

## Effective Complex Treatment at Epithelial-Myoepithelial Carcinoma of Submandibular Salivary Gland- Clinical Case with a Literary Review

Marinova L<sup>1\*</sup>, Vassileva V<sup>1</sup>, Gabrovski I<sup>1</sup> and Yordanova B<sup>2</sup>

<sup>1</sup>Medical Oncology Clinic, Department of Radiation Oncology and Metabolic Brachytherapy, UMHAT “Queen Joanna” Sofia, Bulgaria

<sup>2</sup>Complex Oncology Center; Department of Clinical Pathology - Ruse, Bulgaria

### \*Corresponding author:

Lena Marinova,  
Medical Oncology Clinic, Department of Radiation  
Oncology and Metabolic Brachytherapy, UMHAT  
“Queen Joanna” Sofia, Bulgaria,  
E-mail: rad\_marinova@abv.bg

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## 1. Abstract

Epithelial- Myoepithelial Carcinoma (EMC) is a rare biphasic salivary glands tumor with low malignant potential. Pathohistological Differential Diagnosis (DD) is difficult due to the rare frequency and biphasic cell characteristic of the EMC, which requires Immunohistochemical (IHC) analysis to define the epithelial and myoepithelial cell component. In the article we present a clinical case at a 55 -year -old woman with a rarely diagnosed EMC of submandibular salivary gland, in which a local tumor excision with postoperative radiotherapy (RT) was performed. Strict diagnosis requires a wide immunohistochemical analysis. Despite the low -malignant tumor characteristics, EMC requires radical surgical resection with clean resection lines.

The optimal healing approach to the administration of RT and chemotherapy has not yet been clarified. For 3 years, after complex treatment, including surgery and postoperative RT, our patient has local tumor control with a good quality of life.

## 2. Introduction

Epithelial- Myoepithelial Carcinoma (EMC) is a rare biphasic salivary glands tumor with low malignant potential [1]. The parotid EMC represents <1% of all malignant tumors of the salivary glands [2-4]. Most often it covers the parotid gland, but is also published by localization in submandibular and small salivary glands, as well as in areas with glandular structures outside the oral cavity - breast, lung, kidney and uterine body [2]. The myoepithelial tumor component was first described by Donath et al. in 1972 [5]. Previously, the EMC was defined by various names such as adeno-myepithelioma, rich in glycogen adenoma, rich in glycogen carcinoma,

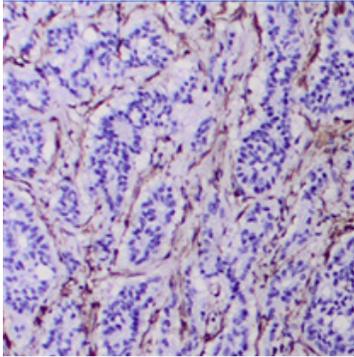
clear cell adenoma and clear cell carcinoma [4, 6]. The EMC of the salivary glands is typically regarded as a low-grade malignancy due to its low rate of nodal and distant metastasis [7]. The World Health Organization (WHO) differentiated this cancer as a separate histopathological disease in 1991 [8]. Dedifferentiation has been reported [9]. Pathohistological Differential Diagnosis (DD) is difficult due to the rare frequency and biphasic cell characteristic of the EMC, which requires immunohistochemical (IHC) analysis to define the epithelial and myoepithelial cell component.

## 3. Clinical Case

We present a 55 -year -old woman with a slow growing, painless formation in the left submandibular area for 2 months. There are no clinical data on enlarged cervical lymph nodes and pathological changes from the facial nerve. From the CT of the head and the neck with contrast - In the left submandibular salivary gland, a rounded, well -limited solid tumor with smooth outer contours, without the presence of calcifications, with an axial plan of -2.5 cm /2.14cm was visualized. There are no evidence of enlarged cervical lymph nodes. A local tumor excision without pathohistological examination of resection lines was performed. Intraoperatively, in depth, a capsule of a solid-elastic tumor, well-separated by the surrounding tissue structures, was found. The same was visible in a healthy one.

Histological result №7213-15/ 23.07.19- Macroscopic description - encapsulated node with a diameter of about 2.5 cm. Microscopic description- large and partly fragmented encapsulated tumor represented by the parenchyma of the salivary gland with lipomatosis and sialoadenosis. The same consists of the glandular compo-

nent, composed of a population of large, polygonal clear cells of myoepithelial type arranged in sheets, nests and tubules, creepy structures and cysts, arranged amidst myxoid stroma with prismatic cells with mild nuclear polymorphism, in places with two -row epithelium and single mitoses. The peripheral tumor component has a bundle construction composed of spindle cells with oval and slightly spindle nuclei with slightly pronounced polymorphism. The cytoplasm is well represented, poorly eosinophilic and partly vacuolized (Figure 1).



**Figure 1:** Immunohistochemical analysis- Glandular cell component and myoepithelial cell component, clearly visible at IHC with alpha SMA positive expression in the outer layer of the glandular component and focal positive in the bundle component.

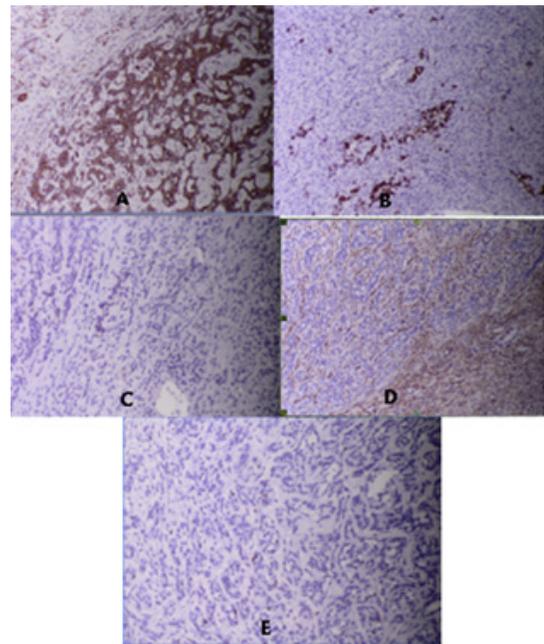
### 3.1. Immunohistochemical (IHC) analysis

The immunohistochemical expression to CK AE1/AE3 is diffusely positive in the glandular component and positive in the myoepithelial component (Figure 2/A); focally positive CK7 expression in the glandular component and negative in the myoepithelial component (Figure 2/ B); for p63 focally positive expression in the glandular component and negative in the myoepithelial component (Figure 2/C); focally positive CD 117 expression in the glandular component and negative in the myoepithelial component; Alpha SMA positive expression in the outer layer of the glandular component and focally positive in the bundle component (Figure 2/D); GFAP is focally positive in the glandular component and negative in the bundle component; The Ki-67 Index is 32% in the glandular component and 10% in the bundle component (Figure 2/ E).

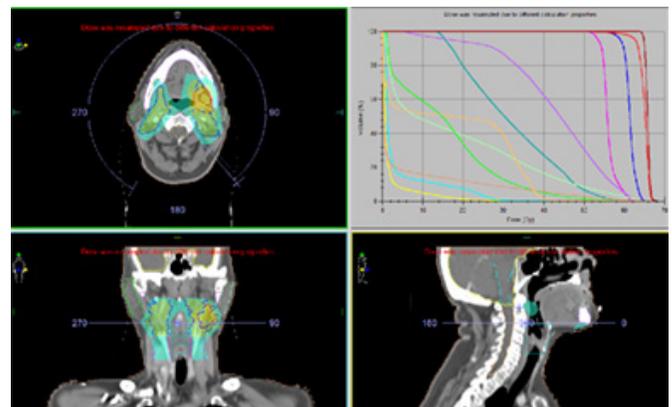
### 3.2. Histological Diagnosis

Pathohistological and immunohistochemical characteristic of epithelial-myoepithelial carcinoma of the salivary gland

Due to the lack of pathohistologically verified resection lines, postoperatively intensively modulated radiation (IMRT) was performed on a linear accelerator with VMAT technique. In the tumor bed was realized up to TD 64Gy, in the left submandibular salivary gland TD up to 60Gy and in the cervical lymph nodes bilaterally up to TD 54Gy (Figure 3). The patient is evaluated for active monitoring. For 3 years he has been in good general condition with good quality of life and without a local recurrence or distant hematogenous spread.



**Figure 2:** Immunohistochemical analysis of epithelial-myoepithelial carcinoma: A/ CK AE1/ AE3 diffuse positive expression in the glandular component and positive in the bundle component; B/ CK7 focal positive expression in the glandular component and negative in the bundle component; C/ P63 focal positive expression in the glandular component and negative in the bundle component; D/ alpha SMA positive expression in the outer layer of the glandular component and focal positive in the bundle component; E/ KI-67 Index 32% in the glandular component and 10% in the bundle component.



**Figure 3:** Postoperative Intensity Modulated Radiotherapy with technique VMAT in the tumor bed up to TD 64Gy and in the cervical lymph nodes bilaterally up to TD 54Gy.

### 4. Discussion

Clinically, EMC is manifested as a bulky, slow -growing tumor with the ability to grow to large volume [2]. In parotid localization, the symptoms are local pain or facial asymmetry. The average tumor diameter is 2 cm to 3 cm, bordering 1 cm to 12 cm in its largest diameter [10]. Usually the lesion is encapsulated, as we see in the clinical case presented. WHO defines EMK as a low malignant glandular neoplasm, composed of a variable ratio of two types of cells forming structural tissue resembling ductules [4, 6, 11].

Typically, there is a multinodular expansion with tumor cell nests separated by dense fibrous connective tissue [12]. Epithelial-myoeithelial carcinoma is a histopathological term used to describe the biphasic pattern of clear staining of the myoeithelial cells surrounding variable proportions of the ducts with an epithelial lining [13]. Bifasic cell morphology is represented by epithelial cell type covering the inner layer of ductules and outer, consisting of clear myoeithelial cells [4, 6, 11, 14]. In the clinical case we have presented, two types of tumor cells are determined- a glandular component made up of prismatic cells with mild polymorphism and single mitoses and a peripheral component with a bundle of oval and slightly spindle nuclei, well slightly eosinophilic and partly vacuolized cytoplasm (Figure 1). IHC analysis is required to clarify the histogenesis of tumor cells [12]. The epithelial component is selectively well expressed Pancytokeratin and Epithelial Membran Antiigen (EMA) [15, 16]. The myoeithelial component is demonstrated with the S100, Smooth Muscle Actin (SMA), P63 and Vimentin [4, 17, 18]. From the IHC analysis in the presented clinical case, we report CK AE1/AE3 diffuse positive in the glandular component and (+) in the bundle component; SK7 focal (+) in the glandular component and (-) in the bundle component; P63 focal (+) in the glandular component and (-) in the bundle component; Alpha SMA (+) in the outer layer of the glandular component and focal (+) in the bundle component; Ki-67 index 32% in the glandular component and 10% in the bundle component (Figure 2). In this way, we prove the epithelial nature of the glandular cellular component and the myoeithelial cellular component of the outer bundle component.

Differential diagnosis (DD) includes all clear cell tumors of the salivary glands (mucoepidermoid carcinoma, acinic cell carcinoma, sebaceous carcinoma) and metastatic renal cell carcinoma [6, 11, 12, 19]. EMC is a low malignancy tumor, of ductal origin, which should be differentiated from ductal salivary gland cancer [12]. Careful DD is needed by clear cell oncocytoma, pleomorphic adenoma, myoeithelioma, polymorphic low malignant adenocarcinoma and clear cell myoeithelial carcinoma [6,11,19]. The adenoid cystic carcinoma (a tubular variant), like EMC, consists of two types of cells (epithelial and myoeithelial) and morphologically resembles EMC in terms of the trabecular model, where visible hyaline stroma surrounds and presses tumor cells to thin threads. Unlike EMC, these cells are smaller and usually with more hyperchromic nuclei [4]. The characteristic that distinguishes the myoeithelioma and the myoeithelial carcinoma from the EMC is the lack of a ductal cell component [4].

The prognosis is difficult to define due to the rare incidence of EMC. Wakasaki et al. reported that myoeithelial carcinoma originating from a minor salivary gland and low proliferation index of Ki-67 labeling indicate favorable prognosis in the patients [20]. Adverse prognostic factors are determined by pathohistological data on solid tumor expansion, nuclear atypia, DNA aneuploidy and high

proliferative activity of tumor cells [21]. The vascular-lymphatic and perineural invasion aggravates the prognosis [6]. The recurrences depend on the condition of the resection edges, the invasion of the blood and lymphatic vessels, the necrosis, the myoeithelial anaplasia [3, 15]. EMC is considered to be a low-grade malignant tumor that may commonly recur locally after resection from 23% to 80% [4, 22], with hematogenous metastases up to 14% [23-26] and 40% disease mortality [24].

#### 4.1. Treatment

Currently, there is no consensus regarding optimal treatment for this salivary gland neoplasm, mainly due to its rare occurrence [27]. Surgical treatment appears to be the mainstay of treatment, with radiation reserved for positive or close margins or patients who are not surgical candidates or who refuse surgery [28]. Although this neoplasm develops relatively slowly and the histological characteristic seems benign, locoregional relapse occur in 50% of patients [6, 29]. This fact requires a radical tumor resection with clean resection lines [11], which is the minimum requirement and the necessary treatment [4]. The efficacy of adjuvant RT and/ or chemotherapy remains unclear because of its relatively indolent biological behavior [30]. For the prevention of local recurrences in tumors with diameter over 4cm., it is recommended to combine the surgery with subsequent RT [6]. Some authors recommend postoperative RT after radical surgical resection with a wide edges [11]. In the case, we conducted a postoperative RT due to lack of histologically verified resection lines, although the tumor is well encapsulated (Figure 3). RT is indicated on positive resection edges and in cases where the wide tumor resection will cause significant cosmetic or functional deficiencies. Lymphatic dissection is required in a local advanced disease with metastatic cervical lymph nodes. Inoperable tumors are subject to combined RT and chemotherapy [31,32] due to the fact that EMCs are sensitive to RT and chemotherapy [29]. In general, lymphatic and hematogenous metastases are rare [33,34]. Distant metastases for EMC with malignant characteristics (nuclear atypia, high proliferative tumor cells activity, vascular-lymphatic and perineural invasion) reaches 47% with high mortality (29%) after an average period of 32 months [15]. 5 and 10- year survival are 87.1% and 67.5% [24] respectively.

#### 5. Conclusion

EMC is a rare biphasic epithelial tumor of the salivary glands. Pathohistological diagnosis is often difficult because of the need for a broad differential diagnosis with a number of benign and malignant salivary glands tumors. Strict diagnosis requires a wide IHC analysis. Despite the low-malignant tumor characteristics, EMC requires radical surgical resection with clean resection lines. Due to a high risk of local recurrence, a strict assessment of adverse pathohistological tumor characteristics (nuclear atypia, high proliferative activity of tumor cells, vascular-lymphatic and perineural invasion) is recommended. The optimal healing approach

to the administration of radiotherapy and chemotherapy has not yet been clarified. For 3 years, after complex treatment, including surgery and postoperative RT, our patient has local tumor control with a good quality of life.

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