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Case Report

Primary Squamous Cell Carcinoma of the Breast Arising from Metaplastic Ductal Epithelium: A Case Report and Literature Review

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Abstract

Introduction: Primary squamous cell carcinoma (PSqCC) of the breast is a rare and aggressive type of carcinoma. It is believed to arise from squamous metaplasia of ductal carcinoma cells or mammary duct epithelium. The tumor is usually estrogen receptor (ER) and progesterone receptor (PR) negative without overexpression of human epidermal growth factor receptor (HER-2/neu). Epidermal growth factor receptor (EGFR) is reported to be expressed in a large percentage of these tumors. It is typically high grade, although lymph node involvement is less common with PSqCC than breast adenocarcinoma. Studies showed that almost seventy percent of patients with PSqCC have no axillary lymph node involvement.

Report: We report a case of a 52-year-old female who presented with a self-discovered breast mass. The mass proved to be a PSqCC of the breast with a minor component of invasive ductal carcinoma. We detail the diagnostic challenges of this entity and discuss management modalities.

Conclusion: It has been hypothesized that PSqCC of the breast arises from metaplasia of pre-existing malignant ductal carcinoma cells. Our case would seem to support this hypothesis. Compared to invasive ductal carcinoma, few cases of PSqCC of the breast have been reported. Due to the rarity and lack of randomized controlled trials, there is a necessity for consensus on the diagnostic criteria, treatment, and prognosis.

Keywords: Breast; Squamous Cell Carcinoma; Primary; Malignancy; Metaplastic; Treatment

Abbreviations

PSqCC: Primary Squamous Cell Carcinoma; ER: Estrogen Receptor; PR: Progesterone Receptor, HER-2/neu: Human Epidermal Growth Factor Receptor; EGFR: Epidermal Growth Factor Receptor, SCC: Squamous Cell Carcinoma; IHC: Immunohistochemistry

Introduction

Breast cancer is the most prevalent cancer in women, affecting around two million women each year. The most common types of breast cancer are adenocarcinomas including invasive ductal carcinoma, ductal carcinoma in situ, and invasive lobular carcinoma. Primary squamous cell carcinoma of the breast is a rare tumor accounting for less than 0.1% of all breast carcinomas [1]. Hennessey et al. [2], classifies PSqCC of the breast as having greater than 90% of the area as SCC, absence of skin involvement, and absence of another primary SCC (oral, cervix, anus, etc.). PSqCC of the breast can be categorized as pure or non-pure (with mixed component). Macia et al. [3], further defines pure forms as having no other neoplastic components such as ductal or mesenchymal elements. The majority of PSqCC of the breast are not pure. Interestingly, when tumors classified as "pure" were subjected to ultra-structural analysis, either separate squamous and glandular cells were present or both histologic features were noted to coexist together [4]. Therefore, tumors classified as primary squamous cell carcinomas typically range from having a spectrum of no ductal component to a small amount of ductal component [2].

The origin of these tumors remains unclear. It has been postulated that the pure form of PSqCC of the breast arises from advanced squamous metaplasia [1]. This metaplasia may arise from reactive reparative changes following benign conditions such as various inflammatory conditions. The aggressive phenotype of PSqCC has directed the attention to the possibility that the tumor may arise from basal progenitor cells of mammary ductal epithelium. Finally, it has been proposed that PSqCC of the breast arises from metaplasia from pre-existing adenocarcinoma.

Literature review revealed that PSqCC of the breast is an aggressive, hormone receptor negative, and treatment refractory tumor. At time of diagnosis, patients typically do not present with axillary lymph node involvement [5]. There is no consensus on survival rates. Due to the rarity of the tumor, there is no universal recommendation for treatment.

Case Presentation

A 52-year-old female presented with a self-discovered

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left breast mass. Her medical history is significant for mild hypercholesterolemia controlled with Lipitor, and well-controlled type-II diabetes mellitus. She had no specific family history and no significant risk for breast carcinoma. Two years prior, she had a suspicious mammographic finding, and a core biopsy showed atypical ductal hyperplasia. After a non-diagnostic core biopsy of the current mass, a repeat core biopsy was suspicious for malignant squamous tissue. The mass was excised.

The gross specimen measured 6 x 3.5 x 2.5 cm and upon sectioning, revealed a 9 mm in diameter oval, tan-white, centrally located, friable mass. Microscopically, there was a dominant mass formed by islands and large sheets of malignant squamous epithelium associated with dense desmoplastic reaction. The dominant lesion showed cystic areas with abundant keratin and extensive necrosis. Although the nuclear grade was low, sufficient atypia was noted with prominent necrosis and scattered abnormal mitosis (3 mitosis/10 HPF). Abundant microcalcifications were noted.

Immunohistochemistry (IHC) studies aided in identifying this tumor as an invasive squamous cell carcinoma with ductal component. The tumor mass showed two components, one major component (9 mm) was purely squamous, and a minor component (2 mm) was invasive ductal carcinoma, both making a single mass (Figures 1,2). The squamous component was positive for HMW-Cytokeratin, E-Cadherin, and P63, but negative for Calponin, ER, PR and Her-2/neu. In addition, the squamous component was positive for EGFR and 40% nuclear staining with proliferation index Ki-67. The invasive ductal component was positive for E-Cadherin, ER (90%) and PR (10%), but negative for HMW-Cytokeratin, Calponin, P63 and EGFR.

There was a spectrum of prominent proliferative fibrocystic changes including multiple foci of atypical ductal hyperplasia, which showed weak to absent staining with HMW-Cytokeratin. Although the tumor was close to the skin (anterior margin), it was not connected or infiltrating into the skin. There was no evidence of squamous carcinoma or other types of carcinoma involving any other organs at the time of diagnosis. Thus, the tumor was diagnosed as a PSqCC of the breast arising from metaplastic components of breast ducts. This is considered a type of metaplastic carcinoma where the metaplastic part is malignant squamous component rather than a sarcomatous component in the presence of a minor invasive ductal component. Sentinel lymph node examination at the time of lumpectomy was negative; therefore, no dissection of axillary lymph nodes was performed.

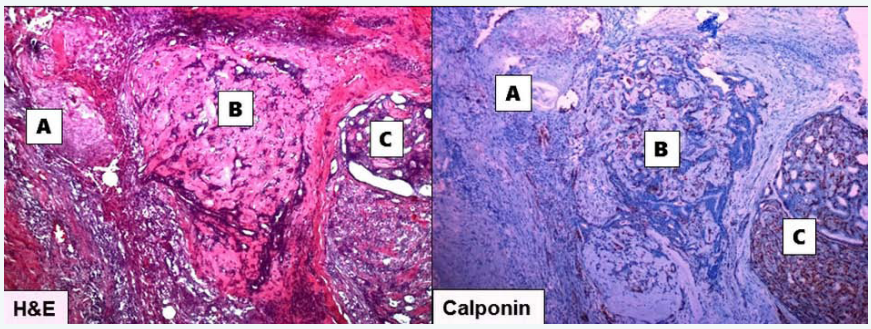

Figure 1 Sections from the breast carcinoma mass, H&E and Calponin stains X20
A. Squamous carcinoma component showing negative Calponin
B. Ductal carcinoma showing only weak scattered stained cells
C. Breast benign tissue showing positive Calponin

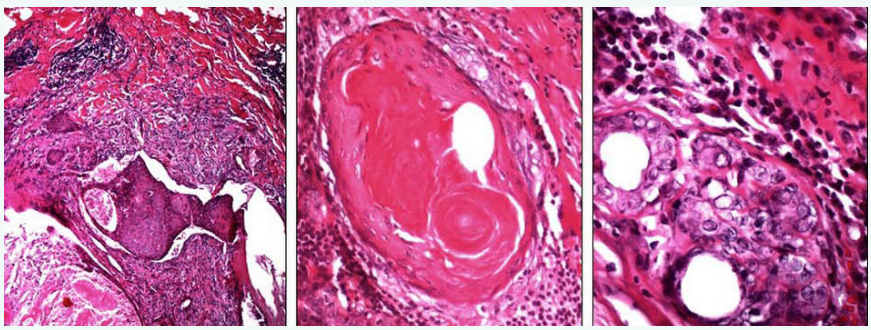

Figure 2 Sections from breast carcinoma mass showing different components of the tumor
A. Squamous component with cystic changes and necrosis H&E X20
B. Squamous component showing prominent keratin pearls H&E X40
C. Ducal adenocarcinoma carcinoma H&E X40

The patient decided to undergo a bilateral mastectomy. Post-operative treatment included six cycles of adjuvant chemotherapy with fluorouracil, epirubicin, and cisplatin followed by postoperative radiotherapy to chest wall and drainage areas for a 6-week period. One-year later, recurrence in the form of 1.2 cm squamous cell carcinoma mass appeared at the chest wall, but no other metastatic sites. The recurrent mass was excised followed by EGFR-tyrosine kinase inhibitors and a combination of pemetrexed with platinum-based regimens. The patient developed multiple treatment related side effects and did not tolerate the new regimen well. However, three years later she was free of recurrence or metastasis then was lost to follow-up.

Discussion

Squamous cell carcinoma is a malignancy that classically involves the skin, head, neck, lung, esophagus, vagina, cervix, and anal canal [6]. PSqCC originating from the breast is a rare occurrence accounting for less than 0.1% of all breast tumors [1]. Frequently, these tumors are reported to be larger than average breast tumors, rapidly progressive, chemotherapy resistant, and receptor negative. An extensive literature review confirms the common characteristics of these tumors as seen in 28 selected cases and retrospective studies of PSqCC of the breast (Tables 1, 2). However, there is still no consensus on survival rates and treatment.

The average age of diagnosis is usually around 57-years-old [1]. PSqCC of the breast tend to be larger than other breast tumors at presentation [1]. Based on our literature review, the size of these tumors ranges from 0.5 cm to 10.5 cm with the average size being 4.8 cm. Our patient's tumor was 1.1 cm including both

Table 1: 28 selected cases of primary squamous cell carcinoma of the breast and current case, listed chronologically.

Author	Year	Age	Mass size	ER	PR	HER2	Axilla LN Mets	Treatment	History of Breast Condition
Clay et al. [current case]	2019	52	6 x 3.5 x 2.5 cm	(-)	(-)	(-)	No	S, R, C	ADH
Anne et al. [21]	2019	68	3.5 cm x 3.4 cm	(-)	(-)	(-)	No	S	None
Mahrous et al. [22]	2018	49	3 x 2.5 cm	(-)	(-)	(-)	No	S, R, C	None
Purkayastha et al. [6]	2018	31	4 x 3 cm	(-)	(-)	(-)	No	S, R, C	None
Lim et al. [8]	2017	62	5.5 cm	(-)	(-)	(-)	No	S	NR
Siripurapu et al. [23]	2017	47	3.0 x 2.5 x 2.0 cm	(-)	(-)	(-)	No	S	None
Siripurapu et al. [23]	2017	54	6.5 x 6.1 x 5.2 cm	(-)	(-)	(-)	Yes	S	Fibroadenoma
Ramos et al. [14]	2016	36	8 × 5.5 × 4 cm	<5%+	(-)	(-)	No	S, R, C	None
Konuk et al. [24]	2017	56	0.5 x 0.3 cm	(-)	(-)	(-)	No	S, R	IDC
Konkankit et al. [25]	2016	67	2.4 x 2.0 x 1.3 cm	(+)	(-)	(-)	No	S, C	None
Akram et al. [26]	2015	50	6 x 5 cm	(-)	(-)	(-)	Yes	S, R, C	None
Seddik et al. [27]	2015	43	9 x 8 x 9 cm	(-)	(-)	(-)	Yes	C	None
Badge et al. [5]	2014	72	8 x 6 x 4 cm	(-)	(-)	NR	No	S	None
Porzio et al. [28]	2014	54	0.6 cm	(-)	(-)	(-)	No	S, C	IDC
Bhosale et al. [29]	2013	60	3 x 3 cm	(-)	(-)	NR	No	S, C	NR
Salemis [12]	2012	61	5 × 4 × 2.5 cm	(-)	(-)	(-)	Yes	S, R, C	None
Accurso et al. [30]	2012	42	6 cm	(-)	(-)	(-)	Yes	S, R, C	NR
Carbone et al. [31]	2012	51	2 cm x 1.9 cm	(-)	(-)	(-)	No	S, R, C	Mastitis
Gupta et al. [19]	2012	63	6 x 3 cm	(-)	(-)	(-)	No	S, R, C	None
Mitra et al. [32]	2011	58	3 x 4 cm	(-)	(-)	NR	Yes	S	None
Temiz et al. [33]	2010	68	5 cm	(-)	(-)	(-)	Yes	S, C	None
Uncu et al. [20]	2009	64	5.5 cm	(-)	(-)	NR	No	S, R, C	NR
Sharma et al. [34]	2009	59	10.5 cm	(-)	(-)	(-)	No	S, C	Phyllodes Tumor
Murialdo et al. [15]	2009	54	4.7 cm	(-)	(-)	(-)	No	S, C	None
Gürsel et al. [35]	2007	60	3 cm	(-)	(-)	NR	No	S, C	NR
Wrightson et al. [13]	1999	73	4.6 cm	(-)	(-)	NR	No	S, R	None
Wrightson et al. [13]	1999	56	4.4 cm	(-)	(-)	NR	No	S	None
Wrightson et al. [13]	1999	74	2.6 cm	(-)	(-)	NR	Yes	S, R, C	None
Wrightson et al. [13]	1999	77	8 cm	(-)	(-)	NR	Yes	S	None

Abbreviations: NR= Not Reported, S= Surgery, R= Radiation, C= Chemotherapy, Mets= Metastasis, LN = Lymph Node, IDC = Invasive Ductal Carcinoma, ADH = Atypical Ductal Hyperplasia

Table 2: Selected retrospective studies of primary squamous cell carcinoma of the breast, listed chronologically.

Author	Year	# of cases	Age	Mass Size	Axilla LN Metastasis	Survival (5-year OS)	Years of Cases
Zhang et al. [10]	2016	30	50*	3.1 cm*	Yes, 36.7%	67.2%	1966-2014
Liu et al. [16]	2015	29	54*	4.5 cm*	Yes, 41.4%	34.5%	1985-2013
Znati et al. [36]	2010	8	48.2*	3-4 cm*	Yes, 12.5%	NR	2004-2009
Grabowski et al. [17]	2009	177	64^	NR	Yes, 32%	68.1%	1988-2006
Hennessey et al. [2]	2005	33	52*	NR	Yes, 50%	40%	1985-2001
^^SEER [2]	2005	137	NR	NR	Yes, 20%	64%	1988-2001
Wargotz and Norris [18]	1990	22	52*	4.0 cm*	Yes, 10.5%	63%	NR-1983

Abbreviations: ^^SEER= Surveillance, Epidemiology, and End Result Database, from Hennessey et al. [2], * = Median, ^= Mean, NR= Not Reported, LN = Lymph Node, S= Surgery, R= Radiation, C= Chemotherapy, OS= Overall Survival

components. PSqCC of the breast are more frequently associated with cystic degeneration compared to metastatic SCC to the breast. Most women present with a mass, while others present with an abscess, cyst, or mastitis. Mammography does not reveal a classic presentation; however, calcifications may be seen [1]. These tumors are rarely well-circumscribed.

These tumors are classically negative for ER, PR, and HER-2/neu, however, EGFR is often overexpressed as is the case in our patient [2]. Since most PSqCC of the breast present with a mixed ductal component, there is a wide variation in tumor marker reporting. As the quantity of ductal component is increased, the likelihood of ER or HER-2/neu expression increases as well [7]. It is our recommendation to report the details of each component separately regarding size and ancillary/therapeutic studies to assist in definitive diagnosis and optimal management.

Although patients typically do not present with axillary lymph node involvement at the time of diagnosis, these tumors are known to be aggressive [5]. One case reports a patient with a 0.5 cm mass on ultrasound who declined treatment, then returned three months later to have the mass removed. The final histopathology revealed a 5.5 cm PSqCC [8]. Despite the aggressive nature of these tumors, only about 22% of patients with PSqCC of the breast present with axillary lymph node metastasis, compared to 40-60% for invasive ductal carcinomas [9]. Also, unlike invasive ductal carcinoma, there is still a large number of distant metastasis without lymph node involvement [9]. Due to the lack of lymph node involvement, Menes et al. [9], recommends a sentinel node biopsy over an axillary node dissection. Zhang et al. [10], suggests that axillary lymph node involvement is an important prognostic factor and affects overall survival rates. Zhang et al. [10], reported a 5-year overall survival in their patients with lymph node involvement as 31.7% vs. a 100% 5-year overall survival in patients with no lymph node metastasis. Just like receptor status, as the ductal component is increased, so does the incidence of lymph node metastasis, and tumor stage has a greater impact on survival [7].

The origin of PSqCC of the breast remains unclear and controversial. There are three main theories of the histogenesis of these tumors. 1) PSqCC of the breast arises directly from basal progenitor cells of mammary ductal epithelium. The aggressive nature of PSqCC of the breast is similar to basal forms of breast cancer. Basal forms of breast cancer are classified based on a set of characteristics: lack of ER, PR, and HER-2/neu expression, positive for HMW-Cytokeratins and/or EGFR, and tend to be aggressive tumors [11]. Because these tumors arise from basal progenitor cells and have similar characteristics to PSqCC of the breast, Hennessey et al. [2], postulates this may be an origin of these tumors. 2) PSqCC of the breast can arise from advanced squamous metaplasia [1]. This metaplasia may arise from benign conditions such as chronic abscesses [12,13], cysts [14], mastitis [15], fibroadenomas, phyllodes tumors, mammary duct ectasia, and breast prosthesis. It is believed that this chronic inflammation may lead to the development of squamous metaplasia, and subsequent malignancy in the already metaplastic tissue [13]. This is thought to be the etiology of the pure form [1]. 3) PSqCC of the breast arises from metaplasia of pre-existing malignant ductal carcinoma cells. Stevenson et al. [4] suggests that when PSqCC of the breast classified as "pure" were subjected to ultrastructural analysis, either separate squamous and glandular cells are present or both histologic features are noted to coexist together. Therefore, tumors classified as primary squamous cell carcinoma typically range from having a spectrum of no ductal component to a small amount of ductal component [2]. Because this malignant ductal component is seen in the background of the squamous carcinoma, this is suggested to be the origin [6,7]. Our patient did not present with any of the aforementioned benign lesions. Our patient had a predominant invasive squamous cell carcinoma portion merging with a small portion of well differentiated ductal carcinoma, indicating that the PSqCC arose from metaplastic malignant ductal epithelium (Figures 1 & 2).

There have been a few cases of PSqCC of the breast reported in literature. This includes individual case reports (Table 1) and larger retrospective studies (Table 2). However, there is great variability in treatment, prognosis, and survival outcomes. The majority of these cases fit the basic criteria of primary squamous cell carcinoma of the breast. The majority are receptor negative. However, some of the older retrospective studies did not have the ability or tissue sample to report immunohistochemistry. In most cases, patients did not have a personal or family history of breast cancer. The majority received surgery, chemotherapy, and radiation. Zhang et al. [10] also reports that due to lack of stringent pathological criteria, early cases of PSqCC of the breast frequently occurred with adenocarcinoma or originated from

adjacent skin. Past literature reviews often combine the "pure" and "mixed" forms in their studies.

There has been controversy over tumor survival rates. Most articles report that PSqCC of the breast is an aggressive tumor. Hennessey et al. [2], and Liu et al. [16], report 40% and 34.5% 5-year overall survival rate respectively. Whereas others reported a 5-year overall survival rate between 63% and 68.1% [2- (SEER Data),10,17,18]. As stated previously, PSqCC of the breast most likely fall on a spectrum between pure and mixed [2]. A study by Pai et al. [7], compared 28 pure squamous tumors with 28 metaplastic ductal carcinomas with squamous components ranging from 10% to <100%. The 5-year disease free survival rate for metaplastic carcinomas was 64% vs. 39.8% for the pure squamous tumors. Most large retrospective studies do not report the degree of squamous differentiation or ductal component; this may be a source of discrepancy between survival rates for these tumors. It is our recommendation to report the details of each component separately regarding size and ancillary/therapeutic studies to assist in definitive diagnosis and optimal management.

For treatment, the majority of patients receive mastectomy, radiation, and adjuvant chemotherapy [1]. However, there is no widely accepted treatment approach. Due to their aggressive nature, they are often treated like invasive ductal carcinomas. Unfortunately, these tumors are well known for being resistant to the standard chemotherapy used for invasive ductal carcinomas [19]. They also tend to be resistant to radiotherapy [2]. Hormonal therapy is usually not utilized due to the majority being ER/PR negative. In addition, most of these tumors show no HER-2/neu amplification. Patients typically do not respond to neoadjuvant chemotherapy [2,10]. Regimens usually include CMF (cyclophosphamide, methotrexate, and fluorouracil) or FAC (fluorouracil, doxorubicin, cyclophosphamide) with or without a taxane. Hennessey et al. [2], showed the effectiveness of platinum-based adjuvant therapy as well. Uncu et al. [20], suggests that combining platinums with adriamycin and cyclophosphamide may be the most ideal combination. Hennessey et al. [2], suggests that since a large amount of these tumors are EGFR positive, this is a treatment that needs to be explored. Our patient showed serious reactive changes related to chemotherapy.

Primary squamous cell carcinoma of the breast is a rare and aggressive malignancy. Due to the rarity of this tumor, there is often controversy of the origin, treatment and prognosis. We presented a case of PSqCC of the breast that arose from a malignant ductal component. Hopefully this case can provide insight into the histogenesis of this relatively poorly understood malignancy.

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