Review Article

Pseudoangiomatous stromal hyperplasia: overview and clinical management

Ashley Estes[1], Lifen Cao[2], Megan E. Miller[2]

[1]Case Western Reserve University School of Medicine, Cleveland, OH, USA; [2]Department of Surgery, University Hospitals, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Contributions: (I) Conception and design: ME Miller, A Estes; (II) Administrative support: All authors; (III) Provision of study materials or patients: ME Miller, L Cao; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: A Estes, ME Miller; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Megan E. Miller, MD, FACS. Assistant Professor, Department of Surgery, University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine, 11100 Euclid Avenue, Lakeside 7009, Cleveland, OH 44106-5047, USA.
Email: Megan.Miller6@UHhospitals.org.

Abstract: Pseudoangiomatous stromal hyperplasia (PASH) is a benign mesenchymal lesion of the breast characterized by dense collagenous stroma forming "pseudoangiomatous" capillary-like spaces lined by slender spindle cells. A rare condition overall, PASH is most common in premenopausal women, though cases have been described at ages ranging from 14 to 86, and in men, usually associated with gynecomastia. While the exact etiology is unknown, PASH is considered hormonally responsive, with myofibroblastic proliferation leading to stromal hyperplasia. It may present as a palpable mass or an incidental imaging finding. The usual appearance on mammography and ultrasound is that of a well-circumscribed mass which must be differentiated from other benign and malignant lesions such as fibroadenoma, phyllodes tumor, and myofibroblastoma; histologically it must be distinguished from angiosarcoma. Core needle biopsy is indicated for diagnosis and must be concordant with imaging and clinical findings. PASH lesions should be surgically excised if enlarging, associated with symptoms, suspicious imaging findings are present, or other lesions are synchronously diagnosed that warrant removal; otherwise, observation with clinical and imaging follow-up can be considered. Progression and recurrence, each reported at rates of approximately 15–20%, indicate change in management and/or additional surgical intervention. PASH is not associated with an increased risk of breast cancer and prognosis is generally favorable.

Keywords: Pseudoangiomatous stromal hyperplasia (PASH); benign breast disease; mesenchymal lesion; stromal hyperplasia; breast cancer risk; breast surgery

Received: 18 August 2020; Accepted: 29 September 2020; Published: 30 December 2020.
doi: 10.21037/abs-20-86
View this article at: http://dx.doi.org/10.21037/abs-20-86

Introduction

First described by Vuitch *et al*. in 1986, pseudoangiomatous stromal hyperplasia (PASH) is a benign mesenchymal breast lesion characterized by the proliferation of myofibroblasts that simulates a vascular lesion (1). It may present as a palpable mass or imaging abnormality, and must be distinguished from other benign and malignant diagnoses including angiosarcoma, phyllodes tumor, and fibroadenoma (2,3). While PASH is uncommon overall with fewer than 1,500 cases documented in the literature, it can also be found incidentally at biopsy for other breast lesions with a reported incidence of 23% (3,4) (*Table 1*). PASH presents most frequently in pre- and peri-menopausal women, though cases have been documented at ages ranging from 14 to 86, as well as in post-menopausal women taking hormone-replacement therapy and in men, usually associated with gynecomastia (9,11). It is thought that hormonal factors contribute to the development of

Table 1 Summary of retrospective studies for patients with pseudoangiomatous stromal hyperplasia (PASH)

Study	Vuitch *et al*., 1986 (1)	Powell *et al*., 1995, (5)	Hargaden *et al*., 2008, (6)	Celliers *et al*., 2010, (7)	Jones *et al*., 2010, (3)	Degnim *et al*., 2010, (8)	Gresik *et al*., 2010, (2)	Bowman *et al*., 2012, (9)	Yoon *et al*., 2020, (10)
Sample size	9	40	149	73	57	579 with PASH *vs*. 8,486 with another benign breast lesion	80	24	61
Age, mean/median, range	Mean 40; 22–52 years	Mean 37; 14–67 years	N/A	Mean 51.1; 24–82 years	Mean 48; 9–76 years	Mean/median N/A; 18–85* years	Median 45; 12–65 years	Mean/median N/A; 18–86 years	Median 41; 14–61 years
Patient population	· 9 (100%) women · 9 (100%) premenopausal	· 40 (100%) women · 4 (10%) post-menopausal; 2 (5%) on HRT · 1 (2.5%) pre-menarchal · Majority premenopausal (number N/A)	· 149 (100%) women · 98 (66%) premenopausal · 51 (34%) postmenopausal; 24 (16%) on HRT	· 73 (100%) women · 22/45 (49%) premenopausal · 23/45 (51%) postmenopausal; 4 (5%) on HRT	· 57 (100%) women · 34 (60%) premenopausal; 1 prepubescent · 23 (40%) postmenopausal; 11 (19%) on HRT · 3 (5%) on oral contraceptives	PASH cohort: · 579 (100%) women · Majority pre- or peri-menopausal · 512 (88%) <55-year-old	· 76 (95%) women · 4 (5%) men · 54 (71%) premenopausal · 22 (29%) postmenopausal women; 2 (3%) on HRT	· 22 (92%) women · 2 (8%) men · 20 (90%) women pre- or peri-menopausal	· 61 (100%) women · 5 (8.2%) with bilateral PASH · 57 (93%) premenopausal · 4 (7%) postmenopausal with 1 (2%) on HRT
Clinical presentation	Most often discrete, painless, breast mass; firm, rubbery	· Most firm, non-tender, palpable unilateral mass · 2 (5%) had ill-defined areas of thickening · 1 (2.5%) non-palpable mass	· 59 (40%) image detected · 90 (60%) palpable mass	· 52 (70.8%) image detected · 21 (29.2%) clinically detected	· 25 (44%) palpable mass · 30 (53%) image detected · 2 (3%) incidental	· 379 (71%) palpable mass *vs.* 4,722 (59.2%) with another breast lesion	· 45 (56%) palpable mass · 33 (41%) image detected · 2 (3%) incidental at pathology	· 8 (33%) pain or focal tenderness · 2 (8%) non-bloody nipple discharge · 23 (96%) with masses on imaging or clinical exam (not specified if either or both)	· 16/66 (24.2%) palpable mass · 8/66 (12.1%) rapid breast enlargement · 42/66 (63.6%) Non-palpable mass
Imaging findings	Mammogram · 1 questionable mammogram result; other imaging results N/A	N/A	Mammogram · Screening group N=59: majority circumscribed mass or asymmetric density · Clinical finding group N=90: 62 (69%) no findings	Mammogram · N=56 · 17 (30.4%) noncalcified mass, 17 (30.4%) localized increased stroma, 9 (16.1%) no abnormality	Mammogram · N=55 · 43 (78%) abnormality such as mass or focal asymmetry, 12 (22%) normal	N/A	Mammogram · N=80 · 71 (88.7%): well- or partially circumscribed mass, noncalcified, hyperdense with irregular margins	Mammogram · N=23 · 12 (52%) isodense, oval/round · 6 (26%) asymmetry · 4 (17%) no visualization due to dense parenchyma	Mammogram · N=43 · 18 (41.9%) normal, 7 (16.3%) circumscribed mass, 10 (23.3%) lobulated mass, 5 (11.7%) calcification
			Ultrasound · N=109 · 52 (48%) abnormalities; 44 (85%) oval, 43 (83%) circumscribed, 29 (56%) hypoechoic, 20 (38%) isoechoic, 40 (77%) acoustic enhancement	Ultrasound · N=49 · 18 (36.7%) well-defined, hypoechoic masses, 6 (12.2%) ill-defined, hypoechoic masses, 16 (32.7%) normal	Ultrasound · N=56 · 48 (86%) noted a lesion; 37 (66%) circumscribed, oval hypoechoic mass · 8 (14%) irregular/poorly defined borders		Ultrasound · N=53 · 50 (94%) mass visualized: homogeneous, well-circumscribed, hypoechoic mass	Ultrasound · N=66 · 1 (4%) architectural distortion	Ultrasound · N=66 · 12 (18.2%) round, 53 (80.3%) oval, 37 (56.1%) circumscribed, 22 (33.3%) hypoechoic, 42 (63.7%) isoechoic
					CT · N=3		MRI · N=12 · No specific findings	· 1 (4%) complex fluid collection Ultrasound · N=24	MRI · N=12 · 9 (75%) mass enhancement, 3 (25%) non-mass enhancement

Table 1 (*continued*)

Table 1 (*continued*)

Study	Vuitch *et al*., 1986 (1)	Powell *et al*., 1995, (5)	Hargaden *et al*., 2008, (6)	Celliers *et al*., 2010, (7)	Jones *et al*., 2010, (3)	Degnim *et al*., 2010, (8)	Gresik *et al*., 2010, (2)	Bowman *et al*., 2012, (9)	Yoon *et al*., 2020, (10)
					· Incidental masses			· 15 (62.5%) oval/round mass, well circumscribed margins	
					MRI			· 10 (67%) homogeneous, 5 (33%) heterogeneous	
					· N=9				
					· 7 (78%) focal or segmental mass-like enhancement				
					PET scans				
					· N=4				
					· 2 positive, 2 negative for FDG uptake				
Size (cm)	Mean/median N/A; 2-7 cm (gross examination)	Mean 6 cm; 1.2–12 cm (gross examination)	N/A	Mean 1.8 cm; 0.3–7.0 cm**	Mean/median N/A; 0.3–7 cm (on US)	N/A	N/A	Mean/median N/A; 0.6–7 cm**	Median 2.3 cm; 0.6–14 cm (on US)
Management	· 8 (89%) excisional biopsy	· 38 (95%) excisional biopsy	· 16 (11%) observation	· 12 (17.4%) excision	· 38 (79%) observation	579 (100%) excisional biopsy	· 27 (34%) observation	· 14 (58%) surgical excision	· 20 (30.3%) observation
	· 1 (11%) excisional biopsy followed by bilateral mastectomies	· 1 (2.5%) incisional biopsy	· 133 (89%) excision	· 1 (1.4%) reduction mammoplasty (PASH incidental)	· 10 (21%) excision		· 45 (56%) excisional biopsy	· 10 (42%) core needle biopsy and observation	· 11 (16.7%) vacuum-assisted excision
		· 1 (2.5%) bilateral mastectomy		· 60 (81.2%) core needle biopsy, additional treatment N/A	· Data N/A for 9 patients		· 8 (10%) mastectomy	· 5 pts (20% of the total cohort) in the surgical excision group converted to surgery after an initial period of observation	· 29 (43.9%) excision
									· 6 (9.1%) mastectomy
Length of Follow-up	Range and mean/median N/A; maximum of 2.5 years	Mean 4.5 years; range 0.6–11 years	Mean/median, range N/A; minimum 4 years	Mean/median N/A; 1–8 years	Mean 4 years; range 0.5–11 years	Mean 19.8 years; range N/A	Median 3.71 years; range, 0.5–9.5 years	Mean/median N/A; range, 0.5–8 years for 10 patients with available data	Median 32 months; range, 0.5–9.5 years
Outcome	· 7 (78%) no recurrence or other notable outcome	· 6 (15%) recurrences at 1 mon-1 year after dx	· 149 (100%) no subsequent cancer	· 73 (100%) no subsequent cancer	· 48 (100% with follow-up) no upgraded lesions or malignancies	· 34 (5.9%) with PASH developed subsequent breast cancers *vs*. 789 (9.5%) in those without PASH	· Note: PASH was found along with DCIS, LCIS, or invasive cancer in 20/80 (25%), though separate from the malignant lesion, i.e., PASH was incidental	· N=14	· 55 (83%) stable
	· 2 (22%) recurrences at 11 and 14 months, underwent repeat excision or mastectomy	· 2/6 (33%) multiple recurrences	· 3 (2%) recurrence; treatment N/A	· 1 (1.4%) recurrence; treated with excision, 12 months later another recurrence at same site and excised, asymptomatic 6 months later	Observation group	· Breast cancer risk lower in PASH patients *vs*. those with other benign lesions (SIR 1.0 *vs*. 1.5, P<0.001)	Observation group	· 8 (57%) stable	· 11 (17%) progression overall at median 26 months: 3 (15%) in observation group, 3 (27%) in vacuum-assisted excision group, 5 (17%) in surgical excision group
		· 1/6 (17%) extensive contralateral PASH treated with HRT then bilateral mastectomy			· N=38/48 (79%)		· 7/27 (26%) progression within 32 months	· 2 (14%) progressed (1.9–2.9 cm in 4 years and 1.4–3.8 cm in 8 years) —treatment N/A	

Table 1 (*continued*)

Table 1 (*continued*)

Study	Vuitch *et al*., 1986 (1)	Powell *et al*., 1995, (18)	Hargaden *et al.*, 2008, (13)	Celliers *et al*., 2010, (10)	Jones *et al*., 2010, (3)	Degnim *et al.*, 2010, (9)	Gresik *et al*., 2010, (2)	Bowman *et al*., 2012, (5)	Yoon *et al.*, 2020, (11)
					· 28 (74%) stable		· 5 treated with excision; 2/5 had DCIS on surgical pathology	· 4 (29%) excision patients had no recurrence (10 excision patients had no follow-up available)	
					· 4 (10%) decreased/ resolved; 6 (16%) progression (further treatment type N/A)		· 2 continued observation without further progression		
					Excision group		Excision group		
					· N=10/48 (21%)		· 5/38 (13%) had recurrence within 15 months		
					· 7 (70%) stable		· 2/5 had PASH alone at repeat excision		
					· 2 (20%) progressive enlargement (treated with mastectomy)		· 3/5 had DCIS along with PASH at initial diagnosis; repeat excision showed focal DCIS in 2 and invasive cancer in 1		
					· 1 (10%) recurrence (treated with excision)				

*, in total cohort of 9,087 pts; age range not specified in the PASH cohort; **, does not specify source of size data. HRT, hormone replacement therapy; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.

PASH based on the population affected and its resemblance to breast intralobular stroma during the luteal phase of menstruation (1,12).

Etiology

PASH is derived from myofibroblasts with variable expression of myoid and fibroblastic features; there may also be glandular hyperplasia. Myofibroblasts are often CD34 immunoreactive, and the presence of CD34 with vimentin, desmin, smooth muscle actin (SMA) support CD34 as a myofibroblastic differentiation marker (13). Myofibroblasts are normally activated by cytokines and growth factors related to inflammation and wound healing. The myofibroblasts in PASH have more secretory activity and contractile filaments, and it is suggested that stromal fibroblast activation results in collagen release and subsequent stromal hyperplasia (8).

Evidence supporting a potential hormonal etiology for PASH include its preponderance in premenopausal women, and those taking oral contraceptives and hormonal-replacement therapy (HRT) (2-4,7,10,14). One series of 149 patients with PASH reported smaller lesions were more often found in post-menopausal women via screening studies compared with the larger palpable masses that brought pre-menopausal women to clinical attention (6). In the same study, there were more post-menopausal women taking HRT in the palpable mass *vs.* screening group (19% *vs.* 8%), suggesting hormonal influence in creating PASH changes large enough to palpate (6). A case report of a 39-year-old woman with cyclical breast pain and progressive bilateral breast enlargement diagnosed with PASH noted improvement in her symptoms when treated with tamoxifen, further suggesting a hormonal relationship (15). PASH has also been diagnosed in men, nearly always in association with gynecomastia (2,16-18). In the largest series of male PASH cases reported by Badve *et al*., 43 of the 44 patients had gynecomastia, which is known to result from an increase in the ratio of estrogen to androgen activity (16). Further, several histopathology studies have demonstrated estrogen receptor (ER) and progesterone receptor (PR) positive stains within the spindle cells and spaces of the breast stroma, although PR positivity is more frequent (5,9,19).

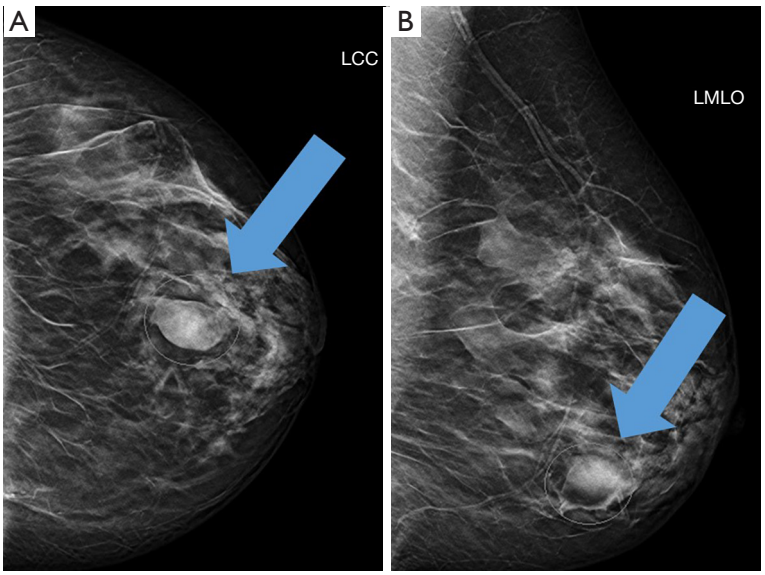

Figure 1 (A,B) Mammography in a 48-year-old female demonstrating PASH lesion as an oval partially circumscribed mass (arrows) in the inferior central left breast; CC and MLO views. PASH, pseudoangiomatous stromal hyperplasia; CC, cranial-caudal; MLO, mediolateral oblique.

Clinical presentation

PASH has a wide spectrum of potential presentations. While most common in pre-menopausal women, it can also affect men, post-menopausal women, and pre-menarchal girls. In men, it is associated with gynecomastia; one case was also reported in a transgender man receiving exogenous hormones (9). Documented ages for women range from 12–86 years (9,20) with mean/median in most series between age 30 and 50 years (1,2,4,5,7,10,14,21,22). Clinically, patients either present with a palpable breast mass, or PASH is discovered as an imaging finding. The lesion can grow slowly or rapidly and is often a painless, firm, mobile mass when palpable (11). In a series of 73 patients, the mean age of those who presented with a palpable mass was 45 years, while that of patients detected on imaging was 53 years (7). In the available literature, 38–60% of PASH cases came to clinical attention due to a palpable mass, with the remainder detected at screening (2,3,6,14).

Less common clinical presentations of PASH can mimic other benign and malignant breast diagnoses. One case report described a 17-year-old girl with a rapidly growing, diffusely tender and firm mass concerning for a phyllodes tumor or giant juvenile fibroadenoma (23), and another identified a 35-year-old woman with gradual breast enlargement accompanied by peau-de-orange skin changes worrisome for inflammatory breast cancer (4). While PASH is most often unilateral and focal, bilateral cases do occur (10,12,24) and PASH may present as diffuse breast enlargement or in a multinodular pattern (25). One case described a menarchal 12-year-old girl with a 4-month history of bilateral breast enlargement and significant reactive hyperemia of the overlying skin on physical exam (20). PASH was confirmed in both breasts and initially treated with subcutaneous right mastectomy and left breast reduction, though due to progressive disease, she completed bilateral mastectomy 8 months after the initial presentation.

Imaging

On mammography, PASH commonly presents as a dense, well-circumscribed, round-oval mass without calcifications (24) (*Figure 1*). It is less frequently detected as a focal asymmetry and is rarely spiculated, but may have indistinct margins (3,25,26) (clinical case #3). While atypical, two studies report PASH associated with calcifications (10,11). Interestingly, in a series of 55 PASH cases, 22% were mammographically occult (3).

Sonographic features of PASH are more variable (24). The most common presentation is a solid, well-circumscribed, homogenous, oval, hypoechoic mass (25) (*Figure 2*). Other findings include heterogeneous or echogenic areas with hypoechoic central portions, cystic

components, and irregular borders (12,21,22) (clinical case #1). The majority of lesions lack posterior acoustic shadowing and demonstrate normal vascularity on color Doppler ultrasound (14,27).

MRI characteristics are non-specific and less well documented. PASH has been described as isointense to breast parenchyma on T1- and T2-weighted images with reticular and cystic areas appearing hyperintense (10,23,25,26). Mass enhancement demonstrates a type 1 curve, suggesting a benign etiology; non-mass enhancement is less common. PASH has been called an imaging mimicker as it can present similarly to fibroadenomas on MRI, mammography and ultrasound, though the slit-like foci on MRI corresponding to the spaces seen on pathology can differentiate PASH when seen (25).

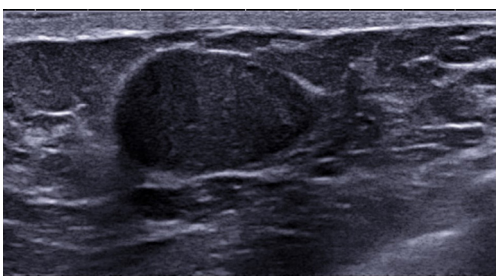

Figure 2 Corresponding left breast ultrasound for PASH lesion in a 48-year-old female demonstrates an oval parallel hypoechoic mass with slightly indistinct margins on anti-radial views. There was no internal flow and it was soft on elastography images. PASH, pseudoangiomatous stromal hyperplasia.

PASH has been detected as an incidental finding on CT and infrequently evaluated with PET. As with MRI, PASH may appear similar to fibroadenomas on PET or present as focal areas of FDG uptake, but findings overall are not specific and suggest a benign process (3,25).

Gross presentation and histopathology

On gross presentation, PASH is often a smooth, solid, oval, rubbery mass that is non-encapsulated but well-circumscribed (5,24). Sectioning reveals a homogeneous tan or gray-white fibrous interior and lack of extensive hemorrhage and necrosis, though cysts up to 1 cm and nodules may be seen (13). The mean size on gross examination is 4–5 cm, with a range of 1.2–15 cm, though the largest documented case was 20 cm (5,13,23).

On microscopy, PASH was first described by Vuitch *et al*. as having intermixed stromal and epithelial components with the epithelial cells ranging from normal to hyperplastic. The name pseudoangiomatous was derived because it mimics vasoformative proliferation, which is characteristic of angiosarcoma. The most prominent feature of the stroma is a complex pattern of interanastomosing empty "slit-like" spaces lined with spindle-shaped myofibroblastic cells (*Figure 3*). The stroma also contains endothelial cells lining small blood vessels and dense collagen (13). Unlike angiosarcoma, PASH lacks erythrocytes, nuclear atypia, mitoses, and pleomorphism. PASH can be classified as simple or fascicular/proliferative; simple is described as above, while the fascicular/proliferative type is characterized

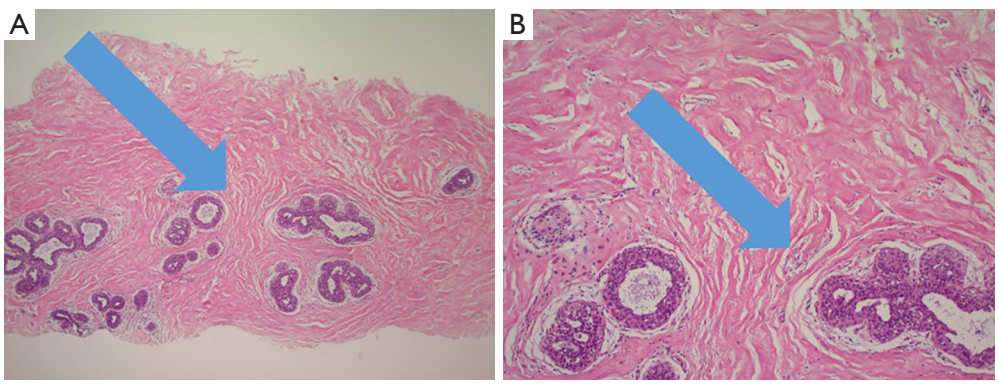

Figure 3 (A,B) H&E 40× and 100×. Pseudoangiomatous stromal hyperplasia (PASH) from an ultrasound guided core needle biopsy specimen for a mass lesion. Histologic sections show a benign myofibroblastic proliferation within a densely collagenized stroma (arrow, A). There are complex interanastomosing spaces within the stroma that imitate the appearance of vessels hence the term "pseudoangiomatous." These spaces are lined by spindle-shaped myofibroblasts that cause PASH (arrow, B). The ducts and lobules within this area of PASH are involved by usual ductal hyperplasia.

by an accumulation of myofibroblasts into distinct bundles in the background of conventional PASH (13,14). While the proliferative areas can obscure underlying PASH, the classic pattern is still present and this is a differentiating factor from myofibroblastoma (5). Of the 26 patients with PASH one series, 18 (69%) of biopsies were classified as simple and 8 (31%) were fascicular/proliferative (14). Histologic markers that identify PASH include CD34, vimentin, desmin, and SMA; calponin is variably reactive (13). Stains for ER and PR are also generally positive, though PR more consistently so. PASH lesions are negative for endothelial markers (CD 31 and factor VIII) and cytokeratin (28,29).

Differential diagnosis

PASH must be differentiated from low-grade angiosarcoma. As the treatment and prognosis of these two lesions is vastly different, histopathology must be carefully examined to ensure the proper diagnosis. Low-grade angiosarcoma is characterized by true vascular spaces, while PASH has pseudoangiomatous slit-like clefts; PASH lacks the erythrocytes, nuclear atypia, mitoses, pleomorphism, destruction of epithelial structures, and endothelial markers found in low-grade angiosarcoma (1). Furthermore, PASH usually is a round, discrete and rubbery mass without the hemorrhagic areas present in angiosarcomas.

Other lesions that are important to differentiate from PASH include fibroadenoma, mammary hamartoma, myofibroblastoma, and additional spindle-cell lesions such as desmoid tumors (also known as fibromatosis), phyllodes (also known as spindle cell sarcoma or cystosarcoma), and leiomyosarcoma (24,30). The clinical presentation of a palpable breast mass in a pre-menopausal woman and the non-specific imaging findings associated with PASH make it especially important to diagnose histologically, and thereby rule out other rare but more serious conditions.

Mammary hamartoma and PASH can present similarly at clinical evaluation and on gross examination as a well-circumscribed breast mass. At histologic comparison, mammary hamartoma may contain glandular breast tissue, fibrous connective tissue, or adipose tissue, while PASH has characteristic dense collagenous breast stroma punctuated by slit like spaces (19). Furthermore, the stroma of PASH stains positive for PR and often ER, while hormone receptor staining is absent in mammary hamartoma. PASH can be distinguished from phyllodes tumors due to absence of the pathognomonic "leaf like" papillary projections of phyllodes, and the lack of true stromal overgrowth, pleomorphism and mitoses seen in malignant phyllodes lesions (22). Myofibroblastoma, another uncommon benign breast lesion, is predominantly seen in older adult men and post-menopausal women, whereas PASH is most common in premenopausal women (26). Both stain positive for vimentin, CD34, and SMA, but PASH expresses PR, while myofibroblastoma expresses androgen receptors (24). Histologically, myofibroblastomas are composed of fascicles and whorls of myofibroblasts intermixed with bands of hyalinized collagen (31). While the fascicular/proliferative subtype of PASH can exhibit a similar pattern, the underlying stromal hyperplasia with slit-like spaces can still be detected to differentiate it from myofibroblastoma. Leiomyosarcoma, a rare breast sarcoma variant, may have areas of hyalinized stromal fibrosis and stain positive for vimentin, desmin, and SMA similar to PASH; characteristics of smooth muscle tumors, nuclear pleomorphism and mitoses separate it from PASH at microscopy evaluation (13).

Diagnostic approach

Since physical examination and imaging findings for PASH are non-specific and mimic other benign and malignant breast lesions, biopsy is necessary for definitive diagnosis. Core needle biopsy is preferred over fine needle aspiration (FNA) or excisional biopsy. PASH was indistinguishable from fibroadenoma on cytology in 70% of cases in one series (7) and others have suggested that PASH may be underdiagnosed due to lack of consensus on minimum volume of PASH necessary for diagnosis (8). Upon histologic diagnosis of PASH, clinical and imaging concordance must be determined. As noted in a series of 80 patients with PASH, 35% underwent core needle biopsy but were not properly diagnosed with PASH until surgical excision, highlighting the utility of excisional biopsy in discordant cases (2).

Treatment and management

Traditional management of PASH has consisted of surgical excision or even mastectomy in rare cases with very large symptomatic masses (20,32). Current evidence-based guidelines recommend that when core needle biopsy is concordant with imaging and clinical findings, the patient may undergo excision or clinical observation (30). Excision is recommended if there are suspicious imaging findings, interval growth of the mass, or accompanying symptoms. Other authors additionally suggest excision for larger lesions

(>2 or 3 cm), and for women with a strong family history of breast cancer and/or an increased risk of developing breast cancer (9,10,25). Complete excision of the lesion should be performed, though there are no definitive guidelines for margin management. If observation is elected, clinical exam and radiologic follow-up should occur at 6-month intervals or based on clinical presentation (2). Since many women are younger than age 40 at diagnosis of PASH, ultrasound and/or MRI can be considered for imaging surveillance in place of mammography.

Though rarely used, anti-estrogen therapy is a potential alternative non-surgical intervention to consider for symptomatic PASH. In a case report utilizing this strategy, a 39-year-old woman with painful, enlarging and persistent PASH in both breasts noted symptom relief when treated with tamoxifen (15). In an earlier published series, one patient with PASH experienced recurrence of an incompletely excised mass and was managed temporarily with hormonal therapy, though the type was not specified (5). The side effect profile of tamoxifen, particularly in pre-menopausal women, likely limits its use to symptom management in patients for whom surgery is contraindicated, and may explain the sparse literature in this area.

Clinical outcomes and risk profile

PASH itself is a benign lesion not associated with an increased risk of breast cancer. While prognosis is generally excellent, progression, recurrence, and concurrent diagnosis of high risk and/or malignant disease have been described. Progression, defined as an increase in size after initial diagnosis, is a possible outcome when PASH is not excised. In a retrospective analysis of 66 PASH cases, progression occurred in 16.6% at median 26 months (range, 6–36 months) and was associated with additional lesions found on CNB, larger lesion size, and symptoms (10). Others have noted progression rates of 0–71% based on serial imaging and/or physical exam (14,21,27), including one study that noted increased lesion size warranting additional biopsy in 15.8% (6/38) of patients at mean follow up of 4 years (range, 6 months to 11 years) (3). The relatively slow growth rate suggests that observation with close clinical follow up is a reasonable strategy after a balanced discussion of surgical risk and benefit in appropriate patients.

Local recurrence has been reported in 15–22% of cases treated with surgical excision (5,21). In their seminal study of 9 patients with PASH, Vuitch *et al*. described two patients (22.2%) with local recurrences at 11 and 14 months following excision; one patient had two recurrences at the same site treated with repeat local excision (1). Powell *et al* found that of 38 patients with PASH undergoing surgical management, 6 (15.8%) experienced recurrence at intervals from one month to one year, of which 5 were ipsilateral and two were multiple (5). Four patients were treated with repeat excision, one did not have further therapy (not specified if this was by patient choice), and one developed bilateral PASH with multiple nodules and was managed temporarily with hormonal therapy before ultimately completing bilateral mastectomies. Accordingly, recurrence could be attributed to incomplete excision, the presence of multiple lesions that were not all excised, or de novo growth of PASH (33).

PASH is often accompanied by other benign and high risk lesions. These include fibroadenoma, fibrocystic change, hamartoma, apocrine metaplasia, intraductal papilloma, atypical hyperplasia, and LCIS, which are synchronously found in 14–65% of cases (7,10). PASH has infrequently been found concurrent with malignancy diagnosed on the same core needle biopsy, though always described as distinct and separate from the primary tumor focus. Until 2010, only one case of invasive ductal carcinoma was reported in association with PASH on core needle biopsy (14). In a later series of 80 patients diagnosed with PASH on core needle biopsy, 38 completed excisional biopsies, and 35% (13/38) were subsequently diagnosed with DCIS, LCIS, or infiltrating cancer on surgical pathology (2). The malignant lesions were found separate from the focus of PASH, and the authors note it was not possible to determine the reason for excision, i.e. discordance of imaging, clinical, and pathology findings which would prompt surgical management. In cases with synchronous diagnoses, the more pathologic (i.e., atypical or malignant) lesion determines the patient's prognosis as PASH itself does not give rise to atypia or malignancy.

Further evidence that PASH is not associated with an increased risk of breast cancer is derived from a comparative study of 9,087 patients who underwent surgical excision of benign breast lesions including PASH (8). Of the 579 (6.4%) patients with PASH at histologic examination, the majority (88%) were under age 55 and most (71%) presented with a palpable mass. At mean follow-up of 18.5 years, subsequent breast cancer developed in 5.9% of patients in the PASH group *vs*. 8.8% in the non-PASH group. Women with histologic PASH had a lower risk of breast cancer (SIR 1.03, 95% CI, 0.71–1.44) than those without PASH (SIR 1.54, 95% CI, 1.43–1.65) (P=0.01). PASH was not associated

Table 2 Clinical pearls for management of pseudoangiomatous stromal hyperplasia (PASH)

Most common patient population	Premenopausal females, age 30–50
Clinical presentation	Either palpable unilateral breast mass, often non-tender; or incidental imaging finding
Imaging characteristics	Mammogram: well-circumscribed, round-oval mass without calcifications
	Ultrasound: solid, well-circumscribed, homogenous or heterogeneous, oval, hypoechoic mass
	MRI: mass enhancement
	The lack of specificity and similarity to other benign (fibroadenoma) and malignant breast lesions is non-diagnostic
Differential diagnosis	Low-grade angiosarcoma, fibroadenoma, mammary hamartoma, myofibroblastoma, and other spindle-cell lesions (i.e., desmoid tumors, phyllodes, leiomyosarcoma)
Histology	Complex, slit-shaped pseudoangiomatous spaces lined by spindle-shaped myofibroblasts in inter- and intra-lobular stroma. Dense collagen and epithelial cell hyperplasia also present
Management	Core needle biopsy for diagnosis. If pathology is concordant with imaging and clinical findings, options include observation *vs*. surgical excision. Observation should include clinical exam and imaging every 6 months or based on initial presentation.
Indications for surgical excision	Increasing size, associated symptoms, suspicious imaging findings, another lesion present indicating excision
Clinical outcomes	Possible recurrence following excision (7–22%), progression during observation (6–17%)
Increased breast cancer risk	No
Classification (benign/high risk/malignant)	Benign

with a family history of breast cancer and was not more commonly found with proliferative lesions, supporting the divergent pathogenesis of PASH and epithelial lesions that increase breast cancer risk. However, interestingly, 85% of subsequent breast cancers in the PASH group developed in the ipsilateral breast, suggesting a potential relationship between the hormonal environment of PASH and the epithelial-stromal interactions in breast carcinogenesis.

Summary and recommendation

PASH is a benign stromal lesion of the breast characterized by "pseudoangiomatous" capillary-like spaces. It is most common in premenopausal women and may present as a palpable mass or an incidental imaging finding. Core needle biopsy is indicated for diagnosis and must be concordant with imaging and clinical findings. PASH lesions should be surgically excised if enlarging, associated with symptoms, or suspicious imaging findings are present; otherwise, observation with clinical and imaging follow-up is appropriate. A discussion of risks and benefits, as well as patient preferences, should be used to facilitate shared decision making and optimal patient care (*Table 2*).

PASH clinical scenarios

Case 1

A 27-year-old female gravida 5 para 2 presented to her OB/GYN with a self-palpated left breast mass and associated pain. Family history included a paternal grandmother with breast cancer at age 68; she had a personal history of systemic lupus erythematosus. Ultrasound examination demonstrated in the left breast at the 3:00 position, 3 cm from the nipple an oval parallel mixed echogenicity mass comprised of hypoechoic vascular tissue with anechoic cysts, minimally stiff on elastography, measuring 3.1×0.7×2.5 cm^3 (*Figure 4*). She was referred to breast surgery and clinical exam showed a 3×2 cm^2 firm mobile mass at the site of her palpable abnormality; no axillary adenopathy was noted. Ultrasound guided core needle biopsy yielded PASH, focal atypical ductal hyperplasia (ADH), apocrine metaplasia and cysts, intraductal papillomatosis, and a benign sclerosing lesion. Pathology was concordant with imaging and clinical exam. Excisional biopsy was recommended due to presence of ADH and clinical symptoms (pain, bothersome palpability). Surgical pathology yielded PASH, florid usual ductal

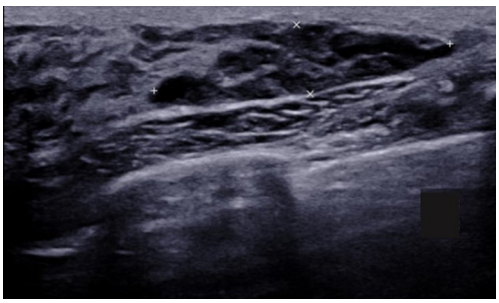

Figure 4 Case 1: ultrasound image of left breast mass with mixed echogenicity, minimally stiff on elastography in radial view; female patient age 27.

hyperplasia, a complex sclerosing lesion with associated microcalcifications, and microcysts. She recovered well post-operatively and continues bi-annual surveillance in a high risk breast cancer program.

Case 2

A 48-year-old pre-menopausal female, gravida 1 para 1, presented with a self-palpated left breast mass. The patient had a strong family history of breast cancer, involving her mother at age 54, a paternal aunt at age 44, and a maternal aunt at unknown age. There was also a history of pancreatic and uterine cancers on the maternal side. Clinical exam demonstrated a 2 cm mass in the left breast lower outer quadrant without axillary lymphadenopathy. Diagnostic mammography showed an oval density in the area of palpable abnormality in the left breast without suspicious calcifications (*Figure 1*). On targeted ultrasound, at 5 o'clock 1 cm from the nipple, there was an oval parallel hypoechoic mass with slightly indistinct margins and without

internal flow, soft on elastography images (*Figure 2*). Ultrasound examination of the left axilla demonstrated 3 unremarkable lymph nodes. Ultrasound-guided vacuum assisted core biopsy yielded PASH, columnar cell change, and usual ductal hyperplasia. The pathology results were concordant with the imaging and clinical exam findings. Surgical excision and clinical observation were discussed. Due to the small size and lack of associated symptoms, observation was elected. There was no interval change in size, imaging characteristics, or symptoms at one year of follow-up (*Figure 5*). The patient was referred to genetics for consultation regarding her family history of breast and other malignancies.

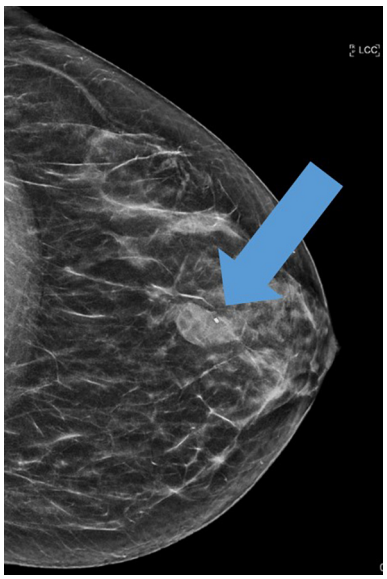

Figure 5 Case 2: one-year follow up mammography for a 48-year-old patient demonstrating stable circumscribed left breast mass (arrow) with biopsy clip; CC view. CC, cranial-caudal.

Case 3

A 44-year-old pre-menopausal female, gravida 2 para 1, presented with a screen-detected right breast mass. Her family history included breast cancer in a post-menopausal maternal great aunt. Right diagnostic mammogram demonstrated a well-circumscribed oval mass in the superolateral aspect at mid to posterior depth (*Figure 6*). Right breast ultrasound showed an oval well-circumscribed mass with mixed echogenicity in the 11:00 position 6 cm from the nipple, measuring 2.3×1.1×2.3 cm^3 with minimal internal vascularity and soft elastography characteristics; categorized BI-RADS Category 4 (*Figure 7*). Clinical exam demonstrated a 3 cm firm, irregular mass in the upper outer quadrant of the right breast without skin or nipple changes. No axillary, infraclavicular, or supraclavicular lymphadenopathy was appreciated on physical exam or ultrasound. Ultrasound guided core needle biopsy yielded PASH and usual ductal hyperplasia. This was concordant with the imaging and clinical exam findings. The patient declined surgical consultation and presented 18 months later due to increased size of the mass. Repeat mammogram and ultrasound showed the size to measure 3.1×1.5×3.3 cm^3 (*Figures 8* and *9*); clinical exam was significant for a 4 cm mass in the upper outer quadrant. Surgical excision was recommended and completed (*Figure 10*). Pathology

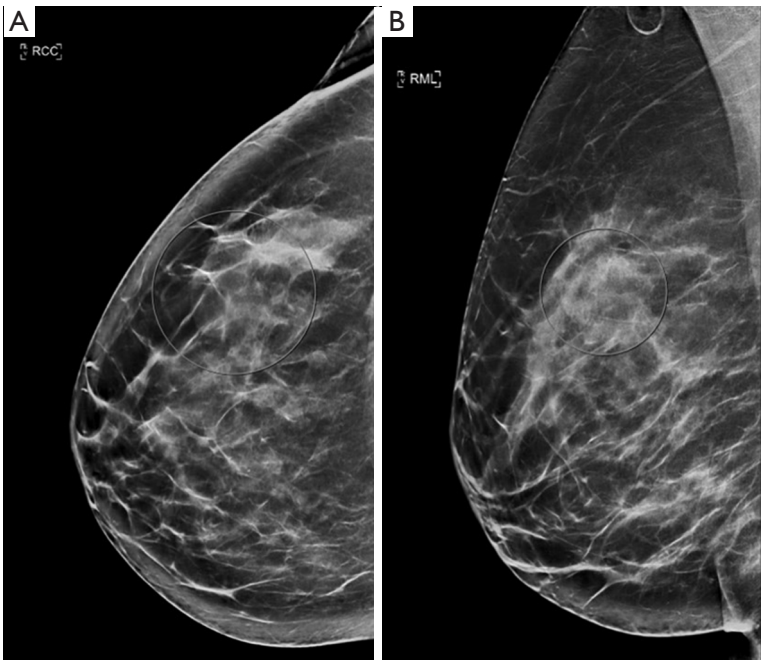

Figure 6 (A,B) Case 3: mammography images at initial presentation in a 44-year-old female; a well-circumscribed oval mass in the superolateral aspect of the right breast at mid to posterior depth is circled on CC and MLO views. CC, cranial-caudal; MLO, mediolateral oblique.

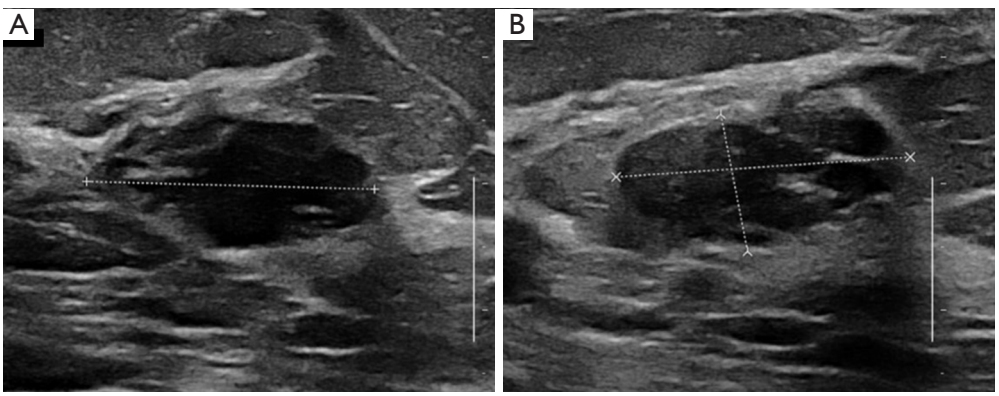

Figure 7 Case 3: ultrasound images at initial presentation for a 44-year-old female patient demonstrating an oval well-circumscribed mass with mixed echogenicity; anti-radial and radial views.

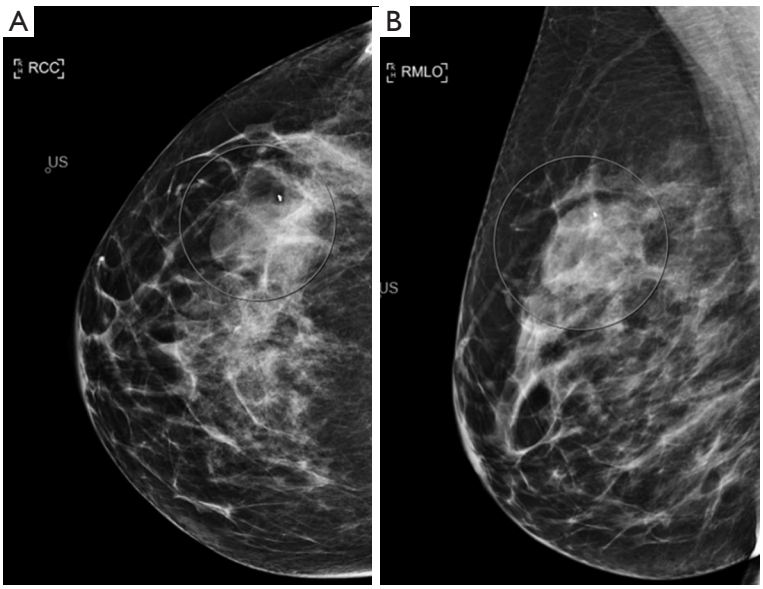

Figure 8 (A,B) Case 3: mammography images for a 44-year-old patient at 18 months after PASH diagnosis via core needle biopsy. Right breast CC and MLO views show an increase in the size of the circled mass with associated biopsy clip. CC, cranial-caudal; MLO, mediolateral oblique.

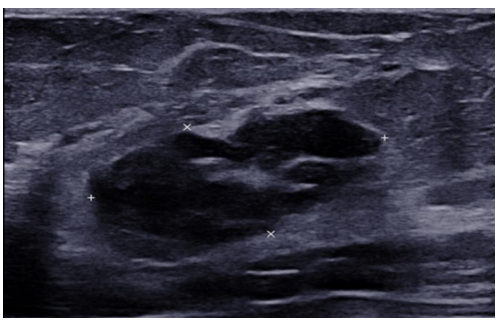

Figure 9 Case 3: Ultrasound image for a 44-year-old patient at 18 months after PASH diagnosis via core needle biopsy; radial view. PASH, pseudoangiomatous stromal hyperplasia.

demonstrated PASH, fibroadenomatous change, and sclerosing adenosis. Her postoperative course was uneventful and no recurrence has been noted at 2 years of follow up.

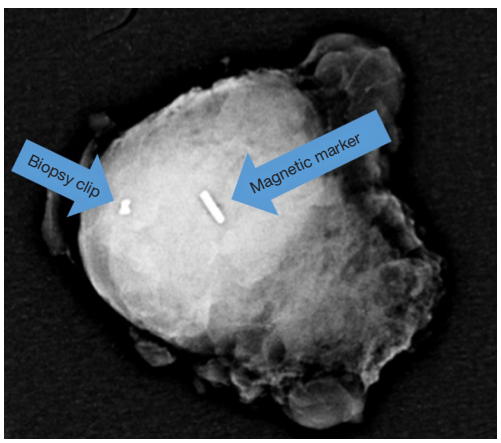

Figure 10 Case 3: surgical specimen after excisional biopsy in a 44-year-old patient demonstrating mass, biopsy clip, and magnetic seed localizing marker. Pathology yielded PASH, fibroadenomatous change, and sclerosing adenosis.

Acknowledgments

We would like to thank Dr. Hannah Gilmore and Dr. Leah Sieck for their contributions to the histology and radiology images.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Katharine Yao) for the series "A Practical Guide to Management of Benign Breast Disease" published in *Annals of Breast Surgery*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/abs-20-86). The series "A Practical Guide to Management of Benign Breast Disease" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Vuitch MF, Rosen PP, Erlandson RA. Pseudoangiomatous hyperplasia of mammary stroma. Hum Pathol 1986;17:185-91.
2. Gresik CM, Godellas C, Aranha GV, et al. Pseudoangiomatous stromal hyperplasia of the breast: a contemporary approach to its clinical and radiologic features and ideal management. Surgery 2010;148:752-7.
3. Jones KN, Glazebrook KN, Reynolds C. Pseudoangiomatous stromal hyperplasia: imaging findings with pathologic and clinical correlation. AJR Am J Roentgenol 2010;195:1036-42.
4. Ibrahim RE, Sciotto CG, Weidner N. Pseudoangiomatous hyperplasia of mammary stroma: some observations regarding its clinicopathologic spectrum. Cancer 1989;63:1154-60.
5. Powell CM, Cranor ML, Rosen PP. Pseudoangiomatous stromal hyperplasia (PASH). Am J Surg Pathol 1995;19:270-7.
6. Hargaden GC, Yeh ED, Georgian-Smith D, et al. Analysis of the mammographic and sonographic features of pseudoangiomatous stromal hyperplasia. AJR Am J Roentgenol 2008;191:359-63.
7. Celliers L, Wong D, Bourke A. Psuedoangiomatous stromal hyperplasia: a study of the mammographic and sonographic features. Clin Radiol 2010;65:145-9.
8. Degnim AC, Frost MH, Radisky DC, et al. Pseudoangiomatous stromal hyperplasia and breast cancer risk. Ann Surg Oncol 2010;17:3269-77.
9. Bowman E, Oprea G, Okoli J, et al. Pseudoangiomatous stromal hyperplasia (PASH) of the breast: a series of 24 patients. Breast J 2012;18:242-7.
10. Yoon KH, Koo B, Lee KB, et al. Optimal treatment of pseudoangiomatous stromal hyperplasia of the breast. Asian J Surg 2020;43:735-41.
11. Castro CY, Whitman GJ, Sahin AA. Pseudoangiomatous stromal hyperplasia of the breast. Am J Clin Oncol 2002;25:213-6.
12. Smilg P. Pseudoangiomatous stromal hyperplasia: presentation and management – a clinical perspective. SA J Radiol 2018;22:1366.
13. Rosen PP. Chapter 38. Benign Mesenchymal Neoplasms. In: Rosen PP, eds. Rosen's Breast Pathology, Third Edition. Lippincott Williams & Wilkins, 2009:839-48.
14. Ferreira M, Albarracin CT, Resetkova E. Pseudoangiomatous stromal hyperplasia tumor: a clinical, radiologic and pathologic study of 26 cases. Mod Pathol 2008;21:201-7.
15. Pruthi S, Reynolds C, Johnson RE, et al. Tamoxifen in the management of pseudoangiomatous stromal hyperplasia. Breast J 2001;7:434-9.
16. Badve S, Sloane JP. Pseudoangiomatous hyperplasia of male breast. Histopathology 1995;26:463-6.
17. Milanezi MF, Saggioro FP, Zanati SG, et al. Pseudoangiomatous hyperplasia of mammary stroma associated with gynaecomastia. J Clin Pathol 1998;51:204-6.
18. Maciolek LM, Harmon TS, He J, et al. Pseudoangiomatous stromal hyperplasia of the breast: a rare finding in a male patient. Cureus 2019;11:e4923.
19. Anderson C, Ricci A Jr, Pedersen CA, et al. Immunocytochemical analysis of estrogen and progesterone receptors in benign stromal lesions of the breast. Evidence for hormonal etiology in pseudoangiomatous hyperplasia of mammary stroma. Am J Surg Pathol 1991;15:145-9.
20. Singh KA, Lewis MM, Runge RL, et al. Pseudoangiomatous stromal hyperplasia. A case for bilateral mastectomy in a 12-year-old girl. Breast J 2007;13:603-6.
21. Polger MR, Denison CM, Lester S, et al. Pseudoangiomatous stromal hyperplasia: Mammographic and sonographic appearances. AJR Am J Roentgenol

1996;166:349-52.
22. Cohen MA, Morris EA, Rosen PP, et al. Pseudoangiomatous stromal hyperplasia: Mammographic, sonographic, and clinical patterns. Radiology 1996;198:117-20.
23. Solomou E, Kraniotis P, Patriarcheas G. A case of a giant pseudoangiomatous stromal hyperplasia of the breast: magnetic resonance imaging findings. Rare Tumors 2012;4:e23.
24. Virk RK, Khan A. Pseudoangiomatous stromal hyperplasia: an overview. Arch Pathol Lab Med 2010;134:1070-4.
25. Raj SD, Sahani V, Adrada BE, et al. Pseudoangiomatous stromal hyperplasia of the breast: multimodality review with pathologic correlation. Curr Probl Diagn Radiol 2017;46:130-5.
26. Schickman R, Leibman AJ, Handa P, et al. Mesenchymal breast lesions. Clin Radiol 2015;70:567-75.
27. Mercado CL, Naidrich SA, Hamele-Bena D, et al. Pseudoangiomatous stromal hyperplasia of the breast: sonographic features with histopathologic correlation. Breast J 2004;10:427-32.
28. Salvador R, Lirola JL, Domínguez R, et al. Pseudo-angiomatous stromal hyperplasia presenting as a breast mass: Imaging findings in three patients. Breast 2004;13:431-5.
29. Kempson RL, Rouse RV. Stanford Pathology Criteria: Pseudoangiomatous Stromal hyperplasia. Stanford University School of Medicine. Published March 6, 2012. Accessed July 23, 2020. Available online: http://surgpathcriteria.stanford.edu/breast/pash/
30. The American Society of Breast Surgeons Consensus Guideline on Concordance Assessment of Image-Guided Breast Biopsies and Management of Borderline or High-Risk Lesions. Published November 2, 2016. Accessed July 23, 2020. Available online: https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Concordance-Assessment-of-Image-Guided-Breast-Biopsies.pdf
31. Magro G. Mammary myofibroblastoma: a tumor with a wide morphologic spectrum. Arch Pathol Lab Med 2008;132:1813-20.
32. Osborne MP, Boolbol SK, Asad J. Chapter 16. Benign conditions of the breast. In: Kuerer HM, eds. Kuerer's Breast Surgical Oncology. McGraw-Hill, 2010. Accessed July 23, 2020. Available online: https://accesssurgery.mhmedical.com/content.aspx?bookid=428&sectionid=39936142
33. Sng KK, Tan SM, Mancer JF, et al. The contrasting presentation and management of pseudoangiomatous stromal hyperplasia of the breast. Singapore Med J 2008;49:e82-5.

doi: 10.21037/abs-20-86
Cite this article as: Estes A, Cao L, Miller ME. Pseudoangiomatous stromal hyperplasia: overview and clinical management. Ann Breast Surg 2020;4:22.

