

Epithelial-myoeplithelial Carcinoma of the Parotid Gland with Adenoid Cystic Carcinoma-like Features: a case report with immunohistochemical study

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ABSTRACT

A 69-year-old Japanese female with epithelial myoeplithelial carcinoma (EMC) in the parotid gland is reported. The tumor, 3.5 × 4.0 × 1.5 cm in size, was located in the left parotid gland. Histopathological examination of the surgically removed tumor revealed that it was composed of double-layered, tubule-like structures formed by inner eosinophilic ductal cells and outer clear cells, as well as solid clear cell nests. The unique histological finding of this tumor was that it had a cribriform-like arrangement of myoeplithelial cells resembling an adenoid cystic carcinoma. On the other hand, the typical ductal and myoeplithelial components of EMC showed the usual biphasic pattern and the expected immunophenotypes, with expression of low molecular weight cytokeratins, CAM 5.2 and EMA in the ductal part, and smooth muscle actin, S-100 protein, and vimentin in the myoeplithelial component.

Key words: Epithelial myoeplithelial carcinoma, S-100 protein, Immunohistochemistry

Epithelial myoeplithelial carcinoma (EMC) is a rare and low grade malignant salivary gland neoplasm that accounts for less than 1% of all salivary gland tumors^{2,8)}. This tumor was described in 1972 by Donath⁷⁾, and established as a distinct clinicopathologic entity by the World Health Organization (WHO) in 1991¹⁴⁾. The most characteristic histological feature of EMC is an inner layer of duct-forming epithelial cells and an outer layer of prominently clear myoeplithelial cells^{4,11)}. The proportion and the growth pattern of each component may vary greatly in individual neoplasms. Here we present a case of EMC with a cribriform arrangement simulating an adenoid cystic carcinoma.

CASE REPORT

Clinical Summary

A 69-year-old woman presented with a painless tumor in her left parotid region. Fine needle aspiration cytology of the lesion showed clusters of cells with the appearance of epithelial cells with clear cytoplasm and small uniform nuclei. These findings were interpreted as indicating a suspected pleomorphic adenoma of the parotid gland. Computed tomography showed a mass of higher density than the normal parotid gland. The mass had irregular margins. A total parotidectomy with facial nerve conservation was then performed. The

surgical specimen showed a solid, well circumscribed, round tumor measuring 40 × 32 × 15 mm involving the deep lobe of the parotid gland. The patient is alive, without evidence of disease, at 6 months after the first surgery.

Pathological Findings

The resected tumor, measuring 40 × 35 × 15 mm, had irregular margins and invaded into the surrounding soft tissues. The cut surfaces were solid and gray-white with focal hemorrhage (Fig. 1).

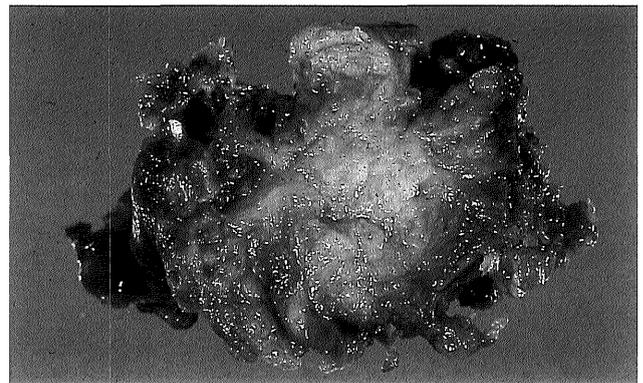


Fig. 1. Gross appearance of the parotid tumor. The cut surface of the tumor shows irregular margins and invasion to the muscle.

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The tumor exhibited a multinodular growth pattern with islands of tumor separated by dense fibrous connective tissue septa (Fig. 2a). It was composed of double-layered, tubular structures

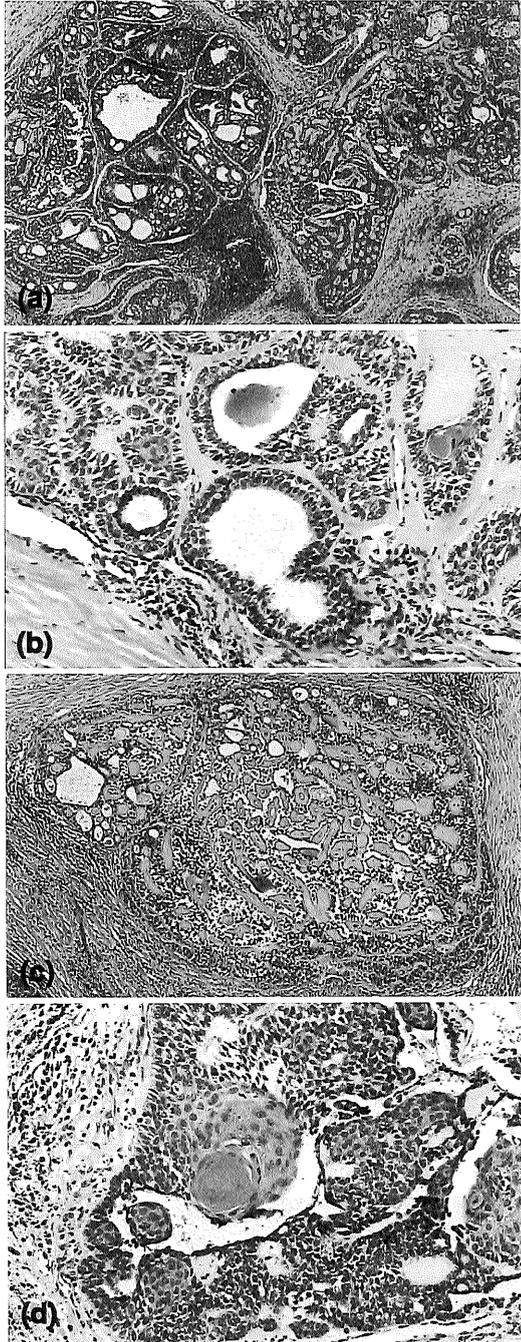


Fig. 2. Microscopic appearance of the tumor tissue. (a) Fibrous connective tissue bands separate lobules of this multilobular tumor. The tumor seems well circumscribed, but residual ducts of parotid parenchyma are present adjacent to and between tumor lobules (HE, $\times 100$). (b) Tumor nests composed of inner ductal and outer clear myoepithelial cells surrounded by hyaline stroma (HE, $\times 200$). (c) The tumor cell nest with cribriform arrangement simulating an adenoid cystic carcinoma. Moreover, there is hyaline material within the round and oval spaces. (d) EMC pattern with clear cell predominance and foci of squamous metaplasia (HE, $\times 200$).

formed by inner eosinophilic ductal cells and outer clear cells, as well as solid clear cell nests. The most common pattern in this case consisted of nests of myoepithelial cells, with or without an epithelial component, arrayed in a hyaline stroma (Fig. 2b). Occasionally, it formed a cribriform

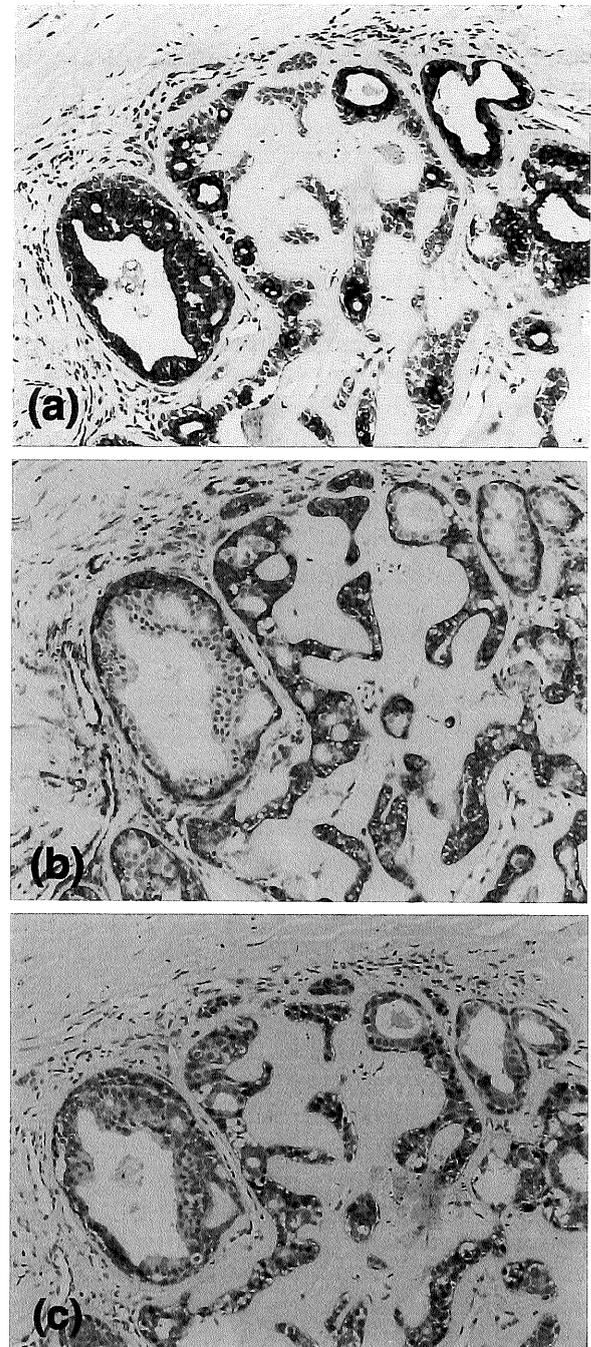


Fig. 3. Microscopic appearance of the immunochemical staining.

(a) The inner ductal cells are positive for CAM 5.2 (Avidin-biotin peroxidase stain, $\times 400$). (b) The outer clear cells react intensely with anti-smooth muscle actin, but the ductal cells are unreactive (Avidin-biotin peroxidase stain, $\times 400$). (c) Immunohistochemical staining for S-100 protein shows intense staining of the clearest cells and less intense staining of the ductal cells (Avidin-biotin peroxidase stain, $\times 400$).

Table 1. Panel of Antibodies used in this study and immunohistochemical results

Antigen	Antibody	Source	Dilution	Immunohistochemical results	
				Ductal cell	Myoepithelial cell
CAM 5.2	M	Becton-Dickinson	1:100	+++	-
EMA	M	DAKO	1:200	+	-
CEA	M	Euro-Diagnostica (Apeldoorn, Holland)	1: 50	+	-
SMA	M	DAKO	1:800	-	+++
S-100	P	DAKO	1:500	-	++
Vimentin	M	DAKO	1:100	-	++
GFAP	P	DAKO	1:300	-	+
p53	M	Novocastra (DO-7)	1:100	-	++
MIB-1 (Ki-67)	M	Immunotech	1: 20	-	++

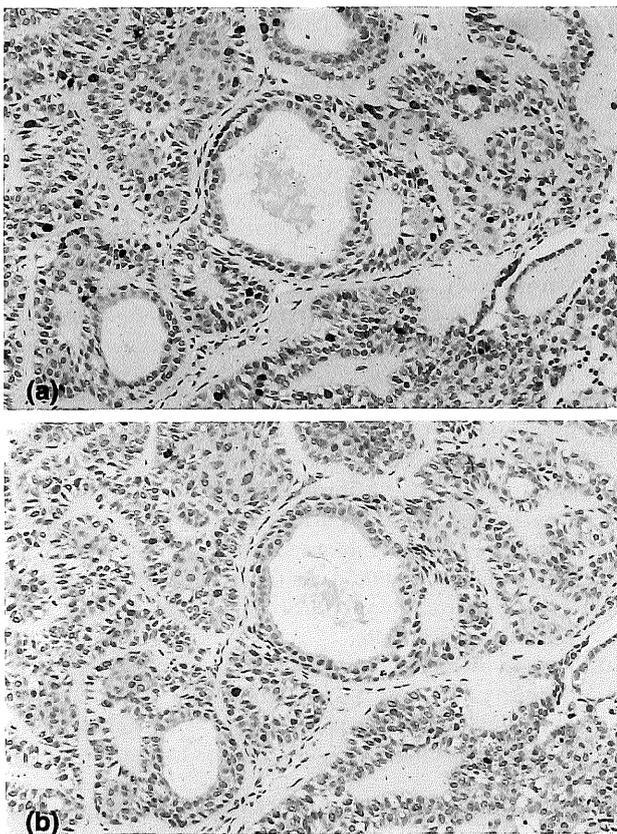


Fig. 4. The Ki-67 (a) and p53 (b) immunostaining was detected in the myoepithelial cells. (Ki-67; 38%, p53; 42%)

appearance with hyaline that mimicked adenoid-cystic carcinoma (Fig. 2c). Moreover, foci of squamous metaplasia among abundant clear cells were seen (Fig. 2d).

An immunohistochemical examination was performed on formalin-fixed paraffin embedded sections using the avidin-biotin-peroxidase complex kit (Vector, Burlingame, CA) and specific monoclonal antibodies against low-molecular-weight cytokeratin (CAM 5.2), epithelial membrane (EMA), carcinoembryonic antigen (CEA), S-100 protein, α -smooth muscle actin (SMA), vimentin,

glial fibrillary acidic protein (GFAP), p53 and MIB-1 (Ki-67). To enhance the immunostaining for p53 and MIB-1 (Ki-67), microwave pretreatment in citrate buffer was performed for 10×3 min. A summary of the source, type and working dilution of each of these antibodies and the results of immunostaining is given in Table 1. The immunoreactivity was graded as - to +++ according to the number of cells stained. Grades were defined as: -, almost no positive cells; +, 5-25% of tumor cells showed immunoreactivity; ++, 25-50% of tumor cells showed immunoreactivity; +++, over 50% of tumor cells showed immunoreactivity. Grades ++ and +++ were regarded as strongly positive. The immunohistological studies demonstrated that the inner eosinophilic cells were positive for CAM 5.2 (Fig. 3a), EMA and CEA, whereas the clear cells were positive for SMA (Fig. 3b), vimentin, GFAP and S-100 protein (Fig. 3c). The MIB-1 (Fig. 4a) and p53 (Fig. 4b) were positive (Ki-67; 38%, p53; 42%) only in myoepithelial cells. The tumor was diagnosed as EMC arising in the parotid gland.

DISCUSSION

EMC is an uncommon neoplasm of the salivary gland. EMC is a rare tumor, accounting for approximately 0.5% to 1% of salivary gland neoplasms^{4,7,15}. EMC usually occurs in the parotid gland, and more rarely in minor salivary glands, with a predilection for females. It is difficult to assess the reported incidence of this tumor among large surveys of salivary gland neoplasms since it has not often been included as a specific entity. Schackelford et al¹³ have reported that the intercalated duct in the minor salivary gland is lacking or shorter than that in the parotid gland. This may explain why most EMCs occur in the major salivary glands.

There are common histomorphologic features among some salivary gland tumors⁹. Moreover, salivary gland tumors have many common mechanisms of differentiation underlying many of the subtypes. Grenco et al⁹ suggest that salivary

gland tumors represent a plastic phenotypic expression of tumor types sharing common differentiation pathways. In this case, the tumor showed, partially, a very typical feature of EMC such as the lobular growth pattern on low magnification, a bicellular appearance formed by eosinophilic epithelial cells and outer clear myoepithelial cells. The differential diagnosis of salivary gland neoplasms with bicellular ducts includes mixed tumor, basal cell adenoma, adenocarcinoma, ACC and EMC. The mesenchymal-appearing myxochondroid tissue that characteristically occurs in mixed tumors was not observed in this case. Moreover, some clear cells can be found in basal cell adenoma or basal cell adenocarcinoma, but they are not a predominant component and are not arranged in a bicellular pattern with ductal cells. This tumor showed a characteristic cribriform-like appearance. Therefore, histologically differential diagnosis between ACC and EMC was tried by immunohistochemistry¹¹. S-100 protein and SMA were detected in the outer clear cells, while the inner ductal cells reacted intensely for CAM 5.2 and EMA¹⁰. These immunohistochemical findings, especially, S-100 protein immunoreactivity favored the diagnosis of EMC.

Cho et al³ suggested that myoepithelial cells play an important part in the growth of EMC, because the proliferative activity measured by Ki-67 immunostaining was observed mostly in the myoepithelial cells. Moreover, Fonseca et al⁸ reported that the only morphological feature that has been found to correlate with prognosis of EMC is the presence of nuclear atypia in more than 20% of the tumor cells. In the present case, MIB-1 (Ki-67) was detected in the myoepithelial cells. This patient has not shown any local recurrence or distant metastasis for 6 months since the surgical operation. Although most reported information indicates that EMC has a low-grade malignancy, some EMC have the possibility of local recurrences and metastasis^{1,4}. Therefore, the current case requires careful follow-up.

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REFERENCES

1. Alos, L., Carrillo, R., Ramos, J., Baez, J.M., Mallofre, C., Fernandez, P.L. and Cardesa, A. 1999. High grade carcinoma component in epithelial myoepithelial carcinoma of salivary glands clinicopathological, immunohistochemical and flow-cytometric study of three cases. *Virchows Arch.* **434**: 291–299.
2. Batsakis, J.G., El-Nagger, A.K. and Luna, M.A. 1992. Epithelial-myoeplithelial carcinoma of salivary glands. *Ann. Otol. Rhinol. Laryngol.* **101**: 540–542.
3. Cho, K.J., El-Naggar, A.K., Ordonez, N.G., Luna, M.A., Austin, J. and Batsakis, J.G. 1995. Epithelial myoepithelial carcinoma of salivary glands. A clinicopathologic, DNA flow cytometric and immunohistochemical study of Ki-67 and HER-2/neu oncogene. *Am. J. Clin. Pathol.* **103**: 432–437.
4. Corio, R.L., Sciubba, J.J., Brannon, R.B. and Batsakis, J.G. 1982. Epithelial myoepithelial carcinoma of intercalated duct origin. A clinicopathologic and ultrastructural assessment of sixteen cases. *Oral Surg. Oral Med. Oral Pathol.* **53**: 280–287.
5. Dardick, I., van Nostrand, A.W.P., Jeans, M.T.D., Rippstein, P. and Edward, V. 1983. Pleomorphic adenoma, I: ultrastructural organization of “epithelial regions”. *Human Pathol.* **14**: 780–797.
6. Dardick, I. and van Nostrand, A.W.P. 1984. Morphogenesis of salivary gland tumors: a prerequisite to improving classification. *Pathology Annual* **22** (pt1): 1–53.
7. Donath, K., Seifert, G. and Schmitz, R. 1972. Zur Diagnose und ultrastruktur des tubularen speichelgangkarzinoms. Epithelial myoepitheliales schaltstuckkazinom. *Virchows Arch.* **356**: 16–31.
8. Fonseca, I. and Soares, J. 1993. Epithelial myoepithelial carcinoma of the salivary gland: A study of 22 cases. *Virchows Arch.* **422**: 389–396.
9. Grenco, R.T., Abendroth, C.S., Davis, A.T., Levin, R.J. and Dardick, I. 1998. Hybrid tumors or salivary gland tumors sharing common pathway? Reexamining adenoid cystic and epithelial myoepithelial carcinomas. *Oral Surg. Oral Med. Oral Pathol.* **86**: 188–195.
10. Luna, M.A., Batsakis, J.G., Ordonez, N.G., Mackay, B. and Tortoledo, M.E. 1987. Salivary gland adenocarcinomas: a clinicopathologic analysis of three distinctive types. *Semin. Diagn. Pathol.* **4**: 117–135.
11. Luna, M.A., Ordonez, N.G., Mackay, B., Batsakis, J.G. and Guillaumondegui, O. 1985. Salivary epithelial myoepithelial carcinoma of intercalated ducts: a clinical, electron microscopy and immunocytochemical study. *Oral Surg. Oral Med. Oral Pathol.* **59**: 482–490.
12. Palmer, R.M. 1985. Epithelial myoepithelial carcinoma: an immunocytochemical study. *Oral Surg. Oral Med. Oral Pathol.* **59**: 511–515.
13. Schackelford, J.M. and Klapper, C.E. 1962. Structure and carbohydrate histochemistry of mammalian salivary glands. *Am. J. Anat.* **111**: 25.
14. Seifert, G. and Sobin, L.H. 1991. Histologic typing of salivary gland tumours. In: World Health Organization international histologic classification of tumours. 2nd ed. Berlin: Springer-Verlag.
15. Seifert, G. 1998. Are adenomyoepithelioma of the breast and epithelialmyoepithelial carcinoma of the salivary glands identical tumors? *Virchows Arch.* **433**: 285–287.