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CASE REPORTS

Low-Grade Intraductal Carcinoma of the Parotid Gland: A Case Report and Literature Review

Daniela Russo[1] · Rosa Maria Di Crescenzo[1] · Silvia Varricchio[1] · Giuseppe Broggi[2] · Maria Eleonora Bizzoca[3] · Stefania Troise[4] · Giovanni Salzano[4] · Gennaro Ilardi[1] · Francesco Merolla[5]

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Abstract

Low-grade intraductal carcinoma is a rare neoplasia with an excellent prognosis, previously classified as low-grade cribriform cystadenocarcinoma and low-grade salivary duct carcinoma. The tumor mainly occurs in the parotid gland and presents a ductal phenotype and an intraductal/intracystic growth pattern. It resembles intraductal breast lesions such as atypical ductal hyperplasia, papillary and cribriform ductal carcinoma in situ. Despite its infrequency, discriminating low-grade intraductal carcinoma from other salivary gland tumors is crucial, especially because of its favorable prognosis. A 74-year-old woman with a history of neurofibromatosis underwent a superficial parotidectomy to remove a sharply demarcated multi-cystic mass, diagnosed as category 4 at FNAC. The histological examination revealed a demarcated but unencapsulated lesion composed of a bigger cyst surrounded by several smaller cysts, lined by a monolayer or bilayer epithelium alternated with a cribriform proliferation, characterized by "Roman-bridges", with occasional micro-papillae. A myoepithelial component, with a basal disposition, was present, confirmed by intense staining for protein p63 and SMA. Immunohistochemical stains showed intense, strong uniform positivity for pan-cytokeratin, protein S100, and SOX10. The Ki67 proliferation index was low (< 10%). A diagnosis of Low-grade Intraductal Carcinoma (LGIC) of the parotid was made. We performed a literature search in PUBMED for "Intraductal carcinoma", "Low-grade Intraductal Carcinoma", "Cribriform Cystadenocarcinoma", "Salivary Duct Carcinoma", and "Low-Grade Salivary Duct Carcinoma". We selected 17 papers published between 1983 and 2020; the most affected anatomical site was the parotid gland (77/90), followed by minor salivary glands (6/90), the intraparotid lymph nodes (3/90) and the submandibular gland (4/90). Their main histopathological features are reported in the paper. Here we present a case report and a review of scientific literature on this topic to provide some essential diagnostic tools to discriminate this rare entity.

Keywords Low-grade intraductal carcinoma · Cribriform cystadenocarcinoma · Low-grade salivary duct carcinoma · Salivary gland · Parotid gland

Introduction

Low-grade intraductal carcinoma (LGIC), previously identified as low-grade cribriform cystadenocarcinoma or low-grade salivary duct carcinoma, is a rare salivary gland tumor.

Daniela Russo and Rosa Maria Di Crescenzo are co-first authors. These authors contributed equally to the work.

✉ Francesco Merolla
francesco.merolla@unimol.it

[1] Pathology Section, Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy

[2] Section of Anatomic Pathology, Department G.F. Ingrassia, University of Catania, Catania, Italy

[3] Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy

[4] Maxillofacial Unit, Department of Neuroscience, Reproductive Sciences and Dentistry, University of Naples Federico II, Naples, Italy

[5] Department of Medicine and Health Sciences "V.Tiberio", University of Molise, Campobasso, Italy

In about 80% of cases, it occurs in the parotid gland and rarely involves other anatomic sites [1]. LGIC displays histological features resembling atypical ductal hyperplasia or ductal carcinoma in situ of the breast [2]. It grossly appears as an unencapsulated uni- or multi-cystic lesion, microscopically characterized by an intra-cystic proliferation of neoplastic epithelial cells associated with a preserved layer of myoepithelial cells [3]. LGIC grows slowly, rarely develops metastases [4], and has never been associated with systemic diseases or cigarette smoking. Since its first description in 1996 by Delgado and colleagues, about 50 cases have been reported worldwide. Its incidence is low in Italian series, being as low as 2% of all salivary gland tumors [1].

Searching our pathology unit's database from January 2000, using the terms "low-grade intraductal carcinoma", "low-grade cribriform cystadenocarcinoma", and "low-grade salivary duct carcinoma", we found no cases that met the above criteria. Here we report an additional case of LGIC occurring in the left parotid gland of a 74-year-old woman affected by neurofibromatosis. The neoplasia presented morphological features generally considered an expression of aggressiveness, such as focal apocrine differentiation and invasive growth pattern. The patient is still alive and disease-free after 15 months from diagnosis.

Case Report

A 74-year-old woman was referred to the Maxillofacial Surgery Department of the University of Naples Federico II, Italy, because of a 6-month-history of left parotid region swelling. The patient was a heavy smoker and reported a history of arterial hypertension, neurofibromatosis, and previous resection of bladder cancer. The clinical examination revealed a well-circumscribed mass in the inferior portion of the left parotid gland near the mandibular angle and the presence of multiple neurofibromas on the skin surface. On palpation, the swelling was not painful and had a firm consistency. It was movable to the deeper tissue and to superficial skin that appeared normal for color and appearance. A CT scan (Fig. 1) of the head and neck region showed a non-homogeneous cystic formation of about 28×15 mm. Following an FNAC examination, the case was categorized as a neoplasm of uncertain malignant potential (diagnostic category 4, according to the Milan System) [5]. A superficial parotidectomy was performed, with the preservation of all facial nerve branches. The tumoral mass was removed "en bloc", and no complications were detected during the post-surgery follow-up (Fig. 2). The patient was discharged from hospital after 5 days.

The specimen consisted of a superficial parotidectomy partially occupied by a sharply demarcated multi-cystic mass of about 2.3×2.7 cm in diameter. Grossly, it showed cysts filled with a serous/mucoid/hemorrhagic fluid. No necrosis was macroscopically detected. The histologic examination showed a demarcated but unencapsulated lesion made up of a bigger cyst surrounded by several smaller cysts. Cysts were lined by a monolayer or bilayer epithelium alternated with a cribriform proliferation, characterized by "Roman-bridge" pattern with occasional micro-papillae. At high power magnification, it was possible to distinguish a neoplastic epithelial proliferation from a myoepithelial component, with a basal disposition. Neoplastic epithelial cells were small to medium-sized and presented mild atypia, eosinophilic cytoplasm, round/oval nuclei, and occasional prominent nucleoli (Fig. 3). Moreover, also apocrine differentiation and cytoplasmic microvacuoles (PAS and mucicarmine positive) were significant histologic features (Fig. 4). Mitotic activity

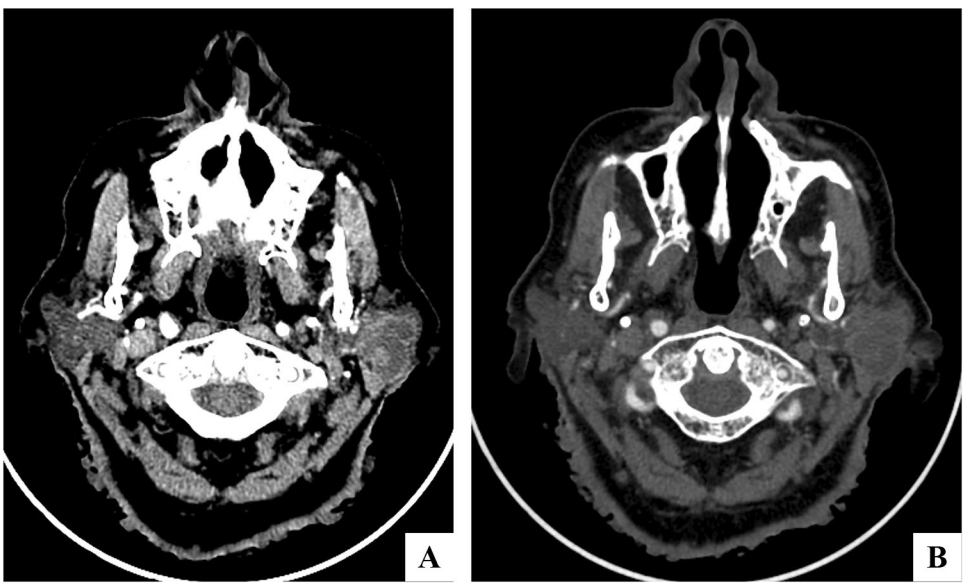

Fig. 1 **a**, **b** Axial CT-Scan: A neoplasm alters the left parotid parenchyma and presents uneven density after enhancement (**a**)

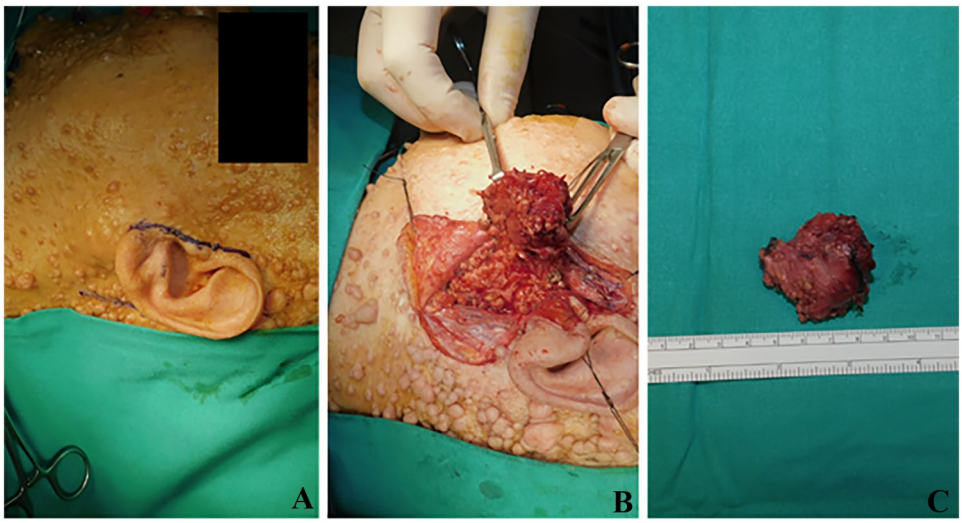

Fig. 2 **a** A 74-year-old female affected by neurofibromatosis with a non-painful and non-tender swelling of the left parotid region; **b** superficial parotidectomy, with preservation of the integrity of all facial nerve branches was performed; **c** the superficial parotidectomy was partially occupied by a clearly demarcated multi-cystic mass of about 2.3 × 2.7 cm in diameter

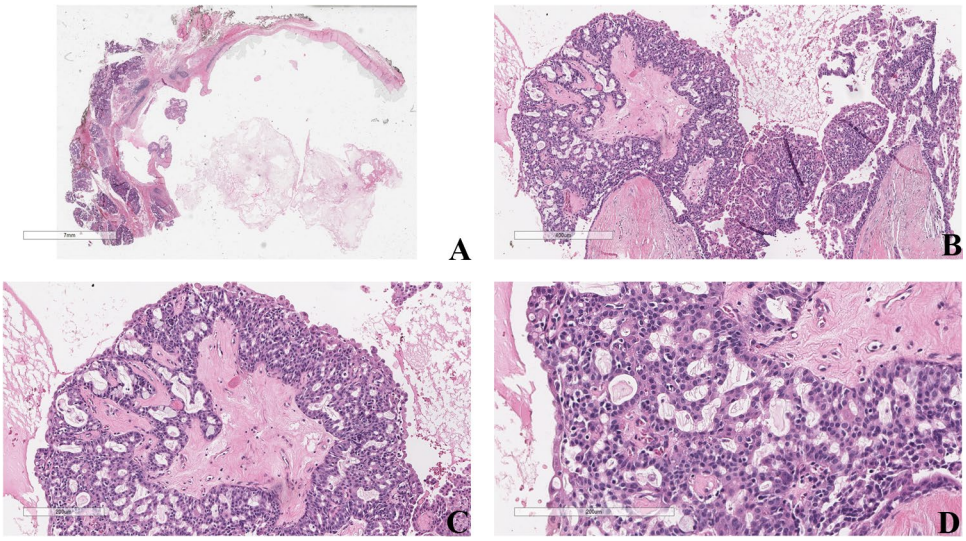

Fig. 3 **a** The low-power field shows a discrete, well-circumscribed cyst filled with serous/mucous material (H&E, 2×,). **b**, **c** At higher magnification, the cyst is lined by a bilayered epithelium with rare islands of cribriform proliferation (H&E, 4× and 10×, respectively). **d** Neoplastic cells present mild atypia and are small to medium-sized with eosinophilic cytoplasm, round/oval nuclei, and prominent nucleoli (H&E 20×)

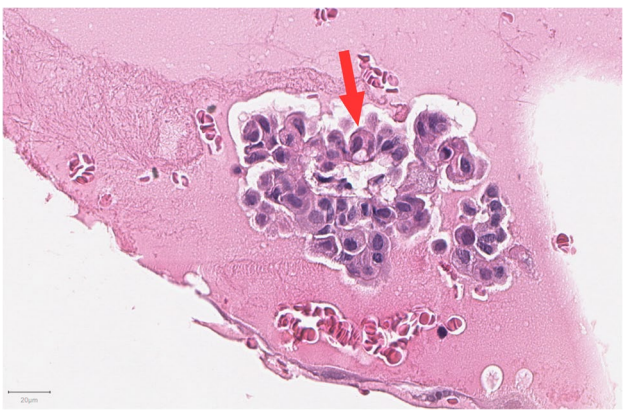

Fig. 4 Apocrine cells show larger nuclei, variable nucleoli, abundant eosinophilic cytoplasm, and cytoplasmic microvacuoles (red arrow) (H&E, 20×)

was low, and atypical mitotic figures were not detected. We observed focal perineural invasion and a focal invasive growth pattern.

Immunohistochemical stains showed intense, strong uniform positivity for pan-cytokeratin, S100, and SOX10 (Fig. 5a,c,d). The presence of a non-neoplastic myoepithelial layer, rimming the cystic spaces, was confirmed by intense staining for protein p63 (Fig. 5b) and Smooth Muscle Actin (SMA) in this cellular population. Myoepithelial rim was lacking in the focal invasive component. The Ki-67 proliferation index was low (< 10%). Immunostaining for Androgen Receptor (AR), PSA, Gross Cystic Disease Fluid Protein 15(GCDFP-15) DOG-1 and Her-2 resulted negative.

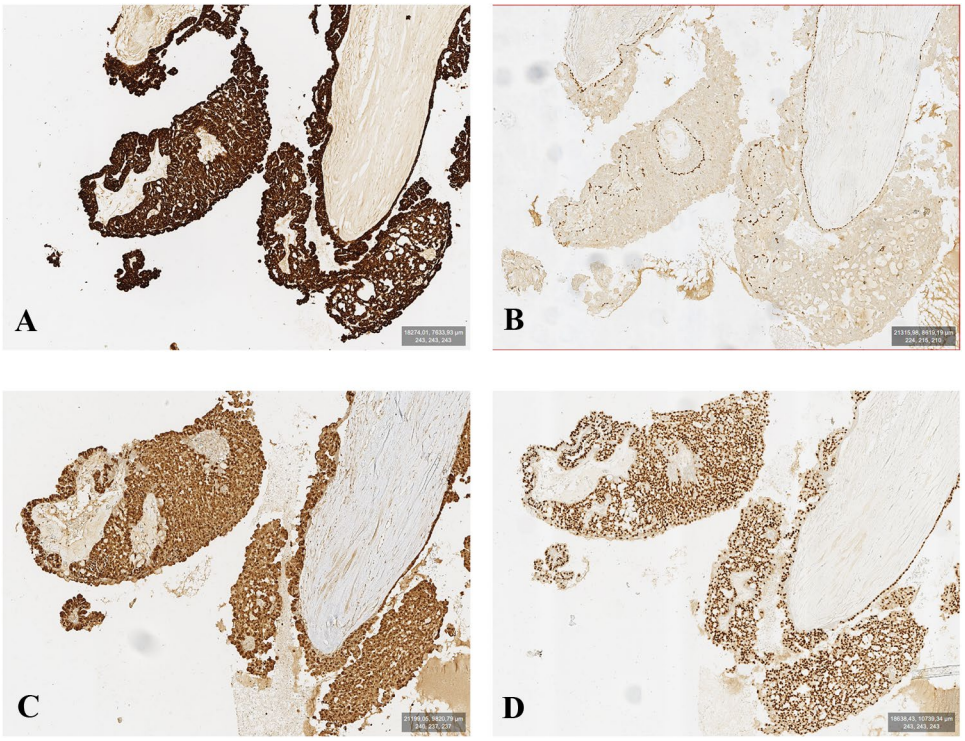

Fig. 5 The figure shows immunoreactivity for pan keratin (**a**) p63 (**b**); S100 (**c**), and SOX10 (**d**). Epithelial neoplastic cells present a strong reactivity for pan keratin, S100, and SOX10; p63 highlights myoepithelial cells with basal disposition (10×)

We concluded for a diagnosis of Low-grade Intraductal Carcinoma (LGIC). After 1-year follow-up, there was no evidence of recurrence or metastases.

Discussion

LGIC is an uncommon malignant tumor of the salivary glands that frequently occurs in the parotid gland. It involves intraparotid lymph nodes, submandibular glands, and, rarely, minor salivary glands [1]. We reviewed the scientific literature concerning Intraductal Carcinomas of Salivary Glands: Table 1 shows the morphological and clinicopathologic features of these tumors. Searching the PUBMED database for "Intraductal carcinoma", "Low-grade Intraductal Carcinoma", "Cribriform Cystadenocarcinoma", "Salivary Duct Carcinoma", and "Low-Grade Salivary Duct Carcinoma" we selected 17 papers published between 1983 and 2020. Table 2 summarizes the key features of the selected case series. The total number of patients included in the sorted series was 90, the median age ranged between 43 and 79 years old; 42 out of the 90 patients were female, 47 male and 1 unknown; the most affected anatomical site was the parotid gland (77/90), followed by minor salivary glands (6/90, 3 of the hard palate, 2 of the buccal mucosa and 1 of the tongue), intraparotid lymph nodes (3/90) and the submandibular gland (4/90). The described lesions ranged, in the largest diameter, between 1 and 4.5 cm. Invasive growth was described in 20 cases. Most of the reported cases showed cells with clear nuclei with dispersed chromatin and prominent nucleoli. The oncocytic appearance was also described. Apocrine features were frequently reported. The architecture of the reported lesions was mostly cystic with the presence of so-called "Roman-arches" or "Roman-bridges". Some cases had a cribriform or papillary/micropapillary pattern of growth. Mitotic figures were absent or mostly few (frequently described as scattered). Except for three cases, the presence of myoepithelial cells was always reported in the analyzed cases. The term Intraductal Carcinoma was introduced by Chen in 1983 [6], but Delgado first described the tumor in 1996, reporting 10 cases of salivary gland lesions with histological features attributable to a low-grade counterpart of salivary duct carcinoma [7]. It had been named Low-Grade Salivary Duct Carcinoma and Low-Grade Cribriform Cystadenocarcinoma before being classified as Intraductal Carcinoma (IC) in the last edition of the WHO classification of Head and Neck Tumors [3]. The intraductal nature of the tumor is demonstrated by the presence of a preserved myoepithelial layer (highlighted by immunostaining for p63), surrounding the neoplastic epithelial component. Neoplastic cells show particular diffuse, co-expression of SOX10, cytokeratin 7, and S100 and are generally arranged in a cribriform, "Roman-bridge" or micropapillary intraductal/intra-cystic growth pattern. Based on the degree of cytological atypia and the number of mitotic figures, IC can be divided into Low-Grade Intraductal Carcinoma (LGIC), Intermediate Grade Intraductal Carcinoma, and High-Grade Intraductal carcinoma (HGIC) [3]. Moreover, IC has been

Table 1 Morphological findings of salivary gland intraductal carcinomas reported in most important scientific papers published between 1983 and 2020

Authors	Year	Number of cases	Median age	Gender	Location	Largest diameter (cm)	Cytology	Myoepithelial cells	Architectural pattern	Invasive growth pattern	Mitotic rate
T.K. Chen [6]	1983	1	60	F	Minor salivary glands	Not reported	Epithelial cells with a small amount of cytoplasm and hyperchromatic nuclei	Not reported	Not reported	No	Frequent mitotic figures
R. Delgado et al. [7]	1996	10	60	5 M, 5 F	9 Parotid, 1 intraparotid lymph node	1.1 (median value)	Apocrine/vacuolated, intercalated duct-like, nonspecific glandular	Present	Cystic ducts with micropapillary projection Intraductal pseudo-cribriform cellular proliferation Ducts with architectural atypia	1 case	Negligible
Y. Tatemoto et al. [15]	1996	1	58	F	Minor salivary glands	1	Tumor cells with eosinophilic cytoplasm and clear large nuclei	Not reported	Ductal structures with intraductal proliferation with cribriform pattern	No	Negligible
W. Cheuk et al. [16]	2004	1	44	F	Minor salivary glands	1.2	Tumor cells with eosinophilic cytoplasm and round/oval nuclei with finely dispersed chromatin and distinct nucleoli	Present	Intraductal/Intra-lobular proliferation with fenestrated or cribriform pattern	No	1–2 mitotic figures/HPF

Table 1 (continued)

Authors	Year	Number of cases	Median age	Gender	Location	Largest diameter (cm)	Cytology	Myoepithelial cells	Architectural pattern	Invasive growth pattern	Mitotic rate
M. Brandwein-Gensler et al. [17]	2004	16	64	7 M, 8 F, 1 unknown	14 Parotid, 1 intraparotid lymph node, 1 submandibular gland	Not reported	Neoplastic ductal cells with finely dispersed chromatin and small nucleoli Ductal cells with apocrine-type microvacuoles and lipofuscin-like granules Oncocytoid cells in 2 cases	Present	Cystic ducts and intraductal proliferation with micropapillary, cribriform (with occasional "Roman-bridge" formations) or solid pattern	4 cases	Scattered mitotic figures in 2 cases
I. Weinreb et al. [9]	2006	3	67	1 M, 2 F	Parotid	2 (median value)	Tumor cells with deeply eosinophilic cytoplasm, nuclei with central eosinophilic nucleoli, apical apocrine snouts and cytoplasmic vacuoles	Present	Large cystic ducts with intraductal proliferation with "Roman-arches", cribriform, papillary or micropapillary architecture	1 case	Scattered mitotic figures
I. Weinreb et al. [18]	2011	1	59	F	Intraparotid lymph node	3.5	Tumor cells with ovoid/round nuclei, inconspicuous nucleoli and granular, amphophilic or focally oncocytic cytoplasm and bubbly microvacuoles	Present	Nests and cystic spaces with cell proliferation with solid, cribriform, micropapillary and "Roman-bridge" architecture	No	No

Table 1 (continued)

Authors	Year	Number of cases	Median age	Gender	Location	Largest diameter (cm)	Cytology	Myoepithelial cells	Architectural pattern	Invasive growth pattern	Mitotic rate
L. Wang et al. [19]	2013	2	53,5	1 M, 1 F	Parotid	2.5	Uniform tumor cells with round/oval nuclei with fine chromatin, prominent nucleoli and pale to amphophilic cytoplasm. Apocrine differentiation of cells in 1 case	Present	Large cystic or solid spaces with cribriform or micropapillary architecture	No	Negligible
S. Kokabu et al. [20]	2015	1	56	F	Minor salivary glands	2	Tumor cells with inconspicuous nuclear atypia	Present	Unilocular cyst with intracystic proliferation with tubular, cribriform or solid architecture	No	Presence of mitotic figures
N. Wakabayashi et al. [4]	2017	1	51	M	Parotid	4.5	Tumor cells with mild atypia, low N/C ratio and intracytoplasmic mucin	Not reported	Tumor cell proliferation with papillary, cribriform pattern	No	Negligible
T. Nishijima et al. [21]	2016	1	75	F	Parotid	4	Tumor cells with mild-to-moderate atypia, round to oval nuclei, dispersed chromatin, and distinct nucleoli	Present	Papillary-cystic proliferation of tumor cells with cribriform and papillary structure (lacking a fibro-vascular core) accompanied by prominent lymphoid stroma	No	1–2 mitotic figures/HPF

Table 1 (continued)

Authors	Year	Number of cases	Median age	Gender	Location	Largest diameter (cm)	Cytology	Myoepithelial cells	Architectural pattern	Invasive growth pattern	Mitotic rate
M. Nakaguro et al. [22]	2018	5	63	3 M, 2 F	4 parotid, 1 submandibular gland	3.3	Tumor cells with medium-sized round nuclei with finely dispersed chromatin and conspicuous nucleoli, abundant granular eosinophilic cytoplasm	Present	Intraductal/ Intra-cystic proliferation with papillary, fenestrated cribriform (with occasional "Roman-bridge" structures) and solid nest pattern	No	Few mitotic figures
F. Giovacchini et al. [1]	2019	1	43	F	Parotid	1.6	Small and monotonous tumor cells with mildly atypical nuclei and pale to eosinophilic cytoplasm	Present	Small nodules and dilated ducts with solid and cribriform pattern and cysts with comedo-like necrosis	No	Rare mitotic figures

Table 1 (continued)

Authors	Year	Number of cases	Median age	Gender	Location	Largest diameter (cm)	Cytology	Myoepithelial cells	Architectural pattern	Invasive growth pattern	Mitotic rate
A. Skálová et al. [2]	2019	33	54	21 M, 12 F	30 parotid, 1 submandibular, 2 minor salivary glands	1.5	Luminal epithelial proliferation with multiple cystic, solid, cribriform or micropapillary pattern Small-medium sized tumor cells with indistinct cell borders, round/ovoid nuclei with dark condensed or finely dispersed chromatin and large pale to eosinophilic cytoplasm. Apocrine features in 6 cases	Present	Luminal epithelial proliferation with multiple cystic, solid, cribriform, papillary or micropapillary pattern	8 cases	Inconspicuous mitoses

Table 1 (continued)

Authors	Year	Number of cases	Median age	Gender	Location	Largest diameter (cm)	Cytology	Myoepithelial cells	Architectural pattern	Invasive growth pattern	Mitotic rate
H. Lu et al. [12]	2019	1	79	M	Parotid	1.7	Monomorphic tumor cells with round to oval nuclei with dispersed chromatin and scant cytoplasm with clear cell change. Apocrine tumor cells with large nuclei, hyperchromasia, variable nucleoli, and abundant eosinophilic cytoplasm with occasional apocrine snouts	Present	Nests or solid pattern with focal cribriform structures or large cystic spaces with cribriform and micropapillary intraductal proliferation	No	Scattered mitotic figures
J.A. Bishop et al. [13]	2020	3	63	3 M	Parotid	1.8	Tumor cells with apocrine features with large round nuclei, prominent nucleoli, abundant granular eosinophilic cytoplasm and apical snouts	Present	Large, dilated cystic spaces, with scattered smaller microcysts or cribriform nests adjacent to the dominant macrocysts with micropapillary or papillary or a "Roman-bridge"-like architecture	No	1–3 mitotic figures/ 10 HPF

Table 1 (continued)

Authors	Year	Number of cases	Median age	Gender	Location	Largest diameter (cm)	Cytology	Myoepithelial cells	Architectural pattern	Invasive growth pattern	Mitotic rate
Min-Shu Hsieh et al. [14]	2020	9	70	4 M, 5F	8 Parotid, 1 Submandibular gland	3.3 (median value)	Cuboidal tumor cells with amphophilic cytoplasm with low- to intermediate-grade features with oval nuclei, inconspicuous nucleoli, and fine chromatin Apocrine cells with eosinophilic cytoplasm, vesicular nuclei with occasionally prominent nucleoli, apical snouts, apocrine snouts, and decapitation secretions	Present	Variable-sized cysts with micropapillary or filigreed epithelial tufts, cribriform, papillary, or solid patterns in variable proportions	6 cases	Not reported

Table 2 Summary of clinicopathological features of salivary gland intraductal carcinomas reviewed in case series

N° of selected papers		17
Year of publication (range)		1983–2020
N° of cases (total)		90
Median age (years)	Min	43
	Max	79
Gender	F	42
	M	47
	Unknown	1
Anatomical site	Parotid gland	77
	Minor salivary gland	6
	Intraparotid lymph node	3
	Submandibular gland	4
Largest diameter (range)	Min	1 cm
	Max	4.5 cm
Tumors with invasive growth pattern		20

recently further divided into two morphologic and immunophenotypic subtypes: intercalated duct type and apocrine type. Strong positivity for S100 and SOX-10, negativity for AR and mild atypia characterize the pure intercalated form. Instead, the apocrine type lacks S100 and SOX10 expression and shows a strong positivity for AR. It is composed of a pure apocrine population of cells with abundant eosinophilic granular cytoplasm, large nuclei with prominent nucleoli and apocrine snouts [8]. The last classification has been recently confirmed by molecular investigations, which revealed a particular association between NCOA4-RET gene fusion and the intercalated variant, and between TRIM27-RET gene fusion and the apocrine variant [2]. The focal invasive pattern of growth has also been reported and well-described [9], especially in the apocrine variant. However, in clinical practice, a clear distinction between these two variants is frequently difficult to make, and mixed/hybrid IC, with morphological, immunohistochemical, and genetic features of both intercalated and apocrine types, are reported [10]. Due to its analogy with atypical ductal hyperplasia and ductal carcinoma in situ of the breast, IC has been considered a preneoplastic lesion. In particular, Delgado first and other authors later investigated the relationship between IC, called low-grade salivary duct carcinoma at the time, and salivary duct carcinoma (SDC), assuming that they were opposite extremities of the same spectrum of salivary gland neoplasms [11]. However, they are currently considered different entities because of their morphological, immunohistochemical, and molecular features. Intercalated duct-type IC shows intense positivity for S100 and SOX-10, and negativity for AR and GCDFP-15. A continuous layer of p63 positive myoepithelial cells surrounds the tumor cells. Conversely, SDC is a high-grade neoplasia made up of pleomorphic apocrine cells, with S100 negative and AR/GCDFP15 positive immunophenotype. Despite the fact that this immunoprofile is shared with apocrine type IC, SDC is widely invasive and never rimmed by myoepithelial cells [12]. Moreover, the recent identification of RET rearrangements in ICs, but not in SDCs, has finally confirmed the clear distinction between these two neoplasms [2]. SDC has specific genomic alterations such as HER2-neu gene amplification and hotspot mutations of PIK3CA and HRAS. The latter two mutations were found in a rare form of ICs with apocrine features, high cellular grade and widespread invasion that could represent a precursor lesion of SDC [13, 14]. Thus, IC is a rare but widely debated neoplasia. It has a good prognosis, and therapy consists of surgical excision only. Therefore, it seems necessary to distinguish IC from other salivary gland neoplasms with more aggressive behavior but similar morphological features.

The WHO Classification term “intraductal carcinoma” is confusing and, according to previous studies [2, 12, 12], it is feasible it will be changed again with a more appropriate definition that summarizes its origin from intercalated ducts, the intraductal or invasive nature of the lesion, and differences from other salivary gland neoplasms [2]. In our experience, this was the first case of intraductal carcinoma of salivary glands and, to the best of our knowledge, is the first case reported in a patient suffering from neurofibromatosis. Moreover, it is particular because of the combination of prominent histological and immunohistochemical features of intercalated duct type LGIC with focal apocrine differentiation and an invasive growth pattern, which complicate differential diagnosis. In our opinion, a reclassification of this pathological entity and a better definition of the morphological and molecular diagnostic parameters could make the diagnosis of this rare neoplasm more straightforward.

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Compliance with Ethical Standards

Conflict of interest No conflict of interest to disclose.

Informed Consent Informed consent was obtained from patient for being included in the study.

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