Case Report

Malignant phyllodes tumor of the breast with heterologous high-grade angiosarcoma

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Abstract

Phyllodes tumors (PTs) account for ~3% of fibroepithelial breast lesions and for 0.3% to 1.0% of primary breast tumors. They occur predominantly in middle-aged women (mean age range, 40–50 years). PTs can be categorized into benign, borderline, and malignant; the first 2 categories are distinguished only by degree of cellular atypia and mitotic activity. Malignant PTs are more frequent among persons of Hispanic ethnicity, especially those born in Central America or South America. Heterologous sarcomatous elements may be present in malignant PTs, predominantly liposarcoma and rarely fibrosarcoma, rhabdomyosarcoma, leiomyosarcoma, osteosarcoma, and chondrosarcoma. Breast angiosarcoma (BA) is a rare heterologous, sarcomatous element that may arise secondary to malignant PT. We report a 47-year-old woman with no history of previous surgery or radiation therapy who presented to the emergency department with a painful right breast mass. She admitted noticing the right breast mass for many years; however, recently it increased in size. Mammography and ultrasonography identified a partially cystic mass. Core needle biopsy showed dense hyalinized fibrous tissue with old blood clots, suggestive of infarcted fibroadenoma. The patient received antibiotics and analgesics; however, she reported intractable pain and a worsening skin rash of her right breast. Chest computed tomography and magnetic resonance imaging showed a doubling in mass size, with pectoralis major muscle involvement. Incisional biopsy showed malignant PT with heterologous high-grade angiosarcoma. The diagnosis of angiosarcoma was confirmed through immunoreactivity for CD31, FLI1, and ERG immunostains. © 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Phyllodes tumors (PTs) are rare fibroepithelial lesions and are considered true neoplasms [1,2]. They historically have been given many names that are misleading and unhelpful. Thus, the term cystosarcoma phylloides is no longer used [2]. The name phyllodes tumor is derived from the Greek word phyllus, meaning leaf. Gross examination shows that PTs can have variable sizes ranging from a few centimeters to 20 cm (mean, 4–5 cm) [2]. Benign PTs are well defined and often lobulated, whereas borderline and malignant PTs are ill defined [2,3]. Microscopic examination shows cellular stroma lined by an epithelial and myoepithelial bilayer, forming a leaflike structure. A focally infiltrative border can be seen in borderline PT [2,4]. Malignant PTs show a prominent infiltrative border, unequivocal sarcomatous areas, and stromal overgrowth [2,5]. Heterologous sarcomatous elements occasionally may be present in malignant tumors [2]. By comparison, angiosarcoma is a rare heterologous sarcomatous element that could arise secondary to malignant PT [2,6].

Breast angiosarcomas (BAs) are rare malignant tumors arising from endothelial cells or their precursors [7]. They comprise about 0.05% of all breast cancers, but they are the second most common mesenchymal malignancy of the breast after malignant PT [8]. Primary or idiopathic BAs are more common in young premenopausal women and are present as a deep breast mass [7,8]. Secondary BAs develop in older postmenopausal patients, frequently 5 to 6 years after radiotherapy, and they are more superficial and usually present as a rash or bruising [9,10]. Radiation treatment of breast cancer has increased the risk of BA of the skin by 9 times [10]; however, radiation treatment for Hodgkin disease increased the risk of breast cancer but not of BA [4]. After breast and axillary surgery, the arm with complicated lymphedema at the surgery site has increased risk of BA of the skin, known as Stewart-Treves syndrome [8–11].

We describe a case of high-grade angiosarcoma secondary to malignant PT in a middle-aged woman.

2. Case presentation

A 47-year-old woman with no history of alcohol or tobacco use or radiation exposure presented to the emergency department with a painful right breast mass. She admitted noticing a right breast mass for many years; however, recently it increased in size. The mass invaded
the overlying skin, deformed the right nipple (Fig. 1A and B), and invaded the right pectoralis muscle.

2.1. Radiologic evaluation

Mammography and ultrasonography identified a partially cystic mass measuring 4.8 × 6.6 × 5.9 cm (Fig. 2A). Ultrasound-guided aspiration revealed 35 mL of old blood, presumed as a hematoma. Core needle biopsy showed dense, hyalinized fibrous tissue with old blood clots, suggestive of an infarcted fibroadenoma. The patient was treated with antibiotics and analgesics. However, the skin ecchymosis and erythema were increasing and covering almost the entire right breast, and the breast pain was intractable. The patient had chest computed tomography and magnetic resonance imaging (MRI) at 2 months after her initial presentation. The imaging showed multicystic complex, heterogeneously enhancing mass in the right breast measuring 11.3 × 14 × 10 cm—double the size seen in the initial ultrasonography examination 2 months previously (Fig. 2B and C). The patient underwent incisional biopsy, which showed malignant PT with heterologous angiosarcoma.

2.2. Gross examination

The specimen was a 6.5 × 3.7 × 3.5-cm, 115-g right breast lumpectomy with a ragged cut surface. It consisted mostly of hemorrhagic tissue with ill-defined cystic lesion that had hemorrhagic contents. No skin or nipple was identified.

2.3. Microscopic examination

Multiple sections demonstrated a fibroepithelial lesion with extensive infarction and an associated malignant epithelioid and spindle cell proliferation involving the stromal component. The latter proliferation showed high-grade cytologic atypia with numerous mitoses and areas of extensive necrosis. Vague areas of vasoformative growth were seen, as well as prominent hemorrhage (Fig. 3A–D).

The differential diagnosis was between angiosarcoma secondarily involving a PT and malignant PT with heterologous angiosarcoma. Given the intimate association of angiosarcoma with the stromal...
component of the underlying fibroepithelial lesion, the latter interpretation was favored, with high-grade morphologic characteristics.

2.4. Immunohistochemistry

Evaluation with immunohistochemical stains (Table 1) was performed to detect the nature of the tumor cells. The angiosarcomatous area tested positive for CD31, FLI, and ERG (Fig. 4A–C) and negative for cytokeratin AE1/AE3, CAM 5.2, and p63.

3. Discussion

PTs are fibroepithelial tumors composed of epithelial elements that project into a hypercellular stroma in a leaflike manner [2,4]. They were first considered a kind of breast sarcoma, but their relatively benign behavior has led to their being considered separately [2,4]. The World Health Organization has subclassified PTs into benign, borderline, and malignant according to stromal cellularity, cellular pleomorphism, and tumor margins; stromal pattern; and heterologous stromal distribution [2,4]. These different elements are explained in Table 2 [4].

The majority of PT tumors (up to 60%) are benign and composed of cellular stroma formed from spindled cells, which are somewhat plump and show mild cytologic atypia and few mitoses (<5 per 10 high-power fields) [2,4]. Occasionally, bizarre pleomorphic stromal cells may be seen, but they should not lead to the diagnosis of malignant PT in the absence of other distinguishing features. The lesion margin is usually relatively well defined, with no stromal overgrowth, defined as absence of epithelial elements within the fields of view at original magnification ×4 and ×10 ocular [2,4].

At the other end of the PT spectrum are lesions composed of markedly atypical stromal cells with abundant mitoses (>10 per 10 high-power fields) in which the stroma has outgrown the epithelial component and infiltrates the adjacent parenchyma [2,4]. Occasionally, specific heterologous sarcomatous elements may be seen, such as predominantly liposarcoma and, rarely, osteosarcoma, chondrosarcoma, fibrosarcoma, or rhabdomyosarcoma. Such malignant PTs account for approximately 20% of all cases [4]. Malignant PTs are more common in the Hispanic population, especially persons born in Central America or South America [4]. Patients who have tumors with an infiltrating tumor margin, severe stromal overgrowth, atypia, and cellularity are at high risk for metastases [12].

Our current case is the fourth case in the literature of angiosarcoma developing in a clinical setting of PT (Table 3). Two previously reported cases occurred in a clinical setting of recurrent PTs (1 benign and 1 malignant).

**Table 1**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clone</th>
<th>Supplier</th>
<th>Dilution</th>
<th>Antigen retrieval method</th>
<th>Platform</th>
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<tr>
<td>AE1/3</td>
<td>AE1/AE3</td>
<td>Dako</td>
<td>Predilute</td>
<td>High pH</td>
<td>Dako/Envision Flex</td>
</tr>
<tr>
<td>CAM 5.2</td>
<td>CAM 5.2</td>
<td>Becton Dickinson</td>
<td>1:21</td>
<td>CC1 56 min</td>
<td>Dako/Envision Flex</td>
</tr>
<tr>
<td>p63</td>
<td>4A4</td>
<td>Ventana Medical Systems</td>
<td>Predilute</td>
<td>High pH</td>
<td>OptiView DAB</td>
</tr>
<tr>
<td>CD 31</td>
<td>JC/70 A</td>
<td>Lab Vision Corp.</td>
<td>Predilute</td>
<td>CC1 mild 30 min</td>
<td>OptiView DAB</td>
</tr>
<tr>
<td>FLI-1</td>
<td>G146–254</td>
<td>BD Pharmingen</td>
<td>1:50 BRD</td>
<td>CC1 mild 30 min</td>
<td>OptiView DAB</td>
</tr>
<tr>
<td>ERG</td>
<td>9FY</td>
<td>Biocare Medical Inc.</td>
<td>1:25 BRD</td>
<td>CC1 mild 32 min</td>
<td>OptiView + OptiView AMP</td>
</tr>
</tbody>
</table>

Abbreviations: BRD, background-reducing diluent; CC1, cell-conditioning solution.

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malignant) [13,14]. Three of the 4 angiosarcomas were high grade; 1 angiosarcoma showed a low-grade tumor occurring in association with recurrent benign PT [13–15].

The mammographic picture of BA is nonspecific. It usually presents as an ill-defined, noncalcified mass or with focal asymmetry as the most common finding. Yang et al. [16] found that 19% of patients had tumors not visible on mammography but visible with sonography and MRI. Ultrasonography is used for mass confirmation when a palpable abnormality is found. Masses may be circumscribed or ill defined [16,17]. MRI of BA shows a heterogeneous mass with low signal intensity on T1-weighted images, but signal intensity is high in images that are heavily T2-weighted [16,17].

Gross examination of BA usually shows an ill-defined hemorrhagic mass, ranging from 1 cm to 20 cm (mean size, 5 cm) [7,8]. Histologically, the tumor consists of abnormal blood vessels in the dermis and breast stroma [7–9]. Blood vessels are increased in number and form complex anastomosing channels. Borders are infiltrative and not well circumscribed. Necrosis and blood lakes may be present [7,8]. Endothelial cells show enlarged, pleomorphic nuclei with frequent mitotic figures [7,8]. Usually, the tumor cells are positive for vascular markers, including CD31, CD34, ERG, and FLI-1 [18]. Tumor cells are typically negative for cytokeratin and EMA [18].

Treatment of BAs is surgical removal with wide margins, and most patients require mastectomy to achieve this goal. Chemotherapy and radiation therapy are also used but have uncertain benefits [8–10]. Many patients with BA have distant metastasis—lungs being the most common site, followed by liver, bone, and contralateral breast. Median recurrence-free survival time is about 3 years; overall survival is <6 years [19].

Primary BA typically follows an aggressive course, with a recurrence rate of approximately 25%, a metastatic rate of 60% (median, 34 months after diagnosis), and, in 1 large series, a 5-year mortality rate of about 50% [8]. Axillary lymph node involvement is exceptional. About one-third of the lesions are high grade. Importantly, in 1 series, patient outcome has not shown a correlation with histologic grade of the angiosarcoma; therefore, some experts have questioned the value of grading such lesions [8].

Surgery is the cornerstone of treatment of primary breast angiosarcomas while the role of both chemotherapy and radiation is still controversial. Biswas et al. [9] showed, in a study of 8 patients identified as having histologically confirmed diagnosis of angiosarcoma of the breast, 7 patients (87%) had a history of prior radiation to the breast, and the other patient had primary de novo angiosarcoma. Median overall survival was 37.4 months (range, 8.7–92.8 months); relapse-free survival was 17.9 months (range, 2.5–69.4 months) [9].

Patients with radiation–associated angiosarcomas have a poor prognosis, with an overall 5-year survival rate of approximately 40% [10]. Among these tumors, 80% are high grade, but the outcome does not appear to be associated with tumor grade [8]. Surgical excision is the main therapeutic modality [8,9].

Table 2
WHO histologic criteria for classification of the different PTs.

<table>
<thead>
<tr>
<th>WHO classification</th>
<th>Benign PT</th>
<th>Borderline PT</th>
<th>Malignant PT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stromal cellularity</td>
<td>Modest</td>
<td>Modest</td>
<td>Marked</td>
</tr>
<tr>
<td>Cellular pleomorphism</td>
<td>Little</td>
<td>Moderate</td>
<td>Marked</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Few, if any</td>
<td>Intermediate</td>
<td>Numerous, ≥10/HPF</td>
</tr>
<tr>
<td>Margins</td>
<td>Well circumscribed (pushing border)</td>
<td>Focally infiltrative</td>
<td>Infiltrative</td>
</tr>
<tr>
<td>Stromal pattern</td>
<td>Uniform stromal distribution</td>
<td>Heterogeneous stromal distribution</td>
<td>Marked stromal overgrowth</td>
</tr>
<tr>
<td>Heterogeneous stromal distribution</td>
<td>Rare</td>
<td>Rare</td>
<td>Not uncommon</td>
</tr>
<tr>
<td>Overall average distribution, %</td>
<td>60</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Abbreviations: HPF, high-power field; PT, phyllodes tumor; WHO, World Health Organization. (Data from Lekhani et al [4].)

Fig. 4. Angiosarcoma confirmed by immunoreactivity to immunostains. A, CD31 immunostain. B, ERG immunostain. C, FLI1 immunostain.

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Table 3
Three published angiosarcoma cases in comparison with the present case.

<table>
<thead>
<tr>
<th>Case</th>
<th>Authors/year</th>
<th>Age, y</th>
<th>Sex</th>
<th>Size, cm</th>
<th>Recurrent</th>
<th>Angiosarcoma grade</th>
<th>Phyllodes tumor grade</th>
<th>IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mamoon et al./2009 [14]</td>
<td>70</td>
<td>F</td>
<td>5.5</td>
<td>Yes</td>
<td>Low</td>
<td>Benign</td>
<td>CD31, CD34</td>
</tr>
<tr>
<td>2</td>
<td>Kumar et al./2012 [13]</td>
<td>22</td>
<td>F</td>
<td>8.0</td>
<td>Yes</td>
<td>High</td>
<td>Malignant</td>
<td>CD31, CD34</td>
</tr>
<tr>
<td>3</td>
<td>Costa et al./2012 [15]</td>
<td>83</td>
<td>F</td>
<td>15.0</td>
<td>No</td>
<td>High</td>
<td>Borderline</td>
<td>ND</td>
</tr>
<tr>
<td>Present</td>
<td>Tranesh et al./2016</td>
<td>47</td>
<td>F</td>
<td>6.5</td>
<td>No</td>
<td>High</td>
<td>Malignant</td>
<td>CD31, ERG, FLI-1, AE1/3, CAM5.2, p63</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; IHC, immunohistochemistry; ND, not done.

Declaration of conflict of interest

None.

References