Tubular Adenoma of the Breast: A Clinicopathologic Study of a Series of 9 Cases

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ABSTRACT: Tubular adenoma of the breast is one of the most rare benign neoplasms, accounting for only 0.13% to 1.7% of all breast benign tumors. Little is known about this rare neoplasm as the current literature offers only some case reports or a few number of small series. The aim of our study is to provide some clinicopathologic features of the breast tubular adenoma. We retrospectively analyzed at our department of pathology all cases of breast tubular adenomas confirmed by immunohistochemistry over a period of 9 years (2009-2017). Nine cases of breast tubular adenoma have been recorded, with an average age of 31.44 years. Five tumors were located at the right side (55.55%), and most cases had suspicious aspects on imaging techniques (6 cases out of 9). The diagnosis has been made on 5 resected specimens (lumpectomy) and on 4 core needle biopsies. The tumor size ranged from 0.9 to 7 cm (mean size of 3.08 cm) and had well-circumscribed margins with elastic consistency. The histopathologic analysis showed a typical pattern of proliferating round and uniform tubules lined by regular epithelial cells surrounded by myoepithelial cells, packed in a small amount of stroma, highlighted by CD34 immunostaining. Tubular adenoma is a rare breast benign neoplasm of young premenopausal women. The radiologic aspects are often worrisome and only the histopathologic analysis can achieve the correct definitive diagnosis by excluding all potential differential diagnoses.

KEYWORDS: Breast, tubular adenoma, pathology

Introduction

Tubular adenoma of the breast is one of the most rare benign neoplasms, accounting for 0.13% to 1.7% of all breast benign tumors.¹⁻³ Typically, tubular adenoma occurs in young women, very rarely before menarche or after menopause.³ The imaging techniques show mostly a benign aspect, although rarely some suspicious features can be suggested.³,⁴ The preoperative diagnosis of tubular adenoma is quite impossible, only the histology can achieve a definitive correct diagnosis.⁵ The cytologic examination is not reliable as it often fails to diagnose correctly the tubular adenoma.⁵,⁶ Biopsies or lumpectomy provide a sufficient tumoral tissue to allow a correct diagnosis. The classical histologic aspect of tubular adenoma is a proliferation of packed tubular structures within a small amount of fibrous stroma. The tubules are lined by regular epithelial and basal myoepithelial cells.¹ However, there are some histologic differential diagnoses, such as certain benign tumors (fibroadenoma, lactating adenoma, phyllodes tumor, adenosis) and malignant tumors (tubular carcinoma), that require the usage of immunohistochemistry.¹,⁷ Also, association with carcinomas has been reported.⁸,⁹

Little is known about tubular adenoma as in the current literature only some case reports or small series are described.¹,²,⁵,⁶ Our aim is to provide clinicopathologic features of breast tubular adenoma through a retrospective study.

Methods

Patients selection

It is a retrospective analysis of all histologically diagnosed cases of breast tubular adenoma over a period of 9 years (2009-2017), in the department of pathology of Hassan II Teaching Hospital, Fès, Morocco. Only cases of tubular adenoma with additional immunohistochemical analysis have been included. Available clinical data (age, tumor site), radiologic aspects, and pathologic features were retrospectively collected through electronic files and request forms archives at our department.

Histopathologic analysis

The histologic analysis has been performed on paraffin-embedded and formalin-fixed specimens stained by hematoxylin-eosin-saffron. The immunohistochemical analysis has also been performed on paraffin-embedded and formalin-fixed tissues. We have used the antibodies according to the manufacturer’s guidelines, with an automated immunohistochemical stainer (BenchMark ULTRA; Ventana, Tucson, AZ, USA). At our pathology department, for all antibodies, positive and negative controls were routinely performed, including processing of normal tissue or tumor sections known to be positive or negative (normal breast tissue, breast carcinomas, normal uterine wall, normal smooth muscle tissue, etc). We have used these
antibodies: anti-SMA (smooth muscle actin; 1A4; Cell Marque, Rocklin, CA, USA), anti-p63 (4A4; Ventana), anti-cytokeratin 5/6 (D5/16B4; Ventana), and anti-CD34 (QBEnd/10; Ventana).

Results
During our study period, we have recorded 9 cases of breast tubular adenoma.

Table 1 summarizes the clinicopathologic features of our 9 patients diagnosed with tubular adenoma. They were all women, with the mean age of 31.44 years (ages ranging from 19 to 55 years). The right breast was slightly more affected (5 cases out of 9).

The radiologic aspects of lesions were suspicious in 6 patients (BI-RADS 4—Breast Imaging-Reporting and Data System) and lumpectomy has been performed in 5 patients (4 with radiologically suspicious lesions and another with radiologically benign lesion (BI-RADS 3)) (Figure 1). The tumor size, as assessed radiologically or on resected specimens, ranged from 0.9 to 7 cm, with an average of 3.08 cm.

Macroscopically, all 5 resected lesions were well circumscribed, elastic, and whitish to tan colored (Figure 2).

The histologic aspect of all cases showed a benign well-circumscribed tumor consisting of a proliferation of small rounded tubules packed in a small amount of loose and fibrous stroma. Tubules are lined by regular epithelial cells and myoepithelial cells with round nuclei, without atypia. In certain areas of the tumor, the lumen of the tubules contain eosinophilic amorphous materials (Figure 3).

The presence of basal myoepithelial cells has been proved by immunohistochemical expression of p63 protein (5 cases), p63+CK5/6 (3 cases) and CK5/6+SMA+p63 (1 case) (Figure 4).

Also, the CD34 immunohistochemical staining highlighted the inconspicuous small amount of the stromal component, characteristically found in tubular adenoma (Figure 5).

Discussion
Our current retrospective series reports some clinicopathologic features of a rare breast neoplasm, the tubular adenoma. Little is known about this tumor, as the current medical literature offers only some case reports and other rare small series.2–9 The incidence of breast tubular adenoma varies from 0.13% to 1.7%.3,4 However, recent 2 series by Sengupta et al5,6 showed higher incidences, 2.9% and 2.83%, over periods of 3 and 10 years, respectively. The tubular adenoma is typically a neoplasm of young premenopausal women, although cases in postmenopausal women have been reported.1,2,10 In our series, one case of tubular adenoma occurred in a postmenopausal patient (case 2); the average age was 31.44 years, supporting that this tumor affect the women at a reproductive age.

The radiologic features of 6 cases out of 9 in our study showed suspicious lesions, classified as BI-RADS 4. The suspicious radiologic pattern is rarely reported in the literature. The classical radiologic features of tubular adenoma are well-circumscribed lesions without calcifications suggestive of ade- nofibroma; however, in older women, calcifications may be present, and this finding may be interpreted as a malignant tumor.1–5

Table 1. Clinicopathologic features of our patients diagnosed with breast tubular adenoma.

| CASES | AGE, Y | SIDE | RADILOGIC FEATURES | SPECIMENS | TUMOR SIZE, CM | MACROSCOPIC FEATURES | MYOEPITHELIAL CELL MARKERS (IMMUNOHISTOCHEMISTRY) |
|-------|--------|------|-------------------|-----------|----------------|---------------------|-----------------------------------------------|
| 1     | 42     | Right| BI-RADS 4         | Lumpectomy | 1.5            | Whitish, well circumscribed, elastic         | p63 CK5/6                                      |
| 2     | 55     | Left | BI-RADS 3         | Biopsy    | 2              |                                    | p63                                           |
| 3     | 35     | Left | BI-RADS 4         | Lumpectomy | 6              | Whitish, well circumscribed, elastic         | CK5/6 SMA P63                                   |
| 4     | 22     | Right| BI-RADS 4         | Biopsy    | 1.6            |                                    | p63 CK5/6                                      |
| 5     | 23     | Right| BI-RADS 3         | Lumpectomy | 0.9            | Tan, elastic, encapsulated                | p63 CK5/6                                      |
| 6     | 48     | Left | BI-RADS 4         | Lumpectomy | 3.5            | Whitish, lobulated                       | P63                                           |
| 7     | 18     | Left | BI-RADS 4         | Lumpectomy | 7              | Tan, well encapsulated                     | P63                                           |
| 8     | 19     | Right| BI-RADS 4         | Biopsy    | 3              |                                    | P63                                           |
| 9     | 21     | Right| BI-RADS 3         | Biopsy    | 2.3            |                                    | P63                                           |

Abbreviation: BI-RADS, Breast Imaging-Reporting and Data System.
The tumor size in tubular adenoma varies from 1 to 7.5 cm, rarely exceeds 5 cm. A case of a giant tubular adenoma of 14 cm in size has been recently reported. Also, another giant tubular adenoma of 15 cm has been reported on accessory breast in a pregnant woman. In our series, tumor size varies from 0.9 to 7 cm, with an average size of 3.08 cm. The macroscopic features of tubular adenoma are often indistinguishable from those of fibroadenoma. Typically, tumors are firm, homogeneous, well circumscribed, with yellowish to tan-brown cut surface. Features suggestive of malignancy, such as a hard consistency, ill-defined margins, skin inflammatory changes, are very rarely associated with tubular adenoma. None of these features have been observed in all of our 9 cases.

The histologic features of tubular adenoma are characteristic. Tumors are well circumscribed and consisted of a proliferation of uniform small round tubules lined by regular epithelial cells surrounded by myoepithelial cells. These tubules are packed in a small intervening stroma. The lumen of the tubules is usually empty but may contain proteinaceous material or mucin. Lymphocytes or mucinous changes can be found in the stroma. Immunohistochemical analysis confirms the presence of myoepithelial cells, ruling out the diagnosis of carcinoma. Markers of these myoepithelial cells are expressed in tubular adenoma: p63 protein, SMA, cytokeratin 14 (CK14), CK5/6, calponin, etc. Vimentine or CD34 highlights the stromal component of the tubular adenoma, and this feature

Figure 1. The radiologic aspects of breast tubular adenoma in our patients. (A) Breast mammography (oblique magnified incidence) showing a lesion with small round clustered calcifications (red circle), classified as BI-RADS 3 and (B) breast mammography showing a tumor with pleomorphic ill-defined calcifications (red arrow), classified as BI-RADS 4. BI-RADS indicates Breast Imaging-Reporting and Data System.

Figure 2. The macroscopic aspects of breast tubular adenoma. (A) A lumpectomy showing a well-circumscribed and lobulated whitish tumor and (B) a resected specimen showing a tan and well-circumscribed tumor.
can easily allow to rule out the diagnosis of other benign breast tumors with more abundant stroma. In our series, we have used p63 and SMA as myoepithelial markers, CK5/6 to exclude atypical hyperplasia or ductal carcinoma in situ, and CD34 to highlight the classical small amount of the stromal component of the tubular adenoma. This approach was intended to rule out any malignancy or any benign breast lesions that can mimic the histologic morphology of the tubular adenoma.

There are a number of histologic differential diagnoses of tubular adenoma, either malignant or benign breast tumors. Tubular carcinoma presented as a proliferation of well-differentiated tubules lined by a single layer of cells. This aspect can easily be mistaken for tubular adenoma, as it is not always easy to see myoepithelial cells at a routine morphologic examination. In tubular carcinoma, tubules have an open lumina with a haphazard distribution. The immunohistochemistry allows to rule out the diagnosis of the tubular carcinoma if myoepithelial cells markers are positive. Other differential diagnoses are some benign breast tumors. It is important to rule out their diagnosis as some benign tumors are associated with a risk of an invasive carcinoma. Atypical hyperplasia or ductal carcinoma in situ sometimes has morphologic features that can be difficult to distinguish from the tubular adenoma but they are negative for CK5/6. Fibroadenoma can be mistaken for tubular adenoma but the later has a characteristic small intervening stroma. Lactating adenoma is supposed to be either a tubular adenoma or a fibroadenoma with secretory changes (vacuolated cytoplasm, secretion in tubular lumen) that occur during pregnancy or lactation. Radial scar or complex sclerosing lesions are a group of benign tumors associated with a risk of cancer. Histologically, they present as a lobulocentric proliferations consisted of a central area of fibrosis surrounded by many tubules lined by regular epithelial and myoepithelial cells. The abundant fibrous stroma and the less monomorphic shape of proliferating tubules are not found in tubular adenoma. Microglandular adenosis is another differential diagnosis of tubular adenoma. It is a suspicious lesion and it is unclear whether it represents a truly benign proliferation or an indolent precursor lesion of an invasive carcinoma. Microglandular adenosis shows a proliferation of small rounded tubules lined by a single layer of epithelial cells. This feature differentiates microglandular adenosis from tubular adenoma, as immunohistochemistry confirms the absence of myoepithelial

Figure 3. (A) The morphologic aspects of the tubular adenoma showing a proliferation of regular small rounded tubules packed in an inconspicuous stroma. An eosinophilic proteinaceous material is seen in the lumen of some tubules (hematoxylin-eosin-saffron, original magnification x100). (B) A higher magnification showing tubules lined by luminal epithelial cells and myoepithelial cells (hematoxylin-eosin-saffron, original magnification x400).

Figure 4. Immunohistochemical analysis shows a prominent expression of CK5/6 (A) and p63 protein (B) by tumors cells (original magnification x200).
cells. Sclerosing adenosis can mimic the morphologic aspects of the tubular adenoma but its stromal component is often abundant. Phyllode tumors, benign or borderline, can also be mistaken for tubular adenoma. Of note, 2 of our patients (cases 3 and 7) with a 6- and 7-cm adenomas have been diagnosed as borderline tumor on core needle biopsy, but after lumpectomy, the diagnosis of tubular adenoma has been made. In fact, phyllode tumors have a characteristic leaf-like appearance, with abundant fibrous stroma.

In summary, the use of myoepithelial cell markers and stromal markers allows to rule out the diagnosis of breast carcinoma and other benign breast neoplasms that can be associated with a cancer risk. Tubular adenoma is not known to be associated with a risk of cancer, but in the literature cases, tubular adenoma associated with carcinoma has been reported. However, this seems to be a fortuitous association. In fact, reported cases of association between carcinoma and tubular adenoma showed generally histologically demarcated lesions and seem to be a collision between a separate tubular adenoma and an invasive carcinoma.

Conclusions

Tubular adenoma is a rare breast benign neoplasm of young premenopausal women. The radiologic features may be suspicious, thus the correct diagnosis relies on the histopathologic analysis. The immunohistochemical analysis by myoepithelial cells markers, combined with stromal markers, allows to rule out the various differential diagnoses, either malignant or benign tumors. This diagnostic approach allows a better clinical management of patients with breast tubular adenoma.

Author Contributions

BE and HEF contributed to study conception and design. ISS and SA helped in acquisition of data. BE, ISS, and SA contributed to analysis and interpretation of data. BE, HN, LC, and HEF contributed to drafting and revision of manuscript.

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