Pseudo-Angiomatous Stromal Hyperplasia of Breast (PASH): A Case report and Literature Review

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ABSTRACT
PASH (Pseudo-angiomatous Stromal Hyperplasia) is a benign disease of breast connective tissue. May be presented as a breast lump or as an incidental radiological or histological finding. This is a case report of a large, rapidly growing PASH in a 43-year-old female patient. The pre-operative tissue diagnosis showed benign changes. The decision for surgical excision triggered by the history rapid growth as well as large size of the lump and indeterminate radiological findings. The lesion has been removed with intact strong capsule. The patient had uneventful recovery. PASH diagnosis is important to differentiate it from angiosarcoma and phyllodes tumours.

Key words: Pseudo-Angiomatous Stromal Hyperplasia, PASH, Breast.

INTRODUCTION
PASH (Pseudo-Angiomatous Stromal Hyperplasia) is a proliferative benign pathological condition of the breast stroma. A characteristic feature is a dense proliferation of stromal mesenchymal cells of myofibroblastic origin. This is seen as a network of empty, slit-like channels lined by endothelial-like spindle cells.1 The term “pseudoangiomatous” narrated this histological manifestation which resembles, without literally forming, an angiomatous proliferation and indeed they emphasised the significance of differentiating this benign lesion from different vascular tumours such as low-grade Angiosarcoma.2 Presentation as a large palpable mass is very rare; huge rapidly enlarged breast is another form of presentation. Clinically they may mimic inflammatory cancer also; their behaviour could be influenced by hormonal activity, and that can mimic fibroadenoma.

CASE PRESENTATION
A breast triple assessment has been done to a 43 years old lady, who attended the breast clinic with a rapid growing lump of the right breast, associated with a significant degree of breast asymmetry. Her Menarche was at 11 and the past medical history and family history were unremarkable. On clinical examination there was obvious breast asymmetry with a larger right breast. A palpable soft cystic lesion felt in the right breast occupying the retro-areolar area and the breast upper inner quadrant. Mammogram revealed a well circumscribed lesion measures about 150 mm. It showed features of high density, lack of microcalcification and is of homogeneous property. This has been graded as M3 using the BIRADS (Breast Imaging-Reporting and Data System). (Figure 1) Breast ultrasound showed a large well defined lesion, hypoechoic, partially solid and partially cystic. Measures about 15 cm, nature indeterminate, and has been graded as U2/3 (BIRADS). (Figure 2) Fine Needle Aspiration Cytology showed benign cells only. Due to indeterminate features in imaging, breast MDT [multidisciplinary team] advised to offer the patient surgical removal of the lump. Surgical excision was performed using a superior circum areolar incision. The lesion has been removed intact and it has a very strong capsule. The histology of the removed lump shows the interlobular stroma is expanded by hyalinated fibro-connective tissue containing anastomosing slits/channels which simulate vascular spaces. These slits are lined by bland spindle and ovoid cells within a hyalinated stroma. The displaced intervening breast ducts and ductules are benign, without significant epithelial proliferation and no breast lobules seen. (Figure 4,5)
The cells lining the spaces are positive for Vimentin (Figure 6), CD34 (Figure 7), Bcl-2 (Figure 8), and SMA (Figure 9). They are negative for FVIII-related antigen (Figure 10), CD31 (Figure 11), and D2-40 (Figure 12). Our case was negative for ER and PR, the PASH negativity for ER & PR has been reported in the literature before. The picture is consistent with extensive, mass forming unusual extent of pseudo-angiomatous stromal hyperplasia (PASH).

The postoperative period was uneventful, and the patient currently has joined annual follow-up program for three years.
PASH (Pseudo-angiomatous Stromal Hyperplasia) of the breast, first has been reported in 1986 when Vuitch, Rosen, and Erlandson presented nine cases with benign well-circumscribed breast masses that simulated vascular lesions consisting of mammary stromal proliferations. PASH is associated with several benign breast conditions including proliferative and non-proliferative fibrocystic changes, fibroadenomas, gynaecomastia, normal breast dense tissue and sclerosing lobular hyperplasia. The aetiology and pathogenesis remain unknown. Pseudoangiomatous stromal hyperplasia is a relatively common lesion of the breast. Age of presentation of Pseudoangiomatous Stromal Hyperplasia of Breast is usually between 12-70 years, the average age of patients with PASH is around 40 years, and usually diagnosed in pre-menopausal and peri-menopausal women after an imaging guidance biopsy or lump excision. PASH has been diagnosed in men also, in a transgender men on hormones and in men with gynaecomastia. Around 30% of focal breast PASH presented as a palpable lump, the other 70% either as incidental radiological finding or incidental histological features. Generally speaking, it is less commonly present as a clinically palpable mass and is more commonly found as incidental microscopic foci. The non-mass forming or diffuse PASH incidence is about 23% in breast biopsies. PASH was found as...
an incidental histological finding in the surgical excised specimens done for benign or malignant pathology was in 23% cases, and in 24-47% of resected gynaecomastia lesions. PASH may presents clinically as a breast lump or nodule, typically solitary, circumscribed, rubbery and mobile, usually in pre-menopausal women, and accordingly is most frequently misdiagnosed as a fibroadenoma.

The radiological findings are indistinguishable from those of the fibroadenoma, and they are categorised as BI-RADS type 3 lesions (probably benign lesions). Mammographic features of PASH can be entirely non-specific and can show a broad spectrum of variation. In mammography, PASH can appear as a partially or well-circumscribed non-calciﬁed mass or as an asymmetric density. The ultrastructural findings reveal that the spaces found in the lesion are not true vascular channels, the impression is as they arise by a process that involves disruption and separation of stromal collagen ﬁbers.9

Macroscopic morphology of the removed lesion usually a well-circumscribed ﬁbrous tumour, may have white or grey colour. The tumour may contain some cystic areas. The removed lesion cut surface is pale, ﬁbrous and has a homogenous character. The reported sizes in literature vary between 1 and 12 cm.17

A high percentage of lesions show positive hormonal receptor staining, and the rarity of PASH in patients older than 50 years concurs with the conclusions of hormonal association.18 The histological similarity of the stromal changes in PASH and gynaecomastia represents a response in the male breast to hormonal stimulation, which also support the hormonal theory. The mammary stroma is classiﬁed into an intralobular hormonal dependent component and an interlobular component that is relatively unresponsive to hormones. There are suggestions that, PASH could be the result of expansion of the intralobular stroma.2

On histological ﬁndings, PASH can be mistaken for a low-grade angiosarcoma and phylloides tumour; however PASH itself is a benign condition. Proper diagnosis of PASH of the breast has crucial management implications for patients. The typical microscopic picture shows a complex network of inter-anastomosing slit-like spaces lined by endothelial-like spindle cells against a background of stromal hyperplasia in the breast parenchyma. PASH tumours are classiﬁed into either simple or fascicular/proliferative subtypes. In the simple type open, slit-like anastomosing channels without erythrocytes appear to be lined by ﬂat cells in a discontinuous layer, while in the fascicular/proliferative type there are areas of cellular proliferation composed of bland spindle cells.4

Cytology is non-speciﬁc and it is impossible to diagnose PASH on ﬁne needle aspiration cytology. Imaging guidance core biopsy is needed to establish the diagnosis prior to surgery, although in some cases the ﬁnal diagnosis is revealed only after excision.4,19 PASH does not exhibit any atypia or mitotic activity.4 It lacks any invasive features, contains no necrosis, and no destruction of mammary epithelial structures.15 There is no evidence that it is a precursor of angiosarcoma or any other malignancy.

The signiﬁcance of the accurate diagnosis is to differentiate PASH from LG-BAS (low grade breast angiosarcoma). LG-BAS is characterised by prominent and freely anastomosing vascular channels invading the breast parenchyma. There is minimal cytological atypia of the hyper-chromatic endothelium and very little endothelial tufting and papillary pattern.10 On the contrary, PASH is not a real vascular space, it is composed of a network of slit-like spaces lined by myofibroblasts that have an appearance of vascular spaces, it is thought to be due to disarrangement of stromal collagen ﬁbres. The role of immuno-histochemistry is crucial at this stage, PASH myofibroblastic cells are persistently positive for DC34 (marker shows expression in early hematopoietic and vascular-associated tissue), Vimentin (is a type III intermediate ﬁlament [IF] protein that is expressed in mesenchymal cells), progesterone receptors, smooth muscle actin, desmin (muscle-speciﬁc, type III intermediate ﬁlament protein that integrates the sarcolemma), and BCL-2,1,11,16,20,21 and weekly positive for ER.16,21 Powell et al found expression of PR in 36% (5 of 14) and ER in 12% (2 of 14) of PASH cases.6,7 Also PASH is negative Factor VIII, Ulex europeus, cytokeratin, S100 p63.11

PASH is consistently negative for CD31 [cluster of differentiation 31], also known as Platelet endothelial cell adhesion molecule (PECAM-1) makes up a large portion of intercellular junctions of endothelial cell. It is the most sensitive and speciﬁc indicator of angio-genic proliferation. CD31 is positive in angiosarcoma. The electron microscope ﬁndings shows spindle stromal cells of PASH with nondescript ultra-structural characteristics. They invariably absence of Weibel-Palade bodies, pinocytic vesicles, and a completely surrounded basement membrane, that is, they have no endothelial features.5,8,20

**Treatment**

Complete surgical excision of the tumour with good safety margins, remain the determining factors to reduce disease recurrence. High PASH recurrence without complete surgery has been reported, even in 12 months period after surgery. A recurrence rate of 15 to 22% has been reported.6,8,22,23 The most used surgical techniques in breast conservation surgery, some authors suggest breast skin sparing mastectomy10, and many papers suggest a regular follow up for few years.11

**CONCLUSION**

PASH of the breast is not uncommon; however it is a benign condition. Large size tumour presentation of PASH is unusual. Complete surgical excision of lesion reduces the recurrence risk. It is very crucial to differentiate between PASH and the low-grade angiosarcoma in histology, immunohistochemical studies are essential to exclude the angiosarcoma diagnosis.

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**REFERENCES**


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