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Case Report

Invasive lobular carcinoma harboring dual PIK3CA mutations and a CDH1 variant with prominent myxoid stroma: a case report

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Abstract: Invasive lobular carcinoma is defined by a characteristic discohesive growth pattern and is frequently associated with alterations in *CDH1*. The clinical interpretation of genomic findings in this tumor type, however, remains challenging. We describe a woman in her 50s with estrogen receptor-positive, HER2-negative invasive lobular carcinoma of the left breast, in whom comprehensive genomic profiling was performed. Histological examination of the primary tumor demonstrated classic lobular carcinoma accompanied by prominent myxoid stromal components surrounding tumor cells. After surgery, the patient received adjuvant endocrine therapy, followed by systemic chemotherapy at recurrence and subsequent treatment with abemaciclib and letrozole after the development of liver metastases, resulting in sustained disease stabilization. Genomic analysis identified two *PIK3CA* mutations (p.E542K and p.E726K) together with a truncating *CDH1* variant (p.Q383*). The variant allele frequency of the *CDH1* alteration was compatible with heterozygosity, raising the possibility of a germline event. Tumor mutational burden was low, and microsatellite instability was not detected. These molecular findings provided a rationale for consideration of PI3K pathway-directed therapy and prompted referral for genetic evaluation. This case illustrates the complexity of genomic interpretation in invasive lobular carcinoma and raises the possibility that stromal features, such as myxoid extracellular matrix, may contribute to tumor behavior and thus deserve further study.

Keywords: Invasive lobular carcinoma, CDH1, PIK3CA, tumor-associated stroma

Introduction

Invasive lobular carcinoma (ILC) is characterized by a discohesive growth pattern and is frequently associated with alterations affecting cell adhesion [1, 2]. Despite its distinct histological features, the clinical course of ILC is heterogeneous, and factors influencing disease progression are not fully understood. Comprehensive genomic profiling (CGP) allows simultaneous assessment of multiple genomic alterations; however, interpretation of these results in ILC can be complex, particularly when multiple variants are detected in a single tumor. In addition to tumor-intrinsic genetic changes, stromal components may modify tumor behavior, although their relevance in ILC has not been clearly defined.

In addition, recent advances in genomic analysis have revealed diverse molecular alterations in ILC, including recurrent mutations in CDH1 and PIK3CA. However, the clinical significance of coexisting multiple genomic alterations and their relationship with histological features, particularly stromal characteristics,

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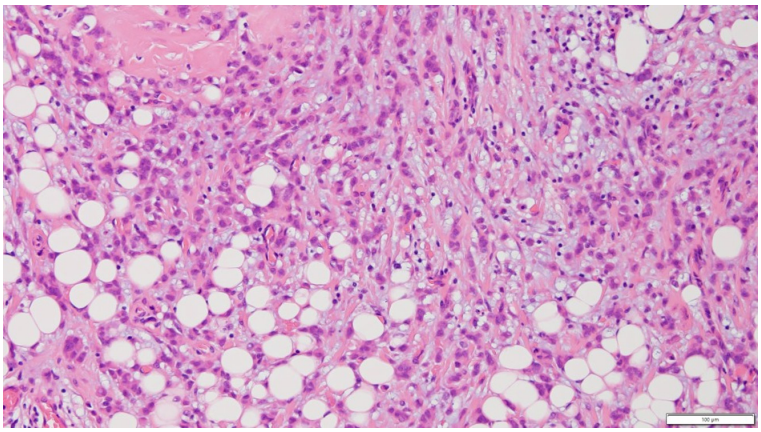

Figure 1. The tumor shows a diffusely infiltrative growth pattern showing a characteristic discohesive growth pattern (Hematoxylin and eosin (H&E) stain, ×40).

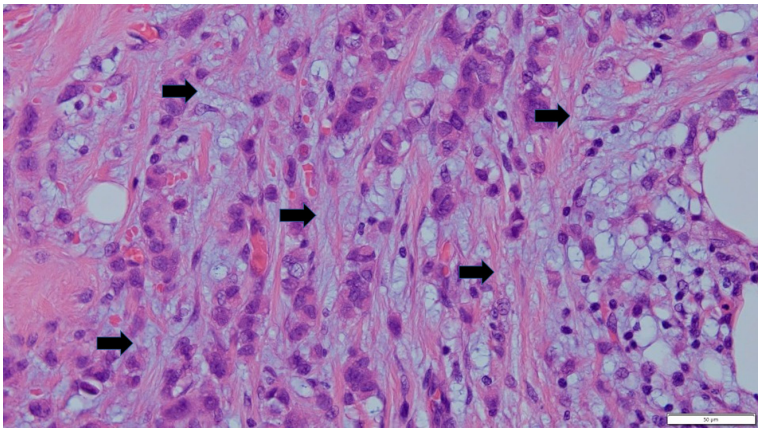

Figure 2. Histopathological image of invasive lobular carcinoma with prominent myxoid stromal components surrounding tumor nests (Hematoxylin and eosin (H&E) stain, ×400). Arrows indicate immature (myxoid) stromal components.

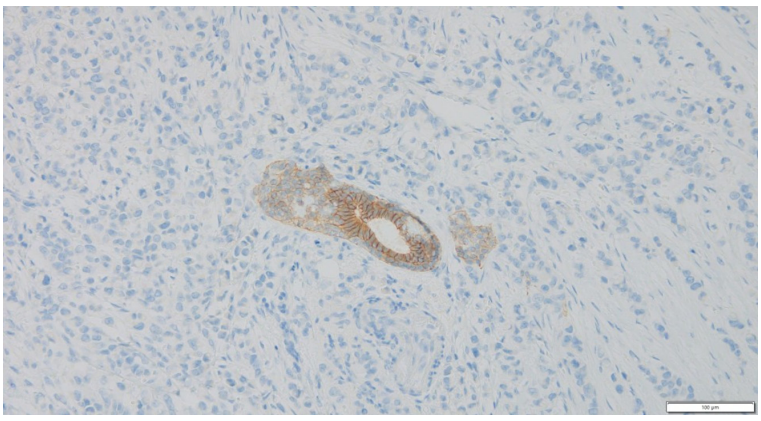

Figure 3. Tumor cells show complete loss of membranous E-cadherin expression, whereas adjacent non-neoplastic ductal epithelium in the center of the figure retains intact membranous staining, serving as an internal positive control (×40).

remains unclear. Therefore, further investigation integrating molecular and pathological findings is needed.

In this report, we describe a case of estrogen receptor-positive, HER2-negative ILC harboring dual PIK3CA mutations and a truncating CDH1 variant, accompanied by prominent myxoid stromal features.

Case report

In July 2021, a woman in her 50s underwent surgical resection of a tumor located in the left breast. Microscopic examination of the resected specimen revealed an infiltrative lesion extending diffusely into the surrounding breast tissue, without formation of a clearly demarcated tumor margin. On scanning magnification, the tumor cells were dispersed in a characteristic single-file arrangement, interspersed with linear cords of neoplastic cells (**Figure 1**). Closer inspection demonstrated small to medium-sized tumor cells with relatively uniform morphology. The nuclei were round to ovoid in shape, with inconspicuous nucleoli and limited cytoplasm. Nuclear atypia was mild to moderate, and mitotic activity was low (**Figure 2**). To further clarify the histological nature of the lesion, immunohistochemical studies were performed. Tumor cells exhibited a complete absence of membranous E-cadherin expression, whereas the adjacent non-neoplastic ductal epithelium showed preserved membranous staining, providing an internal control (**Figure 3**). Taken together with the discohesive growth pattern, these findings supported a diagnosis of invasive lobular carcinoma.

Table 1. Summary of genomic alterations identified by comprehensive genomic profiling

Gene	Variant	VAF (%)	Interpretation
PIK3CA	p.E542K	-	Activating mutation
PIK3CA	p.E726K	-	Potential activating mutation
CDH1	p.Q383*	54.3	Truncating, possible germline
POLE	p.G1065E	52.0	Variant of uncertain significance
GNAS	p.R201H	-	Activating mutation
TBX3	p.Q590*	-	Truncating mutation

Comprehensive genomic profiling revealed dual PIK3CA mutations (p.E542K and p.E726K), a truncating CDH1 variant (p.Q383*) with a variant allele frequency of 54.3%, and additional alterations in POLE, GNAS, and TBX3. Abbreviations: VAF, variant allele frequency; CGP, comprehensive genomic profiling. -: Variant allele frequency not reported by the CGP assay.

One of the most striking pathological features of this tumor was the presence of abundant stromal components with a myxoid appearance (**Figure 2**). Pale basophilic, loosely structured extracellular matrix surrounded both tumor nests and individual tumor cells, without evidence of a dense desmoplastic response. This myxoid stroma was not confined to a focal area but was observed throughout the invasive component, becoming particularly conspicuous at the invasive front. Pathological stage of the tumor was pT2N0M0. Immunohistochemical evaluation demonstrated positivity for estrogen receptor and progesterone receptor, with an Allred score of 8 (5 + 3). HER2 expression was scored as IHC 1+, and the Ki-67 (MIB-1) labeling index was approximately 20%. The same primary tumor specimen was subsequently used for comprehensive genomic profiling. Following surgery, the patient received adjuvant endocrine therapy with tamoxifen. Despite this treatment, disease progression was noted, and liver metastases were detected within three years after the initial diagnosis. Systemic chemotherapy with epirubicin and cyclophosphamide was administered as first-line therapy for recurrent disease. Afterward, treatment was switched to abemaciclib in combination with letrozole. Under this regimen, the disease has remained stable for more than 20 months, with no marked elevation of serum CA15-3 levels. The patient has maintained a good general condition, with an Eastern Cooperative Oncology Group performance status of 0-1, and radiological evaluation by computed tomography has confirmed stable disease according to RECIST version 1.1. The patient's family history was notable for breast cancer in her father, gastric cancer in a paternal uncle, and lung cancer in a maternal uncle.

Genomic profiling

CGP was conducted on formalin-fixed, paraffin-embedded primary tumor tissue (tumor content ~50%), revealing: Somatic mutations: PIK3CA p.E542K, PIK3CA p.E726K, GNAS p.R201H, TBX3 p.Q590*; CDH1 p.Q383* (variant allele frequency [VAF] 54.3%) was reported by the CGP laboratory as a pathogenic variant and was considered suggestive of a germline origin based on the VAF; however, confirmatory testing using matched normal tissue (e.g., peripheral blood) was not performed, and thus a somatic origin cannot be definitively excluded (**Table 1**).

In addition, POLE p.G1065E (VAF 52.0%) was detected. This variant is not listed in ClinVar and lies outside the exonuclease domain; therefore, it is currently best classified as a variant of uncertain significance (VUS), with a germline origin suspected but unconfirmed.

The tumor mutational burden (TMB) was 3.62 Muts/Mb, microsatellite stable.

The dual *PIK3CA* mutations suggest potential benefit from *PI3K/AKT/mTOR* pathway inhibition. The *CDH1* finding warrants genetic counseling and family risk assessment for hereditary diffuse gastric cancer (HDGC). The POLE variant is of uncertain clinical significance at present (**Table 1**).

Discussion

In the present tumor, two distinct PIK3CA mutations were identified within the same lesion. When interpreting this finding, the coexistence of multiple alterations affecting the PI3K pathway was considered potentially relevant to downstream signaling activity and treatment response in this specific clinical context, given that alterations in this pathway are frequently encountered in hormone receptor-positive breast cancer [3]. Experimental and clinical studies have suggested that tumors har-

boring more than one PIK3CA mutation may show enhanced pathway activation compared with single-mutant tumors [4]. In this case, the combination of a helical domain mutation (p.E542K) and a second mutation (p.E726K) raised the possibility of cooperative effects on PI3K signaling. Although functional data for this exact mutation pair are limited, exploratory clinical analyses have indicated that tumors with multiple PIK3CA alterations may derive increased benefit from PI3Kα-targeted therapies [5, 6]. The sustained disease control observed under systemic therapy in the present patient was therefore interpreted as being compatible with a treatment-sensitive molecular profile rather than an indolent disease course.

In addition to alterations in PIK3CA, a truncating CDH1 variant was identified in this tumor. Pathogenic germline variants in CDH1 are well established as the molecular basis of hereditary diffuse gastric cancer syndrome and are also associated with an increased risk of lobular breast carcinoma [7, 8]. In the present case, the variant allele frequency of approximately 50% was compatible with heterozygosity and therefore raised the possibility of a germline origin. However, because matched normal tissue was not available for confirmatory testing, a somatic event cannot be excluded. From a clinical perspective, this uncertainty underscores the importance of genetic counseling and consideration of germline testing when truncating CDH1 variants are detected by tumor-only genomic analyses [9].

A further finding in this case was the detection of a POLE variant (p.G1065E), which is not currently listed in ClinVar and lies outside the exonuclease domain. On this basis, the variant was classified as a variant of uncertain significance. Although pathogenic POLE mutations are best characterized in colorectal and endometrial carcinomas, sporadic reports have described POLE alterations in breast cancer [10]. At present, the clinical relevance of this variant in the current case remains unclear, and its contribution, if any, to tumor biology or cancer predisposition cannot be determined without additional functional or germline studies.

From a clinicopathological standpoint, invasive lobular carcinoma with a luminal immunophenotype is often regarded as having a relatively indolent disease course. Nevertheless, the present patient developed liver metastases within three years of initial diagnosis, indicating a more aggressive clinical behavior than might be expected [1, 2]. Histological examination revealed abundant myxoid stromal components surrounding tumor cells, corresponding to an immature stromal phenotype. While the prognostic or biological significance of stromal features in ILC has not been systematically investigated, studies in other tumor types have highlighted the role of the tumor microenvironment in modulating cancer progression [11, 12].

In breast cancer, particularly in triple-negative subtypes, immature or myxoid stromal patterns have been associated with unfavorable outcomes [13, 14]. Whether similar stromal characteristics exert comparable effects in ILC remains unknown. In the present case, the combination of discohesive tumor growth due to CDH1 alteration and an immature stromal background may have created a microenvironment permissive to tumor dissemination. This interpretation, however, is based on a single observation and should be regarded as hypothesis-generating. Further studies involving larger ILC cohorts are required to determine the prevalence of myxoid stromal features and to clarify their potential biological and clinical significance.

Conclusion

This case illustrates the complexity of genomic interpretation in invasive lobular carcinoma. The presence of dual PIK3CA mutations provides a potential rationale for considering PI3K pathway-directed therapies, while identification of a truncating CDH1 variant emphasizes the importance of evaluating possible germline alterations detected through tumor genomic testing. In addition, the prominent myxoid stromal background observed in this tumor raises the possibility that stromal characteristics may contribute to tumor behavior in ILC. Further studies involving larger cohorts will be required to clarify the biological and clinical significance of these findings.

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Disclosure of conflict of interest

None.

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