Angiocentric Carcinoma Of The Breast: A New Type Of Breast Carcinoma With Analysis Of Immunohistochemical Profile.

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Citation


Abstract

We present a new type of breast carcinoma which recurred locally after modified radical mastectomy, and describe the histomorphologic features, and analyze the immuno-histochemical expression profile to characterize angiocentric carcinoma. Angiocentric carcinoma of the breast is characterized by clustering of tumor cells around vascular spaces with destruction and infiltration of the vascular endothelial lining to come into the lumen along with large areas of necrosis. Angiocentric carcinoma of the breast similar to angiocentric lymphoma and angiocentric glioma is a distinct pathological entity. We coined the term ‘angiocentric carcinoma of the breast’ for this novel histopathological entity.

INTRODUCTION

Angiocentric carcinoma of the breast, a new distinct histopathological entity has not been reported previously in the English literature. The histological feature of this variant is its striking angiocentric and angiodestructive pattern of growth i.e. they tend to cluster around vascular spaces (perivascular) to form rosettid structures along with geographic necrosis and mild lymphocytic infiltration.

In this report we are analyzing the histopathologic features, immuno-histochemistry expression profile of “Angiocentric carcinoma of the breast” and compared with the established prognostic immunohistochemical panels of invasive breast cancer to characterize this novel entity and its pathogenesis.

The immuno-histochemistry profile of this triple negative breast cancer i.e. expression of estrogen receptor (ER), progesterone receptor (PR) and Her2-neu are negative in tumor cells suggesting the basal- like phenotypic characteristic of this invasive carcinoma breast’ but the histomorphologic features of angiocentric carcinoma is quite different.

MATERIAL AND METHODS

A forty year old female presented in the surgical Outpatient Department OPD with a hard partially mobile, non tender lump in the upper outer quadrant of the left breast measuring 5 X 5 cms with defined border and a normal nipple-areola complex. She was subjected to fine needle aspiration cytology (FNAC) of the lump. FNAC yielded blood mixed whitish granular material on aspiration. The cytology report was signed out as ductal carcinoma of the left breast.

Thereafter, she underwent modified radical mastectomy of the left breast with axillary clearance and the resected specimen was sent for histopathological examination. On bread loafing the specimen, after inking of margins, showed a partially well defined solid greenish-white growth measuring 6 cms in greatest dimension with multiple areas of necrosis. Thirteen lymph nodes were dissected out from the axillary tail. The histopathology report was signed out as infiltrating duct carcinoma, NOS with modified Bloom Richardson histological grading as (3+3+1=7). Grade II and Nottingham prognostic index falls into the moderate prognostic group. All the resection margins including the base were negative and all the 13 dissected lymph nodes were free of tumor infiltration. Duct carcinoma in-situ and lympho-vascular emboli were not seen.

The patient was discharged after an uneventful post-operative period and referred to for neoadjuvent therapy and immunohistochemical profile for ER, PR, Her2-neu. But unfortunately she went to her home without taking oncologic consultation and neo adjuvant therapy.

After one year she came back with swelling on left chest wall near the shoulder of 7 days duration. The swelling was
diffuse, ill-defined measuring approximately 3 X 2.5 cms. She was again subjected to FNAC of this swelling which yielded scanty yellowish granular material and the report was signed out as positive for malignant cells suggestive of recurrence of the breast carcinoma. After hematological work-up she was again operated for recurrent swelling in the same breast and chest wall. The resected specimen was again sent for histopathological examination. Grossly, a globular grayish-white solid firm tissue mass was received with attached fibro-fatty tissue measuring 6 X 5.5 X 2.5 cms. Serial sectioning showed a solid grey white cut surface with multiple necrotic foci. Histopathological examination this time revealed striking perivascular tumor growth pattern with cuffing and destruction of the vascular wall with large area of ischemic necrosis and fibrinoid necrosis of occasional vessel wall (Fig. 1) along with mild focal lymphocytic infiltration. Archived previous H&E stained glass slides of the patient were reviewed by the author and he found similar perivascular tumor growth pattern with angiodestruction (Fig. 2) and geographical necrosis.

Figure 1
Fig.1: Hematoxylin & Eosin X 100. Microphotograph shows perivascular pattern of growth of tumor cells with infiltration of the the vascular lumen.

Figure 2
Fig. 2: Hematoxylin & Eosin X400. High power objective: microphotograph shows angiocentricity and angiodestruction with luminal infiltration of the blood vessel.

All the margins were negative. The histopathologic report was signed out as angiocentric carcinoma of the breast with basal cell-like phenotype after doing immunohistochemistry for ER, PR, Her2-neu, CD31, CK7, CK5/6, CK8/18, EGFR, p 53, Ki-67, Bcl-2, VEGF and CD56 on previous archived and recent blocks. The tumor cells were negative for ER, PR, Her2-neu, p 53 expressions (Fig. 3 A-D).

Figure 3
Fig. 3. A: ER X100. Microphotograph shows negative Estrogen receptor expression.
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Figure 4
Fig. 3 B: PR X100. Microphotograph shows negative Progesterone receptor expression.

Figure 5
Fig. 3 C: Her2-neu X400. Microphotograph shows negative Her2-neu expression.

Whereas the tumor cells were positive for CK5/6 & CK8/18 (in < 50 % of tumor cells), CK7 was expressed in most of the tumor cells, and CD31 was expressed on endothelial lining of vascular spaces surrounded by tumor cells (Fig. 4 A-D).

Figure 6
Fig. 3 D: p53 X400. Microphotograph shows negative p 53 expression.
Figure 7
Fig. 4A: CK 5/6 X100. Microphotograph shows cytoplasmic positivity for CK 5/6 in some tumor cells.

Figure 8
Fig. 4B: CK 8/18 X400. Microphotograph shows cytoplasmic positivity for CK 8/18 in few of the tumor cells.

Figure 9
Fig. 4C: CK 7 X100. Microphotograph shows cytoplasmic positivity for CK 7 in many tumor cells.

Figure 10
Fig. 4D: CD 31 X100. Microphotograph shows positively stained endothelial lining cells of blood vessels with CD 31.
The tumor cells showed positive EGFR expression in < 50 % of tumor cells (3+ ve), Bcl-2 positivity in some of the tumor cells, high Ki-67 index (>90 % tumor cells) and high cytoplasmic expression (> 90 % tumor cells) of VEGF (Fig. 5 A-D). CD56 was not expressed in tumor cells. The patient was lost to follow-up for the last 6 months.

**Figure 11**
Fig. 5A: EGFR X400. Microphotograph shows positive expression of EGFR (3+ ve) in few of the tumor cells.

**Figure 12**
Fig. 5 B: bcl-2 X400. Microphotograph shows Bcl-2 expression on tumor cells.

**Figure 13**
Fig. 5 C: Ki 67 X100. Microphotograph shows positive nuclear staining of tumor cells in Ki 67 stain.
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Figure 14
Fig. 5 D: VEGF X400. Microphotograph shows positive cytoplasmic expression of VEGF in most of the tumor cells.

Angiocentricity is defined as the presence of tumor cells around and within vascular spaces with infiltration and destruction of the vessel wall. Perivascular localization is not sufficient for the designation of angiocentricity. Angiocentric carcinoma of the breast has not been described to date and this specific pattern of growth is described neither in any specific type of carcinoma of the breast nor even in a specific type category (NST).

The defining histological features of an angiocentric carcinoma are the presence of a moderately pleomorphic tumor cells clustered around vascular spaces and infiltrating, focally destroying the vessel wall with large areas of tumor tissue necrosis and mild focal lymphocytic infiltrate. Mitoses are frequent indicative of highly proliferative and aggressive nature of tumor. Immunno-histochemical profile of triple negativity for ER/PR/Her2-neu expression with associated EGFR positivity is indicative of carcinoma with basal-like phenotype. CD31 expressions on endothelial cells highlighted the perivascular growth pattern (angiocentricity). Contrary to angiocentric lymphoma CD 56 was negative for neural cell adhesion molecule (NCAM). High Ki-67 index is indicative of highly proliferative tumor and high intracytoplasmic expression of VEGF on tumor cells is hypothesized for angiocentric growth.

It is speculated that different types of carcinomas of the breast arise from target cells of different cellular compartments. Recent studies pointed towards the existence of primary stem cells and so called first-, second- and n-order ‘transit amplifying cells’ corresponding to glandular progenitor stem cells, immediately differentiated glandular cells respectively and glandular cells. Pure progenitor stem cells have a distinct immunohistochemical pattern: CK5/6+, CK8/18- and ER negative. The immediately differentiated cells express CK5/14+ and some other marker, complete glandular differentiated cells show CK8/18+. The cytokeratin expression patterns are partially retained during carcinogenesis and tumor progression. Carcinogenic hit of early progenitor cells may cause evolvement of a subgroup of invasive breast cancer which is characterized by poor differentiation, worse prognosis and more frequently carry BRCA-1 mutation.

The pure basal-like (progenitor cell ) carcinoma accounting for not more than 0.8 % of all invasive breast cancers is a clinically significant subtype of invasive breast carcinoma. Besides constituting at least 80% of triple negative phenotype also shows reactivity for one of the basal type cytokeratin like CK 5/6, CK147 with associated EGFR, p 53 expressions and reduced E-cadherin membranous expression. The majority were grade III ductal/ NST carcinoma with larger size, good circumscription and pushing margins, poorer Nottingham prognostic index, geographical necrosis, recurrence, node negative and distant metastases with poor outcome. These were further subdivided in to two subgroups: (A) those with dominant basal pattern having positive expression for one of the basal keratin in more than 50 % of tumor cells and (B) carcinoma with basal characteristics having 10-50 % of cells positive. Coexpression of CK 5/6 and CK 8/18 indicates abortive glandular differentiation and is seen in < 10 % of invasive carcinoma. Such basal type carcinoma is characterized by similar expression for EGFR, p 53, E-cadherin as pure basal cell carcinoma and grade 3 morphology.

Correlation between the degree of EGFR expression and outcome of triple negative breast cancer have been studied and found that EGFR immuno-reactivity in > or = 50 % invasive tumor cells indicates worse prognosis. Significant correlation exits between high EGFR expression and poor differentiation of tumor. Immuno-reactivity for bcl-2 is more frequently seen in low grade carcinoma and is associated with a better response to hormone therapy regardless of nodal status. It has observed that human breast
cancer cells can express VEGF in the cytoplasm and inverse relationship exists between VEGF level in the tumor cytoplasm and estrogen receptor expression. Patients with higher level of VEGF had a significantly poor prognosis. Unlike basal like carcinoma, in our case p53 expression was not seen, there was low expression for EGFR and CK 5/6 in < 50 % of tumor cells with coexpression of CK 8/18 in few of the tumor cells. The tumor was of lower Modified Bloom Richardson Grade (grade II), lower Nottingham prognostic index (Moderate group) with unique angiocentric, angiodestructive pattern of growth and high cytoplasmic positivity for VEGF expression. All these facts suggest a different genetic cause of tumor genesis and better prognosis than the conventional basal- like carcinoma breast with dominant basal pattern.

Since hypothesis of multiple, predominantly parallel progression cytogenetic pathways exist in breast cancer and these pathways are associated with specific phenotypic and prognostic parameters we think that a cytogenetic study is mandatory.

In conclusion, angiocentric carcinoma is a new distinct type of triple negative breast cancer that have tendency for recurrence. Angiocentric pattern of growth with angiodestruction and large areas of tumor necrosis are characteristic of this tumor. Further cell molecular, cytogenetic studies required to address the issue of pathogenesis and significance of an angiocentric carcinoma.

References
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