# Low-grade cribriform cystadenocarcinoma of the palatal gland: A case report

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**Abstract.** Low-grade cribriform cystadenocarcinoma (LGCCC) is a malignant salivary gland tumor. LGCCC occurs rarely, with the parotid gland being the most commonly afflicted site. Few cases arise in other sites. The present study reports a case of LGCCC that occurred at the palatal gland of the hard palate. A 56-year-old female was referred to Saitama Medical University Hospital (Moroyama, Saitama, Japan) due to an intraoral mass. Since cytological examination and biopsy led to a diagnosis favoring a neoplasm, but with uncertain malignant potential, the tumor was resected with a safe surgical margin. The specimen was thoroughly examined. Microscopically, there was a well-demarcated, unilocular cyst with the lumen lined by tumor cells. The tumor cells were arranged in tubular, cribriform and solid structures in the area of the intracystic mass lesions. Nuclear atypia was inconspicuous, although mitotic figures were observed throughout the tumor. Neither local nor perineural invasion was present. On immunohistochemistry, the tumor cells were diffusely positive for S-100 protein. Myoepithelial markers, calponin and p63, highlighted the cells rimming the cystic mass. The final histopathological diagnosis was of LGCCC. The tumor was completely resected. At 1 year post-resection, the patient exhibited no recurrence or distant metastasis. LGCCC is regarded as clinically indolent. However, there is little literature available to aid with prognosis prediction due to the rarity of LGCCC cases. Thus, greater experience and longer follow-up periods are necessary to find the optimal/curative treatment for patients with LGCCC and to clarify the pathophysiology.

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*Abbreviations:* LGCCC, low-grade cribriform cystadenocarcinoma; PCVACC, papillary cystic variant of acinic cell carcinoma

*Key words:* palatal gland, salivary gland tumor, low-grade cribriform cystadenocarcinoma, salivary duct carcinoma

## Introduction

Salivary gland tumors produce a variety of histological patterns making tumor classification difficult (1).

Low-grade cribriform cystadenocarcinoma (LGCCC) is a malignant salivary gland originally reported as a variant of salivary duct carcinoma (2). However, LGCCC differs from typical salivary duct carcinomas with respect to the growth pattern, a lack of evident nuclear atypia, invasiveness to the surrounding tissues, and regional lymph node metastasis (2,3). Thus, the 2005 World Health Organization classification considers this neoplasm to be a variant of cystadenocarcinoma, mainly due to its cystic morphology, since no definite association has been found between salivary duct carcinoma and LGCCC (1). In this classification system, LGCCC is defined by its histological similarity to breast atypical ductal hyperplasia or low-grade ductal carcinoma *in situ* (1).

LGCCC is extremely rare and thus, the incidence rate of LGCCC remains unknown. The parotid gland is the most commonly involved site. Few cases arise at other sites, such as the submandibular gland and palate (2-7). The present study reports a case of LGCCC that occurred at the palatal gland of the hard palate. Written informed consent was obtained from the patient.

## Case report

A 56-year-old female was referred to Saitama Medical University Hospital (Moroyama, Saitama, Japan) from a local dentist in July 2013 due to the presence of an intraoral mass. The patient had noticed this mass 1 month previously.

The mass, measuring 20x18 mm in diameter, was located on the right side of the hard palate (Fig. 1A). The mass was soft and non-tender, and did not adhere to the oral mucosa. The surface showed normal mucosa. X-ray examination revealed no abnormality of the bone. Computed tomography

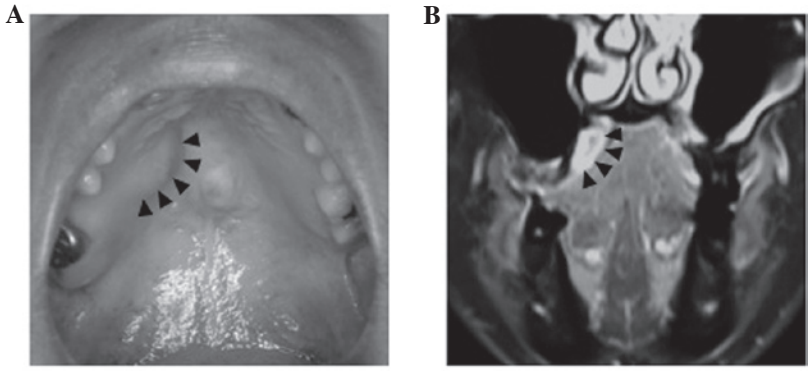


Figure 1. Intraoral findings at the first visit and magnetic resonance imaging view. (A) The mass was located on the right side of the hard palate. The surface showed normal mucosa (arrowheads). (B) Magnetic resonance imaging showed a high-intensity cystic mass with internal fluid on T1-weighted imaging of the right palatal region (arrowheads).

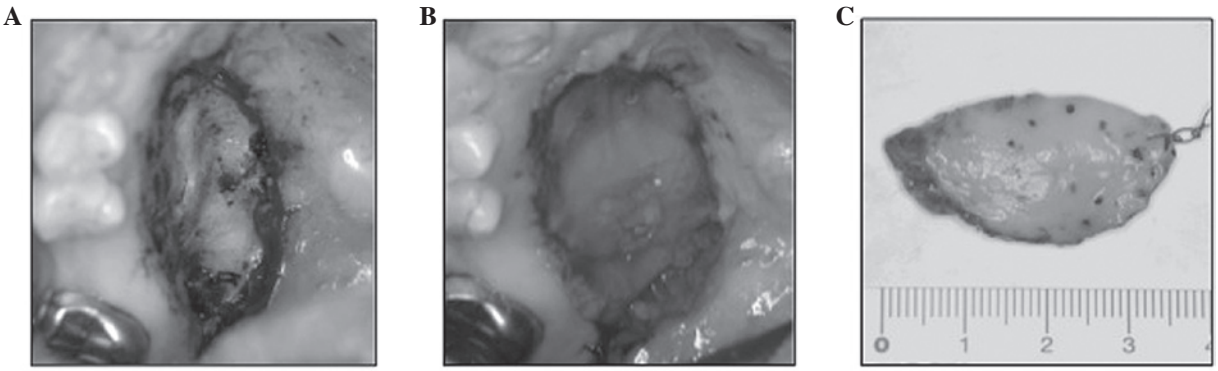


Figure 2. Tumor resection. (A) The tumor was resected with a safe surgical margin and dissected from the adjacent palatal bone. (B) The palatal bone was covered with a poly-glycolic acid sheet and fibrin. (C) Excised tissue, including the tumor.

could not detect any abnormalities at the palatal region, probably as the mass was too small to detect. Magnetic resonance imaging showed a high-intensity cystic mass with fluid internally on T1-weighted imaging of the right palatal region (Fig. 1B). Fine-needle aspiration (FNA) revealed that this mass contained brown-yellow fluid. Cytological examination and biopsy led to a diagnosis favoring a neoplasm, but with uncertain malignant potential. Thus, the tumor was resected with a safe surgical margin. The tumor was easily dissected from the adjacent palatal bone (Fig. 2A). Subsequent to resection, the palatal bone was covered with a poly-glycolic acid sheet and fibrin (Fig. 2B).

The surgical specimen measured 3.5 cm at its largest diameter (Fig. 2C). The specimen was thoroughly examined. Microscopically, there was a well-demarcated, unilocular cyst with the lumen lined by tumor cells (Fig. 3A). The tumor cells were arranged in tubular, cribriform and solid structures in the area of the intracystic mass lesions (Fig. 3B-D). Nuclear atypia was inconspicuous, although mitotic figures were observed throughout the tumor. Neither local nor perineural invasion was present. On immunohistochemistry, the tumor cells were diffusely positive for S-100 protein (Fig. 3E). Myoepithelial markers, calponin and p63, highlighted the cells rimming the cystic mass, confirming the intraductal nature of tumor (Fig. 3F). The final histopathological diagnosis was of LGCCC.

The tumor was completely resected, and 1 year later, the patient exhibited no recurrence or distant metastasis.

## Discussion

To date, there have been 12 published studies reporting a total of 39 cases of LGCCC (2-5,7-14). Characteristics of the reported cases together with the present case are summarized in Table I. From the literature, it is evident that LGCCC commonly occurs among older patients (median age, 60.73 years), with a female predominance (females:males, 23:16; gender was unreported in 1 case). A total of 36 tumors (90%) arose from the parotid glands, including the intraparotid lymph node and accessory parotids. The remaining 4 cases arose in the palate and submandibular gland, suggesting that the present case, which also occurred in the palate, is an rare event. LGCCC is regarded as a low-grade malignant tumor with indolent clinical behavior. Due to this clinical indolence, the majority of cases were treated with tumor excision without radiotherapy. Among the cases with follow-up data available, no patient experienced recurrence of the tumor or succumbed due to the tumor (Table I) (7).

The differential diagnosis of LGCCC includes several salivary tumors, such as papillary cystic variant of acinic cell carcinoma (PCVACC) and other variants of cystadenocarcinoma (1). Indeed, in the present case, when five specialists of

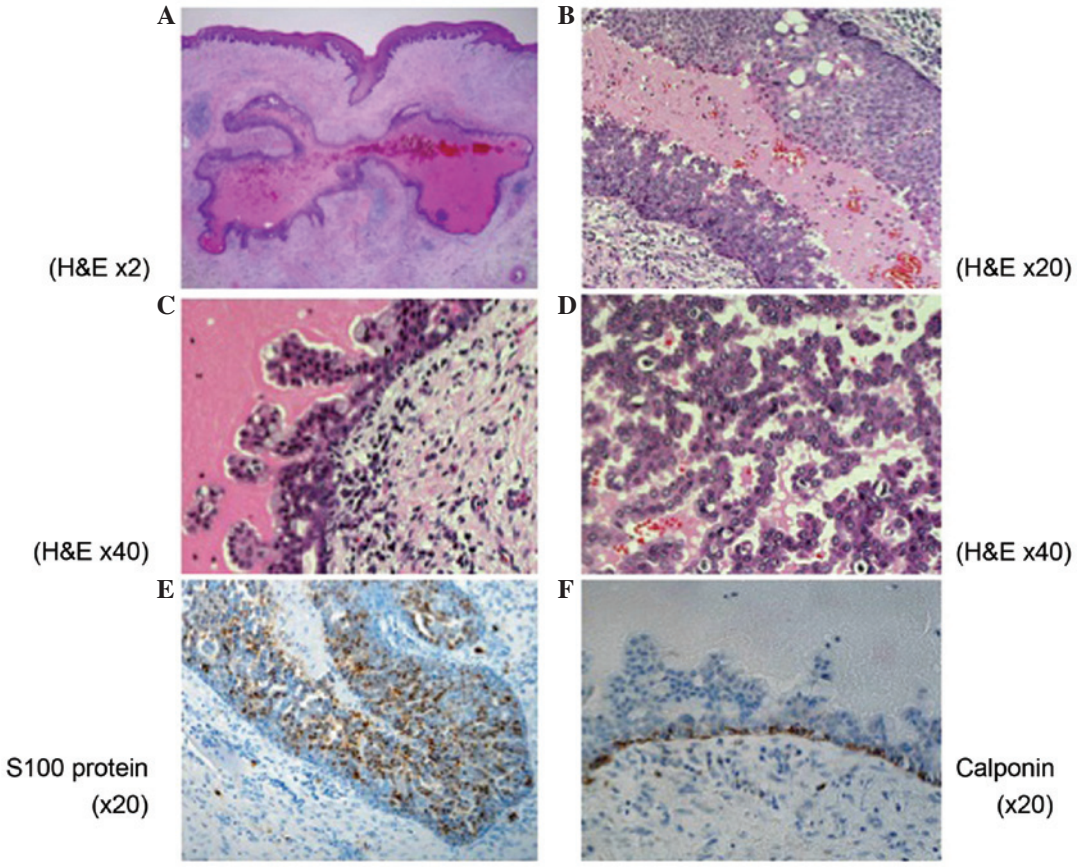


Figure 3. Histopathological findings. (A) Encapsulated tissues consisting of single cyst. The cystic lumens were lined by the tumor cells [hematoxylin and eosin (HE) staining; original magnification, x2]. (B-D) The tumor cells were arranged in (B and C) tubular, solid and (D) cribriform structures [HE staining; original magnification, (B and C) x20 and (D) x40]. (E and F) By immunohistochemistry, the tumor cells were diffusely positive for (E) S-100 protein and (F) the myoepithelial marker, calponin, highlighted the cells rimming the cystic mass (original magnification, x20).

salivary gland pathology were consulted, they listed PCVACC as a differential diagnosis for LGCCC. PCVACC contains vacuolated cells similar to the microvacuolated cells of LGCCC. However, the vacuoles of LGCCC are smaller, refractile and associated with a yellow-brown pigment, while areas with periodic acid Schiff-positive diastase-resistant fine cytoplasmic granules are found in PCVACC (1,15). In contrast to PCVACC (1,16), LGCCC also strongly expresses S-100 protein, as observed in the present case (Fig. 3E). Conventional cystadenocarcinoma differs from LGCCC by the lack of intraductal proliferation, golden brown pigment, solid cellular foci, and an overall resemblance to atypical hyperplasia or carcinoma *in situ* of the breast. Cystadenocarcinoma tends to be an invasive tumor, whereas LGCCC is usually confined to the cystic wall (1,15).

Necrosis of the central region of the proliferating tumor nests frequently occurs (1,17). Necrosis is usually uncommon in LGCCC, although in the present case, the central portion of the tumor exhibited necrosis. Biopsy or FNA, which was performed in the present study, may affect the tumor, and necrosis may occur in a tumor region.

The variability and histological complexity of salivary gland tumors does not allow an easy diagnosis (1,18). The variations appear to be based on the multi-differential potentiality of the salivary gland cells and their stem cells (19-21). Indeed, in the present case, the formation of a final diagnosis was difficult. Although the morphological and immunohistochemical features are comparatively well investigated, little else is known about the genetics or pathogenesis of these tumors (22). Recently, the association between the rearrangement of genes such as *PLAG1* and *HMGA2* with the prognosis of LGCCC have been investigated (22). Such studies may confer novel insights with regard to an understanding of LGCCC and the establishment of novel methods to diagnose the disease.

In conclusion, the present study reported a LGCCC that arose in the hard palate. Although LGCCC is regarded as clinically indolent, there is limited literature on prognosis prediction, since LGCCCs, and particularly those that arise in the palatal salivary gland, are rare tumors. Moreover, several cases have been reported of more aggressive and invasive carcinomas that are presumed to arise in LGCCC (4,6,22). Thus, greater experience and longer follow-periods are necessary to find an optimal/curative treatment for LGCCC and to clarify the pathophysiology.

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Table I. Characteristics of the reported cases and the present case of low-grade cribriform cystadenocarcinoma.

| Case | First author, year (ref.) | Age, years | Gender | Location | Size, cm | Treatment | Follow-up, months |
|---|---|---|---|---|---|---|---|
| 1 | Delgado *et al*, 1996 (2) | 58 | M | Parotid | 1.0 | Parotidectomy | Not mentioned |
| 2 | | 62 | F | Parotid | 0.7 | Parotidectomy | Not mentioned |
| 3 | | 32 | F | Parotid | 1.1 | Parotidectomy, Radiotherapy | NED, 144 |
| 4 | | 63 | M | Parotid | 1.3 | Parotidectomy | NED, 132 |
| 5 | | 74 | M | Parotid | 1.8 | Parotidectomy | NED, 72 |
| 6 | | 56 | F | Parotid | 1.0 | Parotidectomy | NED, 24 |
| 7 | | 42 | M | Parotid | 1.2 | Parotidectomy | NED, 24 |
| 8 | | 69 | F | Parotid | 4.0 | Parotidectomy | NED, 24 |
| 9 | | 69 | M | Parotid | 0.9 | Parotidectomy | Not mentioned |
| 10 | | 52 | F | Parotid | 0.8 | Parotidectomy, Radiotherapy | NED, 9 |
| 11 | Tatemoto *et al*, 1996 (8) | 58 | F | Palate | 1.0 | Not mention | NED, 30 |
| 12 | Brandwein-Gensler *et al*, 2004 (3) | 62 | F | 15 parotid, 1 submandibular gland | N/A | Not mentioned | NED, 12 |
| 13 | | 82 | M | | | | NED, 44 |
| 14 | | 78 | F | | | | NED, 17 |
| 15 | | 72 | F | | | | NED, 108 |
| 16 | | 93 | F | | | | NED, 24 |
| 17 | | 64 | F | | | | NED, 30 |
| 18 | | 66 | U | | | | NED, 62 |
| 19 | | 57 | F | | | | NED, 33 |
| 20 | | 63 | M | | | | Not mentioned |
| 21 | | 57 | F | | | | NED, 30 |
| 22 | | 63 | F | | | | Not mentioned |
| 23 | | 64 | M | | | | NED, 6 |
| 24 | | 62 | M | | | | NED, 132 |
| 25 | | 72 | M | | | | NED, 40 |
| 26 | | 76 | M | | | | NED, 24 |
| 27 | | 54 | M | | | | Not mentioned |
| 28 | Weinreb *et al*, 2006 (4) | 50 | F | Parotid | 2.0 | Parotidectomy | NED, 5 |
| 29 | | 73 | M | Parotid | 1.8 | Parotidectomy and supraomohyoid neck dissection | NED, 60 |
| 30 | | 67 | F | Parotid | 2.5 | Parotidectomy and chemotherapy and radiotion therapy | Not mentioned |
| 31 | Arai *et al*, 2009 (5) | 32 | F | Parotid | 2.8 | Parotidectomy | NED, 24 |
| 32 | Laco *et al*, 2010 (9) | 50 | F | Parotid | 1.5 | Enucleation of the tumor | NED, 24 |
| 33 | Nakazawa *et al*, 2010 (10) | 56 | F | Parotid | 3.0 | Parotidectomy | NED, 12 |
| 34 | Kusafuka *et al*, 2010 (11) | 38 | F | Parotid | 3.5 | Superficial lobectomy of parotid gland | NED, 8 |
| 35 | Weinreb *et al*, 2011 (12) | 59 | F | Parotid | 3.5 | Not mentioned | Not mentioned |
| 36 | Wang *et al*, 2013 (7) | 48 | M | Parotid | 2.0 | Parotidectomy | NED, 16 |
| 37 | | 58 | F | Parotid | 3.5 | Parotidectomy | NED, 7 |
| 38 | Projetti F *et al*, 2014 (13) | 57 | M | Parotid | 2.7 | Not mentioned | Not mentioned |
| 39 | Obokata A *et al*, 2013 (14) | 65 | M | Submandibular | 4.0 | Not mentioned | Notmentioned |
| 40 | Present case | 56 | F | Palate | 2.0 | resection of tumor | NED, 12 |
| Mean | | 59.21 | 23 F, 16 M, 1 U | | | | |

M, male; F, female; U, unknown; N/A, not available; NED, no evidence of disease.

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