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Clinicopathology and treatment of a giant malignant phyllodes tumor of the breast: A case report and literature review

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ABSTRACT

INTRODUCTION: Phyllodes tumors (PTs) of the breast are extremely rare accounting for less than 1% of all breast tumors globally. Case records at the Trinidad and Tobago Cancer Registry show that only 0.003% of the reported breast cancer cases between 1995 and 2009 were PTs.
PRESENTATION OF THE CASE: We report a 45-year-old woman who presented with swelling of the left breast. Ultrasound, mammogram and computed tomography imaging confirmed the presence of a mass in the right upper inner quadrant of the left breast. A biopsy revealed features supportive of a benign phyllodes tumor. A wide local excision was performed with the removal of a $19 \times 11 \times 10$ cm mass. Histopathological analysis revealed features consistent with malignant phyllodes tumor. A complete mastectomy of the left breast was subsequently performed. Follow up over a 5-year period did not reveal any evidence of local recurrence or residual disease. To the best of our knowledge, this is the first case report of a malignant PT from the Caribbean and Latin America.
DISCUSSION: Phyllodes tumors are classified as benign, borderline, or malignant based on histologic features including presence of a clear margin, cellularity, stromal overgrowth, tumor necrosis and mitotic index. The clinical challenge is to assess the risk of local tumor and metastatic recurrence in the context of fluid classifications.
CONCLUSION: Our case management approach shows that for patients with malignant PT, a thorough preoperative workup regimen followed by appropriate surgical intervention can result in a desirable prognosis.

1. Introduction

Phyllodes tumors (PTs) of the breast are circumscribed biphasic fibroepithelial neoplasms analogous to fibroadenomas [1]. PTs are characterized by a double layered epithelial component surrounded by a hypercellular mesenchymal component, typically presenting in leaf-like processes [1]. These tumors are extremely rare, globally accounting for 0.3% to 1% of all breast tumors and 2.5% of all fibroepithelial tumors of the breast [2]. They commonly occur in women 35–55 years (median 45 years) [1].

The World Health Organization (WHO) classification schema grades PTs as benign, borderline, or malignant based on stromal patterns of cellularity, nuclear atypia, mitotic activity, heterologous stromal differentiation, stromal hypercellularity, cellular pleomorphism and tumor margin appearance [1]. However, absent clear defining boundaries for each of these histologic parameters, reliable classification assignment is challenging [3].

The majority (up to 60%) of PTs are benign [1]. Distant metastases have been reported in up to 22% of malignant PTs with expansion to nearly all internal organs, in particular the lung and skeleton [3]. Axillary lymph node metastases are rare. Wide local excision or mastectomy with appropriate margins is the preferred clinical intervention [4].

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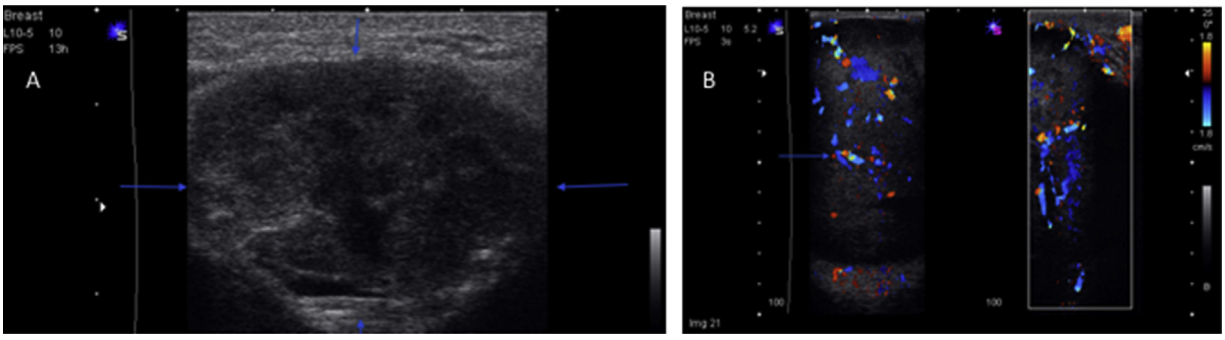

Fig. 1. A) Transverse ultrasound image of the left breast demonstrates a heterogeneous, mostly hypoechoic mass (blue arrows), the full extent of which is not demonstrated on the images. B) Transverse ultrasound image of the left breast with color doppler interrogation demonstrates a heterogeneous, mostly hypoechoic mass with internal vascularity (blue arrows), the full extent of the mass is not demonstrated on the images.

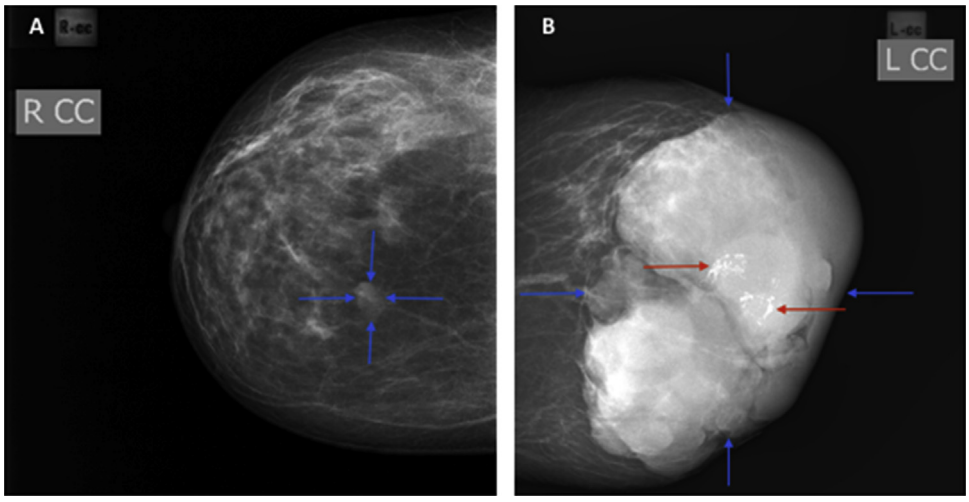

Fig. 2. Mammogram imaging of the left breast. A). The right craniocaudal view showing heterogeneously dense breast tissue with a fairly well defined spherical opacity in the right upper inner quadrant (blue arrows). B). The left craniocaudal view showing a large mass 13 cm (AP) × 13 cm (TS) with lobulated margins replacing most of the left breast parenchyma (blue arrows). A few scattered foci of coarse, punctate and plaque-like calcifications are seen within the mass centrally (red arrows).

We describe the case of a 45-year-old woman who presented to the Eric Williams Medical Sciences Complex (EWMSC), Champ Fleurs, Trinidad and Tobago (TT) with swelling of her left breast, which was later confirmed histologically to be a malignant phyllodes tumor. This case report was prepared according to the Surgical CAse REport (SCARE) guidelines which provides a framework for accuracy in surgical case reports[5,6].

2. Case presentation

A 45-year-old woman of Trinidad and Tobago nationality and East Indian ancestry, presented to the emergency room of the Eric Williams Medical Sciences Complex (EWMSC) with a 3-week history of left breast swelling. She had a body mass index (BMI) of 31.8 kg/m^2, and reported a history of diabetes mellitus type 2 and hypertension. The patient also reported abstinence from smoking and alcohol. She had four children, with the first birth occurring at 26 years.

She reported that the swelling occurred a few days after being accidentally hit on the left breast. Examination revealed a hard, nodular 13 × 10 cm mass, with no palpable axillary lymph nodes. An ultrasound revealed a heterogeneous, mostly hypoechoic mass with internal vascularity (Fig. 1A, and B). A mammogram revealed a heterogeneously dense breast tissue with a well-defined spherical opacity in the right upper inner quadrant (Fig. 2A). Further, a large mass with lobulated margins replacing most of the left breast parenchyma along with a few scattered foci of coarse, punctate and plaque-like calcifications were noted (Fig. 2B). These observations supported a clinical suspicion of phyllodes tumor. Computed tomography (CT) imaging of the chest revealed a large lobulated soft tissue density mass in the left breast (Fig. 3A–C).

An ultrasound-guided Tru-cut needle biopsy demonstrated features such as high stromal cellularity with moderate pleomorphism that would support a differential diagnosis of benign PT (Fig. 4). Histopathological examination revealed that the needle core sections were composed of cellular-stromal spindle cell lesions with hypocellular areas. The spindle cells showed mild pleomorphism, with few mitosis <5/10 high power field (hpf) and the tumor was devoid of glandular elements or foci of necrosis. However, because of heterogeneity of the tumor, wider sampling was considered essential for comprehensive evaluation.

A few weeks later, the patient returned to the hospital complaining of acute pain around the swelling. After counseling by the case management team, the patient agreed to have the mass surgically removed by wide excision. In brief, the patient was sterile prepped, draped and an elliptical incision was made around the affected area leaving 1 cm margins past the involved skin. Hemostasis was achieved using diathermy coagulation after the excision and a silicone drain was placed in situ. Her estimated blood loss was 150 ml. The deep tissues and skin were sutured with 2.0 vicryl and 3.0 prolene (subcuticular stitch looped in the middle), respectively. The operation was uneventful culminating with the excision of the large mass which was invading the skin and superior areolar complex. Postoperatively, the patient received divon (Diclofenac),

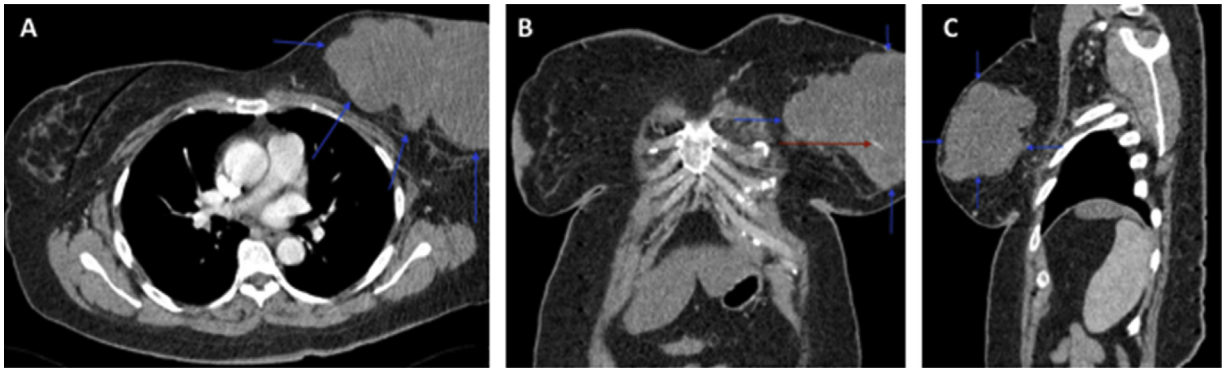

Fig. 3. Images from a CT chest post IV contrast in the arterial phase and in soft tissue window without significant enhancement post IV contrast administration. A). Axial view. Partially seen in the field of view of the scan is a large lobulated soft tissue density mass in the left breast corresponding to the previously seen mammographic mass (blue arrows). The visualized portion measures 9 cm (AP) × 12 cm (TS). No enlarged axillary or internal mammary lymph nodes seen. B). Coronal image. Partially seen in the field of view of the scan is a large lobulated soft tissue density mass in the left breast corresponding to the previously seen mammographic mass (blue arrows). Few central calcifications were observed (red arrow). The visualized portion measures 12 cm (TS) × 12 cm (Cranial-Caudal, CC). C) Para-sagittal image. Partially seen in the field of view of the scan is a large lobulated soft tissue density mass in the left breast corresponding to the previously seen mammographic mass (blue arrows). The visualized portion measures 9 cm (AP) × 12 cm (CC).

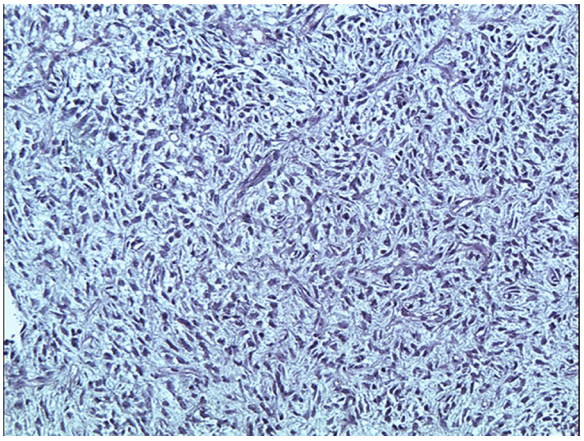

Fig. 4. Phyllodes tumor biopsy shows marked stromal cellularity with mild pleomorphism (Hematoxylin and eosin, H&E; 20×).

Invanz, Flagyl, an analgesic, and anti-embolism stocking. Ambulation was encouraged.

A complete mastectomy of the left breast was performed a few weeks later. In brief, the patient was sterile prepped, draped and Zinacef administered on induction. An incision made along the elliptical line drawn from the clavicle to the 6th rib to the sternum to the axillary tail. The breast was removed with deep margins including pectoralis fascia. Hemostasis was achieved and suturing was as for the prior surgery. Two silicone drains were placed in situ. Postoperatively, the patient received divon, Rocephin, an analgesic, and anti-embolism stocking. As before, ambulation was encouraged.

The excised specimen consisted of a large, firm oval mass partly covered by an ellipse of skin, measuring 20 × 15 × 10 cm. Cut sections revealed a fleshy grey-white tumor measuring 19 × 11 × 10 cm with satellite nodules close to the inferior margin. Histopathological investigations revealed that sections showed marked stromal cellularity with mild pleomorphism. Additionally, a well circumscribed cellular stromal tumor containing occasional glandular elements was observed. The epithelial component in the adjoining tissue and tumor showed ductal and lobular hyperplasia and focal in situ carcinoma (Fig. 5). There were foci of tumor necrosis, mild-moderate atypia foci of marked cellularity resembling fibrosarcoma with a mitotic index >5/10 hpf in the active areas (Fig. 6). No evidence of lympho-vascular invasions was observed. The tumor showed a predominately pushing growth

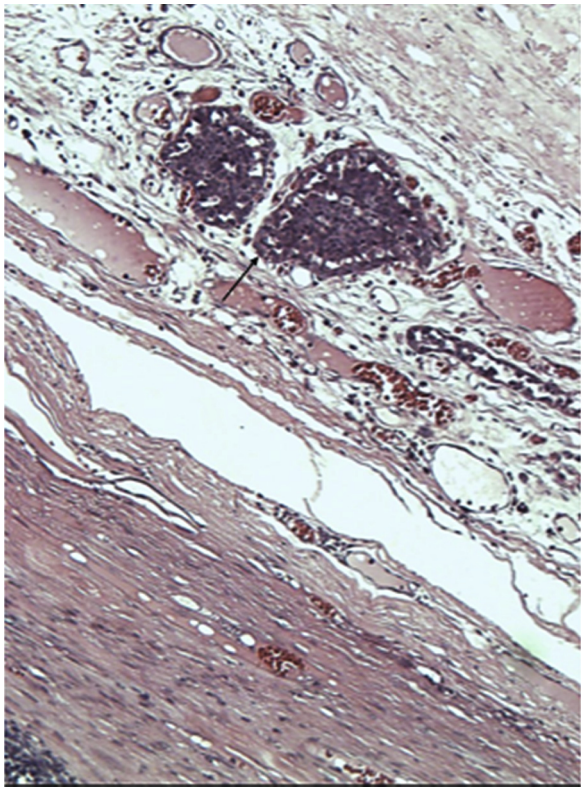

Fig. 5. Phyllodes tumor. Glandular elements showing duct hyperplasia at the periphery of the tumor (black arrow head). (H&E;10×).

pattern (Fig. 7). The medial, superior, and inferior margins were not clear. However, the posterior margin was clear but showed a breach in the capsule, while the lateral and anterior margins were close (<3 mm) but clear. These histologic features are consistent with the WHO grading for a malignant phyllodes tumor. Sections from the mastectomy specimen showed granulomatous inflammatory changes. Residual tumor was not observed in the lesion and all margins were clear.

At her bimonthly follow up appointment, Tramacet was prescribed to alleviate the intermittent pain around the incision site. She had an uneventful postoperative course and ten months later a surveillance CT did not reveal any recurrent or residual mass (Fig. 8).

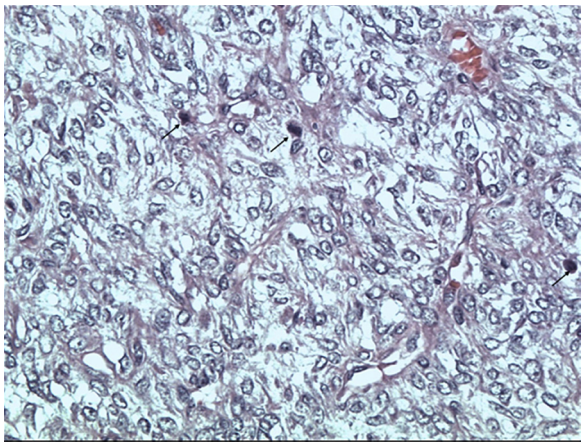

Fig. 6. Phyllodes tumor. Cellular stroma shows brisk mitoses (black arrow heads). (H&E; 40×).

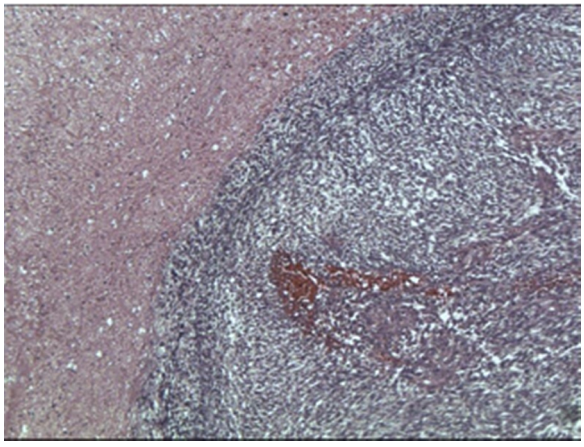

Fig. 7. Tumor showing a pushing growth pattern.

After a three-year absence, the patient returned to the clinic and a surveillance abdomen/pelvis and chest CT imaging regimen did not reveal any evidence of local recurrence or residual disease. A technetium 99 m (^{99m}Tc) hydroxyethylene diphosphonate (HDP) bone scan with anterior and posterior imaging was negative for uptake in the lumbar vertebral region which would have been suggestive of metastatic deposits. Stable disease with stable sclerotic lesions were observed in her lumbar vertebral bodies.

An exhaustive PubMed/Medline and EMBASE medical database search from inception (1946) to present was performed. The search strategy was created using indexing terms/keywords and the AND Boolean operator. For example; in PubMed: (Caribbean OR Latin America OR developing countries) AND (phyllodes tumor OR cystosarcoma phylloides). After limiting final retrieval to English language; humans and case reports; we retrieved one citation for a benign PT [7]. To the best of our knowledge; ours is the first case report of a malignant PT in the Caribbean and Latin America. A search of the TT Cancer Registry records revealed that only 12 (0.003%) of the 4685 reported breast cancer cases between 1995 and 2009 were phyllodes tumors (Table 1). All of the cases were malignant with most patients (11/12; 1 unknown) receiving only surgical intervention. The mean age at presentation was 49.

3. Discussion

In this case, there was a high degree of suspicion for a benign PT based in part, on the biopsy findings of few mitoses. However, histopathological examination of the mass revealed that the mitoses in active areas were >5/10hpf and thus strongly suggestive of malignant PT. Extensive imaging and histopathological workup is critical when a diagnosis of PT is suspected [8]. If the mass has a smooth contours, intramural cysts and low echogenicity on ultrasound, a PT is usually suspected and a core needle biopsy recommended [9,10]. In such cases, cytology specimens should contain both epithelial and stromal elements to confirm the PT diagnosis. However, there is oftentimes discordance between the core biology pathology and surgical histopathology in rendering a differential diagnosis between the various classifications of PT and fibroadenoma due to tumor heterogeneity [11,12].

All of the cases reported to the TT Cancer Registry since 1995 were classified as malignant. This is striking given that globally most PTs are benign. Distinguishing between benign, borderline, and malignant PT is critical to the development of an effective clinical management plan. There is significant variability in the interpretation of the criteria for each designation. Additionally, tumor heterogeneity, sampling errors increase reported variabilities. In fact, studies in which different pathologists have analyzed the same histological slides were marked by a 25% discordance in the final histopathological finding [13]. One approach to better delineate between benign and a malignant PT might be to assess the immunohistochemical (IHC) expression of CD10 in the stromal cells. CD10 immunoreactivity has the potential to inform on the histopathological grading of PTs, given that CD10 expression strongly correlates with PT grade [14,15]. Restaging with 18F-fluorodeoxyglucose positron emission tomography computed tomography (FDG PET-CT) could also be helpful in distinguishing between a benign and malignant PT [8]. This hybrid imaging modality benefits from the sensitivity of the PET component and the specificity of the CT component. However, it is not available in the Caribbean or most low resource countries. The challenges

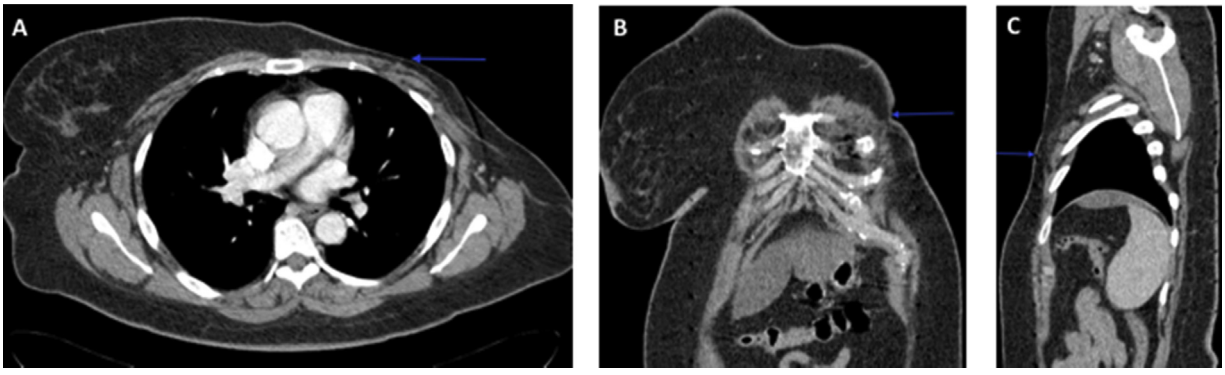

Fig. 8. Selected images of a CT chest post IV contrast in the arterial phase and in soft tissue window. A). Axial view B). Coronal view. C). Sagittal view showing post-surgical changes noted (left mastectomy) with no recurrent/residual masses seen (blue arrow).

Table 1
Reported phyllodes tumor of the breast cases in Trinidad and Tobago,1995–2017.

Ethnicity	Age at incidence	Basis of diagnosis	Stage	Classification	Surgery	Chemotherapy	Status at last contact	Follow up period	Source
Mixed	42	Histology of primary	Localized	Malignant	Yes	No	Alive	1 year	TT Cancer Registry
Unknown	40	Histology of primary	Localized	Malignant	Yes	No	Alive	2 years	TT Cancer Registry
African	57	Histology of primary	Unknown	Malignant	No	No	Expired	1 year	TT Cancer Registry
Mixed	73	Histology of primary	Regional	Malignant	Yes	No	Alive	1 year	TT Cancer Registry
Indian	49	Histology of primary	Localized	Malignant	Yes	No	Alive	2 years	TT Cancer Registry
Unknown	61	Histology of primary	Localized	Malignant	Yes	No	Alive	1 year	TT Cancer Registry
African	43	Histology of primary	Regional	Malignant	Yes	No	Alive	1 year	TT Cancer Registry
Indian	54	Histology of primary	Localized	Malignant	Yes	No	Alive	1 year	TT Cancer Registry
Indian	51	Histology of primary	Unknown	Malignant	Unknown	Unknown	Unknown	None	TT Cancer Registry
Indian	45	Histology of primary	Distant	Malignant	Yes	No	Alive	1 year	TT Cancer Registry
Mixed	49	Histology of primary	Localized	Malignant	Yes	No	Unknown	None	TT Cancer Registry
Indian	29	Histology of primary	Localized	Malignant	Yes	No	Alive	4 years	TT Cancer Registry
Indian	44	Histology of primary	–	Benign	Yes	No	Expired	6 months post-surgery	[7]
Indian	45	Histology of primary	–	Benign	Yes	No	Alive	4 years	This case

*Ethnicity was self-reported. These categories are based on physical observation without any assessment of genetic variants. Indian refers to ancestry from India, South Asia. All patients were nationals of TT.

of expanding nuclear medicine capacity in low resource countries were reviewed elsewhere [16,17]. The addition of FDG PET-CT to the diagnostic arsenal might be of value in developing countries given the increasing cancer burden.

While the molecular basis of phyllodes tumors largely remains unknown, the most frequent genomic insults are mutations in exon 2 of MED12, a subunit of the transcriptional mediator complex and RARA [18–20]. Interestingly, fibroadenomas also share this genetic signature [18–20]. Less frequently, mutations in *FLNA*, *SETD2* and *KMT2D* have also been reported in PT. Loss of function mutations in p53, deleterious mutations in *Rb1* and *NF1*, mutations in *PIK3CA* and *ERBB4*, and high-level copy number variations of *EGFR* were detected in borderline and malignant tumors [20]. However, *EGFR* and *IGF1R* gene amplifications were only detected in malignant tumors [21,22]. These mutational signatures of PT provide a possible framework to distinguish between the three subtypes. This type of genome forward clinical assessment is not available in Trinidad and Tobago and the Caribbean region, in general. Capacity building towards this level of precision medicine is fiscally challenging for the region, but is crucial for long term sustainable improvements in health care [23].

Breast-conserving surgery with appropriate margins (≥1 cm) is the preferred primary therapy for PT in the absence of metastatic disease [4]. In this case, given the histologic confirmation of a malignant tumor, we elected to perform a wide excision in accordance with National Comprehensive Cancer Network guidelines [24] followed by a mastectomy. Axillary dissection was not performed since nodal metastases secondary to PT are very rare. The utility of adjuvant therapy in the management of PT cases is unclear and there are no prospective or randomized studies of adjuvant chemotherapy in this setting. Recent reports recommended adjuvant therapy intervention for borderline cases with maximal diameter greater than 5 cm and those with histologic evidence of stromal overgrowth, since these seem to have greater metastatic potential [4,25]. For metastatic PTs, some studies have reported promising results with administration of ifosfamide, doxorubicin and dacarbazine [26,27].

Given the absence of metastasis or recurrence in the chest wall post mastectomy, radiotherapy was not offered to this patient. In fact, there are no prospective randomized data in support of radiotherapy for PT [24]. Recent studies advocate the use of radiotherapy for borderline and malignant PT, recurrent tumors and in cases where it is not possible to achieve a greater than one-centimeter surgical margin [25,28]. Given the rarity of PT, it might be challenging to derive a randomized controlled trial with adequate sample size.

4. Conclusion

Phyllodes tumors are extremely rare. The major challenge facing clinicians in developing countries is the availability of clinical resources to adequately distinguish between fibroadenoma and PT, and where PT is affirmed, to arrive at the appropriate PT classification. Our experience with this case in TT shows that adequate preoperative workup followed by surgical intervention can result in an improved prognosis for patients with malignant PT.

Conflicts of interest

None to declare.

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Ethical approval

Ethical approval was not required since patient is de-identified.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

All of the authors contributed substantially to the overall study concept, data collection, data analysis or interpretation, and writing the paper.

Guarantor

Wayne A. Warner, Vandana Devika Sookdeo, Maurice Fortuné, Meenakshi Akhilesh, Chalapathi Rao Adidam Venkata, Wayne Mohammed, Cassandra Ramkissoon, Dave Harnanan, Lemuel Pran and Ravi Maharaj.

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