

ORIGINAL PAPER

SEBACEOUS CARCINOMA OF THE BREAST: REPORT OF FOUR CASES AND REVIEW OF THE LITERATURE

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Sebaceous carcinoma of the breast is an exceedingly rare neoplasm. Little is known about the behavior and prognosis of this type of breast cancer. We report clinical, histological and immunohistochemical features of four cases of breast carcinoma with prominent (at least 50%) sebaceous differentiation. The tumors occurred in four women, aged 25-66, and were composed of cords, lobules and solid sheets of tumor cells with sebaceous differentiation, comprising 50-90% of the tumor mass. The second component consisted of cells with non-vacuolated cytoplasm, present mostly around the periphery of the lobules, or which formed separate tumor sheets with no evidence of sebaceous differentiation and were indistinguishable from a classical ductal carcinoma. Immunohistochemically, three tumors expressed hormone receptors; all cases were HER2-negative and had retained expression of the DNA mismatch repair proteins. Three patients had axillary lymph node metastases, and two patients had distant metastases: one in the liver, lung and bones, and one in the mediastinal and supraclavicular lymph nodes. One patient died 28 months after diagnosis, indicating that mammary sebaceous carcinoma is a potentially aggressive neoplasm. In contrast to extraocular cutaneous sebaceous carcinomas, mammary sebaceous carcinoma is probably unrelated to Muir-Torre syndrome. It should be differentiated from morphologically similar but biologically distinct lipid-rich carcinoma.

Key words: breast, sebaceous carcinoma, lipid-rich carcinoma, hormone receptors, HER2.

Introduction

Sebaceous differentiation in a mammary carcinoma is a very rare phenomenon. It has been described in 15 cases so far in the English-language literature, either as a minor or predominant component in a classical ductal carcinoma or as a pure line of differentiation [1-11]. According to the current WHO classification, primary sebaceous carcinoma of the breast must

show sebaceous differentiation in at least 50% of cells and have no evidence of origin from the cutaneous adnexa [12]. Because of its rare occurrence, little is known about the behavior and prognosis of this type of breast cancer. We report clinical, histological and immunohistochemical features of four cases of breast carcinoma with prominent (at least 50%) sebaceous differentiation, and the literature on sebaceous differentiation in mammary tumors is reviewed.

Clinical history

Case 1

A 65-year-old woman presented during regular mammography checkup with an opaque mass lesion in the upper lateral quadrant of her right breast. The mass was a new finding and had not been present on the mammograms two years before. The lesion showed irregular borders and retraction of the surrounding parenchyma (BI-RADS 5); the skin was unremarkable. A quadrantectomy with sentinel lymph node sampling was performed, followed by an axillary lymph node dissection. Macroscopically, the tumor measured 16 mm, had a grayish and yellow cut surface and was localized 15 mm from the overlying skin. The sentinel lymph node showed a metastasis of the carcinoma with a sebaceous morphology. Thirty-two axillary lymph nodes were retrieved; two of them showed a metastasis with a sebaceous morphology and one lymph node showed a micrometastasis with a classical ductal morphology. The patient underwent chemotherapy (four cycles of doxorubicin + cyclophosphamide + four cycles of docetaxel) followed by radiotherapy (total dose 42.56 Gy) and aromatase inhibitor therapy (letrozole). She is alive with no evidence of disease 27 months after diagnosis.

Case 2

The patient was a 61-year-old woman. A routine mammography examination showed an asymmetry in the upper lateral quadrant of the right breast (BI-RADS 2). An ultrasonographic examination revealed a hypoechoic poorly circumscribed mass measuring $17 \times 10 \times 7$ mm (BI-RADS 5) and a suspicious lymph node metastasis in the right axilla. The skin was inconspicuous. A modified radical mastectomy was performed. Grossly, the tumor was grayish-white on the cut surface and was poorly circumscribed. There was no connection to the overlying skin. An axillary lymphadenectomy yielded five lymph nodes; a metastasis was present in three lymph nodes. The patient received six cycles of chemotherapy (fluorouracil + doxorubicin + cyclophosphamide), followed by radiotherapy (total dose 50.0 Gy). Computed tomography examination performed 18 months after diagnosis (12 month after completion of radiotherapy) revealed metastases in the liver and the lungs. One month later, multiple bone metastases developed. The patient received combined paclitaxel and bevacizumab therapy and bisphosphonates to reduce the risk of fracture and bone pain. However, disease progression occurred after five months and third-line chemotherapy was administered (gemcitabine + carboplatin). Three months later the patient underwent surgery because of a pathological metaphyseal fracture of the right femur. The operation was compli-

cated by an arrhythmia and the patient was admitted to the intensive care unit. Her condition deteriorated rapidly and she died 28 months after diagnosis.

Case 3

A 66-year-old woman presented with a history of a palpable mass in the right breast. A modified radical mastectomy with axillary lymph node dissection was performed. Macroscopically, the tumor measured 30 mm in the largest diameter, showed a firm white cut section and had infiltrative borders. The skin above the tumor was unremarkable. One of ten lymph nodes showed a metastasis. The patient was treated postoperatively with six cycles of chemotherapy (fluorouracil + doxorubicin + cyclophosphamide), followed by tamoxifen. Twenty months after diagnosis, the patient underwent radical hysterectomy because of a well-differentiated endometrioid carcinoma. Regional recurrence of the breast cancer appeared 26 months after diagnosis and was treated by surgery, radiotherapy (total dose 50.0 Gy) and chemotherapy (6 cycles of vinorelbine + capecitabine). Disease progression occurred after another 28 months, with metastases in the mediastinal and supraclavicular lymph nodes. Eleven cycles of paclitaxel + bevacizumab were administered, followed by letrozole. She is in a good condition with a clinically stable disease, 70 months after diagnosis.

Case 4

A 25-year-old woman presented during regular medical checkup with a palpable lump in her right breast. Ultrasonographic and mammographic examination confirmed a tumorous mass. Segmentectomy and axillary lymphadenectomy were performed. The cut surface of the tumor was brownish and white. The size of the tumor and number of lymph nodes examined are unknown (consultation case); however, all lymph nodes were free of metastases. Postoperatively, the patient received six cycles of chemotherapy (doxorubicin + cyclophosphamide) followed by radiotherapy (total dose 50.0 Gy) with a high-dose radiation (HDR) boost (15.0 Gy). After the therapy she gave birth to one child. Currently, the patient is on hormonal (anti-estrogen) therapy with no evidence of disease 75 months after diagnosis.

Clinical findings are summarized in Table I.

Material and methods

The tissue specimens were fixed in 10% buffered formalin, routinely processed and embedded in paraffin. Five- μ m thick sections were stained with hematoxylin and eosin. Immunohistochemistry was done manually, according to the manufacturer's protocols. The following antibodies were used: estrogen recep-

Table I. Patient demographics, therapy and follow-up

CASE	AGE	TUMOR LOCALIZATION	pTNM	THERAPY	FOLLOW-UP
1	65	right breast, upper lateral quadrant	T1c N1a M0	quadrantectomy + SLN + axillary dissection; ACT; RAT (42.56 Gy); letrozole	ANOD 27 months
2	61	right breast, upper lateral quadrant	T2 N1a M1	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
3	66	right breast	T2 N1a M1	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
4	25	right breast	Tx N0 Mx	segmentectomy + axillary dissection; AC + RAT (50.0 Gy) + HDR boost (15.0 Gy) + anti-estrogen	gave birth to one child; ANOD 75 months

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

tor (clone 1D5, RTU, Dako, Glostrup, Denmark), progesterone receptor (clone PgR636, RTU, Dako, Glostrup, Denmark), Ki-67 (clone MM1, 1 : 50, Diagnostic Biosystems, Pleasanton, USA), p53 (clone D07, RTU, Dako, Glostrup, Denmark), HercepTest Dako (Dako, RTU, Glostrup, Denmark), EMA (clone E29, 1 : 100, Diagnostic Biosystems, Pleasanton, USA), S100 (clone 4C4.9, 1 : 100, Diagnostic Biosystems, Pleasanton, USA), GCDFP-15 (clone 23A3, 1 : 100, Cell Marque, Rocklin, USA), MLH1 (clone ES05, 1 : 100, Leica, Newcastle, UK), PMS2 (clone EPR3947, RTU, Cell Marque, Rocklin, USA), MSH2 (clone 25D12, 1 : 100, Leica, Newcastle, UK) and MSH6 (clone 44, 1 : 100, Diagnostic Biosystems, Pleasanton, USA). Appropriate positive and negative controls were used.

Results

Histologically, the tumors were composed of cords, lobules and solid sheets of cells with abundant vacuolated cytoplasm, reminiscent of mature sebocytes (Fig. 1). The sebaceous cell component varied from case to case, comprising 50-90% of the tumor volume. The nuclei of the sebaceous component varied from relatively small monomorphic and darkly stained, to large and pleomorphic with more vesicular appearance and prominent basophilic or slightly eosinophilic nucleoli. The nuclei were mostly eccentrically located and scalloped by the intracytoplasmic vacuoles (Fig. 2). The second component of the tumors consisted of cells with non-vacuolated eosinophilic or basophilic cytoplasm. These cells were pres-

ent mostly around the periphery of the lobules but also were focally intermixed with sebaceous cells (Fig. 3) or formed separate tumor sheets with no evidence of sebaceous differentiation and were indistinguishable from a classical ductal carcinoma (Fig. 4). Foci of comedonecrosis in the sebaceous component were present in two cases (Fig. 5). One tumor showed foci of ductal carcinoma *in situ* with sebaceous differentiation (Fig. 6). Squamous differentiation was not seen. Mitotic activity ranged from 5 to 39 mitoses per 10 high power fields. The stroma was densely collagenous or slightly myxoid. Individual cords and small nests of tumor cells were separated by thin collagenous septa with a rich capillary network. Lymphovascular invasion was identified in three cases. Prominent retraction clefts mimicking lymphatic spread were present in one case. None of the tumors reached the dermis or showed pagetoid spread. Histological findings are summarized in Table II.

Immunohistochemically, three tumors expressed hormone receptors and one was completely negative. In the positive cases, estrogen (ER) and progesterone receptors (PR) were expressed in 90-100% and 5-80% of tumor cells, respectively. HER2 (HercepTest Dako) was negative (0 or 1+) in three cases and equivocally positive (2+) in one case; CISH analysis (performed in an external laboratory) did not show amplification of the *HER2* gene. The Ki-67 labeling index, investigated in three cases, was 5%, 30% and 80%. One of the two investigated cases showed p53 overexpression (strong nuclear positivity in 30% of cells). EMA was expressed in three cases, whereas the remaining tumor was negative. S100 protein

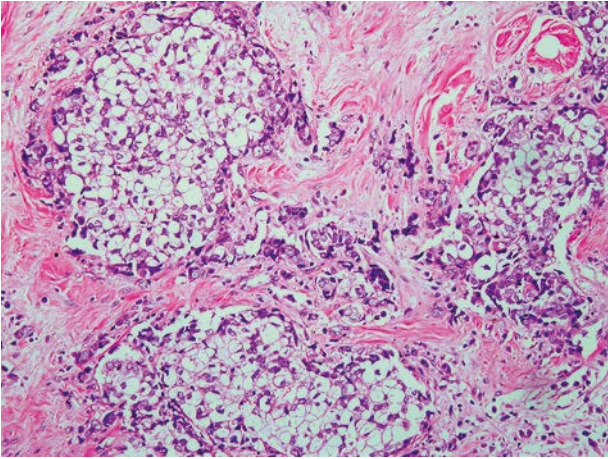


Fig. 1. Sebaceous carcinoma: Lobules of tumor cells with abundant vacuolated cytoplasm. More basophilic tumor cells are present at the periphery of the lobules. The stroma is densely collagenous (case 4, HE, magnification 100 \times)

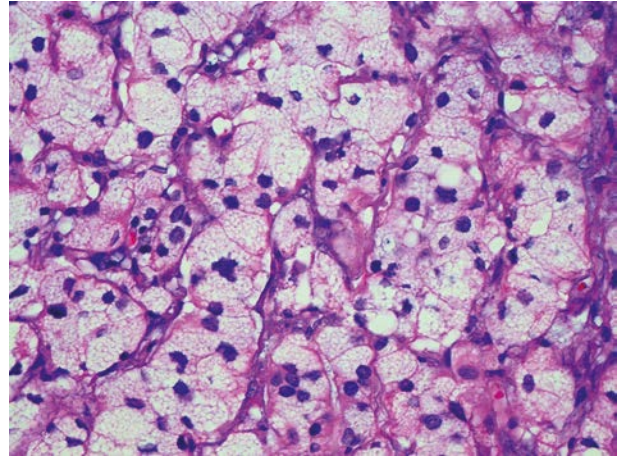


Fig. 2. Relatively uniform proliferation of cells with finely vacuolated cytoplasm and hyperchromatic scalloped nuclei without prominent nucleoli (case 1, HE, magnification 400 \times)

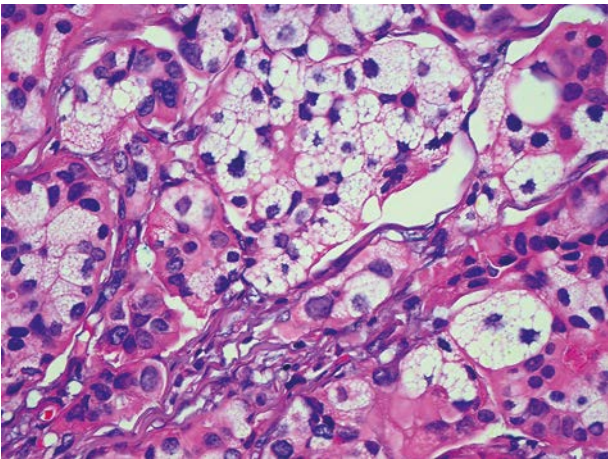


Fig. 3. Cells with non-vacuolated eosinophilic cytoplasm around the periphery of some nests. High-grade nuclear atypia and pleomorphism are more evident in these cells (case 1, HE, magnification 400 \times)

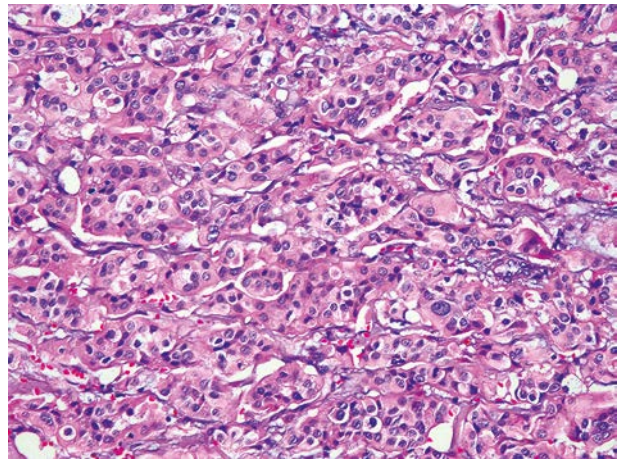


Fig. 4. Separate tumor sheets with no evidence of sebaceous differentiation, indistinguishable from a classical ductal carcinoma (case 1, HE, magnification 200 \times)

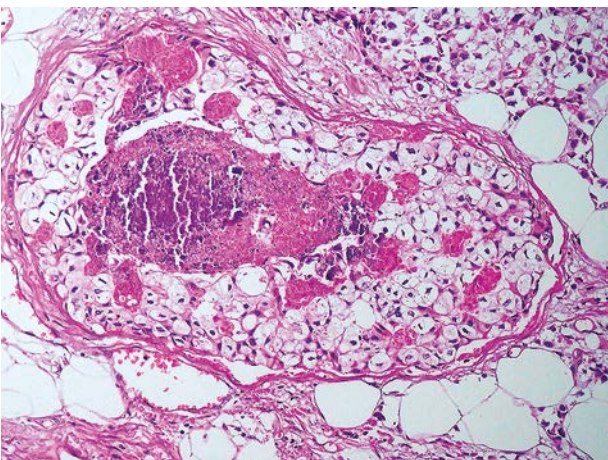


Fig. 5. Foci of comedonecrosis were present in two cases (case 3, HE, magnification 400 \times)

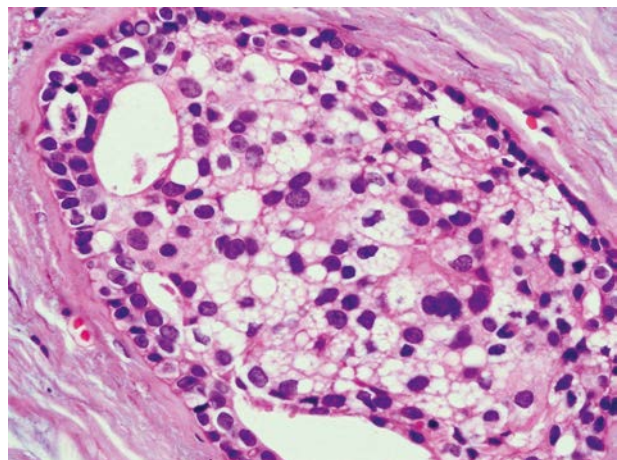


Fig. 6. Ductal carcinoma *in situ* with sebaceous features (case 1, HE, magnification 400 \times)

Table II. Summary of histological findings

CASE	NUCLEAR GRADE	MITOSES (PER 10 HPF)	NOTTINGHAM HISTOLOGIC GRADE	SEBACEOUS COMPONENT (%)	LYMPHOVASCULAR SPREAD	SEBACEOUS DCIS	COMEDO NECROSIS
1	3	15	3	80	+	+	-
2	3	39	3	50	+	-	+
3	2	7	2	> 90	+	-	+
4	3	5	3	60	-	-	-

hpf – high power fields; *DCIS* – ductal carcinoma in situ

Table III. Summary of immunohistochemical findings

CASE	ER (%)	PR (%)	HER2	KI-67 (%)	p53 (%)	GCDFP-15	S100	EMA
1	100	30	0	30	30	NA	-	+
2	0	0	1+	80	0	NA	NA	+
3	90	5	2+ / no HER2 amplification	5	NA	-	-	-
4	100	80	0	NA	NA	-	+	+

NA – not available

and GCDFP-15 expression were investigated in three and two cases, respectively; one tumor showed S100 expression; the rest of the cases were negative for these markers. All tumors had retained expression of the DNA mismatch repair proteins (MLH1, PMS2, MSH2 and MSH6). Immunohistochemical findings are summarized in Table III.

Discussion

Primary sebaceous carcinoma (SC) of the breast is a very rare tumor. It was proposed that SC represents a rare variant of metaplastic breast carcinoma [7, 11]. Carlucci *et al.* observed sebaceous differentiation in a triple-negative carcinoma with ductal, squamous, adenosquamous and spindle cell differentiation in the primary tumor and additional osteochondroid differentiation in the metastasis, respectively [11]. We have also observed sebaceous differentiation in a case of metaplastic high grade spindle cell carcinoma (unpublished personal observation, Z.K.). However, SC of the breast is classified in the current WHO classification as a separate entity along with other exceptionally rare types of carcinoma (i.e. secretory carcinoma, oncocytic carcinoma, lipid-rich carcinoma or glycogen-rich clear cell carcinoma). Sebaceous carcinoma is defined as a breast carcinoma with prominent sebaceous differentiation in at least 50% of cells and no evidence of origin from cutaneous adnexal sebaceous glands [12]. To the best of our knowledge, only ten cases of mammary SC are well documented in the English-language literature conforming to the above definition [1, 3-9]; these cases are summarized in Table IV. One of these cancers occurred in a male patient [3]. These tumors occurred in patients across

a wide age range (25-85 years, including our cases). A few cases of invasive ductal carcinoma with a minor sebaceous component (i.e. < 50%) have also been described [2, 10, 11]. Moreover, sebaceous differentiation rarely occurs in other malignant and benign mammary lesions: adenoid cystic carcinoma [13], cylindroma [14], adenomyoepithelioma [15, 16] or intraductal papilloma [17]. We have also observed sebaceous differentiation in a distinct subset of breast tumors which, in our view, are poorly characterized in breast pathology. They often show areas reminiscent of adenoid cystic carcinoma and constantly manifest plentiful ductal structures lined by an eosinophilic cuticle [18].

Not much is known about the behavior and prognosis of mammary SC. Two reported cases showed metastasis in one regional lymph node [6, 8]; three cases had negative lymph nodes [3-5]. Follow-up is available in three cases only: one patient was alive with no evidence of disease 24 months after the operation [8]; the second patient had no evidence of disease after ten months [3]; the third patient had skin and bone metastases 132 months after surgery [5]. Follow-up of our cases indicates that mammary SC might be a high-grade malignant neoplasm. Three of four patients had axillary lymph node metastases and two patients experienced an aggressive clinical course with distant metastases: one with metastases to the liver, lung and bones, and one with metastases to the mediastinal and supraclavicular lymph nodes. The carcinoma in case 2 proved to be fatal, and this case represents the first documented fatal case of mammary SC.

Regarding the potential therapeutic targets in mammary SC, altogether six cases (including three present cases) were ER and PR-positive [3, 5, 6] and

Table IV. Summary of clinicopathologic features of published cases of mammary sebaceous carcinoma

REFERENCE AND YEAR OF PUBLICATION	CLINICAL DATA	STAGING DATA	ER, PR AND HER2 STATUS	FOLLOW-UP	OTHER FINDINGS / COMMENT
Van Bogaert <i>et al.</i> [1]; 1977	3 cases, gender not stated, age ≥ 33 to ≤ 76 years	tumor size: ≥ 1.2 to ≥ 3.5 cm; lymph node stage NA	NA	NA	all three cases originally described as a "sebaceous-type" lipid-secreting carcinoma
Mazzella <i>et al.</i> [3]; 1995	male, 55 years; left breast	tumor size: 5 cm; negative LN	ER+, PR+, HER2 NA	ANOD, 10 months	case originally described as infiltrating ductal carcinoma with "lipid-rich sebaceous-like" component
Tavassoli [4]; 1992	female, 46 years; right breast	tumor size: 7.5 cm; negative LN	ER-, PR+, HER2 NA	NA	squamoid morules; androgen receptor negative
Varga <i>et al.</i> [5]; 2000	female, 45 years; right breast	tumor size: 2.5 cm; negative LN	ER+, PR+, HER2-	AWD, 132 months; skin and bone MTS	
Hisaoaka <i>et al.</i> [6]; 2006	female, 71 years; right breast	tumor size: 2 cm; one positive LN	ER+, PR+, HER2-	NA	androgen receptor negative
Moinfar [7]; 2007	female, 75 years; right breast	tumor size: NA; lymph node stage NA			squamous differentiation
Murakami <i>et al.</i> [8]; 2009	female, 50 years	tumor size: 2 cm; one positive LN	ER-, PR-, HER2 NA	ANOD, 24 months	androgen receptor positive
Ramljak <i>et al.</i> [9]; 2010	female, 85 years; left breast	tumor size: 7.5 cm; lymph node stage NA	ER-, PR-, HER2-	NA	

NA – not available; LN – lymph nodes; ANOD – alive with no evidence of disease; AWD – alive with disease; MTS – metastases

one case was ER-negative/PR-positive [4]. Three cases were hormone receptors-negative, including one of our cases [8, 9]. Three patients with ER/PR-positive tumors and available follow-up were alive with no evidence of disease, 10, 27 and 75 months after the operation (the case reported by Mazzella *et al.* [3] and cases 1 and 4 from the current report). Another two patients with hormone-positive tumors showed an aggressive clinical course with distant metastases, but were alive after 132 month and 70 months (the case reported by Varga *et al.* [5] and case 3 from the current study). One patient with ER/PR-negative tumor was alive with no evidence of disease 24 months after the operation [8], and one patient died 28 months after diagnosis (case 2 from the present study). All seven cases (including four present cases) that were investigated for HER2 expression/amplification were HER2-negative [5, 6, 9]. One tumor showed androgen receptor expression [8].

Differential diagnosis of mammary SC includes cutaneous SC and mammary lipid-rich carcinoma. Cutaneous SC can rarely involve the skin of the breast [19, 20] or the nipple [21]. The distinction between mammary and cutaneous SC can be made when there

is no connection to the overlying skin, both macroscopically and microscopically, or the tumor is completely surrounded by breast tissue [18]. Importantly, extraocular cutaneous SC can represent a manifestation of Muir-Torre syndrome (MTS), a phenotypic variant of Lynch syndrome (LS)/hereditary nonpolyposis colorectal cancer syndrome [22]. Muir-Torre syndrome/LS is caused by a germline mutation in one of the DNA mismatch repair genes resulting in non-functional protein, leading to microsatellite instability [22, 23]. Immunohistochemical detection of the DNA mismatch repair proteins (MMRP) can be used as a reliable screening method, as the loss of expression of a particular MMRP (most commonly MSH2 in MTS) generally correlates with the underlying germline mutation in the corresponding gene [22, 23]. All our cases showed retained immunohistochemical expression of MMRP. Kinkor *et al.* also did not find loss of MMRP expression in three cases of invasive ductal carcinoma with sebaceous differentiation [10]. Thus, so far, it seems that mammary carcinoma with sebaceous features is not associated with MTS/LS.

Lipid-rich (lipid-secreting) carcinoma is a rare special type of breast cancer. At least 90% of tumor

cells have abundant clear or vacuolated lipid-rich cytoplasm [12]. Interestingly, the first three cases of mammary SC were originally described as a variant (“sebaceous-type”) of lipid-secreting carcinoma [1]. In contrast to SC, which shows a compact lobulated solid growth pattern and finely vacuolated cells, lipid-rich carcinomas infiltrate like a regular invasive ductal carcinoma and vacuolization is much less conspicuous. The second cell population often present in the periphery of the lobules of the SC or squamous differentiation are absent in lipid-rich carcinomas [4]. In two studies, most cases of lipid-rich carcinoma were HER2-positive and ER/PR negative [24, 25].

In conclusion, we have described the clinicopathological features of four cases of mammary sebaceous carcinoma (sebaceous differentiation in at least 50% of tumor cells). Two of our patients had distant metastases and one patient died of the disease. This indicates that mammary SC is a potentially aggressive neoplasm. Most of the cases reported so far were ER/PR-positive, and hormonal therapy could represent a good therapeutic option. On the other hand, HER2 overexpression/amplification has not been reported so far. It seems that SC of the breast is unrelated to MTS/LS. More cases need to be investigated to better define the clinicopathological and prognostic features of this special type of breast cancer.

The following clinicians are acknowledged for providing the clinical follow-up: Radovan Barilla, MD, Department of Oncology and Radiotherapy, Štefan Kukura Hospital a.s., Michalovce, Slovakia; Lubica Legišnová, MD, Department of Radiology, Louis Pasteur University Hospital, Košice, Slovakia; BĽibiana BrezĽinová, MD, Department of Oncology, Hospital Trebišov a.s., Trebišov, Slovakia.

We are also grateful to RNDr. Lucia Lucia FröbliĽchová, Department of Pathology, Louis Pasteur University Hospital, Košice, Slovakia, for performing the immunohistochemical studies.

The authors declare no conflict of interest.

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