Phyllodes Tumor on Male Breast: A Literature Review

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INTRODUCTION

Phyllodes tumor of the breast is a rare type of neoplasm from a group of fibroepithelial lesions. Tumor phyllodes formerly known as “cystosarcoma phyllodes” was first proposed by Johannes Muller in 1838, to denote a tumor that macroscopically resembles flesh with a leaf-like microscopic appearance. The incidence of phyllodes tumor <1% of all breast neoplasms is 0.3–0.5% with the highest incidence occurring in the age range of 30–40 years. Research shows that the incidence increases at older ages, especially at 45–54 years [1].

The incidence of this tumor is increasing in Asian countries. The incidence of this tumor is 6.92% of all malignancies in the breast and occurs at a younger age, ie 25–30 years. Although rare, there have been reports of phyllodes tumors in men. Several case reports were found from 1990 to 2020, there were only 13 articles showing phyllodes tumors in men. In Indonesia alone, there is no data on the number of patients with phyllodes tumors [2]. Based on the 2013 Basic Health Research (Riskesdas) data, the prevalence of tumors/cancer in Indonesia is 1.4 per 1000 population, or about 330,000 people. The frequency of occurrence of this tumor based on histopathological changes (gradation) is 75% benign, 16% borderline, and 9% malignant [3].

In 1981, the World Health Organization (WHO) adopted the naming of phyllodes tumors and divided them into benign, borderline, and malignant types based on stromal characteristics. These characteristics include the degree of atypical stromal cellularity, mitotic activity per ten large visual fields, the presence or absence of stromal overgrowth, and infiltrative tumor boundaries or well-defined tumor boundaries. Benign phyllodes tumors have mild to moderate cellular atypicality with an increase in stromal cells. High mitotic ratio (10 or
more mitoses in 10 large visual fields), presence of infiltration, and stromal overgrowth. Stromal overgrowth has been associated with metastatic activity, which is absent in the benign and borderline types [4]. Despite the rare cases of phyllodes tumors in male breast, this study aims to explore and summarize the risk factors, diagnostic approach, and treatment used for the cases.

METHODS

The main focus of the study

A literature review by collecting the case reports based on the following inclusion criteria: (1) the full-text article can be accessed, (2) the year of publication of the journal is later than 2012, and (3) according to the material raised in this literature review (male patient with phyllodes tumor).

Search Strategy

This literature review description was synthesized using literature review by collecting case reports methods obtained from various online databases, such as NCBI, Google Scholar, Science Direct, Elsevier, Springer Nature, Wiley Online Library, World Health Organization, Ministry of Health of the Republic of Indonesia, and the Indonesian Oncology Association (POI). The keywords used in the literature search were phyllodes tumor, tumor filodes, tumor filodes pada pria, and phyllodes tumor on male breast. All selected literature was analyzed and the material was combined into a logical flow of ideas. There are 13 studies fulfilling inclusion criteria and 7 articles were selected for this study. The literature selection process is in the flow diagram in Figure 1.
RESULTS AND DISCUSSIONS

Phyllodes tumor

Phyllodes tumor is a rare breast neoplasm ranging in severity from benign to malignant. Phyllodes tumors are characterized as tumors that grow rapidly and rarely metastasize. The incidence of phyllodes tumors ranges from 0.3–1% of all breast cancer incidences [2].

The phyllodes tumor has a characteristic microscopic leaf-like appearance within the cystic cavity and a sarcomal stromal appearance. Although phyllodes tumor is a benign tumor, currently according to some literature there is an increase in cases of malignancy up to 10–15%. Malignant phyllodes tumors can metastasize to other organs [2]. WHO classifies phyllodes tumors into benign, borderline, and malignant forms based on histologic findings such as stromal cellularity, nuclear atypia, mitotic activity, stromal overgrowth, and tumor margins. The most common age for finding phyllodes tumors is 45 years with tumor sizes ranging from 4–5 cm [5].

Cytopathology and histopathology of phyllodes tumor

Fine needle aspiration (FNA) is a pre-operative modality used for the diagnosis of phyllodes tumors. Cytologically, phyllodes tumors show a section of cellular fibromyxoid stroma containing spindle cells, ductal epithelium, and admixed myoepithelial cells. This characteristic is also often found in fibroadenoma. However, a phyllodes tumor should be suspected on the findings of large hypercellular stromal fragments, numerous discohesive stromal cells with elongated nuclei and admixed cytoplasm with fibromyxoid stromal components, significant atypical distribution including nuclear enlargement, pleomorphism, and mitoses, poor epithelial-stromal ratio, epithelial fragments. round with mild atypia, and columnar epithelial cells. Malignant phyllodes tumors have high stromal cellularity, high atypical stromal nuclei, and mitotic features [6]. Classification can be seen in Table 1. Histopathological description as can be seen in Figure 2.

| Table 1. Phyllodes tumor classification [6] |
|-----------------|-----------------|-----------------|
| **Histopathology** | **Characteristics** | **Phyllodes Tumor** |
|                 |          | **Border** | **Borderline** | **Malignant** |
| Border          | Definite  | Focal surpass the tumor border | Surpassing the tumor border |
| Stromal hypercellularity | Mild cellularity, heterogenous | Moderate cellularity, can be found non-uniform or diffuse | Severe cellularity and uniform |
| Stromal nucleus atypia | Mild | Moderate | Severe |
| Mitotic activity | <5 in 10 HPF | 5–9 in 10 HPF | ≥10 in 10 HPF |
| Stromal overgrowth | None | Focal | Definite |

Figure 2. Histopathology on phyllodes tumor. (A) The histopathological examination reveals a biphasic tumor composed of both epithelial and stromal elements. The epithelial part forms tubules with irregular shapes, surrounded by a moderately cellular spindle cell stroma. Furthermore, there is a large cystic space lined by squamous epithelium, and these cysts contain keratin. The findings were observed under a hematoxylin and eosin stain at 10x magnification; (B) Several areas of squamous metaplasia are observed within the ductal structures. These findings were visualized under a 40x magnification using H&E stain; (C) Within the ducts, p63-positive myoepithelial cells are detected. Additionally, p63 highlights the metaplastic squamous epithelial cells, while the regular tubular epithelium does not exhibit p63 positivity; (D) Myoepithelial cells within the ducts exhibit positivity for smooth muscle actin immunostaining. [6]
Phyllodes Tumor on Male Breast

Incidence of phyllodes tumor in men

The incidence of phyllodes tumors is quite rare, which is less than 1% of all breast cancer cases. As a result, data on the prevalence and epidemiology of this disease are not very abundant. A study in Los Angeles stated that the incidence of phyllodes tumors was 2.1 per 1 million female population [7].

The majority of the incidence of phyllodes tumors is in women, especially those aged 42-45 years. In men, phyllodes tumors are associated with gynecomastia. Gynecomastia is a benign proliferation of breast tissue (such as ducts and stroma) that occurs in 65% of men, especially in the peripubertal period and over 50 years [8].

Gynecomastia is associated with the incidence of phyllodes tumors in men as a result of hormonal imbalances that will later cause tumors. Gynecomastia has the potential to affect an estrogen/androgen imbalance. Several case studies suggest that there is an incidence of breast tumors in men taking long-term estrogen therapy [8].

Although it is widely stated in the literature that gynecomastia is one of the causes of phyllodes tumors in men, this is still quite debated. A study conducted by Panigrahi et. al. [9] did not show an association of gynecomastia with the incidence of phyllodes tumors in their patients.

In addition to gynecomastia, several case reports also mention that treatment with bicalutamide for men with prostate cancer can also cause malignant phyllodes tumors in men. Bicalutamide acts as an androgen receptor antagonist. This will result in the production of estrogen. So there is a hormonal imbalance that can cause breast cancer in men [8]. All studies that included in this literature review, including their results, can be seen in Table 2.

Clinical manifestation of phyllodes tumor in men

In general, the clinical manifestations of phyllodes tumors in men and women do not differ [16]. Clinical manifestations of tumor filodes in the form of lumps are unilateral, single, painless, and can be palpated. Patients usually complain of a tumor that suddenly appears and continues to enlarge, or a lump that initially persists and suddenly grows in size in the last few months [11].

On physical examination of the breast, the phyllodes tumor is a soft and round lump, similar to a fibroadenoma, but with a large size (>2–3 cm). The tumor can be seen if it enlarges quickly. Although growing rapidly does not indicate its malignant nature. The shape looks shiny with the skin surface as if stretched with the widening of the veins on the skin surface [16]. In cases that are not handled properly, ulcers can occur on the skin as a result of tissue ischemia. Although skin changes like this like in breast tumors always show signs of malignancy (T4 lesions), but not in phyllodes tumors, because ulcers on the skin can occur in benign, borderline, or malignant types of lesions [10].

Metastases can appear simultaneously when the patient comes or at least for the next 12 years. Metastases can spread haematogenously, spreading to the lungs (66%), bone (28%), brain (9%) and in rare cases the liver and heart (8%). These tumors may be accompanied by enlarged regional lymph nodes, even without tumor cells. Not much literature reports the presence of metastases to lymph nodes [16]. Treves [17] in 33 cases, only reported 1 case of metastasis to the axillary lymph nodes. Noris and Taylor [18] of 94 patients, 16 patients had enlarged lymph nodes but only 1 case was histologically proven to have metastases. Reinfuss et al. [19] found 11 cases of enlarged lymph nodes out of 55 cases, but only 1 case showed metastasis. Minkowitz et al. [20] also reported one case with metastases to the axillary glands.

Therapy of phyllodes tumor in men

Management of phyllodes tumors is still debated and is not the same in all cases. The mainstay of therapy is complete surgery with adequate margins. Many investigators recommend a 1 cm margin of excision as a good resection. Recurrence was related to the excision margin and not related to tumor grade and size. Wide excision of small tumors or simple mastectomy generally yield satisfactory results. Excision of the pectoral muscles should be considered if infiltration has occurred. Mastectomy with breast reconstruction may be an option for large tumors [21].

Phyllodes tumors, as well as soft tissue sarcomas, rarely cause lymph node metastases. Most studies show that axillary lymph node dissection is not routinely performed, given the infiltration of the axillary lymph nodes is rare. Norris and Taylor [18] recommend mastectomy with lower axillary lymph node dissection if lymph node enlargement is present, tumor size >4 cm, biopsy shows aggressive tumor type (capsular infiltration, high mitotic rate, and high atypical cellular grade). If there is indication of lymph node involvement clinically or on imaging studies, a needle biopsy with ultrasound guidance can be performed. If the result is negative, a sentinel lymph node biopsy may be considered [22].

The role of radiotherapy and adjuvant chemotherapy is controversial, but the use of radiotherapy and chemotherapy in sarcomas indicates that they can be used in phyllodes tumors. Adjuvant radiotherapy may be useful in the malignant type. Chemotherapy class anthracyclines, ifosfamide, cisplatin, and etoposide are rarely used. There has not been much research on the use of hormonal therapy, such as tamoxifen. Hormonal sensitivity in phyllodes tumors has also not been well identified. Broadly speaking, systemic therapy for phyllodes tumors is no different from treatment for sarcomas [23].
Table 2. Case report of phyllodes tumor on male breast

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Patient Age</th>
<th>Macroscopic</th>
<th>Microscopic</th>
<th>History</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Khalid et al. (2021) [10]</td>
<td>62</td>
<td>A 2.5 x 2.5 cm lump was palpable at 1 o’clock on the right breast. Not fixed to the skin and not metastatic</td>
<td>Increased stromal cellularity in the form of sheets and spindle cells and areas of necrosis</td>
<td>No history of another disease</td>
<td>Malignant phyllodes tumor</td>
</tr>
<tr>
<td>2</td>
<td>Karihtala et al. (2016) [11]</td>
<td>68</td>
<td>Enlargement of the left breast</td>
<td>Cellular stroma with atypical spindle cells and pleomorphic cells, with tubular and papillary structures of epithelial cells without atypia margins</td>
<td>Prostate adenocarcinoma, in bicalutamide treatment, gynecomastia bilateral</td>
<td>Malignant phyllodes tumor</td>
</tr>
<tr>
<td>3</td>
<td>Gyu et al. (2015) [12]</td>
<td>39</td>
<td>Palpable mass in left breast since 20 days before administration to hospital, fixed in subareolar area, firm, painless. There is nipple retraction and thickened skin</td>
<td>Moderate stromal cellularity, minimal atypia stromal cells, no stromal overgrowth. Mitotic activity increased</td>
<td></td>
<td>Gynecomastia</td>
</tr>
<tr>
<td>4</td>
<td>Panigrahi et al. (2021) [9]</td>
<td>32</td>
<td>A 2x2 cm lump on the left breast grew rapidly with heterogeneous consistency and was not fixed to the chest wall. There is a slight discoloration and excoriation of the areola</td>
<td>The stromal and epithelial components are leaf-shaped. Mild to moderate atypical stromal cells. Mitotic activity 6-7 per 10 large visual fields. The cystic contains metaplasia of epithelial cells with keratin debris projection with cystic areas lined by epithelium</td>
<td></td>
<td>Gynecomastia, Squamous metaplasia in borderline phyllodes tumor</td>
</tr>
<tr>
<td>5</td>
<td>Chougulle et al. (2015) [13]</td>
<td>31</td>
<td>Bilateral breast enlargement is painless with a lump in the right breast measuring 5x5x4 cm and growing slowly</td>
<td>Moderate atypia cells with mitosis</td>
<td></td>
<td>Gynecomastia</td>
</tr>
<tr>
<td>6</td>
<td>Hamdy et al. (2019) [14]</td>
<td>73</td>
<td>Large swelling of the left breast from the clavicle to the hypochondriacal region measuring 22x25x26 cm.</td>
<td>Proliferation and hypercellularity form spindle cell fascicles. High degree of anaplasia and pleiomorphism. Large area of necrosis</td>
<td></td>
<td>Gynecomastia, Huge malignant phyllodes tumor</td>
</tr>
<tr>
<td>7</td>
<td>Jagmoohan et al. (2020) [15]</td>
<td>75</td>
<td>Breast lumps and bleeding from the nipple. Hard retroareolar mass</td>
<td>Leaf-like architecture, cystic space lined by epithelium and surrounded by hypercellular spindle areas, stroma overgrowth</td>
<td></td>
<td>Gynecomastia, prostate cancer</td>
</tr>
</tbody>
</table>


CONCLUSIONS

Phyllodes tumor of the breast is a rare type of neoplasm from a group of fibroepithelial lesions. The incidence of phyllodes tumor <1% of all breast neoplasms is 0.3–0.5% with the highest incidence occurring in the age range of 30–40 years. Although rare, there have been reports of phyllodes tumors in men. Several case reports were found from 1990 to 2020, there were only 13 articles showing phyllodes tumors in men.

The phyllodes tumor has a characteristic microscopic leaf-like appearance within the cystic cavity and a sarcomal stromal appearance. In men, phyllodes tumors are associated with gynecomastia. Gynecomastia has the potential to affect an estrogen/androgen imbalance. Several case studies mention that there is an incidence of breast tumors in men who use long-term estrogen therapy. Treatment with bicalutamide for men with prostate cancer can also lead to malignant phyllodes tumors in men.

Phyllodes tumors on male breasts are rare cases that need to be understood by physicians for diagnostic approaches and effective treatment. The male who have a history of gynecomastia or prostate disease should be cautious as they can develop phyllodes tumors in the future.

DECLARATIONS

Competing interest:
The authors declare no competing interest in this study

Acknowledgment
Not applicable

REFERENCES
