Malignant Phyllodes Tumor With Metastases to the Femur the Lung and Bilateral Axillas: A Case Report and Review of Literature

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Case report

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Abstract

Background: Phyllodes tumor is rare accounting for <1% of all breast tumors. It is classified as benign, borderline, or malignant. The lymph node is involved rarely, and the most common metastasis path is through hematogenous channels mainly to the lung the pleura and the bone.

Case presentation: This case report presents a 34-year-old woman suffered from metastases to the femur the lung and bilateral axillas from a malignant phyllodes tumor in 9 years. The most recent recurrence was discovered on bilateral axillas. The patient accepted adjuvant chemotherapy. However, because no obvious benefit of chemotherapy was found, the patient received bilateral axillary lymph node dissection finally. Genetic testing after surgery showed tumor-specific mutations and mutations about the polymorphism of drug metabolism-related enzymes.

Conclusions: The primary treatment modality for phyllodes tumor is surgery. For metastases, adjuvant chemotherapy may be efficient. However, when the effect of chemotherapy is not obvious, aggressive surgical therapies should be performed. Besides, genetic testing can provide advices on effective treatments.

Introduction

Phyllodes tumor (PT) is a rare type of breast tumor accounting for < 1% of all breast tumors. [1] They are classified by the World Health Organization (WHO) into benign, borderline and malignant variants. It usually occurs in middle-aged women, mostly 35–55 years old. [2] Clinically, the size of PT is 4–7 cm on average, [3] only less than 10% of PTs can grow larger than 10 cm. [4] The lymph node is involved rarely, and the most common metastasis path is through hematogenous channels, mainly to the lung the pleura and the bone. [5] Herein, we report a patient with metastases to the femur the lung and bilateral axillas from a malignant phyllodes tumor of the breast and review literature about PT.

Case Presentation

In November 2019, a 34-year-old married premenopausal female was admitted into the department of thyroid and breast surgery of our hospital with a 3-month history of multiple lumps in bilateral axillas. There was no history of similar illness in first degree relatives. The patient attained menarche at the age of 16 years old. She is a non-smoker and denies history of alcohol intake.

On examination in our department, multiple lumps occupying bilateral axillas was observed. The largest lump in the right axilla was about 2*1CM and the largest lump in the left axilla was about 3*2CM. All of the lumps had clear margin, rubbery consistency and had no spontaneous pain or tenderness.

On investigating the patient, ultrasound showed multiple lumps in bilateral axillas, which were considered metastatic tumors (Fig. 1). A chest computed tomography (CT) showed no abnormality and whole body bone scan showed no evidence of metastasis. Needle aspiration biopsy of the lumps revealed borderline

or malignant phyllodes tumors. Mammary tissue and actively proliferous stromal cells was found in the lump of the right axilla and proliferous spindle cells was found in the lump of the left axilla(Fig. 2).

9 years ago, the patient discovered a mass about 8*6cm in her right breast for which she got admitted in our department. Then a lumpectomy was conducted. Histopathological examination showed it was a malignant phyllodes tumor. (supplementary material 1) Immunohistochemical stains showed ER(-), Her-2(-),PR(-),AE1/AE3(-),Vimentin(+),a-SMA(-/+),colponin(-),S-100(-/+),CD34(partially+),P53(-/+),Ki67(30%-40%+). The tumor reappeared within 9 months with a size of 11*8cm in upper inner and lower inner quadrants of her right breast. Then a needle aspiration biopsy was conducted, histopathological examination showed tumor cells according with typical malignant phyllodes tumor cells and no evidence of metastasis to axillary lymph nodes. Therefore, with the agreement of the patient a mastectomy was conducted in Fudan University Shanghai Cancer Center .Histopathological examination showed a typical representation of malignant phyllodes tumor.

3 years later, the patient presented in Fudan University Shanghai Cancer Center for multiple masses in her left breast. After discussions about the possibility of malignant phyllodes tumor, the patient underwent a left mastectomy. Histopathological examination showed malignant phyllodes tumors.

3 years later, the patient was admitted to The Second Affiliated Hospital of Medical School ,Zhejiang University with complaints of pain on the right thigh for 2 weeks. Whole body bone scan showed a high metabolic lesion in the upper side of the right femur. Afterwards she underwent right proximal femur resection and reconstruction. Histopathological examination showed spindle cell tumor considered a metastasis from the malignant phyllodes tumor in her breast, Immunohistochemical stains showed ER(-), AE1/AE3(-), GATA3(-), P63(-), TTF-1(-), PE10(-), NapsinA(-), Ki-67(30%+), SMA(+).

2 years later,the patient was admitted to Department of Thoracic Surgery of The Affiliated Zhongshan Hospital of Fudan University for cough and a lung lesion of the right upper lobe discovered a year ago. The patient underwent a lung wedge resection. Histopathological examination showed a spindle cell tumor. Immunohistochemical stains showed CK(pan)(epithelium+), CD68(PGM1)(histiocyte+), ER(-), PR(-), SMA(muscle+), CD34(interstitium+), AE1/AE3(-), GATA3(-)Ki-67(20%+), SMA(+), P63(-), TTF-1, PE10(-), NapsinA(-). After discussion the lung lesion was considered a metastasis from the malignant phyllodes tumor in the breast.

Combining with the history, our team recommend the patient to receive adjuvant chemotherapy. Adjuvant chemotherapy with doxorubicin liposome (35mg/m² administered intravenously push on day 1) plus isophosphamide (1.2-2.0g/m² administered intravenously push on days1-3) was planned for 1 cycle every 3 weeks. Bilateral axillary ultrasound were performed to evaluate the response to chemotherapy every cycle. When the patient completed 4 cycles of adjuvant chemotherapy ,the ultrasound examination to superficial lymph nodes revealed that the largest lump in the right axilla had decreased to 1*1CM and the largest lump in the left axilla had increased to 3*3CM.

In January 2020, the patient presented in our hospital for right atrial thrombus and received anticoagulation treatment. As the effect of adjuvant chemotherapy was not evident, in March 2020, after the anticoagulation treatment finished the patient received bilateral axillary lymph node dissection. (Fig. 3) The mass excised in the right axilla was about 1*1CM and the mass excised in the left axilla was about 3*3 CM, both of the masses had the characteristics of hard, clear boundary, oval shape and fishy texture. Histopathological examination showed spindle cells proliferated in the lumps excised from bilateral axillas and moderate dysplasia of the spindle cells form intercellular substance. The mitoses are common (> 10/10HPF) and stromal cells proliferate actively. (Fig. 4) Combining with the medical history the lumps were considered as borderline or malignant phyllodes tumors. Immunohistochemical stains showed CD34(+), CD68(+), Desmin(-), Ki67(20%), VIM(+++). The disease progression is shown in Fig. 5.

After bilateral axillary lymph node dissection, a genetic testing for all types of cancers was conducted. The testing covered 425 genes with a total of 1.28Mb of nucleotide sites, exons, fusion related introns, variable shear regions and the specific microsatellite loci of the genes were included. (supplementary material 2) The testing results included the information of point mutations in the coverage area, small fragment insertion and deletion mutations, gene fusion and copy number variation, the analytical results of microsatellite and the information of tumor mutation burden (TMB). Tumor-specific mutations which can lead to tumorigenesis and the development of the tumor were displayed in the testing results. (Table 1) The gene mutations about the polymorphism of drug metabolism-related enzymes were also found. (Table 2) However, no mutations about mismatch repair genes and germline genes were found and no microsatellite instability (MSI) was found. Besides the tumor mutation burden was 5.7 mutations /Mb. The testing results indicated the tumor cells were more sensitive to platinum drugs, fluorouracil drugs and anthracyclines and the toxic effects of irinotecan, etoposide, methotrexate and fluorouracil drugs would increase. However the sensitivity of tumor cells to targeted agents, immunotherapy and inhibitors of poly-ADP-ribose polymerase (PARP) was not affected by the gene mutations.

Table 1
Tumor-specific mutations

Gene	Mutation	Mutant Type	The Abundance of Mutation in Blood	The Abundance of Mutation in Tissue
GNAQ	p.Q209L a missense mutation in exon 5	c.626A > T(p.Q209L)	-	0.9%
NF2		c.1564_1567delGAGA(p.E522Kfs*27)	-	15.7%
RARA		c.631 - 13_641de	-	17.4%
TERT	p.E522Kfs*27 a frameshift mutation in exon 14	c.-124C > T	-	41.4%
MED12		c.97G > C(p.E33Q)	-	30.2%
SMARCB1	c.631 - 13_641del a shear mutation in exon 6	c.1091_1093delAGA(p.K364del)	-	18.4%
	c.-124C > T a mutation in promoter			
	p.E33Q a missense mutation in exon 1			
	p.K364del a deletion mutation in exon 1			
Note: the abundance of mutation is defined as the specific percentage of mutant alleles in a locus				

Table 2
The polymorphism of drug metabolism-related enzymes

Gene	Mutation	Mutant Type
DPYD	p.I543V heterozygous polymorphism	c.1627A > G(p.I543V)
GSTP1	p.I105V heterozygous polymorphism	c.313A > G(p.I105V)
MTHFR	p.A222V heterozygous polymorphism	c.665C > T(p.A222V)
UGT1A1	16/7TA heterozygous polymorphism	c.-55_-54insAT
XRCC1	p.Q399R homozygous polymorphism	c.1196A > G(p.Q399R)

Table 3. Three-Tiered Grading System for Phyllodes Tumors Based on 2012 World Health Organization Classification

Histologic Features	Benign	Borderline	Malignant
Stromal cellularity	Mild	Moderate	Marked
Stromal atypia	Mild	Moderate	Marked
Mitosis (per 10 HPF)	<5	5–9	≥10
Stromal overgrowth	Absent	Absent or focal	Present
Tumor margin	Well-defined	Well-defined or focal infiltrative	Infiltrative

Abbreviation: HPF=high-power field.

Discussion

Phyllodes tumor is a rare type of breast tumor, accounting for < 1% of all breast tumors. [1] PTs are very rare in males and are associated with gynecomastia. [6] In 2012, WHO proposed the classification of PT suggesting that the PTs should be classified into three subgroups benign, borderline and malignant based on a combination of several histologic features including stromal cellularity, nuclear atypia, mitotic activity, stromal overgrowth and tumor margin appearance. (Table 3) Most of PTs behave in a benign fashion, with the risk of local recurrence ranging from 17% in benign PT to 27% in malignant PT. Distant metastasis occurs in up to 22% of malignant PTs. [7] Furthermore, local recurrence occurs in 15% of patients with R0 resections and is more common after inadequate excision. [8] The histologic grading of PT is always connected with prognosis. Nevertheless, in individual, histologic features can't always predict clinical behavior. [9–11] To the best of our knowledge, The pathogenesis and molecular biologic features of PT are still unknown. The most popular theory on the pathogenesis of PT is epithelial-stromal interactions. The most recent genome sequencing studies have identified frequent MDM12 somatic mutations in fibroadenoma and PT, suggesting these two entities may share a common origin. [12–16] A study by Hodges et al showed that the deletion or amplification of some allele may led to the transformation of fibroadenoma into PTs. [17] Moreover, another study by Sapino et al suggested that high expressive ER-β in elderly patients was considered as an independent factor. Besides pregnancy status and a high level of estrogen were also related to this disease. [18]

PTs have long medical history ranged from several months to years and the early performances of PT are not typical. [19] The tumor always be found in a unilateral breast and with the characteristics of hard, clear boundary, oval or phyllodes shape, good tumor mobility, and non-adherence to skin. [5] Clinically, the size of PT is 4–7 cm on average. [3] Only less than 10% of PTs can grow larger than 10 cm. A case report by Islam et al showed a phyllodes tumor with the size of 50 × 50 cm which is the largest one up till now. [4] Huge mass can result in ulcerated, thinned, and tightened skin. The lymph node is involved rarely, and the most common metastasis path is through hematogenous channels, mainly to the lung, the pleura,

and the bone. The presence of metastatic disease usually indicates a bleak prognosis followed by death soon after with no long term survivors. [5, 20] As to this case, the patient has a long history of up to 9 years and had experienced metastases to the femur the lung and bilateral axillas. Preoperative diagnosis of breast PT is difficult. Ultrasound and mammography usually show an unfeatured picture with large, round or lobulated masses with clear boundary. Whereas, some studies found diagnostic differences in magnetic resonance imaging(MRI): the enhancement curve of benign PT was almost ascending type and that of malignant tumor was flat or platform type. [21] Pathological examination is the gold standard in the diagnosis of PT. Core needle biopsy has been widely applied with a accuracy rate as high as 99%, and the positive predictive value and negative predictive value are 93% and 83%. However, the false negative predictive value is 39%. [22] Therefore the definite diagnosis still depends on the complete excision of the tumor. In this case ultrasound showed a typical picture with multiple round lumps with clear boundary in bilateral axillas and needle aspiration biopsy of the lumps revealed borderline or malignant phyllodes tumors. The basic treatment modality for this cancer is surgery including various operation methods such as lumpectomy, wide local excision, and total mastectomy. A study revealed that radical surgery do improve the survival and decreased the rate of local recurrence. [23] The study by Tan et al indicated that the state of surgical margin was an important prognostic factor. [24] The National Comprehensive Cancer Network recommends that the range of negative margin should be more than 1 cm. However, securing a sufficient margin is difficult in most cases because of huge tumor sizes that can occupy the entire breast. In such cases a complete mastectomy is often needed. [25] The absence of skin requires extensive removal during surgery. Besides, some think that due to high recurrence rate in malignant subgroup, as long as the histopathological diagnosis was malignance before or during operation, all patients should undergo total mastectomy regardless of the tumor size. [26] Lymph node is barely involved in PTs, so routine axillary lymph node dissection is often unnecessary, unless lymph node involvement has been diagnosed pathologically. [10] The effect of postoperative comprehensive treatments such as adjuvant chemotherapy against malignant PT is still unclear. For metastatic malignant phyllodes tumors, Ifosfamide may be a active agent [27]. Doxorubicin and dacarbazine have been reported to be effective when combined with cisplatin or ifosfamide. [28] Besides postoperative radiotherapy does not improve prognosis regardless of type of surgery. [29] On the other hand, a reported by Belkacemi et al showed that radiotherapy decreased local recurrence in malignant PT and borderline PTs at 10 years but did not affect overall survival. [30] 58% and 75% of PT has been reported as ER(+) and PR(+) but no defined benefit has been derived from hormone therapy. [31] The patient underwent surgeries several times in 9 years. However no obvious benefit was found. Therefore adjuvant chemotherapy with doxorubicin liposome plus isophosphamide was recommended. However, because of inefficient of the adjuvant chemotherapy, the patient finally received bilateral axillary lymph node dissection. After this, the patient received genetic testing, and it was showed that tumor-specific mutations and mutations about the polymorphism of drug metabolism-related enzymes were discovered. The discovery can direct follow-up treatment.

Conclusion

PT is a rare type of breast disease and easy to recur. Preoperative diagnosis of PT is difficult and pathological examination is the gold standard in the diagnosis of PT. The primary treatment is operation, and the efficiency of adjuvant treatment is still under investigation. For metastases from malignant phyllodes tumor, adjuvant chemotherapy may be efficiency. However aggressive surgical therapies should be performed when adjuvant chemotherapy is ineffective. Besides, genetic test can provide advices on effective treatments.

Abbreviations

CT=chest computed tomography; ER=estrogen receptor; PR=progesterone receptor; HER-2=human epidermal-growth-factor receptor 2; PT=Phyllodes tumor; WHO=the World Health Organization; TMB=tumor mutation burden; MSI-microsatellite instability; PARP=poly-ADP-ribose polymerase; HPF=high-power field; MRI=magnetic resonance imaging

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University and the patient signed a written informed consent.

Consent for publication

The patient has given her written informed consent to publish her case including publication of images.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JZ wrote the manuscript. GG modified the manuscript. The others collected the relevant information. All authors read and approved the final manuscript.

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Figures

Figure 1

A:Ultrasound showed a lump in the right axilla. B:Ultrasound showed lumps in the left axilla.

Figure 2

A:Mammary tissue and actively proliferous stromal cells was found in the lump of the right axilla. It is demonstrated on a hematoxylin and eosin stain at a magnification of 100x. B:proliferous spindle cells was found in the lump of the left axilla. It is demonstrated on a hematoxylin and eosin stain at a magnification of 100x.

Figure 3

A:the mass excised in the right axilla. B:the mass excised in the left axilla.

Figure 4

The spindle cells proliferated in the lumps excised from bilateral axillas and the moderate dysplasia of the spindle cells form intercellular substance. A:It is demonstrated on a hematoxylin and eosin stain at a magnification of 50x.B:It is demonstrated on a hematoxylin and eosin stain at a magnification of 100x.

Figure 5

the flow chart of disease progress.

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