Table 1). The role of adjuvant chemotherapy in EMC is also not well documented. According to Cerda et al., chemotherapy should be considered when irradiation is delivered in doses of 65 Gy or more in the patients with locoregional high-risk salivary gland tumors (close or positive margins) [36].

The diagnostic methods in EMCs of the MSG have basically remained unchanged: combined routine HE with multi-IHC staining (Table 2). Our cases were stained with almost the same variation. However, these accepted diagnostic methods do pose difficulties in the differential diagnosis of EMCs. On microscopic examination, PA is composed of epithelial and myoepithelial cells within variable stroma that may comprise of myxoid, fibrous, chondroid, mucinous, or even osseous/cartilage tissue: the biphasic pattern of epithelial and myoepithelial cells in this tumor resembles EMC. Most EMCs show a multinodular pattern with evidence of invasion and a classic arrangement of myoepithelial cells with clear cytoplasm that strikingly contrast with the inner low-cuboidal luminal cells. The biphasic structures of EMCs have an interface of a thickened, hyaline-like basement membrane, which is distinct from the chondromyxoid matrix intermingling with the outer myoepithelial cells in PAS staining [15]. Cases of an EMC arising in a PA have been described in the literature, and the diagnosis of malignancy in such cases is predicated on the presence of invasion [5, 37, 38]. According to Eneroth et al., the risk of malignancy in PA varies from 1.6 to 7.5% [39]. Our Case 1 might be this type. Also, an analysis of recurrent PAs indicated that 7.1% undergo malignant transformation and that the risk of malignancy increases with disease progression [40]. In general, carcinoma arising in a PA is difficult to diagnose because the mixed tumor component is often small and easily overlooked and the malignant component may be difficult to classify [41]. From this viewpoint, it can be deduced that the diagnostic accuracy of incisional biopsy is not high. In this review, only 3 cases (16.7%) could be diagnosed as EMC by incisional biopsy, indicated the limit of the microscopical diagnosis of EMC of the MSG using a part of small mass. In contrast, El Hallani et al. indicated that 80% of EMCs arising in a PA and the genetic profile of patients with EMCs varies between the absence or presence of preexisting PA and its cytogenetic signature [37]. Moreover, Nakaguro et al. and Urano et al. reported, since the IHC for RAS Q61R is highly sensitive and specific for detecting the HRAS Q61R mutation in EMC which has been reported to be frequent in and specific to EMC, the evaluation of RAS Q61R can be a useful tool to diagnose EMC [18, 42].

In conclusion, diagnosis of EMC of the MSG cases is still difficult, because the tumor is small and a mimicking tumor could be present. Additional other diagnostic methods (e.g., genomic analysis) may be helpful for an accurate presurgical diagnosis. The present review revealed no consensus on treatment strategy for EMC of the MSG other than surgical treatment. More MSG cases should be accumulated to establish accurate treatment approach and to find the prognosticator.

Abbreviations

EMC	Epithelial-myoepithelial carcinoma
MSG	Minor salivary gland
CT	Computed tomography
MRI	Magnetic resonance imaging
HE	Hematoxylin and eosin
IHC	Immunohistochemistry
CK	Cytokeratin
EMA	Epithelial membrane antigen
SMA	α -smooth muscle actin
PA	Pleomorphic adenoma

Declarations

Ethics approval and consent to participate:

This study followed the Declaration of Helsinki on medical protocol and ethics, and the regional Ethical Review Board of Tokyo Medical and Dental University approved the study (Permission no. D2015-600). Patient consent for publication was acquired.

Consent for publication:

The written informed consent to publish the personal and clinical details of the participant was obtained and a copy of the written consent is available for review by the Editor of this journal.

Authors' contributions

KO contributed to the conception and design of the study and wrote and edited the manuscript. KO, YM, YK, HT, HH, MY, YY, TK, YS, and HH contributed the treatment of cases. MT, KK, and TI contributed the pathological diagnosis of the cases. KO and HH critically revised the manuscript. All authors have read and approved the manuscript.

Availability of data and materials

Not applicable.

Conflicts of Interest Statement

The authors declare that they have no conflicts of interests.

Funding

No funding was received.

Acknowledgments

Not applicable.

References

1. Ellis GL, Auclair P. Epithelial-myoepithelial carcinoma. In: Tumors of the Salivary Glands (AFIP Atlas of Tumor Pathology: Series 4). Washington, DC: American Registry of Pathology; 2008. pp. 309–22.
2. Seethala R, Bell D, Fonseca I, El-Naggar A, Chan JK, Grandis J, Takata T, Slootweg P. Epithelial-myoepithelial carcinoma. In: WHO classification of head and neck tumours. Lyon: International Agency for Research on Cancer; 2017. pp. 309–22.
3. Sedassari BT, Dos Santos HT, Mariano FV, da Silva Lascane NA, Altemani A, Sousa S. Carcinoma ex pleomorphic adenoma of minor salivary glands with major epithelial-myoepithelial component: clinicopathologic and immunohistochemical study of 3 cases. *Ann Diagn Pathol.* 2015;19:164–8. <https://doi.org/10.1016/j.anndiagpath.2015.03.011>.
4. Gore MR. Epithelial-myoepithelial carcinoma: a population-based survival analysis. *BMC Ear Nose Throat Disord.* 2018;18:15. <https://doi.org/10.1186/s12901-018-0063-2>.
5. Seethala RR, Barnes EL, Hunt JL. Epithelial-myoepithelial carcinoma: a review of the clinicopathologic spectrum and immunophenotypic characteristics in 61 tumors of the salivary glands and upper aerodigestive tract. *Am J Surg Pathol.* 2007;31:44–57. <https://doi.org/10.1097/01.pas.0000213314.74423.d8>.
6. Vazquez A, Patel TD, D'Aguillo CM, Abdou RY, Farver W, Baredes S, Eloy JA, Park RCW. Epithelial-myoepithelial carcinoma of the salivary glands: an analysis of 246 cases. *Otolaryngol Head Neck*

- Surg. 2015;153:569–74. <https://doi.org/10.1177/0194599815594788>.
7. Shinozaki A, Nagao T, Endo H, Kato N, Hirokawa M, Mizobuchi K, Komatsu M, Igarashi T, Yokoyama M, Masuda S, Sano K, Izumi M, Fukayama M, Mukai K. Sebaceous epithelial-myoeplithelial carcinoma of the salivary gland: clinicopathologic and immunohistochemical analysis of 6 cases of a new histologic variant. *Am J Surg Pathol*. 2008;32:913–23. <https://doi.org/10.1097/PAS.0b013e318160852a>.
 8. Seethala RR. Oncocytic and apocrine epithelial myoeplithelial carcinoma: novel variants of a challenging tumor. *Head Neck Pathol* 7 suppl. 2013;1:77–84. <https://doi.org/10.1007/s12105-013-0461-0>.
 9. Seethala RR, Richmond JA, Hoschar AP, Barnes EL. New variants of epithelial-myoeplithelial carcinoma: oncocytic-sebaceous and apocrine. *Arch Pathol Lab Med*. 2009;133:950–9. <https://doi.org/10.5858/133.6.950>.
 10. Hussaini HM, Angel CM, Speight PM, Firth NA, Rich AM. A double-clear variant of epithelial-myoeplithelial carcinoma of the parotid gland. *Head Neck Pathol*. 2012;6:471–5. <https://doi.org/10.1007/s12105-012-0350-y>.
 11. Fonseca I, Soares JBarnes L, Eveson JW, Reichart P, Sidransky D. Epithelial-myoeplithelial carcinoma. In: *Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press; 2005. pp. 225–6.
 12. Alos L, Carrillo R, Ramos J, Baez JM, Mallofre C, Fernandez PL, Cardesa A. High-grade carcinoma component in epithelial-myoeplithelial carcinoma of salivary glands clinicopathological, immunohistochemical and flow-cytometric study of three cases. *Virchows Arch*. 1999;434:291–9. <https://doi.org/10.1007/s004280050344>.
 13. Roy P, Bullock MJ, Perez-Ordenez B, Dardick I, Weinreb I. Epithelial-myoeplithelial carcinoma with high grade transformation. *Am J Surg Pathol*. 2010;34:1258–65. <https://doi.org/10.1097/PAS.0b013e3181e366d2>.
 14. Cheuk W, Chan JC. Dedifferentiation in salivary gland carcinomas. *Am J Surg Pathol*. 2000;24:469–71. <https://doi.org/10.1097/00000478-200003000-00018>.
 15. Fonseca I, Soares J. Epithelial-myoeplithelial carcinoma of the salivary glands. A study of 22 cases. *Virchows Arch A Pathol Anat Histopathol*. 1993;422:389–96. <https://doi.org/10.1007/BF01605458>.
 16. Kusafuka K, Takizawa Y, Ueno T, Ishiki H, Asano R, Kamijo T, Iida Y, Ebihara M, Ota Y, Onitsuka T, Kameya T. Dedifferentiated epithelial-myoeplithelial carcinoma of the parotid gland: a rare case report of immunohistochemical analysis and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2008;106:85–91. <https://doi.org/10.1016/j.tripleo.2008.01.013>.
 17. Nagao T. “Dedifferentiation” and high-grade transformation in salivary gland carcinomas. *Head Neck Pathol* 7 suppl. 2013;1:37–47. <https://doi.org/10.1007/s12105-013-0458-8>.
 18. Urano M, Nakaguro M, Yamamoto Y, Hirai H, Tanigawa M, Saigusa N, Shimizu A, Tsukahara K, Tada Y, Sakurai K, Isomura M, Okumura Y, Yamaguchi H, Matsubayashi J, Nagao T. Diagnostic significance of HRAS mutations in epithelial-myoeplithelial carcinomas exhibiting a broad

- histopathologic spectrum. *Am J Surg Pathol*. 2019;43:984–94. <https://doi.org/10.1097/PAS.0000000000001258>.
19. Wang F, Li B, Wang Y, Shen Y, Yang H. Clinical and pathological analysis of 10 cases of salivary gland epithelial–myoepithelial carcinoma. *Med (Baltim)*. 2020;99:41. <https://doi.org/10.1097/MD.00000000000022671>.
 20. Lee YS, Ha SM, Paik SW, Yang HJ, Jeon HJ, Park DJ, Hwang CS. Epithelial-myoepithelial carcinoma originating from a minor salivary gland in the nasal septum: A case report and literature review. *Med (Baltim)*. 2020;99:e19072. <https://doi.org/10.1097/MD.00000000000019072>.
 21. Palaniappan R, Chandran J, Purushothaman D, Nandhagopal V. Epithelial myoepithelial carcinoma of the hard palate: A case report with a review of the literature. *EMJ Oncol*. 2019;7:63–7.
 22. Tsuji T, Kitada H, Abe S, Ikeda H, Nakayama E. Epithelial–myoepithelial carcinoma of a minor salivary gland in the buccal mucosa. *Oral Radiol*. 2016;32:130–5.
 23. Oh HJ, Do NY, Kee KH, Park JH. Epithelial-myoepithelial carcinoma arising from the subglottis: a case report and review of the literature. *J Med Case Rep*. 2016;10:45. <https://doi.org/10.1186/s13256-016-0824-8>.
 24. Lima FJ, Porto DE, Cavalcante JR, Oka SC, Godoy GP. Epithelial-myoepithelial carcinoma of high grade transformation: The case report in the buccal mucosa. *Open Dent J*. 2012;6:111–7. <https://doi.org/10.2174/1874210601206010111>.
 25. Angiero F, Sozzi D, Seramondi R, Valente MG. Epithelial-myoepithelial carcinoma of the minor salivary glands: immunohistochemical and morphological features. *Anticancer Res*. 2009;29:4703–9.
 26. Teppo H, Paronen I. Epithelial-myoepithelial carcinoma in minor salivary gland of the hard palate. *J Craniofac Surg*. 2008;19:1689–91. <https://doi.org/10.1097/SCS.0b013e318189723a>.
 27. Yamanegi K, Uwa N, Hirokawa M, Ohyama H, Hata M, Yamada N, Ogino K, Toh K, Terada T, Tanaka A, Sakagami M, Terada N, Nakasho K. Epithelial-myoepithelial carcinoma arising in the nasal cavity. *Auris Nasus Larynx*. 2008;35:408–13. <https://doi.org/10.1016/j.anl.2007.10.001>.
 28. Inoue Y, Nomura J, Hashimoto M, Tagawa T. Epithelial-myoepithelial carcinoma of the palate: A case report. *J Oral Maxillofac Surg*. 2001;59:1502–5. <https://doi.org/10.1053/joms.2001.28295>.
 29. Li CY, Shirasuna K, Ishibashi H, Nakayama H, Kiyoshima T. Epithelial-myoepithelial carcinoma arising in pleomorphic adenoma of the palate. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2000;90:460–5. <https://doi.org/10.1067/moe.2000.108099>.
 30. Friedrich RE, Donath K. Epithelial-myoepithelial carcinoma of the parotid gland with multiple distant metastases: a case report. *J Oral Maxillofac Surg*. 2000;58:690–4. [https://doi.org/10.1016/s0278-2391\(00\)90171-x](https://doi.org/10.1016/s0278-2391(00)90171-x).
 31. Shruthi H, Sumona P. Epithelial myoepithelial carcinoma- A rare case report. *Banglad J Med Sci*. 2012;11:129–33.
 32. Goodwin CR, Khattab MH, Sankey EW, Crane GM, McCarthy EF, Sciubba DM. Epithelial-myoepithelial carcinoma metastasis to the thoracic spine. *J Clin Neurosci*. 2016;24:143–6.

<https://doi.org/10.1016/j.jocn.2015.07.014>.

33. Hamper K, Brüggmann M, Koppermann R, Caselitz J, Arps H, Askensten U, Auer G, Seifert G. Epithelial–myoepithelial duct carcinoma of salivary glands: a follow-up and cytophotometric study of 21 cases. *J Oral Pathol Med*. 1989;18:299–304. <https://doi.org/10.1111/j.1600-0714.1989.tb00401.x>.
34. Corio RL, Sciubba JJ, Brannon RB, Batsakis JG. Epithelial–myoepithelial carcinoma of intercalated duct origin. A clinico-pathologic and ultrastructural assessment of sixteen cases. *Oral Surg Oral Med Oral Pathol*. 1982;53:280–7. [https://doi.org/10.1016/0030-4220\(82\)90304-8](https://doi.org/10.1016/0030-4220(82)90304-8).
35. Simpson RH, Clarke TJ, Sarsfield PT, Gluckman PG. Epithelial–myoepithelial carcinoma of salivary glands. *J Clin Pathol*. 1991;44:419–23. <https://doi.org/10.1136/jcp.44.5.419>.
36. Cerda T, Sun XS, Vignot S, Marcy PY, Baujat B, Baglin AC, Ali AM, Testelin S, Reyt E, Janot F, Thariat J. A rationale for chemoradiation (vs radiotherapy) in salivary gland cancers? On behalf of the REFCOR (French rare head and neck cancer network). *Crit Rev Oncol Hematol*. 2014;91:142–58. <https://doi.org/10.1016/j.critrevonc.2014.02.002>.
37. El Hallani S, Udager AM, Bell D, Fonseca I, Thompson LDR, Assaad A, Agaimy A, Luvison AM, Miller C, Seethala RR, Chiosea S. Epithelial-myoeplithelial carcinoma: frequent morphologic and molecular evidence of preexisting pleomorphic adenoma, common HRAS mutations in PLAG1-intact and HMGA2-intact cases, and occasional TP53, FBXW7, and SMARCB1 alterations in high-grade cases. *Am J Surg Pathol*. 2018;42:18–27. <https://doi.org/10.1097/PAS.0000000000000933>.
38. Hernandez-Prera JC, Skálová A, Franchi A, Rinaldo A, Poorten VV, Zbären P, Ferlito A, Wenig BM. (*In Press*) Pleomorphic adenoma: The great mimicker of malignancy. *Histopathol*. <https://doi.org/10.1111/his.14322>.
39. Eneroth CM. Histological and clinical aspects of parotid tumours. *Acta Otolaryngol Suppl* 188 Suppl. 1964;191:1–99.
40. Phillips PP, Olsen KD. Recurrent pleomorphic adenoma of the parotid gland: a report of 126 cases and a review of the literature. *Ann Otol Rhinol Laryngol*. 1995;104:100–4. <https://doi.org/10.1177/000348949510400203>.
41. Gerughty RM, Scofield HH, Brown FM, Hennigar GR (1969) Malignant mixed tumors of salivary gland origin. *Cancer* 24:471–486. [https://doi.org/10.1002/1097-0142\(196909\)24:3<471::aid-cncr2820240309>3.0.co;2-0](https://doi.org/10.1002/1097-0142(196909)24:3<471::aid-cncr2820240309>3.0.co;2-0)
42. Nakaguro M, Tanigawa M, Hirai H, Yamamoto Y, Urano M, Takahashi RH, Sukeda A, Okumura Y, Honda S, Tasaki K, Shimizu A, Tsukahara K, Tada Y, Matsubayashi J, Faquin WC, Sadow PM, Nagao T. (*In Press*) The Diagnostic Utility of RAS Q61R Mutation-specific Immunohistochemistry in Epithelial-Myoepithelial Carcinoma. *Am J Surg Pathol*. <https://doi.org/10.1097/PAS.0000000000001673>.

Tables

Due to technical limitations, table 1,2 is only available as a download in the Supplemental Files section.

Figures

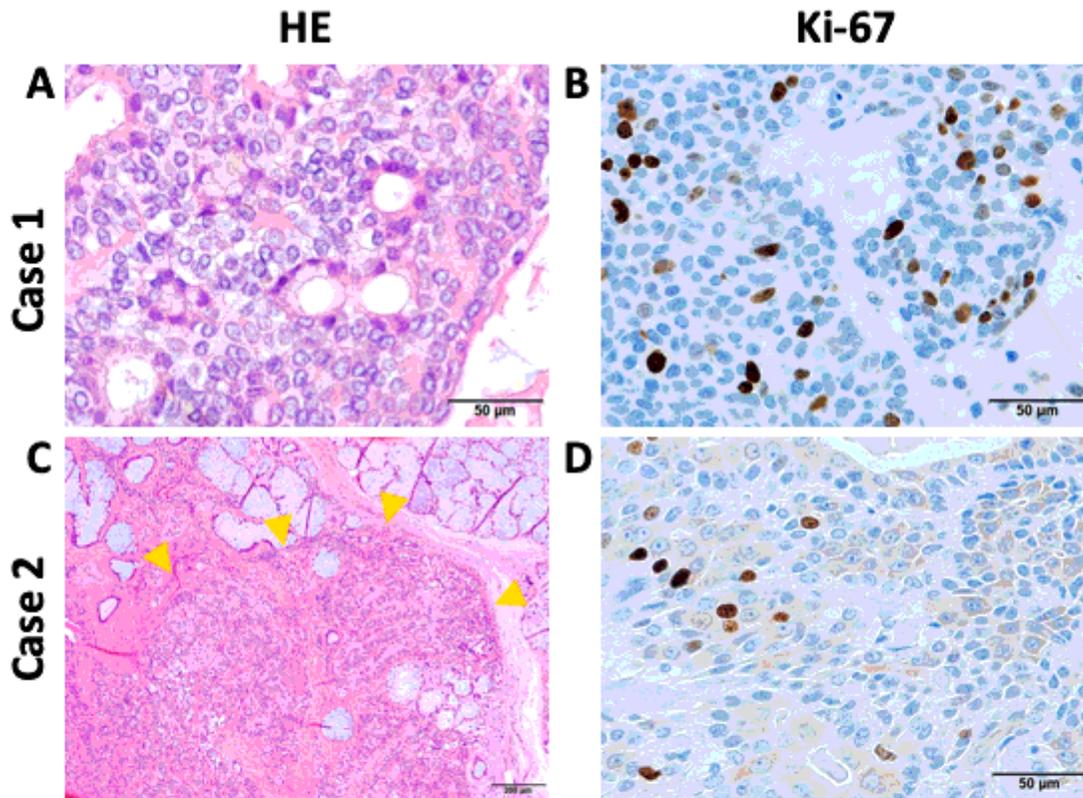


Figure 1

Figure 1

Hematoxylin and eosin and Ki-67 staining images. Morphological and immunohistochemical pattern of the present cases with epithelial-myoepithelial carcinoma. A: Hematoxylin and eosin staining showing a biphasic glandular structure consisting of glandular cavities with acidophilic vesicles and neoplastic myoepithelial cells with clear vesicles outside the cavities. B: Immunohistochemistry with Ki-67 showing active fission images and a high Ki-67 labeling index (10.6%). C, D: Hematoxylin and eosin staining showing a component with dense growth of acidophilic tumor cells and a component with cord-like or network-like growth of epithelioid-like neoplastic myoepithelial cells. Although Ki-67 labeling index was low (3.8%), apparent invasion of preexisting minor salivary glands can be identified (yellow arrowheads), which is a crucial finding of malignancy.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.jpg](#)
- [Table2.jpg](#)