Ductal Carcinoma *In Situ*: Pathology

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Rezumat

Carcinomul ductal *in situ* reprezintă un grup heterogen, din punct de vedere biologic și morfologic, de neoplazii intraductale proliferative ale țesutului mamar și de asemenea, o leziune precursoră importantă a dezvoltării carcinomului mamar invaziv, având o rată crescută de diagnosticare, datorită îmbunătățirii metodelor imagistice de diagnostic. Cu toate acestea, clasificarea exactă și diferențierea de alte leziuni ale țesutului mamar poate reprezenta o provocare pentru medicul anatomopatolog. Prin urmare, articolul de față evidențiază atât aspectul clinic, cât și macroscopic, dar și clasificarea bazată pe histomorfologie și imunohistochimie, pe lângă cele mai importante diagnostice diferențiale și tipuri speciale de carcinom ductal *in situ*.

Cuvinte cheie: carcinom ductal *in situ*, patologie

Abstract

Ductal carcinomata *in situ* (DCIS) are both biologically and morphologically a heterogeneous group of neoplastic intraductal proliferations of the breast tissue, they represent an important precursor lesion for the development of invasive breast carcinoma and their diagnosis increases due to improved imaging. Nevertheless, the exact classification and differentiation from other lesions of the mammary gland tissue is often challenging for the pathologist. Therefore, this article highlights both the clinical and macroscopic presentation as well as the classification based on histomorphology and immunohistochemistry in addition to the most important differential diagnoses and the special types of DCIS.

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Key words: ductal carcinoma *in situ*, pathology

Introduction

Ductal carcinomata *in situ* (DCIS) are genetically and pathomorphologically a hetero-geneous group of neoplastic intraductal proliferations of the breast tissue. They are considered non-obligate precancerous lesions of invasive breast carcinomas.

Material and Methods

A summary of established knowledge and new findings on DCIS.

Results

Clinical Presentation

Today most DCIS are detected via mammography by it's association with microcalcifications in more than 70%. These DCIS normally do not present as a palpable mass.

Mammography often underestimates the histologically determined extent in DCIS in approximately 30% (1), because microcalcification can be irregularly distributed. DCIS tend to grow along ducts and in clusters with spaces sometimes more than 10 mm between them (2).

Prognosis

In untreated DCIS, the risk of subsequent invasive carcinoma is about 50% (3,4). Carcinomas usually develop within 10 years (4,5), are usually of the non special type and are located in the same quadrant. Patients with DCIS can develop another DCIS or invasive carcinoma in the contralateral breast in 22% (6).

The higher the nuclear grade the higher the recurrence rate and the risk of progression to invasive carcinoma. The same goes for size

(especially more than 2.5 cm) and an incomplete removal (7). Lymph node metastases are found in 1-4.5% and are due to undetected (microinvasive) carcinomas due to "sampling errors". Therefore critical cases especially with high grade DCIS require extensive sampling and use of immunohistochemistry regarding myoepithelial markers (8).

Etiology

Etiological risk factors for DCIS are the same as for invasive breast cancer (9) for example nulliparity, late menopause or late age at first childbirth.

Macroscopic Appearance

DCIS rarely presents as a palpable or visible mass. Sometimes you can see pale fibrotic areas with yellowish material in duct structures resembling comedo-type necrosis (*Fig. 1*).

Figure 1. Macroscopic appearance of a later histologically confirmed high grade DCIS (author's archive)

Histopathology

Histologically DCIS are a heterogeneous group.

Classically DCIS is defined as an intraductal proliferation of neoplastic epithelial cells with atypia. DCIS shows a preserved myoepithelial layer (Fig. 2) and is restricted to the ductulo-lobular unit. The proliferates may show a variety of nuclear grades and growth patterns or architecture.

The architecture may be papillary, micro-papillary or solid. Focal or extensive comedo-necrosis may occur. Those are eosinophilic material consisting of cellular and nuclear debris within the duct lumen.

DCIS may involve the adjacent lobules, so called lobular involvement (Fig. 3).

Grading

For grading DCIS is characterized by nuclear grade (low, intermediate, high), presence or absence of comedo-necrosis and architecture, while emphasizing the nuclear grade (10,11). For nuclear grading, in addition to nucleus shape and nucleoli, the size of the nuclei must be taken into account (40x objective) (Table 1, 2).

Pathological Report

The WHO classification recommends documentation of the following parameters in a pathological report:

- grading;
- presence of necrosis;
- architecture;
- size [extent, distribution (continuous/discontinuous) pattern];
- resection margins (if positive: focal or wide; if negative: distance from resection margins in mm).
- presence or absence of: microcalcifications, wire probe, clips (for correlation with radiology report).

In the eighth edition of the UICC TNM classification DCIS is staged „pTis (DCIS)“ (12).

Figure 2. Preserved myoepithelium layer in DCIS high grade (p63, 10x) (author's archive)

Biomarkers

Determination of hormone receptors [estrogen and progesterone receptor (Fig. 8, 9)] in DCIS can be useful, but there is no international agreement or guideline. The evaluation is analogous to that of invasive breast carcinoma.

Her2 neu overexpression occurs especially in high grade DCIS (Fig. 10) and may differ from the expression in an accompanying invasive component (13).

DCIS as a precursor lesion of invasive breast cancer shows similar genomic alterations as invasive breast carcinomas, especially high grade DCIS (14). However, to date, there is no reliable molecular marker that indicates progression of DCIS to invasive carcinoma (15).

Special types

Papillary DCIS

Papillary DCIS consists of fine finger like

Figure 3. High grade DCIS with involvement of adjacent lobules (HE, 10 x) (author's archive)

Table 1. Grading

	nuclear grade	necrosis	calcification	architecture
Low grade	small, monomorphic	extremely rare	lamellar	mainly cribriform or micropapillary
Intermediate grade	moderate variability	maybe	lamellar or amorphous	variable
High grade	large, pleomorphic, irregular contours	often comedo-type	amorphous	mainly solid

Table 2. Nuclear grading (10)

Nuclear grade	shape	size	chromatin	nucleoli	mitosis
I low	uniform	1.5-2 times the size of an erythrocyte	regular	incon-spicious	rare
II intermediate	moderate variability	variable	coarse	sometimes prominent	maybe
III high	pleomorphic with irregular contours	> 2.5 times the size of an erythrocyte	coarse	prominent	brisk

Figure 4. DCIS low grade (He, 10 x)
(author's archive) **Figure 5.** DCIS intermediate grade (HE, 10 x)
(author's archive) **Figure 6.** DCIS high grade (HE, 10x)
(author's archive) **Figure 7.** DCIS high grade with nuclear pleomorphism and comedo-type necrosis (HE, 20x)
(author's archive)

shaped papillae with vessels as well as an atypical epithelial overcoat within a larger epithelial-lined ductal structure. While the fine papillae lack a myoepithelial layer, it is preserved in the outer ductal structure. These account for approximately 3% of all DCIS (16). As with other DCIS, grading is based on the nuclear changes, usually a grade 1 or 2 (16).

Solid papillary carcinoma in situ:

The term "solid papillary carcinoma in situ" is used when there are solid nodules with a sharp roundish contour and are localized, regardless of whether or not a myoepithelial layer is present (17). This type of tumor has an excellent prognosis with few reported lymph node metastases (18).

Paget disease

Paget disease of the nipple shows an intra-epidermal spread of atypical epithelial cells, almost always associated with a high-grade DCIS, which spreads from the subareolar ducts to the epidermis (19,20).

Rare subtypes

DCIS can consist of apocrine, neuroendocrine, signet-ring or clear cells.

Differential diagnosis

The most often and challenging differential diagnosis, especially for low grade DCIS include UDH and ADH.

UDH (usual ductal hyperplasia) shows intraductal epithelial proliferation of benign and regularly distributed whorled cells. There are often slit-like lumina located in the periphery. The cells are irregularly arranged with slightly irregular nuclei. Immunohistochemistry with a high molecular weight cytokeratin reveals a mosaic-like pattern. A preserved myoepithelial layer is seen (21).

ADH (atypical ductal hyperplasia) is an intraductal proliferation that can be differentiated from low grade DCIS only by its size. Both show a preserved myoepithelial layer and are similar in architecture and cell morphology. ADH shows micropapillary epithelial pullouts

Figure 8. Estrogen receptor expression in DCIS high grade (10x) (author's archive)

Figure 9. Progesterone receptor expression in DCIS high grade (10x) (author's archive)

Figure 10. Her2 neu overexpression in DCIS high grade (10x) (author's archive)

or solid proliferates with round or punched out lumina. Compared to UDH the cells are

monomorphic and proliferation is more rigid. ADH can be diagnosed if a maximum of two involved duct structures within less than two involved sites is present and if the lesion is less or equal 2 mm (only applies if ducts are completely affected) (22).

Conclusions

Although DCIS is a long known entity, on the pathology side, better predictive factors, like the nuclear grade needs to be established to predict more safely which DCIS progresses into an invasive carcinoma in order to develop better therapy concepts.

Conflict of Interest

No conflict of interests.

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