Pseudoangiomatous Stromal Hyperplasia
An Overview

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Pseudoangiomatous stromal hyperplasia (PASH) of the breast is a benign, proliferative mesenchymal lesion with possible hormonal etiology. It typically affects women in the reproductive age group. Pseudoangiomatous stromal hyperplasia is frequently an incidental histologic finding in breast biopsies performed for other benign or malignant lesions. Rarely, it can present as a firm, painless breast mass, which has been referred to as nodular or tumorous PASH. Grossly, tumorous PASH is a well-circumscribed, firm, rubbery mass with solid, homogenous, gray-white cut surface. On histologic examination, it is characterized by the presence of open slitlike spaces in dense collagenous stroma. The spaces are lined by a discontinuous layer of flat, spindle-shaped myofibroblasts with bland nuclei. The spindle cells express progesterone receptors and are positive for vimentin, actin, and CD34. The most important differential diagnosis on histopathology is angiosarcoma.

Pseudoangiomatous stromal hyperplasia discovered incidentally does not require any additional specific treatment. Tumorous PASH is treated by local surgical excision with clear margins and the prognosis is excellent, with minimal risk of recurrence after adequate surgical excision. (Arch Pathol Lab Med. 2010;134:1070–1074)

Pseudoangiomatous stromal hyperplasia, more commonly known as PASH, is a well-recognized but poorly understood entity. Pseudoangiomatous stromal hyperplasia is a widely accepted term, but it does not reflect this entity’s true histogenesis. It is believed to originate from mammary myofibroblasts and, for that reason, Leon et al. proposed the term nodular myofibroblastic hyperplasia of the mammary stroma to denote its true histogenesis.

Pseudoangiomatous stromal hyperplasia was first described by Vuitch et al. in 1986. The authors described histologic and ultrastructural features of tumorous PASH in 9 premenopausal women. Each of them presented with a palpable, unilateral breast mass. Approximately 150 cases of tumorous PASH have been described in the literature. The first large series of patients with tumorous PASH, published by Powell et al. in 1995, described the histologic features, immunohistochemical characteristics, and clinical follow-up of 40 cases. More recently, Ferreira et al. compared the histologic findings of tumorous PASH with clinical outcome in 26 patients.

Herein, we review the literature of PASH, including the clinical features, pathogenesis, findings on imaging studies, histopathologic features, along with treatment and prognosis.

CLINICAL FEATURES

Pseudoangiomatous stromal hyperplasia can affect persons in any age group, ranging from 12 to 75 years, but it occurs more commonly in premenopausal women. It was originally described in females and later on, it was documented in males in association with gynecomastia. Pseudoangiomatous stromal hyperplasia may present in a wide clinicopathologic spectrum ranging from incidental histologic finding to clinically palpable breast mass. The patients with tumorous PASH present with a slow-growing breast mass. On physical examination, tumorous PASH is a solitary, firm, painless, well-circumscribed, and freely mobile mass mimicking fibroadenoma. Sometimes, the mass may enlarge rapidly and mimic a malignant tumor. Rarely, the patient may present with diffuse massive enlargement of the breast. Tumorous PASH is typically unilateral, but there are rare documented reports of asymmetric diffuse enlargement of bilateral breasts. It can also arise in the axillary tail of breast and, very rarely, tumorous PASH may involve nipple-areola complex and accessory breast tissue in axilla.

HISTOGENESIS AND PATHOGENESIS

The exact etiology and pathogenesis of PASH is not clearly understood. In the past, some authors considered it to be a hamartomatous lesion and classified it along with the mammary hamartomas. However, The World Health Organization classified PASH distinctively from mammary hamartoma. The widely accepted hypothesis in the literature is that the stromal hyperplasia in PASH results from an exaggerated, aberrant responsiveness of mammary myofibroblasts to hormonal stimuli. The hormonal influence may be endogenous or exogenous. The main hormone implicated to stimulate the myofibroblasts is progesterone. The nuclei of myofibroblasts in PASH have been shown to express progesterone receptors (PR). Anderson et al. studied expression of estrogen receptor (ER) companies described in this article.

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and PR in 5 cases of PASH. Intense, patchy staining of PR was noted in the nuclei of stromal cells in all cases, whereas ER expression was more variable and faint. In contrast, the stromal cells in uninvolved breast tissue did not show any expression of either ER or PR. Powell et al found expression of PR in 36% (3 of 14) and ER in 12% (2 of 14) of PASH cases. They, too, found stronger expression of PR than ER, like the previous study. These studies indicate that progesterone probably stimulates the stromal cells in estrogen-primed breast tissue.12

The epithelial nuclei of the ducts and lobules showed frequent positivity for ER as well as PR.12,13 The hormonal basis is further supported by the similarity of histologic changes seen in PASH and in normal breast during the luteal phase.14 The fact that more than half of postmenopausal women with tumorous PASH, as described in literature, were receiving hormone replacement therapy, further supports the role of hormonal influence in its pathogenesis.3,12,13 Pseudoangiomatous stromal hyperplasia has been described in immunosuppressed patients.15 It shows rapid growth in immunosuppressed patients but it is not clear whether immunosuppression plays a role in its pathogenesis or in its rapid enlargement.

There is no consensus on the origin of slit-like spaces in PASH. Initially, the spaces were considered to be artifacts but their presence in frozen sections, as well as permanent sections, confirmed their true nature.16 Immunohistochemical staining and ultrastructural studies have supported the myofibroblastic origin of the stromal spindle cells. On immunohistochemistry, the spindle cells show expression of myofibroblastic markers such as vimentin, CD34, and smooth muscle actin (SMA).1 In addition, the spindle cells have been shown to be positive for BCL-2.15 Damiani et al18 reported carcinoma infiltrating the slitlike spaces in PASH. They proposed that this could be an unrecognized pathway of tumor spread. Furthermore, they suggested that these spaces may represent prelymphatic channels described in the breast stroma by Hartveit.19 This prelymphatic origin of spaces seen in PASH has not been supported by any other study. Moreover, Damiani et al18 showed that the spindle cells lining the spaces were positive for CD34 and SMA and negative for CD31, which is consistent with the immunophenotype of myofibroblasts. On electron microscopy, the slitlike spaces are lined by incomplete layer of spindle cells joined together by rudimentary cell junctions or, occasionally, by tight cell junctions. The cells show cytoplasmic processes extending along and around the spaces. The cytoplasm contains abundant endoplasmic reticulum, well-developed Golgi apparatus, and small bundles of intermediate filaments.2 Collagen fibrils are seen in stroma, present between the spaces.

**RADIOLOGIC FEATURES**

Mammography and ultrasonography are the 2 most frequently used modalities in clinical practice for breast imaging. Magnetic resonance imaging findings have been described in a limited number of patients with PASH. The mammographic findings consist of a well-circumscribed, round to oval density without calcification.20 The sonographic findings in tumorous PASH are quite variable. Mercado et al21 described the spectrum of sonographic findings in 13 cases of tumorous PASH. They described solid, well-circumscribed, homogenous, hypoechoic mass as the most common appearance of tumorous PASH on ultrasonography. Less commonly, the mass may be ill-circumscribed or hyperechoic. Rarely, it may have cystic component. Wieman et al3 studied the ultrasonographic findings in 22 patients with tumorous PASH and found hypoechogenicity in 83% of cases and ill-defined borders in 62% of cases. Magnetic resonance imaging reveals isointense mass on T1-weighted gradient echo images and may show linear reticular “lacelike” pattern on axial T2-weighted images, indicative of slitlike spaces within the lesion.7 The presence of these linear reticular lines may potentially be a helpful feature in diagnosing PASH. On imaging studies, the most common differential diagnosis is fibroadenoma. Tumorous PASH does not show any unique features on imaging studies, and histologic examination of the lesion is necessary to make a definitive diagnosis and to rule out malignancy.

**PATHOLOGY FINDINGS**

**Gross Features**

The size of tumorous PASH ranges from 0.6 cm to 12 cm.3,4,20 The largest size of tumorous PASH documented in the literature is 20 cm in a 36-year-old woman.23 Grossly, the excised mass is round to oval, well-circumscribed, and rubbery. The outer surface is usually smooth and unencapsulated. The cut surface reveals a homogenous solid lesion with gray-white color and occasional cysts.21 Necrosis and hemorrhage are rare except when induced by previous fine-needle aspiration or needle core biopsy.

**Microscopic Features**

Pseudoangiomatous stromal hyperplasia can occur as an isolated mass or may coexist with any breast lesion ranging from benign to malignant including proliferative and nonproliferative benign breast disease, fibroadenoma, phyllloides tumor, and carcinoma. Ibrahim et al24 demonstrated at least 1 microscopic focus of PASH in 23% (46 of 200) of consecutive breast biopsies and mastectomy specimens. Pseudoangiomatous stromal hyperplasia has been described in the breast stroma in association with gynecomastia in males. Milanezi et al25 described presence of PASH in 23.8% of breast biopsies from men with gynecomastia.

On histologic examination, PASH shows a wide spectrum of morphologic changes ranging from typical appearance to more proliferative lesions. The typical lesion is composed of complex anastomosing, slitlike empty spaces in a dense fibrous stroma (Figures 1 and 2). These spaces are lined by a discontinuous layer of flat, benign spindle cells (Figure 3). No mitosis or nuclear atypia is seen. The stromal hyperplasia may involve perilobular as well as intralobular stroma (Figure 1). Expansion of intralobular stroma may cause effacement of terminal duct–lobular units. Isolated involvement of perilobular stroma is more common than that of intralobular stroma.4 The epithelium of lobules and ducts may be unremarkable or may show ductal hyperplasia and/or apocrine metaplasia. Sometimes, the hyperplasia may also involve myoepithelial cells. The ducts may show gynecomastia-like changes including nuclear overlapping, nuclear hyperchromasia, and nucleoli with hyperplastic myoepithelial cells. The presence of gynecomastia-like changes has been shown to be strongly associated with the involvement of intralobular stroma.4

The proliferative lesions show variable cellularity, ranging from increased stromal cellularity to formation...
of cellular bundles in a dense collagenous background, and these lesions show a lobulocentric growth pattern. In proliferative lesions, the stromal cells may be larger and have conspicuous nuclei but cytologic atypia is rare. More florid areas may show formation of fascicles with obliteration of spaces. The cells in fascicular foci show oval nuclei with indistinct cytoplasmic borders. One recent study found the fascicular growth pattern in 31% of cases of tumorous PASH. The tumors with predominant fascicular architecture are more likely to cause diagnostic confusion. However, the presence of more typical areas of PASH adjacent to fascicular foci is helpful in making the accurate diagnosis. A rare histologic feature includes the presence of multinucleated giant cells. These cells can be seen lining the spaces as well as in the stroma. Pseudoangiomatous stromal hyperplasia with multinucleated giant cells has also been reported in breast biopsies from male patients with gynecomastia and a history of neurofibromatosis.

Sometimes, core needle biopsy is warranted in suspicious cases to exclude malignancy. Wieman et al attempted to characterize PASH preoperatively on the basis of results of imaging studies and needle core biopsies. They found that needle core biopsies had a sensitivity of 83% for diagnosing the lesion. However, careful correlation of histologic features with clinical and radiologic findings is required to ensure that the target lesion has been appropriately and adequately sampled.

Fine-needle aspiration and cytologic examination is not very helpful in making definitive diagnosis. Tumorous PASH does not have any unique features on cytology that can help in making the accurate diagnosis. Differential diagnoses on cytologic examination include fibroadenoma, phylloides tumor, or fibrocystic change due to the overlapping cytologic features. The major utility of cytologic examination lies in ruling out malignant lesion rather than in providing the definitive diagnosis.

Ancillary Studies

On immunohistochemistry, the spindle cells lining the slitlike spaces are positive for myofibroblastic markers including CD34 (Figure 4), vimentin, and SMA. They are negative for cytokeratin, S100, and endothelial markers such as von Willebrand factor antigen (Figure 5) and CD31. Smooth muscle actin expression is seen more conspicuously in lesions with plump spindle cells and fascicular foci. The fascicular areas may show expression of desmin. The stromal cells show nuclear positivity for PR. Estrogen receptor expression may be present but is focal and may show faint positivity. The epithelial nuclei are frequently positive for ER as well as PR.

The spindle cells show myofibroblastic features on ultrastructural studies. The spaces are lined by an incomplete layer of spindle cells with elongated cytoplasmic processes. The cytoplasm contains well-developed Golgi apparatus and abundant endoplasmic reticulum. The cells are joined together by rudimentary cell junctions or, very occasionally, tight junctions.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of PASH include low-grade angiosarcoma, myofibroblastoma, fibroadenoma, and mammary hamartoma. The most important differential diagnosis is angiosarcoma and it must be distinguished from PASH. Grossly, angiosarcoma is an infiltrative,
hemorrhagic, ill-circumscribed mass. On microscopic examination, PASH as well as angiosarcoma show anastomosing spaces lined by spindle cells. On low-power view, the spaces in angiosarcoma dissect interlobular stroma with invasion of surrounding fat, whereas PASH merges gradually with the surrounding stroma. On high-power view, the spaces in angiosarcoma are lined by atypical endothelial cells. The cells show mild to moderate pleomorphism, nuclear atypia, and increased mitotic activity. The cells vary in size and shape and contain hyperchromatic nuclei. Red blood cells may be present within the spaces. In contrast, the spindle cells in PASH are benign and lack cytologic atypia or mitosis. Immunostaining can further help in establishing the diagnosis. The spindle cells in angiosarcoma are positive for endothelial markers such as CD31, CD34, and von Willebrand factor antigen, whereas the spindle cells in PASH are positive for myofibroblastic markers CD34 and SMA and are negative for endothelial markers.

Myofibroblastoma is a rare, benign breast mass predominantly seen in adult males. Upon histologic examination, it is characterized by predominant fascicular architecture. It is composed of bland spindle cells haphazardly arranged in fascicles with interspersed, thick, hyalinized collagen bundles. Tumorous PASH with predominant cellular areas or fascicular foci is more likely to be confused with myofibroblastoma. It is believed that PASH and myofibroblastoma share common histogenesis and represent a spectrum of myofibroblastic proliferation. On immunohistochemistry, the spindle cells in PASH, as well as in myofibroblastoma, express myofibroblastic markers including vimentin, CD34, and SMA. The focal distribution of fascicular areas and presence of more typical areas of PASH adjacent to fascicular foci favor the diagnosis of tumorous PASH. The other feature that differentiates PASH from myofibroblastoma is the expression of progesterone receptors, in contrast to the expression of androgen receptors in myofibroblastoma.

Fibroadenoma is the most common differential diagnosis on clinical and imaging studies. However, it can be easily distinguished on histology. Fibroadenoma is a benign, fibroepithelial tumor. It is composed of glandular elements in characteristic intralobular stroma. Fibroadenoma may show intracanalicular or pericanalicular pattern, depending upon the amount of stroma. In intracanalicular pattern, abundant stroma compresses the ducts with slitlike lumen. The ducts are open in pericanalicular pattern. The ducts are lined by an inner layer of cuboidal to low columnar epithelial cells and an outer layer of myoepithelial cells. The stroma may show myxoid change in fibroadenoma.

Mammary hamartoma is an uncommon, benign neoplasm of breast. The distinctive histologic feature of mammary hamartoma is the presence of mature adipose tissue and nodular aggregates of mammary parenchyma. Tumorous PASH is differentiated from mammary hamartoma by the absence of adipose tissue within the mass.

**CURRENT TREATMENT AND PROGNOSIS**

The treatment of PASH depends upon clinical presentation. No additional specific treatment is required if PASH is an incidental histologic finding in specimens excised for other lesions. The excision, with adequate but close margin, is the recommended treatment for tumorous PASH. Sometimes, diffuse PASH may require wide excision of breast tissue or mastectomy for cosmetic reasons or for persistent pain and discomfort. The recurrence rate after excision ranges from 0% to 22%.

The recurrence is more likely if the lesion is not completely excised. The recurrent PASH occurs in ipsilateral breast but it is also known to occur in contralateral breast. The recurrent lesions behave in a benign fashion and can be managed with reexcision. As reported recently, nonoperative management with close clinical follow-up may be an alternative approach for selected patients with tumorous PASH who have benign findings on pathology and imaging studies. However, the long-term outcome of patients managed conservatively has not been studied.

There is no well-established medical treatment for tumorous PASH. Recently, Pruthi et al documented successful treatment with tamoxifen of bilateral tumorous PASH in a 39-year-old woman. The patient presented with progressive enlargement of bilateral breasts with cyclic pain. The mass disappeared completely after 6 months of treatment. However, this is only 1 case report and further studies will be needed to establish it as a definitive medical treatment.
Tumorous PASH is slow growing and is known to recur after excision. Overall, the prognosis for PASH is excellent. Pseudoangiomatous stromal hyperplasia is not considered a premalignant lesion or a risk factor for malignancy. Only 1 single instance has been reported in which invasive ductal carcinoma was present within tumorous PASH, and the authors considered that to be an incidental finding rather than true malignant transformation.

In summary, PASH is a benign, localized, mesenchymal proliferative lesion with possible hormonal etiology. It is characterized by the presence of slitlike spaces in dense collagenous stroma. The spaces are lined by benign spindle cells, which show myofibroblastic differentiation and express progesterone receptors. It has an excellent prognosis, with very low risk of recurrence. Local surgical excision with adequate margins is the recommended treatment for tumorous PASH.

References