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Case Report

Macrocystic and non-necrotic salivary duct carcinoma of the submandibular gland: A case report ☆,☆☆

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ABSTRACT

Salivary duct carcinoma (SDC) is a major malignant salivary gland tumor that usually forms a solid tumor. Non-necrotic macrocystic SDCs have rarely been reported among salivary gland tumors. A 78-year-old Japanese man with a submandibular gland tumor was evaluated radiologically, pathologically, and immunohistochemically. A multilocular lesion with a maximum size of 6 cm was radiologically observed in the left submandibular region. It had been noticed 20 years earlier. Malignant cytological result was obtained, and surgical resection was performed. Pathological examination revealed a non-necrotic, macrocystic submandibular gland tumor lined with glandular, cribriform, or papillary forms of atypical cuboidal cells. Frankly invasive components were observed in intercystic areas. Intraductal, mucoepidermoid, and secretory carcinomas were identified as pathological differential diagnoses because of their macrocystic morphology. We diagnosed SDC because there was no intraductal growth based on the lack of myoepithelial markers, diffuse immunoreactivity to gross cystic disease fluid protein15, androgen receptor, and mammaglobin and immunoneg-

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ativity to S100 and p63. Postoperative positron emission tomography revealed the absence of lymph node and distant metastases. The patient was disease-free 9 months after surgery. Salivary duct carcinoma can be included in the differential diagnoses of cystic salivary gland tumors.

Introduction

Salivary duct carcinoma (SDC) is a salivary gland tumor with an aggressive clinical course [1]. SDCs mostly arise from the parotid gland and can be derived from pleomorphic adenomas and intraductal carcinoma [2,3]. They usually form a solid mass [1]; however, cystic morphology with small cysts is included in the macroscopic features of SDCs, probably because of tumor necrosis and/or the precursor lesion of intraductal carcinoma [1,4]. Radiologically, a study by Weon et al. reported that 20% (4/20 cases) of SDCs predominantly showed cystic tumors due to extensive tumor necrosis [5].

The SDC in our case presented as a non-necrotic macrocystic mass without a solid component, similar to the presentation of an intraductal carcinoma of the salivary gland. No similar cases have been reported in the past. The clinicopathological findings of our case are presented and discussed in relation to distinguishing features from cystic salivary gland neoplasms [6], including intraductal carcinoma.

Case report

A 78-year-old Japanese man was referred to our hospital for diagnosis and treatment of a left submandibular mass. His medical history included Basedow's disease, pulmonary tuberculosis, bronchiectasis, and lung cancer. Lung cancer was resected 2 years before admission, and the postoperative diagnosis was acinar adenocarcinoma with TNM stage pT1bcN0cM0 and stage IA2. The asymptomatic mass in the left submandibular region had been noticed approximately 20 years earlier and had enlarged since 6 months prior to admission. Physical examination confirmed the presence of a non-tender protruding mass with a maximum size of 6 cm in the left submandibular region. Laboratory test results, except for serum carcinoembryonic antigen (CEA) were unremarkable. High levels of serum CEA (8.3 ng/mL, normal range <5 ng/mL) were observed, possibly due to bronchiectasis, as high levels of serum CEA had been detected during the preoperative period of lung cancer. Computed tomography (CT) confirmed that the mass was a multilocular lesion involving the left submandibular gland (Fig. 1) without metastasis. Fine-needle aspiration cytology confirmed the presence of malignant cells (category VI of the Milan system) suggestive of an adenocarcinoma. Therefore, a cystic salivary gland tumor was suspected. The lesion was surgically resected to confirm its nature of the cystic lesion. During surgery, the cystic tumor was connected to the left submandibular gland, and tumorectomy was performed to include the normal submandibular gland and the surrounding skin tissue.

The resected mass was 6.0 × 5.0 × 3.0 cm and showed a demarcated and multilocular lesion with small- to large-sized cysts (Fig. 2). Small cystic components appeared to be present in the submandibular glands, and the larger cystic component protruded towards the resected skin. Gelatinous material was also present in the cystic space. No solid lesions were observed. Whole-mount preparation of the tumor was performed.

Microscopically, the tumor cells formed macroscopic and microscopic cysts (Fig. 3A and B). In the intercystic areas, cuboidal or polygonal tumor cells with round to oval nuclei with or without distinct nucleoli and abundant cytoplasm invaded in an irregular tubular fashion with fibrous stroma (Fig. 3C). The mitosis of the tumor cells was scattered. In the luminal portion of the cystic lesions, cuboidal tumor cells were arranged in a single layer (Fig. 3D), in a cribriform or Roman bridge-like arrangement (Fig. 3E), papillary, or in a micropapillary fashion (Fig. 3F). The tumor cells lining the cystic lesions showed mild to severe atypia and apical snouts, and included mucinous tumor cells (Fig. 3D, inset). Comedonecrosis was absent. The tumor border was demarcated (Fig. 3A), and the cystic tumor component reached the subcutaneous tissue but not the skin tissue. The submandibular gland tissue was detected at the tumor periphery, and atrophic salivary gland tissue was included in the intercystic lesions. No pleomorphic adenoma was observed. Therefore, salivary gland neoplasia derived from the left submandibular gland was diagnosed. Histological diagnoses included intraductal carcinoma, mucoepidermoid carcinoma, SDC, and adenocarcinoma not otherwise specified. Metastatic lung adenocarcinoma was unlikely but was included in the differential diagnoses. Four lymph nodes without metastases were observed around the tumor.

Immunohistochemically, the tumor cells were diffusely positive for gross cystic disease fluid protein15 (GCDFP15, Fig. 4A), androgen receptor (AR, Fig. 4B), mammaglobin, GATA3 (Fig. 4C), and cytokeratin 19 (CK19); focally positive for human epidermal growth factor receptor 2 (HER2, score 1+, Fig. 4D); and negative for CK5, CK14 (Fig. 4E), p40, p63 (Fig. 4F), alpha-smooth muscle actin, H-caldesmon, S100, SOX10, glial fibrillary acidic protein, estrogen receptor, progesterone receptor, thyroid transcription factor 1, and Napsin A. Although immunostaining for various myoepithelial markers (CK5, CK14, p40, p63, alpha-smooth muscle actin, H-caldesmon) was performed at many tumor sites, intraductal localization of the tumor cells was absent. SDC with macrocystic morphology was diagnosed.

Postoperative 18-fluorodeoxyglucose positron emission tomography/computed tomography showed neither tumor

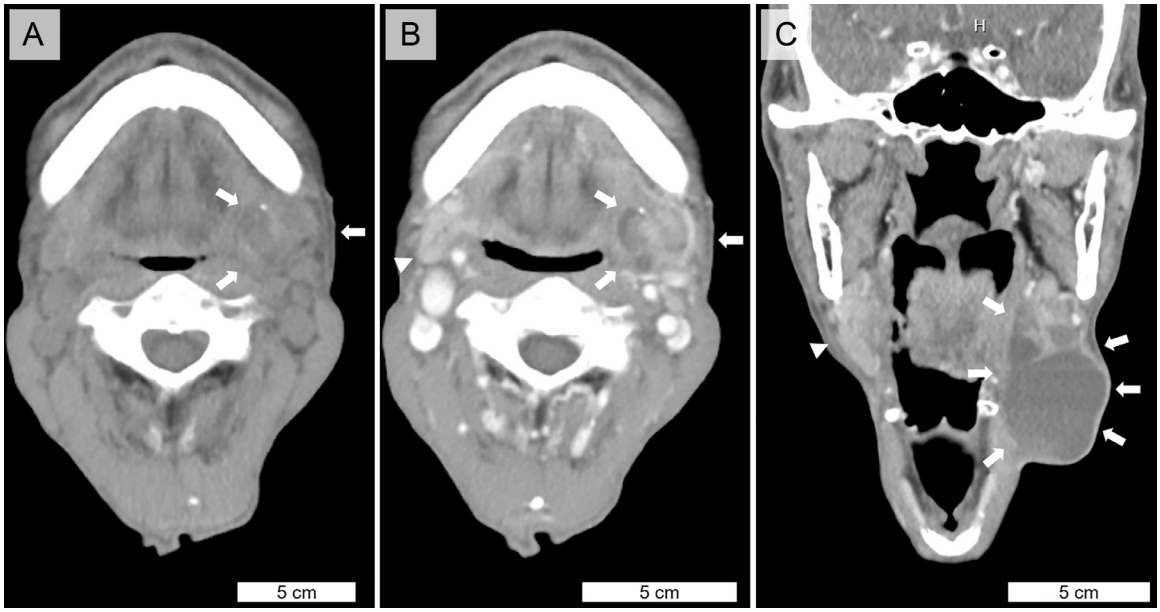

Fig. 1 – Computed tomographic images of a macrocystic salivary duct carcinoma of the left submandibular gland. Axial images (A and B) of the tumor (arrows) showing a vague round nodule with heterogeneous enhancement (B). Contrast-enhanced coronal image (C) showing a cystic tumor derived from the left submandibular gland. The right submandibular gland is intact (arrowheads in B and C). The scale bars are shown in the photos.

metastasis nor lung cancer recurrence. The patient was disease-free 9 months after surgery.

Discussion

Here, we describe a non-necrotic macrocystic SDC, and to our knowledge, such cases have not yet been reported. The radiological examination using CT revealed well-defined cystic features without apparent solid components. Typical CT findings of SDC often present as solid masses with ill-defined tumor borders and heterogenous enhancement patterns [7]. Compared to mucoepidermoid carcinoma, adenoid cystic carcinoma, and acinic cell carcinoma, SDCs are more likely to invade into adjacent tissues and metastasize to lymph node [8]. Weon et al. reported that cystic changes due to tumor necrosis could be seen in SDC [5], in contrast, Kazawa et al. suggested that cystic and necrotic components might be less typical of SDC [9]. The CT findings in our case were notably atypical for SDC.

Radiologically, cystic salivary gland lesion in our case initially suggested dilated ducts or intraductal tumor growth. However, pathology confirmed that the macrocystic SDC exhibited a pushing border-type invasion, with intercystic areas containing frankly invasive nests. Comparing the radiological and pathological findings of our case suggested that the contrast-enhanced tumor area seen in Fig. 1B corresponded to the cyst wall infiltrated by the frankly invasive carcinoma. Additionally, the cystic lesion extending near the skin (Fig. 1C, arrows) demonstrated pushing-type invasion into the subcutaneous tissue. Thus, retrospectively, malignant salivary gland tumor might be radiologically suggested because of the presence of contrast-enhanced tumor area and abnormal localization near the skin. However, heterogenous enhancement of the tumor septa on CT images might have been induced by non-tumor conditions like inflammation. Radiological identification of extra-salivary gland extension of the tumor might be difficult in this case because of the well-defined tumor borders.

The recent UpToDate database highlights that imaging studies are unable to definitively diagnose salivary gland tumors or distinguish between malignant and benign tumors [10]. However, in this case, we investigated whether it was possible to arrive at a qualitative diagnosis based on findings of CT images. Clinically, differential diagnoses of cystic lesions in major salivary glands includes various benign and malignant conditions, including human immunodeficiency virus (HIV) infection, Sjögren syndrome [11], lymphoepithelial cyst [12], cystadenoma, adenoid cystic carcinoma, acinic cell carcinoma, intraductal carcinoma, mucoepidermoid carcinoma, and secretory carcinoma [6,13,14]. CT findings of cystic lesions in major salivary glands are summarized in Table 1. Among benign cystic salivary gland lesions, HIV-associated lymphoepithelial cysts may exhibit multilocular lesions similar to our case; however, they typically present as bilateral lesions [15]. Specific data on cyst size in salivary duct intraductal carcinoma as evaluated by CT are lacking [16], making it challenging to distinguish this case from intraductal carcinoma based solely on CT findings. Nevertheless, the large cystic changes extending near the skin in our case might be atypical for intraductal carcinoma. Typical CT findings for ade-

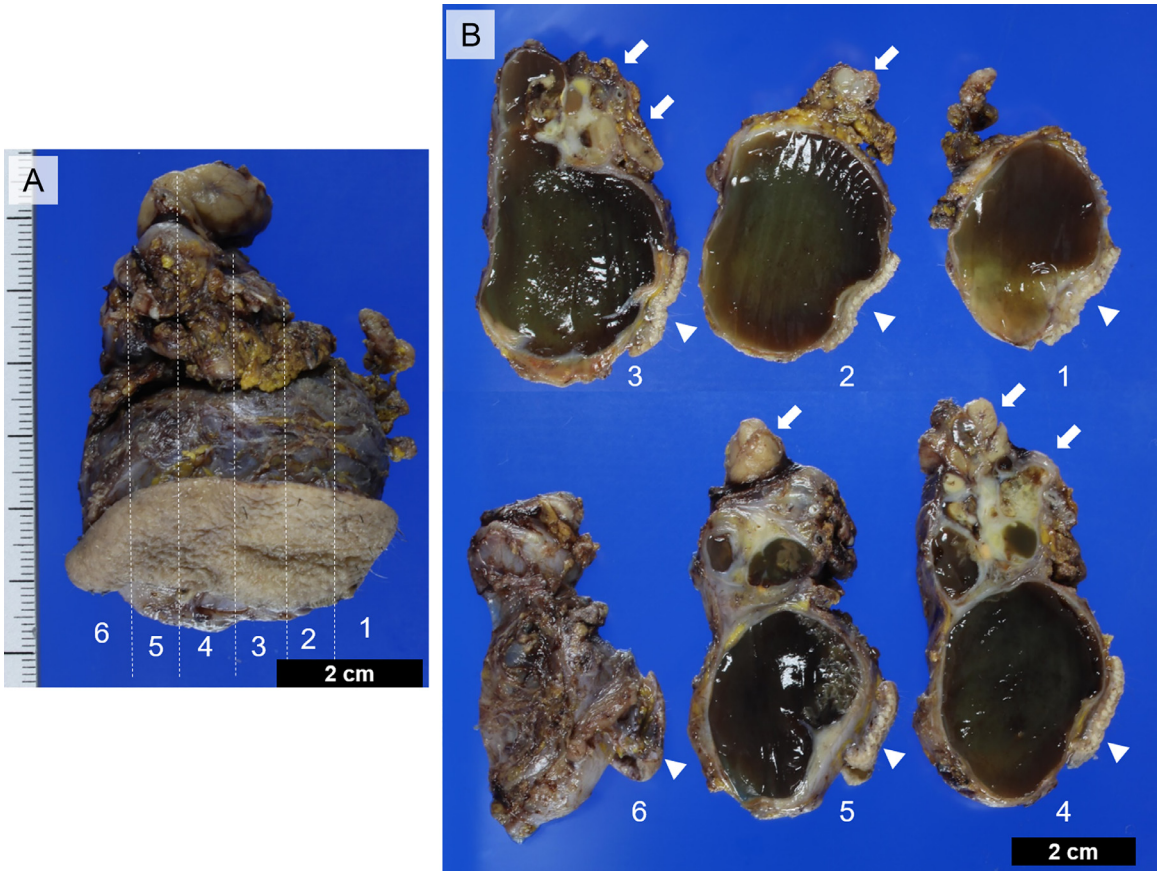

Fig. 2 – Macroscopic images of a macrocystic salivary duct carcinoma of the left submandibular gland. Formalin-fixed resected tissue (A) is indicated with dotted lines, which are the cut lines. The cut surfaces of the resected tissue (B) show multilocular lesions with small-to large-sized cysts. Small cystic components appear to be present in the submandibular gland tissue (arrows), and the larger cystic component appears to protrude from the salivary gland tissue towards the resected skin (arrowheads). The cut section named 3 in (B) corresponds to the coronal section of the tumor seen in Fig. 1C. The scale bars are shown in the photos.

Table 1 – Computed tomographic findings of cystic lesions of major salivary glands.

Diseases	Computed tomography findings
Sjögren syndrome	Bilateral, heterogenous fat deposition, punctate calcification (cysts are usually detected by magnetic resonance imaging) [11].
Lymphoepithelial cyst (HIV infection)	Unilateral and unilocular (HIV-associated lymphoepithelial cysts are often bilateral and multicystic) [15].
Cystadenoma	Unilateral. Typical features are unknown.
Adenoid cystic carcinoma	Unilateral. Typical features are unknown [17].
Acinic cell carcinoma	Unilateral. Typical features are unknown (hypoattenuating regions of central necrosis and irregular enhancing solid component may be seen) [18].
Intraductal carcinoma	Unilateral. Typical features are unknown (case reports have reported well-circumscribed and partially cystic, heterogenous mass with peripheral enhancement, homogenous isodense, or heterogenous mass with enhanced ill-defined border) [14].
Mucoepidermoid carcinoma	Unilateral, well circumscribed, usually cystic [19].
Secretory carcinoma	Unilateral, well circumscribed, uneven density, with or without cystic areas [20].
Salivary duct carcinoma	Unilateral, solid mass with ill-defined borders and heterogenous enhancement patterns (multilocular cystic lesion seen in our case is rare) [7].

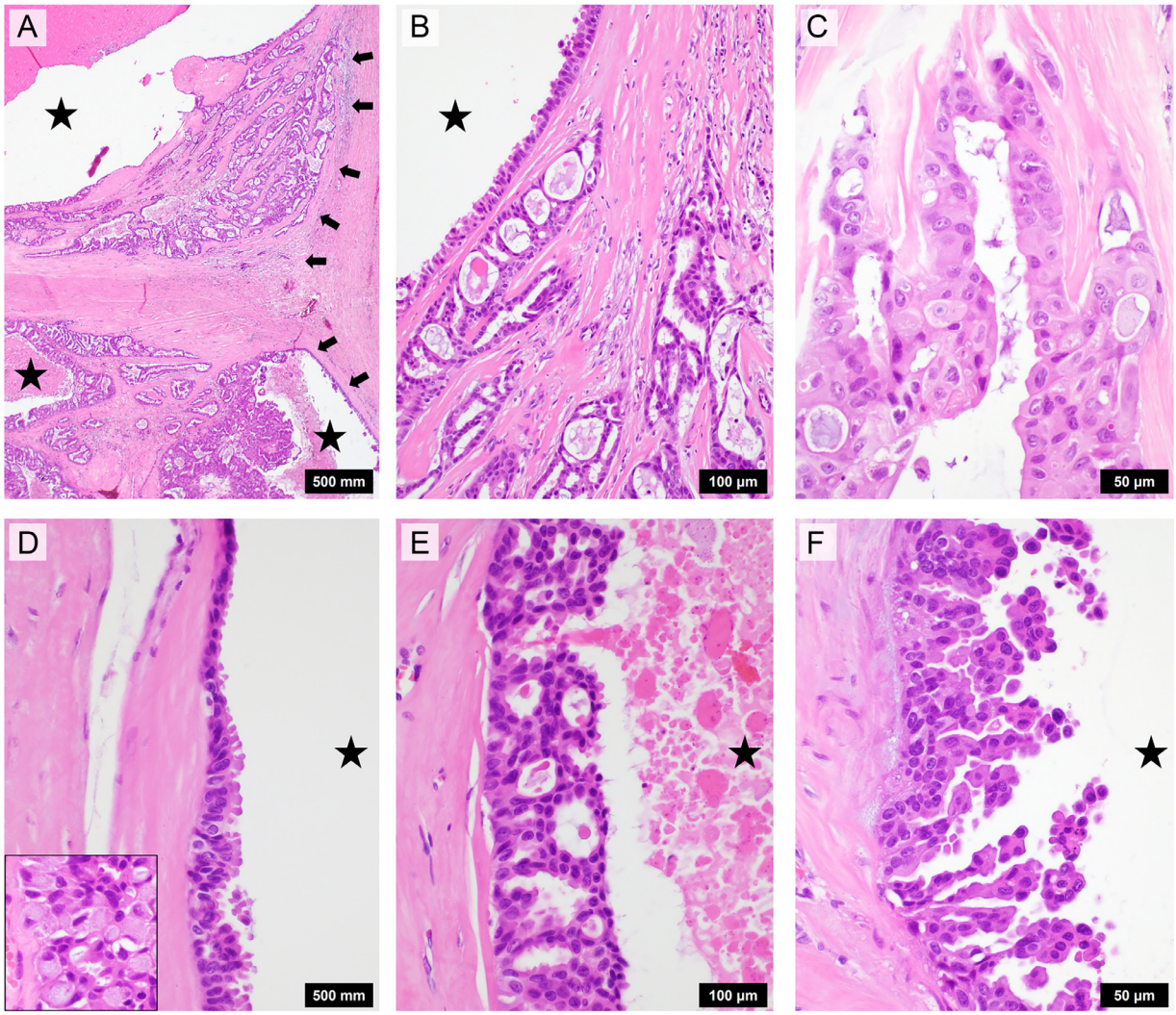

Fig. 3 – Microscopic images of a macrocystic salivary duct carcinoma of the left submandibular gland. Low-magnification image (A) showing a cystic tumor with demarcated borders (arrows). Tumor cells form cysts and invade the intercystic area (B), where atypical tumor cells with enlarged nuclei and nucleoli invade in a tubular fashion associated with the fibrous stroma (C). The cystic tumor components (D-F) consist of a single layer (D), Roman bridge-like or cribriform arrangement (E), or micropapillary arrangement (F). Mucinous tumor cells are included (D, inset). The cystic cavities are indicated by stars. The scale bars are shown in the photos.

noid cystic carcinoma and acinic cell carcinoma are unavailable [17,18], and multilocular cystic lesions detected by CT may be unusual for mucoepidermoid carcinoma and secretory carcinoma [19,20]. Although the CT finding of multilocularity observed in our case might be used to differentiate from other cystic salivary gland tumors, arriving at a radiological diagnosis of SDC was deemed impossible because of the unusual CT findings exhibited by our case.

In our case, pleomorphic adenoma was absent. No morphological features suggesting adenoid cystic carcinoma and acinic cell carcinoma were observed. Intraductal carcinoma was also ruled out, as our case lacked an intact myoepithelial cell layer at the periphery of the cystic components and was negative for S100 and SOX10 immunoreactivity. Other macrocystic salivary gland carcinomas, mucoepidermoid carcinomas and secretory carcinomas were also excluded because of a lack of squamous cells, intermediate cells, p63-positive tumor cells, and S100/SOX10-positive cells. According to the latest AFIP fascicle [21], our tumor could be classified as a cystadenocarcinoma because of its slow-growing, painless, and cystic nature. However, we diagnosed this tumor as SDC instead of cystadenocarcinoma based on several key factors. These included the tumor cells' apocrine morphology, diffuse immunoreactivity for GCDFP15, AR, and mammaglobin. According to the recently-proposed risk stratification of SDC, low-risk tumor was considered in our case [22].

The patient noticed the lesion 20 years earlier, suggesting the possibility of an association with preexisting benign or in situ lesions. SDCs can derive from pleomorphic adenomas and intraductal carcinoma [2,3]. However, these preexist-

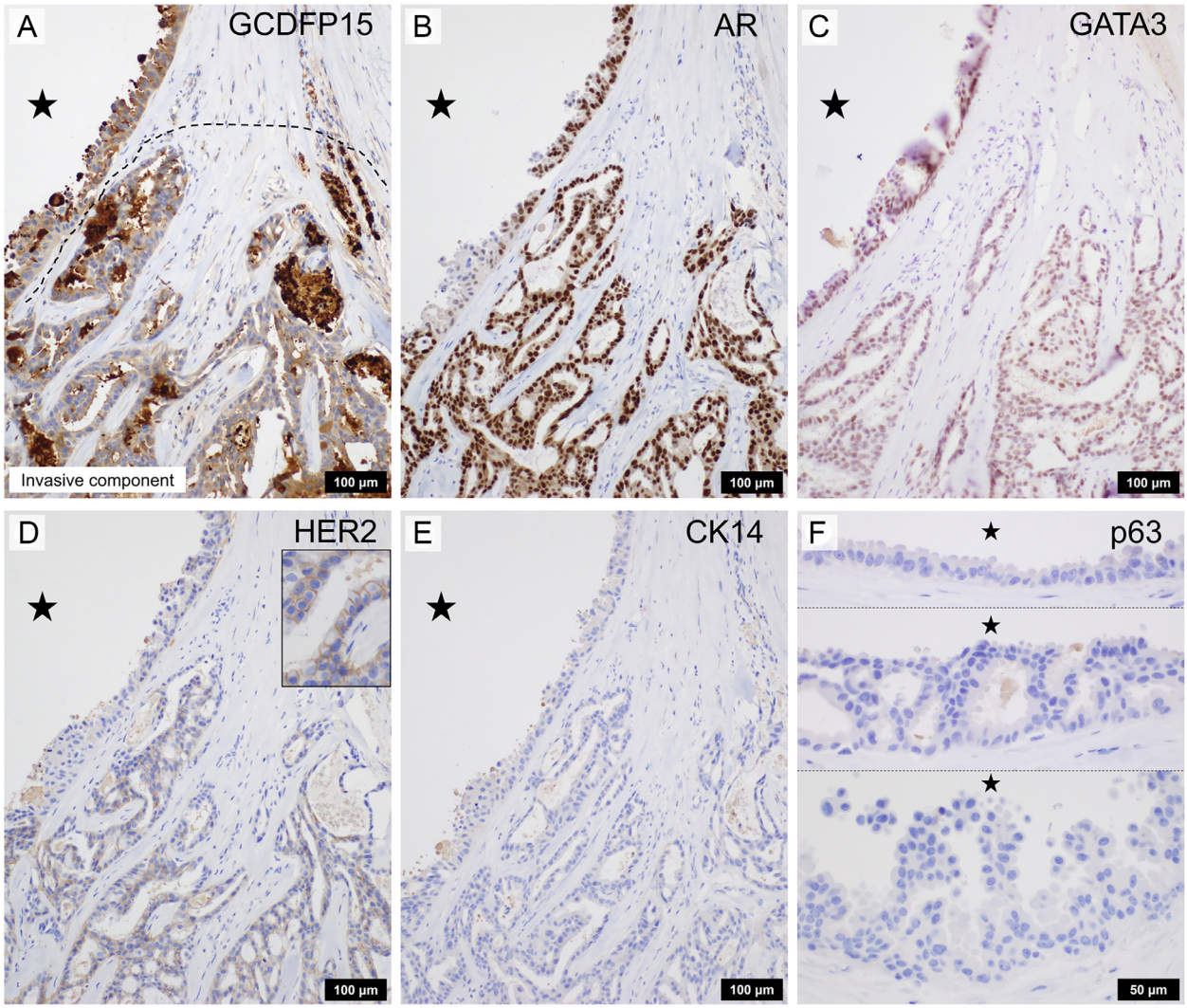

Fig. 4 – Immunohistochemical images of a macrocystic salivary duct carcinoma of the left submandibular gland. Tumor cells of the cystic component (cystic cavities are shown as stars) and the infiltrative component (partly circled by a dotted line in A) were diffusely positive for gross cystic disease fluid protein15 (GCDFP15, A), androgen receptor (AR, B), and GATA3 (C), focally positive for human epidermal growth factor receptor 2 (HER2, score 1+, D), and negative for cytokeratin 14 (CK14, E). CK14 (E) and p63 (F) show no myoepithelial cells in the cystic epithelium. In F, 3 photos of the cystic components are exhibited; a single layer (upper), Roman bridge-like or cribriform arrangement (middle), or micropapillary arrangement (lower). The scale bars are shown in the photos.

ing lesions were absent on histological evaluation with whole-mount preparation of the tumor. Intraductal carcinoma might be not the precursor lesion of SDC in submandibular glands as apocrine intraductal carcinoma has been hardly reported in submandibular glands. Thompson et al. reported a literature review of apocrine intraductal carcinoma of salivary glands in which 39 cases of apocrine intraductal carcinoma in the parotid (n = 38) and minor salivary glands (n = 1) were observed [16].

In conclusion, we have presented a case of macrocystic and non-necrotic SDC of the left submandibular gland. Despite the atypical radiological and pathological features observed in our case, SDC should be included in the differential diagnoses of cystic salivary gland tumors.

Patient consent

Written informed consent was obtained from the patient for the publication of this case report.

Contributions

KY performed the pathological diagnosis, wrote the main text, and prepared the figures. KM, TT, and KT performed the clinical examinations, surgery, and follow-ups. MU, TN, and MN confirmed pathological diagnoses. KN performed radiological diagnosis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.radcr.2024.04.014.

REFERENCES

[1] Nagao T, Licitra L, Loening T, Vielh P, Williams MD. Salivary duct carcinoma. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, editors. WHO classification of head and neck tumours. Lyon: International Agency for Research on Cancer; 2017. p. 173–4.

[2] Bahrami A, Perez-Ordonez B, Dalton JD, Weinreb I. An analysis of PLAG1 and HMGA2 rearrangements in salivary duct carcinoma and examination of the role of precursor lesions. Histopathology 2013;63:250–62. doi:10.1111/his.12152.

[3] McLean-Holden AC, Rooper LM, Lubin DJ, Magliocca KR, Manucha V, Sadow PM, et al. Frankly invasive carcinoma ex-intraductal carcinoma: expanding on an emerging and perplexing concept in salivary gland tumor pathology. Head Neck Pathol 2022;16:657–69. doi:10.1007/s12105-021-01408-3.

[4] Delgado R, Klimstra D, Albores-Saavedra J. Low grade salivary duct carcinoma. A distinctive variant with a low grade histology and a predominant intraductal growth pattern. Cancer 1996;78:958–67. doi:10.1002/(SICI)1097-0142(19960901)78:5⟨958::AID-CNCR4⟩3.0.CO;2-8.

[5] Weon YC, Park SW, Kim HJ, Jeong HS, Ko YH, Park IS, et al. Salivary duct carcinomas: clinical and CT and MR imaging features in 20 patients. Neuroradiology 2012;54:631–40. doi:10.1007/s00234-012-1014-z.

[6] Ribeiro EA, Maleki Z. Cystic salivary gland neoplasms: diagnostic approach with a focus on ancillary studies. Adv Anat Pathol 2022;29:365–72. doi:10.1097/PAP.0000000000000361.

[7] Lodhi T, Knipe H, Ayesa S. Salivary duct carcinoma. Radiopaedia.org (accessed on 13 Mar 2024), Latest revised 18 Jul 2023, https://doi.org/10.53347/rID-99562.

[8] Wu WL, Wang CL, Li D, Luo J, Ye JY, Xu SS. Multiphase contrast-enhanced computed tomography imaging features of salivary duct carcinoma: differentiation from other salivary gland malignancies. Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:543–51. doi:10.1016/j.oooo.2019.05.011.

[9] Kazawa N, Shibamoto Y, Hirose Y, Yamashita Y. The radiologic (CT/MRI)-pathological correlations of the salivary duct carcinoma (SDC) with hyaline degeneration and peripheral nerve invasion. Dentomaxillofac Radiol 2021;50:20200603. doi:10.1259/dmfr.20200603.

[10] Laurie SA. Salivary gland tumors: epidemiology, diagnosis, evaluation, and staging. In: UpToDate. edn. Edited by Brockstein BE, Brizel DM, Fried MP. UpToDate, Waltham, MA (Accessed on Mar 13, 2024). https://www.uptodate.com/contents/salivary-gland-tumors-epidemiology-diagnosis-evaluation-and-staging.

[11] Takagi Y, Katayama I, Eida S, Sasaki M, Shimizu T, Sato S, et al. Three signs to help detect Sjögren's syndrome: incidental findings on magnetic resonance imaging and computed tomography. J Clin Med 2023;12:6487. doi:10.3390/jcm12206487.

[12] Ahamed AS, Kannan VS, Velaven K, Sathyanarayanan GR, Roshni J, Elavarasi E. Lymphoepithelial cyst of the submandibular gland. J Pharm Bioallied Sci 2014;6:S185–7. doi:10.4103/0975-7406.137464.

[13] Hernandez-Prera JC, Holmes BJ, Valentino A, Harshan M, Bacchi CE, Petersson F, et al. Macrocystic (mammary analogue) secretory carcinoma: an unusual variant and a pitfall in the differential diagnosis of cystic lesions in the head and neck. Am J Surg Pathol 2019;43:1483–92. doi:10.1097/PAS.0000000000001309.

[14] Viswanathan K, Sadow PM, Maleki Z, Nishino M, Baloch ZW, Abbott TE, et al. Cytomorphologic features of intraductal salivary gland carcinoma: a multi-institutional study of 13 FNA cases with histologic, molecular, and clinical correlations. Cancer Cytopathol 2021;129:928–46. doi:10.1002/cncy.22504.

[15] Zanelli M, Zizzo M, Sanguedolce F, Annessi V, Ascani S. Benign lymphoepithelial cyst of the parotid gland: mind the underlying cause. Int J Surg Pathol 2021;29:78–9. doi:10.1177/1066896920913620.

[16] Thompson LDR, Bishop JA. Salivary gland intraductal carcinoma: how do 183 reported cases fit into a developing classification. Adv Anat Pathol 2023;30:112–29. doi:10.1097/PAP.0000000000000362.

[17] Saleh E, Ukwas A. Adenoid cystic carcinoma of salivary glands: a ten-year review and an assessment of the current management, surgery, radiotherapy, and chemotherapy. Int J Otolaryngol 2023;2023:7401458. doi:10.1155/2023/7401458.

[18] Weerakkody Y, Atkinson H, Gaillard F. Acinic cell carcinoma (salivary glands). Radiopaedia.org (accessed on 13 Mar 2024), Latest revised 23 Jul 2023, https://doi.org/10.53347/rID-9149.

[19] Gaillard F, Yap J, Sharma R. Mucoepidermoid carcinoma of salivary glands. Radiopaedia.org (accessed on 13 Mar 2024), Latest revised 22 Jun 2023, https://doi.org/10.53347/rID-4284.

[20] Sun J, Liu S, Fu K, Gao N, Li R, He W, et al. Clinicopathological characteristics and outcomes of 23 patients with secretory carcinoma of major salivary glands. Sci Rep 2021;11:22639. doi:10.1038/s41598-021-01970-4.

[21] Bishop JA, Thompson LDR, Wakely PE, Weinreb I. AFIP atlases of tumor and non-tumor pathology: tumors of the salivary glands. Arlington, VA: American registry of pathology; 2021. p. 414–22. fascicle 5.

[22] Nakaguro M, Sato Y, Tada Y, Kawakita D, Hirai H, Urano M, et al. Prognostic implication of histopathologic indicators in salivary duct carcinoma: proposal of a novel histologic risk stratification model. Am J Surg Pathol 2020;44:526–35. doi:10.1097/PAS.0000000000001413.