Microinvasive Carcinoma

12

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Microinvasive breast carcinoma is a rare lesion, in which foci of intralobular or intraductal carcinoma are associated with one or more microscopic foci of atypical cells located outside the basement membrane, in the adjacent intralobular or interlobular stroma [1]. In rare cases, microinvasive carcinoma can be identified without an adjacent in situ lesion (Fig. 12.1). Frequently, microinvasive carcinomas have a multifocal character. There is no international consensus regarding this lesion and its definition and all definitions are arbitrary. Some authors consider that the maximum size of the invasive focus should be 1 mm for the diagnosis of microinvasive carcinoma [1]. Other authors define microinvasive carcinoma as having a single focus with a maximum size less than 2 mm, while others consider 2–3 foci, none exceeding 1 mm in diameter [2]. However, the presence of microinvasive breast carcinoma and distinction from in situ carcinoma may have therapeutic and prognostic implications, consequently recognizing it is of paramount importance. During microscopic examination, the pathologist establishes microinvasion on the basis of several morphological criteria. Sometimes, these criteria may be difficult to assess and may not be perfectly reproducible among pathologists.

Microinvasive breast carcinoma does not display clinical signs and can only be identified on mammography and macroscopic examination due to its association with intraductal or, rarely, intralobular carcinoma. As a consequence, microinvasion is only detected when examining the microscopic slides, making the role of the pathologist essential in the diagnosis of this lesion.

Microscopically, invasive tumor cells usually invade the stroma by forming small nests or tubular structures, while in other cases the cells are isolated (Fig. 12.2). Sometimes we can only detect tongue-like projections of cohesive cells that have not lost continuity with the in situ component through a minor disruption of the basement membrane. Most of the time, however, the invasive cells are found dissociated from the in situ component, infiltrating the stroma. Neither the microscopic type nor the grade of malignancy can be established due to its small size, but mostly, the morphological appearance suggests an infiltrating carcinoma of no special type (NST). A desmoplastic stroma and an inflammatory infiltrate can be noticed around microinvasive foci (especially if the in situ component is of high grade) (Fig. 12.3). Consistency in the recognition of microinvasion significantly improves with the use of additional stains. Immunohistochemically, the absence of myoepithelial cells around the clusters of invasive tumor cells can be demonstrated using stains for Calponin, smooth muscle myosin heavy chain (SMMHC), p63 (these markers being reported with excellent sensitivity and specificity) and more recently, p40, D2–40. Ideally, the three markers should be used in association. However, it is important to keep in mind that myoepithelial cells surrounding spaces involved by ductal carcinoma in situ may show phenotypic differences from normal myoepithelial cells [3, 4]. Ductal carcinoma in situ-associated myoepithelial cells show decreased expression of one or more myoepithelial markers (such as SMMHC, CD10, CK5/6, calponin, p63, p75, smooth muscle actin) when compared with normal myoepithelial cells. As such, for practical implications, it is always advisable to use a panel of markers. Also, the absence of the basement membrane around the nests of microinvasive cells can be demonstrated using Laminin or Collagen IV. However, careful consideration should be given to rare situations in which invasive carcinomas may produce basement membrane components. It is always advisable to combine myoepithelial markers and basement membrane markers with a keratin stain, which can also better determine the extent of the invasive component, especially in cases in which the tumor cells are isolated.

In routine practice, the evaluation of ER, PR, Ki-67, and HER2 is recommended in microinvasive foci as for any other

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foci of certain invasive tumors. In some cases, however, this is not possible due to the small size of the foci. In these particular cases, these four markers can be reported in the adjacent in situ lesion since the molecular profile of the two lesions (in situ and microinvasive) is identical in most of the cases.

The pathology report of a microinvasive carcinoma must necessarily include the number of the microinvasive foci, their size (in case there are multiple foci, the size of the largest one must be mentioned), as well as any special test that was performed for the diagnosis. It is essential that multiple sections should be performed in any intraductal carcinoma (especially if it is extensive) in order to exclude the presence of microinvasive foci. Similarly, it is recommended that multiple sections should be performed in a microinvasive lesion to exclude the presence of an invasive carcinoma of larger size.

Differential diagnosis is performed with intraductal carcinoma. Of interest, the features of ductal in situ carcinoma associated with microinvasion are the following: more extensive in situ component, high-grade, central necrosis, and periductal inflammatory infiltrate. In intraductal carcinoma, the branching layout of the duct on a small cross section can sometimes mimic adjacent invasive foci (Fig. 12.4). In most of these cases, the myoepithelial cells can be detected on hematoxylin-eosin slides (Fig. 12.5). In difficult cases, however, laminin or collagen IV allows the identification of a continuous basal membrane around these foci. If around such a duct with in situ carcinoma there are small portions where laminin is negative and the microscopic appearance suggests a microinvasion, the microinvasion focus being directly connected to the duct, the lesion should be reported as possibly microinvasive. It is noteworthy, however, that some intraductal carcinoma lesions may sometimes have a discontinuous basement membrane, and some microinvasive foci may sometimes have areas of basement membrane around them, so that the diagnosis remains a morphological one. Also, problems in distinguishing ductal in situ carcinoma from microinvasion occur when the in situ component may involve the lobules, sometimes with distortion of involved spaces, tangential sectioning, crushed artifact, cautery effect, and artifactual displacement of cells in ductal in situ lesions. In all these situations, the lesion can be overdiagnosed, but there are also situations in which the microinvasive carcinoma can be under-diagnosed (when the microinvasive foci can be overlooked or may not be sampled). Also, because differential diagnosis includes frank invasive foci with a diameter greater than 1 mm, invasive foci should be carefully measured under the microscope.

Cases of previous biopsy in which the area is associated with architectural distortion, inflammation, hemorrhage, and fibrosis may pose difficulty in diagnosing. Microinvasive diagnosis is difficult especially if intralobular or intraductal carcinoma foci are associated with radial scars, sclerosing adenosis, or complex sclerosing lesions [3]. In these situations, it is important to remember that myoepithelial cells associated with benign sclerosing lesions of the breast may show immunophenotypic differences from normal myoepithelial cells. In one published study, myoepithelial cells associated with benign sclerosing lesions showed reduced expression of SMMHC, CD10, p63 and calponin [3]. This needs to be taken into consideration when selecting myoepithelial markers to help distinguish benign sclerosing lesions from invasive breast cancer.

Microinvasive carcinoma is rarely associated with lymph node metastases. Lack of consensus regarding the definition of the lesion makes the predictability of its evolution difficult, although it is usually favorable.

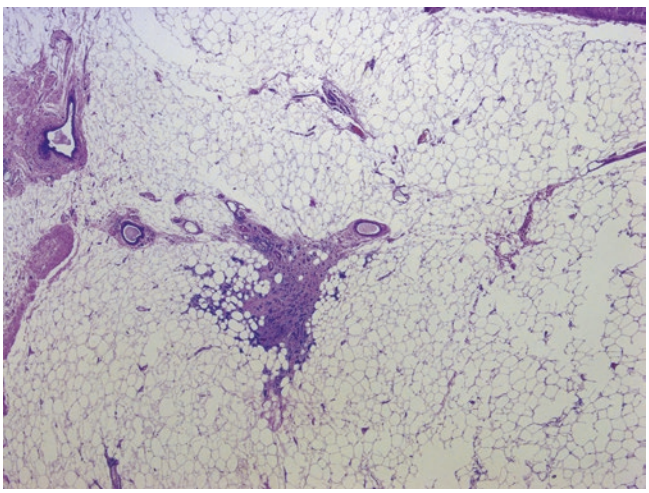

Fig. 12.1 Focus of microinvasive carcinoma (size <1 mm diameter) identified at microscopic examination lacking an adjacent in situ lesion

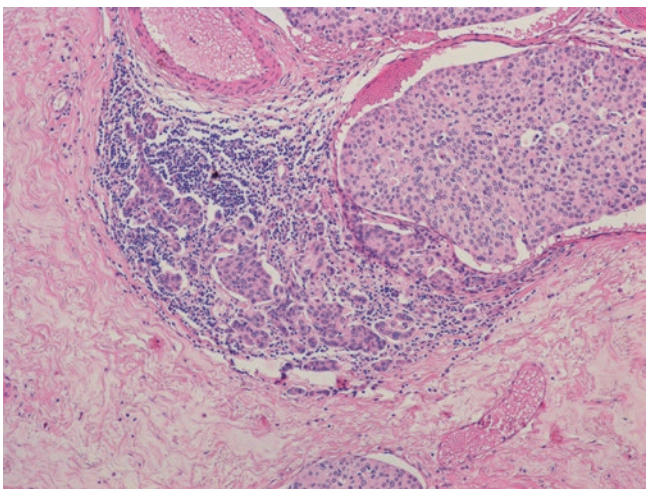

Fig. 12.2 Microinvasive carcinoma: invasive tumor cells invade the stroma in the vicinity of DCIS

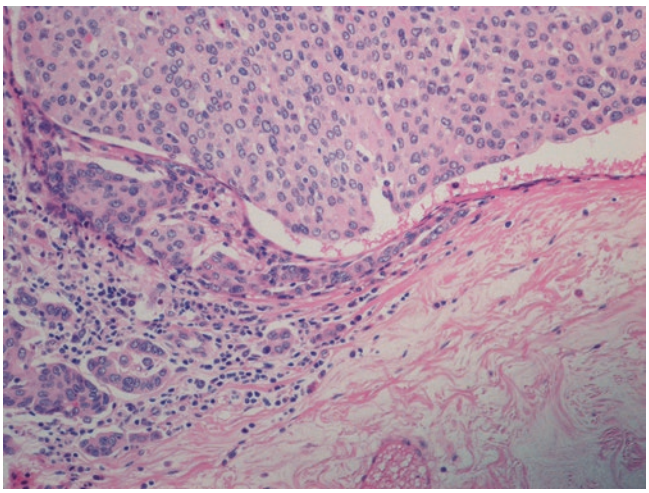

Fig. 12.3 Microinvasive carcinoma: the invasive tumor cells are forming small nests or have a trabecular arrangement while others are isolated into the stroma; an inflammatory infiltrate can be appreciated surrounding the invasive foci

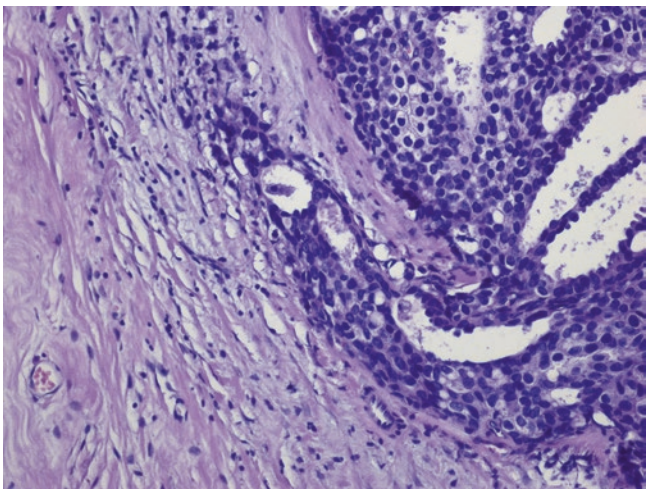

Fig. 12.5 Intraductal carcinoma mimicking a microinvasive focus by the branching layout of the duct; however, the myoepithelial cells can be detected on the hematoxylin-eosin slide

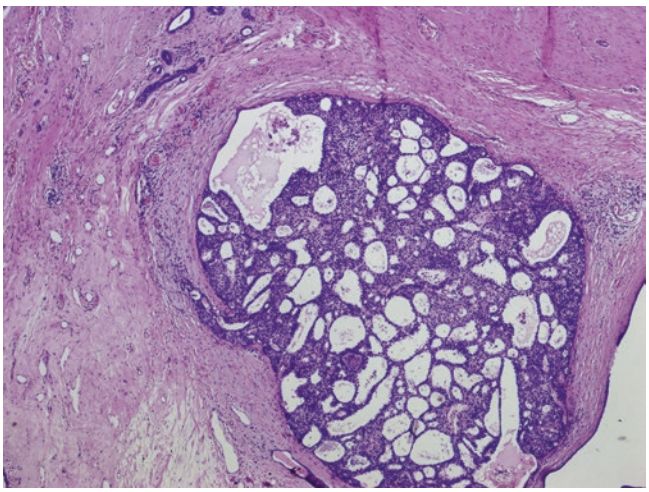

Fig. 12.4 Intraductal carcinoma: the branching layout of the duct on a small cross section can mimic adjacent invasive foci

References

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