

ORIGINAL PAPER

CLINICOPATHOLOGICAL CHARACTERISTICS OF BREAST
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Two middle-aged females presented with a mass located in the lateral quadrant of the breast. Both patients received modified radical surgery for breast cancer, radiotherapy, and chemotherapy and have been living without evidence of disease for more than one year. Under the microscope, we observed that the tumour cells were organised in a solid nest-like or leafy distribution and comprised sebaceous gland cells and oval or fusiform cells. The differences between the two cases are as follows: First, the mass in the first case had a mixed echo pattern on ultrasound, whereas that in the second case had a hypoechoic pattern. Pathology revealed the presence of irregular cysts in the first case, which was consistent with the ultrasound features, and microscopy revealed the presence of necrosis in the tumour. Second, the first case was strongly positive for HER-2 expression, but the second case was negative. In contrast, the second case was positive for ER expression, whereas the first case was negative. Third, the second patient had two axillary lymph node metastases, whereas the first patient had none. We analysed the obtained data to derive the following conclusions: breast sebaceous carcinoma typically occurs in middle-aged women. Under the microscope, two types of cells can be observed in a solid nest-like or leafy distribution. One cell population consists of sebaceous gland-like tumour cells, which are mostly located in the centre of the lobules or cell nests. These represent a more differentiated cell type and are rich in vacuolar cytoplasm. The other cell population consists of smaller oval or fusiform non-vacuolar cells, mostly located at the periphery of the lobules or cell nests. These cells are usually undifferentiated and are thus difficult to distinguish from typical ductal carcinoma cells. Breast sebaceous carcinoma has a high rate of positive expression of ER, PR, p53, and EMA and a low rate of positive expression of HER-2 and GCDFP-15. Primary breast sebaceous cancer has the following diagnostic characteristics: sebaceous differentiation in at least 50% of cells in the absence of any evidence of originating in the cutaneous adnexa; features, such as ductal carcinoma differentiation, lobular carcinoma differentiation, and others, which can be found in primary breast sebaceous cancer, distinct from those in skin sebaceous adenocarcinoma; and a typical transitional structure between the cancer tissue and ductal epithelium. Breast sebaceous carcinoma should be distinguished from skin sebaceous adenocarcinoma, lipid-rich carcinoma, apocrine carcinoma, and glycogen-rich clear cell carcinoma, among others. Furthermore, this is a hormone receptor-dependent type of breast cancer that requires comprehensive treatment. Thus, after extensive analysis, we conclude that breast sebaceous carcinoma has low invasiveness and good prognosis.

Key words: sebaceous carcinoma of the breast, clinical, pathology.

Introduction

Breast sebaceous adenocarcinoma is a rare and special type of invasive breast cancer, with as few as 21 cases reported at home and abroad. Among these cases, six have been reported in China (including the two cases described in this text). The World Health Organisation defines primary sebaceous carcinoma of the breast based on sebaceous differentiation in at least 50% of cells in the absence of any evidence of originating in the cutaneous adnexa [1]. The clinical pathology data and follow-up information of two breast sebaceous adenocarcinoma cases are discussed below with retrospective analysis of information on the clinical and pathological features, diagnosis, differential diagnosis, treatment and prognosis of breast sebaceous adenocarcinoma patients highlighted in studies at home and abroad.

Clinical history

Case 1

A 55-year-old female patient presented with an 8.0 × 8.0 cm hard mass in the outer quadrant of her right breast. On October 18, 2016 the patient was diagnosed with invasive breast carcinoma based on biopsy results. The patient then received two cycles of neoadjuvant chemotherapy (epirubicin + cyclophosphamide) at Wuhan Union Hospital. Afterward, she came to Xiaogan City Centre Hospital for surgery. Prior to surgery, she underwent colour Doppler ultrasound scanning, which showed a mass with a mixed-echo pattern in the right breast (Fig. 1). Her CEA-125 level was 132.40 KU/l, which was higher than the normal range (0-34.9 KU/l). Soon afterwards, she underwent modified radical mastectomy of the right breast. The tumour was approximately

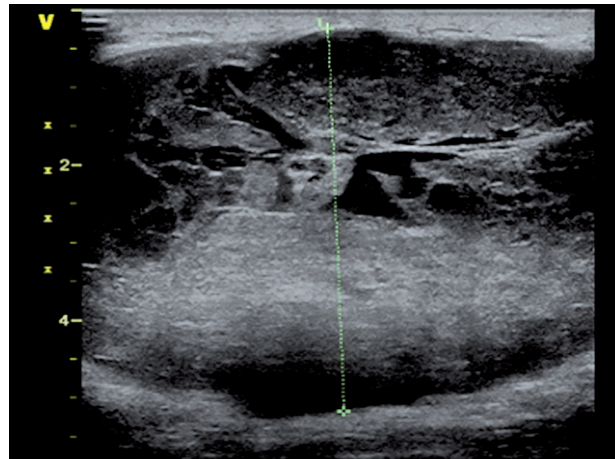


Fig. 1. Colour Doppler ultrasound image showing a mass of mixed echo pattern, with blurry and irregular border and a hypoechoic interior

6.5 × 6.5 cm in size. The tumour sections appeared grey in colour, with many irregular cysts inside. Under the microscope, we observed that the tumour cells were organised in a solid nest-like or leafy distribution and were composed of sebaceous gland cells and oval or fusiform cells (Fig. 2A). The sebaceous gland-like tumour cells were mostly located in the centre of the lobules or cellular nests. These represent a more differentiated cell type and are rich in vacuolar cytoplasm. The other cell population consisted of smaller oval or fusiform non-vacuolar cells, mostly located at the periphery of the lobules or cell nests. These cells are usually undifferentiated and are difficult to distinguish from typical ductal carcinoma cells. The sebaceous gland-like cells accounted for more than half of the total number of tumour cells. We also observed necrosis under the microscope (Fig. 3). The tumour was not connected with

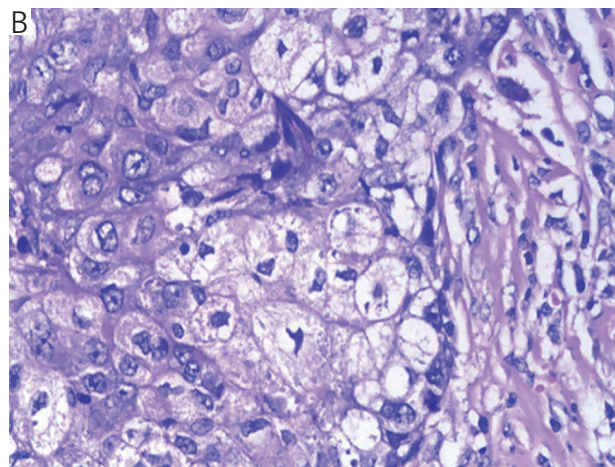
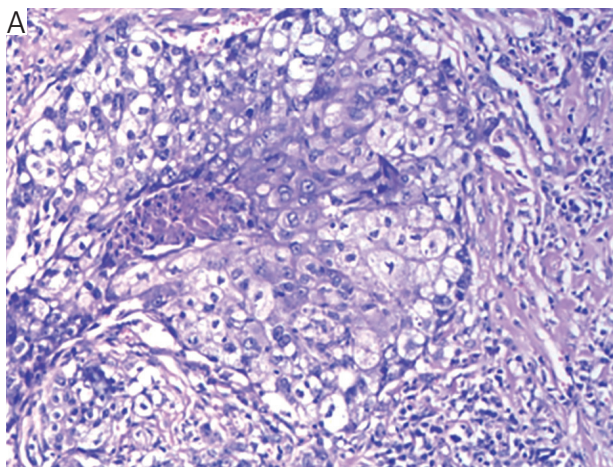


Fig. 2A, B. Two cell types: namely, sebaceous gland cells, which are rich in vacuolar cytoplasm and distributed in the centre of the leafy or nest-like structure, and smaller oval or fusiform cells distributed in the periphery (HE staining; 10 × and 20 ×)

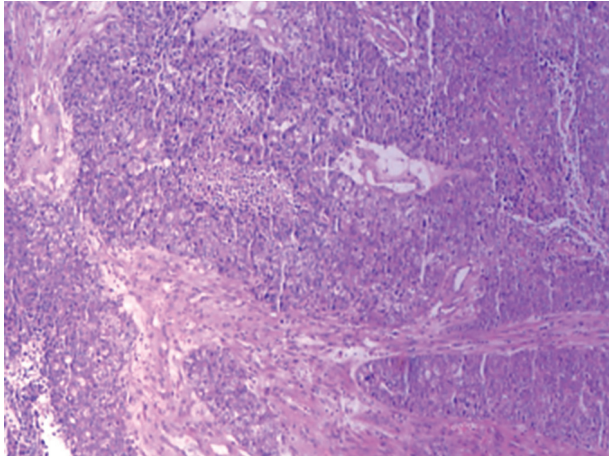


Fig. 3. Tumour cells arranged in solid nest-like or leafy distribution and a necrotic tumour interior; haematoxylin and eosin (HE) staining, 4 ×

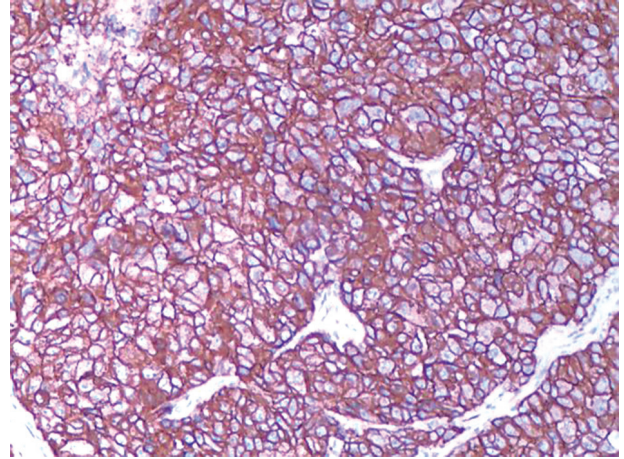


Fig. 4. Positive expression of HER-2 on tumour cells

the skin, and there was no lymph node metastasis (0/31). The immunohistochemistry results were as follows: ER (-), PR (-), Ki-67 (LI: +50%), HER-2 (3+) (Fig. 4), E-ca (+), GCDFP-15 (-), CK5/6 (partial +), and CKH (partial +). Subsequently, the patient received six cycles of chemotherapy (two cycles of epirubicin+cyclophosphamide and four cycles of docetaxel). The patient was diagnosed with HER-2-overexpressing breast cancer, for which targeted treatment is now available. However, she refused the treatment because of financial problems. Because of the large tumour size, the patient received radiotherapy. Until now, she has survived for 13 months without evidence of disease.

Case 2

A 42-year-old woman accidentally discovered a mass in her left breast. Colour doppler ultrasound scanning revealed a hypoechoic mass in the upper and lateral quadrant of the left breast. Mammograms showed a mass approximately 2.0 × 1.5 cm in size in the upper and lateral quadrant of the left breast near the armpit (BI-RADS grade 4A) (Fig. 5). Biopsy showed a fibrous histiocytoma. CEA-125 tumour markers did not exhibit obvious abnormalities. The patient underwent tumour resection on the left breast under local anaesthesia on August 5, 2016. Postoperative pathological examination revealed the presence of invasive cancer. The patient subsequently underwent modified radical surgery of the left breast. The tissue section was white, and the tumour was approximately 2.5 × 2.0 cm in size. Microscopic examination showed the presence of the two types of cells similar to those described above with a nest-like or leafy distribution, and the sebaceous gland cells accounted for more than half of the total number of cells (Fig. 2B). The tumour was not associated with the skin. How-

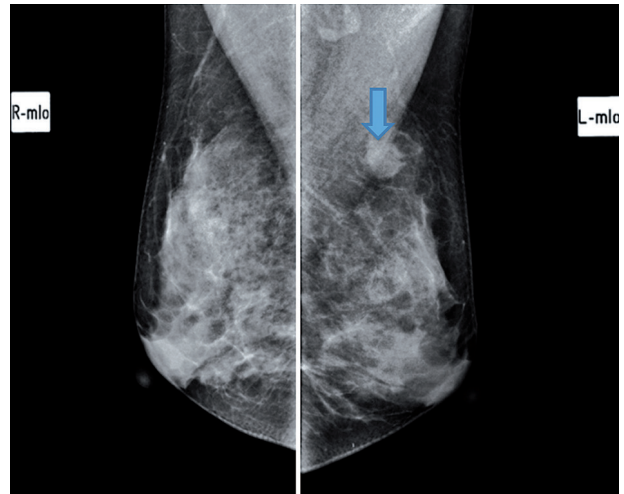


Fig. 5. Mammograms showing a mass of approximately 2.0 × 1.5 cm in size in the upper and lateral quadrant of the left breast near the armpit (BI-RADS grade 4A)

ever, there were two axillary lymph node metastases. The immunohistochemistry results were as follows: ER (+), PR (-), HER-2 (0), Ki-67 (+60%), E-ca (+), FAS (+), FASL (+), P53 (+), GCDFP-15 (-), CK5/6 (+), P63 (-), CD34 (-), SMA (-), and calponin (-). Subsequently, the patient received eight cycles of chemotherapy (four cycles of epirubicin+cyclophosphamide and four cycles of docetaxel), followed by radiotherapy and anti-hormone therapy (toremifene). Until now, she has survived for 15 months without evidence of disease.

Material and methods

First, we collected clinical pathology data and follow-up information from two cases of breast sebaceous adenocarcinoma in Xiaogan City Centre Hospital. Second, we gathered similar data and information from related studies published at home and

Table I. Summary of clinicopathological features and follow-up information of patients with breast sebaceous adenocarcinoma

AUTHORS	YEAR	AGE	SEX	SIDE	DIAMETER (CM)	LYMPH NODE METASTASIS	TREATMENT	FOLLOW-UP
Van Bogaert <i>et al.</i> [4]	1977	33~76			1.2~3.5			
Prescott <i>et al.</i> [5]	1992	74	F	R				
Mazzella <i>et al.</i> [6]	1995	55	M	L	5	+		ANOD 10 months
Tavassolli <i>et al.</i> [7]	1999	46	F	R	7.5	-		
Varga <i>et al.</i> [8]	2000	45	M	R	2.5	-		AWD 132 months, skin and bone MTS
Hisaoka <i>et al.</i> [9]	2006	71	F	R	2	+		
Numoto <i>et al.</i> [10]	2007	49	F	L				
Moinfar <i>et al.</i> [11]	2007	75	F	R				
Murakami <i>et al.</i> [12]	2009	50	F	L	2	+		ANOD 24 months
Ramljak <i>et al.</i> [13]	2010	85	F	L	7.5			
Svajdler <i>et al.</i> [2]	2015	65	F	R	1.6	+	quadrantectomy + SLN + axillary dissection; ACT; RAT (42.56 Gy); letrozole	ANOD 27 months
		61	F	R	1.7	+	mastectomy + axillary dissection; FAC; RAT (50.0 Gy); paclitaxel + bevacizumab + bisphosphonates; gemcitabine + carboplatin	MTS in the liver, lungs and bone; pathological fracture of the femur; arrhythmia; DOD 28 months
		66	F	R	3	+	mastectomy + axillary dissection; FAC + tamoxifen; RAT (50.0 Gy) + vinorelbine + capecitabine; paclitaxel + bevacizumab + letrozole	endometrial carcinoma; local recurrence; mediastinal and supraclavicular lymph node MTS; AWD 70 months
		25	F	R	NA	-	segmentectomy + axillary dissection; AC + RAT (50.0 Gy) + HDR boost (15.0 Gy) + anti-oestrogen	gave birth to one child; ANOD 75 months
Yamamoto <i>et al.</i> [3]	2015	80	F	L	3.5	-	partial mastectomy and sentinel lymph node biopsy	ANOD 16 months
Zhang Junneng <i>et al.</i> [14]	2001	73	M	L	2.5	+	mastectomy + axillary dissection	ANOD 6 months

Table I. Cont.

AUTHORS	YEAR	AGE	SEX	SIDE	DIAMETER (CM)	LYMPH NODE METASTASIS	TREATMENT	FOLLOW-UP
Chen Jian <i>et al.</i> [15]	2005	45	F	L	2.0			
Qiu Zhenying <i>et al.</i> [16]	2016	62	F	R	4.3	–	mastectomy + axillary dissection + four cycles of chemotherapy	ANOD 6 months
Zuo Zhong <i>et al.</i> [17]	2017	70	F	L	4.5	+		
Chen Heng <i>et al.</i> (current case)	2016	55	F	R	6.5	–	neoadjuvant chemotherapy (2 cycles of EC); mastectomy + axillary dissection; chemotherapy (2 cycles of EC + 4 cycles of T)	ANOD 8 months
	2016	42	F	L	2.5	+	mastectomy + axillary dissection; chemotherapy (4 cycles of EC + 4 cycles of T) + RAT + anti-oestrogen (toremifene)	ANOD 10 months

SLN – sentinel lymph node biopsy; ACT – doxorubicin + cyclophosphamide + docetaxel; AC – doxorubicin + cyclophosphamide; FAC – fluorouracil + doxorubicin + cyclophosphamide; EC – epirubicin + cyclophosphamide; T – docetaxel; RAT – radiotherapy; HDR – high-dose radiation; MTS – metastases; ANOD – alive with no evidence of disease; AWD – alive with disease; DOD – dead because of disease

abroad. Last, we retrospectively analysed the clinical and pathological features, diagnosis, differential diagnosis, treatment, and prognosis of patients with breast sebaceous adenocarcinoma.

Results

There are many similarities between the two cases, such as age, tumour location, treatment methods, and microscopic examination results, as described above. The differences between the two cases are as follows: First, their ultrasound performances were different. Pathology revealed the presence of irregular cysts in the first case, which was consistent with the ultrasound features, and microscopy revealed the presence of necrosis in the tumour. Second, their HER-2 expression and ER expression were different. Third, their lymph node metastasis patterns were not the same.

Discussion

Sebaceous gland cancer is rare. It often occurs in the eyelids and is accompanied by Muir-Torre syndrome, which is caused by mutations in DNA mis-

match repair genes leading to the loss of expression of specific DNA mismatch repair proteins (MMRPs). Švajdler *et al.* reported four cases of breast sebaceous adenocarcinoma in the absence of visceral malignancies, but all the tumours retained the expression of DNA MMRPs. Therefore, the authors concluded that breast cancer with sebaceous gland characteristics are not associated with Muir-Torre syndrome [2], and our two cases did not have any visceral malignancy either, consistent with the conclusions of the previous study. Thus, as highlighted below, we analysed the data obtained thus far to derive several conclusions.

Clinical and pathological features

Breast sebaceous carcinoma typically occurs in middle-aged women, with a median age of 65 years. The breast mass is usually discovered accidentally by the patients or during regular physical examination. The clinical features of some breast sebaceous carcinoma tumours are very similar to those of breast fibroadenoma, and thus the tumours are sometimes removed as benign lesions such as in the case reported by Chen Jian *et al.* [15] and in patient 2 described herein.

Table II. Summary of immunohistochemistry data for breast sebaceous adenocarcinoma

Authors	ER	PR	HER-2	Ki-67	P53	GCDFP-15	EMA	AR
Prescott <i>et al.</i> [5]							+	
Mazzella <i>et al.</i> [6]	+	+						
Tavassoli <i>et al.</i> [7]	-	+						-
Varga <i>et al.</i> [8]	+	+	-					
Hisaoka <i>et al.</i> [9]	+	+	-				+	-
Numoto <i>et al.</i> [10]	+	+	-				+	
Murakami <i>et al.</i> [12]	-	-	+				+	+
Ramljak <i>et al.</i> [13]	-	-	-					
Švajdler <i>et al.</i> [2]	+	+	-	30%	+		+	
	-	-	-	80%	-		+	
	+	+	-	5%		-	-	
	+	+	-			-	+	
Yamamoto <i>et al.</i> [3]	-	-	-				+	-
Chen Jian <i>et al.</i> [15]	+	-	-			-		
Qiu Zhenying <i>et al.</i> [16]	+	+	-	10%		--		
Zuo Zhong <i>et al.</i> [17]	+	+	-	35%				
Chen Heng <i>et al.</i> (current case)	-	-	+	50%		-		
	+	-	-	60%	+	-		

In breast sebaceous carcinoma, two types of cells distributed in a solid nest-like and leafy pattern can be observed under the microscope. One cell population consists of sebaceous gland-like cancer cells, mostly located in the centre of the lobules or cell nests. These represent a more differentiated cell type and are rich in vacuolar cytoplasm. These cells have pleomorphic nuclei, which are often pushed to an eccentric position. The other cell population, which is mostly located at the periphery of the lobules or cell nests, consists of smaller oval or fusiform non-vacuolar cells with little cytoplasm. These cells are usually undifferentiated and are difficult to distinguish from typical ductal carcinoma cells. Generally, these cells are mixed with sebaceous gland-like cancer cells. Alternatively, these cells can also form individual clusters. The sebaceous gland-like cancer cells account for more than half of the total number of tumour cells. In breast sebaceous carcinoma, the tumour is typically not connected with the skin. Occasionally, features such as squamous epithelial differentiation, necrosis, lobular carcinoma *in situ*, and transition between the cancer tissue and ductal epithelium are also present. Furthermore, the incidence rate of lymph node metastasis in breast sebaceous carcinoma is 50%, with 1-3 lymph node metastases.

The proportions of positivity for ER, PR, HER-2, p53, EMA, and GCDFP-15 are 64.71%, 58.82%, 13.33%, 66.67%, 88.89%, and 0.00%, respectively

(Tables I, II). Therefore, breast sebaceous carcinoma has a high rate of positive expression of ER, PR, p53, and EMA and a low rate of positive expression of HER-2 and GCDFP-15. The high positive rate of ER and PR expression in breast sebaceous adenocarcinoma indicates that this is a hormone receptor-dependent breast cancer, which is consistent with the view of Varga *et al.* [8]. Gao Renli *et al.* [18] concluded that the high expression of androgen receptor (AR) in breast cancer might indicate a low invasive potential and good prognosis. Until now, the only patient diagnosed with breast sebaceous carcinoma with a positive expression of AR has survived for 24 months without evidence of disease, which supports the notion mentioned above. Fasanella *et al.* [19] reported that the proportion of Ki-67-positive cells in breast carcinoma is approximately $36 \pm 14\%$, which is consistent with our data (36.57%). Based on the hormone receptor status and HER-2 expression status, the number of breast sebaceous cancer cases of the luminal, HER-2-positive, and triple-negative subtype are 9, 3, and 2, respectively, indicating that the luminal type is the more common subtype of breast sebaceous adenocarcinoma.

Diagnosis

Here, we summarise some aspects for the diagnosis of primary breast sebaceous adenocarcinoma according to the views of a number of scholars. Primary

breast sebaceous adenocarcinoma is defined based on sebaceous differentiation in at least 50% of cells in the absence of any evidence of originating in the cutaneous adnexa. Moreover, the tumours have features, such as ductal carcinoma differentiation, lobular carcinoma differentiation, and others, that can be found in primary breast sebaceous cancer distinct from those in skin sebaceous adenocarcinoma. Additionally, a typical transitional structure can be found between the cancer tissue and the ductal epithelium in primary breast sebaceous adenocarcinoma.

Differential diagnosis

Breast sebaceous adenocarcinoma should be distinguished from cancers such as skin sebaceous adenocarcinoma, lipid-rich carcinoma, apocrine carcinoma, and glycogen-rich clear cell carcinoma. The features for differential diagnoses are described below.

The differences between breast sebaceous adenocarcinoma and skin sebaceous adenocarcinoma are as follows: First, in the case of breast sebaceous adenocarcinoma, the tumour is located in the breast, and there is no evidence of origin from the cutaneous adnexa. Second, the tumours have features, such as ductal carcinoma differentiation, lobular carcinoma differentiation and others, which can be found in primary breast sebaceous cancer distinct from those in skin sebaceous adenocarcinoma. Last, even when the tumour is connected to the skin, if a typical transitional structure is observed between the cancer tissue and breast ductal epithelium, a diagnosis of breast sebaceous adenocarcinoma can be made.

The differences between breast sebaceous adenocarcinoma and lipid-rich carcinoma are as follows: First, 90% of lipid-rich carcinoma cells contain varying levels of intracellular lipids. Second, lipid-rich carcinoma consists of more than two types of cells, and there are no undifferentiated cells or cells with squamous epithelial differentiation. Third, in lipid-rich carcinoma, the cells have a cord-like and irregular distribution but not solid nest-like or leafy distribution such as that observed in breast sebaceous adenocarcinoma.

The differences between breast sebaceous adenocarcinoma and apocrine carcinoma are as follows: First, apocrine carcinoma consists of two kinds of cells, which both have large nuclei and obvious nucleoli. These cells include eosinophilic or granulocyte-like cells with abundant cytoplasm and vacuole-like cells. There are no small oval or fusiform non-vacuolar cells or cells with squamous epithelial differentiation. Second, the cells have glandular and tubular distribution and not solid nest-like or leafy distribution such as that observed in breast sebaceous adenocarcinoma. Additionally, apocrine carcinoma is associated with apocrine secretion on the cavity surface. Third, GCDFP-15 expression is positive in both

cell types in apocrine carcinoma, whereas GCDFP-15 expression is negative in the cells of breast sebaceous adenocarcinoma.

The differences between breast sebaceous adenocarcinoma and glycogen-rich clear cell carcinoma are as follows: The cells in glycogen-rich clear cell carcinoma have abundant cytoplasm rich in glycogen. These cells are also positive for periodic acid-Schiff (PAS) staining. Moreover, glycogen-rich clear cell carcinoma lacks vacuole-like features, two cell types, and lobular structures.

Prognosis

There are a total of 12 cases of breast sebaceous adenocarcinoma with follow-up data. Nine cases have no signs of recurrence. The other three cases had metastasis or breast cancer recurrence at 132 months, 18 months, and 26 months; among these three patients, one died from arrhythmia during surgery. The clinical features of some breast sebaceous carcinoma tumours are very similar to those of breast fibroadenoma, and thus, the tumours are sometimes removed as benign lesions, and patients often need a second surgery. Regarding the pathological aspect, the World Health Organisation defines primary breast sebaceous carcinoma based on sebaceous differentiation in at least 50% of cells, indicating that most of the tumour cells are differentiated. Furthermore, the incidence rate of lymph node metastasis in patients with breast sebaceous carcinoma is 50%, with 1-3 lymph node metastases. Additionally, the average proportion of cells positive for Ki-67, which is a tumour proliferation index, is consistent with our findings. Moreover, most breast sebaceous carcinoma belong to the luminal subtype, which has a good prognosis. After a comprehensive analysis of these data, we conclude that breast sebaceous carcinoma has low invasiveness and good prognosis.

Conclusions

Breast sebaceous carcinoma typically occurs in middle-aged women. Under the microscope, two types of cells can be observed in these tumours in a solid nest-like or leafy distribution. One cell population consists of sebaceous gland-like tumour cells, which are mostly located in the centre of the lobules or cellular nests. These represent a more differentiated cell type and are rich in vacuolar cytoplasm. The other cell population consists of smaller oval or fusiform non-vacuolar cells, mostly located at the periphery of the lobules or cell nests. These cells are usually undifferentiated and are difficult to distinguish from typical ductal carcinoma cells. Additionally, breast sebaceous carcinoma has a high rate of positive expression of ER, PR, p53, and EMA and a low rate of positive expression of HER-2 and

GCDFP-15. Primary breast sebaceous carcinoma has the following diagnostic characteristics: sebaceous differentiation in at least 50% of cells in the absence of any evidence of originating in the cutaneous adnexa; features, such as ductal carcinoma differentiation, lobular carcinoma differentiation and others, that can be found in primary breast sebaceous cancer distinct from those in skin sebaceous adenocarcinoma; and a typical transitional structure between the cancer tissue and ductal epithelium. Nevertheless, breast sebaceous carcinoma should be distinguished from skin sebaceous adenocarcinoma, lipid-rich carcinoma, apocrine carcinoma, and glycogen-rich clear cell carcinoma, among others. Furthermore, this is a hormone receptor-dependent type of breast cancer, which requires comprehensive treatment. Therefore, after extensive analysis of the data, we conclude that breast sebaceous carcinoma has low invasiveness and good prognosis.

The authors declare no conflict of interest.

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