Giant Multilobulated Breast Mass, an Uncommon Manifestation of Fibroadenoma: A Case Study and Review of the Literature

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Abstract: A giant multilobulated breast mass is a rare and significant presentation of fibroadenoma characterized by their considerable size, exceeding 5cm and their rapid progression, which frequently results in notable breast distortion. It can cause symptoms such as stretching of the skin with multiple dilated veins, nipple changes and even ulceration that may mimic malignancy. Presented is a case involving a 33-year-old woman with a giant multilobulated breast mass of 6 years duration noticed during lactation. Clinical, imaging and histological evaluation revealed a definitive diagnosis of a giant fibroadenoma. She was offered surgical enucleation with satisfactory outcome. Giant fibroadenoma is rare and may be noticed during lactation simulating malignancy. Hormonal changes during pregnancy and lactation can stimulate the growth of fibroadenoma.Timely histopathological validation through immunohistochemistry is crucial to prevent the unnecessary treatment of benign lesions that resemble malignant condition. Surgical intervention with enucleation is the treatment choice for this benign disease and timely surgical intervention is recommended for the avoidance of complications that may be associated with late presentation of giant lesions.

Keywords: Giant, fibroadenoma, lactation, triple assessment, conservative surgery

INTRODUCTION

A giant multilobulated breast mass is a rare and significant presentation of fibroadenoma, a benign breast tumour composed of fibrous(stromal) and glandular(epithelial) tissue. While most fibroadenomas are small and grow slowly, giant fibroadenomas are characterized by their considerable size, exceeding 5cm and their swift progression, which frequently results in notable breast distortion or even skin ulceration [1,2]. The term multilobulated describes the appearance characterized by a lobed or divided structure for this generally well defined benign lesion [1]. Giant multilobulated fibroadenoma are a rare manifestation, making up a small percentage of fibroadenomawith some estimates placing their incidence at 0.5%-4% of all fibroadenoma [1,3]. The risk factors include genetic predisposition, excessive or hypersecretory oestrogen response in puberty [4]. They exhibit rapid and massive enlargement, quickly outgrowing typical fibroadenomas and causing significant distortion of the breast [4]. These large masses can cause symptoms such as stretching of the skin, nipple changes and even ulceration that mimic malignancy [2]. Atypical clinical and imaging can make them indistinguishable from more serious conditions such as phyllodes tumour and breast carcinoma resulting in a dilemma [1]. A multidisciplinary approach based on triple assessment is key to management [2]. The surgical management require excision biopsy. The significance of the biopsy is to rule out phyllodes tumour with a different treatment and follow up [3]. The prognosis for a giant fibroadenoma is generally good as there are benign tumour that do not increase the risk of malignancy [5,6]. The focus of this report is a case involving a 33-year-old woman with a giantmultilobulated fibroadenoma as a rare and important variant that require thorough histological analysis to rule out malignancy with a more challenging treatment. Furthermore, the lump was noticed during lactation.

Case Report

A 33-year-old female presented to the surgical outpatient with a history of a left breast lump of 6 years duration. She was apparently well until the past 6 years when she noticed a lump in her left breast while breast feeding her child. The lump which was initially small in size comparable to a walnut. It persisted and gradually increased in size over the past 2 yeas prior to her presentation in our facility. There was no history of loss of weight nor the presence of other swelling in any other part of her body. Menarche was at 14 years and her first pregnancy was at 19 years. She has 5 children with all breast fed. There was no family history breast cancer, nor that of trauma and radiation. She did not admit to a history of chronic cough nor having been in

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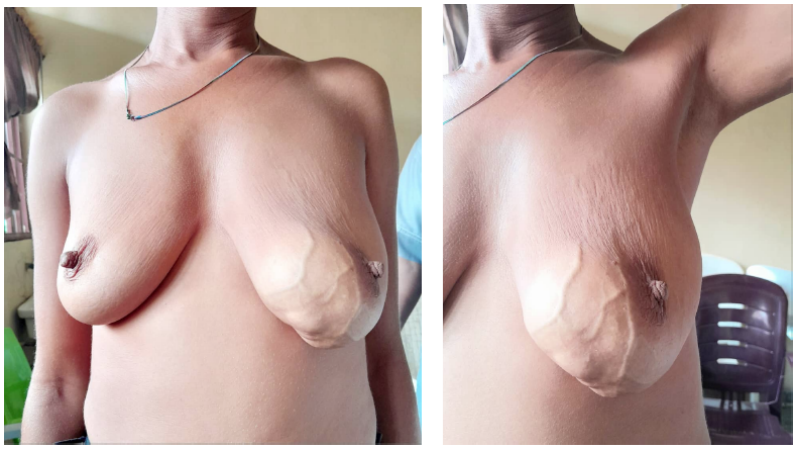


a b

Figure 1: a, b. Clinical photographs of the multilobulated left breast mass with prominent distended veins.

contact with people with chronic cough. She had no low back pain nor weakness in the lower limbs. There was no chest pain or difficulty in breathing. She had no abdominal swelling or yellowness of the eyes. There was no visual problem, headache or convulsion.

Upon clinical examination, she was not in any distress, not pale, anicteric, with no pedal oedema or peripheral lymphadenopathy. Vital signs revealed a temperature of 36.7^{0}C, respiratory rate of 22cycles/min., pulse rate of 80 beats/min. and blood pressure of 120/80mmHg. Chest was clinically clear. The left breast was asymmetrically enlarged with prominent distended superficial veins and no skin changes. The nipple-areolar complex was normal. There was a mass located in the inner lower quadrant extending laterally towards the nipple. It was oblong in shape, multilobulated and well circumscribed with the overlying dilated veins in the skin. It was non tender, firm, mobile and measured 12cm in the widest dimension. There was no axillary lymphadenopathy, Figure **1a**, **1b**. Abdominal examination was unremarkable. A clinical diagnosis of a giant fibroadenoma or phyllodes tumour was made.

The diagnostic evaluation included a packed cell volume of 33% and a total white cell count of 5.4(4.0-12.0) x 10^3/ul with the following differential white cell count: neutrophil at 47%, lymphocytes at 46%, monocytes at 1%, eosinophil at 1% and basophil at 0%. Retroviral serology results were non-reactive and the urinalysis was normal. Breast ultrasound scan (USS) reported: the left breast with a large circumscribed lobulated hyperechoic mass with few cystic foci extending from the left lower inner quadrant to the upper inner quadrant with minimal involvement of the lower outer quadrant measuring about 10 x 11cm. There was minimal flow on doppler study. The retromammary space and axillary tail were normal. There was no axillary or intramammary lymphadenopathy. The overlying skin and nipple were normal – large breast mass BIRADS 3 – hamartoma, phyllodes tumour.

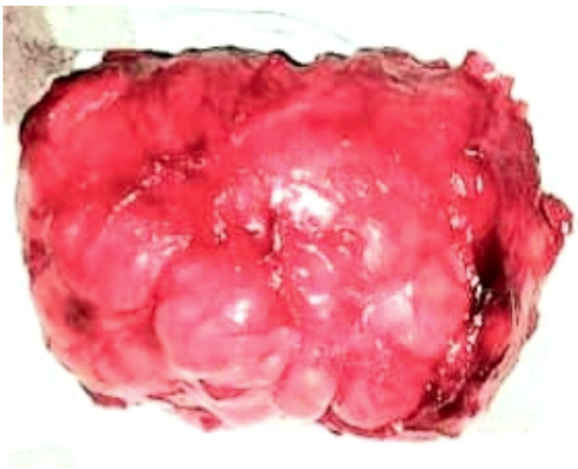
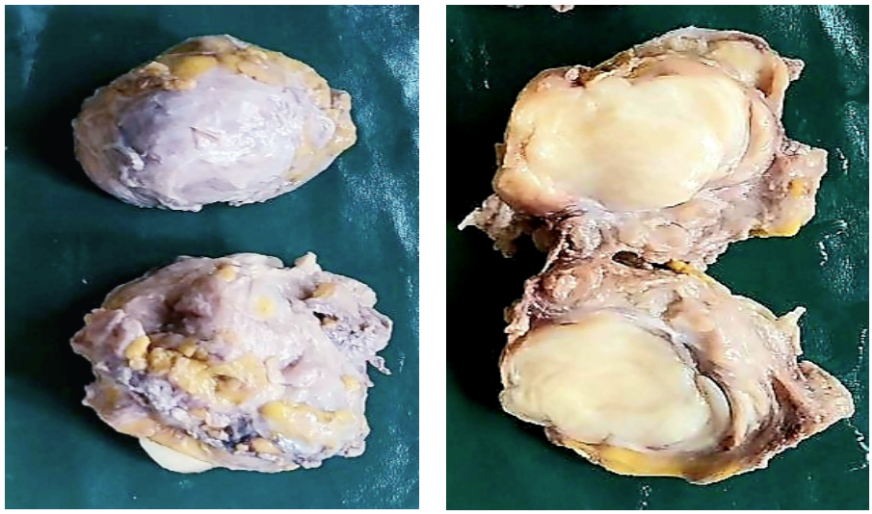


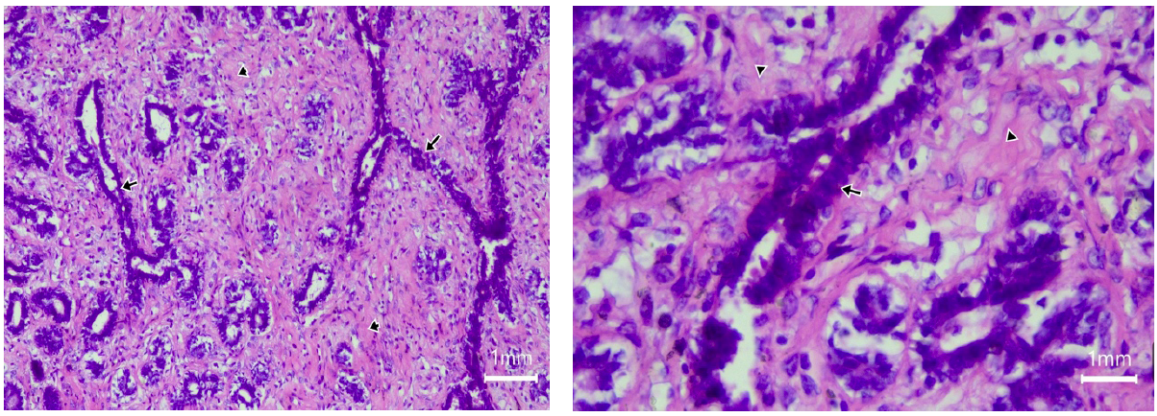
Figure 2: Photograph showing an excised multilobulated left breast mass.

The patient underwent an excision biopsy with a drain in situ with the following findings: a multilobulated mass that measured 12cm in the widest dimension, Figure **2**. It was mobile and not attached to the skin and the deeper structures. The postoperative period was uncomplicated and the patient discharged to the outpatient on the 3rd day after the surgery following the removal of the drain after 48 hours. Follow up examination indicated satisfactory wound healing while the histological analysis revealed: Grossing – breast lump that measured10 x 7.5cm, soft to firm multinodular and greyish tan mass, Figure **3a**. Cut surface showed bulging pale yellow appearance,



a **b**

Figure 3: a,b. Gross pictures – **a**, upper showing the anterior surface of the excised mass and the lower, the posterior surface.



a **b**

Figure 4: a) H&E x100, **b**) H&E x 400. Section of breast tissues showing biphasic proliferation of glands and fibro myxoid stroma. The glands are compressed into slit-like structures lined by outer myoepithelial cells and inner columnar cells. Long arrow – showing the compressed glands, arrow head -myxoid stroma and no atypia.

Figure **3b**. Microscopy: Histological section of breast tissue that showed hyperplasia of ducts and stroma. The ducts are compressed into slit-like spaces by the surrounding fibrocollagenous stroma. Some areas showed variable dilated cystic ducts. The ducts lining consist of inner cuboidal epithelial cells and outer myoepithelial cells with no atypia – Left breast fibroadenoma, Figure **4**. The postoperative evaluation has been conducted over a period of six months during which no indication of recurrence have been observed. The patient conveyed a sense of satisfaction regarding the aesthetic results.

DISCUSSION

Fibroadenoma is common benign lesion of the breast characterized by proliferative epithelium and stromal tissue [7]. Giant fibroadenoma is rare subtype of fibroadenoma classified when its size is greater than 5cm and weighs more than 500gm or replaces more than 80% of the breast [8]. Fibroadenomas are typically found in women in the second and third decades of life with a prevalence of 2.2% [8]. Giant fibroadenoma are rare and represent less than 4% of all fibroadenomas [4,8]. They usually occur in adolescent women or older female during pregnancy and lactation in keeping with our presentation[7]. Bhargava *et al* [9] and Bairwa [10] described giant fibroadenoma in a perimenopausal female and a postmenopausal female respectively. It commonly affect women with African, Asian descent and the African-American female has an increased risk [3,4].

There is no consensus regarding the exact aetiology of giant fibroadenoma; however, the risk

factors may be genetic or hormonal [4]. Abnormal response to oestrogen receptor sensitivity as evidenced by their increased frequency during puberty, oral contraceptive and cyclical hormones decreased oestrogen antagonist level during puberty have been implicated in the pathogenesis of fibroadenoma [3]. It is also hypothesized that the mediator complex subunit 12 (MED 12) gene plays a role in the pathophysiology of fibroadenoma [8]. Mutations in the MED12 gene are frequently observed in benign breast tumours, such as fibroadenomas, and are associated with changes in gene expression, as well as interactions with the stromal-epithelial microenvironment. These alterations, along with the influence of oestrogen and progesterone receptors, contribute to tumour proliferation and involve a complex regulatory network that may impact tumorigenesis [11-13]. MED12 somatic mutations are particularly prevalent in benign breast tumours, occurring in approximately 70% of fibroadenomas, and are also linked to benign and borderline phyllodes tumours. As a critical component of the mediator complex, MED12 is essential for the regulation of gene transcription. The mutations of MED12 are significant in the pathogenesis of specific breast tumours, as they can modify the expression of genes associated with signalling pathways, including WNT and TGF-beta [11]. Gene expression profiling has revealed additional differentially expressed genes in giant fibroadenomas, such as FN1, CDC6, IL23A, CCNAS, and MCM4, which are associated with pathways including P13K-AKT signaling and cell cycle regulation [14]. The interaction between stromal tissue (connective tissue) and epithelial tissue (lining of glands and ducts) is dynamic and vital for both mammary gland development and tumour growth. The influences of oestrogen receptor (ER) and progesterone receptor (PR) are of paramount importance in breast development and serve as major drivers of growth in various breast cancers. The dysregulation of oestrogen and progesterone signalling pathways has been implicated in the initiation and progression of breast cancer [13,15].

Giant fibroadenoma are fast growing masses that can cause pressure atrophy to the adjacent breast tissue, dilated veins and sometimes skin ulceration, mimicking a malignancy [8,16]. It is usually unilateral in 90% of cases frequently in the upper outer quadrant. Ours waslocated in the lower inner quadrant [3]. Clinical diagnosis may be difficult because of the similarity with other breast lesions [16] as shown in Table **1**.

The second pillar of the triple evaluation is imaging. It is difficult to distinguish between giant fibroadenoma and phyllodes tumour because of considerable overlap in imaging features [17]. USS is the recommended imaging modality for patients less than 30 years. Mammography is recommended for patients greater than 40 tears, while those between 30-40 years may be evaluated first by USS followed by diagnostic mammogram. The image should always be staged per breast imaging reporting and data system (BIRADS) [18]. Our patient report was BIRADS 3 and suggested hamartoma or phyllodes tumour. Data from sonographic measurements related to breast diseases entails a detail analysis of various characteristics of a lesion, including its shape, margins, orientation, echogenicity, vascularity and posterior features. Subsequently a BIRADS category ranging from 0 to 6 is assigned to indicate the degree of suspicion for malignancy. The BIRADS classification serves as an interpretative framework, encompassing findings from negative results (BIRADS) to confirmed malignancy identified through biopsy (BIRADS 6), Table **2** [19]. Standard radiological examination; USS and mammogram might not be conclusive in the diagnosis.

In some cases of giant fibroadenoma, a triple assessment may not help in a final diagnosis with the definitive diagnosis only revealed after surgery [2]. Histological analysis is indicated and helpful in the final diagnosis. Histological features of fibroadenoma include glandular (epithelial) and fibrous (stromal) components characterized by a uniform proliferation of spindle shaped cells and benign ducts [20]. Immunohistochemistry (IHC) can help distinguish

Table 1: Differential Diagnosis of Giant Fibroadenoma

Non-neoplastic	Neoplastic – Benign	Neoplastic – Malignant
Hamartoma	Benign phyllodes tumour	Malignant phyllodes tumour
Haematoma	Giant lipoma	Breast cancer
Large breast abscess		
Breast tuberculosis		
Large cyst of fibrocystic disease		
Parasitic cyst		

Table 2: BIRADS Description

Category	Description	Probability of malignancy
0	Incomplete – Need additional imaging evaluation and/or prior images for comparison	Nil
1	Negative – Symmetric, no masses, architectural distorsion or suspicious calcification	0%
2	Benign – Findings are definitely benign (Simple cyst)	0%
3	Probably benign – Findings that are very likely benign, but require short interval follow up to confirm stability	<2%
4	Suspicious for malignancy – Finding are sufficiently suspicious to warrant a biopsy	2-95%
5	Highly suggestive of malignancy – Findings are highly suggestive of malignancy	>95%
6	Known biopsy proven malignancy – Imaging performed after biopsy confirms malignancy prior to definitive surgery	-

phyllodes tumour from fibroadenoma by assessing the expression of markers like CD10 and Ki-67 in the tumour stroma. Increased stromal cell CD10 expression is associated with phyllodes tumours while higher Ki-67 (a proliferative marker) is often seen in the stroma of more aggressive phyllodes tumours to fibroadenoma. The combined use of multiple marker such as p53 and CD117 can enhance diagnostic accuracy of these overlapping lesions [21]. Furthermore, the field of breast pathology, CD34 serves as a marker for identifying endothelial cells within blood vessels and evaluating micro-vessel density, which is indicative of tumour proliferation and invasiveness. Ki-67 functions as a proliferation marker, reflecting the rate at which cancer cells are dividing; elevated levels of this marker are associated with more aggressive tumours and can inform treatment strategies. Additionally, B-catenin is linked to cell adhesion mechanisms and the WNT signaling pathway; its abnormal accumulation in the nucleus or cytoplasm may signify a more invasive and aggressive tumour phenotype, associated with a poor prognosis

Table 3: Comparative Features of Fibroadenoma, Phyllodes Tumour and Hamartoma

Investigation	Fibroadenoma	Phyllodes tumour	Hamartoma
Imaging - USS	Uniformly hypoechoic: a well circumscribed oval, solid mass with homogenous internal echoes Margin: smooth and well defined Vascularity: Typically hypo-vascular on doppler USS	Heterogenous: A solid mass with heterogenous echogenicity and non-homogenous echo pattern Internal cysts: The presence of internal cysts and fluid filled clefts is a key distinguishing feature. Vascularity: Hyper-vascular more common than in fibroadenoma	Mixed echogenicity: mixed echogenicity (fibro-glandular) and anechoic (fat) component. Margins: smooth and well defined.
Histology	Epithelial and stromal components: Consists of benign elements and a fibrous stromal component. Growth pattern: Characterized by either a peri-canalicular (stroma surround ducts) or intracanalicular(stroma compresses ducts into clefts) pattern. Stroma: uniform and has low cellularity Mitosis: minimal mitotic activity.	Leaf-like architecture: Characterized by an exaggerated intracanalicular pattern forming leaf-like clefts and fronds. Stromal cellularity: varies from mild to highly cellular often with high cellularity surrounding the ducts Mitosis: mitotic activity nuclear atypia and stromal overgrowth are key features used for grading (benign, borderline or malignant).	Disorganized tissue: A mix of normal breast tissue components – including mature fat, glandular elements and fibro-stroma, arranged in a disorganized but benign manner Encapsulated: Surrounded by thin fibrous capsule.
Immunohistochemistry (IHC)	Stroma: uniformly low Ki-67 proliferation index Epithelium: Hormone receptors (oestrogen and progesterone) are typically positive. Stromal component: CD34 expression may be present in the stroma.	Stroma: can show increased Ki-67 proliferation index especially in borderline and malignant subtypes. p53 expression can also be increased in high grade tumours. Genetic mutation: High grade tumours may show TERT promoter mutations.	No specific markers: mirrors normal breast tissue a marker for proliferation e.g., Ki-67 are low.

[22,23]. Fibroadenoma, phyllodes tumour and hamartoma are all fibroepithelial breast lesions, they differ significantly in their imaging, histology and immunohistochemical features [24]. Table **3** shows the comparative features of fibroadenoma, phyllodes tumour and hamartoma based on USS, histologic and IHC features.

Surgical enucleation is less invasive and the mainstay of treatment of giant fibroadenoma to allow compressed normal surrounding breast tissue retain normal function and appearance. A sub-mammary incision is preferred to provide excellent cosmesis. The challenges of breast asymmetry or deformity result in cosmetic problem leading to psychological disturbance [21]. In some cases, reconstruction techniques and plastic surgical expertise are required [1]. Surgical excision remains the predominant treatment for giant fibroadenomas, particularly when these tumours result in pain or cosmetic concerns. This intervention, however, has the potential to induce notable postoperative cosmetic issues, such as deformity or asymmetry, particularly in adolescent patients. For giant fibroadenomas that arise during pregnancy, it is generally advised to postpone surgery until after lactation to allow for potential tumour shrinkage prior to any surgical intervention. If significant deformity occurs, reconstruction surgery may be necessary, although this is typically carried out only after the breast has achieved skeletal maturity and any initial swelling has subsided, which can be up to one year following the initial excision [20]. Although less common, cryoablation serves as an alternative method for fibroadenoma removal. Giant fibroadenomas are influenced by hormones such as estrogen and progesterone, with gene expression research identifying markers including MED12, FN1, CDC6, and IL23A as potential contributors to their development [14]. Hormonal fluctuations, particularly those associated with pregnancy, can precipitate rapid tumor growth; hence, surgical excision is the primary management strategy. However, this approach carries potential risks of cosmetic deformity or asymmetry. While alternative treatments, such as cryoablation, may be utilized, surgical excision continues to be the most prevalent method for addressing large fibroadenomas [25]. Fibroadenomas are responsive to hormonal changes, with their growth often accelerating during periods of elevated hormonal activity, including puberty, pregnancy, and the menstrual cycle [20,25]. In pregnancy, the increased levels of estrogen, progesterone, and prolactin can lead to a rapid enlargement of giant fibroadenomas, sometimes necessitating surgical excision postpartum. Although some giant fibroadenomas may shrink following the cessation of lactation, it is advantageous to delay surgical intervention until hormonal levels stabilize, allowing for the potential for smaller excisions [25].

CONCLUSION

Giant fibroadenoma is a rare occurrence. Hormonal changes during pregnancy and lactation can stimulate the growth of fibroadenoma. Prompt histopathological verification using immunohistochemistry is crucial in order to prevent unnecessary treatment of benign lesion that can be mistaken for malignant conditions.Timely surgical intervention for large benignbreast tumour is recommended to prevent potential complications that could arise from delayed diagnosis of large benign lesions.

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