Parotid sclerosing mucoepidermoid carcinoma: a case report and immunohistochemical study

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Abstract
Here we report the case of a 63-year-old female with a parotid sclerosing mucoepidermoid carcinoma diagnosed and treated at the Department of Oral and Maxillofacial Surgery, Emergency County Hospital of Craiova, Romania. The clinical and imaging investigation revealed a parotid malignant tumor with central fluid-filled cystic formation. Histopathology found an intermediate grade sclerosing mucoepidermoid carcinoma that invaded the adjacent adipose and striated muscle tissues, but without perineural and lymphovascular invasion. The immunohistochemistry investigated mainly biomarkers involved in the induction of a local aggressive behavior. This case report describes a rare parotid sclerosing mucoepidermoid carcinoma with peculiar clinical and morphological characteristic features. The immunohistochemical study sustained its intermediate grade malignancy highlighting the prognostic value of some of the used biomarkers.

Keywords: sclerosing mucoepidermoid carcinoma, immunohistochemistry, parotid gland, tumor grade malignancy.

Introduction
Mucoepidermoid carcinoma (MEC) is the most common malignant primary salivary gland tumor composed of varying proportions of mucous, intermediate and epidermoid cells, with columnar, clear cell and oncocytoid features [1]. Salivary MEC as a malignant glandular epithelial neoplasia is believed to arise from pluripotent reserve cells of the excretory ducts that are capable of differentiating into such variety of cell types [2]. Exposure to ionizing radiation [3–4] and MECT1-MAML2 translocation and somatic TP53 and POU6F2 mutations [5] seems to be the most important factors involved in the pathogenesis of such salivary gland tumor.

Another important feature of salivary MEC is its variety of biological behaviors that generally is correlated with the histological grade of the tumor. However, there are still many controversies in defining the high-grade MEC variant, none of the proposed MEC grading systems being widely accepted [6–8]. Most studies indicate for patients with salivary MEC a favorable outcome, death being reported in cases with high-grade tumors because of distant metastasis [8, 9].

We report here a case of right parotid MEC developed in a 63-year-old female. A comprehensive immunohistochemical study was performed concerning the local aggressive behavior of this tumor. Written informed consents were obtained from the patient for publication and images usages.

Case presentation
A 63-year-old female presented to our institution with painless swelling in right parotid region for one year, which was slowly grown to the present size. Extraoral examination revealed a mild, firm swelling of about 3 cm in size at the right preauricular area. Patient did not present lymphadenopathy and neither facial nerve involvement. Also, its personal or family records were not significant. Ultrasound examination revealed a solitary mass in the superficial lobe of the right parotid gland with dimensions of 27×20 mm, with heterogeneous echotexture, with peripheral intense vascularization, irregular shape, and with distal acoustic enhancement divided by a vascularized septum (Figure 1, A and B).

Under general anesthesia, following a modified Blair incision a superficial parotidectomy with facial nerve preservation was performed. The tumor was completely excised with negative margins.

On gross examination, a whitish gray, firm mass of 4×2.5×2 cm was identified. On cut section, it appeared as solid mass with poorly defined edges that in the central part had a mucin-filled cyst of 0.7 cm diameter surrounded by other smaller cystic structures.

Histopathological examination
Microscopic examination of the tumor revealed a mixture of malignant epithelial cells with different morphology, respective neoplastic cells with squamoid differentiation, mucous cells (most of goblet-like type), “intermediate” cells, clear cells, columnar apocrine-like cells and sebaceous-like cells (Figure 2, A–F). The neoplastic cells had moderate cellular pleomorphism and rare mitotic figures.
The prevalent neoplastic cell type was the “intermediate” and clear cell types mostly with solid island growth pattern (Figure 3, A and B). However, in the center we noticed a large flattened cavity with eosinophilic, secretory material filling the lumen, lined by varying number of cell layers of variable thickness (Figure 3C). Also, adjacent to it were present few small cystic structures with tick lining neoplastic epithelium. The Periodic Acid–Schiff (PAS) and Alcian blue stainings show the intra- and extracellular mucin secretion (Figure 3, D and E).

One of the histopathological peculiarities of this case was the existence of a large number of neoplastic clear cells admixed with the “intermediate” cells and those with epidermoid feature in the form of variably sized, irregular or rounded cellular aggregates. The clear cells were only focally positive to PAS staining.

Another peculiar histological feature was the presence of an extensive central sclerosis that enclosed the cystic and solid epithelial neoplastic proliferation (Figure 4A). Also, a dense hyalinized fibrous tissue was seen at the tumor periphery along with a rich lymphoid infiltrate with follicles and even formation of germinal centers (Figure 4B).

The tumor edges were infiltrative with invasion of the adjacent adipose and striated muscle tissues, but without perineural and lymphovascular invasion.

Taken together all these histological aspects led us to classify our case as a sclerosing MEC subtype with intermediate grade malignancy.

Figure 1 – Ultrasonography in B-mode (A) and color Doppler mode (B): a solitary mass in the superficial lobe of the right parotid gland of 27×20 mm dimensions with heterogeneous echotexture, with peripheral intense vascularization, irregular shape, with distal acoustic enhancement divided by a vascularized septum.

Figure 2 – The main histomorphological features of the tumor. The tumor was composed of a mixture of malignant epithelial cells with different morphology: (A) mucous cells (most of goblet-like type), (B) neoplastic cells with squamoid differentiation, (C) clear cells and (D) “intermediate” cells. Hematoxylin–Eosin (HE) staining, ×200.
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Figure 2 (continued) – The main histomorphological features of the tumor. The tumor was composed of a mixture of malignant epithelial cells with different morphology: (E) columnar apocrine-like cells and (F) sebaceous-like cells. HE staining, ×200.

Figure 3 – The main histomorphological features of the tumor (continuation): Neoplastic epithelial cells were arranged in solid island (A and B) and a central large cyst (C) (composed of four images of original magnification ×40); (D and E) Some neoplastic cells presented intracellular mucin secretion, mucin that were also present in the cystic lumina. HE staining: (A and C) ×40; (B) ×200. PAS and Alcian blue stains: (D and E) ×100.
Immunohistochemical findings

The mucous and columnar neoplastic cells from our case showed an immunoprofile specific to glandular phenotype by expressing CK7 (Figure 5A), CK8/18, and CEA (Figure 5B). Also, these cells were intensely positive to EMA (Figure 5C) and variable positive for MUC5AC (Figure 5D), CK5 and p63. The “intermediate” and epidermoid neoplastic cells presented variable reactivity for EMA (Figure 5E), CK5 (Figure 5F), p63 and vimentin, and in addition the “intermediate cells” were also positive for CK7 and CK8/18. Also, the neoplastic clear cells had a phenotype close to the epidermoid differentiation with variable positivity for EMA, CK5 and p63. None of the malignant cells showed reactivity for α-SMA and MUC2.

In order to evaluate its malignancy, we investigated tumor cell immunoreactivity for a number of markers used as prognostic markers in other known human malignancies, as listed in Table 1.

Table 1 – Characteristics of the antibodies utilized in the study

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CK: Cytokeratin; α-SMA: α-Smooth muscle actin; CEA: Carcinoembryonic antigen; EMA: Epithelial membrane antigen; MUC: Mucin; MMP: Matrix metalloproteinase; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; EGFR: epidermal growth factor receptor; ER: Estrogen receptor; PgR: Progesterone receptor; CXCR: Chemokine receptor.
Figure 5 – Immunohistochemical patterns of the tumor: (A and B) Neoplastic epithelial cells positive to CK7 and CEA most of them being of mucous or “intermediate” type (immunostaining, ×100); Variable reactivity of tumor cells to EMA (C and D) and respective to MUC5AC (E) mostly being of mucous type (immunostaining, ×100); (F) CK5 was intense positive especially in the intermediate and squamous neoplastic cells type (immunostaining, ×100); (G and H) A weak to moderate positive reaction for VEGF and VEGFR2 was observed in neoplastic cells regardless their morphology (immunostaining, ×100).
Screening for tumor reactivity to the main growth factor receptors and their ligands we found a weak to moderate positive reaction for VEGF and VEGFR2 (Figure 5, G and H), a similar reactivity for EGFR (Figure 6A) but a negative reaction for Her2/neu, ER and PgR. The VEGFR2 was also positive at the level of endothelial cells and VEGF was also identified in tumor associated stromal cells (Figure 5F).

Regarding the involvement of protein that regulates the cell cycle we found a weak to moderate nuclear reactivity to p53 in more than 50% of tumor cells (Figure 6B) and also a weak cytoplasm reaction to Bcl-2 in the majority of tumor cells compared to more intense reaction of the lymphoid infiltrate from the tumor periphery. The Ki-67 mitotic index was low with less than 5% of tumor cells positive to this marker, without any significant difference regarding the tumor topography.

Investigation of tumor angiogenesis with CD105 and CD34 highlighted the existence of intense active process especially at the tumor periphery (26.43±12.5 versus 12.53±9.3 for CD105 and 41.43±11.6 versus 21.35±13.7 for CD34) (Figure 6C). The CD117 staining proved the existence of a great number of mast cells at the tumor periphery, their density being correlated with the micro-vessels density.

Investigation of markers involved in matrix remodeling and consequently in tumor invasiveness revealed increase reactivity especially for MMP-9, more obviously in cytoplasm of “intermediate” neoplastic cells, especially from the solid proliferation from the tumor periphery (Figure 6D).

Investigation of markers involved in cell adhesion showed a positive reaction with prevailing membranous pattern in the tumor cells for E-cadherin (Figure 6E) and CD44, a more obvious the reactivity being present at the level of neoplastic mucous cells and diminished in the solid proliferations, especially form the tumor edges. In addition, at the tumor advancing edge, the small groups or cords of infiltrating tumor cells were cytoplasm and nuclear positive to N-cadherin.

The chemokine receptor 4 (CXCR4) reactivity was also noticed in tumor cells, with prevailing membrane and cytoplasm pattern (Figure 6F). In addition, we observed intense nuclear and cytoplasmic tumors’ reactivity for galectin-3, staining that was also noticed in tumor stromal cells (endothelial cells, cancer-associated fibroblasts, myofibroblasts, and mesenchymal stromal cells).

A final diagnosis of sclerosing MEC of intermediate grade malignancy was made. After six months of follow-up, at the time of publication, the patient did not present any clinical or radiographic evidences of recurrence.

Discussion

MECs account for approximately 30% of all malignant tumors of the salivary gland being the most common salivary malignancy in adults and children [1, 10]. The literature data report a 3:2 female predilection with 45 years as the mean patient age for such malignant salivary gland tumor [1, 11]. More than 50% of MECs occur in major glands, the parotid glands being the most affected, while the palate and retromolar area of the mandible are the most commonly involved site for the minor salivary glands [1, 7]. Our case fits in the general epidemiological profile of such salivary tumors, the tumor affecting the right parotid of a 63-year-old female and was the 5th reported case from our Hospital casuistry since 1995.

It seems to have been first described in the literature by Masson & Berger as “épithélioma à double métaplasie” [12]. Subsequently, in 1945, Stewart et al. introduced the term “mucoepidermoid tumor” [13]. However, because over time it has been proved that all salivary mucoepidermoid tumors had malignant potential this term was replaced in 1996 by Ellis & Auclair with the term “mucoepidermoid carcinoma” [14].

Our case of parotid MEC presented as a painless, soft mass of 3 cm in diameter that developed during about one year. The literature data shows that the major salivary glands MECs usually had a mean duration of 1.5 years, presenting as solitary painless masses, with variable skin or deeper tissue fixation [10, 15, 16]. Generally, regardless of the MECs location only 13% of patients experience associated pain [10]. Usually, high-grade MEC presents as a rapidly enlarging mass with variable fixation to the surrounding tissues, facial nerve paralysis, and tumor ulceration.

In terms of tumor grading, our case was classified as intermediate grade MEC being composed of few and small neoplastic cysts and solid islands of predominant intermediate neoplastic cells. The neoplastic cells had moderate cellular pleomorphism and rare mitotic figures. Tumor stroma was predominantly of fibrous type and at the periphery presented a chronic inflammatory reaction with lymphoid aggregates formation. Also, we noticed tumor invasion of the adjacent adipose and striated muscle tissues, but without perineural and lympho-vascular invasion.

Although, there is no uniformly accepted grading system for MEC, it is generally accepted that a three-level grading approach to classify these tumors it is absolutely necessary to evaluate their prognosis and to establish the most appropriate therapeutic approach. Currently, the salivary MECs are graded as low-, intermediate- and high-grade tumors investigating a series of parameters such as cytomorphologic and architectural aspects, the degree and patterns of invasion, perineural and angiolymphatic invasion, necrosis and mitotic rate [17–19]. However, these grading systems are not infallible considering the fact that the Armed Forces Institute of Pathology (AFIP) system [19] tends to downgrade tumors while the Brandwein system [18] seems to upgrade tumors, with an obvious impact on therapeutic attitude to be followed in case of such patients [20].

As histological variant, our case was classified as sclerosing MEC since we noticed extensive central sclerosis that enclosed the cystic and solid epithelial neoplastic proliferation and at the tumor periphery was present a lymphoid infiltrate with follicles and even germinal centers formation. According to the literature data, this MEC variant is very rare with no more than 20 cases that almost exclusively were reported in the major salivary glands [21]. As possible mechanisms of this reactive fibrosis were proposed: (1) tumor infarction and (2) host tissue reaction due to extravasated mucin [22, 23]. Most
of the reported cases where classified as low-grade MEC, but at least in two cases the presence of metastasis were noticed [24]. Other histological variants of MEC described in the literature are: clear cells, oncocytoic, sebaceous, spindle cell and with areas mimicking thyroid follicles [1, 18, 19, 25]. Given this variety of histopathological aspects becomes clear that many times the accurate diagnosis of such an entity requires the exclusion of other salivary gland tumors with similar histological aspects such as: squamous cell carcinoma adenosquamous carcinoma, cystadenoma, cystadenocarcinoma, sebaceous carcinoma, and other clear cell tumors such as acinic cell carcinoma, hyalinizing clear cell carcinoma, clear cell oncocytoic, and metastatic renal cell carcinoma [1, 7, 10].

Although it is well known that salivary MEC is an aggressive malignancy, the prognostic factors as well as treatment strategies remain controversial [26–28]. Throughout time there were proposed many prognostic factors for patients with MECs such as: sex, age, tumor location, clinical stage, tumor grade, lymph node status, surgical margins, postoperative radiotherapy and some molecular markers [7, 10, 26, 29].

Figure 6 – Immunohistochemical patterns of the tumor (continuation): (A) A moderate reactivity mainly in the intermediate and squamous neoplastic cells type was noticed for EGFR (immunostaining, ×100); (B) p53 was positive in more than 50% of tumor cells regardless their morphology (immunostaining, ×100); (C) CD105 positive reaction especially at the tumor periphery as a proof of an intensely active angiogenic process (immunostaining, ×40); (D) A moderate reactivity for MMP-9 noticed mainly at the tumor periphery in the cytoplasm of intermediate and squamous neoplastic cells (immunostaining, ×100); (E) The membranous E-cadherin pattern diminished in the solid proliferations especially form the tumor edges (immunostaining, ×100); (F) A moderate membrane and cytoplasm chemokine receptor 4 (CXCR4) reactivity was also noticed in tumor cells (immunostaining, ×100).
As we mentioned, our MEC case developed at a 63-year-old female in the superficial lobe of right parotid, presented with a clinical stage II and the pTNM stage III, without perineural and lymphovascular invasion, but with the adjacent adipose and striated muscle tissues invasion, and with tumor free margins. The literature data showed a poor prognosis of MEC among men at older ages (more than 40–50 years old) [19, 30, 32], with submandibular gland involvement [11, 26], with high-grade tumors, in advanced clinical stages (III/IV stage) with lymph node metastasis and positive surgical margins [26, 27, 31–33].

In the last decades, researchers have focused on finding prognostic biomarkers that could guide the therapeutic management in order to increase the survival time of these patients. Thus, investigating the mucin profile of these tumors revealed that high MUC1 expression associated a high histological grade, high rate of recurrence and metastasis and short disease-free interval, while MUC4 expression was related to low grade, low recurrence rate and a long disease-free interval [29, 34]. Another independent prognostic factor for MEC is the Ki-67 index, values higher than 10% suggesting an unfavorable prognosis, associated with high recurrence and metastasizing disease [35]. High Bcl-2 expression was related to low-grade tumors [36], while cyclooxygenase-2 expression was reported to be high in MECs with lymph node metastasis [37]. Also, p27, a universal cyclin-dependent kinase inhibitor, was proved to correlate inversely with histological grade of MEC of the intraoral minor salivary gland and was selected as an independent risk factor for both disease-free and overall survivals [38]. p53 expression is not only considered as an early event in MEC carcinogenesis but also correlates to tumor behavior and local recurrence, high expression being related to high grade tumors [39].

Regarding salivary MECs reactivity to growth factor receptors, their ligands and their prognostic significance the results are inconsistent. Thus, while some studies have shown an association between EGFR and high-grade MECs [40, 41], others reported its overexpression in low-grade tumors [42]. Also, Her2/neu has been shown to be an indicator of poor prognosis in MECs, independent of histological grade, and T or N status [43]. Even if it was shown that this receptor is expressed in less than 20% of MEC cases [44], Her2 and EGFR genomic alterations play a key role in the development of high-grade MEC, favoring also the progression from MAML2 fusion-positive low-/intermediate-grade to high-grade in a subset of MEC [45]. However, it has been proved that activated protein kinase intracellular molecules (phosphorylated ERK-1/ERK-2) expression in MECs did not correlate with Her2/neu or histological grading, but its high reactivity was associated with worse prognosis and high proliferative activity (Ki-67 index) [46]. TGF-β1 was proved to play a key role in the progression of MECs by increased MMP-9 activation in the carcinomatous cells, suggesting that these patients could benefit from targeted therapies blocking effectors of this signaling pathway [47].

On the other hand, although hormonal therapy has been shown to be useful in treatment of breast and prostate cancers, studies regarding ER, PgR and AR (androgen receptor) expression and their prognostic implications in salivary gland malignancies are inconsistent. Thus, concerning ER reactivity in MECs it was showed that three of 10 cases studied by Jeannon et al. were positive [48], while Nasser et al. reported only one of 10 MEC as being positive for this marker [49] and other authors did not reveal any ER expression in MEC cases [50]. For PgR reactivity, Jeannon et al. reported that only one from the 10 studied cases was positive [48], while other authors did not find any reactivity for this hormone receptor in MEC cases [49, 50]. Regarding AR expression, Nasser et al. revealed that two of 10 MEC were positive [49], while Ito et al. found only two positive cases from 30 MECs [50].

Several studies reported a higher rate of angiogenesis and cellular proliferation in malignant tumors compared to benign tumors, with highest vascularization in the MECs [51, 52]. This fact may reflect the invasiveness potential of such tumors and thus the usefulness of monoclonal anti-human CD105 antibodies in MEC anti-angiogenetic therapy [53].

Moreover, Uchida et al., found CXCR4 overexpression in MECs suggesting its contribution to the metastatic potential of such tumors [54]. Also, galectin-3 expression was related to a more aggressive behavior of salivary glands malignancies, including MECs [55].

Summarizing, our immunohistochemical results have showed a tumor immunoprofile that certified its locally aggressive behavior. Thus, we found an intercellular adhesion loss especially at the tumor periphery with an increased MMP-9 reactivity both for tumor cells and tumor stromal cells at this level. Also, we have proved that at the tumor periphery there was an intense angiogenic process sustained by high value of CD105+ microvessel density and high VEGF and VEGFR2 tumor cell reactivity. In addition, we noticed high tumor CXCR4 reactivity especially at the tumor edges, and also galectin-3 reactivity was observed both in tumor cells and stromal tumor cells.

**Conclusions**

Here we report a rare case of a parotid sclerosing mucoepidermoid carcinoma with peculiar clinical and morphological characteristic features, reasons that may pose serious diagnosis problems for clinicians and even pathologists. The histopathological and immunohistochemical examinations revealed its intermediate grade malignant behavior highlighting the usefulness investigation of some prognostic markers for such salivary gland tumors.

**Conflict of interests**

The authors declare no conflict of interests.

**Author contribution**

All authors contributed equally to the study and the publication.

**References**


