Pseudoangiomatous stromal hyperplasia: An observation on its microscopic involvement in breast carcinoma and the presence of lymph node metastases

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Abstract. The spaces of pseudoangiomatous stromal hyperplasia (PASH) are postulated to be important in the intramammary spread of breast carcinoma. The present study aimed to note the prevalence of inconspicuous, microscopic foci of PASH (identified as CD34+ve, CD31-ve and D2-40-ve spaces containing tumour emboli) involved in breast carcinoma and to establish the significance of its relationship to lymph node metastases. A total of 80 cases of breast carcinoma were examined for microscopic foci of PASH permeated by carcinoma and, of the four cases found to demonstrate such involvement, three had lymph node metastases.

Introduction

In order to determine whether microscopic involvement of pseudoangiomatous stromal hyperplasia (PASH) by breast cancer is associated with lymph node metastases, 80 cases of breast carcinoma in different categories were examined for microscopic foci of PASH. Of the 80 cases, 4 contained microscopic foci of PASH permeated by carcinoma. The results support the premise that PASH is an underestimated pathway of tumour spread.

Materials and methods

A total of 80 cases of infiltrating breast carcinoma in four different categories were examined. The materials used in this study were archived consecutive cases (mastectomy or wide local excisions) obtained from the files of the Department of Pathology at the University Hospital of South Manchester and were selected based on histological type, with and without nodal involvement. Carcinomas with vascular invasion were excluded. The categories included 10 grade 2 infiltrating ductal carcinomas with lymph node metastases, 10 grade 2 without lymph node metastases, 10 grade 3 infiltrating ductal carcinomas with lymph node metastases and 10 grade 3 carcinomas without lymph node metastases, respectively. In addition, four groups of infiltrating lobular carcinoma grades 2 and 3, with and without lymph node metastases were examined. All of the slides from the cases were reviewed. Any cases showing evidence of vascular invasion were excluded and a block from each case was randomly selected for immunohistochemistry. The sections were stained with CD34 (Novocastra) and smooth muscle actin (Sigma) to confirm or negate the presence of PASH with involvement by carcinoma (Figs. 1 and 2). A total of 4 cases with foci showing such involvement were additionally stained with antibodies to podoplanin (AngioBio), D2-40 (Zymed) and CD31.

Results

Of the 80 cases, 4 (2 grade 2 and 2 grade 3 infiltrating ductal carcinomas) contained microscopic foci of PASH measuring up to one high-power field, confirmed immunohistochemically, which was permeated by carcinoma. None of the cases displayed foci of vascular invasion. The 4 cases were also stained with antibodies to podoplanin (AngioBio), D2-40 (Zymed) and CD31 (Dako), and the CD34+ve spaces were unstained with these lymphatic and vascular markers. Lymph node involvement was noted in 3 of the 4 cases (Table I).

Discussion

Pseudoangiomatous stromal hyperplasia consists of slit-like anastomosing spaces lined by flattened elongated myofibroblasts with small nuclei and scanty cytoplasm. The spaces are separated by hyalinised connective tissue, and the cells are negative for vascular endothelial markers, including factor VIII and CD31, and for the lymphatic endothelial marker D2-40, but are positive for CD34 and smooth muscle actin (1,2). Vuitch *et al* described PASH as a form of stromal hyperplasia considered to be the result of artefactual disruption and separation of collagen fibres with resulting open inter-anastomosing spaces (3). Findings by Hartveit showed that the ultrastructure of attenuated lymphatic

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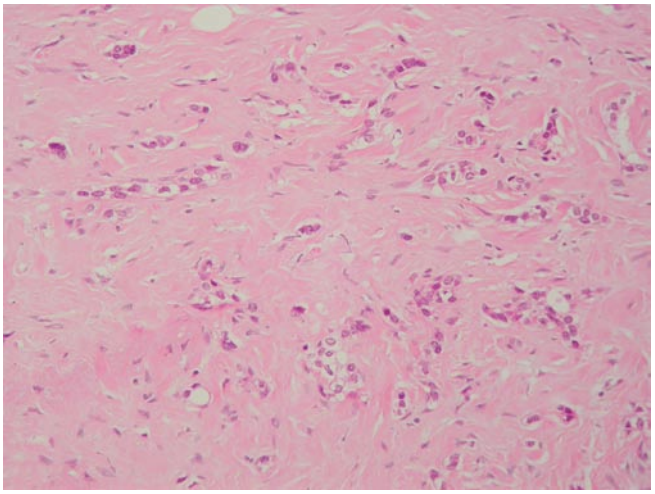

Figure 1. A barely conspicuous microscopic focus of pseudoangiomatous stromal hyperplasia involved by invasive carcinoma (H&E).

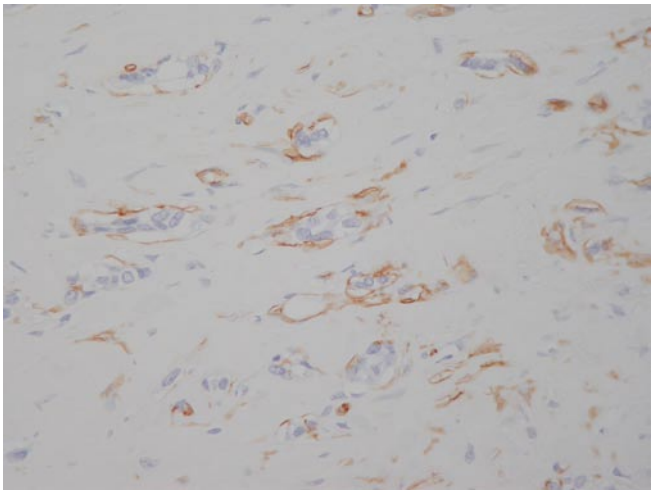

Figure 2. The same focus of invasive carcinoma within the microscopic spaces of pseudoangiomatous stromal hyperplasia highlighted by CD34 immunohistochemistry.

Table I. Pseudoangiomatous stromal hyperplasia; an observation on its presence in breast carcinoma and lymph node metastases.

Case no.	Age (years)	Carcinoma	Size (mm)	Vascular invasion	Nodes
1	64	Infiltrating ductal grade 2	18	Not found	1 of 13
2	56	Infiltrating ductal grade 3	15	Not found	4 of 15
3	72	Infiltrating ductal grade 3	25	Not found	1 of 24
4	59	Infiltrating ductal grade 2	10	Not found	0 of 17

endothelial cells form sheets rather than vessels within the breast stroma and that these potential spaces form the missing lymphatic system of the breast, the lymphatic labyrinth (4,5). Fisher *et al* concluded that PASH and this lymphatic labyrinth (spaces ultrastructurally lined by slender cells with tapering cytoplasmic processes that are either fibroblasts or lymphatic endothelial cells) are related structures (6). Recently, Asioli *et al*, in a three-dimensional study of two cases of normal breast tissue and one case of PASH, demonstrated direct anastomoses between pre-lymphatic channels and true lymphatics of the breast (2).

The missing lymphatic labyrinth described by Hartveit is now considered to be the normal counterpoint of the spaces that constitute pseudoangiomatous hyperplasia (7). Due to the fact that these channels communicate between breast epithelial/stromal structures and the main lymphatic system, it is also suggested that these pre-lymphatics should be considered in the intramammary spread of tumours, a suggestion previously posited by Damiani *et al* (1). These authors' observations, although not statistically valid, are supportive of this premise.

Axillary lymph node involvement is a powerful prognostic indicator (7). Undetected or unsampled lymphatic involvement in these 4 cases cannot be excluded, while the correlation of two findings does not necessarily establish a cause and effect relationship. However, the involvement of PASH may be a marker of such involvement, given the results of this study and the findings of Damiani *et al* (1) and Asioli *et al* (2). Furthermore, we cannot exclude such undetected or unsampled lymphatic involvement in other cases with lymph node metastases, but without vascular involvement and the absence of PASH foci. A recent study using antibodies to D2-40, podoplanin and Prox-1 concluded that lymphangiogenesis does not occur in breast cancer (8). Three additional studies documented the correlation between prominent separation/retraction artefact in breast cancer and lymph node metastases (10-12). One of these studies suggested that separation artefact may be early 'lymphovasculogenesis' prior to the mesenchymal cell being converted to the endothelial cell (10). An additional study postulates that retraction spaces are likely related to altered tumour-stromal interactions and are possibly an early stage of lymphatic tumour spread (12).

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