An isolated metastasis to the heart from a malignant phyllodes tumor with osteosarcomatous differentiation

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SOUHRN

A 74-year-old woman was admitted in a serious condition due to the failing right heart. A CT scan revealed a tumor infiltration through the interventricular septum in the right heart, spreading from the apex as far as under the tricuspid valve. The tumor penetrated into the conus of the pulmonary artery, bulging and markedly narrowing the lumen. As a result of the tumor infiltration, the patient died from cardiac failure.
Histological examination of the tumor revealed atypical elongated cells and areas of large cells with significantly enlarged hyperchromatic and lobulated nuclei. In some portions, the tumors had a biphasic appearance. The tumor cells resembled epithelial tissue but immunohistological analyses to detect cytokeratins yielded negative results. The elongated cells expressed desmin and smooth muscle actin. A vast majority of the tumor was solid or hard, histologically corresponding to osteosarcoma. Later, it was found that the patient undergone right-sided mastectomy for a malignant phyllodes tumor with osteosarcomatous differentiation three years previously. The metastasis to the heart was the only metastasis detected by the autopsy.

Keywords: malignant phyllodes tumor with osteosarcomatous differentiation - metastasis to heart - cardiac failure

Izolovaná metastáza do srdce z maligního fyloidního nádoru s osteosarkomatózní diferenciací

SUMMARY

74-letá žena byla přijata v těžkém stavu pro selhávající pravé srdce. CT vyšetření ukázalo tumor, který infiltrativně prorůstal mezikomorovým septem v pravé části srdce a šířil se od hrotu srdečního až pod trojcípou chlopeň. Nádor pronikal do konusu a. pulmonalis, kde se polokulovitě vyklenoval a výrazně zužoval lumen. V důsledku nádorové infiltrace pacientka zemřela na selhání srdeční.
Histologicky nádor tvořily atypické protáhlé buňky někde s velkými buňkami, které měly výrazně zvěšená hyperchromní a laločnatá jádra. V některých úsecích měl nádor bifazický vzhled. Nádorové buňky připomínaly epitel, ale imunohistologická vyšetření na průkaz cytokeratinů byla negativní. Protáhlé buňky exprimovaly desmin a hladkosvalový aktin. Převážná část nádoru byla tuhé až tvrdé konzistence a histologicky odpovídala osteosarkomu. Dodatečně bylo zjištěno, že u pacientky byla před třemi roky provedena pravostranná mastektomie pro maligní fyloidní nádor s osteosarkomatózní diferenciací. Metastáza do srdce byla jedinou metastázou zjištěnou při pitvě.

Klíčová slova: maligní fyloidní nádor s osteosarkomatózní diferenciací - metastáza do srdce - selhání srdce

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Malignant phyllodes tumors (PTs) account for approximately 20 % of all PTs. They are also responsible for local recurrences (1-3). Approximately one-fifth of them metastasize but a lethal course is rare (2,3). Most frequently, hematogenous metastases to the lungs, soft tissues, bones and pleura are observed. Spread to the heart is rare and isolated metastases may mimic primary tumors of the heart (4,5). Occasionally, tumors exhibit heterologous elements, for instance, liposarcomatous, fibrosarcomatous, osteosarcomatous, chondrosarcomatous and rhabdomyosarcomatous (6). In such cases, the original biphasic features disappear and the tumors are sarcomatous.

We present a case of a patient who developed a tumor in the right heart three years after right-sided mastectomy. The tumor led to stenosis in the area of the tricuspid valve and conus arteriosus and, subsequently, to cardiac failure.

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MATERIAL AND METHODS

Tissue samples from autopsy and mastectomy three years previously were fixed in 10 % formalin and processed by the paraffin technique. Then the tissues were stained with hematoxylin and eosin; immunohistochemical staining was performed with the avidin-biotin complex (ABC) method. The antibodies including clone numbers, working dilutions and results are shown in Table 1.

CASE REPORT

A 74-year-old woman was admitted due to progressive dyspnoea over several months and chest tightness. The examination revealed a tumor in the right ventricle causing stenosis in the tricuspid valve region and cardiac failure. When endomyocardial

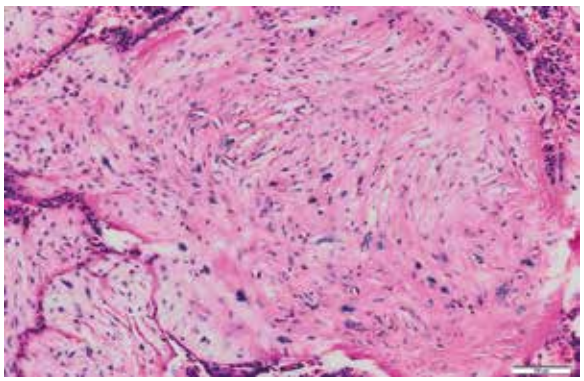


Fig. 1. Malignant phyllodes tumor of the breast, HE.

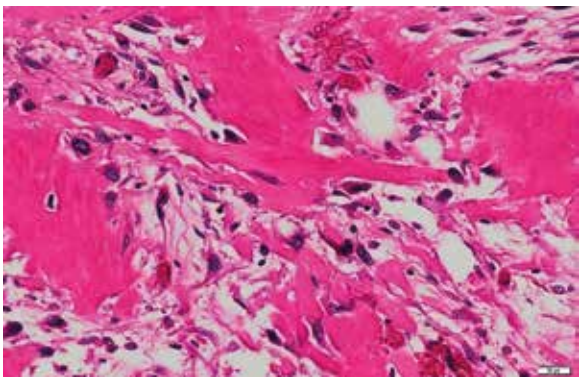


Fig. 2. Osteosarcomatous differentiation of a malignant phyllodes tumor of the right breast. HE, scale bar 20 µm.

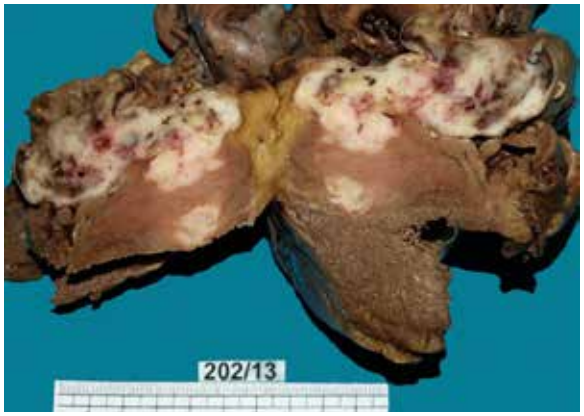
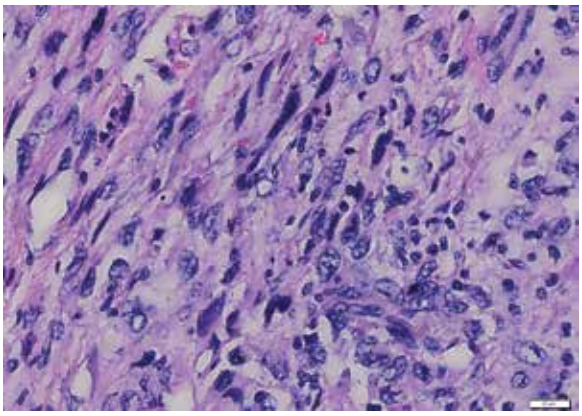


Fig. 3. Heart – a metastasis mostly infiltrating the right ventricular myocardium and ventricular septum.



Obr. 4. Elongated tumor cells of the metastasis to the heart, with no signs of storiform arrangement. HE, scale bar 20 µm.

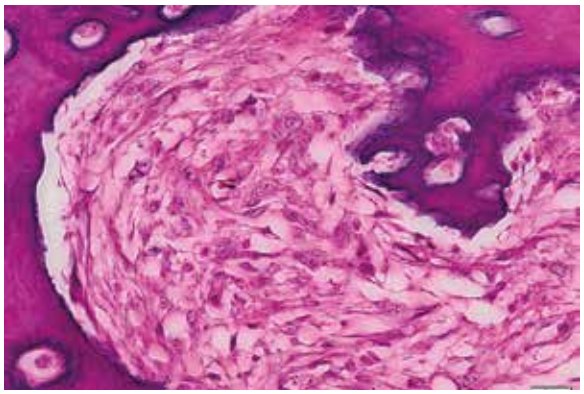


Fig. 5. Irregular bone trabeculae of the metastasis of a malignant phyllodes tumor with osteosarcomatous differentiation to the heart. Close to the trabeculae, elongated tumor cells are seen. HE, scale bar 20 µm.

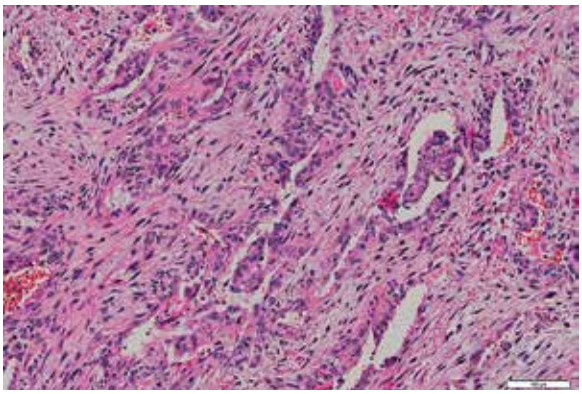


Fig. 6. Metastasis of the tumor to the heart – biphasic structures were present in some portions. HE, scale bar 100 µm.

biopsy was attempted, iatrogenic cardiac tamponade and circulatory instability occurred. After drainage of the pericardial cavity, the patient's condition improved but her dyspnoea at rest continued to be present. The condition gradually progressed, resulting in bradycardia and respiratory and circulatory failure.

It was ascertained from the patient's history that at the age of 71 years, she underwent right-sided mastectomy for a tumor sized 10 x 8 x 7 cm in a health care facility outside the University Hospital Ostrava. In the center of the tumor, a cystic cavity was found. The tumor was solid to hard. Originally, it was diagnosed as a malignant PT with osseous metaplasia. Later, the diagnosis was revised to a malignant PT with osteosarcomatous differentiation. Histologically, the tumor comprised structures of a fibroadenoma transforming into a malignant PT (Fig. 1). Mesenchymal lesions markedly narrowed tubular epithelial structures. Some mesenchymal cells were atypical, with large irregular hyperchromatic nuclei. Some portions of the mesenchyme just under the epithelium of compressed tubules contained areas of osteoid and bone trabeculae transforming into larger segments with bone trabeculae and atypical osteoblasts in their close proximity. Adjacent to bone trabeculae there were elongated cellular elements with relatively large hyperchromatic cells. The mi-

totic index was 5 mitoses per 10 HPF. The finding was classified as a malignant PT with osteosarcomatous differentiation (Fig. 2).

Tumor in the heart: macroscopic findings

The tumor was located in the region of the right ventricular apex. From there, it spread along the muscular ventricular septum to the tricuspid valve. Irregular tumor nodules bulging into the right ventricular lumen were covered with the endocardium. The tumor grew into the conus arteriosus, forming a bulging polypoid structure that narrowed the space under the pulmonary valve (Fig. 3). The size of the tumor from the right ventricular apex to the tricuspid valve region was 7.5 x 8 x 6 cm. In the region between the apex and the tricuspid valve, the tumor was solid to hard.

Histological pattern of the tumor in the heart

The tumor was made up of elongated cells with irregular hyperchromatic nuclei. The tumor cells formed intertwined fascicles (Fig. 4). The tumor contained necrotic deposits. These tumor structures were smoothly continuous with irregular bone trabeculae surrounded by elongated tumor cells (Fig. 5). In some portions, structures with a biphasic appearance were formed (Fig. 6). Immunohistochemical evaluation with antibodies against cytokeratins yielded negative results. The tumor was penetrated by numerous irregular thin-walled capillaries expressing the CD34 antigen. The tumor cells themselves were negative with an antibody against the antigen. Sporadically, small amounts of lipoblast-like cells were seen. The immunohistochemistry results are shown in Table 1. Positive results were achieved with antibodies against desmin in approximately 40 % of cells and against SMA in 50 - 60 % of cells. The other antibodies did not react with the tumor.

DISCUSSION

PTs are classified into benign, borderline and malignant. Benign and borderline tumors have a very favorable prognosis and may be treated by surgical removal. Malignant tumors may recur and metastasize. Despite intensive research in this area, immunohistochemical methods have failed to predict behavior of malignant PTs (7-9) and attention has turned to molecular pathology methods (10).

Although malignant PTs mostly metastasize to the lungs and bones, distant metastases may occur, for example to the adrenals (11) and heart. Two cases of malignant PTs metastasizing to the heart have been published (4,5). In both cases, tumors occupied the right ventricle. In one case, a metastatic tumor was detected 3 years after mastectomy. This was similar to our case of a tumor metastasizing to the right ventricle and right atrium 3 years after mastectomy.

PTs with osteosarcomatous differentiation are estimated to account for approximately 1.3 % of all malignant PTs (6,12). As in other locations, osteosarcomas in PTs are classified based on prevailing morphological patterns into fibroblastic, osteoclastic and osteoblastic. According to Tavassoli (14), the osteosarcomatous component can occupy a variable percentage of a PT, ranging from 25 % to 100 %. Rare cases have been reported (13) of the osteosarcomatous component being detected not in the primary tumor but only in lung metastastases. In these cases, very rare primary pulmonary osteosarcoma must be ruled out. In another case, telangiectatic osteosarcoma was detected in a recurrent tumor but not in the primary mass (15).

Some PTs are quite large and tiny areas of osteosarcomatous differentiation cannot be completely ruled out. In the mammary gland, sarcoma may rarely occur as the primary tumor or as a part of a malignant PT. Silver et al. (6) studied Armed Forces Institute of Pathology material collected in the last 30 years to detect 22 malignant PTs with osteosarcomatous differentiation. In 11 cases, axillary lymph nodes were histologically examined and found to be free of tumor. The mean size of the neoplasms was 6.4 cm. According to the authors, neoplasms larger than 5 cm are potentially aggressive. Of the set of 22 PTs with osteosarcomatous differentiation, metastases were clinically apparent within 1 year of diagnosis in 8 patients and 7 died within 12 months of detection of initial metastases. Thus, biological

Table 1. Results of immunohistochemical examination of the metastasis to the heart.

Antibody	Producer	Clone	Dilution	Result
S100 protein	DAKO	polyclonal	1: 600	**Neg.**
Desmin	BioGenex	33	prediluted	**40 % +**
SMA	DAKO	1A4	1:100	**50 - 60 % +**
Myo D1	DAKO	5.8A	1:50	**Neg.**
Myogenin	DAKO	F5D[1]	1:50	**Neg.**
Caldesmon	DAKO	h-CD[1]	1:50	**Neg.**
Cytokeratins	DBS (Diagnostic BioSystems)	AE1-AE3	1:50	**Neg.**
CK7	DAKO	OV-TL 12/13	1:100	**Neg.**
CK20	DBS	KS20.8	1:100	**Neg.**
CK 5/6	DAKO	D5/16 B4	1:100	**Neg.**
CK HMW	DAKO	34βE12	1:50	**Neg.**
EMA	DAKO	E29	1:100	**Neg.**
p63	ZYTOMED	4A4	1:50	**Neg.**
CD10	NOVOCASTRA	56C6	1:100	**Neg.**
GFAP	ZYTOMED	EO672Y	prediluted	**Neg.**
CD 117	DAKO		polyclonal rabbit	**Neg.**
ER	NOVOCASTRA	6F11	1:50	**Neg.**
PR	NOVOCASTRA	16	1:200	**Neg.**

behavior of these neoplasms is similar to that of soft tissue osteosarcomas.

In our case, transformation of connective tissue into osteosarcoma was observed just under the ductal epithelium. Other segments contained numerous irregular bone lamellae with atypical osteoblasts in their close proximity. Differential diagnosis must distinguish the tumor from other neoplasms potentially containing cartilaginous or osseous structures such as breast cancer or metaplastic carcinoma (16). In such cases, metaplastic cartilaginous or osseous segments are a part of, for example, invasive ductal carcinoma in the adjacent areas.

Rarely, the epithelial component may undergo malignant transformation in PTs. Such cases are very low in numbers, with fewer than 30 cases having been reported (17-19). Very sporadically, metaplastic spindle cell carcinoma was noticed in a PT (1).

In metaplastic carcinoma, elongated sarcomatous cells transforming into carcinoma structures may be observed, with immunohistochemical findings revealing cytokeratin-positive isolated elongated cells or clusters of such cells. Kinkor et al. (1) reported sarcomatoid (metaplastic) spindle cell carcinoma in a PT. The authors pointed to potential confusion with primary sarcoma of the mammary gland, especially in small or core-cut biopsies. Sarcomas, however, are always negative in immunohistochemical reactions for cytokeratin (12). It must be stressed that elongated cells in PTs may focally express cytokeratins (20). In such cases, immunohistochemistry results should be interpreted with caution. The prognosis of patients with metaplastic breast carcinoma containing osteocartilaginous heterologous elements is no worse than in infiltrating ductal carcinomas (21).

Treatment of primary osteosarcomas of the mammary gland is similar to that of malignant PTs with osteosarcomatous differentiation (22-24). These patients undergo radical mastectomy, simple mastectomy or complete resection of the tumor. In spite of hematogenous spread of the tumor, resection of axillary lymph nodes is recommended.

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