Malignant transformation of the salivary gland pleomorphic adenoma in myoepithelial carcinoma – the report of two cases

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ABSTRACT: Pleomorphic adenoma is the most commonly diagnosed benign tumour of the salivary glands. In the majority of patients, surgical resection of the tumour with adequate surrounding tissue of the salivary gland allows for complete recovery. A small percentage of the cases is constituted by recurring pleomorphic adenoma. Diagnosis of carcinoma ex pleomorphic adenoma is even more rare. The study presents two clinical cases of malignant transformation of pleomorphic adenoma into the myoepithelial carcinoma. Surgical treatment and additional radiotherapy were performed in both cases.

KEYWORDS: salivary gland tumours, carcinoma ex pleomorphic adenoma, pleomorphic adenoma, myoepithelial carcinoma

INTRODUCTION

Pleomorphic adenoma (PA), previously known as mixed tumour, is the most common benign salivary gland tumours. Epithelial, myoepithelial and mesenchymal cells are identified histopathologically in the tumour in various proportions. It is most common in the parotid (about 80% of cases). The incidence rate is higher in women. In about 6% of cases PA can transform into carcinoma ex pleomorphic adenoma (CAxPa) [1]. CAxPA is defined as cancer originally arising in PA (‘de novo’) or in recurrent PA [2,3]. Based on the analysis of 60 papers regarding CAxPA, Gnepp concluded that it constitutes around 3.6% of all salivary gland tumours, 6.2% of all PA and 1.6% of all malignant tumours of salivary glands [2]. The maximum incidence falls on the 6th and 7th decade, i.e. 1-2 decades later than for PA [4]. The current edition of WHO classification of head and neck cancer suggests that CAxPA diagnosis should not be the only diagnosis [4]. For prognostic reasons, it is important to determine the extent of infiltration and histological subtype of the cancer. The most commonly diagnosed histopathological types in CAxPA are adenocarcinoma (either ductal or not otherwise specified– NOS) and myoepithelial carcinoma. Morphological types of mucoepidermal, carcinoma adenoids cysticum and myoepithelial cancers are identified less frequently.

Due to the extent of invasion, CAxPA can be classified as intra-capsular, minimally invasive and extensively invasive. However, the size of infiltrate beyond the tumour capsule still remains controversial for the minimally invasive form. The initially accepted limit of <1.5 mm seems to be too strict, and some authors have shown that even 4-6 mm infiltration is not associated with deterioration of prognosis [1, 4-7]. Hence, further research is neces-
scar, most of the lesions were regularly shaped, from 4.5 to 18.4 mm, without increased vascularisation in the Power Doppler ultrasound. Cervical lymph nodes were not enlarged. (Photograph 1). PA recurrence was suspected. Surgical resection of all cancer sites was performed; they were well-demarcated from the surrounding tissues. (Photograph 2). Histopathological examination of the removed lesions revealed solid white nodules surrounded by adipose tissue. Microscopically, multifocal myoepithelial carcinoma was present in each of the lesions, built of nests formed of fairly monomorphic, epithelioid and spindle cells with clear cytoplasm. It was found that the foci of cancer, although most of them have expansive growth, focally infiltrate the surrounding adipose tissue (Photograph 3). Immunohistochemical stains showed a positive reaction for CKAE1/AE3, S100 and p63, and negative for SMA, EMA, c-kit. The proliferation index measured with Ki67 marker was up to 90% in areas with the highest proliferation activity, which were located in the expansive front of the cancer foci (Photograph 4). The patient was referred for radiotherapy (RT). She received a dose of 60 cGy to the scar area and 50 cGy to the lymphatic system of the neck on the side of the lesion. She remains in observation for 20 months without local recurrence. There is no evidence of regional or metastatic progression.

Case 1
84-year old woman was admitted to the Department of Otolaryngology of the Medical University of Warsaw due to tumour in the right submandibular region, which had appeared 57 years earlier. From 2014 to 2016 there was a rapid increase of the tumour size, painless and causing a difficulty during head rotation. The tumour with submandibular gland was removed in 2016. PA was diagnosed histopathologically. The tumour was excised completely. Six months after surgery, the patient palpated 4 nodules in the scar area, the largest of which was 1.5 cm long. The lesions were well-demarcated, painless, the skin around the scar was unaltered, and facial nerve function was normal. Ultrasound examination confirmed the presence of six focal, hypoechogenic, well-demarcated lesions in the submandibular region around the scar, most of the lesions were regularly shaped, from 4.5 to 18.4 mm, without increased vascularisation in the Power Doppler ultrasound (arrows indicate changes).

Clinical symptoms of CAXPA are most often similar to pleomorphic adenoma, because a relatively large percentage is non-invasive. Pain occurs in the case of local expansion of the tumour into the neighbouring soft and/or hard tissues. CAXPA infiltrate into the facial nerve causes paresis or paralysis of this nerve [9,10]. Typically, ulceration or other skin lesions may occur over the tumour for salivary gland malignancies [10], as well as cervical lymphadenopathy.

Case 2
63-year old woman was admitted to the hospital with the tumour of the left parapharyngeal space, which was growing gradually for about 10 years. The patient reported pain and a pulling sensation on the neck on the side of the lesion. Asymmetry of palatal arches was observed in physical examination. Magnetic resonance imaging (MRI) aroused a suspicion of 26 x 33 mm tumour originating from the parotid gland. A hard, polycyclic
parapharyngeal space tumour reaching the base of skull was resected from cervical approach. Histopathological examination confirmed the diagnosis of PA. During follow-up visits after 3 and 6 months of surgery, the patient did not report any symptoms. A year after surgery, the patient reported a sensation of a foreign body in the throat and a visible nodule in the scar, as well as intensifying pain radiating to the ear persisting for a month. Physical examinations revealed left-sided medialisation of the lateral pharyngeal wall. Function of the facial nerve was normal on both sides. Two tumours were detectable in the postoperative scar area. Magnetic resonance imaging (MRI) performed at that time revealed a 60x30x35mm tumour, well-demarcated, with a non-uniform signal, litho-cystic. The tumour heterogeneously strengthened after administration of contrast media, accentuated towards the nasopharyngeal region and modelled the throat while maintaining its adipose tissue surface. Tumour mass adheres to the deep part of parotid gland with abolition of planes between them, which entailed the conclusion of probable connectivity of the lesion with the parotid gland. Cervical lymph nodes were not enlarged. The transparotid–transcervical approach was chosen for reoperation and the superficial and deep part of the parotid gland was excised with preservation of the facial nerve, followed by excision of polycyclic tumour of the parapharyngeal space (Photograph 5). Histopathological examination revealed the presence of multifocal myoepithelial carcinoma in tissue removed from the parapharyngeal space. In macroscopic description, the tumour was well-demarcated and consisted of numerous cystic and solid, cohesive and whitish lesions with a diameter of 0.5 to 3.5 cm. Microscopic evaluation revealed tumour made of large epithelioid nests and spindle cells with clear cytoplasm (Photograph 6). Individual foci had a connective tissue pseudocapsule, however invasion of cancer outside the pseudocapsule to surrounding soft tissues was found. No invasion of vessels or nerves has been revealed. Ten mitoses/10 high power fields (HPF) were found. Additional immunohistochemical staining revealed a positive reaction for CKAE1/AE3, p63, PAS, CD10, uncertain for S100, GFAP, and negative for PAS+diastase, SMA, EMA, p53. Proliferative index measured with Ki67 marker was up to 50% in areas with the highest proliferative activity, which were localised in the expansive front of the cancer foci. Infiltration of myoepithelial carcinoma was also found in the excised deep part of parotid gland. The superficial part of the parenchyma displayed normal glandular structure.

The patient was referred to complementary RT treatment, where she received a dose of 60 cGy to the parapharyngeal space and 50 cGy for the lymphatic system of the neck on the side of the lesion. Six months after the end of RT, the patient reported left-sided facial pain, left ear pain and dysphagia. RM examination revealed extensive litho-cystic infiltration of 55x55x90 mm in the left parapharyngeal area and the base of skull. The lesion penetrated into the sphenoid sinus, infiltrated the cavernous sinus and Meckel cave, enhancement of the mandibular branch of the trigeminal nerve in the oval foramen was shown. Destruction of the apex of the pyramid of the temporal bone, left part of the sphenoid sinus, and partially of the clivus as well as slight thickening of the dura of middle cranial fossa with suspicion of their infiltration were revealed. The patient was referred for palliative treatment with chemotherapy. 

**DISCUSSION**

Most tumours of the salivary glands are benign. The most common type is pleomorphic adenoma. The standard treatment for PA of the parotid gland is resection of the tumour with the surrounding salivary gland tissue and preservation of the facial nerve. PA recurrence is diagnosed in approximately 3% of patients [11]. The method of PA extracapsular enucleation is not widely accepted due to the significantly higher relapse rate of 45% [12]. The use of postoperative radiotherapy in the case of recurrent PA is controversial. According to some authors it prevents further recurrences, while according to others it creates the possibility of malignant transformation [1,11,12].

In 1.8-6.2% of cases, PA can transform to to malignant neoplasm – carcinoma ex pleomorphic adenoma (CAxPA). The risk of malignant PA in case of the relapse is 23% [11].

The usefulness of radiological examinations in the differentiation of PA and Ca ex PA is poorly understood. RM seems to constitute a better diagnostic tool than tomography due to greater sensitivity in detecting the malignant component of tumour [13]. The most typical symptom indicative of CAxPA is the history of slow, year-long growing tumour of the salivary gland, which has recently significantly enlarged. Most often CAxPA is initially misdiagnosed as a benign lesion. BAC sensitivity for pre-operative CAxPA diagnosis is relatively low and amounts to only 29-54% [14]. Surgical parenchymal resection of the occupied salivary gland remains the treatment of choice, with preservation of the facial nerve, in the case of non-confirmed infiltration of the nerve by the cancer. Superficial parotidectomy is an accepted method of treatment of intracapsular or minimally invasive tumours, limited to the superficial part of the parotid gland. Complete or radical parotidectomy is recommended for invasive cancer. The presence of metastases to the lymph nodes of the neck requires selective lymphadenectomy [3,10]. Radiotherapy is used as complementary treatment in highly advanced cancers, close or uncertain surgical margins, the presence of lymph node metastases or perineural spread of the cancer. Patients may also receive combined radiotherapy with chemotherapy, but there is insufficient data in the literature confirming the effectiveness of chemotherapy in the treatment of CAxPA [3,15]. The prognosis for CAxPA depends on the severity of cancer, lymph nodes involvement, presence of distant metastases, radical surgical excision and histological type of cancer [2,16]. An important
sis of myoepithelial cancer in PA (MECxPA) is almost impossible, and prognostic factors in this cancer are uncertain due to low prevalence. There are no unambiguous guidelines for adjuvant treatment after surgical resection.

Wakasaki et al. summarised data from the literature and showed that a less aggressive course, with a lower rate of recurrences and distant metastases occurs in myoepithelial tumours derived from minor salivary glands and with diagnosed histopathological component of clear cells [14]. On the other hand, negative prognostic factors are: tumour size and clinical stage, extensive invasion of cancer into surrounding tissues, invasion along the nerves, ‘spindle cell’ histopathological type, positive immunohistochemical staining for p53 and p63 and high Ki67 proliferative index [14]. In both cases of MECxPA, clear cells and a positive reaction for p63 were present, while a negative reaction was observed for p53, and cancer cells showed a relatively high Ki67 proliferative index (90% and 50%).

The basic method of treatment of myoepithelial cancer is radical surgical resection with a wide margin due to tumour aggressiveness and a tendency to local recurrence. There is no consensus regarding the preservation of the facial nerve as well as elective lymph node surgery [17,19]. Postoperative RT is recommended for tumours with high grade of malignancy, positive or close surgical margins, perivascular and perineural invasion, lymph node metastases and salvage surgery for recurrent tumours [14, 22]. Chemotherapy combined with radiotherapy in postoperative treatment is used to treat relapses or distant metastases [21].

prognostic factor in CAxPA is also tumour size [16]. The five-year survival rate in patients with CAxPA is 25-65% [2], and local recurrence is the main factor decreasing the prognosis rates [10]. In both cases, malignant PA transformation did not occur ‘de novo’, but up to a year after removal of PA and was multifocal. Both patients had a long history of tumours with accelerated growth before the first surgery, but histopathological examination did not show characteristics of malignancy in primary PA.

Myoepithelial cancer (MEC) is a rare malignant tumour of the salivary glands. It occurs between the 5th and 7th decade of life, without any predilection to either of the sexes [17,18]. It is most often diagnosed in the parotid gland (29-82% of cases) [17, 18]. Typically, MEC displays an oligosymptomatic growth, often reaching large sizes within months or years [17, 18]. The accompanying facial nerve palsy is described relatively rarely - 10-15% of cases, and pain in 10-29% of patients [19,2]. Pre-operative diagno-
There are no results in the literature comparing relapse-free survival for ‘de novo’ and MECxPA cancers. Lim et al. compared the survival in 52 patients with primary, high-grade parotid cancer with survival in 21 patients with CAxPA in the same location [23]. The largest percentage in both groups was ductal carcinoma of the salivary glands. The authors showed that CAxPA is a more aggressive cancer compared to primary parotid cancer. The extent of CAxPA occurred significant in prognosis.. Suzuki et al. demonstrated 3-year disease free survival for non-invasive CAxPA at a level of 79.9% and 76%, respectively for histopathological types of ductal carcinoma and adenocarcinoma [24]. In the same work, the percentage of recurrence-free survival for invasive forms of both CAxPA types was 60% and 30%, respectively.

Due to the rare occurrence of CAxPA, and thus even more rare cases of particular histopathologic types of salivary carcinomas in PA, both uniform criteria of therapeutic treatment and prognosis are difficult to determine. It is necessary to report individual cases or their series to accurately assess cancer biology.

Molecular studies indicate that the development of CAxPA is a consequence of a multi-stage carcinogenesis model, with progressive loss of heterozygosity on the arms of chromosome 8q, then 12q and finally 17p [25]. In the future, detailed results of these studies may provide guidance for more accurate diagnosis and aggressive treatment of patients with CAxPA and improve their survival.

CONCLUSIONS

CAxPA constitutes a histopathological diagnosis of a specific type of salivary gland cancer that arises in co-existing PA or on the grounds of pre-existing and excised PA. The advanced patient’s age, large size of the tumour and location in the submandibular gland are factors that increase the risk of malignant transformation of PA. Histopathologically observed features of significant hyalinisation and increased mitotic activity up to (10xHPF) may also indicate a greater likelihood of malignant PA. Patients with intracapsular and minimally invasive CAxPA have a more favourable prognosis than patients with extensively invasive cancer.

References

CASE REPORT


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