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Secretory breast carcinoma: a clinicopathological and immunophenotypic study of 15 cases with a review of the literature

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Secretory breast carcinoma is a rare breast cancer with indolent clinical behavior. Recent research showed that secretory breast carcinoma belongs to the phenotypic spectrum of basal-like breast carcinomas. In this study, a clinicopathological and immunophenotypic analysis of secretory breast carcinomas from 15 Chinese patients was conducted. This patient group consisted of 2 males and 13 females, with ages ranging from 10 to 67 years old (median, 36 years old). All patients presented with a painless and firm mass. Tumor size ranged from 10 to 55 mm. Most tumors were located in the outer upper quadrant of the breast. Two patients (2 of 13, 15%) displayed positive axillary lymph nodes. At the microscopic level, the presence of intracellular and extracellular secretory material was the most remarkable feature. Most cases showed mild dysplasia cytologically. All cases were negative for estrogen receptor, progesterone receptor and HER2. The expression rate of the basal-like marker (CK5/6 or epidermal growth factor receptor) was 87% (13 of 15). The basal-like phenotype was identified in 13 cases (87%). Follow-up time ranged from 10 to 55 months (median, 19 months). None of the cases had evidence of recurrence and metastasis. Our study reveals that secretory breast carcinoma is a distinct subset of invasive breast carcinoma, with expression of basal-like markers. It should be noted that secretory breast carcinoma is different from conventional basal-like breast carcinomas. Future studies are required to further understand the prognostic significance of the basal-like markers expression in secretory breast carcinomas.
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Secretory breast carcinoma was originally recognized in 1966 by McDivitt and Stewart[1] as an uncommon variety of mammary carcinoma in children, which they designated as 'juvenile carcinomas'. Tavassoli and Norris[2] subsequently reported 19 cases ranging in age from 9 to 69 years old; therefore, they recommended replacing the term 'juvenile carcinoma' with the descriptive term 'secretory carcinoma'. Secretory breast carcinoma has distinctive features that differ from other typical breast ductal carcinomas, such as the presence of large amounts of intracellular and extracellular secretory material. These neoplasms have indolent clinical behavior, late local recurrences and prolonged survival, even with lymph node involvement.[3,4] Immunochemically, the tumor usually has shown strong reactivity for S-100 and is negative for estrogen receptor (ER), progesterone receptor (PR) and HER2.[4–7] In 2002, Tognon *et al*[8] were the first to report that secretory breast carcinoma expresses the *ETV6-NTRK3* gene fusion in 12 out of 13 of their cases. Recently, Laé *et al*[7] demonstrated that secretory breast carcinoma with the *ETV6-NTRK3* fusion gene belongs to the phenotypic spectrum of basal-like breast carcinomas, and immunohistochemical, as well as genetic features of secretory breast carcinomas, distinguished them from other basal-like breast cancers. Here, we performed a clinicopathological and immunophenotypic analysis of 15 cases of secretory breast carcinoma to delineate the characteristic features of this entity in Chinese patients.

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Patients and methods

Patient Samples

A search for secretory breast carcinoma cases was performed in the surgical pathology and consultation files of the Department of Pathology, Fudan University Shanghai Cancer Center, between 2006 and 2010. Fifteen cases were accepted as secretory breast carcinoma after a detailed clinicopathological and immunophenotypic analysis. All cases were confirmed by at least two pathologists. Available data including clinical presentations, therapeutic regimens and follow-up information were evaluated.

Morphology and Immunohistochemistry

Formalin-fixed biopsy or resection specimens of 15 secretory breast carcinomas were routinely processed, embedded in paraffin and stained with hematoxylin–eosin. The invasive component of all cases was graded according to the modified Scarff–Bloom–Richardson system. Histological features including the growth pattern of tumor cells, cell morphology, mitotic figures and vascular invasion were evaluated.

Immunohistochemical staining was performed on paraffin-embedded sections from all cases by the standard Envision method using a panel of antibodies: ER (1D5, dilution 1:150; Dako), PR (PgR 636, dilution 1:125; Dako), HER2 (polyclonal, dilution 1:175; Dako), S-100 protein (polyclonal, dilution 1:300; Dako), CK5/6 (D5/16B4, dilution 1:50; Dako), epidermal growth factor receptor (EGFR; EGFR.113, dilution 1:50; Dako), mammaglobin (304-1A5, dilution 1:500; Dako), gross cystic disease fluid protein-15 (GCDFP-15; 23A3, dilution 1:50; Dako) and Ki-67 (MIB-1, dilution 1:100; Dako). Appropriate positive and negative control samples were used.

Evaluation of the Staining

Samples were defined as immunopositive if they had the following: at least 10% of tumor cells with nuclear immunoreactivity for ER and PR; at least 30% of tumor cells with continuous strong membranous reactivity for HER2; nuclear staining for Ki-67 and S-100; membranous/cytoplasmic reactivity (weak or strong) for CK5/6 and EGFR; and cytoplasmic reactivity for mammaglobin and GCDFP-15. The Ki-67 labeling index was determined by counting the number of positive cells in a total of 1000 tumor cells. If either CK5/6 or EGFR was positive immunohistochemically, the tumor was considered to express basal-like markers. A basal-like phenotype was defined as a ER−, HER2− and CK5/6 + /EGFR + expression.

Results

Clinical Features

The clinical features of the 15 patients are summarized in Table 1. There were 2 males and 13 females, with a male to female ratio of 1:6.5. Patient ages during the initial examination ranged from 10 to 67 years old (median, 36 years old). In 10 cases, the neoplasm was located in the right breast (one in the right axilla) and in the left breast in five cases. The tumors were mostly confined to the outer upper quadrant of the breast (7 of 15), and 3 were located in the subareolar region. All patients presented with a mass (two patients also had nipple discharge).

Table 1 Summary of clinical data

Case no./sex /age (yo)	*Symptoms/ duration (mo)*	*Site/locations*	*Size (mm)*	*Treatment*	*Axillary status*	*Recurrence*	*Follow-up (mo)*
1/M/10	Mass/ND	R/subareolar	20	MRM	−(0/11)	None	Well, 12
2/M/18	Mass/60;nipple bloody discharge/3	R/subareolar	25	MRM+CT	+(2/17)	None	Well, 13
3/F/17	Mass/ND; nipple discharge/5	R/upper outer	55	LE+SLNB	+(2/2, SLN)	None	Well, 10
4/F/27	Mass/3	R/subareolar	10	MRM	−(0/16)	None	Well, 19
5/F/30	Mass/ND	R/upper outer	10	LE	NE	NA	NA
6/F/34	Mass/1	L/lower outer	10	SM+SLNB+CT	−(0/4, SLN)	None	Well, 33
7/F/35	Mass/ND	R/subareolar	15	LE	NE	NA	NA
8/F/36	Mass/12	R/subareolar	10	MRM+CT	−(0/16)	None	Well, 15
9/F/39	Mass/126	R axillary	20	WLE+ALND+CT+RT	−(0/17)	None	Well, 21
10/F/39	Mass/ND	L/upper outer	15	MRM	−(0/12)	None	Well, 18
11/F/41	Mass/ND	L/upper outer	10	MRM+CT	−(0/18)	None	Well, 31
12/F/42	Mass/ND	L/upper inner	20	MRM	−(0/25)	None	Well, 13
13/F/59	Mass/2	L/upper outer	10	WLE+ SLNB+CT	−(0/3, SLN)	None	Well, 30
14/F/66	Mass/1	R/upper outer	20	MRM+CT	−(0/16)	None	Well, 55
15/F/67	Mass/ND	R/upper outer	20	MRM	−(0/30)	None	Well, 36

Abbreviations: ALND, axillary lymph node dissection; CT, chemotherapy; F, female; L, left; LE, local excision; M, male; MRM, modified radical mastectomy; mo, months; NA, not available; ND, not defined; NE, not examined; R, right; RT, radiotherapy; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; SM, simple mastectomy; WLE, wide local excision; yo, years old.

None of the patients had received chemotherapy before surgery. Lumpectomy was performed in five patients (two also with sentinel lymph node biopsy and one with axillary lymph node dissection), simple mastectomy and sentinel lymph node biopsy in one case, and modied radical mastectomy in nine patients. Seven cases received postoperative chemotherapy, and one of them also had radiotherapy. Two out of thirteen patients (15%) showed positive axillary lymph nodes. Follow-up data were available for 13 patients. Follow-up time ranged from 10 to 55 months (median, 19 months). None of them had evidence of recurrence and metastasis.

Pathological Findings

All cases presented with a painless and firm mass. Grossly, two cases showed obscure boundaries and inltrating margins, whereas others were well demarcated and non-encapsulated. The cut sections were greyish white to tan or yellow. Tumor size ranged from 10 to 55 mm, with a mean of 18 mm. Microscopically, the presence of intracellular and extracellular secretory material was the most remarkable feature. Several histological patterns, such as microglandular, glandular, cystic, microcystic and solid area, were present in varying proportions among the tumors. The honeycomb pattern can be observed in all cases (Figure 1a). Tumor cells were arranged in nests separated by dense collagen stroma (Figure 1b). Sometimes irregular or oval microcysts of varying sizes containing abundant secretion resembled thyroid follicular structure, even with absorption vacuoles (Figure 1c). A typical papillary growth pattern can be observed in some regions of case 10 (Figure 1d). Dilated cysts filled with eosinophilic secretion were presented in case 15 (Figure 1e). Tumor cells were mild-to-moderate atypia with pale-to-clear, pink or amphophilic cytoplasm. Nuclei were small round-to-oval, with or without a prominent nucleolus. Mitosis was rare or absent. In the solid area, there was no extracellular secretion and the tumor cells were slightly granular with intracellular secretory material (Figure 1f). Two cases (13%) were grade 2 and 13 cases were grade 1 (87%). No necrosis or vascular invasion was observed. Perineural infiltration was present in two cases. Pushing margins can be observed in three cases. The metastatic carcinoma in axillary lymph nodes also displayed a growth pattern similar to the primary tumor with abundant secretion (Figure 1g).

Immunohistochemical Findings

Immunohistochemical findings are summarized in Table 2 and illustrated in Figure 2. All cases were triple-negative (negative for ER, PR and HER2). The expression rate of basal-like markers was 87% (13 of 15), with a positive staining rate of 80% (12 of 15) for CK5/6 and 40% (6 of 15) for EGFR. Thirteen cases (87%) were identified as the basal-like phenotype. The mean value of Ki-67 index was about 6%. All cases showed positive staining for S-100 protein and mammaglobin. No reactivity was observed for GCDFP-15.

Discussion

Secretory carcinoma is a very rare type of breast carcinoma, accounting for less than 0.15% of all breast cancers.[7] In this retrospective study, 15 cases of secretory breast carcinoma were retrieved from a series of 10 000 newly diagnosed breast cancers between 2006 and 2010, with an incidence of only 0.15%. The reported male–female ratio is approximately 1:6,[9] which is similar to the distribution in our data set.

It is well known that breast cancers are highly heterogeneous malignancies. Patients with the same clinical stage, histological type and treatment may have diverse outcomes. Molecular differences are considered to be the main reason for this disparity. In 2000, Perou *et al*[10] initially produced a molecular portrait of breast cancer. Complementary DNA microarrays were employed to identify five biologically distinct subtypes of breast tumors, including luminal A and B, HER2 overexpression, normal breast-like tumors and basal-like tumors.[10–12] Many studies have demonstrated that basal-like tumors are associated with poor clinical outcome.[11,13] However, gene chip technology is expensive and not suitable for daily clinical application. Therefore, an immunohistochemical surrogate for the five molecular subtypes has been studied. The basal-like phenotype was found to have markedly reduced expression of ER and HER2 while it expressed markers present in the normal myoepithelial cell.[14] Studies by Nielsen *et al*[15] and Rodríquez-Pinilla *et al*[16] have proposed that a combination of ER−, HER2− and CK5/6 + /EGFR + markers can accurately diagnose basal-like breast cancer with a sensitivity of 76% and a specificity of 100%.[15] This immunohistochemical definition is the most frequently quoted definition of basal-like breast cancer.

In our cohort, the basal-like phenotype was identified in 13 (87%) cases according to the aforementioned criteria. Nevertheless, unlike other typical basal-like carcinomas (usually with features of high histological grade, pushing growth pattern, conspicuous lymphocytic infiltrate, central necrotic zones, geographic tumor necrosis, high mitotic rate, notable cellular pleomorphism, vesicular chromatin and high cell proliferation activity), most of our basal-like secretory breast carcinomas showed mild dysplasia without necrosis and active cell proliferation. They did not show local recurrence or distant metastases after a short follow-up period. Additionally, we also noticed that all of the cases in our series presented with higher histological grade, or pushing

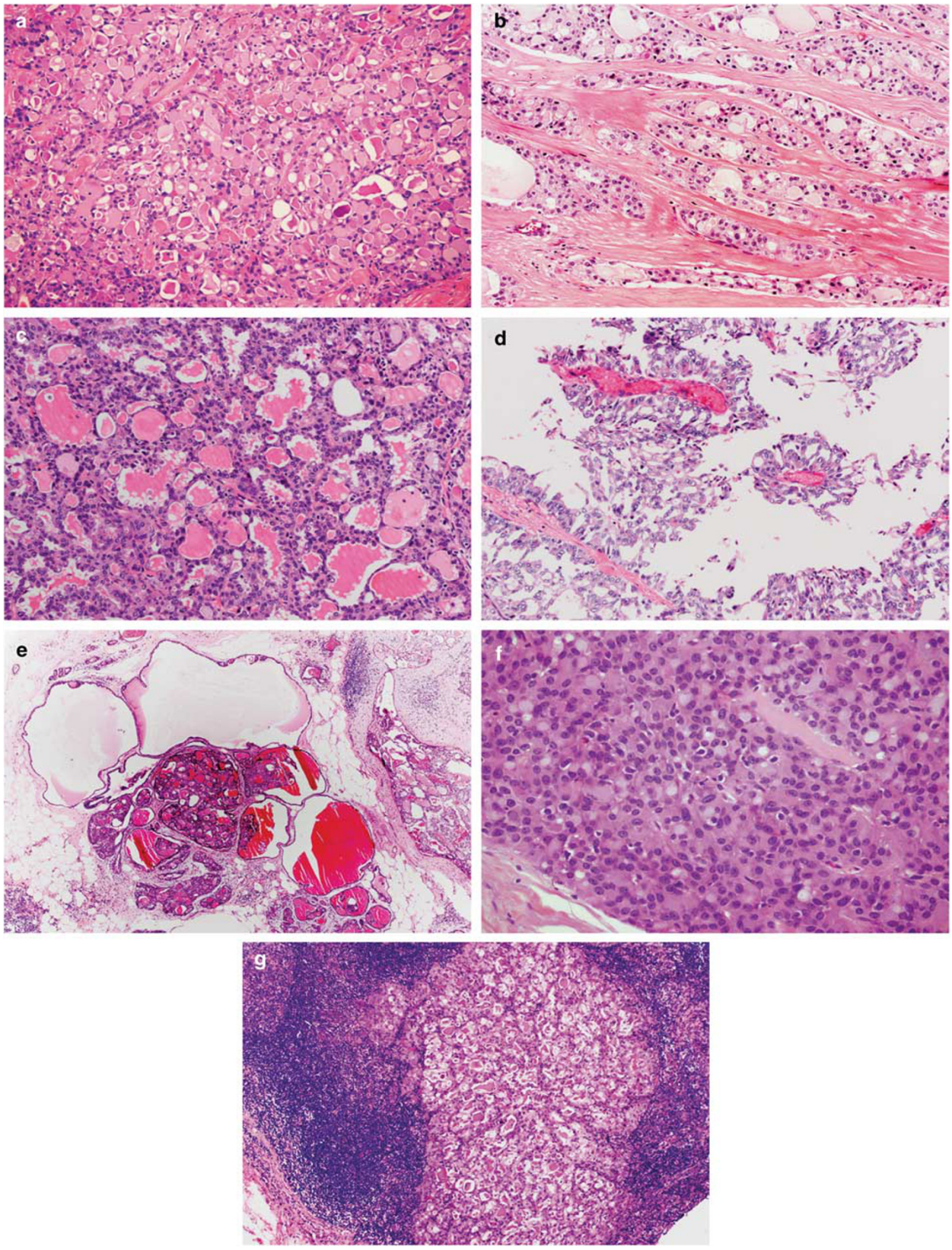

Figure 1 Secretory breast carcinoma with intracellular and extracellular secretory material (**a**). Tumor cells are arranged in nests and separated by dense collagen stroma (**b**). Follicle-like structures are filled with homogeneous eosinophilic secretion with absorption vacuoles (**c**). A papillary growth pattern with an edematous fibrovascular core can be observed (**d**). Large cysts containing eosinophilic secretion (**e**). Solid area with no extracellular secretion (**f**). The metastatic carcinoma in axillary lymph node, displaying a growth pattern similar to the primary tumor with abundant secretion (**g**).

Table 2 Immuophenotype of 15 cases of secretory breast carcinoma

Markers	*ER*	*PR*	*HER2*	*CK5/6*	*EGFR*	*S-100*	*Mammaglobin*	*GCDFP15*	*Ki-67 (%)*
Case 1	−	−	−	+	−	+	+	−	5
Case 2	−	−	−	+	−	+	+	−	6
Case 3	−	−	−	+	−	+	+	−	8
Case 4	−	−	−	−	+	+	+	−	4
Case 5	−	−	−	+	+	+	+	−	5
Case 6	−	−	−	+	−	+	+	−	2
Case 7	−	−	−	+	+	+	+	−	7
Case 8	−	−	−	+	−	+	+	−	5
Case 9	−	−	−	+	+	+	+	−	10
Case 10	−	−	−	−	−	+	+	−	4
Case 11	−	−	−	+	+	+	+	−	8
Case 12	−	−	−	−	−	+	+	−	5
Case 13	−	−	−	+	−	+	+	−	7
Case 14	−	−	−	+	−	+	+	−	6
Case 15	−	−	−	+	+	+	+	−	5

Abbreviations: ER, estrogen receptor ; EGFR, epidermal growth factor receptor; GCDFP15, gross cystic disease fluid protein-15; PR, progesterone receptor.

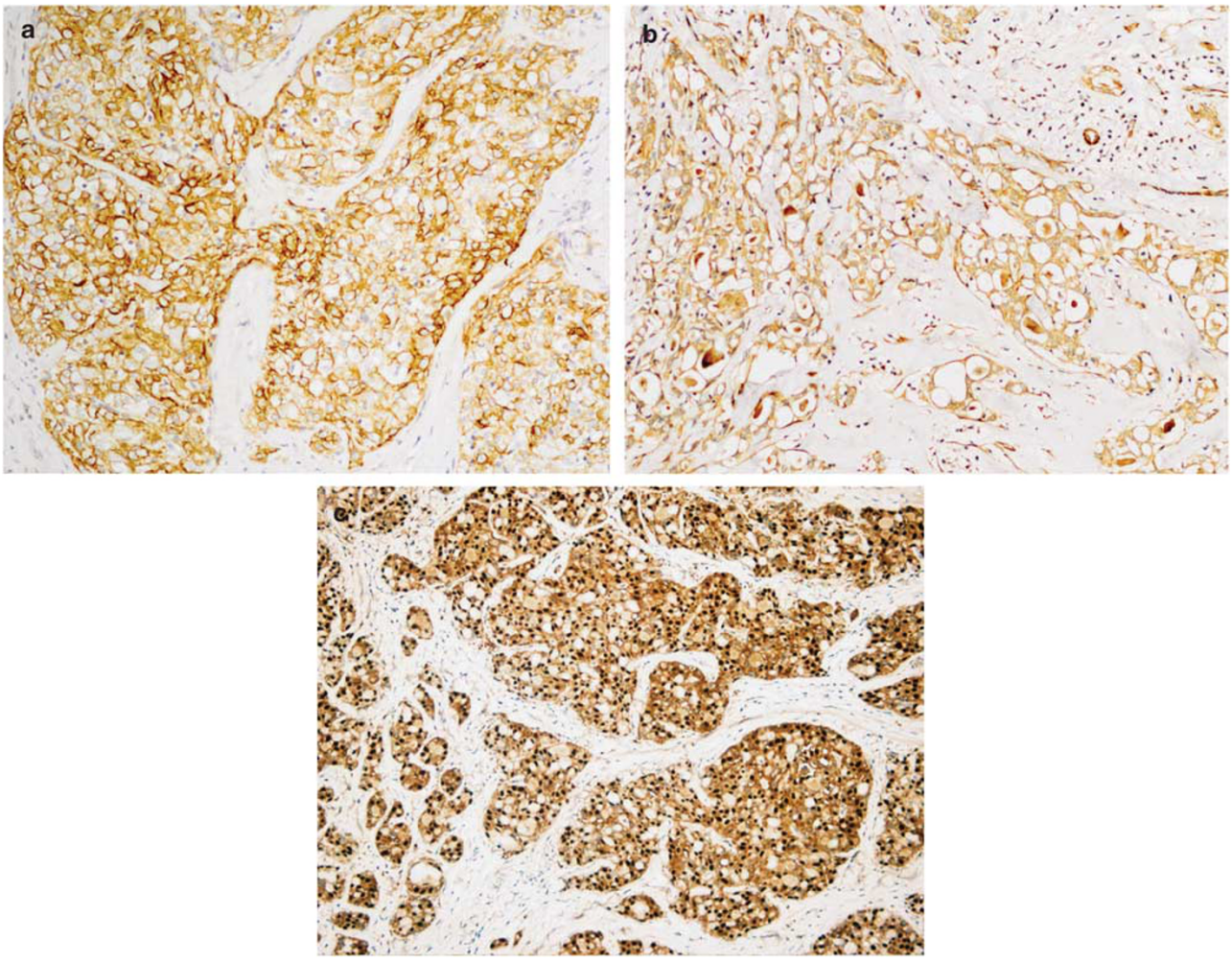

Figure 2 Secretory breast carcinoma with positive CK5/6 (**a**), positive epidermal growth factor receptor (EGFR; **b**) and positive S-100 (**c**).

margins express basal-like markers. Thus, we believe that some secretory breast carcinoma has a few basaloid characteristics. Tumors with basal-like immunophenotype constitute a heterogeneous group of tumors, and secretory breast carcinoma is one of the basal-like tumors that have good

prognosis.[7] This view is confirmed by our present study. However, the clinical significance of this finding is not clear at this time. Future studies are required to further understand the prognostic significance of the basal-like markers expression in secretory breast carcinoma.

The reported incidence rate of axillary lymph node metastasis of secretory breast carcinoma is 15–30%,[6,17] and most patients involved no more than four lymph nodes.[18–23] Studies have shown that lymph node metastasis is rare in children and teenagers.[9,24,25] In our series, there were two cases (case 2 and 3) with axillary lymph nodes metastases. Both of them were adolescents and had a tumor larger than 20 mm. Furthermore, both were grade 2 and expressed CK5/6. Sentinel lymph node biopsy has been used in several studies and has proven to be a useful evaluation method for the lymph node status of secretory breast carcinoma.[6,20,22] Three patients in our series received a sentinel lymph node biopsy, and one of these cases showed a positive result. However, considering that the patient was very young, lumpectomy without axillary dissection was adopted. Follow-up of the three patients to date has shown no evidence of recurrent or metastatic carcinoma. It suggests that sentinel lymph node biopsy can be a good replacement for axillary lymph node dissection in secretory breast carcinoma patients to predict the axillary status and achieve a satisfied treatment.

Though most secretory breast carcinoma cases are female, male sufferers have also been reported. A total of 27 cases (including 2 cases from our study, see Table 3) of male patients with secretory breast carcinoma could be identified in the literature.[2,3,6,9,23,25–44] Most affected patients were children and adolescents with a median age of 27 years. The tumors are usually located subareolarly. Tumor size varies from 8 to 120 mm, with an average diameter of approximately 30 mm. An asymptomatic, firm, mobile mass is the most frequent clinical presentation. The duration of symptoms varies from 2 weeks to 21 years. Case 2 had a lump below the right areola that was asymptomatic for approximately 5 years, but a cauliflower-like neoplasm with bloody discharge then began to gradually grow on the nipple several months before admission. This is not common in male secretory breast carcinoma patients. Nearly half (8 of 19, 42%) of the reported cases with axillary lymph node metastasis were confirmed. This rate was higher than the reported overall incidence. Six (six of eight, 75%) of the node metastatic cases had a tumor larger than 20 mm. Though secretory breast carcinoma usually behaves in an indolent manner, a few researchers have proposed that secretory breast carcinoma in men appeared to be more aggressive.[37] However, we only find three (3 of 20, 15%) patients resulted in death after a review of the literature.[5,26,39] Two of them had a tumor larger than 20 mm. Another patient was an old man with multiple foci and high Ki-67 expression (34%). A few male patients of secretory breast cancer also encountered recurrence and even distant metastases.[3,40,41] These patients merely underwent a lumpectomy or simple mastectomy during their first visit and had a tumor larger than 40 mm. Therefore, we advocate that sentinel lymph node biopsy should be added to the surgical regimen for male secretory breast carcinomas, especially those with a tumor larger than 20 mm.

In our cohort, we also had a patient (case 9) who developed secretory carcinoma in axillary breast tissue. This axillary mass had been present for more than 10 years before the carcinoma was diagnosed. Her pectoral breasts were normal. During her first pregnancy, the mass became itchy and a milky liquid could be squeezed out, but the epidermis was intact. This patient has not had another baby since then, and the mass remained dormant without enlargement or any discomfort. She recently visited the hospital because she was experiencing 'slight pain'. A wide local excision and axillary lymph node dissection were performed by surgeons. The mass was 20 mm and no metastatic axillary lymph node was found. Microscopically, the lesion was located in the deep dermal-subcutaneous region and was shaped in lobules. Normal mammary lobules were observed adjacent to the tumor. The evidence suggested that this tumor might have arisen from ectopic breast tissue. To our knowledge, this is the third report of secretory carcinoma taking place in axilla ever documented.[19,45]

Though most secretory breast carcinomas express the basal-like markers, we do not think that the treatment will be affected, and aggressive treatment should be avoided. To date, there is no consensus on the treatment of secretory breast carcinoma. Most children and adults have been treated by surgical excision techniques ranging from local resection to radical mastectomy. Secretory breast carcinoma is considered by a few researchers to be more aggressive in adult women than in children.[25,46] Wide excision is potentially adequate due to few occurrences of metastasis in children. For patients over 20 years old, an initial simple mastectomy with axillary node dissection might be adequate.[2] However, recently the technique of sentinel lymph node biopsy has replaced conventional axillary lymph node dissection to become the standard of care for early breast cancer. Thus, conservative surgery (adequate local excision or quadrantectomy) with sentinel lymph node biopsy has been chosen by some surgeons when neoplasms are smaller than 20 mm, and simple mastectomy with sentinel lymph node biopsy has been preferred for neoplasms larger than 20 mm.[20,22] If the result of sentinel lymph node biopsy is negative, the patient can be exempted from axillary lymph node dissection. The real value of postoperative radiotherapy and chemotherapy has not been examined.

In conclusion, secretory breast carcinoma is a distinct subset of invasive breast carcinoma, which

Table 3 Data on 26 male secretory breast carcinoma patients

Author	*Age (y)*	*Duration of symptoms (m)*	*Location*	*Size (mm)*	*Axillary status*	*Treatment*	*Hormone receptors*	*HER2*	*ETV6-NTRK3*	*Follow-up (m)*
Simpson[27]	5	ND	ND	ND	−(Clinical)	LE	NE	NE	NE	NED 48
Tavassoli[2]	9	ND	ND	ND	−(Clinical)	LE	NE	NE	NE	NED 21
Karl *et al*[28]	3	1	L subareolar	15	+(1/4)	SM+ALNS	NE	NE	NE	ND
Roth *et al*[25]	23	252	L Upper outer	20	−(0/21)	MRM	NE	NE	NE	NED 48
Krausz *et al*[26]	24	Many years	L subareolar	40	ND	SM+RT(axilla)	NE	NE	NE	DOD 240
Serour *et al*[9]	17	48	L subareolar	15	−(0/3)	WLE+ALND+RT	ER− PR+	NE	NE	NED 60
Lamovec[29]	20	ND	R subareolar	12	−(0/?)	MRM	ER+ PR+	NE	NE	NED 12
Pohar-Marinsek[30]	20	72–84	R medial	12	−(Clinical)	SM	ER+ PR+	NE	NE	NED 6
Kuwabara *et al*[31]	66	36	L subareolar	30	+(2/?)	MRM	ER− PR−	NE	NE	NED 8
Vesoulis[32]	33	120	R subareolar	15	ND	MRM	ER+ PR+	NE	NE	ND
Kameyama *et al*[33]	51	ND	L subareolar	30	−(0/?)	MRM	ER+	NE	NE	ND
Chevallier *et al*[34]	9	168	L subareolar	20	−(0/?)	LE+ALND	ER− PR−	NE	NE	NED 45
Yildirim *et al*[35]	11	12	R subareolar	15	+(1/18)	MRM+CT+RT	ER−	NE	NE	NED 12
Bhagwandeen[36]	9	1	R subareolar	12	−(0/15)	MRM	ER− PR−	NE	NE	NED 20
Titus *et al*[44]	9	1	R subareolar	10	−(0/15)	SM+ALND	ER− PR−	NE	NE	NED 20
de Bree *et al*[37]	17	24	R subareolar	30	−(0/14)	MRM	ER− PR−	NE	NE	NED 9
[a]Diallo *et al*[38]	74	ND	ND	8	+(Clinical)	EB	ER− PR−	—	NE	Died at the time of dx
Szántó *et al*[6]	7.5	6	R subareolar	17	−(SLNB)	RM+SLNB	ER− PR−	NE	NE	NED 5
Woto-Gaye *et al*[39]	20	ND	ND	120	+(3/?)	SM+ALND	NE	NE	NE	DOD a few months
[b]Kavalakat *et al*[40]	17	ND	R subareolar	60	+(10/12)	MRM+CT+RT	ER−	NE	NE	NED 13
[c]Niveditha *et al*[41]	19	24	R chest wall	40, 20	ND	LE	ER− PR−	NE	NE	ND
Alenda *et al*[42]	79	ND	L subareolar	30	− (0/?)	SM+ALND	ER− PR−	—	NE	ND
[d]Grabellus *et al*[43]	46	ND	L	35	ND	LE	ER− PR−	—	Present	ND
Arce *et al*[3]	52	120	L	70	+(2/24)	MRM+CT	ER− PR−	—	Present	AWD 25
Iglesias *et al*[23]	63	12	R subareolar	20	+(1/10)	SM+ALND	ER− PR−	—	NE	NED 71
Our case number 1	10	0.5	R subareolar	20	−(0/11)	MRM	ER− PR−	—	NE	NED 12
Our case number 2	18	60	R subareolar	25	+(2/17)	MRM+CT	ER− PR−	—	NE	NED 13

Abbreviations: ALND, axillary lymph node dissection; ALNS, axillary lymph node sampling; AWD, alive with disease; CT, chemotherapy; DOD, died of disease; dx, diagnosis; EB, excisional biopsy; ER, estrogen receptor; L, left; LE, local excision; m, months; MRM, modified radical mastectomy; ND, not defined; NE, not examined; NED, no evidence of disease; PR, progesterone receptor; R, right; RT, radiotherapy; SLNB, sentinel lymph node biopsy; SM, simple mastectomy; WLE, wide local excision; y, years.

[a]The patient had multifocal tumors.

[b]The patient underwent excision of a lump 2 years ago, then developed a recurrence on the same site within 6 months.

[c]The patient underwent a lumpectomy in the right breast, then two small lumps reappeared on the right chest wall 3 months after surgery.

[d]The patient was a male-to-female transsexual.

expresses basal-like markers such as CK5/6 and EGFR. Distinguished from the typical basal-like breast carcinomas, it only shows mild dysplasia. Aggressive treatment should be avoided in such kind of patients. At this time, the importance of the expression of basal-like markers of secretory breast carcinoma is unclear. Future studies are required to further understand the prognostic significance of the expression of basal-like markers in secretory breast carcinoma.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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