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Diagnostic Approach to Soft Tissue Tumour of the Breast and Phyllodes Tumour in Ilorin, North Central with Review of Institutional Experience

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Abstract: Background: Primary soft tissue tumour (primary mesenchymal tumour) of the breast comprised of spectrum of neoplasm that arise from mammary stroma with comparable tumour biology of primary mesenchymal tumour at other sites. There are palpable diagnostic challenges which can be resolved by considering histomorphologic analysis that characterized each tumour entity regardless of the site and the use immunohistochemical markers. Methodology: This is an analytical hospital based retrospective study of patients with primary breast mesenchymal tumour and phyllodes diagnosed during 2014–2019 at the Department of Pathology, University of Ilorin Teaching Hospital. The histopathological diagnosis of primary mesenchymal tumour of the breast and phyllodes tumours with documented age and other inclusion criteria were used for the study but excluded patients with incomplete information. Result: This study analysed 39 patients with histological diagnosis of soft tissue tumour of the breast and phyllodes. The youngest patients was found to be 16 years of age while the oldest patients was 70 years with the mean age of 37.82±12.86. Benign phyllodes tumour accounted for 19 (48.7%), followed by borderline phyllodes 3 (7.7%) and 1 case of malignant phyllodes. Fibrosarcoma is the most common primary mesenchymal tumour of the breast which accounted for 6 (15.4%), followed by undifferentiated pleomorphic sarcoma 3 (7.7%) and 1 (2.5%) case of the following tumours, Neurofibroma, Granular cell tumour, Myofibroblastoma, Dermatofibroma, Low grade fibromyxoid sarcoma, Rhabdomyosarcoma and, Malignant phyllodes and Angiosarcoma. Conclusion: Primary mesenchymal tumour of the breast are rare or underdiagnosed, biopsy must be interpreted with caution in order to rule out their mimics that is phyllodes and metaplastic carcinoma with histomorphological analysis and complementary ancillary test.

Keywords: PT (Phyllodes Tumour), UPS (Undifferentiated Pleomorphic Sarcoma), FA (Fibroadenoma), ER, (Oestrogen)

1. Introduction

Most pathologic lesions in the breast arise from the epithelium. However, the components of the mammary stroma may also give rise to various neoplasm which are similar in clinical, macroscopic, microscopic and tumour biology with comparable prognosis to the primary mesenchymal tumour at other sites. [1] Majority of benign and malignant mesenchymal lesions which were reported in the other part of body have been described in the breast with view of differential diagnosis that might needs to be resolved through the use immunohistochemical markers.

Primary mesenchymal tumours of the breast comprised of broad spectrum of lesions that usually pose diagnostic challenges to surgical pathologists. The site-specific mimics that accounted for the majority of tumour in the breast with a sarcomatoid appearance which must be rule out based on histomorphological analyses and ancillary studies are metaplastic carcinoma and phyllodes tumour. These tumours might show fibroblastic, myofibroblastic, adipocytic, vascular differentiation may be encountered comprising of benign and malignant lesions. [2]

Benign mesenchymal tumours are lipoma, angiolipoma, neurofibroma, leiomyoma, schwannoma, granular cell tumor

and myofibroblastoma of the breast. Granular cell tumor is a benign tumour derived from Schwann cells of peripheral nerves which is commonly found in the adult female and male in the head & neck, tongue, and other parts of the body. Majority are benign, however, it may appear malignant clinically (irregular and firm mass), radiologically (ill-defined spiculated lesion), and pathologically (infiltrative growth pattern). [3] Malignant mesenchymal tumors of the breast are rare but might include angiosarcomas, leiomyosarcoma, rhabdomysarcoma, fibrosarcoma, malignant peripheral nerve sheath sarcoma and liposarcoma.

Mammary mesenchymal tumours require a careful approach to morphological clues and consideration of histologic mimics and pitfalls. A tumour of the breast with sarcomatous-appearance is far more likely to be a metaplastic carcinoma (spindle cell carcinoma) or a malignant phyllodes tumor rather than a primary sarcoma. Therefore, extensive sampling of the tumor with immunostained tissue sections are essential for correct diagnosis. The aim of this study is to highlight histopathological profile of the primary mesenchymal tumour of the breast and their mimics in Ilorin, North-Central.

The aim and objectives of this study are;

To determine the age of patients with primary mesenchymal breast tumour and phyllodes.

To determine histological patterns of primary mesenchymal breast tumour and phyllodes.

To determine the side of the breast.

To determine association between age of patients with primary mesenchymal breast tumour and phyllodes.

2. Methodology

This is an analytical hospital based retrospective study of patients with primary mesenchymal tumour of the breast and phyllodes diagnosed during 2014–2019 at the Department of Pathology, University of Ilorin Teaching Hospital. The study was conducted at the Department of Pathology University of Ilorin Teaching Hospital (U. I. T. H) Ilorin, Kwara state, a tertiary health facility in the North Central geopolitical zone of Nigeria. It is bordered by neighbouring states like Kogi, Niger, Osun, Oyo and Ekiti. There are four consultants in the Department of Pathology. There were facilities for routine H&E, Cytopathology. Immunohistochemistry services were recently suspended due to logistic challenges.

The inclusion criteria includes women with diagnosis of primary mesenchymal tumour of the breast and phyllodes tumours with documented age and other inclusion criteria.

The exclusion criteria are patients with incomplete information necessary for including patients into this study.

The surgical biopsies were promptly immersed in adequate volume of fixative of 10% neutral buffered formalin in an appropriate tight-fitting correctly labelled container for fixation. Then each specimen with an accompanying complete filled request form was sent to the Pathology Department. Thereafter, grossing of specimens was done by measuring the dimensions, colour, consistency, and weight of the tumour. Representative tumour tissue sections were submitted in tissue cassettes, subsequently tissue processing, embedding, and routine microtomy and staining were done. The slides were examined with histological diagnosis using the 2012 WHO classification system.

2.1. Method of Analysis

Data were subjected to statistical software analysis, SPSS, version 20 (SPSS, Inc., Chicago, IL, USA). Data obtained from the study were presented in tables, charts, and photomicrograph. Data were presented as the mean±standard deviation for quantitative variables and percentage for qualitative variables.

2.2. Ethical Issues

This study was conducted in compliance with the guidelines of the Helsinki declaration on biomedical research in human subjects. Confidentiality of the identity of the patients and personal health information was maintained.

3. Result

Table 1. *Age distribution of patients with primary soft tissue tumour of the breast and phyllodes.*

Age groups (years)	Frequency	Percentage
< 30	10	25.6
30 – 39	16	41.0
40 – 49	6	15.4
≥ 50	7	17.9
Mean±SD	37.82±12.86	
Age Range (years)	16 – 70	

This study analysed 39 patients with histological diagnosis of primary mesenchymal tumour of the breast (soft tissue tumour) and phyllodes in the University of Ilorin Teaching Hospital. The youngest patients was found to be 16 years while the oldest patients was 70 years and the mean age was 37.82±12.86. This is illustrated in table 1.

Benign phyllodes tumour accounted for 19 (48.7%), followed by borderline phyllodes 3 (7.7%) and 1 case of malignant phyllodes. Fibrosarcoma is the most frequently diagnosed soft tissue tumour of the breast which accounted for 6 (15.4%), followed by undifferentiated pleomorphic sarcoma (UPS) 3 (7.7%) and 1 (2.5%) case of the following tumours, Neurofibroma, Granular cell tumour, Myofibroblastoma, Dermatofibroma, Low grade fibromyxoid sarcoma, Rhabdomyosarcoma, Malignant phyllodes and angiosarcoma. This is shown in table 2. Left breast were affected in 25 (64.1%) cases while right breast was found in 14 (35.9%) as illustrated in figure 1. Majority of benign phyllodes tumour was found predominantly in patients less than 30 years with mean age of 28.95±5.24 and range of 16 to 35years. Borderline phyllodes most commonly found in the 5th decade, youngest patient was 39 years while the oldest found at the age of 45 years. Only 1 case of malignant phyllodes tumour which accounted by 2.5%. Fibrosarcoma is the commonest soft tissue tumour of the breast found

predominantly in the 5th and 6th decade, mean age of 50.00±8.51 and range of 40-60years followed by undifferentiated pleomorphic sarcoma in the 6th decade. Table 3.

Table 2. *Spectrum of Histological diagnosis of primary soft tissue tumour of the breast and phyllodes.*

Diagnosis	Frequency	Percentage
Benign phyllodes tumour	19	48.7
Borderline phyllodes tumour	3	7.7
Fibrosarcoma	6	15.4
Undifferentiated Pleomorphic Sarcoma	3	7.7
Others	8	20.5

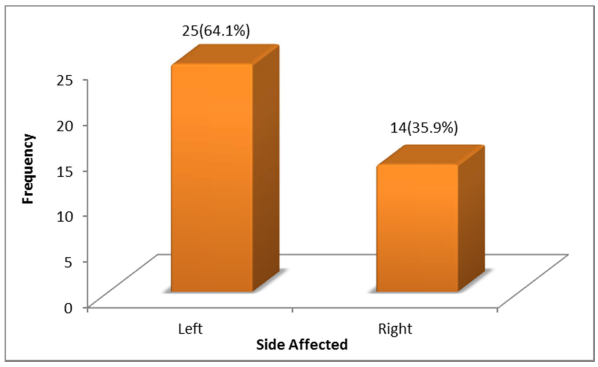

Figure 1. *Side of the breast affected with primary breast soft tissue tumour and phyllodes.*

Table 3. *Association between age of patients and Histologic diagnosis.*

Age groups	Diagnosis						
Years	**Benign phyllodes tumour (%)**	**Borderline phyllodes tumour (%)**	**Fibrosarcoma (%)**	**UPS**	**Others (%)**	**χ^2**	**ρ**
< 30	10 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**28.694[y]**	**0.004**
30 – 39	9 (56.3)	1 (6.3)	0 (0.0)	0 (0.0)	6 (37.5)		
40 – 49	0 (0.0)	2 (33.3)	3 (50.0)	0 (0.0)	1 (16.7)		
≥ 50	0 (0.0)	0 (0.0)	3 (42.9)	3 (42.9)	1 (14.3)		
Ranges	16 – 35	39 – 45	40 – 60	60 – 65	30 – 70		
Mean±SD	28.95±5.24	41.33±3.21	50.00±8.51	62.33±2.52	39.25±12.81		

[y] = *Yates corrected value* UPS: Undifferentiated pleomorphic sarcoma.

Table 4. *[3] WHO classification of Phyllodes tumor subtyping into benign, borderline, and malignant Subtype.*

Subtype	Stromal hypercellularity	Stromal cytologic atypia	Mitotic activity (stromal) per 10 high-power fields (10 hpf)	Tumour border	Comments
Benign	Mild	Minimal	<5	Pushing border (well-defined)	Stromal overgrowth not present
Borderline	Moderate/high	Moderate	Frequent (5–9)	Pushing±focal infiltrative	Features intermediate between benign and malignant
Malignant	High	Marked; + pleomorphism	>10	Infiltrative	High-grade sarcoma features with marked stromal overgrowth;±focal fibrosarcomalike appearance; ±heterologous elements

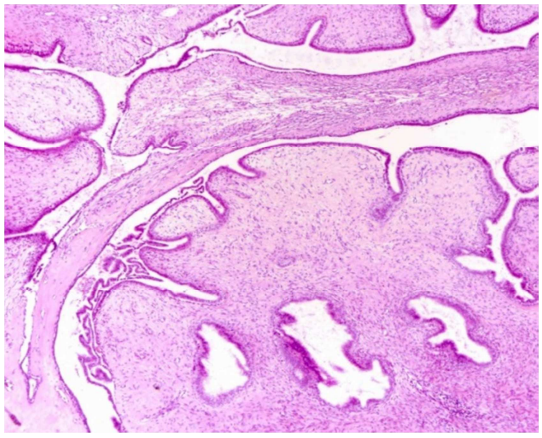

Figure 2. *Section shows intracanalicular leaflike architecture with stromal hypercellularity and lined by benign epithelial cells.*

4. Discussion

This study intends to highlight diagnostic features of the soft tissue tumour of the breast and phyllodes tumour with their prevalence from institutional experience. Phyllodes tumour was first described in the 19th century by Johannes Mu¨eller who introduced the term cystosarcoma phyllodes to an unusual type of fleshy tumor characterized by the formation of leaflike fronds projecting into cystic spaces. [1] It arises from fibroblasts of the specialized stroma of the breast with potential for limitless, invasive growth and the ability to stimulate the proliferation of entrapped glands. The stromal cells proliferate unchecked with growth advantage which leads to formation of large masses completely admixed with benign glandular elements, a phenomenon referred to as stromal overgrowth.

Grossly, the cross section of the tumour is lobulated with cleft-like spaces, a reflection of its classic "leaf-like" architecture. Necrosis may be present which might be secondary to either ischemic changes or inherent tumor necrosis. The overlying skin changes are not uncommon and range from discoloration to skin ulceration.

Phyllodes tumors (PTs) are diagnosed based on the presence of the following stromal features: stromal cellularity, stromal cytological atypia, stromal mitotic activity, and

prominence of stromal overgrowth. This tumour is stratify into the following major histologic subtypes: benign, borderline, and malignant. This histologic classification is based on recommendations from the World Health Organization. [3] Benign PT are characterized by stroma hypercellularity, mild or no cytologic stroma atypia, pericanalicular leaflike architecture and pushing border. An attempt has been made to standardize grading of stoma hypercellularity by Jacob et al [4] who used normal perilobular stroma cellularity as reference. Mild hypercellularity is characterized by stroma cellularity with overlapping of the stroma cells, high cellularity by extensive overlapping of the stroma cells and moderate is in-between. Borderline PT show features of benign PT with cytologic atypia, mitotic figures and stroma invasion. In this index study, Benign phyllodes tumour accounted for 19 (48.7%), followed by borderline phyllodes 3 (7.7%) and 1 case of malignant phyllodes. Phyllodes tumour and its subtypes in this study were categorized based on the WHO classification as illustrated in table 4. [3] A study done few years ago in the study centre reported 2 (0.38%) cases of malignant PT [5]. Review of PT showed varied regional reports in Nigeria, Egypt and Malaysia. [6-11] The surgical practice in the study centre involves clinical assessment, radiological with use of Ultrasound and pathological diagnosis from Fine needle aspiration and cytology (FNAC) and histopathological analyses of excised surgical specimens. Surgeon excised the palpable masses which was submitted inside 10% Neutral buffered formalin (NBF) together with request form and were diagnosed by pathologist. Accurate diagnosis and grading of phyllodes tumors are important for patient management and prognosis because grade correlates with increasing local recurrence and metastasis. A commonly encountered problem at the benign end of the spectrum is the distinction of benign phyllodes tumor from cellular fibroadenoma, which is largely due to the overlap in the histologic features. Thus, distinction is based on clinical, radiological and histomorphological features.

However, some centres performed core or needle biopsies for the diagnosis of PT with presence of only stromal component. The pathologist should make diagnosis of fibroepithelial lesion with a qualifying statement that the differential diagnosis includes Fibroadenoma (FA) and (PT). A study conducted to investigate diagnostic features overlap between FA and PT showed that 44 patients with phyllodes tumours had previous core biopsy specimens which were reported as fibroadenoma in 11 cases, spindle cell lesion of uncertain nature in 1 case and PT in 32 cases. [10] Thirty-eight cases of fibroadenoma had previous core biopsy specimens reported as fibroadenoma in 37 cases and 1 as phyllodes tumour. [11] The following four features were significantly more common in cores from phyllodes tumours and had a kappa statistic of > 0.6 in a reproducibility study: stromal cellularity increased in at least 50% compared with fibroadenoma, stromal overgrowth (x10 field with no epithelium), fragmentation and adipose tissue within stroma. [11]

Moreover, malignant PT, metaplastic carcinoma, fibromatosis and myofibroblastoma should also be considered based on cellularity and sarcomatoid appearance. Immunohistochemistry plays an important role during handling of core biopsies showing proliferating fibroblast without epithelial component. Malignant PT is more common than primary soft tissue tumour of the breast or metastatic sarcoma of the breast, however, malignant PT is less common than metaplastic carcinoma. [3] Metaplastic carcinoma will be positive for cytokeratin whereas malignant PT will be negative. In this index study, 6 (15.4%) and 3 (7.7%) were diagnosed as fibrosarcoma and undifferentiated pleomorphic sarcoma of the breast respectively. Fibrosarcoma is more cellular arranged in herringbone pattern or fascicles with greater degree of cytologic atypia and mitotic activity. This tumour is very rare in the breast, borderline PT, malignant PT or spindle cell metaplastic carcinoma should be excluded. These cases will benefit from re-classification with availability of immunohistochemistry test which were not done in the study. Morphologic features favouring fibromatosis composed of less cellular spindle shaped or stellate cells arranged in sweeping fascicles with interspersed myxoid or hyaline stroma, positive for nuclear beta catenin while myofibroblastoma is composed of spindle shaped cells arranged in long fascicles, uniform spindle cells with bland oval nuclei with interspersed ropy pink collagen, positive for Desmin, BCL-2, Oestrogen (ER) and C34. There is paucity of data on the prevalence of mesenchymal tumour of the breast, owing to under-diagnosis, paucity of specialist in Anatomic pathology especially in Africans countries, manpower and facilities for immunohistochemistry.

Angiosarcoma of the breast is a malignant vascular tumour which may be primary arises de novo within breast parenchyma, or it may be secondary developing in the skin, chest wall, or breast parenchyma after radiation treatment for breast cancer or lung cancer. [12] Primary angiosarcoma is the second-commonest sarcoma of the breast accounting for 0.05% of all primary breast malignancies. [12] The median age of patients with primary angiosarcoma is 40 years which is compatible with findings in this study and other review of angiosarcoma. [13, 14] while another report showed that angiosarcoma can occur in 17 years old patient. [15] Patients present with diffuse mass, breast enlargement and skin discolouration.

Grossly, angiosarcomas are haemorrhagic on appearance, borders are ill-defined, solid to firm and spongy consistency

Microscopic features are infiltrative, arborizing irregular, anastomosing vessels dissect through the breast parenchyma arranged in lobules and sheets lined endothelial cells with marked atypia. Necrosis and mitotic figures may be present. The endothelial cells are immunoreactive for CD31, CD34 or factor VIII.

Primary rhabdomyosarcoma of the breast is rare and poses challenges to pathologist especially in low resource countries where ancillary diagnostics tests are not available. It is a malignant neoplasm arising from mesenchymal supportive breast tissue that shows variable differentiation toward primitive skeletal muscle. Patients presented with painless

breast lump of varying sizes with or without metastasis.

Microscopic features are composed of sheets of spindle to stellate, or round to oval cells with increased nuclear cytoplasmic ratio, dense clumped chromatin pattern, hyperchromatic nuclei, and scanty eosinophilic cytoplasm. The stroma may be fibrocollagenous tissue or myxoid with variable cellularity often show alternating hyper- and hypocellular zone ("marbled" pattern). The cellularity is higher around stromal blood vessel with round or spindle cells with eccentric nuclei and prominent eosinophilic cytoplasm reminiscent of rhabdomyoblast which includes "strap cells," "tadpole cells," and "spider cells. These tumour cells will be immunostained with desmin, myogenin and MyoD1. This study reported a case of primary rhabdomyosarcoma of the breast in a 38 year old woman which accounted for 2.5% of all cases seen. Similar case reports were made by other authors at younger age of 16, 12, and 13 years respectively. [16-18] Although, immunohistochemistry of the tumour cells was not done in this study to confirm the histological diagnosis. It is also important to rule out malignant phyllodes tumour with heterologous differentiation that is rhabdomyoblastic with presence of rhabdomyoblast. This tumour cells will be immunostained positively for high molecular weight cytokeratin and negative for Myogenin and MyoD1.

Granular cell tumour is a benign tumor of schwann cell origin composed of round to polygonal cells with abundant eosinophilic cytoplasm. It is usually arises in skin and subcutaneous tissue with wide anatomic distribution commonly in the tongue, head and neck but rare in the breast. Patient present with solitary, slowly progressive mass, painless nodule or plaque.

Microscopically composed of overlying skin demonstrate pseudoepitheliomatous hyperplasia or parakeratosis and the sub epithelium showed sheets, nests, and cords of round to polygonal cells with abundant eosinophilic cytoplasm and fibrocollagenous tissue stroma. Histochemistry will show PAS positive diastase-resistant cytoplasmic granules and strong immunoreactive with diffuse S100 protein (+). A case of granular cell tumour was recorded in this study which accounted for 2.5% in a 30 year old woman while Nwafor et al [9] showed that it constituted 2 (0.3%) cases in Uyo. Similar findings were reported by other researchers at varying age of 52 years, 57 years and 32 years respectively. [19-21]

Neurofibroma is a rare benign mesenchymal tumour of the breast which arise from peripheral nerve sheath composed of Schwann cells, fibroblasts, and residual nerve axons within extracellular matrix. It may be cutaneous, diffuse and plexiform, however, plexiform type is essentially pathognomonic for neurofibromatosis type 1 (NF1). It is well circumscribed or well demarcated or plaque-like cutaneous growth and cross section is grey-white, firm to hard, fibrous to gelatinous cut surface. Microscopically it is composed of loosely or densely arranged spindle cells in sheets, with elongated, hyperchromatic, wavy or buckled nuclei and variable myxoid to fibrocollagenous tissue. The tumour is dermal based with subcutaneous proliferation that entraps adnexa and breast parenchyma. The tumour cell will stained positively for S100 protein. This study showed that breast neurofibroma in 45 year old female patient accounted for 2.5% which is concordant with other similar findings in 48 year old male and 33 year old female patients respectively. [22, 23]

The dermatofibroma arise from breast skin dermis, however, it can extend into the deep dermis and subcutis. Microscopically, it is composed of proliferating spindle shaped cells arranged in fascicles admixed with foamy histiocytes, Touton giant cells and hemosiderin deposits. A prominent storiform pattern is absent, no cytologic atypia, and mitoses are rare. Immunoreactivity to dermatofibroma is CD34 negative but Stromelysin is positive in dermatofibroma. This index study recorded a case of dermatofibroma in 32 year old female which constituted 2.5% and concordant with similar review. [24]

5. Conclusion

Primary mesenchymal tumour of the breast are rare or underdiagnosed, biopsy must be interpreted with caution in order to rule out their mimics that is phyllodes and metaplastic carcinoma with histomorphological analysis and complementary ancillary test. Pathologist should make diagnosis of fibroepithelial lesion in the presence of only stromal component in biopsy with a qualifying statement that the differential diagnosis includes fibroadenoma, phyllodes, metaplastic carcinoma and other soft tissue tumour based on his/her assessment of the biopsy together with adjunct immunohistochemical test. Risk assessment tool for predicting patients with risk of recurrence of phyllodes tumour was created by Singapore General Hospital's Department of Pathology is available for further comparative studies. (https://mobile.sgh.com.sg/ptrra/)

Conflict of Interest Statement

There is no competing or conflict of interest.

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