Intraductal Papilloma Arising From the Minor Salivary Glands of the Larynx: A Case Report

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Abstract
It is rare for intraductal papilloma, a benign papillary tumor, to occur in the salivary glands. To our knowledge, intraductal papilloma occurring in the minor salivary glands of the larynx has not been reported. In this report, we describe a case of intraductal papilloma that occurred in the minor salivary glands of the larynx. A woman in her 30s presented with hoarseness and dyspnea since a year. Fiber-optic laryngoscopy revealed a submucosal tumor involving the left aryepiglottic fold and the left false vocal fold. Computed tomography and magnetic resonance imaging revealed a 17 × 15 × 10 mm3 mass with homogenous isodensity, with regular, well-defined margins located on the left aryepiglottic fold and the left false vocal fold. Surgical resection was performed, and subsequently a diagnosis of intraductal papilloma was made by pathologic evaluation. During the follow-up period of over 3 years, the lesion has not recurred. In conclusion, intraductal papilloma of the minor salivary glands should be considered in the differential diagnosis of laryngeal submucosal tumors.

Keywords
laryngeal tumor, intraductal papilloma, papilloma, minor salivary gland

Introduction
Ductal papillomas include intraductal papilloma, inverted ductal papilloma, and sialadenoma papilliferum. Among these, intraductal papilloma in the salivary gland is a rare benign papillary tumor.1 On the basis of histogenesis, intraductal papilloma is considered to originate from the salivary gland duct epithelium.2,3 These papillomas more frequently involve the minor salivary gland than the major salivary gland.4 Of the minor salivary glands, those of the lips, buccal mucosa, soft palate, hard palate, and ventral tongue have been reported to be involved.2,5–9 However, there has been no reported case of intraductal papilloma arising from the larynx. Herein, we report a case of the intraductal papilloma arising from the minor salivary glands in the larynx.

Case Report
A woman in her 30s was referred to our department from a previous clinic for the evaluation of a tumor in the larynx. The patient reported having hoarseness and dyspnea since a year. Fiber-optic laryngoscopy revealed a submucosal and rounded tumor involving the left aryepiglottic fold and the left false vocal fold (Figure 1). The superficial mucosa of the tumor was intact. The shape of the true vocal folds was normal and both vocal folds were mobile. Nevertheless, incomplete glottic closure was seen. In her neck, there were no palpable masses. The results of the laboratory tests were within normal limits. Computed tomography (CT) revealed a 17 × 10 mm2 homogeneous, isodense, and regular mass located on the left
aryepiglottic fold and the left false vocal fold. The lesion was contained within the laryngeal framework. Cartilage destruction was not evident.

Magnetic resonance imaging (MRI) revealed a mass with a similar shape as observed on CT. T1- and T2-weighted images showed an isointense tumor, whereas short T1 inversion recovery (STIR) images showed a $17 \times 15 \times 10$ mm$^3$ high-intensity unicystic, regular mass with well-defined margins located on the left aryepiglottic fold and the left false vocal fold (Figure 2).

Using the endoscopic procedure, a biopsy sample was obtained from the laryngeal mass. Microscopic examination revealed papillary proliferations with fibrovascular cores and minor salivary glands. The tumor was suspected of being a benign papilloma. Under general anesthesia, transoral video surgery (TOVS) was performed with a WEERDA Distending Video Operating Laryngoscope (Karl Storz). The tumor was completely resected in 2 parts using the tumor splitting approach. There were no complications associated with the surgical procedure.

Following the surgical procedure, the patient experienced a satisfactory course of recovery, and the patient’s symptoms improved. The patient has undergone regular postoperative follow-up as an outpatient once a month for the first 6 months, followed by twice a year for 3.5 years. During the follow-up, the lesion did not recur.

Histologically, the microscopic section showed a submucosal tumor, measuring a maximum of $13 \times 10$ mm$^2$, located within the duct of the minor salivary gland (Figure 3). The tumor cells were growing into the lumen of the submucosal cystic space. A higher power view of the tumor showed that the papillary tumor was composed of tall columnar epithelial cells with squamous metaplasia and fibrovascular cores. The cyst was lined by cuboidal and goblet cells. No tumor extension beyond the cyst wall was seen microscopically. The tumor cells showed no evidence of malignancy. A diagnosis of intraductal papilloma was made.

Sections from the paraffin-embedded tissue were examined immunohistochemically, using the primary antibodies listed in Table 1. The percentage of Ki-67-positive cells was recorded as the Ki-67 labeling index. The results of the immunohistochemical studies are summarized in Table 1. In this case, the tumor cells expressed cytokeratin (7, 20), CAM5.2, p63, and MUC1. The cells showed no immunoreactivity to cytokeratin (5 of 6), S100 protein, mammaglobin, vimentin, p53, HER2, CEA, α-SMA, MUC2, MUC4, MUC5AC, and M-GGMC-1.

Discussion

We report a case of the intraductal papilloma arising from the minor salivary glands of larynx. Histopathologically, intraductal papilloma is recognized as a luminal papillary proliferation of the duct epithelium that arises from a segment of the interlobular or excretory duct and causes unicystic dilatation.$^{10}$ In this case, the microscopic section did not show a typical unicystic tumor because the tumor was resected in 2 parts.
However, CT and MRI that were performed before biopsy showed a homogeneous mass with isodensity and regular, well-defined margins. In addition, fiber-optic laryngoscopy showed that the mucosa of the larynx was intact. It has been reported that the cyst wall in intraductal papilloma is lined by a layer of cuboidal or columnar cells, as found in our case. Therefore, a diagnosis of intraductal papilloma was made.

The literature shows that the main differential diagnoses for intraductal papilloma of the larynx include benign laryngeal tumors (neurofibroma, lipoma, adenoma, osteoma, chondroma,

### Table 1. Results of the Immunohistochemical Staining.

| Antigen          | Source       | Clonality | Dilution | Results                          |
|------------------|--------------|-----------|----------|----------------------------------|
| Cytokeratin 5/6  | DAKO         | Monoclonal| 1:200    | Negative                         |
| Cytokeratin 7    | DAKO         | Monoclonal| 1:2000   | Positive                         |
| Cytokeratin 20   | Leica        | Monoclonal| 1:75     | Positive                         |
| CAM5.2           | BD           | Monoclonal| Prediluted| Positive                        |
| S-100 protein    | Leica        | Polyclonal| 1:800    | Negative                         |
| Mammaglobin      | DAKO         | Monoclonal| 1:100    | Negative                         |
| Vimentin         | Leica        | Monoclonal| 1:800    | Negative                         |
| p40              | BIO CARE     | Monoclonal| 1:100    | Positive for squamous metaplasia |
| p53              | Thermo       | Monoclonal| 1:800    | Negative                         |
| p63              | DAKO         | Monoclonal| 1:200    | Positive for squamous metaplasia |
| HER2             | Roche        | Monoclonal| Prediluted| Negative                        |
| CEA              | Leica        | Monoclonal| 1:200    | Negative                         |
| α-SMA            | DAKO         | Monoclonal| 1:200    | Negative                         |
| MUC1             | Leica        | Monoclonal| Prediluted| Positive                        |
| MUC2             | Leica        | Monoclonal| Prediluted| Negative                        |
| MUC4             | SANTA CRUZ   | Monoclonal| 1:200    | Negative                         |
| MUC5AC           | Leica        | Monoclonal| Prediluted| Negative                        |
| M-GGMC-1         | Kanto Kagaku | Monoclonal| 1:20     | Negative                         |
| Ki-67 (MIB-1), % | Roche        | Monoclonal| Prediluted| 3.7                             |
paraganglioma, schwannoma), non-neoplastic lesions (laryngocele, ectopic thyroglossal duct cyst, laryngeal cyst), and malignant neoplasms. However, it is most important to distinguish intraductal papillomas from malignant and precancerous neoplasms, such as mammary analogue secretory carcinoma (MASC), mucoepidermoid carcinoma, and intraductal papillary mucinous neoplasm (IPMN).

It has been reported that MASC is immunohistochemically positive for S-100 protein, mammaglobin, and vimentin. In our case, the immunohistochemical analysis did not show immunoreactivity for vimentin, mammaglobin, and S-100. Mucoepidermoid carcinoma shows a multicystic, multinodular, and infiltrative growth pattern compared to that shown by intraductal papilloma. It has been reported that MUC1 and MUC5AC are more frequently expressed in salivary gland mucoepidermoid carcinoma than in normal salivary glands. However, previous studies have shown conflicting results of MUC1 expression in salivary gland mucoepidermoid carcinoma. In our case, these histopathological findings were not identified and the immunohistochemical analysis did not show immunoreactivity for MUC5AC. Additionally, the Ki-67 labeling index of the tumor was low (3%). Intraductal papillary mucinous neoplasm of the minor salivary gland was proposed as a new entity. It has been reported that the typical IPMN expresses MUC5AC, shows architectural atypia, and has no recognizable basal cell layer on immunohistochemical analysis. However, the typical pathological findings of IPMN were not observed in our case. Therefore, we excluded these malignant and precancerous neoplasms from the diagnosis.

The possible methods of preoperative evaluation of this lesion were biopsy, CT, and MRI. In this case, the biopsy sample was obtained using the endoscopic procedure because the submucosal tumor was located in the larynx. The microscopic examination of the biopsy specimen revealed that the mass was a benign papilloma. Although a confirmative diagnosis of intraductal papilloma should be made on the basis of histopathological findings of the surgical specimen, biopsy may be useful for the exclusion of malignancy and preoperative clinicopathological diagnosis of papillary tumor of the larynx.

According to a previous report, CT and MRI are helpful for evaluating the location, internal features, and behavior of the tumor; however, it is difficult to make a diagnosis of this tumor preoperatively through radiologic studies because intraductal papillomas are very rare and small. In previously reported cases of intraductal papilloma arising from major salivary glands, CT showed both cystic and solid features. Furthermore, MRI showed high intensity in T1-weighted images, and various levels of intensity in T2-weighted images of the lesion. In our case, the CT and MRI findings were not the same. Our CT images showed a solid tumor, while the MRI images showed both iso intensity in T1- and T2-weighted images. In the CT and MRI images, STIR images showed that the margins of the tumor were well defined, which was helpful for making the diagnosis. Therefore, STIR images may be especially useful for locating the tumor.

As no case of intraductal papilloma of the larynx has been reported previously, it is difficult to discuss the best treatment for this case. Mostly, intraductal papilloma is benign; however, cases of malignant intraductal papilloma have also been reported. Confirmative diagnosis of intraductal papilloma is mostly made on the basis of the histopathologic findings of the surgical specimen, even if a biopsy is performed. Hence, surgical resection can be the first-line treatment for intraductal papilloma of the larynx. It has been reported that the treatments for pleomorphic adenoma arising from the minor salivary glands in the larynx include pharyngotomy or transoral surgery under microdirect laryngoscopy, depending on its size and location. This treatment policy could have been applied in the present case. Because intraductal papilloma is a benign tumor, a less invasive surgery should be performed, as far as possible. Transoral surgery is a minimally invasive approach that requires no skin incision and limits the extent of tissue dissection, disruption of speech and swallowing muscles, blood loss, damage to the major neurovascular structures, and injury to normal tissue. In our case, we performed TOVS and there were no complications associated with the surgical procedure.

Only 4 cases of this tumor with adequate postoperative follow-up (2-2.5 years) have been reported. In all of them, there was no evidence of recurrence. Our patient has been followed up for 3.5 years, the longest period, and has undergone regular follow-up as an outpatient once a month for 6 months and twice a year for 3.5 years, until the time of this study. During the follow-up, endoscopic examination and CT showed no recurrence of the tumor. However, as a risk of recurrence of this tumor remains, long-term follow-up will be needed.

**Conclusion**

In summary, intraductal papilloma of the minor salivary glands should be considered as a differential diagnosis of laryngeal submucosal tumors. Although it is difficult to make a preoperative diagnosis of such a tumor by radiologic studies, STIR images of MRI may be useful in making a diagnosis. Surgical resection can be the first-line treatment for such a lesion; a less invasive surgical technique, such as transoral surgery, should be adopted. As there is a risk of recurrence, long-term follow-up is necessary.

**Authors’ Note**

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

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**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
References

1. El-Naggar AK, Chan JK, Grandis JR, Takata T, Slootweg PJ, eds. *World Health Organization Classification of Tumours. 4th ed.* International Agency for Research on Cancer; 2017.

2. Ishikawa T, Imada S, Ijuhin N. Intraductal papilloma of the anterior lingual salivary gland. Case report and immunohistochemical study. *Int J Oral Maxillofac Surg.* 1993;22(2):116-117. doi:10.1016/s0901-9077(05)80812-1

3. Nagao T, Sugano I, Matsuzaki O, Hara H, Kondo Y, Nagao K. Intraductal papilloma of the minor salivary glands. *Acta Cytol.* 1999;43(3):457-463. doi:10.1159/000331100

4. Brannon RB, Scuibba JJ, Giuliani M. Ductal papillomas of salivary gland origin: a report of 19 cases and a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001;92(1):68-77. doi:10.1067/moe.2001.115978

5. Abbey LM. Solitary intraductal papilloma of the minor salivary glands. *Oral Surg Oral Med Oral Pathol.* 1975;40(1):135-140. doi:10.1016/0030-4220(75)90357-6

6. Goldman RL. Melanogenic papillary cystadenoma of the soft palate. *Am J Clin Pathol.* 1967;48(1):49-52. doi:10.1093/ajcp/48.1.49

7. Kerpel SM, Freedman PD, Lummer H. The papillary cystadenoma of minor salivary gland origin. *Oral Surg Oral Med Oral Pathol.* 1978;46(6):820-826. doi:10.1016/0030-4220(78)90314-6

8. Neville BW, Damm DD, Weir JC, Fantasia JE. Labial salivary gland tumors. *Cancer.* 1988;61(10):2113-2116. doi:10.1002/1097-0142(19880515)61:10<2113::aid-cnrc2820611030>3.0.co;2-b

9. Sher L. The papillary cystadenoma of salivary gland origin. *Diastema.* 1982;10:37-41.

10. Barnes L, Eveson JW, Sidransky D, Reichart P, eds. Pathology and genetics of head and neck tumours. In: Kleihues P, Sobin LH, series ed. *World Health Organization Classification of Tumours.* International Agency for Research on Cancer; 2005.

11. Iguchi K, Urano M, Takahashi RH, et al. Cytological features of mammary analogue secretory carcinoma of salivary gland: fine-needle aspiration of seven cases. *Diagn Cytopathol.* 2014;42(10):846-855. doi:10.1002/dc.23139

12. Handra-Luca A, Lamas G, Bertrand J C, Fouret P. MUC1, MUC2, MUC4, and MUC5 AC expression in salivary gland mucoepidermoid carcinoma: diagnostic and prognostic implications. *Am J Surg Pathol.* 2005;29(7):881-889. doi:10.1097/01.pas.0000159103.95360.e8

13. Shemirani N, Osipov V, Kolker A, Khampang P, Kerschner J E. Expression of mucin (MUC) genes in mucoepidermoid carcinoma. *Laryngoscope.* 2010;120(1):167-170. doi:10.1002/lary.21164

14. Nakaguro M, Urano M, Ogawa I, et al. Histopathological evaluation of minor salivary gland papillary-cystic tumours: focus on genetic alterations in sialadenoma papilliferum and intraductal papillary mucinous neoplasm. *Histopathology.* 2020;76(3):411-422. doi:10.1111/his.13990

15. Agaimy A, Mueller SK, Bumm K, et al. Intraductal papillary mucinous neoplasms of minor salivary glands with AKT1 p. Glu17Lys mutation. *Am J Surg Pathol.* 2018;42(8):1076-1082. doi:10.1097/PAS.0000000000001080

16. Iguchi H, Yamane H, Nasako Y, Nishiura H, Nakamura A, Wakasa K. Intraductal papilloma in the parotid duct. *Acta Otolaryngol.* 2002;122(3):314-317. doi:10.1080/00016480275368231

17. Choi G, Choi CS, Choi JS, Choi JO. Intraductal papilloma of the parotid gland in a child. *Otolaryngol Head Neck Surg.* 2001;125(3):280. doi:10.1067/moh.2001.115978

18. Hara H, Oyama T, Omori K, et al. Fine needle aspiration cytology of an intraductal papilloma originating in a sublingual gland. A case report. *Acta Cytol.* 1999;43(3):457-463. doi:10.1159/000331100

19. Shiotani A, Kawaura M, Tanaka Y, Fukuda H, Kanzaki J. Papillary adenocarcinoma possibly arising from an intraductal papilloma of the parotid gland. *ORL J Otorhinolaryngol Relat Spec.* 1994;56(2):112-115. doi:10.1159/000276621

20. Tateya I, Shiotani A, Satou Y, et al. Transoral surgery for laryngeal cancer – The paradigm shift of the head and cancer treatment. *Auris Nasus Larynx.* 2016;43(1):21-32. doi:10.1016/j.anl.2015.06.013

21. Sawaisubashi M, Tuda K, Tokunaga O, Shin T. Pleomorphic adenoma of the larynx: a case and review of the literature in Japan. *Otolaryngol Head Neck Surg.* 1997;117(4):415-417. doi:10.1016/S0194-5998(97)0137-221

22. Sun S, Wang P, Wang Y, Su W, Wang F, Yang H. Intraductal papilloma arising from the accessory parotid gland: a case report and literature review. *Medicine (Baltimore).* 2018;97(20):e10761. doi:10.1097/MD.0000000000010761