Case Report

Epithelial-myoepithelial carcinoma ex pleomorphic adenoma of the parotid gland with unique histologic differentiation: A rare case report

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Abstract

Epithelial myoepithelial carcinoma (EMC) is an uncommon low-to-intermediate grade salivary gland malignancy that accounts for 1% of all tumors arising in salivary glands. About 80% of these tumors affect the parotid gland. These lesions either arise *de novo* or from existing pleomorphic adenoma (PA). Histologically, these tumors reveal a biphasic cell population with inner ductal epithelial cells and peripheral myoepithelial cells. There are many histologic variants of EMC, but sebaceous, verocay-like differentiation and high-grade transformation is very rarely reported. This article describes a 48-year-old female patient diagnosed with EMC ex PA with unique histologic differentiation.

Keywords: Carcinoma ex pleomorphic adenoma, dedifferentiation, epithelial-myoepithelial carcinoma, high-grade transformation, histology, oncocytic differentiation, parotid gland, sebaceous differentiation, squamous differentiation, verocay-like differentiation

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INTRODUCTION

Epithelial-myoepithelial carcinoma (EMC) is a rare malignancy which accounts to 1% of all tumors arising in salivary glands. Clinically it often presents as a slowly progressing asymptomatic mass and shows classic biphasic histology composed of variable amounts of small ductal and large myoepithelial cells. EMC mainly affects elderly women of 60 years and involves the parotid gland most commonly. Various histologic variants have been described.[1] EMC with sebaceous, verocay-like differentiation and high-grade transformation (HGT) is rarely reported in published literature.

CASE REPORT

A 48-year-old female reported to the outpatient department with a chief complaint of a painless swelling in the right parotid region of 1-year duration, which was small, to begin with and had slowly progressed to the present size. On examination, a solitary, well-defined, nodular mass with a smooth surface measuring approximately 3 cm × 2.5 cm

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was present in the right parotid region pushing the ear lobule upward with normal overlying skin [Figure 1]. The mass was painless, mobile and firm. There was no cervical lymphadenopathy and no paresthesia. History revealed that the patient had undergone partial parotidectomy in the same region 3 years back with a diagnosis of pleomorphic adenoma (PA). A provisional diagnosis of recurrence or carcinoma ex PA was made.

Contrast-enhanced magnetic resonance imaging (MRI) scan revealed a hyperdense mass involving both superficial and deep lobes of the right parotid gland [Figure 2a-c]. Fine needle aspiration cytology was done. Smears studied showed few atypical mucous cells in small clusters and few dispersed squamous cells in a mucoid background. Most of the cells showed degenerative changes. Few macrophages, polymorphs and necrotic foci were also seen in the background. Based on these findings, a diagnosis of mucoepidermoid carcinoma (MEC) was given. The patient underwent a total conservative parotidectomy followed by reconstruction by rotating and suturing of the posterior belly of digastric with tissues above the parotid under general anesthesia [Figure 3a and b]. The lesion was close to the branches of the facial nerve intraoperatively; from which it was dissected off, taking 1 cm margins. Postoperatively, mild facial paresis was present. The excised tissue was sent for histopathologic examination [Figure 4]. The gross specimen revealed a nodular, well-circumscribed mass which was yellowish-brown in color. The patient is under regular follow-up for the past 1 year, and her facial nerve functions have recovered completely [Figure 5].

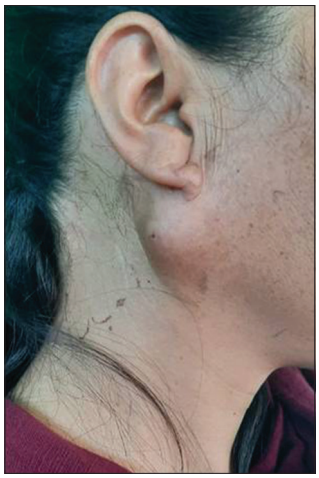

Figure 1: Clinical photograph showing the presence of tumor in the right parotid gland

Histopathology showed the tumor cells invading the stroma with irregular infiltrating margins. Tumor cells were arranged in sheets and lobules separated by bands of hyalinized fibrous tissue in a myxoid stroma reminiscent of PA [Figure 6a]. Biphasic cell population comprising myoepithelial cells having abundant clear vacuolated cytoplasm and pleomorphic hyperchromatic vesicular nuclei with distinct nucleoli and eosinophilic cuboidal cells was observed [Figure 6b and c]. Some areas revealed ducts and tubular structures surrounded by ductal cells and myoepithelial cells [Figure 6d and e]. Few abnormal mitoses in foci of HGT were evident along with spindle-shaped cells showing higher nuclear pleomorphism, prominent nucleoli, acidophilic cytoplasm and mitotic activity [Figure 6f]. Some areas of cystic degeneration and necrosis were evident [Figure 6g]. Some cells with sebaceous differentiation [Figure 7a], verocay-like differentiation [Figure 7b], squamous differentiation [Figure 7c] and oncocytic differentiation [Figure 7d] were also evident. The peripheral areas revealed

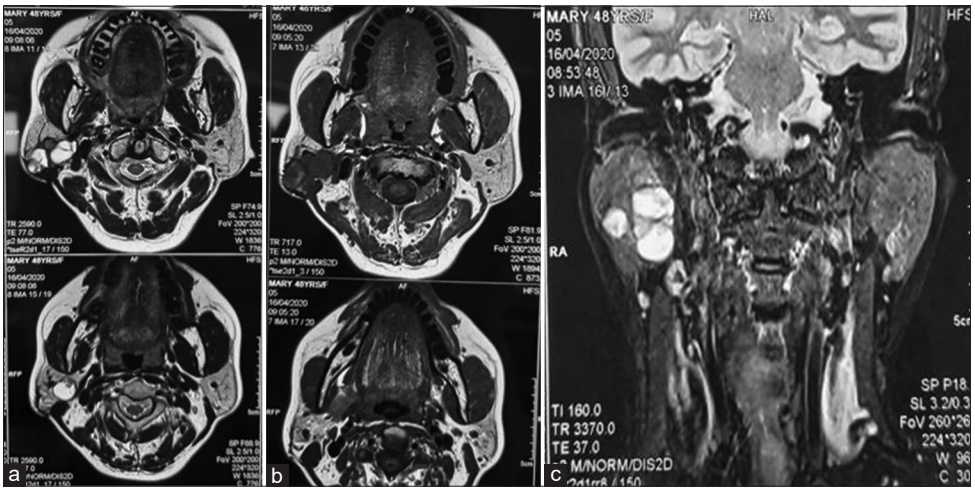

Figure 2: Contrast-enhanced magnetic resonance imaging revealed a lobulated hyperdense mass in the right parotid gland involving both deep and superficial lobes a) axial section b) axial section c) coronal section

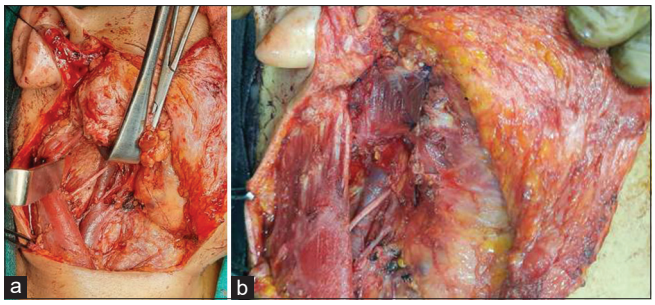

Figure 3: Intraoperative photographs (a) before tumor removal, (b) after tumor removal

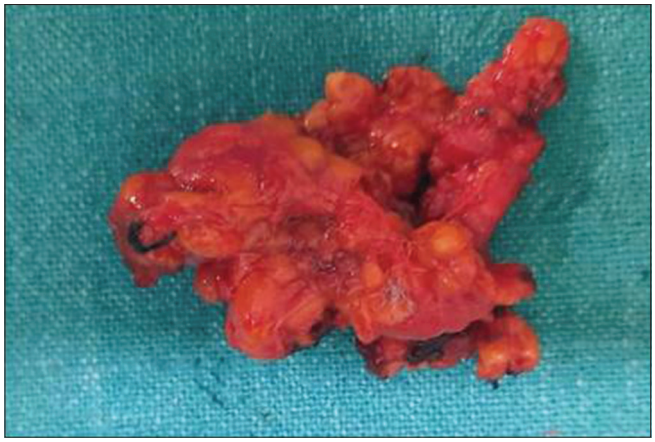

Figure 4: Excised tissue specimen

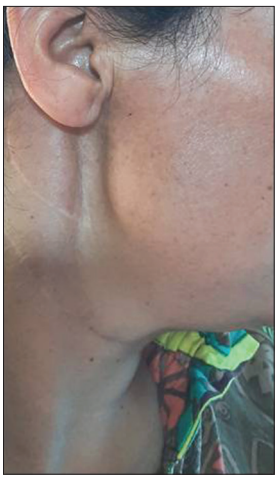

Figure 5: Clinical photograph at 1-year follow-up

parotid tissue with lymphoplasmocytic infiltration. Neural and vascular involvement was not evident.

Immunohistochemical staining (IHC) was carried out to rule out other clear cell tumors and to confirm the biphasic differentiation and final diagnosis. Neoplastic cells revealed positivity for S-100, cytokeratin and high-grade component was negative for epithelial membrane antigen (EMA). Nuclear positivity for p63, S-100 and cytoplasmic positivity for calponin in the surrounding myoepithelial cells, and intense positivity for epithelial markers, like cytokeratin-7 in the luminal tumor cells was seen. Sebaceous cells were S 100 negative and intensely positive for EMA membranous and cytoplasmic staining (with a characteristic bubbly pattern). Ki67 index was 5%. The IHC workup was done in a private laboratory so the pictures were not available. A final diagnosis of EMC ex PA with sebaceous, verocay-like differentiation and foci of HGT was given.

DISCUSSION

EMC was first described in 1972 by Donath.[2] Most cases are seen in parotids (83.74%), followed by the submandibular gland (13.01%) and minor salivary glands of the oral cavity, especially palate, maxillary sinus, trachea, larynx and hypopharynx. Females are twice more commonly affected than males. It is common in individuals in the 6th to 7th decades and rarely seen in children.[3-5]

Clinical features

EMC is a low-to-intermediate grade malignancy often with slow growth potential and present for a long duration. Tumors involving mucosa commonly present with ulcerations. Nasal tumors may cause pain, nasal obstruction, or rhinorrhea. Occasionally, high-grade tumors with aggressive and painful clinical courses causing nerve palsies have been reported.[6] Facial asymmetry, palsy and lymphadenopathy may be rare presenting symptoms. Usually, high-grade tumors are invasive and can invade nerves, blood vessels and bones. Nevertheless, EMC has a lower mortality rate. Local and distant metastases are about 15% and a 5-year survival rate of 80% is reported.[7]

Etiology

The origin of EMC is not clear. The origin may be *de novo* or in preexisting or recurrent PA. The latter origin seems to hold good in the present case. It is believed to arise from the stem cells with dual differentiation forming myoepithelial and ductal epithelial cells. It is thought to arise from the intercalated duct.[8] *De novo* EMCs are believed to have aggressive course with a shorter history.

p53 and Harvey rat sarcoma viral oncogene homolog (HRAS) mutations seen in EMC mainly depend on preexisting lesions. EMC developing in preexisting PA often show *PLAG1* or *HMGA2* rearrangement and one-third exhibit *HRAS* mutation. Eighty percent of EMC arise from PA.[9,10]

Radiographic features

Preoperative diagnosis based on imaging alone is challenging. Computed tomography may reveal a

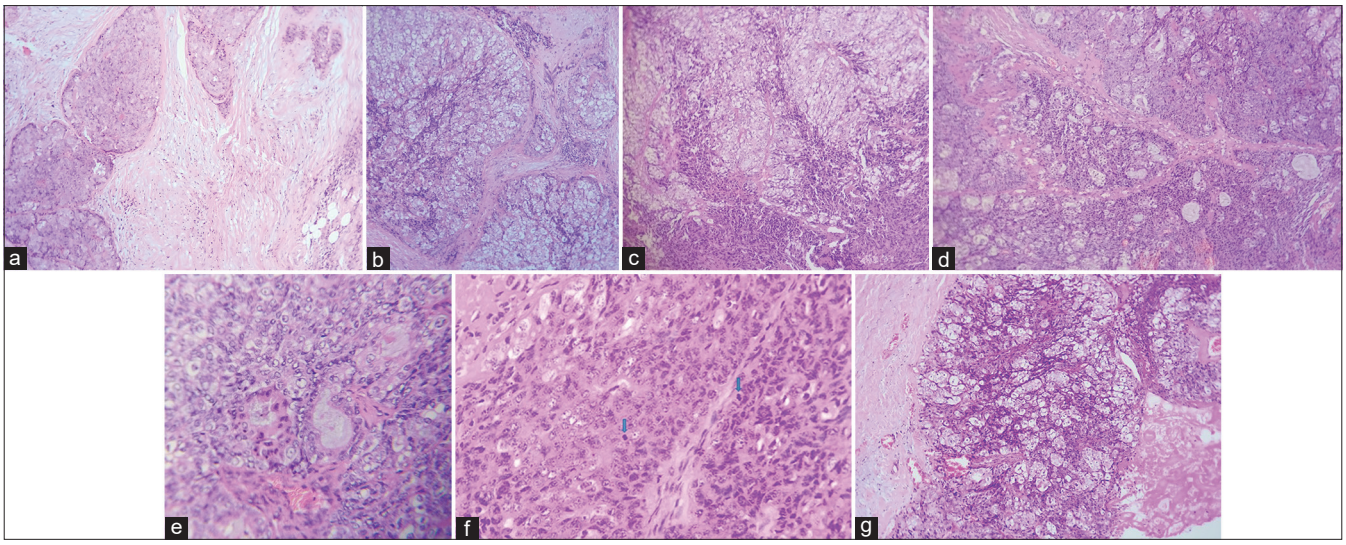

Figure 6: Photomicrograph showing (a) Multinodular growth pattern with the invasion of tumor islands in a background of myxoid stroma reminiscent of pleomorphic adenoma (×4, hematoxylin and eosin); (b) Biphasic cell population with clear myoepithelial cells and eosinophilic cuboidal cells (×4 hematoxylin and eosin stain); (c) Biphasic cell population with clear myoepithelial cells and eosinophilic cuboidal cells (×10, hematoxylin and eosin stain); (d) Rare ducts are surrounded by ductal eosinophilic cuboidal and myoepithelial cells (×4 hematoxylin and eosin stain); (e) Rare ducts are surrounded by ductal eosinophilic cuboidal and myoepithelial cells (×20, hematoxylin and eosin stain); (f) Abnormal mitosis in foci of high grade transformation (×20, hematoxylin and eosin stain); (g) Areas of necrosis (×20, hematoxylin and eosin stain).

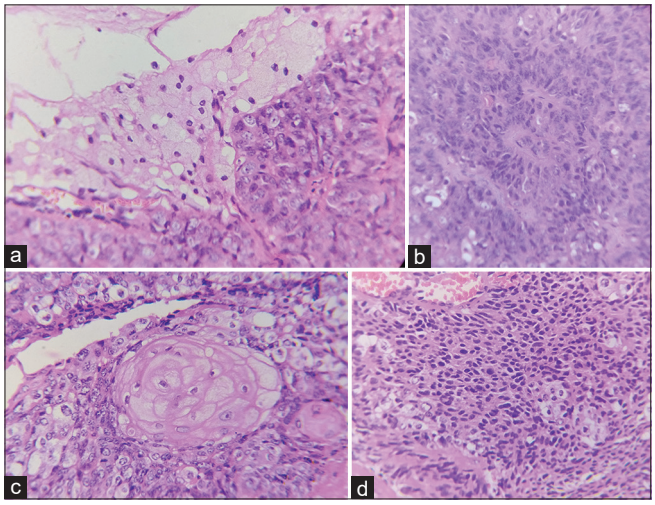

Figure 7: Photomicrographs showing tumor cells with (a) Sebaceous differentiation, (b) verocay-like differentiation (c) Squamous differentiation, (d) Oncocytic differentiation (×40, hematoxylin and eosin stain)

heterogeneously soft tissue shadow with the destruction of the adjacent structures. The radiological appearance of EMC is nonspecific and cannot be used to differentiate from other neoplasms. MRI and ultrasound are recommended for the initial radiological assessment of parotid and submandibular lesions.[11]

Cytology

The characteristic cytological feature of EMC includes three-dimensional cellular aggregates, vacuolated cytoplasm in the peripheral cells and the presence of acellular hyaline globules.[12] Misdiagnosis on fine-needle aspiration cytology is common because of the various cell types making the interpretation difficult, which was in agreement in the present case. These lesions are diagnosed on conventional light microscopy features, confirmed by the IHC and ultrastructural investigation.[13]

Gross features

Macroscopically, EMC characteristically shows a multinodular appearance, 2–8 cm diameter, and firm to rubbery consistency. Cut surfaces are often gray-white or brownish due to hemorrhage, necrosis and cystic degeneration. The tumor often is a well-defined grossly, but partial encapsulation and cystic change are noted in 30% of cases.

Histopathology

EMC often shows multinodular growth pattern with infiltrative margins, perineural invasion and rarely vascular invasion. Classically, neoplastic cells are seen as solid lobules or islands separated by hyalinized stroma showing duct-like structures. These duct-like structures show inner luminal cuboidal cells having granular eosinophilic cytoplasm and basal nucleus and outer, abluminal myoepithelial cells having clear cytoplasm and a vesicular nucleus located toward the basement membrane (one or more layers). Classic or conventional EMC accounts for 40.2% of all cases. Various histologic variants have been described making the diagnosis challenging, such as double clear,

oncocytic, sebaceous, apocrine-type, cribriform-type, basaloid, EMC ex PA, papillary-cystic, squamous, psammomatous, verocay-like, EMC with adenoid cystic carcinoma (AdCC)-like areas with pseudocyst formation and EMC with HGT and with anaplasia.[5,9,14,15] Concurrent occurrence with other neoplasms has been reported by Yanagawa *et al*.[16] These histologic types are attributed to pluripotent stem cells which can undergo multidirectional differentiation. It is still uncertain whether histologic types have any clinical and prognostic significance. Solid infiltrative invasion, nuclear pleomorphism, aneuploidy and rapid proliferation suggest a poorer outcome. EMC often reveals infiltrating margins, hyalinized stroma and split artifacts between dual cell populations. These form unique areas when EMC has origin from PA and help in differentiating EMC from cellular PA.[10] The ultrastructure of EMC reveals microvilli and zymogen granules in luminal cells with glycogen and peripheral smooth muscle myofilaments in myoepithelial cells.[17]

The transition of cells to more disorderly pattern with features of dysplasia is termed as HGT or dedifferentiation. In salivary gland neoplasms the term HGT is preferred than dedifferentiation. "It remains unsettled whether the process of HGT represents a failure of differentiation in stem cells or whether differentiated neoplastic cells undergo dedifferentiation." These tumors exhibit aggressive behavior clinically and hence require long-term follow-up after treatment. HGT in EMC is commonly seen in myoepithelial components (spindle-shaped cells, clear cells and the presence of plasmacytoid cells), often affects the parotid gland and occurs in slightly elderly (72 years) than conventional EMC. Increased mitosis, pleomorphism, cytologic atypia, necrotic areas, lack of ductal structures and original distinct histology may give a hint of HGT.[18]

Differential diagnosis

EMC may mimic myoepithelioma (ME), myoepithelial carcinoma (MYC), PA and AdCC, MEC, acinic cell carcinoma (ACC), oncocytoma, oncocytic carcinoma, mammary analog secretory carcinoma, metastatic clear-cell renal cell carcinoma (MRCC) and clear-cell carcinoma.[19,20] IHC is needed for correct diagnosis. It is recommended to distinguish the type of tumor using myoepithelial markers. α-Smooth muscle actin (α-SMA) and calponin are positive in EMC, ME and MYC, but not in the other tumors. EMA-positive staining in the apical portion differentiates EMC from ME and MYC. ME and MYC are devoid of ductal cell components, unlike EMC.

Myoepithelial component in EMC shows a sharp peripheral margin, unlike PA where it merges into adjacent stromal tissue giving a "melting pattern." In addition, conventional EMC lacks any mucinous or myxochondroid stroma seen in PA. AdCC may have EMC-like areas, but the tumor cells are uniform and resembling basal cells in appearance with few myoepithelial cells compared to EMC. In MEC, clear cells contain glycogen and mucous cells secrete mucin that shows per-iodic acid Schiff (PAS) stain and alcian blue positivity and are p63-negative. In ACC, there is serous differentiation, and clear cells do not stain positive for PAS and p63, differentiating it from EMC. Oncocytic tumors may be differentiated by selective markers for mitochondria such as positive phosphotungstic acid-hematoxylin staining and anti-mitochondrial antibody 113-1.[20] MRCC is positive for CD10 and negative for p63, unlike EMC. Mammary analog secretory carcinoma shows mammoglobin positivity unlike, EMC. Clear-cell carcinoma does not reveal myoepithelial differentiation.

Sebaceous adenoma as well as sebaceous carcinoma may be differential diagnoses if sebaceous cells are seen. Clear cells in sebaceous tumors fail to stain for glycogen and show a foamy cytoplasm. These cells show strong staining for EMA with bubble-like patterns, adipophilin and perilipin. Androgen receptors can differentiate poorly differentiated sebaceous carcinomas.[21]

Immunohistochemical findings

EMC is diagnosed by the histologic identification of ductal and myoepithelial cells with confirmation by IHC staining. Smooth muscle actin, p63, p40 and calponin, and rarely S100 protein highlight the myoepithelial cells. Luminal cells stain intensely for low-molecular-weight cytokeratins and EMA, while myoepithelial cells show negative staining.[4]

Treatment

Surgery with a clear margin is the primary modality of the treatment since the tumor infiltrates locally. Even with complete surgical resection, recurrences and distant metastases remain a concern and may occur from a few months to years later to treatment. Radiotherapy is suggested to prevent local recurrence by some authors. However, whether radiotherapy and/or chemotherapy are helpful in treating EMC remains debatable.[22]

Prognosis and predictive factors

Significant prognostic factors like patient age of >80 years at initial diagnosis, tumor size more than 4 cm in diameter, positive margin status, presence of regional nodal or distant metastases, solid invasive pattern, nuclear pleomorphism, DNA aneuploidy and high proliferative activity, HGT, presence of myoepithelial anaplasia, necrosis and angiolymphatic invasion may indicate a poorer prognosis.[3,6]

Patients with EMC have the risk of developing second primary malignant tumors in the salivary gland itself or in tissues like breast or thyroid separately, warranting long-term follow-up. About 35%–50% recurrence is reported with a metastatic rate of 8.1%–25%.[23]

CONCLUSION

Diagnosing EMC is challenging due to its histologic diversity. Even though EMC is the low-grade tumor, long-term follow-up is needed to prevent recurrence and metastasis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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