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Original Article

Columnar cell lesions and pseudoangiomatous hyperplasia like stroma: is there an epithelial-stromal interaction?

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Abstract: The significance of association between cancer and its microenvironment has been increasingly recognized. It has been shown in animal models that interaction between neoplastic epithelial cells and adjacent stroma can modulate tumor behavior. Carcinoma associated stromal cells can transform normal epithelial cells into neoplastic cells. In breast, columnar cell lesions are non-obligate precursors of low grade ductal carcinoma in situ. Columnar cell lesions can be seen intimately associated with PASH-like-stroma, a lesion we termed as CCPLS. Our aim is to investigate epithelial-stromal interactions in CCPLS and compare them to PASH without columnar cell lesions in breast core needle biopsies. Normal terminal duct lobular unit (TDLU) epithelium was seen in association with columnar cell lesions as well as PASH. Eight (8) cases of each category were examined by a panel of immunostains: CD117 (C-kit), CD34, CD105, bFGF, AR, ER-beta, MIB-1. We observed a markedly decreased expression of c-kit in columnar cell lesions compared to TDLU-epithelium. CD105 showed a quantitative increase in activated vessels in CCPLS compared to PASH. A subset of CCPLS and PASH were androgen receptor positive. A strong nuclear positivity for ER-beta is observed in the epithelium and stroma of all CCPLS cases. We conclude that (1) activated blood vessels predominate in CCPLS; (2) A molecular alteration is signified by c-kit loss in columnar cell lesions; (3) ER-beta and androgen receptor positivity indicate CCPLS are hormonally responsive lesions. Our study suggests an intimate vascular and hormone dependent epithelial-stromal interaction exists in CCPLS lesions.

Key words: Columnar cell, pseudoangiomatous stromal hyperplasia, c-kit, AR, ER-beta

Introduction

Columnar cell lesions arise from terminal duct lobular unit (TDLU), and are characterized by a columnar cell lining with prominent apical snouts and luminal secretions, divided by histomorphology into columnar cell change, columnar cell hyperplasia, columnar cell hyperplasia with atypia, and ductal carcinoma in situ (DCIS) of micropapillary /cribriform types [1, 2]. Loss of heterozygosity (LOH) and comparative genomic hybridization (CGH) analysis have demonstrated molecular similarities between columnar cell lesions and invasive carcinomas [1, 3, 4], suggesting this lesion to be considered an early neoplastic rather than hyperplastic proliferation. The significance of association between cancer and its microenvironment has been increasingly recognized. Animal models have shown an interaction between neoplastic epithelial cells and adjacent stroma, which can modulate tumor behavior. Carcinoma associated stromal cells can transform normal epithelial cells into neoplastic cells. It was also demonstrated that an activated stroma produces numerous substances called tumor-stroma-associated antigens [5] that are necessary for development of normal and neoplastic mammary cells, supporting the theory of an epithelial-stromal interaction necessary for breast tumorigenesis [6-9]. The importance of epithelial-stromal interactions in breast cancer is increasingly recognized.

In our practice we have frequently encountered an intimate association of columnar cell lesions with PASH-like stroma in core needle biopsies, a lesion we designated as CCPLS. We believe the histological association of both lesions is not a mere coincidence but a lesion representing epithelial-stromal interaction. We used a panel of immunohistochemical markers to investigate the presence of hormonal and angiogenic factors that might play a role in epithelial-stromal interaction of CCPLS lesions.

Material and methods

Cases were retrieved from our Magee Women's Hospital tumor registry. The original hematoxylin and eosin (H&E) slides and paraffin blocks of eight core needle biopsies with CCPLS lesions. Eight core needle biopsies with PASH without columnar cell lesions were selected. Normal terminal duct lobular unit (TDLU) epithelium was seen in association with columnar cell lesions as well as PASH. All core biopsies were performed for primary diagnoses, and none of the patients had received prior treatment. The Institutional Review Board approved the study. The original H&E slides were examined blindly and independently by three pathologists (MC, RR, DD). The histological criteria for the **epithelial component** of CCPLS include:

- The presence of one or two epithelial cell layers of crowded and overlapping cuboidal to tall columnar cells lining TDLU, often showing cystic dilatation.
- The nuclei were usually elongated and mildly enlarged in comparison to normal ductal cells.
- Snouts were present in the apical surface of the cell, resembling apocrine-type cytoplasmic protrusions.
- Granular amorphous basophilic material and calcifications were also noted.
- No distinction of simple changes, hyperplasia or atypia was made on the columnar cell lesions of CCPLS.

Stromal features of CCPLS

A dense collagenous tissue with complex anastomosing slit spaces lined by myofibroblasts with no nuclear atypia reminiscent of PASH stroma and thin wall vessels intimately associated with columnar cell lesions (**Figures 1**, **2**).

Immunohistochemistry

Immunohistochemical stains were performed on formalin-fixed paraffin-embedded 4-μm thick sections of tissue on the Benchmark XT (Ventana, Tucson, AZ). Briefly, heat-induced epitope retrieval (HIER) and antigen retrieval

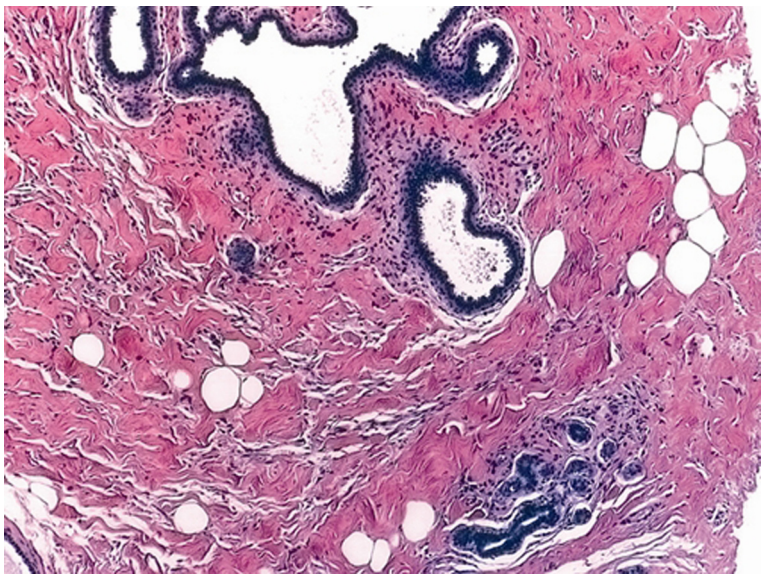

Figure 1. CCPLS lesion demonstrates intimate association of CCL and PASH-like stroma (H&E, 10×).

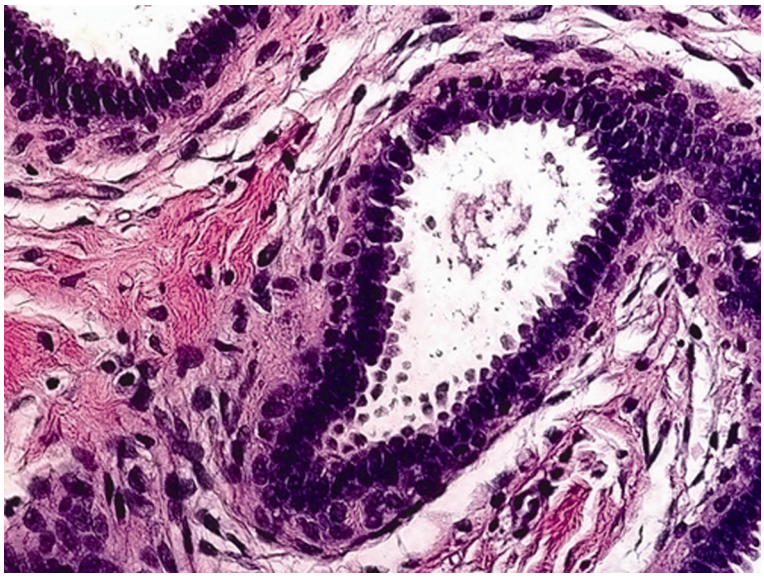

Figure 2. CCL showing apical snouts in columnar cells (H&E, 20×).

with 0.05 M tris-HCl buffer containing 0.1% Tween was performed prior to staining. Staining was performed using commercial primary antibodies c-kit, CD34, CD105, basic fibroblast growth factor [bFGF], androgen receptor [AR], estrogen receptor beta [ER-β], MIB-1 (**Table 1**) using 3,3'-diaminobenzidine as chromogen followed by enhancement with 1% copper sulfate in all immunohistochemical stains. Positive and negative controls were evaluated and found to be satisfactory.

The presence of cytoplasmic staining for CD34, c-kit, and bFGF was considered a positive reaction. The results were reported in a semiquantitative fashion as: *negative* (0) if <5% of the cells had cytoplasmic staining, *weakly positive* (1+) if 5 to 20% of the cells were stained, *moderately positive* (2+) if staining was present in 21 to 50% of the cells and *strongly positive* (3+) if >50% of the cells showed cytoplasmic staining. Similar semiquantitative criteria were utilized for the nuclear staining (AR, ER- β, and MIB-1).

CD105 was considered positive if cytoplasmic staining was present. CD105 was quantitatively addressed by counting the number of vessels in three separate 20 HPF areas in the ductal and stromal components of CCPLS and PASH core biopsies; a mean number of vessels were obtained.

All stains were analyzed by three pathologists (MC, RR, and DD).

Results

The semiquantitative immunohistochemical results are summarized in **Table 2**.

AR and ER-beta Six out of 8 cases (75%) of CCPLS and 4 out of 7 cases (57%) of PASH expressed AR. One case (*PASH #14*) lost area of interest in recuts. We observed concurrent staining of the epithelial and stromal component staining in most of the positive cases of CCPLS and PASH. ER-β was consistently positive in all CCPLS and PASH cases (100%), in both epithelial and stromal components (**Figure 3**).

bFGF showed consistent cytoplasmic positivity in the collagenized stroma of CCPLS and PASH. A "halo effect" (negative staining of stroma around ductal components) is seen in CCPLS (**Figure 4**).

CD34 showed positive cytoplasmic staining of the myofibroblastic lining of anastomosing channels of CCPLS and PASH stroma in all our cases (16/16; 100%). The epithelial components of CCPLS and PASH were negative (**Figure 5**).

MIB-1 showed higher expression in CCPLS (4/8, 50%) compared to PASH (2/8; 25%) (**Figure 6**).

CD117 (C-kit) was weakly positive in only one CCPLS case (*CCPLS #3*) (1/8; 13%). All PASH cases were negative for C-kit. Rare mast cells

Table 1. Summary of Immunohistochemistry Reagents

Antibody	Vendor	Clone	Dilution	Pretreatment	Detection	Staining Platform
CD117 (C-kit)	Dako	rabbit polyclonal	1:50	CC1 mild, pH 8.0; Ventana Medical Systems	Iview DAB, Ventana	BenchMark XT, Ventana
CD34	Dako	QBEnd10	1:50	CC1 mild, pH 8.0	Iview DAB	BenchMark XT
CD105	Dako	SN6h	1:50	Proteinase K, 5 min; Dako	Mouse Envision +; Dako	Dako Auto Stainer
bFGF	BioGenex	rabbit polyclonal	Predilute	no Pretreatment	Rabbit Envision +; Dako	Dako Auto Stainer
Androgen Receptor	Dako	AR441	1:60	Trilogy Steam 20 min; Cell Marque	Mouse Envision +	Dako Auto Stainer
ER-beta	BioGenex	rabbit polyclonal	1:50	TRS, pH 6.0 Steam 20 min; Dako	Rabbit Envision +	Dako Auto Stainer
Ki-67	Dako	MIB-1	1:100	CC1 standard, pH 8.0	Iview DAB	BenchMark XT

Ventana Medical Systems, Inc.; Tucson AZ Dako; Carpinteria, CA Cell Marque; Hot Springs, AR BioGenex; San Ramon, CA.

Table 2. Summary of immunohistochemistry results in both CCPLS and PASH core biopsies. CCPLS is composed of CCL in association of PLS. PASH core biopsies contained PASH stroma and TDLU

CASES	STROMA						DUCTS			
	CD34	**CD117**	**AR**	**ER-beta**	**bFGF**	**MIB-1**	**CD117**	**AR**	**ER-beta**	**MIB-1**
CCPLS 1	3+	0	2+	3+	3+	0	1+	3+	3+	1+
CCPLS 2	3+	0	2+	3+	2+	1+	2+	2+	3+	1+
CCPLS 3	3+	2+	2+	3+	3+	2+	1+	2+	3+	1+
CCPLS 4	3+	0	1+	3+	3+	0	1+	1+	3+	2+
CCPLS 5	3+	0	0	3+	3+	1+	1+	0	3+	2+
CCPLS 6	3+	0	3+	3+	2+	0	2+	3+	3+	0
CCPLS 7	3+	0	2+	3+	3+	2+	2+	3+	3+	2+
CCPLS 8	3+	0	2+	3+	3+	0	0	2+	3+	0
PASH 9	3+	0	0	3+	3+	0	2+	0	3+	1+
PASH 10	3+	0	1+	3+	3+	1+	3+	3+	2+	1+
PASH 11	3+	0	2+	3+	3+	0	3+	2+	3+	1+
PASH 12	2+	0	3+	3+	3+	0	2+	3+	3+	1+
PASH 13	3+	0	3+	3+	3+	1+	3+	3+	3+	2+
PASH 14	3+	0	n/a	3+	3+	0	3+	n/a	2+	1+
PASH 15	3+	0	3+	3+	3+	0	0	2+	3+	2+
PASH 16	2+	0	0	3+	3+	0	3+	0	3+	2+

n/a – not available for study

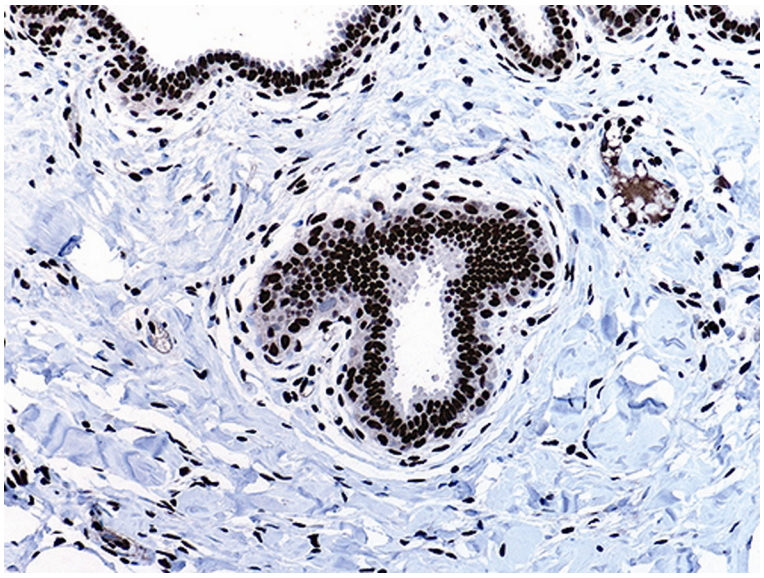

Figure 3. ER-beta was consistently positive in both the ductal and stromal components of CCPLS and PASH with strong nuclear positivity. AR was positive in a subset of cases (40×).

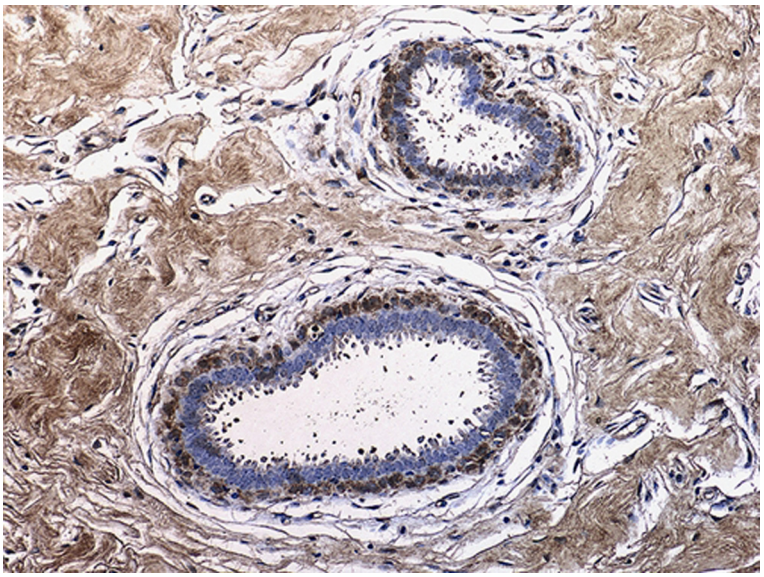

Figure 4. bFGF was positive in the collagenized stroma of PLS and PASH (20×).

were seen within the stroma of CCPLS and PASH. C-kit showed strong cytoplasmic positivity in 7 of 8 cases (88%) of normal TDLU. Columnar cell lesions showed c-kit expression ranging from negative to weak positivity in five of eight cases (5/8; 63%), (**Figure 7**).

CD105, an early angiogenesis marker, demonstrated significantly (**$p < 0.0001$**) more number of small vessels in CCPLS [mean number of vessels per 3 (20 HPF) = 25] in comparison to PASH [per 3 (20HPF) = 3] (**Tables 3, 4 and Figure 8**).

Discussion

The recognized hyperplasia-atypia-carcinoma spectrum of histologic changes within columnar cell lesions and its frequent presence adjacent

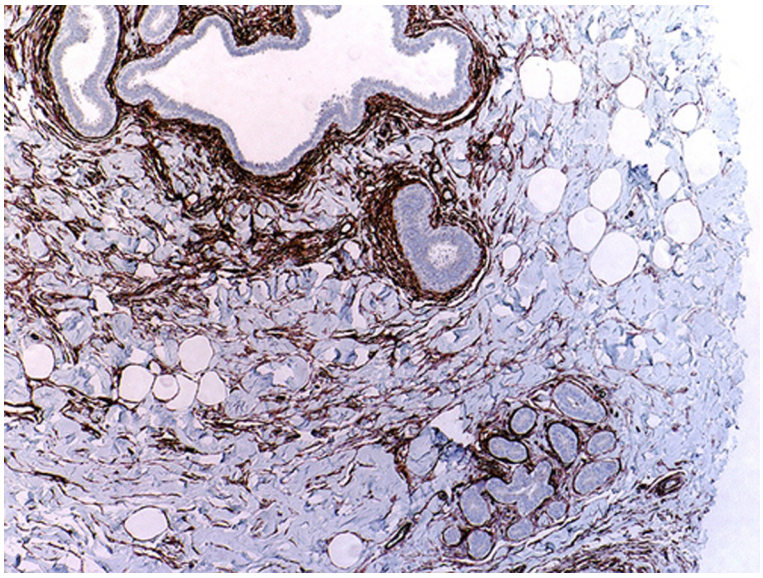

Figure 5. CD34 highlights PASH-like stroma (10×).

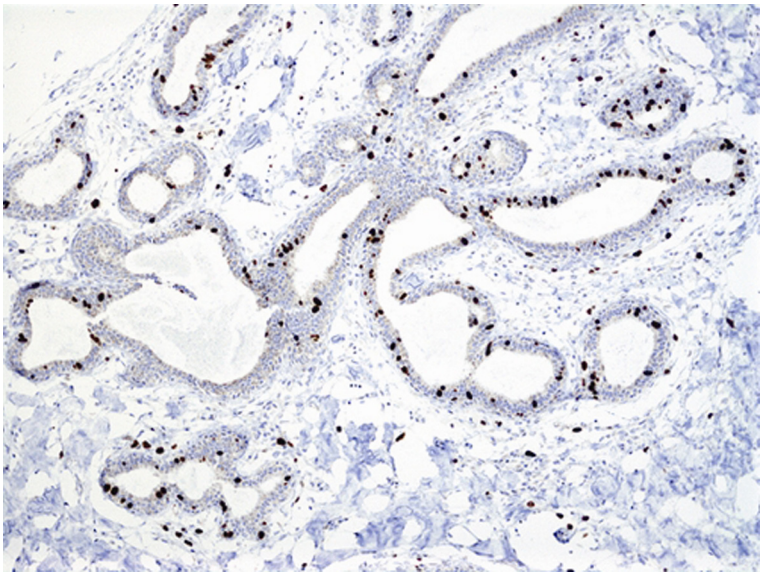

Figure 6. MIB-1 showed variably positivity in ductal components of both CCPLS and PASH, although the stromal component of CCPLS showed slight more positivity (20×).

to more severe lesions like tubular carcinoma implies an association of progression to atypia/carcinoma [1, 2]. Columnar cell lesions with atypia (flat epithelial atypia, atypical ductal hyperplasia) are considered a "step behind" in the progression to ductal carcinoma in situ (DCIS). Molecular studies have corroborated that columnar cell lesions share similar genetic alterations as invasive breast carcinomas, such as LOH (loss of heterozygosity) at 11q21-23.2, 16q23.1-24.2 and 3p14.2 [4]. Dabbs et al demonstrated allelic loss damage in columnar cell change, with preferentially targeted loci at 9q, 10q, 17p, and 17q, consistent with the hypothesis that a select group of atypical columnar cell lesions are very early precursors to invasive breast carcinoma [1]. Columnar cell lesions should therefore be considered *clonal and neoplastic* rather than a hyperplastic proliferation [1, 3, 4].

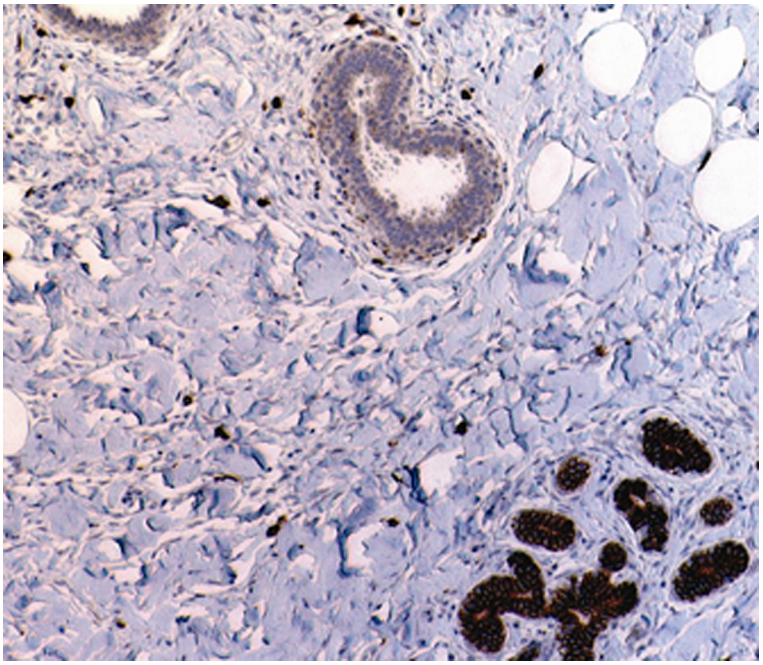

Figure 7. C-kit shows strong staining of normal TDLU in comparison to the negative staining of CCL lesion. Some spindle myofibroblasts of the PASH-like stroma show immunoreactivity (10X).

Table 3. Mean number of blood vessels around the ductal components (CCL of CCPLS; TDLU present in PASH biopsies) counted in three separate areas at 20HPF

CASES		CD105 DUCTS		# vessels/3 (20HPF)	Mean
CCPLS 1	30	3	8	41	14
CCPLS 2	7	7	17	31	10
CCPLS 3	11	25	14	50	17
CCPLS 4	30	30	23	83	28
CCPLS 5	53	32	28	113	38
CCPLS 6	40	27	28	95	32
CCPLS 7	45	50	36	131	44
CCPLS 8	15	28	15	58	19
				MEAN	25.25
PASH 9	12	10	6	28	9
PASH 10	7	3	5	15	5
PASH 11	0	4	4	8	3
PASH 12	3	3	6	12	4
PASH 13	12	12	12	36	12
PASH 14	5	4	6	15	5
PASH 15	5	11	12	28	9
PASH 16	4	7	5	16	5
				MEAN	6.5

Table 4. Mean number of blood vessels within stromal component (PLS of CCPLS biopsies; PASH biopsies) counted in three separate areas at 20HPF

CASES	CD105 STROMA			# vessels/3 (20HPF)	Mean
CCPLS 1	6	4	8	18	6
CCPLS 2	16	7	9	32	11
CCPLS 3	9	7	7	23	8
CCPLS 4	21	15	10	46	15
CCPLS 5	14	10	22	46	15
CCPLS 6	12	10	15	37	12
CCPLS 7	25	15	20	60	20
CCPLS 8	6	6	6	18	6
				MEAN	**11.625**
PASH 9	6	2	0	8	3
PASH 10	4	1	3	8	3
PASH 11	2	2	1	5	2
PASH 12	4	3	1	8	3
PASH 13	7	5	3	15	5
PASH 14	5	3	5	13	4
PASH 15	5	3	6	14	5
PASH 16	1	2	2	5	2
				MEAN	**3.375**

PASH is considered to be “benign” or “hamartomatous” by some [10-12], and neoplastic process by others due to its frequency of presentation, multifocality, and its potential to recur [13, 14].

Stromal microenvironment is necessary for normal mammary tissue development and breast cancer tumorigenesis. This is shown most strikingly in orthotopic transplants of normal human mammary epithelial cells (MEC) into the mouse mammary fat pad. Human MEC fail to develop into normal mammary structures when injected into mouse mammary fat pads. However, the presence of human stromal cells created an environment permissive for normal ductal development and function [7, 8, 15]. Similar epithelial-stromal interaction influenced by some hormonal and angiogenic factors were observed by our group in CCPLS, further demonstrated by immunohistochemical stains.

Our CCPLS and PASH cases expressed AR, ER-beta and PR; therefore we raise the possibility that these proliferating ducts have the capacity to induce hormones in the surrounding stroma as well. Investigations on embryonic mouse mammary epithelium rudiments demonstrate their capacity to induce AR in the adjacent stroma, which is normally AR negative. Thus, as the breast tissue differentiates the mammary ducts are surrounded by AR positive stroma, as seen in our cases as well [16] (**Figure 4**).

Angiogenesis is an important component of tumorigenesis. CD105 (endoglin) is a 95 kD cell surface protein that functions as an endothelial marker and an accessory receptor for TGF-β [17-19]. CD105 is expressed in endothelial cells, activated monocytes, differentiated macrophages and fibroblasts among other cells.It has been found to be up-regulated in tumor endothelial cells of breast and shown to be a useful marker of neoangiogenesis in this neoplasm [17, 19]. Studies have demonstrated that hypoxia, which is a common feature of proliferative lesions as tumors, is a potent stimulator of CD105 gene expression in vascular endothelial cells, and this effect can be potentiated by the presence of TGF-β. Expression of CD105 in these tumors correlates with vascular density and, most importantly, poor prognosis [5]. In our cases, CD105 staining demonstrated significantly increased numbers of small-activated

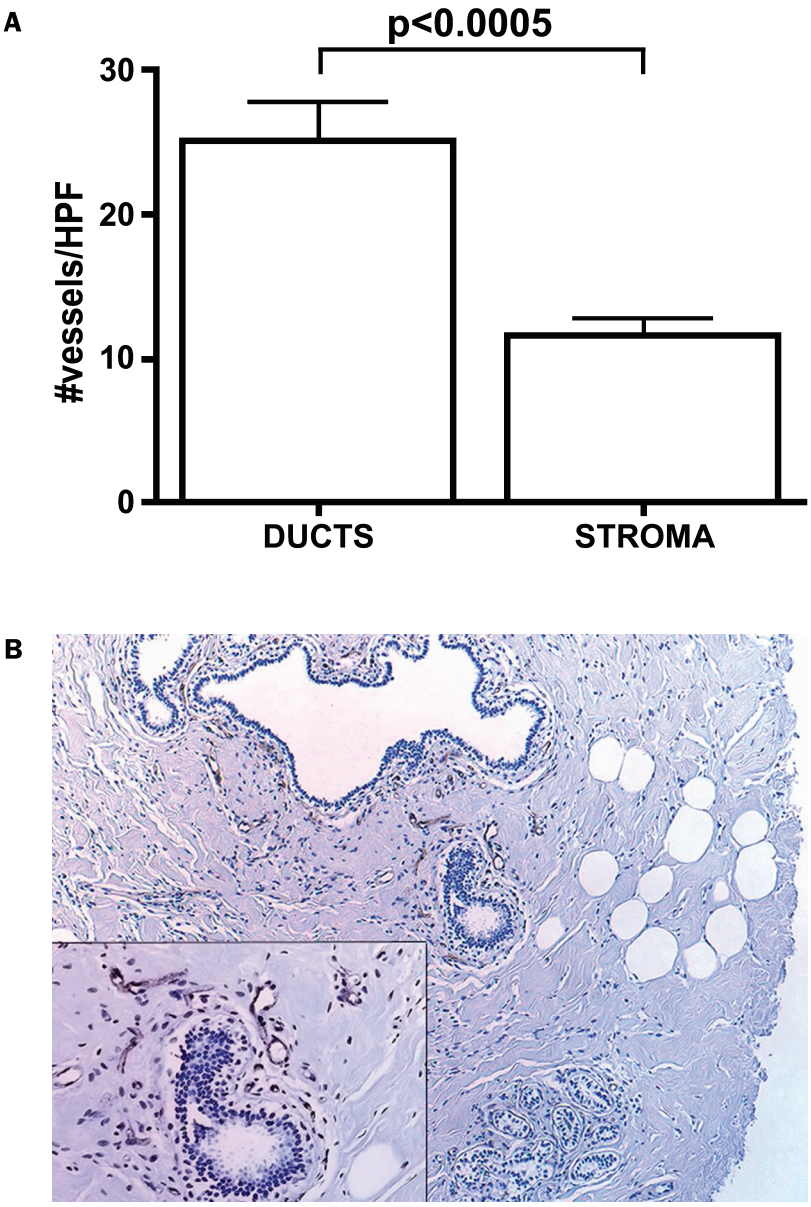

Figure 8. a: Comparison of CD105 (+) blood vessel numbers in both ductal and stromal components of CCPLS and PASH core biopsies. b: CD105 (20×) staining blood vessels around CCL (inset, 40×). Compare to decrease staining of TDLU (right bottom, arrow head).

vessels in CCPLS. In contrast, TDLU and PASH show a lesser number of vessels. Through these observations we question if columnar cell epithelium is responsible for angiogenesis within the stroma of CCPLS, in turn a demonstration of epithelial-stromal interaction (**Figure 9**). Many of our CCPLS cases were Magnetic Resonance Imaging (MRI) guided core biopsies. Since this is a modality that detects vascular aberrations in the breast, it further supports our observations of angiogenesis associated with these lesions.

A strong expression of bFGF in CCPLS is also indicative of the vascular nature of these lesions. bFGF is a fibroblastic marker, demonstrated by expression in our PASH cases. The lack of immunostaining for bFGF in the stroma immediately surrounding breast epithelium suggests that this epithelium modulates the function of the stroma cells, dampening their bFGF production, which we described histologically as "halo effect". This may represent an important endogenous mechanism of tumor suppression. The

lack of bFGF in the immediate vicinity of potentially malignant epithelium may inhibit the angiogenesis necessary for the survival of these tumors (**Figure 5**).

CD34, a marker of hematopoietic progenitor cells in the bone marrow, stains a variety of tissues [20-22]. CD34 highlighted the myofibroblastic differentiation in CCPLS cases. MIB-1 was variably positive, and we agree with other studies that columnar cell lesions do not display high proliferation [23], although CCPLS stroma can be slightly more proliferative than the normal TDLU (**Figures 6 and 7**).

C-kit (CD117) is a receptor-tyrosine kinase that is structurally similar to platelet derived growth factor and colony stimulating growth factor-1 [24]. C-kit signaling promotes cell survival, cell differentiation, adhesion and chemotaxis [24, 25]. Expression of c-kit has been reported in both normal and neoplastic breast epithelium, and the results are quite variable. In most studies c-kit expression in breast carcinomas is shown in less than 20% of cases [25], although the range is vast (1%-82% of cases) [24], attributed to different methodologies for its detection. Loss of c-kit expression has been associated with increased numbers of lymph nodes involved by metastatic carcinoma, suggesting prognostic implications for this marker in breast carcinomas [24]. Only one case of CCPLS demonstrated weak positivity for this marker in the stroma. We observed a reduced expression of c-kit in columnar cell lesions in comparison to stronger expression in TDLU. To our knowledge, our study is the first to report c-kit expression in columnar cell lesions. Our observations might represent a downregulation of c-kit protein expression corresponding with the "early precursor" nature of these lesions. Definitively, c-kit is of interest and future studies are needed to confirm its prognostic implications and possible therapeutic effects in these aggressive neoplasms (**Figure 8**).

In conclusion, we have verified the presence of an epithelial-stromal interaction in CCPLS. The presence of hormonal and angiogenic factors in our cases of CCPLS is a good example of demonstration of epithelial-stromal interactions. Future studies with larger number of cases are needed to evaluate the significance of these factors and possible prognostic and therapeutic implications. The decreased expression of c-kit in columnar cell lesions is an interesting finding in our study, which needs to be further evaluated. Due to the small number of cases in our study no meaningful statistical analysis could be obtained. Though our study does not reflect a diagnostic utility, it emphasizes an observation of epithelial-stromal interaction in early preneoplastic lesions of the breast.

Acknowledgments

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