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Primary Small Cell Carcinoma of the Breast: When a Rare Tumour is Real

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ABSTRACT

Background: Extra-pulmonary small-cell neoplasms are rare, and treatment planning is challenging for clinicians. The lack of guideline-based management undermines and isolates patients for whom these cancers are not just rare but also real. Small-cell breast cancer (SCBC) is a rare, aggressive disease that accounts for less than 1% of all invasive breast cancers. Here, we report a case of SCBC and discuss the complexities of case management.

Case Presentation: A 46-year-old patient presented with a self-detected right breast lump. Mammogram and ultrasound examination showed a 69x47mm dense lesion in the upper outer aspect of the right breast and a 17mm pathologic node in the inferior right axilla. The triple assessment demonstrated a localised high-grade malignant neuroendocrine neoplasm. Management extrapolated from small cell lung cancer management and case reports, consisted of chemotherapy with carboplatin, and etoposide introduced with concurrent radiotherapy, followed by mastectomy with axillary lymph node dissection. A complete pathological response was obtained. Six months following her surgery, metastatic disease in the brain, chest wall, lymph nodes, and lungs developed. Rechallenge with carboplatin and etoposide led to a brief response, and subsequent immunotherapy was ineffective.

Conclusion: This case report highlights the challenges of rare tumor management. Establishing registries for these and other rare tumors would facilitate care, reduce patient uncertainty and assist in founding protocol-based care.

INTRODUCTION

Neuroendocrine breast cancer was defined in 2003 by the World Health Organization as a separate subtype of breast cancer, the diagnosis of which requires the existence of neuroendocrine features in at least 50% of malignant cells, the absence of evidence of non-mammary primary tumors, and an *in situ* component in breast histology, for diagnosis.[1]

SCBC is a rare subtype of extra-pulmonary small cell cancer (EPSCC) first described in 1983 by Wade *et al.* and constitutes less than 1% of all invasive breast cancers.[2] Due to its rarity, the optimal management strategy for the disease is derived from existing therapeutic strategies for Small cell lung cancer (SCLC), which typically comprise

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chemotherapy, and radiotherapy, with the primary chemotherapy being etoposide and platinum agents.[3] SCBCs are rarely reported in the literature, and according to an article published in June 2021, fewer than a hundred case reports exist.[4] We highlight the challenges of caring for such patients and suggest strategies to improve their care pathways.

CASE PRESENTATION

A previously healthy 45-year-old Caucasian woman presented with a rapidly developing uncomfortable lump in her right breast. She was never a smoker. She had no family history of cancer other than gastric cancer in her grandfather. At triple assessment, an 8 cm firm irregular mobile mass in the right upper outer quadrant and a small 1 cm palpable mass lateral to the large lump were found. Mammogram and ultrasound (US) demonstrated a 69x47mm dense lobulated opacity in the upper outer aspect of the right breast and a 17mm pathologic node in the inferior right axilla (Figure 1).

US-guided core needle biopsy revealed a high-grade malignant neoplasm composed of predominantly intermediate-sized tumor cells with condensed chromatin, indistinct nucleoli, scant to moderate cytoplasm, nuclear moulding, crush artefact, high mitotic rate, abundant apoptosis and extensive necrosis (Figure 2).

Immunohistochemistry was positive for neuroendocrine tumor markers; Synaptophysin, chromogranin and CD56, and also for TTF1 (Figure 3). Ki67 was positive in >95-100% of tumor cells. Immunohistochemistry for estrogen/ progesterone receptors and HER-2 was negative. US fine needle aspiration of the right axilla confirmed malignancy.

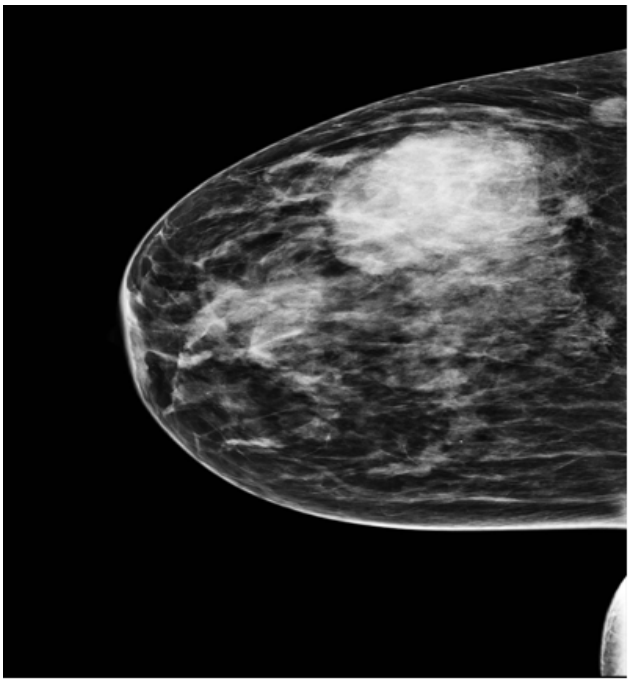

Figure 1. Mammogram showing a 69x47mm dense lobulated opacity in the upper outer aspect of the right breast

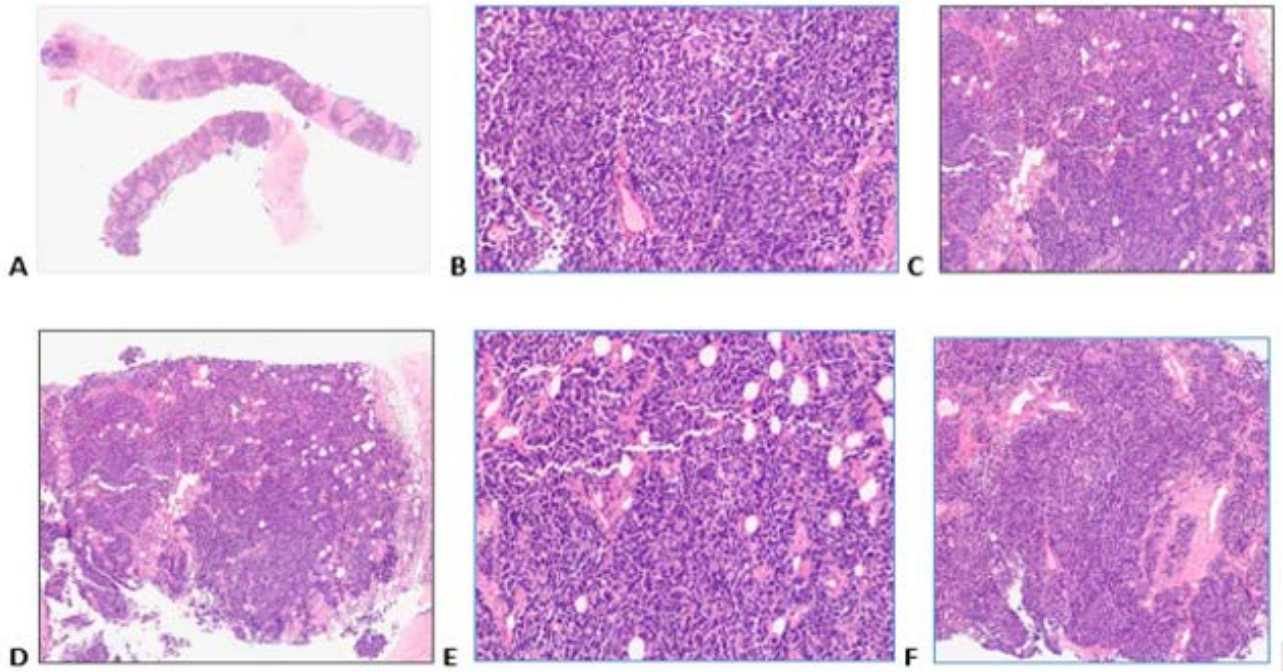

Figure 2. (A-F) Hematoxylin and Eosin (H&E) stain shows high grade malignant neoplasm composed of predominantly intermediate sized tumor cells with condensed chromatin, indistinct nucleoli, scant to moderate cytoplasm, nuclear moulding, crush artefact, high mitotic rate, abundant apoptosis and extensive necrosis (magnification 1x, 20x, 10x, 4x, 20x and 10x, respectively)

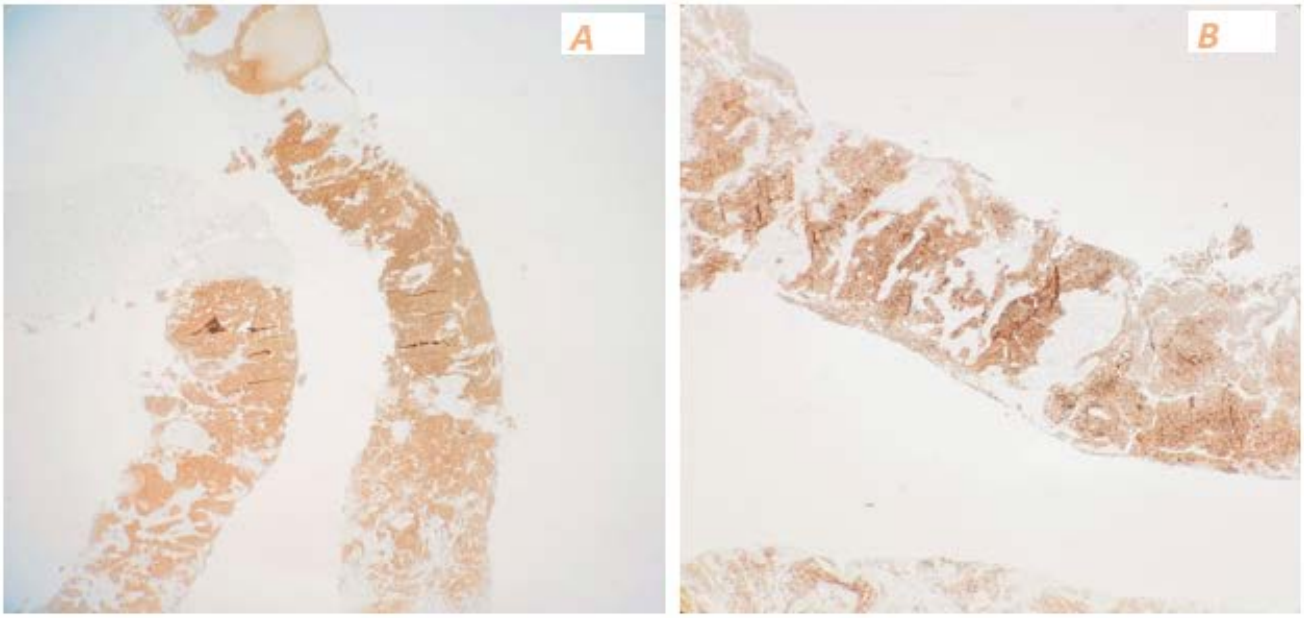

Figure 3. A. Immunohistochemistry showing homogenous diffuse strong positivity for Synaptophysin (2x). B. Showing diffuse strong positivity for CD56 in the malignant cells (4x)

A Positron Emission Tomography (PET) scan revealed an FDG avid right breast mass SUV 10.6 with adjacent satellite nodule or lymph node SUV 4.3 and no other FDG avid disease (Figure 4). MRI brain with gadolinium contrast was normal.

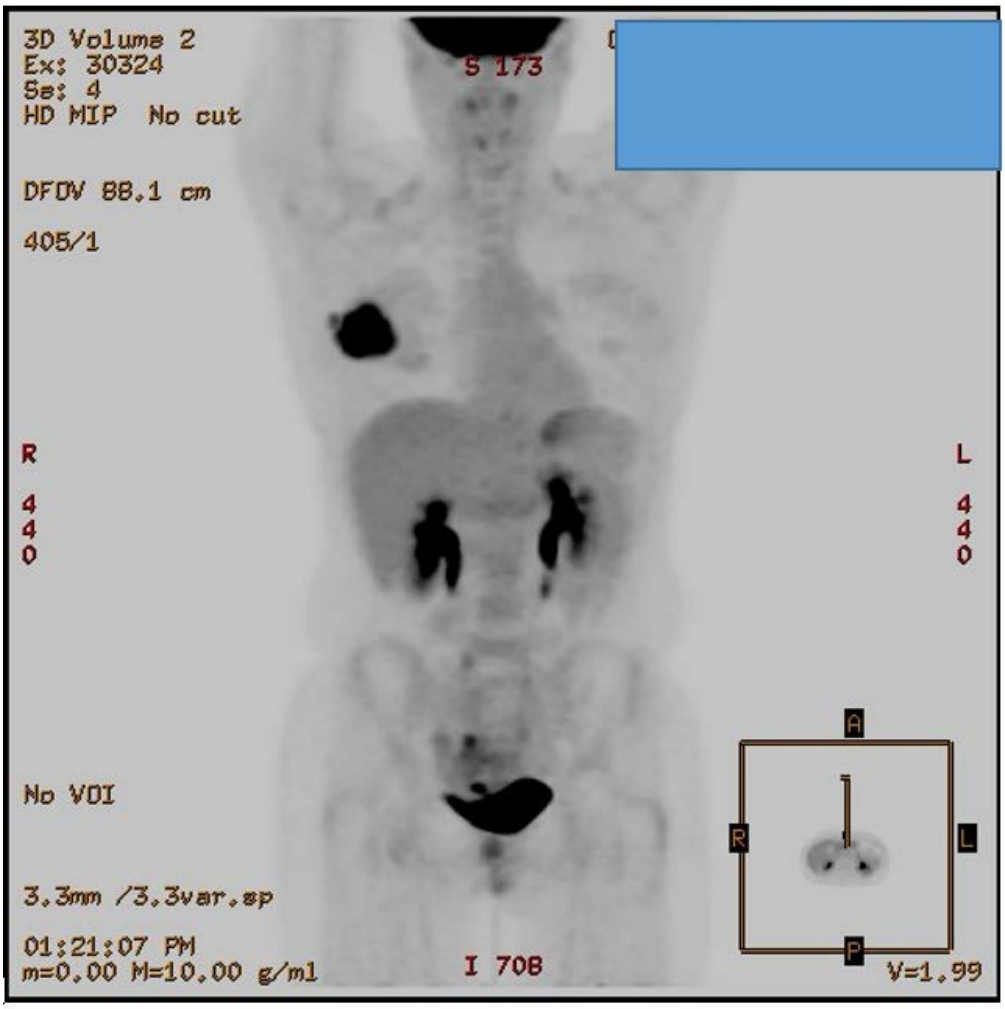

Figure 4. PET/CT showing FDG avid right breast mass with satellite nodule

Foundation One, next-generation sequencing testing analysing 324 genes revealed a tumor mutation burden score of 3Muts/Mb and alteration in PTEN-C25fos*6, IRF2-E294*, RB1-Q471fs*7, and TP53-R213*.

Chemotherapy treatment consisted of four courses of chemotherapy with Carboplatin AUC 5 (day 1) and Etoposide 100mg/m^2 (day 1-3) every 21-day cycle with concurrent breast radiotherapy with a dose of 50gy/25 fractions to whole right breast, whole right axilla, right supraclavicular and right internal mammary chain followed by a boost of 10 greys in 5 fractions.

Subsequently, she underwent a right mastectomy, and axillary lymph node clearance. Pathology assessment demonstrated a complete pathological response.

Six months after surgery, she presented with weight loss and dyspnoea. Computed tomography (CT) confirmed recurrent disease with multifocal right chest wall soft tissue nodules, bulky hilar and mediastinal adenopathy and a heavy burden of pulmonary metastatic nodules. Brain MRI detected a new 7mm metastatic lesion in the right parietal lobe.

She proceeded to receive palliative chemotherapy with Carboplatin and Etoposide. CT post two cycles showed a mixed response in lung nodules; however, brain imaging revealed significant progression with an interval increase in the size of the pre-existing right parietal metastatic deposit and multiple small new ring-enhancing lesions throughout the brain.

Immunotherapy with nivolumab secured on an expanded access programme was initiated. She subsequently developed severe dyspnoea, and the assessment demonstrated hypoxia with oxygen saturation of 77% in room air. Pulmonary CT angiogram demonstrated significant disease progression with extensive thoracic and supraclavicular adenopathy, innumerable bilateral pulmonary metastasis, bilateral pleural effusions, diffuse bilateral lymphangitis carcinomatosis and left lower lobe collapse/consolidation due to invasion of the left lower lobe bronchus.

She was discharged home on an oxygen supply and, with the support of the community palliative care team and social work, to have end-of-life care with her family at home and passed away ten days later in a hospice.

DISCUSSION

Primary SCBC is a rare entity with a poor prognosis. This case highlights the challenges of such rare tumor management, the lack of guidelines, reliance on extrapolation, and the importance of case reports. Importantly, the lack of security in treatment planning compounds the sense of isolation experienced by patients for whom these cancers are considered to be real rather than rare.

In the present case, treatment recommendations are made using retrospective, single-centre institutions or extrapolating evidence from SCLC studies. Brennan *et al.* conducted a retrospective review of 120 patients with EPSCC managed in a tertiary referral centre.[5] Patients were staged according to the Veterans Administration Lung Study Group Classification System used in managing SCLC and treated with multimodal therapy, including four cycles of cisplatin/carboplatin and etoposide, radiation to the primary site and surgical resection if possible. Recurrence-free survival at one year ranged from 13% (primary genitourinary site) to 64% (head and neck). The overall 5-year survival rate was 25.4% for patients with limited stage and 0% for the extensive stage. Surgical resection was not associated with improved clinical outcomes, and they identified a lower rate of brain metastases compared to small-cell lung cancer. Of note, no patients with known SCBC were included in this study. Our patient developed brain metastases six months after radical treatment.

For locally advanced SCBC, management is typically multimodal and includes a radical-modified mastectomy and axillary lymph node clearance with chemotherapy in the adjuvant or neoadjuvant setting.[6,7] Chemotherapy regimens used typically include a platinum-backbone and etoposide; however, there have been case reports of FAC (fluorouracil, cyclophosphamide and doxorubicin) and CAE (cyclophosphamide, doxorubicin and etoposide).[8,9]

The molecular landscape of SCBC is poorly understood. In one of two available studies, McCullar *et al.* used Immunohistochemistry and a 47-gene panel to characterise the genomic landscape of small cell carcinoma of the breast. Of the 19 patients with SCBC included in the study, 31% expressed *ER*, 13 % expressed *PR*, and 16% expressed *AR*.[10] Furthermore, 75% of the patients had a *TP53* mutation identified. Bean *et al.* identified a co-occurring *TP53* and *RB1* mutation in 86% of patients with small-cell neuroendocrine carcinoma of the breast.[11] In the present case, compassionate access genetic testing was used to explore potentially actionable mutations. As with other cases, our patient also had a *TP53* and *RB1* co-alteration on next-generation sequencing, but actionable changes were not observed. In contrast, some degree of molecular characterisation has been achieved in other EPSCC subgroups such as prostate, bladder, uterine, cervix, and head and neck, according to a comprehensive overview of newly emerging molecular vulnerabilities of EPSCC by Frizziero *et al.*[12]

The immune landscape is also not fully characterised in EP-SCLC. IHC expression of PD-L1 in EPSCC is more predominant in tumor-associated immune cells than in tumor cells and is most commonly of low intensity and restricted to a small proportion of the tumor sample. Moreover, EPSCC exhibits a lower median TMB (1.7-7.1mut/Mb), indicating less sensitivity to immune checkpoint inhibitors.[12,13] In reality, the duration of therapy in our patient was short. During second-line therapy, protracted attempts were made to secure immune checkpoint inhibitor access, which was ultimately successful. In our jurisdiction, many patients self-pay or crowd-fund for such therapies.[14] Developing real-world databases for patients with rare tumors would help clinicians and patients in treatment selection and reduce the moral hazard involved.

Rare cancers are defined as those with an annual incidence of less than 6/100,000 per year, accounting for 22% of all newly diagnosed cancers.[15] For patients, these cancers are not rare; they are actual cancers. These rare cancers account for at least 5,200 annually diagnosed cancer cases in Ireland. Lack of information and guidelines on their management leads to more isolation and distress for patients and their families.[16] Challenges in managing these rare cancers also include their heterogeneity and lack of first-hand evidence from clinical trials resulting in inadequate diagnosis and treatment.[17,18,19] Consequently, contemporaneous registry-based studies have documented poorer 5-year survival rates for rare cancers compared to common ones and a failure for the former group to benefit from the gains in cancer survival in recent decades.[20] Recognition of the significance of rare cancers has led to several initiatives, including RARECARE (The project Surveillance of Rare Cancers in Europe), the establishment of European Reference Networks (ERNs) and, in particular, EUROCAN, the ERN for rare adult solid cancers, and the International Rare Cancers Initiative.[15,21,22]

A situational analysis of our experience with the present case would suggest several mechanisms to improve care for others. This would include the appointment of a national lead clinician for rare breast cancer subtypes, a real-world mandatory reporting database with an available opt-out option for patients and a nurse navigator to assist in care management and support patients and healthcare teams. Such a strategy has been integrated into gestational trophoblastic disease management in Ireland as part of a rare cancer initiative by the National Cancer Control Programme. Such an exemplar would have greatly reassured and assisted in the present case.

CONCLUSION

Small cell carcinoma of the breast is a rare, aggressive type of breast cancer with morphological and immunohistochemical similarities to neuroendocrine carcinoma of the lung. Our case highlights the multidisciplinary nature of its management and the need to characterise better the molecular subtypes, immune landscape, and tumor microenvironment to expand therapeutic options and improve outcomes. The lack of knowledge of biology and molecular drivers for SCBC has hampered the development of effective treatments; therefore, we highlight the need for a national registry and database for this rare breast cancer subtype to gather clinical information on the entire patient journey and help describe the natural history and biology of the disease. Integrating with other international registries can provide multidisciplinary second opinions for the management and facilitate access to clinical trials to deliver more therapeutic options.

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CONFLICT OF INTEREST:

None to declare.

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