Epithelial myoepithelial carcinoma of parotid gland-a case report

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Abstract

Epithelial-Myoepithelial Carcinoma is a rare malignant salivary gland neoplasm. It is also known as adenomyoepithelioma. It accounts for less than 1% of all salivary gland neoplasms. This unusual salivary gland tumors is first described by Donath et al in 1972. This tumor occurs in sixth decade and beyond having a female predominance. Parotid gland is the most commonly involved followed by submandibular gland and palate. Herein we are presenting a rare case of Epithelial-myoepithelial carcinoma of parotid gland.

Keywords: Epithelial–myoepithelial carcinoma, Adenomyoepithelioma, Parotid gland tumors

Access this article online

Website:
www.innovativepublication.com

DOI:
10.5958/2395-6194.2016.00035.7

Introduction

Epithelial-myoepithelial carcinoma (EMEC) of the salivary glands was described by Donath et al in 1972[1]. It is a rare tumor, accounting for less than 1% of all salivary gland neoplasms that arises most commonly in the parotid gland but has also been described in the submandibular gland and in the minor salivary glands[2,3]. There is a female predominance with a peak occurrence in the seventh decade[4]. Epithelial-myoepithelial carcinoma also known as adenomyoepithelioma is low grade malignant salivary gland neoplasm composed of clear myoepithelial cells that surround epithelial lined ducts resembling intercalated ducts. In 1991, the WHO recognized Epithelial-myoepithelial carcinoma as a distinct entity and subtype of salivary gland adenocar- cinoma and it became part of the new classification system[5]. Epithelial-myoepithelial carcinoma tends to grow in a bulky lobulated fashion with necrosis and hyalinization of large tumor nodules. The tumor has a distinctive histopathologic pattern with a proliferation of ductular structures. The inner cells of these ductules constitute the epithelial component of Epithelial-myoepithelial carcinoma. These mildly to moderately pleomorphic cells have irregular ovoid shapes may overlap and have prominent nucleoli and fine chromatin. Local spread to lymph nodes has been reported[4]. The usual treatment is wide surgical resection including adjacent lymph nodes however there is a high reported rate of local recurrence approaching 50%[6,7,8]. Therefore adequate resection with negative soft-tissue margins is the minimum recommended and necessary therapy. It chiefly occurs in the parotid gland representing about 1% of all salivary gland tumors[9,10,11]. In addition, the major sites of involvement are the maxillary sinus, trachea, larynx, hypopharynx, and minor salivary glands. Patients are mostly women in their fifth to eighth decades[12,13]. Epithelial-myoepithelial carcinoma is a malignant biphasic salivary-type tumor and the diagnosis is based on conventional light microscopy confirmed by immunohistochemical and ultrastructural investigation. Histologically the tumor is characterized by well-defined tubules with two cell types: an outer layer of myoepithelial cells with clear cytoplasm surrounding an inner lining of eosinophilic cuboidal epithelial cells[14] resembling intercalated ducts. It has been suggested that it derives from the intercalated ducts of the salivary glands because the tubular growth pattern of this tumor epitomizes this phenotype[15,16]. It has been observed that some morphologically low-grade myoepithelial carcinomas behave aggressively[16]. Thus in the absence of frankly malignant cytomorphology, an invasive growth pattern is the single most useful criterion for establishing malignancy in salivary Epithelial-myoepithelial carcinoma. It was first described by Donath et al. in 1972 and recognized as a distinct entity by the World Health Organization (WHO) in 1991[17,18,19]. Soft palate seems to be the site of predilection of minor salivary gland Epithelial-myoepithelial carcinoma[18,19]. Histologically, the tumor is characterized by a biphasic cytomorphology comprised of an inner layer of duct lining cells and an outer layer of clear myoepithelial cells[20,21,22]. It can also show a multinodular growth pattern with tumor islands separated by a basement membrane and dense fibrous connective tissue bands. In many cases, the clear myoepithelial cell components are more predominant than the typical biphasic character[23]. Based on the primary histological characteristics, the Epithelial-myoepithelial carcinoma can be classified in four

categories: solid, tubular, pappilary and cribriform[21]. In some cases, the local rate of recurrence is high, ranging from 31.3% to 43%, and most recurrences manifest within 5 years[24,25]. This may be partly because Epithelial-myoepithelial carcinoma often appears histologically benign and this can result in its incomplete excision[26]. Metastasis to regional cervical lymph nodes has been reported in about 19.6% ofpatients[27] and distant metastasis to the kidney, lung and brain have been reported in 9.8%[28]. The diagnosis of Epithelial-myoepithelial carcinoma is difficult, partly because of the rarity of the tumor, partly because of the complicated histopathological characteristics and it has been speculated that most reported cases are not correctly diagnosed. Some authors divide Epithelial-myoepithelial carcinoma into 2 subtypes: 1) a tubular cribriform type characterized by a double-layered tubule ductal structure and 2) a solid type dominated by clear cells[29]. The solid variant of Epithelial-myoepithelial carcinoma is found to be associated with a more aggressive behavior compared with the other histological types[30]. Other microscopic features of Epithelial-myoepithelial carcinoma include periodic acid-Schiff (PAS) positivity of the clear cells, with corresponding negativity on diastase digestion; markedly PAS-positive basement membrane, with minimal cellular atypia; infrequent mitoses and a tendency to exhibit ductal differentiation[17]. The differential diagnosis of Epithelial-myoepithelial carcinoma includes clear cell dominated tumors such as myoepitheliomas, acinic cell carcinomas, mucoepidermoid carcinomas, and metastatic clear cell tumors[31,32,33]. Because adenoid cystic carcinoma(ACC) can also show a double-layered, duct-like structure, it can be mistaken for Epithelial-myoepithelial carcinoma[17] but different immunostaining characteristics are useful for distinguishing between Epithelial-myoepithelial carcinoma and ACC. The identification of S-100 protein can help in this differentiation. The inner ductal cell layer in ACC will stain positive whereas only the outer ductal cell layer in EMC is positive for this protein[19]. For Yamada et al[19] the value of image examination such as computed tomography, magnetic resonance imaging and positron emission tomography for the pathologic diagnosis of EMC has yet to be established. Epithelial-myoepithelial carcinoma is a rare biphasic tumor of the salivary gland. It is generally composed of variable proportions of two cell types: An inner layer of duct lining cells and an outer layer of clear cells, which typically form doublelayered duct-like structures. Clear cells, which are of myoepithelial origin, often predominate in number[34]. EMC is a rare, low-grade malignant neoplasm characterized by a dual cell population of luminal ductal cells surrounded by large, polygonal clear myoepithelial cells. The criteria proposed to identify more aggressive lesions are a solid growth pattern, nuclear atypia, DNA aneuploidy, necrosis, positive surgical margins and high proliferative activity; such cases generally have a more aggressive behavior and a higher frequency of local recurrences and metastases. Adenoid cystic carcinoma, as EMC, is a tumor comprising a dual cell population of epithelial and myoepithelial cells and it can have a morphology similar to that of EMC in terms of its trabecular pattern, where the prominent hyalinised stroma surrounds and squeezes the tumor cells into thin strands. In contrast to EMC, these cells are smaller and usually have more hyperchromatic, irregular and angulated nuclei. The feature that distinguishes myoepithelioma and myoepithelial carcinoma from EMC is the lack of a ductal cell component. Because EMC is considered to be a low-grade malignant tumor, adequate resection with negative soft-tissue margins is the minimum recommended and necessary therapy. Neck node dissection should be considered in cases of lymph node positivity along with chemotherapy and radiotherapy in patients with highly advanced disease, positive surgical margins, or surgically unresectable disease. Other synonyms of epithelial-myoepithelial carcinoma include epithelial carcinoma, myoepithelial carcinoma and clear cell carcinoma of salivary gland origin[35]. The tumor is usually encapsulated, and may exhibit areas of necrosis and cystic degeneration. It may show one or more of spindle cells, epithelioid cells, plasmacytoid hyaline cells and clear cells. Nuclear atypia ranges from mild to marked. Solid, fascicular, trabecular and lace-like growth patterns are common. There can be various amounts of myxoid, collagenous or hyaline stroma[36]. Di Palma and Guzzo considered epithelial-myoepithelial carcinoma to be low grade when it arose in a pleomorphic adenoma and high grade when it arose de novo[37]. These tumor cells secrete extracellular matrix, proteinases and proteinase inhibitors and also inhibit angiogenesis, and modification of these attributes could affect their biological behavior[38]. Donath et al. postulated that the cell of origin was from intercalated ducts[1].The occurrence of intercalated duct hyperplasia has been observed in association with EMC in the case described by Di Palma[37] and in three of the cases described by Chetty[39]. The integration of the two elements probably means that the EMC started from preceding intercalated duct hyperplasia[39,40]. CT and MR appearances of EMC are nonspecific, and that EMC cannot be differentiated from other parotid neoplasms[41]. The usual treatment is wide surgical resection, including adjacent lymph nodes; adequate resection with negative soft-tissue margins is the minimum recommended therapy[42].

Case Report

A 28year old male patient (**Fig. 1**) reported to us with chief complaint of swelling involving right side of face since 3 years. The swelling was progressively increasing in size. There was no associated pain or bleeding. The swelling was causing disfigurement in

right side. There was no significant past medical/ dental history. He has normal gait and posture. He has normal intelligence and well oriented to surroundings. He had normal vitals. On extra-oral examination a firm, non-tender swelling of 4x4 cm is noted in right tragus area extending from right tragus to middle of canthus- tragus line antero-posteriorly. Superio-inferiorly the swelling was extending from lower hairline to middle of ramus of mandible(**Fig. 2**). The right ear lobe was elevated. The skin overlying the swelling was of normal texture and colors however it was erythematous at its apex. There was no associated dysfunction with swelling. Intra-orally no significant finding in noted. The mouth opening was normal (**Fig. 3**). On the basis of clinical and radiological findings a provisional diagnosis of parotid gland neoplasm is reached. The patient was advised for radiographic investigations and FNAC of right parotid swelling. The panoramic radiograph shows a well-defined radiolucency of 3x3 cm extending from medial side of condyle to lateral side of coronoid process antero-posteriorly and till middle of right ramus ineriorly(**Fig. 4**). All the other structures were within normal limit. The contrast enhanced CT shows ill-defined heterogeneously enhancing soft tissue attenuation lesion measuring (4.5x4.8x5.0cm) in size is noted in right infratemporal fossa. The lesion is seen thinning and remodeling of ramus of mandible with deepening and widening of mandibular fossa. Anterolaterally the lesion is causing thinning and buckling of posterior wall of right maxillary sinus. The lesion is also seen abutting and displacing the masseter and temporalis muscle with focal loss of fat plane. Medially the lesion seen abutting left lateral and medial pterygoid with loss of fat plane. The lesion is also causing thickening and remodeling of right lateral pterygoid plate(**Fig. 5a, 5b, 5c**). All other structures were normal. The FNAC from right parotid region shows benign epithelial and myoepithelial cells with bland nucleoli arranged in clusters as well as dispersed singly in a chondromyxoid matrix.The individual myoepithelial cells are predominantly spindle shaped. There is no evidence of granuloma and atypia(**Fig. 6**). The radiological features and FNAC were suggestive of malignant tumor of parotid gland. The patient was advised for right parotidectomy with radical neck dissection under GA in ENT department (**Fig. 7**). The histopathology of resected section shows.

Gross:

Vail 1- Labelled as right level 1B and level II lymph node, received as two grayish brown soft tissue pieces larger measuring 1x0.5x0.2 cm. Larger soft tissue piece- outer surface smooth cuts firm. Cut surface shows grayish white areas. Whole sanctioned maller soft tissue piece-- outer surface smooth cuts firm. Cut surface shows grayish white areas.

Vial 2- Labeled as infratemporal fossa tissue, received as multiple grayish white soft tissues measuring 3x2x1cm.

Microscopic features- (Fig. 8a & 8b)

Vial 1- The section shows malignant biphasic tumor of salivary gland comprising of epithelial and myoepithelial component. The individual myoepithelial component is disposed in glandular and acinar pattern having round to ovoid nuclei, hyperchromatic chromatin, have high nucleocytoplasmic ratio, inconspicuous nucleoli and scanty cytoplasm. The individual myoepithelial / stromal components are comprising of ovoid or spindled cells having high nucleocytoplasmic ratio, coarse chromatin, inconspicuous nucleoli and moderate eosinophillic cytoplasm.

Vial 2. Section shows three lymph nodes showing reactive lymphoid hyperplasia and are free from tumor invasion.

The histopathology was suggestive of Epithelial-Myoepithelial carcinoma of right parotid gland.

So on the basis of radiological and histopathological investigations a final diagnosis of Epithelial-Myoepithelial carcinoma of right parotid gland has reached. The patient is referred to radiotherapy department for further management by radiation. The patient is treated in radiotherapy department for 1 year. The patient is followed for 2 years but no active lesion has been detected.

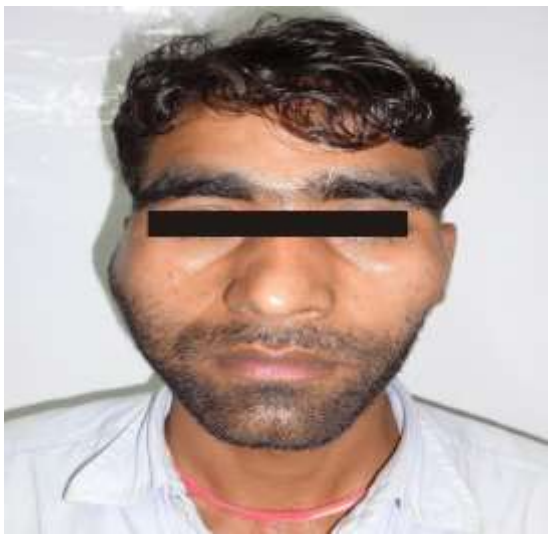

Fig. 1: Profile photo of patient

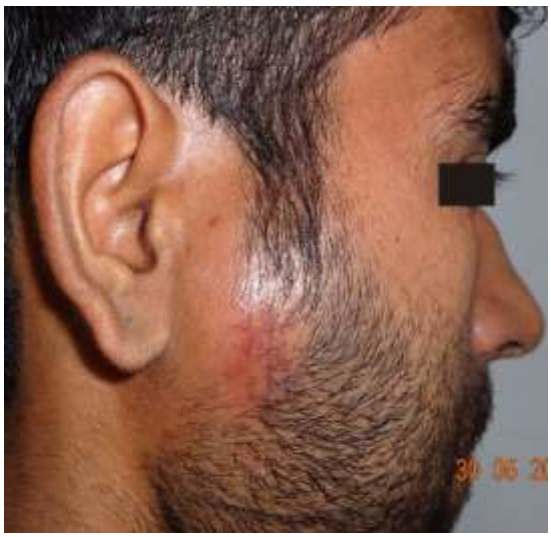

Fig. 2: Showing swelling of 4x4 cm is noted in right tragus area extending from right tragus to middle of canthus- tragus line antero-posteriorly. Superio-inferiorly the swelling was extending from lower hairline to middle of ramus of mandible

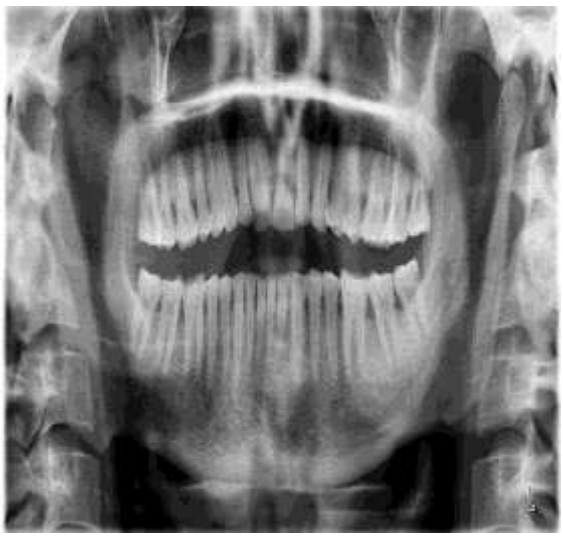

Fig. 4: Panoramic radiograph showing a well-defined radiolucency of 3x3 cm extending from medial side of condyle to lateral side of coronoid process antero-posteriorly and till middle of right ramus inferiorly

Fig. 3: Intra-oral view showing no significant findings

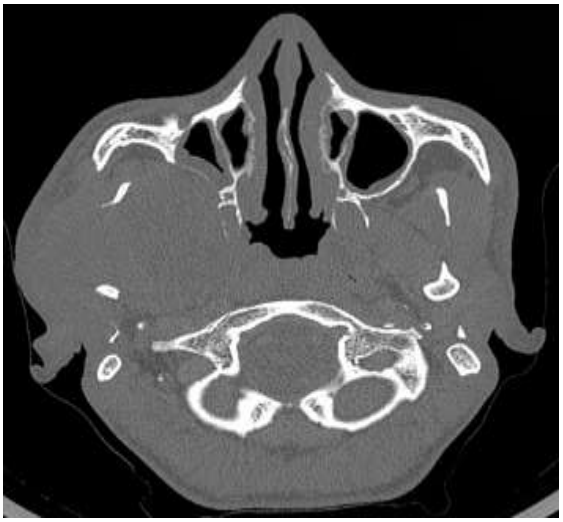

Fig. 5a: CECT (Axial) showing ill-defined heterogeneously enhancing soft tissue attenuation lesion measuring (4.5x4.8x5.0cm) in size is noted in right infratemporal fossa

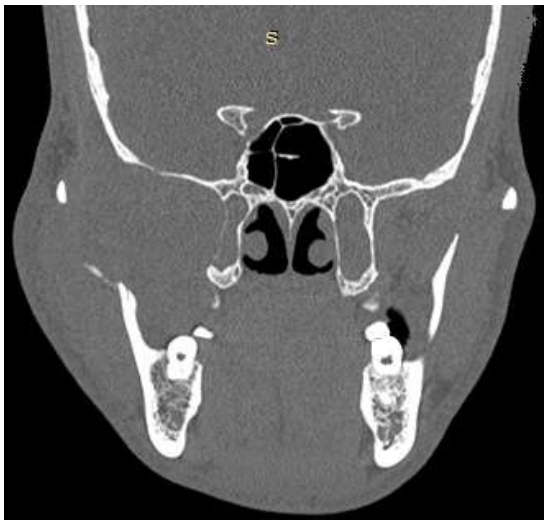

Fig. 5b: CECT (Coronal section) showing thinning and remodeling of ramus of mandible with deepening and widening of mandibular fossa. Anterolaterally the lesion is causing thinning and buckling of posterior wall of right maxillary sinus

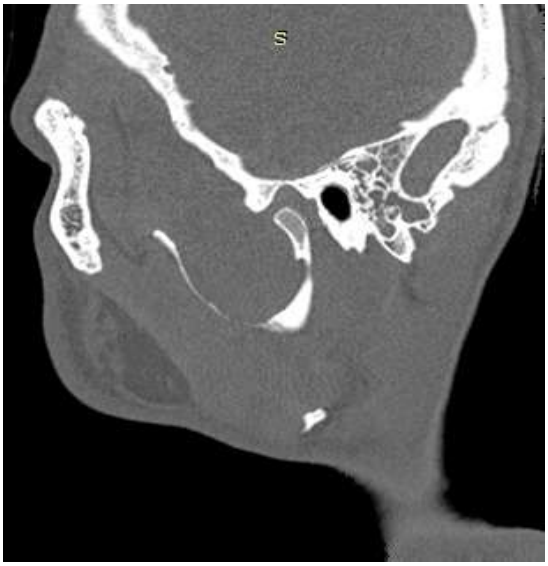

Fig. 5c: CECT (sagittal section) The lesion is also seen abutting and displacing the masseter and temporalis muscle with focal loss of fat plane

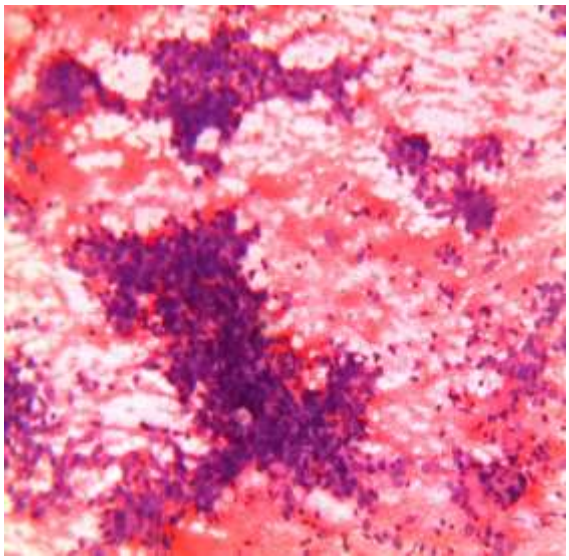

Fig. 6: FNAC shows benign epithelial and myoepithelial cells with bland nucleoli arranged in clusters as well as dispersed singly in a chondromyxoid matrix. The individual myoepithelial cells are predominantly spindle shaped

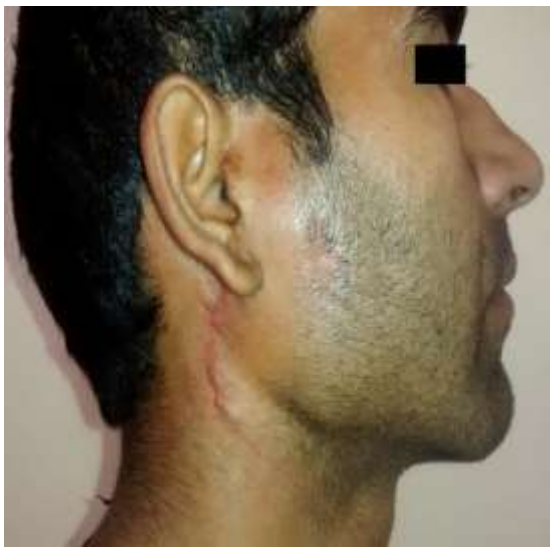

Fig. 7: Profile view of patient showing the surgical scar of total parotidectomy with radical neck dissection

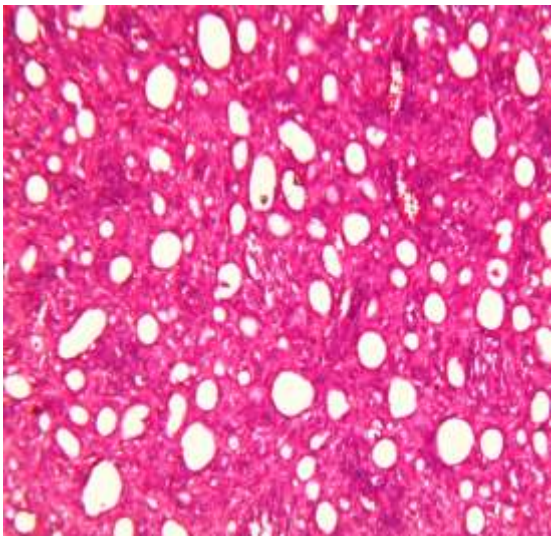

Fig. 8a

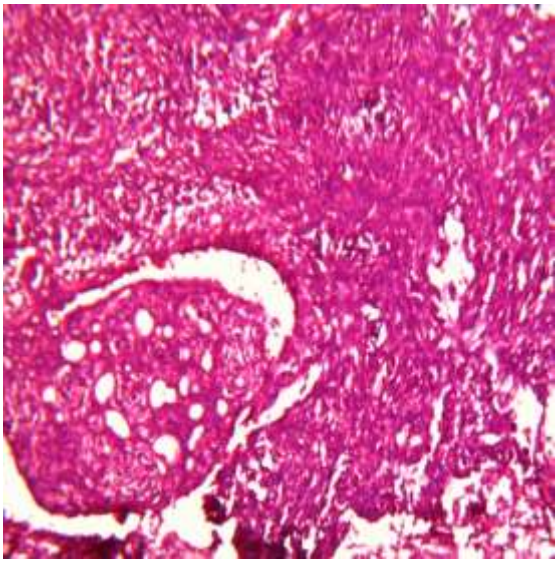

Fig. 8b

Fig. 8a & 8b: The section shows malignant biphasic tumor of salivary gland comprising of epithelial and myoepithelial component. The individual myoepithelial component is disposed in glandular and acinar pattern having round to ovoid nuclei, hyperchromatic chromatin, have high nucleocytoplasmic ratio, inconspicuous nucleoli and scanty cytoplasm

Discussion

Pleomorphic adenoma is the most common neoplasm of both the major and minor salivary glands. It is composed of an array of tissue types of both epithelial and mesenchymal origins and is regarded as benign in clinical behavior but has the potential to undergo malignant transformation. Epithelial-myoepithelial carcinoma (EMC) is a rare biphasic tumor of the salivary glands typically arising in the parotid[43]. Epithelial-myoepithelial carcinoma (EMC) is a rare type of malignant tumor accounting for about 1% of all salivary gland tumors[44,45] and recognizes a typical biphasic pattern: a central ductular structure often containing eosinophilic material surrounded by clear cells of myoepithelial origin. It was firstly described as a glycogen rich or clear cell adenoma because of the clear cell component. Epithelial-myoepithelial carcinoma (EMC) is a rare biphasic tumor of the salivary gland. It is generally composed of variable proportions of two cell types: An inner layer of duct lining cells and an outer layer of clear cells which typically form double-layered duct like structures. Clear cells which are of myoepithelial origin often predominate in number[46]. The first description of this tumor with the terminology of EMC was introduced by Donath in 1972[47]. EMC is primarily a tumor of older adults with a peak incidence in the sixth and seventh decades of life. Our case is one of the rarest described arising in a younger patient 28 years old[48]. Clinical presentation is not specific and is usually that of a long-standing and progressively enlarging painless mass. Facial nerve palsy occurs only rarely[49]. The clinical behavior and histologic findings of EMC originally prompted its previous classification as an adenoma (so called glycogen-rich, clear cell adenoma) or adenomyoepithelioma[50]. Most tumors arise in the major salivary glands, especially the parotid, but cases have been described in the minor glands of the mouth and even in the maxillary sinus. The history is typically that of a mass enlarging over several months or even years[51]. Perineural and vascular invasion are frequent and recurrence occurs in around 40% of cases and metastasis in 14%[52]. The association of EMC with other salivary gland tumors may also be a reflection of a common differentiation pathways as suggested by multidirectional differentiation that may be mediated through intercalated duct hyperplasia[53]. Analogous to its breast and skin counterparts, this neoplasm comprises two populations of cells: myoepithelial and epithelial as adenomyoepithelioma and clear cell hydradenoma respectively. Microscopically on histological examination the tumor is biphasic and characterized as in this case by tubules lined by an inner layer of cytokeratin-positive bland cuboidal epithetlial cells surrounded by an outer layer of S100 positive myoepithelial cells[43]. Fine needle aspiration cytology is widely used in the initial investigation of salivary gland swellings and whilst the cytological features of this tumor have been described they are not well recognized. It has been suggested that there is bidirectional differentiation from a stem cell to form myoepithelial and intercalated ductal epithelial cells[54]. CT and MR appearances of EMC are nonspecific, and that EMC cannot be differentiated from other parotid neoplasms[55]. The morphological features of epithelialmyoepithelial carcinoma are generally quite distinct from other salivary tumours. Monomorphic or pleomorphic adenomas do not invade locally and the

latter often contain abundant alcian blue positive stromal mucin. Salivary duct adenocarcinoma is aggressive and resembles ductal carcinoma of the breast. Terminal duct carcinoma[51] or polymorphous low grade adenocarcinoma is a locally invasive tumour arising almost always in minor salivary glands and is characterised by cytological uniformity and histological diversity single lined ducts often with intraluminal papillae are typical, but a biphasic ductal lining is not a feature[56]. The pathologic differential diagnosis includes other clear cell salivary tumors as clear cell carcinoma, acinar cell carcinoma, mucoepidermoid carcinoma, metastatic renal cell carcinoma, clear cell oncocytoma and pleomorphic adenoma[57,58]. The usual treatment is wide surgical resection, including adjacent lymph nodes; adequate resection with negative soft-tissue margins is the minimum recommended therapy[59]. EMC is considered to be a low-grade malignant tumor that may commonly recur locally after resection in 23-50% of cases. This is often because the capsule which normally delimits this neoformation may be incomplete. Less frequent is the finding of lymph node and hematogenous metastasis[60]. Distant metastases to kidney, lung, and brain have also been reported.

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