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In situ lobular neoplasia of the breast with marked myoepithelial proliferation

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Running Title: In situ lobular/ myoepithelial proliferation

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Abstract

Aims: To present four new cases of in situ lobular neoplasia associated with marked proliferation of myoepithelial cells

Methods and Results: Four recently seen cases showing extensive foci of in situ lobular neoplasia, as confirmed by negative E-Cadherin staining, were stained for myoepithelial cells using CD10, smooth muscle actin and cytokeratin 5/6. Invasive lobular carcinoma was also present in two cases, one case was associated with multiple foci of collagenous spherulosis and one was associated with a radial scar. Marked myoepithelial proliferation was seen around most of the in situ lobular foci or mingled with lobular cells.

Conclusions: Marked proliferation of myoepithelial cells is sometimes encountered in association with extensive in situ lobular neoplasia. It is suggested that this proliferation might have a role in maintaining the in situ status of these lesions or, alternatively, that there is a shared factor responsible for the simultaneous proliferation of certain 'lobular' cell types and myoepithelial cells.

Introduction

We previously reported a case of mixed in situ lobular/ myoepithelial **proliferation** that developed in a 31 year old woman (1). No similar cases were reported before that, but a report with three cases was later published showing some of the features encountered in our case (2). We here present four further cases that we have seen recently with features similar to those previously reported, but with each developing in a different background. **Two were associated with foci of invasive lobular carcinoma, one with extensive foci of lobular carcinoma in situ and collagenous spherulosis, and one present in a radial scar.**

Case Reports

Case 1

A 64-year old woman presented with an ill-defined mass in the upper outer quadrant of the right breast that was thought clinically to be malignant. A core biopsy confirmed the presence of invasive carcinoma. Wide local excision and sentinel lymph node biopsy were carried out.

The excision biopsy had multiple well defined relatively large foci of in situ lobular neoplasia with adjacent smaller foci of invasive carcinoma. The invasive elements were composed of lobular type neoplastic rounded cells with uniform rounded nuclei, arranged in alveolar pattern.

E-cadherin staining was negative in the invasive tumour cells. The in situ tumour cells were mostly E-cadherin negative, but some foci also included groups of E-cadherin positive cells. These cells proved to be positive for the myoepithelial markers CD10, SMA (Fig 1) and cytokeratin 5/6.

Case 2

A 53-year-old woman had indeterminate calcification detected in her right breast on mammographic screening. A core biopsy showed widespread foci of in situ lobular neoplasia, some associated with fine microcalcification. Fibrocystic and columnar cell changes were also present. A wire guided excision biopsy was carried out.

The specimen excised weighed 25g and consisted of fibrofatty tissue with no defined lesions. Microscopic examination showed extensive foci of in situ lobular neoplasia, some associated with microcalcification. Foci of in situ lobular/ myoepithelial

proliferation, similar to those previously described (1), were also present. These consisted of well defined solid structures composed of two separate populations one being neoplastic lobular (E-cadherin negative, CD10 negative, cytokeratin 5/6 and 14 negative, smooth muscle actin negative, and cytokeratin 8/18 and ER positive), and the other is myoepithelial (positive for E-cadherin, CD10, cytokeratin 5/6, 14 and 8/18 and smooth muscle actin, and negative or weakly positive for ER). Some of these foci exhibited an appearance like that seen in collagenous spherulosis, where the proliferating cells had cribriform gaps some containing an amorphous eosinophilic material (Fig 2), and gave positive staining for laminin. There were also foci of pure myoepithelial cell proliferation.

Case 3

A 58-year old woman with a past history of left breast invasive ductal carcinoma, developed microcalcification of the right breast for which she had a core biopsy-. Features suggestive of a radial scar in the form of fibroelastosis associated with epithelial hyperplasia and cysts were detected and a wire guided excision biopsy was carried out.

The excision biopsy showed foci of columnar cell change, flat epithelial atypia, apocrine cysts, in situ lobular neoplasia as well as foci of solid proliferation of cells that on immunohistochemistry proved to be a mixture of lobular (E-cadherin, CD10 and SMA negative) and myoepithelial cells (E-cadherin, SMA, CK 5 and CD10 positive) (Fig 3). No invasive carcinoma was present.

Case 4

A 62-year old woman presented with 2 lumps in the left breast. Core biopsies showed that both lumps were grade 2 invasive lobular carcinomas, classical type, associated with multiple foci of in situ lobular neoplasia. Mastectomy was carried out and confirmed the presence of 3 foci of invasive lobular carcinoma 32, 17 and 8 mm in maximum dimension respectively. All were associated with extensive foci of in situ lobular neoplasia, many showing marked proliferation of CD10, SMA and cytokeratin 5 positive myoepithelial cells (Fig 4).

Discussion

The cases presented here highlight the previously reported observation of the presence of marked proliferation of myoepithelial/ basal cells in some cases of in situ lobular neoplasia (1). It is interesting to note that in 1983 Azzopardi mentioned that association, in passing, in one of his articles, noting that myoepithelial cells persist around foci of LCIS more frequently than around DCIS, and that in some cases myoepithelial cells increase in number and intermingle with the neoplastic lobular cells (3). We suspect that this association is more common than is thought, and may include at least some of the cases reported as mixed ductal/ lobular in situ carcinoma (4-8).

The additional presence of foci of collagenous spherulosis in one of the cases is in agreement with studies demonstrating a high incidence of that condition in association with lobular carcinoma in situ (9,10), although the proportion of cases of lobular neoplasia with associated collagenous spherulosis has been recently reported to be low (11). Collagenous spherulosis has also been described in association with an adenocarcinoma (12). The associated presence of columnar cell change and flat epithelial atypia in another case is also consistent with the presence of a relationship between these lesions and in situ lobular neoplasia (13,14). We have never seen this marked proliferation of myoepithelial cells in association with DCIS or usual type or atypical ductal hyperplasia. Although the cells are best demonstrated with CD10, they also show similar positivity with other myoepithelial markers like smooth muscle actin, S100 and cytokeratins 5/6, cytokeratin 5 and 14 (1). **The positive staining with all these markers, particularly with SMA, would exclude the possibility that the lesions represent lobular neoplasia involving foci of florid usual type epithelial hyperplasia.** However, as these markers can also be positive in 'epithelial basal' cells ; the proliferation mentioned in this article may best be labeled as 'myoepithelial/ basal' to include that possibility. **On the other hand, in florid usual type ductal hyperplasia, CD10 produces a mosaic pattern, similar to that obtained with markers like CK5, but no 'lobular' E-Cadherin negative cells are present.**

The phenomenon is probably worth investigating in a large series of cases of in situ lobular neoplasia to assess its real incidence and significance. In particular, molecular studies may be useful in finding out whether the proliferating myoepithelial/ basal cells are neoplastic or reactive in nature. Also, it would be interesting to try to find out whether

the proliferating cells play a role in maintaining the in situ status of these foci, whether or not there are factors produced by certain 'lobular' cells that stimulate the proliferation of myoepithelial cells, or the other way round; or, alternatively, there is a shared factor that is responsible for the simultaneous proliferation of certain 'lobular' cell types and myoepithelial/ basal cells.

Acknowledgment

Case 1 was referred to me by Dr S Gharaie, Kingston Hospital, Surrey, UK.

For Peer Review

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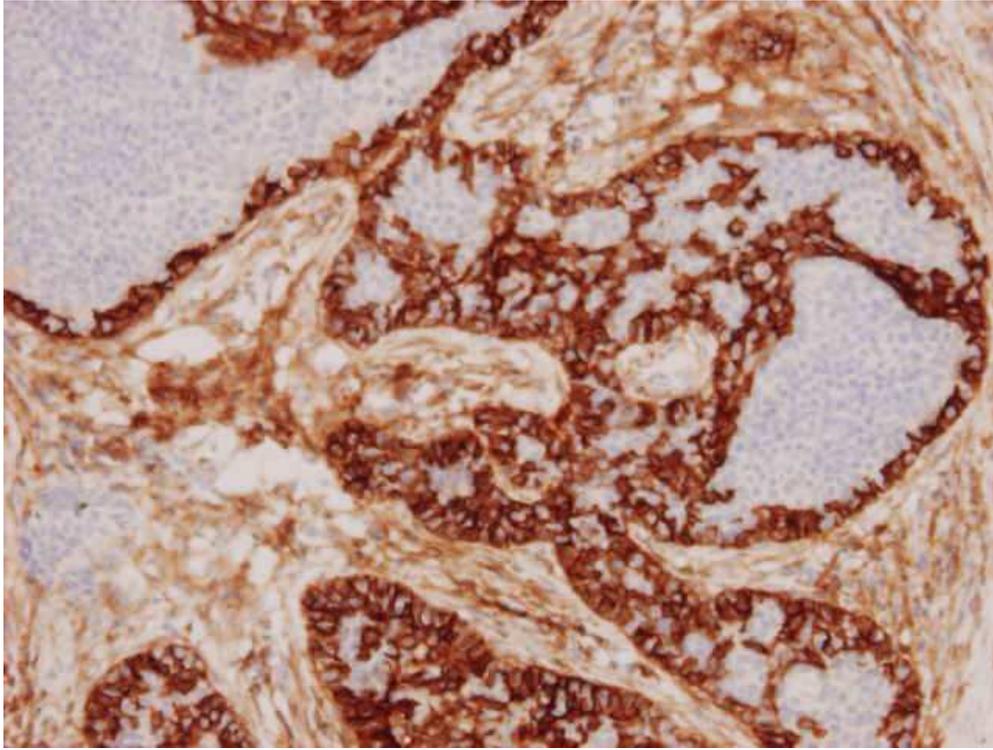
Legends to Figures

Fig 1: Case 1: Foci of in situ lobular neoplasia (unstained) surrounded and mingled with extensive proliferation of myoepithelial/ basal cells which show strong positive brown staining for CD10 (immunoperoxidase)

Fig 2: Case 2: (a) Foci of collagenous spherulosis stained with H & E. (b) Marked proliferation of CD10 positive myoepithelial/ basal cells associated with the spherulosis cavities, with abundant (unstained) in situ lobular cells present at the periphery of the focus (immunoperoxidase).

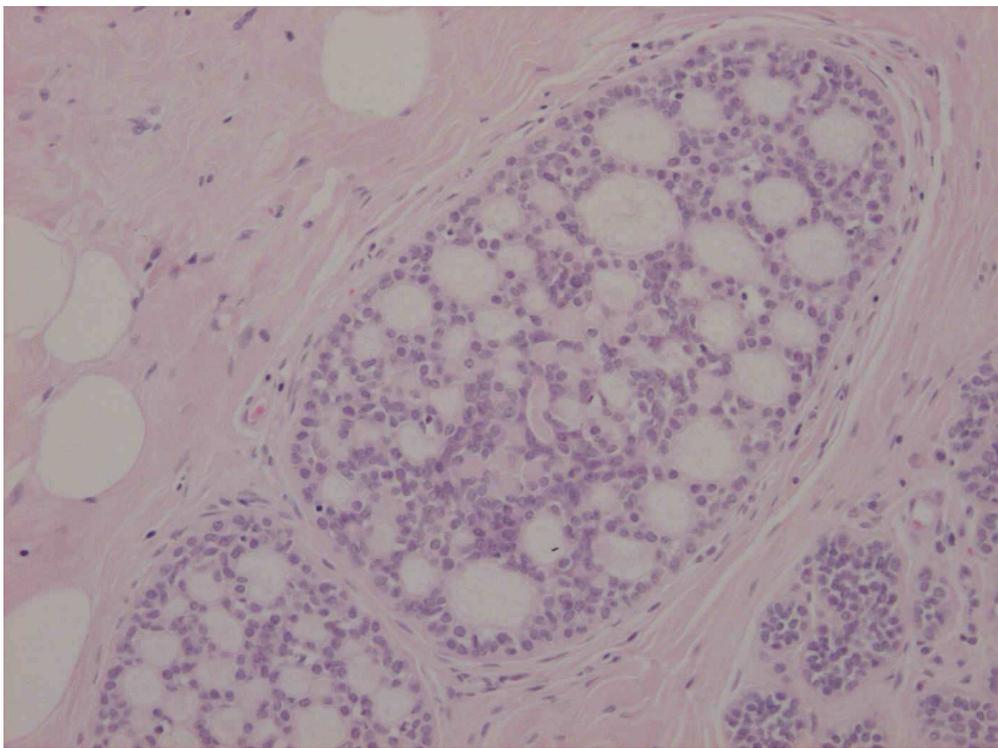
Fig 3: Case 3: (a): H & E stained foci of in situ lobular neoplasia intermingled with myoepithelial/ basal cells, seen at the periphery of a radial scar. The same foci stained for E-Cadherin (b), SMA (c) and CK5 (d) showing negative in situ lobular cells mingled with positive myoepithelial/ basal cells (immunoperoxidase).

Fig 4: Case 4: foci of (unstained) in situ lobular neoplasia associated with marked, mostly central, proliferation of CD10 (a) and CK5 (b) positive myoepithelial/ basal cells (immunoperoxidase).



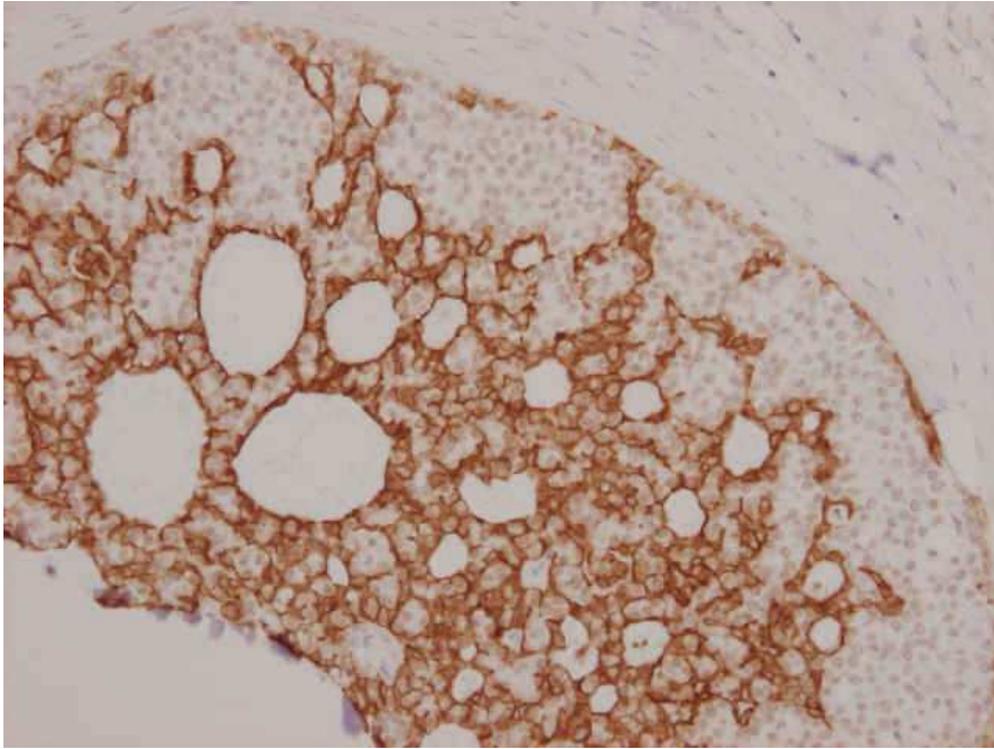
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Review



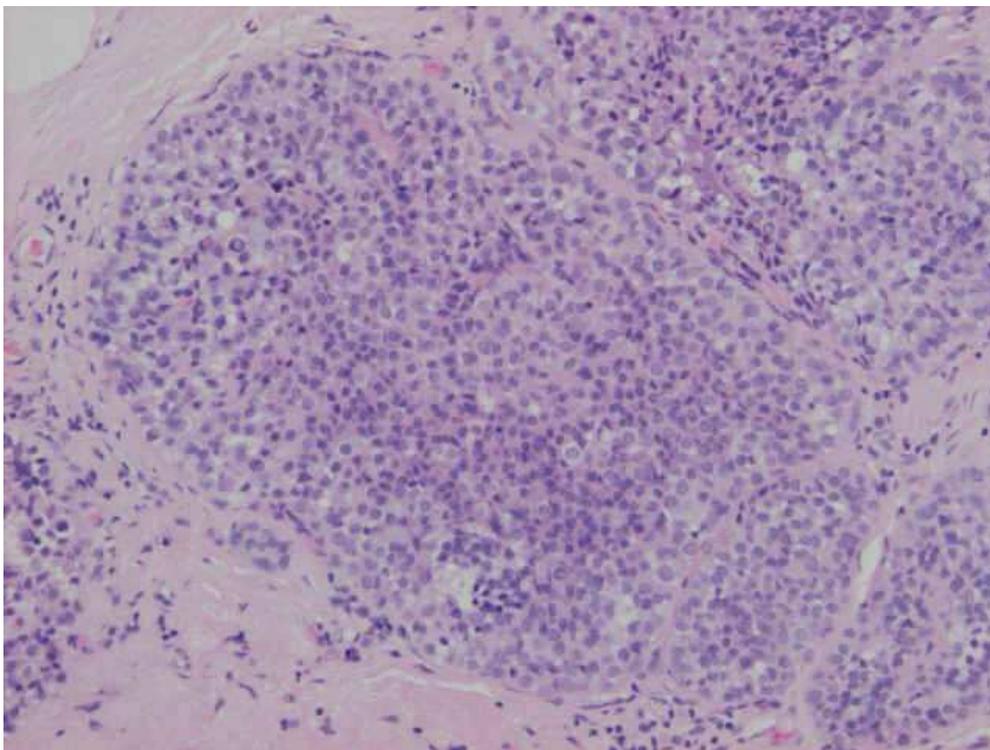
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Review



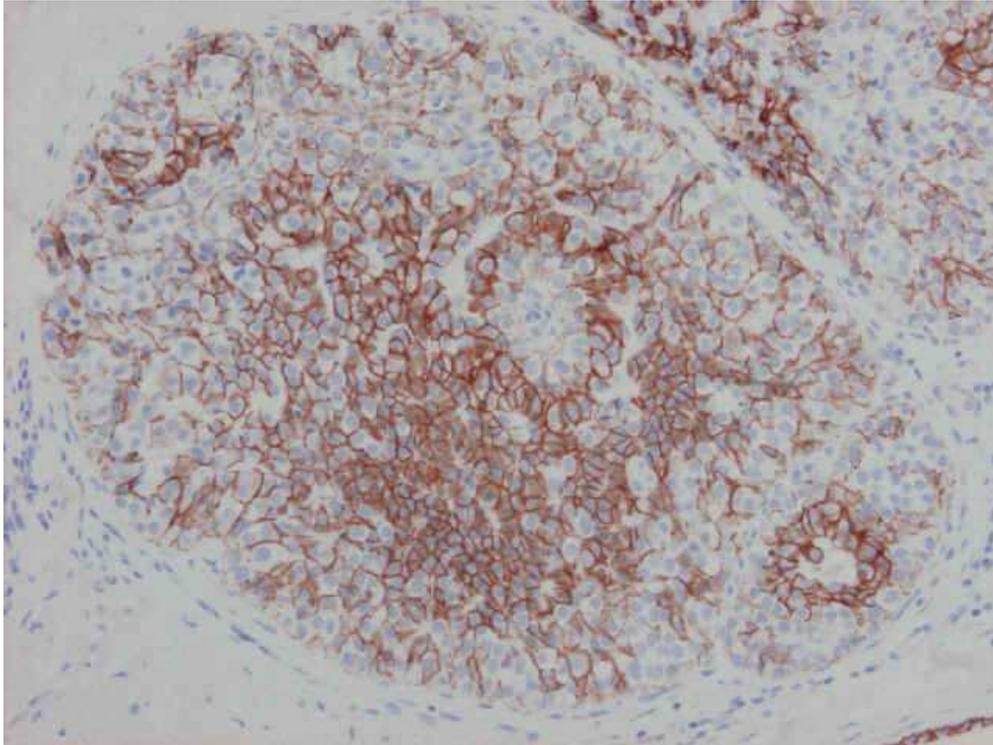
Case 2, CD10
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Review



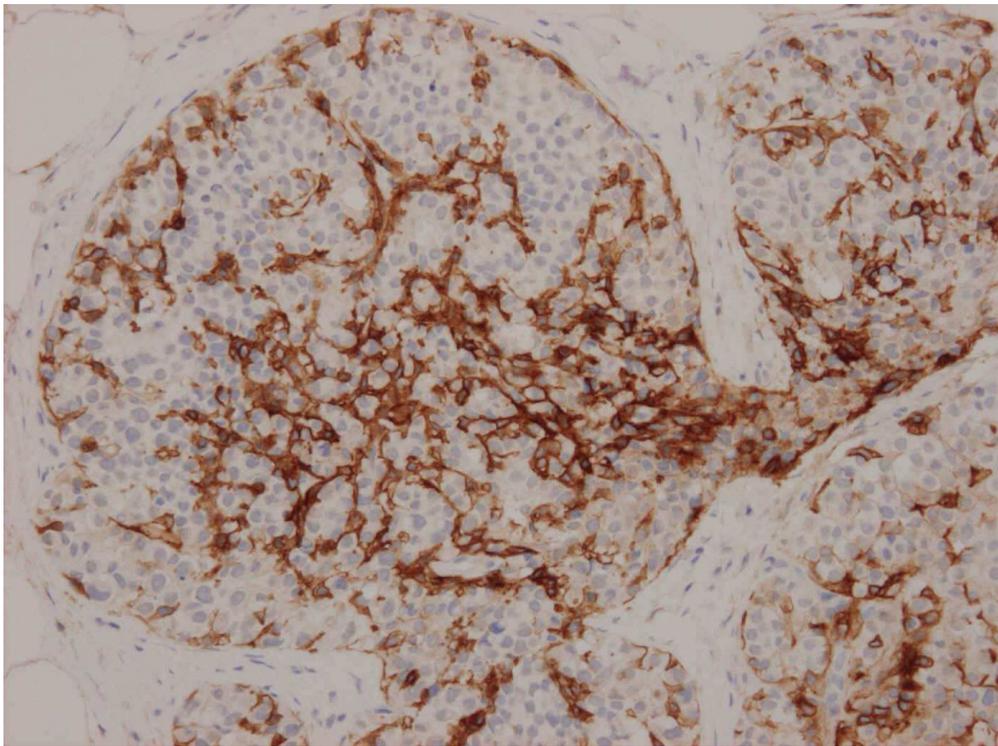
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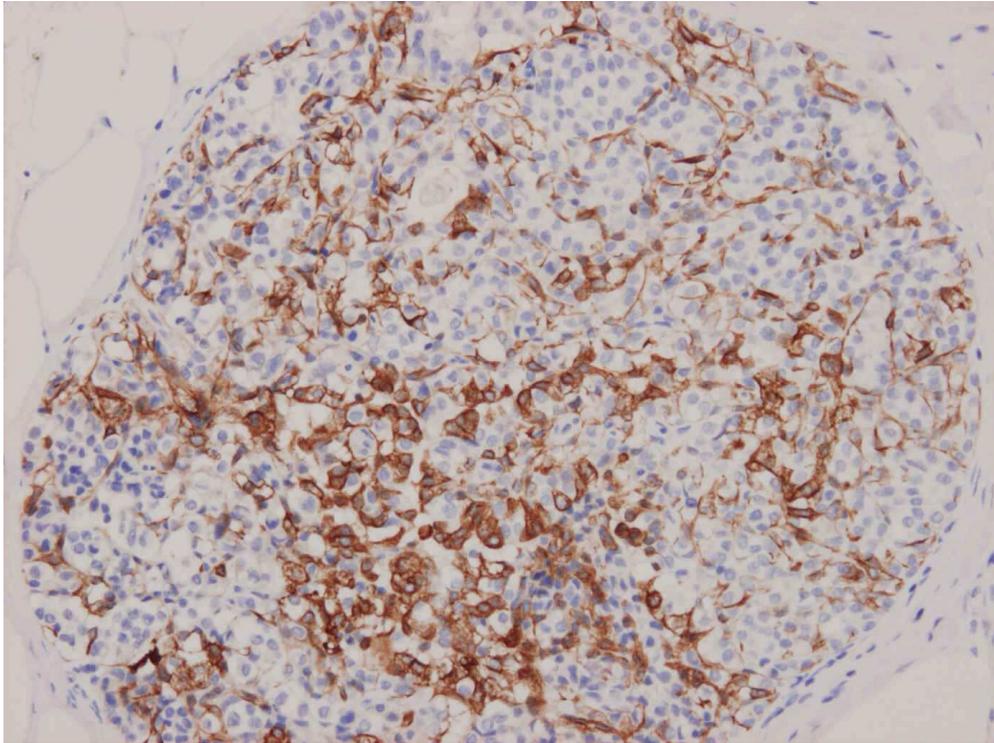
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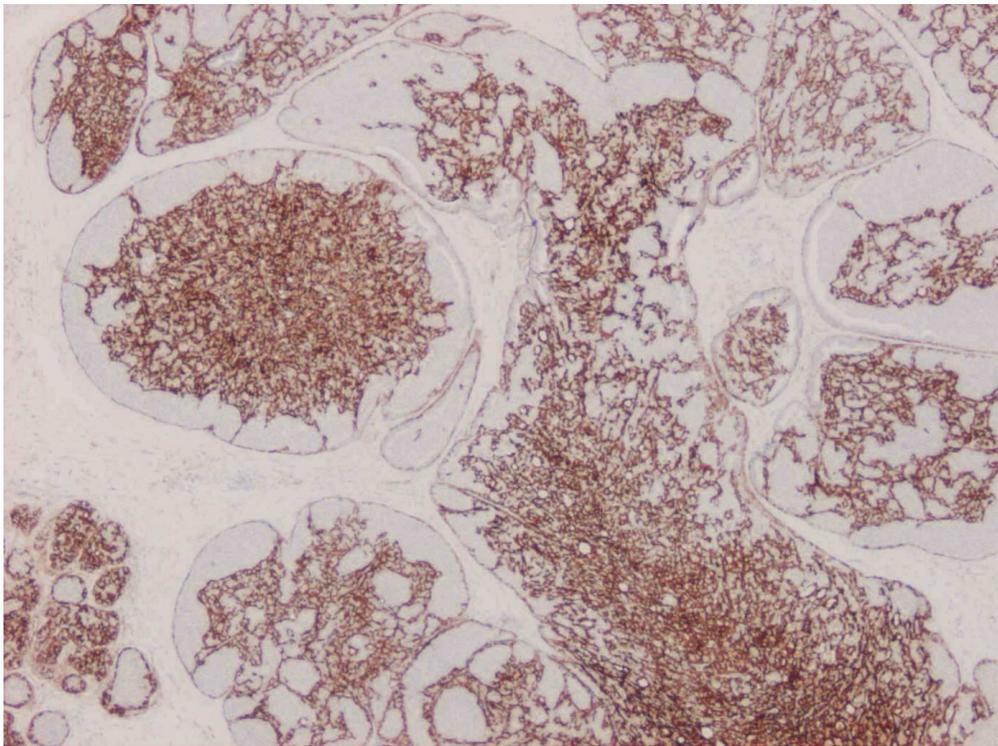
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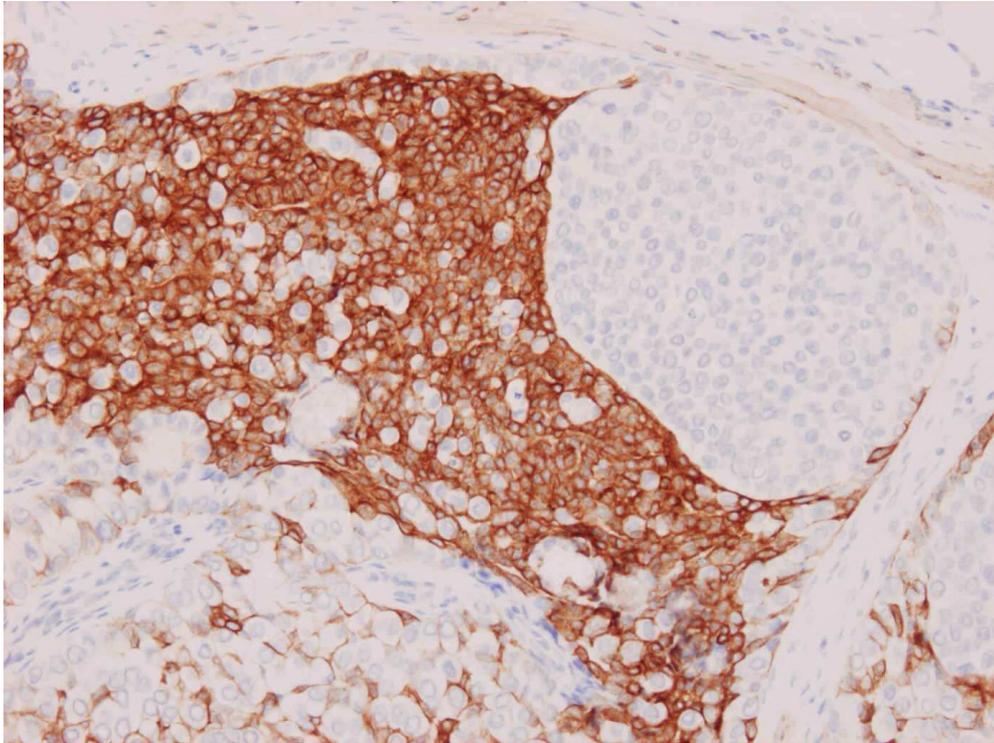
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