

# Cystosarcoma phyllodes with lymph node metastasis

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Cystosarcoma phyllodes is a rare breast tumor with a low incidence of metastasis. Lymph node metastasis is even rarer. We report here a case of a 45-year-old woman who presented with a large lump in her left breast and involvement of multiple ipsilateral axillary lymph nodes. Clinical findings and cytologic examination (fine-needle aspiration) were suggestive of cystosarcoma phyllodes, for which she underwent a radical mastectomy. Postoperative histopathologic findings revealed cystosarcoma phyllodes with multiple lymph node metastases. Postoperative radiotherapy was given to the locoregional area.

Cystosarcoma phyllodes was first described by Chelius in 1928. However, Johannes Muller was the first person to use the term *cystosarcoma phyllodes*, denoting the cystic appearance and leaflike growth pattern of these large tumors, which he believed were benign.<sup>1</sup> Calling this tumor a “sarcoma” is somewhat misleading because it connotes malignancy, but it is now well known that both benign and malignant forms can occur. Although the term is still used, it is now qualified by the words *benign* or *malignant* to differentiate the two forms. Division into benign or malignant is a function of the stroma.

## Case history

A 45-YEAR-OLD-FEMALE, mother of three, presented with a large, painful mass in her left breast. She had noticed a small mass 12 years prior, while breast feeding her youngest child, which she then correlated with trauma and ignored. For 12 years, the mass stayed the same size and was painless. Four months prior to admission, however, the mass started increasing in size and became painful.

Clinical examination revealed a well-nourished woman whose left breast was replaced by a large, solid, irregular mass fixed to the chest wall. No ulceration, bleeding, or discharge was observed. The axillary lymph nodes were palpable. Results of a routine blood and urine analysis were normal, as were a chest x-ray film, a computed tomographic

scan of the chest and abdomen, and a bone scan. Fine-needle aspiration cytology from the mass revealed features of cystosarcoma phyllodes. The patient was clinically diagnosed with a stage IIIB (T4a, N1, M0) breast tumor.

A modified radical mastectomy of the left breast, with wide resection of the skin, was performed, and the surgical wound was covered with a myocutaneous graft. The patient was given postoperative radiotherapy (5,000 cGy in 25 fractions) by conventional fractionation to the chest wall and regional lymph nodes, and she is being followed closely.

## Pathologic findings

On gross examination, the external surface of the breast tissue was covered with shiny, stretched skin, and a few hard to firm satellite nodules, 0.5–1 cm in diameter, were palpable close to the mass. Cutting the surface revealed a soft, myxoid, necrotic, lobulated mass measuring 11 cm × 8.5 cm × 8 cm, with a variegated, pale-yellow surface.

On microscopy, the tumor showed pleomorphic atypical spindle cells with eosinophilic cytoplasm and elongated hyperchromatic nuclei infiltrating the adjacent fibroadipose tissue. Satellite nodules displayed features similar to those of the main mass, with 13 out of 24 axillary lymph nodes posi-

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tive. All findings were suggestive of cystosarcoma phyllodes with axillary lymph node metastasis.

## Discussion

Cystosarcoma phyllodes is an uncommon tumor of the breasts, accounting for only 0.4%–1% of all breast tumors.<sup>2</sup> Although phyllodes tumors can occur in women of any age, they are most commonly seen in women 35–55 years of age.<sup>3</sup> The tumor is usually benign but can recur locally and occasionally spreads systemically in a lethal manner.

Although the malignant potential of a tumor, in general, is related to its microscopic features, such as considerable cellular atypia, excessive proliferation of the stromal cells with an intensified pleomorphism, high mitotic activity, and increased vascularity, the clinical picture correlates little with the microscopic appearance of these tumors.

Based on these histopathologic criteria, several classifications of cystosarcoma phyllodes have been proposed.<sup>4–6</sup> The World Health Organization classification was proposed in 1982 to promote uniformity in the recording and reporting of breast diseases and to facilitate international comparisons. However, a tumor is considered malignant if the stromal component shows a clear pattern of sarcoma. Generally, 10%–40% of these tumors take a malignant course, with a high tendency toward local recurrence and systemic dissemination.

Patients usually present with a large encapsulated tumor without infiltration of the surrounding tissues. The skin may be stretched over the tumor and may have a shiny appearance, sometimes with prominent veins. The mass is usually nontender, free from overlying skin, and mobile. Pain or ulceration indicates pressure necrosis secondary to a bulky tumor. Approximately 3%–12% of malignant phyllodes tumors metastasize.<sup>5,7</sup> Metastasis may occur ei-

ther at the time of presentation or as late as 12 years later,<sup>2</sup> spreading hematogenously to the lungs (66%), bones (28%), and brain (9%) and, in rare instances, to the liver and heart.<sup>5</sup> Regional lymph node enlargement is common, but the lymph nodes are rarely involved by tumor.<sup>2,4,7</sup>

Only a few cases of cystosarcoma phyllodes with lymph node involvement have been reported in the literature. Treves, in his series of 33 cases, reported only 1 case that showed metastasis to the axillary lymph nodes.<sup>4</sup> In Norris and Taylor's series of 94 patients, 16 (17%) had enlarged lymph nodes, but only 1 patient had histologically proven metastasis.<sup>7</sup> Reinfuss et al found axillary lymphadenopathy clinically in 11 (20%) of 55 patients, but only 1 showed metastasis.<sup>8</sup> Staren et al found axillary lymph node involvement in 1 out of 26 patients.<sup>9</sup> Thus, in these series the incidence of axillary lymph node involvement ranged from 1.1% to 3.8%. Minkowitz et al also described a single case of cystosarcoma phyllodes with involvement of axillary lymph nodes.<sup>10</sup>

## Management

Management of cystosarcoma phyllodes has always been controversial and cannot be standardized for all patients. Treatment is directed at complete removal of tumor with adequate margins. Wide local excision for small tumors and simple mastectomy for larger ones are usually satisfactory. Excision of the pectoralis major muscle may be necessary if the fascia or muscle is infiltrated. Most of the studies showed that axillary node clearance is not required because of a very low incidence of lymph node involvement. Norris and Taylor<sup>7</sup> suggested a mastectomy with low axillary node dissection should be performed if the axillary lymph nodes are enlarged, the tumor is 4 cm or larger, and biopsy shows an aggressive tumor (as determined by the presence of an infiltrating margin,

high number of mitotic figures, and a higher degree of cellular atypia).

The role of adjuvant radiotherapy and chemotherapy remains uncertain, but encouraging results using radiotherapy and chemotherapy for soft-tissue sarcomas suggest that consideration be given for their use in cases of malignant cystosarcoma phyllodes. Chaney et al<sup>11</sup> found adjuvant radiotherapy to be beneficial in patients with adverse features (eg, bulky tumors, close or positive surgical margins, hypercellular stroma, high nuclear pleomorphism, high mitotic rate, presence of necrosis, and increased vascularity within the tumor and tumor recurrence). Chemotherapy, including anthracyclines, ifosfamide (Ifex), cisplatin, and etoposide, has been mentioned in various studies, though rarely used.<sup>12,13</sup> The use of hormonal therapy, such as tamoxifen, has not been fully investigated in cystosarcoma phyllodes. However, because estrogen and progesterone receptors have been documented in these tumors, further studies with hormonal manipulation in cystosarcoma phyllodes might be warranted.<sup>14</sup>

## Summary

Our patient had silent disease for 12 years, followed by rapid growth in the past 4 months. The rare finding of histologically proven metastases to multiple, ipsilateral axillary lymph nodes at presentation suggested the presence of aggressive disease. Following mastectomy, she received postoperative radiotherapy of 5,000 cGy over 5 weeks by conventional fractionation to the locoregional area and was closely followed thereafter.

We reviewed the literature with the intention of finding prophylactic measures that could have been used in such patients with clinically aggressive localized disease to prevent metastatic spread. We found instead that the literature on cystosarcoma phyllodes is mainly focused on the optimal surgical approach for these

tumors. The role of postoperative radiotherapy and chemotherapy in particular received little attention.

A review of the available literature on phyllodes tumors suggests that more radical treatment fails to prevent metastases; therefore, conservative surgery, followed by close observation, is all that is needed. We would suggest that multi-institutional randomized trials be carried out using new chemotherapeutic agents to define and update the optimum management of patients with these tumors.

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# Phyllodes tumors: about this rare cancer

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The case presented by Agrawal and colleagues describes a malignant phyllodes tumor with metastatic spread to the ipsilateral axillary lymph nodes. A 45-year-old woman presented with a solid irregular mass replacing her left breast. The 11 cm × 8.5 cm × 8 cm tumor had pleomorphic atypical spindle cells, eosinophilic cytoplasm, and elongated hyperchromatic nuclei. The tumor invaded the surrounding fibroadipose tissues, and the satellite nodules had features similar to those of the large tumor. Thirteen of 24 ipsilateral axillary lymph nodes were positive for metastatic spread.

Multimodality treatment consisted of a left modified radical mastectomy with wide resection of the

skin, a myocutaneous graft, and postoperative radiation therapy (5,000 cGy) to the chest wall and regional lymph nodes.

#### Histologic characteristics

Johannes Muller,<sup>1</sup> in 1838, originally described fleshy breast lesions as cystosarcoma phyllodes based on their gross appearance; however, these lesions are not true sarcomas. Therefore, in 1981, the World Health Organization adopted the term *phyllodes tumors*, and these tumors are now subclassified as benign, borderline, or malignant, based upon stromal characteristics.<sup>2</sup> These characteristics include the degree of stromal cellular atypia, mitotic activity per 10 high-powered fields, the presence or absence of stro-

mal overgrowth, and infiltrative versus circumscribed tumor margins.

Benign phyllodes tumors have mild to moderate cellular atypia within increased stromal cellularity. Mitotic rates of less than four dividing cells per 10 high-powered fields are common, along with a well-circumscribed tumor margin. Borderline phyllodes tumors have a background of increased cellularity and atypia, with mitotic rates of four to nine mitotic figures per 10 high-powered fields. The margins can be microscopically invasive. Malignant phyllodes tumors have high mitotic rates (10 or more mitotic figures per 10 high-powered fields), infiltrative borders, and areas of stromal overgrowth.

This characteristic of stromal overgrowth, which has been associated with metastatic behavior in multiple series, is absent in the benign and borderline subgroups.<sup>3-6</sup> In some series, the majority of phyllodes tumors (35%–64%) are classified as benign, and the remainder is split somewhat evenly between the borderline and malignant subtypes.<sup>7-9</sup>

### Prevalence and survival

These tumors are not common. An epidemiologic evaluation of malignant phyllodes tumors based upon Surveillance, Epidemiology, and End Results (SEER) data has estimated the incidence to be 2.1 per 1 million women.<sup>10</sup> Retrospective analyses of databases from institutions indicate that 0.3%–0.5% of breast masses are due to phyllodes tumors.<sup>7,11</sup>

The different histologic subtypes of phyllodes tumors appear to predict survival. The retrospective review by Chaney et al<sup>6</sup> from the University of Texas M. D. Anderson Cancer Center, Houston, describes the natural course of surgically treated phyllodes tumors. In all, 101 patients were treated and followed at their institution; 71 of these patients had nonmalignant disease (59, benign; 12, indeterminate [borderline]), and 30 patients had malignant disease.

After a median follow-up of 47 months, the 5- and 10-year overall survivals in the nonmalignant group were 91% and 79%, respectively. The malignant group had statistically significant lower 5- and 10-year survivals of 82% and 42%, respectively ( $P = 0.0151$ ). No patients in this review had metastases to the axillary lymph nodes. Of the eight patients with metastatic disease, all involved the lungs and all exhibited stromal overgrowth. Other reports of metastatic disease describe

a hematogenous pattern involving the lungs, bone, liver, heart, and, occasionally, distant lymph nodes.<sup>12,13</sup>

Tse et al<sup>14</sup> evaluated the epithelial and stromal components of phyllodes tumors for estrogen receptor (ER) and progesterone receptor (PR) expression. The stromal component, which metastasizes, expresses ER and PR less than 5%. The epithelial component generally expresses a higher percentage, but this expressivity decreases inversely with the degree of malignancy.

### Recommended treatment

Much of the literature regarding the incidence of axillary lymph node metastases is reported in isolated case studies.<sup>15-17</sup> Staging of phyllodes tumors follows the guidelines for sarcoma. Thus, nodal metastases constitute stage IV disease.<sup>18</sup> Treatment of malignant phyllodes tumors is based upon retrospective reviews in the literature. Institutions with multiple phyllodes tumor patients have attempted to describe the population and outcomes based upon treatment. Because of the rarity of these cases and the variety of therapies utilized, it is difficult to extrapolate data and use the information to treat individual patients.

Surgical therapy is aimed at complete excision of the tumor with at least 1-cm margins. This can be accomplished by either lumpectomy or mastectomy, depending upon the size of the tumor relative to the breast. Geisler et al,<sup>11</sup> at the University of Oklahoma Health Sciences Center, Tulsa, reviewed all cases of phyllodes tumors treated at their institution over 24 years and found an increased recurrence of all tumors, whether benign or malignant, when the margins were positive. Mastectomy has not shown a survival advantage over wide local excision.<sup>19,20</sup> The strongest independent predictor of local recurrence is a positive margin.<sup>21,22</sup>

The patient in the case presented

by Agrawal et al underwent postoperative radiation therapy. Chaney et al<sup>23</sup> described a subset of eight patients with phyllodes tumors who received postoperative radiation for one or more indications, including malignant tumors, tumors larger than 10 cm, or a positive margin. One patient had a previous recurrence. No patient had metastatic disease at presentation. Radiotherapy of 7,000 cGy was administered to the chest wall/breast of the eight patients. No local or distant failures were seen at a median follow-up of 36.5 months. The use of radiotherapy remains controversial, as other retrospective studies have failed to prove any benefit.<sup>13,24,25</sup>

A current clinical prospective trial, "Phase II Study of Adjuvant Radiotherapy After Resection in Patients With Borderline or Malignant Phyllodes Tumors of the Breast,"<sup>26</sup> has accrued 34 of the projected 50 patients since 1998. Eligible patients have borderline or malignant histology, breast conservation with negative margins, no prior in situ or invasive cancer in the breast, and no prior radiotherapy to the breast. The study's objective is to determine local recurrence rates and survival in these select patients. Radiotherapy begins within 12 weeks after local excision.

Chemotherapy has not been used routinely for patients with phyllodes tumors. Sarcoma chemotherapy regimens have been attempted in these patients without success. Isolated case reports exist that demonstrate rare responses to cytotoxic drugs. Burton et al<sup>27</sup> administered cisplatin and etoposide to three patients. Two of the patients had a significant clinical response. Further studies are needed to determine whether cytotoxic drugs are useful in treating malignant phyllodes tumors.

Agrawal et al suggest a multi-

institution trial to determine the most beneficial selection of chemotherapy. As previously mentioned, the incidence of malignant phyllodes tumors is 2.1 per 1 million women in the US (SEER data). To predict a 10% difference in treatment with a 90% confidence interval, a trial would require more women than the population of the entire United States.

Appropriate treatment of phyllodes tumors involves surgical resection with at least 1-cm margins. Adjuvant radiotherapy is currently under investigation in a phase II trial. The results of this trial will be vital to future treatment. Chemotherapy is currently used in a variety of combinations. The usefulness of these regimens remains to be proven.

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