

Multifocal Tumorous Pseudoangiomatous Stromal Hyperplasia Presenting as Asymmetric Bilateral Breast Enlargement

Multifokale tumoröse pseudoangiomatöse Stromahyperplasie mit bilateraler asymmetrischer Makromastie

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Key words

- benign mammary gland tumor
- hormonal receptor
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Schlüsselwörter

- Mamma
- benigne Mammatumoren
- Hormonrezeptor

Abstract

PASH is a benign proliferation of stromal myofibroblasts that affects mostly premenopausal women and typically shows estrogen and progesterone receptor expression, allowing speculation regarding a hormonal cause. It usually presents as an incidental finding on a mammogram or as a palpable mass. We present a case of diffuse asymmetrical massive breast enlargement in a premenopausal woman with history of previous multiple PASH excisions for recurrent lesions, caused by multifocal tumorous PASH virtually replacing the breast parenchyma. Immunohistochemistry examination showed no hormone receptor expression. Despite its benign nature, such presentation of PASH is managed with bilateral mastectomy and immediate reconstruction with expanders for cosmetic and comfort reasons, while tumor excision or expectant management is deemed to lead to recurrence and progression. Although a hormonal origin is speculated based on hormone expression studies and typical patient profile, this case showed 0% estrogen/progesterone expression in the final histology specimen.

Zusammenfassung

PASH ist eine gutartige Proliferation der stromalen Myofibroblasten. Betroffen sind überwiegend prämenopausale Frauen. Die typischerweise vorliegende Estrogen-/Progesteron-Rezeptorexpression legt die Vermutung einer hormonellen Ursache nahe. Häufig zeigt sich die PASH zufällig in der Mammografie oder als tastbarer Herd in der Mamma. Wir stellen den Fall einer massiven asymmetrischen Makromastie bei einer prämenopausalen Frau vor, die anamnestisch mehrere vorangegangene Tumorektomien wegen rezidivierenden PASH-Herden hatte. Nahezu das gesamte Brustdrüsenparenchym wurde durch die multifokalen tumorösen PASH-Herde ersetzt. Ungeachtet der Gutartigkeit der Herde wurde bei der Patientin eine bilaterale Mastektomie mit Sofortrekonstruktion mit Implantaten aus kosmetischen Gründen durchgeführt, da ein abwartendes Verhalten zu einer weiteren Progression geführt hätte. Trotz der Vermutung einer hormonellen Ursache der PASH zeigte unser Fall keine Hormonrezeptorexpression.

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Clinical Case Description

A 45-year-old pre-menopausal woman presented in 2008 with a palpable mass in the right breast. She had no family history of breast diseases and had not been taking any medications. A mammogram, an ultrasound and a breast MRI were undertaken (• Fig. 1 a to c). The mammogram revealed a dense breast parenchyma without suspicious abnormalities, while the ultrasound revealed a hypoechoic mass correlating with the palpable abnormality in the right breast. The MRI revealed a “cauliflower-like cluster” and the diagnosis of pseudoangiomatous stromal hyper-

plasia (PASH) was made through an ultrasound-guided core needle biopsy. The lesion was excised upon request of the patient, and the diagnosis confirmed. Immunohistochemistry staining revealed neither estrogen nor progesterone expression (0%). In 2009 the patient noted palpable masses on both breasts, revealing bilateral tumorous PASH on ultrasound-guided core needle biopsy, and bilateral tumor excision was undertaken, again showing no hormone receptor expression. In 2011 the patient noted again the presence of bilateral breast masses, which were diagnosed as PASH through ultrasound-guided core needle biopsies. The patient was advised against excision

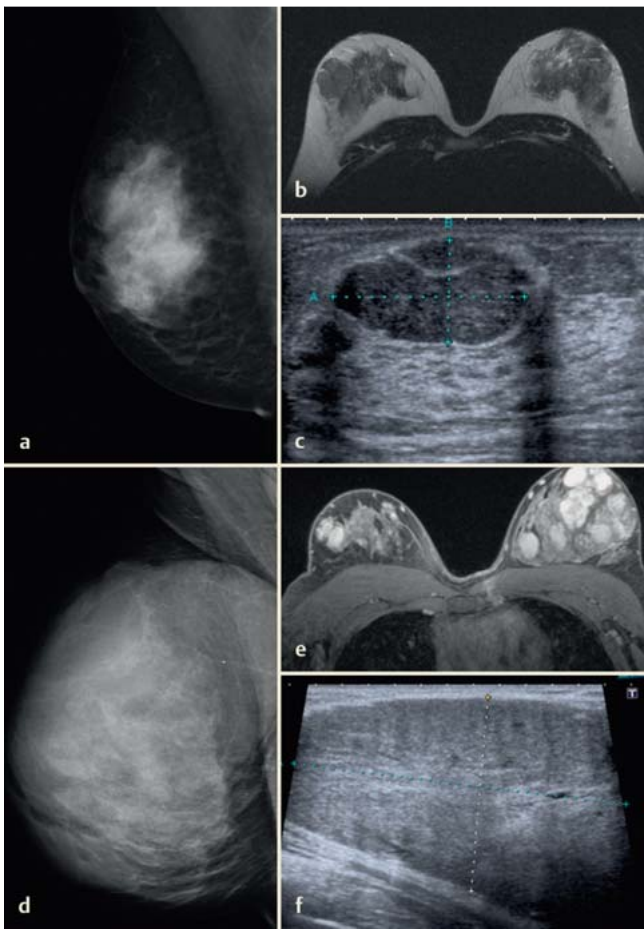


Fig. 1 a to f **a** Right mammogram from 2008 revealing no abnormalities. **b** Breast MRI from 2008 showing a “cauliflower-like cluster” in the right breast. **c** Ultrasound from the right breast from 2008 showing a hypoechoic, well-defined, oval mass. **d** Right mammogram from 2013 showing multiple low-density radiopaque lesions obscuring the surrounding parenchyma. **e** Breast MRI from 2013 showing asymmetric enlargement of solid fibroglandular tissue with multiple cauliflower-like lesions diffusely scattered throughout both the breasts, particularly the left one. **f** Breast ultrasound from 2013 showing a large oval, sharply circumscribed, hypoechoic mass.

of these lesions by her attending physician given the benign nature of the lesion and the history of previous excisions. In 2013 she presented with rapid lesion progression in both number and size, resulting in marked aniso-macromastia. On examination, both breasts showed several tumorous masses and were very enlarged (► Fig. 2a). A mammogram, an ultrasound and a MRI were undertaken (► Fig. 1 d to f). The mammogram revealed multiple low-density radiopaque lesions obscuring the surrounding parenchyma, while the ultrasound revealed multiple oval, sharply circumscribed, hypoechoic masses with varying diameter and scarce breast parenchyma. The MRI showed asymmetric enlargement of solid fibroglandular tissue with multiple cauliflower-like lesions showing a heterogeneous enhancement pattern diffusely scattered throughout both breasts, particularly the left one. Core-needle biopsy specimen examination revealed PASH with no evidence of malignancy (NHBSP Classification: B2). For cosmetic reasons and persistent discomfort the patient chose to undergo a bilateral mastectomy with immediate breast reconstruction with Siltex Contour Profile Becker™ 35 expanders



Fig. 2 a and b **a** Preoperative view of the patient showing asymmetrically enlarged breasts. **b** Postoperative view 4 weeks after bilateral mastectomy with immediate breast reconstruction with expanders and free nipple grafting.

using the dual plane technique originally published by Bostwick [1] (► Fig. 2b). The breast tissue had been replaced by several large tumors (► Fig. 3a) and the final report confirmed the diagnosis of PASH (► Fig. 3 right panel b and c). The final histology specimen immunohistochemistry examination revealed neither expression of estrogen (0%) nor expression of progesterone receptors (0%).

Discussion

▼ Epidemiology and pathogenesis

Pseudoangiomatous Stromal Hyperplasia (PASH) is a benign proliferation of stromal myofibroblasts and was described in 1986 by Vuitch et al. as a “stromal proliferation with the formation of interanastomosing slits that simulate vascular space” [2]. In the breast it can present as tumorous form or as microscopic diffuse form, as an incidental finding, as a mass or as multifocal disease. Since its description, approximately 285 of the published cases

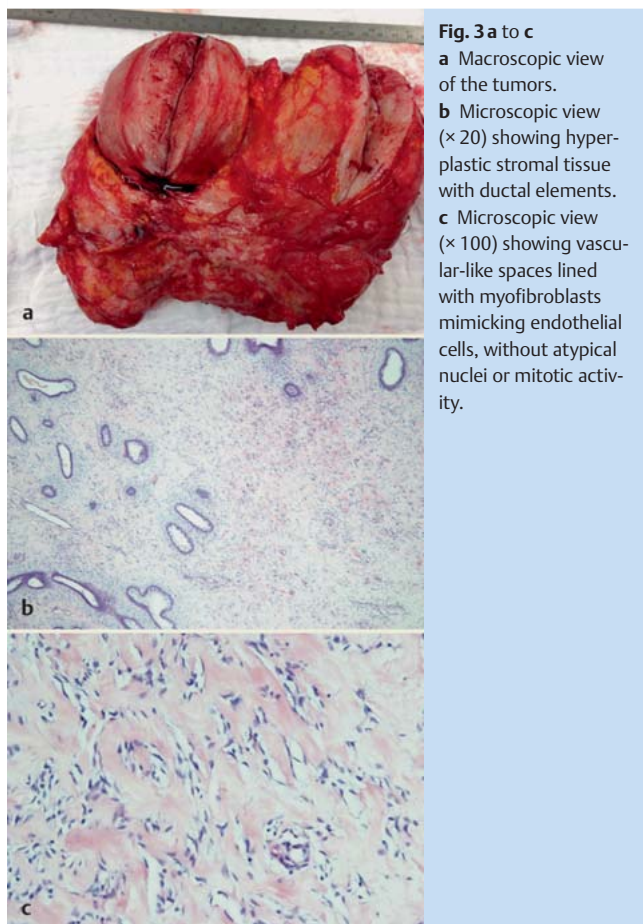


Fig. 3 a to c
a Macroscopic view of the tumors.
b Microscopic view ($\times 20$) showing hyperplastic stromal tissue with ductal elements.
c Microscopic view ($\times 100$) showing vascular-like spaces lined with myofibroblasts mimicking endothelial cells, without atypical nuclei or mitotic activity.

presented as a mass, although it can present as an incidental finding in its non-tumorous microscopic form in up to 23% of core needle biopsy specimens [3]. The published literature includes some case reports and small case series, insufficient to create management guidelines or standardized treatment. The biggest series from PASH cases includes 80 patients, mostly women of reproductive age or women under hormone replacement therapy [4]. This seems to be a constant finding in other case series [5–7]. Women are typically in their 4th decade of life and 60–79% of them are pre-menopausal [4–7]. This, together with estrogen and progesterone receptor expression, allows speculation regarding a hormonal cause. In a study of 200 consecutive biopsies, 65 women were shown to have incidental microscopic PASH, of which only 5 were older than 50 years of age [3]. PASH was also described in a transsexual man undergoing hormonal therapy [8]. Estrogen is expressed in 12–77% of the cases and progesterone in 36–63% [8,9]. Interestingly, although our patient was premenopausal, the histological specimen revealed no hormone receptor expression, so that a hormonal cause appears to be unlikely in this case.

Clinical presentation and radiologic findings

Clinically, it presents as an incidental finding on a mammogram in 40–62% of the cases and as a palpable mass in 38–53% of the cases [5–7]. The mass usually presents as solitary, firm, painless, well-circumscribed and freely mobile mass mimicking a fibroadenoma (as was the initial presentation in this case). Occasionally it can grow quickly, resembling malignancy or a phyllodes tumor. Rarely, it can present as multifocal disease with diffuse asymmet-

rical breast enlargement [10,11] (this type of progression occurred in our case approximately 5 years after the initial presentation). It occurs more commonly unilaterally [5–7], rarely in axillary tail [6,12] or in the nipple-areola complex [13]. In the ultrasound examination PASH again mimics the fibroadenoma as an oval, well-circumscribed, hypoechoic, parallel mass. Rarely it can present as an irregular hypoechogenic mass with hyperechogenic areas and indistinct margins [14]. In a series of 22 women with PASH, 62% showed irregular margins and 83% a hypoechogenic mass [15] with normal color Doppler vascularity [6,16]. In the mammograms it presents as a well-circumscribed, round-oval hyperdense mass without calcifications [6,16]. In its diffuse form it can present in the mammogram as a diffuse hyperdense area without a mass and in the ultrasound as a poorly circumscribed isoechogenic area [16]. In magnetic resonance imaging it shows as an isointense mass in T1 and a hyperintense reticular mass in T2 [16]. PASH has also been described in men, as a form of gynecomasty [5,8,17]. In men with gynecomasty PASH is shown in up to 23% of the cases [18].

Pathologic findings

Likewise, PASH is very difficult to distinguish from a fibroadenoma through fine needle aspiration (FNA). In a small retrospective series of 10 PASH cases, none of the cases was pre-operatively identified through FNA. The most common misdiagnosis was fibroadenoma (5/10), but schwannomas, neurofibromas and fibrocystic changes were also reported [19]. The cytological characteristics of PASH were described by Vicandi et al. as the presence of medium to small monolayered clusters of ductal epithelium with variable amounts of single, bipolar, naked nuclei in the background, fragments of acellular and/or cellular stroma, fibroadenoma-like patterns, and loosely cohesive clusters of atypical ductal epithelium mimicking malignancy [20]. To exclude malignancy, core-needle biopsy showed a sensitivity of 83% [15]. Clinically PASH mimics a fibroadenoma, however histologically the differential diagnosis between these two entities is not challenging. Here, phyllodes tumors and low-grade angiosarcomas represent the biggest diagnostic challenges [21]. Macroscopically angiosarcomas show indistinct margins and an infiltrative-hemorrhagic mass [21]. On the contrary, PASH constitutes a well-circumscribed, firm, rubbery-like, homogeneous, and gray-white mass, without a capsule. The reported diameter in its tumorous form ranges between 0.1 to 11 cm, with an average diameter of 2–4 cm [5,6,8]. The largest reported mass measured 20 cm in diameter [22]. Microscopically, PASH shows anastomosing channels lined by fusiform cells that mimic angiosarcoma's endothelial cells [2,21]. In angiosarcomas the channels dissect the interlobular stroma and invade the circumscribing fat tissue, while in PASH these gradually merge with the neighboring stroma [21]. The endothelial cells in angiosarcomas are light to moderate pleomorphic, showing nuclear atypia and high mitotic activity. On the contrary, the spindle cells in PASH are benign and hence do not show cytological atypia or mitotic activity [21]. To further overcome this problem immune histochemical studies are of use because myofibroblasts express characteristic markers such as CD34, Vimentin, Desmin, SMA (smooth muscle actin) and BCL-2, as opposed to vascular cells that express CD31, S100, Factor VIII, cytokeratin and von Willebrand Factor [9,21,23,24]. ERG is an emerging endothelial marker that has a very high sensitivity and specificity [25]. Seldom a giant cell component may be present in the pseudovascular spaces and stroma. These giant cells are CD34 positive, Factor VIII negative, present abundant cy-

toplasm and are moderately pleomorphic [26]. Such cells have also been described in phyllodes tumors [27]. Distinguishing PASH from a phyllodes tumor may at times be challenging because both lesions may be infiltrative and may form slit-like stromal spaces. However, in PASH the expanded stroma is predominately collagenous with a distinct cuff of specialized stroma remaining around the glands, while phyllodes tumors present an expanded stroma that is primarily myxoid and is in continuity with the periglandular stroma. Stromal mitotic activity, cytological atypia and tortuous glands strongly favor the diagnosis of phyllodes tumor [28].

Tumorous PASH is unifocal in about 80% of the cases, while multifocal disease occurs in approximately 12% of the cases and the diffuse form in ca. 6% of the cases [5]. The association with proliferative changes is common, occurring in approximately 60% of the patients. The coexistence of invasive cancer and/or ductal carcinoma in situ (DCIS) has likewise been described, albeit seldom [5,6]. In a study including 9065 core needle biopsy specimens PASH was discovered in 579. Invasive breast cancer affected 8.8% of the women without PASH and 5.9% of the women with PASH (SIR 1.03 95% CI = 0.71–1.44), so that it was concluded that PASH does not constitute a risk factor for invasive breast cancer [29]. The presence of PASH within the stroma of phyllodes tumors has been described in as many as 70% of phyllodes tumors when one low power field of characteristic slit-like changes in the stroma was used as the cut off. Interestingly, PASH is shown to be inversely correlated to tumor grade, translating into its presence in a phyllodes tumor being less likely to be associated with malignancy [30].

Treatment options

The treatment of PASH depends upon clinical presentation. No additional specific treatment is required if PASH is an incidental histologic finding. Excision is the recommended treatment for tumorous PASH. Although it represents a benign condition with no malignant potential by itself (neither as invasive breast cancer nor as a mesenchymal tumor such as angiosarcoma), it does have a propensity to grow and recur over time and requires clinical surveillance. Reported rates of recurrence after excision have been highly variable, ranging from 0 to 28.5% [6,7,14]. In a case series including 40 women, 12.5% of patients were found to have clinically important ipsilateral recurrences, despite aggressive operative excision [9]. Recurrent lesions behave in a benign fashion and, although they can rapidly progress in size, can be managed with reexcision. Diffuse and multifocal PASH may require mastectomy for cosmetic reasons or for persistent pain and discomfort. One case report described the successful treatment of a patient with extensive bilateral PASH tumors with tamoxifen [31], but there is lack of evidence to substantiate this as a treatment option. If this treatment form is to be undertaken, we strongly recommend beforehand determination of hormonal receptors, as in case of negative expression (as in this case) this approach is unlikely to be successful.

Concluding Remarks

In summary, we present an unusual form of multifocal tumorous hormone receptor negative PASH with rapid asymmetrical breast enlargement and a history of previous multiple excisions for recurrent lesions. Despite its benign nature, such presentation of

PASH is managed with bilateral mastectomy and immediate reconstruction with expanders for cosmetic and comfort reasons, while tumor excision or expectant management is deemed to lead to recurrence and progression in both size and number of lesions. Although an excessive responsiveness of mammary myofibroblasts to hormonal stimuli is the speculated origin, based on hormone expression studies and typical patient profile, this case showed 0% estrogen/progesterone expression in the final histology specimen. This indicates a probable independent myofibroblast process as a major role in the histogenesis of this case, as also previously alternatively hypothesized [5]. There has been a report of successful management of PASH with tamoxifen, the use of which we advocate only after hormone receptor determination and with an experimental character, with the patient being informed about the lack of evidence to support this treatment form.

Conflict of Interest

None.

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