Virchows Arch (2000) 436:421–430

ORIGINAL ARTICLE

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Mammographically detected in situ lobular carcinomas of the breast

Received: 23 July 1999 / Accepted: 22 October 1999

Abstract We present ten cases of mammographically detected lobular carcinoma in situ (LCIS), involving a single area of variable size (up to a quadrant) in seven cases and the entire gland in three cases. Histologically, calcifications were associated with necrotic central areas within the in situ carcinomatous foci. Multiple foci of LCIS were observed in all five cases in which mastectomy had been performed. Cytologically, the lesions were characterized by a solid proliferation of round noncohesive cells with nuclei of intermediate size. Immunocytochemically, all cases were E-cadherin and p53 negative, and c-ErbB-2, GCDFP-15 and estrogen receptor positive. The proliferation index, evaluated with Ki67, was in the low range. Four cases were associated with foci of infiltrating lobular carcinoma (ILC). These findings contradict the commonly held opinion that LCIS is not mammographically detectable because of its lack of necrosis and calcification. This study documents the existence of a variant of LCIS exhibiting the mammographic features and central necrosis classically associated with ductal carcinoma in situ (DCIS), while retaining the spatial distribution, cytological composition and immunocytochemical features of lobular carcinoma.

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Key words Breast · Calcification · In situ · Lobular carcinoma · Mammography

Introduction

In situ carcinomas of the breast share a common origin from terminal duct units (TDLU), but are classified into two separate entities: lobular carcinoma in situ (LCIS), and ductal carcinoma in situ (DCIS). Both types carry an increased potential risk for the development of invasive carcinoma, but further treatment is generally not advised for the former.

The widespread use of mammographic screening has focused attention on DCIS, which is recognized because calcifications are present [8, 9, 16]. Conversely, classic LCIS is usually the result of a chance histological finding; when microcalcifications are present they are usually located in a benign lesion adjacent to LCIS [6, 19]. Because of this, mammography is not regarded as an effective method of detecting LCIS and cannot be depended upon for assessment of the extent of the disease or determination of whether it is bilateral [14].

In this paper, we describe ten cases of in situ carcinoma of the breast having the spatial distribution, cytological composition and immuno-phenotype of lobular carcinoma, which had been detected by mammography because there were calcifications associated with necrosis. Four of these cases were associated with areas of stromal infiltration, featuring the classic and pleomorphic varieties of invasive lobular carcinoma (ILC). We define the radiographic and histological profiles of this variant of LCIS and compare it both with classic LCIS and with DCIS with a solid growth pattern and comedo-type necrosis.

Materials and methods

Case selection

All lesions were nonpalpable and radiologically recognized by the presence of calcifications. In two of the cases, these were com-

Table 1 Clinical data and follow- up of 10 cases of lobular carcinoma in situ (*LCIS*) with central necrosis and calcification (*L.N.* lymph node, *Mts* metastases, *NED* no evidence of disease, ILC infiltrating lobular carcinoma, *AWD* alive with disease, *N.A.* not available, *UIQ* upper internal quadrant, *UEQ* upper external quadrant, *Neg* no metastases)

Case . no	Patient's age (years)	Invasive component	Bilaterality	Radiographic findings	Treatment	L.N.	Follow-up (months)
1	56	No	No	Diffuse coarse granular calcifications in round clusters or single elongated calcifications	Wide resection followed by simple mastectomy	N.A.	NED (24)
2	51	Yes, ILC	Yes, papilloma LCIS	Clusters of fine or coarse granular calcifications	Wide resection followed by mastectomy	Neg	NED (10)
3	55	No	No	Single round cluster of fine granular calcifications	Wide resection	N.A.	NED (11)
4	58	No	No	N.A.	Mastectomy	Neg	NED (8)
5	55	Yes, ILC	No	Clusters of coarse granular calcifications	Wide resection	Mts	AWD (6)
6	64	Yes, ILC	No	Distortion with a round cluster of calcifications	Wide resection followed by mastectomy	Mts	NED (5)
7	51	No	Yes, comedo DCIS	Distortion with diffuse round clusters of fine granular calcifications or single elongated calcifications	Wide resection followed by simple mastectomy	N.A.	NED (6)
8	58	No	No	Cluster of coarse granular calcifications	Lumpectomy	N.A.	NED (2)
9	52	Yes (tubulolobular carcinoma, in different quadrant from LCIS)	No	Spiculated mass in UEQ, and coarse granular calcifications in UIQ	Two biopsies followed by mastectomy	Neg	NED (26)
10	49	Yes, ILC	No	Cluster of fine granular calcifications	Lumpectomy followed by mastectomy	Mts	NED (12)

Table 2 Antibodies used in this study

Antibody	Antigen	Source	Dilution and antigen retrieval	Specificity
E-cadherin monoclonal	E-cadherin (120 kDa glycoprotein)	Transduction Lab, Lexington, Ky.	1:1000 microwave	Membrane of epithelial cells
GCDFP-15 polyclonal	Gross cystic disease fluid protein	Dr. D.E. Haaghensen, Sacramento, Calif.	1:5000	Apocrine cells
HMFG-2 monoclonal	Human milk fat globulin membrane	Dr. J. Taylor Papadimitriou, London, UK	1:50	Luminal epithelial cells
ER-1D5 monoclonal	Estrogen receptor	Dakopatts, Glostrup, Denmark	1:50 pressure cooker	Nuclei of luminal epithelial cells
PGR-ICA monoclonal	Progesterone receptor	Abbott Diagnostic, Wiesbaden-Delkenheim, Germany	1:10 pressure cooker	Nuclei of luminal epithelial cells
HER-2/neu monoclonal	c-erbB-2 protein	Pabisch, Pero, Italy	1:30 pressure cooker	Membrane of carcinoma cells
DO-7 monoclonal	p53 protein	Biogenex, San Ramon, Calif.	1:100 microwave	Nuclei of carcinoma cells
1A4 monoclonal	Alpha smooth muscle actin	Dakopatts	1:100	Myoepithelial cells
MIB1 monoclonal	Ki67-related antigen	Immunotech, Marseille, France	1:10 microwave	Nuclei of proliferating cells

bined with parenchymal distortions, and in one case with a spiculated mass. The propositus case (case 1) was detected by screening mammography because of the presence of suspect calcifications scattered in the right breast. A stereotactic preoperative fine-needle aspiration biopsy in the areas with calcifications resulted in a cytological diagnosis of carcinoma. Histologically the case was diagnosed as LCIS with necrosis and calcifications. Review of a series of 37 mammographically detected in situ carcinomas yielded one additional case (case 7) of pure LCIS with necrosis and calcifications. Three cases (case 3, 4 and 8) were seen in consultation following referral. Five other cases (cases 2, 5, 6, 9 and 10) were identified after a review of invasive carcinomas associated with extensive in situ changes, most of them featuring multiple foci of ILC within a prevalent LCIS.

Clinical data

None of the patients had any symptoms of breast disease or any family history of breast pathology. Patient 5 initially presented with a thyroid nodule that proved to be a metastasis from a pleomorphic ILC of the breast. The mammographic report on this case (not available for review) described only clusters of coarse granular calcifications. The patient refused mastectomy, and just a wide resection was performed. Bilateral LCIS was known to be present in two cases (2 and 7). Patient 2 had a subareolar papilloma and foci of classic LCIS in the contralateral breast, and case 7 had a contralateral high-grade DCIS with microinvasion and negative lymph nodes. At the time of the last follow-up all patients were alive. The most important clinical data including follow-up are listed in Table 1.

Tissue processing

The surgical specimens were fixed in formalin. Areas containing the mammographic abnormality were selected with the assistance of radiographs (Faxitron Cabinet X-ray System, Hewlett Packard, Ore.) of the sliced specimen. Between 12 and 23 blocks were examined. Sections were stained with hematoxylin–eosin, Alcian Blue (AB) at pH 2.5, periodic acid–Schiff (PAS), and elastic–van Gieson.

Representative sections of the tumors were selected and processed for immunohistochemistry using a standard avidin–biotin–peroxidase complex procedure. The primary antibodies used are listed in Table 2. When necessary, heat-induced antigen retrieval was performed pretreating sections in a pressure cooker [12] or in a microwave oven (Table 2).

The main morphologic and immuno-phenotypic features of the cases were compared with those of other variants of in situ carcinoma, such as classic LCIS, solid DCIS, and comedo-type DCIS.

Results

Mammographic features

Mammograms were available and reviewed in eight cases. In two cases (cases 1 and 7) multiple, small (5–15 mm) round or oval clusters of calcifications showing a lobular distribution were widely scattered in a large area of the gland, extending over a quadrant (Fig. 1). Radiologically these calcifications were dense, mostly round or coarsely granular (case 1). Sometimes “crushed stone”-like calcifications, with some casting and powdery patterns suggestive of a ductal distribution were also present (case 7). In case 7, a 2.5-cm area of parenchymal distortion was also present. In case 2, there were three clusters 5–20 mm wide of fine granular-type calcifications, and one 6- to7-mm cluster of more prominent, coarse granular-type calcifications. In these cases (1, 2 and 7) calcifications were also present in the subareolar quadrant, very close to the nipple. In four cases (cases 3, 8, 9, and 10) fine granular or coarse granular calcifications were grouped in single clusters ranging from 0.7 to 2.5 cm in diameter. In case 9 a 1.4-cm spiculated mass was observed in a different quadrant than that containing the calcifications. In case 6 a 2.5-cm area of architectural distortion associated with parenchymal retraction and a very few, mostly finely granular, calcifications were visible on the film.

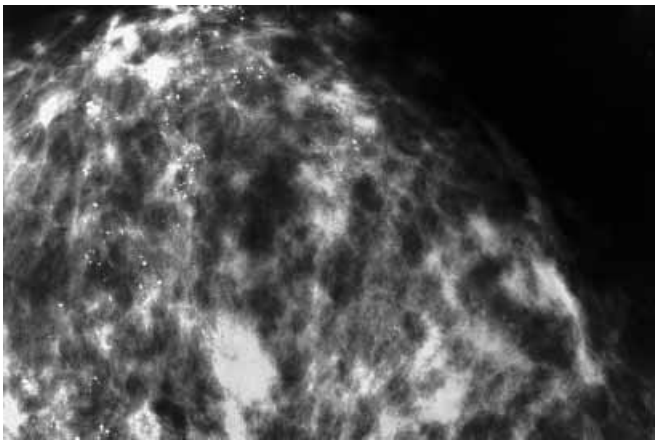


Fig. 1 Case 1. This mammogram shows multiple small (5–15 mm) clusters of calcifications with a lobular distribution, widely scattered over the extent of a quadrant and in the subareolar region very close to the nipple (*upper area*). These calcifications are dense, mostly round or coarse granular

Pathological features

Grossly, in cases 1 and 7 pink nodules measuring 1–2 mm in diameter, some containing cheese-like necrotic material, were scattered in the fibro-adipose tissue. In cases 6 and 7, the areas of parenchymal distortion seen on the radiograph corresponded grossly to a stellate white area of fibrosis punctuated by small pink nodules sometimes containing comedo-like material. The other cases lacked specific gross features.

Microscopically, the spatial distribution was that of a multicentric lesion. In all seven mastectomy specimens multiple foci of in situ carcinoma were seen in different quadrants, and in three of the seven cases foci of LCIS were present in the subareolar region, from where they extended to the main ducts by pagetoid spread. On low-power examination, the most striking feature in all cases was the presence of multiple lobular structures distended by solid cell nests, some of them containing central areas of necrosis (Fig. 2, insets a, b). Amorphous calcifications with irregular shapes and jagged or spiculated edges and granular calcifications were detected within the necrotic

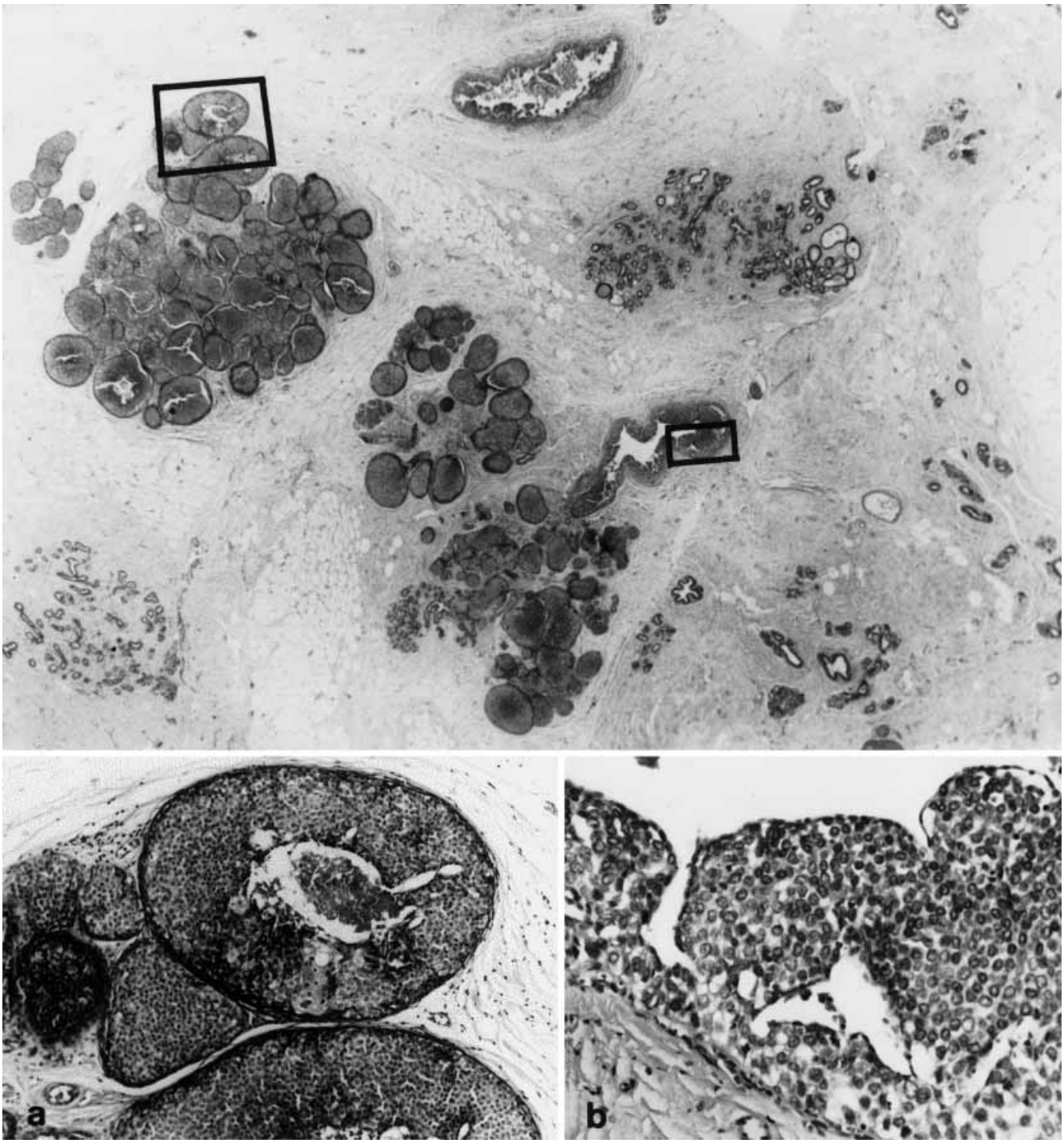


Fig. 2 Case 2. At low magnification, three lobular structures show widely distended lobules (*inset a*) and ducts lined by several cell layers (*inset b*). At higher magnification, the lobules are enlarged by a solid cell proliferation sometimes containing central areas of necrosis (*inset 2a*), while the duct is involved by a pagetoid spread of neoplastic cells beneath the residual luminal epithelium (*inset 2b*). Hematoxylin–eosin

material (Fig. 3a, b). In some cases a hyaline sclerotic tissue bordered the calcification and compressed the tumor cells at the periphery in a crescentic fashion (Fig. 3b, c). Even the most severely distended lobules (which reached 1075 μm in diameter) retained their round shape and tight-knit appearance, exhibiting little or no intervening stroma (Fig. 4a, b). The lobular nature of the proliferation was confirmed by the absence of surrounding elastic fibers. Peripheral myoepithelial cells were always present, as identified by anti-actin antibody.

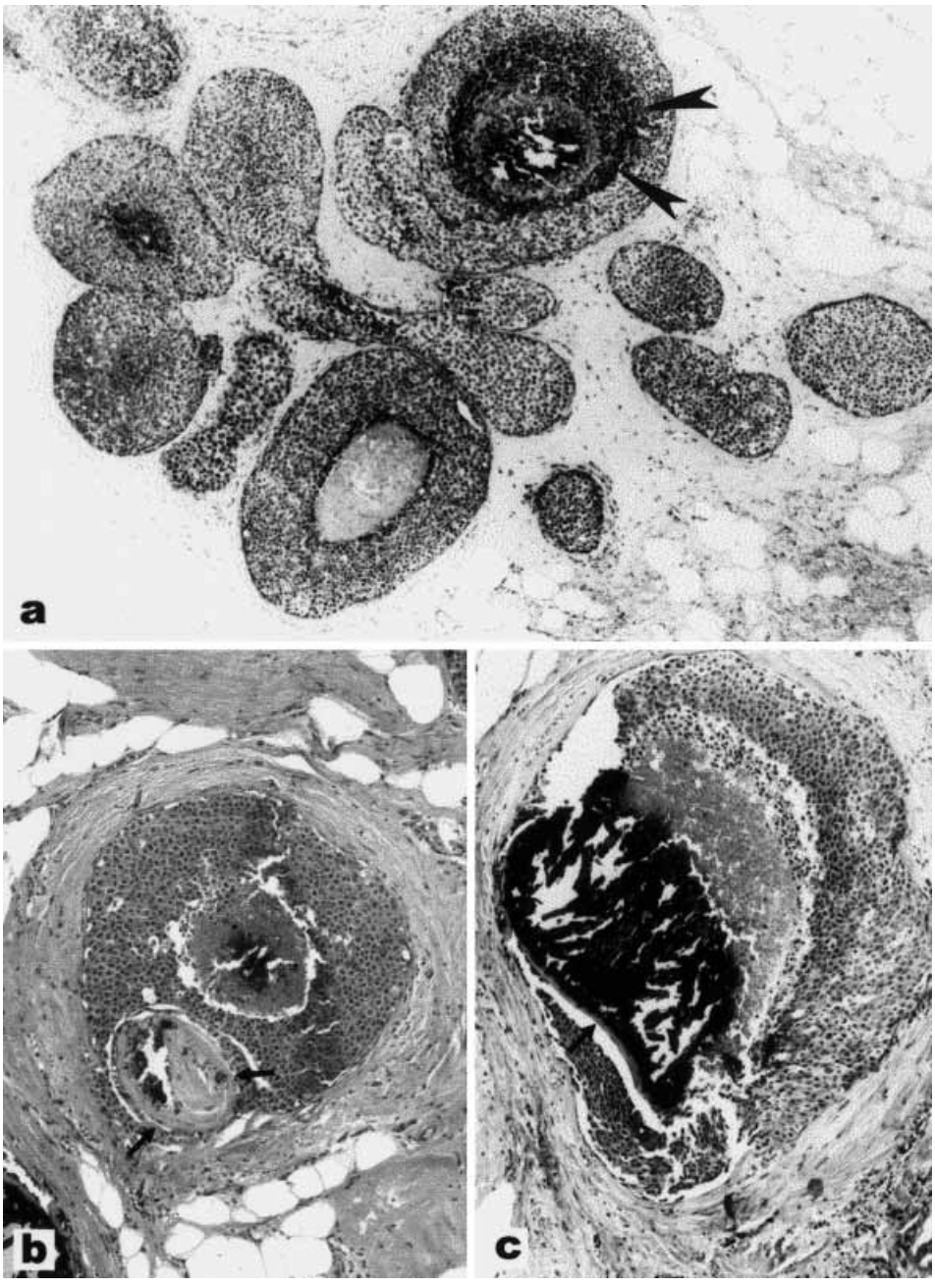


Fig. 3a–c Case 1. Granular calcifications (**a**) are detected within the necrotic material in a neoplastic lobule (*arrow*). Amorphous calcifications with irregular shapes are present within central necrosis. A thin band of hyaline sclerotic tissue separated the cells from calcification (*arrows*). The neoplastic cells are compressed at the periphery in a crescentic fashion (**b, c**). Hematoxylin–eosin

Focally, typical pagetoid spread of the tumor cells beneath residual ductal epithelium was observed (Fig. 2b, inset). Necrosis and calcifications were present in some of these affected ducts (Fig. 5). The stellate area grossly identified in case 7 corresponded histologically to a radial scar containing foci of LCIS, whereas that in case 6 corresponded to a focus of fibrosis containing LCIS and multiple small foci of ILC. In case 9 the spiculated mass identified in the upper outer quadrant far from the area of calcification corresponded to an invasive carcinoma of the tubulo-lobular type.

Cytologically, the lesions were composed of roughly uniform round noncohesive cells with pale cytoplasm containing very fine granules which were positive for AB and PAS stains. Numerous tumor cells had a typical "target" appearance owing to the presence of intracytoplasmic lumina containing a PAS- and HMFG2-positive central globule (Fig. 6). The nuclei, while retaining their monomorphic quality, were larger than those of the usual LCIS, often eccentrically located, and had sparse chromatin and usually a single nucleolus (Fig. 6). In case 4, the tumor cells had a signet ring-like appearance owing to cytoplasmic vacuoles which were mucin positive.

In all cases, foamy macrophages were sometimes admixed with the neoplastic cells. The specimens obtained from mastectomies showed many foci of classic LCIS without calcification admixed with LCIS exhibiting central necrosis and larger cells.

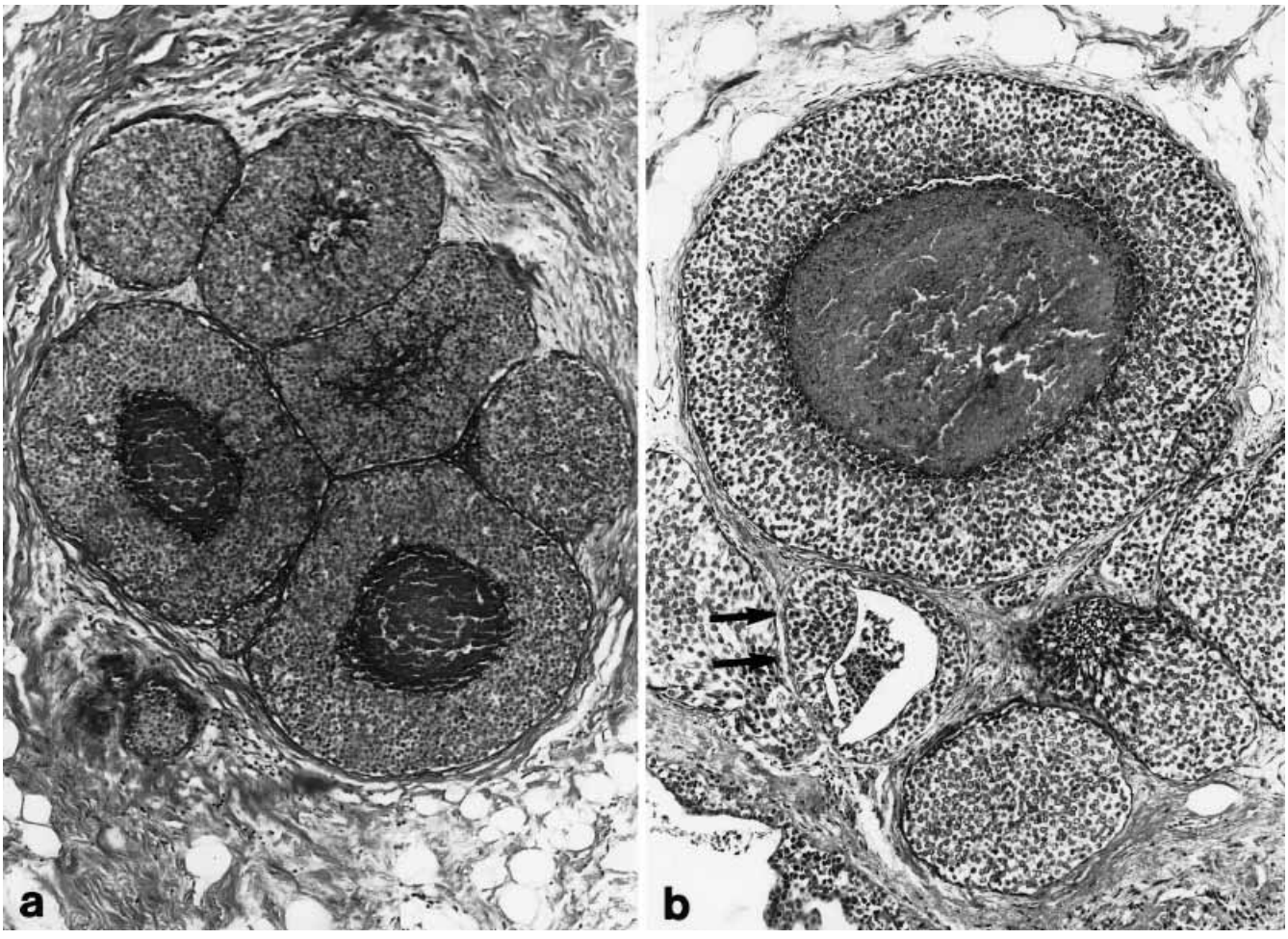


Fig. 4a, b Cases 9 and 1. In greatly distended lobules, the individual units are round and tightly packed, exhibiting little or no interductular stroma (**a**). A duct in the center is involved by pagetoid spread (**b** *arrow*). Hematoxylin–eosin

Five cases were pure LCIS and one case was associated with a distant invasive carcinoma of the tubulo-lobular type, whereas in four cases (cases 2, 5, 6 and 10) multiple foci of ILC with a pleomorphic appearance, ranging from 0.5 to 2.2 cm in width, were present around the in situ carcinoma. In cases 5, 6 and 10 lymph node metastases were already present.

Marker expression

E-Cadherin was expressed at the cell membrane of the normal epithelial cells in the surrounding parenchyma. In all types of lobular carcinomas, the cells were negative for E-cadherin, whereas the protein was detected on the normal residual epithelial cells of ducts involved by pagetoid spread (Fig. 7a).

The apocrine marker GCDFP-15 was detected in a variable percentage of large-cell LCIS, and also in the ILC cells of case 5.

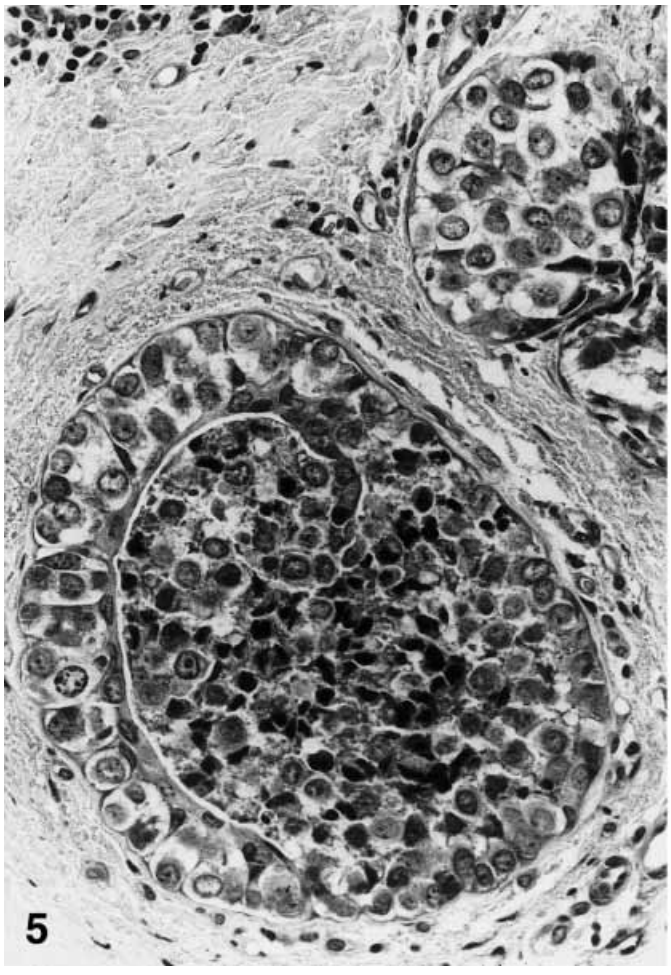
Estrogen receptor was present in more than 50% of large cells in LCIS, whereas progesterone receptor was either absent or present in only a low percentage of these cells.

p53 was always negative both in LCIS and in ILC, whereas c-erbB-2 antibody decorated the cellular membrane of large cells in LCIS and in ILC and not the cells of classic-type LCIS (Fig. 7b).

The proliferation rate of LCIS large cells exceeded the 20% cut-off point in case 5 only, whereas in the other cases it varied from 2% to 15%. The proliferating cells were typically located along the basal layer.

Differential diagnosis (Table 3)

The main morphologic and immuno-phenotypic features that distinguish this LCIS variant from classic LCIS are larger nuclei, a slightly greater degree of pleomorphism, the presence of central necrosis, and constant positivity for c-erbB-2 antigen. On the other hand, the presence of attributes traditionally associated with LCIS, such as multicentricity, pagetoid spread, growth pattern with lack of cohesiveness, cytoplasmic vacuoles, and loss of expression of E-cadherin, clearly distinguish LCIS with necrosis from both the solid low- or intermediate-grade type of DCIS and the comedo forms of DCIS.



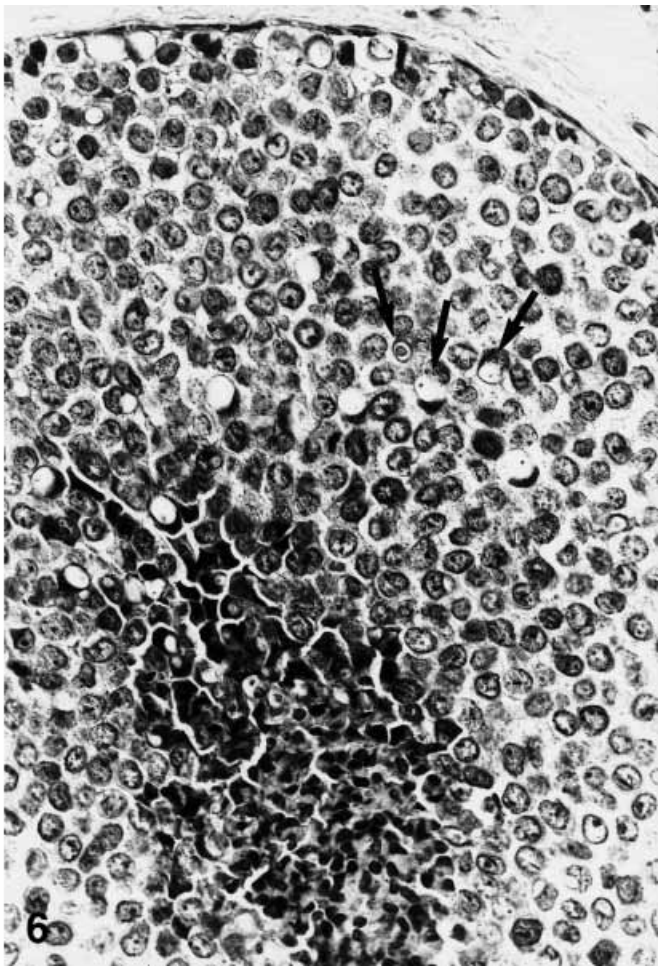


Fig. 5 Case 4. Typical pagetoid spread of the tumor cells beneath persisting ductal epithelium. The lumen is filled by necrotic cells. Hematoxylin–eosin

Fig. 6 Case 1. At high power, the tumor cells are relatively uniform with pale finely granular cytoplasm, large nuclei, and a single nucleolus. Necrotic debris is evident in the center. Some tumor cells show intracytoplasmic lumina and a small central globule, resulting in a targetoid appearance (*arrows*)

Discussion

We describe ten cases of LCIS with a mammographic pattern suggestive of or compatible with DCIS in the occurrence of central necrosis and calcification. At variance with previous works on histologically proven cases of LCIS, where review of the mammographic findings demonstrated only nonspecific mammographic abnormalities [10, 11, 17], all our cases showed calcifications histologically located within the neoplastic lobules.

Multifocality and multicentricity, two important properties of LCIS [18, 20], were observed in all five cases in which mastectomy was performed. Recent studies have confirmed previous observations to the effect that DCIS typically is not multicentric within the breast [16], even acknowledging that the mammographic estimates (based on the extent of calcifications) frequently underestimate its size, particularly in the case of the noncomedo form [9]. In some of our cases calcifications involved extensive areas involving a whole quadrant, but in the mastectomy specimens multiple foci of LCIS were demonstrated in almost all quadrants, including those lacking any radiologic signs of neoplasia.

The more frequent radiological pattern was that of coarse granular calcifications arranged in round or oval clusters suggestive of a lobular location. A pattern of powdery calcifications consistent with either lobular proliferation or low-nuclear-grade DCIS [9] was clearly recognizable in some areas. Still other patterns were present which, on the whole, were more in keeping with an intermediate- to high-grade in situ carcinoma or, in one case (case 7), a pure high-grade DCIS.

In contrast to the radiologic findings, the multicentric distribution and the histological architecture at low magnification immediately suggested the diagnosis of LCIS. This refers to the presence in different quadrants of tightly packed ductules that maintained a round shape even when massively distended, corresponding to the “macrolobules” described by Haaghensen [6, 7] in LCIS. Recently, Fisher and coworkers [5] labelled as ductolobular carcinoma in situ (DLCIS) cases very similar to those we are reporting. However, in contrast to these authors (who also included cases showing a cribriform pattern), in the

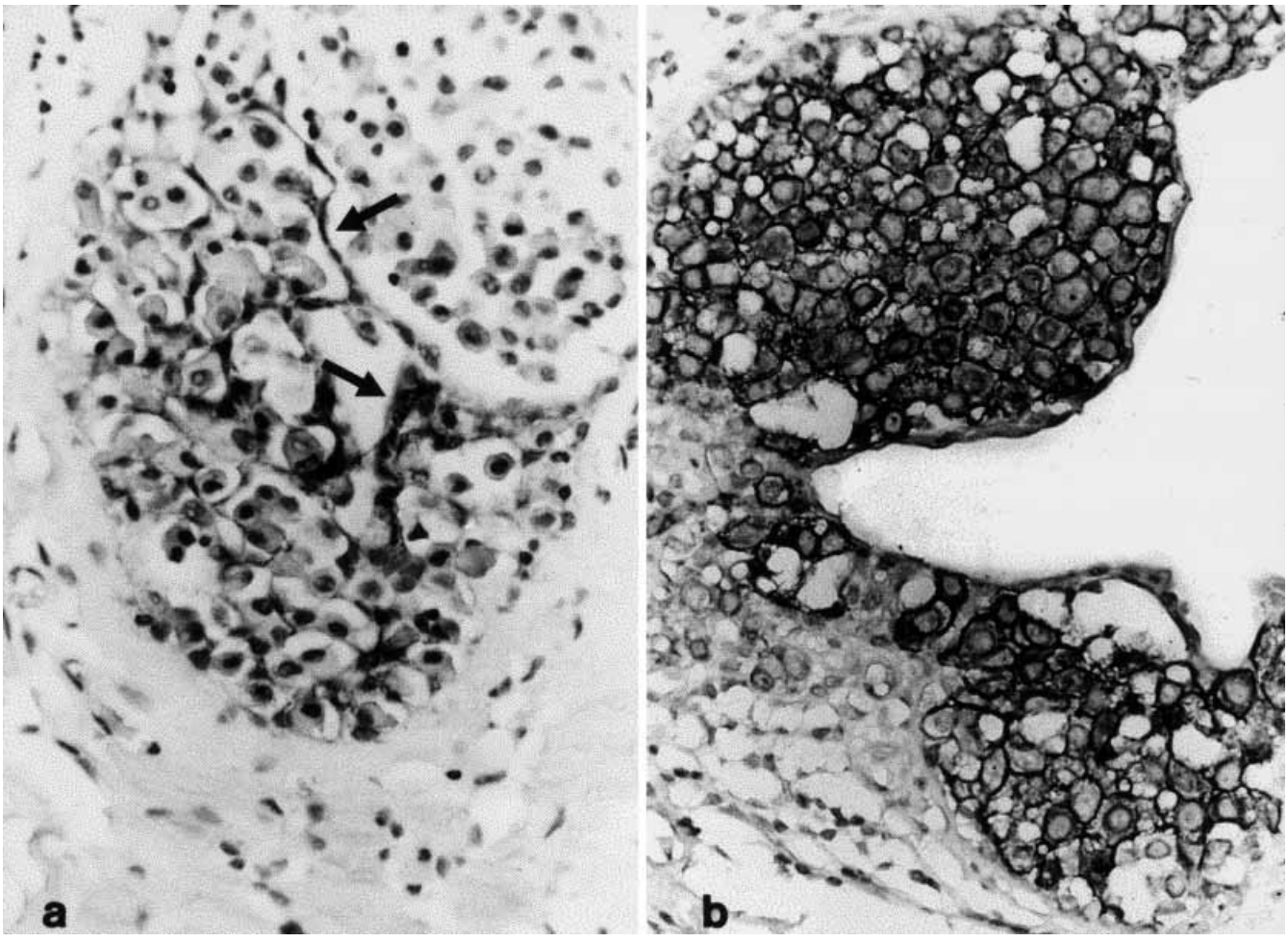


Fig. 7a, b Case 10. **a** In a duct featuring pagetoid spread by lobular carcinoma in situ (LCIS) cells, the immunocytochemical expression of E-cadherin is limited to residual epithelial cells towards the lumen (*arrows*), whereas the carcinomatous cells are completely negative. **b** In the same duct, immunocytochemical staining for cErbB-2 is present at the cell membranes of the neoplastic elements but not the residual luminal epithelial cells

Table 3 Histological and immuno-phenotypical differences of LCIS with central necrosis with classic LCIS, solid DCIS, and comedo type DCIS

	LCIS with central necrosis	Classic LCIS	Solid DCIS	Comedo-type DCIS
Histology				
Spatial distribution	Multicentric	Multicentric	Rarely multicentric	Not multicentric
Pattern of spread	Pagetoid	Pagetoid	Lobular cancerization	Lobular cancerization
Nucleus	Intermediate grade	Low grade	Low intermediate grade	High grade
Cytoplasm	Round, pale, large, with intracytoplasmic vacuoles or signet ring features	Scant with intracytoplasmic vacuoles	Cuboidal, rarely with eosinophilic granules	Pleomorphic, large
Lack of cohesiveness	Yes	Yes	No	No
Growth pattern	Solid	Solid	Solid, with rare intercellular spaces	Solid
Central necrosis	Present	Absent	Absent	Present
Shape of neoplastic ducts	Regular, round	Regular, round	Regular, round	Irregular
Myoepithelial cells	Present	Present	Present	Present, but thin and attenuated
Periductal fibrosis	Absent	Absent	Absent	Present
Immuno-phenotype				
E-cadherin	Negative	Negative	Positive	Positive
c-erbB-2	Positive	Negative	Variable	Positive
p53	Negative	Variable	Variable	Positive
Ki67 (proliferative index)	Variable (generally low)	Low	Low	High

present study we have included only cases with a solid growth pattern without any lumen formation and with foci of central necrosis. The patterns described here fit in with the so-called lobular neoplasia grade 3 (LN3) described by Tavassoli [20]. Reportedly, the most important features that distinguish LN3 from other types of lobular neoplasia (called LN1 and LN2) are the massive degree of lobular distension, the barely evident interacinar stroma, and the more atypical tumor cells. In addition, in LN3 necrosis and calcifications may be present and involve almost all lobules within a biopsy.

The lack of cohesiveness, the absence of lumina, the pagetoid spread and the presence of target cells, as seen in our cases, are all features that (though not entirely specific) are certainly more common in LCIS than in DCIS [4]. Two different cell types of LCIS have been described. Cells with scant, pale cytoplasm and round bland nuclei that lack nucleoli and have a diploid DNA pattern [7, 22] have been referred to as type A, whereas cells with larger nuclei, more pleomorphism and a hyperdiploid DNA have been designated type B [22]. The latter probably correspond to those present in our cases.

Four of our cases were associated with ILC, which is a high frequency [15]. All four cases were of the pleomorphic variant. Previous investigations have already demonstrated that pleomorphic patterns and apocrine differentiation in lobular carcinomas are associated with an aggressive behavior [3, 21].

In previous work, the only pathologic parameter found to be significantly predictive for invasive ipsilateral breast tumor recurrence in LCIS was marked ductular and lobular distension, with the occurrence of areas exhibiting little or no interductular stroma [5]. Other authors have demonstrated that the recurrence rate in LCIS, either as infiltrating carcinoma or as in situ carcinoma, correlates with the number of neoplastic lobules and the nuclear size in the original biopsy [15]. Our cases showed marked lobular distension, numerous neoplastic lobules and large nuclear size, i.e. all the features recognized as aggressive parameters in LCIS [5, 15].

The immuno-phenotype of these cases, particularly the loss of E-cadherin expression, is in keeping with the diagnosis of LCIS. In fact, it has been demonstrated that presence of E-cadherin is a feature of ductal, as opposed to lobular, in situ carcinomas. As a result of the molecular defect in E-cadherin expression, the cells in LCIS can easily dissociate and freely move along the ductal system, thus explaining their lack of cohesiveness and the intraductal pagetoid spread [2, 13]. Furthermore, the potential for biological aggressivity is heralded by the expression, mainly in the larger cell type, of c-erbB-2 protein, a protein consistently present in high-grade DCIS [1].

In conclusion, our cases exhibit radiologic and histological patterns characterizing a distinct variant of LCIS. Unlike classic LCIS, this variant was mammographically detected because of extensive necrosis and microcalcifications. However, these patterns still ought to be classified as lobular (as opposed to ductal) in situ lesions, on the basis of the following criteria: (a) *spatial distribution*, in that the lesions were multicentric, involved many lobular structures and showed typical intraductal pagetoid spread; (b) *cytological features*, with absence of gland-like structures and lack of cell cohesiveness (c) *immuno-phenotype*, and specifically loss of E-cadherin expression.

Our data suggest that the distinction between LCIS and DCIS is drawn too rigidly in the literature. In fact, the use of mammographic screening selects a specific variant of LCIS which approaches DCIS in appearance in terms of cell size, pleomorphism, necrosis and calcification and should be regarded as a more aggressive lesion than classic LCIS, so that further treatment (i.e. simple mastectomy) should be advised in such cases.

Acknowledgements This work was supported by grants from the M.U.R.S.T. (Ministero della Ricerca Scientifica e Tecnologica, Rome) and from the Associazione Italiana per la Ricerca sul Cancro (A.I.R.C.), Milan, Italy. We are deeply indebted to Prof. J. Rosai for criticism and revision of the manuscript.

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