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Lobular and ductal intraepithelial neoplasia

Lobular intrapepithelial neoplasia

Introduction

In 1941, Foote and Stewart [8] described lobular carcinoma in situ (LCIS) in detail and emphasized the morphologic similarity of the cells comprising LCIS and invasive lobular carcinoma. Clinically, mammographically, and grossly occult, LCIS is often detected incidentally; the multicentricity and high frequency of bilaterality of these lesions were recognized early on. Occurring generally in younger women, microcalcification is not a feature of these lobular lesions, in contrast to the high frequency of microcalcifications seen with ductal proliferative lesions. Microscopically, LCIS is generally characterized by a solid, occlusive proliferation of a loosely cohesive, uniform population of cells, some of which may contain intracytoplasmic lumens. A quantitatively more limited version of the lesion was subsequently designated as atypical lobular hyperplasia (ALH). This resulted in mastectomy for those women who were diagnosed as having LCIS and follow-up for those with a diagnosis of ALH. The morphologic and clinical features outlined by Foote and Stewart [8] still characterize a vast majority of „LCIS," but accumulated experience over the past several decades has expanded the pathologic spectrum and modified the clinical implications of „LCIS."

Classic studies on LCIS/LN with divergent conclusions

In a study of 210 women with a diagnosis of „LCIS" from a biopsy and no further therapy after the biopsy, Haagensen [10] found that only 10% of the women developed subsequent invasive carcinomas with a median follow-up of 14 years. Noting the low frequency of progression of „LCIS" to subsequent invasive carcinoma, in 1978 Haagensen proposed the term lobular neoplasia (LN) for the spectrum of ALH and LCIS. Furthermore, he advocated patient follow-up after a diagnosis of LN by biopsy rather than mastectomy at a time when mastectomy was the standard management of patients with a diagnosis of in situ carcinoma, whether ductal or lobular in type and regardless of quantity or extent of the disease. Interestingly, another paper by Rosen et al. [21] in 1978 found that 23% of women with no further therapy after a diagnosis of „LCIS" after a biopsy develop an invasive carcinoma after a mean follow-up of 23 years. Rosen et al. [21] advocated ipsilateral mastectomy and mirror-image biopsy of the contralateral breast; if the contralateral breast also harbored LCIS, bilateral mastectomy was recommended. This reflected a drastic difference in terminology and management of the same lesion at two distinguished medical centers (Columbia University Hospital and Memorial Sloan Kettering Cancer Center) in New York City. Shortly after the publication of Haagensen's study [10], we adopted the LN terminology at the Armed Forces Institute of Pathology (AFIP), where I practiced at the time, and enthusiastically supported his management recommendations [27]. Later on, we changed the term to lobular intraepithelial neoplasia (LIN) because invasive carcinomas could also fall under the umbrella of LN. In 2003, 25 years and many unnecessary mastectomies after the introduction of the term lobular neoplasia (LN), it was selected as the optimal term by the World Health Organization (WHO) for the spectrum of atypical lobular hyperplasia and lobular carcinomas in situ [28]. My preference is for the more specific designation of LIN.

Evolution of LIN

Over the past several decades, the morphologic spectrum of LIN has been modified by some new and rare subtypes (necrotic and macroacinar LIN) that are detected mammographically because of microcalcifications [7] and cytologic variants (pleomorphic and signet ring-cell LIN) that are more frequently associated with invasive carcinoma. Together, these lesions comprise the LIN3 group of the three-tiered grading of LIN lesions proposed at the AFIP [3]; LIN3 lesions accounted for 12% of the 775 LIN cases in that study based on consultation material, but they most probably account for less than 5% of LIN in the general practice of pathology.

The finding of similar frequencies of chromosomal gains of 6q, 2p11, and 20q13.13 along with losses of 16p, 16q, 17p, 19q13.2, and 22q in „ALH" and „LCIS" by comparative genomic hybridizations (CGH) further supports the validity of the term LIN for this spectrum [15].

Management of LIN

In contrast to invariable mastectomy performed in the past, the current management of a vast majority of women with LIN is directed at follow-up along with hormonal therapy for preventive purposes. For a select group of women (BRCA-related familial breast cancer), bilateral mas-

Tab. 1 DIN translational table

Ductal intraepithelial neoplasia (DIN) terminology	Conventional terminology
Low-risk DIN	Intraductal hyperplasia (IDH)
Flat DIN 1	Flat epithelial atypia
DIN 1	<2 mm: atypical ductal hyperplasia (ADH)
	>2 mm: ductal carcinoma in situ, low grade (DCIS, grade 1)
DIN 2	Ductal carcinoma in situ, intermediate grade (DCIS, grade 2)
DIN 3	Ductal carcinoma in situ, high grade (DCIS, grade 3)

tectomy, often with reconstruction, is an option. The current general consensus is that classic LIN is generally a risk factor for subsequent development of invasive carcinoma in either breast; interestingly, the associated or subsequent invasive carcinoma may be either ductal or lobular in nature. The presence of classic LIN at the resection margin of excisional biopsies does not require reexcision as the multicentricity of LIN is well recognized. The lesions that comprise LIN3 (necrotic, pleomorphic, etc.), however, are often associated with invasive carcinoma, and reexcision is advised when they are identified at the resection margin or in a core biopsy even if the general policy of a given institution is not to perform excision for LIN identified in core biopsies.

Ductal intraepithelial neoplasia

Introduction

The term ductal intraepithelial neoplasia (DIN) refers to the spectrum of diverse intraductal proliferations that are associated with an increased risk, albeit of variable magnitude, for subsequent development of invasive ductal carcinoma.

As noted above, the use of the term neoplasia instead of the spectrum of atypical hyperplasia and carcinoma in situ was first introduced for lobular lesions by Haagensen in 1978 [10]. In 1991, Rosai [20] suggested the terminology of mammary intraepithelial neoplasia because of the significant interobserver variability in the diagnosis of intraductal proliferative lesions. The terminology of ductal intraepithelial neoplasia was proposed and initially used at AFIP in the mid-1990s [25]. In 2003, the WHO accepted the ductal intraepithelial neoplasia (DIN) terminology and classification as an alternative to the DCIS terminology [28]. Some of the details of the terminology have changed with time as expected, and further modifications are expected as we learn more about these lesions. The most recent version that we use is shown in **Tab. 1** along with the equivalent in the conventional classification.

- In the conventional classification, this spectrum has been divided into benign and malignant and designated as intraductal hyperplasia (IDH), atypical intraductal hyperplasia (AIDH), and ductal carcinoma in situ (DCIS), which is further subdivided into low, intermediate, and high grades.
- The introduction of widespread screening mammography has resulted in substantial changes in the frequency, presentation, dominant types, treatment of, and survival from „DCIS." Mammography has also resulted in the detection of a variety of proliferative lesions, the biologic significance of which is not well established.
- The changes resulting from application of technologic advances and the modifications necessary in interpretation, designation, and, ultimately, management of this spectrum are addressed below.

Impact of screening mammography

It is estimated that approximately 67,770 cases of DCIS will be diagnosed in women in the United States in 2008 [12]. The proportion of breast carcinomas diagnosed as DCIS increased from 2.8% in 1973 to 14.4% in 1995, and DCIS currently accounts for 25–30% of all mammographically detected carcinomas and 10% of all breast carcinomas [5]. The clinical presentation of DCIS has shifted from a palpable mass in the premammographic era to a nonpalpable lesion detected on the basis of mammographic microcalcifications or density. The vast majority (>90%) of premammography „DCIS" were of the comedo type, whereas this variant accounts for about 40% of the postmammography „DCIS." Treatment has shifted from mastectomy to lumpectomy with or without radiation and hormonal therapy in a large proportion of women. Mortality from „DCIS" at 10 years has decreased from 3.4% after mastectomy in the 1978–1983 period (premammography) to 1.9% in the 1984–1989 period (postmammography) despite the more limited surgical excisions [6]. This reduction in death is probably due to improved treatment options, a change in the biology of the detected lesions, and more accurate exclusion of any associated invasive carcinoma in thoroughly sampled biopsies in recent years compared with suboptimal sampling characteristic of premammographic-era tissue processing. DCIS is considered a curable disease with a 10-year cause-specific survival of 97% [22].

Despite all these changes, the breast committees of major societies have made no attempt to adopt a more appropriate terminology for these lesions. This failure of breast specialists to make any modifications in the conventional terminology is in sharp contrast to specialists in other areas, who have dropped the term carcinoma in situ and switched to the intraepithelial neoplasia terminology in the cervix, vulva, vagina, prostate, pancreas, etc.

Problems with the conventional classification of IDH, AIDH, and DCIS

The conventional classification has divided the spectrum of intraductal proliferations into cancer (DCIS) and noncancer (hyperplasia) and has proposed a linear progression of the proliferation from hyperplasia to atypical hyperplasia, DCIS (with low-grade DCIS progressing to intermediate and ultimately high-grade DCIS), and finally invasive ductal carcinoma. It is now well recognized, however, that low-grade „DCIS" progresses to low-grade invasive carcinoma, while high-grade „DCIS" progresses to high-grade invasive carcinoma [11, 14, 17]. By CGH, low-grade „DCIS" shows frequent gains of 1q and losses of 16q, while high-grade

„DCIS" shows gains on 8q and 17q22–24 and losses on 17p–alterations they share with their invasive counterparts. These parallel progression pathways are far more common and easily documented at the morphologic and molecular levels.

The emphasis placed on hyperplasia in the conventional system has resulted in a failure to recognize the flat epithelial atypias that were lucidly described by Azzopardi [1] in his excellent book *Problems in Breast Pathology*. This important lesion, which frequently manifests mammographically as microcalcifications, was not even recognized in the USA until we proved its neoplastic nature and illustrated its similarity at the molecular level to"DCIS" and well-differentiated invasive carcinomas, particularly tubular carcinoma [16].

Another major problem of conventional classification is interobserver variability that results in the interpretation of a lesion as noncancerous (atypical intraductal hyperplasia) by some, while the same lesion is interpreted as carcinoma (ductal carcinoma in situ) by other pathologists. It is important to note that the studies proposing separation of AIDH from low-grade DCIS were based predominantly on premammographic material that was poorly sampled and had no assessment of margins. The criteria proposed by one group [18] required complete involvement of two spaces by the cribriform, solid, or micropapillary patterns of low-grade DCIS without any qualification as to the size of the two spaces. Therefore, two adjacent 1-mm ducts showing complete involvement by these patterns would have qualified as DCIS, whereas a 3- or 4-mm duct with similar complete involvement would not. Why this illogical criterion continues to be used is difficult to understand. Another approach [29] was to require the complete involvement of one or more adjacent ducts by the same changes, but the maximum dimension of the duct cross-section(s) had to exceed 2 mm to qualify as DCIS. This group emphasized that, qualitatively, AIDH and low-grade DCIS are the same, but quantitatively, AIDH is too small to warrant mastectomy–which was the standard therapy for a lesion diagnosed as DCIS regardless of its size or type in the era when these studies were published. In effect, the only difference between AIDH and low-grade DCIS is a quantitative one. It is important to note that the findings of these studies based on poorly sampled material that had no assessment of margins is no longer relevant to our current practice, in which most excisions are image-guided and we have extensive sampling of the tissue samples.

It is important to emphasize that the consequences of lack of reproducibility are numerous and include the following: assignment of a lesion diagnosed as carcinoma to a cancer protocol, reexcision if the lesion is at or close to the inked resection margin, variable assessment of lesion size, interpretation of similar lesions in the future as recurrent „DCIS," and, most importantly, an adverse psychosocial impact on the patient. The same lesion interpreted as AIDH would have significantly different consequences. When two studies in the early 1990s confirmed the presence of significant interobserver variability even among expert breast pathologists [20, 23], it was argued that educating the pathologists would improve the situation. But a recent study that included both expert breast pathologists and those whose major responsibility is breast pathology showed the persistence of significant interobserver variability [9].

The disappointing results of the reproducibility studies in the 1990s were the impetus to consider the alternate classification and terminology of ductal intraepithelial neoplasia.

Before proposing the DIN classification, we asked two major questions:

1 Is IDH neoplastic?
2 Should we combine AIDH and low-grade DCIS?

Our answer to both questions was yes.

It is clear that IDH is a new growth that is unrelated to a physiologic state, and there is no evidence that it is spontaneously reversible. Furthermore, a study assessing the loss of heterozygosity (LOH) in IDH, AIDH, and DCIS found overall LOH in at least one of 15 loci evaluated among 37–40% of IDH unassociated or associated with carcinoma, respectively, compared with 42–44% of AIDH and 70–80% of DCIS lesions. The difference between IDH and AIDH was only 5%! Because 20% of comedo DCIS lesions also

Zusammenfassung · Abstract

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Lobuläre und duktale intraepitheliale Neoplasie

Zusammenfassung

Lobuläre und duktale intraepitheliale Neoplasien stellen Proliferationen dar mit immunphänotypisch variablen, biologisch und morphologisch unterschiedlichen Zellen. Beide haben das (nicht immer realisierte) Potenzial zur Progression in ein Karzinom, indem sie die Barrieren der myoepithelialen Zellschicht und der Basalmembran durchbrechen und schließlich in das Stroma eindringen.

Beginnend mit den lobulären und dann den duktalen Proliferationen, schildert dieser Übersichtsartikel die Entwicklung von unserem Verständnis dieser Läsionen, die Probleme, die mit der konventionellen Terminologie der duktalen Hyperplasie, der atypischen Hyperplasie und des Carcinoma in situ einhergehen, sowie die Gründe für die Vorteile einer Terminologie für die intraepitheliale Neoplasie.

Schlüsselwörter

Duktal · Lobulär · Intraepithelial · Neoplasie · Hyperplasie · In-situ-Karzinom

Lobular and ductal intraepithelial neoplasia

Abstract

Lobular and ductal intraepithelial neoplasias reflect proliferations of immunophenotypically variable, biologically and morphologically diverse cells with a potential, not always realized, for progression to carcinoma by breaking through the barriers of the myoepithelial cell layer and basement membrane, ultimately invading the stroma.

Starting with the lobular and then the ductal proliferations, this review will address the evolution of our understanding of these lesions; the problems associated with the conventional terminology of ductal hyperplasia, atypical hyperplasia, and carcinoma in situ; and reasons for and advantages of the intraepithelial neoplasia terminology.

Keywords

Ductal · Lobular · Intraepithelial · Neoplasia · Hyperplasia · Carcinoma in situ

failed to show any LOH, one could argue that 20% of comedo DCIS are also nonneoplastic. It is important to also note that the comparison of alterations in IDH with those present in the common infiltrating duct carcinomas is most likely inappropriate. Maybe IDH should be compared to basal-like carcinomas that express CK5/6 or CK903–a feature that is characteristic of IDH.

Our answer to the question on combining AIDH and DCIS was also yes because the two are morphologically and immunohistochemically similar; they share significant similarities at the molecular level; and the only difference separating them is quantity [25].

It has been suggested that AIDH differs from DCIS in the location of subsequent carcinomas, with AIDH being a risk for both breasts, whereas DCIS indicates a risk for the ipsilateral breast [2]. It is doubtful that there is any validity to this statement, as Degnim et al. [4] have noted that women with AIDH actually have a higher risk for subsequent ipsilateral invasive carcinoma within 10 years of follow-up. Even if this were the case in studies based on premammographic material, it could be that complete excision of a small lesion (AIDH) equates the subsequent risk for invasive carcinoma in both breasts, while complete excision is far more difficult to attain in the case of larger lesions (DCIS), thus increasing the chances of ipsilateral recurrences. Assuming that there are differences in the behavior of AIDH and low-grade DCIS, do differences in behavior justify giving one a designation of cancer and the other a designation of noncancer? If so, why do we designate a 3-mm invasive carcinoma that practically never metastasizes or kills the patient as being the same as a 4-cm invasive carcinoma with its significant likelihood of nodal and distant metastases as well as significant chances that it will kill the patient? Finally, all subsequent invasive carcinomas following low-grade DCIS in one study actually occurred in the contralateral breast [24], in total contradiction to these claims.

Advantages of and rationale for adopting DIN

While waiting in anticipation of the „ideal" classification with incorporation of molecular findings, my preference is to use a terminology that causes the least anxiety among the patients, eliminates the use of drastically different terms of cancer and noncancer for the same lesion, and allows for individualized management. I believe that DIN is actually as close to the ideal terminology as we will get. Some of its advantages are as follows:

1 It diminishes the anxiety and emotional stress associated with the emotionally charged designation of cancer for the patient and her family.
2 It diminishes the impact of having two drastically different designations of cancer and noncancer applied to the same lesion by different observers, while allowing an individualized approach to management based on the quantity of the lesion just as we do for invasive carcinomas. For instance, a 3-mm or a 3-cm invasive carcinoma is designated the same, even though their behavior and management are drastically different.
3 It obviates upstaging up to 50–65% of breast fine-needle aspiration and core biopsy diagnoses from AIDH to grade 1 DCIS on subsequent excision biopsies.
4 It combines AIDH and low-grade DCIS in the category of DIN1, thereby diminishing a major source of interobserver variability.
5 It applies the unifying concept of intraepithelial neoplasia as it is already used in many other organs, including the cervix, vagina, vulva, prostate, pancreas, and colorectum.

Another advantage derived from this terminology is that we could drop the „invasive" or „infiltrating" qualification from breast carcinomas; the term carcinoma would be used only for lesions with stromal invasion.

What will our clinical colleagues think?

It is quite surprising that more of our clinical colleagues have not actually demanded that we switch to the DIN terminology. Why is it that gastrointestinal specialists, gynecologic oncologists, and genitourinary specialists have had no problems with the intraepithelial neoplasia concept replacing the carcinoma in situ terminology? If so many oncologists and surgeons in other subspecialties have switched, what is the issue with the breast specialists? Interestingly, in two excellent reviews, Leonard and Swain [13] state that „DCIS is a benign lesion," and Sakorafa et al. [22] refer to DCIS „as a lesion with malignant potential." If this lesion is benign and has only a potential for malignancy, why are we calling it a carcinoma?

Dr. Umberto Veronesi, a distinguished European oncologist, has actually advocated using the DIN and LIN terminology and replacing the T(is) of TNM classification by T(in). It is a simple switch that should be incorporated in TNM.

The concept of ductal intraepithelial neoplasia and the logic behind it are clear and easy to follow. It has been accepted as an alternate classification by WHO, and there is no need to delay bringing its advantages to our patients.

Conclusion

As we learn more about these neoplastic lesions, modifications and adjustments will become necessary, but there is no reason to continue using the emotionally charged terms of „LCIS" and „DCIS" while we are improving our knowledge base. Eliminating the term"carcinoma" for these intraepithelial lesions would also facilitate individualized treatment of patients. There are, without question, some small „DCIS" lesions that get no significant benefit, if any, from radiation therapy. Radiation therapy for these cases actually prevents the use and potential benefits of this therapeutic modality if a subsequent carcinoma develops in the same breast. With retention of the term „DCIS," however, many patients may even feel obligated to accept radiation therapy, and physicians may fear mal-

practice issues if they do not use radiation therapy for a „carcinoma."
The rapid advances in technology have made realities of many dreams. I look forward to a day in the near future when we will be able to completely eliminate these lesions simply by modifying the mammary microenvironment in which they proliferate, or even prevent their development by altering the lining cells of the duct system in women over 50 years of age.

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