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Tubular Carcinoma of the Breast: A Clinicopathological Analysis of Two Cases

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Abstract

Tubular Carcinoma (TC) of the breast, also known as tubular carcinoma or well-differentiated adenocarcinoma, is defined as a special type of breast cancer consisting of well-differentiated tubular structures with excellent prognosis by WHO (2019) pathological and genetic classification of breast neoplasms. Two cases of breast tubular carcinoma admitted to our hospital were reported. The relevant literature was reviewed and the clinical features, histological morphology (microscopic features and differential diagnosis), molecular changes and clinical prognosis were summarized.

Keywords

TC, Clinical Pathology, Differential Diagnosis, Prognosis

1. Case Presentation

1.1. Case 1

A 50-year-old female patient came to our hospital because of her 10 years of backache which worsened in 3 months. Lumbar computed tomography (CT) showed spinal disc herniation. She also brought her three-year-ago mammary ultrasound to other hospitals, which suggested bilateral breast hyperplasia and a right breast cyst that were considered BI-RADS 2. Our physical examination found no obvious mass in the right breast, but palpable granularity in the outer upper quadrant of the left breast. So we went over mammary ultrasound again, this time it revealed a lesion located in the right mammary gland at 9 o'clock, about 4 cm from the nipple, single, elliptical, 0.8 × 0.6 cm in size. The mass was hypoechoic, ill-defined, irregular, and rich in blood flow. The other lesion on the left breast was about 1 cm from the nipple at 10 o'clock. The lesion was single, hypoechoic, ill-defined and had sparse blood flow. Ultrasound diagnosis is right

breast lesion, nature undetermined, BI-RADS 4b; left breast lesion, hyperplastic nodules, BI-RADS 3. Bilateral breast lesions are considered cysts. No abnormal enlarged lymph nodes in the bilateral axilla. Ultrasound-guided puncture biopsy of breast mass was performed and sent to pathology.

1.2. Case 2

A 40-year-old female patient presented with a history of breast lump one week ago in the right breast. On examination, her breast surface is smooth, with no dimpling and venous engorgement, no peau d' orange appearance, and no fissuring, fungating and eczema seen. Nipples were normally located bilaterally. She doesn't complain of any symptoms of chills, fever or dyspnea. Ultrasonography revealed a single lesion beside the glands of the right breast at 10 o'clock, shaped oval, 0.6 × 0.6 cm in size, with the hypoechoic area, unclear boundary and strip flow signal. Ultrasound diagnosis is right breast lesion, nature undetermined, BI-RADS 4a. No abnormal enlarged lymph nodes in the bilateral axilla. A mammotome biopsy had been taken and the tissue was sent to pathology.

2. Methods

Surgically resected specimens were fixed with 10% formalin, generally embedded in paraffin, sliced and stained with haematoxylin and eosin. Immunohistochemical analyses of 4‐micrometer sections of whole tumour tissues containing *in situ* and/or invasive regions were performed using autostainers (DakoCytomation), according to the manufacturer's instructions. All the used antibodies including ER, PR, ERBB2, Ki-67, S-100, P63 and Calponin were from DakoCytomation.

2.1. Imaging Examinations

The tumor tissues of the two cases were basically the same. The tumor tissues were surrounded by a single layer of cells in clear tubules, which were mild in shape and uniform in size. The tubules were arranged in a single row into a well-defined lumen. The volume and nuclei of the cancer cells were small, the nuclei were hyperchromatic, the nucleoli were unclear, the atypia was not obvious, and there was no mitotic figure or necrosis. The tubules were randomly distributed, and the surrounding cancer tissue invaded the normal breast ducts, lobules and adipose tissue. Tumor stroma was mostly dense fibers (**Figure 1(a)** and **Figure 1(b)**, **Figure 2(a)** and **Figure 2(b)**).

2.2. Immunohistochemical Analysis

The nucleoli of the tumor cell stained diffusely positive for the presence of Estrogen (ER) and Progestogen (PR). The presence of Ki-67 was about 2% - 4%. On the other hand, Herceptin-2 (Her-2) and S-100 was negative, P63, Calponin showed no myoepithelial surrounding the cancer nest (**Figures 1(c)-(f)**, **Figures 2(c)-(f)**).

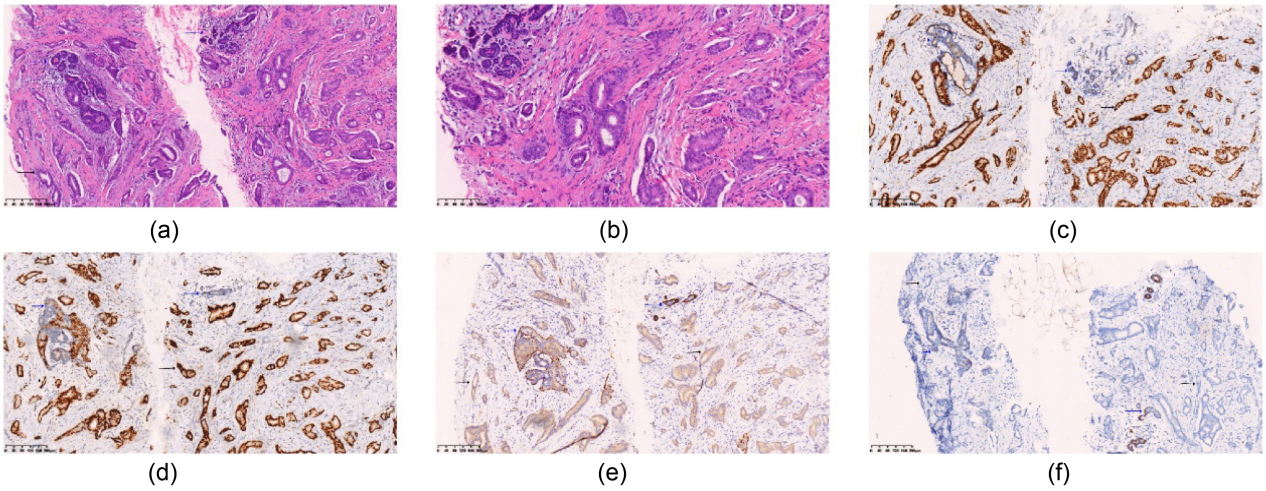

Figure 1. Case 1: Histopathology of tubular carcinoma of the breast. (a) The ductal epithelium of the breast (blue arrow) was surrounded by tubular carcinoma (black arrow) with an invasive growth pattern. (b) Neoplastic tubules are small to medium in size, with open lumen and pointed at one end, described as teardrop-shaped. The tubules are lined with a single layer of epithelium, which are mildly dysplasia, not obvious nucleoli, and mitosis is rare. The tubules have no surrounding epithelium. (c)-(d) Tubule cancer cells with diffuse positive ER and PR (black arrows). Ductal epithelial cells were mottled positive for ER and PR. (e)-(f) Negative P63 and S-100 surrounding tubule cancer cells indicate the absence of myoepithelial cells (black arrows). Positive P63 and S-100 surrounding ductal epithelial cells indicate the presence of myoepithelium cells (blue arrow).

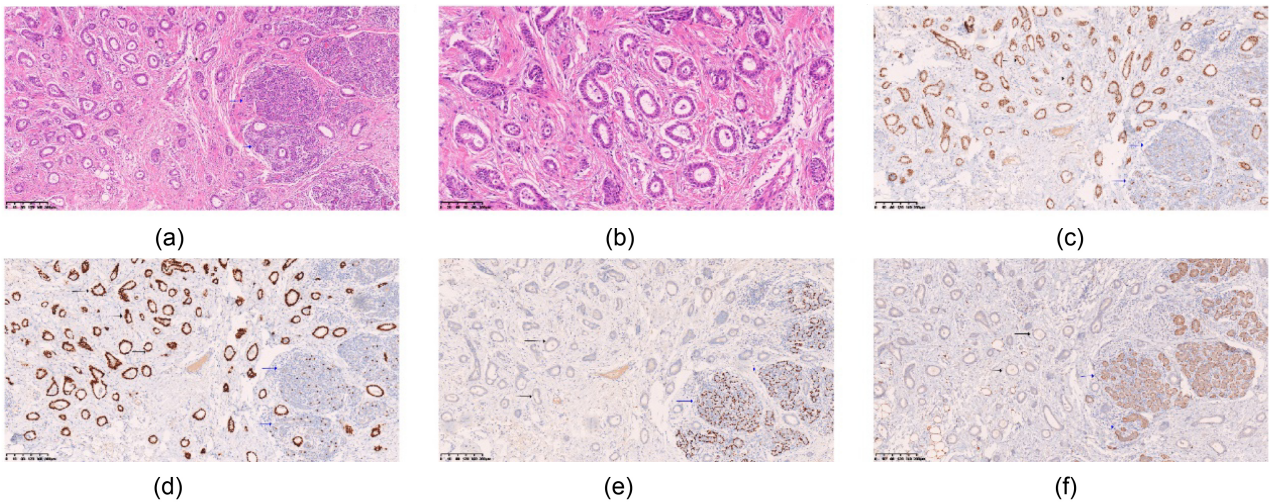

Figure 2. Case 2: Histopathology of tubular carcinoma of the breast. (a) Invasive growth of tubule carcinoma (black arrow) around ductal epithelium in breast tissue (blue arrow). (b) Neoplastic tubules are small to medium in size, with open lumen, pointed at one end, described as angular edges. The tubules are lined with a single layer of epithelium. The epithelial cells are without overt cytologic atypia, the nucleoli are not obvious, the mitosis is rare. (c)-(d) ER and PR were diffusely positive in tubule cancer cells (black arrows), while ER and PR were patchy in ductal epithelial cells. (e)-(f) Negative P63 and S-100 surrounding tubule cancer cells indicate the absence of myoepithelial cells (black arrow). Positive P63 and S-100 surrounding ductal epithelial cells indicate the presence of myoepithelium cells (blue arrow).

3. Discussion

3.1. Diagnosis

3.1.1. Clinical Features

This type of cancer is generally considered rare, and if strictly diagnosed ac-

cording to the criteria, its incidence in breast cancer is lower than 2% [1]. Tubular cancer can occur in women between 23 and 84 years of age, with an average age of about 50 years (often in postmenopausal women) [2], mostly in the outer upper quadrant of the breast, often unilateral, can also be multifocal or bilateral, male mammary glands also occur. Tumors generally grow slowly, so it is called well-differentiated cancer. Most tubular carcinomas today present as untouchable radiographic abnormalities of the breast or incidental findings of breast biopsy due to other unrelated lesions.

3.1.2. Macroscopic General Features

The margin of the tumor was ill-defined and hard. The tumor volume was small, with an average diameter of about 1 cm, and only 4% of the cases were larger than 2 cm [2] [3].

3.1.3. Microscopic Histologic Features

The histologic features of tubular carcinoma are proliferation of well-differentiated glands or tubules, arranged in a disorderly and often radial pattern, with glands extending irregularly into adjacent fibrous stroma and adipose tissue. The tubules and glands are composed of a single layer of cuboidal to columnar epithelial cells with no surrounding myoepithelial cells. The tubules were mostly oval and clearly angulated with tapered ends and open lumens. The cells that make up these tubules have low-grade nuclei with frequent apocrine cytoplasmic processes. The histologic features of tubular carcinomas, which are often desmoplastic stromal tubulocarcinoma [3], are proliferation of well-differentiated glands or tubules that are arranged in a disorderly, often radial pattern, with glands extending irregularly into adjacent fibrous stroma and adipose tissue. The tubules and glands are composed of a single layer of cuboidal to columnar epithelial cells with no surrounding myoepithelial cells. The tubules were mostly oval and clearly angulated with tapered ends and open lumens. The cells that make up these tubules have low-grade nuclei with frequent apocrine cytoplasmic processes [4] [5].

Most tubular carcinomas contain components of ductal carcinoma *in situ* and are often low-grade with cribriform and micropapillary structures, although evidence sufficient to diagnose ductal carcinoma *in situ* is sometimes lacking Atypical Ductal Hyperplasia (ADH) and Flat Epithelial Atypia (FEA) [6]. In addition, Atypical Ductal Hyperplasia (ADH) and Flat Epithelial Atypia (FEA) are often present in tubular carcinoma. Tubular carcinomas often have a desmoplastic stroma.

3.1.4. Biomarkers and Molecular Pathology

Tubular carcinomas are always ER positive, PR positive in most cases, and HER2 protein overexpression or gene amplification is rare [7] [8]. Ki-67 proliferation index was low, and myoepithelial markers such as P63, calponin, SMA and S-100 were negative as we can see in **Figure 1**. In gene expression profile studies, tubular carcinoma belongs to luminal type A [9]. At the genomic level, tubular

carcinomas usually show a 16q deletion, similar to other lesions in the low-grade breast tumor pathway, including columnar cytopathies, FEA, ADH, and low-grade DCIS, among others [6]. Almost all tubular carcinomas are diploids with low proliferative rates and rarely show HER-2 overexpression or P53 protein aggregation [7] [10] [11]. Compared with invasive ductal carcinoma NOS, there were fewer chromosomal alterations in tubular carcinoma [12] [13].

3.1.5. Electron Microscopic Scanning

Under electron microscope, uniformly sized tumor cells were arranged into a monolayer to form neoplastic glands, myoepithelial cells were rarely seen or absent, and basement membranes were absent or discontinuous. Tumor cells are connected by numerous desmosomes and filaments terminalis. There were a large number of microfilaments arranged in bundles in the cytoplasm. The microfilaments were 8 nm in diameter and did not attach to desmosomes or other structures. Cytoplasmic organelles such as ribosomes, rough endoplasmic reticulum, mitochondria and tension filaments are distributed around the nucleus. The surface of luminal epithelial cells was covered with a large number of lacy microvilli. These microvilli were small processes secreted by apical plasma in lumen seen under light microscope [14].

3.2. Differential Diagnosis

1) Sclerosing adenosis

Histological examination at low magnification is valuable in distinguishing tubular carcinoma from benign sclerosing lesions. Sclerosing adenosis has organ-like, lobular, or tufted structures in contrast to the disorganized, star-shaped glands of tubular carcinoma. In Complex sclerosing lesions, buried glands are confined to areas of interstitial sclerosis/fibroelastic tissue hyperplasia and do not extend irregularly beyond the margin of the sclerosing area and into adjacent fibrous interstitial and adipose tissue as tubular carcinoma glands do.

However, in some cases, it is difficult to distinguish tubular carcinoma from these benign lesions by histomorphology alone, and the correct diagnosis must be made by immunostaining. Absence of myoepithelial cell layer around glands in tubular carcinoma; In contrast, myoepithelial cells are present around benign sclerosing lesions (*i.e.* sclerosing adenosis/complex sclerosing lesions) [15] [16].

2) Microglandular adenosis

The duct of microglandular adenosis is randomly distributed and rounder and the lumen is obvious. It is also covered by a single layer of epithelium, lacks myoepithelial cells, and can infiltrate adipose tissue similar to tubular carcinoma. However, the edge of microglandular adenosis is not radially arranged and does not show true infiltrative growth, and the lumen is round and irregular.

Myoepithelial cell labeling is not helpful in differentiating tubular carcinoma from MGA because there is no myoepithelial cell layer around the glands in either case, but S-100 protein and ER immunostaining are helpful in differentiating [17], as we can see S-100 in **Figure 1(f)** and **Figure 2(f)**.

3) Radial scar: There were myoepithelial cells in the ducts proliferating in the radial scar, and there was no intraductal carcinoma or other types of invasive carcinoma in the surrounding tissues.

4) Grade I invasive ductal carcinoma of the breast: In general, Grade I invasive ductal carcinoma glands do not have the oval shape, angular ends, or apical cytoplasmic processes that are characteristic of tubular carcinoma glands. Because tubular carcinoma has a better prognosis than Grade I invasive ductal carcinoma, it is important to distinguish between them [2] [4] [18].

3.3. Prognosis and Therapy

The prognosis of tubular carcinoma is better than that of other types of breast cancer, and some studies have shown that even lymph node metastasis does not affect disease-free survival and overall survival in patients with tubular carcinoma [2] [7]. In the 35 cases of tubular carcinoma reported by Carstens *et al*., axillary lymph node metastasis occurred in only 3 cases [19]. However, only 4% of the 135 patients reported by McDivitt *et al*. who were followed for an average of 72 years had recurrence or metastasis. No lymph node metastasis was found in the 2 cases. Axillary lymph node metastases occur in approximately 10% of cases [2] [20], but this does not appear to affect the outcome, even in the absence of systemic chemotherapy [2] [7]. Tubule carcinoma rarely metastases to other sites, unless combined with other types of breast cancer. When tubular carcinoma is accompanied by a common type of invasive ductal carcinoma, the prognosis of this mixed type of tumor is much worse than that of pure tubular carcinoma. However, when tubular carcinoma is the main component, it is still better than ordinary ductal carcinoma [2]. Therefore, modified radical mastectomy is generally used for the treatment of tubular carcinoma.

In addition, the life expectancy of patients with TC appears to be close to normal, so adjuvant systemic therapy may not be justified in their routine management [21] [22].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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