A Rare Case of Breast Malignant Phyllodes Tumor With Metastases to the Kidney

Case Report

Bożenna Karczmarek-Borowska, MD, PhD, Agnieszka Bukala, MD, Karolina Syrek-Kaplita, MD, Mariusz Ksiązek, MD, Justyna Filipowska, MD, and Monika Gradalska-Lampart, MA

INTRODUCTION

The first descriptions of phyllodes tumors of the breast come from the end of the 18th century, while the term was suggested for the first time in 1838. The tumors are composed of an epithelial component and hypercellular connective tissue—stroma whose spindle cells form leaf-like structures. The tumor is rare; it constitutes 0.3% to 1% of all breast neoplasms in women. In Poland, 473 cases of phyllodes tumor were diagnosed between the years 2000 and 2012, which constituted 0.2% to 0.3% of all neoplasms of the breast diagnosed per year. The greatest number of new cases (86 patients) was noted among patients 45 to 49 years old (Polish National Cancer Registry, Warsaw. 85.128.14.124/KRN/English/index.asp).

In most cases, phyllodes tumors are diagnosed in patients between the ages of 35 and 55 although it can affect people of any age. The mean age of patients is 50 years. The highest incidence among patients 45 to 49 years old (Polish National Cancer Registry, Warsaw. 85.128.14.124/KRN/English/index.asp).

According to the World Health Organization (WHO) criteria, phyllodes tumors can be classified based on their microscopic appearance as benign, borderline, or malignant. However, this classification does not always allow the physician to accurately predict the prognosis as the tumors show a tendency toward rapid growth and are characterized by a biphasic growth pattern. During the first phase, which can last even for years, the growth is slow. Afterward, the growth rapidly accelerates over several weeks or months. The average size of the tumor at the time of diagnosis was 4 cm; however, available literature documents cases in which phyllodes tumors reached significant sizes, even up to 20 to 40 cm.

In our work, we present the case of a female patient with diagnosed malignant phyllodes tumor of the breast with metastases in the kidneys, lungs, liver, and bones.

CASE REPORT

A 41-year-old female patient presented herself to our outpatient oncological clinic in the middle of July 2012. Two months earlier, she noticed a rapidly growing tumor in her right breast. She had breast ultrasonography performed; in the right breast were revealed numerous focal lesions with heterogeneous echogenicity, poorly circumscribed with few fluid-filled spaces. The patient was admitted to the surgical
department wherein abdominal ultrasonogram and chest x-rays were obtained, but no significant abnormalities were found in both the examinations. An open surgical biopsy of the tumor was performed and histopathological examination revealed the presence of phyllodes tumor. The patient was again admitted to the surgical department and a right-sided mastectomy with removal of the enlarged lymph nodes of the inferior level of the right axilla was performed. Postoperative histopathological examination confirmed malignant phyllodes tumor of the breast (Figure 1): phyllodes tumor with foci of extensive necrosis of a coagulative type and hypercellular type of stroma. Borderline pattern predominates; however, in areas that are more hypercellular, there is clear cellular atypia present and mitotic activity of 13 to 15/10 high power field, which is a criterion of malignancy of the fibrosarcoma type without heterologous elements. Expanding type of growth is seen in most of the periphery; however, there are also areas with infiltration of the surrounding structures. No emboli were found in the blood vessels. Lymph nodes were free of metastases. The tumor was completely excised.

Mammography of the left breast performed after the surgery showed a nonhomogeneous, a hyperechogenic structure, 37 × 18 × 38 mm in size, located in the upper outer quadrant. Fine-needle aspiration biopsy of this lesion was performed with the diagnosis: “in the smear, there are sparse fragments of benign glandular structures of the breast and morphotic elements of blood. The overall appearances are in keeping with a benign lesion.” In the following months, the patient was subjected to a routine checkup procedure. At the end of May 2013, the patient came for a checkup to the oncological outpatient clinic. She reported symptoms of left-sided ischias and dysuria with urinary bleeding lasting for 2 weeks and dysuria with periodic urinary bleeding. Imaging examinations (abdominal ultrasonogram, mammography, breast ultrasonography, chest radiogram) and laboratory tests were ordered. The patient was instructed to return for a follow-up visit with the results in 1 week. However, on June 2, 2013, she was admitted to the urology department because of severe abdominal pain.

A computed tomography (CT) scan of the abdomen and pelvis showed a tumor of the left kidney, 110 × 100 × 130 mm in size, with evidence of renal vein thrombosis, a tumor-like lesion of the right kidney, metastatic-type lesions in the sacral bone and lungs, as well as a lesion in the liver suspected of being a metastasis (Figures 2 and 3). Thoracic angiography CT scan confirmed the presence of numerous metastatic foci up to 26 mm in size (Figure 4). As a primary tumor of the kidney was suspected, on June 5, 2013, a left-sided nephrectomy with adrenalectomy was performed. The results of the postoperative histopathological examination of the specimens was as follows: “Spindle cell sarcoma of kidney with tumor invading renal sinus fat, renal pelvis, fibrous capsule, perirenal fat, and ipsilateral adrenal gland with extension into renal vein. Immunohistochemical examination—positive Vimentin, CD34, CD10 in about 70%, negative: CK-Pan, CK-7, CK-20, CD-5/6, CD31, Des, Estr, HMB-45, melan-A, S-100, and SMA. Ki-67 proliferation index high, focally up to 90%.” (Figure 5). As the neoplastic process had spread to the bones and the patient suffered from intense pain, she qualified for palliative radiotherapy for the sacral bone metastasis. She received 20 Gy in 5 fractions. Then she was admitted to the Department of Clinical Oncology in good general condition—Karnofsky score: 100. On physical examination, a tumor, approximately 30 mm in diameter, was palpable in the upper outer quadrant of the left breast, and no other abnormalities were detected. A core-needle biopsy revealed hyalinized fibroadenoma. The slides of the right breast tumor and the left kidney tumor were reviewed.
again and analysis of the slides indicated that sarcomatous phyllodes tumor/malignant phyllodes tumor of the breast was the primary tumor, whereas the renal tumor was recognized as being metastatic. In addition, the case was sent for a second opinion to a reference center where the diagnosis was confirmed. The patient was qualified for CyVaDIC chemotherapy (dacarbazine 250 mg/m² on days 1–5, vincristine 1.5 mg on day 1, doxorubicin 50 mg/m² on day 2, cyclophosphamide 500 mg/m² on day 2). After the patient received 4 courses of chemotherapy, partial regression of the lesions in the lungs with stabilization of the lesions in the sacral bone and progression in the abdominal cavity (manifesting itself as the occurrence of a pathologic mass in the postoperative bed after nephrectomy and new foci in the liver) were found in a CT. The patient was qualified for second-line treatment—ifosfamide 1.7 g/m² on days 1 to 7 in a cycle repeated every 21 days. The patient received 3 courses of the treatment with good tolerance. The last course ended in December 2013. The patient did not present herself for the next course of chemotherapy. According to information obtained from the patient’s family, she died several days after she had left the hospital.

DISCUSSION

Phyllodes tumors of the breast are rare tumors that exhibit a wide range of clinical behaviors. An appropriate method of treatment, as well as their prognosis, remains under dispute. In the majority of cases, the course of the disease is mild and surgical treatment results in long-term survival. However, in other cases, the tumors demonstrate a tendency toward recurrence in the form of distant metastasis and/or local recurrence.

The statistical data presented in the “Introduction” section as well as the data from the Polish National Cancer Registry
both confirms that the disease is rare and that in most cases, the tumor is benign. Histologically, phyllodes tumors are described as mixed tumors that are composed of a benign epithelial component and a connective tissue stroma, which is a main feature of this tumor and the main indicator of malignancy. The WHO classification into benign, borderline, and malignant tumors is based on a microscopic evaluation of the degree of stromal cellularity and expansion, cellular atypia, and mitotic activity. The appearance of the tumor’s margin is also taken into account—it is believed that a sharp and clear demarcation from the surrounding tissue is a good prognostic factor.\textsuperscript{2,5,6,7} The malignant form is characterized by high mitotic activity, stromal hypercellularity, and high cellular atypia. In malignant tumors, necrotic areas, cellular pleomorphism, and high Ki-67 expression occur more often than in benign tumors. The histological features mentioned earlier are used to determine the degree of malignancy of phyllodes tumors; however, definitive cutoff criteria, allowing the physician to foresee the course of the disease, have not been precisely defined. Many authors stress that not a single unique microscopic feature, but a whole complex of such features, may have a prognostic value.\textsuperscript{2,6} Histologically, the breast tumor in this case report was characterized by high mitotic activity, high cellular atypia, pleomorphism, and necrosis.

A wide surgical resection with a 1 to 2 cm margin is the treatment of choice for phyllodes tumors of the breast. If it is impossible to obtain an appropriate surgical margin, it is necessary to perform a simple mastectomy as in this case.\textsuperscript{5,6} It has been observed that when the surgery is not radical, the risk of local recurrence and the possibility of distant metastasis is significantly increased.\textsuperscript{7} Thus far, there is no consensus on the role of postoperative chemotherapy and radiotherapy. Currently, there is no conclusive evidence indicating that they improve the efficiency of the treatment.\textsuperscript{6,8} It remains in dispute whether and when a postoperative chemotherapy is necessary to perform a simple mastectomy as in this case.\textsuperscript{5,6}

A study by Haberer et al.\textsuperscript{9} demonstrated that adjuvant chemotherapy offers minimal benefit, as it lowers the rate of patients with distant metastases. The role of adjuvant radiotherapy has not been proven,\textsuperscript{5} although publications attesting to its positive value in the prophylaxis of local recurrence. It refers to patients with the borderline and malignant forms of the tumor and with a high tumor mass and a lack of radical surgical margins. One of the latest studies that confirm that theory was carried out and published by Barth et al.\textsuperscript{10} in 2009. In this connection, the patient left in observation.

Our patient was 41 years old and she did not suffer from any other disease. There was only one case of breast cancer in distant relatives (no more data) in the patient’s family history. Therefore, in this case, genetic predisposition is unlikely. There was no data that the younger age was a risk factor for early appearance of metastases.\textsuperscript{2} Basically, literature does not report any correlation between the patient’s age and the micropscopic appearance of phyllodes tumor. A few authors suspect that the malignant forms appear more frequently in women over the age of 30. The majority of authors stress that none of analyzed factors (age, tumor location in the breast, and tumor size) is independent prognostic factor in the group of women with phyllodes tumor.\textsuperscript{3,6,11} The microscopic appearance of phyllodes tumor is the only generally accepted independent prognostic factor.\textsuperscript{3,6,11}

Distant metastases occur at different times after the primary therapy. Available publications present cases of both very early metastases occurrence (after approximately 1 month from the surgical treatment), as well as cases wherein metastases occurred over a dozen years after the treatment.\textsuperscript{3,6} The average time till generalization of the disease was from 15 to 26 months.\textsuperscript{2,6} Based on the available data, it can be estimated that distant metastases occur in up to 5% to 20% of patients with phyllodes tumor of the breast.\textsuperscript{2,5} Large discrepancy in data on the number of patients with metastatic disease stems from the imprecise determination by the authors of microscopic forms and diverse clinical composition of the patient group. Such metastases occur significantly more often in patients with the malignant form of the tumor, although there are reports on their occurrence in patients with benign tumors, which confirms that it is hard to predict the clinical course of a phyllodes tumor.\textsuperscript{6}

Metastatic lesions are most commonly localized in the lungs (66%–84.5%) and bones (28%–39%), more seldom in the liver and brain.\textsuperscript{3,5,6} They can also occur in the nasal cavity, oral cavity, larynx, salivary glands, thyroid glands, heart, pleura, adrenal glands, kidneys, spleen, pancreas, stomach, small intestine, large intestine, ovary, vulva, and skin.\textsuperscript{2,12–14} Distant metastases can appear without coexisting local recurrence,\textsuperscript{3} as it was in the case of our patient.

Having analyzed the available data, we have not discovered a description of a case of phyllodes tumor metastasis to the kidney in a patient who was alive at the time the generalized disease was diagnosed, as it was in the case of our patient. There is only 1 report available from 1980 with metastases of phyllodes tumor in the kidney, which were found during the autopsy on a 33-year-old female patient. In her case, metastases were also found in the lungs, liver, intestine, pleura, and the bones of the pelvis and spinal column. Histologically, they were exclusively composed of the mesenchymal component.\textsuperscript{14} In our case, the patient was initially suspected of having a primary tumor of the kidney with generalized metastasis. It was the comparison of histopathological slides from the kidney and the breast that showed it was a metastasis of the phyllodes tumor.

In patients with a spread of the phyllodes tumor, systemic treatment is the therapy of choice. A multiagent chemotherapy regimen based on doxorubicin is most commonly utilized.\textsuperscript{6} It exhibits a slightly higher efficiency, when compared to a monotherapy with ifosfamide or cyclophosphamide.\textsuperscript{15}

The occurrence of metastasis is an unfavorable prognostic factor, as the efficiency of the treatment of such cases is low and the average time from generalization of the disease to death ranges, in available literature data, approximately from 5 to 24 months.\textsuperscript{2,10} Although cases of a positive response to the treatment were reported, in the majority those remissions were for the short term. Precise evaluation of the chemotherapy efficacy is difficult, because the number of presented cases is low.

Over the last years, there are more and more publications that describe both various clinical pictures of phyllodes tumors and new therapeutic options available in their treatment, namely, adjuvant chemotherapy and radiotherapy. The role of the microscopic analysis of phyllodes tumors is to be stressed as it often allows for the identification of patients at high risk for local relapse and distant metastasis.\textsuperscript{6,7} Identification of that group of patients and the introduction of uniform rules for the management of such patients would make planning an efficacious treatment possible.

The presented clinical course of a phyllodes tumor in the patient with metastasis that occurred 1 year after a surgical treatment demonstrates not only a unique localization of metastases of the tumor (in the kidneys), but also the aggressive course of the disease. Despite the treatment introduced, a rapid progression of the disease resulted in the death of the patient 18 months after the diagnosis had been established and 6 months after the spread of the neoplastic process had been recognized.
REFERENCES

1. Tavassoli FA, Devilee P. Pathology and Genetics of Tumours of the Breast and Female Genital Organs: World Health Organization Classification of Tumours Lyon: IARC Press; 2003:99–103.

2. Mitus JW, Reinfuss M, Skotnicki P, et al. Population, clinical and microscopic picture, treatment outcomes and prognostic factors in patients with tumor phyllodes of the breast. Oncol Radiother Med Proj. 2013;1:45–50.

3. Reinfuss M, Mitu J, Duda K, et al. The treatment and prognosis of patients with phyllodes tumor of the breast: an analysis of 170 cases. Cancer. 1996;77:910–916.

4. Khajotia R, Poovaneswaran S, Pavadai T, et al. Unusually large breast tumour in a middle-aged woman. Can Fam Physician. 2014;60:142–146.

5. Khoravi-Shahi P. Management of non metastatic phyllodes tumors of the breast: review of the literature. Surg Oncol. 2011;20:143–148.

6. Telli ML, Horst KC, Guardino AE, et al. Phyllodes tumors of the breast: natural history, diagnosis, and treatment. J Natl Compr Canc Netw. 2007;5:324–330.

7. Tan PH, Thike AA, Tan WJ, et al. Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. J Clin Pathol. 2012;65:69–76.

8. Morales-Vásquez F, Gonzalez-Angulo AM, Broglio K, et al. Adjuvant chemotherapy with doxorubicin and dacarbazine has no effect in recurrence-free survival of malignant phyllodes tumors of the breast. Breast J. 2007;13:551–556.

9. Haberer S, Laé M, Seegers V, et al. Management of malignant phyllodes tumors of the breast: the experience of the Institut Curie. Cancer Radiother. 2009;13:305–312.

10. Barth RJ Jr, Wells WA, Mitchell SE, et al. A prospective, multi-institutional study of adjuvant radiotherapy after resection of malignant phyllodes tumors. Ann Surg Oncol. 2009;16:2288–2294.

11. Chen WH, Cheng SP, Tzen CY, et al. Surgical treatment of phyllodes tumors of the breast: retrospective review of 172 cases. J Surg Oncol. 2005;91:185–194.

12. Collin Y, Chagnon F, Mongeau CJ, et al. Adrenal metastasis of a phyllodes tumor of the breast: case report and review of the literature. Int J Surg Case Rep. 2013;4:687–689.

13. Suárez Roa Mde L, Ruiz Godoy Rivera LM, Vela Chávez T, et al. Breast malignant phyllodes tumour metastasising to soft tissues of oral cavity. Clin Transl Oncol. 2007;9:258–261.

14. Hanada M, Maeda T, Takeuchi N. Cystosarcoma phyllodes of the breast with features of malignant fibrous histiocytoma. Acta Pathol Jpn. 1980;30:91–99.

15. Hawkins RE, Schofield JB, Wiltshaw E, et al. Ifosfamide is an active drug for chemotherapy of metastatic cystosarcoma phyllodes. Cancer. 1992;69:2271–2275.