RESEARCH ARTICLE

Can Ultrasound be Used to Differentiate Tubular Adenomas of Breast from Fibroadenomas or Carcinoma?

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Abstract

Breast tubular adenomas are rare benign breast tumors and detailed descriptions of their sonographic appearance are necessary for differential diagnosis from fibroadenomas or breast cancers. This study investigated twenty-one histology-proved tubular adenomas in 17 patients and also included 48 fibroadenomas in 35 patients as a control group. There was no significant difference between the two groups with clinical presentation, which was age, tumor location, tumor number ($p>0.05$). Statistic analysis showed three significant factors in the differential diagnosis of tubular adenomas and fibroadenomas, including macro-lobulation ($p=0.01$), "tiny branch like" patterns ($p=0.001$) and vascularity ($p=0.02$). Other ultrasonographic features such as echogenicity, border, uniformity of echotexture, posterior acoustic enhancement, lateral wall shadowing were of no clinical significance ($p>0.05$). Calcifications were seen in three tubular adenomas which were different from those of carcinomas. Although tubular adenomas have some typical characteristics on sonography, surgery and core needle biopsy are still needed for complex cases to exclude progress to malignancy.

Keywords: Ultrasonography - breast - adenoma - diagnosis - differential

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Introduction

Breast tubular adenomas (TA) are rare benign tumors of epithelial origin, which accounted for 0.13% -1.7% of benign breast tumors. TA are relatively rare neoplasms that usually occur in young, non pregnant girls and women (Tavassoli et al., 2003). It was first described as a distinctive classification of adenomas in 1968 by Persaud et al. (1968). This uncommon lesion can be distinguished from fibroadenoma by the predominance of epithelium and relative lack of stroma. There have been few reports describing the imaging features of TA (Nishimori et al., 2000; Soo et al., 2000; Salemis et al., 2012). However, it generally was difficult to distinguish from fibroadenoma (FA) in this regard (Soo et al., 2000; Salemis et al., 2012). To the best of our knowledge, detailed descriptions of the ultrasonography (US) appearances of TA were sparse. The purpose of this study was to evaluate the gray-scale and Doppler US features of TA of breast and to compare with FA.

Materials and Methods

After institutional review board approval, a retrospective review of medical and imaging records of patients of histology-proved as TA and FA was performed.

Patients

Study cases were 21 pathological confirmed TA that underwent US examinations in our department during 2002-2012. They were all female, age 14-54 years (25.1±11.6 years). There were no women in pregnancy and lactation. Eleven cases had single breast lesion. The remaining 6 cases had two or three lesions, and only the lesion which was pathology-proved was used for imaging analysis. There were 8 patients with lesions located at the right breast, 8 patients with lesions located in the left breast and one patient with lesions at both breasts. Lesions in 12 patients were surgically removed, and the remaining 5 were removed by a Mammotome biopsy system (Johnson & Johnson Corp., New Brunswick, NJ) using an ultrasound-guidance.

One thousand and eight consecutive cases that underwent ultrasound examination were pathologically confirmed as FA. Among these cases, we random selected 35 cases who served as control group. Random sampling was made through mechanical methods as picking strips of paper with names written on it from a box while the researcher was blindfolded. There were 35 females, age 16-49 years (mean 27.3±8.4 years). There were 18 patients with lesions located at the right breast, 10 patients with lesions located in the left breast and 7 patients with lesions at both breasts. Lesions in 20 patients were surgically

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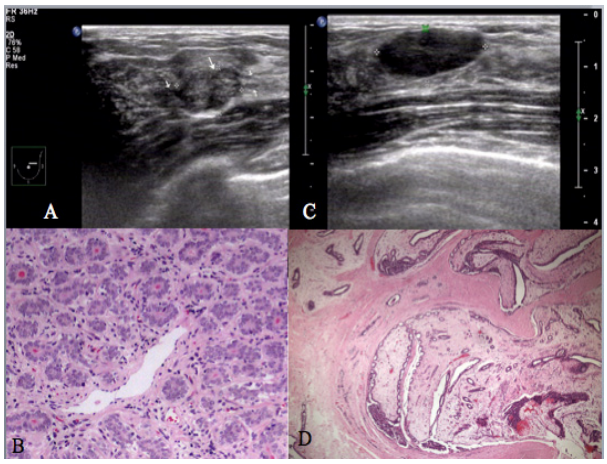

Figure 1. A 21-year-old Girl Was Found to Have Two Nodules Located at Both Breasts. (A) The left lesion was heterogeneous, well-defined and demonstrated a gentle lobulated contour (large arrow) and thin "branch type" (small arrows). On color Doppler flow imaging, the lesion showed minimal blood flow signal. (B) Pathologic diagnosis of the left lesion was tubular adenoma. The lesion was characterized by tightly packed acinar units with sparse intervening connective tissue. A large crack-like thin-wall vessel was also seen within the lesion. (H and E, ×100). (C) The mass of the right breast was hypoechoic compared to fat. The mass was well circumscribed with slight posterior acoustic enhancement and demonstrated the typical ultrasonic features of fibroadenomas. On color Doppler flow imaging, the mass also showed minimal blood flow signal. (D) The histologic finding of the right lesion was fibroadenoma. The image demonstrated abundant myxoid connective tissue and large dilated ducts, which was distinctly different from the image of tubular adenomas (H and E, ×40)

removed, and 6 patients were diagnosed and cured by the Mammotome biopsy system, and 9 patients were diagnosed by biopsy without surgical resection.

Instrument and methods

The equipment used included Logic 9 (General Electric Healthcare, WI, USA) and iU22 (Philips Medical Systems, Bothell, WA, USA) with 7-17MHz linear array probes. Standard equipment settings dedicated for breast were used, and Doppler was set at low wall filter and low velocity scale. The color areas were carefully searched with no extra pressure used, and color gain was adjusted to optimize the color flow signals without causing excessive noise. The US images were reviewed by two radiologists experienced in breast ultrasound with more than 10-year experiences. Features of enrolled lesions were evaluated in shape, border characteristics, echogenicity, uniformity of echo texture, posterior acoustic enhancement, lateral acoustic shadow, calcification, and vascular pattern.

A lesion with a ratio of anteroposterior to transverse diameter (A/T)≤1 (parallel to the skin) was defined as oval shape, and a ratio of A/T>1 as round shape. Border characteristics included whether there was well-defined border, macro-lobulations, and branch pattern extensions (Figure 1). Lesion with distinctive border related to surrounding tissues was considered well-defined. Macro-lobulations were defined as 2-4 mild, smooth, round lobulations on the surface of a solid breast nodule. "Thin branch-like pattern" was defined as multiple small and thin projections (parallel to the chest) from the nodule extending into the surrounding tissues (Figure 1). The presence of the thin branch-like pattern usually indicates an incomplete capsule. The echogenecity of the tumor was classified as hyper-, iso- and hypo-echoic compared with fat. Homogeneous tumor had one level of internal echoes, while heterogeneous tumor had various echoes levels.

On color Doppler US, that no flow signals detected inside the lesion was defined as avascular type. The vascularity types of tumor were determined to be minimal, moderate, or marked (Adler et al., 1990). One or two pixels containing flow (usually less than 1 mm in diameter) was considered minimal flow. If a main vessel was seen in the area and/or several small vessels were visualized, the blood flow was judged to be moderate. Tumors with more than four internal vessels on color or power Doppler imaging were considered marked vascular.

Table 1. Clinical Information of the Patients with Tubular Adenomas (TA) and Fibroadenomas (FA)

Clinical presentation	TA (n=17)	FA (n=35)	*P* value
Mean age (years)	25.1±9.8	27.3±8.4	0.932
Tumor size (longest diameter)	2.39±2.0 cm	2.18±1.5	0.401
Tumor number			0.943
Single	11	23	
Multiple	6	12	
Tumor location			0.238
Right	8	10	
Left	8	18	
Both	1	7	
Breast background			0.202
Gland hyperplasia	10	21	
Normal	7	14	

Statistical Analysis

All quantitative data are expressed as mean±S.D. and range unless otherwise indicated. Comparison of continuous variables was performed using the independent sample t test. Comparison of categorical variables was performed using the chi-square test (or Fisher's exact test where appropriate). The level of significance was set at 0.05 for all tests. All data were analyzed with SPSS 13.0 software (SPSS Inc., Chicago, Illinois).

Results

General features

Table 1 showed the clinical presentations of the 17 cases of TA and 35 cases of FA.

In TA group, the mean age was younger than that of FA group (25.1 vs 27.3 years), although there was no significant difference (p=0.932). The mean diameter of TA was 2.39±2.0cm (0.6-9.0cm), while the mean diameter of FA was 2.18±1.5cm (0.6-10cm). There was no significant difference in tumor size (F=0.716, p=0.401). Clinically, 58.8% of the patients with TA (10/17) presented mammal gland hyperplasia, which was similar to the presentation of FA (60.0%, 21/35).

Table 2. Sonographic Features of Tubular Adenomas (TA) and Fibroadenomas (FA)

Sonographic features	TA (n=21)	FA (n=48)	χ^2	*P* value
Echogenecities*			_	0.218
Hypoechoic	19	47		
Isoechoic	2	1		
Margin			0.003	0.957
Well-defined	18	43		
Ill-defined	3	5		
Macro-lobulation			6.6	0.01
Present	7	3		
Absent	14	45		
Texture			0.308	0.579
Homogeneous	13	33		
Heterogeneous	8	15		
Posterior acoustic enhancement			0.088	0.766
Present	10	21		
Absent	11	27		
Lateral acoustic shadow			2.772	0.096
Present	4	29		
Absent	17	19		
"Thin branch-like" pattern			10.971	0.001
Present	8	2		
Absent	13	46		
Calcification			2.915	0.088
Present	3	1		
Absent	18	47		
Vascularity			5.441	0.02
Avascular	5	26		
Present	16	22	0.19	0.552
Minimal	10	14		
Moderate	2	5		
Marked	4	3		

Unless otherwise indicated, the chi-square test was used as the statistical method. Data are number of breast lesions. *Fisher's exact test was used

Sonographic features

The shape of the lesions was all oval. Table 2 showed the US features of TA and FA.

In TA group, 90.5% (19/21) lesions represented hypo-echoic, 38.1% (8/21) heterogeneous in texture, 85.7% (18/21) had well-defined margin, 47.6% (10/21) had posterior acoustic enhancement, and 19.0% (4/21) with lateral acoustic shadow. There was no significant difference between the two groups with the above mentioned US features.

There were 7 out of 21 (33.3%) TA showed macro-lobulations, 8 out of 21 (38.1%) TA showed "thin branch type", while 3 out of 48 (6.23%) FA showed macro-lobulations (p= 0.01), 2 out of 48 (4.2%) FA showed "thin branch type" (p=0.001).

Five out of 21 (23.8%) lesions were avascular, while 26 out of 48 (54.2%) lesions in FA group were avascular (p=0.02). There was no significant difference between the two groups as for the different vascular types of tumor (p=0.552).

In TA group, there were three lesions with dot-flake calcification (14.3%) (two of the three lesions were in the same patient). In FA group, there was only one lesion with flake calcification (p=0.088).

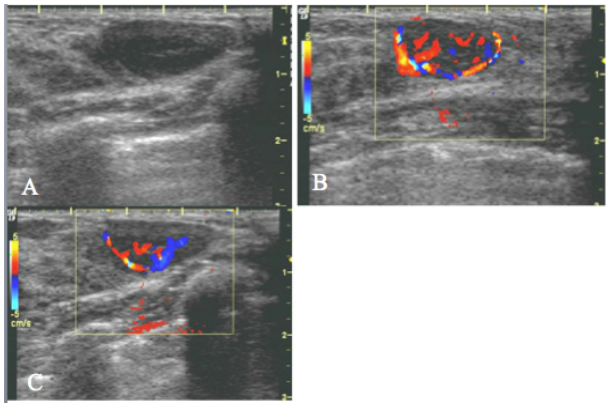

Figure 2. A 24-year-old Woman with Left Breast Nodule Palpable on Physical Exam. (A) The breast nodule located in the 4 o'clock position of the left breast, measuring 2.0x0.7cm. The nodule was well-defined, hypoechoic and with lymph node-like structure to a certain extent. (B-C) On color Doppler ultrasound, multiple feeding vessels (marked type) within the nodule was observed. In some ultrasound sections, central hilar-like vasculature was showed (C). The nodule was misdiagnosed as inflammatory lymph node of breast on ultrasound. By histological section from surgical specimen, it was finally diagnosed as tubular adenomas

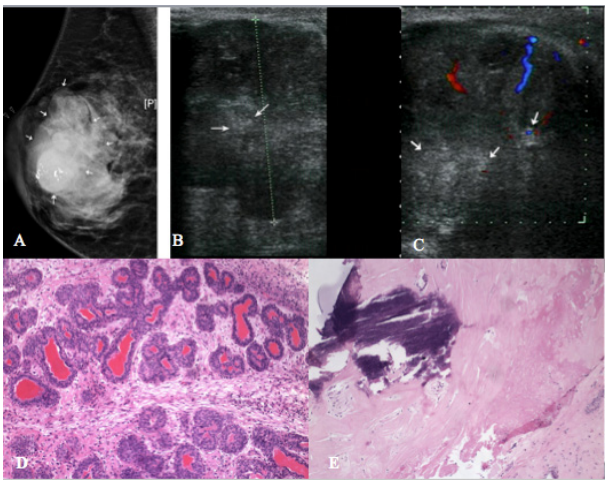

Figure 3. A 54-year-old Woman with Calcified Tubular Adenoma in Both Breasts, Which Was Misdiagnosed as Phyllodes Tumor by Ultrasound. (A) Right craniocaudal mammogram showed a large mass (arrows) containing multiple irregular, popcorn-like with sharp boundary and high density calcifications, associated with partial skin thickening (△). (B-C) Ultrasonography showed a heterogeneous macro-lobulated hypoechoic gaint mass with multiple echogenic foci (arrows). On color Doppler flow imaging, the tumor showed marked vascularity (C). (D-E) Pathologic diagnosis was tubular adenomas with irregular and coarse stromal calcifications (H and E, magnification×40)

Diagnostic performance of US and follow-up

Sixteen lesions in TA group were diagnosed as FA. One case was misdiagnosed as reactive lymph node because of features of hilum-like structure and central hilar vasculature to a certain extent (Figure 2). One case with bilateral lesions was misdiagnosed as potential malignant tumors because the lesions were ill-defined, lobulated and with multiple patchy calcifications (Figure 3). It was misdiagnosed as phyllodes tumor. The patient also received mammography and was diagnosed as

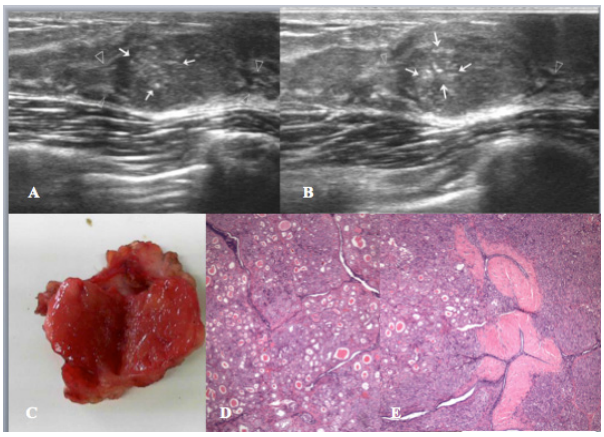

Figure 4. A 22-year Old Woman with a Palpable Breast Nodule Located in the 12 o'clock Position of the Right Breast. (A-B) Baseline ultrasound showed a 1.8x1.2cm hypoechoic nodule with thin "branch type" (△), heterogeneous texture and suspicious calcifications (arrows). A maximum transverse ultrasound view of the nodule showed multiple punctuate foci, which might be calcifications within the nodule (B). The lesion was diagnosed as suspected malignant by ultrasound. Furthermore, the patient received mammography examination and there was not calcification found. Finally, the patient received lumpectomy. (C) Gross findings showed a well demarcated and isolated nodules with no true capsule appeared gray-red in color. The nodule was of medium and fine texture. (D) Histological section from surgical specimen, the nodule was composed by tightly packed tubular structures. In some areas, eosinophilic protein aceous material was present within the cystically dilated tubules. (H and E, magnification×40). (E) In some area, the areas of hyaline degeneration and collagen deposition were found, which would be the areas of suspicious calcifications found by ultrasound (H and E, magnification×40)

breast cancer. Then, the patient was planned to receive breast-conserving surgery. Intra-operative frozen-section pathologic findings revealed it was benign lesion. So, the patient received lumpectomy instead of breast-conserving surgery. As of this writing, this patient has survived for 22 months without recurrence. The other patient with the lesion of multiple punctate calcifications was diagnosed as suspected malignancy (Figure 4). However, there was not calcification found on the mammography. Finally, the patient received lumpectomy. The remaining patient was with diagnostic uncertainty and also received breast lump excision.

In FA group, only 3 cases with complex performance of FA were with diagnostic uncertainty, while the remaining lesions were all diagnosed as FA (32/35 cases, 91.4%).

After a mean follow-up period of 37.7±27.1 months (6-120 months), all the 17 patients are alive and no local or remote recurrence is developed. In FA group, the mean follow-up period was 30.6±20.9 months (5-74 months). Recurrent FA of breast was seen in three patients after lumpectomy. There was enlargement in size in two patients of FA who received biopsy during follow-up. No local or remote recurrence is developed in the remaining 30 patients.

Discussion

US is widely used to evaluate palpable breast lesions, and FA represents the most common benign breast masses. In contrast, TA is rare benign epithelial tumor arising from the terminal ductal-lobular units (TDLUs) and accounting only for 0.13-1.7% of benign breast masses (Tavassoli et al., 2003). Histologically, TA is distinguished from FA by the predominance of acinar epithelium and sparse stroma. Microscopically, the lesion is sharply demarcated from the surrounding mammary tissue but has no true capsule (Moross et al., 1983). It consists of tubular structures of regular size and shape, indistinguishable from normal breast tissue. The tubules are lined by one layer of epithelial cells and an attenuated layer of myoepithelial cells.

The definitive identification of TA of breast as a distinct clinic-pathological entity was achieved by Hertel et al. in 1976 (Hertel et al., 1976). However, the true nature of the neoplasm remains controversial. Some researchers supported a common histogenesis for TA, lactating adenoma and FA (LE GAL, 1961). They suggest that the lesion is simply an extreme variant of FA. An immune-histochemical study of TA and FA revealed that several cell components of both epithelial and mesenchymal origin (epithelial cells, myoepithelial cells and myofibroblasts) were involved in the genesis of tubular adenomas. The morphological and immune-histochemical features of TA closely resemble to those of FA in some areas of the tumors (Maiorano et al., 1995). The result of our research seems to give further strength to the hypothesis that TA and FA are closely related tumors.

In the present study, most tubular adenomas appear as a well-defined lesion, and share common features of simple FA, such as oval shape, hypoechoic, posterior acoustic enhancement, etc. Also, there are several different features between the two groups, that is macro-lobulations, thin branch-type and present of vascularity. The proportion of macro-lobulated lesions in TA group is greater than that of FA (41.2% vs 6.3%). The explanation may be that the tumor was often fleshy gross appearance and softer in texture than FA because of little intervening stroma (LE GAL, 1961). With the tumor growth, fibrous stroma or fibrous septa are easy to divide the tumors in nodular appearance or to form a contour with four or fewer gentle lobulations.

In general, the finding of a "branch pattern" suggests that a process is spreading along the ductal system and increases the likelihood of malignancy (Stavros et al., 1995). Thin branch pattern here means multiple thin extensions from the main mass into the surrounding duct. A branching pattern tends to indicate the not well-defined margin of the nodule or the continuity between the tumor tissue and the surrounding duct. In the present study, thin branch pattern was rarely seen in FA group (4.2%). This feature may reflect the distinct feature of TA, because it consists of tubular structures of regular size and shape, indistinguishable from normal breast tissue on pathology and there is no true capsule of TA. Moreover, the larger tubules might give rise to thin branches in the mammary gland parenchyma. Although, the feature alone will cause more concern of radiologist and surgeon, we hypothesized that the combined criteria of oval shape, macro-lobulations, present of vascularity could improve

the predictive ability of sonography for TA instead of malignant breast tumor. Thus, excessive resection and biopsy may be avoided.

On color Doppler flow imaging, most of the tubular adenomas (76.2%) tended to have blood flow signals, including 4 cases of lesions with marked vascular signals. The contribution of blood flow information for differential diagnosis is controversial. Previously published results suggest the presence of Doppler signals within a solid breast mass is a nonspecific finding (McNicholas et al., 1993; Holcombe et al., 1995; Birdwell et al., 1997; Strano et al., 2004). The presence of color Doppler flow has been detected in up to83% of FA (Strano et al., 2004). Some emphasized that detectable blood flow in breast masses is more common in cancer than in fibroadenoma and is highly suggestive of malignancy if the mass is less than 13 mm in size (Holcombe et al., 1995). In this study, TA is easier to show blood flow signals than FA.

TA usually occurs in young women of childbearing age, rare in post-menopausal women (Goto et al., 2009). Detailed case reports of TA in old women are sparse. It was difficult to distinguish from malignant tumor which usually occurred in old women and the preoperative examinations are often misdiagnosed both on radiologic and cytohistologic examinations (Domoto et al., 2002; Rovera et al., 2006; Salemis et al., 2012). In older women, the features of TA may resemble that of malignant mass, such as obscure boundary, irregular shape, uneven echotexture and some with microcalcifications (Nishimori et al., 2000; Soo et al., 2000). There was only one old woman of bilateral lesions with multiple large (>2mm) calcifications in our research (Figure 3). The calcifications here are patchy, irregular, popcorn-like with sharp boundary and high density, which are different from that in breast carcinoma. In general, morphology alone in some well-defined instances (popcorn, eggshell or tram-track calcification) can be used to identify the benign nature of a breast nodule, and may be considered as "benign-looking" (Limite et al., 2013), whereas small, branching and casting types and heterogeneous calcifications will always be highly suspicious of malignant. However, there are many morphological possibilities. Calcifications may be a sign of benign changes but they can also be a product of malignant process. For our case, active cell secretion, calcium deposits after cellular necrosis are the most possible reasons for the formation of calcifications in the old woman. In a recently published research of TA (Soo et al., 2000), they found three of the five screening-detected lesions contained microcalcifications and all occurred in patients who were 38 years old or older. In these patients, microcalcifications forming inspissated secretions were located within the dilated acinar glands. The morphology of calcifications was dense, punctate, or irregular without castlike or branching forms and the microcalcifications were tightly grouped within a mass which was similar to the calcifications of the other case in our group (Figure 4). They speculated that morphology features of microcalcifications may prove to be a distinctive feature of TA. Anyway, we should pay more attention on calcification for it may be a precursor of malignant process from a radiological point of view.

Rare cases have been described of in situ and/or invasive carcinoma involving adenomas. To the best of our knowledge, there were only four case report of carcinoma arising in TA of the breast (Hill et al., 1954; Fechner, 1987; Domoto et al., 2002; Saimura et al., 2012). In 1954, Hill and Miller described the first case of invasive carcinoma within the area of TA, and the liver metastasis of the breast carcinoma. The most recent case was a 33 years woman with a tumor existence for 18 years. The carcinoma component was suspected due to the increasing microcalcifications. It was diagnosed as ductal carcinoma in situ (DCIS) arising in the preexisting tubular adenoma. Although the histological transition between DCIS and TA was not determined, DCIS was found to be completely surrounded by the tubular adenoma and it had also spread within it. The same phenomenon is also known to occur in FA (Limite et al., 2013). The relative risk of breast carcinoma development is believed to be increased 1.8-3.88 fold in women who have previously had a FA (Kriegeret al., 1992; Dupont et al., 1994). And the incidence of carcinoma within FA is estimated as 0.1-0.3% (Stafyla et al., 2004). As mentioned above, TA may be simply an extreme variant of FA, so, TA also has the potential of malignant transformation. Radiologists should keep in mind that the possibility of a carcinoma arising in a tubular adenoma or a collision of the two separate entities will exist, especially in the elderly.

The differentiation between TA and FA is also very difficult by other imaging modalities except for US (Soo et al., 2000; Yoo et al., 2013). Senga et al reported that 201T1-chloride was concentrated in TA, therefore, 201T1-chloride scintigraphy was very valuable for differentiating TA from FA (Senga et al., 1992). However, scintigraphy is not applied to screen breast lesions routinely, the clinical value of scintigraphy imaging is limited.

Surgical excision and core needle biopsy are necessary to establish a definitive diagnosis of TA. It might be difficult to diagnose TA on fine needle aspiration cytology from the point of view of existing cases reported (Rovera et al., 2006; Calderaro et al., 2010). As for treatment, lumpectomy is sufficient for the treatment of TA, and further clinical observation did not show recurrence or malignant transformation of the 21 lesions in the group. If histopathological examination confirms a benign character of the lesion and the patient who refused to have visible scars by general incision, surgery may be avoided but regular follow-up is recommended. For patient suspected of TA with calcification, surgery is warranted and exploratory lumpectomy maybe the most appropriate treatment for this tumor.

Several limitations in the present study should be addressed. Firstly, the retrospective nature of this study may be considered an important limitation, and the data should be confirmed by prospective studies. Secondly, the incidence of TA is far lower than FA. We randomize choose 35 patients among FA. There was a selection bias. Thirdly, we considered these two kinds of breast tumors had similar imaging finding and were easy to be misdiagnosed, so, we choose FA as control group. Our research finding may be helpful to understand the relationship of TA and FA. Sometimes, TA can take

on a malignant behavior, further differential diagnoses with other breast tumor, especially those with complex appearances should be also considered.

In conclusion, TA of breast is rare benign breast tumor that usually occurs in patients younger than 39 years, and it is often misdiagnosed as FA. TA are more commonly seen with macro-lobulation (p=0.01), tiny "branch like pattern" (p= 0.001) and presence of vascularity (p=0.02) related to FA in the present study. A comprehensive US analysis may be helpful in preoperative differential diagnosis and avoid excessive surgery.

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