CLINICAL VIGNETTE

Secretory Carcinoma of the Breast

Merry L. Tetef, MD

Case Report

A 54-year-old woman underwent annual screening mammogram which revealed a 5 mm nodule in the left upper outer quadrant. Ultrasound-guided biopsy revealed secretory carcinoma of the breast, Estrogen Receptor (ER) positive- with 40% of the cells staining 1-2+, Progesterone Receptor (PR) negative, HER2-neu negative, and molecular studies revealing FISH positive for ETV6 gene rearrangement. She then underwent partial mastectomy and was found to have stage IA T1cN0M0 low grade secretory carcinoma of the breast. This was followed with whole breast radiation therapy, after which the patient was started on adjuvant anastrazole therapy.

Discussion

Secretory breast carcinoma (SBC) is a rare malignancy, accounting for 0.15% of all breast cancers. Initially called "juvenile secretory carcinoma" as the first descriptions were in children, over two-thirds of the cases of SBC occur in adults. Although SBC has distinctive morphologic features and a chromosomal translocation, the clinical symptoms are not uniform.

The presentation of SBC can be varied, with reports of cases diagnosed with bloody nipple discharge, palpable masses, or image findings.[1] Given that there is not a specific imaging pattern for SBC, biopsy is critical for the diagnosis.

This histopathologic features of SBC include cells containing vacuolated cytoplasm and the presence of intracellular and extracellular secretory material. When such secretory features are present in a breast cancer, the diagnosis of SBC must be considered.

Most case reports and small series of SBC describe a triple negative phenotype-negative for ER, PR and HER2-neu- which expresses high molecular weight cytokeratins similar to basal-like breast carcinomas. A larger data base study revealed that the majority of cases were indeed hormone receptor positive.[2] In the patients with SBC who do express the triple negative pattern, unlike triple negative infiltrating ductal cancers, these cancers usually have a good prognosis, with rare nodal and distant metastases.[3]

In 2002, Tognon et al showed a translocation that previously was described in other malignancies such as some pediatric spindle cell tumors, acute myeloid leukemia, and mammary analogues secretory carcinoma (MASC) of the salivary gland, is also seen in all SBC.[4] This chromosomal translocation t(12;15) results in the fusion of the ETS variant gene 6 (ETV6) on 12p13 with the neurotrophic tyrosine kinase receptor 3 (NTRK3) on 15q25. This ETV6-NTRK3 is seen in SBC and is negative in other breast carcinomas. The ETV6-NTRK3 fusion activates RAS-MAP kinases and PI3K Akt pathways responsible for breast call proliferation and survival.

Of note, MASC, is also defined by the ETV6-NTRK3 fusion gene. This malignancy comprises a significant portion of low-grade adenocarcinomas of the salivary glands, particularly outside of the parotid gland. MASC has a similar morphology to SBC and interestingly shows positivity for the breast marker mammoglobin and also GATA3. The diagnosis is supported by the presence of an ETV6 rearrangement. MASC has a low rate of locoregional recurrence and excellent survival.

In 2016, Jacob et al reviewed 246 cases of SBC from the National Cancer Data Base.[2] This registry was established in 1989 and contains data from more than 30 million patients treated at more than 1,500 hospitals in the United States, estimated as 70% of all U.S cancer patients. It compared 246 cases of SBC to more than 1.5 million cases of invasive ductal cancer (IDC) reported in the same timeframe of 1998 to 2011. They found that the age range of presentation of SBC was 56 years of age, 4 years younger than for IDC. The stages at presentation were similar, but SBC was more likely to be low grade. The majority (64%) of SBC was ER positive compared with 76% of IDC, PR was positive in 44% of SBC and in 66% of IDC, and HER2-neu was negative in all SBC. The average tumor size for SBC was 19.9 mm and 32% were node positive, not statistically different than in the IDC cases. The overall survival of SBC was better than with IDC, with median of 14.8 years for IDC and median survival not reached for the SBC patients. Earlier studies found a predominance of hormone-receptor negativity in the SBC patients reported, while this much larger data base from the National Cancer Data Base demonstrated that the majority of SBC cancers were hormone-receptor positive.

In conclusion, SBC is a rare but distinct subtype of breast cancer with characteristic morphologic features and the ETV6-NTRK3 fusion. Large databases do not exist for this malignancy. Although both basal-like patterns and hormone sensitive subtypes have been described, the prognosis for SBC is more favorable than for IDC. Optimal treatment is not known given

the rarity of this disease. The patient discussed in this case report had early stage disease of this good-prognosis cancer, and likely will do well after completing 5 years of adjuvant endocrine therapy.

REFERENCES

1. **Lee SG, Jung SP, Lee HY, Kim S, Kim HY, Kim I, Bae JW**. Secretory breast carcinoma: A report of three cases and a review of the literature. *Oncol Lett*. 2014 Aug;8(2):683-686. Epub 2014 Jun 3. PubMed PMID: 25009650; PubMed Central PMCID: PMC4081125.
2. **Jacob JD, Hodge C, Franko J, Pezzi CM, Goldman CD, Klimberg VS**. Rare breast cancer: 246 invasive secretory carcinomas from the National Cancer Data Base. *J Surg Onco*l. 2016 Jun;113(7):721-5. doi: 10.1002/jso.24241. Epub 2016 Apr 4. PubMed PMID: 27040042.
3. **Horowitz DP, Sharma CS, Connolly E, Gidea-Addeo D, Deutsch I**. Secretory carcinoma of the breast: results from the survival, epidemiology and end results database. *Breast*. 2012 Jun;21(3):350-3. doi: 10.1016/j.breast.2012.02.013. Epub 2012 Apr 10. PubMed PMID: 22494666.
4. **Tognon C, Knezevich SR, Huntsman D, Roskelley CD, Melnyk N, Mathers JA, Becker L, Carneiro F, MacPherson N, Horsman D, Poremba C, Sorensen PH**. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. *Cancer Cell*. 2002 Nov;2(5):367-76. PubMed PMID: 12450792.

Submitted October 14, 2018