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A case of oncocytic papillary cystadenocarcinoma of the parotid gland—Pathological and molecular features of a rare tumor

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ABSTRACT

We present histological, immunohistochemical and molecular features of oncocytic papillary cystadenocarcinoma, a rare neoplasm of the salivary and parotid glands, in an 82-year-old Japanese man. The resected tumor was solid nodular mass with fibrous capsule. The tumor was composed of papillary proliferation of tall columnar cells with thin vascular cores. The cytoplasm of the tumor cells was granular and eosinophilic. The tumor cells showed clear positive reaction for mitochondria and androgen receptor. GCDFP15 and HER2 were negative. Electron microscopy demonstrated numerous mitochondria in the cytoplasm of the tumor cells. Ki-67 index was 30%. Most of the tumor cells were positive for TP53, and single nucleotide polymorphism was found at codon 151. The invasion into the lymphatic spaces and capsule was noted. Although recurrence and metastasis were not noted at one and a half years after the resection, the patient needs to be followed up under careful observation.

1. Introduction

Papillary cystadenoma and cystadenocarcinoma are rare histological subtypes of neoplasms of the salivary and parotid glands, and it constitutes approximately 2% of malignant tumor [1]. Oncocytic variant of these neoplasms is extremely rare. In the salivary and parotid glands, to date, seven cases of oncocytic papillary cystadenoma (OPCA) [2–7] and only two cases oncocytic papillary cystadenocarcinoma (OPCCa) [8] were reported in the literature. The tumors are characterized by the papillary growth of the cells with eosinophilic cytoplasm. However, the immunohistochemical features and genetic alteration of these tumors were not fully described. We here present the histopathological and molecular features of OPCCa of the parotid gland.

2. Case report

2.1. Clinical history

An 82-year-old Japanese man complained of a firm nodular mass in the left parotid region. Computed tomography showed a well-circumscribed tumor at the middle to lower pole of the left parotid gland. The size of the tumor was approximately 45 mm in diameter. Systemic examination did not show distant metastasis or lymph node metastasis. Fine needle aspiration cytology demonstrated the tumor cells with oncocytic feature and mild atypia. The patient underwent partial resection of the left parotid gland. The resected tumor was subjected for the pathological examination, and a diagnosis of OPCCa was made. The patient has been followed up without any additional treatment. At one and a half years after the surgery, recurrence or metastasis is not noted.

2.2. Pathologic findings

The resected tumor was a firm mass located in the lower part of the left parotid gland, and the size was 45 mm in diameter. The tumor had fibrous capsule, and there was no invasion to the surrounding parotid

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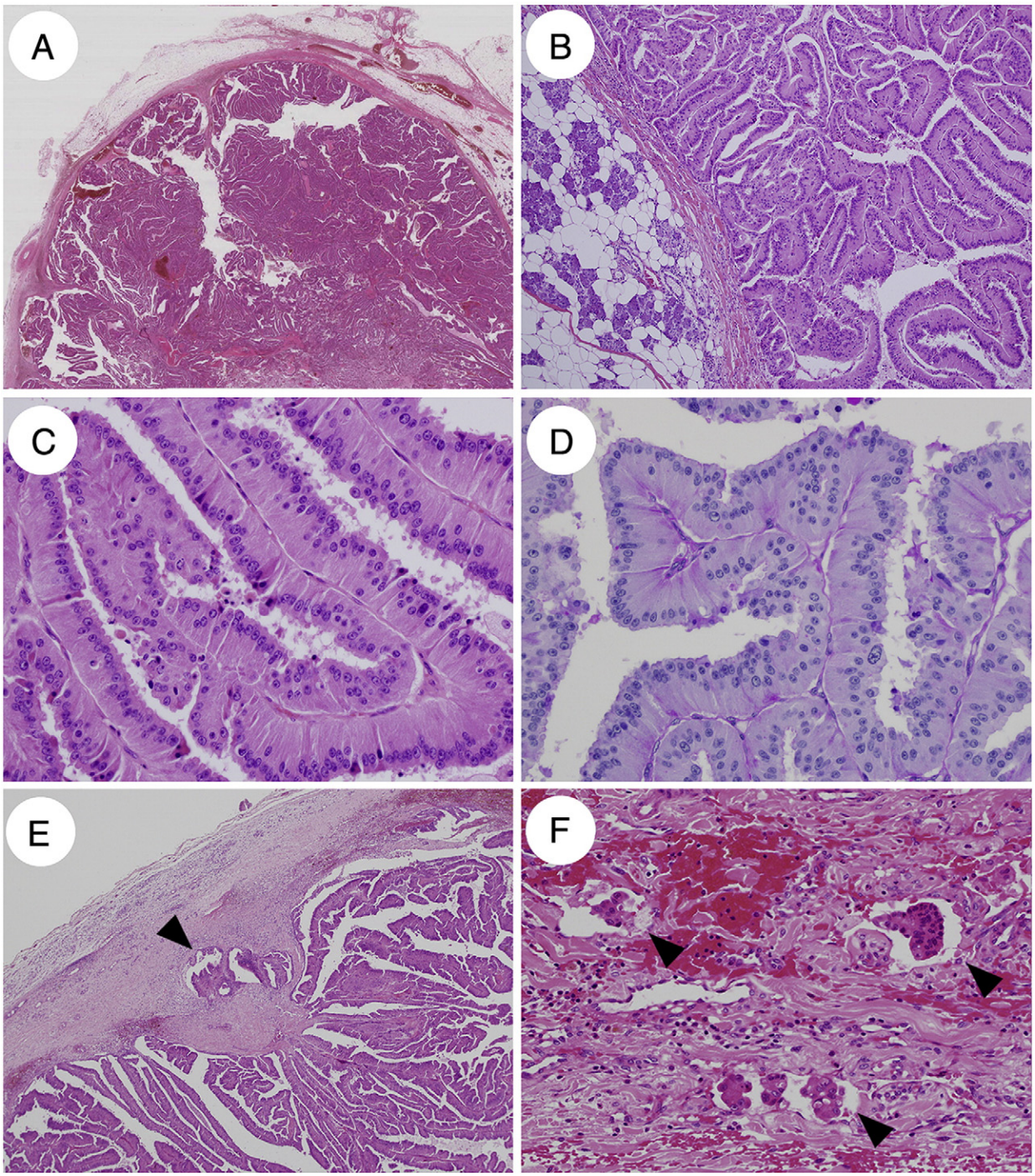

Fig. 1. Histological findings of the parotid tumor. (A) Low power image of the tumor. (B) Medium magnification depicted the papillary growth of the tumor. (C) High magnification of papillae with lining of single layer of tall columnar cells. (D) Periodic acid-Schiff was negative in the tumor cells. (E and F) Invasion into the capsule (E, arrow head) and lymphatic spaces (F, arrow heads) was noted.

gland (Fig. 1A). Large cystic space was not evident inside of the tumor. Necrosis was not found. The histology of the tumor is characterized by proliferation of papillae, forming irregular slit-like spaces (Fig. 1B). Mucus production and crystalloid materials were not found in the spaces. The papillae had thin fibrovascular core, and they were covered with single layer of tall columnar epithelial cells with eosinophilic and granular cytoplasm. The nuclei were round to oval, and nucleoli were conspicuous (Fig. 1C). Pleomorphism of the nuclei was not seen, and mitosis was 1/10 high power field. The tumor cells were negative for periodic acid-Schiff (Fig. 1D) and mucicarmine. Infiltration and aggregation of lymphoid cells were not observed. The tumor showed invasion into the capsule (Fig. 1E) and lymphatic spaces (Fig. 1F).

2.3. Immunohistochemical findings

The immunohistochemical staining was performed by Ventana GX System (Roche Diagnostics, K.K., Tokyo, Japan) with antibodies against mitochondria (Abcam, Co., Tokyo, Japan), GCDFP15 (Leica

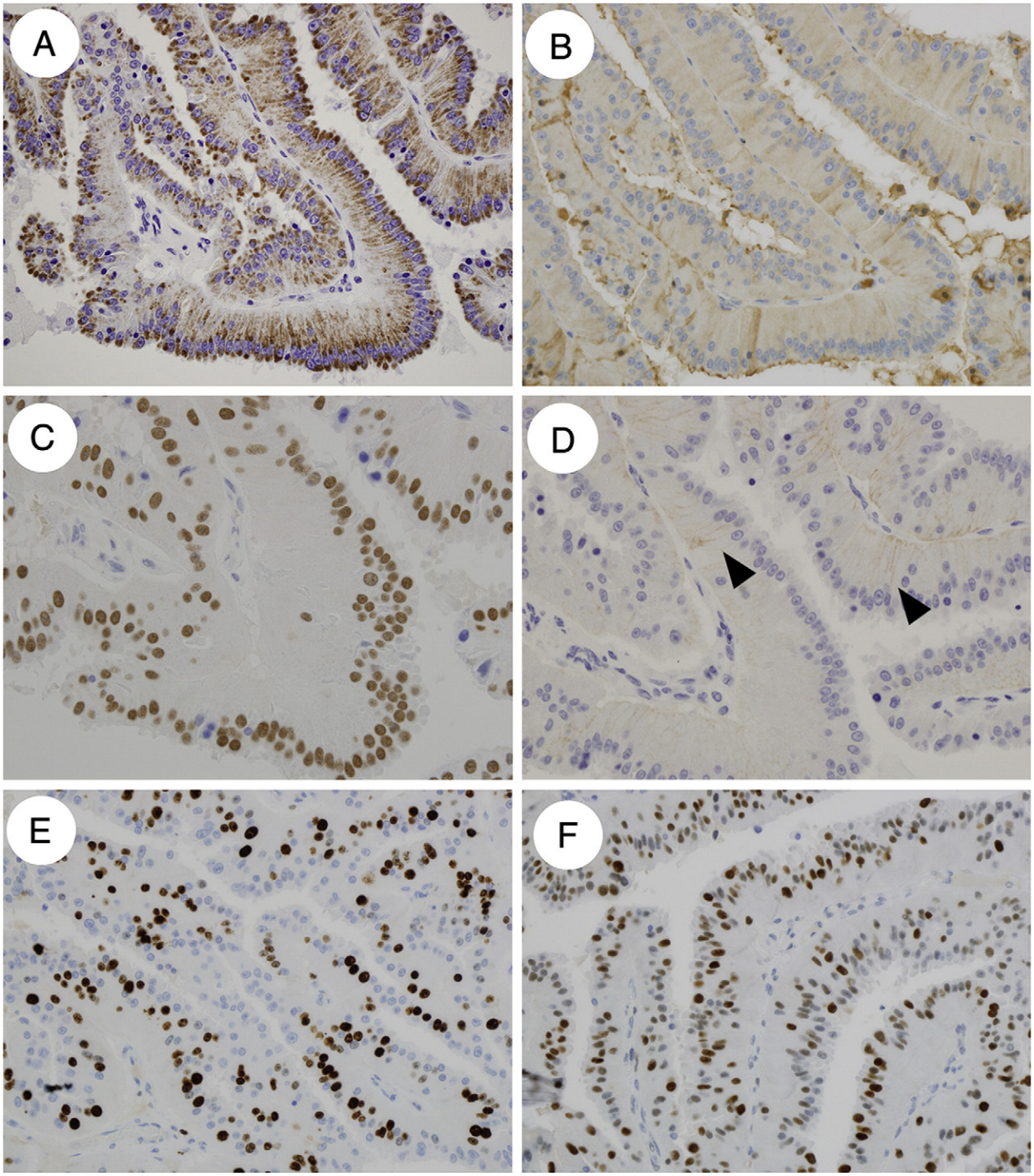

Fig. 2. Immunohistochemical findings. (A) The cytoplasm of the tumor cells was positive for anti-mitochondria antibody. (B) The cells were negative for GCDFP15. (C) Androgen receptor was positive in the nucleus of the epithelial cells. (D) The cell membrane of the columnar cells was faintly positive for HER2 (arrow heads). (E) Ki-67 index was approximately 30%. (F) The epithelial cells were positive for TP53.

Microsystems K.K., Tokyo, Japan), androgen receptor (AR) (Cell Marque, Co., CA, USA), estrogen receptor (ER), progesterone receptor (PgR), TP53 and Ki-67 (Dako Japan, KK, Tokyo, Japan). Immunostaining of HER2 was done with HercepTest (Dako Japan, KK). Strong granular positive reaction for anti-mitochondrial antibody was found in the cytoplasm of the tall columnar cells (Fig. 2A). The cells were negative for GCDFP15 (Fig. 2B). AR was clearly positive in the nuclei of the epithelial cells (Fig. 2C). Neither ER nor PgR was detected. A faint reaction for HER2 was found on the cell membrane of some epithelial cells (Fig. 2D). Ki-67 index was 30% (Fig. 2E), and TP53 was positive in 90% of the epithelial cells (Fig. 2F).

2.4. Electron microscopic findings

Pathological specimen was dewaxed, and it was processed and embedded in Epon812 for the examination by electron microscopy (EM). EM depicted the papillae lined with tall columnar cells (Fig. 3A). Most of the cells had prominent nucleoli. The cytoplasm of the columnar

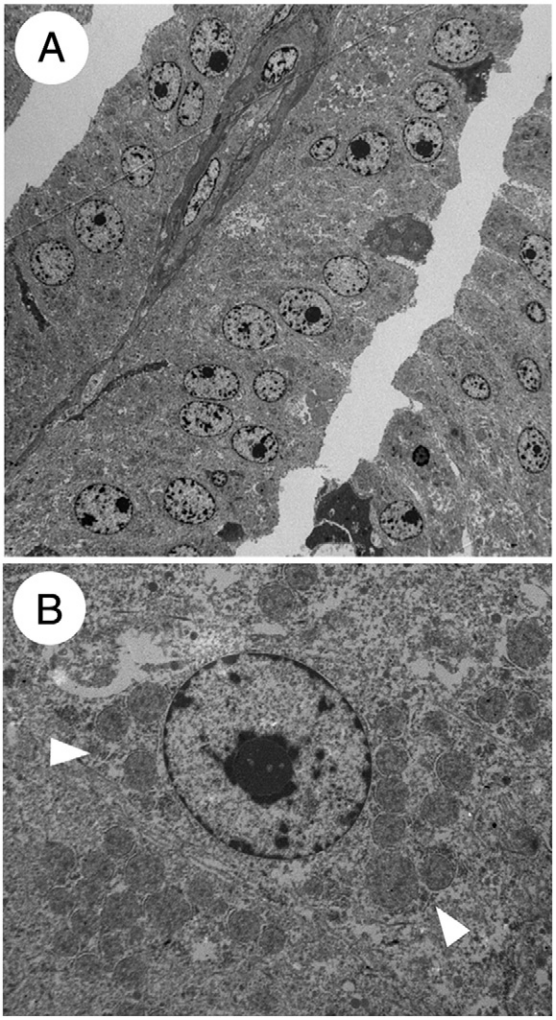

Fig. 3. Electron microscopic findings. (A) High magnification of proliferating papillae. (B) The lining columnar epithelial cells were packed with numerous mitochondria (arrow heads).

cells was packed with numerous mitochondria (Fig. 3B). Zymogen granule was not identified in the tumor cells.

2.5. Sequencing of TP53 gene

Using DNA extracted from paraffin sections of tumor tissue, fragments of exon 5–8 of *TP53* were amplified and sequenced. In the exon 5, substitution of nucleotide C to A, which causes substitution of amino acid of proline to threonine at codon 151, was detected. This missense mutation is known as single nucleotide polymorphism (SNP, rs28934874).

3. Discussion

The current study, the first, demonstrated the histological and genetic features of OPCCa of the parotid gland. The tumor was characterized by papillary growth of tall columnar cells with eosinophilic cytoplasm. The cells showed strong positive reaction with anti-AR and anti-mitochondrial antibodies. The presence of numerous mitochondria in the cytoplasm of the columnar cell was further confirmed by EM. The invasion into the capsule and lymphatic spaces was noted by histological examination. The invasion may not be due to the displacement of tumor cells by aspiration cytology. The capsular invasion was found in the inner side of the tumor, where the aspiration needle did not reach. The lymphatic endothelial cells were confirmed by immunostaining with D2-40 (data not shown). This evidence prompted a diagnosis of OPCCa.

To date, only two cases of OPCCa and seven cases of OPCA in the salivary glands are reported in the literature [2–8]. Including the current case, seven cases were male [2,5–8], and three cases were female [3,4,6]. There is no apparent trend of the age in the development of the tumor. The pathogenesis and behavior of the tumor are largely unknown. Since one case of OPCCa follows an aggressive clinical course [8], it is necessary to elucidate the expression and alteration of molecules related to the pathogenesis and behavior of the tumor.

In the routine pathological diagnosis, it is essential to differentiate OPCCa from Warthin tumor, papillary variant of acinic cell carcinoma, salivary duct carcinoma, and mucoepidermoid carcinoma [10]. Careful histological evaluation of lymphoid aggregation and mucous production needs to be evaluated. Immunohistochemical examination of HER2 and AR is also useful for the differential diagnosis of these neoplasms [11]. For the definitive diagnosis of OPCCa, it is necessary to demonstrate the positive staining with anti-mitochondria antibody by immunostaining or the presence of numerous mitochondria in the cytoplasm of the tumor cells by EM.

The expression of AR in OPCCa was not described before. The association between AR expression and oncocytic change of the tumor cells is not known. The expression might be associated with male predominance of these rare histological subtypes of salivary tumor. It is plausible that the strong expression of AR is involved in the pathogenesis or proliferation of tumor cells, and the molecule may serve as a therapeutic target of the tumor [9].

The malignant potential of OPCCa is not fully elucidated. In the previous report, 8-year-old child followed an aggressive clinical course, showing lymph node metastasis and multiple recurrences [8]. Another case followed a favorable course at eight months after the surgery. In the current case, although there was invasion into the capsule and lymphatic spaces, recurrence and metastasis were not noted at one and a half years after the resection. Follow-up duration may be too short to evaluate the prognosis. The tumor cells showed strong reaction for TP53, and the sequencing of *TP53* gene disclosed the presence of SNP at codon 151. The SNP is suspected to be pathogenic alteration in breast cancer [12]. The loss of heterozygosity is not examined in the current case. The presence of SNP may serve as a pathogenic background in the development of the tumor in the current case.

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