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ORIGINAL ARTICLE

Optimal treatment of pseudoangiomatous stromal hyperplasia of the breast

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Summary *Background:* Pseudoangiomatous stromal hyperplasia (PASH) is a benign mesenchymal proliferative lesion of the breast. Owing to the rarity of PASH, the pathogenesis, clinical manifestation, and optimal treatment of this condition remain unclear. We aimed to clarify the appropriate management of PASH.
Methods: We performed a retrospective analysis of the clinicopathological data of 66 cases with a diagnosis of PASH, confirmed by core needle biopsy (CNB) or surgical excision at Severance Hospital between 2000 and 2016. The primary endpoint was pathologic results after surgical excision of the lesion that confirmed PASH by CNB. The secondary endpoint was progression after the first treatment.
Result: The median age of patients was 41 years (range, 14–61 years). Findings on medical imaging were nonspecific. CNB was performed in 61 cases, with a diagnosis of PASH confirmed in 39 cases (63.9%). No malignant or premalignant cells directly arising from PASH were identified after surgical excision that confirmed PASH via CNB. The progression rate after the first treatment was 16.6%, with lesion size, enlargement of palpable mass size, and a diagnosis other than PASH on CNB being factors associated with progression.
Conclusion: CNB is sufficient to confirm PASH what is necessary for an abnormal imaging or suspicious physical examination finding. Surgical excision is not necessarily indicated to rule out occult malignancy after a diagnosis of PASH. Close monitoring or surgical excision are required to manage large lesions (>3 cm) or progressive growth of a PASH lesion.

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1. Introduction

Pseudoangiomatous stromal hyperplasia (PASH) is a benign mesenchymal proliferation of myofibroblasts of the breast. Due to the rarity of PASH, its pathogenesis, clinical presentation, diagnosis, and proper management are poorly understood.

Although PASH mainly occurs in perimenopausal women, the incidence of PASH has also been reported in men associated with gynecomastia, and in menopausal women on hormone replacement therapy.[1] The pattern of incidence of PASH supports a hormonal etiology. It has been postulated that PASH results from activation of stromal myofibroblasts by endogenous and exogenous hormone stimulation, which results in excessive secretion of collagen.[2] The collagenous stroma comprises spindle cells, containing an anastomosing slit-like pseudovascular space, without red blood cells.[3] This pseudovascular space is the most typical histological finding of PASH, especially in its simple form.[4] PASH lesions are usually located in interlobular or intralobular stroma, have a low mitotic count, and none-to-mild nuclear atypia.[5] These are specific distinctive features of PASH that differentiate it from a low-grade angiosarcoma or phyllodes tumor.[6]

Clinically, PASH can mimic a fibroadenoma.[6] In addition, PASH can coexist with other breast lesions[7] and even present as significantly enlarged breast.[8] On imaging, PASH presents with benign features that are generally nonspecific.[9] PASH is most commonly diagnosed incidentally during histological examination of another benign or malignant lesion.[10] With regard to treatment, surgical excision has traditionally been recommended to confirm the absence of occult malignancy and to prevent progression or recurrence.[11] The management of PASH has become significantly standardized in recent years. The American Society of Breast Surgeons does not recommend routine excision; however, supportive data are limited.[12] Furthermore, there is currently no statistical evidence of disease progression or credible evidence for the appropriate management of PASH.[13]

Accordingly, our aim in this study was to review the clinical, radiological, and histological features of PASH and recommend an appropriate strategy for its diagnosis and treatment.

2. Material and methods

2.1. Patient selection

We conducted a retrospective review of patients who were diagnosed with PASH at Severance Hospital (Seoul, South Korea), between January 2000 and December 2016. The inclusion criterion was a diagnosis of PASH confirmed by core needle biopsy (CNB) and/or surgical excision. Patients with a follow-up of less than six months after confirmation of the diagnosis were excluded. The following clinicopathological variables were extracted from the medical records for analysis: menopausal status for women; breast disease history; medication history; chief complaints; findings on physical examination; findings on imaging [mammography (MMG), ultrasonography (US), and/or magnetic resonance imaging (MRI)]; treatment methods; pathologic reports; and follow-up data.

This study was approved by the Institutional Review Board of the Severance Hospital, Yonsei University Health System (2018-0878-001). The requirement for patient consent was waived owing to the retrospective design of our study and the use of de-identified data.

2.2. Clinicopathological characteristics of PASH

Medical imaging was performed by experienced radiologists, with images recorded using the breast image and reporting data system (BI-RADS), which was developed by the American College of Radiology. CNB was performed under US guidance using a 14-gauge automated core needle to obtain tissue samples. CNB was indicated for pathological confirmation of the diagnosis in patients with suspicious findings on imaging (a BI-RADS grade $\geq$4a). All pathological data were interpreted by pathologists specialized in breast diseases.

The first treatment option was based on clinical manifestation and findings on images and pathological results, and could include observation, vacuum-assisted excision (VAE), or surgical excision. VAE was performed under either stereotactic or US guidance using an 8- or 11-gauge needle. Progression was defined as an increase in the volume of a lesion that had confirmed PASH on following image studies after diagnosis or the first treatment.

2.3. Data and statistical analysis

For analysis, patients were divided into the CNB-positive group (patients with PASH confirmed by CNB), CNB-negative group (patients with other lesions confirmed by CNB) and diagnosed by mastectomy group (patients who had mastectomy without pathologic confirmation) (Fig. 1). We analyzed the pathologic results after surgical excision or VAE in the CNB-positive group to evaluate for occult malignancy with PASH lesion. Subsequently, all PASH cases were divided into the progression and non-progression groups. Clinicopathological and treatment variables were compared between the two groups using the Mann–Whitney U test for quantitative variables (without a normal distribution) and a chi-squared test or the Fisher's exact test for nominal data. A binary logistic regression model was used for multivariate analysis to identify

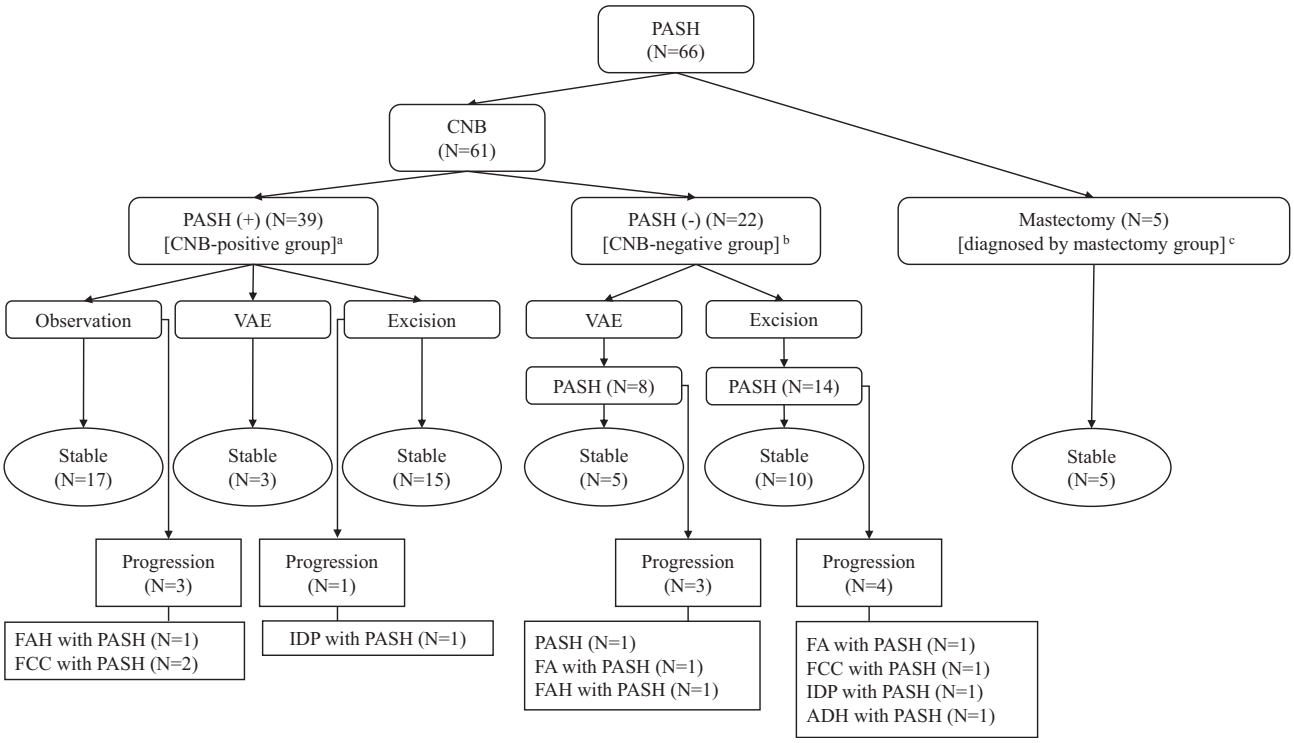

Figure 1 Flowchart of management strategies including follow-up data and pathologic diagnosis of progression group. PASH pseudoangiomatous stromal hyperplasia, CNB core needle biopsy, VAE vacuum-assisted excision, FAH Fibroadenomatoid hyperplasia, FCC Fibrocystic change, IDP intraductal papilloma, FA Fibroadenoma, ADH atypical ductal hyperplasia. [a] confirmed PASH by initial CNB, [b] confirmed other lesion by initial CNB, these group confirmed PASH by VAE or excision after CNB, [c] confirmed PASH by mastectomy except pathologic confirmation.

predictive factors of PASH progression after the first treatment. The multivariate analysis was adjusted for confounding variables that were significant in the univariate analyses. Due to the small sample size and therefore low statistical power of our model, we calculated the discriminative effect of our multivariate logistic analysis for PASH progression using the area under the receiver operating characteristics (ROC) curve. All statistical tests were two-sided, with a P-value <0.05 considered significant. Analyses were performed using IBM SPSS v. 23.0 (Armonk, NY, USA).

3. Results

3.1. Characteristics of patients

Sixty-six cases of PASH confirmed by CNB or surgical excision in 61 patients because of five patients had bilateral PASH. Their characteristics are presented in Table 1. Median follow-up duration was 32 months (range, 6—114 months). All patients were women, with a median age of 41 years (range, 14—61 years). Four patients had post-menopause status and one was on hormone replacement therapy at the time of PASH diagnosis. The medical and medication histories of the participants were unremarkable, with the exception of 12 (19.6%) patients, who were taking levothyroxine for the management of hypothyroidism or were following bilateral thyroidectomy for thyroid cancer. Seven patients had a prior history of breast disease, and among them two patients had a history of breast malignancy, both of whom were on ongoing tamoxifen treatment prior to diagnosis of PASH. These two patients underwent pathological examination for diagnosis of newly developed suspicious findings on post-operative follow-up imaging. For the majority of the patients, PASH lesions were identified during health screening imaging tests, with no subjective symptoms. However, a non-tender mass was palpable in most patients on physical examination.

Five patients had bilateral PASH, including PASH located at bilateral accessory breasts in the axillary area in one patient; four patients presented with significantly enlarged bilateral breasts. In two of these latter four patients, the rapid growth of the breast was associated with signs of infection (redness, swelling, and localized sense of heat) on physical examination at the time of the first hospital visit. The prolactin level in one of these two patients rarely exceeded the 100 ng/mL threshold; the patient had no evidence of hypothyroidism and was neither pregnant nor breast-feeding. This patient was treated conservatively for breast infection, with signs of infection resolving within two months, including a normalization of prolactin level. Another patient was treated using bromocriptine, with rapid growth and congestion resolving in both breasts within one month. This initial treatment was changed to tamoxifen for symptom relief. However, the patient did not respond well to tamoxifen and redeveloped rapid growth

Table 1 Characteristics of patients with pseudoangiomatous stromal hyperplasia.

Characteristic	No. (%) (N = 66)
Follow up (months)	
Median (IQR)[a]	32 (13, 52)
Age (years)	
Median (IQR)[a]	41 (36, 46)
BMI	
Median (IQR)[a]	22.1 (19.8, 24.1)
Menopausal status	
Premenopausal	62 (93.9%)
Postmenopausal	4 (6.1%)
Previous breast disease history	
None	59 (89.4%)
Benign	5 (7.6%)
Malignancy	2 (3.0%)
Detection	
Health screening image test	33 (50%)
Subjective symptom	24 (36.4%)
Incidental finding during evaluation other lesion	9 (13.6%)
Subjective symptom	
None	42 (63.6%)
Rapid growing huge breast	8 (12.1%)
Palpable mass	16 (24.2%)
Tenderness on physical examination	
None	54 (81.8%)
Yes	12 (18.2%)
Palpability on physical examination	
None	26 (39.4%)
Yes	40 (60.6%)
PASH Site	
Right	34 (51.5%)
Left	32 (48.5%)
PASH Location	
Subareolar area	7 (10.6%)
Upper outer quadrant	37 (56.1%)
Upper Inner quadrant	10 (15.2%)
Lower outer quadrant	5 (7.6%)
Lower Inner quadrant	5 (7.6%)
Accessary breast	2 (3.0%)

BMI body mass index, IQR interquartile range, PASH pseudoangiomatous stromal hyperplasia.
[a] The Shapiro–Wilk test suggests that the data are not normally distributed.

Table 2 Radiologic findings of pseudoangiomatous stromal hyperplasia lesion.

Characteristic	No. (%) (N = 66)
Lesion size by diagnostic sonogram	
Median (IQR)[a]	2.3 (1.3, 3.1)
Mammographic finding	(N = 43)
Normal	18 (41.9%)
Circumscribed mass	7 (16.3%)
Lobulated mass	10 (23.3%)
Focal asymmetry density	3 (7.0%)
Calcification	5 (11.7%)
Sonographic mass shape	(N = 66)
Round	12 (18.2%)
Oval	53 (80.3%)
Irregular	1 (1.5%)
Sonographic mass margins	(N = 66)
Circumscribed	37 (56.1%)
Microlobulated	25 (37.9%)
Indistinct	4 (6.1%)
Sonographic mass echo pattern	(N = 66)
Hypoechoic	22 (33.3%)
Isoechoic	42 (63.7%)
Complex	2 (3.0%)
Breast MRI finding	(N = 12)
Mass enhancement	9 (75.0%)
Non-mass enhancement	3 (25.0%)
Breast MRI Category	(N = 12)
BI-RADS 2	2 (16.7%)
BI-RADS 3	3 (25.0%)
BI-RADS 4a	5 (51.7%)
BI-RADS 4b	2 (16.7%)

PASH pseudoangiomatous stromal hyperplasia, BI-RADS breast imaging-reporting and data system, MRI magnetic resonance imaging.
[a] The Shapiro–Wilk test suggests that the data are not normally distributed.

and inflammation of her breasts, requiring termination of tamoxifen treatment.

3.2. Image findings of PASH

US, MMG, and MRI were performed on all, 43, and 12 cases, respectively (Tables 2 and 3.). The median lesion size on US was 2.3 cm (range, 0.6–14 cm), with generally benign features of the shape and margins of the mass. BI-RADS category 4a or 4b findings on US, indicative of a low-to-moderate suspicion of malignancy, were identified in 51.5% of cases. Microcalcifications in the PASH lesion were identified in five cases on MMG. A BI-RADS category of $\leq$3 was reported in about 80% of patients who had MMGs. The distribution of BI-RADS category score by US and MMG is presented in Table 3. MRI was performed in 12 cases, including five patients in whom PASH was diagnosed incidentally on MRI during preoperative evaluation for a malignancy, three patients who underwent MRI due to significant enlargement of bilateral breasts, and one patient who was undergoing routine follow-up after contralateral mastectomy for malignancy. The MRI finding of three patients with enlarging bilateral breasts was PASH-specific. Multiple delineated and heterogeneous nodules were identified on MRI, with edematous changes and replacement of stromal tissue observed on T2 short tau inversion recovery image.

3.3. Diagnosis and treatment

A PASH diagnosis was confirmed incidentally (when the actual histological examination was performed for another

Table 3 Distribution of BI-RADS category scores by ultrasonography and mammography.

Mammographic BI-RADS Category	Sonographic BI-RADS Category					Total
	1	2	3	4a	4b	
1	0	0	9	7	2	18 (41.9%)
2	0	0	6	3	1	10 (23.3%)
3	0	0	4	2	1	7 (16.3%)
4a	0	0	2	3	2	7 (16.3%)
4b	0	0	0	1	0	1 (2.3%)
Not done	0	0	11	12	0	0
Total	0	0	32 (48.5%)	28 (42.4%)	6 (9.1%)	

The kappa value of the mammogram and ultrasonogram BI-RADS score among patients who underwent mammography is 0.13 (*p*-value = 0.51).
BI-RADS breast imaging-reporting and data system.

breast lesion) in nine cases (13.6%), with four of these cases being benign and the other five being malignant. Five cases (diagnosed by mastectomy) underwent subcutaneous mastectomy with immediate reconstruction without pathological confirmation, because of clinical diagnosis of bilateral PASH based on specific MRI finding and clinical feature of significantly enlarged bilateral breasts. Subsequent to CNB, due to indeterminate findings on US examination, only one patient among four with significantly enlarged bilateral breasts underwent subcutaneous mastectomy with immediate reconstruction. CNB was performed in 61 cases, with confirmation of PASH by CNB made in 39 (63.9%) of these cases. In the other 22 cases (36.1%), the diagnosis of PASH was confirmed on subsequent surgical excision or VAE. The pathologic report of PASH after final treatment, including CNB results of 17 cases without progression in the CNB-positive group, is presented in Table 4.

The first treatment option for PASH was determined by physician's preference based on CNB results, imaging, and clinical presentation. The treatment was subdivided into observation (routine surveillance), VAE, or surgical excision, including mastectomy. The progression rate according to first treatment method is presented in Table 5. One patient in the observation group had adjuvant chemotherapy for breast malignancy, with resultant decrease in the size of the PASH lesion. There were three cases of a proliferative lesion with atypia that were identified on final treatment; in all 3 cases, a lesion other than PASH was confirmed on CNB. Progression was confirmed in 11 cases (16.6%) and median progression period was 26 months (range, 6–36 months) after the first treatment. On univariate logistic regression analysis for progression, the CNB results, symptoms, and lesion size were identified as factors associated with progression after the first treatment (Table 6). On multivariate logistic regression analysis, after adjusting for CNB results, symptoms, and lesion size were regarded as independent factors for progression. Of note, multicollinearity, with variance inflation factor, was not detected on this multivariate regression model. The Hosmer–Lemeshow test of goodness-of-fit was not significant (P value = 0.676). The AUC for this multivariate analysis was 0.78 (95% CI, 0.68–0.88).

Table 4 Pathologic diagnosis after the final treatment.

Pathologic finding	No. (%) (N = 66)
PASH	29 (43.9%)
Apocrine metaplasia with PASH	2 (3.0%)
Fibroadenomatoid hyperplasia with PASH	5 (7.6%)
Fibrocystic change with PASH	7 (10.6%)
Fibroadenoma with PASH	17 (25.8%)
IDP with PASH	3 (4.5%)
ADH with PASH	2 (3.0%)
LCIS with PASH	1 (1.5%)

Core needle biopsy results are the pathologic results in patients with observation after confirmation of pseudoangiomatous stromal hyperplasia.
PASH pseudoangiomatous stromal hyperplasia, IDP intraductal papilloma, ADH atypical ductal hyperplasia, LCIS lobular carcinoma in situ.

4. Discussion

In our cohort, PASH was largely diagnosed in women of reproductive age. It was detected during health screening imaging tests; the patients had no subjective symptoms and presented with palpable non-tender mass on physical examination. The clinical presentation widely varied, from asymptomatic lesion to significantly enlarged bilateral breasts. The findings on US and MMG were nonspecific, and 63.9% (39/61) had pathological confirmation of PASH by CNB. The local progression rate of PASH after the first treatment was 16.6% (11/66), with progression being associated with CNB results, lesion size, and symptoms.

The estimated incidence rate of PASH varied from 0.4% to 23.0% in several studies.[10,11] This range of incidence rate might reflect the disparate administration of pathological diagnosis across different centers. A relatively high number of PASH cases in our center reflects the nature of our hospital as being a tertiary care center for the treatment of breast cancer patients. The threshold for using CNB was lower among breast cancer patients who undergo preoperative imaging assessment or follow-up surveillance after treatment. Generally, the majority of PASH lesions detected on MMG or US were under the threshold for proceeding with CNB. In our center, a few patients with PASH, with probably benign findings on image study, underwent CNB

Table 5 Follow-up data after the first treatment.

First treatment	No. (%) (N = 66)	Stable disease (N = 55)	Progression (N = 11)	p-value
Observation	20 (30.3%)	17 (85%)	3 (15%)	0.58
VAE	11 (16.7%)	8 (72.7%)	3 (27.3%)	
Excision	29 (43.9%)	24 (82.8%)	5 (17.2%)	
Mastectomy	6 (9.1%)	6 (100%)	0	

VAE vacuum-assisted excision.

Table 6 Univariate and multivariate analyses of the progression of PASH.

Variables	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Pathology result by CNB				
Diagnosis PASH	ref		ref	
Diagnosis other than PASH	29.2 (3.4–252.3)	0.01	13.6 (1.9–94.3)	0.01
Symptom				
None	ref		ref	
Rapid growing huge breast	0.4 (0.1–9.4)	0.57	0.5 (0.1–9.2)	0.70
Palpable mass enlargement	5.4 (1.3–21.3)	0.02	6.1 (1.4–21.6)	0.01
Lesion size by diagnostic US				
$\leq$ 3 cm	ref		ref	
$>$ 3 cm	4.3 (1.2–21.9)	0.04	2.8 (0.4–16.9)	0.24
First treatment method				
Surgical excision	ref		ref	
VAE	1.1 (0.2–4.9)	0.94	1.8 (0.4–8.9)	0.89
Observation	2.3 (0.4–11.5)	0.33	2.4 (0.1–94.4)	0.75

PASH pseudoangiomatous stromal hyperplasia, CNB core needle biopsy, US ultrasonography, VAE vacuum-assisted excision, ref reference, OR odds ratio, CI confidence interval.

during the preoperative evaluation period for another lesion. It is possible that wide application of CNB increased the incidence rate of PASH. Because of the possibility that pathologic examination may not have been performed for actual PASH lesions, the incidence rate of PASH is difficult to be fully clarified based on our data.

The etiology and pathophysiology of PASH are unclear, but a hormone-dependent stromal change is widely accepted as being causative.[14] The hormonal etiology is supported by the following evidence: the expression of progesterone receptor on the nuclei of myofibroblasts in PASH lesions, the high prevalence of premenopausal women among patients with PASH, and a case report that associated reduction in PASH progression with tamoxifen.[15] Other hypotheses include an abnormal proliferation of lymphatic channels, based on electron microscopy findings.[16] Another hypothesis is that PASH is an independent myofibroblastic lesion of the breast.[17] In our study cohort, PASH developed in two women with the use of tamoxifen as an adjuvant endocrine therapy. Hypothyroidism was observed in 12 of our 61 patients. Signs of infections were observed in a few patients with significantly enlarged bilateral breasts, with these signs being relieved with bromocriptine treatment. It is known that prolactin is an essential hormone for normal production of breast milk and that it promotes normal breast proliferation and differentiation.[18] Hyperthyroidism induces subsequent hyperprolactinemia. Hyperprolactinemia leads to the accumulation of the static secretion and nuclear factor kappa-light-chain-enhancer of the activated B cells (NF-kB) signaling pathway, which triggers an inflammatory response in mammary epithelial cells.[19] Based on this evidence, we suggest that prolactin might also be associated with the development of PASH.

PASH might mimic fibroadenoma, as well as co-exist with other breast lesions. Therefore, PASH could present with a wide spectrum of clinical and radiological manifestations. There were no specific findings on US and MMG in our data. However, patients with significantly enlarged bilateral breasts had PASH-specific MRI finding and clinical presentation. In our experience, these specific conditions of PASH were not necessary for CNB for diagnosis of PASH. CNB was indicated only for another suspicious finding that indicated a lesion other than PASH on imaging finding.

Traditionally, surgical excision is recommended for confirmation of occult malignancy. In our dataset, a premalignant lesion that combined with PASH was identified in three cases. All three cases were in the CNB-negative group, with confirmation of atypical ductal hyperplasia (ADH), and lobular carcinoma in situ by CNB, respectively. PASH was diagnosed by surgical excision, with PASH forming only a small portion of the premalignant mass. In the CNB-positive group, there was no evidence of underestimation of an angiosarcoma for PASH.

Although PASH is a benign breast disease, it can progress. CNB results, enlargement of a palpable mass, and $>$3 cm on US were associated with progression. The AUC for multivariate analysis was 0.78 (95% CI, 0.68–0.88), indicative of a relatively good predictive power of the factors. Selected cases associated with progression should be considered for surgical excision of PASH lesions for symptomatic relief or cosmetic effect.

There are several limitations to our study. First, this is a retrospective study. Our data were affected by possible selection bias. We included only cases with at least 6 months follow-up after PASH diagnosis. Furthermore, data were uncertain with regard to the accuracy of medical records. Second, although factors associated with PASH can be identified in this design, a cause-and-effect relationship cannot be determined. Serum prolactin levels were only available for patients with a diagnosis of hypothyroidism; therefore, the possible relationship between PASH and prolactin requires further research. Third, PASH can coexist with other breast lesions; it is possible that the progression may be triggered by a coexisting lesion. To lower this possible effect, we defined progression as an increase in the volume of a lesion after diagnosis or the first treatment, with the diagnosis of PASH confirmed for progressive lesions by surgical excision or VAE.

In conclusion, PASH is a benign mesenchymal proliferative lesion of the breast. Our findings indicate that CNB is sufficient to confirm diagnosis of PASH what is necessary for an abnormal imaging or physical examination finding. Surgical modalities may not be indicated to rule out occult malignancy after a diagnosis of PASH by CNB. The progression of PASH was associated with lesion size (>3 cm), enlargement of palpable mass, and a diagnosis other than PASH on CNB. Surgical excision or VAE or close monitoring are required to manage progression of PASH. Furthermore, surgery might be helpful in PASH with bilateral huge breasts. With regard to treatment method, the modality may be selected based on evidential data, surgeon's preference, or patient's need.

Declaration of Competing Interest

The authors have no financial support or potential conflicts of interest to declare.

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