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Precision Medicine Clinic: Molecular Tumor Board

Histologic Discordance Between Primary Tumor and Nodal Metastasis in Breast Cancer: Solving a Clinical Conundrum in the Era of Genomics

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Key Words. Breast cancer • Histologic discordance • Genomic sequencing • Next-generation sequencing • Occult breast cancer • Cancer stem cells

Abstract

Next-generation sequencing (NGS) technologies have become increasingly used for managing breast cancer. In addition to the conventional use of NGS for predicting recurrence risk and identifying potential actionable mutations, NGS can also serve as a powerful tool to understand clonal origin and evolution of tumor pairs and play a unique role in clarifying complex clinical presentations. We report an unusual case of early-stage breast cancer in which the primary tumor and draining axillary node were histologically discordant. The primary tumor was invasive lobular carcinoma, whereas the nodal metastasis was invasive ductal carcinoma. This discordance led us to question whether the tumors had the same origin. NGS performed on both specimens identified no overlapping variants, leading us to conclude that the patient had two separate primary breast cancers, with the nodal tumor representing metastasis from an occult breast cancer. DNA sequencing of the primary tumor and the nodal metastasis allowed us to predict the patient's recurrence risk, and we initiated adjuvant chemotherapy and hormonal therapy based on these results. This case illustrates the utility of NGS for successfully managing a rare and challenging case. ***The Oncologist*** 2021;26:1000–1005

Key Points

- A degree of molecular concordance is expected for tumors originating from a common stem or progenitor cell. Histological discordance and absence of any genomic overlap should raise suspicion for two separate primary tumors.
- Paired DNA sequencing of the primary tumor and nodal metastasis can inform clinical decisions when primary breast tumor and axillary metastasis are histologically discordant. Molecular/Precision Oncology Tumor Board is the best setting to facilitate such decisions in these challenging cases.
- Paired DNA sequencing under these rare circumstances may suggest an occult breast tumor.

Introduction

Next-generation sequencing (NGS) technologies have become increasingly used in the management of breast cancer (BC). In early-stage BC, these assays can help predict the risk of distant recurrence and benefits of chemotherapy, thereby guiding treatment decisions. We describe a rare presentation of early-stage BC in which the primary tumor and metastasis in a draining axillary node were histologically discordant. Genomic data were used to determine the tumor of origin and guide subsequent management, highlighting the value of these data as diagnostic, prognostic, and predictive tools for atypical clinical presentations when used in conjunction with expert review through Multidisciplinary Molecular Tumor Board (MTB).

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Patient Story

A 49-year-old postmenopausal woman was diagnosed with right-sided BC by screening mammography at an outside hospital. The mammogram displayed moderate-to-marked fibroglandular density with an area of asymmetry in the right breast, which was confirmed by subsequent diagnostic mammography and ultrasonography (US). US of the right breast revealed four hypoechoic masses: a 1.1-cm irregular solid periareolar mass at the 5:30 position (mass 1); a 0.7-cm hypoechoic, lobulated solid mass at the 10:30 position (mass 2); a 1.3-cm ovoid hypoechoic mass at the 12:00 position (mass 3); and a 0.9-cm hypoechoic mass at the 2:30 position (mass 4). Left breast US demonstrated a 0.8-cm hypoechoic lobulated mass at the 9:00 position (mass 5).

The patient underwent four-site US-guided core biopsy at the outside institution. Biopsy of mass 1 revealed grade 1 invasive lobular carcinoma (ILC) (estrogen receptor [ER] 60%, progesterone receptor [PR] 1%, and human epidermal growth receptor 2 [HER2] immunohistochemistry [IHC] 0+); mass 2 biopsy revealed dense sclerosis and fat necrosis; and mass 3 biopsy revealed a benign fibroadenoma and papilloma. Mass 4 was not biopsied, as it was not suspicious for malignancy on breast imaging. Biopsy of mass 5 (left breast) showed a benign fibroadenoma.

The patient presented to our institution for further management. Bilateral breast magnetic resonance imaging (MRI) with and without contrast revealed postbiopsy changes, no residual enhancement at the cancer site, no lymphadenopathy, and no evidence of a second primary malignancy. MRI and repeat breast US results confirmed that tissue sampling of mass 4 was unnecessary. As there was no evidence of multicentric disease, the patient was offered breast-conserving treatment (BCT) or mastectomy. She subsequently underwent BCT (right partial mastectomy), with sentinel lymph node (SLN) biopsy and excisional biopsy of the papilloma.

Surgical pathology revealed multifocal grade 2 ILC with extensive lymphovascular invasion. The largest focus was 2.4 cm, and there were at least four microscopic foci measuring 1–2 mm. Biomarker analysis revealed ER 90%, PR <1%, and HER2 IHC 1+ (Fig. 1), with a Ki-67 proliferation index of <10%, which is typical for lobular carcinoma. One of three SLNs in the right deep axilla was positive for metastatic carcinoma. Histology showed a 3-mm focus of metastatic ductal carcinoma (ER >90%, PR focally positive [2%], HER2-negative [2+, not amplified by fluorescence in situ hybridization]), with no extranodal extension (Fig. 2). Ki-67 proliferation index was not determined. As these findings differed from those of the primary tumor, the pathologist pursued further testing with repeat molecular profiling to assure that the nodal metastasis originated from the breast. Positive ER/PR staining as well as absent Pax8 and Wilms' Tumor1 (WT1) staining excluded a gynecologic primary malignancy and confirmed the breast as the site of metastasis origin. The breast surgical specimen margins were free of tumor, and no other tumor was identified in the breast specimen to suggest another primary or a composite malignancy. Postoperative computed tomography scan of the chest, abdomen, and pelvis and a bone scan showed no local or distant metastases or other primary tumor.

Molecular Tumor Board

Cancer stem cells (CSCs) are a subgroup of tumor cells characterized by their tumor-initiating capacity, low proliferation rate, self-renewal capacity, pluripotency, and chemoresistance [1]. They occupy different regions in the primary tumor and are thought to account for the spatial heterogeneity observed between cell populations within a single tumor and the temporal heterogeneity observed between the primary tumor and metastatic clones [2]. Our patient exhibited two histologically different breast carcinomas in the primary tumor and nodal metastasis—the breast mass was ILC and the axillary SLN contained metastatic ductal carcinoma. Their similar biomarker expression profiles are not unexpected, as hormone receptor–positive, HER2-negative BC is the most common subtype [3]. However, synchronous diagnosis of two histologically different tumors led us to question whether the tumors arose from a common CSC with divergent differentiation, resulting in clonal heterogeneity and aberrant morphology variation, or whether they represented two separate entities.

This case was presented at our MTB, and the decision was made to pursue tumor NGS to help answer our question. NGS can reveal novel insights regarding tumor heterogeneity, clonal evolution, and the metastatic process [4]. Primary and locally relapsed breast tumors usually have similar genomic profiles and morphology, suggesting that the metastasis originated from the primary tumor [5]; however, differences in biomarker expression [6], degree of lymphovascular invasion [7], and progression of histologic grade [8] can occur between the primary tumor and recurrent or distant metastatic breast tumors.

NGS results, as well as IHC and genomic features, of the primary and SLN tumor specimens are summarized in Table 1. The SLN tumor had a lower mutational burden than the primary breast tumor. There was no overlap in somatic variants between tumors to suggest a shared origin with additional mutations acquired over time. Additional bioinformatics analyses using DNA alterations and RNA expression revealed no overlap in variants between the two specimens, even below the assay's 5% limit of variant allele frequency detection. Expression of DNA mismatch repair proteins (MSH2, MSH6, MLH1, PMS2) was normal in both specimens, which is typical for BC. Germline component of the tumor testing showed a variant of uncertain significance in *T53* gene, TP53 c.986C > T, consistent with the same result of patient's comprehensive genetic testing.

Comparative genomic analysis of primary tumors and corresponding metastatic lesions in BC has historically revealed obvious overlap or moderate primary/metastases concordance of variants, with a higher mutational burden in metastasis specimens [9, 10]. In our case, the observed nonoverlapping genomic profiles of the primary ILC and SLN tumor, in addition to lower tumor mutational burden in the SLN, suggest that they are not a primary-metastatic tumor

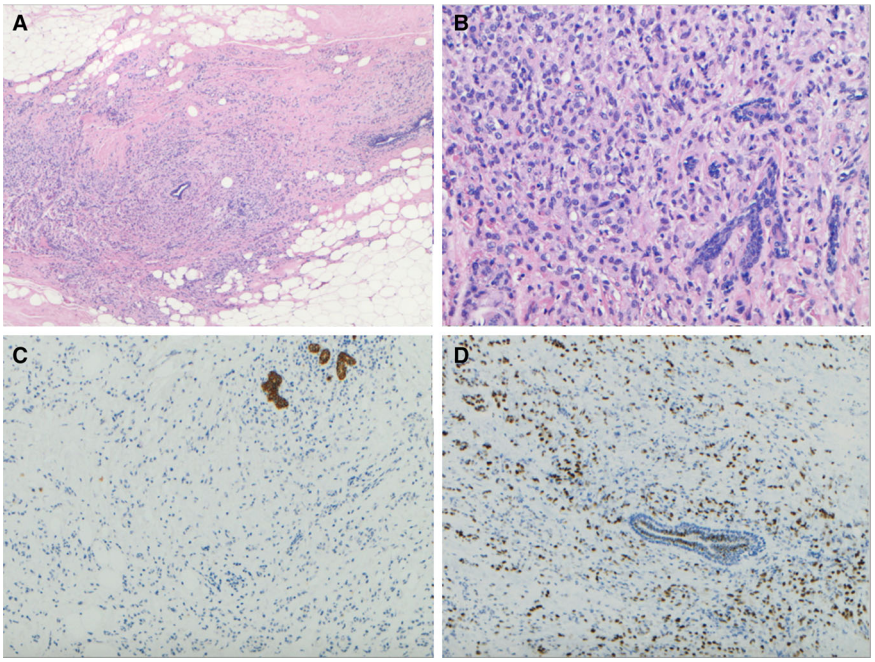

Figure 1. Hematoxylin and eosin staining of invasive lobular carcinoma specimen at ×4 magnification **(A)**, with normal ductal histology seen at ×20 magnification **(B)**. **(C):** Staining for E-cadherin is negative in the lobular carcinoma but positive in the normal ducts. **(D):** Estrogen receptor staining of nuclei in tumor cells (and internal controls).

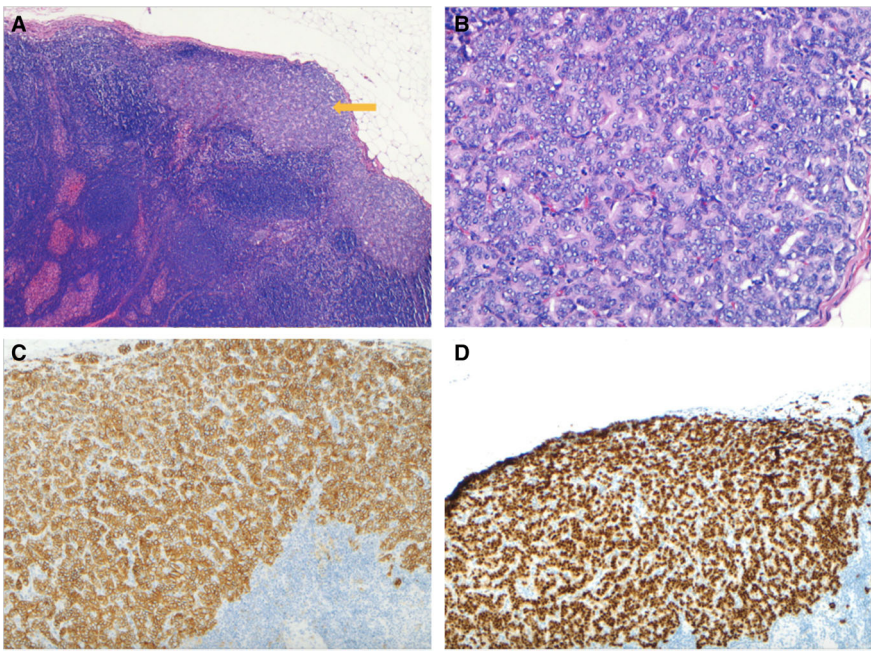

Figure 2. Hematoxylin and eosin staining of metastatic ductal carcinoma in the sentinel lymph node (arrow) at ×4 magnification **(A)** and ×20 magnification **(B)**. **(C):** Staining for E-cadherin is positive in the tumor cells. **(D):** Estrogen receptor staining of nuclei in tumor cells (and internal controls).

pair. Because of differences in histology, molecular expression, and genomic expression, we interpreted the lobular and ductal samples as representing two separate primary tumors. The ductal SLN tumor may have originated from a separate occult breast cancer (OBC) or perhaps represented the rare occurrence of regional primary BC developing in the axillary fat pad [11]. We considered the latter possibility less likely, as the tumor was encased entirely by lymphoid tissue. OBC represents the presence of an axillary metastatic carcinoma with no clinically or radiographically identified primary breast tumor. The high sensitivity of MRI (approximately 96%) to identify OBC presenting with axillary metastasis [12], in combination with the genomic results, led us to believe that our patient had both an ILC of the breast and a secondary OBC presenting as nodal ductal carcinoma (IDC). As mentioned, the patient's primary tumor

Table 1. Summary of breast and nodal specimen histologic and molecular features

	Surgical specimen site	
Feature	**Breast**	**Sentinel lymph node**
Pathology		
Histology	Invasive lobular carcinoma, classical type	Invasive ductal carcinoma
Histologic grade	Grade 2	Not reported
Lymphovascular invasion	Extensive lymphovascular invasion	No extranodal extension
Receptor expression	ER-positive (90%), PR-negative (<1%), HER-2 negative (1+)	ER-positive (>90%), PR focally positive (2%), HER2-negative (2+, not amplified by FISH)
Ki-67 proliferation index	Favorable (<10%)	Not determined
Next-generation sequencing		
PD-L1 expression	<1% tumor cell staining (membranous) 1% tumor-associated immune cell staining	Negative <1% tumor cell staining (membranous) <1% tumor-associated immune cell staining
Tumor mutational burden	2.1 mutations/MB (27th percentile) Stable microsatellite	0.5 mutations/MB (41st percentile) Stable microsatellite
Somatic genomic variants: potentially actionable/biologically relevant	PTEN c.165-2A > G: splice region variant – LOF, VAF 15.4% TP53 p.R213*: stop-gain variant – LOF, VAF 6.5% CDH1 p.Y228fs: frameshift variant – LOF, VAF 4.3%	No reportable pathogenic variants found
Somatic variants: unknown significance	XPO c.3085G > A p.D1029N: missense variant, NM_003400, VAF 10.2% ERBB4 c.2720G > C p.G907A: splice region variant, NM_005235, VAF 7.0% HAS3 c.763G > C p.E255Q: missense variant, NM_138612, VAF 6.2% KMT2D c.1522G > A p.E508K: missense variant, NM_003482, VAF 5.3%	BRD4 c.766dup p.Q256fs: frameshift variant, NM_058243, VAF 9.1%
Germline genomic variants: pathogenic/likely pathogenic	No pathogenic variants found	No pathogenic variants found
Germline variants: unknown significance	TP53 c.986C > T p.T329I: missense variant, chr17:7576860 NM_000546	TP53 c.986C > T p.T329I: missense variant chr17:7576860 NM_000546
DNA mismatch repair protein expression	Normal	Normal
70-gene signature test		
Molecular subtype	Low-risk, luminal type (A)	High-risk, luminal type (B)
Average 10-year risk of recurrence, untreated	10%	29%
Predicted DMFI at 5 years	96% with hormonal therapy alone	93% with chemotherapy and hormonal therapy
Absolute chemotherapy benefit	<1.5%, no potential significant chemotherapy benefit	>12%, potential chemotherapy benefit

Abbreviations: DMFI, distant metastasis–free interval; ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth receptor 2; LOF, loss of function; MB, megabase; PD-L1, programmed death ligand 1; PR, progesterone receptor; VAF, variant allele frequency.

was multifocal and we cannot exclude the possibility of one of these small foci metastasizing to the axillary lymph node. However, the foci appeared morphologically the same as the primary ILC and were too small for tumor DNA analysis.

Management of OBC remains challenging because of a paucity of available data to guide therapy. A 2010 population-based analysis of Surveillance, Epidemiology, and End Results data from 1983 to 2006 of patients with OBC presenting with axillary LN metastasis showed no survival benefit from mastectomy compared with BCT and radiation therapy (RT) [13]. This study was based on data from an era predating routine use of breast MRI during preoperative assessment. Recent studies specifically evaluating MRI-negative OBC have also demonstrated no differences in survival outcomes between these therapeutic approaches [14]. Accordingly, the consensus of the MTB discussion after obtaining the additional genomic

studies was that BCT with RT was sufficient for local management of the primary tumor and suspected second OBC. Thus, further surgery was not recommended.

With regard to adjuvant therapy, the MTB recommended sending both the breast and SLN specimens for a 70-gene molecular testing (MammaPrint) to stratify recurrence risk and guide therapy. Genomic assays such as MammaPrint (Agendia Inc., Irvine, California, U.S.A) and Oncotype DX (Exact Sciences corp, Madison, WI) are validated for use on primary breast cancer tissue but not SLN specimens [15]. The MINDACT [16] and TAILORx [17] trials, which explored the role of these assays in determining which patients would benefit from adjuvant chemotherapy, did not incorporate nodal specimens as part of study inclusion criteria. However, nodal testing may be considered for instances of OBC or histologically discordant specimens.

The 70-gene signature test predicted that the patient's two tumors would respond differently to therapy, with the risk of metastatic disease from the IDC nodal metastasis decreasing with chemotherapy. Although ILC is less likely than IDC to be classified as high risk for recurrence, patients with nodal involvement have a higher risk of distant metastases than those with a node-negative primary tumor, regardless of histology [18]. Our patient's ILC primary tumor was classified as low risk for cancer recurrence, whereas her IDC metastasis was classified as high risk.

We decided to treat the patient with adjuvant chemotherapy to reduce the recurrence risk of the higher-risk nodal IDC, while also using standard endocrine therapy to treat both tumors. Based on the SLN metastasis 70-gene signature test results and genomic testing, we recommended four cycles of adjuvant cyclophosphamide and docetaxel (TC), followed by RT, and at least 5 years of antihormonal therapy with an aromatase inhibitor (letrozole).

Current guidelines recommend standard chemotherapy for hormone receptive–positive, HER2-negative early BC with node-positive disease [19]. Typically, dose-dense doxorubicin and cyclophosphamide, followed by dose-dense paclitaxel, is recommended; however, TC is a reasonable alternative for low-risk node-positive BC [20]. Patients with node-positive OBC have better overall survival rates than matched patients with T1N1 disease [21, 22]. The favorable prognosis may be explained by immunoediting, whereby differences in immunogenicity between tumor cell populations result in elimination of the primary tumor by the immune system so that only the metastatic tumor remains [23, 24]. We therefore considered a less intensive chemotherapy regimen with TC to be appropriate for this patient after weighing the risks associated with anthracycline therapy.

There are limitations to single-region sampling of primary tumors. Differences in molecular signatures between primary tumors and paired recurrences or metastases have been described, although this is a relatively rare phenomenon [10, 25]. Ellsworth and colleagues demonstrated that primary carcinomas exhibit genetic heterogeneity and recommended multiple-region sampling to adequately assess intratumor variability within the primary tumor [26]. To overcome the challenges of temporal and spatial tumor heterogeneity resulting from divergent evolution, phylogenetic genomic analyses performed from multiple-region sampling of the primary tumor may reveal multiple/different clonal lineages in the primary malignancy. Although this may allow mapping of the genomic blueprint of SLN metastases to specific clones within the primary tumor, multiple sampling may not be practical from cost and tissue availability perspectives. In these instances, careful analysis and discussion of clinical and molecular data are warranted to guide clinical decision-making.

Patient Update

The patient tolerated chemotherapy well without complications. She completed adjuvant RT and began antiestrogen therapy with letrozole. Repeat surveillance breast MRI a year later showed no evidence of disease. She currently remains on letrozole with no evidence of disease 27 months after initial diagnosis.

Conclusion

This Precision Medicine Clinic case highlights the utility of genomic data when encountering conflicting features between a breast primary tumor and presumed nodal metastasis. For tumors originating from a common stem or progenitor cell, we expect some degree of molecular concordance between breast and SLN specimens. The complete molecular discordance between specimens observed in our patient suggested that the SLN tumor originated from a separate primary tumor. Genomic sequencing not only has enhanced our understanding of cancer pathophysiology and led to the development of targeted therapies but also serves as a powerful diagnostic, prognostic, and predictive tool when encountering complex clinical presentations.

Glossary of Genomic Terms and Nomenclature

Clone: An identical copy of a DNA sequence or entire gene; one or more cells derived from and identical to a single ancestor cell OR to isolate agene or specific sequence of DNA.

Frameshift variant: An insertion or deletion involving a number of base pairs that is not a multiple of three, which consequently disrupts the triplet reading frame of a DNA sequence. Suchvariants (or mutations) usually lead to the creation of a premature termination (stop) codon and results in a truncated (shorter-than-normal) protein product. Also called frameshift mutation.

Genomics: The study of the complete set of DNA (including all of its genes) in a person or other organism. Almost every cell in a person's body contains a complete copy of the genome. The genome contains all the information needed for a person to develop and grow. Studying the genome may help researchers understand how genes interact with each other and with the environment and how certain diseases, such as cancer, diabetes, and heart disease, form. This may lead to new ways to diagnose, treat, and prevent disease.

Genomic sequencing: A laboratory method that is used to determine the entire genetic makeup of a specific organism or cell type. This method can be used to find changes in areas of the genome. These changes may help scientists understand how specific diseases, such as cancer, form. Results of genomic sequencing may also be used to diagnose and treat disease.

Germline variant: A gene change in are productive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. A variant (or mutation) contained within the germline can be passed from parent to offspring, and is, therefore, hereditary. Also called germline mutation.

Microsatellite: A short sequence of DNA, usually 1 to 4 base pairs (a unit of DNA), that is repeated together in a row along the DNA molecule. There is

variation from person to person in the number of repeats. There are hundreds of places in human DNA that contain microsatellites.

Missense variant: A genetic alteration in which a single base pair substitution alters the genetic code in a way that produces an amino acid that is different from the usual amino acid at that position. Some mis sense variants (or mutations) will alter the function of the protein. Also called missense mutation.

PD-L1: A protein that acts as a kind of ''brake'' to keep the body's immune responses under control.

Somatic variant: An alteration in DNA that occurs after conception and is not present within the germline. Somatic variants can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. Somatic variants can (but do not always) cause cancer or other diseases.

Splice region variant: A genetic alteration in the DNA sequence that occurs at the boundary of an exon and an intron (splice site). This change can disrupt RNA splicing resulting in the loss of exons or the inclusion of introns and an altered protein-coding sequence. Also called splice-site mutation.

Stop-gain variant: A DNA sequence change which results in a new stop codon. Tumor mutational burden (TMB): the total number of mutations found in the DNA of cancer cells.

Variant allele frequency (VAF): The percentage of sequence reads observed matching a specific DNA variant divided by the overall coverage at that locus.

Variant of unknown significance: A variationin a genetic sequence for which the association with disease risk is unclear. Also called unclassified variant, variant of uncertain significance, and VUS.

NOTE: The primary source of definitions is the NCI Dictionary of Cancer Terms: https://www.cancer.gov/publications/dictionaries/genetics-dictionary/

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Disclosures

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