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Malignant Myoepithelioma of the Salivary Gland – an Untypical Clinical Course

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A case of malignant tumor developing from myoepithelial cells (malignant myoepithelioma) is presented. The primary focus was located in the region of the left submandibular salivary gland. A relapse and metastases were disclosed in the same salivary gland, in the lung and the left breast. Immunohistochemical studies demonstrated positive reactions for S-100 protein, cytokeratins, smooth muscle actin, vimentin, GFAP protein, p53 protein and Ki-67 antigen, and allowed for establishing the final histopathological diagnosis of malignant myoepithelioma.

Introduction

Under physiological conditions, myoepithelial or basket cells are located between cells of the secretory epithelium on one side and the basement membrane of ducts in the mammary gland, sweat, salivary and lacrimal glands on the other [2–4, 9, 12]. In the mammary gland, they are present already at the fetal stage of development. They are thought to play a role in the development of the mammary gland and in lactation. Their contraction induces the ejection of milk. Numerous reports describe the effects of myoepithelial cells on the biology of breast cancer. A loss of basket cells in the breast cancer architecture is one of the more important traits of the tumor invasion [1, 3]. The typical trait of myoepithelial cells involves their bidirectional differentiation to both epithelial and smooth muscle cells.

Neoplastic proliferation of myoepithelial cells is extremely rare and it is classified first of all as benign lesions of the myoepitheliosis or adenomyoepithelioma type. The respective malignant lesions, termed malignant myoepithelioma or myoepithelial carcinoma, develop sporadically. They are frequently defined as myoepithelial tumors of an unspecified malignant potential [3]. The lesions develop in the age range from 31 to 72 years (mean, 50 years) [11] and, according to some authors [3, 13], occur mainly between the 22nd and 87th year of age, with the peak incidence in the 6th decade of life (i.e. about 10 years later than benign lesions). The size of the tumor ranges from 1.4 to 17cm (mean, 3.5cm). It may arise spontaneously, *de novo* or from preexisting lesions of the pleomorphic adenoma or myoepithelioma type in the salivary gland [2, 3, 7, 8, 12]. Malignant myoepithelioma is a moderately or well-differentiated tumor. Relapses following an incomplete excision occur in 8–59% of cases and in 29–50% of cases the process is fatal [2, 8, 12]. Distant metastases develop first of all in the liver and spinal bones [3]. The present report aims at drawing the reader's attention to the potential for development of such a tumor, which occasionally is misdiagnosed due to its frequently predominant, spindle-shape cell component.

A Case Description

A presently 40-year-old female noted a small tumor in the region of her left submandibular salivary gland in April 1995. The lesion was removed in a regional hospital and the histopathological examination resulted in the diagnosis of a fibroma. In 1997, at the site of the previous operation, a new tumor, about 12cm in diameter, appeared. The patient reported to the Lower Silesia Center of Oncology, in which the lesion was completely removed. Histopathology established the diagnosis of a malignant myoepithelioma. In January 1998, in the course of follow-up in the outpatient clinic of the Lower Silesia Center of Oncology, a chest X-ray examination revealed a round shadow 6×5cm in size in the middle field of the left lung. In February 1998, the lesion-containing lower lobe of the left lung was surgically re-

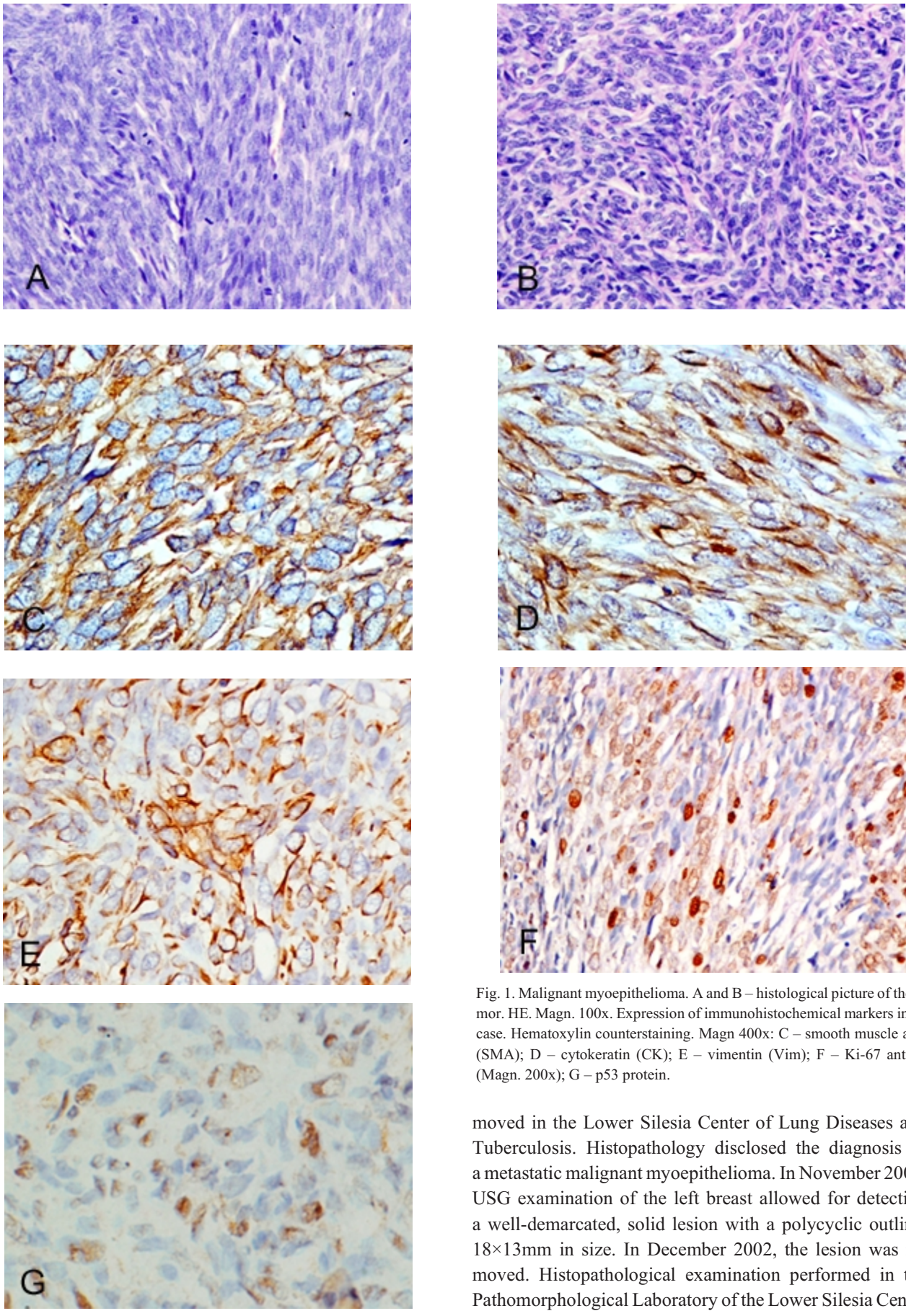

Fig. 1. Malignant myoepithelioma. A and B – histological picture of the tumor. HE. Magn. 100x. Expression of immunohistochemical markers in our case. Hematoxylin counterstaining. Magn 400x: C – smooth muscle actin (SMA); D – cytokeratin (CK); E – vimentin (Vim); F – Ki-67 antigen (Magn. 200x); G – p53 protein.

moved in the Lower Silesia Center of Lung Diseases and Tuberculosis. Histopathology disclosed the diagnosis of a metastatic malignant myoepithelioma. In November 2002, USG examination of the left breast allowed for detecting a well-demarcated, solid lesion with a polycyclic outline, 18×13mm in size. In December 2002, the lesion was removed. Histopathological examination performed in the Pathomorphological Laboratory of the Lower Silesia Center

TABLE 1

Expression of selected myoepithelial cell markers in benign and malignant tumors originating from the cells as compared to results obtained in the presented case. SMA – smooth muscle actin, S-100 protein, CK – cytokeratins, GFAP – glial fibrillary acidic protein, Vim – vimentin, MT – metallothionein, Ki-67 antigen, p53 protein, maspin

Tumor	SMA	S-100	CK	GFAP	Vim	MT	Ki-67	p53	Maspin
Malignant myoepithelioma	+	+	+	+/-	+	+/-	+	+	+/-
Benign myoepithelioma	+	+	+	+/-	+	+/-	+/-	-	+
Presented case	+	+	+	+	+	-	+	+	-

of Oncology documented the diagnosis of a malignant tumor. In January 2003, the re-evaluation of the entire material and immunohistochemical tests established the final diagnosis of malignant myoepithelioma with metastases to the lung and breast. In March 2003, a follow-up USG examination of the breasts allowed for detecting two solid lesions in the left breast, 11 and 5mm in diameter. The lesions were non-palpable. The patient was qualified to a mammotomic biopsy, which was performed in the same month. Histopathology confirmed the diagnosis of a malignant myoepithelioma. In May 2003, a quadrantectomy was performed in the surgical ward of the Lower Silesia Center of Oncology, removing the upper-external quarter of the left breast. Histopathology confirmed the earlier diagnosis (malignant myoepithelioma). In order to corroborate the diagnosis, a number of immunohistochemical reactions were performed using antibodies manufactured by DAKO, Denmark. They included anti-S-100 (clone DAK-S100A1/1), anti-cytokeratin (clone MNF116, reacting with cytokeratins 5, 6, 8, 17 and 19), anti-Glial Fibrillary Acidic Protein (GFAP – clone 6F2), anti-Smooth Muscle Actins (SMA – clone 1A4), anti- vimentin (clone V9), anti-Desmin (clone D33), anti-metallothionein (MT – clone E9), anti-Ki-67 (clone MIB-1), anti-p53 (clone DO-7), anti-maspin (clone S-20, Santa Cruz Biotechnology). Positive reactions with antibodies directed to S-100, cytokeratins, smooth muscle actin (SMA), vimentin, GFAP, p53 protein and Ki-67 antigen (expression in over 10% of the tumor cells) were found (Fig. 1, Table 1).

Discussion

Macroscopically, malignant tumor that originates from myoepithelial cells frequently forms non-capsulated, multinodular lesions with centrally located cysts, or coagulative necrosis of varying extent. Only occasionally are the lesions encapsulated. In most cases, the lesions exhibit marginal infiltration, usually of the multinodular form, cell atypia and, significantly, a high mitotic activity. The trait, which differentiates the benign form from malignant proliferation of myo- epithelial cells involves the mitotic index higher than 7/10 hpf and/or the expression of proliferation-associated antigen Ki-67 in more than 10% of tumor cells. In benign lesions, the expression of Ki-67 antigen is assumed to affect up to 5% of tumor cells. Tumors with a marked cellular pleomorphism, invasion to the nerves, a high mitotic index, a high index of Ki-67 antigen expression and overexpression of p53 antigen are always associated with a poor prognosis [3, 8, 10, 12]. On the other hand, the rare cases of malignant proliferation of myoepithelial cells are characterized by a low mitotic index and only their infiltrative growth provides a base for their malignant character and poor prognosis [3, 8]. Spindle, epithelioid, plasmacytoid, oncocyte-like and clear cells growing in solid, streak-like or trabecular patterns are frequently embedded in myxomatous, hyaline or collagenous stroma. The frequent presence of spindle and plasmacytoid cells, which exhibit positive immunohistochemical reactions to vimentin, cytokeratin (CK), S-100 protein, GFAP and to SMA, points to neoplastic proliferation of myoepithelial cells. Some authors [1, 4] noted positive reaction to SMMHS (Smooth Muscle Myosin Heavy Chain), calponin and maspin. Immunohistochemical studies are most useful in differential diagnostics of benign and malignant proliferations of myoepithelial cells, distinguishing them from spindle cell sarcomas, carcinosarcomas and spindle cell amelanotic malignant melanomas. In the latter case, apart from a positive reaction to S-100 protein, a negative reaction for HMB-45 and/or Melan A antigens allow for diagnosing a malignant myoepithelioma. Due to the occurrence of spindle cells in myoepithelial cell proliferation, a differential diagnosis of breast lesions should also include malignant fibrous histiocytoma, synovial sarcoma, as well as malignant peripheral nerve sheath tumor, which can exhibit positive immunohistochemical reactions to individual antigens (vimentin and -1-antichymotrypsin; cytokeratins 7 and 19; S-100 protein and vimentin). According to several authors [1, 5, 6, 14], a positive immunohistochemical reaction in myoepithelial cells should be expected when anti-cytokeratin 14 (100%), anti-SMA (70–80%), anti-calponin (100%), anti-S-100

(100%), anti-GFAP (50%) and anti-EMA (Epithelial Membrane Antigen – 100%) antibodies are applied. When epithelial differentiation of myoepithelial tumors is dealt with, the application of anti-cytokeratin antibodies is recommended (clone LP34, reactive with cytokeratins 1, 5, 6, 8, 10, 14, 18 and clone D5/16 B4, reactive with cytokeratins 5, 6, 7, 8, 10, 13, 14, 18, 19, and clone AE1/AE3 reactive with all cytokeratins of the 40–67kDa range). When antibodies directed to cytokeratins CK7, CK8, CK13, CK18, and CK19 are employed, the reaction is negative in myoepithelial cell proliferation, what has been used in differential diagnostics with synovial sarcoma (yielding positive reaction). In our case, we applied with success the anti-cytokeratin reagent, produced by the clone MNF 116 and detecting CK5, CK6, CK8, CK17 and CK19. The reagent may also be used in the panel for differential diagnostics of myoepithelial tumors.

Summing up, we should note that a rarely occurring proliferation of myoepithelial cells of a variable location and variable morphology, as well as a difficult to predict clinical course may pose several problems in histopathological diagnostic management, both in cases of primary tumors and, in particular, metastases. The application of a broad panel of immunohistochemical tests provides a valuable diagnostic tool, which allows not only for a correct diagnosing of the lesion, but also for predicting its clinical course.

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