Case Report

rare tumors

Rare Tumors
Volume 12: 1–5

DOI: 10.1177/2036361320972866
journals.sagepub.com/home/rtu
SAGE

Pancreatic metastases and first reported gallbladder metastasis from phyllodes tumor of the breast

Salsabil Nasri[1], Fehmi Hamila[1], Rym Bourigua[2], Sarra Mestiri[3] and Mohamed Amine Elghali[1]

Abstract

Distant metastases from breast phyllodes tumor (PT) are very rare. They usually occur in lung and bones. We report a case of a 51-year-old woman who was hospitalized in the digestive surgical department for atypical epigastric pain. Her medical history started 2 years ago when she underwent a curative left mastectomy for a malignant PT of the breast. Radical surgery was indicated to her resectable pancreatic tumor diagnosed on computed tomography. Histological exam confirmed that it was pancreatic metastases of her breast PT. Adjuvant chemotherapy was indicated. Three months after the surgery, the patient developed gallbladder and brain metastases. She died 5 weeks later. With this case, we enrich the literature with another example of pancreatic metastasis from PT and we report, for the first time, gallbladder metastasis. The very high aggressiveness of this tumor suggests that markers of tumor malignancy need to be sought after by subsequent studies.

Keywords

Breast phyllodes tumor, pancreatic metastasis, gallbladder metastasis, case report

Date received: 3 September 2020; accepted: 21 October 2020

Highlights

1. Distant metastases from breast phyllodes tumor (PT) are very rare. They usually occur in lung and bones.
2. Tumor size, stromal atypia, mitotic activity, local recurrence, surgical excision margin and the positivity of CD117 have been described as predictors for developing distant metastasis.
3. Metastases to the pancreas from phyllodes tumor are extremely rare. Only seven cases are reported in the literature.
4. With this case, we enrich the literature with another example of pancreatic metastasis of breast PT and we report, for the first time, gallbladder metastasis.
5. This case highlights that markers of tumor malignancy need to be sought after by subsequent studies.

Introduction

Phyllodes tumors of the breast are rare and usually benign. They are graded as benign, borderline or malignant based on the World Health Organisation (WHO) classification, according to a constellation of five histologic parameters. Metastases are very rare: The overall

[1]Department of Visceral Surgery, Farhat Hached University Hospital, Sousse, Tunisia
[2]Department of Medical Oncology, Farhat Hached University Hospital, Sousse, Tunisia
[3]Department of Pathology, Farhat Hached University Hospital, Sousse, Tunisia

Corresponding author:
Salsabil Nasri, Department of Visceral Surgery, Farhat Hached University Hospital, Ibn Eljazzar Street, Sousse 4000, Tunisia.
Email: salsabil_nasri@yahoo.fr

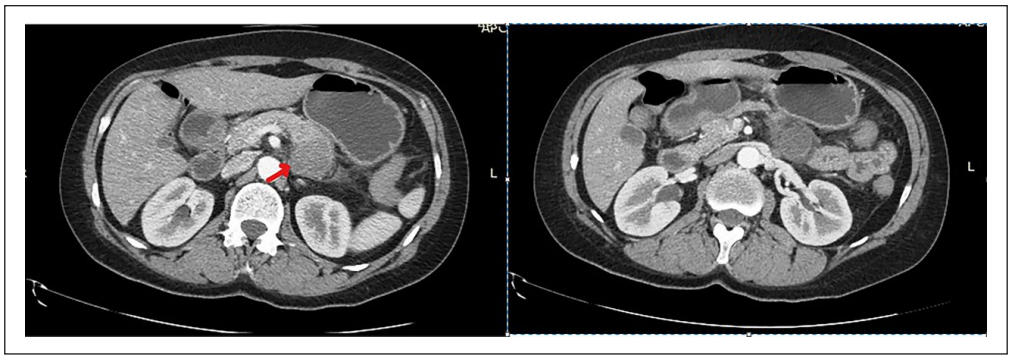

Figure 1. CT scan: pancreatic metastasis of phyllodes tumor.

rates of distant metastases in PTs range from 1.7% to 27.1%, with an average of 5.6%, and vary according to tumor grade.[1] They usually occur in lung and bones. Predictive factors of malignancy of phyllodes tumor of the breast are size, mitotic index, stromal atypia, overgrowth, surgical margins,[1] and expression of CD117.[2]

We report a case of very aggressive phyllodes tumor of the breast that metastasized in lung, brain and in unusual sites: pancreas and gallbladder.

While most invasive primary breast cancers are epithelial derived adenocarcinomas, rare neoplasms such as phyllodes tumor may arise from mesenchymal tissue. Phyllodes tumors represent 0.3% to 1.0% of the entire mammary tumors.[3] Cystosarcoma phyllodes was first described in 1838 and was originally considered to be a benign tumor until 1931 when metastasis from a cystosarcoma phyllodes was reported for the first time.[3] In fact, fibro-epithelial breast neoplasms exhibit a spectrum of clinical behavior ranging from benign tumors, which may be indistinguishable from fibroadenomas and may be healed by local surgery, to aggressive malignant tumors which have a propensity for rapid growth metastatic spread.[4] Pancreatic metastases from breast phyllodes tumors have rarely been reported in the literature, typical sites of the metastases being lungs and bones.[4] This case enriches the literature with another example of pancreatic metastasis of phyllodes tumor. We also report, for the first time in the literature, gallbladder metastasis from phyllodes tumor.

Case observation

A nulliparous woman aged 51 years old was hospitalized in our general surgical department for atypical epigastric pain associated with some vomiting episodes. Her medical history started 3 years ago when a mammogram was performed and the found lesion was considered a fibroadenoma. One year later, a second mammogram showed an increase in tumor size measuring $4 \times 5 \times 6$ cm. She had a left mastectomy. Pathological and immunohistochemical examination of the specimen showed that it was phyllodes tumor with highly cellular and diffuse proliferation of malignant mesenchymal round and spindle cells, displaying marked nuclear atypia and mitotic figures, focally surrounding a residual acinar stricture. Cells expressed Vimentin, but not CKs or neuroendocrine markers. CD117, CD99, and TTF1 were negative. Surgical margins were satisfactory. The tumor was considered malignant. A full-body CT scan was performed which didn't show the presence of secondary lesions.

Two months after surgery, she underwent adjuvant radiotherapy of the chest wall on the site of mastectomy. She received a 52.2 Gy spread over 2 months at a rate of 1.8 Gy per fraction and 5 fractions per week.

The patient was followed at the outpatient clinic with a clinical examination every 3 months and a full-body CT scan at 6 months, which suddenly showed 5.5 cm metastatic pulmonary nodule. She had left upper pulmonary lobectomy with ganglionic lymphadenectomy. The metastatic nature of this nodule was confirmed with its histopathological examination. Surgical margins were satisfactory.

The patient was followed up with a clinical examination every 3 months and a full-body CT scan every 6 months. Two years after mastectomy, about 18 months after pulmonary metastasis surgery, she complained of abdominal pain mimicking pancreatitis pain leading to her hospitalization in the surgical department.

Abdominal CT scan showed solid exophytic pancreatic masses of 56 and 33 mm longer axe each one, with no signs of vascular, lymphatic or neighboring organs spread (Figure 1).

The diagnostic dilemma was whether this was a case of primary pancreatic cancer or a recurrent phyllodes tumor presenting as pancreatic metastasis, which is very rare. In this context of two pancreatic metastatic localizations (corporeal and caudal), we have concluded to pancreatic metastases.

Radical surgery was indicated to that resectable pancreatic tumor in a good general condition patient. Therefore, she had laparoscopic splenopancreatectomy and she needed cuneiform resection of the stomach because it was adhering to the tumor.

Histological examination confirmed that it was pancreatic tumor metastases of her breast phyllodes tumor. Macroscopically, we found two metastatic pancreatic oval

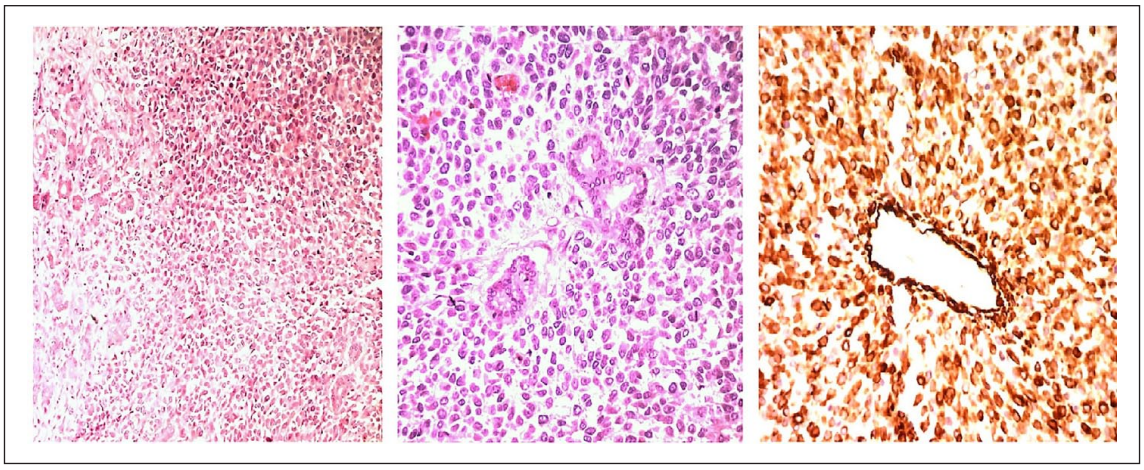

Figure 2. Immunohistochemical examination of the specimen.
At right: IHC × 100: pancreatic parenchyma, infiltrated by a highly cellular, malignant neoplastic proliferation.
In the middle: IHC × 200: neoplastic proliferation displays a biphasic feature, with a predominant mesenchymal component and an epithelial component – displaying a glandular differentiation. Nuclear atypia are moderate and mitoses are numerous.
At left: IHC × 400: diffuse and intense expression of Vimentin by neoplastic cells.

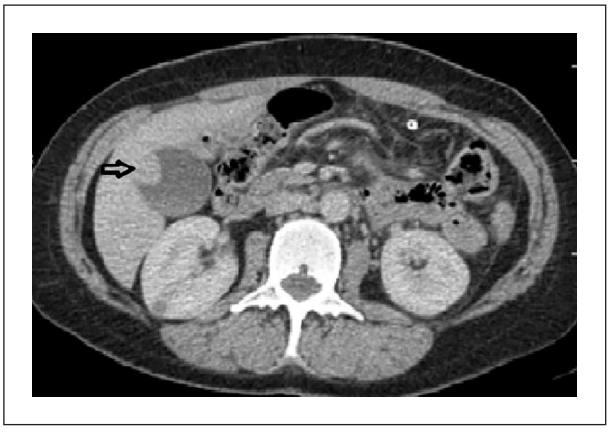

Figure 3. CT scan: metastasis in gallbladder.

whitish masses both of 7 cm on their large diameter, well limited, rearranged by necrosis and hemorrhage, and separated by normal pancreatic tissue. Lesions were rich in blood vessels. Cells expressed Vimentin, but not CKs (CK7−, CK20−, CK19−). There was also no expression of neuroendocrine markers, of CD117, of CD99 and of TTF1. Surgical pancreatic margins were satisfactory. The spleen and the resected gastric part were not infiltrated by tumor (Figure 2).

Chemotherapy based on doxorubicin and cyclophosphamide was indicated. Three months after the last surgery, a new CT scan showed a bulging mass in the gallbladder that 3 months ago did not exist on previous computed tomography imaging (Figure 3). We concluded that this was a new metastasis of her aggressive phyllodes tumor.

A whole body MRI has been conducted and has revealed two asymptomatic cerebral metastatic lesions. The patient died 5 weeks later.

Discussion

Phyllodes tumors of the breast are infrequently encountered fibroepithelial neoplasms, comprising 0.3% to 1.0% of all primary breast tumors in Western countries.[1] Most phyllodes tumors occur in women between the ages of 35 and 55 years old,[4] and according to Surveillance, Epidemiology, and End Results (SEER) data, the median age at diagnosis of women is 50 years.

Phyllodes tumors were further classified as benign, borderline, or malignant on the basis of features of the stromal cells. About 10% to 20% of those tumors are classified as malignant.[3] Traditionally, predictors of malignant behavior include tumor size, cytological atypia, mitotic rate, tumor necrosis, stromal atypia, overgrowth, surgical margins.[1,3,5] Malignant phyllodes tumors are diagnosed when there are marked stromal hypercellularity, atypia, increased mitoses of $\geqslant$10/10 HPFs, permeative tumor borders, and stromal overgrowth. The presence of a malignant heterologous component places the tumor into the malignant category regardless of other histological features.[6]

Most recently, expression of CD117 (KIT) was shown to be associated with unfavorable pathologic criteria and worse prognosis in patients with phyllodes tumor, although no mutation in the CD117 gene has been identified.[2]

Treatment of phyllodes tumor is remaining primarily surgical. Nonsurgical therapies are still controversial and uncertain. Neoadjuvant treatment was reported in one isolated case, with the patient demonstrating no response after three cycles of doxorubicin prior to surgical resection.[7] The role of adjuvant radiotherapy was demonstrated for high-risk phyllodes tumors.[8,9] The National Comprehensive Cancer Network (NCCN) suggested radiation therapy for local recurrence, but it did not prevent

distant metastasis and had no effect on disease-free survival or overall survival.

The real question was whether we should systematically indicate adjuvant chemotherapy for patients that gather all high-risk phyllodes tumor criteria or not. In a study of 101 patients with phyllodes tumor, of whom four received adjuvant chemotherapy, the authors suggested that adjuvant chemotherapy should be considered in patients with stromal over-growth.[10] But according to many other studies, there was no established role for adjuvant chemotherapy in phyllodes tumors.[6,11,12]

The overall metastatic rate of phyllodes tumor in general has been reported at $<5\%$.[12] Tumor size, stromal atypia, mitotic activity, local recurrence and surgical excision margin have been described as predictors for developing distant metastasis.[4,11] Malignant phyllodes tumor is not a particularly lethal neoplasm when resected, but average survival time of patients with phyllodes tumor metastasis was reported to be at 30 months.[12]

Metastases to the pancreas from phyllodes tumor are extremely rare. A comprehensive review of the literature identified only seven case reports.[13–19] Among the four resected cases of pancreatic metastasis,[15–18] two cases showed early relapse;[16,17] whereas one patient survived for a long time after resection.[14]

Gallbladder metastasis of phyllodes tumor has never been described before in the literature. In this case, it was a proof of that special tumor aggressiveness and it suggested its spread through biliary tract, because it happened after pancreatic metastasis.

However, initial histological findings were not suggesting that high grade of malignancy, when they specially revealed absence of CD117 expression, which is known to be associated with worse prognosis.[2]

Complete surgical removal of the involved pancreatic metastatic site is benefic, but when new metastases appear in a short time, systemic treatment should be considered early. Chemotherapy that includes ifosfamide was reported to be effective.[10] More pooling of data may be beneficial to identify specific findings that increase pre-test probability, prior to making a decision whether to treat systemically the metastatic mass or to proceed to surgery.

Conclusion

Malignant phyllodes tumor of the breast is an unpredictable and sometimes very aggressive neoplasm. Stromal overgrowth in malignant phyllodes tumor carries a severe prognosis. Adjuvant treatment for phyllodes tumor is currently limited to radiation therapy as chemotherapeutic intervention is consistently proven ineffective. Genomic-level research performed on resected phyllodes tumors has the potential to identify novel drug targets in the future. Current guidelines from the NCCN indicate that malignant phyllodes tumor should be treated as sarcomas rather than typical breast carcinomas.

Author contributions

S.N.: writing the paper, bibliography. F.H.: reviewing the paper. R.B.: bibliography and writing the paper. S.M.: reviewing the paper. M.A.E.: writing the paper, reviewing the paper.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Where ethical approval is not required for our article. In fact, it is just a report of an observation after obtaining the consent of the family of the defunt and it's not an experimental study.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent has been provided by family to publishing this case and all figures.

References

1. Koh VCY, Thike AA and Tan PH. Distant metastases in phyllodes tumours of the breast: an overview. *Appl Cancer Res* 2017; 37(1): 15.
2. Tan WJ, Thike AA, Tan SY, et al. CD117 expression in breast phyllodes tumors correlates with adverse pathologic parameters and reduced survival. *Mod Pathol* 2015; 28(3): 352–358.
3. Vajpeyi R. WHO classification of tumours: pathology and genetics of tumours of the breast and female genital organs. *J Clin Pathol* 2005; 58(6): 671–672.
4. Reinfuss M, Mituś 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(5): 910–916.
5. Park HJ, Ryu HS, Kim K, et al. Risk factors for recurrence of malignant phyllodes tumors of the breast. *In Vivo* 2019; 33(1): 263–269.
6. Tan BY, Acs G, Apple SK, et al. Phyllodes tumours of the breast: a consensus review. *Histopathology* 2016; 68(1): 5–21.
7. Korpanty G, Power DG, Murphy C, et al. Phyllodes tumor of the breast. *Med Oncol* 2011; 28(1): 62–64.
8. August DA and Kearney T. Cystosarcoma phyllodes: mastectomy, lumpectomy, or lumpectomy plus irradiation. *Surg Oncol* 2000; 9(2): 49–52.
9. Belkacémi Y, Bousquet G, Marsiglia H, et al. Phyllodes tumor of the breast. *Int J Radiat Oncol Biol Phys* 2008; 70(2): 492–500.
10. Chaney AW, Pollack A, McNeese MD, et al. Primary treatment of cystosarcoma phyllodes of the breast. *Cancer* 2000; 89(7): 1502–1511.
11. Hawkins RE, Schofield JB, Fisher C, et al. The clinical and histologic criteria that predict metastases from cystosarcoma phyllodes. *Cancer* 1992; 69(1): 141–147.
12. Guerrero MA, Ballard BR and 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.

13. Yukawa M, Watatani M, Isono S, et al. Pancreatic metastasis from phyllodes tumor presenting initially as acute retroperitoneal hemorrhage. *Int Canc Conf J* 2013; 2(4): 238–242.
14. Serikawa M, Sasaki T, Kobayashi K, et al. Malignant phyllodes tumor metastatic to the pancreas: a case report. *Nihon Shokakibyo Gakkai Zasshi* 2012; 109(5): 795–803.
15. Ang TL, Fock KM, Teo EK, et al. Diagnosis of a metastatic phyllodes tumor of the pancreas using EUS-FNA. *JOP* 2007; 8(1): 35–38.
16. Yu PC, Lin YC, Chen HM, et al. Malignant phyllodes tumor of the breast metastasizing to the pancreas: case report. *Chang Gung Med J* 2000; 23(8): 503–507.
17. NAKAHARA R. A case of metastasizing cystosarcoma phyllodes to the pancreas and lung. *Rinsho Geka* 1986; 41: 1709–1713.
18. Wolfson P, Rybak BJ and Kim U. Cystosarcoma phyllodes metastatic to the pancreas. *Am J Gastroenterol* 1978; 70(2): 184–187.
19. Amir RA, Rabah RS and 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.