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Case Report

Primary Squamous Cell Carcinoma of the Breast with Metastasis to the Lung: A Case Report of a Rare and Aggressive Breast Cancer with Literature Review

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Abstract

While breast cancer is the most prevalent form of cancer in women worldwide, the rare and aggressive subtype of primary squamous cell carcinoma of the breast represents an area of unmet need in breast cancer diagnosis and management. Currently, there is no agreed consensus on primary treatment options, neoadjuvant and adjuvant therapy, or prognosis of this rare type of carcinoma. In addition, definitive diagnosis of this entity represents a significant diagnostic challenge and strict criteria should be applied to make such diagnosis. We present a case of a 78-year-old female who presented to her physician with a left breast mass. The final diagnosis proved to be a primary squamous cell carcinoma of the breast. Here, we discuss and detail the diagnostic criteria and what we currently know regarding possible management options. It is our hope that this report raises awareness of clinicians and pathologists to this uncommon entity and promotes continued investigation to drive further development of efficacious diagnosis and safe treatment options to improve patient outcomes.

Keywords: Breast cancer; Neoplasm; Squamous cell carcinoma; Metaplastic carcinoma; Fine needle aspiration; Sentinel lymph node; Axillary lymph node; Prognosis; Treatment; Chemotherapy; Radiotherapy

Abbreviations

PSqCC: Primary Squamous Cell Carcinoma; SCC: Squamous Cell Carcinoma; IDC: Intraductal Carcinoma; IHC: Immunohistochemistry; ER: Estrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receptor; MBC: Metaplastic Breast Cancer; OS: Overall Survival; HPV: Human Papilloma Virus

Introduction

Primary squamous cell carcinoma (PSqCC) of the breast is an extremely rare breast malignancy, accounting for approximately 0.1% of all breast carcinomas [1]. Diagnostic criteria for PSqCC of the breast have been described by the World Health Organization (WHO) and cited in many articles. Notably, Macia et al., defined PsqCC as a tumor with the following characteristics: 1. No other neoplastic components, such as ductal or mesenchymal elements, are present in the tumor. 2. The tumor origin is independent from the overlying skin and nipple. 3. There is absence of an associated primary squamous cell carcinoma in a secondary site [2]. Later reports have added further description to distinguish PSqCC from other types of breast carcinomas. It must first be established that the squamous cells present in the tumor are of primary origin, rather than a secondary metastatic carcinoma from a different primary site, and it must be determined that the tumor origin is independent from the overlying skin and nipple [1-4]. Additionally, the diagnosis is made when more than 90% of the malignant cells found in the tumor are of squamous cell type and no other neoplastic elements are detected in the tumor mass [2,4,5,6]. Debate exists around the origin of squamous cell differentiation; some believe the cells are secondary to squamous metaplasia of breast glandular tissue in response to benign inflammatory processes while others believe the cells are of basal progenitor mammary ductal epithelial origin [7,8]. An additional hypothesis postulates that PSqCC may exist on a disease continuum as an extreme form of squamous metaplasia within pre-malignant and adenocarcinoma cells [9,10]. Though the pathophysiology of PSqCC of the breast is not well understood, this rare subtype of breast cancer is considered far more aggressive and less responsive to standard therapy when compared to other breast carcinomas [12].

This case represents an extremely rare entity with a small amount of associated published reports. At this time there is no agreed consensus on primary treatment options, neoadjuvant and adjuvant therapy, or prognosis of PSqCC. A literature review revealed that cases of PSqCC typically had an outcome comparable to a poorly differentiated ductal carcinoma of the breast with a median overall survival (OS) of 37-39 months

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and a relapse rate of approximately 70% [4,7,10-12]. The tumors are often very large in size, without regional lymph node involvement, and many cases reported that PSqCC of the breast were characterized by absent expression of hormone receptors (ER/PR) and human epidermal growth factor receptor (HER2), contributing to their aggressive nature and propensity to metastasize both locally and distantly [13,14]. Because this pathologic variant is so rare, targeted treatment options have yet to be identified and management decisions are typically made from experience with breast ductal carcinomas [11]. Due to lack of universal understanding of this breast cancer subtype, this case provides the opportunity to raise awareness among clinicians and pathologists to this uncommon entity. Additionally, this case may serve to drive further development of efficacious diagnosis and safe treatment options for cases of PSqCC of the breast.

Case Presentation

A 78-year-old female presented to her physician with a left breast mass. An initial fine needle aspiration cytology and core biopsy of the mass revealed malignant neoplasm with squamous features. The mass was excised along with the overlying skin and sentinel lymph node sampling from the left axilla. The mass grossly measured 1.5 x 1.3cm and histomorphologic examination revealed infiltrating moderately to poorly differentiated squamous cell carcinoma involving the breast tissue and deep dermal tissue without attachment to the overlying epidermal skin (Figure 1 A). Cytohistologic examination was consistent with reported cases of PSqCC of the breast, revealing malignant squamous cells, some with keratinizing cytoplasm, but most showed hyperchromatic, dense nuclei, thickened nuclear membranes, and a necrotic background (Figure 1 B). Additionally, the sample revealed overlying skin with moderate chronic inflammation and associated reactive/reparative changes at the superior aspect of the tumor. The epidermis was free of tumor and all excised margins were free from carcinoma with the closest margin inferiorly at 6mm. Though the tumor was seen infiltrating the skin adnexal glands, there was no evidence that the adnexal glands were the point of squamous origin and there was no evidence of an in-situ component in these adnexal structures. The infiltrating component of the breast cancer was of squamous cell type (> 90%) and there were no other invasive ductal or mesenchymal neoplastic elements identified in the tumor. There was no evidence of a glandular carcinomatous component, in-situ component, vascular invasion, perineural invasion, or microcalcification. The sentinel lymph node from the left axilla was negative for carcinoma, and no subsequent axillary dissection was performed.

Immunohistochemistry (IHC) studies helped to identify the origin of the tumor cells as squamous cells and revealed that they were strongly positive for P63, a nuclear myoepithelial cell stain associated with basal cells and myoepithelial cells (Figure 1 C). HMW-CK 903, a cytokeratin present in all squamous epithelium and their carcinomas as well as other specific types of carcinoma (Figure 1 D). The tumor cells were also strongly positive for E-Cadherin (Figure 1 E), and BCL-2, but negative for Mammaglobin, Calponin, ER (1D5), PR (PgR 636), and HER2. Ki-67 proliferation index was unfavorably high at 45%. The sentinel lymph node from the left axilla was negative for Cytokeratin stain AE1/AE3. Full body imaging survey proved the absence of any other primary carcinoma, ruling out the possibility of metastatic carcinoma. HPV testing was performed on the tumor cells and was negative for all HPV subtypes. This IHC profile along with the histomorphology of the mass was diagnostic of PSqCC of the breast.

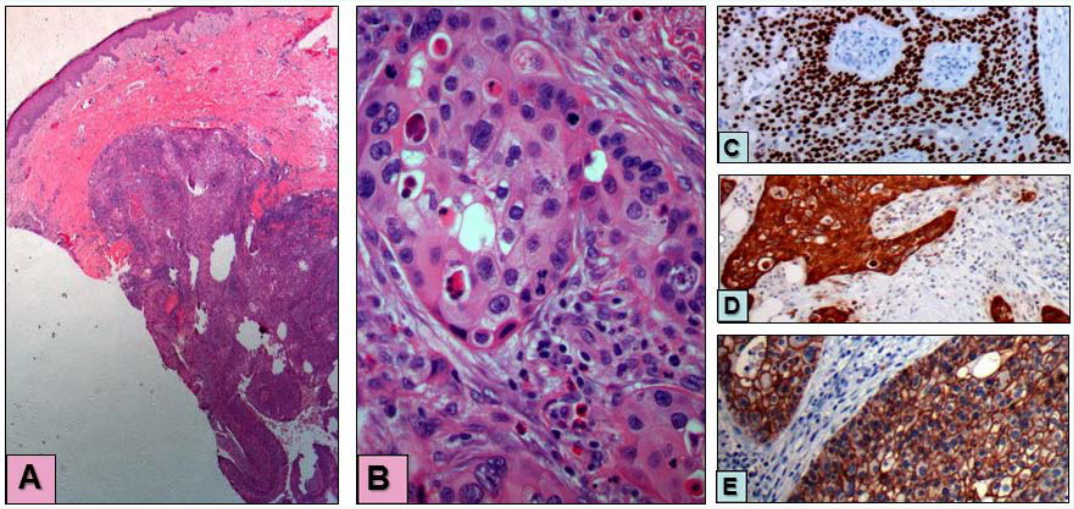

Figure 1 Sections from left breast mass
A: Tumor dermal mass, infiltrating breast tissue and not connected to the overlying skin. H&E X20
B: High power view showing squamous cells with large pink cytoplasm, pleomorphism, cellular keratinization and abnormal mitosis. H&E X100
C: p63 positive with nuclear staining
D: HMW-CK 903 positive with cytoplasmic staining
E: E-Cadherin positive with membranous staining.

The patient underwent surgical intervention followed by adjuvant chemotherapy typically used for IDC and radiotherapy for 30 days at 70 Gy dose. No hormonal/endocrine therapy was initiated due to the triple-negative nature of the tumor cells. Three months after initial diagnosis, the patient was found to have developed masses in the lung. Biopsy of the lung masses showed metastatic squamous cell carcinoma similar to the original samples taken from the breast mass (Figure 2 A&B). Treatment with additional chemotherapy and radiotherapy was initiated, but unfortunately, the patient expired 9 months later due to widespread metastasis.

Discussion

PSqCC of the breast is a relatively uncommon disease. The prognosis of this type of breast cancer is still a subject of controversy; many reports suggest that the outcome of PSqCC is comparable to poorly differentiated ductal carcinoma of the breast, while some reports suggested a more aggressive course [1,2,5,15-17]. In the literature reviewed, a standard of care has yet to be established. Much of what we know regarding treatment of PSqCC of the breast has been extrapolated from management options for breast ductal carcinomas in combination with known treatment options for squamous cell carcinoma (SCC) in extra-mammary locations such as head and neck, cervix, vagina, and anus [11].

PSqCC of the breast is classified as a "purely epithelial" subtype of a heterogenous group of malignancies known as metaplastic breast cancer (MBC), which as a group overall, accounts for less than 1% of all breast carcinomas (3,6,18). Review of multiple case reports reveals some general shared characteristics of PSqCC, which Clay et al., summarizes in a review of 28 selected cases. The average age of diagnosis is usually in the post-menopausal period, around 57 years old, the tumors present as palpable masses and tend to be large and bulky in size (average size of 4.8cm) with non-specific physical exam and mammographic findings, and a large percentage of cases present without expression of steroid hormone (ER/PR) and HER2 receptors [8]. Cytodiagnosis can be made with fine needle aspiration and confirmation with excisional or core breast biopsy, as seen in our patient [16]. While our patient presented at a much older age and with a significantly smaller tumor size on gross excision, she did exhibit the triple-negative feature reported by other cases. Another characteristic noted in multiple cases is the lack of axillary lymph node involvement, despite the aggressive clinical course of the tumor. Per Menes et al, only 22% of patients with PSqCC of the breast experienced axillary lymph node involvement at time of presentation, compared to 40-60% noted in cases of IDC [14,15,19,20]. This also differs from classic extra-mammary SCC presentation, which frequently metastasizes to local lymph nodes. Despite lack of local lymph node metastasis in most cases, many reported that PSqCC of the breast was likely to skip regional lymph nodes and present with distant metastasis, with rates reported in the range of 30-33% [13,15,19,20,21]. Sites of common metastasis include the soft tissues of the neck, mediastinum, and lungs, as seen in our patient [15]. Additionally, per review of 33 patients treated at The University of Texas M.D. Anderson, 71% of patients with initial localized disease experienced a relapse, with a median survival of 14 months after recognition of recurrent or metastatic disease, reinforcing what we know about the aggressive nature of these rare tumors [4]. Of note, the role of human papilloma virus (HPV) in breast carcinoma, and in particular PSqCC, has been examined and is still considered a debatable issue [8,22]. In our case, the tumor cells were negative for all types of HPV, which precluded further investigation into the role of HPV when discussing the pathogenesis of PSqCC

To better determine prognosis and appropriate management options for this subtype of breast carcinoma, it is important to continue to collect and condense the information that has been gathered from case reports of PSqCC of the breast. A large amount of uncertainty continues to center around a lack of universal understanding of the origin of the cancerous squamous

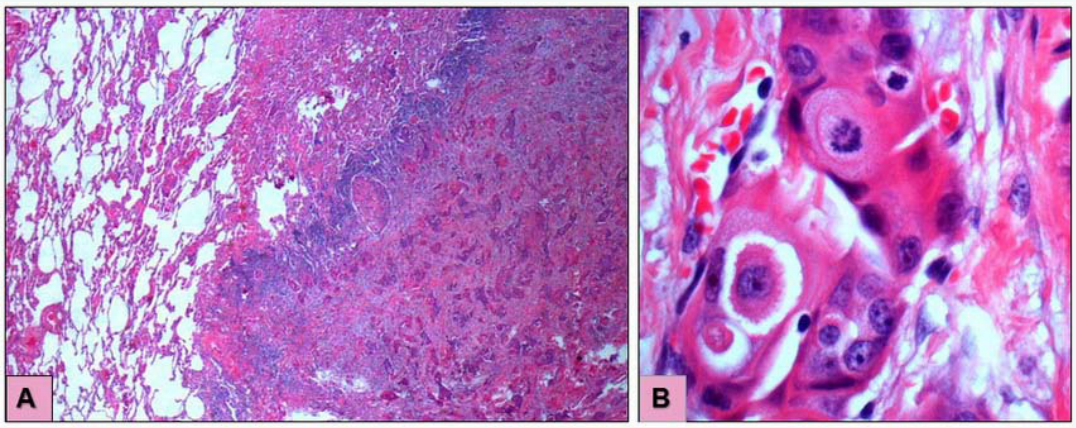

Figure 2 Sections from metastatic lung mass showing similar histomorphology and immunohistochemistry profile as compared to original breast mass
A: Lower power view showing large mass of squamous tissue infiltrating lung parenchyma. H&E X20
B: High power view showing malignant squamous cells similar to the cells identifies in the primary breast carcinoma. H&E X100

cells. The available literature proposes many theories regarding the histogenesis of squamous cell differentiation. One theory suggests that PSqCC of the breast arises directly from basal progenitor cells of the mammary duct epithelium, producing a basal-like, triple-negative breast cancer that lacks expression of steroid hormone receptors (ER/PR) and HER-2 [4,5,8]. These basal-like characteristics distinguish PSqCC of the breast from IDC (which typically experience overexpression of ER) and limit targeted therapeutic options and often contribute to the aggressive and relapsing nature of PSqCC of the breast. Another popular theory suggests that the origin of PSqCC is squamous metaplasia secondary to chronic benign breast conditions such as dermatoid cysts, chronic abscesses, fibroadenomas, and phyllodes tumors [2,20,23]. Lastly, Stevenson et al., suggests that PSqCC of the breast may exist on a disease continuum, with cases revealing a heterogenous group of infiltrating carcinomas of the breast with varying degrees of squamous differentiation. He argues that a "pure" form of PSqCC of the breast may not actually exist and that cases of PSqCC actually represent an extreme form of squamous metaplasia within adenocarcinoma [9]. This is supported by the aforementioned criteria required to diagnosis a breast carcinoma as PSqCC. While 90% of malignant cells found in a tumor must be comprised of squamous cells, the additional 10% of malignant cells may be of alternate origin (such as ductal adenocarcinoma), creating what he calls "intermediate" cells. It is postulated that this "intermediate" or "mixed" nature may contribute to the tumor's resistance to standard adjuvant radiation and chemotherapy.

Though knowing the exact origin of PSqCC appears clinically insignificant, treatment regimens and management decisions are often made based on experience treating IDC which typically involves surgical intervention and adjuvant chemotherapy with agents such as 5-fluorouracil (5-FU), cyclophosphamide, methotrexate (MTX), or Adriamycin. What is known is that patients with triple-negative metaplastic breast cancer such as PSqCC of the breast who receive identical chemotherapy regimens as patients with IDC showed a poorer 3-year disease-free survival rate [1]. Because this entity is so rare and the tumor has an unclear behavioral pattern, no randomized clinical trials have been published studying the appropriate treatment regimen for PSqCC of the breast and many management decisions are made using the little information available in the reported case studies. After diagnosis, initial treatment includes surgical intervention. Given the large tumor size and typical locally advanced disease at presentation, most cases opted for mastectomy as the surgical option of choice. Of note, some cases of lumpectomy/breast conservative surgery were reported with similar OS rates between breast conservative surgery and mastectomy [11]. Given the low rate of axillary lymph node involvement at presentation, Menes et al., has recommended sentinel node biopsy over routine axillary dissection [19]. Neoadjuvant chemotherapy use has proven futile in cases reported by Hennessey et al., and Nayak et al [4,12]. Because most cases of PSqCC of the breast exhibit triple negativity, targeted hormone receptor and HER2 receptor therapies are usually not an option. The tumors have also demonstrated an unusual resistance to radiation therapy even though SCC are considered generally radiosensitive [4,9,10,20]. Instances of locoregional and metastatic disease progression in previously irradiated sites have even been reported at a mean of 6 months after treatment [4]. This lack of response is frequently attributed to the heterogenous/mixed cell types present in the tumor. The determination of appropriate adjuvant chemotherapy regimens seems to be an area of debate. As previously mentioned, typical IDC chemotherapy regimens have not proven efficacious in the treatment of PSqCC. A report by Dejager et al., reported great success using a SCC-centered multimodal treatment approach including cisplatin, 5-FU, and radical mastectomy. The patient remained disease free at 2.5 years after initial diagnosis [24]. Since this case report was published in 1995, many succeeding case reports have recommended a similar regimen with or without the addition of doxorubicin and many cases have reported successful disease-free follow ups after the use of adjuvant cisplatin [9,10,19,24,26].

Although prognosis for PSqCC of the breast has never been formally studied outside of case reports and small case series, even after treatment, the 21 cases reviewed by Nayak et al., revealed a 40% locoregional recurrence within 4-16 months (median of 11 months) in the ipsilateral breast, axilla, or chest wall. Distant metastasis was described in 30% of the patients within 4-22 months (median of 13 months), with the lung being the most common site of metastasis. At last follow up, it was reported that 40% of the patients had died of the disease within 3-37 months (median of 18 months) from onset of the disease [12]. Many case series have published statistics on 5-year OS in patients diagnosed with PSqCC of the breast, mostly ranging between 50-70% [1,11,12,19]. Nayak et al., stratifies 5-year OS by age and tumor histology, stating that these two features were the only factors found to be statistically significant in regard to OS. Patients greater than 60 years old, such as our patient, experience a greatly reduced 5-year OS when compared to patients less than 60 years old (36%, SD 12% vs. 60%, SD 16%, respectively).

As mentioned previously, a few number of published reports currently exist regarding PSqCC of the breast, and what we currently know is based on a small cohort of case studies and case series. Many of these cases have yielded inconsistent results and statistics, leaving much unknown regarding the appropriate management options for this type of breast carcinoma. Overall, through literature review and experience with this case, it is obvious that a standard of care has not been established for this rare subtype of breast carcinoma. In conclusion, given the unique nature and characteristics of this tumor, we feel that standard therapy used to treat IDC is not appropriate when treating PSqCC of the breast. We are in agreement with multiple other case reports and believe that neoadjuvant and adjuvant therapy with cisplatin should be further investigated. Additionally, some reports have suggested further investigation into Epidermal Growth Factor Receptor (EGFR) inhibitors administered concurrently with radiation in attempt to minimize risk of locoregional recurrence [4]. While this breast cancer subtype has proven somewhat allusive, we hope this case report will add to the repertoire of research on this topic and provide clinicians and pathologists with more insight about PSqCC of the breast,

allowing for appropriate diagnosis and informed management decisions until definitive conclusions can be established by future randomized clinical trials.

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