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REVIEW ARTICLE

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DCIS, cytokeratins, and the theory of the sick lobe

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Abstract We postulate that ductal carcinoma in situ (DCIS), and consequently breast carcinoma in general, is a lobar disease, as the simultaneously or asynchronously appearing, often multiple, in situ tumor foci are localized within a single lobe. Although the whole lobe is sick, carrying some form of genetic instability, the malignant transformation of the epithelial cells may appear localized to a part or different parts of the sick lobe at the same time or with varying time difference. It may be confined to terminal ductal lobular units (TDLUs), to ducts or both. The malignant transformation is often associated with aberrant branching and/or aberrant lobularization within the sick lobe. Involvement of a single individual TDLU or of a group of adjacent TDLUs generates a unifocal lesion. Multifocal lesions appear if distant TDLUs are involved. Diffuse growth pattern in DCIS indicates involvement of the larger ducts. The extent of the involved area in multifocal or diffuse cases varies considerably. Diffuse growth pattern with or without evidence of aberrant arborisation within the sick lobe seems to characterize a subgroup of DCIS with unfavourable prognosis. In this paper, we discuss the anatomical, embryological and pathological background of the theory of the sick lobe and present supporting evidence from modern radiological breast imaging, long-term follow-up studies and from our own series of 108 DCIS cases.

Keywords Breast · Ductal carcinoma in situ · Cytokeratins · Neoplasia · Hypothesis

Introduction

Breast carcinoma is a heterogeneous and progressive disease with many variations in morphological appearance, which has always made attempts of classification of breast tumors very difficult. Mammography screening during the last decades has changed the panorama of breast carcinoma, detecting small invasive tumors in asymptomatic women and also detecting malignant lesions in their non-invasive state [3, 16]. Under the circumstances of adequate surgical removal of the lesions, proper histopathologic work-up and systematic mammographic-pathologic correlation, this evolution offers the opportunity of studying breast carcinoma at the earliest stages in its natural history, which in turn may offer a key to better understanding the many variations of breast cancer morphology.

Classical whole organ studies had long ago demonstrated that the vast majority of in situ and invasive breast carcinomas are multifocal/multicentric/diffuse [10, 12]. However, the traditional technique used routinely in most breast pathology laboratories today does not allow repetition of the results of whole organ studies in most cases. The "modern" approach of focusing on histological, immunohistological and molecular analysis of the dominant invasive lesion may lead to underestimation of the importance of the alterations in the tissue adjacent to the dominant mass. In our laboratory, the diagnostic routine is specially adapted to the work-up of quadrantectomy specimens (the method of choice in breast conserving surgery in Scandinavia). This method of two- and three-dimensional large (up to 10×8 cm) histological sections gives the contiguous piece of tissue necessary for proper analysis of the extent and distribution of the lesions belonging to a breast carcinoma and represents an ideal background for detailed and systematic radiopathologic correlation [13, 31, 33]. Based on our 20 years experience and more than 5000 consecutive breast cases documented and analysed this way, we have become more and more convinced that the multiple malignant lesions exhibit a lobar distribution within the breast. Thus, we postulate that ductal carcinoma in situ, and consequently breast carcinoma in general, is a lobar disease, which means that the simultaneously or asynchronously appearing, often multiple, in situ (and invasive) tumor foci belong to a single lobe in one breast [34]. While in situ carcinomas keep their lobar distribution

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during their entire development, invasive carcinomas may step out from this frame and grow beyond the borders of the sick lobe, especially in their advance phase.

The diagnosis of breast carcinoma always reflects the actual status of the process of malignant transformation within the sick lobe in the moment of perception. Prolonged time of evolution of the neoplastic process may lead to development of new tumor foci and/or to growth of the already existing foci. Thus, the morphology of breast carcinoma is clearly time-related, which means that the malignant transformation of the cells within the sick lobe may depend on complex genetic-biological timing.

Complex lobar anatomy of the breast

The breast is a glandular organ with lobar morphology [5]. A typical lobe consists of one lactiferous duct opening on the nipple, branching into segmental, subsegmental and terminal ducts and ending up in thousands of lobules. The terminal duct and the corresponding lobule represent the so-called terminal ductal-lobular unit (TDLU), which is considered to be the most important morphologic-functional unit in the breast [32, 36]. Although rare anastomoses between the lobes have been described in one study [22], the breast lobes are considered to be well-defined individual units in the related literature [11, 18]. However, the lobar division of the breast parenchyma is complex, with considerable variation in origin, size and shape of the lobes [5, 11, 18, 31].

A normal lobe of the breast is a complex dynamically evolving and involuting structure during the woman's entire lifetime [31]. There are relatively few TDLUs before puberty [35]. During the reproductive period the numerous TDLUs undergo cyclical changes following the menstrual cycle [17]. The number of the TDLUs is highest during the period of late pregnancy and lactation and is substantially reduced after the menopause [33]. Thus, TDLUs may appear and disappear, the number of them being dependent on the woman's age, constitution and hormonal status. This is probably correct for the smaller ducts, too. The number of the lactiferous ducts and the number of the openings on the nipple is, however, independent of hormonal influences and age. Thus, the number of the breast lobes is constant during the woman's lifetime, but their size and shape and the number of their ducts and lobules varies and depends on anatomical variations, hormonal and age related influences [31]. The actual morphology of the lobe is maintained by the finely regulated equilibrium of development and involution of the ducts (arborisation) and lobules (lobularization).

In one study [11], the breast lobes varied in size, representing between 2% and 23% of the breast volume. Although a malignant transformation may lead to considerable enlargement of the sick lobe, the original size of the lobe may be crucial in determining the extent of the eventually developing disease and the chances for successful breast-conserving surgery. The surgical method of quadrantectomy (segmentectomy) represents an attempt to radically excise the sick lobe and not only the radiologically and/or clinically evident lesion(s). As the lobar morphology of the breast is complex, the surgical intervention is often inaccurate (with local recurrence rate up to 30% in cases without radiotherapy) [24].

Embryological background

The lobes of the breast (the epithelium and the myoepithelium of their ducts and lobules) are of ectodermal origin. During the 21st week of the intrauterine life, buds from the embryonal ectoderm are formed as non-luminated, solid protrusions into the embryonal mesenchyme [2]. All the buds represent an initiation of one potential breast lobe, but some of them probably are abortive. Some of the buds (at least those in the accessory breasts developing along the embryonal mammary line) disappear during intrauterine life. Luminalization begins during the 26th week [2]. The next steps are ramification (branching of the luminated buds, forming smaller and smaller ducts) and lobularization (forming the lobules as groups of blindly ending vesicles on the terminal ducts) [15]. The ramification process is almost completed during intrauterine life, while lobularization mainly characterizes the postpubertal period [33].

Luminalization of the buds, ramification and lobularization represent a complex process related to changes of the expression of different genes and to consequent changes in the phenotype of the epithelial cells. This process can be successfully monitored, determining the cytokeratin (CK) phenotype of the structures of the breast at different stages of intrauterine development. The buds in the initial stage have the same immunophenotype as the basal cells in the embryonal ectoderm and express CK14, vimentin, S-100-beta and p63 [2]. During the period between weeks 21–26 of intrauterine life, expression of CK17, CD10 and alpha-smooth muscle actin appears [2, 15]. Luminarization of the buds is associated with the appearance of cells expressing CK19, while ramification is related to cells not expressing CK19. Lobularization, in turn, seems to be associated with expression of CKs 8 and 18 in the epithelial cells [2, 15]. As demonstrated in several studies, the hyperplastic breast epithelium exhibits "basal cell type" CKs, but DCIS does not [23].

The embryonal development of CK phenotype within the breast lobe may reflect a complex and sensitive genetic regulatory mechanism behind the processes of initialisation, arborisation and lobularization. The similarity of the neoplasia-related and embryonic phenotypic variations may indicate that the malignant transformation is somehow related to lobularization and/or arborisation within the sick lobe, targeting and altering these processes. According to our observations on two- and three-dimensional large histologic sections and to the experience from radiopathologic correlative studies, low-grade DCIS targets most often the process of lobularization while the high-grade DCIS may also alter the process of arborisation.

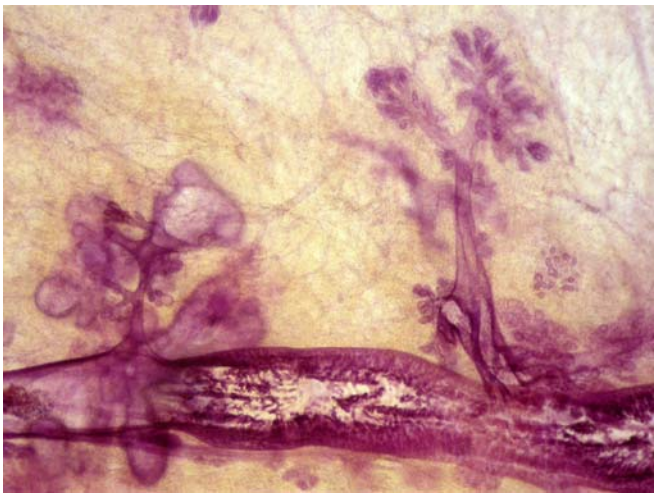

Fig. 1 DCIS involving a segmental duct, but not the related terminal ducts and TDLUs (thick section image, 20×) Note the regular branching into relatively long, narrower ducts

In addition to changes related to the epithelial cells, the embryonal mesenchyme surrounding the mammary buds, and partly the newly formed ducts also exhibits some changes. Overexpression of tenascin C, as demonstrated by immunohistochemistry, is considered to be a sensitive indicator of remodelling of the mesenchyme into a specific periductal stroma [28]. Thus, tenascin C overexpression may represent an indirect indicator of initialisation of a breast lobe during the embryonal period and a sign of arborisation within the lobe. Tenascin C overexpression can also be demonstrated surrounding some duct-like structures in a proportion of cases of (often high-grade) DCIS [14, 28], which may additionally prove the involvement of this type of malignancy in the process of arborisation within the sick lobe. This phenomenon is sometimes designated as "duct neogenesis" [30].

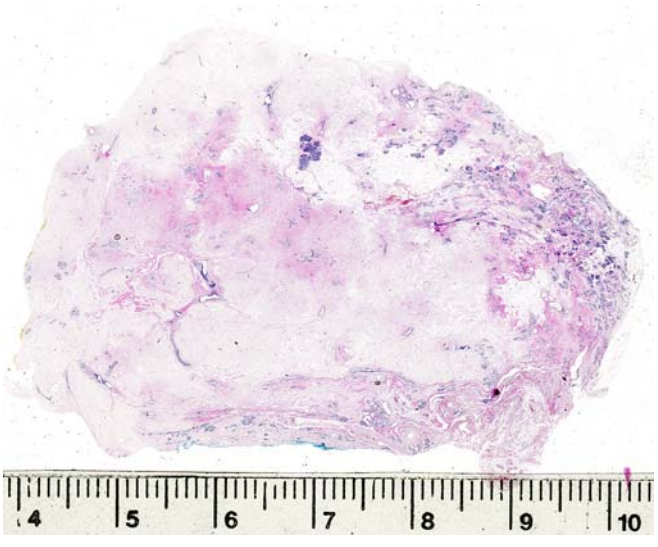

Fig. 2 Unifocal lesion in DCIS. Large histologic section

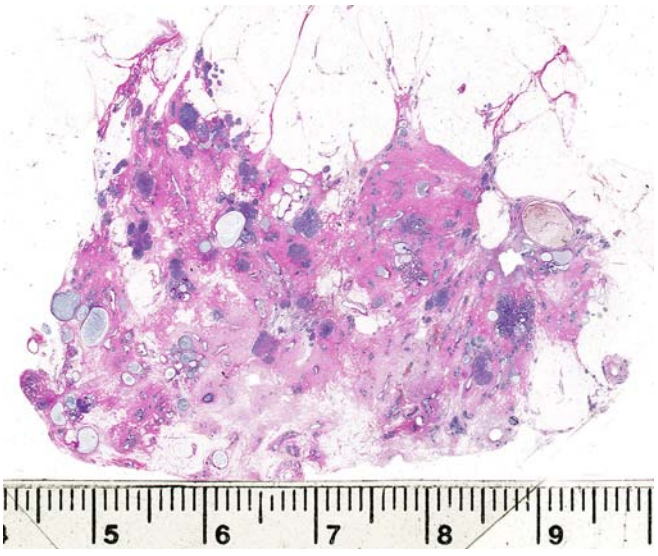

Fig. 3 Multifocal DCIS involving many distant TDLUs, leaving uninvolved tissue in between

Subgross morphology of ductal carcinoma in situ

Our observation based on examination of the large histologic sections and stereomicroscopic analysis of three-dimensional large thick sections, in concordance with the results of previous published similar studies [8, 9] can be briefly summarized in the following. Structures of carcinoma in situ may be demonstrated in TDLUs as well as in ducts. The ductal epithelium may be involved without demonstrable DCIS in the related TDLUs (Fig. 1). The ductal epithelium may be discontinuously involved with "gaps" exhibiting seemingly normal epithelium [9].

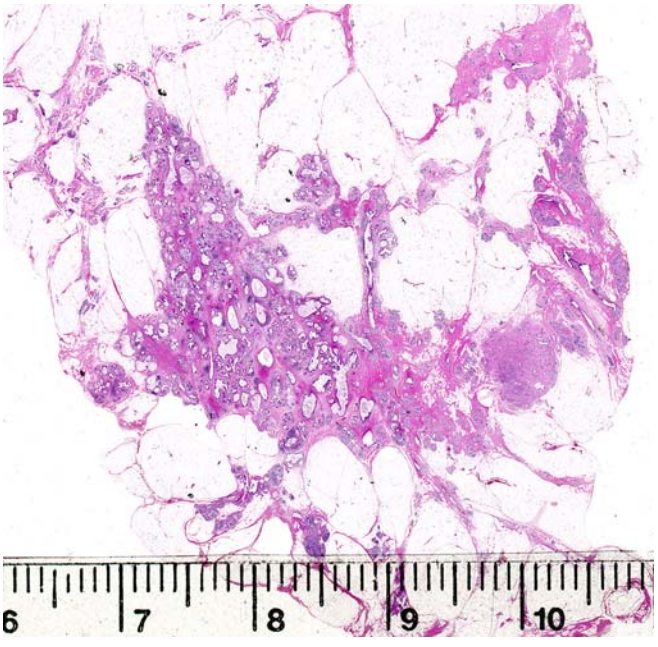

Fig. 4 Diffuse growth pattern in DCIS: the lesion involves the ducts system without well-outlined TDLUs in the left half of the image. The round structure to the right is a fibroadenoma

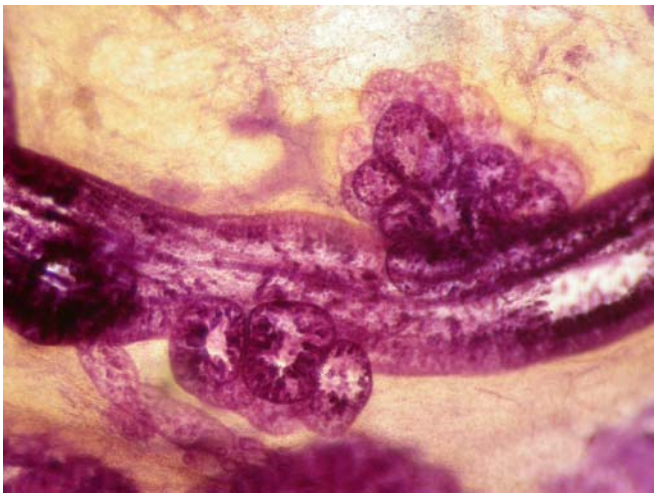

Fig. 5 Aberrant arborisation in DCIS. Note the absence of narrower branches as compared with previous image in Fig. 1 (thick section image, 20×)

The presence of the structures of an in situ carcinoma in a TDLU leads to considerable enlargement and distortion of this structure. The size of the involved individual TDLUs may vary between 1–2 mm to 20 mm or even more. The enlarged TDLU is regularly perceived as a round (spherical) or oval, well outlined structure (Fig. 2). If there are several distant TDLUs containing structures of in situ carcinoma, they are also seen as individual, well-delineated lesions, giving the impression of multifocality of the malignant process (Fig. 3). Involved TDLUs adjacent to each other may form a conglomerate, where the units are no longer separable as individual on radiology or gross examination. In addition to an enlarged single TDLU, this conglomerate is another example of the unifocal lesions. Involvement of the larger ducts may lead to their dilatation, but the long, branching tree of the involved duct system is perceived rather as a diffuse network of tubes than a well-outlined individual structure (Fig. 4). In conclusion, DCIS may manifest as a unifocal, multifocal or diffuse lesion (as well as a combination of multifocal and diffuse lesions) indicating involvement of one individual TDLU or a conglomerate of adjacent TDLUs (unifocal DCIS), simultaneous involvement of several distant TDLUs (multifocal DCIS) or involvement of the larger ducts (diffuse DCIS).

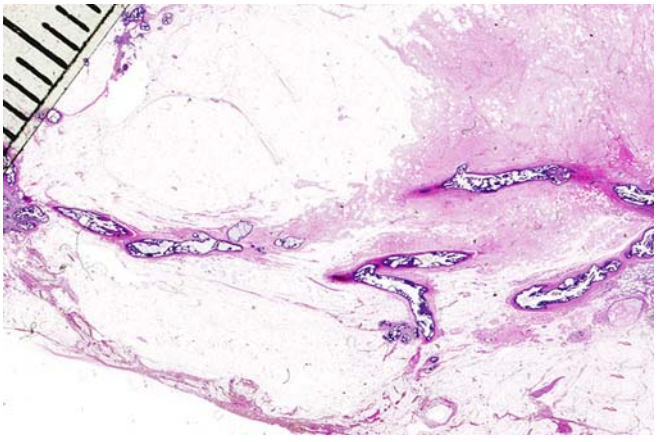

Fig. 6 Duct involvement in DCIS without evidence of altered arborisation. The number of the involved ducts corresponds to normal anatomy and the branching is regular

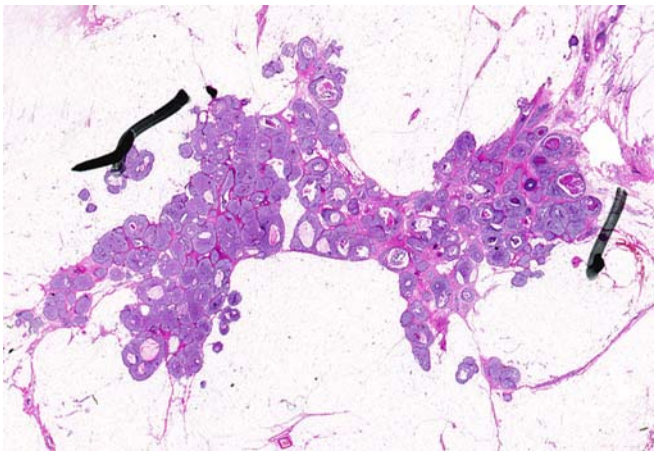

Fig. 7 DCIS with evident disturbance in arborisation as the number of the duct-like structures exceed the anatomically expected number (duct-neogenesis)

While involvement of the TDLUs alters these structures on a relatively uniform way, distending and distorting them similarly, involvement of the ducts may or may not be associated with different changes in ramification of the duct system. In the normal situation, the ducts give raise to smaller and smaller branches, which end up in TDLUs. If this process is altered, the ducts may give abortive branches (Fig. 5) without narrower ducts and TDLUs. In more severe cases, an abnormally large number of duct-like structures are seen in the area of the in situ carcinoma, regularly lacking smaller branches and TDLUs. Already, the tightness of the ducts indicates that they are newly formed, "neogenetic" and cannot represent a part of an anatomically normal lobe (Figs. 6 and 7). As these duct-like structures are often surrounded by a remodelled stroma overexpressing tenascin C (and regularly associated with periductal lymphoid cell infiltration), we assume that this phenomenon corresponds to an aberration in the process of arborisation within the sick lobe.

Theory of the sick lobe

Based on the anatomical, embryological and pathological data discussed above, we postulate that ductal carcinoma in situ, and consequently breast carcinoma in general, is a lobar disease. This means that the simultaneously or asynchronously appearing, often multiple, in situ tumor foci are localised in a single lobe of one breast. We assume that this sick lobe is genetically malconstructed from birth, carrying some kind of genetic instability from its initiation during fetal life. Further accumulation of genetic changes during the decades of the postnatal period may lead to malignant transformation of the epithelial cells in any part of the sick lobe. We believe, that this is a life-long process initiated

during the fetal period of life, which can be influenced or even interrupted by radical excision of the sick lobe and, possibly, with other therapeutic interventions. In addition to malignant transformation at the cellular level, there are two sensitive points in morphogenesis of the sick lobe, which are also regular targets of the neoplastic events: the process of lobularization and the process of arborisation. Altered lobularization is regularly seen in the majority of cases of DCIS, while different alterations in arborisation represent the hallmark of high-grade DCIS.

The biological timing of the malignant transformation of the cells within the sick lobe may be very variable [4, 6, 7]. Simultaneous involvement of most of the epithelial cells within the sick lobe leads to rapid development of extensive, diffuse, usually high-grade, DCIS. The malignant transformation may also be microfocal and localized to one or more individual TDLUs (as in low-grade DCIS, lobular carcinoma in situ or in atypical ductal or lobular hyperplasia). In these cases, the transformation may involve very distant TDLUs within the sick lobe with time difference varying up to several years or decades.

Supporting evidence

Radiological observations on individual extensive DCIS cases support the theory of lobar distribution of multiple and diffuse lesions. Cases with nipple discharge in extensive micropapillary DCIS may manifest such a distribution of the individual filling defects in a lobe filled with contrast on galactography (Fig. 8a and b). The microcalcifications on the mammogram in high-grade DCIS may also exhibit a distribution resembling the anatomy of the duct system of a single lobe. Magnetic resonance images in cases of high-grade DCIS often outline a whole involved breast lobe, including the lactiferous ducts (Fig. 9), [20].

We studied a series of 108 consecutive DCIS cases diagnosed in period 1996–2001 on our department. The so-called “special type DCIS” such as intracystic papillary carcinomas and papillomas with DCIS were excluded, as their growth pattern depends on the morphology of pre-existent lesions. Most of the cases were initially treated with breast conserving surgery and radiotherapy. In 30 cases, based on close or dirty margins (less than 10 mm circumferential margin), the surgical intervention was completed with re-resection or mastectomy. The cases were reviewed by the author and followed up to 31 December 2004. The cases were grouped according to their distribution as unifocal, multifocal and diffuse (as defined above), according to their extent (the area including all the structures corresponding to DCIS within a large histologic section) as extensive (more than 20 mm in largest diameter) and non-extensive. They were also graded as low-grade (low nuclear grade without central necrosis), intermediate (low nuclear grade with central necrosis or intermediate nuclear grade with or without necrosis) and high-grade (high nuclear grade with or without necrosis). The diffuse cases were further divided into a neogenetic group (with evidence of alterations in arborisation of the lobe often

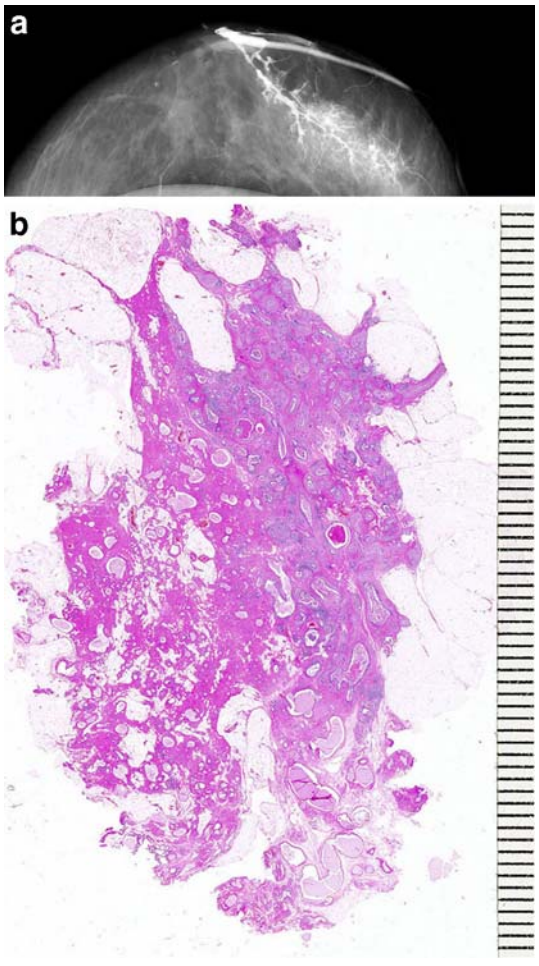

Fig. 8 **a** Galactogram showing a lobe-like distribution of filling defects and parenchymal lesions surrounding the duct system. **b** The corresponding large histologic section showing extensive, diffuse DCIS

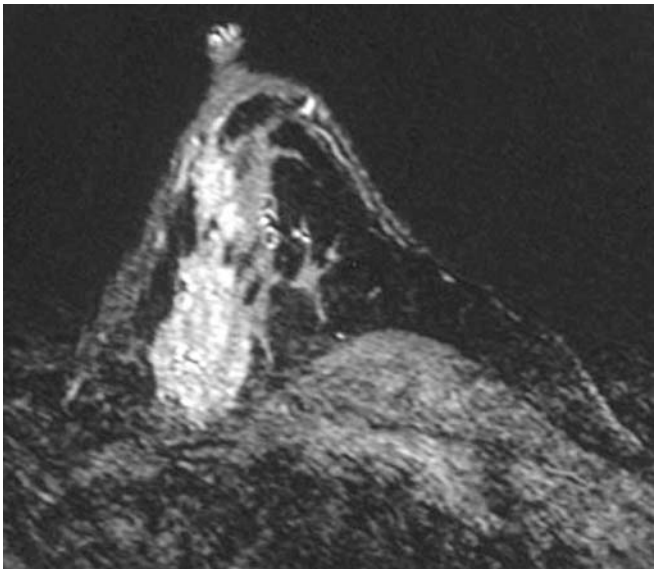

Fig. 9 Lobar distribution of the lesions in a case of high-grade DCIS indicated on a magnetic resonance image

Table 1 Local recurrences by extent and distribution of the lesions in 108 consecutive cases of ductal carcinoma in situ

Extent	Unifocal	Multifocal	Diffuse, non-neogenetic	Diffuse neogenetic	Mixed	Sum
Extensive	0/0	4/24	3/18	4/14	0/2	19% (11/58)
Non-extensive	1/41	0/5	0/3	0/1	0/0	2% (1/50)
Sum	2% (1/41)	14% (4/29)	14% (3/21)	27% (4/15)	0% (0/2)	11% (12/108)

manifesting in tightly packed ductal structures without TDLUs) and a non-neogenetic group. The results are presented in Table 1 and in the diagram in Fig. 10 and indicate that the extensive cases recurred significantly more often compared to non-extensive ones, the diffuse neogenetic subgroup being the prognostically most unfavourable. The same study also demonstrated that low-grade DCIS tends to be multifocal, the cases with intermediate grade tend to be unifocal, while the diffuse cases are mostly of high grade. In fact, the duct-neogenetic subgroup contained exclusively high-grade DCIS cases. One patient with extensive high-grade DCIS without demonstrable invasion, but with evident alterations in arborisation of the duct system developed metastases and died later on of the disease, as was verified on autopsy.

Several long-term follow-up studies have demonstrated that mammographially detected casting-type microcalcification are associated with higher risk of local recurrence of DCIS and with associated invasive carcinoma than the other types of microcalcifications. [21, 26]. As the casting-type microcalcifications most often indicate presence of duct-neogenetic high-grade DCIS, these studies represent an indirect evidence for unfavourable prognosis of this DCIS subtype. Further, small invasive breast carcinomas (less than 15 mm in size) have a more unfavourable outcome in overall survival if associated with casting type microcalcifications [29, 30]. The other types of microcalcifications indicating presence of intermediate or low-grade DCIS, were not associated with increased mortality in the cited studies.

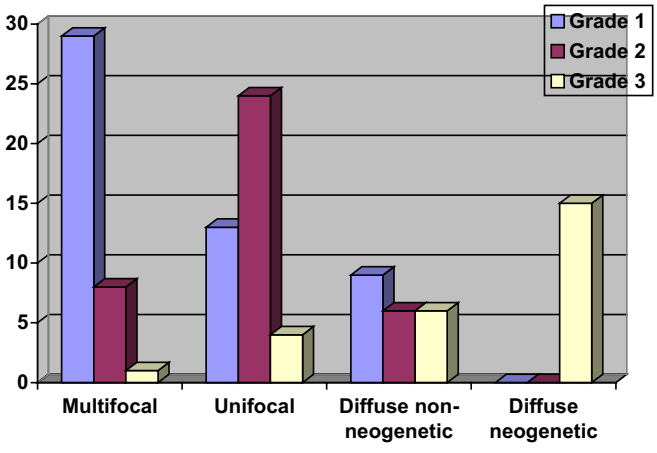

Fig. 10 Grade distribution by growth pattern in 108 consecutive cases of ductal carcinoma in situ

The presented evidence indicates that diffuse involvement of large areas of the sick lobe in DCIS, with altered arborization of the duct system is a characteristics of the unfavourable subgroup of DCIS. Extensive and/or multifocal involvement of the sick lobe with altered lobularization, but with normal arborization is typical of grade I, less often grade II DCIS and is associated with higher local recurrence rate compared to the unifocal cases. The unifocal DCIS cases seem to represent the prognostically most favourable subgroup.

Discussion

Several investigators have previously assessed the extent and the distribution of carcinoma in situ within the breast, however, multicentricity and multifocality in breast carcinoma in situ remains a debated topic in the literature. The reported incidence of multicentricity ranges from 0 to 78%, depending on the used criteria and methods [9, 27]. The group of Holland and Faverly, using the technique of whole organ sectioning and thick section images, demonstrated that ductal carcinoma in situ may exhibit either a continuous or a discontinuous growth; they divided the cases with discontinuous growth into multifocal (less than 4 cm gaps between the foci) and multicentric (larger gaps) and concluded that most of the in situ carcinomas are unicentric (showing a segmental distribution) [9]. Page believe that "multicentricity is a misconception" and that the majority of in situ carcinomas are limited to a single focus with continuous growth pattern, which may be perceived in histological preparations as discontinuous after artificial fragmentation [25]. Andersen et al. divided the cases of ductal carcinoma in situ into microfocal, tumor forming, diffuse and mixed. Their microfocal cases correspond to the low-grade lesions targeting the terminal ductal-lobular units of the sick lobe. The diffuse cases in their series mostly correspond to the diffuse extensive high-grade cases in our concept [1]. Analysing the three-dimensional distribution of in situ and invasive breast carcinomas, Mai et al. concluded that the in situ component is often located in a single duct, the small invasive carcinomas appear adjacent to the in situ and the whole tumor may form a pyramid with the summit towards the nipple [19]. Thus, the suspicion that DCIS and invasive breast carcinoma may have a segmental (lobar) distribution has been expressed previously. The theory of the sick lobe adds the dimension of time to morphological findings and connects the malignant transformation to an anatomically well-defined

structure of the breast lobe and to disturbances in the dynamically maintained processes of arborisation and lobularization within it.

The most widely accepted concept of breast cancer development, the Wellings concept, connects the initiation of the malignant transformation to changes in the TDLUs [36]. According to this concept, breast carcinoma develops from the individual TDLUs with secondary involvement of the ducts by spread of the tumor cells as well as invasion of the tumor cells through the basement membrane. This concept is considered valid in many benign breast lesions, too, with only a small minority of the lesions developing primarily in the ductal system (e.g. papillomas). Although many in situ carcinomas exhibit the distribution corresponding to the terminal units, the continuous "spread" of the in situ cancer along the ducts in a several cm large area, seen not rarely in cases of DCIS, is difficult if not impossible to explain by the origin of the process in a few individual 1–2 mm large units; the signs of migration of the tumor tissue are seldom evident. Studying the three-dimensional morphology of the early stage breast carcinomas, however, evidenced involvement of large areas of the ductal tree in addition to lobular involvement or, at least partially, without lobular involvement. As discussed above, new insight into this process gave the recent anatomical and embryological studies, and first of all, the new radiological imaging methods enabling the definition of a new concept, the theory of the sick lobe, challenging the classical concept of Wellings. The theory of the sick lobe, in contrast to the concept of Wellings, is based on a hypothesis that the malignant transformation may appear in any part(s) of the sick lobe, not only in the TDLUs. The so-called "pagetoid spread" or other forms of tumor spread in DCIS may be explained as malignant transformation of the cells of the ducts distant to the TDLU, rather than spreading of the malignant cells from the involved TDLU. Thus, the biological timing of the malignant transformation, the involved structures of the lobe and the involved morphogenetic processes (lobularization and arborisation) determine the morphology and the natural history of DCIS subtypes.

Consequences/future perspectives

Provided that the theory of the sick lobe is correct, the extent of the disease in breast cancer in situ can no longer be defined as the area including all the detected lesions, but becomes equal to the area delineated by the borders of the sick lobe. Radical interventions have to shift their target from the detected lesion(s) to aiming to excise or otherwise destroy the entire sick lobe. Multicentricity of breast carcinoma may be redefined as the presence of two or more sick lobes within a single breast, the large majority of cases remaining unicentric. Multifocality, in turn, may be defined as presence of more than one individual tumor foci within the sick lobe.

As the sick lobe is formed already during intrauterine life, this theory assumes that prenatal influences of different noxious factors may play a role in predisposing the individual to breast cancer. On the other hand, decades of postnatal life are necessary for the development of breast carcinoma. The surgical intervention itself interrupts this otherwise life-long process only if it leads to excision or destruction of the entire sick lobe. Involvement of different structures and processes into the morphogenesis of breast carcinoma may indicate different pathways of malignant transformation in various categories of breast carcinoma.

Further development of modern imaging methods may play a crucial role in proving or questioning this theory, as methods effectively outlining the sick lobe and the lesions within it at the same time may become routinely used. If proved as correct, in general or in a substantial proportion of cases, the theory of the sick lobe may represent a real challenge in diagnostic breast pathology in the near future.

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