Primary Small Cell Carcinoma of the Breast: A Case Report and Review of Current Challenges

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Introduction

Primary neuroendocrine tumors of the breast were recognized as a distinct subtype of breast carcinoma in the 2003 WHO Classification of Tumours with further refinements made in 2019.[1] Breast neuroendocrine neoplasms (NENs) are classified as neuroendocrine tumors or neuroendocrine carcinomas, the latter further subdivided into small cell and large cell neuroendocrine carcinomas based on tumor morphology.

Primary small cell carcinoma of the breast (PSCCB) accounts for only 0.1% of breast cancers and 4% of extrapulmonary small cell carcinomas.[2] It is aggressive, often presenting with axillary node metastasis and rapid progression. Treatment follows protocols for small cell lung cancer due to pathologic similarities and typically involves multimodal approaches.[3] However, optimal strategies for PSCCB remain unclear due to its rarity and limited data. Here, we present a case of PSCCB with axillary lymph node metastasis and highlight the challenges in diagnosis, treatment and disease monitoring.

Helpful diagnostic features: the presence of ductal carcinoma in situ (DCIS), exclusion of metastatic non-mammary NENs, and estrogen receptor expression.

Case Report

A 39-year-old perimenopausal female presented with a 6-month history of a firm, enlarging mass in her right breast. Imaging revealed a 3 cm mass and core needle biopsy confirmed high-grade carcinoma with neuroendocrine differentiation (**Figure 1**). Immunohistochemistry (IHC) showed diffuse reactivity for synaptophysin, CD56 and INSM-1. Breast carcinoma predictive markers were as follows: ER 100%, PR 95%, HER-2 negative and a Ki-67 proliferation index of 85%. Genetic testing revealed a heterozygous *BRIP1* variant of unknown significance. A whole-body PET-CT described a focal breast malignancy with no evidence of distant metastatic disease. However, an ultrasound-guided core needle biopsy of a right axillary lymph node demonstrated a high-grade carcinoma with neuroendocrine differentiation involving lymphoid tissue with a similar histomorphology and immunoprofile of the patient's previous right breast core biopsy, confirming a metastasis (**Figure 2**). The patient underwent six cycles of Cisplatin and Etoposide-based neoadjuvant therapy, declining the final cycle due to side effects. Post-treatment mastectomy revealed residual small cell carcinoma, DCIS, metastasis in four axillary lymph nodes, and Residual Cancer Burden Class III (**Figure 3**). An axillary dissection was performed at a later date which confirmed five additional metastatic nodes.

Results

Figure 1: Core-needle biopsy of the right breast. (1a) H&E at 10x; (1b) H&E at 40x.

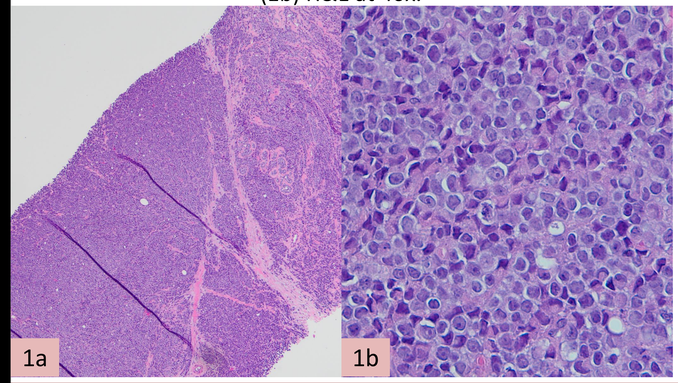


Figure 2: Core-needle biopsy of the right axillary lymph node. (2a) H&E; (2b) Pancytokeratin highlights metastatic carcinoma. 10x.

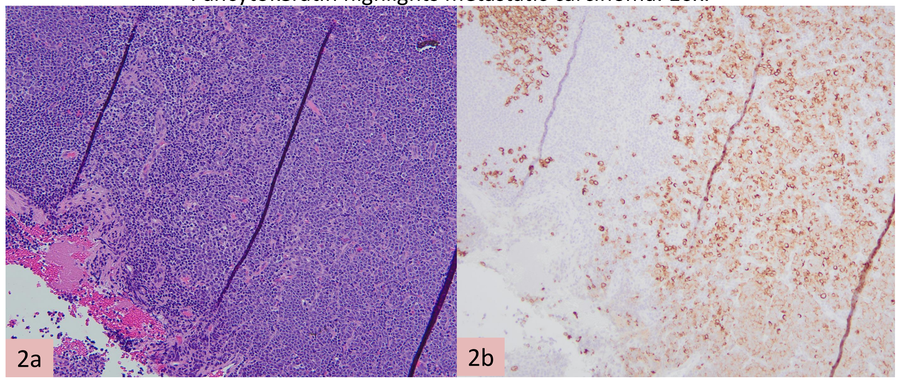
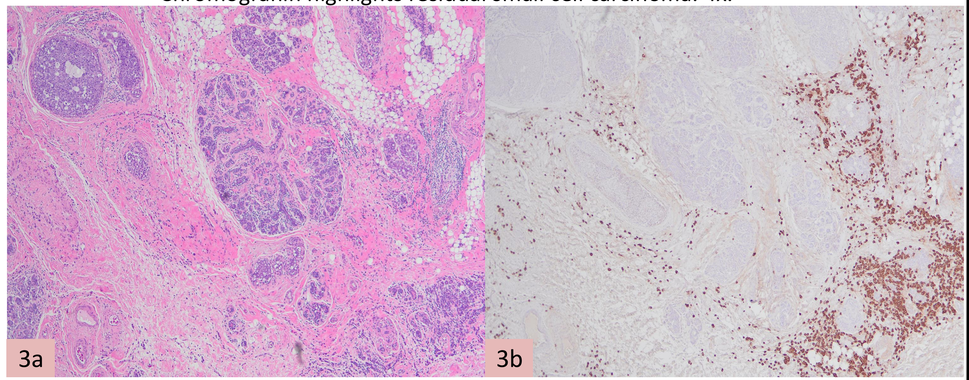


Figure 3: Right post-treatment mastectomy specimen with DCIS. (3a) H&E; (3b) Chromogranin highlights residual small cell carcinoma. 4x.



Discussion

Challenges in Neoadjuvant Therapy: Neoadjuvant therapy aimed to reduce tumor size and facilitate surgery. Despite initial response, significant residual disease persisted raising questions about the efficacy of current chemotherapy regimens for PSCCB. This highlights the need for tailored approaches and further research into optimal neoadjuvant strategies.

Diagnostic Limitations: Standard imaging modalities inadequately detected disease extent, particularly in axillary lymph nodes. This case underscores the need for advanced imaging techniques, such as somatostatin receptor imaging, which may enhance diagnostic accuracy in neuroendocrine tumors.

Tumor Biology: The findings of DCIS within the small cell carcinoma component on excision helped to support a primary breast tumor. Hormonal receptor reactivity supports the potential use of hormonal therapies, though their role in PSCCB is not well established. Genetic findings suggest a possible hereditary component, warranting further exploration of *BRIP1* and other predisposition genes.

Future Directions: Standardized management protocols and robust clinical trials are essential for PSCCB. Advances in molecular studies may identify biomarkers for targeted therapies, while improved imaging modalities could aid in early detection and monitoring.

References & Acknowledgements

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