

Original Article

Epithelial-myoeepithelial Carcinoma - Review of Clinicopathological and Immunohistochemical Features

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Abstract

Introduction: Epithelial-myoeepithelial carcinoma is a low-grade malignant salivary gland neoplasm with a biphasic cell population that encompasses around 1% of all salivary neoplasms.

Method: We present different cases of epithelial-myoeepithelial carcinoma, with special emphasis on histopathology, differential diagnosis, relevant prognostic factors and follow-up.

Results: This study included 8 patients who were diagnosed with epithelial-myoeepithelial carcinoma and treated surgically including a follow-up period of at least 19 months.

Conclusion: Clinical and histopathological characteristics of these rare tumors are extremely valuable for accurate diagnosis and further therapy planning.

Keywords: Clinical features, epithelial-myoeepithelial carcinoma, histopathology, immunohistochemical features salivary glands

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Introduction

Malignant salivary neoplasms comprise less than 1% of all malignancies and around 5% of all head and neck cancers.¹

Epithelial-myoeepithelial carcinoma (EMCa) is defined as a low grade malignant salivary gland neoplasm with expansive borders and lacking a true capsule, composed of two cell types, which was first described in 1972 by Donath *et al.*^{2,3} It encompasses about 1% of all salivary gland neoplasms, with the most common localization being the parotid gland but also minor salivary gland sites such as oral mucosa and the upper and lower respiratory tract.^{1,4,5} Women are affected the most with the peak occurrence in the 6th decade. Patients usually present with a painless, slow-growing, multinodular mass in the parotid that may be present for several years prior to diagnosis but on minor salivary gland sites the tumor may present as an ulcerated sub-mucosal mass with ill-defined margins.^{1,6,7}

Surgery is the therapy of choice for EMCa, on both major and minor salivary gland sites. Size and rapid tumor growth are associated with worse prognosis while margin status is a major pathological prognostic factor because incomplete surgical excision is followed by local recurrence and metastasis.^{2,5}

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Materials and Methods

This study included 8 patients who were diagnosed with EMCa and treated surgically including a follow-up period of at least 19 months (average 52 months), with special emphasis on histopathology, differential diagnosis and relevant prognostic factors.

Results

The patient age ranged from 44 to 86 years (average 60 years). In five cases, the patients were female (62%). In five cases, the tumor was localized in the parotid gland (three in superficial lobe, two in superficial and deep lobe). In three cases, tumors were diagnosed on minor salivary gland sites: the tongue base, nasal cavity and soft palate (Table 1). Parotid patients usually presented with an asymptomatic mass, but two patients also had pain sensations prior to diagnosis. On minor salivary gland sites, the symptoms varied slightly and included dysphagia and speech difficulties, foreign body sensation, nasal obstruction symptoms and intermittent nasal bleeding. Duration of symptoms before clinical examination and diagnosis ranged from 1 month to 84 months (average 32 months). Patients with tumor of soft palate and tongue base underwent, as part of a diagnostic procedure, panendoscopy; patients with tumor of the nasal cavity underwent nasal endoscopy. Prior to surgery, all patients underwent computerized tomography (CT), and patients with parotid localization also had an ultrasonographic examination (US). In one case, CT scan showed the presence of exophytic tumor originating from minor salivary gland at the tongue base with well defined margins, heterodense, with cystic changes,

Table 1. Clinicopathological features features of epithelial-myoepithelial carcinoma.

Gender & Age	Localization	Duration of symptoms	Treatment/tumor diameter	Margin status	Perineural/angiolympathic invasion	Mitotic count/10 HPF	Follow-up
1. ♀ 51	Nasal cavity (lateral nasal wall)+maxillary sinus	12 months (nose obstruction, bloody nasal discharge)	May 2001 Nasal cavity tumor extirpation (2×2 cm) April 2005 Reoperation January 2013 Reoperation	Cannot be determined	-/-	1	149 months NED
2. ♀ 70	Parotid salivary gland (superficial and deep lobe)	6 months (Asymptomatic mass, late pain sensation)	June 2005 Total parotidectomy (5×5 cm)	-	-/-	1	58 months Died April 2010 NED
3. ♀ 56	The tongue base	40 months (Dysphagia, speech problems)	September 2009 Base of tongue tumor resection (8×7 cm) Neck dissection	-	-/-	1	49 months NED
4. ♂ 44	Parotid salivary gland (superficial lobe)	84 months (Asymptomatic mass)	March 2010 Superficial parotidectomy (3×3 cm)	-	-/-	1	43 months NED
5. ♂ 47	Parotid salivary gland (superficial lobe)	48 months (Asymptomatic mass)	October 2010 Superficial parotidectomy (5×4 cm)	-	-/+	1	36 months NED
6. ♀ 66	Soft palate	2 months (speech problems, dysphagia)	November 2010 Soft palate tumor extirpation (6×4 cm) September 2011 Reoperation	+	-/-	1	35 months NED
7. ♀ 58	Parotid salivary gland (superficial lobe)	60 months (Asymptomatic mass)	October 2011 Superficial parotidectomy (4×3 cm)	-	-/-	2	24 months NED
8. ♂ 86	Parotid salivary gland (superficial and deep lobe)	6 months (Asymptomatic mass, late pain sensation)	March 2012 Total parotidectomy (6×4 cm) Neck dissection	+	-/+	4	19 months LR
Average: 60 years		Average: 32 months					Average: 52 months

NED-no evidence of disease; LR- Local recurrence; HPF-High power field.

signs of necrosis, and slight enhancement (Figure 1). The tumor spread from the base of the tongue to the level of hyoid, and caused significant obstruction. The tumor size ranged from 2 cm to 8 cm (Figure 2A).

All patients with EMCa were treated surgically; three cases underwent superficial parotidectomy, two cases were treated with total parotidectomy whilst on minor salivary gland sites tumor excision was performed. Frozen sections were made during surgery in each case and confirmed the malignant nature of the neoplasm. Neck dissection (ND) was performed in two patients, one with total parotidectomy and one case of EMCa localized at base of the tongue. Lymph nodes were enlarged clinically and on CT scan, but histopathologically showed only reactive changes, with no evidence of regional metastasis.

Patients were followed up from 19 to 149 months (average 52 months). During follow-up, one patient died after 58 months from other causes without clinical signs of recurrence. Local recurrence was diagnosed in three patients. Two cases of EMCa on minor salivary gland sites (nasal cavity and soft palate) with local recurrence were re-operated and are currently dis-

ease-free. One patient with local recurrence in deep parotid region was not re-treated because of poor general condition at 87 years of age. Adjuvant therapy was not applied in our patients.

Grossly, all tumors were nodular, with invasion of the adjacent salivary gland structures (Figure 2A). Surgical margins were positive in two cases, negative in five and in one case margin status could not be assessed because of tumor fragmentation during surgery. EMCas were diagnosed on conventional light microscopy that showed the presence of duct-like structures with luminal and abluminal cells (Figure 2B); each diagnosis was confirmed by immunohistochemical analysis (IHC) that showed epithelial and myoepithelial tumor component. IHC analysis showed that ductal cells were positive for low-molecular weight cytokeratins such as cytokeratin 7 (Figure 2C). Myoepithelial cells were positive for abluminal markers such as smooth muscle actin, calponin and p63 (Figure 2D).

Mitotic count ranged from 1 to 4 per 10 in high power field (HPF). There was no evidence of perineural invasion, but signs of vascular invasion were detected in two patients.

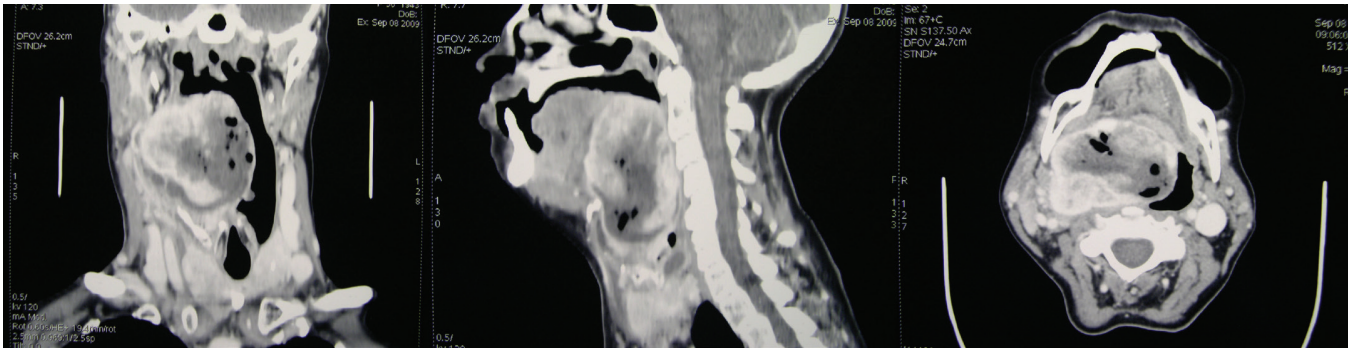


Figure 1. CT scan coronal, sagittal, and axial, shows an exophytic tumor originating from minor salivary localized at the tongue base.

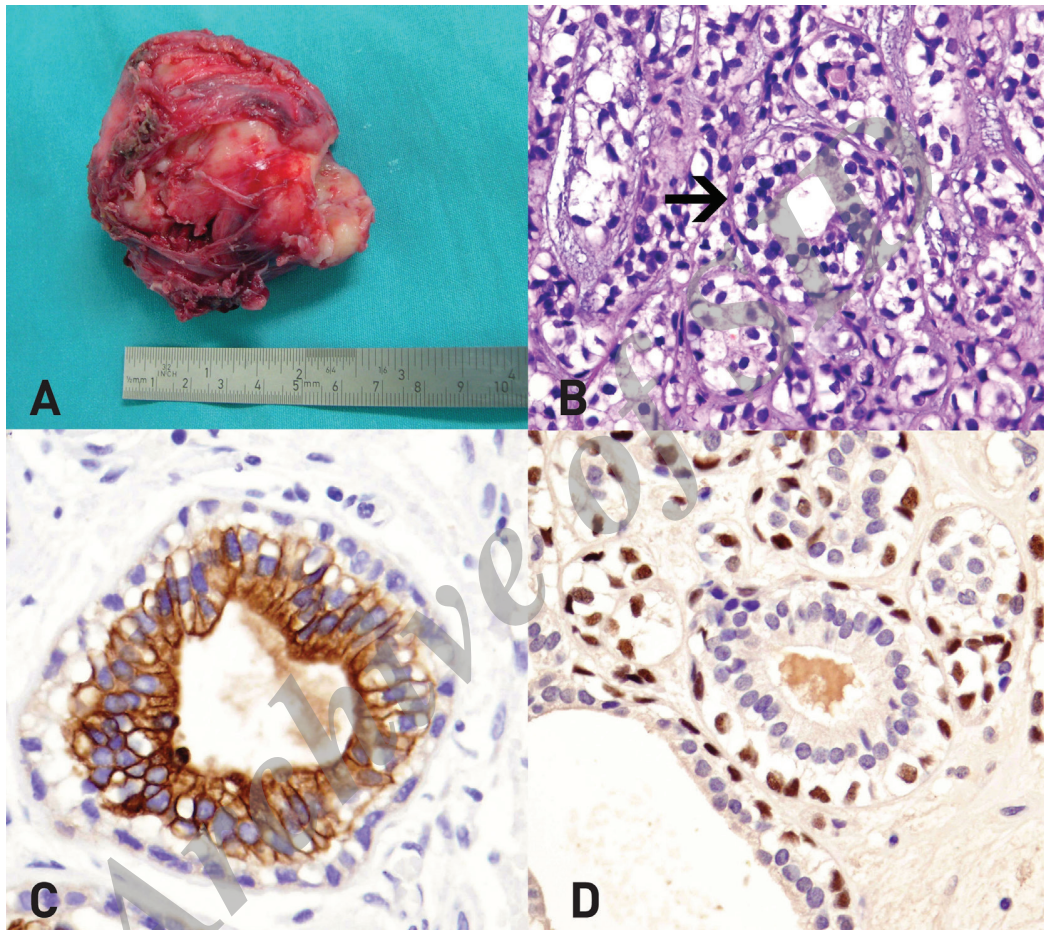


Figure 2. **A)** Excised EMCa of minor salivary gland origin at the tongue base. **B)** Presence of bi-layered duct-like structures (arrow) composed of myoepithelial and ductal cells is the hallmark for histopathological diagnosis. Hematoxylin & eosin, original magnification $\times 400$. **C)** Epithelial-myoepithelial carcinoma: cytokeratin 7 immunoreactivity of luminal, ductal cells. Streptavidin-biotin, original magnification $\times 400$. **D)** Epithelial-myoepithelial carcinoma: p63 immunoreactivity of clear, abluminal cells. Streptavidin-biotin, original magnification $\times 400$.

Discussion

Malignant salivary gland tumors account for less than 5% of head and neck cancers. EMCa belongs to a small group of rare entities that comprise only 1% to 2% of all salivary tumors.^{5,7}

Clinical presentation

EMCa is primarily a tumor of the parotid gland, but it can also occur in the submandibular gland and on minor salivary gland sites.^{1,7,8} In our case series, five patients were diagnosed

with EMCa in the parotid and three on minor salivary gland sites. Our patients showed female predilection which has been also reported in previously published papers.^{1,2,4-11} EMCa usually has an indolent presentation, with the peak incidence in the 6th decade.^{1,7} The average age of our patients was 60 years and the average duration of symptoms was 32 weeks. Patients with parotid EMCa presented with a slowly growing mass; if present, pain sensations occurred late and prompted the visit to a physician. The duration of symptoms of tumors on small salivary gland locations was 2, 12 and 40 months, respectively.

The tumor localized on the soft palate had the shortest duration of symptoms because of dysphagia and speech difficulties.

EMCa imaging

According to previously published series, clinical examination should be followed by certain additional imaging techniques such as US, CT and magnetic resonance imaging (MRI).⁹ During the diagnostic process in our clinic, US has always been the first line imaging technique in radiological assessment of parotid lesions. CT was applied in all cases in our series, and was very useful for evaluation of the overall extent of tumor growth, the relationship to adjacent vessels, assessment of resectability and planning of the extent of neck dissection.¹⁰⁻¹³

Surgical therapy

Since EMCa can radiologically simulate benign lesions, frozen sections were performed during surgery in all patients in order to confirm the malignant nature of the lesions.⁹ Since surgery is the treatment of choice for EMCa for parotid tumors, the therapy included superficial parotidectomy in three cases and total parotidectomy in two cases; one patient with total parotidectomy also had ND.⁷⁻¹¹ Patients with EMCa on minor salivary gland sites underwent tumor extirpation (EMCa located in the nasal cavity) with two re-interventions during a follow-up period of 12 years, tumor resection and ND (EMCa at the tongue base) and tumor extirpation (soft palate EMCa) followed by reoperation after 11 months. Four patients with parotid EMCa were disease-free during the follow-up period. Low grade, stage I salivary tumors are curable with surgery alone; radiation therapy may be used for tumors in which resection involves significant cosmetic or functional deficit or as an adjuvant to surgery when positive margins are present.^{7,8,11,14} All our cases were treated with surgery alone; two NDs performed histopathologically showed no evidence of metastatic disease. Prophylactic neck dissections are not mandatory for EMCa because of its low metastatic potential.⁷

Gross features and histopathology

EMCa is usually deceptively multinodular and well circumscribed, sometimes even with a capsule.^{5,7} In published series, tumor size ranged 0.5–20 cm.^{5,8,9,12,14} In our case series, all tumors were multinodular but unencapsulated and ranged from 2 cm to 8 cm in size, the largest tumor being the EMCa at tongue base (8 × 7 cm). These tumors are generally low-grade, with a deceptive pushing, multinodular pattern of infiltration; rarely, these tumors may show evidence of high-grade transformation or evidence of variant morphological features such as oncocytic, sebaceous, apocrine, spindled, or even some “ancient” changes.⁷ All tumors in our case series showed prototypical biphasic tubular arrangement that consisted of inner, cuboidal ductal cells and an outer layer of clear, myoepithelial cells. There was minimal nuclear pleomorphism and low mitotic rate that ranged 1–4 mitoses/10 HPF, which is in accordance with previously published data.^{1,5} Histopathological diagnosis was made on conventional light microscopy and always confirmed by IHC. Epithelial and myoepithelial markers were used for IHC confirmation: cytokeratin 7 for ductal, epithelial cells and p63 for myoepithelial cells.^{7,11,13} IHC analysis performed by Seethala *et al.*⁵ showed p63 positivity in 100% of myoepithelial cells with 100% sensitivity and specificity. Seethala also used

AE1/AE3, CAM 5.2 and pankeratin antibodies for assessment of epithelial cells. In our case series, cytokeratin 7 was strongly positive in all ductal epithelial cells. As for differential diagnosis, one should consider other clear cell tumors in cases with classic histopathological presentation of EMCa; variants of EMCa should be emphasized by IHC analysis.

Clinical outcome

Necrosis, angiolymphatic invasion and positive margin status correlate with an aggressive behavior of EMCa.⁷ Seethala *et al.*⁵ reported a local recurrence rate of 36.3% and metastatic disease in 5.2% with a 5-year survival of 93.5%. Fonseca *et al.*² reported that local recurrence occurred in up to 50% of patients with a 5-year survival of 87%. In our case series, one patient with parotid EMCa died after 58 months, but due to other causes and without recurrent disease. The oldest patient (86-year-old male) treated with total parotidectomy and ND had a recurring disease after 19 months. Tumor localization, extent of the disease and negative margins are essential for complete surgical excision.^{1,3,5,7} Two patients were re-operated and disease-free throughout the follow-up period. In our case series, surgical re-interventions were performed because surgical margins were positive or because margins could not be determined (in one case, tumor fragmentation occurred during surgery on minor salivary gland sites). Angiolymphatic invasion was present in two cases, one of which had a recurrent disease.

In conclusion, the current information and review of literature indicates that EMCa is generally a low grade malignant tumor of salivary glands, with distinct histopathological appearance. EMCa has a low incidence of regional and distant metastasis and relatively high tendency for local recurrence. Knowing the clinical and histopathological features of these tumors is essential for establishing the accurate diagnosis and planning further treatment. Surgery is the therapy of choice for EMCa, on both major and minor salivary gland sites, with tendency to achieve tumor free margins and good prognosis.

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