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Case Report

Sonographic, microscopic, and immunohistochemical features of nipple adenoma coexisting with intra-ductal papillary carcinoma: a rare case report

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Abstract: Nipple adenoma is an uncommon benign mammary lesion derived from the lactiferous ducts. This is the first case of nipple adenoma coexisting with intra-ductal papillary carcinoma with sonographic, microscopic, and immunohistochemical analysis. In this report, a case of nipple adenoma coexisting with intra-ductal papillary carcinoma is presented from a 72-year-old female patient. Ultrasonography showed a hyperechoic lesion with abundant blood flow signal in the right papilla. Histologically, there was infiltrating growth or compression deformation of gland ducts in the sub-epithelial stroma. The myoepithelial cells of the gland ducts were p63 positive, CK5/6 positive, and smooth muscle actin (SMA) positive. In addition, there was a local lesion of intra-ductal papillary carcinoma. The epithelial cells arranged in papillary shape, and the nuclei of epithelial cells have low or moderate atypia. CK5/6 negative, p63 negative; SMA negative; estrogen receptor (ER) and progesterone receptor (PR) heterogeneous positive; Ki67 index was about 70%. The patient was alive with no tumor recurrence during 4 years of postoperative follow-up period. Nipple adenoma coexisting with intra-ductal papillary carcinoma is exceptionally rare. This kind of case is reported based on ultrasonic characteristics, microscopic features, and immunohistochemical testing, which highlights the possibility of nipple adenoma coexisting with intra-ductal papillary carcinoma and provides most effective basis for the diagnosis and treatment of this disease.

Keywords: Nipple adenoma, intra-ductal papillary carcinoma, immunohistochemistry

Introduction

Nipple adenoma is an uncommon lesion of the benign mammary tumor. It generally happens in females aged 40 to 50 [1-3]. This benign tumor is also termed superficial papillary adenomatosis and erosive adenomatosis. Clinically, the patient with nipple adenoma often has nipple discharge, papillae thickening, erosion, etc [4]. Ultrasonography shows that there is a hyperechoic mass with or without blood flow in the lesion. Microscopically, it includes adenosis pattern, papillomatosis pattern and sclerosing pattern with pseudoinfiltration. These histological patterns are often mixed [5]. Nipple adenoma is characterized by positive expression for p63, SMA and CK5/6 in myoepithelial cell [2]. The cases of nipple adenoma with malignant tumors are very rare [6]. Here, a case of nipple adenoma coexisting is reported with intra-ductal papillary carcinoma, undergoing the surgery of endometrial carcinoma.

Case presentation

The patient was a 72-year-old Chinese woman. She suffered an operation of endometrial carcinoma in 2008, undergoing 6 cycles of chemical therapy. At the beginning of 2013, the patient unintentionally touched a mass lesion under right nipple but didn't feel the pain. The medium size of the lesion was 0.6 cm and the shape of the mass lesion was irregular. The patient noticed that the mass lesion increased in size and caused clear-yellow discharge and blood discharge before she was admitted to the hospital. There was no inflammation in the skin. Bilateral axillae did not reveal any lymphadenopathy on local examination.

The patient was admitted to the First Affiliated Hospital of China Medical University and a highly suspicious mass was found with associated calcifications by targeted ultrasonography. The result showed that there is a hyperechoic lesion

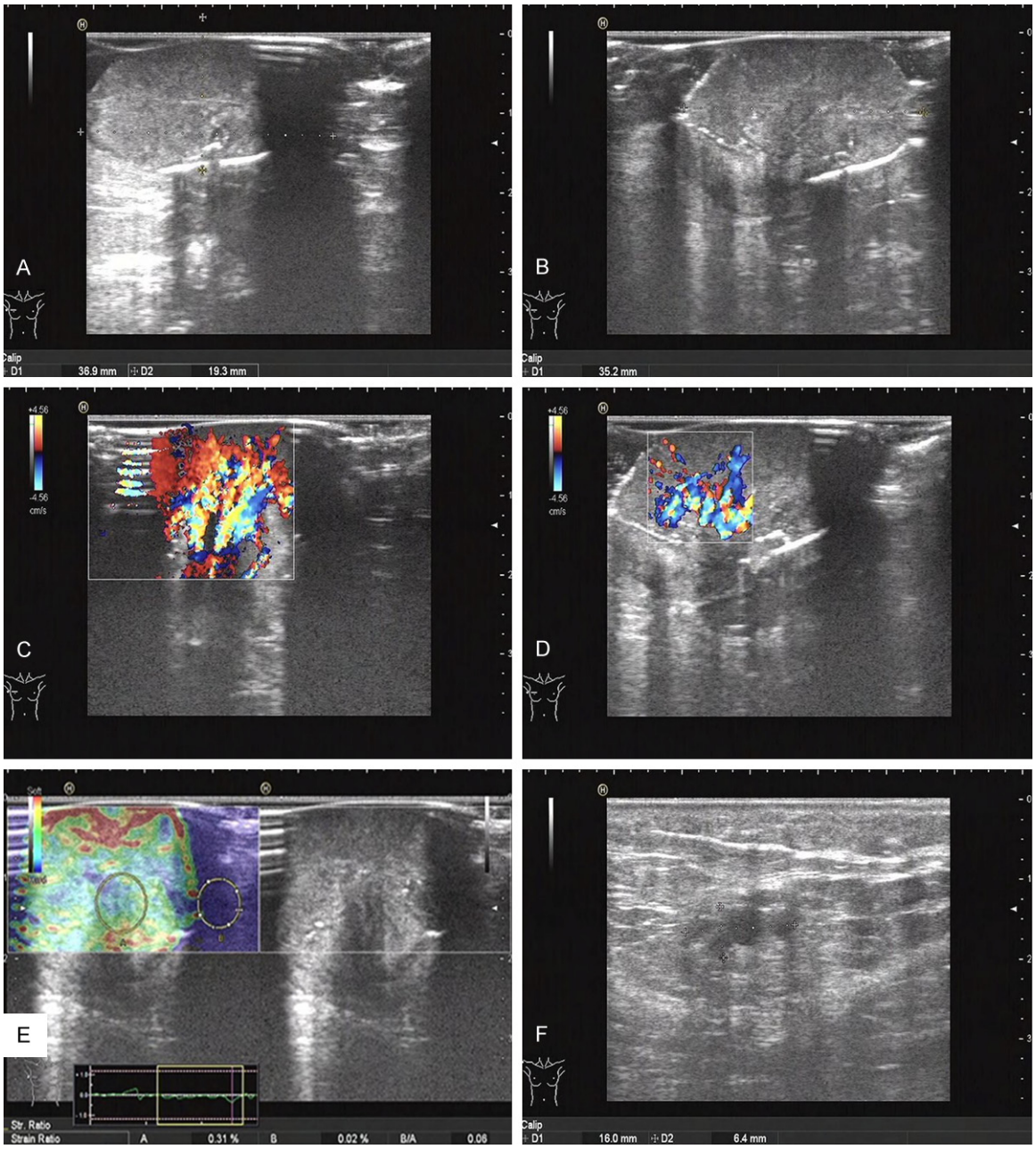

Figure 1. Ultrasound images of the lesion characteristics of the tumor on the right nipple and the lymphonodus on the right axillary fossa.

in right papilla measuring 3.69 × 1.93 × 3.52 cm, with abundant blood flow (**Figure 1A-D**). Most of the lesions were deformed, and the inspection of ultrasonic elastography showed blue-green mosaic like appearance (**Figure 1E**). The score was 2, and the value of strain ratio in ultrasound elastography is 0.06. There was a hypoechoic lymph node in the right axillary fossa measuring 1.6 × 0.64 cm (**Figure 1F**). A tumor with a cauliflower-like shape (approximately the yolk size) was completely resected (It is the surgery record, which is provided by the Department of Surgical Oncology and Breast Surgery, the First Affiliated Hospital of China Medical University). After 4 years of follow-up, the patient was alive with no tumor recurrence.

Materials and methods

The tumor tissue was fixed with 10% formalin and embedded in paraffin. The paraffin

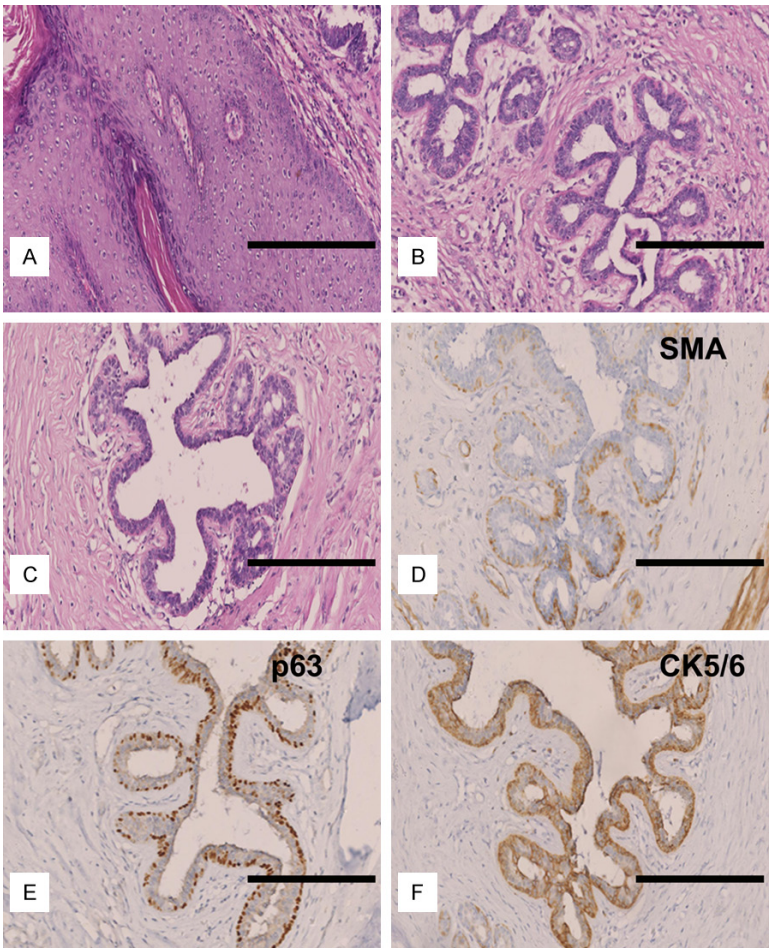

Figure 2. Nipple adenoma: (A-C) Histopathological findings of nipple adenoma. Immunohistochemistry examination of SMA (D), p63 (E), and CK5/6 (F). Bar = 600 μm.

block was cut into serial sections (4 μm) and then H&E staining was performed followed by immunohistochemistry staining. A streptavidin peroxidase system (Ultrasensitive; Mai Xin, Fuzhou, China) was used for immunohistochemistry staining. The tissue was immunestained with the following antibodies: CK5/6, smooth muscle actin (SMA), estrogen receptor (ER), progesterone receptor (PR), p63, and Ki67. The above antibodies were purchased from Mai Xin Inc., Fuzhou, China. The primary antibody was replaced with phosphate buffered saline (PBS) for the negative controls. This study was approved by the Ethics Committee of the First Affiliated Hospital of China Medical University. Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Results

Microscopic and immunohistochemical features in the lesion of nipple adenoma

The epidermis of the nipple was papillary proliferative with hyperkeratosis. There was infiltrating growth or compression deformation of gland ducts in the sub-epithelial stroma, as well as lymphocytes and smooth muscle distributed sparsely (**Figure 2A**, **2B**). The tubules were covered with two layers composed of glandular epithelium and myoepithelial cells. The glandular epithelium was flattened or cuboidal, and the centre of the cell was a spherical or oval nucleus (**Figure 2C**). The myoepithelial cells of the tubules were SMA positive, p63 positive, and CK5/6 positive (**Figure 2D-F**).

Microscopic and immunohistochemical features in the lesion of intra-ductal papillary carcinoma

A local lesion of intra-ductal papillary carcinoma was observed. The papillary structure was thin, and the epithelium was composed of one to several layers of monomorphic epithelial cells, arranged in papillary shape. Fibrosis is rare. The nuclei of epithelial cells have low or moderate atypia. The nuclear to cytoplasmic ratio increased significantly (**Figure 3A**, **3B**). In the papillary structure, p63 and SMA are negative, but they are positive in a few myoepithelial cells; CK5/6 negative; ER and PR heterogeneous positive; Ki67 index was about 70% (**Figure 3C-H**).

Discussion

Nipple adenoma is a rare benign tumor of the breast, which was first described by Jones in 1955 [7]. It is mainly a female adult disease [8, 9], occurring most often in 40 to 50 years old patients [10]. It is defined as a type of intra-

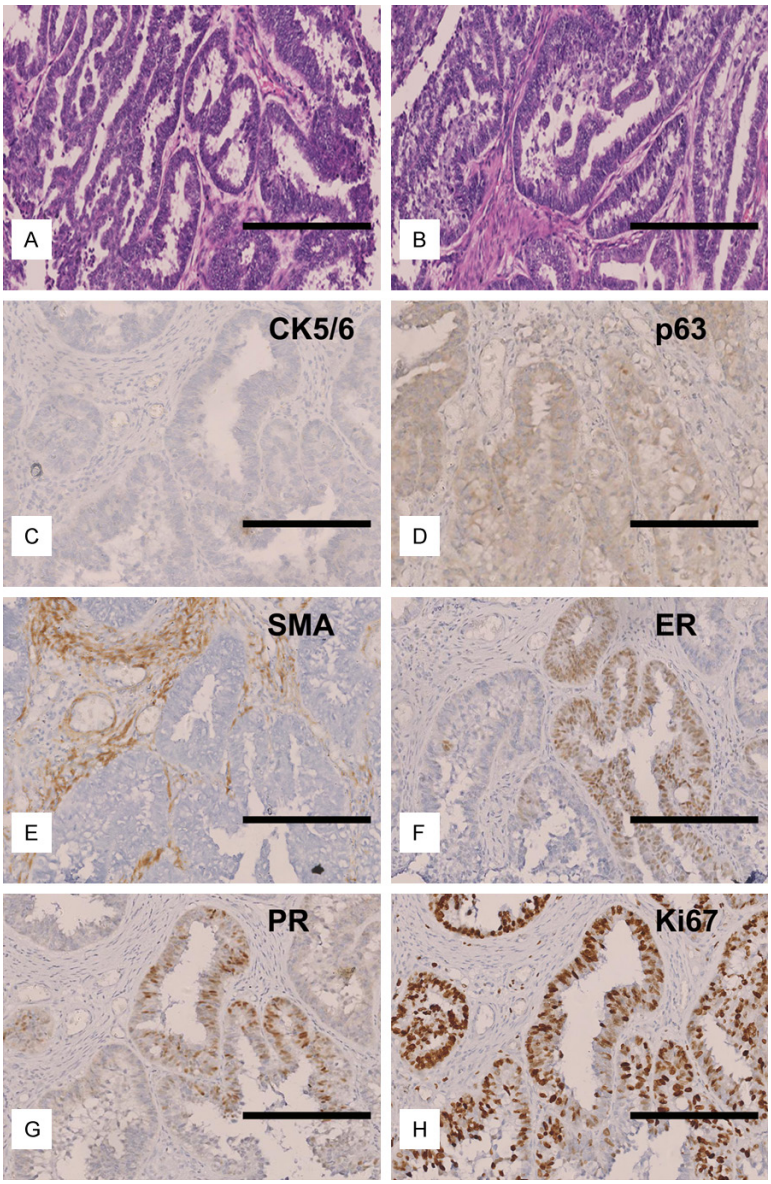

Figure 3. A local lesion of intra-ductal papillary carcinoma: (A, B) Histopathological findings of a local lesion of intra-ductal papillary carcinoma. Immunohistochemistry examination of CK5/6 (C), p63 (D), SMA (E), ER (F), PR (G), and Ki67 (H). Bar = 600 μm.

ductal papilloma that arises within the lactiferous ducts that are located within the nipple. It is well documented that incidental breast cancer has been detected at the time of the excision of nipple adenoma [6, 11], and the morbidity is very low [12]. It is still unclear that whether there is a relationship between nipple adenoma and breast cancer. Our case was a patient with nipple adenoma coexisting with intra-ductal papillary carcinoma. In addition, this patient had the operation of endometrial carcinoma.

Nipple adenoma is easy to be mistaken for Paget disease, especially in ultrasonic testing. The feature of Paget's disease in ultrasound showed an irregular, ill-defined, and hypoechoic lesion [13]. Limited reports indicated relatively increased blood flow signal in the nodule of nipple adenoma lesion [14], also in the periphery of the nodule [13]. Most of the nodules were well-circumscribed in the superficial part of the nipple. The lesions are usually very small in size (0.5-1.5 cm). Our case showed that blood flow was abundant in the lesion, but the size was too large and a hypoechoic lymph node was in axillary fossa on the same side. So the nipple adenoma in this study coexisted with malignant disease.

Microscopically, nipple adenoma contains three histological patterns. In the first place, adenosis pattern, there is interstitial fibrosis, which makes the shape of duct distorted; in the second place, papillomatosis pattern, papillary endothelial hyperplasia, accompanying a partial or total obliteration of the lumen; in the third place, sclerosing pattern with pseud-oinfiltration in which there are irregular ducts in sclerosing interstitial, and parts of them have infiltrative growth pattern, which is easy to confuse with invasive carcinoma. In this case, nipple adenoma was mainly based on the first histological pattern.

The presence of myoepithelial cell is important for distinction between invasive breast cancer and carcinoma *in situ*, as well as invasive breast cancer and pseudo-invasive lesion. It surrounds the epithelium of the ductal lobule, located on epithelial basement membrane. Myoepithelial cells surround gland ducts in the benign lesions of the breast. p63 was only posi-

tively expressed in the nucleus of the mammary myoepithelial cells, but not the cytoplasm. So p63 is good for judging the interstitial invasion of cancerous tissue. SMA is often combined with p63. CK5/6 is often positive expressed in myoepithelial cell of nipple adenoma [15, 16]. In this case, p63, SMA and CK5/6 were all positive expressed in myoepithelial cells, supporting the diagnosis of nipple adenoma.

SMA is the most common marker for myofibroblasts identification. It is used to stain smooth muscle or myoepithelial cells, as well as stromal myofibroblasts and pericytes, ER positive is good for patients who can benefit from endocrine therapy. Receptor expression for progesterone is induced by estrogen. Ductal carcinoma *in situ* in the breast showed high scores for ER, but was mostly negative for CK5/6 and p63 [17]. Intra-ductal papillary carcinoma is a type of ductal carcinoma *in situ*. In this case, there was some papillary structure, composed of monomorphic epithelial cells with cellular atypia. ER is heterogeneous positive, as well as PR, but SMA, CK5/6 and p63 is negative in papillary structure. p63 and SMA were positive in a few myoepithelial cells. In addition, Ki67 majority positive cells indicates strong proliferative activity. These results support intra-ductal papillary carcinoma.

Based on the above, nipple adenoma coexisting with intra-ductal papillary carcinoma is an exceptionally rare case. The morbidity of nipple adenoma is very low, and its coexisting with malignant disease is very rare. Careful ultrasonic testing and strict histological detection are important for accurate diagnosis. Complete resection of this tumor is correct treatment for this disease.

Conclusion

Nipple adenoma coexisting with intra-ductal papillary carcinoma is a rare case. We report for the first time this case with ultrasonic characteristics, microscopic features, and immunohistochemical testing. This case highlights the possibility of nipple adenoma coexisting with intra-ductal papillary carcinoma and provides a more effective basis for the diagnosis and treatment of this disease.

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Disclosure of conflict of interest

None.

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