Case Report

ISSN 2771-9057

Recent Advances in Clinical Trials

First Case Report of Synchronous Presentation of Tumoriform Psudoangumatous Stromal Hyperplasia (PASH) and Malignant Phyllodes Tumor in One Breast Lesion

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Received: 01 Nov 2023; **Accepted:** 08 Dec 2023; **Published:** 16 Dec 2023

Citation: Zainab AlDawood, Amal Al-Habib, Miral Mashhour, et al. First Case Report of Synchronous Presentation of Tumoriform Psudoangumatous Stromal Hyperplasia (PASH) and Malignant Phyllodes Tumor in One Breast Lesion. Recent Adv Clin Trials. 2023; 3(4); 1-6.

ABSTRACT

Pseudoangiomatous stromal hyperplasia (PASH) of the breast is a benign proliferative mesenchymal lesion with possible hormonal etiology. PASH is mostly identified as an incidental finding in the final histopathology of excised breast specimens. However, another less common presentation of PASH is the tumoriform palpable lesion. Herein, we report an unusual case of tumorous PASH of the breast with a deceiving clinical presentation mimicking invasive mammary carcinoma, and a surprising final histopathological diagnosis. Our report indicates that widening the differential diagnosis of a breast mass, to include rare and uncommon diseases, as well as careful decision making are essential measures to avoid overlooking a serious diagnosis or over treating a simple disease.

Keywords

Pseudo-angiomatous stromal hyperplasia, PASH, Breast mass, Phyllodes tumors, Type II Diabetes mellitus.

Introduction

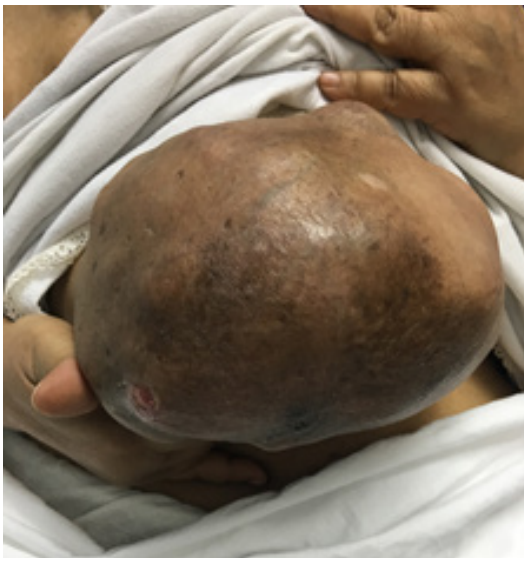
Pseudo-angiomatous stromal hyperplasia (PASH) is a benign mesenchymal proliferative lesion of the breast, which was first described in 1986 by Vuitch et al. They described it as a benign lesion comprising stromal myofibroblastic proliferation and having the appearance of anastomosing slit-like pseudovascular spaces lined by spindle-shaped cells [1]. PASH is most commonly found in premenopausal females with an average age of 37 years. However, it has been observed in postmenopausal women, pediatric patients and males as well. Although the exact etiology is unknown, PASH is thought to be derived by hormonal imbalances, with aberrant response of myofibroblasts to endogenous or exogenous hormones being an important etiopathogenic factor. Thus, the use of oral contraceptives has been observed in most women with PASH. Well-developed nodular PASH in postmenopausal women has been linked with the use of hormone replacement therapy [2]. PASH is a common incidental finding in breast tissue, mostly appearing as scattered foci within various benign and malignant breast lesions. However, a palpable mass or a radiologically detected lesion consisting predominantly or entirely of stromal cells (tumoriform PASH) has been rarely described. Occasionally, PASH exhibits an accelerated growth and can occur as bilateral lesions [3]. Radiographically, tumoriform PASH presents as a mass without calcification. Ultrasonography usually reveals a well-defined hypoechoic mass while magnetic resonance imaging may show non-mass-like contrast enhancement. On microscopy, PASH is a myofibroblastic proliferation intermixed with epithelial elements. The lobular and duct structures are separated by an increased amount of hyalinized stroma. The stromal cells form a complex pattern of empty, often inter-anastomosing spaces in the

densely collagenous stroma. Myofibroblasts with attenuated nuclei rimming the empty spaces resemble endothelial cells. Rarely, the myofibroblasts may accumulate in distinct bundles and fascicles in a background of conventional PASH, forming fascicular PASH. The most pronounced examples of this cellular form of PASH are reminiscent of mammary myofibroblastoma. PASH itself usually lacks mitotic figures and atypia. There is no destruction of the normal breast tissue, and no fat necrosis or invasion [2].

Phyllodes tumors (PT) are the most commonly occurring non-epithelial neoplasms of the breast, although it represents only 1% of breast neoplasia [4]. Their etiology is unknown. In 1981 the World Health Organization adopted the term Phyllodes tumor and as described by Rosen, it sub-classified them histologically as benign, borderline, or malignant according to the microscopic features such as tumor margins, stromal overgrowth, tumor necrosis, cellular atypia, and number of mitosis per high power field [5]. Because of limited data, the relative percentages of benign and malignant PT are not well defined. Reports have suggested, however, that about 85-90% of PT are benign or borderline, and that approximately 10-15% are malignant [6]. Clinically, PT presents as a firm, smooth, sharply demarcated mass and typically is freely movable. It is a relatively large tumor, with an average size of 5 cm (though lesions larger than 30 cm have been reported) [7,8]. Very large tumors may erode the skin and cause skin ulceration. If inadequately treated, malignant PT have a propensity for rapid growth and hematogenous metastatic spread. The commonest sites for distant metastases are the lungs (66%), bones (28%), and brain (9%) and in rare instances, the liver and heart. The risk of metastatic disease does not appear to be influenced by the extent of the initial surgery and seems to be predetermined by tumor biology. Metastatic PT have a poor prognosis and long-term survival [9]. According to the latest National Comprehensive Cancer Network (NCCN) guidelines, the treatment of PT including all its subtypes (benign, borderline, and malignant) is surgical, as no strong clinical evidence exists to support other treatment modalities like radiation or systemic therapy [10]. Therefore, accurate preoperative pathological diagnosis allows correct surgical planning and avoidance of reoperation for either achieving wider excision of close margin or for subsequent tumor recurrence. With such differences in management and prognosis between the two breast diseases, the simultaneous co-existence of PASH and malignant PT in the same lesion is a challenging presentation, especially if the more serious disease is covered by the dominant benign disease. To our knowledge, this is the first reported case of synchronous presentation of tumoriform PASH with malignant PT in the same breast lesion.

Case Report

A 57 year-old lady, known to have diabetes mellitus type II, hypertension and bronchial asthma, presented with right breast painful mass. The mass was increasing in size over a year and was associated with breast swelling, redness, itching and bloody nipple discharge. The patient was postmenopausal, P12+0, who breastfed all her offspring. She gave a history of long use (>5years) of oral contraceptive pills. Family history was negative for breast, ovarian or uterine cancer. Right breast examination revealed a gigantic mass occupying the whole breast, measuring 34 X 32 cm with skin ulceration and distortion of nipple (Picture 1). Left breast examination was unremarkable. There were no axillary or supraclavicular lymph nodes enlargement.



Picture 1: Picture of right breast giant mass with skin ulceration and nipple distortion.

Mammography showed right breast tissue replaced by a huge mass, with peripheral course calcifications (BIRADS 0), and a normal appearing left breast, classified BIRADS II (Figure 1).

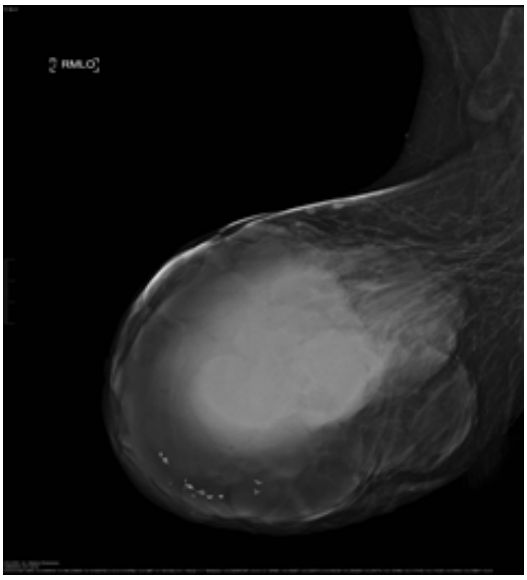


Figure 1: Mammogram MMG of right breast showing right breast hyperdense lobulated central mass, with peripheral course calcifications BIRADS 0.

Ultrasonography showed right breast occupied by a large hypo-echoic mass with cystic degeneration, measuring 14 x 12 cm, suspicious for malignancy, BIRADS 4B. Axillary lymph nodes were normally looking, bilaterally (Figure 2).

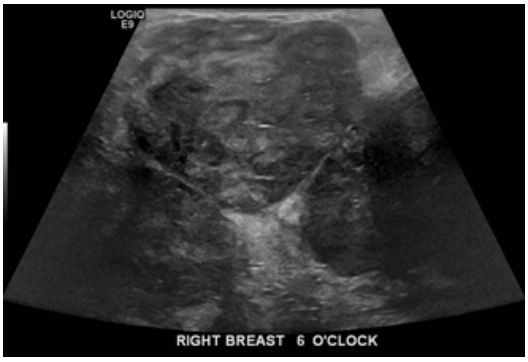


Figure 2: Ultrasound (US) showed right breast occupied by a hypo-echoic mass with cystic degeneration BIRADS 4B.

Microscopic examination of an US guided core needle biopsy of that lesion revealed breast tissue with exuberant interlobular and intralobular proliferation of partially hyalinized collagenous stromal tissue. Numerous Psudoangiomatous slit-like clefts and anastomosing empty spaces are present in the stroma focally, and partially lined by a single layer of flattened, bland spindle cells. On immunohistochemical staining, the stromal spindle cells were positive for vimentin and negative for estrogen receptors, CD31, CD34, or P63. There was no evidence of in situ or invasive malignancy, supporting the diagnosis of PASH (Figure 3). However, due to the suspicious clinical presentation, US guided core needle biopsy was repeated twice from two different locations of the same lesion. Our differential diagnosis included malignant PT and invasive mammary carcinoma (IMC). The results of both additional biopsies revealed PASH features with absence of any malignant cells.

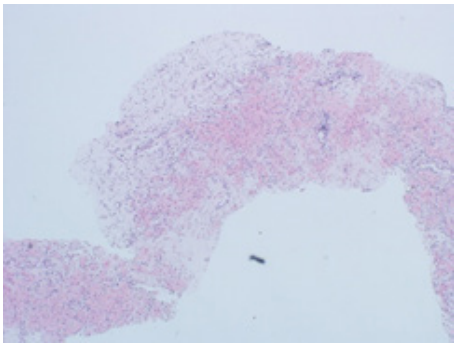


Figure 3: (a) 4X H/E of Peusoangiomatous stromal hyperplasia.

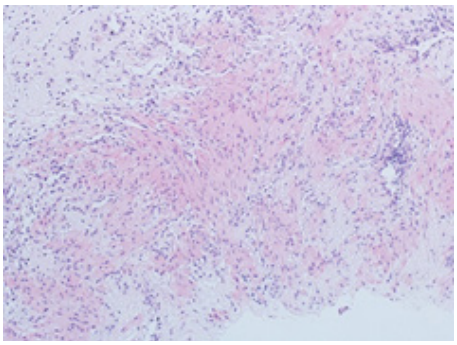


Figure 3 (b): 10X H/E showing plumped spindle cells in dense keloid like stroma and around empty spaces.

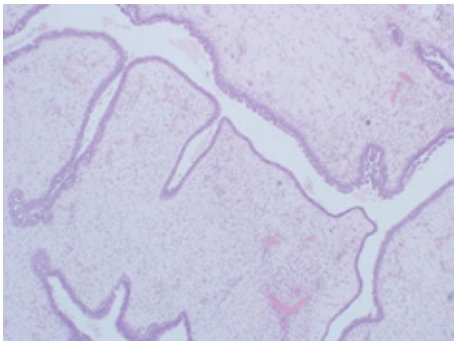


Figure 3 (c): 10x H/E spindle spindle cells with severe atypia, increase in mitotic cells and infiltrative borders.

The discordant biopsy result to the clinical presentation raised the suspicion of additional undiagnosed pathology. Therefore, a computed tomography (CT) scan of the chest, abdomen and pelvis was performed before any surgical intervention to rule out any metastatic disease. The CT scan showed a large fungating right breast mass with skin ulceration and suspicious right axillary and right internal mammary lymph nodes. In addition, two nodules were identified in the left lung, with intermediate suspicion of metastasis (Figure 4). There were no evidence of bony or other visceral metastasis.

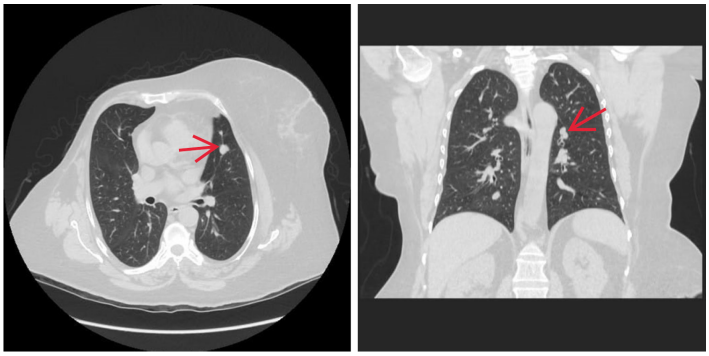


Figure 4: Image of CT scan showing suspicious pulmonary nodules.

The case was discussed in the multidisciplinary breast tumor board (MDBT). A malignant disease appeared more likely based on the clinical picture and the radiological appearance. The CT scan report of metastatic disease raised the possibility of invasive mammary carcinoma. However, in the absence of definitive histopathology, no systemic chemotherapy was recommended, as it would be indicated in a locally advanced or metastatic mammary carcinoma. Upfront surgery was the best and safest approach in order to provide a definitive diagnosis. Because of the size of the tumor and the skin ulceration, mastectomy was planned. Whether to perform sentinel lymph node biopsy (SLNB), axillary dissection, or no axillary surgery at all, was a difficult decision to make. The suspicious lymph nodes on CT were not accessible to core biopsy. Therefore, SLNB was determined appropriate with mastectomy, due to the possibility of IMC, and its lower risk of upper limp lymphedema compared to axillary dissection.

The patient underwent right breast mastectomy with SLNB. Intra-operatively, the lesion was not attached to the pectoralis muscle, sentinel lymph nodes frozen section was negative for malignant cells, and no axillary dissection was performed. Skin was closed primarily with no skin graft required. The final histopathology reported malignant Phyllodes measuring 17.5X12.5X8.5 cm, extensive PASH at the background of mass tissue with extensive adenosis and seborrhoeic keratosis (Figure 5). Nipple was negative for malignancy and skin ulceration was not involved by malignancy. All surgical margins were >1cm away from malignant Phyllodes.

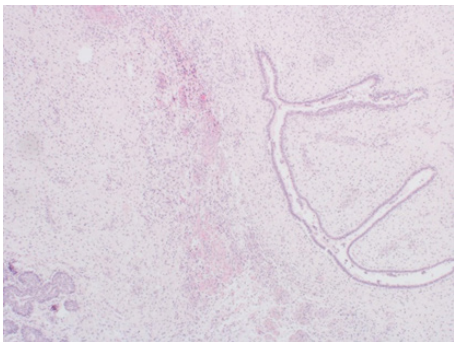


Figure 5: Surgical pathology specimen image: 4X H/E of malignant phyllodes with leaf-like areas.

The final diagnosis was re-discussed in the MDBT. Short-term follow up CT chest showed resolution of the pulmonary nodules, eliminating the possibility of distal metastasis. Based on NCCN recommendations [10], no adjuvant treatment was recommended after surgery. The patient was followed for 5 years post operatively, with no evidence of local or distal recurrence.

Discussion

Synchronous existence of tumorous PASH with malignant PT is not reported. To our knowledge, this is the reported first case in literature. The typical presentation of PASH when associated with other tumors was reported to be an incidental finding of breast biopsies performed for benign or malignant neoplasia in females and also males due to absence of specific imaging patterns [11,12]. Recently, one association of PASH and benign phyllodes was reported in a 41-year-old multiparous woman, however unlike our case each lesion occurred separately in the contralateral breasts [13]. In another case, PASH and benign PT were co-diagnosed from the same breast mass samples in a 42-year-old woman. Histological analysis was crucial for the diagnosis as the mass was first attributed to a giant fibroadenoma based on clinical and imaging patterns [14]. Oppenheimer et al. performed mastectomy for PASH causing macromastia in a 29-year-old woman, which had led to subsequent identification of histopathological patterns of coexisted benign PT [15].

According to a large study, PASH was present in 73.1% (245/335) of women diagnosed with PT [16]. Concurrent presence of PASH with other malignancies such as invasive ductal carcinoma, ductal carcinoma in situ, invasive micropapillary carcinoma, lobular carcinoma in situ has been described [17]. Nevertheless, in these cases the diagnosis of associated breast cancer was evident and established prior to the diagnosis of PASH as the former was an incidental finding of malignant mass sample histological analysis. Oppositely, in our patient the diagnosis of PASH was first made and confirmed by three biopsies obtained from different locations in the mass, while the diagnosis of malignant PT was the secondary finding after surgical excision.

PASH rarely presents as a large tumor by itself. Raza et al. described a case of huge firm mass with skin thickening and palpable left axillary lymph nodes in a lactating female, primarily diagnosed as breast malignancy, but turned out to be PASH of the breast after excision [18]. Masannat et al. reported a case of large PASH in a young lady, clinically mimicking an inflammatory carcinoma [19]. Similarly, in our case, PASH presentation was mimicking metastatic invasive mammary carcinoma.

The size of the PASH tumor in our case was less surprising after the diagnosis of a co-existing malignant PT in the same lesion. Malignant PT tumors are frequently reported to be huge and rapidly growing lumps that can present as more than 30 cm breast mass [20]. Prakash et al. identified a case of malignant PT measuring $45 \times 35 \times 20$ cm and weighing 12 kg [21]. However, the median size of malignant PT is reported around 8.7 cm with very huge size lesions being the rarity [20,21].

Despite the lack of sufficient knowledge, PASH and malignant PT may share the same pathogenic mechanism as both diseases appear to be attributed to hormonal stimuli [9,17] but a major difference is that PASH does not transform into malignancy [13]. The etiopathogenic role of female hormones was supported by the positive staining for estrogen and progesterone receptors (ER and PR) in PASH samples and the development of PASH in males with hormonal imbalance including the use of female hormones by transgender or males with gynecomastia [22], as well as the expression of ER by PT cells [23]. Nonetheless, similar to our immune-histochemial staining results, other authors found that PASH myofibroblastic cells have poor expression for ER. These cells are stained positive for virmentin and other markers of stromal origin such as CD34, smooth muscle actin, and BCL-2 [17].

Upon reviewing the risk factors in the literature, we concluded that the use of OCP by our patient may have increased her risk of developing malignant PT, but it remains unclear if that would be the case for PASH, considering that the IHC staining was negative for ER in the PASH. The old age, postmenopausal status, and the presence of diabetes mellitus may be other risk factors for malignant PT in our patient. In one of the largest cohorts of PT including 307 cases, Patients with malignant PT were found to be older, more diabetics, less breastfeeding, more smokers, more postmenopausal, and older age at menopause (51.5 years) compared with the remaining subtypes of benign and borderline PT ($P<0.05$) [20].

The decision to perform mastectomy with SLNB in our case was derived from combining the treatment recommendation of all three possible differential diagnoses, with the least possible complication. The appropriate treatment for PASH varies. When the lesion is small and asymptomatic, surgical excision is not indicated [24]. If there are suspicious features of malignancy on clinical or radiological evaluation, wide local excision is recommended for treatment [19]. For giant tumorous PASH, surgical excision should be performed as the treatment of choice. Some cases with diffuse involvement or multiple recurrences may necessitate mastectomy [25]. The standard treatment of invasive mammary carcinoma requires surgical excision with negative margin (no tumor on ink) and staging of the axillary lymph nodes (ALN), with or without adjuvant radiation and systemic therapy, depending on the phenotype and the final disease stage. The mainstay treatment for malignant PT is surgical. Lumpectomy or partial mastectomy is the preferred surgical therapy. Total mastectomy is necessary only if negative margins (1 cm or more) cannot be obtained by breast conserving surgery. Since PT rarely metastasize to the ALN, surgical axillary staging or ALN dissection is not necessary unless the lymph nodes are pathologic on clinical examination [7].

There is no prospective randomized data supporting the use of radiation treatment with PT. However, in the setting where additional recurrence would create significant morbidity, e.g., chest wall recurrence following salvage mastectomy, radiation therapy may be considered, following the same principles that are applied to the treatment of soft tissue sarcoma [7]. While the epithelial component of most PT contains ER (58%) and/or PR (75%), endocrine therapy has no proven role in the treatment of PT. Similarly, there are no evidence that adjuvant cytotoxic chemotherapy provides benefit in reduction of recurrences or death [7]. Therefore, no adjuvant radiation or systemic therapy was offered to our patient after complete surgical excision. In a large study of patients with PT, The presence of PASH had a prognostic significance; the risk of PT recurrence dropped by 51.3% in patients with coexisted PASH when compared with those without PASH [11]. This observation is in alliance with our reported patient, who did not develop recurrence of malignant PT after 5 years of follow up.

Conclusion

PASH is a benign entity of the breast that should be treated with caution. On one hand, an underlying hidden and more serious disease that will require different management like malignant PT or IMC might be missed. On the other hand, Tumorous form of PASH might be mistaken for a more aggressive disease leading to inaccurate diagnosis and over treatment, due to their camouflaging clinical presentation and the low histopathological yield of biopsy. Although this situation remains very rare, breast surgeons should be cautious when dealing with PASH lesions, especially in post-menopausal women. Following the least invasive and safest approach is essential to avoid overlooking a serious diagnosis or over treating a simple disease.

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