Eur J Cancer, Vol. 29A, No. 13, pp. 1824–1831, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

Sarcomatoid Tumours of the Breast in Denmark from 1977 to 1987. A Clinicopathological and Immunohistochemical Study of 100 Cases

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One hundred sarcomatoid breast tumours, which had been diagnosed and registered in Denmark from January 1977 to January 1987, were subclassified using a combination of conventional morphological evaluation and immunohistochemistry, and the diagnosis was in each case related to clinical follow-up of 5–14 years or until death of the patient. Conventional histological examination resulted in 36 benign, 19 borderline and 18 malignant phyllodes tumours, 1 angiosarcoma and 26 non-specified sarcomatous tumours, 6 with small carcinoma-like foci. Immunohistochemical staining revealed that 23 of the non-phylloid sarcomatous tumours showed a tumour cell reaction for epithelial markers, predominantly cytokeratin and, therefore, the tumours were interpreted as metaplastic carcinomas. Clinical follow-up showed for phyllodes tumours and for the three cytokeratin-negative sarcomatous tumours local recurrence rates of 21 and 33%, respectively, whereas metastases only occurred from the angiosarcoma and from one borderline phyllodes tumour with five recurrences (5%). In contrast, metaplastic carcinomas gave rise to distant metastases in 50% of cases but no local recurrences. Axillary lymph nodes had been examined in 28 cases, 13 from metaplastic carcinomas. Only two of these showed metastatic spread, both with a pattern similar to the primary tumour. The differences in survival between patients with metaplastic carcinoma and patients with a borderline/malignant phyllodes tumour or a cytokeratin-negative sarcomatous tumour has in this study proven to be highly significant ($P < 0.0001$), and we find it of importance to use immunohistochemistry in the subclassification of sarcomatous breast tumours for appropriate surgery, reliable prognostic outlook and optimal postoperative therapy.
Eur J Cancer, Vol. 29A, No. 13, pp. 1824–1831, 1993.

INTRODUCTION

SARCOMATOID BREAST tumours form a heterogenous group of rare mesenchymal neoplasms with the phyllodes tumour as the commonest and best known subtype. The phyllodes tumour (or cystosarcoma phyllodes) is a mixed tumour characterised by an epithelial, generally benign component and a mesenchymal component of varied malignancy [1–4]. Mitotic index, nuclear anaplasia, cellularity, the character of tumour margins and the presence of stromal overgrowth, defined as complete absence of ductal epithelium in at least one ×40 low power field, have been used to determine malignancy and predict the risk of recurrence/metastatic spread from these tumours [2–8]. The treatment of phyllodes tumours and other sarcomatoid tumours of the breast is surgery, either resection or simple mastectomy. Local recurrences are frequent but do not affect prognosis [2, 3, 9, 10], except in rare cases of direct extension through the chest wall [2, 5, 11, 12]. Metastatic rates for phyllodes tumours range from 3 to 24% [6, 7], and for non-phylloid sarcomatous tumours from 40 to 63% [12, 13].

Histo- and pathogenesis of sarcomatous breast tumours, or stromal sarcomas, comprising only mesenchymal components, has been the subject of considerable speculation. With the advent of electron microscopy and immunohistochemistry it has been increasingly clear that at least four possibilities exist: (1) they may arise *de novo* through transformation of normal mesenchymal cells, as has been described following irradiation [14, 15], (2) they may result from stromal overgrowth of a phyllodes tumour [8, 13], (3) they may represent a carcinoma with sarcomatous metaplasia (metaplastic carcinoma) [16, 17] or (4) a myoepithelial carcinoma [18].

The present study was carried out with the purpose of obtaining a more specific subclassification of sarcomatoid breast tumours and—by relating this to their metastatic potential—to find the optimal surgical approach to each of these tumour types and a more reliable prognostic outlook at the time of diagnosis.

PATIENTS AND METHODS

From January 1977 to January 1987 all sarcomatoid breast tumours diagnosed in Denmark were reported consecutively to the Danish Breast Cancer Cooperative Group (DBCG), and the patients were subjected to clinical follow-up at regular intervals. 104 cases, one bilateral, were registered, and tissue samples from these tumours underwent standardised formalin fixation, dehydration and paraffin-embedding procedures. The age of the patients ranged from 13 to 94 years with median and mean values of 49 and 50 years, respectively. Two tumours turned out to be metastases from primary soft tissue sarcoma elsewhere, and another two were metastases from malignant melanoma. These four were excluded leaving a total of 100 tumours from 99 women.

Between five and 32 histological slides (average 10) from the primary tumours, their recurrences and metastases were reviewed and reclassified by two pathologists, and additional

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Revised 7 Feb. 1993; accepted 25 Mar. 1993.

Table 1. Original (a) and revised (b) diagnoses (of 100 sarcomatoid breast tumours based on morphology (a + b) and after immunohistochemistry

Tumour type	(a) Original diagnosis (*n*)	(b) Revised diagnosis (*n*)	Immunohistochemical diagnosis (*n*)
Benign phyllodes tumour	41	36	36
Borderline phyllodes tumour	14	19	19
Malignant phyllodes tumour	25	18	18
Non-phylloid sarcomatous tumour	19	26 (6)	3
Angiosarcoma	1	1	1
Metaplastic carcinoma	—	—	23
Total	100	100	100

No. of tumours with small carcinoma-like foci in parentheses.

sections were cut for immunohistochemistry. On the basis of the criteria proposed by Pietruszka and Barnes [3] and Azzopardi [19], the series was divided into two main groups: phyllodes tumours and non-phylloid sarcomatous tumours. The phyllodes tumours were morphologically classified into benign, borderline and malignant subtypes depending on cellularity, cellular atypia, number of mitoses, necroses, type of borders (e.g. pushing vs. infiltrating) [2, 3, 10] and the presence of stromal overgrowth [4] (Table 1).

Malignant mesenchymal tumours lacking the epithelium-lined clefts were classified as sarcomatous tumours with various cellular patterns, and tumours containing small carcinoma-like foci were classified as metaplastic carcinomas (Table 1b). For further characterisation of the different cell types and the nature of the extracellular tissues, immunostaining by the peroxidase–antiperoxidase method was performed using a panel of monoclonal and polyclonal antibodies against α-smooth muscle actin (α-actin), α-1-antichymotrypsin (α-1-ACT), B 72.3, carcinoembryonic antigen (CEA), cytokeratins, desmin, von Willebrand factor (factor 8), fibronectin, keratin (wide spectrum screening; keratin WSS), keratin, laminin, leucocyte common antigen (LCA), L 26, lysozyme, MT 1, neuron specific enolase (NSE), S-100 protein (S-100) and vimentin (for details, see Table 2). Prior to immunostaining with most antibodies (excluding LCA, L26, MT1, B 72.3, NSE and actin) sections received a 5-min proteolytic digestion with 0.5 mg/ml protease (Sigma type 24, P 8038), which in the case of fibronectin was further followed by a 30-min incubation with testicular hyaluronidase (2×10^6U/l) (Leo, Sweden) in Tris-buffered saline (TBS) at 37°C.

Clinical records and a complete clinical follow-up were available in all cases via hospitals and general practitioners (range 44–171 months, mean 100 months). Of the 30 patients who died from 1 to 118 months after the first operation, 14 died with metastatic breast cancer (one bilateral). This was verified by a complete autopsy investigation in 8 cases and in 6 cases by X-ray examinations combined with needle biopsy findings (3 cases).

The primary surgical treatment of the tumours included simple mastectomy in 40 cases, excision in 57 cases and enucleation in 3. The exact localisations of the morphologically different tumour subtypes appear from Fig. 1. In 5 cases surgical

Table 2. Immunohistochemistry staining protocol used for subclassification of 100 sarcomatoid tumours

Component	Brand	Antibody	Dilution	Cells and tissues
α-Actin	DAKO*	Monoclonal	1:25	Smooth muscle cells Myofibroblasts Myoepithelial cells
α-1-ACT	DAKO	Polyclonal	1:400	Histiocytic cells
B 72.3	Biogenex†	Monoclonal	1:50	Adenocarcinoma cells
CEA	DAKO	Polyclonal	1:200	Epithelial cells
Cytokeratin	DAKO	Monoclonal	1:15	Epithelia with keratins 10, 17, 18
Cytokeratin	Becton Dickinson‡	Monoclonal	1:15	Epithelia with keratins 8, 18
Desmin	DAKO	Monoclonal	1:15	Smooth muscle cells
Factor 8	DAKO	Polyclonal	1:50	Endothelial cells
Fibronectin	DAKO	Polyclonal	1:200	Connective tissue in breast carcinoma
Keratin (WSS)	DAKO	Polyclonal	1:200	Keratins with molecular weights of: 51, 52, 56, 59, 60 kD
Keratin	DAKO	Polyclonal	1:200	Well-differentiated squamous cells
Laminin	Reidar Albrechtsen§	Polyclonal	1:100	Basement membranes
LCA	DAKO	Monoclonal	1:5	Leukocytes Monocytes
L 26	DAKO	Monoclonal	1:50	B Lymphocytes
Lysozyme	DAKO	Polyclonal	1:400	Histiocytic cells
MT 1	DAKO	Monoclonal	1:50	T Lymphocytes
NSE	DAKO	Polyclonal	1:400	Neuroendocrine cells
S-100	DAKO	Polyclonal	1:100	Glial/Schwann cells, ependyma, melanocytic/myoepithelial cells
Vimentin	DAKO	Monoclonal	1:10	Mesenchymal cells

*DAKO A/S, Glostrup, Denmark; †BioGenex Laboratories, San Ramon, U.S.A.; ‡Becton Dickinson, Erembodegem, Belgium; §Reidar Albrechtsen, Institute of Pathology, University of Copenhagen, Denmark.

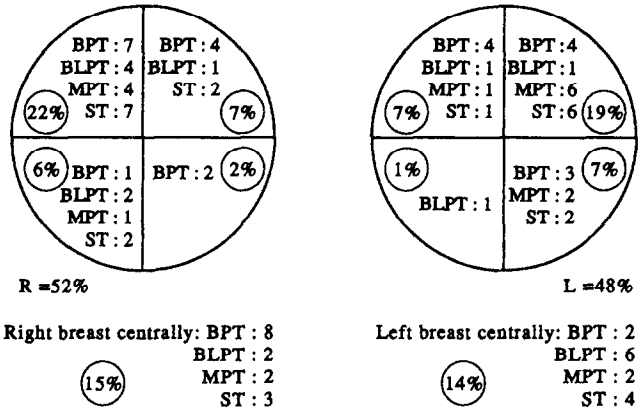

Fig. 1. Schematic presentation of the primary localisation of 100 sarcomatoid breast tumours. BPT, benign phyllodes tumour; BLPT, borderline phyllodes tumour; MPT, malignant phyllodes tumour; ST, sarcomatous tumour (non-phylloid).

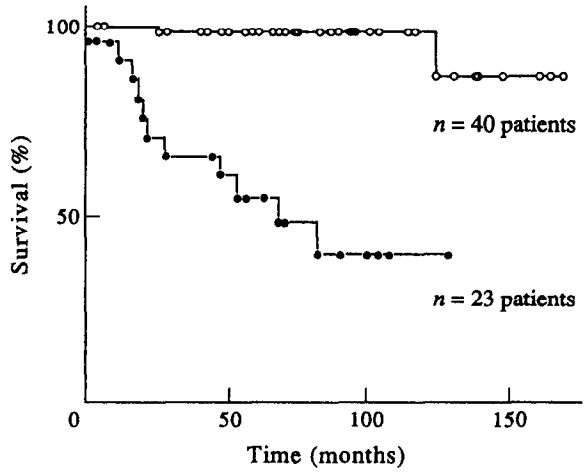

Fig. 2. Kaplan–Meier plot of life tables for patients (pts) with borderline phyllodes, malignant phyllodes and cytokeratin-negative sarcomatous tumours (open circles), and for patients with metaplastic carcinomas (closed circles).

intervention was followed by radiotherapy of the operation field and in 2 cases chemotherapy was administered.

Axillary lymph nodes were removed and examined at the primary operation in 13 cases of phyllodes tumours and in 15 cases of other sarcomatous tumours.

Statistical analyses included life tables constructed according to Kaplan–Meier (Fig. 2). The survival of (1) patients with borderline/malignant phyllodes tumour or cytokeratin-negative malignant sarcomatous tumour and (2) patients with metaplastic carcinoma was compared using the log rank test and the χ^2 test for trend.

RESULTS

Histology

Phyllodes tumours. An overview of the 73 phyllodes tumours is given in Tables 1 and 3. Tumour size ranged from 1 to 35 cm with an average of 4.7 cm. The benign subtype was the most common, and all tumours in this group had pushing borders. Borderline and malignant tumours occurred with the same frequency and displayed an increased incidence of stromal metaplasia with increasing features of malignancy (Table 3). The ratios between pushing and infiltrating borders were for the borderline tumours 12/7 and for tumours characterised as malignant 6/11.

Stromal overgrowth was found in only two malignant phyllodes tumours. The epithelium lining the elongated ducts was hyperplastic in 85% of the tumours, with an even distribution among the three subgroups, and *in situ* carcinoma of ductal type (DCIS) occurred in 2 benign, 6 borderline and 1 malignant case, corresponding to 12% of the whole series of phyllodes tumours. These *in situ* changes were of the small cell type in 5 cases with a combination of cribriform/papillary type patterns (Fig. 3a), and in 4 of the large cell type with a solid/cribriform pattern (Fig. 3b).

Invasive breast carcinoma of metaplastic spindle cell type was discovered along with the fourth local relapse of a borderline phyllodes tumour (Fig. 4). This was interpreted as a collision tumour originating from non-phylloid breast tissue rather than a carcinoma having developed from the epithelial component of the phyllodes tumour, as neither ductal nor lobular *in situ* changes had been present in the primary tumour or its first three recurrences.

Table 3. Predominant stromal pattern in 100 sarcomatoid breast tumours before and after immunohistochemistry (IHC)

Stromal metaplasia	Tumour type before IHC				Tumour type after IHC				
	BPT	BLPT	MPT	ST	BPT	BLPT	MPT	TS	MC
Leiomyo	1	4	4	1	1	4	5	1	1
Lipo				2					2
Leiomyo/lipo			1				1		
Chondro			2	1			2		1
Osteo				1					1
Osteo/chondro				1					1
Giant cell			3	3			3	1	2
Angio				1				1	
Spindle	35	15	8	17	35	15	7	1	15
Total	36	19	18	27	36	19	18	4	23

BPT: Benign phyllodes tumour; BLPT: borderline phyllodes tumour; MPT: malignant phyllodes tumour; ST: non-phylloid sarcomatous tumour; TS: cytokeratin-negative ST; MC: Metaplastic carcinoma.

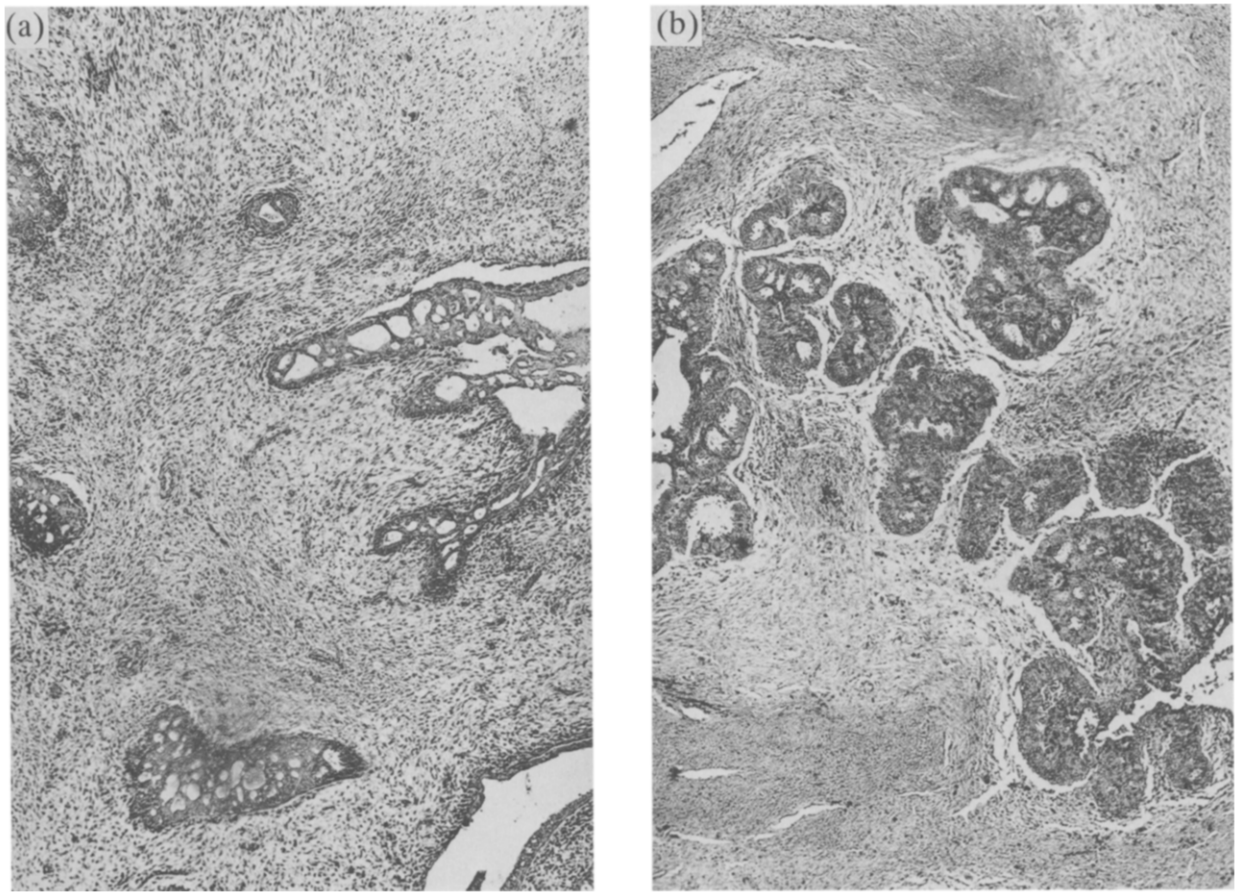

Fig. 3. (a) ***In situ*** **carcinoma with a cribriform/papillary pattern (small cell type) of the duct epithelium in a borderline phyllodes tumour. (b)** ***In situ*** **carcinoma of cribriform/solid type (large cell pattern) in a borderline phyllodes tumour.**

Sarcomatous tumours

These 27 tumours were all cellular mesenchymatous, cytologically malignant neoplasms, which lacked the epithelial-lined clefts characteristic of the phyllodes tumour [Tables 1(b) and 3]. Their sizes ranged from 1.5 to 12 cm with an average of 4.5 cm. One tumour was readily diagnosed as angiosarcoma, due to the abundance of vessels surrounded by abnormal cells, and six tumours raised suspicion of metaplastic carcinoma because the sarcomatous tumour tissue contained small carcinoma-like foci [Table 1(b)]. The remaining 20 neoplasms were diagnosed as sarcomatous with frequencies of osteoid, chondroid, lipomatous and giant cell patterns comparable to the ones observed for the malignant phyllodes tumours (Table 3).

Immunohistochemistry

The panel of polyclonal and monoclonal antibodies revealed a surprising variety in reactivity patterns, when applied to different tumours (Table 4). In many tumours only a proportion of the tumour cells or stroma were stained, but in some cases all tumour tissue was stained.

The mesenchymal cell marker vimentin could be demonstrated within the sarcomatoid tumour cells in all cases (Table 4). Smooth muscle or myofibroblastic origin was generally established by a positive reaction for vimentin and α-actin combined with a negative reaction for epithelial markers (Table 4). Tumours with giant cells and a storiform spindle cell pattern like that of malignant fibrous histiocytoma showed cellular immunoreactivity for histiocytic markers (α-1-ACT and/or lysozyme) (Table 4).

Whenever the mesenchymatoid tumour cells showed a positive reaction for one or more of the epithelial markers, generally cytokeratin, the tumour was classified as a metaplastic carcinoma (Table 4, Figs 5a, 6, 7). This resulted in a surprisingly large number of metaplastic carcinomas [20] and a corresponding reduction in the number of non-phylloid sarcomatous tumours [3]. In many cases only 5–10% of the tumour cells were positive for the epithelial markers, whereas most of them were vimentin positive (Table 4, Fig. 5a, b). One tumour showing positivity for both α-actin, cytokeratin and vimentin met the criteria of a myoepithelial carcinoma [18]. Some of the cytokeratin-positive sarcomatous tumour cells also reacted with the adenocarcinoma marker B 72.3 and keratin WSS, whereas EMA only stained the more epithelial-looking cells (Table 4). Fibronectin was used to screen sections for foci of epitheloid tumour cells within the metaplastic carcinomas because of its intense stromal reactivity around weakly stained or negative epithelial tumour cells (Table 4, Fig. 5c).

Only the angiosarcoma and three sarcomatous, non-phylloid tumours remained, which did not react with any of the epithelial markers. Two of the latter were of the spindle cell type, and one had the features of a malignant fibrous histiocytoma (Table 4).

Among the metaplastic carcinomas were two with a predominant liposarcomatoid pattern (Table 3). Being exceedingly rare these 2 cases will be given special attention:

Case 1. A 65-year-old woman with no previous breast disease or malignancy had radical mastectomy with removal of 12 axillary lymph nodes for a 5-cm white, rubbery, lobular, well

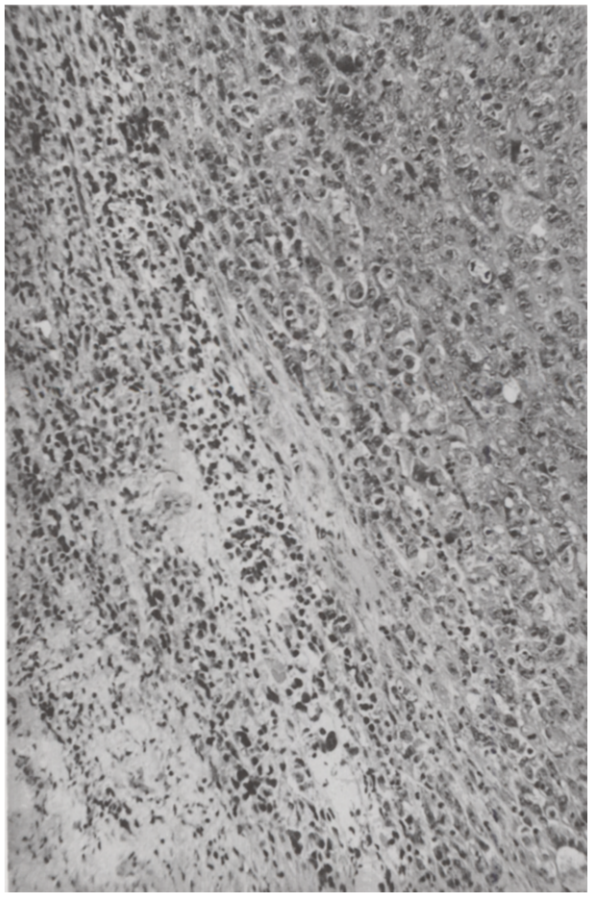

Fig. 4. Collision between a recurrent borderline phyllodes tumour (top) and an invasive carcinoma of spindle cell type (bottom). Numerous lymphocytes are seen in the border zone between the two tumours.

Table 4. Immunohistochemical staining pattern of mesenchymatoid tumour cells in 100 sarcomatoid breast tumours. Only antibodies with positive, tumour cell-related reaction patterns are shown

Antibody	BPT	BLPT	MPT	ST
α-Actin	1	4	6	12 (11*)
α-1-ACT			3	4
B 72.3				16
Cytokeratin (DAKO)				23
Cytokeratin (Becton-Dickinson)				22
EMA				7
Factor-8				1
Fibronectin				23*
Keratin (wide spectrum)				5
Lysozyme			2	2
Vimentin	36	19	18	27

BPT: Benign phyllodes tumour; BLPT: borderline phyllodes tumour; MPT: malignant phyllodes tumour; ST: non-phylloid sarcomatous tumour.
*Staining of benign stroma immediately around tumour cells.

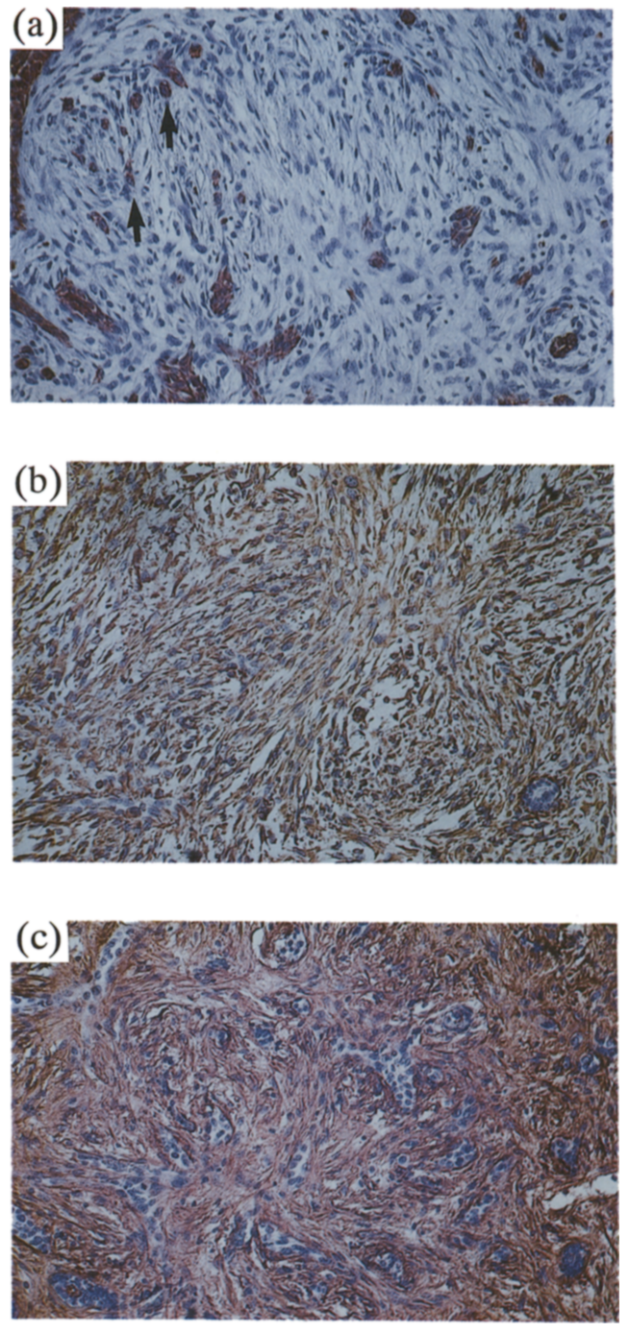

Fig. 5. Spindle cell metaplastic carcinoma. Immunoreactivity for cytokeratin is apparent within tumour cells, which are arranged in small groups or infiltrating individually (a, arrows). Immunoreactivity for vimentin is seen in both malignant tumour cells and benign stroma cells. Only the epithelium of a normal duct (bottom right) is negative (b). Immunoreactivity for fibronectin shows an intense fibrillar staining pattern of the stroma surrounding the unreactive tumour cells (c).

circumscribed tumour located in the upper lateral quadrant of the left breast. Histological diagnosis: myxoid liposarcoma, based on morphology, electron microscopy and positively stained tumour cells in Sudan black and oil red O lipid stains. The patient died 7 years later with wide-spread lung metastases, only verified radiologically. No autopsy was performed.

Case 2. A 48-year-old woman with severe fibrocystic breast disease verified histologically 6 years previously was admitted

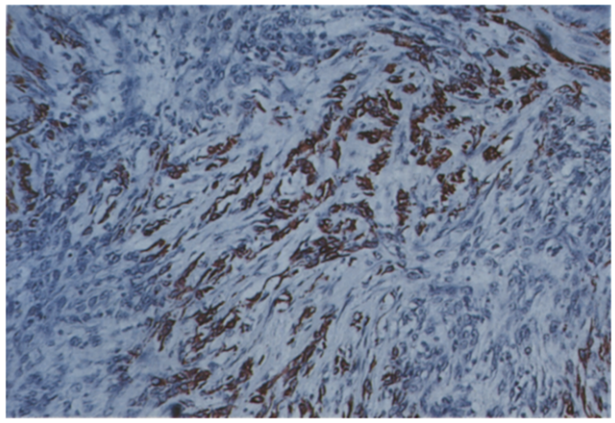

Fig. 6. Another spindle cell metaplastic carcinoma with large patches of cytokeratin-positive tumour cells.

with sclerosing metastases to the spine. Histology: pleomorphic tumour tissue. Shortly after, an 8-cm white, hard tumour was discovered centrally in the left breast and a similar 3-cm tumour centrally in the right breast. Bilateral mastectomy was performed along with removal of one tumour-infiltrated lymph node in the left axilla. Histological diagnosis: pleomorphic liposarcoma of the left breast with metastasis to one axillary lymph node (Fig. 7) and the contralateral breast. Diagnosis was based on morphology and conventional fat stains (see Case 1). The patient died 1 month later, and at autopsy metastases to the brain, the liver and the spine with pleomorphic tumour tissue were all verified histologically.

Axillary lymph nodes

At the primary operation axillary lymph nodes were removed and examined in a total of 28 cases, i.e. in 2 cases of benign phyllodes tumour (two and 10 nodes), 7 cases of borderline phyllodes tumour (two to eight nodes, mean five), 4 cases of malignant phyllodes tumour (two to seven nodes, mean four), 1 case of angiosarcoma (four nodes), 1 case of cytokeratin-negative sarcomatous tumours (three nodes), and in 13 cases of cytokeratin-positive sarcomatoid tumours (one to 23 nodes, mean eight).

Metastatic spread at the primary operation was only seen in 2 cases, both from metaplastic carcinomas (1/1 and 1/5 lymph nodes). In the first case only the metaplastic liposarcomatous component of the primary tumour was apparent (Fig. 7). The other showed a giant cell sarcomatoid pattern similar to that of the primary tumour.

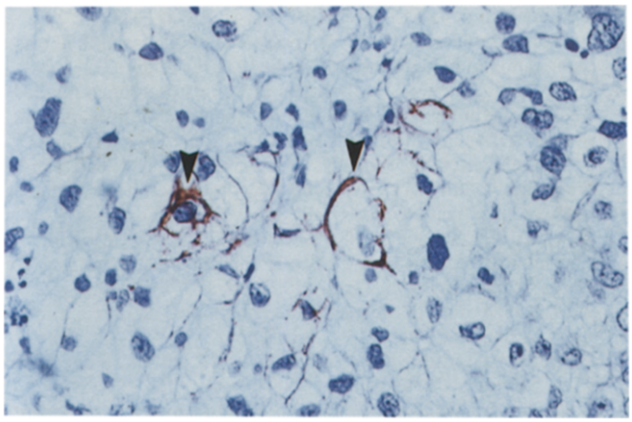

Fig. 7. Metaplastic carcinoma with liposarcomatous metaplasia (axillary lymph node metastasis). Lipoblast-like tumour cells display a distinct, cytokeratin-positive reaction pattern (arrowheads).

Clinical follow-up

Local recurrences. Local recurrences occurred from one to five times (mean two) in 21% of the phyllodes tumours, i.e. seven benign, six borderline, two malignant phyllodes tumours, and in one cytokeratin-negative sarcomatous tumour (33%). Three recurrences appeared after enucleation of the primary tumour, and the remaining 13 following excision. Recurrences tended to show a more malignant cytological stromal pattern than the primary tumour, and four of the six recurrent borderline tumours became cytologically malignant in contrast to the benign phyllodes tumours, where only one recurred with borderline features. One borderline phyllodes tumour recurred five times showing stromal overgrowth in the last four recurrences. This was the only phyllodes tumour of the study, which gave rise to distant metastases (see below).

No local relapse was found for the metaplastic carcinomas, but 1 patient with a borderline phyllodes tumour had developed a metaplastic, cytokeratin-positive spindle cell carcinoma along with the fourth recurrence (Fig. 4) and died with carcinomatous lung metastases.

Distant metastases

14 patients (14%) have died with metastatic disease, 13 within the first 7 years after diagnosis, and 1 after 10 years. 16 patients died with no sign of recurrence (16%), although 3 in this latter group died from other malignancies (ovarian carcinoma, associated invasive duct carcinoma and subsequent metaplastic carcinoma of the breast). 13 patients died from unrelated causes (13%). 69 patients (69%) are still alive and well after 44–171 months (mean 100 months).

Distant metastases developed from the only angiosarcoma of this study, and from 12 metaplastic carcinomas (52%). 1 patient with a phyllodes tumour died after 125 months with metastatic spread to the lung and the supraclavicular region after having recurred locally five times. The epithelial component was absent in the metastases. Twelve metaplastic carcinomas showed a combination of metastatic spread to lung (9 cases), bones (3 cases), brain (4 cases), liver (1 case), mediastinal/abdominal lymph nodes (2 cases) and contralateral breast (1 case).

Statistical evaluation

As it appears from the Kaplan–Meier plot of life tables in Fig. 2, the survival pattern of patients with borderline/malignant phyllodes tumours and cytokeratin-negative sarcomatous tumours differed from that of patients with metaplastic carcinomas in a highly significant manner ($P < 0.0001$).

DISCUSSION

With the advent of immunohistochemical technique it has been apparent that many breast tumours previously diagnosed morphologically as stromal sarcoma are metaplastic carcinoma with an extensive sarcomatous component [16, 19, 21]. This is accomplished by their immunoreactivity for epithelial markers, mainly keratins of the low molecular weight subtypes [22, 21], and by their intense stromal immunoreactivity for the connective tissue glycoprotein, fibronectin [20]. However, although the three non-phylloid sarcomatous tumours of this study, whose tumour cells failed to react with any of the epithelial markers, may be "true" stromal sarcomas or phyllodes tumours with an excessive stromal overgrowth, they may also be metaplastic

carcinomas, which fail to react with any of the available epithelial markers.

A dual immunoreactivity for keratin and vimentin of sarcomatous, α-actin-negative tumour cells, as was registered in this study, has been observed by others [16, 19, 21] and suggests a transition form between epithelial and mesenchymal phenotypes. Transition from epithelial to mesenchymal phenotypes with rearrangements of desmosomal and cytoskeletal proteins has been described in functional studies on cultured rat bladder carcinoma cells, which were found to assume phenotype dependent on extracellular matrix components of the growth substrate [23, 24]. Considering the vast qualitative and quantitative changes in extracellular matrix components known to occur in invasive breast carcinoma [25, 26], it is plausible that the phenotypic changes seen in the tumour cells of metaplastic carcinomas are accomplished by a similar mechanism.

Phyllodes tumours have a characteristic macro- and microscopic two-component appearance, which differs from that of the intracanalicular fibroadenoma by the nature of the stroma cells (large embryonic-looking fibroblasts) and their quantity [3]. The histological feature is of limited value in predicting biological behaviour of the tumour [2, 27], although two parameters have been found to be closely associated with poor prognosis: infiltrating borders [2] and stromal overgrowth [8]. The only metastasing phyllodes tumour of this series had an infiltrating border and showed stromal overgrowth in the last four local recurrences.

In the first national Danish series of sarcomatoid breast tumours covering the years 1943–1973, malignant phyllodes tumours, borderline phyllodes tumours and "other" sarcomatous tumours were diagnosed in 24, 7 and 22 cases, respectively [13]. The corresponding figures in the present national Danish series covering only 10 years (1977–1987) are 18, 19 and 4, reflecting an overall increase in these tumours as well as a proportional change between the three subtypes. The overall increase in sarcomatous tumours may be attributed to the increase in population and an improved registration system and possibly a genuine increase in incidence, as it has been seen for carcinomas of the breast.

Immunohistochemistry performed on all the tumours has in this study proven a major reason for the radical changes in the ratio between different subcategories of sarcomatoid tumours. In a recent report of 32 primary breast sarcomas only 15 had been subjected to staining with immunohistochemical markers, including cytokeratins. The other 17 tumours remained to be ruled out as metaplastic carcinomas by immunohistochemistry [28]. In our opinion this staining method is mandatory for the identification of sarcomatous tumours devoid of morphologically recognisable epithelial components as metaplastic carcinomas through its labelling of cell- and matrix-specific molecules.

The practical implications for reaching an exact diagnosis appear from the fact that apart from the angiosarcoma, which is known for its fatal course [29], and one recurrent phyllodes tumour, which eventually metastasised and caused death of the patient after 125 months, the only metastasising tumours were metaplastic carcinomas. Patients with metaplastic carcinomas have been shown to have a 5-year survival of 47–68% [30, 19, 29, 31]. We found that 50% of these patients died with metastatic disease within the first 7 years after diagnosis, although only 9.7% of the tumours (two out of 23) showed metastatic spread to the regional axillary lymph nodes. The contrasting results of this investigation compared with those of our previous study regarding the metastatic potential of phyllodes tumours and cytokeratin-negative sarcomatous tumours are probably not attributed to the underdiagnosis of metaplastic carcinomas alone. Histological examination of metastatic tissue, including immunohistochemistry, has revealed that also primary invasive breast carcinoma arising before, after or concurrently to the phyllodes tumour is responsible for the metastatic spread. Coexistence of carcinoma and phyllodes tumour of the breast occurs—and the risk seems to increase with each local recurrence of the phyllodes tumour [32]. In this study 85% of the phyllodes tumours showed hyperplasia and 12% *in situ* carcinoma of ductal type. Invasive carcinoma was found along with only one borderline phyllodes tumour, recurring locally for the fourth time, and although it was interpreted as the collision between a phyllodes tumour and a carcinoma with origin in the surrounding non-phylloid breast tissue, we cannot exclude the possibility that some of the metaplastic carcinomas stem from the epithelial component of a phyllodes tumour, which they have partially or completely replaced.

In accordance with others we have shown that phyllodes tumours, in contrast to carcinomas, run a low risk of metastatic behaviour [3, 4, 9, 11, 12]. It is possible that the stromal proliferations seen in the phyllodes tumour reflect a growth disturbance in response to hormonal changes, eventually leading to neoplasia. This would explain the high recurrence rate and low metastatic potential of these tumours, as well as the frequent finding of hyperplastic duct epithelium.

In conclusion, we have found that phyllodes tumours of the breast are relatively benign (i.e. non-metastasising) tumours, which only in case of several recurrences and cytological/histological criteria of malignancy (i.e. invasive borders, stromal overgrowth) may run a low malignancy course with fatal spread. We believe that tumours, mimicking sarcomas morphologically but displaying epithelial markers within their mesenchymatoid tumour cells, should be referred to as metaplastic carcinomas. Like other breast carcinomas, these tumours have a high metastatic potential despite frequently negative lymph nodes, as observed in this and other studies [10, 21, 31, 32], and it is mandatory for clinical treatment and control that these tumours are separated from the more benign phyllodes tumours.

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Acknowledgements—The authors wish to thank the Departments of Pathology at the following hospitals for providing original sections and extra unstained sections for immunostaining: Bispebjerg, Frederiksberg, Esbjerg, Hillerød, Holstebro, Hvidovre, Kommunehospitalet, KAS Gentofte, KAS Glostrup, KAS Herlev, Nykøbing Falster, Næstved, Odense, Randers, Roskilde, Skive, Slagelse, Sundby, Svendborg, Sønderborg,Vejle, Ålborg, Århus Amtssygehus, Århus Kommunehospital. The Danish National Register and general practitioners all over the country are gratefully acknowledged for their assistance in clinical follow-up and information on death causes.

The study was supported by grants from Martha Margrethe and Christian Hermansens Foundation, Åge Henningsen's Foundation, the Danish Medical Research Council and the Danish Cancer Society.

Eur J Cancer, Vol. 29A, No. 13, pp. 1831–1835, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

Adjuvant Chemotherapy with a Nitrosourea-based Protocol in Advanced Malignant Melanoma

C. Karakousis and L. Blumenson

173 patients with regional lymphatic metastases (n = 139) or distant disease (n = 34) were prospectively randomised, following resection of all clinically detectable tumour, to observation (n = 88) or adjuvant chemotherapy (n = 85). The treatment group received 1, 3-bis(2-chloroethyl)-1-nitrosourea (BCNU) 80 mg/m² intravenously (i.v.) every 4 weeks, and actinomycin-D 10 μg/kg, vincristine 1.0 mg/m² i.v. every 2 weeks for 6 months. The disease-free survival curves between the two groups were significantly different (P = 0.03). The estimated 5-year disease-free survival rate for the observation group was 9% and for the treatment group 29%. However, the overall survival curves were not significantly different for the two groups. Nitrosoureas may have a weak effect as adjuvant treatment in malignant melanoma.
Eur J Cancer, Vol. 29A, No. 13, pp. 1831–1835, 1993.

INTRODUCTION

PATIENTS WITH recurrent melanoma generally have a poor outlook. Those with regional node involvement attain a 5-year survival rate ranging from 10–13% [1, 2] to 37% [3] following therapeutic node dissection. The majority of these patients, however, manifest recurrence and die of progression of their disease.

Patients presenting with distant, haematogenous metastases generally have diffuse, non-resectable disease, although occasionally this may be limited to one or two sites and hence can be resected. Following resection this group of patients may be expected to have a worse prognosis when compared with prognoses of patients with clinical involvement limited to the regional nodes.