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Carcinoma of the Breast With Medullary-like Features:

Diagnostic Challenges and Relationship With *BRCA1* and *EZH2* Functions

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Abstract

This case presentation reviews the histologic distinction between pure medullary carcinoma and breast carcinomas with medullary-like features. This particular case prompts us to analyze the relationship among medullary carcinoma, basal-like breast carcinomas and carcinomas associated with germline *BRCA1* mutations. In addition to now well-defined features, such as expression of high-molecular-weight cytokeratins and *EGFR* (epidermal growth factor receptor), basal-like tumors have a deficiency or dysfunction of *BRCA1*. This association in part explains the histologic features of *BRCA1*-associated breast cancers. Recent studies in our laboratory demonstrate that BRCA1 protein is regulated by a recently described gene, *EZH2*. These concepts illustrate the important relationships among histopathologic features; genomic profile; single gene abnormalities, such as *BRCA1* and *EZH2*; and growth regulation in this subset of breast carcinomas.

REPORT OF A CASE

The patient is a 63-year-old woman with a 1-cm tumor discovered on mammogram. Relevant clinical history includes a personal history of clear cell carcinoma of the ovary 8 years earlier and a paternal grandfather diagnosed with prostate cancer at 70 years old. On histologic examination (Figure 1, A through F), the breast tumor is well circumscribed with a pushing border. Already at low-power magnification, we can appreciate a mixture of cells. On closer study, the neoplasm is composed of malignant cells that are not forming glands but, instead, large sheets with no architectural pattern. In addition, there is a rim of lymphocytes and mononuclear cells. At high magnification, highly atypical cells with vesicular nuclei and prominent single or multiple nucleoli are apparent. There is nuclear pleomorphism and numerous mitotic figures. We start to see that the cells form syncytia as we don't really know where one cell ends and the other begins. Lymphocytes are very prominent and are mixed in with the tumor cells. Focally, the tumor has infiltrated fat. Immunohistochemical stains for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (*ERBB2*, formerly *HER2/neu*) are negative.

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Because of her history of ovarian cancer, the patient was encouraged to undergo genetic testing for *BRCA* gene mutations.

COMMENT

In this article we will discuss this case, a carcinoma with medullary features, in the context of the recently described basal-like phenotype of breast cancer and hereditary breast cancer with *BRCA1* mutation. The World Health Organization defines medullary carcinoma of the breast as a well-circumscribed, invasive carcinoma, composed of poorly differentiated cells, arranged in sheets, without gland formation. Collagenous stroma is usually scant, and there is a very prominent lymphoplasmacytic infiltrate. Macroscopic features are illustrated in Figure 2. Note the circumscribed, pushing borders. An important gross characteristic of pure medullary carcinomas is a shiny, pearly white appearance distinct from the yellow, gritty appearance of an invasive ductal carcinoma of no special features. Medullary carcinomas are rare. The average age at presentation is 45 to 52 years, compared with 55 years for patients with invasive ductal carcinomas, not otherwise specified. Medullary carcinomas are almost always ER^-, PR^-, and *HER2/neu*$^-$. Overexpression of p53 protein resulting from *TP53* mutation is common.

The histologic features of medullary carcinoma are illustrated in Figure 3, A through C. Medullary carcinomas can have a multinodular pattern, as well as areas of geographic necrosis. Tumor cells are very atypical; they have multiple nucleoli, and there are atypical mitoses. Tumor cells form sheets, so we don't see boundaries between the cells. Smudged cells, usually not described in textbooks, are common in medullary carcinomas. Multinucleated tumor cells may also be present. There is an intimate mixture of lymphocytes and plasma cells with these highly atypical tumor cells.

Diagnosis of medullary carcinoma requires that the tumor exhibits all of the diagnostic features noted above. Cases with some, but not all, diagnostic criteria used to be designated as *atypical medullary carcinomas*. However, the World Health Organization does not favor that term. In our practice, we use the designation *invasive carcinoma with medullary features* when we encounter tumors with some, but not all, the histologic features of medullary carcinomas. Our patient is an example of such a case; we have highly atypical cells growing in a syncytial pattern with a heavy lymphoplasmacytic infiltrate, but we also have infiltration of the fat, thereby ruling out a diagnosis of pure medullary carcinoma. Another important point to remember is that the diagnosis of medullary carcinoma cannot be made on core needle biopsy because we have to study the histologic features of the whole tumor to make the diagnosis.

The cases meeting the strict diagnostic criteria of medullary carcinoma have a favorable prognosis. In spite of rigid histological criteria, the diagnosis of medullary carcinoma is difficult and controversial among pathologists, likely reflecting their low incidence and morphologic overlap with atypical medullary lesions. This is not the case for oncologists. To illustrate this, I informally asked the breast oncologists at our institution for impressions of a diagnosis of medullary carcinoma and how they manage carcinoma with medullary features. Here are some of the answers: Clinician 1 said, “If you call it pure medullary, I don't treat

(with chemotherapy). If you call it with medullary features, I give full package of adjuvant chemo." Clinician 2 said, "We consider pure medullary to have a better prognosis, and we are less likely to treat with chemotherapy. When it is with medullary features, we look upon it as no specific features." Clinician 3 said: "Medullary features—treat. Pure medullary—let it ride." So it is clear from the literature and from discussions with our clinical colleagues, that the diagnosis of medullary carcinoma has important treatment implications. Therefore, we must reserve that term for the few cases that are histologically classic.

BASAL-LIKE BREAST CARCINOMAS

Medullary carcinomas often exhibit basal-like features.[1,2] What is a basal-like carcinoma? I would like to emphasize that, at this time, the definition of basal-type breast carcinoma is not morphologic or immunohistochemical. The concept that some invasive breast carcinomas have a basal phenotype derives from gene-expression profiling studies examining thousands of genes in a single tumor, providing a comprehensive picture of which genes are up-regulated or down-regulated.[3,4,5] These studies observed that invasive carcinomas of the breast can be separated into different groups because of characteristic clustering of overexpressed or underexpressed genes. The importance of these groups is that they may have prognostic and therapeutic implications.[4,5] In addition to basal-like carcinoma, genetic profiles also describe a *HER2/neu*-overexpressing group and the luminal groups, which are ER^+.[4]

Basal-like breast carcinomas are triple (ER, PR, and *HER2/neu*) negative, but we now know that the basal-like category is not composed of morphologically uniform breast cancers.[6,7,8] In fact, basal-like carcinomas include special morphologic types, such as metaplastic carcinomas, adenoid cystic carcinomas, carcinomas with medullary features, medullary carcinomas, and invasive carcinomas arising in the setting of *BRCA1* mutations. The basal-like group also comprises invasive ductal carcinomas of no special features. The invasive carcinoma, not otherwise specified, cases included in the basal-like molecular group usually have some medullary features, such as pushing margins, areas of geographic necrosis, and central fibrosis. These tumors are usually high grade, with focal or absent ductal carcinoma in situ and a brisk lymphocytic host response.[8] Of note, basal-like breast carcinomas have been associated with a favorable response to neoadjuvant chemotherapy.[9]

Large efforts have been devoted to unambiguously defining basal-like breast carcinomas based on immunohistochemical profiles. Apart from triple-negative status, they express high-molecular-weight keratins, such as CK5/6, CK14, and CK17. Many are EGFR, c-Kit, and vimentin positive.[10,11] However, there is still no consensus on the minimal required immunostains to make the diagnosis of basal-like invasive carcinoma. In fact, at this time, there is no consensus on whether making a diagnosis of basal-like carcinoma has relevance in daily practice. At present, patient management strongly driven by ER, PR, and *HER2/neu* status; stage; and clinical parameters. As we shall see, histology is also of utmost importance in driving the decision to test for *BRCA1*.

There are 2 important issues that pathologists will have to deal with in the near future regarding basal-like breast carcinomas. One is the association of basal-like carcinomas with

BRCA1 mutations and function. Among the multiple functions of *BRCA1*, its roles in DNA repair mechanisms and maintenance of genomic stability open new therapeutic possibilities. To this effect, drugs, including cisplatin and poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors which target DNA repair pathways, are currently undergoing testing in clinical trials. The other important issue about basal-like breast carcinomas is that these tumors often overexpress EGFR, opening the possibility for the use of EGFR inhibitors as a treatment option. There are clinical trials currently evaluating this therapeutic possibility as well.

BRCA1, BASAL SUBTYPE, AND MEDULLARY FEATURES

There are several described *BRCA1* mutations. Germline *BRCA1* mutations confer up to an 80% lifetime risk to develop breast cancer, as well as increased risk to develop ovarian cancer, fallopian tube carcinomas, peritoneal carcinomas, and pancreatic, colon, and hepatocellular carcinomas.

The Breast Cancer Linkage Consortium has devoted large efforts to defining the histologic features of *BRCA1* and *BRCA2* breast carcinomas to help pathologists make a precise diagnosis and help guide their discussions with patients about the need for genetic testing.[12] It should be kept in mind that, although approximately 13% of *BRCA1* tumors have pure medullary histology, 60% of *BRCA1* tumors have some medullary features. One study compared 114 *BRCA1*-mutated tumors with a large number of controls.[12] They found 3 features independently associated with *BRCA1* mutations: high mitotic count, lymphocytic infiltrate, and pushing margins. These are also the features associated with medullary carcinomas and carcinomas with medullary features.

Why is the recognition of medullary histology important in guiding testing for a germline mutation? Histopathologic features are useful indicators of which gene, *BRCA1* or *BRCA2*, should be screened first in families that have both breast and ovarian carcinoma. In addition, medullary histology can suggest *BRCA1* testing in women younger than 35 years, with an ER-invasive carcinoma with medullary features.[13,14] As this is an area of intense investigation, the relationship between these diagnostic designations may change as additional data become available.

Investigators have found that one of the key abnormalities in the basal-like carcinomas is a reduction of BRCA1 protein and messenger RNA levels. Even in the cases in which there is no germline mutation, basal-like tumors have a deficiency or dysfunction of BRCA1. In some cases, decreased expression is caused by promoter methylation or transcriptional repression. Other mechanisms that control BRCA1 levels are still under study.

NEW DIRECTIONS: INSIGHTS FROM RECENT TRANSLATIONAL STUDIES

As discussed above, the basal subgroup of breast cancers is characterized by a reduction of BRCA1 expression. It is hypothesized that breast cancer progression in this setting could be halted by restoration of BRCA1 expression and function. Our laboratory has been concerned with this hypothesis. For several years, we have been studying a transcriptional regulatory gene, *EZH2*.[15] Expression of this gene is very low in ER^+ breast carcinomas but is up-

regulated in invasive, ER^- carcinomas, especially those with medullary features and decreased BRCA1 protein levels. In fact, recent data from our laboratory show that *EZH2* is a marker of the ER-negative breast carcinomas, and especially of triple negative tumors.[16] To investigate the role of *EZH2* in promoting growth of triple-negative breast carcinomas, we concentrated our efforts on ER-negative breast cancer cell lines with high expression of EZH2 protein. We found that if *EZH2* expression is blocked using short hairpin RNA (shRNA; and use of an assay in which cell lines are injected in the mammary fat pad of nude mice), there is a significant decrease in cancer cell proliferation in vitro as well as tumor growth and volume in vivo.[17]

Based on the finding that triple-negative, invasive carcinomas have high levels of EZH2 and low levels of BRCA1 proteins, we hypothesized that the effect of EZH2 in ER^- breast cancer growth requires BRCA1.[17] Indeed, down-regulation of EZH2 in triple-negative breast cancer cell lines was sufficient to restore BRCA1 protein levels in vivo and in vitro. We have recently shown that the effect of EZH2 on breast cancer growth requires BRCA1 protein. These results are promising because they suggest that therapies targeting EZH2 protein may restore BRCA1 expression and function in triple-negative breast cancers and may decrease their progression.

CONCLUSION

Now, let us return to the 63-year-old woman. Genetic testing revealed a common *BRCA1* germline mutation (185 del). This finding emphasizes the relevance and potential effect of histologic observation in patient care. This case also illustrates how the confluence of clinical medicine, histopathology, and translational research themes intersect to define our fascinating profession. What are the key take home points?

1. Histologic criteria for medullary carcinoma are very strict. Appropriate diagnosis requires that all features be present, which is important because it can help avoid unnecessary chemotherapy.
2. If we see medullary-like features, I believe it is necessary to mention that in the pathology report. This will help clinicians guide genetic testing decisions.
3. Both medullary and medullary-like tumors fall into the basal-like molecular subtype, which has frequent *BRCA1* mutations and protein deficiency.
4. In our practice, we do not use of the term basal-like carcinomas in our pathology report at this time because this category is morphologically heterogeneous.
5. In our practice, we do not perform basal keratins and we do not test for EGFR at present. However, this practice may change in the near future. Intensive research is ongoing in this area, so we will hear more about the basal subtype of breast cancer, new molecular markers and therapeutic targets, and how to better define these tumors in the years to come.

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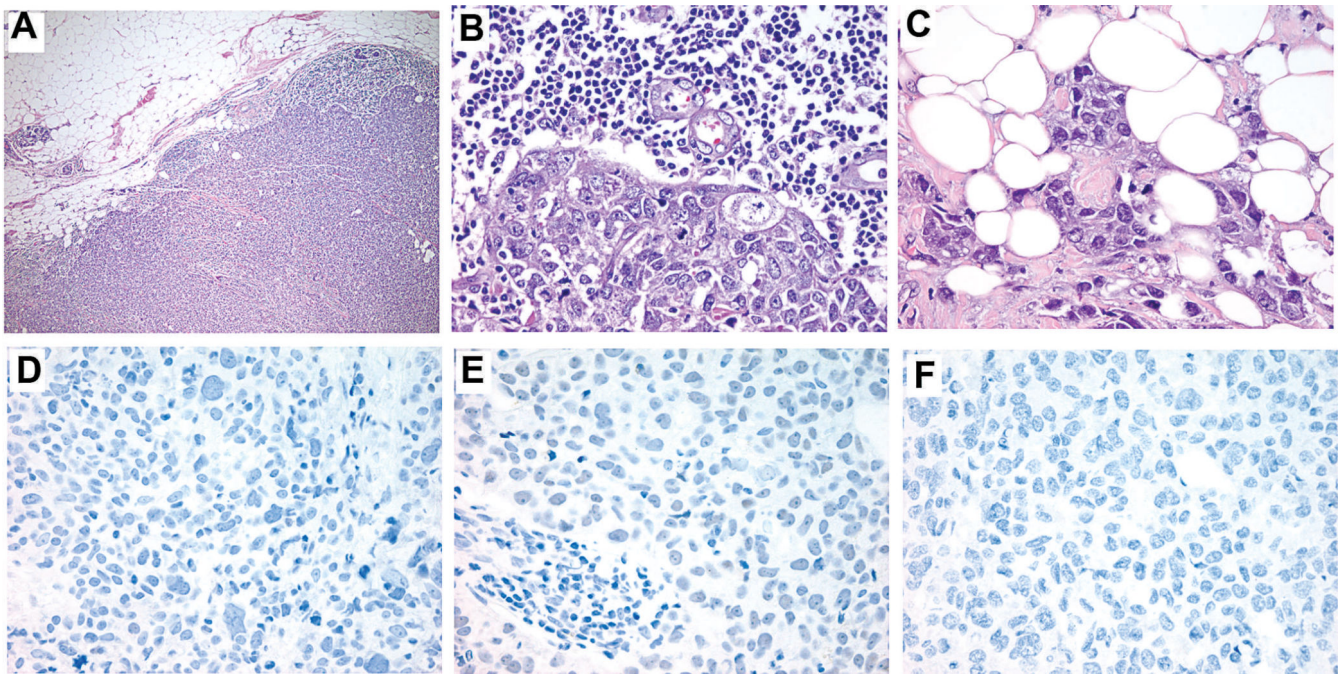

Figure 1.

A 63-year-old woman with a breast tumor. A, Low-power magnification showing well-circumscribed borders. B, The tumor cells are highly atypical and mixed with lymphocytes and plasma cells. C, There is focal infiltration into the fat. D through F, Immunohistochemical stains for estrogen receptor (ER), progesterone receptor (PR), and HER2/neu are negative, respectively (hematoxylin-eosin, original magnifications ×2 [A], ×40 [B], ×20 [C]; immunostains for ER [D], PR [E], and HER2/neu *[F], original magnifications ×40).*

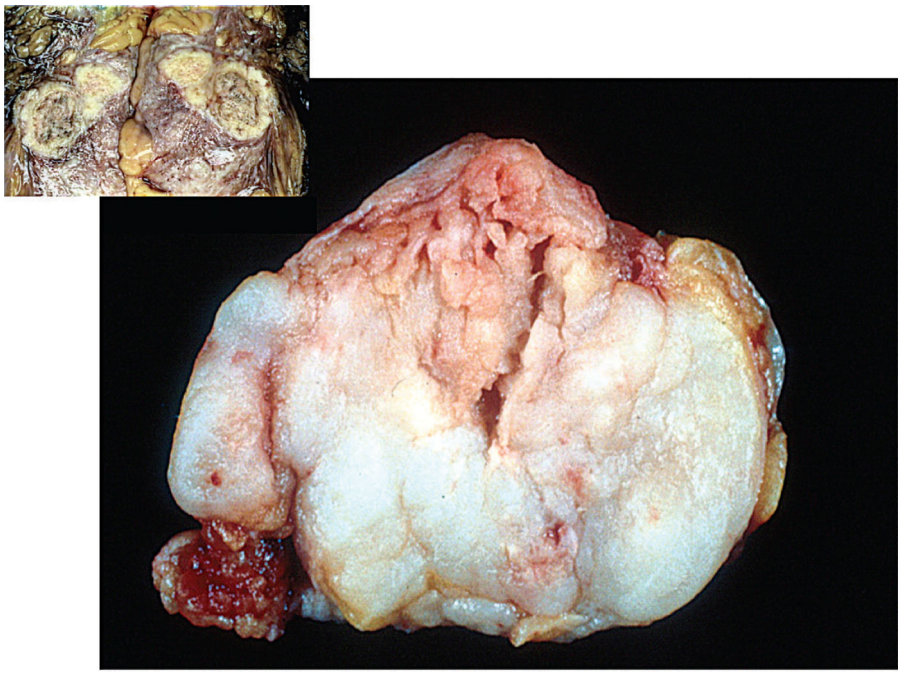

Figure 2.
Macroscopic picture of a pure medullary carcinoma of the breast. Note the pearly white color and glistening appearance. The inset shows an invasive ductal carcinoma, not otherwise specified, with the characteristic yellow and gritty macroscopic look.

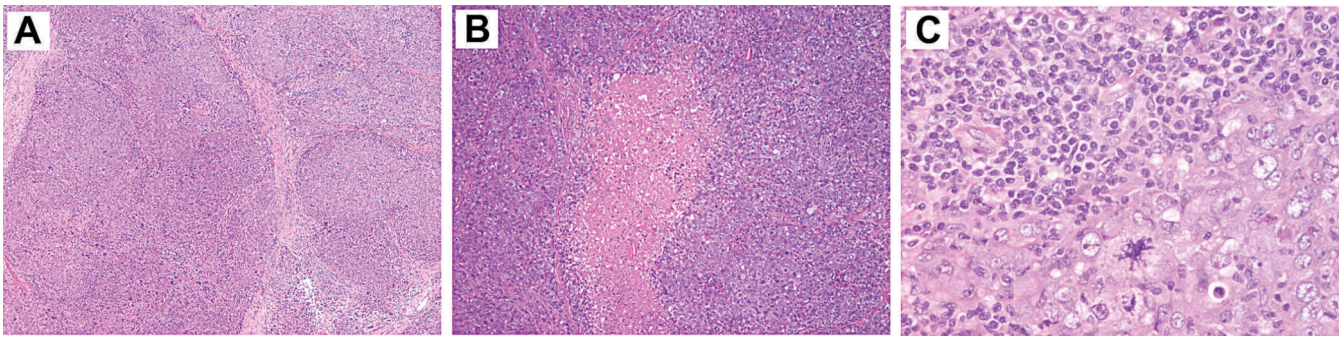

Figure 3.

Medullary carcinoma of the breast. A, Multinodular architecture. B, Geographic necrosis. C, Pleomorphic cells arranged in syncytia, with multiple mitoses and mixed with lymphocytes and plasma cells (hematoxylin-eosin, original magnifications ×10 [A], ×20 [B], and ×40 [C]).