Lobular-like Invasive Mammary Carcinoma: Is This A Ductal Cancer, Lobular Cancer, or A Distinct Entity?

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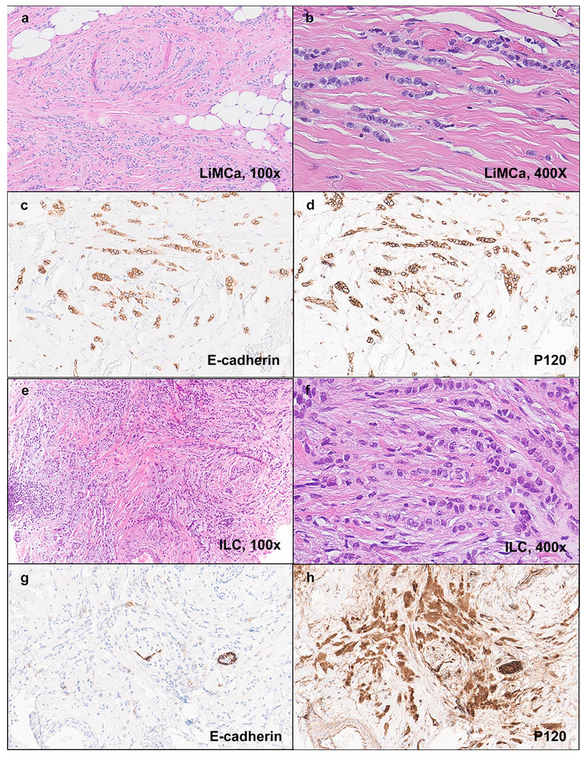
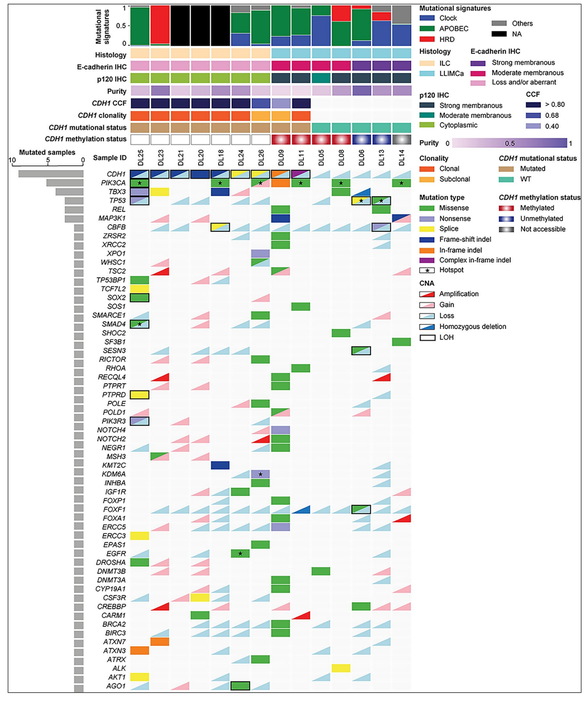
Breast pathologists classify breast cancers into 2 major subtypes based on the tumor's ability to form ducts. This is often accomplished by assessing tumor features on light microscopic examination of a hematoxylin and eosin (H&E) stained section. Ductal cancers form ducts or duct-like structures but lobular cancers show single cell infiltrative growth. In difficult to classify cases, pathologists assess the presence of cell-cell adhesion membrane proteins E-cadherin and p120 by immunohistochemistry (IHC). In ductal cancers, e-cadherin and p120 are identified in the membranes. In lobular cancers, there is absence of e-cadherin (due to mutation of e-cadherin gene) and p120 is present in the cytoplasm instead of the membranes. We have identified a group of breast cancers that resemble lobular cancers on H&E but shows e-cadherin and p120 within the cell membranes. We call these lobular-like invasive mammary carcinoma (LiMCa).

We examined the clinical and pathologic features of an unusual group of breast cancers that we termed as lobular-like invasive mammary carcinoma (LiMCa) and compared these with 100 invasive ductal carcinoma (IDC) and 104 invasive lobular carcinoma (ILC). We defined LiMCa as a low to intermediate grade invasive breast carcinoma with single cell infiltrative growth pattern (i.e. "lobular-like") but with retained circumferential membranous expression for cell adhesion proteins, E-cadherin and p120 (a property of ductal cancers). Based on exploratory molecular analysis of select cases, we found that LiMCa generally lack the typical *CDH1* gene mutations seen in lobular carcinomas but a proportion of them demonstrate *CDH1* gene promoter methylation. LiMCa demonstrate clinical-pathologic features that are intermediate between invasive ductal carcinoma and invasive lobular carcinoma. Tumor prognosis is related to pathologic tumor and nodal stage as well as multivariable prognostic score (Magee Equation).

Biallelic inactivation of the *CDH1* gene, i.e. *CDH1* mutation coupled with loss of heterozygosity of the other allele is considered a hallmark of lobular carcinoma which results in typical discohesive growth pattern of the tumor cells. These molecular events result in loss of E-cadherin protein or aberrant reactivity (i.e. lack of circumferential membranous staining) by immunohistochemistry in lobular carcinoma. This study describes an unusual type of carcinoma with low- to intermediate-grade nuclei with discohesive, diffusely infiltrative cells but showing retained circumferential membranous immunoreactivity for both E-cadherin and p120. We termed these "lobular-like invasive mammary carcinomas" (LiMCa). We analyzed the clinical-pathologic features of 166 LiMCa and compared them with 104 classical invasive lobular carcinomas (ILCs) and 100 grade 1 and 2 invasive (ductal) carcinomas of no special type (IDCs).



LiMCa showed individual cells in single-files and cords within the fibrous stroma (a-H&E, 100X and b-H&E, 400X). The tumor cells showed circumferential membranous staining for E-cadherin (c, 200X) and p120 (d, 200X). ILC displayed similar individual cells in single-files and cords within the fibrous stroma (e-H&E, 100X and f-H&E, 400X). The tumor cells showed negative or aberrant partial membranous staining for E-cadherin (g, 200X) and predominantly cytoplasmic reactivity for p120 (h, 200X).



An exploratory, hypothesis generating analysis of the genomic features of 14 randomly selected LiMCa and classical ILCs (7 from each category) was performed utilizing an FDA-authorized targeted capture sequencing assay (MSK-IMPACT). Sequencing analysis revealed 5 out of 7 LiMCa were *CDH1* wild-type, whereas all ILCs analyzed harbored *CDH1* loss of function mutations coupled with loss of heterozygosity of the *CDH1* wild-type allele. However, 4 of the 6 evaluable LiMCa were positive for *CDH1* promoter methylation.

Table 1. Comparison of Pathological and Radiological Characteristics

	LiMCa (n=166)	ILC (n=104)	IDC (n=100)	LiMCa vs ILC (P-value)	LiMCa vs IDC (P-value)	ILC vs IDC (P-value)
Pathology size (cm)						
Mean	1.9	2.7	1.55	<0.0001*	0.012*	<0.0001*
Range	0.4-10	0.5-16	0.4-4			
Radiology size (cm)						
Mean	1.35	1.7	1.5	0.010*	0.202	0.119
Range	0-8.6	0.4-8	0.4-3.5			
Path:Rad size >1						
No	34 (21%)	20 (19%)	47 (47%)	0.755	<0.0001*	<0.0001*
Yes	118 (71%)	78 (75%)	50 (50%)			
Not available	14 (8%)	6 (6%)	3 (3%)			
Path:Rad size ratio						
Mean	1.6	1.8	1.1	0.255	<0.0001*	<0.0001*
Range	0.4-8.8	0.2-8	0.6-1.6			
Margin (1st surg)						
Negative	104 (63%)	67 (65%)	81 (81%)	0.261	0.003*	0.002*
Close	42 (25%)	19 (18%)	16 (16%)			
Positive	20 (12%)	18 (17%)	3 (3%)			

*Statistically significant. LiMCa: Lobular-like Invasive Mammary Carcinoma; ILC: Invasive lobular carcinoma; IDC: Invasive ductal carcinoma.

LiMCa showed an intermediate pathologic tumor size between ILC and IDC; however, displayed an underestimation of tumor size on imaging and frequent positive margins on first resection similar to ILC.

Table 2. Kaplan-Meier survival analysis log rank test p-values for tumor types and known prognostic variables

Variables	RFS	DRFS	OS	BCSS
ILC vs Others (IDC+LiMCa)	0.074	0.071	0.736	0.148
IDC vs Others (ILC+LiMCa)	0.113	0.059	0.202	0.248
Grade	0.007*	0.016*	0.080	0.041*
Nodal status	0.695	0.294	0.661	0.987
pT stage	0.002*	<0.0001*	0.014*	0.005*
pN stage	0.004*	0.001*	<0.0001*	0.003*
ME2 score	<0.0001*	0.003*	0.020*	<0.0001*

*Statistically significant. ILC: Invasive lobular carcinoma; IDC: Invasive ductal carcinoma; LiMCa: Lobular-like invasive mammary carcinoma; pT: Pathologic tumor stage; pN: Pathologic nodal stage; ME2: Magee Equation 2; RFS: Recurrence free-survival; DRFS: Distant recurrence-free survival; OS: Overall survival; BCSS: Breast cancer-specific survival.

Survival outcomes of all groups were similarly influenced by traditional prognostic factors and the multivariable prognostic score of Magee Equation 2 (ME2).

Despite histomorphologic similarities to classical ILC, the discohesion in LiMCa was independent of E-cadherin/p120 immunophenotypic alteration. *CDH1* promoter methylation may partially explain the typical morphology seen in LiMCa; however, further studies are warranted to better define the molecular basis of the discohesive cellular morphology in LiMCa.