

Aggressive Giant Fibroepithelial Lesion with Unusual Vascular Stroma—A Case Report

Wedad Hanna, F.R.C.P.C., J. AL-Maghrabi, M.D., Abha Malik, M.D.

Department of Anatomical Pathology, Sunnybrook and Women's College Health Science Center, University of Toronto, Toronto, Canada

The stroma of fibroadenoma and phyllodes tumor usually consists of fibroblastic proliferation. Rarely the stroma contains bundles of smooth muscle. Pseudoangiomatous hyperplasia of the mammary stroma has been described in fibroadenomas. However, true benign vascular stroma has not been reported. We report a case of a 34-year-old Chinese woman who presented with a large mass occupying the entire left breast. Left mastectomy was performed and showed a large, well-circumscribed, lobulated, rubbery-firm tumor measuring 13 × 10 × 6 cm. Microscopic examination revealed a fibroepithelial tumor formed by an organoid pattern of ductal structures with a very striking stromal appearance composed of extensive vascular proliferation and that demonstrated strong immunoreactivity for CD31, CD34, and Factor VIII. Ultrastructural examination revealed intercellular junctions, basal lamina, pinocytotic vesicles, and Weibel-Palade bodies in the cells lining the vascular spaces, confirming their endothelial nature. These findings rule out the diagnosis of pseudoangiomatous hyperplasia. The patient developed local recurrence a year later, and the resection showed malignant phyllodes tumor with ductal carcinoma *in situ*. The extensive vascular stroma noted in the primary tumor may have played a role in the malignant transformation of the epithelial and stromal components in this tumor.

KEY WORDS: Angiogenesis, Giant fibroepithelial lesion with vascular stroma, Phyllodes tumor, Vascular breast lesions.

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A 34-year-old Chinese woman presented with a large mass occupying the entire left breast. Left mastectomy was performed that showed a remarkable fibroepithelial lesion with stroma showing extensive vascular proliferation. The patient developed a local recurrence a year later, and the resection was diagnosed as malignant phyllodes tumor with ductal carcinoma *in situ*. The patient had had right mastectomy 5 years ago in China before coming to Canada. No information on the pathology could be obtained.

MATERIALS AND METHODS

All specimens were received fixed in 10% neutral formalin. Paraffin-embedded blocks and sections were prepared in the conventional manner and stained with hematoxylin and eosin. Immunohistochemistry was performed using avidin-biotin complex technique (ABC) with appropriate positive and negative controls. The immunohistochemistry panel included antibodies against CD31 (DAKO, 1/50), CD34, Factor VIII (DAKO, 1/1200), S100 (DAKO, 1/500), actin (Enzo, 1/50), desmin (Biogenex, 1/50), vimentin (Novocastra, 1/75), E-cadherin (Transduction, 1/2500), and CAM 5.2 (Becton Dickinson, 1/8).

For electron microscopy, paraffin-embedded, formalin-fixed tissue was postfixed in osmium, and ultrathin sections were cut after appropriate area was selected from semithin sections.

Pathologic Findings

The initial breast tumor was large, well-defined, lobulated, rubbery firm, measured 13 × 10 × 6 cm, and was surrounded by a narrow rim of breast tissue. The cut surface showed focal areas of hemorrhage (Fig. 1). Microscopic examination showed a fibroepithelial tumor formed by an organoid pattern of regularly spaced ductal structures surrounded by dense and cellular fibrous stroma. There was no stromal overgrowth despite the cellularity of the stroma, with no evidence of necrosis.

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Address reprint requests to: Wedad Hanna, F.R.C.P.C., Anatomic Pathology, Sunnybrook and Women's College, Health Sciences Center, 2075 Bayview Avenue, M5S 1B2, Toronto, Ontario, Canada 30322; fax: 416-480-4271; e-mail: wedad.hanna@swchsc.on.ca.

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FIGURE 1. Gross appearance of primary tumor. Large, well-defined, lobulated mass showing areas of hemorrhage and a rim of normal breast tissue.

The margins were well circumscribed, with no evidence of an infiltrative border. The morphology of the stroma was quite striking. There were numerous arborizing, well-formed vascular channels that were present throughout the stroma (Fig. 2A). In some areas, this was associated with marked edema and extravasation of red blood cells. 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 positivity for CD31, CD34, and Factor VIII (inset, Fig. 2B). The spindle cell fibroblastic stroma showed mild nuclear atypia, and the mitotic activity ranged from 1 to 2 per 10 HPF. These stromal cells showed strong positivity for vimentin and were negative for S-100. Staining with a low molecular weight keratin cam 5.2 was positive only in the ductal elements and completely negative in the stroma, ruling out the possibility of an unusual metaplastic carcinoma. The surrounding breast tissue showed lobular atrophy and stromal fibrosis. No significant epithelial changes were seen. Sections from the nipple were unremarkable, and the lesion

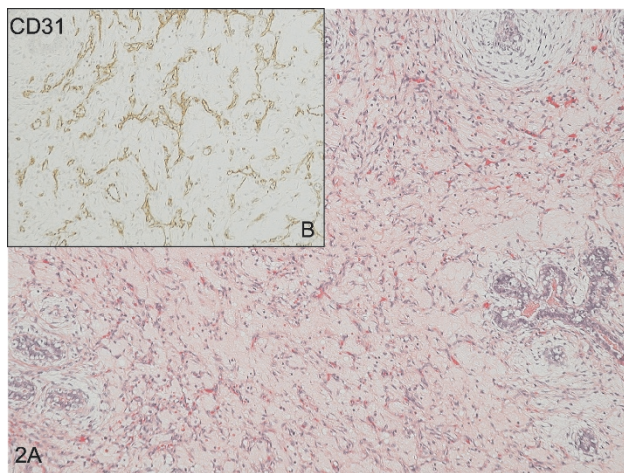


FIGURE 2. A–B, H&E of primary tumor showing stromal cellularity with prominent benign vascular proliferation (CD31 stain in inset). Note the regular spacing of the epithelial component (magnification, 10 \times).

appeared completely excised in the plane of the sections examined.

The recurrent tumor was large, soft, well-defined, and measured 10 \times 6 \times 4 cm. The cut surface of the tumor was bulging, with a nodular contour, and it extended down to the fascia. Microscopic examination showed a variable appearance. In most areas, it had the characteristic appearance of malignant phyllodes tumor that had an extremely cellular stroma, with definite stromal overgrowth. The stroma was formed by highly atypical spindle-shaped cells, with a mitotic rate that ranged from 5 to 6 per 10 HPF. There was a focal area showing a prominent network of vascular proliferation as seen in the primary tumor; however, the vascularity was not as diffuse as in the primary tumor (Fig. 3A–D). A malignant vascular component was not seen (Fig. 4A–B). The other very unusual feature in this recurrent tumor was the marked atypical proliferation of the epithelial element, which had histological features for *in situ* carcinoma on H&E sections (Fig. 5). The monotonous appearance of the cells favored lobular carcinoma *in situ*; however, E-cadherin expression in all the cells was more in keeping with that of ductal carcinoma *in situ* (inset, Fig. 5).

Transmission Electron Microscopy

Ultrastructural examination of the primary tumor confirmed the endothelial nature of the lining of the vascular channels in the stroma with the presence of intercellular junctions, basal lamina, pinocytotic vesicles and Weibel-Palade bodies.

DISCUSSION

The stromal cells in fibroadenomas are usually fibroblasts (1). Rare forms of stromal differentiation

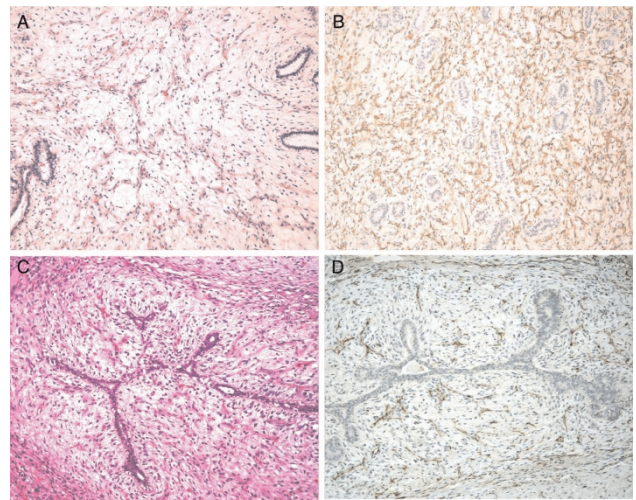


FIGURE 3. H&E and CD31 staining of the primary illustrating the marked vascular proliferation (A, B) as compared with the reduced vascularity in the recurrence (C, D; magnification, 10 \times)

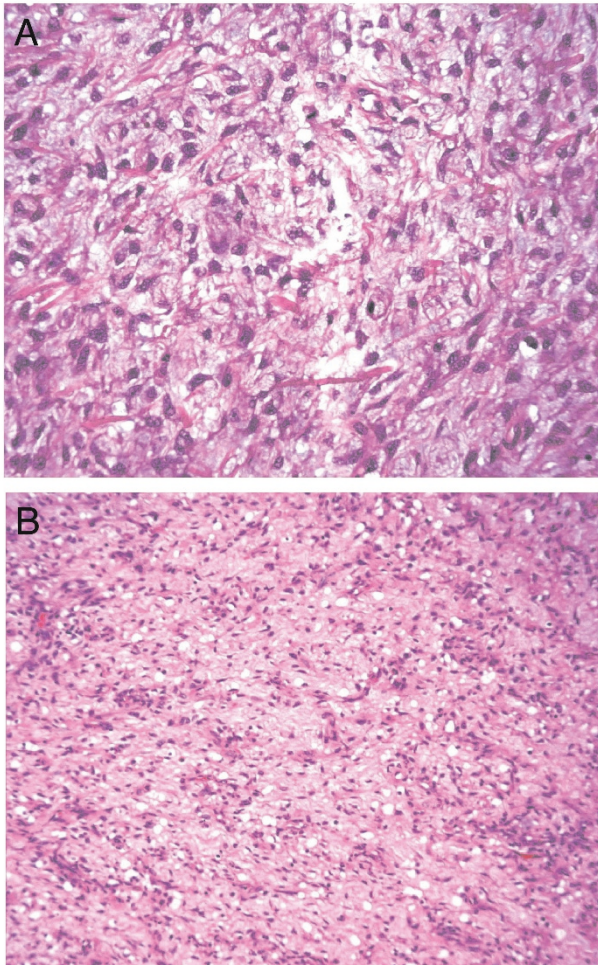


FIGURE 4. The predominantly spindle and atypical stroma of the recurrence (A) with (B) areas of prominent vascularity (magnification, 20×).

include smooth muscle metaplasia (2) or adipose differentiation (3).

Multinucleate stromal giant cells have also been noted in fibroadenomas and phyllodes tumors (4). Osteochondroid metaplasia of the stroma may also be encountered infrequently (5).

In our case, the primary tumor showed a fibroepithelial lesion with an unusual and peculiar stroma composed of extensive vascular proliferation throughout the tumor. The endothelial nature of the lining of these vascular channels was confirmed on immunohistochemistry and electron microscopic examination, which ruled out the possibility of extensive pseudoangiomatous hyperplasia. The slitlike pseudovascular spaces in pseudoangiomatous hyperplasia showed positivity for vimentin and CD34 but were negative for Factor VIII, CD31, or other endothelial markers (5–9). Ultrastructural examination of the lining of pseudoangiomatous hyperplasia showed an incomplete layer of fibroblastic cells. The pattern of vascular proliferation seen in the primary tumor did not resemble that of

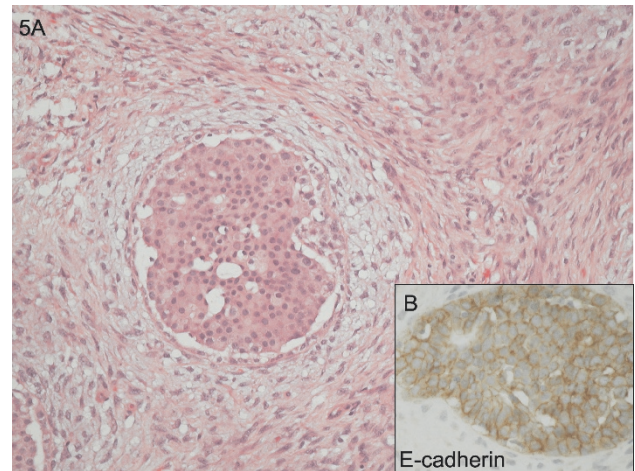


FIGURE 5. Recurrent tumor shows cellular stroma with atypical cells and mitosis surrounding a duct with *in situ* carcinoma (magnification, 40×). **Inset** shows E-cadherin expression in the cells consistent with ductal carcinoma in situ (magnification, 40×).

any previously described vascular lesion in the breast (10–18). A case of angiosarcoma but not benign vascular proliferation was reported in a case of phyllodes tumor (19). The primary tumor, though large in size, had only focal areas of cellular fibroblastic stroma, and stromal overgrowth was not observed as one would expect to see in a phyllodes tumor. The stroma was unusually vascular, with a benign arborizing network of capillaries present in many parts of the stroma. The primary fibroepithelial lesion could not be categorically classified as either phyllodes tumor or a fibroadenoma with cellular stroma because of this unusual feature. The recurrence, on the other hand, showed classic features of malignant phyllodes tumor that included stromal overgrowth, nuclear atypia, and a high mitotic rate. The role of vascular stroma in the pathogenesis and progression of both the epithelial and mesenchymal components is speculative. Recently, epithelial and mesenchymal interactions and in particular the role of angiogenesis in breast cancer has attracted the attention of investigators. Vascular stroma reportedly plays a role in the growth of the primary tumor as well as in invasion and metastasis in breast cancer (20). Angiogenesis and microvessel density have been implicated as important prognostic factors in breast cancer (21, 22). Da Silva *et al.* (23) 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. However, others found that vascularity in breast carcinoma was similar to that of normal breast intralobular stroma (24). 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 that genetic alterations (loss of heterozygosity and p53 mutation) occur in fibroblastic stroma of breast carcinoma, similar to those detected in the epithelial component, which indicates a possible role of tumor stroma in mammary carcinogenesis.

Recently, Tse *et al.* (27) found that there was a correlation between intratumoral vessel density and the histological grade when judged on CD-31-stained slides and that microvessel density could be used as an additional histological parameter to distinguish between benign and malignant phyllodes tumor. Hasebe *et al.* (28) examined vascular endothelial growth factors (VEGF) in conventional fibroadenoma, cellular fibroadenoma, and phyllodes tumor and found that stromal cells in conventional fibroadenoma had the lowest frequency of VEGF protein expression and that those in phyllodes tumor had the highest frequency of expression. The belief that phyllodes tumor is a stromal neoplasm has recently been challenged. Both the stroma and the epithelium in phyllodes tumor can show distinct molecular changes, suggesting that both are part of the neoplastic process (29). It has also been observed that there is an interdependence of growth between the stromal and the epithelial components that explains the complex morphology seen in these tumors (30, 31). Stromal mitotic activity occurs in close proximity to the epithelial component, strengthening the role of stromal-epithelial interactions in progression of phyllodes tumor (30). The stromal-epithelial interaction can both be direct or systemic as a result of the release of angiogenic factor, particularly VEGF and VEGF receptor. This systemic effect might have played a role in our case as there was no preferential increased vascularity around the malignant epithelial component of the recurrent tumor.

Although the epithelial component in the primary tumor in our case did not show any significant atypia, the recurrence showed *in situ* ductal carcinoma. The vascular stroma might have played a role in the quick recurrence and malignant transformation of the epithelial and mesenchymal components. *In situ* carcinoma has been reported before in association with phyllodes tumor, and most have been *in situ* lobular carcinomas (32–34). Positive E-cadherin expression in our case, which had histologically equivocal features, confirmed the presence of ductal carcinoma *in situ* (35, 36).

This case appears to be a unique “aggressive giant” fibroepithelial lesion with cellular stroma showing abnormal vascular proliferation that recurred as malignant phyllodes tumor with *in situ* ductal carcinoma. The exuberantly vascular stroma in the primary tumor may have led to its quick progression to malignancy.

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