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Lobular neoplasia displaying central necrosis: A potential diagnostic pitfall

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ABSTRACT

The distinction between intraepithelial proliferations of ductal and lobular type is often straightforward. However, a small number of cases create diagnostic problems even for experienced pathologists. Among those is the recognized, but not always kept in mind, lobular neoplasia with "comedo-type" necrosis.

Herein, we present six cases of lobular neoplasia with comedo necrosis. Three cases were classified correctly, whereas the three remaining cases were initially misdiagnosed as ductal carcinoma *in situ* with necrosis. Of these three misdiagnosed cases, one patient underwent radiation therapy before this study was carried out. The two other patients were correctly reclassified as lobular type in subsequent excisional biopsies. One case showed a focus of microinvasion. All six lesions were negative by E-cadherin immunohistochemistry. Our experience highlights that the correct differentiation between intraepithelial neoplasias of ductal and lobular type may be challenging, and that the correct differentiation is extremely important for prognostic information and therapeutic decisions.

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Introduction

Intraepithelial proliferations of lobular type are morphologically characterized by small and loosely cohesive epithelial cells [5]. According to the degree of proliferation and expansion of the acini, they have been subdivided in atypical lobular hyperplasia (ALH) and lobular carcinoma *in situ* (LCIS). However, there are no universally accepted criteria for this distinction and, currently, the term lobular neoplasia (LN) is widely used.

Although the majority of intraepithelial proliferations are easily divided into ductal or lobular type on morphologic grounds alone, a small group has indeterminate morphologic features, such as the presence of central necrosis and/or calcifications, which has been regarded as a feature of ductal proliferations [7]. In these cases, the use of E-cadherin plays an important role for the diagnosis [24].

The distinction between lobular neoplasia and intraductal neoplasms of ductal type has important therapeutic and prognostic implications. Patients with lobular neoplasia are often managed by careful follow-up, while treatment of ductal carcinoma *in situ* is intended at eradication of the lesion. In addition, assessment of the surgical margins status is important in ductal carcinoma *in situ*, but not in lobular neoplasia [21]. The aim of this study is to highlight the diagnostic issues surrounding cases of lobular neoplasia with central necrosis (LNCN) to ensure that these cases are correctly classified and accordingly treated.

Material and methods

In order to identify all possible cases, the Pathology Department computer system was searched from November 2006 to July 2009. The search criteria included: lobular neoplasia with necrosis, lobular carcinoma *in situ* with necrosis, pleomorphic lobular carcinoma *in situ*, low nuclear-grade ductal carcinoma with necrosis, ductal carcinoma *in situ* with comedo necrosis, and solid ductal carcinoma *in situ* with necrosis. A total of 22 cases meeting these search criteria were found and retrieved for independently microscopic review by three pathologists (MR, AM, and SM).

All cases except one received for consultation were routinely processed at our department for microscopic examination. Briefly, tissue sections were fixed in 10% neutral-buffered formalin, processed, embedded in paraffin, and stained with Hematoxylin and Eosin. For immunohistochemistry, 4-μm thick, formalin-fixed sections were stained with antibodies to E-cadherin.

After reviewing these 22 cases, immunostain for E-cadherin was performed only in those with unclear morphologic criteria for the differentiation between lobular or ductal type. E-cadherin staining was considered positive when the epithelial cell population of interest showed complete circumferential cell membrane staining. Tumors in which there was cytoplasmic staining without distinct cell membrane staining were scored as negative. All controls reacted properly.

In all cases, a profile including Her2/neu, estrogen (ER), progesterone (PR), and Ki-67, was performed. The Her2/neu assays were performed on a DAKO auto-stainer. ER and PR were considered positive if there was nuclear staining in >5% of neoplastic cells. HER2/neu was scored on the standardized 0–3 scale, accord-

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Table 1
Source and dilution of antibodies used in this study.

Antibody/clone	Source	Dilution
E-cadherin/4A2C7	Zymed	1:40
Estrogen/6F11	Leica	1:15
Progesterone/IE2	Ventana Med. System	Prediluted
Her2/neu/Herceptest	Dako	Prediluted
Ki-67/MIB-1	Dako	1:100

ing to the intensity of cytoplasmic membrane staining present in at least 30% of the neoplastic cells. Ki-67 was classified as negative (nuclear staining in less than 10% of cells), borderline (nuclear staining in more than 10% but less than 20% of cells), and positive (nuclear staining in more than 20% of cells). Table 1 includes a list of antibodies used in this study.

Results

Six cases of lobular neoplasia with central or "comedo-type" necrosis were identified (Fig. 1). Of these, three (cases # 1, 4, and 5) were correctly classified as LNCN. Immunohistochemical staining for E-cadherin was used as confirmation. Case # 1 displayed a higher degree of pleomorphism when compared with misclassified cases (pleomorphic variant of LN), more abundant mitotic figures, and lacked signet ring forms (Fig. 2a). The lack of cohesion between cells raised suspicion and led to performing the E-cadherin immunostaining which allowed a correct classification in this case.

Case # 4 also represented a pleomorphic variant of LN involving an area measuring 1.0 cm with a focus of microinvasion (stromal invasion within 1 mm from the *in situ* component). Central necrosis and calcifications were also prominent (Fig. 2b). This patient underwent subsequent radiation therapy based on the presence of microinvasive carcinoma and very close surgical margins of resection. Case #5 represented the classical variant of lobular neoplasia exhibiting central necrosis.

Three other cases were initially mistakenly diagnosed as ductal carcinoma *in situ* (DCIS) with necrosis (Cases # 2, 3, and 6). Case # 2 was diagnosed as low nuclear-grade ductal carcinoma *in situ*, solid pattern with necrosis (Fig. 1a). Although infrequent, low nuclear-grade ductal carcinoma *in situ* may have necrosis, which is not of comedo type. In this case, the diagnosis was made in core-needle biopsy, and the case was correctly re-classified as lobular neoplasia with central necrosis after reviewing the follow-up excisional biopsy and applying E-cadherin to both biopsies.

Case # 3 was initially called ductal carcinoma *in situ*, comedo type, and identified in retrospective review, when immunohistochemistry for E-cadherin was performed in morphologically ambiguous cases for the purposes of the present study (Fig. 1b).

Case # 6 was received as a consultation. The patient had undergone core-needle biopsy at an outside institution with findings of ductal carcinoma *in situ*, comedo type. A follow-up excisional biopsy, in the same hospital, was classified as LNCN. The patient requested a second opinion, and both cases were sent to us for consultation. On retrospective review, the lesion seen in core-needle biopsy and excisional biopsy showed similar histologic features characterized by distended acini with loosely cohesive atypical but monomorphic cells and central comedo-type necrosis. Immunohistochemistry for E-cadherin was negative in both specimens, and the core biopsy was re-classified as LNCN. The patient was lost to follow-up, and no additional treatment information was available to us.

Clinicopathologic data concerning all cases is summarized in Table 2.

The common features in all cases were a variable expansion of the acini by proliferation of cells and focal to extensive areas of comedo-type necrosis, some of them associated with dystrophic calcifications. Pagetoid spread of the tumor cells to the residual ductal epithelium was frequently observed. On low-power examination, all cases had the typical features of ductal carcinoma *in situ*, comedo type (Fig. 1). However, when examined at higher magnification, they were characterized by low nuclear-grade monomorphic and dyscohesive cells (Cases 2, 3, 5, and 6). Cases 1 and 4 represented the pleomorphic variant of LN and displayed a higher degree of pleomorphism and atypia (Fig. 2). Occasionally, signet ring cells with intracellular mucin and mitotic figures were seen (Fig. 3). In contrast to this morphology, ductal carcinoma *in situ* with comedo necrosis is characterized by having cohesive malignant cells with moderate to high degree of pleomorphism (Fig. 4).

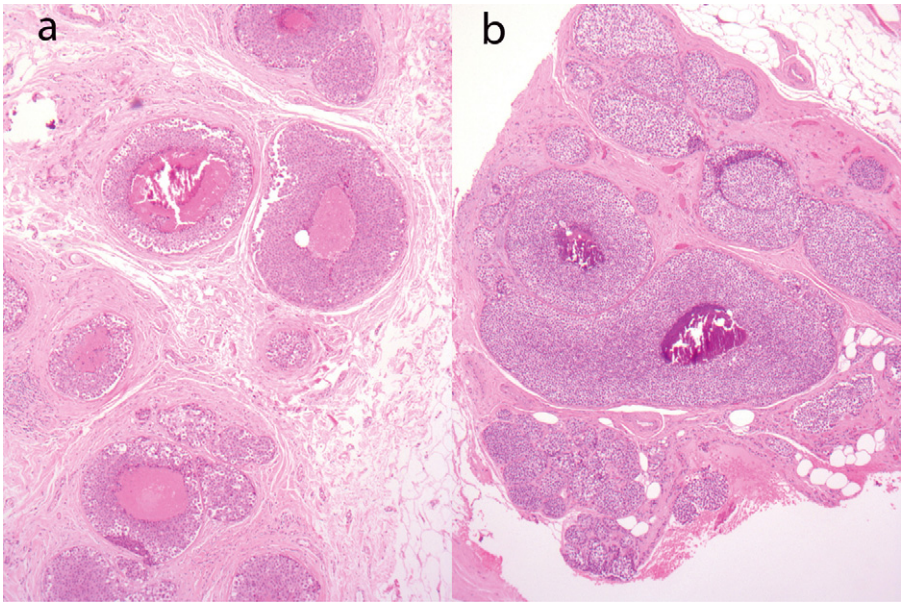

Fig. 1. (a and b) Low magnification of cases 2 and 3, respectively, showing distended acini displaying central necrosis. Dystrophic calcifications are also seen (H&E, original magnification ×50).