



## Pseudoangiomatous Stromal Hyperplasia (PASH) in Adolescence: A Systematic Review

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### Abstract

**Objective:** Pseudoangiomatous Stromal Hyperplasia (PASH) of the breast is a benign mesenchymal proliferative lesion occurring most commonly in middle-aged, premenopausal women and it's exceptionally rare in adolescents. The aim of this study is to present a review of the literature on PASH in childhood, comparing its results with our new cases, and to define a standard approach for its treatment.

**Design and Patients:** We describe PASH in 3 pediatric patients and compare them with 24 adolescent cases described in literature.

**Main Outcome Measures:** Primary outcome was the type of treatment in adolescent patients with diagnosis of breast PASH. Secondary outcomes were the evidence of recurrence and the cosmetic results, associated with the patient satisfaction.

**Results:** All 24 patients described in literature underwent surgical excision of the lesion, the large majority a breast-conserving procedure. None of them had a recurrence, except for an adolescent female. Our 3 patients underwent surgically excision through breast-conserving circumareolar incisions. A slight breast asymmetry was still remaining, but it is improving spontaneously with the patient's growing.

**Conclusion:** PASH benign nature and complete healing after surgical resection represent aspects of tranquility which must be communicated to the patient, often worried because of the big size and the fast growth of the lesion. Preoperative core biopsy and hormonal therapy could be two new instruments to avoid surgery in some patients, but more likely in adults.

**Keywords:** PASH; Adolescence; CD31; CD34

### Introduction

Pseudoangiomatous Stromal Hyperplasia (PASH) is a rare benign mesenchymal proliferative lesion of the breast. Since its first description by Vuitch, Erlandson and Rosen in 1986, about 200 cases had been documented in the literature [1], including only around 20 adolescents. It occurs most commonly in middle-aged, premenopausal women; the age of the diagnosis varies between 14 to 74 years, but it's exceptionally rare in adolescents [2,3].

PASH is a clinical entity now well-known, but which still eludes knowledge of biological characteristics of the tumor. Breast tissue affected by PASH is characterized by dense myofibroblastic proliferation of mammary stroma, associated with inter anastomosing capillary-like space. Such morphology is the basis of the name of the lesion: Leon et al. proposed the term myofibroblastic hyperplasia of the mammary stroma to denote its true histogenesis. More recently it has been proposed to rename the injury to put greater emphasis on the characteristic type of cell PASH (Figure 1).

The exact etiology and pathogenesis of PASH is still unknown, but there are much evidence showing that the basis of the development of PASH is a prolonged hormonal (primarily progestogenic) stimulus. In general, it is believed to be an aberrant reactivity of myofibroblasts to endogenous or exogenous hormones. This strong hormonal component is supported by the fact that PASH appears most commonly in premenopausal women or in older women taking estrogen replacement. PASH is very similar histologically to the normal mammary stroma during the luteal

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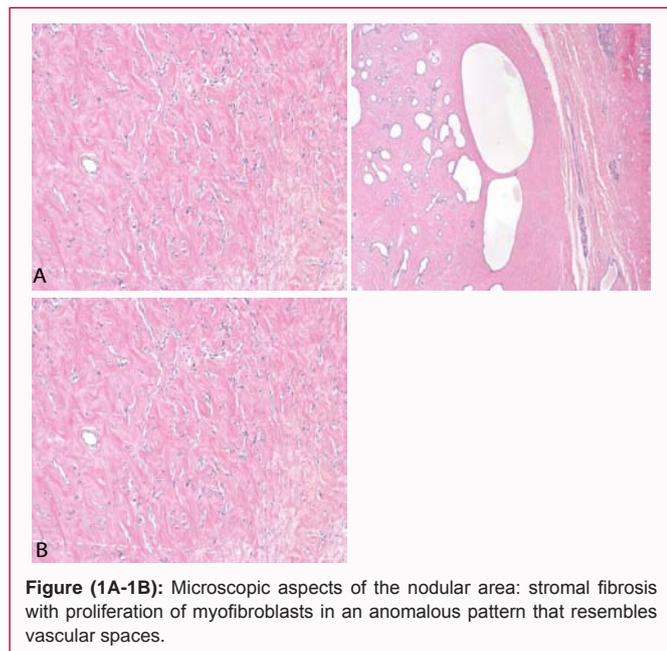
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**Figure (1A-1B):** Microscopic aspects of the nodular area: stromal fibrosis with proliferation of myofibroblasts in an anomalous pattern that resembles vascular spaces.

phase of the menstrual cycle.

More often, PASH clinically presents as a firm, painless and movable single mass, with no associated nipple or skin changes, but it can infrequently be diffuse or multinodular. The size of PASH usually ranges between 0.6 cm to 12 cm with most cases ranging from small to medium size. It may present in a wide clinicopathologic spectrum, ranging from incidental focal microscopic findings to clinically symptomatic and mammographically evident breast masses [4]. In young patients it usually presents as a fast-growing palpable lesion; this may be attributed to the hormonal milieu of puberty and adolescence [5,6].

Mammography of breast masses arising from PASH reveals a discrete, dense homogenous lesion lacking calcifications, however, mammography has had limited application in adolescence because of the more fibrotic nature of the breast tissue, which may either obscure identification of lesions or lead some to interpret normal development as possible suspicious lesions.

Unfortunately, neither the ultrasound, nor the RM is specific enough to allow a definitive diagnosis to be obtained. The cytology also rarely provides a diagnosis, thus a histological examination is necessary. On gross examination, PASH commonly occurs as a sharply circumscribed and well encapsulated breast lesion, occasionally presenting in a diffuse form. Typically, the cut surface is smooth, firm or rubbery. It has typically a glistening surface and varies in color from gray to tan-pink, yellow or white.

Breast lesions are uncommon in children and adolescents. The most common masses are benign tumors like fibroadenomas or are associated with inflammation due to infection [7]. Among breast masses in adolescent females, some pathologic lesions such as giant fibroadenoma, phyllodes tumor, PASH, juvenile papillomatosis (Swiss cheese disease) and virginal breast hypertrophy (juvenile macromastia) rapidly and massively increase in size over a short time period. Other less common causes are lipoma, mammary hamartoma, breast abscess, fibrocystic change and adenocarcinoma.

The differential diagnosis of a large breast mass in adolescent



**Figure 2:** Macroscopic tumor appearance: 12 cm x 10 cm x 6 cm in diameter, homogeneous appearance with a smooth whitish-gray surface, weighing 395g.

females is important for determine treatment modalities. PASH may grow quickly and often is mistaken for fibroadenoma or phyllodes tumors, but the most important differential diagnosis on histopathological examination is low-grade angiosarcoma. Angiosarcoma is characterized by interanastomosing vascular channels with invasion into the breast parenchyma, papillary endothelial growth and hyperchromatic endothelial cells. In problematic cases immunohistochemistry can be helpful.

Immunohistochemical staining of PASH expresses CD34, vimentin and at least focally smooth muscle actin, desmin and bcl-2, but not endothelial markers (CD31, Factor VIII), S100 or cytokeratin [8,9].

Treatment strategies for PASH remain controversial. Wide surgical resection or mastectomy is requested when there is an important mass-effect by PASH, whereas other cases may only require local excision or conservative therapy. However, some cases with diffuse involvement or multiple recurrences may necessitate mastectomy to achieve complete resection, while in others close interval follow-up with careful clinical and imaging correlation could be acceptable, rather than surgical excision [10]. Importantly, even though it is benign, PASH has a tendency to recur if incompletely excised, so it must be resected with careful attention to resection around the capsule of the tumor with breast conservation as a goal.

Regardless of a benign origin of the lesion and good prognosis, long-term follow-up is recommended for all patients, as some have been reported to recur.

We describe PASH in 3 pediatric patients and compare them with 24 adolescent cases described in literature.

## Methods and Materials

We performed a systematic search of the PubMed database from inception to June 2018 using database-specific syntaxes of keywords relevant to 'pseudoangiomatous stromal hyperplasia', 'childhood' and 'adolescent'. We then compared these results with that one from a retrospective review of our institution's surgical pathology database for the histologic diagnosis of PASH from January 2000 through April 2018 among patients between 10 and 18 years of age. Patients' medical records were retrospectively reviewed for information regarding the patient's demographics, personal and family history

of cancer, presentation, clinical, imaging and pathological diagnoses and treatment. Clinical follow-up, imaging and pathological findings were also recorded, where available. All patients' identifiers were kept confidential.

## Results

Only 24 cases of PASH in adolescent patients are described in literature until 2018. The study published by Shehata et al. in 2009 presented the largest number of pediatric patients with PASH, including 9 females and 3 males [11]. Other studies are all case reports describing one or two young female patients.

Almost all of these patients went to breast clinics because of a fast growing breast mass causing them breast asymmetry. Frequently there were no other associated symptoms and only 2 of the 24 patients [12,13] had a painful mass. First of all, clinical examinations always revealed rapidly growing and mobile masses, with no lymphadenopathy, and after that all patients underwent bilateral breast ultrasonography: lesions appeared often well-defined, hypo-echoic and slightly heterogeneous, but the results were not specific.

Mammography is only once described [10], probably because of its low sensitivity in young people: it showed a likely benign mass with asymmetric margins that tailed off into the surrounding breast tissue without microcalcifications. RMN was performed in 2 of the 24 patients for staging the breast tumor. Core-biopsy had been performed and permitted the diagnosis before surgery in 6 cases, while 18 of the 24 patients were diagnosed on surgical excision of the breast mass.

All 24 patients underwent surgical excision of the lesion; the large majority had a breast-conserving procedure. A few patients, instead, underwent a mastectomy: two because of a gynecomastia associated [11,14] and two because of a markedly enlarged breast [15]. Five patients presented with breast asymmetry with masses in both breast and needed bilateral surgery [11,13,15,16].

Conservative surgery needs healthy breast tissue margins to avoid recurrence. None of the 24 patients had a recurrence of their PASH after surgical excision, except for an adolescent female, described in Singh case report, which required bilateral mastectomies after surgical excisions secondary to PASH recurrence before the age of 13.

We report 3 cases of adolescent girls who presented in our breast clinic between 2010 and 2018 with unilateral breast PASH. The clinical history of all them was similar and not significant; they were in good general health. They presented to the breast clinic, sent by general doctor because of a voluminous and rapidly growing breast mass causing breast asymmetry. All cases occurred after menarche with regular menses, normal timing of pubertal development and were not associated alteration with hormonal imbalances. The gonadotropin-Releasing Hormone (GnRH) stimulation test showed values of LH and FSH in the normal pubertal range. None of the girls took any medications, specifically no oral contraceptive or hormonal medications; their clinical history was not significant and they were in good general health.

Clinical examinations revealed palpable masses with elastic and movable hard texture than the superficial and deep planes ranging in size from 5 cm to 10 cm in diameter. Normal breast development was evident on the opposite side. There was no axillary, supraclavicular or lateral cervical lymphadenopathy.

The patients were submitted to bilateral breast ultrasonographic examination that showed solid and homogeneous masses, with no cystic component. Fine-needle aspiration cytology was performed sonographically in one of the 3 girls and did not show cells with features of malignancy, but the result was nonspecific and inconclusive; this patient underwent also an MRI for staging of breast cancer, which showed an 11 cm × 9 cm × 8 cm well-circumscribed mass lesions with plateau and washout enhancement kinetics. On the T1-weighted images the lesion was homogeneously hypointense, while on the T2-weighted image it was heterogeneously hyperintense.

Although all these patients' findings were nonspecific, they were suggestive of a benign process, such as fibroadenoma, Phyllodes tumor, hamartoma or PASH. We decided not to carry out core-cut biopsy sampling before surgical intervention to obtain a specific differential diagnosis because surgery was anyway necessary given the big size of the lesions and the resulting severe breast asymmetry.

Lumps were surgically excised through breast-conserving circumareolar incisions under locoregional anaesthesia and sedation. Histological examinations revealed oval masses with well-defined margins, coloring to greyish (Figure 2).

A slight breast asymmetry was still remaining, but it is improving spontaneously with the patient's growing. The patients were happy with the cosmetic result and enough normal breast tissue had been preserved to enable breast development.

Patients were discharged on the day after surgery.

Histology and immunohistochemistry were diagnostic for PASH. In particular immunohistochemical staining showed intense and diffuse positivity of the myofibroblasts for actin and CD34 and less than 15% of the cells were ER and PR positive in each patient.

None of the patients showed evidence of clinical or ultrasonographic recurrence after a follow-up of at least 10 months.

## Discussion

PASH is gaining acceptance as an important entity in the differential diagnosis of adult breast lesions ever since it was first described in 1986. While PASH is well established in adult breast pathology, little has been reported about it in the pediatric population, where only 24 case reports in adolescent patients exist.

PASH is frequently an incidental histologic finding in breast biopsies performed for other reasons. Sometimes, it can present as a firm, painless and rapidly growing breast mass, as in our patients.

Many evidences showed that the basis of the development of PASH is a prolonged progestogenic stimulus, which can be either endogenous or exogenous. In our patients the definitive histological examination showed the lesion to positive PR as well as fully described in the literature.

Our preoperative diagnostic procedures failed to identify the nature of the lesion and the clinical suspicion addressed to a benign fibroadenoma or borderline phyllodes tumor. It was difficult to suspect and/or diagnose PASH also because of the rarity of PASH in adolescence.

Recently it has been proposed by Wieman et al. to use core-biopsy as a preoperative high sensitivity diagnostic method [17-20]. It is essential especially if you decide to start a close follow-up or medical treatment of the lesion instead of a surgical pathway. Sometimes

PASH is diagnosed in conjunction with malignant breast lesions, so it is necessary to ensure that the sample is sufficiently representative. After performing biopsy, it is crucial to compare histological findings with clinical and imaging data.

Breast-conserving surgery is the current standard of care for PASH. The lumpectomy is technically simple thanks to the solid and well-defined structure and the recurrence rate is extremely low if the tumor is removed with safety margins of healthy tissue. In case of diffuse or multifocal PASH, mastectomy is required to ensure the surgical radicality.

Recently, clinical trials have gone beyond the current standard of care by investigating new and more conservative treatments, with surgery only if needed. Many authors proposed short-interval follow-up or medical therapy, instead of an initial surgical treatment. In favor of this approach it has been described in the literature a case of PASH regression after hormonal therapy with tamoxifen.

In our cases we opted for surgery given the asymmetry of the two breasts, as well as obvious cosmetic problems, which caused a distress in the young patients and could, generated a spoiled column posture. Moreover, although preoperative diagnosis was not conclusive, the rapid growth of the lesions, in contrast to the cytological findings of mercy, forced to surgery. It is more likely that conservative approaches will be mostly useful for adult patients in whom PASH is frequently an incidental histologic finding in breast biopsies performed for other reasons and not a big breast mass clinically evident.

## Conclusion

PASH is a rare event in the wide spectrum of breast lesions. Its benign nature and complete healing after surgical resection represent aspects of tranquility which must be communicated to the patient, often worried because of the big size and the fast growth of the lesion.

Preoperative core biopsy and hormonal therapy could be two new instruments to avoid surgery in some patients, especially adults. New studies are therefore desirable to determine the best approach for this type of injury in pediatric patients.

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