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## *Myoepithelioma* of the Parotid Gland – Diagnosis and Surgical Treatment Difficulties: a Case Study

### *Myoepitelioma* przyusznicy – rozpoznanie i trudności w leczeniu chirurgicznym: opis przypadku

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article

#### Abstract

In the article, a rare case of parotid gland neoplasm pre-surgically diagnosed as fibrous histiocytoma which mid-surgically displayed the features of malignancy was reported. On the basis of histopathological and immunohistochemical examination, the neoplasm was diagnosed as *myoepithelioma*. Discrepancies between the pre-surgical examination results and the biological features of the neoplasm, and also the expectations in relation to the immunohistochemical examination were emphasized.

On the basis of recent literature, possibilities were reported of pre-surgical assessment of a tissue fragment complemented with immunohistochemical examination, as well as a smear assessment acquired during FNAB complemented with immunocytochemical examination. Histopathological examination of the fragments stained with H-E, as a basic examination, and the complementing role of immunocytochemical and immunohistochemical examinations, were emphasized. Understanding that *myoepithelioma* is a neoplasm with a clinical course not always possible to foresee on the basis of its morphology led us to seek the reports of *myoepitheliomas* whose aggressive growth did not correlate with the diagnosis of a benign tumor in the literature. The reports found on the tumors were mentioned in the article, and they correlate with the findings in our patient. There was a remarkable lack of the influence of certain pre-surgical diagnostics on surgery planning and its course. Since 2011 in our hospital, immunocytochemical and immunohistochemical examinations have been performed with all neoplasms formed of myoepithelial cells (**Dent. Med. Probl. 2016, 53, 2, 282–290**).

**Key words:** salivary gland tumors, *myoepithelioma*, fibrous histiocytoma, diagnosis difficulties, surgical treatment difficulties.

**Słowa kluczowe:** guzy ślinianek, *myoepitelioma*, fibrohistiocytoma, trudności diagnostyczne, trudności w leczeniu chirurgicznym.

*Myoepithelioma* is a rare benign neoplasm composed of myoepithelial cells. The neoplasm accounts for less than 1.5% of large salivary glands tumors. According to repeated case descriptions, the parotid gland and minor palatal salivary glands are the most common locations of the neoplasm, which is rarely present in the oral cavity, nasal cavity, nasopharynx, lungs, skin, retroperitoneal area or stomach [1–8]. In the last decade, in north-eastern China, a significantly greater percentage – in comparison to other parts of the world – of *myo-*

*epithelioma* neoplasm among the tumors of small salivary glands of almost 15% was recorded. They were mostly tumors of the palate and cheek [9]. In the parotid gland, *myoepithelioma* appears as independent primary tumors, usually well bounded from the background and usually unencapsulated, which can pose a problem in differentiation from mixed tumors, especially those lacking components of cartilaginous and mucosal patterns.

They can also grow as a part of *adenoma polymorphum* [3, 10]. The capsule of the gland is the

limitation of *myoepithelioma*'s painless growth observed from a few months up to a few years in young or middle-aged patients [1, 11].

Microscopically, *myoepithelioma* can be of lined, myxoidal or reticular pattern. The tumor contains spindle cells in 70% of cases, and in 20% of cases it contains epithelioid or plasmacytoid cells. The cytoplasm of the *myoepithelioma* cells is eosinophilic or bright. The nucleus is oval or round with regularly dispersed chromatin, and it is localized eccentrically [12]. Diversity in the microscopic images of the neoplasm may be the cause of microscopic diagnosis difficulties, especially when only hematoxylin- or eosin-stained substances are assessed. In the majority of cases, the tumor is recognized as *adenoma polymorphum* [13]. In *myoepithelioma* differentiation from other salivary glands tumors, immunohistochemical examinations are used.

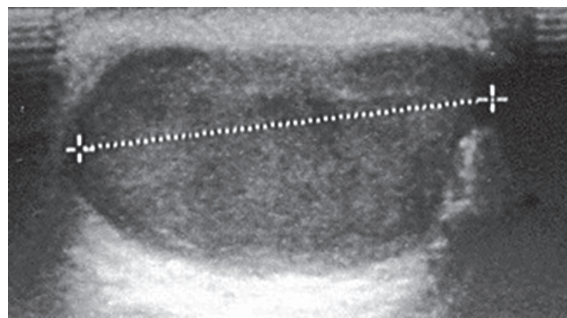
A differential clinical course not correlating with a morphologic structure and repetitive diagnostic difficulties cause that, apart from over 200 *myoepithelioma* case reports in the literature since the first description by Sheldon in 1943, and 2005 and 2012 observation summaries on the tumor [11, 12], the tumor is still difficult to diagnose and treat.

## Case Report

A 57-year-old man presented with a quite hard, painless mass in the left preauricular area. The patient had not been diagnosed or treated earlier. At the time of admission to the hospital, he did not report any other symptoms apart from the neoplasm growing slowly for two years. The neoplasm caused a bump in the left parotid area, which was hard, painless, and slightly movable in relation to the surrounding tissues. The color of the covering skin was not homogenous; there were brighter discolorations of a rice grain size on the skin surface of 3 cm x 2 cm. The skin was movable against the background to varying degrees; the least moveable part was in the upper area of the neoplasm. Mimic muscle activity was preserved bilaterally. Laboratory examinations did not show any deviations beyond the normal range. Radiological examination of the chest showed chronic bronchitis in the lungs. The patient informed us during the interview that he had been smoking at least 20 cigarettes a day and often drank alcohol.

USG image showed a hypoechogenic lesion with a diameter of 32 mm in the left parotid gland area, and reactive lymph nodes of 10 mm diameter on the neck (Fig. 1).

FNA (fine-needle aspiration) of the lymph nodes showed a hypertrophic reaction.



**Fig. 1.** USG image of the hypoechogenic lesion with a diameter of 32 mm in the left parotid gland area, and reactive lymph nodes of 10 mm diameter on the neck

FNA of the left parotid area neoplasm showed a few groups and dispersed spindle-like cells, which indicated histopathological verification.

Presurgical histopathological examination – the biopsy of three neoplasm fragments (1 cm, 1.2 cm, 1.4 cm) was performed under general anesthesia.

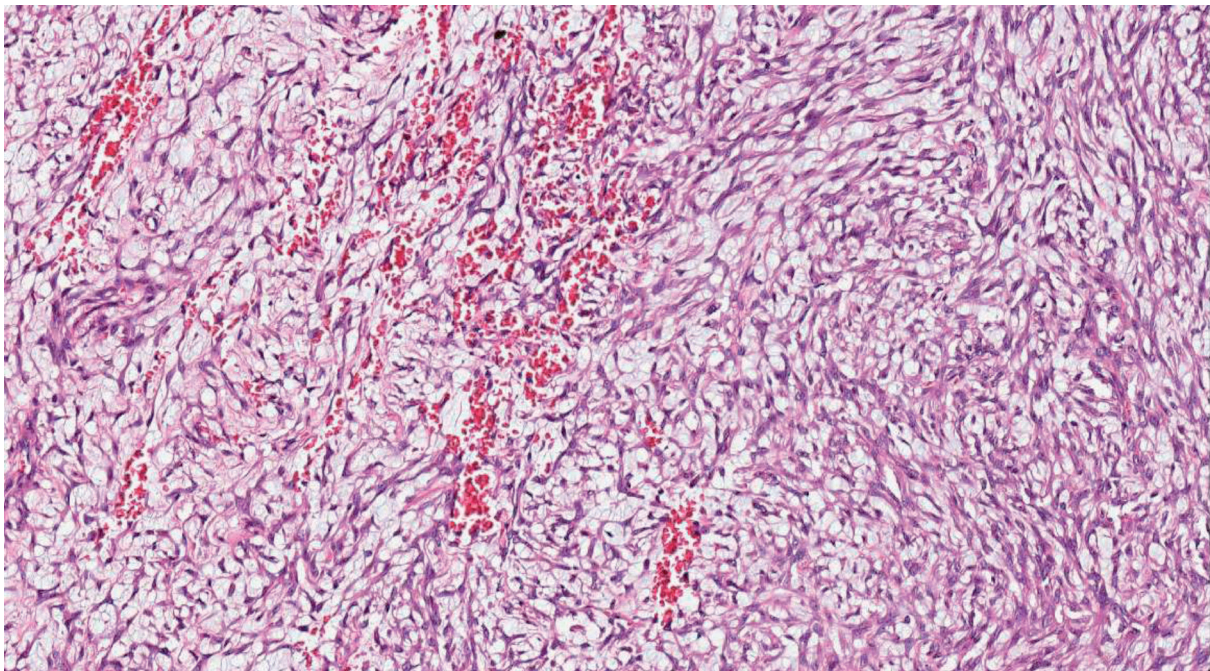
The histopathological examination results showed a histopathological picture indicating *fibrous histiocytoma*.

Surgery: the neoplasm of the parotid gland was excised with the surrounding microscopic healthy tissue under general anesthesia with the preauricular section extended to the neck, with a healthy tissue margin and covering skin. Facial nerve branch control was maintained. In its upper part, the neoplasm did not have a capsule. The neoplasm infiltrated the capsule of the parotid gland and the adjacent muscle. The upper branch of the facial nerve was surrounded by the infiltration, and was excised together with the neoplasm. Suturing and drainage were performed. The wound was sutured after reducing the left eyelid gap of 1/3. The wounds healed without any complications.

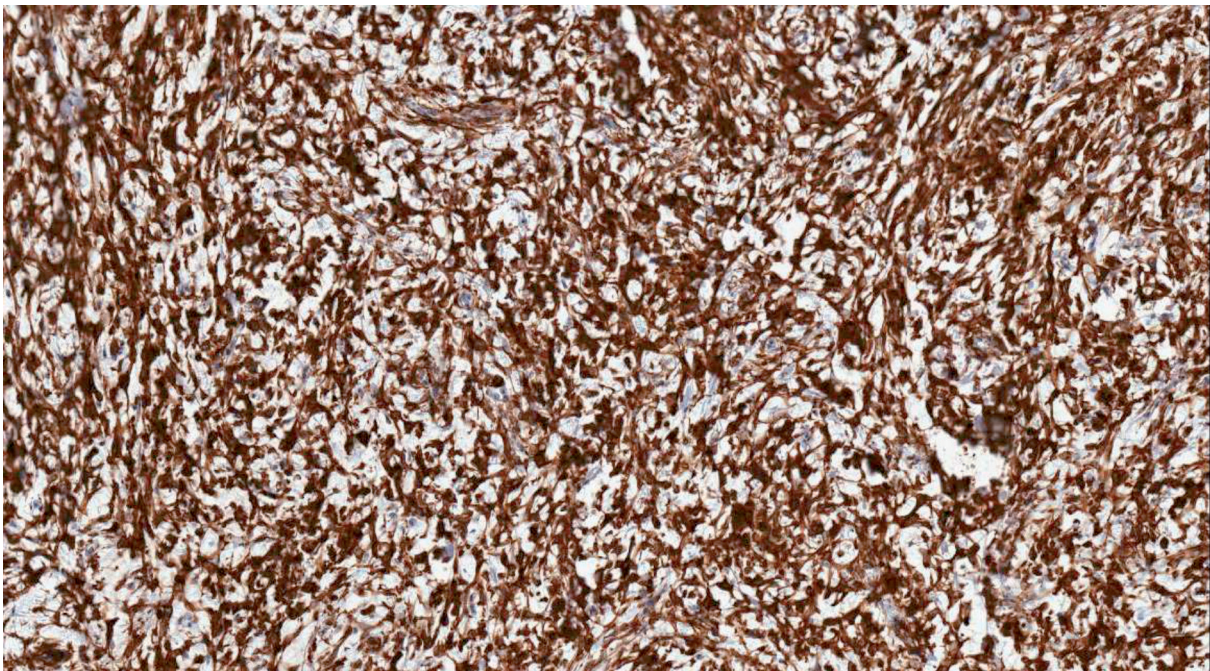
The result of the surgery sample examination showed *myoepithelioma*. The tissue sample with the greatest size, of 6 cm x 3.8 cm, was analyzed. Histologically, the tumor tissue was composed of solid, proliferated spindle cells with a vesicular chromatin pattern and prominent central nucleoli with cell borders and amorphophilic, eosinophilic and clear cell cytoplasm (Fig. 2).

Considering the inaccurate pre-surgical diagnosis, mid-surgical observations not compliant with the USG image performed 2 months before the surgery, and the result of the post-surgical histopathologic examination not similar to the previous results, an immunohistochemical examination was performed.

By immunohistochemistry, tumors are reactive for epithelial markers CK AE1/AE3, CK5/6, S-100 and V-9 (Fig. 3, 4, 6) and are negative for epithelial membrane antigen (EMA), smooth muscle ac-



**Fig. 2.** *Myoepithelioma* (spindle-cell type). The neoplasm consists of spindle-cell type with slightly acidophilic cytoplasm and centralized nucleus. Bright cells visible focally. Stained with HE



**Fig. 3.** *Myoepithelioma* (spindle-cell type). Cytokeratin AE/AE3 (+)

tin (SMA) and glial fibrillary acid protein (GFAP). Cell proliferation marker Ki-67 is low (1%) (Fig. 5).

The examination showed immunoexpression of cytokeratin AE1/AE3, cytokeratin 5/6, Ki-67, S-100, and vimentin V-9 (Fig. 3–7). The examination performed made possible the diagnosis of *myoepithelioma*.

The follow-up examination after 1 month post-surgically showed efficiency of the left eye protective system. Regular three-month follow-up

oncologic examinations were recommended to the patient. The patient has stayed under medical supervision for four years, without recurrence.

## Discussion

The results of fine-needle biopsy and the histopathological examination of the tissue sample of the patient suggested a benign type of tumor, how-

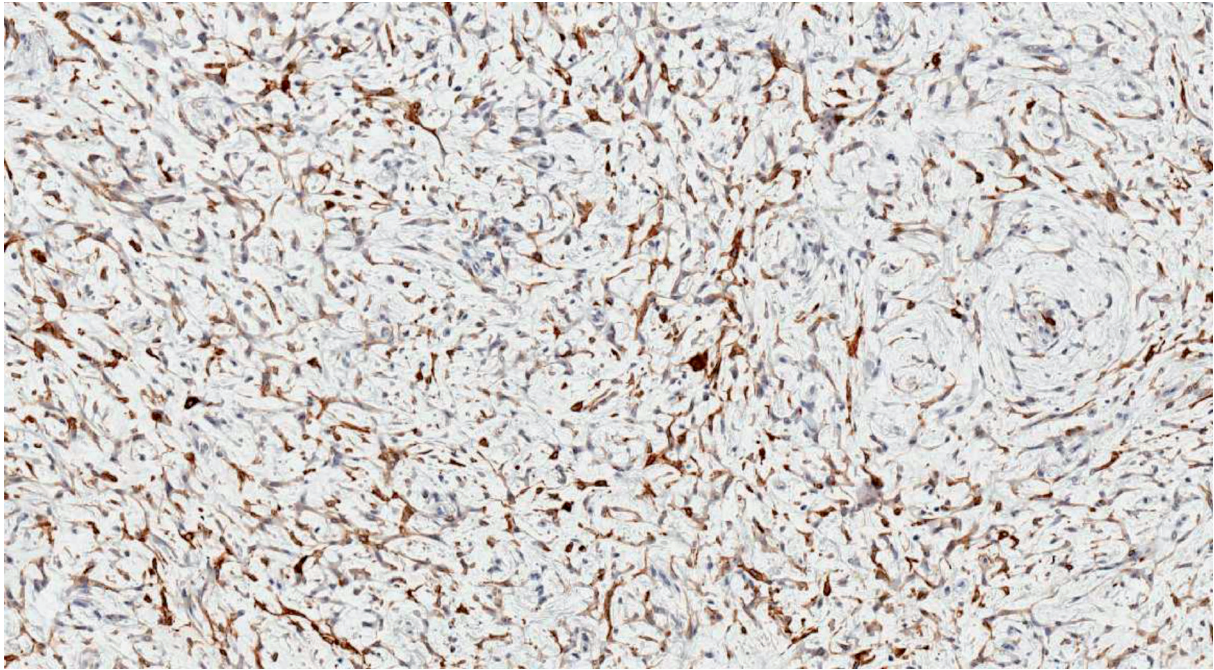


Fig. 4. *Myoepithelioma* (spindle-cell type). Cytokeratin 5/6 (+)

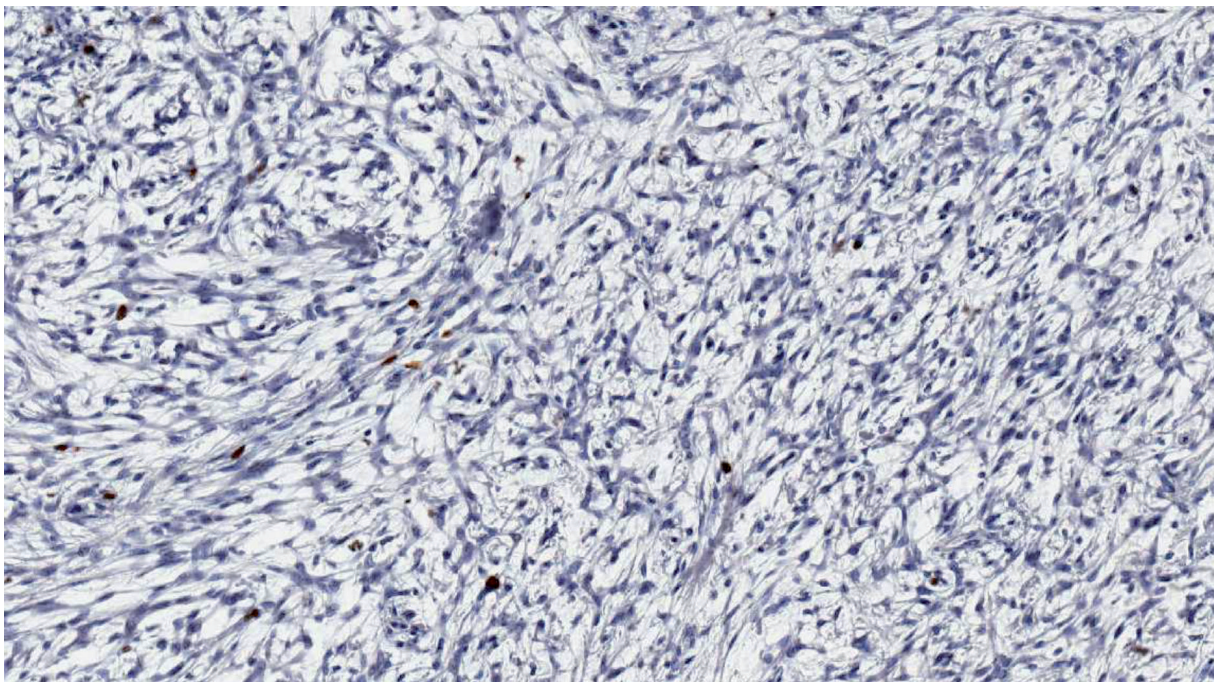


Fig. 5. *Myoepithelioma* (spindle-cell type). Ki-67 (ca. 1% of the cell nucleuses +)

ever they did not clearly indicate its morphological type. USG image showed the presence of the tumor, well distinguished from its surroundings, possibly cystic. Mid-surgical observation was different from the pre-surgical insights; the neoplasm was not fully cystic. It had been growing, infiltrating the parotid gland in its upper part, its capsule and the adjacent muscle. The observations helped to decide not to prepare the facial nerve branch. Total excision of the neoplasm was performed.

Neoplasm localization in the upper part of the superficial flap of the parotid gland caused the excision of part of the facial nerve upper branch. The aggressive growth of the tumor, especially its upper part, salivary gland capsule and the muscle infiltration, demanded the tumor be treated as a malignant neoplasm.

Fine-needle biopsy might be (in case of *myoepithelioma*) an examination which does not give a final diagnosis, however it is believed that the

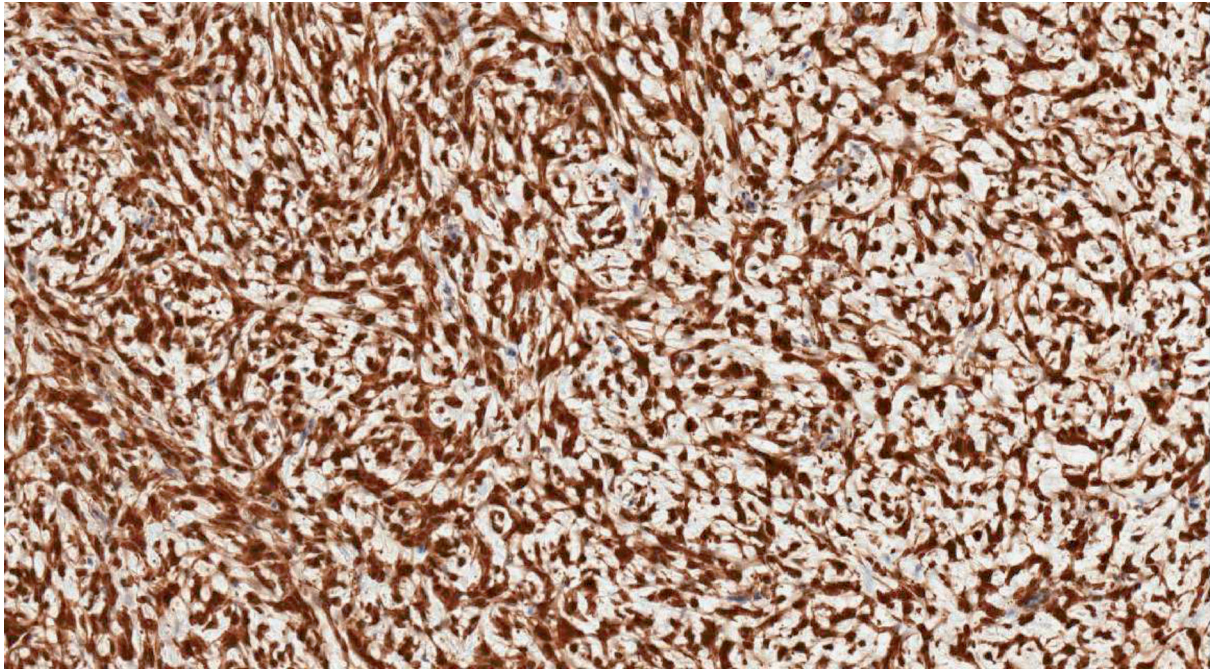


Fig. 6. *Myoepithelioma* (spindle-cell type). S-100 (+)

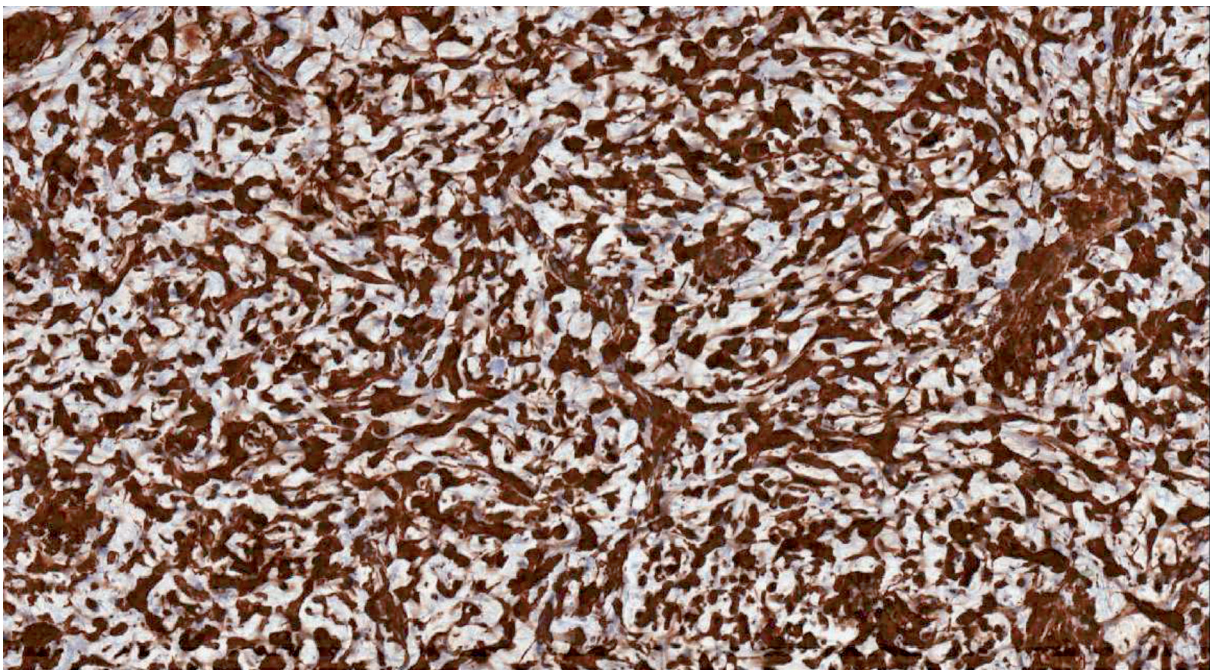


Fig. 7. *Myoepithelioma* (spindle-cell type). Vimentin V-9 (+)

examination, along with a histopathologic examination of a tissue fragment, is the basis of diagnosis [1, 13].

A histopathological assessment of *fibrous histiocytoma* obtained in our patient was perceived as possible, as it seemed to have its confirmation in skin changes observed above the neoplasm. Similar changes were described by Wiley et al. [14]. The neoplasm's benign character was observed in its slow and painless growth, USG image, and

reactive character of the nearest lymph nodes hypertrophy. Cases of a malignant *fibrous histiocytoma* of the parotid gland described in the last decade [15–17], which in pre-surgical diagnosis were assessed as non-malignant, recommend caution in the morphologic interpretation of pre-surgical examinations. The authors of the aforementioned reports emphasize the possibility of invalid diagnosis of benign *fibrous histiocytoma*, *adenoma pleomorphum*, and spindle-like

cell *myoepithelioma*. Faults in diagnosis, which were the same in the case of our patient's diagnosis, are associated with the fact that *myoepithelioma* forms from proliferating myoepithelial cells. It might also have the features of *adenoma polymorphum*, and despite the fact that the quantity of ductal elements in the neoplasm is non-significant, it is often confused with this neoplasm [11]. Despite the fact that the growth of *myoepithelioma* is described as more aggressive than that of *adenoma polymorphum*, the neoplasm is benign, surrounded by a fibrous capsule in the case of parotid gland neoplasms, or without a capsule in the case of palatal neoplasms [6, 12]. Occasionally, it can infiltrate and give metastases [1]. Focal infiltration of the gland capsule without lying beneath glandular tissue infiltration reported by Gun et al. [18] is, according to the authors, the evidence of indefinite malignancy potential in the benign parotid gland neoplasm described by them. Hunt et al. [19] described *myoepithelioma* infiltration of the floor of mouth to the mandible, causing pressure resorption of the lingual mandibular cortex, at the same time emphasizing the rare intercostal presence of the tumor. Buccal muscle infiltration by *myoepithelioma* growing from buccal mucosa was described by Park and Seo [20], who enhanced the description with the information of a lack of vascular invasion of the capsule and the neoplasm free margin to excise.

The aforementioned examples of *myoepithelioma* infiltrating growth concerned benign tumors at the moment of diagnosis, however infiltration, areas of necrosis, cellular atypia, high mitotic index, cellular polymorphism and infiltration along the nerves are features of malignant tumors.

Vast infiltration in the case of malignant *myoepithelioma* enforces a bad diagnosis [10, 21–23]. Differentiation between benign and malignant *epithelioma* is difficult despite accurate diagnostic features.

Treatment of the benign type of *myoepithelioma* is similar to the one applied in the case of *adenoma pleomorphum*, based on total excision of the neoplasm mass with a margin of healthy salivary gland tissue. Local recurrence is similar to the one described in *pleomorphic adenoma*, and it accounts for 15–18% of all cases. There has not been any clear relationship detected between the morphologic type of *myoepithelioma* and its biological features, or its tendency for recurrence. According to Hornick and Fletcher [3], the mitotic index is significant for the prognosis. In benign *myoepithelioma* with recurrence and metastases, the index was the highest [3, 24]. The authors emphasize a significantly greater possibility of recurrence with a non-significant possibility of

metastases in benign *myoepithelioma* with a high mitotic index.

Spindle-like cell *myoepithelioma* (exactly the same as the one diagnosed in our patient) should be differentiated from *pleomorphic adenoma*, *fibrous histiocytoma*, *schwannoma*, *leiomyoma*, *leiomyosarcoma*, *hemangiopericytoma* or *synovial sarcoma*. *Myoepithelioma* in which plasmacyte-like cells are in the majority should be differentiated from *plasmacytoma* [11, 12, 15, 16].

According to Zhu et al. [25], immunohistochemical examinations may be very helpful in defining the differentiation of the cells of rare tumors or in defining variations of common tumors. According to the author, myoepithelial cells are usually positive for p63, SMMHC, SMA, calponin, vimentin, S 100 protein and high molecular-weight keratins (CK 5/6, 34bE12), but they show weak expression for keratins CK7 and CAM, as well as having no expression for epithelial membrane antigen EMA.

Kapoor et al. [26] reviewed the literature and also performed their own examinations which confirm that vimentin and S 100 protein cause a positive reaction in neoplastic myoepithelial cells, not reacting to contact with the myoepithelial cells of the parotid gland, whereas cytokeratins and vimentin react positively with *myoepithelioma* cells. The same authors think that a combination of keratins along with the positivity for S 100, vimentin and one more myogenic marker for stamping the diagnosis of ME is a rough criterion.

Nagao et al. [27] also report immunohistochemical markers which are useful in salivary gland tumor diagnostics. Pan-cytokeratin (CK) [AE1/AE3],  $\alpha$ -smooth muscle actin (SMA), calponin, muscle-specific actin (MSA), p63, CK14, glial fibrillary acidic protein (GFAP), S-100 protein, and vimentin, Ki-67 [MIB-1] are useful in the differentiation of myoepithelial tumors of the salivary glands. High sensitivity is characteristic of SMA, calponin and MSA, therefore they are useful in diagnosis. A low specificity but great utility in screening are characteristic of S 100 protein and vimentin. According to the cited author, the greatest role of immunohistochemistry in the case of myoepithelial cell tumors is to explain if neoplastic myoepithelial cells take part in the tumor or not. Approximately 70% of salivary gland tumors exhibit myoepithelial cell differentiation. *Myoepithelioma* and *myoepithelial Carcinoma* are in the group of tumors which do not reveal luminal cell differentiation.

Marker Ki-67 is helpful in the proliferative activity assessment of *myoepithelioma* cells; if the marker is equal to or greater than 10, it indicates a diagnosis of *myoepithelial carcinoma*.

The immunoeexpression of cytokeratin AE1/AE3, cytokeratin 5/6, S-100, vimentin V-9, and Ki-67 (ca. 1% of the cells) demonstrated in our patient made the diagnosis of *myoepithelioma* possible.

The importance of immunohistochemical examination in salivary gland tumors is highlighted mainly after an assessment of tissue samples tinted with hematoxylin and eosin to refine the diagnosis. Through immunohistochemistry, cases of *myoepithelioma* were shown to be reactive for epithelial markers (keratin and/or epithelial membrane antigen); about 90% expressed keratins (most often AE1/AE3 or PAN-K), about 90% S-100 protein, 50–60% epithelial membrane antigen, 40–50% glial fibrillary acidic protein, and 30–40% smooth muscle actin [25–27]. Pre-surgical diagnosis of *myoepithelioma* on the basis of cytological assessment of the fine-needle biopsy material and immunohistochemical examination of the smear, confirmed by the histopathological examination of excised neoplasm described by Das [28] suggests the possibility of rationalizing and shortening pre-surgical diagnostics. However, post-surgical diagnostics, according to Ogawa et al. [29], should be based on a detailed examination of subsequent fragments of the neoplasm, because dedifferentiation of a cell group in the neoplasm of low malignancy is possible. Cells of another population form another neoplasm of high malignancy, capable of salivary gland tissue and facial nerve infiltration. Postponing the exact assessment of the subsequent fragments of the neoplasm might be the cause of the omission of the dedifferentiated cell presence in the neoplasm, which determines its high malignancy.

We support the opinion that more and more precise pre-surgical diagnostics (morphology and imaging) of salivary gland neoplasms in the case of *myoepithelioma* of the parotid gland does not reduce the surgeon's precariousness arising mid-surgically concerning the range of the neoplasm excision. Features that determine local malignancy of the neoplasm such as muscle infiltration beyond the salivary gland capsule, even in a case of lack of morphologic features of malignancy assessed in routine histopathological examination,

are in favor of the need for vaster excision range, much wider than is assumed for benign neoplasms. Aggressive in relation to the surrounding tissues, the infiltrating growth of the neoplasm, which is often reported, can be a symptom of further local recurrence [25–27]. Neoplasm infiltration of the perineural spaces is reported much more rarely; reports mainly concern malignant *myoepithelioma* [29–31]. The possibility of *myoepithelioma* transformation into *myoepithelial carcinoma*, and to be more precise, into the co-existence of *myoepithelial carcinoma* with *myoepithelioma* of the soft tissues described by Mahdi et al. [32], is a reminder of the necessity of caution while interpreting histopathological examination results and the possibility of *myoepithelioma* transformation from a benign into malignant form.

The lack of certainty as far as the morphologic character of the tumor in our patient (who was diagnosed and surgically treated 5 years ago) was concerned, influenced our decision not to reconstruct the continuity of the excised facial nerve branch in one stage along with tumor excision. The patient did not agree to reconstruction of the continuity in the next surgery.

Recurring faults in neoplasm diagnosis and doubts as far as surgery range is concerned, present during surgery planning and the surgery itself, are evidence of the need to perform immunohistochemical examination in the pre-surgical diagnostics. Since 2011 in our hospital, immunohistochemical examinations of all neoplasms formed of myoepithelial cells have been performed in pre-surgical diagnostics.

The unique character of *myoepithelioma* is expressed in: the possibility of the creation of a malignant form inside the benign tumor; the fact that infiltrating growth which does not respect anatomical boundaries can be present in some benign tumors; the appearance of local recurrence after radical excision, which is a malignant form of *myoepithelioma*. All of the aforementioned characteristics demand extreme caution in interpreting a morphological examination, as well as in planning the surgical treatment.

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