



DOI: 10.19187/abc.20207144-48

Progressive Metastatic Breast Phyllodes Tumor Turns into Spindle Cell Sarcoma: Report of Two Cases and Review of the Literature

 Nahid Nafissi^a, Seyed-Mohamad-Sadegh Mirahmadi^b, Majid Samsami^c, Nafiseh Ansarinejad^{*d}
^a Breast department, Rasoul-Akram Hospital, Iran university of medical sciences, Tehran, Iran

^b School of Medicine, Iran University of Medical Sciences, Tehran, Iran

^c Department of Surgery, Shahid Beheshti university of medical sciences, Tehran, Iran

^d Department of Hematology and Oncology, Iran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Received:
08 November 2019
Revised:
18 December 2019
Accepted:
10 January 2020

Key words:
Phyllodes tumor,
breast sarcoma,
early recurrence

ABSTRACT

Background: Breast fibroepithelial lesions encompass a wide variety of tumors from benign fibroadenomas to malignant phyllodes tumors (PTs). Local recurrence was reported in 20% of all subgroups and 20-25% risk of distant metastasis though superaggressive tumors are rare. Two young patients with nonresponsive, frequent recurrences of phyllodes tumors turned into the aggressive metastatic sarcoma are presented.

Case Presentation: *Case 1:* A 34-year-old married woman referred with the chief complaint of a mass and pain in her right breast. There was a 3cm well defined mass in right breast. An intermediate grade benign phyllodes tumor was confirmed in biopsy. Patient underwent surgical wide excision, radiotherapy. Three weeks later the mass recurred in her right breast with severe pain and nonproductive cough without hemoptysis. A single lung metastasis is conformed in the CT scan. Total mastectomy and thoracoscopic metastasectomy was performed and spindle cell sarcomas in both specimens is confirmed. Chemotherapy was done. Two weeks after chemotherapy she presented with multiple bilateral lung metastasises and thoracic wall involvement. No regression in metastasis was seen receiving the second line chemotherapeutic agents. *Case 2:* A 17-year-old young girl was referred to the breast clinic with a 2 cm firm mobile mass in left breast. The histopathology of the mass was benign phyllodes tumor. (1.5 cm margins) The tumor recurred 3 months later treated. During radiotherapy, the patient referred to the emergency department with the complaint of dyspnea and sever pleural effusion. The cytology reported malignant cells. CT-guided biopsy showed a high grade sarcoma. During chemotherapy, large ulcer in the site of the breast was appeared and mastectomy with Latissimus dorsi flap was performed and angiosarcoma was confirmed. Despite the second and third line chemotherapy the disease was progressed and multiple lung metastasis were confirmed in chest CT scan.

Conclusion: It seems that some subtypes of breast sarcomas could have an extremely an aggressive behavior which threatens the life of the patients in a short period of time. Further studies is suggested to discriminate the aggressive subtypes at the first step.

Introduction

Breast fibro-epithelial lesions encompass a wide variety of tumors from benign fibroadenomas (FAs)

to malignant phyllodes tumors (PTs).¹ As some tumors show similar characteristics of PTs and fibroadenoma, there is not a distinct boundary between FA and PT and it is still a considerable challenge to differentiate PTs from FAs due to morphology integration.²

In 1883, Johannes Müller introduced cystosarcoma phyllodes in mammary tissue with leaf shape growth.³ As the phyllodes tumors (PTs) can have different

*** Address for correspondence:**

Nafiseh Ansarinejad, MD
 Address: department of hematology-oncology, Rassoul Akram Hospital, Sattarkhan-Niyesh Avenue, Tehran, Iran
 Tel: +98 21 64352390
 Fax: +98 21 64352486
 Email: nafisse@yahoo.com



natural histories, World Health Organization (WHO) suggested the classification of PTs into three forms, including benign, premalignant (borderline), and malignant lesions.⁴ Furthermore, there is no correlation between tumor categories with its clinical manifestation. It is also hard to distinguish between subgroups with radiological and histopathological findings.⁵

PTs are rare biphasic fibro-epithelial tumors that account for 0.3 to 1% of all primary breast neoplasms.⁶ The PTs invasion is unpredictable. Local recurrence was reported in 20% of all subgroups of breast PTs. Although distant metastasis commonly occurs in the malignant and borderline subgroups (20-25%), it can be rarely found in benign breast PTs. The common sites of distant metastasis are lung and bone as a consequence of hematogenous spreading of the tumor cells.^{7,8} The breast PTs challenge women mostly in the age range of 35 to 55.⁹

Regarding the low efficacy of adjuvant treatment, the primary line of treatment is the aggressive removal of the tumor and its adjacent healthy tissue during surgical intervention. Although chemotherapy and radiotherapy are not approved as main adjuvant treatments, radiotherapy is shown to have limited benefits in selected patients.⁸

In this article, we present two uncommon cases of young females with frequent early recurrences of phyllodes tumor along with the phyllodes tumors turned into the aggressive metastatic sarcoma.

Case Presentation

Case No 1:

A 34-year-old married woman was referred to the surgical oncology outpatient clinic of Rasoul-e-Akram hospital with the chief complaint of a mass in her right breast. The patient had two children, and had her first childbirth at the age of 20. She had a family history of gastric cancer in her father and her paternal aunt. The patient had a personal history of multiple sclerosis (MS) and minor depression and used Gabapentine, Assentra, Doxepin, and Azaram to control the neurologic and psychological symptoms. Also, she had a history of breast pain and breast cysts in both breasts approved by ultrasonography and an examination by her family physician.

On the recent physical examination, there was a mass in the lower outer quadrant of her right breast 5 cm far from the border of the nipple-areola complex, measured about 3 cm. The well-defined mass was firm in palpation and had a lobulated margin. Ultrasonography showed a 30- mm benign mass with a regular border in the lower outer quadrant of the right breast, mostly suggesting fibroadenoma. A core needle biopsy was performed, and the pathologist reported it as an intermediate grade benign phyllodes tumor. Preoperative investigations, including Chest X-ray, were performed. All the lab tests and radiology findings were normal except for

the breast mass.

According to the histopathology report, she underwent surgical excision of the mass with a one-cm margin from each side of the tumor. The histopathological evaluation of the surgical specimen revealed a high-grade malignant phyllodes tumor with a focally positive margin. The records of the patient were presented in the Multidisciplinary Tumor Board (MDT). Since the patients strongly preferred not to do a mastectomy, the recommendation of the panel of experts was radiation therapy and close follow-ups. The patient received 50 Gy to the whole breast, followed by a boost dose of 16 Gy to lumpectomy bed totally in 33 fractions. There was no significant complication for the irradiation rather than redness and skin burning.

Three weeks after the last session of radiotherapy, the patient referred back to the clinic because of palpation of mass in her right breast near the location of the primary excised tumor. The mass was palpable on the physical examination. Also, she suffered from severe pain with radiation to the axilla and nonproductive cough without hemoptysis. Magnetic Resonance Imaging (MRI) of the breasts was performed and the recurrence of the tumor was suggested. Also, in the Computed Tomography (CT) scan of the chest, a single metastasis of the lung was confirmed. According to the second discussion in MDT, the brain MRI was performed though it did not show any abnormality compared to the previous multiple brain MRIs for the follow-up of multiple sclerosis. The patient underwent a total mastectomy and thoracoscopic metastasectomy by means of lung-wedge resection. Histopathological evaluation of the surgical specimen revealed spindle cell sarcomas in both specimens. The patient referred to the medical oncology department for chemotherapy. She received Ifosfamide and Adriamycin for four courses as the first line of chemotherapy agents. Two weeks after the concluding session of chemotherapy, the patient returned to the emergency department of the hospital with complaints of chest pain and dyspnea. Computed tomography (CT) scan showed multiple bilateral lung metastases and thoracic wall involvement. By the progression of the disease, the chemotherapy regimen was changed to Gemcitabine and Docetaxel based on the opinion of MDT. Unfortunately, there was no regression in metastasis by receiving three sessions of the second line chemotherapeutic agents. Finally, the patient referred to the supportive care department and received supportive care. The patient died 12 months after the diagnosis of her disease.

Case No 2:

A 17-year-old young girl was referred to the breast clinic of Rasoul-e-Akram hospital with the chief complaint of a mass palpation in her left breast. In the past medical history of the patient, there was neither any risk factor for the breast cancer nor any



other underlying disease. The mass was well defined, 2 cm in diameter, firm and mobile. In the ultrasonography of the breasts, there was a benign-appearing well-defined 25-mm mass in the lower outer quadrant of her left breast compatible with fibroadenoma. Although in our opinion taking a core needle biopsy was the first step, the mass was excised based on the request of the patient and her mother.

Surprisingly, the histopathology of the mass was reported as benign phyllodes tumor. Since in the first operation, we performed tumor enucleation, there was not a safe margin excised along with the mass, and the pathologist reported the margins as involved. The second surgery for the resection of the margins was performed, and 1-1.5 cm of breast tissue around the lumpectomy cavity was excised. The pathology report confirmed the breast tissue with no remnant of the tumor. The patient was considered for a short time follow-up.

In her first follow-up visit after three months, the tumor recurred according to the physical examination and ultrasonography. We presented the history of the patient in breast cancer MDT of the hospital and they recommended Nipple-sparing mastectomy and immediate direct to implant breast reconstruction. The patient did not accept the aggressive surgery and asked for the second option, which was a quadrantectomy and irradiation. In the third surgery, we performed a quadrantectomy and an oncoplastic repair of the breast. Soon after the surgery, the patient referred to the radiation oncology department to receive radiation. Radiation therapy started one month after the surgery, and after the 15th session of the radiotherapy, the patient referred to the emergency department with the complaint of dyspnea and cough. In the physical examination, the pulmonary sounds decreased in the lower part of her left lung. In Chest X-ray, there was a considerable amount of pleural effusion and a consolidated mass on the left side.



Figure 1. Pleural effusion and mass lesion in left hemithorax

A thoracostomy tube was placed in the left hemithorax, and 1500 cc serous fluid was evacuated gradually. A sample of the pleural effusion liquid was sent to the pathology department for the cytologic evaluation. The cytology report confirmed the presence of malignant cells, the type of which was hard to differentiate. Metastatic work-up was performed at the same admission.

Computed tomography (CT) scan of the thorax and abdomen revealed the same mass in the left pleural cavity, and the whole-body Tc-99 scan study showed focal hyperactivity in the T10 vertebrae. A CT-guided biopsy of the sub-pleural lesion was carried out, and a high-grade sarcoma was confirmed in the specimen.(Figure 1)

Soon after, chemotherapy was started for the



Figure 2. Recurrence of tumor during radiotherapy



patient with the regimen of ifosfamide and Adryamicime. Following two sessions of chemotherapy, the patient returned with the complaint of a large mass in her left breast. In clinical examination, there was a 7*4*6 cm large mass, which was impending to become a large ulcer in her breast.(Figure 2) There was significant lymphadenopathy in her left axillary region. The patient underwent radical mastectomy with the resection of all skin and pectoralis muscles. The lymph nodes in the first level of the axilla were excised as well. Latissimus dorsi muscle flap was used for the coverage of the surgery defect. (Figure 3)

The pathology reported the tumor as a high-grade angiosarcoma with large reactive lymph nodes. The patient referred to the medical oncology department to continue chemotherapy.



Figure 3. Mastectomy and coverage of the defect by Latissimus dorsi flap

Discussion

Breast sarcoma is typically a rare phenomenon that may present similar symptoms to other primary breast malignancies. Primary breast sarcoma is divided into three subgroups of primary breast sarcoma, aroused sarcoma from the post-irradiated breast (secondary to the irradiation), and malignant phyllodes tumors (cystosarcoma phyllodes). Malignant phyllodes tumor is a biphasic malignant stromal neoplasm consisting of epithelial and spindle cell elements, which demonstrates a wide variety of morphologies.^{10, 11} Phyllodes tumor of the breast is reported in the younger age compared to the typical breast carcinoma in the case of our patients.⁹

A systematic review by Lu et al. in 2019 illustrates that the age and the size of the phyllodes tumor are not related to the rate of local recurrence though the breast-conserving surgery and margin involvement are significantly associated with a higher rate of local recurrence. The local recurrence rates from 8 percent in benign phyllodes tumor, 13 percent in borderline tumors, and 18 percent in the malignant sarcomas. Most tumors relapses occur within two years after the surgery, and it is not common for a tumor to recur in a limited period of time (less than one month) as observed in our patients.¹² Tan et al. evaluated 37 patients with breast

The oncologist started Gemcitabine and Docetaxel as the second line of chemotherapy. The response to these agents was satisfactory and all the pleural and pulmonary lesions disappeared after the third session.

Two months after the completion of the chemotherapy, the patient referred with the complaint of a mass in the left axilla. A biopsy was obtained from the new mass, which was reported as spindle sarcoma with prominent vascular differentiation. A few weeks later, multiple round masses on the thoracic wall and latissimus dorsi flap appeared. (Figure 4) Also, there were multiple lung metastases in the CT scan of the thorax. The patient was referred to the palliative care department of the hospital and died four months afterwards.



Figure 4. Local recurrence of the tumore in less than 4 weeks

phyllodes tumors with a mean age of 39.6±7.6 years. Of them, 22, 9, 6 patients had benign, borderline and malignant PTs, respectively. The median duration of local recurrence was 20 months. In this series, only one patient with malignant PT was reported with lung metastasis.¹³

Distant metastasis in breast sarcoma is an outstanding finding which predicts the overall survival.⁷ The time lapse between the surgery to distant metastasis in breast PTs is reported from 2 to 57 months (average 21 months). Although an early metastasis is not common in breast PTs, our patient showed the signs and symptoms of lung metastasis in a month after the first surgery. The common sites of metastasis are lung (75.7%), bone (18.9%), brain (10.8%), and liver (5.4%). The mean survival of breast PTs patients with distant metastasis was reported as long as 7 months in a study by Mitus and colleagues. The longest survival is seen in patients with bone metastasis, and the shortest survival can be seen after brain metastasis.⁷ Despite the short survival, our patient did not have any metastatic lesion in her brain.

Regardless of the tumor subgroup, the first-line treatment of PTs is a surgery including lumpectomy, wide local excision, and total mastectomy. Recent reports confirmed the safety of a more conservative



surgical approach in the treatment of phyllodes tumors. Nowadays, in most protocols, breast conservation with a sufficient margin is an acceptable treatment. MacDonald et al. reported that the size of the tumor could be influenced by surgeon's decisions regarding the limitation of recurrence and cosmetic outcome.¹⁴ They stated that thirty-six percent of the patients with a tumor of larger than 5 cm could undergo breast-conserving surgery. Nevertheless, 75% of patients with tumors of smaller than 5 cm can be treated safely to avoid total mastectomy.¹⁴ All in all, it is more of consensus that mastectomy versus breast-conserving surgery is significantly associated with a lower rate of local recurrence and distant metastasis, particularly in malignant PTs.^{7, 12, 13} Also, adequate surgical margin reduced the rate of local recurrence, particularly in malignant PTs though it did not have any impact on distant metastasis.^{9, 12, 13}

In the reported patients, the early local recurrence can be justified by insufficient surgical treatments in the first operation but the distant metastasis was not related to the surgical treatment. It seems that some subtypes of breast sarcomas could have an extremely aggressive behavior which threatens the life of the patients in a short period of time. Further studies is suggested to discriminate the aggressive subtypes at the first step. The outcome of the patients may differ by selecting more aggressive local treatments and a different systemic therapies.

Conflict of Interests

None

Ethical Consideration

The written consent was signed by the patients when they were alive to report their medical history and to anonymously publish the images in medical literature for educational and research purposes.

References

- Pareja F, Geyer FC, Kumar R, Selenica P, Piscuoglio S, *et al.* Phyllodes tumors with and without fibroadenoma-like areas display distinct genomic features and may evolve through distinct pathways. *NPJ Breast Cancer.* 2017; 3:40.
- Lee AH, Hodi Z, Ellis IO, Elston CW. Histological features useful in the distinction of phyllodes tumour and fibroadenoma on needle core biopsy of the breast. *Histopathology.* 2007;51(3):336-44.
- Telli ML, Horst KC, Guardino AE, Dirbas FM, Carlson RW. Phyllodes tumors of the breast: natural history, diagnosis, and treatment. *J Natl Compr Canc Netw.* 2007;5(3):324-30.
- Zhang Y, Kleer CG. Phyllodes Tumor of the Breast: Histopathologic Features, Differential Diagnosis, and Molecular/Genetic Updates. *Arch Pathol Lab Med.* 2016;140(7):665-71.
- McKenna AM, Pintilie M, Youngson B, Done SJ. Quantification of the morphologic features of fibroepithelial tumors of the breast. *Arch Pathol Lab Med.* 2007;131(10):1568-73.
- Abdelkrim SB, Trabelsi A, Bouzrara M, Boudagga MZ, Memmi A, *et al.* Phyllodes Tumors of the Breast: A Review of 26 Cases. *World J Oncol.* 2010;1(3):129-34.
- Mitus JW, Blecharz P, Walasek T, Reinfuss M, Jakubowicz J, *et al.* Treatment of Patients with Distant Metastases from Phyllodes Tumor of the Breast. *World J Surg.* 2016;40(2):323-8.
- Guerrero MA, Ballard BR, Grau AM. Malignant phyllodes tumor of the breast: review of the literature and case report of stromal overgrowth. *Surg Oncol.* 2003;12(1):27-37.
- Amir RA, Rabah RS, Sheikh SS. Malignant Phyllodes Tumor of the Breast with Metastasis to the Pancreas: A Case Report and Review of Literature. *Case Rep Oncol Med.* 2018;2018: 6491675.
- Confavreux C, Lurkin A, Mitton N, Blondet R, Saba C, *et al.* Sarcomas and malignant phyllodes tumours of the breast--a retrospective study. *Eur J Cancer.* 2006;42(16):2715-21.
- Wang F, Jia Y, Tong Z. Comparison of the clinical and prognostic features of primary breast sarcomas and malignant phyllodes tumor. *Jpn J Clin Oncol.* 2015;45(2):146-52.
- Lu Y, Chen Y, Zhu L, Cartwright P, Song E, *et al.* Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. *Ann Surg Oncol.* 2019;26(5):1263-75.
- Tan EY, Tan PH, Yong WS, Wong HB, Ho GH, *et al.* Recurrent phyllodes tumours of the breast: pathological features and clinical implications. *ANZ J Surg.* 2006;76(6):476-80.
- Macdonald OK, Lee CM, Tward JD, Chappel CD, Gaffney DK. Malignant phyllodes tumor of the female breast: association of primary therapy with cause-specific survival from the Surveillance, Epidemiology, and End Results (SEER) program. *Cancer.* 2006;107(9):2127-33.