Clinics in Oncology

Case Presentation
Published: 13 Mar, 2017

Rare Breast Myoepithelial Carcinoma with a Distinctive Genetic Profiling Study

*Kerolos Abadeer[1], Judith S. Kaur[2], Mohd E.M. Ibrahim[4] and Aziza Nassar[3]**

[1]Division of Nephrology and Hypertension, USA

[2]Division of Hematology and Oncology and Cancer Center and Breast Clinic, USA

[3]Department of Laboratory Medicine and Pathology, Mayo Clinic, USA

[4]Division of Pathology, Massey Cancer Center/VCU, USA

Abstract

We describe a 74-year-old woman with no family history of breast cancer who presented with a high-grade myoepithelial carcinoma. Diagnosis was supported by immunohistochemical staining for both epithelial (ie, keratin) and myoepithelial (eg., p63, S-100, actin) differentiation. Because the patient reported that her family had an extensive history of neoplasm, a genetic study was ordered. To our knowledge, this is the first case to be reported in the literature with a complete genomic profiling study in which a 4-gene alteration has been detected. Molecular genetics profiling of the tumor using a genetic profile showed a genetic alteration in *NF1* (L494fs*4), *IRS2* amplification, *RB1* loss, and *TP53* (Y107D). The patient underwent lumpectomy with sentinel lymph node biopsy and chemotherapy treatment with carboplatin and taxol. She is alive and free of disease.

Keywords: Breast; Genetics; Genomic profiling; Immunohistochemistry; Metaplastic carcinoma; Myoepithelial carcinoma; p63

Abbreviations

SMA; Smooth Muscle Actin

Introduction

Myoepithelial breast carcinoma is a rare breast cancer that arises from the myoepithelial cells and shares overlapping phenotypic features with metaplastic carcinoma [1]. It has a unique immunphenotypic profile with positive immunoexpression for cytokeratins (AE1/3), including high-molecular weight keratin (CK 14, CK903) and myoepithelial differentiation (p63, S100), as well as immunoreactivity to antibodies against myofilaments (Smooth Muscle Actin [SMA]). EGFR expression is also common in myoepithelial carcinomas. They are typically negative for hormonal receptors and HER2; therefore they are often considered triple negative breast cancer.

Myoepithelial carcinoma has a propensity for distant metastasis [1]. The molecular profiling of these tumors has not been studied thus far. Herein, we describe a distinctive case of myoepithelial breast carcinoma with its genomic profiling study showing alteration in 4 genes. No known treatment regimen is available for this kind of tumor.

Case Presentation

A 74-year-old woman with hypertension presented to our medical center because of an asymptomatic, non tender lump in her right breast and no palpable axillary or Supraclavicular lymph nodes. The patient had been committed to having her annual mammogram, and her last mammogram was less than a year ago. Nevertheless, neither she nor her doctors believed that mammography screening helped to discover the current tumor. The patient had been pregnant 4 times and had given birth to 4 healthy children. She had an extensive history of cancer in her family: Her father and 2 brothers had died of prostate cancer, and she had both a sister who had lung cancer and a sister who had received a diagnosis of cancer of unknown type. No family history of breast cancer existed, according to the patient. Her surgical history included a hysterectomy. The remainder of the initial physical examination was unremarkable, and the patient had no other concerns. She received a clinical diagnosis of carcinoma in the upper outer quadrant of the right breast that was pathologically staged as a T2N0M0 tumor.

OPEN ACCESS

Correspondence:
Aziza Nassar, Department of Laboratory Medicine and Pathology, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224, USA, Tel: 904-956-3318; Fax: 904-956-3336;
E-mail: nassar.aziza@mayo.edu

Received Date: *13 Dec 2016*
Accepted Date: *03 Mar 2017*
Published Date: *13 Mar 2017*

Citation:
Abadeer K, Kaur JS, Ibrahim MEM, Nassar A. Rare Breast Myoepithelial Carcinoma with a Distinctive Genetic Profiling Study. Clin Oncol. 2017; 2: 1215.

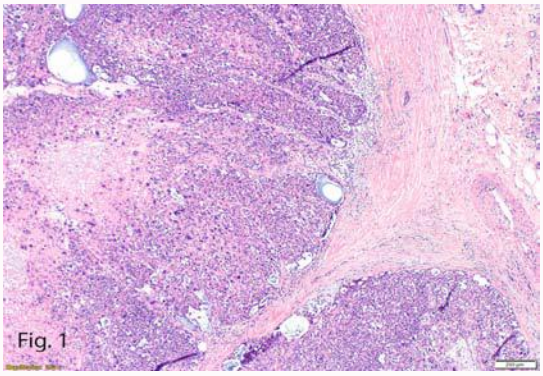

Figure 1: Pushing Borders of High-Grade Malignant Neoplasm at the Interface With Normal Adjacent Breast Parenchyma Showing Microcystic Spaces and Sheets of Epithelioid With Marked Cytologic and Nuclear Atypia and Bizarre Nuclei (hematoxylin-eosin, original magnification ×10).

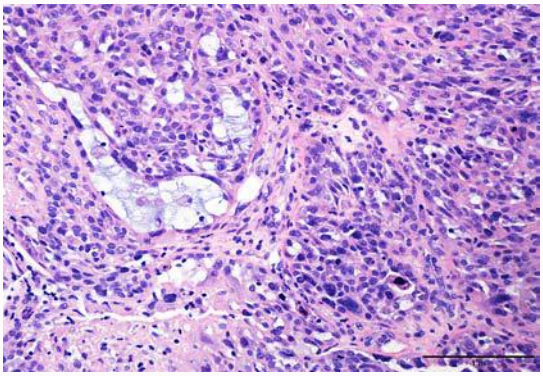

Figure 2: High-Grade Cytologic Atypia. Occasional sheets of spindle neoplastic cells are admixed with epithelioid cells that exhibit marked high-grade cytologic atypia with nuclear pleomorphism and bizarre nuclei and show occasional mitotic figures (hematoxylin-eosin, original magnification ×40).

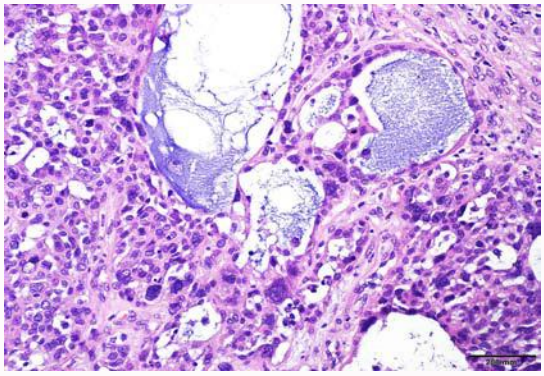

Figure 3: Basophilic and Basement Membrane–Like Material. Cystic spaces with basophilic and basement membrane–like material (hematoxylin-eosin, original magnification ×40).

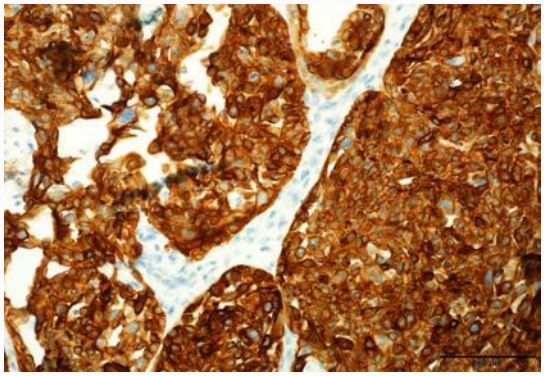

Figure 4: Pancytokeratin (AE1/3) Cytoplasmic Immunostain in the Neoplastic Cells. Immunostain indicates epithelial differentiation (original magnification ×40).

Three weeks after her original breast cancer diagnosis, the patient underwent a right lumpectomy and right sentinel lymph node biopsy. The excised sentinel node was found to be a single lymph node measuring 1.2 cm in its greatest dimension. The gross breast specimen was a red-yellow rubbery breast tissue fragment measuring 9.5×6.5×1.5 cm. The specimen was serially sectioned, showing cut surfaces remarkable for an eccentrically located firm lesion measuring 2.4×1.5×1.8 cm. The remainder of the breast tissue was histologically unremarkable.

Multiple paraffin-embedded sections were studied, which revealed breast parenchyma infiltrated by high-grade malignant neoplasm, composed of sheets and nests of mixed epithelioid and occasional spindle cells with nuclei ranging from low grade to markedly pleomorphic and of bizarre shapes (Figures 1 and 2). Several atypical mitotic figures were found. Cystic spaces were noted that were filled with basophilic and basement membrane–like materials (Figure 3). Sections also showed a single benign lymph node with no evidence of metastatic disease. Furthermore, sections of the surgical margins surrounding the cancer had benign breast parenchyma with focal atypical lobular hyperplasia despite no evidence of invasive disease.

Immunohistochemistry results were strongly positive for pancytokeratin (*AE1/3*) (Figure 4), SMA, smooth muscle myosin, p63 (Figure 5), and S-100 (Figure 6) while being negative for *HER2* and estrogen receptor and weakly positive for progesterone receptor. The final diagnosis was high-grade myoepithelial carcinoma of the breast.

Given the extensive family history of malignancy provided by the patient, a thorough genetic study was ordered. The test was a next-generation, sequencing-based assay that identifies genomic alteration within hundreds of cancer-related genes (Foundation One; Foundation Medicine). The current assay interrogates 315 genes, as well as introns of 28 genes involved in rearrangement, both the genes and introns known to be altered in cases with solid tumors. The test result identified 4 genomic alterations, featuring *NF1* (L494fs*4), *IRS2* amplification, *RB1* loss, and *TP53* (Y107D).

The genomic study also reported identification of certain variants of unknown significance, including *ASXL1* (A1312V) and *CIC* (T295M). These variants may not have been adequately understood or characterized in the literature, but we choose to include them in our report in case they become clinically meaningful in the future for targeted therapy.

Discussion

Myoepithelial carcinoma of the breast is a rare lesion, with about 38 cases reported in the English literature [2]. Therefore, the need is becoming urgent to understand the nature of this rare entity. In addition, our patient's extensive family history of other cancers raises questions about the genetic component of these types of lesions; only a few studies in the literature have demonstrated the association between *EWSR1* gene rearrangements and myoepithelial carcinomas. To our knowledge, this case report is the first of myoepithelial

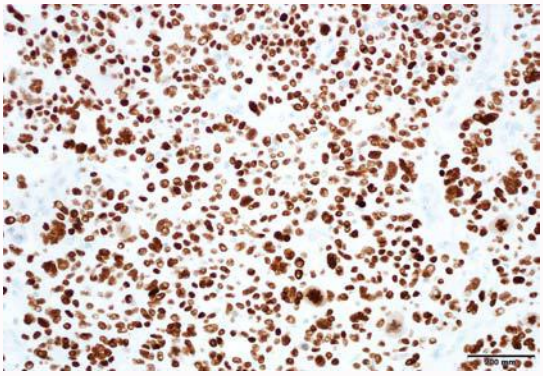

Figure 5: P63 Nuclear Immunostaining in the Neoplastic Cells. Immunostain confirms myoepithelial differentiation (original magnification ×40).

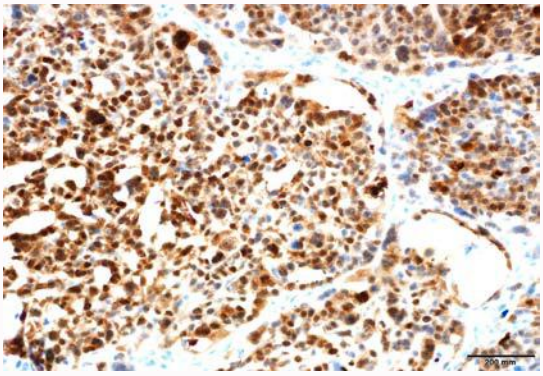

Figure 6: S100 Nuclear Staining in the Neoplastic Cells. Immunostain confirms myoepithelial differentiation (original magnification ×40).

carcinoma of the breast that involved complete genomic evaluation showing multiple genetic alterations, including *NF1*, *IRS2* amplification, *RB1* loss, and *TP53*. More molecular studies should be conducted in this regard to illuminate the pathogenesis and genetic profiling of this distinctive tumor.

Normal breast tissue architecture is composed of networks of branching ducts lined with an inner luminal epithelial layer that regulates the differentiation of the ductal epithelial cells from which the more common adenocarcinoma of the breast originates. Yet, the outer layer that envelops the branching ducts consists of myoepithelial cells that rarely develop into the malignant lesion [3] discussed in the present case report.

The structure of myoepithelial cells closely expresses their function. Major components are desmosomes and hemidesmosomes, by which the cells adhere to the luminal cells and the basement membrane, respectively. They have a contractile function achieved by the actin and myosin filaments embedded in their structure [1].

In 1991, Tavassoli [4] divided the myoepithelial lesions into 3 types: myoepitheliosis, adenomyoepithelioma, and myoepithelial carcinoma. Adenomyoepithelioma was further categorized into tubular, spindle-cell, and lobulated variants depending on the architectural and histologic features. Only myoepithelial carcinoma is composed of pure myoepithelial cells, and it is rare.

Even though the cytologic criteria to diagnose myoepithelial carcinoma of the breast are still elusive, the World Health Organization's definition and certain descriptive histologic literature describe the components of spindle and epithelioid cells as having nuclear atypia and marked mitotic activity. In our present case, we found epithelioid cells with bizarre nuclei. In addition, we recognized cystic spaces filled with basophilic and basement membrane–like materials, and the cytoplasm was pale eosinophilic. Other soft tissue tumors that mimic myoepithelial carcinoma are leiomyosarcoma, fibrosarcoma, and malignant phyllodes tumors. However, these entities can be excluded by immunohistochemistry (eg., SMA, desmin, CD10, CD34). Another important differential diagnosis is metaplastic carcinoma of the breast, which is an uncommon breast tumor but can be differentiated by immunohistochemical stains (eg., AE1/3, MNF-116, p63) [1,5]. In addition, metaplastic breast carcinoma has a unique genomic profiling. It is characterized by a complex array of genomic alterations including multiple gene copy number gains and losses, in addition to mutations in p53 (*TP53*) (20%), loss of *CDKN2A* (*p16*) (20%) and *PTEN* (25%), as well as recurrent mutations of *PIK3CA* (40%), and of genes pertaining to the Wnt pathway [6]. Furthermore, amplification and high polsomy of the *EGFR* gene has been reported in 10% to 25% of metaplastic breast cancers, as well as amplification of *MYC* (30%) [1,6].

Myoepithelial cell–derived neoplasms express both epithelial and myoepithelial antigens on their cell surface. Therefore, immunohistochemical antibodies can react to these antigen types and especially to keratins and myofilaments. For example, antibodies to basal keratins (5, 5/6, 14, and 17) react with most of the myoepithelial tumors; in addition, SMA, muscle-specific actin, calponin, and S-100 are immunostains that can be used to detect the myoepithelial origin of these tumors [2]. p63 is another important immunohistochemical stain that can distinguish the myoepithelial cells of the breast, but unlike other antibodies, p63 stains the nuclei rather than the cytoplasm, as noted by the other antibodies [7].

In our case, the patient had extensive familial history of different types of carcinomas—prostate (father and brothers), lung (sister), and breast (index case). Four gene alterations have been reported in our next gene sequencing study. Few studies have shown the involvement of the *EWSR1* gene rearrangement in many cases of myoepithelial carcinoma, and in particular the cytologic appearances of epithelioid cell nests are known to be associated with such specific gene fusions as *EWSR1-POU5F1* [8,9].

NF1 gene encodes a GTPase activating protein called *neurofiromin*, which acts as a tumor suppressor gene by negatively regulating the RAS signaling pathway [10,11]. Mutations in the *NF1* gene cause the well-known autosomal dominant disorder called *neurofibromatosis type 1*, which is associated with multiple types of cancers, including sarcoma, glioma, hematologic neoplasm, and breast carcinoma [12,13]. An association between *NF1* gene mutations and breast cancer is rare and has been reported in only 2% of breast tumors [14]. Nonetheless, in 1 study of 14 metastatic breast cancers, the *NF1* gene mutation was frequently reported [15]. Studies have shown that the risk of breast cancer is relatively high for women having neurofibromatosis type 1 associated with germline *NF1* mutation [16,17].

The amplification of the *IRS2* gene has been reported in cancer cases and has been found in about 2% of invasive breast carcinoma [18]. *IRS2* encodes insulin receptor substrate 2, which is considered a cytoplasmic signaling molecule. It also is essential in the negative feedback loop between mTOR and Akt. Porter et al. [19] showed in their study that high *IRS2* expression was noted in invasive ductal

carcinoma of the breast. Furthermore, increased *IRS2* expression has been associated with increased cell migration, leading to metastasis and cancer spread in breast cancer cells [20]. This latter gene might have contributed to the high propensity of metastasis associated with these tumors.

Another altered gene found in our study was the *RB1* gene. It normally encodes the retinoblastoma protein that suppresses tumors and acts as a negative regulator of the cell cycle [21]. *RB1* gene mutation or loss has been reported in approximately 2% of breast cancer cases [18].

Because of the unique nature of myoepithelial carcinoma, no therapy is known or approved by the US Food and Drug Administration that is specific to the reported genomic alterations, despite many studies having shown that myoepithelial carcinoma has a high tendency for recurrence and distant metastasis. Therefore, an effective treatment regimen is greatly needed. Most studies in the literature have shown that constructive breast surgery combined with adjuvant chemotherapy and radiotherapy may be effective [22].

Our genomic study reported 2 therapies with potential clinical effect associated with *NF1* gene mutation in another tumor type but none in our patient's tumor type. These 2 medications with potential benefit are cobimetinib and trametinib, which are MEK inhibitors approved by the US Food and Drug Administration for treatment of unresectable or metastatic melanoma with *BRAF V600E* mutation [23,24].

In conclusion, myoepithelial carcinoma of the breast is a rare neoplasm that needs further molecular genetic study and review. Unique cytologic morphologic characteristics could be detected that mostly show nests of epithelioid cells with bizarre nuclei and atypia. Immunohistochemistry can be conclusive in establishing the diagnosis through both epithelial and myoepithelial antibodies (eg., keratin, p63, S-100). Myoepithelial carcinoma of the breast shows association with some gene mutations and fusion, such as *NF1* gene, *IRS1* amplification, *RB1* loss, and *TP53*. No treatment regimens are established in the literature regarding this rare entity.

Acknowledgment

The authors are grateful for Foundation Medicine performing the genetic profiling of this distinctive tumor.

References

1. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ. WHO classification of tumours of the breast. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2012.
2. Liao KC, Lee WY, Chen MJ. Myoepithelial carcinoma: a rare neoplasm of the breast. Breast Care (Basel). 2010; 5: 246-249.
3. Santhosh R, Padu K, Bipin Singh TH, Sharma MB, Singh THSC. Myoepithelial carcinoma of the breast. J Clin Diagn Res. 2013; 7: 1191-1193.
4. Tavassoli FA. Myoepithelial lesions of the breast: myoepitheliosis, adenomyoepithelioma, and myoepithelial carcinoma. Am J Surg Pathol. 1991; 15: 554-568.
5. Sauer T. Cytologic findings in malignant myoepithelioma: a case report and review of the literature. Cytojournal. 2007; 4: 3.
6. Ross JS, Badve S, Wang K, Sheehan CE, Boguniewicz AB, Otto GA, et al. Genomic profiling of advanced-stage, metaplastic breast carcinoma by next-generation sequencing reveals frequent, targetable genomic abnormalities and potential new treatment options. Arch Pathol Lab Med. 2015; 139: 642-649.
7. Tse GM, Tan PH, Lui PC, Gilks CB, Poon CS, Ma TK, et al. The role of immunohistochemistry for smooth-muscle actin, p63, CD10 and cytokeratin 14 in the differential diagnosis of papillary lesions of the breast. J Clin Pathol. 2007; 60: 315-320.
8. Antonescu CR, Zhang L, Chang NE, Pawel BR, Travis W, Katabi N, et al. *EWSR1-POU5F1* fusion in soft tissue myoepithelial tumors: a molecular analysis of sixty-six cases, including soft tissue, bone, and visceral lesions, showing common involvement of the *EWSR1* gene. Genes Chromosomes Cancer. 2010; 49: 1114-1124.
9. Jo VY. Myoepithelial tumors: an update. Surg Pathol Clin. 2015; 8: 445-466.
10. Hattori S, Ohmi N, Maekawa M, Hoshino M, Kawakita M, Nakamura S. Antibody against neurofibromatosis type 1 gene product reacts with a triton-insoluble GTPase activating protein toward ras p21. Biochem Biophys Res Commun. 1991; 177: 83-89.
11. Morcos P, Thapar N, Tusneem N, Stacey D, Tamanoi F. Identification of neurofibromin mutants that exhibit allele specificity or increased Ras affinity resulting in suppression of activated ras alleles. Mol Cell Biol. 1996; 16: 2496-2503.
12. Jett K, Friedman JM. Clinical and genetic aspects of neurofibromatosis 1. Genet Med. 2010; 12: 1-11.
13. Patil S, Chamberlain RS. Neoplasms associated with germline and somatic *NF1* gene mutations. Oncologist. 2012; 17: 101-116.
14. Salemis NS, Nakos G, Sambaziotis D, Gourgiotis S. Breast cancer associated with type 1 neurofibromatosis. Breast Cancer. 2010; 17: 306-309.
15. Craig DW, O'Shaughnessy JA, Kiefer JA, Aldrich J, Sinari S, Moses TM, et al. Genome and transcriptome sequencing in prospective metastatic triple-negative breast cancer uncovers therapeutic vulnerabilities. Mol Cancer Ther. 2013; 12: 104-116.
16. Guran S, Safali M. A case of neurofibromatosis and breast cancer: loss of heterozygosity of NF1 in breast cancer. Cancer Genet Cytogenet. 2005; 156: 86-88.
17. Wang X, Levin AM, Smolinski SE, Vigneau FD, Levin NK, Tainsky MA. Breast cancer and other neoplasms in women with neurofibromatosis type 1: a retrospective review of cases in the Detroit metropolitan area. Am J Med Genet A. 2012; 158A: 3061-3064.
18. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012; 490: 61-70.
19. Porter HA, Perry A, Kingsley C, Tran NL, Keegan AD. IRS1 is highly expressed in localized breast tumors and regulates the sensitivity of breast cancer cells to chemotherapy, while IRS2 is highly expressed in invasive breast tumors. Cancer Lett. 2013; 338: 239-248.
20. Gibson SL, Ma Z, Shaw LM. Divergent roles for IRS-1 and IRS-2 in breast cancer metastasis. Cell Cycle. 2007; 6: 631-637.
21. Burkhart DL, Sage J. Cellular mechanisms of tumour suppression by the retinoblastoma gene. Nat Rev Cancer. 2008; 8: 671-682.
22. Endo Y, Sugiura H, Yamashita H, Takahashi S, Yoshimoto N, Iwasa M, et al. Myoepithelial carcinoma of the breast treated with surgery and chemotherapy. Case Rep Oncol Med. 2013; 2013: 164761.
23. Jessen WJ, Miller SJ, Jousma E, Wu J, Rizvi TA, Brundage ME, et al. MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors. J Clin Invest. 2013; 123: 340-347.
24. Jousma E, Rizvi TA, Wu J, Janhofer D, Dombi E, Dunn RS, et al. Preclinical assessments of the MEK inhibitor PD-0325901 in a mouse model of neurofibromatosis type 1. Pediatr Blood Cancer. 2015; 62: 1709-1716.