Presence of Basement Membrane Material around the Tubules of Tubulolobular Carcinoma

Gábor Cserni

Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary

Key Words

Basement membrane · Breast cancer · Collagen IV · Tubulolobular carcinoma

Summary

Background: Core needle biopsies represent only a small portion of a breast lesion. Rare lesions with overlapping features may be underestimated in such small samples.

Case Report: A 67-year-old female underwent core needle biopsy of a 27-mm breast tumour demonstrating infiltrative glands without significant desmoplasia. Periglandular collagen IV immunostaining and the small glands were reminiscent of microglandular adenosis, and despite the infiltrative look of the microglands, the lesion was interpreted as suspicious for malignancy. Finally, the tumour proved to be a tubulolobular carcinoma. **Conclusions:** The tubules of tubulolobular carcinoma may show a basement membrane-like staining pattern with collagen IV, and this must be considered in the differential diagnosis of mammary lesions with small glandular architecture.

Schlüsselwörter

Basalmembran · Mammakarzinom · Kollagen IV · Tubulolobuläres Karzinom

Zusammenfassung

Einleitung: Stanzbiopsien der Mamma enthalten stets nur kleine Anteile der biopsierten Läsion. Seltenerer Läsionen mit überlappenden Anteilen können daher in solchen Proben unterbewertet werden. **Fallbericht:** Die Stanzbiopsie eines 27 mm großen Mammatumors einer 67-jährigen Patientin zeigte histologisch infiltrierende Drüsen ohne erkennbare Desmoplasie. Auf Grund eines immunhistologischen periglandulären Kollagen-IV-Nachweises wurde der Tumor trotz des infiltrativen Wachstumsmusters der kleinen Drüsen lediglich als «verdächtig für Malignität» eingestuft. Am Operationspräparat wurde schließlich ein tubulolobuläres Karzinom diagnostiziert. **Schlussfolgerungen:** Die Tubuli des tubulolobulären Karzinoms können basalmembranartige Kollagen-IV-Färbungen aufweisen. Dies sollte bei der Differentialdiagnose von Mammaläsionen mit mikroglandulärer Architektur berücksichtigt werden.

Introduction

When Fisher et al. [1] first described tubulolobular carcinoma, they stated that it remained a philosophical question whether the growth pattern or the structure should be given more weight in the nomenclature and when placing this entity among tubular or lobular carcinomas. They opted for a variant of lobular carcinoma on the basis of the cellular composition

and an outcome worse than that of pure tubular carcinoma (although better than that of classical lobular carcinoma) [1]. Since then, a number of studies have evaluated this rare histological subtype of breast carcinoma, and most have concluded that it has overlapping features of both ductal and lobular cancers, but is better considered as a variant of ductal [2–5] or even tubular carcinoma [2]. Likewise, reports suggest that tubulolobular carcinomas are always [2, 3, 5] or nearly always

Fig. 1. Small infiltrative glands devoid of myoepithelium (HE $\times 100$; inset: HE $\times 400$).

[4] E-cadherin-positive, and HMWCK stains most of them the same way as it stains lobular carcinomas [5].

Microglandular adenosis is a very rare pseudoneoplastic benign lesion of the breast which is characterised by small glands haphazardly arranged in a fibrofatty background [6, 7]. It is devoid of myoepithelial cells and is therefore a mimic of well differentiated invasive carcinomas. It has a peculiar immunostaining pattern, and is reported to be distinctively EMA-negative and S-100-positive [8]. The presence of a basement membrane around the glands is also a recognised feature of the lesion [8].

Case Report

An ultrasound-guided core needle biopsy was obtained from a right-sided, non-palpable, but radiologically malignant lesion of a 67-year-old woman. Tissue was fixed in formalin and embedded in paraffin, and slides were stained with haematoxylin and eosin (HE). Small infiltrative glands were seen in a fibrofatty background (fig. 1). No desmoplastic stromal reaction was noted. The small glands clearly lacked myoepithelium, and some of them contained eosinophilic secretory material. Because of the small glands, microglandular adenosis was considered in the differential diagnosis. The infiltrative glands were epithelial membrane antigen-, oestrogen receptor- and progesterone receptor-positive, S-100-negative, and collagen IV but not laminin demonstrated a basement membrane-equivalent staining pattern around them (fig. 2). The lack of a myoepithelial layer around the small glands strongly favoured a malignant preoperative diagnosis, especially in the light of the mammographic and ultrasonic images supporting such a diagnosis. Despite the fact that the immunophenotype did not support the diagnosis of microglandular adenosis, the core biopsy was interpreted as B4, suspicious of malignancy [9, 10], because of the disturbing presence of the periglandular collagen IV staining. The patient underwent breast conserving surgery, and the final diagnosis of a sentinel lymph node-negative, 2.7-cm tubulolobular carcinoma was issued from the resection specimen. The tumour predominantly displayed the microglandular infiltrative pattern seen in the core biopsy specimen,

Fig. 2. Small infiltrating glands surrounded by a somewhat discontinuous rim of collagen IV-positive layer suggestive of a basement membrane (arrowheads). In contrast to collagen IV, laminin (inset) did not show any staining around the glands (collagen IV $\times 400$; inset: laminin $\times 400$).

but also contained areas more reminiscent of classical lobular carcinoma. In keeping with the majority of publications, it demonstrated E-cadherin positivity [2, 5] and weak high-molecular-weight cytokeratin (HMWCK, 34Beta-E12) positivity [2].

Discussion

Both myoepithelial and basement membrane stains are generally recommended in the differential diagnosis of tubular or well differentiated ductal carcinomas versus microglandular adenosis or complex sclerosing lesions [8–10]. Very small glands can be seen, but are not the most typical in tubular carcinoma. Such glands are the features of microglandular adenosis, ductal carcinomas demonstrating a microglandular adenosis-like pattern [11], and classically, tubulolobular carcinoma which on the basis of the above considerations can be considered a misnamed special type of ductal cancers.

To note is the fact that the glands of tubulolobular carcinomas may display a basement membrane-equivalent staining pattern with collagen IV. Invasive breast carcinomas generally lack an epithelial basement membrane, although several authors have shown that a fragmented basement membrane can be visualised in a minority of cases with immunostains to laminin or collagen IV [12–15]. It was also proposed that the presence of basement membrane staining in carcinomas (always in a discontinuous pattern in contrast to the continuous staining seen in benign lesions) was correlated with better differentiation, and high grade cancers generally lacked staining or demonstrated more severe disruption of their basement membrane [12, 15]. As current guidelines [9, 10] stress on the usefulness of basement membrane immunostains in differentiating benign (staining positively) from malignant (lacking staining) lesions, the presence of a slightly disrupted, nearly

Fig. 3. Similar case of tubulolobular carcinoma from another patient; small infiltrating glands in this area and periglandular collagen IV staining (inset) (HE $\times 100$; inset: collagen IV $\times 400$).

continuous staining pattern in some well differentiated breast carcinomas, including tubulolobular carcinoma with its small non-angulated glands, should be remembered when making the distinction between microglandular adenosis and these

cancers. The mysterious perinodal tubules demonstrating focal peritubular collagen IV but not laminin staining recently reported by Nga and Putti [16] were also interpreted as extracapsular spread of a metastasis from an occult carcinoma with tubular features [17]. With this knowledge in mind, the core needle biopsy might and should have been interpreted as B5, diagnostic of malignancy [9, 10].

Conclusions

To support the notion in the title, a similar periglandular collagen IV (but not laminin) staining from another patient with E-cadherin-, EMA-, and HMWCK-positive and S-100-negative tubulolobular carcinoma is shown in figure 3. Benign apocrine glands devoid of myoepithelium have also been recently reported [18]. With this and the present case in mind, the dogmatic approaches suggesting that the presence of a basement membrane is diagnostic of a benign lesion or that the lack of a myoepithelial layer is a proof of malignancy should be considered with more caution, even if microglandular adenosis can be excluded on other grounds. A discontinuous basement membrane staining may not infrequently be present around the tubules of well differentiated breast carcinomas.

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