Secretory carcinoma of breast: A diagnostic dilemma

Editor,

Secretory carcinoma of the breast is a rare form of breast carcinoma seen primarily in children,[1] but it can also occur in adults and account for <0.15% of all breast cancers.[2] These lesions appear to have an excellent prognosis in women under the age of 20 years. The behavior in older women is less favorable with late recurrence. The World Health Organization fascicle on Breast (2012) classifies it as an exceptionally rare type and variant of breast cancer.[3] Its cytological features overlap with many benign as well as malignant lesions of breast and histology mimics with other primary breast tumors and even metastatic tumors of the breast. Recognition of the entity is important because it has a low-grade clinical course and is associated with a favorable prognosis.[4]

Herein, we present a case of secretory carcinoma in postmenopausal female and highlight the diagnostic challenges on cytdiagnosis in which there is florid proliferation of monomorphous epithelial cells and also pitfalls in interpreting hematoxylin and eosin (H and E) stained sections.

A 60-year-old female presented with subcutaneous left breast nodule that she had noted 2 months previously. It was gradually increasing in size. Physical examination revealed a 2.5-cm painless mobile nodule just below the areola of the left breast and no axillary nodes were palpable. Mammography showed well-defined, capsulated, lobulated lesion of size 28 × 25 × 28 mm (volume approximately 10.0 cc) at 12 o’clock position, which belongs to BI-RADS category IV lesion [Figure 1a]. Fine needle aspiration (FNA) of the nodule performed with a 22-gauge needle attached to a 20-cc plastic syringe mounted on a handle yielded mucoid material. Multiple smears stained with May-Grunwald-Giemsma, H and E, and Papanicolaou stain were studied. FNA smears were highly cellular and consisted of numerous papilloroid fragments, cell balls, and clusters of epithelial cells [Figure 1b]. The cells are having hyperchromatic nuclei, inconspicuous nucleoli, and abundant granular and vacuolated cytoplasm [Figure 1c]. Some mucinous material was seen in the background [Figure 1d] and no mitotic activity was identified in the tumor cells. Possibility of epithelial proliferative lesion was considered, and in view of high cellularity of FNA cytological material and absence of bipolar nuclei, a malignant pathology was suggested. Chest X-ray, abdominal ultrasound, and a bone scan did not show any evidence of metastatic disease. The patient underwent modified radical mastectomy and the specimen showed a subcutaneous lesion in the upper outer quadrant of the breast [Figure 2a]. Cut section of the specimen revealed well circumscribed, soft to firm, gray–tan lesion with pushing margins along with the area of hemorrhage measuring 2.5 cm in diameter [Figure 2b]. On microscopic examination, the sections revealed tumor cells arranged in tubuloalveolar, papillary, and microcystic pattern [Figure 2c and d]. The cystic spaces showed eosinophilic secretions. The tumor cells were round to polygonal exhibiting mild atypia and intracytoplasmic vacuolation. Mitotic activity is infrequent. The secretion in the lumen of microcysts was Periodic acid-Schiff (PAS) stain positive. On immunohistochemistry the tumor cells were positive for Pan CK, CK7, CK5/6, S-100 protein [Figure 2e], and Vimentin [Figure 2f]. Carcinoembryonic antigen (CEA) was patchy positive, while CK20, GCDFP, estrogen receptor (ER), progesterone receptor (PR), Her2, and P63 were negative. Based on morphology and immunohistochemistry, a diagnosis of secretory carcinoma was confirmed. Polymerase chain reaction (PCR)-based translocation assay for ETV6–NTR3 translocation was performed and a positive result was obtained for the same.

Secretory carcinoma of the breast was initially termed as “Juvenile breast cancer” by McDivitt and Stewart,[5] based on the fact that the average age of the seven patients described in their series was 9 years (range 3–15). Subsequently, a number of cases were reported in adults, even in postmenopausal females and male patients.

The patients generally presented with painless and firm mass and most tumors are located in the outer upper quadrant of the breast. FNA diagnosis of this rare type of carcinoma with relatively bland cytology may be extremely difficult, especially in a younger woman in whom benign proliferative and secretory lesions far outnumber carcinoma. Cytology of lactational changes or lactating adenoma may mimic with secretory carcinoma in young patients, but in the latter case the cytoplasm will be abundant and fragile, and round central nuclei have distinct small nucleoli. Important diagnostic clues suggesting malignancy are high cellularity of the FNA cytologic material and absence...
of bipolar naked nuclei.\[6\] Other possibilities on cytology are primary papillary carcinoma, apocrine carcinoma, clear cell carcinoma (glycogen rich), lipid-rich carcinoma, and mucinous carcinoma. All these have to be excluded. In papillary carcinoma, columnar cells are seen in row, palisade, and single cell with variable nuclear enlargement and necrosis. Apocrine carcinoma is having highly atypical nuclear morphology, in clear cell carcinoma (glycogen rich) cell population is dispersed in the tigroid background, and in lipid-rich carcinoma microvacuolated cytoplasm with pleomorphic nuclei is seen. Small clumps of mucin-like material are seen in our case but absence of abundant mucin in the background and cells in small aggregate are not in favor of mucinous carcinoma. Adenoid cystic carcinoma, benign epithelial hyperplasia including collagenous spherulosis must also be differentiated from secretory carcinoma.\[8\]

Tumor in our case was seen in the subcutaneous region; therefore we also thought of salivary gland or skin adnexal tumors which although rare, occur in adult or elderly women and present as circumscribed tumor in subareolar area without connection to the overlying skin.

On gross examination, the tumor is well circumscribed and usually small. Microscopically margins are of pushing type and prominent hyalinization is often present in the central portion. Tubuloalveolar and focally papillary formations lined by cells with a vacuolated cytoplasm are seen forming lumina filled by eosinophilic PAS positive secretions. These histological features have to be differentiated from acinic cell carcinoma (ACCA), cystic hypersecretory carcinoma, invasive ductal carcinoma, as well as metastatic carcinoma from thyroid by immunohistochemistry.\[9\] Tumor cells of secretory carcinoma show strong reactivity for α-lactalbumin and S-100 protein, while ER, PR, HER2, and p63 are negative.\[10\]

Ultrastructurally, the tumor cells contain numerous membrane-bound intracytoplasmic secretory vacuoles.\[9\] Genetic abnormality found in secretory carcinoma is balanced translocation t(12;15), which leads to the formation of ETV6–NTRK3 gene.\[9\]

Demonstration of ETV6–NTRK3 is important not only for confirmation of diagnosis but also to exclude ACCA, which lacks hypernephroid features and proteins of salivary gland counterpart and ACCA does not show t(12;15) ETV6–NTRK3.\[10\]

Secretory carcinoma is a rare variant of breast carcinoma that must be considered in the differential diagnosis of a circumscribed lesion of the breast both in young as well as elderly patient. It is not only important that the pathologist is aware of the cytological features, but also that he/she carefully interprets cytological features, morphological features, and immunohistochemistry to ensure that the correct diagnosis is made.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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There are no conflicts of interest.

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