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Low-grade intraductal carcinoma of salivary glands: A systematic review of this rare entity

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ABSTRACT

Background: Low-grade intraductal carcinomas are rare, malign tumors of salivary glands most commonly affecting parotid gland. It is a slow-growing tumor considered with a favourable prognosis after surgical excision.
Methods: To define the characteristics and management of low-grade intraductal carcinoma a systematic review was performed using the electronic databases Pubmed, Cochrane and Scopus. A new case report was also described.
Results: Including this case the review of literature identified only 54 cases reported thus far. Demographics, clinical presentation, diagnostic tools, treatment, follow-up and recurrence rate, histological and immunohistochemical patterns of this kind of tumor were summarized.
Conclusion: Low-grade intraductal carcinoma has already been well defined but is important to focus on the fact that in few cases component of high-grade infiltrations have been reported: this may modify surgical approach because a simple tumorectomy may not be enough.

1. Introduction

Low-grade intraductal carcinoma (LG-IC) is a rare salivary gland tumor that more frequently affects the parotid gland (80,4%), only rarely noted at other sites. The oldest name of LG-IC was “Low-grade cribriform cystoadenocarcinoma” or “Low-grade salivary duct carcinoma”, but it was reclassified according to the 4th WHO Classification of Head and Neck Tumors in 2017.[1] LG-IC was first described in a case series by Delgado and colleagues in 1996 as an entity resembling benign or atypical mammary duct hyperplasia, different from conventional salivary duct carcinoma (similar to an invasive ductal breast carcinoma).[2] From that moment on only 54 cases, including the present one, were described in literature.

These tumors affected adults ranged from 27 to 93 years and were more frequent in female (57%). Patients generally presented with an asymptomatic and slow growing mass without facial nerve involvement.

Macroscopically, LG-ICs were well-circumscribed, non-encapsulated and cystic lesions ranged from 7 mm to 53 mm, containing serous to haemorrhagic fluid. These tumors exhibited multiple cysts (92%) and a typical intraductal growth with three possible architectural patterns[3]:

1 Cystically dilated ducts with tufted, micropapillary anastomosing proliferations;
2 Distended ducts with solid “pseudocribriform” fenestrations or solid papillary proliferations;
3 Intraductal proliferations with Roman Bridges akin to the cribriform architectural pattern typical of low-grade intraductal breast carcinoma.

At cytological analyses, the tumor cells showed a heterogeneous morphology.[3] LG-IC generally lacked cellular or nuclear pleomorphism, prominent nucleoli, significant mitotic activity and necrosis. Furthermore these tumors had no local or perineural invasion, described only in 6 cases[2,4,5]; foci of high grade were described only in 5 cases, including the present case. However all cases illustrated no local or remote metastasis; just a case of invasive ductal carcinoma were observed after 9 months in a patient with positive surgical margin.[2]

Immunohistochemical analyses showed a typical ductal phenotype with diffuse expression of S100 protein; myoepithelial markers such as Calponin or Smooth Muscle Actin (SMA), p63 and Cytokeratin 14 highlighted cells rimming the cystic spaces and ducts.[6]

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Therapeutic management of LG-IC involved complete resection of the tumor, without neck dissection and additional therapies such as chemotherapy or radiotherapy.

Because of its favourable outcome, differentiating LG-IC from other salivary gland tumors is important; these tumors might mimic malignant ones such as cystoadenocarcinoma, salivary duct carcinoma in-situ/high grade intraductal carcinoma, conventional salivary duct carcinoma, acinic cell carcinoma, mammary analogue secretory carcinoma, cystadenoma, sclerosing polycystic adenosis, ductal adenoma with striated duct differentiation and intercalated duct lesions.[7]

2. Case report

2.1. Clinical summary

A 43-year-old Russian woman presented to the Maxillo-Facial Surgery Unit at the S. Maria della Misericordia Hospital of Perugia (Italy) with a 5-years history of a mass in the right parotid region. The lesion remained painless but the patient reported it changed in size in the last 6 months. The mass was consistent and well palpable and adhered to the skin. There was no palpable adenopathy or masses appreciated in levels I-VI of the neck. The tumor was staged as a clinical T1 according with the TNM Classification.[8] Contrast-enhanced computer tomography (CT) revealed a 10 × 16 mm mildly enhancing mass in the anterior superficial lobe of the right parotid gland. On fine needle aspiration biopsy (FNAB), there was no evidence of frank malignancy; FNAB showed very small tissue fragments consisting of epithelial cells without obvious atypia, sometimes arranged in a papillary fashion. A cytological diagnosis of epithelial neoplasia not otherwise specified was made.

The written informed consent was obtained and the patient underwent a superficial parotidectomy with facial nerve preservation extended to the surrounding skin. The final histological diagnosis was low-grade intraductal carcinoma with foci of infiltrating carcinoma (not otherwise specified) of the parotid gland.

Surgical margins were negative, but we recommended that the patient received adjuvant radiotherapy due to the invasive component of the tumor. Postoperative investigation using MRI revealed no residual tumor or lymph node metastasis. The patient was alive and well with no recurrent disease 12 months after the surgery.

2.2. Histological findings

The surgical specimens consisted of superficial parotidectomy (one grey-brownish fragment, lacking orientation, of 4,6 × 2 × 1 cm), two yellowish fragments of subcutaneous tissue (0,6 and 0,3 cm) and a skin fragment of 1,3 × 0,8 cm, overlying the parotid gland. The whole parotidectomy specimen was cut in serial sections and FFPE (formalin fixed-paraffin embedded) tissue blocks were obtained. Two fragments and skin biopsy were included in separated tissue blocks.

On microscopic examination of Haematoxilin&Eosin stained sections, most part of the bigger specimen consisted of normal siero-mucinous salivary gland tissue, while a less amount showed an epithelial proliferation arranged in small nodules, both in solid and cribriform pattern of growth, and cysts, that sometimes displayed comedo-like necrosis. Some adjacent duct structures were dilated and presented a similar epithelial proliferation.

The epithelial cells were small, monotonous, with mildly atypical nuclei and pale to eosinophilic cytoplasm. Mitoses were exceedingly rare. A basal cell population demarcating the nodules and cysts was somewhere evident and immunohistochemical positivity for p63 and Cytokeratin 14 confirmed the myoepithelial cell nature.

The luminal epithelial cells displayed wide positivity for Cytokeratin pool (CK5/6/8/18, marker of epithelial nature), S-100 and focal positivity for GCDFP-15. Other markers such AR, ER, PgR, PLAP, PSA, PLAG1, HMGA1 and HER2 were negative (Fig. 1). Markers details were summarized in Table 1.

No sign of strict invasion was demonstrated in the main specimen of parotidectomy.

In both fragments of subcutaneous tissue and in skin biopsy, instead, there was an epithelial proliferation with different pattern of growth, made of small nodules or single cells. Such cells infiltrated the fibro-adipose tissue and the dermis. No evidence of any positivity for p63 or Cytokeratin 14 was demonstrated in the subcutaneous fragments neither in the dermis of skin biopsy; neoplastic cells showed the same immunohistochemical profile of luminal ones in the main specimen.

Those findings established the diagnosis of low-grade intraductal carcinoma in the main specimen and infiltrating carcinoma (NOS, not otherwise specified) in the subcutaneous and skin ones.

Pathological TNM resulted in pT4a staging.[8]

3. Materials and METHODS

A Systematic Review Protocol was performed according to the PRISMA (Preferred.

Reporting Items Systematic review and Meta-Analyses) Statement.[9]

3.1. Eligibility criteria

All studies in patients with low-grade intraductal carcinoma were considered eligible.

The inclusion criteria were:

- Study design: all kinds of studies describing cases of LG-IC
- Studies in English

The exclusion criteria were:

- Studies in which uncertain diagnosis of LG-IC

3.2. Information sources and search strategy

The literature search for the present systematic review was conducted at Pubmed, Scopus and Cochrane Library up to 30 June 2017.

The search strategy used a combination of the following keywords on the three databases: “low-grade salivary duct carcinoma OR low-grade intraductal carcinoma OR low grade cribriform cystadenocarcinoma OR lg-sdc”.

The additional filter “Language: English” was used.

3.3. Study selection

Studies were selected in two-stage screening by two independent reviewers; the first-stage screening of title and abstract was carried out to eliminate irrelevant article or article that didn't meet the inclusion criteria. At the second-stage screening of full-texts, the study eligibility was verified. The level of agreement between the two reviewers was calculated using Kappa statistics for the first and second-stage screening; disagreements about inclusion or exclusion of studies were resolved by consensus.

3.4. Data collection process/data items

Data were extracted based on the general study characteristics (author and year of publication, country, study design) and case characteristics (number of cases, age, ethnicity, sex, history of the lesion, location, size, evidence of malignant cells at fine needle aspiration biopsy, treatment, follow-up, diagnostic findings, histological findings and immunohistochemical findings).

3.5. Statistics

Categorical variables were summarized by frequency and

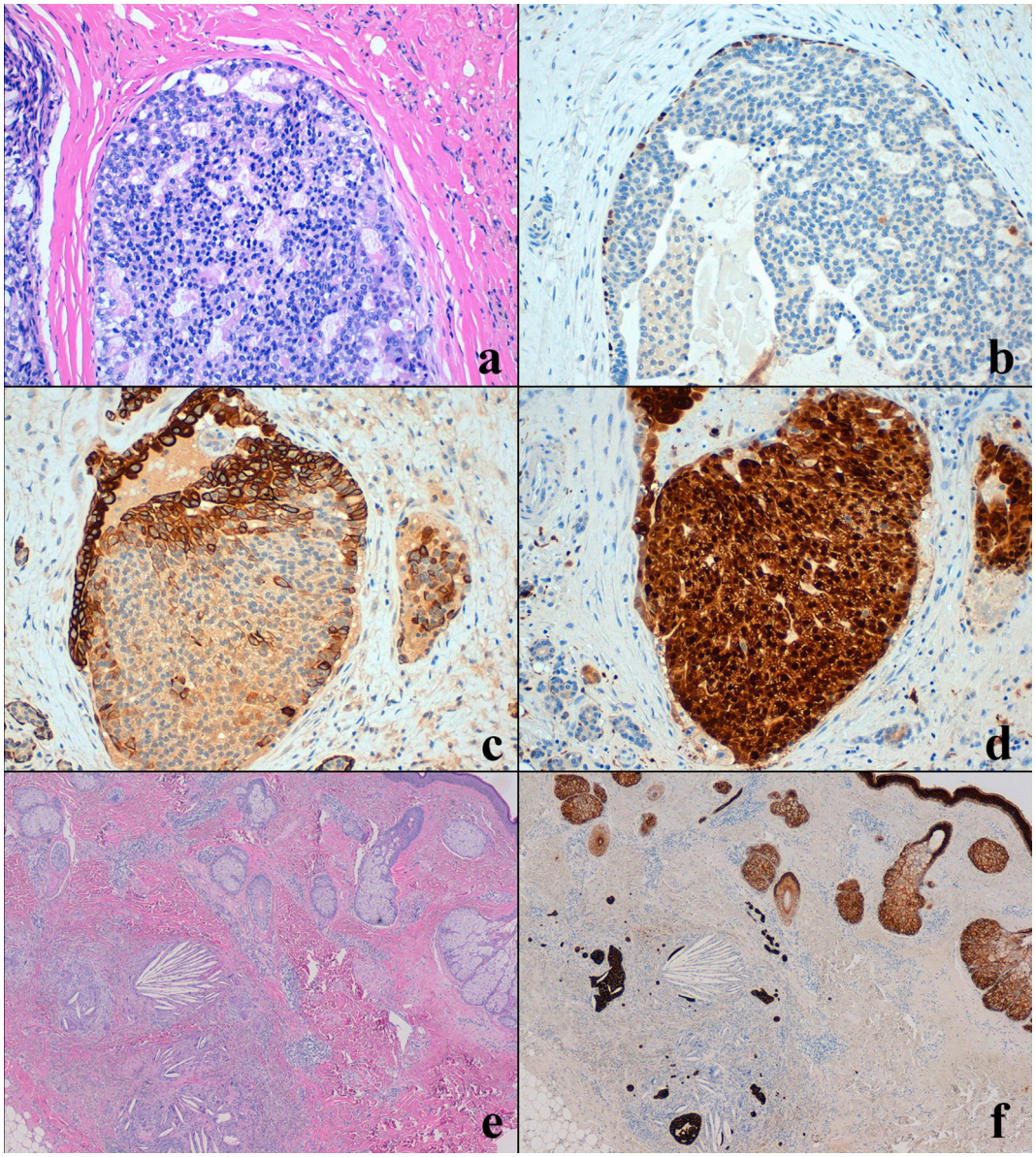

Fig. 1. a–d: low-grade intraductal carcinoma; e–f: intradermal infiltrating carcinoma, NOS; a. H&E; b p63; c Cytokeratin 14; d S100; e H&E; f Cytokeratin pool (CK5/6/8/18). Original Magnification ×20 (a, b, c, d), ×4 (e, f).

percentage; continuous variables were summarized by mean ± standard deviation and range where appropriate.

4. RESULTS

4.1. Search results

PRISMA flow chart describing study selection and inclusion is reported in Fig. 2. The initial search resulted in 559 articles at Pubmed, Scopus and Cochrane Library, after duplicates exclusion (37 duplicate articles). After first-stage screening of titles and abstracts, 29 articles were qualified for second-stage screening of full-text: 24 articles met the inclusion criteria and 5 were excluded. The reasons for exclusion were as follow: 1 full-text was not available (it was not possible to contact the authors) and 4 studies didn't fit inclusion criteria.

The kappa value for inter-reviewer agreement was 0,92 at title and abstract screening and 0,96 at full-text screening, describing good agreement between the reviewers.

4.2. Study design

Of the selected studies, 16 are case reports, 4 are case series and 4 are clinical trials (histology, immunohistochemistry and molecular analyses). Collectively, these studies accounted for 54 cases of LG-IC, including the present case (Table 2). Five cases belonged to consultation files of MBG were described in 2 articles[4,10] but have been considered only one time in the current review.

4.3. Population epidemiology and diagnosis

The patient population consisted of 28 females (57%) and 21 males (43%), with a mean age of 60 ranging from 27 to 93 years. The parotid gland was the most commonly involved anatomic site (n = 40, 80%), followed by intraparotid lymph node (n = 3, 6%), palate (n = 3, 6%), submandibular gland (n = 2, 4%), minor salivary gland (n = 1, 2%) and masseter muscle (n = 1, 2%). Most of the cases were described in USA (n = 27, 50%), followed by Japan (n = 14, 26%), Canada (n = 5, 8%), China, (n = 2, 4%), Korea (n = 2, 4%), Taiwan (n = 2, 4%),

Table 1
Antibodies tested in the present case.

ANTIBODY	CLONE	DILUITION	BRAND	RESULT
S100[a]	polyclonal	Ready to use	Leica	Positive (both component)
Pancytokeratin	5D3 and LI34	1:100	Leica	Positive (both component)
GCDFP15[c]	23A3	Ready to use	Leica	Focally positive (Intraductal component)
p63	7JUL	Ready to use	Leica	Positive (myoepithelial) (Intraductal component)
CK14	LL02	Ready to use	Leica	Positive (myoepithelial) (Intraductal component)
Ki-67 (proliferative index)	MIB1	1:100	Dako	2–3%
Her-2/Neu[b]	Hercept Test™	Ready to use	Dako	Negative (Score 0)
ARc	AR27	1:25	Leica	Negative
ER[d]	6F11	Ready to use	Leica	Negative
PR[d]	6F16	Ready to use	Leica	Negative
PLAP[e]	8A9	Ready to use	Leica	Negative
PSA[e]	35H9	Ready to use	Leica	Negative
PLAG1[f]	3B7	1:50	Abnova	Negative
HMGA2[f]	D1A7	1:400	Cell Signaling	Negative

[a] S-100 marker is usually negative in salivary duct carcinoma, acinic cell carcinoma and high-grade intraductal carcinoma.
[b] 25% of salivary duct carcinoma and carcinoma ex-pleomorphic adenoma show amplification of HER-2.
[c] Androgen Receptor and GCDFP-15 (BRST-2) are useful markers of apocrine differentiation and they are usually positive in salivary duct carcinoma and high-grade intraductal carcinoma.
[d] Estrogen Receptor and Progesterone Receptor are usually negative in salivary duct carcinoma.
[e] Prostate specific antigen and Prostatic alkaline phosphatase can be positive in few salivary duct carcinoma.
[f] Markers useful, if positive, for identification of pleomorphic adenoma, carcinoma ex-pleomorphic adenoma and salivary duct carcinoma ex-pleomorphic

Czech Republic (n = 1, 2%) and Italy (n = 1, 2%); but only 5 studies described the ethnicity of patients as Japanese (n = 4, 80%) and Russian (n = 1, 20%). Lesion size was available for 23 cases, with a mean of 21,67 mm ranging between 7 and 53 mm. The mean history lesion time for patients was 49,7 ± 104,6 months. Only 16 studies (n = 16, 30%), including the present case, described diagnostic modalities employed; the most used diagnostic tool was fine needle aspiration biopsy (FNAB; n = 16, 84%), followed by magnetic resonance

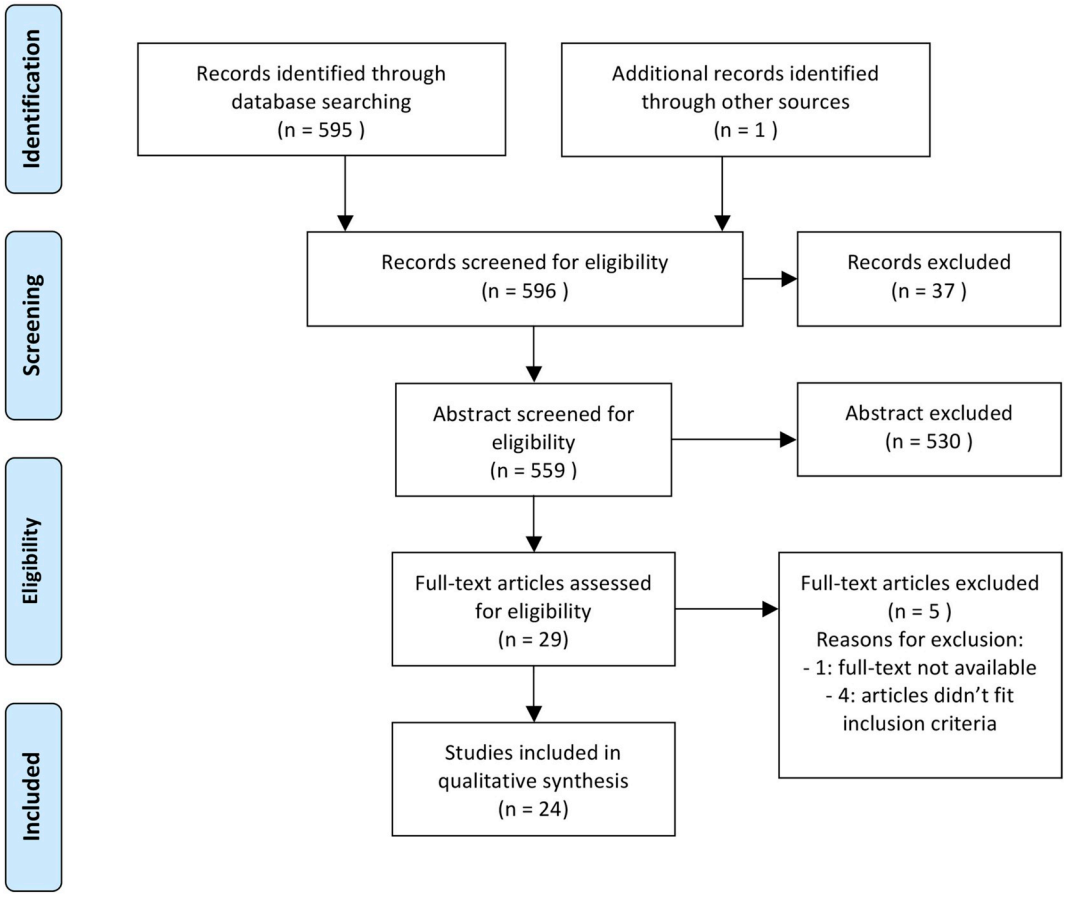

Fig. 2. PRISMA flow chart of included studies.

Table 2
a systematic review of literature.

Study Characteristics				Case Characteristics								
Authors	Year	Country	Study design	Case	Age	Etnicity	Sex	History of the lesion	Location	Size (mm)	Treatment	FU (months)
Delgado R.	1996	USA	Case series	1	58	NA	M	NA	P-sl	10	Superficial parotidectomy	NA
				2	62	NA	F	NA	P	7	Parotidectomy	NA
				3	32	NA	F	NA	RP-sl	11	Parotidectomy, radiotherapy	144
				4	63	NA	M	NA	RP-sl	13	Parotidectomy	132
				5	74	NA	M	NA	LP	18	Parotidectomy	72
				6	56	NA	F	NA	RP	10	Parotidectomy	24
				7	42	NA	M	NA	LP-sl	12	Parotidectomy	24
				8	69	NA	F	NA	RPILNT	40	Parotidectomy	24
				9	69	NA	M	NA	LP	9	Parotidectomy	NA
				10	52	NA	F	NA	RP-dl	8	Parotidectomy, radiotherapy	9 (recurrence)
Tatemoto Y.	1996	Japan	Case report	11	58	NA	F	First presentation 2 weeks before	RHPL	10 × 5	Surgical excision of the tumor	30
Ide F.	2004	Japan	Letter to editor/ case report	12	58	NA	M	First presentation 38 years before	PL	30 × 20	Simple excision	228
Brandwein-Gensler M.	2004	USA	Case series	13	62	NA	F	NA	- 14 P	NA	- 15 cases: parotidectomy	12
				14	82	NA	M	NA	- 1 ILNT	NA	- 1 case: submandibular excision	44
				15	78	NA	F	NA	- 1 SGT	NA		17
				16	72	NA	F	NA		NA		108
				17	93	NA	F	NA		NA		24
				18	NA	NA	F	NA		NA		30
				19	NA	NA	NA	NA		NA		62
				20	64	NA	F	NA		NA		33
				21	66	NA	M	NA		NA		NA
				22	57	NA	F	NA		NA		30
				23	63	NA	F	NA		NA		NA
				24	64	NA	M	NA		NA		6
				25	62	NA	M	NA		NA		132
				26	72	NA	M	NA		NA		40
				27	76	NA	M	NA		NA		24
				28	54	NA	M	NA		NA		NA
Weinreb I.	2006	Canada	Case series	29	50	NA	F	First presentation 5 months before	RP	20	Superficial parotidectomy	5
				30	73	NA	M	First presentation 9 months before	LP	18 × 13 × 10	Superficial parotidectomy, sopraomohyoid neck dissection	60
				31	67	NA	F	First presentation 7 years before	RP[b]	25 × 25 × 20	Total parotidectomy, radical neck dissection with facial nerve preservation, radiotherapy, chemotherapy	
Arai A.	2009	Japan	Case report	32	32	NA	F	First presentation 3 months before	RP	Tumor with 2 cysts: 26,7 × 19,3 × 28,5; 20,5 × 19,5 × 26,2	Parotidectomy	24
Kusafuka K.	2010	Japan	Case report	33	38	Japanese	F	First presentation 2 years before	LP	30 × 17	Superficial lobectomy of the left parotid	8
Laco J.	2010	Czech republic	Case report	34	50	NA	F	First presentation 9 months before	RP	14 × 12	Enucleation of the tumor	24
Nakazawa T.	2011	Japan	Case report	35	56	Japanese	F	First presentation 8 months before	LP-sl	30 × 25	Parotidectomy	12
Weinreb I.	2011	Canada	Case report	36	59	NA	F	NA	ILNT	35	NA	NA
Nakatsuka S-i.	2011	Japan	Case report	37	27	NA	M	First presentation more than 1-year before	LMM	15 × 7	Surgical excision of the tumor	3
Wang L.	2013	China	Case series	38	48	NA	M	NA	LP	21 × 12	Parotidectomy	16
				39	59	NA	F	NA	RP	35 × 21 × 22	Parotidectomy	7

(*continued on next page*)

Table 2 (*continued*)

Study Characteristics				Case Characteristics								
Authors	Year	Country	Study design	Case	Age	Etnicity	Sex	History of the lesion	Location	Size (mm)	Treatment	FU (months)
Obokata A.	2013	Japan	Case report	40	65	NA	M	First presentation 15 years before	SGT	42 × 42 × 35	Tumor resection and regional lymph node dissection	72
Jeong J.Y.	2013	Korea	Case report	41	90	NA	M	First presentation 3 years before	LP	53 × 45 × 4	Parotidectomy	NA
Ko Y.S.	2013	Korea	Case report	42	57	NA	M	First presentation 9 months before	RP-sl	7	Resection of the tumor	2
Schwartz L E.	2013	USA		43	NA	NA	NA	NA	NA	NA	NA	NA
Urano M.	2015	Japan	Clinical Trial[c]	44	46	NA	F	First presentation 6 months before	P	15 × 5	NA	NA
				45	50	NA	F	First presentation 12 months before	P	10 × 5	NA	NA
Kokabu S.	2015	Japan	Case report	46	56	NA	F	First presentation 1 month before	RHPL	20 × 18	Resection of the tumor	12
Stevens T.M.	2015	Canada	Clinical Trial[c]	47[a]	NA	NA	NA	NA	NA	NA	NA	NA
Hsieh M.S.	2016	Taiwan	Clinical Trial[c]	48	NA	NA	NA	NA	NA	NA	NA	NA
				49	NA	NA	NA	NA	NA	NA	NA	NA
Ohta Y.	2016	Japan	Case report	50	44	Japanese	F	NA	RP-sl	8 × 7 × 11	Superficial parotidectomy	NA
Kimura M.	2016	Japan	Case report	51	72	Japanese	M	First presentation 2 months before	MSG	8 × 8	Resection of the tumor	24
Wakabayashi N.	2017	Japan	Case report	52	51	NA	M	First presentation 5 years before	RP	45	Superficial parotidectomy	54
Nishijima T.	2017	Japan	Case report	53	75	NA	F	First presentation 1 year before	LP	40 × 38 × 35	Resection of the tumor	3
Present case	2017	Italy	Case report/ systematic review	54	43	Russians	F	First presentation 5 years before	RP-sl	46 × 20 × 10	Superficial parotidectomy and radiotherapy	12

NA: not available; F: female; M: male; FU: follow-up; P: parotid; RP: right parotid; LP: left parotid; P-sl: parotid superficial lobe; RP-ls: right parotid superficial lobe; LP-sl: left parotid superficial lobe; RPILNT: right parotid intraparotid lymph node; RP-dl: right parotid deep lobe; RHPL: right side of hard palate; PL: palate; ILNT: intraparotid lymph node tumor; SGT: submandibular gland tumor; MSG: minor salivary gland; LMM: left masseter muscle.

[a] The article described 6 cases; 5 of these were already included in Brandwein-Gensler M et al. (2004).

[b] With involvement of skin and subcutaneous tissue and extension to the external auditory canal; clinically palpable lymphadenopathy.

[c] Histology immunohistochemistry and molecular analyses.

Table 3
Use of diagnostic tools.

Study	Case	Ultrasonography	Magnetic resonance Imaging	X-ray examinations	Computer Tomography	Positron emission tomography–computer tomography	EMC-FNAB	Original diagnosis
Delgado R.	1	NA	NA	NA	NA	NA	NA	Low-grade papillocystic adenocarcinoma
	2	NA	NA	NA	NA	NA	NA	Papillocystic carcinoma
	3	NA	NA	NA	NA	NA	NA	Acinic cell carcinoma
	4	NA	NA	NA	NA	NA	NA	Acinic cell carcinoma
	5	NA	NA	NA	NA	NA	NA	Acinic cell carcinoma
	6	NA	NA	NA	NA	NA	NA	Acinic cell carcinoma
	7	NA	NA	NA	NA	NA	NA	LG-SDC
	8	NA	NA	NA	NA	NA	NA	LG-SDC
	9	NA	NA	NA	NA	NA	NA	LG-SDC
	10	NA	NA	NA	NA	NA	NA	LG-SDC
Tatemoto Y.	11			X			NA	Benign salivary gland tumor
Ide F.	12	NA	NA	NA	NA	NA	NA	NA
Brandwein-Gensler M.	13	NA	NA	NA	NA	NA	NA	NA
	14	NA	NA	NA	NA	NA	NA	NA
	15	NA	NA	NA	NA	NA	NA	NA
	16	NA	NA	NA	NA	NA	NA	NA
	17	NA	NA	NA	NA	NA	NA	NA
	18	NA	NA	NA	NA	NA	NA	NA
	19	NA	NA	NA	NA	NA	NA	NA
	20	NA	NA	NA	NA	NA	NA	NA
	21	NA	NA	NA	NA	NA	NA	NA
	22	NA	NA	NA	NA	NA	NA	NA
	23	NA	NA	NA	NA	NA	NA	NA
	24	NA	NA	NA	NA	NA	NA	NA
	25	NA	NA	NA	NA	NA	NA	NA
	26	NA	NA	NA	NA	NA	NA	NA
	27	NA	NA	NA	NA	NA	NA	NA
	28	NA	NA	NA	NA	NA	NA	NA
Weinreb I.	29						Present	NA
	30	NA	NA	NA	NA	NA	NA	NA
	31		X				Present	
Arai A.	32	X	X		X		Absent	Benign parotid tumor
Kusafuka K.	33		X		X		NA	Low grade malignant tumor such as a mucoepidermoid
Laco J	34	X					Not performed	Warthin tumor
Nakazawa T.	35		X	X	X		Uncertain	Tumor with uncertain malignant potential
Weinreb I.	36	NA	NA	NA	NA	NA	NA	NA
Nakatsuka	37		X				NA	Fibroma/granuloma
Wang L.	38	X					Not performed	NA
	39	X					Not performed	NA
Obokata A.	40				X		Present	Mucoepidermoid carcinoma
Jeong J.Y.	41		X			X	Present	Low grade malignancy of the parotid gland
Ko Y.S.	42	X			X[a]		Uncertain	Neoplasm with uncertain malignant potential
Schwartz L E.	43	NA	NA	NA	NA	NA	NA	NA
Urano M.	44	NA	NA	NA	NA	NA	NA	NA
	45	NA	NA	NA	NA	NA	NA	NA
Kokabu S.	46		X	X	X		Uncertain	NA
Stevens T.M.	47	NA	NA	NA	NA	NA	NA	NA
Hsieh M.S.	48	NA	NA	NA	NA	NA	NA	NA
	49	NA	NA	NA	NA	NA	NA	NA
Ohta Y.	50		X				Uncertain	Uncertain such as cystadenocarcinoma or cystadenoma
Kimura M.	51		X				Uncertain	Adenoma with uncertain malignant potentially
Wakabayashi N.	52		X				Absent	NA
Nishijima T.	53		X				Absent	NA
Present case	54	X			X		Uncertain	Neoplasm with uncertain malignant potential

EMC-FNAB: evidence of malignant cells at fine needle aspiration biopsy; NA: not available.
[a] Contrast-enhanced computer tomography.

imaging (MRI; n = 11, 58%), ultrasonography (n = 6, 32%), computer tomography (CT; n = 7, 37%), x-ray examinations (n = 3, 16%) and positron emission tomography–computer tomography (PET-CT; n = 1, 5%) (Table 3).

4.4. Treatment, follow-up, histological and immunohistochemical analises

Most of the cases underwent parotidectomy (n = 27, 57%), followed by excision not well defined (n = 8, 17%), superficial

parotidectomy (n = 6, 14%), parotidectomy and adjuvant radiotherapy (n = 3, 6%), superficial parotidectomy and neck dissection (n = 1, 2%), excision and lymph nodes dissection (n = 1, 2%), and total parotidectomy, radical neck dissection with facial nerve preservation, radiotherapy and chemotherapy (n = 1, 2%). The mean follow-up time for patients was 41,8 ± 48,5 months with recurrence observed in 2% (n = 1) of cases.

Histologically, the main architectural patterns were Pattern 1 and Pattern 2 (n = 43, 36%; n = 42, 36%, respectively), followed by Pattern 3 (n = 33, 28%); lesions (n = 34) were more frequently nonencapsulated cystic tumors (n = 32, 94%) with multiple cysts (n = 34, 92%). In many cases, small, round to oval nuclei with dispersed or condensated chromatin and small nucleoli (n = 40) were observed and apocrine differentiation was described (n = 43). Tumor cells with yellow to brown pigments (n = 33, 94%) were also present; instead, tumor necrosis and/or mitotic figures were observed just in few cases (n = 5, 15%). Local or perineural invasion was described in 15% (n = 6) of cases, while component or transitional area of high-grade malignancy was reported in 9% (n = 5) of cases (Table 4). Immunohistochemically, most tumor cells were positive for S-100 (n = 34, 92%), Cytokeratin AE-1/AE-3 (n = 10), Mammaglobin (n = 8), GCDFP-15 (n = 10, 67%), Calponin (n = 16, 94%), p-63 (n = 17), DOG1 (n = 6, 86%), CK14 (n = 10, 91%), SMA (n = 19, 95%), CEA (n = 7, 70%) and CK7 (n = 8, 11%). Instead, most tumor cells were negative for Her-2/ neu (n = 19, 95%), AR (n = 8, 62%), ER (n = 9, 90%), PR (n = 9, 90%) and p-53 (n = 6, 75%). The mean KI-67 labeling index was 6, ranging between 2 and 19,6 (Table 5). Only 2 cases, including the present case, were monitored for recurrence with MRI and once with PET-CT.

5. Discussion

LG-IC was first described by Delgado in 1996 with the name of "Low-grade salivary duct carcinoma" (LG-SDC): it represented the low-grade end of the spectrum of salivary duct malignant neoplasms exhibiting differentiation towards an intercalated duct-like cell phenotype[2]; thus it was not a well-accepted entity. In the 2005 WHO publications LG-SDC debuted as "low-grade cribriform cystoadenocarcinoma" (LG-CCC), a variant of cystoadenocarcinoma.[11] According to the last classification of Head and Neck tumors of WHO in 2017[12] LG-CCC were categorized as "Low-grade intraductal carcinoma" (LG-IC).[1] In literature, LG-IC was called more frequently LG-SDC (n = 32, 60%),[2,4,5,10,13–15] followed by LG-CCC (n = 15, 28%)[6,14,16–27] and LG-IC itself, including the present case (n = 6, 12%).[28–30]

Demographically, LG-IC is known to localize more frequently to the parotid gland (80%) in a widely distributed age ranged from 27 to 93 years (mean age 60 years) and with a slight predilection for female (28/49). Patient ethnicity were reported just in few studies (n = 5); lesions occurred most commonly in Japanese (n = 4),[5,6,18,26] followed by Russians with the current case (n = 1).

LG-IC is generally painless and asymptomatic; only in a case it caused paresthesias along the ear and upper neck.[29]

Because of its favourable outcome, differentiating LG-IC from other salivary gland tumors is important for appropriate treatment decisions and to maximize the quality of life of the patient. The most used diagnostic tools and gold standard was FNAB; however, it is very difficult to make a differential diagnosis by cytologic finding in the salivary gland.[23]

The smear showed cells appearing solitary or in clusters with nuclei of mildly irregular shape and inconspicuous nucleoli and little atypia; some had single, large, clear cytoplasmatic vacuoles. Inflammatory cells, including lymphocytes, neutrophils, macrophages and eosinophils were scattered across the background suggesting a cystic lesion.[18,23,25]

According to literature, FNAB is not able to differentiate this kind of tumor in fact evidences of malignancy were underlined just in 4 cases (31%),[22,23,29] while them were absent and uncertain, including the present case, in 23% (n = 3)[16, 27, 30] and 46% (n = 6)[6, 18, 21, 25, 26] respectively.

On cytomorphological diagnosis, it may be relatively easy to discriminate LG-IC from usual salivary duct carcinoma because the smears of which usually exhibit moderate to markedly anaplastic cells and contain evident necrosis in the background.[18]

In regards to treatment, all published reports recommended surgical excision with a negative margin; in most of the cases, patients underwent parotidectomy (n = 27), followed by excision not well defined (n = 8) and superficial parotidectomy (n = 6). Few articles, including the present case (n = 6), described adjuvant therapies such as radiotherapy,[2,29] chemotherapy[29] and neck dissection.[22,29]

Weinreb et al.[29] presented 2 cases treated with superficial parotidectomy with supraomohyoid neck dissection, and total parotidectomy with radical neck dissection and facial nerve preservation; the invasive treatment of the second case was justified by the additional invasive adenosquamous carcinoma component.

Delgado et al.[2] described 2 cases treated with parotidectomy and radiotherapy because of the positive margins of excision.

In the study of Obokata et al.,[22] the patient underwent surgical resection of the tumor and regional lymph node dissection with the initial diagnosis of mucoepidermoid carcinoma of the submandibular gland.

Instead, Nakatsuka et al.[19] recommended that the patient received adjuvant radiotherapy because the tumor was close to the surgical margin and for the invasive component of the tumor, but the patient did not wish to undergo the therapy.

Thus, as results from previous studies, an adjuvant radiotherapy is no justified for tumor resections with negative margins, but it may be recommended just in cases of positive margins or invasive component of the tumor. Even the presence of close margins is not an indication to radiotherapy.

Furthermore, a more aggressive LG-IC treatment with neck dissection is not indicated with a clinically and radiologically N0 neck, as shown in literature by the absence of recurrence after tumorectomy.

Weinreb et al.[29] also used chemotherapy, with a regimen not specified, for the treatment of a mixed tumor composed both by a LG-IC and an invasive adenosquamous carcinoma. According to the literature, this may be the only indication for the use of chemotherapy; in fact, it is not necessary for the treatment of LG-IC because of its favourable outcomes.

Even though LG-IC is a low-grade tumor, few cases (n = 5, 9%) with an invasive component were described in literature. Brandwein-Gensler et al.[4] presented 2 tumors that demonstrated transition from low-grade citology to more high-grade. Weinreb et al.[29] described a case with an invasive adenosquamous carcinoma in addition to LG-IC. Nakatsuka et al.[19] reported a case of LG-IC with a component of invasive adenocarcinoma of the accessory parotid gland. Finally, the current article described a case of LG-IC with an invasive component of infiltrating carcinoma not otherwise specified.

The mean age of patients with a high-grade component (n = 3) was 46 years (versus 60 years in patients without high-grade component) with a slight predilection for female (2/3).

Some authors questioned about a possible relationship between LG-IC and conventional SDC but many studies considered the two tumors as separate entities.[1,3,7]

In a study of Bahrami et al.[31] the possible role of precursor lesions in SDC were analysed; they described that some of the cases of SDC did arise in association to LG-IC, in fact 13,6% of their cohort study contained a low-grade putative precursor lesion.

The prognosis of the condition following excision is considered favourable; in this review, only a case (2%) were found to recur: Delgado et al.[2] reported a recurrence at 3 months in a patient with positive surgical margin.

Immunohistochemically, the ductal cells in LG-IC show diffuse and strong nuclear and cytoplasmic immunoreactivity with S100 protein in

Table 4
Summary of the main histological characteristics.

Study	Case	Number of cysts	Pattern 1	Pattern 2	Pattern 3	Nonencapsulated cystic tumor	Tumor cells with pale or eosinophilic cytoplasm	Small, round to oval nuclei with dispersed or condensated chromatin and small nucleoli
Delgado R.	1		+	+		+		+
	2							
	3							
	4							
	5							
	6							
	7							
	8							
	9							
	10							
Tatemoto Y.	11	M				+	+	
Ide F.	12	M	+		+			
Brandwein-Gensler M.	13	M	+	+	+	+		+
	14							
	15							
	16							
	17							
	18							
	19							
	20							
	21							
	22							
	23							
	24							
	25							
	26							
	27							
	28							
Weinreb I.	29	M	+		+		+	+
	30	M	+	+	+		+	+
	31	M	+		+		+	+
Arai A.	32	M	+		+	+		
Kusafuka K.	33	M	+	+	+	+		+
Laco J	34	M	+	+	+	+	+	+
Nakazawa T.	35	M	+	+	+		+	+
Weinreb I.	36	M	+	+	+			+
Nakatsuka	37	M	+			–	+	+
Wang L.	38	M	+	+	+	+	+	+
	39	M	+	+	+			+
Obokata A.	40	M	+	+	+		+	+
Jeong J.Y.	41	M		+	+	+	+	+
Ko Y.S.	42	M	+	+				
Schwartz L E.	43	NA	NA	NA	NA	NA	NA	NA
Urano M.	44							
	45							
Kokabu S.	46	S	+	+	+	–		
Stevens T.M.	47			+				
Hsieh M.S.	48	NA	NA	NA	NA	NA	NA	NA
	49							
Ohta Y.	50	M	+	+	+			
Kimura M.	51	S	+		+			
Wakabayashi N.	52	S		+				

(*continued on next page*)

Table 4 (*continued*)

Study	Case	Number of cysts	Pattern 1	Pattern 2	Pattern 3	Nonencapsulated cystic tumor	Tumor cells with pale or eosinophilic cytoplasm	Small, round to oval nuclei with dispersed or condensated chromatin and small nucleoli
Nishijima T.	53	M		+				+
Present case	54	M		+	+		+	+

Study	Nuclear/ cytoplasmatic ratio	Apocrine differentiation	Tumor cells with yellow to brown pigments	Tumor necrosis and/or mitotic figures	Tumor cells with intra cytoplasmic mucus	Local or perineural invasion	Nuclear atipia	Psammoma bodies	High grade component
Delgado R.		Mr-V	+		–	Only 1 case with	–	+	
Tatemoto Y.				–		–			
Ide F.				+					
Brandwein-Gensler M.		Mr-V	+	Only 2 cases with*	+	4 cases with focal limited invasion	Only 2 cases with	Only 1 case with	Only 2 cases with
Weinreb I.		AS	–	–	+		–	–	
		AS	+	–	+		–	+	
		AS	–	–	+		+	–	+
Arai A.			+		+	–	Ml		
Kusafuka K.		Mr-V		–		Lim			
Laco J		–		–			–		
Nakazawa T.	L	VS-V	+	–	–	–	–		
Weinreb I.		Mr-V		–		–	–	+	
Nakatsuka		AS/ Mr-V	+						+
Wang L.		–		–			–		
		LC		–			–		
Obokata A.		VS-V		–	–	–	Ml	+	
Jeong J.Y.		VS-V		–	–	–	Ml	+	
Ko Y.S.	L	Mr-V		–	+	–	–		
Schwartz L E.	NA	NA	NA	NA	NA	NA	NA	NA	NA
Urano M.						–	Ml		
Kokabu S.				+		–	–		
Stevens T.M.			+			–			
Hsieh M.S.	NA	NA	NA	NA	NA	NA	NA	NA	
Ohta Y.	LM	VS-V		–	+				
Kimura M.	MI	Mr-V	+		+				
Wakabayashi N.	L				+		Ml		
Nishijima T.						–	LM		
Present case	LM	–	+	+ (necrosis)	–	–	Ml	–	+

Pattern 1: cystically dilated ducts with tufted, micropapillary anastomosing proliferations.
Pattern 2: distended ducts with solid “pseudocribriform” (lacey) fenestrations or solid papillary proliferations.
Pattern 3: intraductal proliferations with “conventional architectural atypia” (Roman bridges) akin to the cribriform architectural pattern typical of low-grade intraductal breast carcinoma.
NA: not available; S: single; M: multiple; MI: marginally increased; L: low; LM: low-to-moderate; VS-V: various sizes vacuoles; Mr-V: microvacuoles; Ml: mild; Lim: limited; AS: apical snouts; LC: locally.

Table 5
Summary of the markers most used.

Study	Case	Mucicarmine	PAS	S-100	Cytokeratin AE-1/AE-3	Mammaglobin	GCDFP-15 (BRST-2)	Ki-67 LI (+%)	SOX10	Calponin	P-63	Her-2/neu	Vimentin	HMWCK	CK19	MMG	MUC1
Delgado R.	1			+			+										
	2			+			+										
	3			+													
	4			+													
	5			+													
	6																
	7																
	8																
	9																
	10																
Tatemoto Y.	11	–	–	–									–				
Ide F.	12			+				< 2									
Brandwein-Gensler M.	13		+	+ + + +		+ + + +				+ + + +		–					
	14			+ + + +		+				+ + + +							
	15			+													
	16																
	17																
	18																
	19																
	20																
	21																
	22																
	23																
	24																
	25																
	26																
	27																
	28																
Weinreb I.	29			+	+		+			+	+	–			+		
	30			+	+		+			+	+	–			+		
	31			–	+		+			+	+	–			+		
Arai A.	32		+	–				< 10									
Kusafuka K.	33			F			P	19,6		+	+	P					+
Laco J.	34		–	+	+		I				+	–					
Nakazawa T.	35		+	+			–	2–3			+	–					
Weinreb I.	36			+	+		F			+	+						
Nakatsuka	37			+	+		–	5			+						
Wang L.	38			+	+			< 5			+	–					
	39			+	+			< 5			+	–					
Obokata A.	40		+	+				< 5									
Jeong J.Y.	41			+				< 5			+						
Ko Y.S.	42	+	+	+							+						
Schwartz L E.	43																
Urano M.	44			+			–	4,4	–	+	+		+	+	+	+	+
	45									–							
Kokabu S.	46			+						+	+						
Stevens T.M.	47			+		+				+		–					
Hsieh M.S.	48								+								
	49																
Ohta Y.	50			+			–	10			+	–					
Kimura M.	51	+	+	+	+	+	P	< 9									

(*continued on next page*)

Table 5 (*continued*)

Study	Case	Mucicarmine	PAS	S-100	Cytokeratin AE-1/AE-3	Mammaglobin	GCDFP-15 (BRST-2)	Ki-67 LI (+%)	SOX10	Calponin	P-63	Her-2/neu	Vimentin	HMWCK	CK19	MMG	MUC1
Wakabayashi N.	52			+				3									
Nishijima T.	53			+		+	–	5			+	–					
Present case	54			+	+		F	2–3			+	–					

Study	Adipophilin	GATA3	AMY	DOG1	LMWCK	IgA	CK14	CD10	ETV6	SMA	CEA	AR	ER	PR	EGFR	CK7	CK20
Delgado R.										+	+						
										+	+						
										+	+						
										+	+						
										+	+						
Tatemoto Y.										–	–						
Ide F.										+							
Brandwein-Gensler M.				++++ +[a]					——+			–					
Weinreb I.							+			+		+	–	–		+	
							+			+		+	–	–		+	
							+			+		+	–	–		+	–
Arai A.										+	–						
Kusafuka K.							+				F	P	P	+		+	
Laco J.							+			+		–	–	–	–	+	–
Nakazawa T.										+		–	–	–			
Weinreb I.							+			+		F					
Nakatsuka							+			+	+					+	–
Wang L.										+	–	–	–	–	–	–	
										+		–	–	–	–	+	–
Obokata A.										+							
Jeong J.Y.										+							
Ko Y.S.																	
Schwartz L E.		–															
Urano M.	–	–	–	–	+	+	+ –	–									

(*continued on next page*)

Table 5 (*continued*)

Study	Adipophilin	GATA3	AMY	DOG1	LMWCK	IgA	CK14	CD10	ETV6	SMA	CEA	AR	ER	PR	EGFR	CK7	CK20
Kokabu S. Stevens T.M. Hsieh M.S.				+[a]					–								
Ohta Y. Kimura M. Wakabayashi N.												–	–	–			
Nishijima T.							+			+		–				+	–
Present case							+					–	–	–			

Study	GFAP	CK18	p-53	CK5/6	EMA	MUC6	MUC2	MUC4	Cam 5.2	MSA	HMWK	*E*-cadherin	*c*-erbB-2	Lactoferrin	PCNA (+%)	Cytokeratin ma 903	CD34
Delgado R.									+ + + + +							+ + + + +	
Tatemoto Y.			–		5%								–	–	5		
Ide F.			< 2										< 2				
Brandwein-Gensler M.																	
Weinreb I.			– – –						+ + +	+ + +	+ + +	+ + +					
Arai A.					P												
Kusafuka K.				+	+	+	F	F									
Laco J.		+	I	+													
Nakazawa T.																	
Weinreb I.										+							
Nakatsuka	I		–		P												–
Wang L.																	
Obokata A.	–																

(*continued on next page*)

Table 5 (*continued*)

Study	GFAP	CK18	p-53	CK5/6	EMA	MUC6	MUC2	MUC4	Cam 5.2	MSA	HMWK	*E*-cadherin	*c*-erbB-2	Lactoferrin	PCNA (+%)	Cytokeratin ma 903	CD34
Jeong J.Y.																	
Ko Y.S.																	
Schwartz L. E.																	
Urano M.																	
Kokabu S.																	
Stevens T.M.																	
Hsieh M.S.																	
Ohta Y.																	
Kimura M.																	
Wakabayashi N.																	
Nishijima T.			–						+								
Present case																	

LI: labeling index; P: partially positive; F: focally positive; I: isolated tumor cells positive.
[a] Limited to cells at the periphery of the ducts.

most cases (n = 34, 92%). Only three cases reported S100 as negative[13,16,29]; however, the case of LG-IC described by Weinreb et al.[29] with S100 negative had an invasive adenosquamous carcinoma component. Arai et al.[16] reported a case of LG-IC in which the tumor cells were negative for S100 but with a percentage of MIB-1 labeling index under 10%, suggesting that the tumor was not a high-grade SDC (with an average MIB-1 labeling index of 43%, ranging between 25 and 80%).[11]

PAS-D-positive granules were present in 21 cases (91%); it could help in the differential diagnosis with MASC in fact Khurram et al.[32] described its negativity for PAS.

Neoplastic cells are positive for AE1/AE3 (n = 10), CAM 5.2 (n = 9), cytokeratin 7 (n = 8, 89%), cytokeratin 19 (n = 4) and epithelial membrane antigen (n = 4), while cytokeratin 20 is negative in all reported cases (n = 5).[7] The layer of myoepithelial cells rimming the ducts and cyst spaces is positive for smooth muscle actin (n = 19, 95%), calponin (n = 16, 94%),[33] p63 (n = 17) and cytokeratin 14 (n = 10, 91%).[7] Estrogen receptor (n = 9, 90%), progesterone receptor (n = 9, 90%) and HER-2 (n = 19, 95%) are usually negative, while expression of androgen receptor (n = 5, 38%) and GCDFP-15 (n = 10, 67%) have been noted in less cases.[7] No expression of p53 has been found in the few cases investigated.[7] In LG-IC, GATA-3 was generally negative (n = 2); it may be useful in distinguishing LG-IC from mammary secretory carcinoma, metastatic squamous cell carcinoma, mucoepidermoid carcinoma, salivary duct carcinoma and Wartin tumor, which are usually positive.[34]

As summarized by Kuo et al.,[7] the multicystic architecture of LG-IC raise a wide differential diagnosis which includes:

- Cystadenocarcinoma: unlike LG-IC, cystadenocarcinomas are clearly infiltrative neoplasm which lack cribriform architecture and non-neoplastic myoepithelial cells when stained with SMA, MSA, and other myoepithelial markers;
- Salivary Duct Carcinoma In-Situ/High-Grade Intraductal Carcinoma (HG-IC): the differences between the two kind of tumors are nuclear grade and the presence of necrosis. The expression of S100 protein may help to separate these two lesions since HG-ICs have been either negative or only partially positive for S100 protein;
- Conventional Salivary Duct Carcinoma: SDC resembles high grade ductal carcinoma of breast, with both intraductal and widely invasive components. Immunohistochemically, the tumor cells are positive for AR and GCDFP-15, and usually negative for S100 protein;
- Acinic Cell Carcinoma, Papillary Cystic Pattern: by immunohistochemistry, acinic cell carcinoma is negative for S100 protein;
- Mammary Analogue Secretory Carcinoma (MASC): The tumor is positive for mammaglobin, S100 protein, vimentin, CK19, CK8; CK18, MUC1, MUC4, HMWK and focally with GCDFP-15, while negative for p63 and calponin;
- Cystadenoma;
- Sclerosing Polycystic Adenosis;
- Ductal Adenoma with Striated Duct Differentiation (DAS): unlike LG-IC, DASs are grossly solid and encapsulated;
- Intercalated Duct Lesion (IDLs): in contrast to the multicystic appearance of LG-IC, IDLs are composed of small ducts with mixture of bland ductal, acinic and mucus cells surrounded by a continuous layer of myoepithelial cells.

In conclusion, due to the rarity of the LG-IC, there is limited experience in dentists, oral and maxillofacial surgeons, otolaryngolosists, and primary care physicians in the diagnosis and treatment of the pathology. A right diagnosis is really important to minimize the treatment invasively, avoiding adjuvant and unnecessary therapies considering the good overall prognosis, and maximize the patient quality of life.

Conflicts of interest

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Ethical approval

Not required.

Patient content

The written consent was obtained by the patient.

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