How to manage pseudoangiomatous stromal hyperplasia: our clinical experience

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Background/aim: Pseudoangiomatous stromal hyperplasia (PASH) is a rare and benign mesenchymal proliferative breast lesion. Our aim is to review the clinical and radiological features of PASH and define a standard approach for its diagnosis and management.

Materials and methods: Clinical records of 35 consecutive patients with PASH were retrospectively reviewed between 2009 and 2015. Patients with clinically or radiologically detected mass and patients who underwent biopsy for other indications and were diagnosed incidentally were included in the study.

Results: There were 34 female patients and one male patient with gynecomastia. Twenty-three patients had palpable masses, and 16 of them were diagnosed as PASH with a median size of 3.1 cm. PASH did not show any specific features in radiological imaging. Core needle biopsy was performed for 3 patients before surgical excision; however, the lesions had not been diagnosed as PASH. In pathological examination, lesions associated with PASH showed nonproliferative changes in 14 patients, proliferative changes without atypia in 17, one phyllodes tumor, one in situ tumor, and one invasive cancer.

Conclusion: Imaging findings of PASH are nonspecific. It is difficult to give a true prognostic diagnosis through pathological evaluation of big masses with core needle biopsy. We recommend surgical excision, especially for big lesions with suspicious features.

Key words: Pseudoangiomatous stromal hyperplasia, breast, diagnosis, treatment

1. Introduction

Pseudoangiomatous stromal hyperplasia (PASH) is a rare and benign mesenchymal proliferative breast lesion. Its clinical and radiological findings and optimal treatment are still not clear. It was first described in 1986 by Vuitch et al. (1) in nine patients having nodular mass lesions with a histological pattern, which simulated, but did not in fact constitute, a vasoformative proliferation. PASH is often seen as a microscopic lesion detected incidentally (2); sometimes as a clinically palpable mass or as multiple nodular lesions; or, rarely, as a giant mass causing asymmetry of the breasts (2–4). The clinical and radiologic features of PASH often mislead to a prediagnosis of fibroadenoma, phyllodes tumor, or hamartoma (5–9). Initially thought to be a variant of breast hamartoma, PASH is now accepted as a benign proliferation of stromal myofibroblasts. The histologic appearance is characterized by interanastomosing angulated and slit-like empty spaces, lined by slender spindle cells and surrounded by dense collagenous stroma. These slits lined by myofibroblasts may be a fixation artifact caused by the retraction of the collagenous stroma. Although there are no red blood cells

in these spaces, i.e. they are not vascular spaces, PASH is occasionally misdiagnosed as low-grade angiosarcoma (10).

The aim of this study is to review the clinical and radiological features of PASH by adding our institutional experience with the purpose of helping define a standard approach for the diagnosis and management of PASH.

2. Materials and methods

Following approval by the Institutional Review Board of the Ankara Oncology Education and Research Hospital, a pathology database search was compiled to identify cases with a diagnosis of PASH from January 2009 to September 2015. Over a 6-year period, 35 cases of PASH were determined and the clinical records of the 35 consecutive patients who underwent excisional breast biopsy, lumpectomy, or mastectomy at our hospital were retrospectively reviewed. All patients with either palpable or radiologically detected mass diagnosed as PASH, and patients with PASH found incidentally in breast specimens included in the study. All patients who were 40 years old and above were examined both with mammography

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and sonography, whereas others were evaluated just with sonography. Mammography was performed only in one younger patient, who was 33 years old with a suspected breast mass. Magnetic resonance imaging was performed in 3 patients; one had multiple breast lesions with confusing characteristics in other imaging modalities, and 2 patients had inconclusive findings of a breast lesion on sonography. All patients underwent surgical excision, except for two, who had malignancy and underwent lumpectomy or mastectomy with sentinel lymph node biopsy. Follow-up procedures included clinical breast examination, breast sonography, and mammography, which were recommended to all patients aged 40 years and above, initially 6 months after surgery and then annually. For patients younger than 40 years, follow-up was performed with clinical breast examination and sonography 6 months after surgery, then annually. Magnetic resonance imaging was used in all patients when necessary.

Initially, all pathological specimens were examined at the time of diagnosis by experienced pathologists at the high-volume specialty breast center of our hospital's pathology department. Then, following approval by our Institutional Review Board, microscopic slides of all cases identified as PASH were re-reviewed by a single pathologist. Immunohistochemical studies were performed on formalin-fixed tissue from PASH cases containing cellular areas using anti-CD34, anti-CD31, antidesmin, and antismooth muscle antibodies as well as the iView DAB detection kit (Ventana Medical Systems Inc., Tucson, AZ, USA).

Age at diagnosis, sex, menopausal status, use of hormone replacement therapy, personal and family history of cancer, predominant physical examination findings, radiological findings, presence of previous needle biopsy, associated breast pathologies as benign nonproliferative changes, benign proliferative changes without atypia, benign proliferative changes with atypical hyperplasia and malignant pathology with PASH, length of surgical margins, and treatment modalities were noted. In the follow-up period, patients were divided into 3 groups as adjacent, 1–2 cm, and more than 2 cm, according to the surgical margin width.

2.1. Statistical analyses

Data were descriptively summarized using frequencies and percentages for categorical variables and medians for continuous variables. The association of the recurrence rate and the surgical margin width were compared using the Fisher exact test or the Pearson chi-square test. The duration of follow-up was defined as the time between the date of the diagnosis of PASH to the last contact. $P < 0.05$ was considered statistically significant. All analyses were carried out using SPSS 21.0 (IBM Corp., Armonk, NY, USA).

3. Results

Approximately 12,000 breast biopsies were performed at the Ankara Oncology Education and Research Hospital between January 2009 and September 2015, and about 3000 of these biopsies were wire-localized by image guidance. Nearly 4300 of all breast biopsies were malignant and 35 were determined as PASH cases. Nineteen of 35 PASH diagnoses (54.3%) were incidental. All patients were female except one; two out of 34 patients were postmenopausal. Among nonincidental PASH patients, there was only one postmenopausal woman, and 15 patients with nonincidental PASH were premenopausal. Postmenopausal patients had not received hormone replacement therapy. The male patient had gynecomastia. None of the patients had a family history of breast cancer. Median age of the enrolled female patients was 39 years (range: 15–66 years) while the male patient was 27 years old. Figure 1 shows age distribution according to nonincidental PASH.

Painless palpable breast mass was found in 23 patients (65.7%) on physical examination. Other lesions were detected by sonography and/or mammography. Lesions diagnosed as PASH (i.e. 16 nonincidental PASH lesions) were defined as round or oval, heterogeneous, hypoechoic lesions with regular margins and without posterior acoustic enhancement at sonography in 14 patients; as round or oval heterogeneous, hypoechoic lesions with lobulation in 1 patient; and a heterogeneous hypoechoic lesion with irregular margins in 1 other patient. When classified according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS), these nonincidental, PASH-diagnosed lesions were BI-RADS Category 4 in 14 patients due to mixed echotexture, lobulation or irregular margins, and clinically growing size. Conversely, 2 patients, one female with a giant mass of 8.5 cm and the single male patient with a 0.7-cm palpable heterogeneous hypoechoic round lesion next to the areola, were categorized as BI-RADS-3. Mammographic examination was performed for 14 patients, and only in 3 of them was the PASH diagnosis not incidental. The mammographic finding in these 3 nonincidental PASH patients was a solid, well-circumscribed hyperdense lesion. In the mammographic findings of incidentally detected PASH, there was a mass with irregular shape and spiculated margins in one patient and pleomorphic microcalcifications in the other 2 patients. The remaining patients had nonspecific mammographic findings. Magnetic resonance imaging was performed in 3 patients, and only in one of them was the PASH diagnosis not incidental, with a circumscribed nodular mass hypointense in T1-weighted images, hyperintense in T2-weighted images, and revealing type 2 kinetics in the postcontrast series.
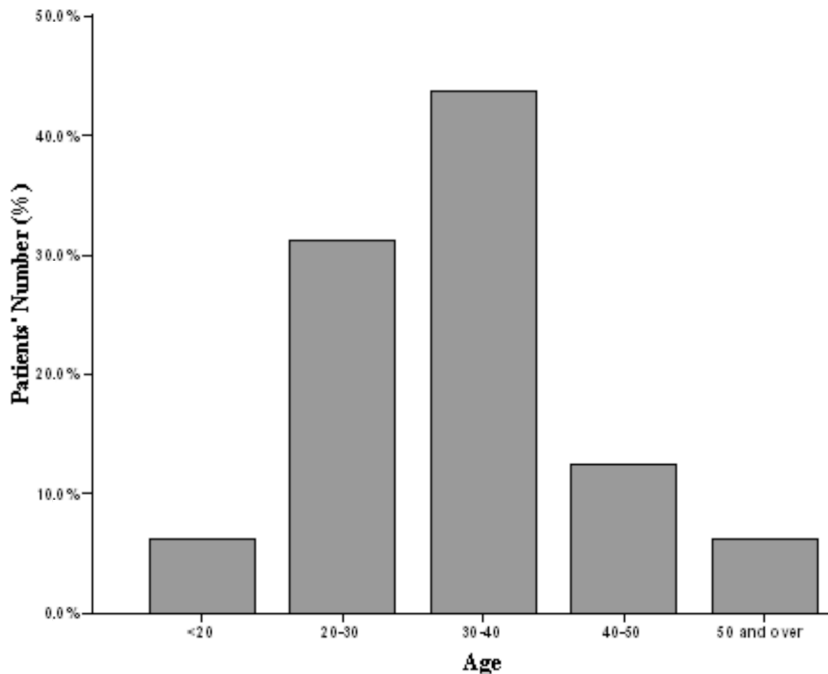
Figure 1. Nonincidental PASH presentation by age.

Twenty patients with palpable lesions underwent surgical excision, and only 3 patients had core needle biopsy before complete surgical excision. Diagnosis of PASH was not possible with core needle biopsy in any of these patients. Finally, all 23 palpable lesions were surgically excised and 12 nonpalpable suspicious lesions were removed by wire-localized, image-guided biopsy. Sixteen of 23 palpable lesions (65.2%) were diagnosed as PASH in final pathology, and the median size of these tumors was 3.1 cm (range: 0.7–8.5 cm). In these nonincidental PASH patients, lesion size was greater in premenopausal women than it was in postmenopausal ones, especially in the most hormonally active ages (Figure 2). Other palpable lesions associated with PASH were diagnosed as fibroadenoma in 2 patients, benign proliferative changes without atypia in 2 patients, low-grade phyllodes tumor in one patient, ductal carcinoma in situ in one patient, and invasive carcinoma in another patient. The patient with the in situ tumor was a postmenopausal woman, whereas all others with palpable lesions were premenopausal women or the male patient.

On pathological examination, 32 cases had typical microscopic appearance for PASH. Lesions were composed of anastomosing slit-like empty spaces lined with spindle cells (Figure 3). In the other three cases, lesions were cellular, and immunohistochemical studies were performed for differential diagnosis. Lesions were CD34- and SMA-positive while CD31 and desmin were negative. In this series, other lesions associated with PASH were benign nonproliferative changes in 14 patients and benign

proliferative changes without atypia in 17 patients. In the same breast, in addition to PASH, there was a concurrent phyllodes tumor in one patient, ductal carcinoma in situ in another patient, and invasive ductal carcinoma in a third patient.

Follow-up data were available for 23 patients. The median follow-up time was 35 months (range: 8–70 months). Among the followed patients, surgical margin width was adjacent in 16 patients, 1–2 cm in 2 patients, and more than 2 cm in 5 patients. During this period, none of the patients had recurrence of PASH.

4. Discussion
PASH is a rare, benign proliferative breast lesion detected mostly in premenopausal women. Its etiology and pathogenesis remain unclear, but hormonal factors are thought to play a role. In the literature, it was reported that the stromal cells in PASH were progesterone receptor-positive (11) and that the histology of PASH resembles that of intralobular stroma during the luteal phase of the menstrual cycle (12). These findings support the hypothesis that PASH is a hormone-dependent proliferation of intralobular stromal cells (1,2,11). However, several cases have been reported in postmenopausal women, men, adolescents, and even in children (13). Our study, having a majority of premenopausal patients (91%) and a male patient with gynecomastia, seems to sustain this, although there were two postmenopausal patients who had not received hormone replacement therapy. Another
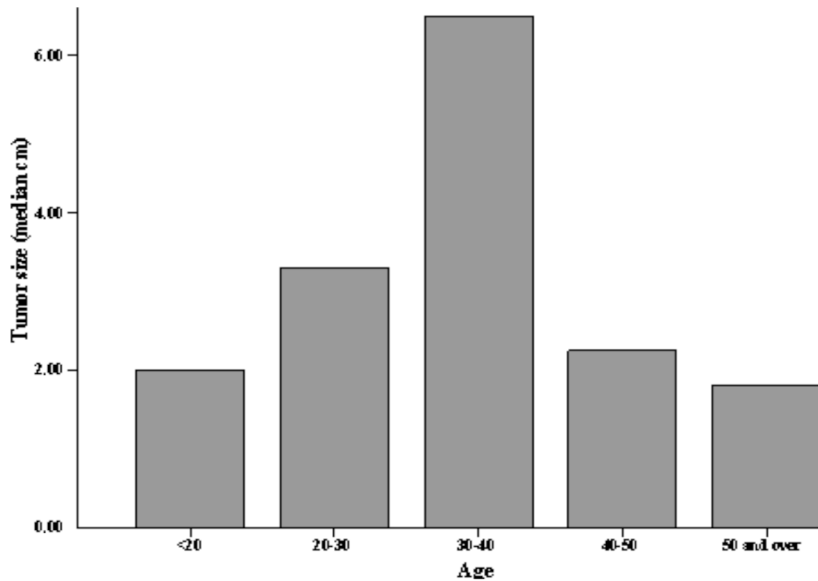
Figure 2. Median size of nonincidental PASH lesion relative to patient age.
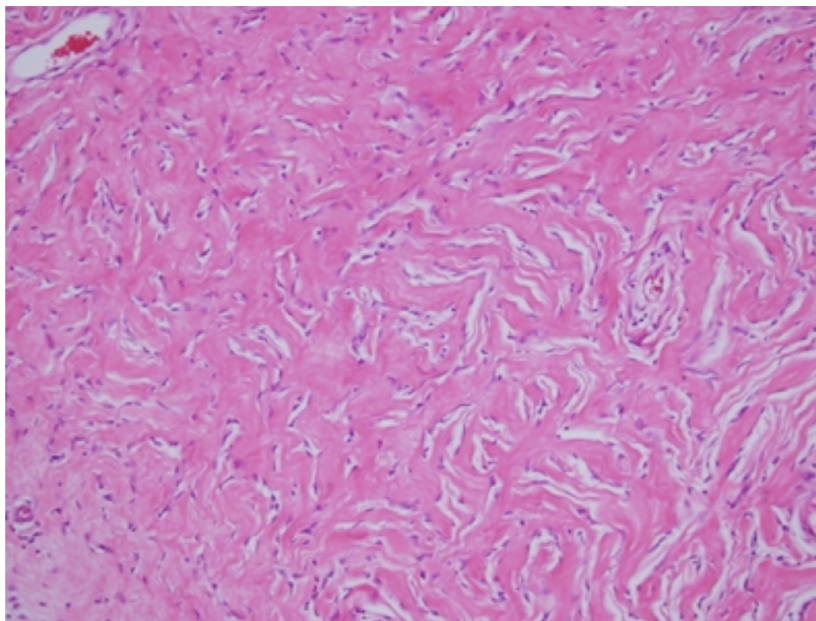
Figure 3. Anastomosing, slit-like spaces lined by spindle cells are seen in a dense collagenous stroma (hematoxylin and eosin, original magnification 200×).

study in the literature supports the hormonal etiology of PASH by reporting that the largest masses were seen in premenopausal women, whereas the smallest were seen in postmenopausal patients (10). Our study demonstrated the same distribution pattern (Figure 2).

PASH cases are mostly identified as incidental microscopic focus associated with various benign nonproliferative and proliferative breast lesions. According to Ibrahim et al. (2), it could be seen in as many as 23% of

all breast specimens. However, the nodular nonincidental form determined by physical examination or imaging modalities, i.e. by mammography or sonography, is less frequent. Palpable nodules are usually firm, painless, and mobile, without nipple or skin changes. Radiological findings are nonspecific; a well-defined oval hypoechoic nodular lesion resembling fibroadenoma is usually seen in sonography. Hargaden et al. (5) described the imaging characteristics of 149 cases of PASH on mammography

and sonography. The most common presentations on mammography were a circumscribed mass and, less commonly, a focal asymmetric density. They found no spiculated lesions, and asymmetric density and microcalcifications were rare and unrelated to PASH. On sonography, it was most commonly a well-circumscribed hypoechoic or isoechoic oval mass with enhanced through transmission. There are limited data in the literature on magnetic resonance imaging. However, especially in the mass-forming type of PASH, bright T2 slit-like spaces and cystic components in the lesion favor PASH diagnosis. Recent studies have described nonspecific magnetic resonance findings, including variable signal intensity in T1-weighted, T2-weighted, and contrast-enhanced sequences usually with a type 1 (progressive) enhancement curve (14). In our study, nonincidental PASH lesions were mostly (14 of 16) benign-appearing round or oval heterogeneous hypoechoic lesions in sonography, which might have been considered as fibroadenomas inadvertently.

In cases with suspicious features, surgical excision should be considered, because PASH can coexist with a malignant process and should not be accepted as a final diagnosis on the basis of fine needle aspiration biopsy (FNAB) or core needle biopsy alone. FNAB often produces acellular specimens. If the cellularity is adequate, PASH does not have any unique features on cytology and fibroadenoma, phyllodes tumor, or fibrocystic changes should be ruled out in differential diagnosis. The importance of FNAB is to rule out malignant lesions rather than provide a definitive diagnosis. On the other hand, core needle biopsy provides more tissue than FNAB to diagnose PASH. Nevertheless, a diagnosis with core biopsy may not be possible in every case. Gresik et al., in their series of 80 patients, reported that 65 patients had undergone core biopsy but only 65% of the core biopsies ended with a diagnosis of PASH (9). In our study, only 3 patients had core biopsy before total surgical excision. Decisions for surgical excision of the lesion without core needle biopsy seemed to be primarily the surgeon's preference, although it could be related to the patient's anxiety over a palpable lesion and to clinical concerns such as enlarging size, as reported by Protos et al. (15). In our series, none of the core biopsies were sufficient for diagnosis of PASH. Instead, they were diagnosed as suspicious for malignancy. If these lesions were followed only with core biopsy, 2 cases of malignancy associated with PASH could have been misdiagnosed.

On histologic examination, PASH shows a wide spectrum of morphological changes, ranging from typical appearance to more cellular spindle lesions. Cellular spindle lesions can be confused with other breast lesions, especially phyllodes tumors or low-grade angiosarcomas. Immunohistochemical staining with clinical and radiologic findings can help to establish the diagnosis. On immunohistochemistry the spindle cells are positive for myofibroblastic markers such as CD34 and SMA but are negative for endothelial markers such as CD31 and von Willebrand factor antigen. PASH rarely presents as a localized mass. More commonly it is an incidental finding, coexistent with many benign and malignant breast lesions. Previous studies have reported that up to 10% of specimens had invasive carcinoma with PASH. If a diagnosis of PASH is rendered on core biopsy, careful correlation of histologic features with clinical and radiologic findings is required to ensure that the target lesion has been appropriately and adequately sampled. As a result, PASH in core biopsies has pitfalls in diagnosis and may require complete excision (16,17).

Criteria for total surgical excision include a size greater than 2–3 cm, symptomatic tumors, or a diagnosis that is questioned, such as with imaging findings of vascularity or irregular margins. Additionally, an increase in size documented by sonography or clinical examination raises skepticism about the diagnosis and warrants removal of the lesion (10,18,19). Moreover, in the literature there is a PASH case with malignant transformation (20), and some cases of PASH are reported to be in association with concurrent malignancy, as in our series (21,22). Moreover, there are some reports favoring follow-up of PASH lesions after diagnosis with core needle biopsy (14,15), though these authors pointed out that a palpable, symptomatic mass with or without susceptible imaging findings should be excised surgically.

In the literature, highly variable recurrence rates are reported, ranging from 0% to 28.5%. Rates of lesion growth were also reported as ranging from 0% to 71.4% (1,23). In our study, all patients underwent complete surgical excision. In the followed-up patients (23 of 35 patients, 65.7%), there was no recurrence or malignancy occurrence in a median follow-up time of 35 months. It was seen that surgical margin width did not affect recurrence or malignancy occurrence.

Among all PASH cases, 45.7% were mass-forming PASH with a median size of 3.1 cm, ranging from 0.7 to 8.5 cm. Their clinical and radiological features were indistinguishable from other probable benign lesions.

When planning treatment and follow-up, it should be considered that malignancy may accompany PASH and a pathological evaluation by core needle biopsy may fail to give a true diagnosis, especially in the mass-forming type.

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