Low-grade Intraductal Carcinoma of Salivary Gland
Report of 3 Cases With Marked Apocrine Differentiation

Ilan Weinreb, MD,*† Rosa Tabanda-Lichaucuo, MD,‡ Theodorus Van der Kwast, MD,§ and Bayardo Perez-Ordoñez, MD, FRCPC*†

Abstract: Low-grade intraductal carcinomas (LG-IDCs) of salivary gland are rare neoplasms that resemble atypical ductal hyperplasia or LG-IDCs of the breast. They have been referred to as “low-grade salivary duct carcinomas” or “low-grade cribriform cystadenocarcinomas.” Herein, we describe 3 additional cases of LG-IDCs, 2 were pure intraductal carcinomas, although 1 demonstrated increasing cytologic atypia and progression to an invasive adenosquamous carcinoma. The latter had been present for 7 years before demonstrating clinical and pathologic progression to a widely invasive malignancy. The intraductal component in all cases exhibited a remarkable degree of apocrine differentiation. The tumor cells were positive for AE1:AE3, Cam 5.2, high molecular weight keratin, CK7, CK19, BRST-2, and androgen receptors (ARs). S-100 was positive in 2 cases and negative in 1 case. The intraductal neoplastic cells were surrounded by myoepithelial cells positive for CK14, actins, calponin, high molecular weight keratin, and p63. All the tumors were negative for CK20, estrogen and progesterone receptors, Her2Neu, and p53. Extensive apocrine differentiation, expression of ARs, CK7, and CK19, and progression to a widely invasive carcinoma after a long clinical latency have not been reported in LG-IDCs previously. These tumors share some histopathologic features with salivary duct carcinoma including apocrine differentiation, and expression of ARs and BRST-2. The terms “low-grade salivary duct carcinomas” and “low-grade cribriform cystadenocarcinomas” should be abandoned in favor of LG-IDC of salivary gland, which better reflects their predominantly noninvasive, intraductal nature.

Key Words: parotid gland, low-grade intraductal carcinoma, low-grade salivary duct carcinoma, low-grade cribriform cystadenocarcinoma, apocrine carcinoma

Intraductal or in situ carcinomas (IDCs) of salivary gland are rare. Their initial description is attributed to Chen in 1983 with several subsequent case reports and small series.1,3,6,12,22,23 Recently, Cheuk and collaborators6 recognized that these tumors may exhibit low, intermediate, or high cytologic grade and proposed specific criteria for the diagnosis of pure ductal carcinoma in situ in salivary glands. These criteria include: (a) a tumor resembling mammary intraductal carcinoma with cribriform, micropapillary, solid, comedo, or clinging patterns; and (b) exclusion of an invasive component by extensive sampling or demonstration by immunohistochemistry of a basal or myoepithelial layer surrounding the intraductal epithelial nests.6

Another subject of controversy in salivary gland tumor pathology is the possible relation of conventional salivary duct carcinoma (SDC) and the so-called “low-grade SDC” (LG-SDC). In 1996, Delgado et al9 described 10 cases of a distinctive LG-parotid neoplasm with a predominantly intraductal pattern resembling atypical ductal hyperplasia or LG-intraductal carcinomas (LG-IDCs) of the breast. In view of some pathologic similarities to SDC but low cytologic grade, the authors proposed the term “LG-SDC”. They also concluded that LG-SDC was primarily in situ (intraductal) neoplasm.9 Despite these reports, the existence of salivary gland malignancies with an exclusive or predominant intraductal component has yet to gain widespread recognition. In fact, the 2005 World Health Organization Classification of Head and Neck Tumors has not specifically included IDCs in their classification of salivary gland neoplasms, instead it regarded LG-SDC as a variant of cystadenocarcinoma and bestowed on them the descriptive term of “LG-cribriform cystadenocarcinoma” (LG-CCC).2 We believe that the terms LG-SDC and LG-CCC should be replaced by LG-IDCs which better communicates its noninvasive, intraductal nature.

To further our understanding of LG-IDCs, we report 3 additional cases showing a marked degree of apocrine differentiation. We also describe their keratin and sex steroid receptor expression pattern, which have not been comprehensively studied previously. One case had been present for 7 year before developing sudden and rapid progression to a poorly differentiated adenosquamous carcinoma, a hitherto unreported occurrence in these tumors.
MATERIALS AND METHODS

All 3 surgical specimens were fixed in neutral-buffered formalin. Hematoxylin and eosin, Mayer mucicarmine, and periodic acid-Schiff (PAS) and PAS-D stains were performed in 3 to 4 μ thick sections of formalin-fixed paraffin-embedded tissue. Immunohistochemical stains were performed in sections from a representative paraffin block from each case using the ultrastreptavidin-HRP detection system (ID Labs Biotechnology, London, Ontario, Canada). Color development was performed using the NovaRed substrate kit (Vector Labs, Burlingame, CA). All the immunohistochemical studies, with the exception of androgen receptor, were performed in a Ventana stainer. The antibodies employed in this study are listed in Table 1.

CASE REPORTS

Case 1

A 50-year-old woman presented with a 5-month history of an asymptomatic right parotid mass with recent change in size. Clinical examination revealed a 2.0-cm mass in the right parotid. A fine needle aspiration biopsy revealed malignant cells and a superficial parotidectomy was performed. A follow-up magnetic resonance imaging 5 months after surgery revealed no recurrent disease.

Case 2

A 73-year-old man with a history of Parkinson disease presented with an asymptomatic mass involving the tail of the right parotid. The mass had been present for 9 months with no change in size. He had a superficial parotidectomy and supraomohyoid neck dissection with an unremarkable postoperative course. The surgical specimen demonstrated a parotid tumor measuring 1.8 × 1.3 × 1.0 cm. No lymph node metastases were present. He was alive and well with no recurrent disease 60 months after diagnosis.

Case 3

A 67-year-old woman presented with a 7-year history of a right parotid mass. The mass had been asymptomatic, but recently she developed paresthesias along the right ear and upper neck. The mass changed in size over the preceding 2 months. She had no facial nerve dysfunction or constitutional symptoms or signs. A preoperative magnetic resonance imaging showed a diffuse mass in the right parotid tail with involvement of skin and subcutaneous tissue and extension to the external auditory canal. She also had clinically palpable lymphadenopathy. A fine needle aspiration biopsy was diagnosed as showing a poorly differentiated carcinoma. Between her first appointment and her preoperative clinic 1 month later, she developed rapidly increasing paresthesias in the greater auricular nerve distribution. She underwent right total parotidectomy, with resection of the right sternocleidomastoid, accessory nerve and external jugular vein with facial nerve preservation. The surgical specimen revealed a multinodular mass with cystic and solid areas measuring 2.5 × 2.5 × 2.0 cm. Postoperative imaging revealed no residual neck disease and no lung metastases. She is currently receiving chemotherapy and radiation therapy.

RESULTS

Histopathologic Findings

Cases 1 and 2 were composed exclusively of a LG-intratumoral component whereas case 3 demonstrated a significant intraductal component together with a high-grade adenocarcinoma with lymph node metastases. The IDC in all the 3 cases had similar microscopic features and was composed of large cystic ducts of variable diameter admixed with smaller ducts showing cribriform architecture (Figs. 1A, C). The cysts were lined by a single layer or multilayered flat, low-cuboidal cells, polygonal, and columnar cells arranged in plaques, micropapillae with a “clinging” pattern, and so-called “Roman arches” (Figs. 1B, D). Case 2 also showed scattered foci of intracystic papillae with thin delicate fibrovascular cores (Fig. 1E). The cysts contained mucin or eosinophilic debris (Fig. 1F) but no comedonecrosis was present. The tumor cells possessed variable amounts of pale to brightly eosinophilic or granular cytoplasm (Figs. 1B–F) with many cells showing apical apocrine snouts and cytoplasmic vacuoles (Figs. 1D–F). Variable numbers of bright PAS-positive D-resistant eosinophilic cytoplasmic granules were also seen. The nuclei were oval or round and ranged from small to large with finely dispersed to vesicular chromatin with inconspicuous, small, or prominent nucleoli (Figs. 1E, F). A layer of flat, thin, or elongated myoepithelial cells beneath neoplastic ductal cells was visible at the periphery of ducts and cysts. This layer was only distinctively recognizable at high-power magnification.

The ducts with cribriform architecture exhibited a typical arrangement of peripheral cells with abundant cytoplasm and central small cells with dark nuclei (Fig. 1C). Case 2 demonstrated abundant psammoma bodies in the cribriform areas. Although the tumor cells demonstrated a wide size range, there was no significant cytologic atypia in cases 1 and 2, whereas case 3 demonstrated foci of increased nuclear atypia in the in situ component (Fig. 2A). All the 3 cases had low mitotic activity characterized by isolated mitotic figures in the
intraductal components. Foci of epithelial cells with brown lipofuchsin pigment were seen in case 2. Secondary changes including hemorrhage, abundant foam cells, cholesterol clefts, and hemosiderin were also present. Case 3 had in addition to the LG-intraductal component, an invasive adenosquamous carcinoma composed of large pleomorphic cells with abundant eosinophilic cytoplasm, which often had a glassy appearance (Fig. 2B). The tumor cells were arranged in nests, sheets, trabeculae, and single cell infiltrative growth pattern with extensive perineural invasion. Numerous foci demonstrated glandular and squamous differentiation with intercellular bridges (Figs. 2C, D) although no keratinization was identified. Interestingly, the invasive component was accompanied by a marked inflammatory infiltrate with numerous eosinophils (Figs. 2B–D). Metastatic adenosquamous carcinoma was present in multiple periparotid and cervical lymph nodes.

**Immunohistochemical Findings**

The immunohistochemical findings are summarized in Table 2. The intraductal component of all the 3 cases showed strong and diffuse staining of intraductal cells for AE1:AE3, Cam 5.2, CK7, CK19, and high molecular weight keratin (HMWK) (34βE12) (Figs. 3A–C). Patchy cytoplasmic staining for BRST-2 was also noted in the intraductal component of all the 3 cases (Fig. 3D). Calponin and CK14 clearly demonstrated a well-defined and continuous layer of myoepithelial cells surrounding cystic and cribriform spaces (Figs. 3E, F). This layer was incomplete in several foci in case 3 indicative of transition to invasive carcinoma. Although actins and p63
immunoreactivity were also present in this myoepithelial layer, the intensity of staining was weaker than seen with calponin and CK14. Case 2 showed diffuse and strong expression of S-100 (Fig. 4A), whereas case 1 exhibited patchy staining. Case 3 was negative. The IDC in all cases demonstrated strong nuclear expression of androgen receptors (ARs) (Fig. 4B) with the invasive component in case 3 being negative. The myoepithelial cells also lacked detectable ARs. The invasive carcinoma in case 3 was strongly positive for CK14, HMWK (Fig. 2E), and p63 (Fig. 2F). Patchy but strong staining for CK7, AE1:AE3, and Cam 5.2 was also observed. Unlike the intraductal component, the invasive carcinoma was negative for CK19. No staining for CK20, Her2Neu, estrogen and progesterone receptors, or p53 was noted in any of the lesions. An E-cadherin stain showed strong staining of the intraductal and invasive components of case 3.

**DISCUSSION**

We describe 3 cases of LG-IDCs, 2 were pure intraductal neoplasms and 1 showed progression to a high-grade adenosquamous carcinoma, a hitherto unreported event in these tumors. The intraductal component in all cases was characterized by an epithelial proliferation resembling atypical ductal hyperplasia or LG-intraductal mammary carcinomas with extensive apocrine differentiation. The tumor cells showed deeply eosinophilic cytoplasm, cytoplasmic vacuoles, nuclei with central eosinophilic nucleoli, apical blebs and decapitation, and staining for BRST-2 with nuclear expression of
ARs. This extent of apocrine differentiation in salivary gland neoplasms is uncommon; although in their original description of LG-SDC, Delgado et al.9 commented on the apocrine nature of at least part of every tumor with 2 cases being focally positive for BRST-2. Brandwein-Gensler et al.3 also described “apocrine-type” PAS-positive apical microvacuoles in their series. Thus, LG-IDCs resembles not only conventional atypical ductal hyperplasia or LG-intraductal mammary carcinomas but also borderline apocrine lesions of the breast. The expression of ARs in LG-IDCs had been previously reported in only 1 case which was found to be negative.3 Nuclear expression of ARs in LG-IDCs is not surprising as AR expression is a common finding in apocrine lesions of the breast.17,21

The phenotype, particularly keratin profile, of LG-IDCs has not been widely studied. Delgado et al.9 showed that all their 5 cases investigated were positive for Cam 5.2, HMWK, pCEA, and S-100. Brandwein-Gensler et al.3 found that all 9 cases investigated were positive for S100 and negative for Her2Neu. Another case described by Chen was positive for S-100 and HMWK. In addition to S-100, we studied our cases with a broad panel of keratins and other markers. In general we found similar results for HMWK, AE1:AE3, and Cam 5.2; however, we found some new and interesting results. Firstly, all the tumors were positive for CK7 and CK19 and unlike previously reported, we found strong nuclear staining for ARs in all cases. We also found 2 positive cases for S-100 and 1 negative. The lack of S-100 expression in the latter case is intriguing and we do not have an explanation for this finding because the phenotype in all cases was otherwise remarkably similar. It is possible that LG-IDCs has a wider phenotypic diversity than previously reported with some cases lacking S-100 expression; or alternatively the loss of S-100 expression may be an early indication of dedifferentiation because this lesion showed progression to a high-grade invasive carcinoma. In summary, the phenotype of LG-IDCs shows a distinctive ductal pattern resembling the keratin profile of striated and interlobular ducts with aberrant expression of S-100.7,13,14 They seemed to be negative for CK20, Her2Neu, estrogen receptor, and progesterone receptor.

Although the number of cases is small and the follow-up has been limited, LG-IDCs have an excellent prognosis. Thus far no lymph node metastases, local recurrences or deaths attributed to tumor have been reported in 21 patients with follow-up ranging from 6 months to 11 years.3,5,9 Nonetheless, LG-IDCs has the potential of progression to invasive carcinomas. Delgado et al.9 reported 1 case with focal high-grade cytologic atypia associated with stromal microinvasion. Brandwein-Gensler et al.3 also described 4 tumors with focal and limited invasion, 2 of them showing progression to high-grade cytologic atypia. One of our cases showed progressive cytologic atypia within the intraductal component and developed a widely invasive adenosquamous carcinoma. This case may represent a case of “dedifferentiation” because the invasive carcinoma lacked expression of CK19, BRST-2, and ARs—found in the intraductal component—and the invasive carcinoma did not resemble conventional SDC. Ide et al.12 described a LG-IDC which had been present for 38 years before resection. In addition to the LG-component, the tumor also contained foci with comedonecrosis and “small nests of high-grade ductal carcinoma” lacking S-100 immunoreactivity. The patient had no recurrences or metastases 19 years after simple excision.12 In summary, approximately 20% of reported cases of LG-IDCs have been associated with limited invasion or “microinvasion” and

### TABLE 2. Immunohistochemical Results

<table>
<thead>
<tr>
<th>Antibody</th>
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<th>Case 2</th>
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<th>Case 3 Invasive</th>
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*Staining present only in myoepithelial cells.
†Staining present in both ductal tumor cells and myoepithelial cells.
FIGURE 3. Immunohistochemical profile of intraductal carcinomas with strong and diffuse expression for CK19 (A), CK7 (B), and HMWK (34βE12) (C). D, Patchy but strong staining for BRST-2. The intraductal nature of the tumors is confirmed by a prominent myoepithelial layer highlighted by calponin (E), and CK14 (F).

FIGURE 4. A, Case 2 showing diffuse and strong staining of intraductal carcinoma with S100 protein. B, All cases showed strong nuclear expression of ARs.
only 1, described herein, with a widely invasive carcinoma; and 17% have been associated with foci of severe cytologic atypia. Although not strictly defined in the literature, the presence of “microinvasion” or “limited” invasion in LG-ICDs does not appear to affect prognosis; therefore, these cases can be diagnosed as “LG-ICDs with microinvasion”. The treatment of these tumors should be complete surgical resection either by superficial parotidectomy or total parotidectomy with preservation of the facial nerve. Given the conspicuous absence of lymph node metastases in the reported cases LG-ICDs, it seems that there is no need for routine neck dissection. There is no data in the literature at this moment to advocate for the routine use of radiotherapy in the management of these tumors after complete surgical resection; nevertheless there may be a role for adjuvant radiotherapy in the treatment of tumors with positive surgical margins. One of the cases reported by Delgado et al9 showed focal invasion and positive surgical margins. The patient had no evidence of recurrent disease 9 months after surgical resection and radiotherapy.

The existence of IDCs in the salivary gland has yet to gain widespread acceptance and recognition. In a recent report describing a pure IDC of the buccal mucosa, Cheuk et al6 analyzed the literature and reviewed the controversy surrounding these neoplasms, and provided strict pathologic criteria for their diagnosis. Their criteria are summarized and slightly modified in Table 3. IDCs of salivary gland origin are epithelial proliferations resembling apocrine or conventional atypical ductal hyperplasia or intraductal mammary carcinomas. They can have low, intermediate, or high cytologic grade and may exhibit cribriform, micropapillary, solid, “comedo,” or clinging architectural patterns. In making this diagnosis, the presence of invasion should be excluded by extensive sampling and by demonstrating the presence of a continuous myoepithelial or basal layer surrounding the intraductal neoplastic proliferation. The presence of ducts with angulated or irregular appearance, desmoplastic reaction, or an inflammatory infiltrate may also be indicative of invasion. It is of paramount importance that the surgical margins of resection are adequately assessed to ensure complete resection of the tumor.

LG-ICDs are probably the most common type of IDCs of the salivary gland but they have been a controversial entity because their initial description as LG-SDCs by Delgado et al9 The 2005 World Health Organization Classification of Head and Neck Tumors has listed these tumors as a variant of cystadenocarcinoma and bestowed on them the descriptive term LG-CCC.2 We agree with the inclusion of LG-SDC/LG-CCC in the category of LG-ICDs as suggested by Cheuk et al.6 These tumors have distinctive morphologic features and immunohistochemical studies have shown that most of the neoplastic cells express CK7, CK19, HMWK, and S-100 and are surrounded by non-neoplastic myoepithelial cells.3,5,9 Indeed, Delgado et al9 remarked that these tumors were primarily an in situ or intraductal process. In contrast, the largest series of salivary gland cystadenocarcinomas included cases of LG-ICDs, but it also described tumors with features not seen in LG-ICDs.10 Furthermore, no immunohistochemical studies were performed to investigate the tumors phenotype or the presence of myoepithelial cells. The rare cases of salivary cystadenocarcinoma studied by immunohistochemistry suggest that salivary cystadenocarcinomas are S-100 negative and lack myoepithelial cells.16,20 The histopathology and phenotype of salivary gland cystadenocarcinomas remain inadequately defined and in need of further investigation. The inclusion of LG-ICDs—a lesion with distinctive morphology and immunophenotype—in an imperfectly defined group of tumors is difficult to support.

LG-ICDs is predominantly a neoplasm of major salivary glands with only 1 case reported in the palate.12 In contrast, almost all IDCs reported in minor salivary gland have been intermediate or high-grade lesions.4,6,22,23 The differential diagnosis of IDCs in minor salivary glands includes the rare cribriform adenocarcinoma of tongue (CAT).19 The clinical, architectural, and cytologic features of these 2 neoplasms are significantly different. Unlike IDCs, CAT is an infiltrative tumor with no demonstrable myoepithelial layer, which clinically presents with cervical lymph node metastases.19 CAT does not have large cystic spaces, micropapillary architecture, or comedonecrosis and furthermore, the neoplastic cells of CAT show clear or oxyphilic cells with overlapping nuclei exhibiting pale, vesicular “ground glass” appearance resembling papillary carcinoma of thyroid.

The question of whether there is a relationship between SDC and LG-ICDs remains unanswered. The evidence suggests that LG-ICDs and SDC are probably related entities. Both neoplasms share some histopathologic characteristics and exhibit ductal phenotype, with variable degrees of apocrine differentiation and expression of BRST-2 and ARs.11,15,18 However, they differ in other significant features. Approximately 75% of cases of SDC occur in males whereas LG-ICDs are more common in females, the diagnosis of LG-ICDs is much rarer than

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**TABLE 3. Proposed Diagnostic Criteria for Intraductal Carcinoma of Salivary Glands (Modified From Cheuk et al6)**

<table>
<thead>
<tr>
<th>Epithelial proliferation with round, smooth borders resembling conventional or apocrine atypical ductal hyperplasia or intraductal mammary carcinoma</th>
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<tr>
<td>Cribriform, micropapillary, solid, “comedo,” or clinging architecture</td>
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<tr>
<td>Low, intermediate, or high cytologic grade</td>
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<tr>
<td>Exclusion of an invasive component (by thorough sampling and by immunohistochemistry (using calponin, actins, CK14, or p63 to demonstrate the presence or absence of a myoepithelial or basal cell layer)</td>
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SDC, and lastly SDC is not preceded by a long clinical course. Another possible difference between SDC and LG-IDCs is the expression of CK19. All of our cases were positive for CK19, whereas 5 cases of SDC investigated by de Araujo et al\textsuperscript{8} were negative. S-100 is only expressed by 4% of SDC\textsuperscript{18} but it is almost always positive in LG-IDCs. Thus far only in the case reported by Ide et al.,\textsuperscript{12} the invasive carcinoma has demonstrated features of SDC. The invasive case in our series was an adenosquamous carcinoma not a SDC. It appears that the histopathologic and phenotypic spectrum of LG-IDCs is wider than previously thought and in certain cases overlap with those of SDC.\textsuperscript{5,12} More comprehensive clinicopathologic, phenotypic, and molecular studies are needed to answer the many questions surrounding these two types of tumors.

The indolent clinical course, morphologic appearance, characteristic phenotype, and the presence of a residual layer of myoepithelial cells with only occasional stromal invasion, support the view that LG-IDCs represents an intraductal salivary gland neoplasm with variable apocrine differentiation. The terms LG-SDC and LG-CCC should be abandoned in favor of LG-IDC of variable apocrine differentiation. The terms LG-SDC and LG-IDC Salivary Gland better reflects their predominantly intraductal and noninvasive nature and thereby avoids confusion with either SDC or cystadenocarcinoma.

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