Abstract: Low-grade cribriform cystadenocarcinoma (LGCCC) is a recently described rare tumor of the salivary gland; this tumor most frequently arises from the parotid gland. Here, we describe a case of LGCCC arising from a minor salivary gland in the buccal mucosa. A 72-year-old man had a small mass on the left buccal mucosa. The mass was completely resected, and the postoperative course was uneventful. Histopathologically, the tumor comprised a single cyst with intraductal proliferation. Based on these histopathological findings along with immunohistochemistry a diagnosis of LGCCC arising from a minor salivary gland was made.

Keywords: cytology; immunohistochemistry; low-grade cribriform cystadenocarcinoma; minor salivary gland.

Introduction

Low-grade cribriform cystadenocarcinoma (LGCCC) is a neoplasm of the salivary gland. According to the 2005 World Health Organization (WHO) classification it is defined as “a rare, cystic, proliferative carcinoma that resembles the spectrum of breast lesions from atypical ductal hyperplasia to micropapillary and cribriform low-grade ductal carcinoma in situ” (1). This tumor was initially described as a low-grade salivary duct carcinoma by Delgado et al. (2). Histopathologically, LGCCCs are unencapsulated and consist of single or multiple cysts with intraductal proliferation. Within the cystic areas, cells are typically arranged in a cribriform pattern and frequently form anastomosing, intracystic micropapillae lining the cavity that may contain fibrovascular cores (1). LGCCCs arise from the parotid gland, palate, submandibular gland, intraparotid lymph node, and accessory parotid glands (Table 1). Differential diagnoses of LGCCC include cystadenoma, cystadenocarcinoma, sclerosing polycystic adenosis, salivary duct carcinoma in situ, high-grade intraductal carcinoma, and papillary cystic variant of acinic cell carcinoma. Immunohistochemistry can help establish a definitive diagnosis (3,4). LGCCCs have a ductal phenotype with diffuse expression of S100 protein. Furthermore, myoepithelial markers, such as calponin or smooth muscle actin (SMA), highlight cells rimming the cystic spaces and ducts (1). To date, there have been five reports describing the cytomorphological findings of LGCCC (5-9). However, it is difficult to definitively diagnose LGCCC based on cytomorphological findings. To the best of our knowledge, we describe the first reported case of LGCCC arising from a minor salivary gland in the buccal mucosa and report the clinical, histopathological, and cytological findings of the tumor.
Case Report

A 72-year-old Japanese man visited our hospital with the complaint of a small lump on the left buccal mucosa. He first noticed the lesion 2 months previously. The lesion remained painless and had not changed in size. Intraoral examination revealed a well-circumscribed mass (8 mm × 8 mm) in the left buccal mucosa (arrowheads). The lesion was distant from the parotid papilla. On palpation, the lesion was hard, nontender, and mobile. T2-weighted magnetic resonance imaging showed a well-defined round mass with high signal intensity (Fig. 1b). Fine-needle aspiration (FNA) cytology of the lesion was performed, and it yielded cellular smears. Papanicolaou and May Giemsa staining of the smears revealed ductal epithelial cells arranged in a vague cribriform pattern. The cells had abundant cytoplasm and central bland nuclei (Fig. 2a-c). A few tumor cells had cytoplasmic vacuoles and peripherally dislocated nuclei (Fig. 2b). These cytological examinations indicated a diagnosis of adenoma with uncertain malignant potential.

A provisional diagnosis of a minor salivary gland tumor was established, and the mass was surgically excised along with the adjacent glandular tissue under local anesthesia (Fig. 3a). The postoperative course was uneventful for 2 years. At 1 year post-surgery, the patient underwent 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT); however, there was no evidence of recurrence or metastases.

Histopathologically, the tumor comprised a single cyst with intraductal proliferation. Minor salivary glands were observed in the vicinity of the tumor (*). The cells exhibited a cribriform architecture with Roman bridges and intracystic micropapillae. The cells were uniform and exhibited slight nuclear hyperchromasia and marginally increased nuclear/cytoplasmic ratio. Some tumor cells exhibited cytoplasmic microvacuoles. Some tumor cells contained lipofuscin-like yellow to brown pigments. Immunohistochemical findings were performed (Fig. 4). Tumor cells exhibited diffuse expression of S100 protein and mammaglobin and partial expression of GCDFP-15. Immunostaining for the myoepithelial markers, such as p63 and calponin, showed these cells rimming the cystic space.
from a minor salivary gland was established. Based on these findings, a diagnosis of LGCCC arising luminal cells, and sclerotic nodules were also absent. There was no admixture of myoepithelial cells with % (Fig. 4 d,e). The Ki-67 proliferation index was <9.

Immunohistochemically, the tumor cells showed partial expression of GCDFP-15 (Fig. 4 a-c). In addition, AE-3 (data not shown), and mammaglobin as well as diffuse expression of S100 protein, cytokeratin AE-1/ AE-3, and calponin, revealed cells rimming the cystic space and periodic acid-Schiff (PAS) staining and resistant to diastase treatment (data not shown). This material was positive for mucicarmine and periodic acid-Schiff (PAS) staining and resistant to diastase treatment (data not shown). In the cystic space, eosinophilic or amphophilic secretory material like yellow to brown pigments (Fig. 3 d,e). In the cystic space, eosinophilic or amphophilic secretory material like yellow to brown pigments (Fig. 3 d,e). Nuclear/cytoplasmic ratio. Some tumor cells exhibited nuclear hyperchromasia and a marginally increased nuclear/cytoplasmic ratio. Some tumor cells exhibited cystadenoma; however, according to previous clinicopathological reports, this tumor differs from typical salivary carcinoma; however, according to previous clinicopathological reports, this tumor differs from typical salivary duct carcinoma with regard to its growth pattern, lack of remarkable nuclear atypia, invasiveness into surrounding tissue, and metastasis to regional lymph nodes (2). To the best of our knowledge, 43 cases of LGCCC have been previously reported with no incidence of recurrence, metastasis, or mortality because of the tumor (Table 1). Although most LGCCCs were found to arise from the parotid gland, only two cases have been reported to arise from minor salivary glands of the hard palate. Therefore, clinicopathological features of LGCCC of the minor salivary gland remain unclear. We believe that the present case is the first documented case of LGCCC arising from

Table 1 Summary of low-grade cribriform cystadenocarcinoma

| No. | Author Year | Age | Sex | Anatomic location | Size (cm) | Histological type | Treatment |
|-----|-------------|-----|-----|-------------------|----------|-----------------|-----------|
| 1   | Delgado et al. 1996 | 58 | M   | Parotid gland (superficial lobe) | 1 | Single cyst | Superficial parotidectomy |
| 2   | Ide et al. 2004 | 62 | F   | Parotid gland | 0.7 | Multiple | Parotidectomy |
| 3   | Laco et al. 2010 | 50 | F   | Parotid gland (superficial lobe) | 1.1 | Multiple | Parotidectomy, radiotherapy |
| 4   | Ide et al. 2004 | 63 | M   | Parotid gland (superficial lobe) | 1.3 | Multiple | Parotidectomy |
| 5   | Ide et al. 2004 | 74 | M   | Parotid gland | 1.8 | Multiple | Parotidectomy |
| 6   | Ide et al. 2004 | 56 | F   | Parotid gland | 2 | Multiple | Parotidectomy |
| 7   | Ide et al. 2004 | 42 | M   | Parotid gland (superficial lobe) | 1.2 | Multiple | Parotidectomy |
| 8   | Ide et al. 2004 | 69 | F   | Intraparotid lymph node | 4 | Multiple | Parotidectomy |
| 9   | Ide et al. 2004 | 69 | M   | Parotid gland | 0.9 | Multiple | Parotidectomy |
| 10  | Ide et al. 2004 | 52 | F   | Parotid gland (deep lobe) | 0.8 | Multiple | Parotidectomy, radiotherapy |
| 11  | Tatamoto et al. 1996 | 58 | F   | Hard palate | 1 | Multiple | Resection of the tumor |
| 12  | Chen et al. 2000 | 83 | F   | Parotid gland (superficial lobe) | 2 | Multiple | Superficial parotidectomy |
| 13  | Weinreb et al. 2011 | 67 | M   | Parotid gland (superficial lobe) | 0.8 | Multiple | Superficial parotidectomy |
| 14  | Weinreb et al. 2011 | 72 | F   | Parotid gland | 0.7 | Multiple | Superficial parotidectomy |
| 15  | Weinreb et al. 2011 | 76 | M   | Parotid gland | 3 | Multiple | Superficial parotidectomy |
| 16  | Weinreb et al. 2011 | 78 | F   | Parotid gland | 0.7 | Multiple | Superficial parotidectomy |
| 17  | Weinreb et al. 2011 | 93 | F   | Parotid gland | 0.7 | Multiple | Superficial parotidectomy |
| 18  | Unknown | Unknown | Unknown | Parotid gland | 14 cases | Not mentioned | Not mentioned |
| 19  | Unknown | Unknown | Unknown | Intraparotid lymph node | 1 case | Not mentioned | Not mentioned |
| 20  | Unknown | Unknown | Unknown | Submandibular gland | 1 case | Not mentioned | Not mentioned |
| 21  | Ide et al. 2004 | 64 | F   | Parotid gland | 3 | Multiple | Simple excision |
| 22  | Weinreb et al. 2006 | 66 | M   | Parotid gland (superficial lobe) | 2 | Multiple | Simple excision |
| 23  | Weinreb et al. 2006 | 57 | F   | Parotid gland (superficial lobe) | 1.8 | Multiple | Simple excision |
| 24  | Weinreb et al. 2006 | 63 | F   | Parotid gland | 2.5 | Multiple | Parotidectomy / chemotherapy / radiation therapy |
| 25  | Weinreb et al. 2006 | 64 | M   | Parotid gland (superficial lobe) | 2.9 and 2.6 (two lesion) | Multiple | Parotidectomy |
| 26  | Weinreb et al. 2006 | 62 | F   | Parotid gland | 1.4 | Multiple | Parotidectomy |
| 27  | Weinreb et al. 2006 | 72 | M   | Parotid gland | 1.5 | Multiple | Parotidectomy |
| 28  | Weinreb et al. 2006 | 76 | M   | Parotid gland | 3 | Multiple | Parotidectomy |
| 29  | Weinreb et al. 2006 | 54 | M   | Parotid gland (superficial lobe) | 1.8 | Multiple | Parotidectomy |
| 30  | Weinreb et al. 2006 | 58 | M   | Palate | 3 | Multiple | Simple excision |
| 31  | Weinreb et al. 2006 | 50 | F   | Parotid gland (superficial lobe) | 2 | Multiple | Simple excision |
| 32  | Weinreb et al. 2006 | 67 | F   | Parotid gland | 2.5 | Multiple | Parotidectomy / chemotherapy / radiation therapy |
| 33  | Weinreb et al. 2006 | 32 | F   | Parotid gland (superficial lobe) | 1.5 | Multiple | Parotidectomy |
| 34  | Weinreb et al. 2006 | 32 | F   | Accessory parotid gland | 3 | Multiple | Parotidectomy |
| 35  | Weinreb et al. 2006 | 32 | F   | Parotid gland | 3.5 | Multiple | Parotidectomy |
| 36  | Weinreb et al. 2006 | 27 | M   | Accessory parotid gland | 2 | Multiple | Parotidectomy |
| 37  | Weinreb et al. 2006 | 27 | M   | Accessory parotid gland | 3 | Multiple | Parotidectomy |
| 38  | Weinreb et al. 2006 | 27 | M   | Accessory parotid gland | 3.5 | Multiple | Parotidectomy |
| 39  | Weinreb et al. 2006 | 39 | M   | Parotid gland | 2 | Multiple | Parotidectomy |
| 40  | Weinreb et al. 2006 | 59 | F   | Parotid gland | 3 | Multiple | Parotidectomy |
| 41  | Weinreb et al. 2006 | 59 | F   | Parotid gland | 0.7 | Multiple | Resection of the tumor |
| 42  | Weinreb et al. 2006 | 59 | F   | Parotid gland | 5.3 | Multiple | Parotidectomy |
| 43  | Weinreb et al. 2006 | 65 | M   | Submandibular gland | 4.2 | Multiple | Resection of the tumor / regional lymph node dissection |
| 44  | Weinreb et al. 2006 | 72 | M   | Minor salivary gland in the buccal mucosa | 0.8 | Single | Resection of the tumor |

Discussion

LGCCC is a rare neoplasm of the salivary glands and is listed in the current WHO classification as a variant of cystadenocarcinoma (1). Previously, this tumor has been reported as a low-grade variant of salivary duct carcinoma; however, according to previous clinicopathological reports, this tumor differs from typical salivary duct carcinoma with regard to its growth pattern, lack of remarkable nuclear atypia, invasiveness into surrounding tissue, and metastasis to regional lymph nodes (2). To the best of our knowledge, 43 cases of LGCCC have been previously reported with no incidence of recurrence, metastasis, or mortality because of the tumor (Table 1). Although most LGCCCs were found to arise from the parotid gland, only two cases have been reported to arise from minor salivary glands of the hard palate. Therefore, clinicopathological features of LGCCC of the minor salivary gland remain unclear. We believe that the present case is the first documented case of LGCCC arising from
minor salivary glands of the buccal mucosa. However, because the pathological features of LGCCC resemble those of breast cancer, such as adenoid cystic carcinoma (ACC) and other ductal carcinomas, there is a possibility that this tumor may have metastasized from the breast. However, no evidence of a breast tumor or metastasis was detected by FDG-PET-CT.

Histopathologically, LGCCC is unencapsulated and is composed of single or multiple cysts with intraductal proliferation of finely dispersed chromatin and small nucleoli. Although most previously reported cases of LGCCC demonstrated multiple cysts with intraductal proliferation, the present case was composed of a single cyst (Table 1). The correlation between this finding and the origin of LGCCC from a minor salivary gland remains unknown because the number of cases with LGCCC arising from minor salivary glands is limited. Thus, further investigation is required to clarify this correlation. On the other hand, this finding assists in distinguishing the present case from polycystic lesions, such as sclerosing polycystic adenosis.

The tumor had a cribriform pattern with sieve-like spaces similar to that observed in breast proliferations. Usually, these tumor cells display no significant nuclear and cytological atypia. Focal invasion into the surrounding tissue can be observed in approximately 23% LGCCCs (4). Perineural and/or vascular invasion and comedonecrosis are absent in this type of tumor, and these features were also absent in the present case.

Many superficial cells have PAS-positive/disastate-resistant microvacuoles and lipofuscin-like yellow to brown pigments (1,3). These are considered to be associated with hemorrhages, cholesterol clefts, and hemosiderin-laden macrophages deposited during cyst rupture (3).

Immunohistochemically, the tumor cells demonstrate diffuse expression of S100 protein in most cases. Previously, three cases of LGCCC have been reported to be negative for the S100 protein (10). Detection of myoepithelial markers, such as p63, CK5/6, CK14, and SMA, may confirm the presence of a continuous myoepithelial rim around most of the tumor structures and thus clarify the in situ nature of the neoplasm (3,4). Mammary analogue secretory carcinoma (MASC) is a newly described tumor of the salivary gland that is associated with the ETV6-NTRK3 genetic translocation. This tumor shows a microvacuolar appearance similar to that of LGCCCs and may have solid, cystic, or papillary architecture. Furthermore, the tumor cells demonstrate an expression of S100 protein and mammaglobin on immunohistochemical staining. These characteristics make it difficult to distinguish between LGCCC and MASC. However, a previous study has shown that most MASCs were negative for p63 and calponin, and no cases of MASC with an intraductal growth pattern have been described in the literature (3). Therefore, the presence of a complete myoepithelial layer around tumor nests is considered specific to LGCCCs compared to MASCs (3). Although we did not conduct molecular genetic tests for ETV6-NTRK3, the presence of a complete rim of myoepithelial cells around the tumor cell nests, indicating intracyctic or intraductal growth, is a specific feature of LGCCC that assists in distinguishing the present case from an MASC. The differential diagnosis of LGCCC also includes the conventional cystadenocarcinoma. The 2005 WHO classification of head and neck tumors considered LGCCC to be a variant of cystadenocarcinoma (1). Although both LGCCC and cystadenocarcinoma share a cystic appearance, cystadenocarcinomas are clearly infiltrative neoplasms that lack a cribriform architecture and exhibit the presence of non-neoplastic myoepithelial cells when stained for SMA, MSA, and other myoepithelial markers (4). In a recent review of LGCCC reported by Kuo et al. (4), there were no data supporting the continuous classification of LGCCC as a variant of the cystadenocarcinoma; therefore, considering that most LGCCCs are noninvasive...
neoplasms, the term “cribriform cystadenocarcinoma” should be replaced by “low-grade intraductal carcinoma” (4). The data in the present report also support this previous report.

Therapeutic management of LGCCC involves complete resection, and additional therapies, such as chemotherapy and radiotherapy, are not required (6). Because of its favorable outcome, differentiating between LGCCCs and other salivary gland tumors during preoperative FNA diagnosis is important for selecting appropriate treatment options (8). However, to date, there have been only five reports describing the cytomorphological findings of LGCCCs (6-9). Therefore, it is difficult to diagnose LGCCC based on cytomorphological findings. The findings from these reported cases as well as the present case are summarized in Table 2. These five cases shared the following cytomorphological findings: 1) ductal epithelial proliferation with tight connections; 2) mild nuclear atypia and minimal size variation; and 3) cytoplasmic vacuoles and squamoid or metaplastic changes of tumor cells. Based on cytomorphological features, the differential diagnosis of LGCCC includes salivary duct carcinoma, papillary cystic variant of acinic cell carcinoma, mucoepidermoid carcinoma, and ACC (6). It is easy to differentiate LGCCC from a conventional salivary duct carcinoma based on histopathological smears; histopathological smears of conventional salivary duct carcinoma usually exhibit moderate to markedly anaplastic cells and contain evidence of necrosis in the background. These findings were absent in all the previously reported cases of LGCCC (6-9). It may be considered that ACC has a similar cytology to LGGCC at low magnification. However, the cribriform architecture of LGCCC differs from that of ACC (7), and can be described as “less defined” or “more vague” compared to that of ACC because basaloid cells are not identified in the cribriform area of LGCCC (7). The papillary cystic variants of acinic cell carcinoma and mucoepidermoid carcinoma also share cytomorphological findings with LGCCC. In the present case, mucoepidermoid carcinoma can be ruled out because the cytomorphological samples were completely devoid of intermediate cells and a mucinous background (Fig. 2). Differentiating LGCCCs from the other salivary gland tumors through preoperative FNA is difficult; however, cytopathologists should consider the possibility that a cystic tumor exhibiting these findings could be an LGCCC. In this report, we described the third case report of an LGCCC arising from a minor salivary gland. This lesion can arise not only from major salivary glands but also from minor salivary glands. Further reports on cases of LGCCC are required to definitively establish the characteristics of this tumor, and we hope to encourage further reports on its cytomorphological features to contribute toward establishing cytologic criteria for diagnosing LGCCC.

Acknowledgments
The authors would like to thank Dr. H. Hayashi (Ogaki Municipal Hospital) for discussion on the cytological features of the LGCCC.

References
1. Gnepp DR, Brandwein-Gensler MS (2005) Low-grade cribriform cystadenocarcinoma. In: World Health Organization classification of tumours. Pathology and genetics of head and neck tumours. Barnes L, Eveson JW, Reichart P, Sidransky D eds, IARC Press, Lyon, 233.
2. Delgado R, Klimstra D, Albores-Saavedra J (1996) Low-grade salivary duct carcinoma. A distinctive variant with a low grade histology and a predominant intraductal growth pattern. Cancer 78, 958-967.
3. Wang L, Liu Y, Lin X, Zhang D, Li Q, Qiu X et al. (2013) Low-grade cribriform cystadenocarcinoma of salivary glands: report of two cases and review of the literature. Diagn Pathol 8, 28.
4. Kuo YJ, Weinreb I, Perez-Ordonez B (2013) Low-grade salivary duct carcinoma or low-grade intraductal carcinoma? Review of the literature. Head Neck Pathol 7, Suppl 1, S59-67.
5. Chen KT (2000) Cytology of salivary duct carcinoma. Diagn Cytopathol 22, 132-135.
6. Nakazawa T, Kondo T, Yuminomochi T, Nakazawa K, Ishii Y, Mochizuki K et al. (2011) Fine-needle aspiration biopsy of low-grade cribriform cystadenocarcinoma of the salivary gland. Diagn Cytopathol 39, 218-222.
7. Ko YS, Koo JS (2013) Cytomorphological findings and histological correlation of low-grade cribriform cystadenocarcinoma of salivary gland in fine-needle aspiration: a case study. Korean J Pathol 47, 592-595.
8. Jeong JY, Ahn D, Park JY (2013) Fine-needle aspiration cytology of low-grade cribriform cystadenocarcinoma with many psammoma bodies of the salivary gland. Korean J Pathol 47, 481-485.
9. Obokata A, Sakurai S, Hirato J, Sakamoto K, Takekoshi T, Aoki J (2013) Cytologic features of low-grade cribriform cystadenocarcinoma of the submandibular gland: a case report. Acta Cytol 57, 207-212.
10. Arai A, Taki M, Mimaki S, Ueda M, Hori S (2009) Low-grade cribriform cystadenocarcinoma of the parotid gland: a case report. Auris Nasus Larynx 36, 725-728.