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Pseudoangiomatous hyperplasia of mammary stroma: clinical cases

Relevance. *Pseudoangiomatous stromal hyperplasia (PASH) is a rare benign breast pathology. Less than 300 cases of PASH are described in the literature; in most cases, the disease appears as a histological finding during a biopsy performed on a different diagnosis. PASH is often associated with other benign breast changes, and these changes may dominate in the clinical and radiological presentation. The BI-RADS scale classifies PASH as category 2 (benign changes). Differential diagnostics shall include fibroadenoma, phylloid tumor, and diabetic mastopathy. PASH is not a precancerous condition and does not require active surgical treatment or dynamic monitoring. After surgery, the risk of relapse occurs in 15-22% of cases.*

PASH diagnostics is challenging due to the variety of radiological patterns and the absence of pathognomonic radiological signs.

Purpose of this study *is to familiarize with this pathology and improve differential diagnosis.*

This article presents clinical cases of three patients with pseudoangiomatous stromal hyperplasia of mammal glands with different clinical and radiological patterns.

Conclusions. *In the case of questionable results of radiation examination, biopsy followed by histological examination is required to clarify the diagnosis.*

Keywords: *Pseudoangiomatous stromal hyperplasia, mammography, breast ultrasonography.*

Introduction. Pseudoangiomatous stromal hyperplasia (PASH) is a rare benign breast pathology first described in 1986 by Vuitch and coauthors in 9 patients with palpable neoplasms in the mammary gland [1]. The scientific literature in English offers a range of publications devoted to this pathology and its diagnostics [2-5]. However, no publications on that topic could be found in Russian-language literature.

This article presents the results of a radiation examination of three patients to demonstrate the differences in clinical and radiological manifestations of histologically confirmed PASH.

The correct and timely PASH diagnostics at the preoperative stage allows for avoiding unnecessary invasive interventions. Despite the low prevalence of this pathology, practical radiologists should be aware of the disease, know its clinical symptoms, radiation semiotics, and tactics to ensure optimum management of patients.

Description of cases.

Case 1 (Figures 1-4).

A female patient, 47 years old, presented complaints on a neoplasm in her right breast, accidentally detected during the screening in 2012 and painfulness in the place of neoplasm. The neoplasm was not palpable; over the years, it slowly increased in size. Histological diagnosis of a core-needle biopsy has shown a mammary fibroadenoma.

The oval neoplasm of average density, precise contour, with dimensions 2.2x1.2 cm at a distance of 6 cm from the nipple was detected on a mammography study of the lower inner quadrant of the right mammary gland.

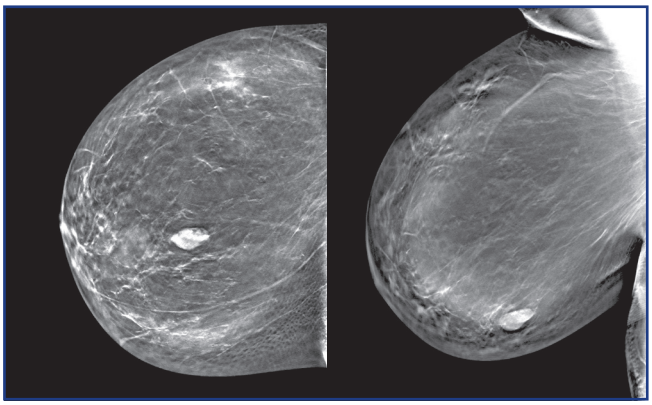


Figure 1 - Mammograms of the right mammary gland, frontal and oblique views. Neoplasm in the lower inner quadrant, with medium intensity, and precise contour.

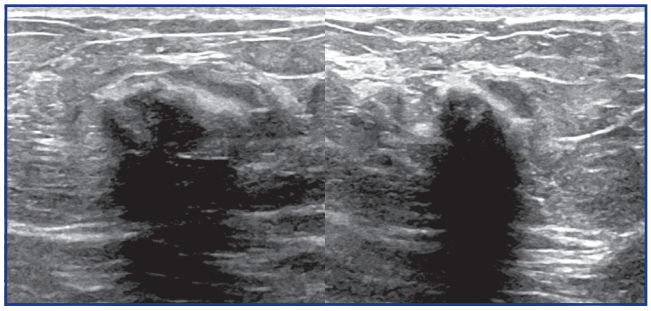


Figure 2 - Ultrasound examination of the right mammary gland. A hypoechoic mass with a fuzzy contour and heterogeneous structure.

Ultrasound examination: a hypoechoic neoplasm with a fuzzy contour, parallel to the skin, with a heterogeneous internal echo-structure and a marked distal acoustic shadow. The

patient was recommended surgery due to neoplasm growth.

Postoperative histology conclusion: PASH with foci of fibroadenomatous changes, without any signs of atypia.

Case 2 (Figures 3-5).

A female patient, 72 years old, without complaints. Screening mammography showed a locus of developing asymmetric tissue 4.5x2.0 cm in size, in the upper-outer quadrant of the mammary gland, 6.3 cm away from the nipple.

Ultrasound examination: an irregular shape neoplasm difficult to measure due to its ductal distribution. BI-RADS 4.Histological diagnosis after of core-needle biopsy: PASH with a simple ductal hyperplasia.

The patient was recommended to continue the routine mammography screening.

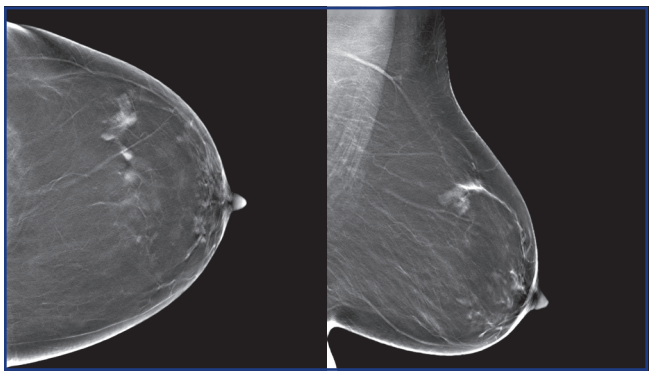
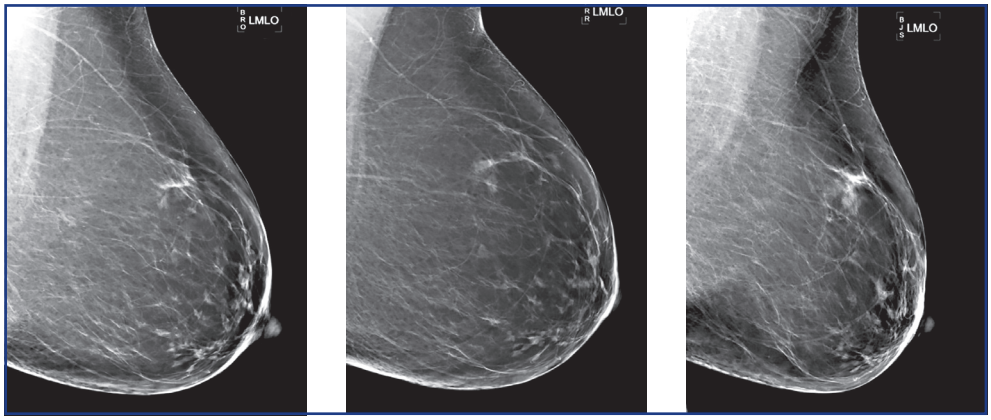


Figure 3 - Tomosynthesis (performed in 2019). In the upper-outer quadrant of the right mammary gland - the locus of focal asymmetry



Picture of 2016. Picture of 2017. Picture of 2019.

Figure 4 - Mammograms of the right mammary gland taken in 2016, 2017 and 2019: the developing asymmetry locus in the upper-outer quadrant

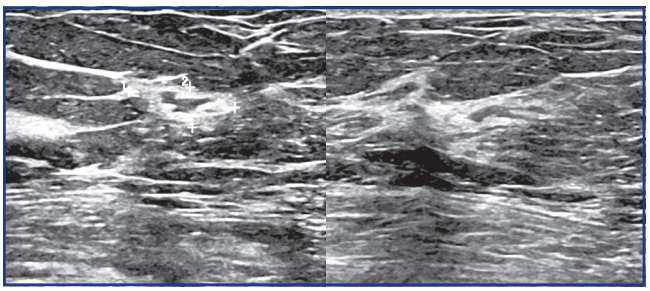


Figure 5 - Ultrasound examination of the right mammary gland: a neoplasm, irregular shaped

Case 3 (Figures 6-7).

A female patient, 45 years old, presented complaints on a neoplasm in the left mammary gland, accidentally detected during the screening mammography about 3 years ago, with the slow growth of the neoplasm. The biopsy showed a fibroadenoma. No other complaints were recorded; the neoplasm was not clearly palpable.

The mammography of the upper-outer quadrant of the left breast showed an oval neoplasm with partially indistinct contours, and low density sized 4.0x3.1 cm.

Ultrasound examination: a hypoechoic mass with precise contours, parallel to the skin, heterogeneous internal echo-structure, size 4.1x4.1 cm.

The patient was recommended surgery due to neoplasm growth.

The postoperative conclusion of the histology examination was the following: PASH associated with fibroadenomatous changes, steatonecrosis, and apocrine metaplasia.

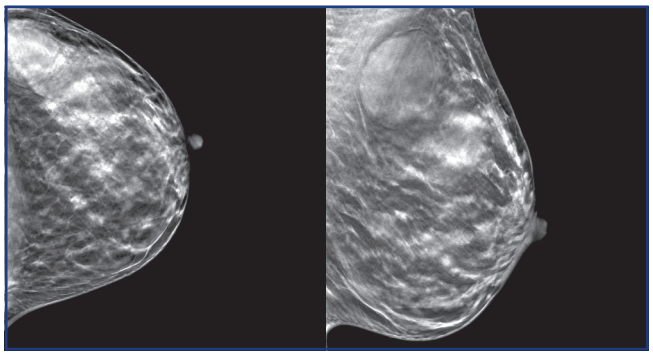


Figure 6 - Tomosynthesis: the neoplasm with partially indistinct contours in the upper-outer quadrant of the left mammary gland

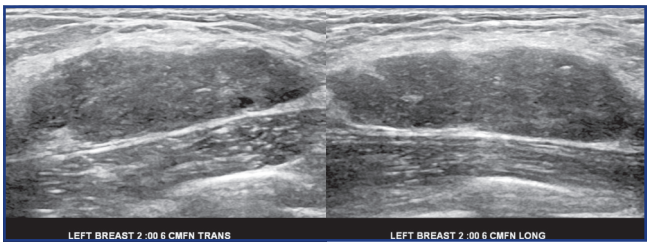


Figure 7 - Ultrasound examination of the left mammary gland: a hypoechoic neoplasm with precise contours and heterogeneous structure

Discussion

Pseudoangiomatous stromal hyperplasia is a benign condition of the mammary gland associated with a collagen proliferation. In most cases, that disease is an incidental histological finding during a biopsy performed because of a different diagnosis.

Less than 300 cases of PASH were described in English-language scientific literature; the most extensive series of cases included 79 patients [6]. In one of the studies, PASH was detected in histological samples of 23% of patients after sectoral resection for another reason [7].

That pathology is observed in both women and men; in men, it is often associated with gynecomastia. In a study, PASH as a comorbidity was detected in 24-47% of men with gynecomastia [8].

The etiology and pathogenesis of PASH are not thoroughly studied; however, hormonal factors are known to play a significant role in PASH development. PASH is more common in women in the premenopausal and perimenopausal period [9].

PASH affects patient of different ages and has been reported in women of 14 to 67 years, with the highest prevalence at the age of 30-50 years [10, 11]. This pathology is rare in patients after 50 years in the postmenopausal period without a hormone replacement therapy. This fact confirms the hormonal etiology of PASH.

Several studies reported the change in the size of neoplasms depending on the phase of the menstrual cycle phase what reconfirmed its hormonal genesis [12]. Histological findings showed a positive sensitivity of stromal cells to progesterone receptors and moderate stromal nuclear sensitivity to estrogen receptors, while the nuclei of the stromal cells in control cases without PASH stained none of the receptors [9].

Clinical and radiological manifestations

Clinically, PASH is usually manifested as moving palpable neoplasm in a mammary gland with a tendency to growth [13].

PASH is often detected during a histological examination with no clinical symptoms [14].

On a mammogram, PASH may look like a round or oval neoplasm which resembles a fibroadenoma, with a precise contour of high X-Ray density, more often with no signs of microcalcifications [15].

During a mammary gland ultrasound examination, PASH commonly manifests itself as a hypoechoic, oval, or round neoplasm, with slightly heterogeneous internal echo-structure [15].

The dimensions of the neoplasm may range from 1 to 23 cm [16].

On MRI study of the mammary glands, the PASH pattern is not specific and varies from a neoplasm accumulating the contrast to a focal accumulation of contrast no developing a neoplasm, usually with benign parameters on kinetic tests [17].

PASH is often associated with other benign breast changes, and these changes may dominate in clinical and radiological patterns.

Histology

The proliferation of stromal cells, more precisely, the proliferation of collagen, forms slit-like channels which are lined by myofibroblasts (spindle cells) and resemble vascular channels [18]. It should be taking into account that this is not a true angiomatous proliferation, and these channels are not the blood vessels. In this regard, PASH may be wrongly viewed as a vascular neoplasm.

A spindle tumor cells are positive to Vimentin, CD34, BCL2, CD99, and α-smooth muscle actin, but negative to CD31 and Factor VIII (endothelium-specific marker). Also, the cells exhibit a hormonal sensitivity and often express the progesterone and estrogen receptors [19].

Differential diagnosis

The clinical and radiological methods should be applied to differentiate PASH from other benign breast diseases such as fibroadenoma, phylloid tumor, and diabetic mastopathy [20].

Morphologically, PASH should be differentiated from low-differentiated angiosarcoma and tumors containing spindle cells such as phylloid tumors and desmoid [21].

Tactics

PASH is a benign breast disease. It is not a pre-cancerous condition or not the risk factor for breast cancer development [13]. The literature does not describe any cases of synchronous PASH and breast cancer; however, it is theoretically possible.

The literature also does not describe malignant PASH variants, except two cases of PASH with marked cytological atypia, multinucleated cells and high mitotic activity in adolescent girls finally diagnosed with myofibroblastic sarcoma. These cases were described by Rosen in his "Breast Pathology" [22].

The BI-RADS scale classifies PASH as category 2 (benign changes).

In the case of questionable results of radiation examination, biopsy followed by histological examination is required to clarify the diagnosis.

No active surgical tactics or dynamic observation is required for PASH management. The surgical resection may be indicated in the following cases: the neoplasm growth, the diffuse PASH with the mammary gland growth, and in case of non-conformity between the histological diagnosis and the radiation pattern. After surgery, the relapse occurs in 15-22% of cases [15].

There are no generally accepted recommendations for PASH conservative treatment. This disease is sensitive to tamoxifen; however, the treatment outcome is supported only within the long-term anti-estrogen therapy [23]. The long-term intake of tamoxifen has many side effects and cannot be recommended for young women in the pre-menopausal period.

Conclusion. The analysis of available literature has revealed no pathognomonic radiation signs of PASH, this rare benign breast pathology. The most frequent radiological manifestation is a round neoplasm of a precise contour with sonographic heterogeneous internal content. In a majority of cases, the solid nature of the neoplasm requires a histological verification using core-needle biopsy. The detection of PASH in pathological specimens can verify the benign nature of the neoplasm that requires no further dynamic observation.

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