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Case Report

Flat epithelial atypia in a mammary hamartoma: case report & clinicopathologic correlates

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Abstract: Mammary hamartoma is a rare benign breast neoplasm, composed of all breast tissue elements in variable proportions. It accounts for 4.8% of benign mammary tumors. Herein, we present a case of a 42-year-old woman who underwent right breast lumpectomy for a solitary well defined breast tumor. Histologic features were consistent with mammary hamartoma and an associated columnar cell changes including flat epithelial atypia. This is, to the best of our knowledge, the first reported case of such an association/finding. The paper will highlight the clinico-pathologic and molecular characteristics of hamartomas in general and summarize the current understanding on it's the pathogenesis.

Keywords: Mammary hamartoma, columnar cell changes, columnar cell hyperplasia, flat epithelial atypia, pseudoangiomatous hyperplasia, lobular neoplasia, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her2/neu)

Introduction

Mammary hamartoma is a rare well demarcated benign breast tumor, it consists of all breast tissue elements in variable proportions. Hamartoma forms 4.8% of benign mammary neoplasms [1]. This entity was initially described by Prym in 1928 as mastomas [2]. However, the term hamartoma was introduced by Arrigoni in 1971 [3]. In 1981, the WHO first recognized this entity in their classification [4].

Mammary hamartoma is an under-recognized entity, therefore the incidence may in fact be higher than that quoted in the medical literature. Histologically, the lesion display normal breast constituents. Correlation with the clinical and radiologic finding of a mass lesion is of paramount importance in arriving an accurate diagnosis [2]. However, with the implementation of breast screening cancer programs, more hamartomas will be identified [5].

Epithelial proliferative changes may occur in hamartomas, the commonest of which is epithelial hyperplasia, and rarely lobular or ductal neoplasia [5, 6]. We report the first case, in the English medical literature of a mammary hamartoma with associated columnar cell lesions including flat epithelial atypia.

Report of a case

A 42-year-old pre-menopausal female, presented with right sided breast mass. The patient first noticed the mass two years prior her current presentation. She noticed a recent increase in tumor size. At the initial presentation, the patient was investigated by radiology and the mass was biopsied. The initial pathology report was consistent with fibrocystic changes without evidence of malignancy. Consequently, she was offered a regular follow up. Physical examination revealed a right sided retro-areolar mobile mass, measuring approximately 4 cm in greatest dimension. There was no evidence of axillary lymphadenopathy. The left breast was unremarkable. Right breast mammography showed retro-areolar well circumscribed mass measuring 4.8×4.7×4.5 cm, two years earlier

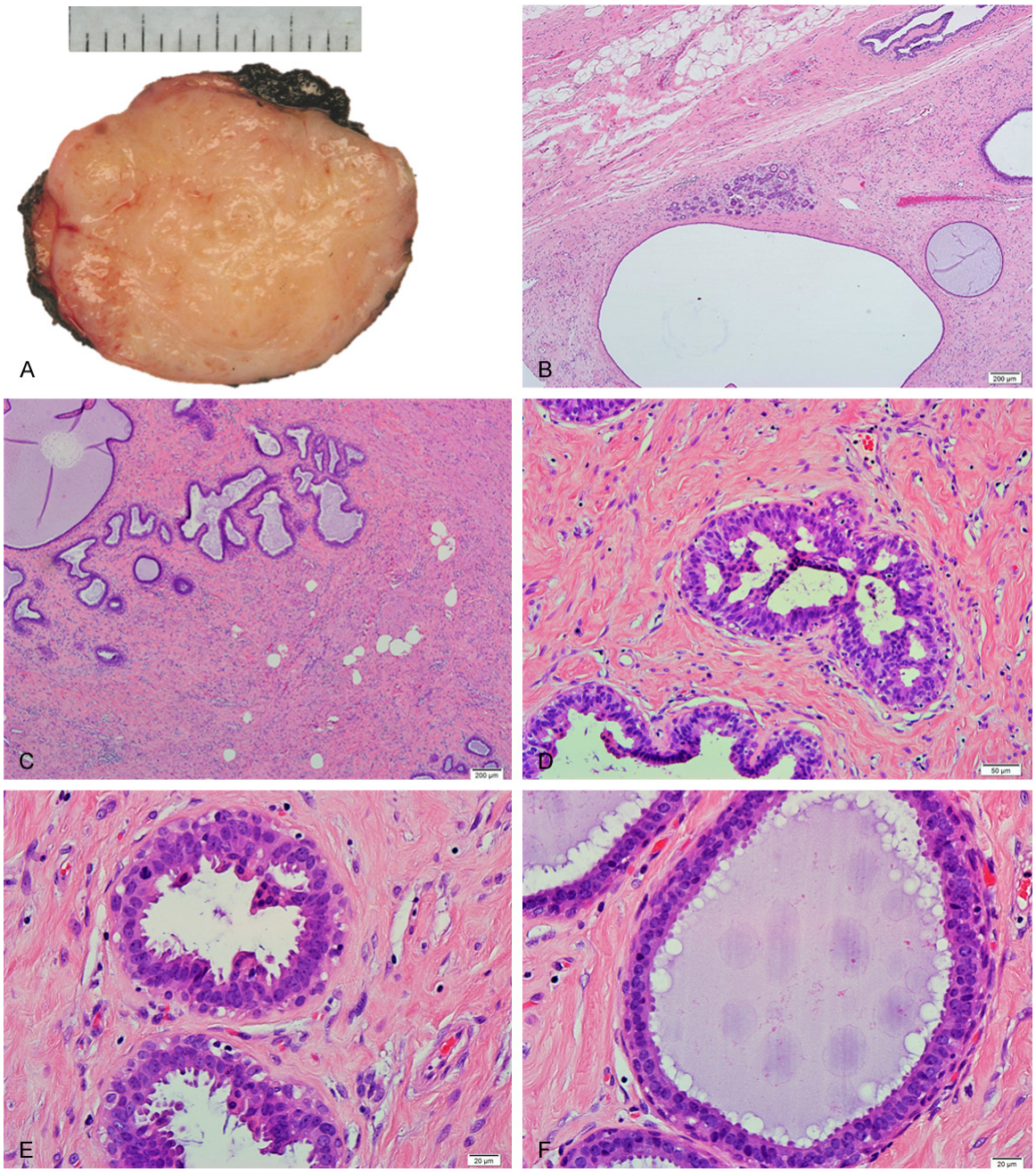

Figure 1. Breast. A. Gross image of a well circumscribed mass with white tan, rubbery cut surface showing vague lobulation. B. Low-power view of a circumscribed non-encapsulated mass (lower right) composed of different elements of mammary tissue, note a rim of compressed non-lesional tissue (upper left). C. Medium-power view highlight stroma composed of bland smooth muscle cells fascicles, and adipocytes. A focus of columnar cell change illustrating a more basophilic terminal duct lobular unit with variably dilated acini and irregular contours. D. Medium-power view of usual ductal hyperplasia, characterized by heterogeneous cellular proliferation with poorly defined cell borders and thin cellular bridges. E, F. High-power view of flat epithelial atypia, demonstrating dilated acini with relatively round contours, and lined by one to several layers of cuboidal epithelial cells with apical snouts. The cells display monomorphic-type low grade cytologic atypia, and nuclei lack perpendicular orientation to the basement membrane and exhibit clumped chromatin and prominent nucleoli.

the mass measured 3.7×3.6×3.6 cm. In addition, the tumor contain punctate clusters of micro-calcifications. Right breast ultrasound confirmed the presence of a well circumscribed

hypo echoic mass measures 4.7×4.7×2.7 cm with an associated anechoic areas. The patient opted for surgery, she underwent a right sided breast lumpectomy.

Gross examination revealed a circumscribed ovoid mass, measuring 5×4.5×3 cm and weighing 35 grams. Outer surface was smooth. Cut surface was white tan rubbery and lobulated, few small cysts were identified. There was no area of necrosis or hemorrhage (**Figure 1A**).

Microscopic examination demonstrated a circumscribed nodule of mammary tissue compressing a thin rim of benign surrounding tissue. The tumor was composed of mammary acini, ducts, adipose tissue, fibrous tissue and smooth muscle. In addition, patchy stromal mononuclear inflammatory cell infiltrates, and pseudoangiomatous stromal hyperplasia were noted. Foci of columnar cell change, illustrating a more basophilic terminal duct lobular unit with variably dilated acini and irregular contours were identified (**Figure 1B**, **1C**). Ducts demonstrating heterogeneous cellular proliferation of poorly defined cell borders, nuclear streaming and thin cellular bridges were evident (**Figure 1D**). Flat epithelial atypia, displaying dilated acini of relatively rounded contours, and lined by one to several layers of cuboidal epithelial cells with apical snouts. The cells display monomorphic-type low grade cytologic atypia, and nuclei lack perpendicular orientation to the basement membrane and exhibit clumped chromatin and prominent nucleoli (**Figure 1E**, **1F**). Intraluminal secretions were noted.

The Histopathologic features of the tumor were consistent with mammary hamartoma. Additional pathologic findings in association with the hamartoma included flat epithelial atypia, columnar cell change, columnar cell hyperplasia, usual ductal hyperplasia, apocrine cysts and adenosis. Twenty seven months following her operation, the patient is well and without any evidence of tumor recurrence.

Discussion

Mammary hamartoma is a rare benign breast tumor, it forms 4.8% of benign mammary neoplasms [1]. The tumor occurs mainly in women of third or fourth decade, and occasionally in adolescent females. A single case has been reported in a 36-year-old male patient [7]. Patients commonly present with painless circumscribed mass. Tumors may attain appreciable size, reaching up to 27 cm [1, 8, 9]. The tumor may recur if excision is inadequate [10].

The pathogenesis of breast hamartoma is largely unknown. Hamartomas are not associated with ethnicity or dietary habits [4]. Many authors perceive it as dysgenesis, or a focal malformation rather than true neoplastic transformation, in which a portion of the breast separates during fetal development from the rest of the tissue [9, 11, 12]. Some investigators speculate an etiological role of estrogen hormone [13, 14]. The ductal epithelium in hamartomas express hormonal receptors estrogen and progesterone, similar to surrounding nonlesional breast tissue [12]. Accordingly, there is no overexpression of c-erbB-2/Her2-neu protein, no expression of p53 and low labeling for Ki-67 proliferative marker, usually in the range of 2-3% [4].

Radiologic studies may propose the hamartoma diagnosis. Since mammographic round to oval mass surrounded by a radiolucent halo and corresponding to a sonographic heterogeneous mass with an echogenic or echo-lucent circle is characteristic of this lesion [15].

Hamartoma consists of all breast tissue elements disposed in a disorganized fashion and in variable proportions. The Histopathologic features are non-specific. However, the diagnostic possibility of hamartoma should be considered, when fibrosis surrounds lobules, fat within stroma, and pseudoangiomatous stromal change are present [14].

Diagnostic misinterpretation may arise if the pathologist is unaware of the clinical radiological findings. The case might be labeled as fibrocystic disease or normal breast with gynecomastia like changes. Furthermore, mammary hamartoma may be confused with fibroadenoma or even with low grade phyllodes tumors. Differentiation from fibroadenoma, a common benign neoplasm of the breast is challenging on limited needle biopsy material [1].

Few hamartoma display myoid differentiation, with positive immunohistochemical staining for muscle markers such as actin and desmin. These are termed myoid hamartoma. The mus-

cle component may be derived from blood vessels, areolar smooth muscle, or possibly from myoepithelium [16]. The smooth muscle cells in myoid hamartoma may assume an epithelioid morphology, a potential diagnostic pitfall with infiltrating lobular carcinoma. But the immunohistochemical profile of the epithelioid cells should aid the diagnosis [17]. In addition, the stroma in some tumors exhibit pseudoangiomatous hyperplasia [4, 14, 18].

There is an association between breast hamartoma and Cowden syndrome, an autosomal dominant cancer syndrome. Affected patients carry an increased risk for multiple skin, brain, breast, thyroid and gastrointestinal tract tumors and hamartomas [19, 20].

Epithelial proliferative changes may occur, albeit uncommon. The most frequent is epithelial hyperplasia in the order of 22-27% in reported series [4, 21]. Hamartomas bear histologic similarity to the surrounding normal breast, so on rare occasions lobular or ductal neoplasia may develop [4, 22-26]. The present case describes a mammary hamartoma with an associated columnar cell changes and flat epithelial atypia. The latter, is considered a neoplastic process involving the terminal duct lobular units. In flat epithelial atypia, the lining ductal epithelium is replaced by one to several layers of cuboidal to columnar cells that demonstrate monomorphic type low grade cytologic atypia [1]. There is an abnormal polarization of luminal epithelium. The nuclei are round to ovoid with prominent nucleoli. The involved ducts and acini are variably dilated, more basophilic and may show flocculent luminal secretions and apical cytoplasmic snouts. The cytologic features in flat epithelial atypia are reminiscent of those seen in low grade ductal carcinoma in situ (DCIS), but without the architectural complexity characteristic of DCIS [27]. Some molecular studies suggest that flat epithelial atypia is a precursor lesion of low grade malignancy in the breast. However, this data has been challenged recently. A Mayo cohort study showed that flat epithelial atypia is not an independent risk factor of breast cancer beyond associated epithelial proliferative lesions including those with and without atypia [28].

Few tumors have been investigated using molecular techniques, and aberration involving the 12q Multiple Aberration Region [29] is reported.

In summary, hamartoma is an uncommon benign breast neoplasm. Awareness of the clinical and radiological context is essential in arriving an accurate diagnosis. Neoplastic transformation in hamartomas, though exceedingly rare, do occur. Thus, careful sampling of the specimen is necessary.

Disclosure of conflict of interest

None.

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