Tamoxifen in the Management of Pseudoangiomatous Stromal Hyperplasia

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Abstract: Pseudoangiomatous stromal hyperplasia (PASH) is a relatively uncommon histologic finding in breast specimens. The clinicopathologic spectrum of this disease entity can range from a focal nonsignificant microscopic finding to a dominant palpable breast mass. To confirm the diagnosis, a biopsy is required primarily to distinguish PASH from a low-grade angiosarcoma. The mammographic description of PASH is a round or ovoid, circumscribed or partially circumscribed mass. The sonographic feature is a hypoechoic mass. PASH is similar to a fibroadenoma in clinical and imaging features. Progressive breast enlargement associated with engorgement, cyclical breast pain, and burning sensation is of significant concern for some women. The management of the palpable mass and associated symptoms has included excisional biopsy, often leading to recurrent excisions and even mastectomy. This report documents an impressive response to tamoxifen in a patient with PASH presenting with breast enlargement, pain, and breast masses. To our knowledge, there are no reports on the use of tamoxifen or other selective estrogen receptor modulators in the management of this benign breast condition.

Key Words: benign breast diseases, low-grade angiosarcoma, stromal hyperplasia, tamoxifen

Since the recognition of pseudoangiomatous stromal hyperplasia (PASH) as a discrete entity (1), knowledge of its clinicopathologic features has increased. PASH is a benign disease of the breast that is characterized by proliferation of mammary stroma, forming a complex pattern of slitlike pseudovascular spaces. Its manifestations range from clinically insignificant focal microscopic changes to the development of one or more symptomatic breast masses. Despite refinements in diagnostic criteria, effective management of PASH in symptomatic patients has been limited to surgical excision of discrete lesions. Symptomatic recurrence is uncommon (2). Currently, there is no effective systemic treatment for patients with PASH. We describe the response to tamoxifen in a patient with symptomatic PASH.

CASE REPORT

A 39-year-old White woman presented in February 1996 with a 13-month history of cyclical breast pain and progressive bilateral breast enlargement. Her
brassiere cup size had increased from D to G. Approximately 2 years before her evaluation, a biopsy of a left breast mass showed a fibroadenoma. One year later, she was treated with antibiotics for left breast tenderness, erythema, and thickening in the periareolar region, but there was no improvement.

Additional evaluation included a mammogram that revealed an area of increased density in the left subareolar region. A 4 cm mass believed to represent ectopic breast tissue was visualized in the right axilla. Over 4 months, biopsies of the left breast mass were reported to show nonspecific dermatitis with periductal fibrosis. The patient was treated with hydroxychloroquine for possible discoid lupus, but there was no improvement.

The patient was gravida 3, para 3 and had breast fed her children with no adverse outcomes. Her past medical history was unremarkable; specifically, there were no previous diagnoses of breast conditions, such as cyclical mastalgia. She did not use oral contraceptives or hormonal medications. She had a tubal ligation in 1990. There was no family history of breast, ovarian, colon, or prostate cancer.

When she presented for evaluation at our institution, the patient had considerable bilateral asymmetric breast engorgement, with the left breast larger than the right. In addition to healed surgical scars, she had a 3 × 3 cm, well-circumscribed, fixed, palpable mass with an accessory nipple in the right axilla. In the left axilla, there was an accessory nipple without a mass; just inferior to the left areolar region, there was a 4 × 4 cm, well-circumscribed, fixed, hard mass. The lymph nodes were not palpably enlarged. Previous mammograms showed dense fibroglandular changes increasing over 2 years. A dominant density was seen in the axillary tail of the right breast. Ultrasonography revealed ectopic breast tissue with dilated ducts and small cysts in the upper outer quadrant of the right breast (Fig. 1) and a dominant 2 × 5 cm hypoechoic solid mass in the left lower breast (Fig. 2). The left breast mass was sampled with four 14-gauge, large-core biopsy needles guided by ultrasound. Evaluation revealed changes consistent with PASH.

To exclude a coexisting malignancy associated with the growth of the breast masses, an excisional biopsy was performed. Evaluation revealed proliferative fibrocystic changes with marked PASH and a right extra-nerumery nipple. Immunoperoxidase staining showed the stromal cells to be negative for estrogen and progesterone receptors.

Because breast engorgement and pain persisted, reduction mammoplasty and hormonal therapy were discussed. The patient agreed to a trial of tamoxifen. For the first year, she took tamoxifen, 20 mg daily, for 3 months on and 3 months off. She noted improvement within 2 weeks of initiating therapy. There was a 50% improvement in her prior symptoms of burning, erythema, and pain. Brassiere cup size decreased to DD within 2 months of initiating therapy, and the patient reported that her breasts were “almost normal again.” After 1 year of using tamoxifen, she discontinued therapy and noted recurrence of bilateral breast pain and engorgement, as well as palpable masses in the left inferior and right inferior breast.

Repeat ultrasound-guided core biopsies of both breasts confirmed the persistence of PASH. Tamoxifen, 20 mg daily, was resumed, and her symptoms improved within 2 weeks. After 2 months, the development of side-effects necessitated a reduction in dose to 10 mg daily for 6 more months. The side-effects included hot flashes and menstrual irregularity. After dilation and curettage, which revealed unremarkable endometrial tissue, she became amenorrheic.Raloxifene, 60 mg, 1 tablet daily, was initiated.

In July 1996, follow-up mammography (Fig. 3) and ultrasonography continued to show dense parenchyma bilaterally. A mass seen in the lateral right breast in February 1996 was no longer present. Nodularity was seen sonographically in the left lower breast.
DISCUSSION

Incidence and Pathology

The prevalence of PASH is difficult to estimate. In a report of 1,661 breast biopsies, seven patients (0.4%) were found to have PASH (3). In a report of 200 consecutive breast biopsies, PASH was noted in at least one microscopic focus in 23% of cases and was multifocal in at least 60% of cases, with only one case having PASH as the major finding (4).

In the first description of this condition, Vuitch et al. described PASH as a benign tumor composed of mixed stromal and epithelial elements (1). However, the epithelial component within these lesions shows only mild hyperplasia; the characteristic feature is the prominent stromal component. The stromal component is made up of diffuse and complex interconnected slitlike spaces resembling vascular structures (Fig. 4). These spaces are lined by stromal myofibroblasts, which lack atypia and mitotic activity and are devoid of red blood cells (1,2). PASH is found in areas of stromal fibrosis and often surrounds breast lobules in a concentric fashion. It is important to understand the clinicopathologic distinction between PASH and low-grade angiosarcoma. The clinical presentation of a discrete mass and the low-power microscopic appearance of anastomosing channels lined by endothelial-like spindle cells suggests a malignant vascular lesion. However, mammary angiosarcoma is characterized by

![Figure 2](image2.png)

Figure 2. Sonogram of palpable mass at the 6 o’clock position in the left breast. Note the large hypoechoic mass (arrows).

![Figure 3](image3.png)

Figure 3. Follow-up mammograms after 4 months of treatment at our institution. (A) Craniocaudal views of both breasts show diffusely dense parenchyma without specific mammographic masses. (B) Mediolateral oblique views of both breasts show the same changes. Arrowheads indicate a mass density in right upper breast seen earlier on mammograms from another institution. This corresponds to area seen sonographically in Figure 1.
open anastomosing vascular channels that infiltrate all components of breast tissue.

PASH has been found occasionally with invasive adenocarcinomas. However, it is generally believed that in the appropriate clinical circumstance, a finding of PASH after a breast biopsy need not prompt an exhaustive investigation for associated malignancy. PASH is not considered premalignant, and in situ or invasive carcinoma has not been reported within a PASH nodule. Other coexisting changes that have been associated with PASH include proliferative fibrocystic changes in 51% of patients with PASH, nonproliferative fibrocystic changes in 15.7%, invasive adenocarcinoma in 9.8%, and fibroadenomas in 13.7% (4). PASH also has been seen in otherwise normal breast tissue and in association with hamartomas, gynecomastia, and lobular hyperplasia (4).

Etiology

Because gynecomastia is believed to occur in response to hormonal factors, it is possible that the stromal changes in PASH are due to hormonal stimulation of the female breast. These changes may represent a stage in the maturation of newly formed mammary stroma.

In aggregate, there is evidence to support the hormonal dependence of PASH. Similar histologic results are seen in normal mammary stroma during the luteal phase of the menstrual cycle, suggesting that PASH may originate as a response to progesterone in estrogen-primed tissue (1). Furthermore, 41 of 46 patients that Ibrahim et al. reported were premenopausal women (4).

It has been suggested that PASH represents a progesterone-primed autonomous proliferation of myofibroblasts that escape the normal physiologic control mechanisms of the menstrual cycle. This leads to cessation of cycling within the remaining breast and, in turn, the capacity for independent myofibroblastic proliferation (2). In the limited number of cases studied, the stromal cells in PASH were found to be strongly positive for progesterone receptor by immunocytochemical staining (5).

Clinical Presentation

Age at presentation ranges from 14 to 67 years, with most women being premenopausal. Patients typically present with one or more discrete, firm, or rubbery, well-circumscribed palpable masses that can be bilateral and as large as 7 cm in diameter (4). PASH is clinically indistinguishable from a fibroadenoma. In most women, investigation of asymptomatic mammographic abnormalities leads to a diagnosis of PASH. Males with gynecomastia have been found to have PASH (6). In the report by Powell et al. (2), only one male patient presented with breast tenderness and enlarging breast masses. Thus, PASH occurs on a clinicopathologic spectrum from clinically insignificant focal microscopic changes to the development of a breast mass secondary to PASH.

Results of Imaging Studies

On mammography, findings include a round or ovoid circumscribed or partially circumscribed mass. On sonography, findings include a hypoechoic, solid mass (3). The mass is most often circumscribed, and cystic changes can be seen within it. PASH is similar to fibroadenoma in clinical and imaging features. It appears that PASH has no specific features that
contribute to a prospective diagnosis by imaging. A core biopsy is sufficient to confirm the presence of PASH.

Treatment

The management of PASH requires careful, studied consultation by the clinician, the pathologist, and the radiologist who perform the imaging and biopsy. It is prudent to perform a core biopsy to exclude coexisting malignancy. Pathologic evaluation is crucial in differentiating PASH from a low-grade angiosarcoma. Thereafter, reassurance that the condition is benign is the mainstay of management. Progression of the lesion often prompts simple excision, which is believed to be adequate treatment initially and for infrequent recurrences. Diffuse involvement of the breast with PASH rarely may necessitate mastectomy. How to manage frequently recurring, biopsy-proven lesions is unclear.

Recurrence rates range from 15% to 22% (1,2). In the original report by Vuitch et al. (1), seven of nine women with PASH were free from recurrence at 30-month follow-up. Two patients had local recurrence within 14 months of the initial operation, requiring subsequent excisions. One patient had bilateral subcutaneous mastectomies after the lesion was initially diagnosed as an “atypical vasoformative process.”

In the report by Powell et al. (2), after a mean follow-up of 4.5 years, 6 of 40 patients with PASH had a recurrence 1 month to 1 year after diagnosis. One patient developed contralateral PASH and was temporarily given “hormonal therapy,” which was not specified. Extensive contralateral PASH developed in another patient, who required bilateral mastectomy for multiple nodules. One patient in this series was a premenarchal girl. Nine patients were known to have used oral contraceptives, but only one was documented to be taking oral contraceptives at diagnosis. Four patients had never used oral contraceptives. Two of four postmenopausal women were receiving supplemental hormones. In 21 patients, the information on hormonal use was unknown.

To our knowledge, there are no reports on the use of tamoxifen or other selective estrogen receptor modulators in the management of PASH. Although often referred to as an antiestrogen, tamoxifen is in fact an attenuated estrogen. Tamoxifen blocks estrogen from binding to the estrogen receptor, indicating that patients with estrogen receptor-positive disease may be more likely to respond than those with estrogen receptor-negative disease. Tamoxifen also has been used in the management of breast pain. In a randomized, double-blind trial, approximately 70% of patients receiving tamoxifen and 38% of patients receiving placebo reported a reduction of breast pain (7). Toxicities of tamoxifen include venous thromboembolism, endometrial cancer, and cataracts. Other side-effects include hot flashes, bleeding, fluid retention, irregular menses, irritability, and headache. Tamoxifen has beneficial effects on bone and lipids. It is a well-tolerated agent, and less than 5% of women with early breast cancer discontinue therapy because of side-effects (8).

CONCLUSION

PASH is an uncommon histologic finding in breast biopsy specimens, and its clinicopathologic spectrum ranges from clinically insignificant focal microscopic changes to palpable breast masses. It is prudent to perform a core needle biopsy to confirm the diagnosis, with the distinction between PASH and low-grade angiosarcoma being of primary importance. For some women, the mass is often symptomatic, and breast enlargement is a major concern. The management of the palpable mass and associated symptoms has included excisional biopsy, often recurrent excisions, and even mastectomy. The case we report illustrates a response to tamoxifen in a patient presenting with breast enlargement, pain, and breast masses.

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