Clinical Case Report

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Submandibular oncocytic carcinoma

A case report and literature review

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Abstract

Background: Oncocytic carcinoma (OC) arising in the submandibular gland is an unusual malignant neoplasm, with <20 cases previously reported. The cancer is characterized by numerous morphologically abnormal mitochondria present in the cytoplasm and marked cellular pleomorphism. At its most severe, the tumor may invade into the surrounding tissues, including intravascular, lymphatic, or perineural invasion, and lead to regional nodal or distant metastasis.

Methods: The current study describes a novel OC case in a 46-year-old male, the youngest case of the review. The patient presented with a 5-month history of an intermittently painful mass.

Results: Following magnetic resonance imaging, excisional biopsy, hematoxylin-eosin staining, phosphotungstic acid-hematoxylin staining, and immunohistochemical examination, an OC of the submandibular gland was diagnosed.

Conclusion: The current study summarizes the pathogenesis, diagnosis, therapeutics, and the prognosis of OC. The literature review regarding this rare disease is also presented to emphasize the lack of specific markers of OC and the risk of cervical lymph metastasis.

Abbreviations: CK = pan-cytokeratin, EMA = epithelial membrane antigen, FNA = fine-needle aspiration, OC = oncocytic carcinoma, PTAH = phosphotungstic acid-hematoxylin, SMA = α-smooth muscle actin.

Keywords: immunohistochemistry, malignant oncocytoma, malignant oxyphilic adenoma, salivary gland, submandibular gland

1. Introduction

Oncocytic carcinoma (OC) of the submandibular gland is a rare malignant neoplasm, with <20 cases reported since Bauer's first description of OC in 1953.[1] It is also recognized to exhibit adenocarcinomatous architectural phenotypes characterized by the proliferation of morphologically abnormal mitochondria in the cytoplasm, local invasion, and regional or distant metastasis. Due the rarity of submandibular OC, the disease features and indicators of prognosis are poorly defined. The present study describes an original case of submandibular gland OC and summarizes the current literature on the disease pathogenesis, diagnosis, therapeutics, and prognosis.

1.1. Case report

A 46-year-old male with a 5-month history of an intermittently painful mass on the right submandibular gland was referred to the First Affiliated Hospital of Gannan Medical University (Ganzhou, China) in August, 2015. Considering the gradually increasing mass, a series of examinations were performed. The physical examination indicated a fixed, hard mass in the right submandibular region, ~5.2 × 4.5 cm in size. Notably, swelling of the lymph nodes was not observed on either side of the maxillofacial region and neck. The submandibular branch of the facial nerve, the hypoglossal nerve, and the mandibular nerve were functionally normal. Magnetic resonance imaging demonstrated a 48 × 26 mm inhomogeneous mass in the right submandibular gland. Other examinations, including intraoral examination, did not demonstrate any abnormalities.

Following assessment of the condition, an excisional biopsy was performed on day 6 of hospitalization and the mass was initially diagnosed as myoepthelioma. However, due to the small size of the biopsy specimen and the lack of knowledge, the diagnosis was uncertain. Following examination of the medical history of the patient, surgery in the submandibular region was performed again. The tumor (60 × 30 × 15 mm) was unencapsulated and macroscopic observation demonstrated a red mass with pale-grey cut surface. Microscopic analysis using hematoxylin-eosin staining demonstrated that the mass was composed of large round/polyhedral-shaped cells arranged in solid sheets, islands, duct-like structures, and cords. The cytoplasm was enriched with eosinophilic granular staining and the nuclei were characteristically round (often with large red nucleoli). In addition, the tumor

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HX and TW contributed to the work equally and should be regarded as cofirst authors.

The patient signed informed consent for the publication of this case report and any accompanying images. Ethical approval of this study was obtained by the ethics committee of Gannan Medical University.

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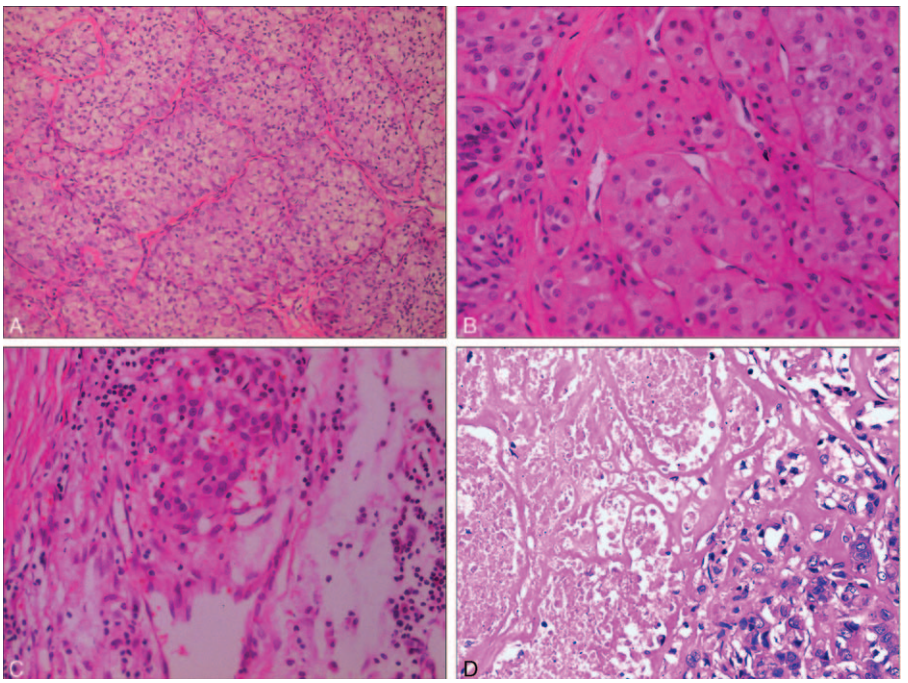

Figure 1. Hematoxylin-eosin staining of OC. (A) Solid sheets and island structures in OC. (B) Eosinophilic granular cytoplasm and round vesicular nuclei in tumor cells. (C) Tumor cells invasion into the blood vessels. (D) Necrotic OC cells. OC = oncocytic carcinoma.

cells were observed to be invading into surrounding tissues and blood vessels (Fig. 1). Immunohistochemical staining of the neoplasm was performed using antibodies against pan-cytokeratin (CK), CK7, epithelial membrane antigen (EMA), α-smooth muscle actin (SMA), CD10, p63, S-100, actin, calponin, thyroid transcription factor-1, and thyroglobulin (Table 1). The stained tumor cells were positive for CK, CK7, and EMA (Fig. 2A, B). The staining with all other antibodies was negative (Fig. 3). The Ki-67 labeling index was approximately 7% in regions of high staining intensity (Fig. 2C). Furthermore, intense positive phosphotungstic acid-hematoxylin (PTAH) staining was observed in the cytoplasm, which indicated marked proliferation of morphologically abnormal mitochondria (Fig. 2D). Ultimately, an OC of the submandibular gland was diagnosed. Upon follow-up, the patient exhibited no evidence of disease recurrence following discharge.

2. Discussion

OCs are extremely rare, accounting for ~0.5% of all epithelial salivary gland malignant neoplasms and 0.18% of all epithelial salivary gland tumors,[2] with occurrence of OC arising in the submandibular gland even less common. The terminologies OC, oncocytic tumors, oncocytic adenocarcinoma, oncocytic neoplasms, malignant oncocytoma, malignant oncocytic adenoma, malignant oxyphilic adenoma, and oxyphilic adenocarcinoma are synonymous. In addition, OC tumors have been demonstrated to occur in a wide variety of tissues, including the neuroendocrine system, pituitary, paraganglion, paranasal sinuses and pleura, thyroid, parathyroid and lacrimal glands, respiratory tract, adrenal cortex, kidney, liver, stomach, pancreas, colon and rectum, genital tracts, skin, and soft tissues.[3] To the best of our knowledge, only 14 cases of submandibular gland OC have been previously reported (Table 2).[4–17] In this context, this review summarizes the pathogenesis, diagnosis, therapeutics, and prognosis of OC.

2.1. Pathogenesis

There is currently no consensus regarding the pathogenesis of OC. However, as demonstrated in Table 2, males appear to be more prone to developing submandibular OC, with a ratio of 13:3 (male:female). The average age of onset was 62.4 years and the case reported in the present study is the youngest patient described in the literature (46 years old). However, the mean age of oncocytoma development was reported to be 58.7 years, with a male-to-female ratio of 1.0.[4] Thus, the age of patients with submandibular OC appears to be higher than oncocytoma in general, suggesting that OCs arise de novo.

In addition, the present study demonstrated that the OC tumor was positive for CK, CK7, and EMA expression. Previous reports

Table 1

Antibodies used for immunohistochemistry.

Antibody	Source	Dilution	Reaction
CK	Maixin	Ready to use	Positive
CK7	Maixin	Ready to use	Positive
EMA	Maixin	Ready to use	Positive
SMA	Maixin	Ready to use	Negative
Calponin	Maixin	Ready to use	Negative
Actin	Maixin	Ready to use	Negative
p63	Maixin	Ready to use	Negative
S-100	Maixin	Ready to use	Negative
CD10	Maixin	Ready to use	Negative
TTF-1	Maixin	Ready to use	Negative
TG	Maixin	Ready to use	Negative

CK = pan-cytokeratin, EMA = epithelial membrane antigen, SMA = α-smooth muscle actin, TG = thyroglobulin, TTF-1 = thyroid transcription factor-1.

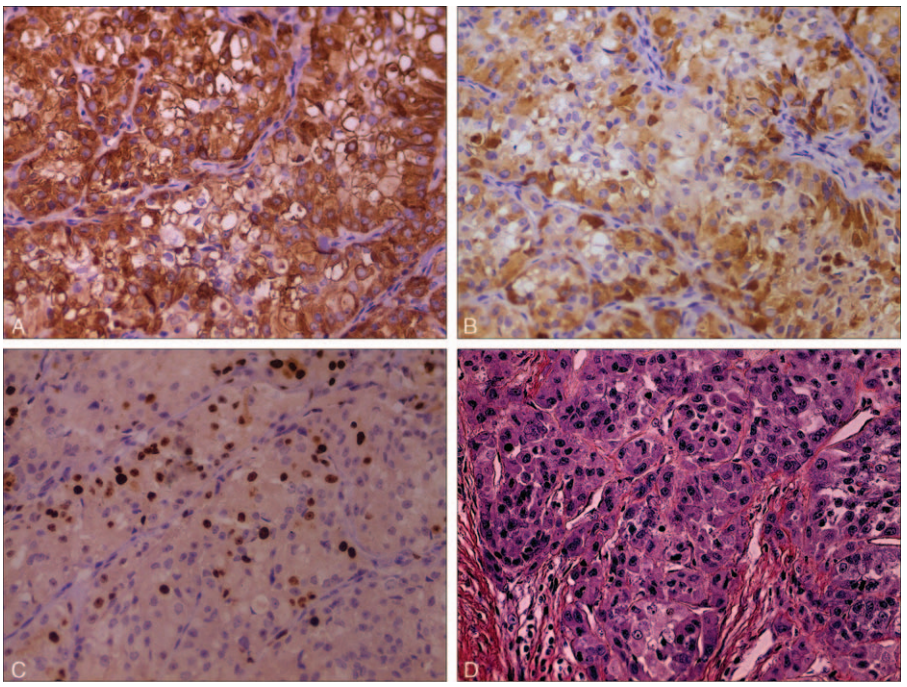

Figure 2. Immunohistochemical reactivity of the tumor cells with (A) pan-cytokeratin and (B) epithelial membrane antigen. (C) Ki-67 positive nuclear staining in malignant oncocytes. (D) Phosphotungstic acid-hematoxylin stain with positive cytoplasmic granules (mitochondria).

have indicated that both luminal and abluminal cells in the normal salivary gland were CK-positive, and the EMA was a luminal cell marker with positive staining in luminal cells only.[18] Furthermore, in the current case, the tumor staining was negative for SMA, calponin, actin, P63, and S-100. These immunohistochemical markers suggest that the origin of the submandibular OC was associated with luminal cells, and not with myoepithelial cells. The immunohistochemical analysis and oncocyte distribution suggest that the OC may be derived from cells in the intercalated ducts.

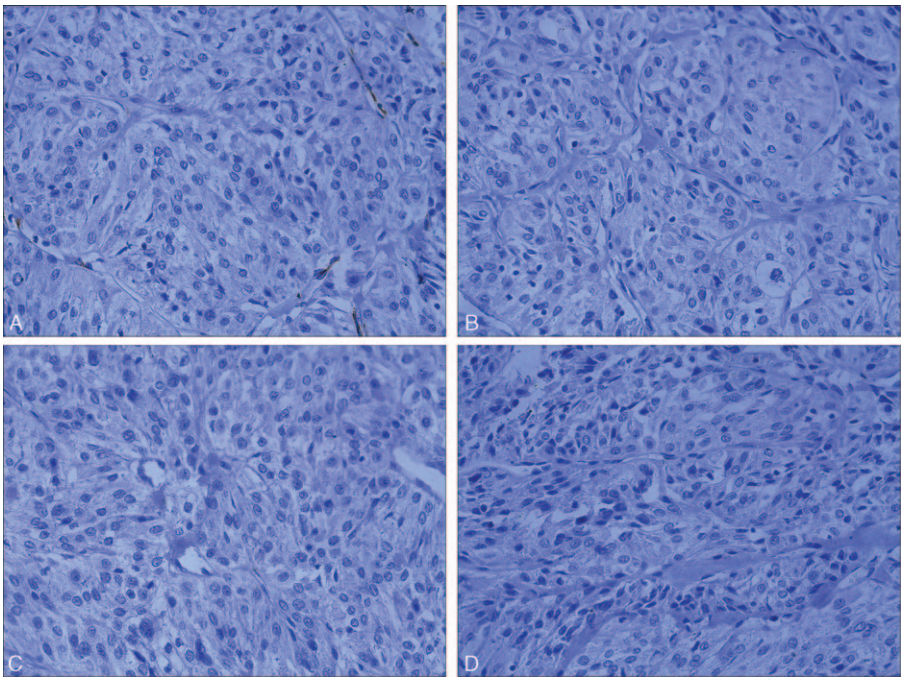

Figure 3. Immunohistochemical reactivity of the tumor cells with (A) α-smooth muscle actin (SMA) (B) CD10. (C) hyroid transcription factor-1. (D) Thyroglobulin negative nuclear staining in malignant oncocytes.

Table 2

Summary of previously reported cases of oncocytic carcinoma arising in the submandibular gland.

Author (reference no.)	Year	Age, y	Gender	Treatment	Metastasis	Prognosis
Mukai et al[8]	1978	61	M	RE + CH + RA	No	Alive, 3 y
Goode and Corio[6]	1988	74	M	RE	CL	Alive, 9 y
		60	F	RE	Unknown	N/A
Brandwein et al[9]	1991	62	M	Unknown	CL	Alive, 6 mo
Ziegler et al[10]	1992	56	F	RE	Unknown	Alive, 9 mo
Wu et al[11]	1998	77	F	RE	CL	Alive, 6 mo
Nakada et al[7]	1998	69	M	RE + Ra	CL	Alive, 1.5 y
Manhnke et al[12]	1998	47	M	RE + Ra	No	N/A
Wischerath et al[5]	2002	59	M	RE + Ra	CL	N/A
Muramatsu et al[13]	2003	82	M	RE	CL + liver	Died after 1 y
Mizutari et al[14]	2005	55	M	RE + RA	No	Alive, 20 mo
Lee et al[15]	2009	67	M	RE + CH	Bone	N/A
Lee et al[16]	2010	54	M	RE + RA	CL	N/A
Wei et al[17]	2014	53	M	RE	No	Alive, 116 mo
Tamai et al[4]	2015	76	M	RE + CH	CL + LN + MED	Alive, 80 mo
Present case	2016	46	M	RE	No	Alive, 8 mo

CH = chemotherapy, CL = cervical lymph, F = female, LN = lung, M = male, MED = mediastinal, N/A = not available, RA = radiotherapy, RE = resection.

2.2. Diagnosis

The clinical symptoms of OC are varied. It normally presents as a rapid growth mass with no obvious symptoms, although in a small proportion of cases, pain, numbness, lymphadenectasis, or facial paralysis occurs. Specifically, on the basis of the World Health Organization Histological Typing of Salivary Gland Tumors,[19] the diagnostic indicators of OC arising in the salivary gland include a lack of encapsulation, regional nodal or distant metastasis, intravascular, lymphatic or perineural invasion, and mitoses or cellular pleomorphism. The majority of these indicators, which also suggest a malignant phenotype, were present in the current submandibular OC case.

In addition, various auxiliary examinations may be used to diagnose OC or differentiate from other similar diseases, including hematoxylin-eosin staining, PTAH-staining, electron microscopy, fine-needle aspiration (FNA), and immunohistochemistry. Light microscopy and hematoxylin-eosin staining can indicate whether the cytoplasm is filled with eosinophilic granules. PTAH staining and electron microscopy were may be used to examine the mitochondria. PTAH staining can indicate profuse dark-blue cytoplasmic granules and mitochondrial immunostaining may indicate positive, finely granular immunoreactivity in the cytoplasm of oncocytes. FNA can be used to aid the diagnosis of OC when the tumor is highly atypical. Otherwise, it may be challenging to differentiate OC from benign oncocytoma and other benign oncocytic tumors. Furthermore, Tamai et al[4] reported that the nuclear size was significantly larger in OC than in oncocytomas ($P < 0.001$). Regarding immunohistochemistry, recent studies have demonstrated that the combined use of several antibodies may be able to distinguish OC from other oncocytic subtype carcinomas, although more specific markers are required. Tamai et al[4] demonstrated the usefulness of immunostaining for p63 and SOX10 to differentiate between OC and oncocytic mucoepidermoid carcinoma or acinic cell carcinoma (Table 3).

2.3. Therapeutics

The combination of complete surgical resection of the tumor mass and metastatic area is the widely accepted treatment for OC.[1] However, adjuvant radiotherapy may be useful for local control of OC.[5] As for chemotherapy, it is rarely considered in symptomatic patients, due to its low efficacy.[20]

2.4. Prognosis

A previous report suggested that OC arising in the submandibular gland commonly recurs locally or metastasizes to the cervical lymph nodes. Fujita et al[21] reported that the argyrophilic nucleolar organizer regions score of OC was 2-fold higher than other salivary gland tumors. This may be a factor in the poor prognosis of OC. In addition, Goode and Corio[6] reported that OC of <2 cm exhibited preferable prognoses compared with larger neoplasms. Furthermore, Nakada et al[7] indicated that the most significant prognostic indicator of OC is distant metastasis,

Table 3

Differentiation of oncocytic carcinoma from other oncocytic subtype carcinomas.

Disease	Diagnosis
Oncocytic carcinoma	Large nuclear size; SOX (-); p63 (-); intensity positive of ki-67
Oncocytoma	Low-grade atypia; SOX 10 (-); p63 (+); low positive of Ki-67
Salivary duct carcinoma	Comedo-like necrosis in the solid center; duct-like spaces with papillary or cribriform growth
Acinic cell carcinoma	Amphophilic or basophilic cytoplasmic granules; growth with microcystic or papillary; SOX 10 (+); P63 (-)
Oncocytic mucoepidermoid carcinoma	Diffusely positive for p63
Metastatic renal cell carcinoma	CD10 (+); CK20 (+)
Metastatic thyroid carcinoma	TTF-1 (+); TG (+)

SOX = SRY-box containing gene, TG = thyroglobulin, TTF-1 = thyroid transcription factor-1.

whereas regional nodal metastasis is not necessarily a good indicator. In the current case, no metastases were observed, potentially due to the short follow-up period.

3. Conclusion

To the best of our knowledge, the morphological features of OC have not been sufficiently investigated and the elucidation of specific immunohistochemical diagnostic markers is required. In addition, further research is important to improve the prognosis of patients with OC.

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