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Pseudoangiomatous Stromal Hyperplasia (PASH) of the Breast: An Uncommon Finding in an Uncommon Patient

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Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 30-year-old
Final Diagnosis: Pseudoangiomatous stromal hyperplasia (PASH)
Symptoms: Breast mass
Medication: —
Clinical Procedure: Lumpectomy
Specialty: Obstetrics and Gynecology

Objective: Unknown ethiology
Background: Pseudoangiomatous stromal hyperplasia (PASH) is an uncommon benign breast lesion.
Case Report: PASH is reported in a young female in treatment for neurological diseases with multi-drug therapy (clonazepam, valproate and risperidone). Her menstrual cycles are irregular, and she reached menarche very late.
Conclusions: The higher PASH prevalence in premenopausal woman (the majority of whom are actively taking oral contraceptive pills), in 24% to 47% of men with gynecomastia and during pregnancy supports a hormonal etiology; the interaction between clonazepam, valproate, risperidone and progesterone could increase the level of progesterone that could stimulate PASH growth.

MeSH Keywords: Breast Diseases • Breast Neoplasms • Drug Therapy, Combination • Mastectomy, Segmental

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Background

Pseudoangiomatous stromal hyperplasia (PASH) in an uncommon benign breast lesion that generally presents as a fast-growing palpable lesion or gynecomastia. PASH etiology is unknown, but hormonal influences are supposed. Our case report deals with a young woman with irregular menstrual cycles, delayed menarche and multi-drug therapy, who developed a breast lump increasing in volume.

Case Report

A 30-year-old female presented to our hospital with a left breast mass in February 2017. Her past medical history included intellectual disability and epilepsy from age of 2, secondary to neonatal hypoxia. She was receiving sodium valproate, phenobarbital, clonazepam and risperidone. She had no family history of breast disease or ovarian cancer. Her body weight was normal (body mass index 21 kg/m^2). She reached menarche at 22 years; her parents referred the use of estro-progestinic pills before the age of 22 years, unsuccessful in drug-induced menstrual flow. At PASH diagnosis, her menstrual cycle was irregular with a normal menstrual flow every 40 to 60 days. She had no pregnancies in the past.

Physical examination showed a 3 cm fixed and firm lump with a not-defined border below left nipple areola complex. Ultrasound examination showed a solid, not homogenous lesion measuring 20×10 mm in size in left Q3-5 with mild peripheral vascularization at color-doppler evaluation, irregular margins, ductal ectasia, without acoustic shadowing (Figure 1). There was likely bilateral reactive axillary lymphadenopathy. Fibrous mastopathy signs and fibroadenomas were found in both breasts. The ultrasound finding was suspicious for malignancy. Under ultrasonography guidance, core needle biopsy was performed, and histopathologic report showed benign fibroepithelial node, enriched in vascular space, suggestive for PASH. Considering the breast mass dimension, lumpectomy was performed. During surgery, the lump was hardly dissociable from adjacent tissue. The tumor resected from the left breast measured 25 mm. She was discharged on day 1 after surgery. Pathology confirms hamartoma-like fibroepithelial lesion with PASH features. No recurrence of disease is observed at 32 months follow-up.

Discussion

Pseudoangiomatous stromal hyperplasia (PASH) is an uncommon breast benign stromal lesion, first described by Vuitch in 1986 [1]. Incidental microscopic PASH can be found in up to 23% of consecutive breast specimens [2]. In contrast, PASH as

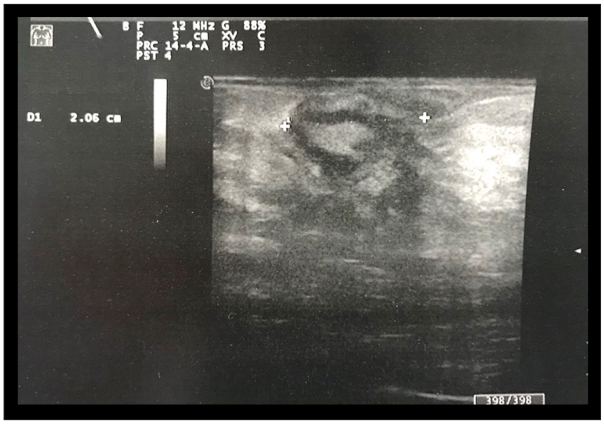

Figure 1. A lump found during the ultrasound examination.

a main pathological finding is a rare entity. Preoperative core biopsy fails to diagnose PASH in 35% of cases [3]. Ultrasound imaging is not specific: generally, it appears like a hypo-echoic ovoidal mass with regular margin. Treatment is usually surgical excision, although "watch and wait" strategy can be applied if PASH diagnosis is made on core biopsy and if the lump is less than 2 cm in size. Rapidly increased lump needs surgical approach to valuate contextual presence of ductal carcinoma *in situ* (DCIS). Recurrence rate is 9% to 21% [4], probably due to the persistence of a residual mass after surgery [5,6]. PASH is related to benign and malign breast lesions in up to 23% of cases but is not associated with an increased risk for malignity [7], rather it seems to be protective [8] although 2 case of synchronous tumoral PASH in the breast and axillary tissue are reported in literature [9,10]. On the other hand, there is an increased ipsilateral breast cancer prevalence in patients treated for PASH more than 5 years after PASH biopsy [11].

PASH is a complex network of slit-like spaced lined by endothelial-like spindle cells surrounded by dense collagenous stroma [12]. Fibroblasts and myofibroblasts proliferation and collagen over-secretion create a solid tissue with cystic areas resembling ectatic vessels (pseudo vascular spaces).

PASH stromal cells nuclei express high density progesterone receptors [13]; estrogen receptors expression is more variable [14]. Normal mammary stroma that showed no progesterone receptor staining instead. Progesterone is metabolized by cytochrome P450, that is inhibited by clonazepam [15]; valproate and risperidone are metabolized by cytochrome P450, so it could be a competition for the cytochrome between our patient multidrug therapy and progesterone. These interactions could increase the level of progesterone that could stimulate PASH growth. A hormonal etiology is also supported by the higher PASH prevalence in premenopausal woman (the majority of whom are actively taking oral contraceptive pills) [16], in 24% to 47% of men with gynecomastia [17] and by reported case of PASH in a transgender male during

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hormone therapy [18] or during pregnancy [19]. PASH affects pre-menopausal women or menopausal women in hormone replacement therapy (HRT). Anti-hormonal therapy could theoretically reduce PASH mass: a case report suggests tamoxifen use as alternative approach in management of PASH [20,21] but the lack of evidence does not support anti-hormonal therapy as adjuvant therapy.

Conclusions

PASH is an uncommon but benign lesion of the breast. Its origin is still unclear, but it seems to be related to hormone stimulation (primarily progesterone stimulation).

Efforts are necessary to recognized PASH lesion during diagnostic examinations (ultrasound, breast core-biopsy) in order to consider watch and wait management, procrastinating surgery if not necessary. A multidisciplinary approach is the best way to manage breast lesions, including PASH.

Knowledges about risk factor (related to hormonal etiology previously described) is essential to report suspected PASH lesion to the pathologist and help him to distinguish PASH from invasive cancer and support a conservative management if possible.

Department and Institution in which the work was done

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