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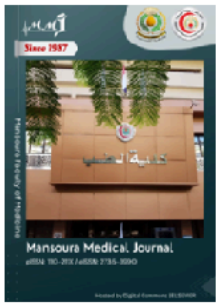


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Jaudah Al-Magharbi

*Department of Pathology', Faculty of Medicine, King Abdulaziz university, King Abdulaziz university Hospital*

Wedad Hanna

*Jeddah, Saudi Arabia. Sunnybrook and Women's College Health Science Centre , Department of Pathology, University of Toronto, Toronto, Ontario, Canada*

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# BREAST GIANT FIBROADENOMA WITH VASCULAR STROMA AND RECURRENCE AS MALIGNANT PHYLLODES TUMOR

*By*

**Jaudah Al-Magharbi**, Wedad Hanna*****

*From*

*Department of Pathology*, Faculty of Medicine , King Abdulaziz university, King Abdulaziz university Hospital**, Jeddah, Saudi Arabia. Sunnybrook and Women's College Health Science Centre***, Department of Pathology, University of Toronto, Toronto, Ontario, Canada.*

## ABSTRACT

The stroma of fibroadenoma and phyllodes tumor consists of fibroblastic proliferation. Rarely the stroma contains bundles of smooth muscle. Vascular stroma is not a feature of fibroadenoma. We report a case of a 34-year old Chinese woman presented with a huge mass occupying much of the entire left breast. Left mastectomy was performed and showed a large well-circumscribed lobulated rubbery firm tumor measure 13x10x6cm. Microscopic examination revealed a remarkable neoplasm in a form of fibroepithelial tumor formed by an organoid pattern of ductal structures with very striking stromal appearance composed of extensive vascular proliferation throughout the tumor confirmed by strong immunoreaction for the endothelial cell markers CD31, CD34 and factor VIII. Ultrastructural examination confirm the endothelial nature of the lining of the vascular channels in the stroma which showed spindle cells with intercellular junctions, Basal lamina, Pinocytotic vesicles and some weibel-Palade bodies. Those finding rule out the diagnosis of pseudoangiomatous hyperplasia. The patient developed a local recurrence few months latter and the resection showed a malignant phyllodes tumor with ductal carcinoma in situ.

In conclusion we described the first reported case of a unique giant fibroadenoma with abnormal vascular proliferation with recurrence as malignant phyllodes tumor associated with

in situ carcinoma. This extensive vascular stroma may play a role in the malignant transformation of the epithelial and stromal components.

*Key words :* Giant fibroadenoma-Cellular fibroadenoma-Phyllodes tumor-Vascular breast lesion-Angiogenesis.

### CASE HISTORY

A 34- year old Chinese woman presented with a huge mass occupying much of the entire left breast. Left mastectomy was performed and showed a remarkable neoplasm in a form of fibroepithelial lesion (giant fibroadenoma) with cellular stroma and extensive vascular proliferation through out the tumor, which confirmed by immunohistochemistry and Ultrastructural examination. The patient developed a local recurrence few months latter and the resection showed a picture of a malignant phyllodes tumor with ductal and lobular carcinoma in situ. A past history of right mastectomy 5 years ago was obtained (no pathology available).

## MATERIAL AND METHODS

All specimens were received fixed in 10% neutral formalin. Paraffin-embedded blocks and sections were prepared in the conventional manner and stained using hematoxylin and eosin. The immunohistochemistry was performed by using avidin-biotin complex technique (ABC) with appropriate positive and negative controls. The immunohistochemistry panel included antibodies against CD31, CD34, f VIII, S100, Actin, Desmin and vimentin. The sources and dilution of the antibodies are shown in Table 1. For electron microscopy paraffin-embedded formalin fixed tissue was post fixed in osmium and ultrathin sections were cut after appropriate area were selected from semithin sections.

## PATHOLOGIC FINDING

The initial breast tumor was a large well-circumscribed lobulated rubbery firm tumor, which measure 13x10x6cm. The cut surface showed focal area of hemorrhage but no definite necrosis. The tumor was surrounded by a narrow rim of breast tissue. No other focal lesions were seen.

Microscopic examination showed a fibroepithelial tumor formed by an organoid pattern of regularly spaced ductal structures surrounded by a dense and cellular fibrous stroma.

The morphology of the stroma was quite striking. There were numerous arborizing, well-formed vascular channels that are present through out the stroma. In some areas this was associated with marked edema and some extravasation of red blood cells. The lining of these vascular channels consisted of plump endothelial cells with no evidence of significant atypia or increased mitotic activity. This lining endothelium showed strong positivety for CD31, CD34, and factor VIII, ruling out the possibility of extensive pseudoangiomatous hyperplasia. The spindle cell fibroblastic stroma showed mild nuclear atypia and the mitotic rate ranged from 1-2/10 HPF. They showed strong positively for vimentin and they were negative for S100. The lesion had well-circumscribed margins that was nodular and lack the infiltrative border. The surrounding breast tissue showed lobular atrophy and stromal fibrosis. There was no evidence of any significant epithelial changes. Sections from the nipple were unremarkable and the lesion appeared completely excised.

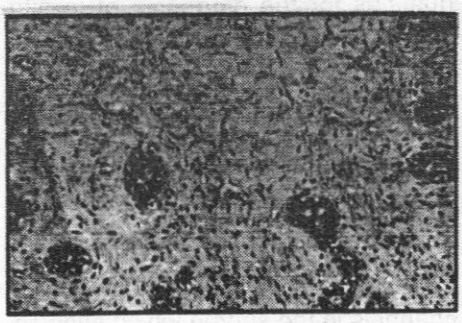
The recurrent tumor was a large rubbery soft well-circumscribed mass measure 10x6x4 cm. The cut surface of the tumor was bulging with a nodular contour and extended down to the fascia. Microscopic examination showed a variable appearance. In some area it had the characteristic appearance of malignant phyllodes tumor with extremely cellular stroma having atypical spindle shaped cells and showing a mitotic rate that varied from 5-6/10 HPF. There was a focal area showing a prominent network of vascular proliferation as seen in the primary tumor, however that did appear to be a diffuse feature as in the primary tumor. No evidence of malignant vascular component was seen. The other very unusual feature in this recurrent tumor was the marked and severe atypical proliferation of the epithelial elements, which qualifies for the diagnosis of in situ ductal carcinoma.

*TRANSMISSION ELECTRON MICROSCOPY:*

Ultrastructural examination of the primary tumor confirm the endothelial nature of the lining of the vascular channels in the stroma which showed spindle cells with intercellular junctions, Basal lamina, Pinocytotic vesicles and some weibel-Palade bodies.

TABLE I.Antibodies used for immunohistochemical studies

| Antibody | Type | Dilution | Pretreatment | Source |
|---|---|---|---|---|
| FVIII | Polyclonal | 1:600 | Digestion with pepsin | DAKO Cat#A082 |
| CD31 | Monoclonal | 1:40 | Microwaving with citric Buffer PH6.0 | DAKO Cat#M0823 |
| CD34 | Monoclonal | 1:2 | Digestion with pepsin | Biogenex Cat#AM286 |
| Actin | Monoclonal | 1:500 | - | DAKO Cat#M0635 |
| Desmin | Monoclonal | 1:500 | - | Biogenex |
| Vimentin | Monoclonal | 1:100 | Microwaving with citric Buffer pH 6.0 | SA NBIO |
| S100 | Polyclonal | 1:2500 | - | DAKO Cat#Z311 |



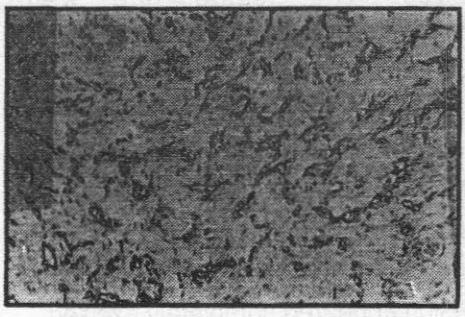


Figure 1. A, The primary tumor showing a fibroepithelial lesion with numerous arborizing vascular channels in the stroma (Hematoxline-eosin, original magnification x100)

B, Immunohistochemistry of CD31 showing a strong positive staining in the lining of the vascular channels(original magnification x100).

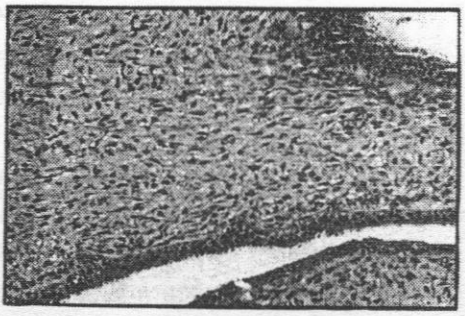
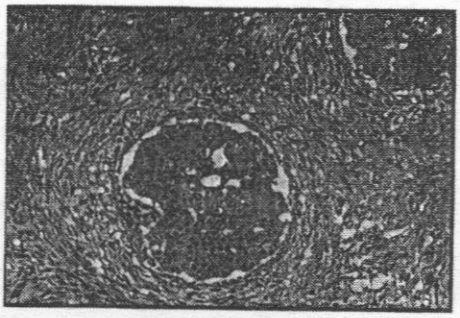


Figure 2. A, The recurrence tumor showing from area with a malignant phyllodes appearance with high mitotic figure in the stroma. (original magnification x400)



B, The recurrence tumor . with area of in sit ductal carcinoma( original magnification x200)

## DISCUSSION

The stroma of fibroadenoma consist of fibroblastic proliferation 1. Rarely the stroma contain bundles of smooth muscle 2. Vascular stroma is not a feature of fibroadenoma.

In our case the microscopic examination of the primary tumor showed a fibroepithelial lesion with features of fibroadenoma accompanied with unusual and peculiar stroma composed of extensive vascular proliferation throughout the tumor. The endothelial nature of the lining of these vascular channels confirmed by immunohstochemistry and electron microscopy examination, which rule out the possibility of being extensive pseudoangiomatous hyperplasia, since the spindle cell lining of the psudoangiomatous hyperplasia exhibit reactivity for Vimentin and CD34 but no reactivity for fVIII or CD31 other endothelial markers 3-8. The Ultrastructural examination of the lining of pseudoangioma-

tous hyperplasia shows incomplete layers of fibroblastic cells.

Although the tumor had a focal areas of cellular fibroblastic stroma, however it did not qualify for a diagnosis of cystosaroma phyllodes. The pattern of this vascular proliferation does not resemble any previously described vascular lesion in the breast9-17. The role of the vascular stroma in the pathogenesis and progression of both the epithelial and mesenchymal components is interesting. Recently the epithelial/mesenchymal interaction and in particular the role of Angiogenesis has attracted the attention of investigators. The Angiogenesis and microvascular density have been reported recently as an important prognostic factor in breast cancer18-20. However a contradictory studies have been published[21]. Da Silva et al [22] found that the number of vessels counted in invasive ductal carcinoma was significantly higher than the number of vessels counted in fibroadenoma and in the adjacent breast tissue and there was no difference between fibroadenoma and adjacent breast stroma. However other found that vascularity of breast carcinoma are similar to that of normal breast intralobular stroma [23]. Haseb et al[24]examined different growth factors expression including vascular endothelial growth factors (VEGF) in conventional fibroadenoma, cellular fibroadenoma and phyllodes tumor and found that conventional type fibroadenoma stromal cells had the lowest frequency of VEGF protein expression and the phyllodes tumor stromal cells had the highest frequency of expression. Valtola et al 25 demonstrated that the expression of VEGFR-3 becomes up-regulated in the endothelium of angiogenic blood vessels in breast cancer. Wernert et al 26 reported genetic alteration (allelic losses, microsatellite instabilities and p53 mutation) occurred in fibroblastic stroma of breast carcinoma, similarly to that detected in the epithelial component, which indicate a possible significant rule of tumor stroma in carcinogenesis.

Although the epithelial component of the primary tumor in our case did not show any significant atypia, however the vascular stroma might have played a role in the quick recurrence and in the malignant transformation of the epithelial and mesenchymal components. The other interesting finding in this case was the relatively quick recurrence and the different morpho-

logic pattern with a clearly malignant phyllodes tumor associated with in situ lobular carcinoma. In situ carcinoma have been reported before in association with phyllodes tumor including both the in situ lobular27 and the in situ ductal28, 29. Although in certain foci, the in situ carcinoma resemble in situ lobular carcinoma, E-cadherin expression was strongly positive favoring in situ ductal. Recently E-cadherin immunostaining has been found to be of value in helping to characterize breast carcinomas in situ with indeterminate features 30-32. In conclusion we report a unique case of giant fibroadenoma with cellular stroma and abnormal vascular proliferation with recurrence as malignant phyllodes tumor associated with in situ carcinoma.

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