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Original Research

The Relationship of Pseudoangiomatous Stromal Hyperplasia (PASH)-Like Appearance in Invasive Breast Carcinomas with PASH Areas in Non-Tumoral Breast Parenchyma as Well as on Axillary Lymph Node Involvement

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Abstract

Objectives: The aim of this study were to determine the relationship of pseudoangiomatous stromal hyperplasia (PASH)-like appearance in invasive breast carcinomas (IBCs) with PASH foci in the non-tumoral breast parenchyma as well as axillary lymph node involvement.

Methods: In this study, 200 consecutive cases with IBC were re-examined. Cases with and without PASH-like appearance in IBC were determined. Each case was assessed regarding the presence of accompanying PASH foci (CD34+, CD31-) in the non-tumoral areas in addition to other clinicopathological parameters.

Results: PASH-like appearance within the IBC was present in 22 of the 200 cases (11%) and absent in 178 (89%). The presence of PASH foci in the non-tumoral breast parenchyma was significantly more common in IBC with PASH-like appearance compared to the group without such areas. However, there was no significant difference between the groups regarding other clinicopathological parameters (age, tumor size, nuclear and histological grade, Estrogen receptor/Progesterone receptor status, HER2 status, and Ki-67 proliferation index), lymphovascular invasion (LVI), and axillary lymph node involvement. There was no significant difference between the two groups regarding the histopathological findings observed in the non-tumoral areas.

Conclusion: PASH-like appearance within IBC was found to be associated with higher rate of PASH foci in the non-tumoral breast parenchyma. However, such cases do not show a difference as regards LVI and axillary lymph node metastasis.

Keywords: Axillary lymph node involvement, Lymphovascular invasion, Pseudoangiomatous stromal hyperplasia, Tumor spreading

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Pseudoangiomatous stromal hyperplasia (PASH) is a benign stromal proliferation consisting of slit-like spaces lined by spindle cells that anastomose with each other within a dense collagenized stroma.[1] Vuitch et al.[2], have observed vascular structure-like slitting in the breast stroma of nine women in 1986 and named this PASH for the first time.

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Leon et al.[3], have suggested naming PASH "myofibroblastic hyperplasia of the breast stroma" based on its structure of a stromal lesion created by myofibroblasts in 2002.

Although PASH has previously been defined as a lesion seen in premenopausal women, it is now known that it can be seen in males and females aged 12–75 years.[1,4] These lesions can be detected in premenopausal women taking oral contraceptives or postmenopausal women taking hormone replacement treatment (HRT), transsexual males or those with gynecomastia taking exogenous hormones, and children and/or adolescents with other disorders such as neurofibromatosis type 1, morbid obesity, or precocious puberty.[4-9] This has emphasized the association of the lesion with hormonal factors.[4,10]

PASH is most commonly found within the breast parenchyma during routine pathological evaluation as incidental small microscopic foci.[11] It less commonly forms unilateral, palpable, painless, slow-growing, and well-defined nodular masses and can mimic fibroadenoma on clinical/radiological investigations. These masses can appear as non-calcified, homogenous, and hyperechogenic images on USG.[12] Cases causing bilateral and asymmetrical diffuse growth of the breast have also rarely been reported.[1] In general, these lesions are localized in the upper outer quadrant of the breast, but they can also be found in the accessory breast tissue in the axilla or encompassing the nipple-areola complex.[1,10,13]

PASH is composed of slit-like cavities that anastomose with each other in the collagenized breast stroma and that are lined with myofibroblasts with small spindle nuclei but no atypia.[10] This morphological appearance can mimic vascular lesions of the breast due to the slit-like spaces. Whereas PASH shows positive staining for smooth muscle actin (SMA), desmin and calponin that reflect the myofibroblastic origin of the lesion, it shows no staining for vascular markers such as CD31, D2-40, and Factor 8. In addition, the lesion displays positive staining for CD34 and particularly progesterone but negative staining for cytokeratin.[8] PASH can be found in the interlobular or intralobular stroma. There is no atypia or mitosis in the myofibroblasts in classic PASH, but mitosis, atypia, hyperchromasia, and multinucleation have been reported in some cases.[12]

In invasive breast tumors, lymphatic invasion is associated with lymph node metastasis. Lymphatic invasion is important in detecting early local recurrence and distant metastasis.[14] The PASH lesion has been hypothesized to be a precursor to the lymphatic vessels and reflects a specific type of tumor spread in some studies.[11] The aim of this study was to (i) investigate the relationship of PASH-like appearance in invasive breast carcinoma (IBC) with PASH areas in the non-tumor breast parenchyma and (ii) investigate the relationship of PASH-like appearance with other clinicopathological parameters, especially PASH-like appearance. Lymphovascular invasion (LVI) and axillary lymph node involvement.

Methods

Our study was designed as a single-center retrospective study. It was carried out in accordance with the Declaration of Helsinki and was initiated after an approval of the Ethics committee from the Ethical committee of the university of health sciences Istanbul Training and Research hospital (approval number: 1287, date: June 01, 2018).

Two hundred and thirty consecutive cases who were diagnosed with IBC and underwent surgical excision (breast conserving surgery in 52 cases, modified radical mastectomy in 83 cases, and simple mastectomy in 95 cases) in our department were included in the study. The H&E sections of 230 consecutive cases from patients (In addition to tumoral areas, surgical margins, and lymph nodes in mastectomy cases, there is routine sampling of non-tumoral sites from four different quadrants, and in breast-conserving surgery cases, there are at least two non-tumor site samples) were obtained from the archive and retrospectively evaluated. Cases with dense collagenized stroma and accompanying PASH-like appearance within the IBC were noted. Among these cases, those with artifacts or suspect changes that could be due to the preanalytic and analytic process were excluded from the study. All the consultation cases were also excluded due to uncertain preanalytic/analytic processes. Cases showing PASH morphology in at least size of one terminal ductal lobular unit in the non-tumoral breast parenchyma were determined and all then underwent CD34 and CD31 immunohistochemical staining to confirm PASH diagnosis. Thus, cases that stained positively with CD34 and negatively with CD31 were accepted as PASH. Mean patient age, mean tumor size, nuclear and histological grade of the tumor, estrogen receptor (ER)/progesterone receptor (PR) status, HER2 status, Ki-67 proliferation index, LVI, and axillary lymph node metastasis status are effective parameters in the prognosis of the cases. These parameters were re-evaluated and noted to evaluate their relationship with PASH cases. Any accompanying changes in the non-tumoral areas (such as columnar cell changes, fibrocystic changes, and apocrine metaplasia) were also noted. The clinical data of the cases were obtained from the hospital electronic record system.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) package program. All data are presented as mean for parametric variables, as

percentage for categorical variables in descriptive statistics. Chi-square test was used for categorical data and student t-test was used for continuous data.

Results

The clinicopathological data of 200 of the 230 cases that had undergone surgical excision for IBC were considered. Table 1 shows the clinicopathological features of the groups. Accordingly, PASH-like appearance was found within the tumor area in 22 cases (22/200, 11%). All of these cases were female with an age range of 33–76 years (median age: 58.5). The histology of these 22 cases consisted of invasive ductal carcinoma in 17 (77%), mixed type IBC in 2 (9%), classic type invasive lobular carcinoma in 2 (9%), and invasive tubular carcinoma in 1 (5%). PASH foci in non-tumoral breast parenchyma were found in 5 (22.7%) of the 22 IBC cases with PASH-like appearance (focal in two cases and multifocal in three cases) (Fig. 1).

Evaluation of the group without PASH-like appearance in IBC (n=178) revealed PASH foci in the non-tumoral areas in four cases (4/178, 2.2%) (Fig. 2). Accordingly, the rate of finding PASH in non-tumoral areas was significantly higher in the group with PASH-like appearance in the IBC (22.7%) compared to those without (2.2%) (p<0.001) (Table 1).

All of the 178 cases without PASH-like appearance were female, with an age range of 31–84 years (median age: 57). There were 143 cases with invasive ductal carcinoma histology (81%), 13 mixed type IBC (7,3%), ten classic type of invasive lobular carcinoma (5.5%), three invasive mucinous carcinoma (1.5%), two invasive tubular carcinoma (1.1%), two invasive cribriform carcinoma (1.1%), one invasive mi-

Table 1. Clinicopathological and histopathological parameters between the groups of IBC with and without PASH-like appearance

	PASH-like focus in invasive tumor (+) (n=22)	PASH-like focus in invasive tumor (-) (n=178)	p
Age (Year)	59.4±13.2	56.1±13.4	0.277
Tumor size, cm	2.8±2.6	2.6±1.4	0.594
Nuclear grade, % (n)			
1	0	3.98 (7/128)	0.344
2	59.1 (13/22)	49.4 (88/178)	0.393
3	40.9 (9/22)	46.68 (83/178)	0.612
Histological grade, % (n)			
1	9.1 (2/22)	7.9 (14/178)	0.842
2	59.1 (13/22)	56.7 (101/178)	0.834
3	31.8 (7/22)	35.4 (63/178)	0.740
LVI, % (n)	40.9 (9/22)	39.9 (71/178)	0.926
ER/PR (+), % (n)	95.5 (21/22)	82.6 (147/178)	0.120
ER (Aps)	62.9±32.5	61.7±37.1	0.880
PR (Aps)	54.7±27.6	43.8±36.5	0.177
HER2 (+), % (n)	36.4 (8/22)	23.0 (41/178)	0.191
KI-67 ≥ %14, % (n)*	92.3 (13/14)	83.7 (87/103)	0.415
KI-67 < %14, % (n)*	7.7 (1/14)	16.3816/103)	0.415
KI-67, % (average ki-67 value)	28.0±12.5	30.4±18.7	0.659
Molecular subtypes			
Lumional group, % (n)**	93.8 (15/16)	75.8 (91/120)	0.104
Triple-negative group, % (n)**	5.98 (1/16)	7.5 (9/120)	0.810
Her2 (+) group,% (n)**	0	16.7 (20/120)	0.077
Aln metastases (+), %, (n)***	52.4 (11/21)	55.6 (95/171)	0.782
In non-tumoral area			
PASH areas (n)	22.7 (5/22)	2.2 (4/178)	<0.001
Apocrine changes, % (n)	36.4 (8/22)	32.0 (57/178)	0.682
Fibrocystic changes, % (n)	68.2 (15/22)	80.3 (143/178)	0.187
Columnar cell changes with atypia, % (n)	9.1 (2/22)	16.9 (30/178)	0.349
Columnar cell changes Without atypia, % (n)	31.8 (7/22)	24.2 (43/178)	0.434

PASH: Pseudoangiomatous stromal hyperplasia; ER: Estrogen receptor; PR: Progesterone receptor; ALN: Axillary lymph nodes; LVI: Lenfovascular ınvasion; APS: Average percentage of staining; *n: 117, **n: 137, ***n: 192.

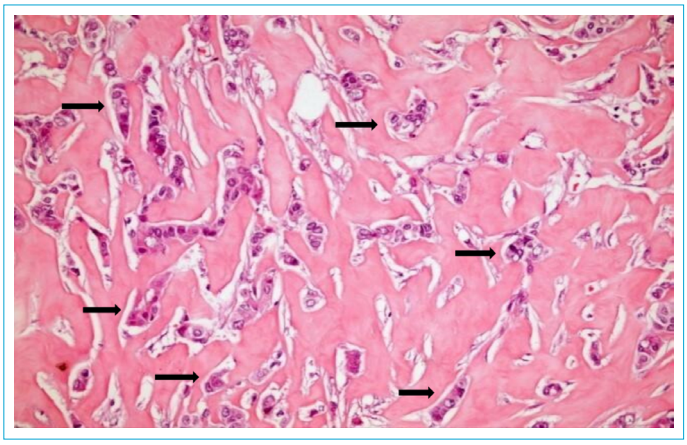

Figure 1. The nests and trabeculae of invasive groups of tumor cells seen within PASH-like areas. (H&E ×200).

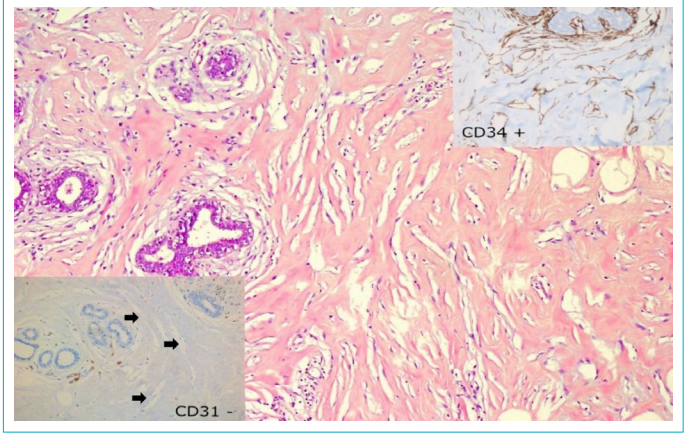

Figure 2. True PASH areas surrounding columnar cell changes with atypia. The lesion shows positivity for CD 34 and negativity for CD 31. (H&E ×200).

cropapillary carcinoma (0.5%), one IBC with medullary features (0.5%), one metaplastic carcinoma (0.5%), one breast carcinoma with neuroendocrine features (0.5%), and one invasive solid papillary carcinoma (0.5%).

There was no significant difference for LVI, axillary lymph node metastasis, mean patient age, mean tumor size, nuclear and histological grade, ER/PR status, HER2 status, Ki-67 proliferation index, and other findings noted in non-tumoral areas (columnar cell changes with or without atypia, fibrocystic changes, and apocrine metaplasia) between the groups of IBC with and without PASH-like appearance (Table 1).

Discussion

PASH used to be considered a hamartamous breast lesion but has first been defined as a separate entity in the World Health Organization (WHO) breast tumors booklet in 2003 and has taken its place among the mesenchymal tumors of the breast.[8] Although it is currently thought to develop following an aberrant response of the myofibroblasts in the breast stroma to endogenous or exogenous stimuli, the etiopathogenesis is still controversial. Progesterone is the hormone thought to be responsible for this effect.[1,8] Another hypothesis is that PASH is a myofibroblastic lesion. This hypothesis is based on the possibility of PASH being present as multifocal foci within the breast parenchyma, the fact that it can be seen together with other breast tumors, and its recurrence at rates up to 22% following excision.[15] PASH can accompany other lesions of the breast (benign and/or malignant) and such concurrence has been reported at a rate of 6.4% to 23% in the literature.[11,16] Incidental microscopic PASH foci can be seen in fibrocystic changes and fibroepithelial lesions of the breast (such as fibroadenoma and benign phylloides tumor) and also as a stromal lesion accompanying columnar cell epithelial changes.[17,18]

Columnar cell changes (especially columnar cell lesions with atypia/flat epithelial atypia) are non-essential precursor lesions for low-grade malignant epithelial carcinomas of the breast.[8] Finding PASH areas in the stroma surrounding these lesions indicate a suspect morphological change found in the early period in the peritumoral stromal tissue.[17] These lesions can also rarely accompany the malignant tumors of the breast and some authors believe they are a special type of tumoral spread.[11]

The presence of PASH has not been shown to be a risk factor for malignancy and there is nothing to support its being a premalignant lesion.[18] However, a concurrent invasive carcinoma focus has been found in approximately 10% of the cases.[19] Drinka et al. [15] have reported concurrent invasive carcinoma in 9 (11%) cases in their study including 79 cases with a PASH diagnosis. The diagnosis was invasive ductal carcinoma in eight, and invasive micropapillary carcinoma in one of these cases. The mean invasive tumor diameter was 2 cm (0.1–5 cm). However, the invasive tumor cells were not within the PASH areas in this study and the two lesions were not in direct contact with each other. Another study by Damiani et al. [20], has found concurrence with a malignant tumor showing an unusual style of distribution within the PASH areas in a total of five cases, and the diagnosis was IBC in three and non-Hodgkin lymphoma in three of these patients. Using these morphological findings, the authors postulated that the PASH foci could be prelymphatic spaces opening into the lymphatic system and act as a precursor for tumor metastases, although they are not real lymphatic channels.[20] Another study retrospectively evaluating breast needle biopsy material has found PASH foci in 37 of 412 cases (8.9%) together with concurrence with invasive carcinoma in one case (0.2%).[17]

Hormonal factors (endogenous or exogenous) and espe-

cially the progesterone hormone are known to influence PASH etiology. Some studies have detected nuclear staining that was strong with the PR and weak with the ER in the myofibroblastic cells lining the PASH areas on immunohistochemical staining.[8,21,22] In addition, the more frequent observation of the lesion in premenopausal women, postmenopausal women with a history of HRT use, males with gynecomastia, and adolescents with the early puberty supports a relationship between the PASH lesion and the hormonal status.[4-9,23] Half of the cases where a PASH focus was found in our study were premenopausal and the other half were postmenopausal. There was no known history of OC or HRT use. Although the difference was not statistically significant, most of the tumors in this group showed hormone receptor positivity (95.5% vs. 82.6) together with a higher rate of PR expression (54.7% vs. 43.8%) (Table 1).

PASH-like appearance in the IBC may resemble tissue retraction. Acs et al. [24-26], searched for the significance of retraction artifacts in IBC and its clinical consequences. The authors defined the term "retraction artefact" for the clear spaces without endothelial lining,which seperated the tumor cells from the adjacent stroma. They first revealed that the extent of retraction artefact showed a significant correlation with tumor size, histologic type, histologic grade, presence of LVI, axillary lymph node metastasis, as well as poor overall and disease-free survival.[24] Therefore, retraction artifacts were suggested as a morphological finding that reflects biologic alterations between tumor cells and stroma instead of being a consequence of inadequate fixation as previously believed. Therefore, they changed the term "retraction artefact" to "retraction clefts." The authors also searched for the correlation between the extent of retraction clefts and lymphangiogenesis, by examining the lymphatic vessel density and vascular endothelial growth factor-C (VEGF-C) expression in cases with the early stage breast carcinomas.[25] IBC with extensive retraction clefts (> 20% of tumor volume) was found to have significantly more lymphatic vessel density and VEGF-C expression levels. In addition, extensive retraction clefts, peritumoral lymphatic vessel density, and VEGF-C expression were demonstrated to be associated with poor clinic outcome. Due to these findings, retraction clefts were suggested as real potential spaces that may represent "pre-lymphatic spaces" facilitating initial lymphatic invasion.[25] It was also validated in a prospective study composed 2742 consecutive cases that the presence of extensive retraction clefts were found to be correlated with aggressive tumor features and lymphatic tumor spread.[26] However, there are significant differences between the retraction clefts mentioned in these studies and the PASH areas mentioned in our study. PASH areas are covered with spindle cells, whereas cells lining the retraction slits are absent. Retraction slits show staining with D2-40 and VEGF-C, which can support their vascular origin, while PASH areas show expression with dyes that promote myofibroblastic origin such as desmin, calponin, and SMA. While tumor cells are seen in the retraction clefts, there are no tumor cells in the PASH areas in our cases. In the light of these findings, PASH areas and retraction artifacts seem to be two separate entities with different characteristics.

This study had some limitations. One of them was that it was a retrospective study. The other was that the nontumoral field sampling of the cases was limited. If there were more samples belonging to non-tumoral areas, the histopathological findings observed in these areas could also be more.

Conclusion

PASH-like appearance within IBC was found to be associated with higher rate of PASH foci in the non-tumoral breast parenchyma in this study. However, the presence of PASH-like appearance within the IBC did not show any association with LVI or axillary lymph node involvement. Therefore, unlike retraction clefts, the presence of PASH-like appearance in the IBC may not be a morphological marker to reflect axillary lymph node metastases. On the other hand, these types of IBC showed more hormone receptor expression, similar to the literature. This may signify the role of a hormonal effect in the shaping of these lesions.

Disclosures

Ethics Committee Approval: Our study was designed as a single-center retrospective study. It was carried out in accordance with the Declaration of Helsinki and was initiated after an approval of the Ethics committee from the Ethical committee of the university of health sciences Istanbul Training and Research hospital (approval number: 1287, date: June 01, 2018).

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