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Invasive Breast Carcinoma With Tubular Features Mimicking Flat Epithelial Atypia: A Case Report

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Abstract

Invasive breast carcinoma of no special type (IBC-NST) demonstrates significant morphological heterogeneity, which may create diagnostic challenges, particularly in limited biopsy specimens. We report a rare case of IBC-NST with extensive tubular morphology closely mimicking columnar cell lesions (CCLs), specifically flat epithelial atypia (FEA). A 49-year-old female patient presented with a palpable breast mass, and imaging revealed an ill-defined lesion associated with widespread microcalcifications. Core needle biopsy of the mass confirmed IBC-NST; however, biopsy of the calcifications showed an atypical glandular proliferation with bland cytologic features and architecture resembling FEA. Immunohistochemical studies demonstrated absence of myoepithelial cells, raising concern for invasive carcinoma, though definitive classification remained challenging preoperatively. Mastectomy revealed an extensive infiltrative carcinoma composed predominantly of dilated tubular structures lacking a desmoplastic stromal response and closely resembling FEA, comprising approximately 80% of the tumor. The final diagnosis was low-grade IBC-NST with tubular features, estrogen receptor/progesterone receptor positive and HER2 negative. This case highlights an unusual morphological presentation of invasive breast carcinoma that may closely mimic benign or precursor lesions, emphasizing the importance of careful histological assessment and immunohistochemical evaluation to avoid underdiagnosis.

Categories: Pathology
Keywords: columnar cell lesions, flat epithelial atypia (fea), invasive breast carcinoma nst, myoepithelial markers immunohistochemistry, tubular morphology in breast carcinoma

Introduction

Invasive breast carcinoma is a malignant process of the breast epithelium characterized by the absence of a peripheral myoepithelial cell layer and invasion into the stroma. Morphologically, it demonstrates diverse histological features. Tumors exhibiting a distinct histological pattern in ⩾90% of their composition are classified as pure special types, such as mucinous carcinoma and tubular carcinoma. Tumors lacking such specific features are categorized as invasive breast carcinoma of no special type (IBC-NST), which constitutes the majority of cases, including those with mixed patterns. IBC-NST thus exhibits significant histological variability, both between cases and within individual tumors [1]. The stromal component also varies widely, ranging from a highly cellular fibroblastic proliferation to marked hyalinization [1-2].

Tubular carcinoma is an IBC in which >90% of the tumor consists of round to ovoid or angular tubules with open lumina, set within a fibrous or fibroelastotic desmoplastic stroma. These tubules are lined by a single layer of cuboidal to columnar cells with low-grade nuclei and sparse mitosis. Apical snouts may be seen on the luminal aspect of the tubules, and secretions or calcifications may be present in the lumina [3].

Columnar cell lesions (CCLs), including flat epithelial atypia (FEA), are commonly encountered in breast biopsies and are frequently associated with microcalcifications. FEA is a low-grade epithelial lesion characterized by one or more layers of cytologically bland, often columnar cells and may coexist with other lesions within the low-grade breast neoplasia pathway, including atypical ductal hyperplasia, low-grade ductal carcinoma in situ (DCIS), and tubular carcinoma [4-8]. Although FEA is not an invasive malignancy, its morphologic similarity to the unusual invasive carcinoma described in this case creates a potential diagnostic pitfall, particularly in limited biopsy specimens.

This case report presents a rare IBC-NST with an unusual tubular morphology, in which the infiltrating tubules closely resemble CCLs, particularly FEA. The unusual morphology and lack of a prominent stromal reaction presented a significant diagnostic challenge in the biopsy material. This unusual combination of extensive FEA-like tubular morphology and invasive growth without a prominent desmoplastic response has not been well-characterized.

Case Presentation

A 49-year-old female patient presented with a palpable mass in her left breast. Mammography revealed an

asymmetric density at the 12 o'clock position with scattered microcalcifications in the upper inner quadrant. Ultrasound identified an ill-defined hypoechoic mass measuring 1.5 cm, with calcifications spanning 7 cm adjacent to the mass. While ultrasound-guided biopsy of the mass revealed IBC-NST, a stereotactic core needle biopsy of the microcalcifications, performed to assess the extent of disease and presence of DCIS, showed an atypical cystic and glandular/tubular proliferation. These atypical glands and cysts were haphazardly distributed among the terminal duct lobular units (TDLU) and lined by one or a few layers of bland oval to round cells with apical snouts, fine chromatin, and inconspicuous nucleoli. Microcalcifications were seen within the lumina. Immunohistochemistry for myoepithelial markers including p63, CK5/6, smooth muscle actin (SMA), smooth muscle myosin (SMM), calponin, CD10, S100, and SOX10 was negative, suggesting invasive malignancy (Figure *1*). Due to the unusual morphology, the biopsy was reported as an atypical glandular proliferation; low-grade invasive carcinoma cannot be excluded. The managing team opted for mastectomy due to the large extent of disease.

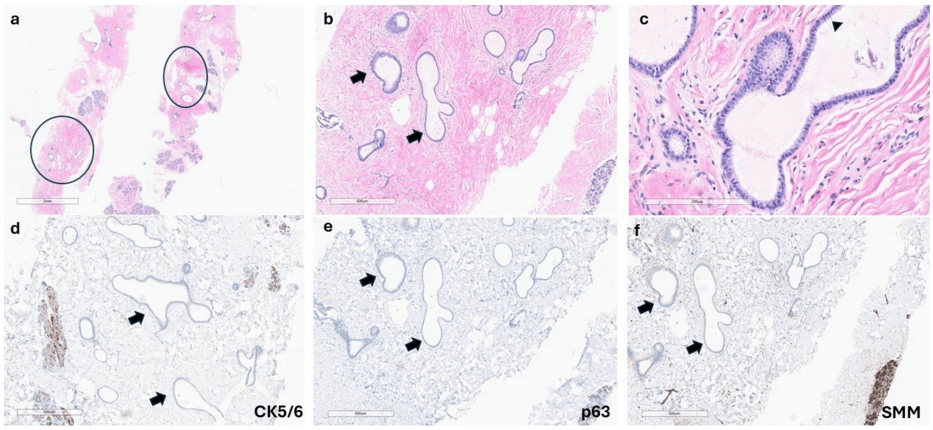


FIGURE 1: H&E and IHC stained images of a stereotactic core needle biopsy performed for microcalcifications

H&E: hematoxylin and eosin; IHC: immunohistochemistry

(a) and (b) Atypical cystic and glandular proliferation haphazardly infiltrating the stroma without desmoplastic response (a. H&E, 1X; b. H&E, 4X). Representative atypical infiltrative glands are circled in (a) and indicated by arrows in (b). (c) Atypical glands lined by one or a few layers of bland oval to round cells with apical snouts (arrowhead), mimicking flat epithelial atypia (H&E, 20X). (d-f) IHC stains demonstrating absence of myoepithelial cells around the atypical glands; representative atypical glands are indicated by arrows: CK5/6 (d, 4X), p63 (e, 4X), and smooth muscle myosin (f, 4X). IHC internal controls stained appropriately. Images were captured using Aperio ImageScope

The patient underwent a left mastectomy and sentinel lymph node biopsy. Gross examination of the mastectomy specimen revealed a solid mass in the upper inner quadrant, measuring 1.6 x 1 x 1 cm. Specimen radiographs confirmed microcalcifications extending over 5 cm (Figure *2*).

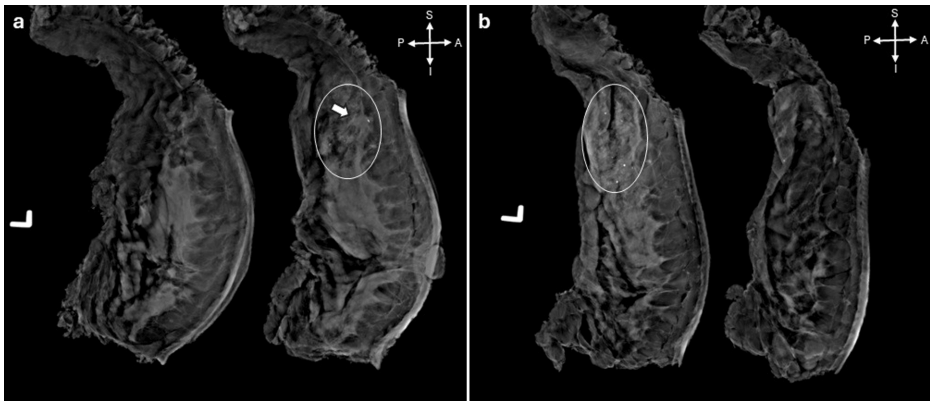


FIGURE 2: Radiograph of mastectomy specimen slices demonstrating the mass (arrow) and associated surrounding microcalcifications (circled)

Microscopic examination showed an extensive atypical dilated glandular proliferation, resembling FEA, infiltrating the breast parenchyma haphazardly without a desmoplastic reaction corresponding to the atypical glandular proliferation observed in the stereotactic core biopsy specimen. In contrast to conventional FEA, the atypical glands were irregularly and haphazardly distributed within the breast parenchyma rather than being confined to TDLU. The glands were also in continuity with overt invasive carcinoma and lacked a myoepithelial layer, supporting their invasive nature. Collectively, the atypical dilated glandular component constituted approximately 80% of the invasive carcinoma (Figure *3*). No unequivocal separate focus of FEA was identified.

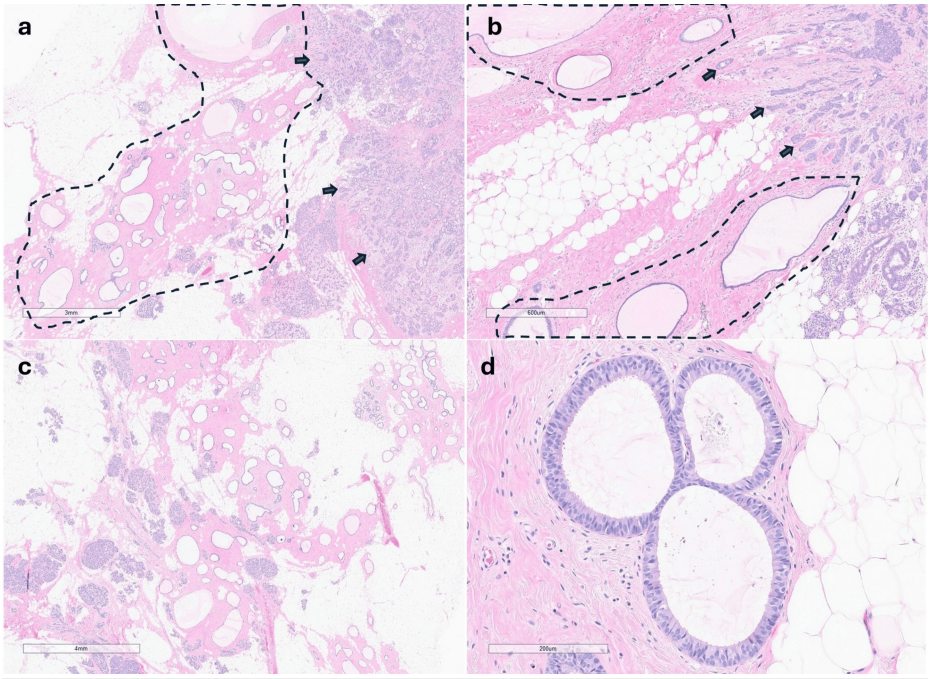


FIGURE 3: H&E stained microscopic images of the mastectomy specimen

H&E: hematoxylin and eosin; FEA: flat epithelial atypia

(a-b) FEA-like atypical cystic and glandular proliferation (dashed outline) appearing continuous with invasive carcinoma of no special type (arrows) (a. H&E, 1X; b. H&E, 4X). (c-d) FEA-like low-grade invasive carcinoma located away from the invasive carcinoma of no special type, spanning an area of approximately 80 mm. The FEA-like atypical dilated glands are lined by one to several layers of oval to round cells with apical snouts. Some dilated glands/cysts are lined by flattened epithelium (c. H&E, 1X, d. H&E, 15 X). All images were captured using Aperio ImageScope

Distinguishing the atypical dilated glandular invasive component from benign fibrocystic changes or FEA was challenging in the absence of immunohistochemical evaluation. Subsequent staining for multiple myoepithelial markers confirmed the absence of myoepithelial cells in the atypical glands (Figure *4*). Some glands showed a reduced or fragmented collagen IV-positive basement membrane, while laminin was completely negative.

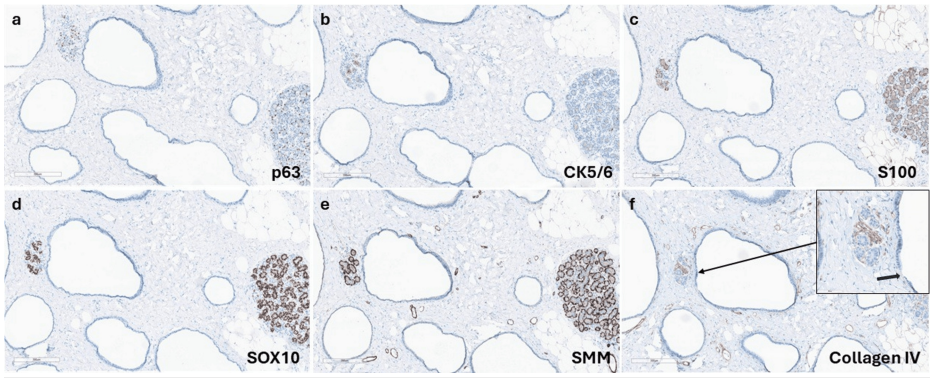


FIGURE 4: IHC of the FEA-like atypical glandular proliferation in the mastectomy specimen

IHC: immunohistochemistry; FEA: flat epithelial atypia; SMM: smooth muscle myosin

The atypical glands were negative for myoepithelial markers, including p63 (a), CK5/6 (b), S100 (c), SOX10 (d), and SMM (e). (f) Some glands show partial/fragmented retention of collagen IV along the basement membrane (arrows) (IHC, 8X; inset, 20X). Internal controls stained appropriately. All images were captured using Aperio ImageScope

The final diagnosis was IBC-NST with extensive tubular features, Nottingham grade I/III (tubule formation score I, nuclear grade II, mitotic count I). DCIS with cribriform architecture and low-to-intermediate nuclear grade was also present. The invasive carcinoma was estrogen receptor/progesterone receptor (ER/PR)-positive, HER2-negative. Sentinel lymph nodes were negative for metastasis, and surgical margins were clear. The size of the invasive carcinoma, including the atypical dilated glands, was estimated at 8 cm, based on microscopic mapping. The patient was placed on adjuvant endocrine therapy and remains free of recurrence or metastasis one year postmastectomy.

Discussion

This case highlights a rare variant of IBC-NST with tubular features that mimic CCLs, in particular FEA. The unusual morphology and absence of a desmoplastic stromal response posed a significant diagnostic challenge in the biopsy material. Recognizing the invasive nature of the atypical glands was essential, as their resemblance to CCLs/FEA could have led to underdiagnosis.

CCLs of the breast represent a spectrum of alterations within TDLUs, ranging from benign to neoplastic [4]. CCLs are classified into columnar cell change, columnar cell hyperplasia, and FEA. FEA, in particular, is characterized by replacement of the native epithelial cells of the TDLUs by one or several layers of monomorphic cuboidal-to-columnar cells with round nuclei, an increased nuclear-to-cytoplasmic ratio, smooth rigid contours, and frequent calcifications [5-6]. While FEA is associated with a relatively low risk of upgrade to malignancy, it often coexists with atypical ductal hyperplasia, low-grade DCIS, and tubular carcinoma, suggesting a possible relationship with the low-grade breast neoplasia pathway [7-13]. A systematic review and meta-analysis of 2,482 cases of pure FEA diagnosed on core needle biopsy reported a pooled upgrade rate of 5% to breast cancer, including 1% to invasive carcinoma and 2% to DCIS [9].

Notably, tubular carcinoma frequently arises in association with FEA. Prior studies have shown a high prevalence (up to 84%) of FEA in pure tubular carcinomas, often accompanied by ADH or DCIS [10]. Clonal analysis has demonstrated shared molecular alterations between FEA and tubular carcinoma, supporting a possible clonal relationship and precursor role for FEA [11-13].

The absence of desmoplastic stroma in this case is particularly noteworthy. Desmoplasia, characterized by peritumoral collagen deposition, results from the activation of tumor-associated fibroblasts and leads to the formation of a new extracellular matrix [14]. The desmoplastic response is a hallmark of many invasive carcinomas, including breast carcinoma, and may contribute to the clinical presentation of a palpable mass [2]. In breast carcinoma, the stromal component varies widely, ranging from a highly cellular fibroblastic proliferation to pronounced hyalinization [1-2]. However, the lack of a desmoplastic response in this case is unusual. The FEA-like morphology raises the possibility that this tumor may share features with the low-grade breast neoplasia pathway; however, the absence of an unequivocal separate focus of FEA and the lack of molecular studies preclude establishing such a relationship. Although unequivocal FEA was not identified in this case, the reduced and fragmented basement membrane in some atypical glands may be relevant to the assessment of their invasive nature, although its significance remains uncertain.

This case underscores the critical importance of recognizing the unusual FEA-like morphology of this

invasive carcinoma and distinguishing it from CCLs. Misinterpretation could lead to inadequate treatment, as FEA is often managed conservatively. Therefore, careful morphological observation, especially of the unusual distribution of dilated glands, along with a comprehensive immunohistochemical panel and heightened awareness of this variant, is essential for accurate diagnosis in challenging cases.

This report has several limitations. First, it describes a single case and therefore cannot establish the frequency or clinical significance of this unusual morphology. Second, molecular studies were not performed, limiting further characterization of the relationship between the FEA-like component and the conventional invasive carcinoma. Finally, follow-up was limited to one year, precluding assessment of longer-term clinical outcomes. This case report adheres to the CAse REport (CARE) Guidelines [15].

Conclusions

This case illustrates a diagnostically challenging presentation of IBC-NST with extensive tubular morphology mimicking FEA. The lack of a desmoplastic stromal response and the close resemblance to CCLs may lead to underdiagnosis, particularly in limited biopsy specimens. Recognition of subtle infiltrative features, together with appropriate use of myoepithelial markers, is essential for accurate diagnosis.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Moreen Haddad, Edi Brogi, Hongming Qiu

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Drafting of the manuscript: Moreen Haddad

Critical review of the manuscript for important intellectual content: Angela E. Schellenberg, Edi Brogi, Hongming Qiu

Supervision: Hongming Qiu

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. University of Manitoba Bannatyne Research Ethics Board issued approval HS26851. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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