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. 1a 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 hyperplasia (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.
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. 1d to f). The mammogram revealed multiple low-density radiopaque lesions obscuring the surrounding parenchyma, while the ultrasound revealed multiple oval, sharply circumscribed, hypoechogenic masses with varying diameter and scarce breast parenchyma. The MRI showed asymmetric enlargement of solid fibro glandular tissue with multiple cauliflower-like lesions diffusely scattered throughout both the breasts, particularly the left one. Breast ultrasound from 2013 showing a large oval, sharply circumscribed, hypoechogenic mass.

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 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%).
Rarely, it can present as multifocal disease with diffuse asymmetry. It can grow quickly, resembling malignancy or a phyllodes tumor. Occasionally, it can present as a well-circumscribed and freely mobile mass mimicking a fibroadenoma (as was the initial presentation in this case). Clinically, it presents as an incidental finding on a mammogram. The mass usually presents as solitary, firm, painless, well-circumscribed and freely mobile mimicking a fibroadenoma, however histologically the difference in 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, vWF, cytokeratin and 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 cyto-...
topsism 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 tu-

Sorous PASH is unifocal in about 80% of the cases, while multi-
tific disease occurs in approximately 12% of the cases and the diffuse form in ca. 6% of the cases [5]. The association with prolif-
erative 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% Cl = 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 tu-
mors 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 and 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 treat-
ment 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 rece-

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 re-
current lesions. Despite its benign nature, such presentation of

PASH is managed with bilateral mastectomy and immediate re-
construction 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 myo-

fibroblasts 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 histol-

ogy specimen. This indicates a probable independent myofibro-

blast process as a major role in the histogenesis of this case, as al-
so previously alternatively hypothesized [5]. There has been a re-
port of successful management of PASH with tamoxifen, the use of which we advocate only after hormone receptor determina-
tion and with an experimental character, with the patient being informed about the lack of evidence to support this treatment form.

Conflict of Interest

None.

References

1 Bostwick J J. Plastic and reconstructive Breast Surgery. St Louis: Qual-

ity Medical Publishing Inc.; 1990


4 Geslik CM, Godellas C, Aranha CV et al. Pseudoangiomatous stromal hyper-

plasia of the breast: a contemporary approach to its clinical and radiolog-


5 Drinka EK, Bargyie A, Erasahin CH et al. Pseudoangiomatous stromal hyper-


6 Ferreira M, Albarracin CT, Resetkova E. Pseudoangiomatous stromal hyper-


7 Jones KN, Glazebrook KN, Reynolds C. Pseudoangiomatous stromal hyper-

plasia: imaging findings with pathologic and clinical correlation. AJR Am J Roentgenol 2010; 195: 1036–1042

8 Bowman E, Oprea G, Okoli J et al. Pseudoangiomatous stromal hyper-


9 Powell CM, Cranor ML, Rosen PP. Pseudoangiomatous stromal hyperplasia (PASH). A mammary stromal tumor with myofibroblastic differen-

10 Byu EM, Whang IV, Chang ED. Rapidly growing bilateral pseudoangio-


12 Lee JS, Oh HS, Min KW. Mammary pseudoangiomatous stromal hyper-

plasia presenting as an axillary mass. Breast 2005; 14: 61–64


15 Wieman SM, Landercasper J, Johnson JM et al. Tumoral pseudoangi-


16 Teh HS, Chiang SH, Leung JW et al. Rapidly enlarging tumoral pseudo-

angiomatous stromal hyperplasia in a 15-year-old patient: distinguishing sonographic and magnetic resonance imaging findings and correlation with histologic findings. J Ultrasound Med 2007; 26: 1101–1106