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Mucoepidermoid mammary carcinoma

Immunohistochemical and biochemical analyses of intermediate filaments*

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Summary. The histological features of mucoepidermoid mammary carcinomas (MMCs) are presented, and criteria for distinguishing these tumours from squamous epithelial metaplasia in other mammary carcinomas are considered. Immunohistochemical and gel-electrophoretic analyses of the intermediate-filament proteins in one MMC case revealed a complex pattern of cytokeratin polypeptide expression. The simple-epithelium-type cytokeratins 7, 8, 18, and 19 were detected mainly in nonsquamous (including mucinous) cells, while the stratified-epithelium-type cytokeratins 5, 6, 14, 16, and 17 were present in squamous cells. However, in both the nonsquamous and squamous regions of the tumour, cytokeratins of the "reverse" type were detected in individual cells. This pattern of single-cell heterogeneity with respect to cytokeratin polypeptide expression suggests that the mixed phenotype of this tumour is not caused by the clonal divergence of tumour cell types. Rather, histogenetically, a pluripotent stem cell with the ability to differentiate into squamous (epidermoid) or mucinous cells might be the starting-point of such a tumour and such differentiation processes may continue to occur during tumour growth. The present case also revealed that mucoepidermoid tumours are not necessarily of low malignancy; there are highly malignant forms with rapid metastasis.

Key words: Mucoepidermoid mammary carcinoma – Squamous metaplasia – Cytokeratins – Histogenesis – Malignancy status

Introduction

The term "mucoepidermoid tumour" was first coined by Stewart et al. (1945) to describe a tumour of the salivary glands that was a compound of two different cell types, epidermoid (squamous) epithelium and mucinous cells. Subsequent studies reported the presence of such tumours at other sites (Hamperl and Hellweg 1957) including the portio uteri, the nasal and oral cavities, the larynx, the bronchial system, the oesophagus (Ming 1973), the mucous layer of the urinary bladder, and the anus.

In a more recent investigation, Patchefsky et al. (1979) described the clinical and histological features of mammary tumours that seem to be identical with the low-grade mucoepidermoid carcinomas of the salivary glands. In contrast, Kovi et al. (1981) and Ratanarapee et al. (1983) classified the mucoepidermoid tumours that they observed as being high-grade tumours (Table 1). The clinical course of these lesions involved the appearance of many metastases in the axillary lymph nodes and, later, in the brain and lungs. In a large study dealing with breast carcinomas, Fisher et al. (1983) observed two further cases with low malignancy, which failed to exhibit regional or distant metastases over an observation period of 10 years. These observations are in agreement with our findings in the case of an 81-year-old woman suffering from a low-grade carcinoma (Lüchtrath 1984), in whose long case history there was no evidence of metastases. Meanwhile, Leong and Williams (1985) and Hastrup and Sehested (1985) have reported two additional cases, both of which were highly malignant and rapidly led to a fatal outcome (Table 1). The recent occurrence of such a high-grade tumour among our patients gave us the opportunity to perform immunohistochemical investigation of this type of carcinoma.

Clinical course. According to her own report, the 60-year-old female patient had discovered a firm node in her breast 3 months before hospitalization. Biopsy followed by radical mastectomy revealed the presence of a carcinoma measuring

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Table 1. Published cases of mucoepidermoid mammary carcinoma

Authors	Age (years)	Grade of malignancy	Axillary lymph node metastases	Distant metastases	Therapy	Follow-up (months)[a]
Patchefsky et al. 1979	66	low	0/20	0	Radical mastectomy (R.M.)	94:0
	70	low	–[b]	0	local excis.	10:0
Kovi et al. 1981	46	high	17/19	–[b]	R.M.	–[b]
Fisher et al. 1983	65		–[b]		local excis.	60:0
	71		0/19		R.M.	48:0
	57	low	0/11	0	R.M.	120:0
	49		0/13		R.M.	108:0
	60		–[b]		R.M.	48:0
Ratanarapee et al. 1983	27	high	6/15	brain, lung	R.M.	13:deceased
Lüchtrath 1984	81	low	–[b]	0	Simple mastectomy	–[b]
Hastrup and Sehested 1985	59	high	0/14	lung, bone, liver	R.M.	26:deceased
Leong and Williams 1985	57	high	0/20	bone, lung	R.M.	6:deceased
Lüchtrath and Moll (present study)	60	high	12/18	bone	R.M.	30:deceased

[a] 0 = no tumour relapse and no metastasis observed
[b] no information available

5 × 4 × 3 cm. Of the 18 lymph nodes in the axilla, 12 exhibited metastases. Despite radio- and chemotherapy, four local relapses occurred. Generalized metastases caused the patient's death 30 months after the mastectomy.

Materials and methods

We obtained tissue from each of these four local relapses as well as histological specimens from the primary tumour. As some of the surgical material had not been fixed, it was possible to freeze this tissue for later use in making a cytoskeletal preparation. For purposes of comparison, normal mammary tissue (including mamillary tissue) of postmenopausal patients was frozen (unfixed) in liquid nitrogen.

The rest of the tumour material studied was fixed in formalin, embedded in paraffin, and cut into sections 3–5 μm thick.

In addition, we examined paraffin-embedded specimens of solid mammary carcinomas (with and without squamous epithelial metaplasia) and mucoepidermoid tumours from other sites (e.g., conjunctiva and salivary glands) as well as material obtained from a previously described mucoepidermoid mammary carcinoma (Lüchtrath 1984).

Sections were stained with haematoxylin and eosin (H&E) and we also used a combination of Alcian-blue and PAS staining. We also applied silver staining according to the procedure of Gomori as well as Prussian-blue staining. For the immunohistochemical study, we used various antibodies against intermediate-filament proteins (listed in Table 2). Paraffin sections were subjected to either the avidin-biotin method or the alkaline-phosphatase anti-alkaline-phosphatase (APAAP) technique. All of the reagents used were purchased from Dakopatts (Hamburg, FRG). During the study, a combined Alcian blue/immunohistochemical staining procedure was developed which allowed mucous matter to be distinguished; this involved Alcian-blue staining followed by washing in distilled water and immunohistochemical staining. Cryostat sections that had been prepared from frozen material and fixed with acetone were subjected to a previously described indirect immunoperoxidase method (Franke and Moll 1987). In some cases, we applied indirect immunofluorescence microscopy using secondary antibodies labeled with Texas Red (Franke and Moll 1987). Negative controls were performed by replacing the primary antibody with phosphate-buffered saline (PBS) or an irrelevant monoclonal antibody. These controls consistently yielded negative results.

For biochemical analyses of cytoskeletal proteins, 20-μm-thick cryostat sections were cut. The target structures (tumour tissue, normal ductal and lobular structures) were separated by microdissection, and cytoskeletal fractions were then obtained by extracting the soluble components. The cytoskeletal proteins were analyzed using two-dimensional gel electrophoresis (for details, see Moll et al. 1982, 1983a).

Results

The primary tumour and the four tumour relapses exhibited similar histological features. The former was localized in the central, submamillar portion of the mammary gland; the major lactiferous ducts were also affected.

Histologically, this case of mucoepidermoid mammary cancer was characterized by the presence of extensive epidermoid structures (Fig. 1). These often contained variably sized foci of rela-

Table 2. List of antibodies used

Antibody[a]	Specificity	Commercial source	Reference
Paraffin sections			
KL 1	several cytokeratins	Immunotech, Marseille, France	Viac et al. 1983
AE 1/AE 3	many cytokeratins	Hybritech/Camon, Wiesbaden, FRG	Tseng et al. 1982
DAKO-CK 1 (LP 34)	several cytokeratins[b]	Dakopatts, Hamburg, FRG	Lane et al. 1985
Cryostat sections			
K_s18.174	cytokeratin 18	Progen, Heidelberg, FRG	Moll et al. 1988
K_s19.2.105	cytokeratin 19	Progen	Franke and Moll 1987
CK 7	cytokeratin 7	Amersham-Buchler, Braunschweig, FRG	Toelle et al. 1985
GP-IT	IT-protein	–	Moll et al. 1987
KA 1	cytokeratin 14	–	Nagle et al. 1986; Jarasch et al. 1988
6 B 10	cytokeratin 4	Euro-Diagnostics, Apeldoorn, Netherlands	Van Muijen et al. 1986
1 C 7	cytokeratin 13	Euro-Diagnostics	Van Muijen et al. 1986
K_K8.60	cytokeratins 10, 11	Bio-Makor, Rehovot, Israel	Huszar et al. 1986
VIM-9	vimentin	Viramed, Martinsried, FRG	Pitz et al. 1987
G-A-5	glial fibrillary protein (GFP)	Boehringer, Mannheim, FRG	Debus et al. 1983

[a] All antibodies are monoclonal murine antibodies (IgG) except for GP-IT which is a polyclonal guinea-pig-antibody preparation. Commercially obtained antibodies were diluted according to the instructions of the distributors. In the other cases, tissue culture supernatants were used undiluted or diluted up to 1:5 whereas ascites fluid (antibody KA 1) was diluted 1:100 with phosphate-buffered saline (PBS). [b] According to the information available from the distributor, only those cells in the paraffin material are recognized which contain cytokeratin proteins (e.g., cytokeratins 6 and 18) in a large quantity

tively mature, squamous-type epithelium consisting of large cells that were rich in cytoplasm, had large, pale nuclei, and exhibited intercellular bridges (Fig. 1a, c). Single-cell keratinization was frequently observed, while abortive horn-pearl formation was occasionally encountered (Fig. 1c). In the peripheral zones of such squamous foci, there were smaller cells that were often arranged in elongated groups and whose nuclei were darker, more compact, and round to fusiform in shape (Fig. 1c); these cells seemed to form a matrix from which the more mature squamous epithelium emerged.

Other tumour segments consisted of areas of simple epithelium that were either solid-trabecular, containing disseminated mucus-filled goblet cells, or exhibited lumina of different sizes filled with Alcian-blue-positive mucus (Fig. 1b). In places, the lumina appeared to have merged into variably large cysts (cf. Lüchtrath 1984).

In some regions, small groups of so-called intermediate cells were observable (these were much more abundant in the case discussed in Lüchtrath 1984); the cells were medium sized, fairly rich in cytoplasm and formed cords and sheets as in squamous epithelia, and were characterized by the presence of a nucleus with honeycomb-like structure.

Squamous epithelial metaplasia in otherwise solid mammary carcinomas exhibited a similar structure, characterized by the occurrance of squamous layers with intercellular bridges; however, the formation of mucus was not observable in these cases.

Immunohistochemical analysis of the present case using KL 1 (a broad-spectrum cytokeratin antibody) resulted in positive reactions in all of the tumour epithelia tested. In contrast, the vimentin antibody, VIM-9, only stained stroma cells. The antibody G-A-5 against glial fibrillary protein (GFP) did not produce a positive reaction (not shown). The antibody (K_s18.174) against cytokeratin 18, whose presence is a typical feature of simple and glandular epithelia, stained most of the relatively small cells forming the solid-trabecular and tubular (nonsquamous) structures of the tumour, including goblet cells. In contrast, the foci and sheet layers of (larger) squamous cells were mostly cytokeratin 18 negative (Fig. 2a). The arrays of positive and negative cells were closely associated with each other. Often, small cytokeratin-18-positive cells were localized immediately next to larger, negative squamous cells. However, on occasion the tumour-cell sheets composed of both nonsquamous and squamous cells were predominantly negative for this cytokeratin. However, scattered single or small groups of cytokeratin-18-positive cells were sometimes visible in squamous epithelium-type tumour sheets otherwise completely negative (Fig. 2a, inset). The antibody CK 7 which is directed against the simple-epithelial-type cytokeratin 7 demonstrated a staining pattern similar to

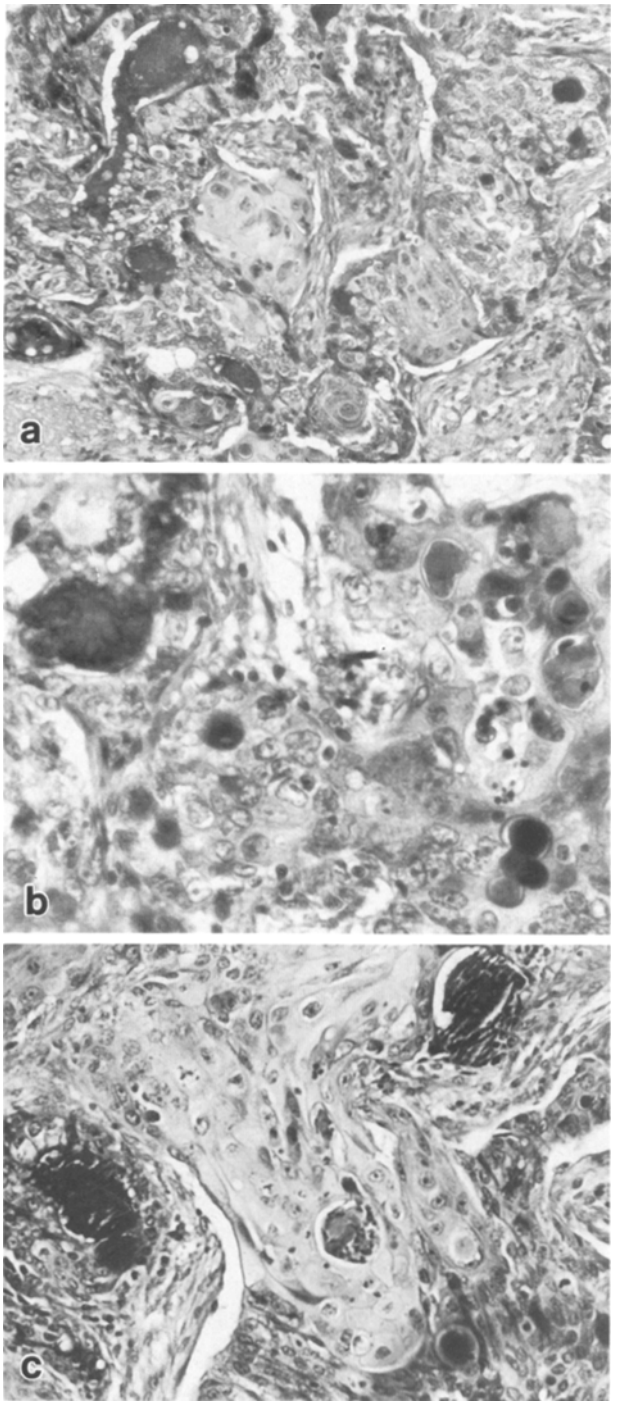

Fig. 1a–c. Mucoepidermoid carcinoma of the breast. **a** Squamous areas and glandular formations (Alcian blue/PAS). **b** Nonsquamous region showing formation of mucus which is visible in lumina and goblet cells (Alcian blue/PAS). **c** Squamous epithelia exhibiting keratin pearls and the formation of mucus in adjacent areas (Alcian blue/PAS). **a, b** ×460; **c** ×230

that produced by the antibody against cytokeratin 18. Cytokeratin 19 was also found to be strongly expressed in tubular and trabecular areas; parts of the squamous epithelial areas were slightly positive for this cytokeratin (Fig. 2b). Tests using antibodies against IT-protein were negative.

The antibody KA 1, which is directed against stratified-epithelial cytokeratins, labelled the foci and sheet layers of large squamous cells primarily, although individual cells and small cell groups in solid-trabecular (and more microcellular) areas, including some goblet cells, were also positive; this resulted in a distinctive mosaic-like staining pattern (Fig. 2d). Comparison of serial sections suggested that some cells were positive for both the antibody against cytokeratin 18 and KA 1, although the patterns were in general very different. In the tumour, cytokeratin 13 was only found in sparsely distributed individual cells (Fig. 2d). The reaction for cytokeratin 4 was essentially negative, with scattered tumour cells providing rare exceptions. The tumour cells were negative for the antibody K_K 8.60, which is directed against cytokeratins 10 and 11, both of which are typically expressed in keratinizing cells.

When a mixture of antibodies AE 1 and AE 3 was applied to paraffin sections, a large proportion of the tumour cells were stained, whereas squamous areas exhibited no reaction. Tests using antibody DAKO-CK1 produced virtually the opposite reaction pattern. Alcian-blue staining combined with immunohistochemical procedures showed that larger, mucus-filled lumina and cysts were lined by cylindrical cells positive for simple-epithelial cytokeratins. Application of the antibody DAKO-CK 1 allowed cellular maturation in the epidermoid areas to be examined in detail. These areas were frequently surrounded by fusiform cells (see above) that reacted negatively with this antibody. The inner layers were progressively more positive, with the strength of the reaction corresponding to the degree of squamous maturation. The reaction of this antibody on paraffin-embedded material can therefore be used to determine the grade of squamous-epithelial differentiation.

Two-dimensional gel electrophoresis of a cytoskeletal preparation of the tumour tissue revealed the presence of cytokeratins 5, 6, 14, 16, and 17, these being typical of stratified squamous epithelia, as well as cytokeratins 7, 8, 18, and 19, which are typical of simple epithelia (Fig. 3).

Furthermore, the large lactiferous ducts of the mamilla were analyzed immunohistochemically. In paraffin sections, parts of the epithelia of the inner layer reacted positively with DAKO-CK 1, although the distribution patterns were varied. When examined biochemically, microdissected large lactiferous ducts of the mamilla were found to contain cytokeratins 5, 6, 14 and 17, as well as cytokeratins 7, 8, 18, and 19. The small lactiferous ducts exhib-

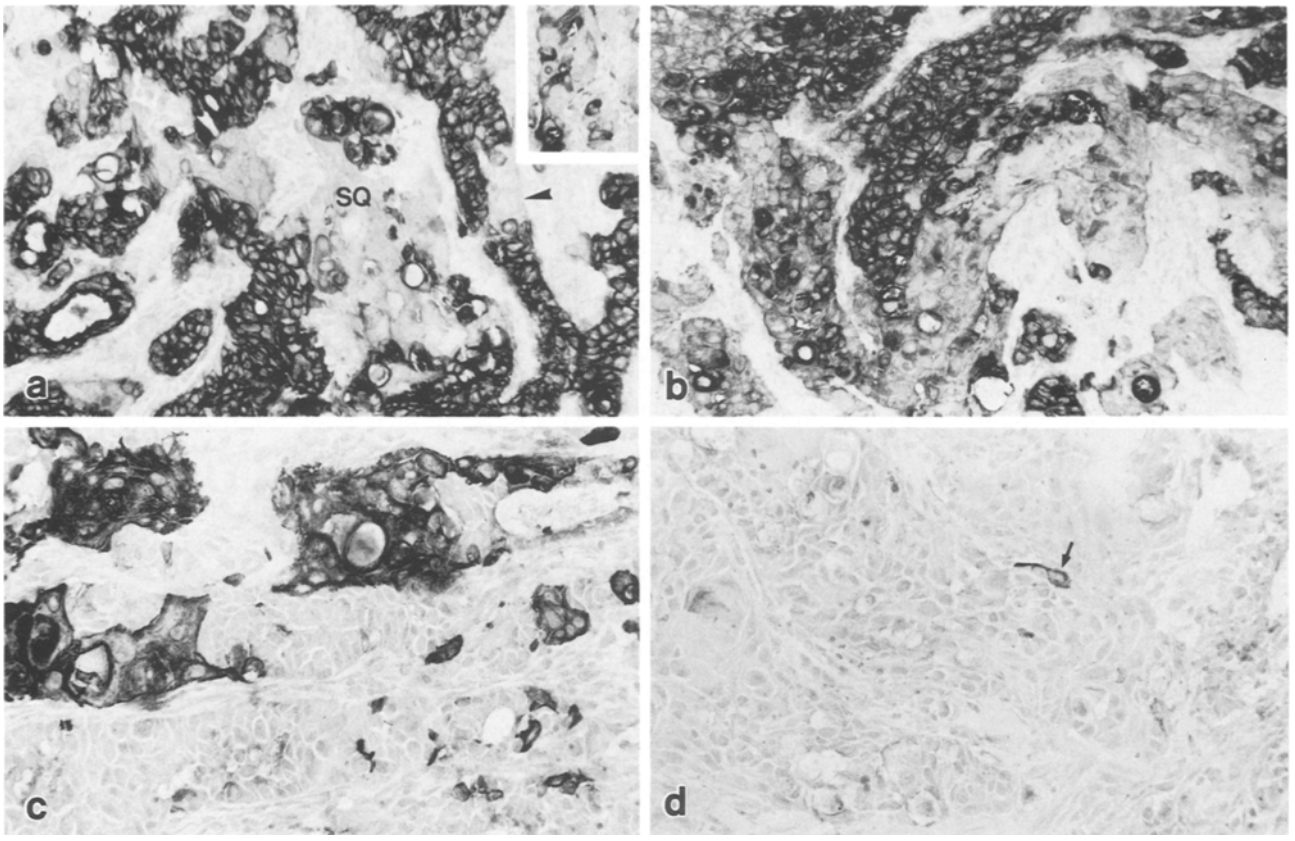

Fig. 2a–d. Immunohistochemical detection of various cytokeratins in a mucoepidermoid mammary carcinoma (immunoperoxidase microscopy, frozen sections). **a** Cytokeratin 18 (antibody K_s18.174) produced a positive staining of glandular and trabecular structures, whereas squamous regions (SQ) were essentially negative or showed a few single positive cells (*inset*). Note that some negative squamous cells border directly on the stroma (*arrowhead*). **b** Cytokeratin 19 (antibody K_s19.2.105) was predominantly present in nonsquamous regions but also reacted positively in squamous regions. **c** Strong expression of stratified-epithelial cytokeratins (antibody KA1) in squamous regions (*upper half*) as well as in some cells of apparently nonsquamous regions (e.g., *lower right*). **d** A single tumour cell (*arrow*) positive for cytokeratin 13 (antibody 1C7). ×110

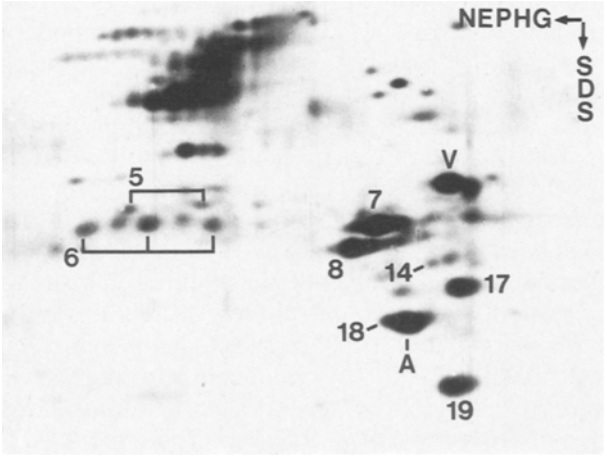

Fig. 3. Two-dimensional gel electrophoresis of cytoskeletal proteins of a mucoepidermoid mammary carcinoma (*NEPHG*, first dimension of electrophoresis using nonequilibrium pH gradient electrophoresis; SDS, second dimension of electrophoresis in the presence of sodium dodecyl sulfate; silver staining). Cytokeratins are denoted by *numbers* according to Moll et al. (1982). The spot denoted "17" probably also includes cytokeratin 16. *V*, vimentin derived from stromal cells

ited a similar pattern (Moll et al. 1983a), although the squamous-epithelium-type cytokeratin 6 was not detectable. This was also the case for microdissected lobular structures of inactive mammary tissue, which exhibited cytokeratins 5, 14, 15, and 17, as well as cytokeratins 7, 8 (in larger amounts than in the small ducts), 18, and 19.

Discussion

Although a mucoepidermoid tumour is an unusual occurrence at any site, mucoepidermoid mammary carcinomas (MMCs) are particular rarities. In the literature, we have only been able to find 13 cases of this kind of carcinoma (including our own) three of which were in Europe (Table 1). Their real incidence is probably higher than these figures suggest – Fisher et al. (1983) have estimated that MMCs account for 0.2% of all mammary carcinomas. The tumours may often be overlooked due to incorrect diagnoses of common types of mammary carcinoma exhibiting squamous differentiation (Cornog

Table 3. Differential diagnosis of mammary carcinomas with squamous features

	Mucoepidermoid mammary carcinomas	Squamous epithelial metaplasias in common mammary carcinomas
Extent of squamous foci	Large squamous areas	Squamous foci
Glycogen	+	+
Keratinization	+	+
Mucous cells within squamous epithelium	+	0
Mucous cysts	+	0
Intermediary cells	+	0

et al. 1971). Even when this potential source of error is taken into account, correct diagnosis may still be difficult. In common mammary carcinomas, squamous epithelial metaplasia is usually focal, whereas in MMCs, squamous epithelial sheets dominate the histological picture and form the main distinguishing feature of such tumours. In metaplasia, mucus formation is completely absent and, therefore, cyst formation is never encountered. In Table 3, the criteria for distinguishing the two types of carcinoma are listed. It is also possible to distinguish MMCs from purely squamous epithelial carcinomas (Cornog et al. 1971) because only the former exhibit mucus formation. Furthermore, undifferentiated large cell carcinomas (Fisher et al. 1983), particularly those with apocrine metaplasia (Azzopardi 1979), need to be distinguished from true squamous tumours and tumour areas (both in MMCs and squamous metaplasias). The presence of glycogen (Fisher et al. 1983) and intercellular bridges are important criteria for identifying whether tumours are of a true squamous character.

The histological structure of MMCs corresponds with that of mucoepidermoid tumours at other sites (salivary glands Seifert (1966) Freytag (1986), cervix uteri (Hamperl and Hellweg (1957) and oesophagus Ming (1973)).

Among MMCs, there are conspicuous differences in maturation. In our first case (Lüchtrath 1984) intermediary cells were dominant throughout large areas of the tumour; the present tumour consisted of large squamous complexes exhibiting areas of keratinization. Intermediary cells need not necessarily be present; indeed, Fisher et al. (1983) found such cells in only one of five tumours. Another source of difference concerns the formation of mucus. Most cases (including our first) exhibited cisternae filled with mucus (Lüchtrath 1984; Leong and Williams 1985). These features are typical and provide macroscopic indicators concerning the nature of the lesion. In our present case, mucus was also evident but in far smaller amounts than usual.

In the study of MMCs Leong and Williams (1985) have applied immunohistochemical procedures, using antisera against keratin. They observed strongly positive reactions in "epithelial pearls". In the present study, all cells of the MMC contained intermediate filaments composed exclusively of keratin (cytokeratin) proteins, which are general markers of epithelial differentiation (Franke et al. 1979; Sun et al. 1979), but no vimentin-type intermediate filaments. In this respect, MMCs are comparable with the majority of common mammary carcinomas (Altmannsberger et al. 1981). However, our immunohistochemical and biochemical analyses of the various subtypes of cytokeratins revealed a complex situation in MMC, in contrast to the relatively simple and uniform cytokeratin composition of most common mammary carcinomas (mainly the simple-epithelium-type cytokeratins 7, 8, 18, and 19; Altmannsberger et al. 1986; Moll and Franke 1986; Nagle et al. 1986). Immunohistochemical analysis for specific individual cytokeratins allowed two major structural components of the MMC to be distinguished. The first was the squamous component consisting of foci and sheets of large, maturing squamous cells: these areas were positive for antibody KA1, which recognizes cytokeratins typical of stratified squamous epithelia (probably cytokeratin 14; Jarasch et al. 1988). Positive reactions with antibody KA1 and the related antibody CK-B1 have been described in rare cases of invasive ductal mammary carcinoma, but this finding has yet to be related to specific morphological features (Altmannsberger et al. 1986; Nagle et al. 1986; Jarasch et al. 1988). Using biochemical procedures, we were able to identify several stratification-related cytokeratins (nos. 5, 6, 14, 16, 17) in the MMC tumour tissue; among these, cytokeratins 6 and 16 may be correlated with more advanced squamous-epithelial maturation (Stoler et al. 1988).

The other structures of the tumour expressed cytokeratins of the simple-epithelial (glandular) type, this being consistent with the mucus produc-

tion detected at these sites. Although cytokeratin analysis revealed the MCC to have an essentially dual composition (squamous vs. nonsquamous), each component contained a proportion of cells expressing the cytokeratins found in the other component. This feature, along with the co-expression of stratified- and simple-epithelial cytokeratins observed in some cells, emphasizes that squamous and glandular characteristics may be closely combined in this kind of tumour. Thus, the immunohistochemical staining patterns are of no clonal significance. It can therefore be assumed that such tumours are not composed of two different, independent, and self-proliferating elements, but rather are basically uniform, containing cells of simple-epithelial (glandular) and squamous character at different stages of differentiation. This accounts for the marked phenotypic tumour heterogeneity that is apparent both morphologically and in the cytokeratin expression. This view is further supported by the fact that all four local tumour relapses showed a cell mixture similar to that observed in the primary tumour. Such differentiation changes can be considered as being metaplastic processes, such as squamous metaplasia, which (for example, in the cervix uteri) has been shown to be associated with changes in cytokeratin expression (Moll et al. 1983b; Gigi-Leitner et al. 1986; Levy et al. 1988). Our results therefore show that, histological features aside, it is possible to identify the components of a tumour consisting of a mixture of squamous epithelial and glandular elements on the basis of molecular biological findings.

With regard to histogenesis, most common mammary carcinomas are thought to originate from "terminal ductal lobular units" (Wellings et al. 1975), in which it is hypothesized that stem cells of the mammary epithelium may be present; however, the question of the localization of such stem cells has given rise to differing theories (Bartek et al. 1985; Dulbecco et al. 1986). When considering the histogenesis of MMCs, it is important to bear in mind that a mixture of cell types (basal/myoepithelial and luminal cells) with divergent cytokeratin patterns is found throughout the mammary parenchyma, including the most peripheral structures (Moll et al. 1983a; Bartek et al. 1985; Nagle et al. 1986; Dairkee et al. 1987). Therefore, our finding of a complex cytokeratin pattern in an MMC does not allow the definitive establishment of a particular histogenetic pathway. Several arguments suggest that MMCs may originate in the large lactiferous ducts and in the majority of MMCs observed so far, these ducts have been found to be involved in the tumour (Kovi et al. 1981; Fisher et al. 1983; the present study). Furthermore, in the present case, a link with the large mamillary lactiferous ducts can be deduced from shared features with respect to cytokeratin distribution, that is, the presence in the tumour and ducts of cytokeratin 6 and the similar staining pattern for antibody DAKO-CK1. Finally, estrogen and progesterone receptors have never been detected in MMC tumours analyzed for these components (Lüchtrath 1984; Hastrup and Sehested 1985; in the present case, we were only able to use lectin binding, which also produced a negative result). However, because of the rarity of MMCs, definitive proof concerning their histogenesis is very difficult to obtain. It is conceivable that a histogenetic role is played by squamous-epithelia metaplasia of ductal or lobular mammary epithelium, or metaplasia occurring in phylloid cystosarcomas, dysontogenetic cysts, or otherwise differentiated carcinomas (Bässler 1978). In any case, the development of such a tumour presupposes the existence of pluripotent cells that are capable of differentiating in two directions; toward squamous epithelium and mucin producing elements (Hamperl and Hellweg 1957). In addition, these cells and their progeny must still be able to select a different type of differentiation during the growth of the tumour (see above).

In the much more common mucoepidermoid tumours that arise in the salivary glands, expression of cytokeratins has also been found (Caselitz et al. 1981) and recent immunohistochemical results suggest that they have a relatively complex cytokeratin composition (Gustafsson et al. 1988). However, in this last study, it proved impossible to distinguish the different cell types present. In contrast to the present MMC, salivary-gland mucoepidermoid tumours have previously been reported to be positive for GFP (Hamper et al. 1989).

There can be no doubt that MMCs should be assigned a malignant status. The previous cases, reported by Patchefsky et al. (1979), Fisher et al. (1983), and ourselves (Lüchtrath 1984) were all tumours of low malignancy. Lymph node and distant metastases were absent, which led Fisher et al. (1983) to ask whether highly malignant MMCs exist at all. However, Kovi et al. (1981) and, more recently, Hastrup and Sehested (1985) and Leong and Williams (1985) have described high-grade MMC tumours to which our present case can be added. The clinical course of such tumours is characterized by a short survival time and many metastases. In the present case, despite radical mastec-

tomy and chemotherapy, there were four relapses and generalized metastasis, leading to death 30 months after diagnosis. This indicates that the degree of malignancy cannot be ascertained from the histological picture alone. Our highly malignant case exhibited a rather mature structure with a high level of squamous differentiation. We had the impression, though, that the proportion of squamous epithelium increased with each relapse. This would seem to point to the conclusion that, as in salivary-gland tumours, the degree of malignancy can be determined from the proportion of squamous epithelium present in MMCs.

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