

CASE REPORT

Intraductal Carcinoma of Salivary Gland Originating from an Intraparotid Lymph Node: A Case Report

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Abstract

Introduction: Salivary gland intraductal carcinoma (IDC) is rare. We present the second case of IDC originating from an intraparotid lymph node (LN) with a more detailed description of the histogenesis, immunohistochemistry (IHC) and updated molecular information. **Case Report:** An 87-year-old male had a tumour nodule over the left parotid tail for about 20 years. Physical examinations revealed a 4.5 cm soft, non-tender and fixed mass. After the left parotidectomy, pathology confirmed the diagnosis of IDC arising within an intraparotid lymph node. The cystic component of the tumour was lined by single to multilayered ductal cells with micropapillary growth pattern. The solid part showed intraductal proliferation of neoplastic cells in solid, cribriform, micropapillary and Roman bridge-like structure. By immunohistochemistry (IHC), the tumour cells were positive for S-100, CK (AE1/AE3), mammaglobin, SOX10, and estrogen receptor (ER), with myoepithelial cell rimming highlighted by positive p63 and calponin IHC stains. The prognosis of this patient is excellent after complete excision. **Discussion:** The mechanism of salivary gland tumour arising in the intra-parotid gland LN was assumed to be related to salivary duct inclusion within the intraparotid gland LN which is a normal occurrence during embryology development. Although the terminology may raise some confusion about the relationship between IDC and conventional salivary duct carcinoma (SDC), they are different in immunophenotype and clinicopathologic features. IDC is characterised by S100 (+) ER (+) with predominant intraductal growth and excellent prognosis; while SDC features S100 (-) androgen receptor (+) with predominant invasive growth and aggressive behavior. Recent discovery of recurrent *RET* gene rearrangement in IDC but not SDC also supports that IDC is not precursor lesion of the SDC.

Keywords: Cribriform cystadenocarcinoma, low-grade, low-grade salivary duct carcinoma, intraductal carcinoma.

INTRODUCTION

The low-grade salivary duct carcinoma (LGSDC) was proposed firstly by Delgado et al.¹ in 1996. World Health Organization (WHO) defined this entity as the low-grade cribriform cystadenocarcinoma with the similar spectrum of breast lesions ranging from atypical ductal hyperplasia to micropapillary and cribriform low-grade ductal carcinoma in-situ in 2005.² The entity is now termed intraductal carcinoma

(IDC) in 2017 WHO classification of head and neck tumours.³

IDC is rare, and there is only one case report of IDC arising from intraparotid lymph node.⁴ We present the second case of IDC originating from an intraparotid lymph node, comparing with the previous report, with a more detailed description of the histogenesis, immunohistochemistry (IHC) and updated molecular information.

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CASE PRESENTATION

An 87-year-old male came to our out-patient department with chief complaint of a tumour nodule over the left parotid area. He noticed that the tumour, which has persisted for about 20 years, became enlarged progressively in recent two years. At outpatient attendance, physical examinations revealed a 4.5cm soft, non-tender and fixed mass over the tail of the left parotid gland. There was no facial palsy. CT scan was arranged and showed a left parotid gland tumour, 4.5cm x 3.1cm x 3.3cm, with mixed solid and cystic parts. (Fig. 1) There was no neck lymphadenopathy.

The patient received left superficial parotidectomy, which is corresponding to left parotidectomy I-II of European Salivary Gland Society (ESGS) classification, and the entire lesion was totally removed by en bloc resection with the surrounded parotid gland.⁵ Grossly, the tumour was well circumscribed, solid-cystic and yellow-brown on cut. Microscopically, the sections showed a mixed solid and cystic lesion within an intra-parotid LN. (Fig. 2A) The cyst was lined by single to multilayered ductal epithelial cells with foci of micropapillary growth along the cystic wall. (Fig. 2B) The solid part was composed of intraductal proliferation of neoplastic cells in solid, glandular, cribriform, micropapillary and Roman bridge-like structures. (Fig. 2C) The growth patterns were reminiscent of those seen in mammary usual and atypical ductal hyperplasia or low-grade ductal carcinoma



FIG. 1: Left parotid gland tumour sized 4.5 x 3.1 x 3.3cm with the mixed content of solid and cystic parts on CT scan with contrast.

in situ. Most of the neoplastic cells had indistinct cell border, round to ovoid vesicular nuclei, small distinct nucleoli and eosinophilic cytoplasm. There was no tumour necrosis or mitotic activity. Diastase resistant periodic acid-Schiff (PAS) positive eosinophilic secretions in microcystic and tubular spaces were prominent in some areas. Focal keratinizing squamous metaplasia was identified lining the cystic wall and shedding necrotic squamous epithelium and keratin into the cystic cavity. Yellow-brown pigment within the ductal epithelial cell was noted focally. The tumour was localised within an intraparotid lymph node characterised by lymphoid tissue surrounded by fibrous capsule with subcapsular sinus. Diffuse reactive follicular hyperplasia with germinal center was identified in the LN. Surgical margin was free of tumour. By IHC, the tumour cells were positive for S-100 (Fig. 3A), cytokeratin (CK)-AE1/AE3, mammaglobin (Fig. 3B), SOX10, and estrogen receptor. Her2 IHC stain demonstrated only focally weak positive in less than 10% the tumour cells. p63 (Fig. 3C) and calponin IHC stains highlighted rimming of myoepithelial cells depicted on the periphery of the tumour nests. Ki-67 proliferating index was less than 1%. A diagnosis of IDC, low grade, was made. After the operation, close observation was suggested to the patient without further treatment.

DISCUSSION

In the last released 2017 WHO classification of head and neck tumours, the low-grade cribriform cystadenocarcinoma and salivary duct carcinoma (SDC) in situ are regarded as synonyms for the IDC, which has a range of cytological features and can be graded as low-grade, intermediate-grade, or high-grade IDC on the basis of the degree of the cytological abnormalities.^{3,12} However, it may raise some confusion about whether this group of IDC (synonym: SDC in situ) is related to the conventional SDC (synonym: high-grade ductal carcinoma). Recently, Weinreb et al.⁶ found the recurrent *RET* gene rearrangements present in 47% of patients with low-grade IDCs positive for S-100 and characteristic of intercalated type, which was much less invasive than apocrine intraductal lesions of the conventional SDC bearing usual mutations in *PIK3CA* and *HRAS*. The combined features of the IDC (ICD-O code 8500/2) with diffuse S100 (+) ER (+), predominant intraductal growth and excellent prognosis, are also in contrast to those of the

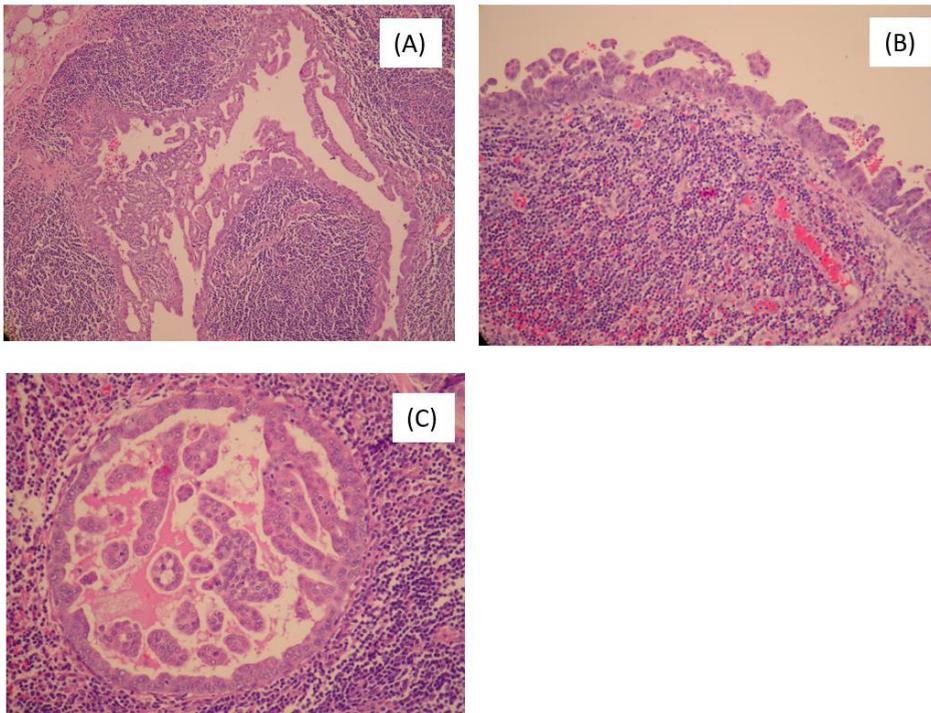


FIG. 2: (A) Intraductal proliferation resembling usual ductal epithelial hyperplasia of the breast. The lesion is located within a lymph node showing capsule with subcapsular sinus (left upper). (B) Cystic epithelial lining with micropapillary proliferation. (C) Micropapillary and Roman bridge-like structure.

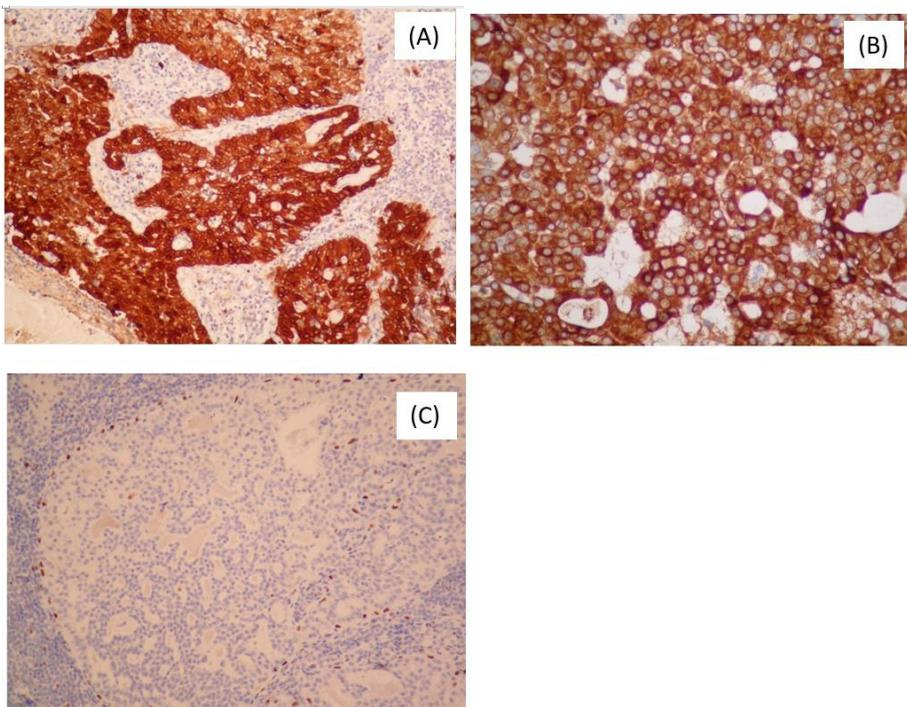


FIG. 3: The tumour cells are diffusely positive for S-100 (A) and mammaglobin (B) by IHC stains. (C) Rimming of myoepithelial cells, highlighted by p63 IHC stain, around the tumour nest.

SDC (ICD-O code 8500/3) which shows S100(-) AR(+), predominantly invasive growth and aggressive behavior.⁷ Further categories beyond current WHO classifications may be developed after analysis of bigger series in the future.

Differential diagnosis of the IDC may include Warthin tumour, secretory carcinoma (synonym, mammary analogue secretory carcinoma), acinic cell carcinoma, and a variant of adenocarcinoma, NOS. Warthin tumour is composed of cystic and papillary structures lined by inner columnar and outer cuboidal cells in a background of lymphoid stroma with germinal centers.⁸ Squamous metaplasia can be identified and the oncocytic epithelium can form closely packed tubules, but rarely solid and micropapillary, or to the degree resembling mammary atypical ductal hyperplasia or ductal carcinoma in situ as observed in the IDC. Warthin tumour does not show diffusely positive for S-100 and myoepithelial cell rimming. The presence of the myoepithelial cell rimming along with the bland nuclear features also excludes the possibility of salivary duct carcinoma arising in Warthin tumour.⁹ In our case, the presence of abundant eosinophilic homogenous secretions in microcystic and tubular spaces raised concerns about secretory carcinoma (synonym: mammary analogue secretory carcinoma) which is also characteristically positive for S100 protein and mammaglobin. However, secretory carcinoma characteristically exhibits a lobular growth pattern with fibrous septa. The presence of Roman bridge-like epithelial proliferation and peripheral rimming of myoepithelial layer also help exclude this mimic.¹⁰ In difficult circumstances, molecular methods assessing the presence of *ETV6-NTRK3* fusion confirm a diagnosis of secretory carcinoma.^{11,12} The acinic cell carcinoma features solid, microcystic, follicular and occasionally papillary cystic structure with microvacuolar and basophilic granular cytoplasm. In addition, the tumour cells are negative for S-100 and lack intraductal proliferation as seen in IDC.

In our case, the tumour cells exhibit low-grade nuclei and low Ki-67 proliferating index without necrosis or mitosis. This low-grade morphology corresponds to the tumour having been persisting for 20 years. However, the tumour became enlarged in recent two years. The mechanism of progressive enlargement may be caused by the occurrence of the cystic structure and imbalance between secretion and reabsorption, resulting in accumulation of cystic fluid with time. In intermediate and high-grade IDC with cellular

atypia and frequent mitoses, the presence of myoepithelial cell rimming around tumour nests helps to exclude metastatic carcinoma.^{4,13}

The origin of salivary gland tumour arising from intraparotid gland LNs was assumed to be associated with ectopic salivary gland tissue within the intraparotid gland LN.¹⁴ The histogenesis of this phenomenon has been related to embryonic development. In the fetus, the parotid gland is closely related to lymphoid tissue from the beginning of the 2nd month. By the 3rd month, the epithelial structures are arranged in lobules, and the mesenchyme of the parotid gland is colonised by numerous lymphocytes that are later disposed in intraglandular and extraglandular LNs. During the process of progressive development of an LN in the salivary lobules, salivary inclusions into the LN is in fact a constant feature of fetal parotid gland.^{15,16} Ectopic salivary gland tissue can be found in many other sites including the soft tissue of the neck, the middle ear, the mastoid, and pituitary region. In addition to the intraparotid LN, paraparotid and upper cervical LNs were also noted as sites of heterotopic salivary tissue.¹⁷ The tumour that most commonly arises in ectopic salivary gland tissue is the Warthin's tumour.¹⁴ According to the above histogenesis, the lymphoid component of the Warthin tumour is actually an LN within the parotid gland, and the epithelial component of the Warthin tumour corresponds to altered included or heterotopic salivary ducts inside the intraparotid LN.¹⁵ Other tumours arising within lymph nodes, such as pleomorphic adenoma, basal cell adenoma, acinic cell carcinoma, mucoepidermoid carcinoma, and sebaceous gland carcinoma, have been reported.^{14,18,19}

Surgery alone remains the mainstream of the treatment for LGSDC, and the prognosis is excellent after complete excision.²⁰ The significance of focal invasion in IDC is uncertain. However, nodal and distant metastases have not been reported to date.³ Considering the low-grade histology in general salivary gland carcinomas, adjuvant therapy was not favoured for the tumour in pathological stage T3 without positive margins and lymph node metastasis.²¹ To the clinical aspect, this case was more suitable for a limited surgery with a proper surgical margin due to its well-encapsulated inside the lymph node.⁴

In conclusion, IDC is rare, and only one case of IDC arising in an intraparotid LN has been reported. We reported the second with updated information. The histogenetic mechanism of salivary gland neoplasm arising in intraparotid

LN has been related to their intimate relationship during their embryology development. The current diagnostic terminology of IDC may raise concerns about its relationship to the conventional SDC. However, the difference in the immunophenotype and clinicopathological features, combined with the recent discovery of recurrent *RET* gene rearrangement in IDC but not SDC support that IDC is not precursor lesion of SDC, and should be categorised as separate entities as it is in the current WHO 2017 classification.

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