# Mucinous Carcinoma of the Skin, Primary, and Secondary

## *A Clinicopathologic Study of 63 Cases With Emphasis on the Morphologic Spectrum of Primary Cutaneous Forms: Homologies With Mucinous Lesions in the Breast*

*Dmitry V. Kazakov, MD, PhD,* Saul Suster, MD,† Philip E. LeBoit, MD,‡ Eduardo Calonje, MD, Dip RCPath,§ Michele Bisceglia, MD,‖ Heinz Kutzner, MD,¶ Arno Rütten, MD,¶ Thomas Mentzel, MD,¶ Jörg Schaller, MD,# Bernhard Zelger, MD, MSc,** Mehmet Baltaci, MD,** Ilmo Leivo, MD,†† Christian Rose, MD,‡‡ Masaharu Fukunaga, MD,§§ Roderick H. W. Simpson, BSc, MB, ChB, MMed (Anat Path), FRCPath,‖‖ Yu Yang, MD,¶¶ J. Andrew Carlson, MD, FRCPC,## Alberto Cavazza, MD,*** Ondrej Hes, MD, PhD,* Petr Mukensnabl, MD,* Tomas Vanecek, MSc,* Ana Fidalgo, MD,††† Karel Pizinger, MD,‡‡‡ and Michal Michal, MD**

**Abstract:** We present the largest series of mucinous carcinoma involving the skin, describing the histopathologic, immunohistochemical, electron microscopic, and cytogenetic findings. Our aim was fully to characterize the clinicopathologic spectrum and compare it with that seen in the breast. In addition, we wished to reevaluate the differential diagnostic criteria for distinguishing primary mucinous carcinomas from histologically similar neoplasms involving the skin secondarily, and study some aspects of their pathogenesis. We demonstrate that primary cutaneous mucinous carcinomas span a morphologic spectrum compatible to their mammary counterparts. Both pure and mixed types can be delineated morphologically, and some lesions have mucocele-like configurations. Most lesions seem to originate from in situ lesions that may represent, using mammary pathology terminology, ductal hyperplasia, atypical ductal hyperplasia, or ductal carcinoma in situ or a combination of the three. Inverse cell polarity appears to facilitate the progression of the changes similar to lesions in the breast. The presence of an in situ component defines the neoplasm as primary cutaneous, but its absence does not exclude the diagnosis; although for such neoplasms, full clinical assessment is essential. Mammary mucinous carcinoma involving the skin: all patients presented with lesions on chest wall, breast, axilla, and these locations can serve as clue to the breast origin. Microscopically, cutaneous lesions were of both pure and mixed type, and this correlated with the primary in the breast. Dirty necrosis was a constant histologic finding in intestine mucinous carcinomas involving the skin, and this feature may serve as a clue to an intestinal origin.

**Key Words:** mucinous carcinoma, gelatinous carcinoma, mucocele-like tumors, in situ, inverse cell polarity, signet-ring cells, globoid cells, dirty necrosis, HER-2/*neu* gene

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From *Sikl's Department of Pathology, Charles University, Medical Faculty Hospital, Pilsen, Czech Republic; †Department of Pathology, Ohio State University Medical Center, Columbus, OH; ‡Dermatopathology Section, University of California, San Francisco, CA; §Department of Dermatopathology, St. John's Institute of Dermatology, St. Thomas's Hospital, London, UK; ‖Department of Pathology, IRCCS-Ospedale "Casa Sollievo della Sofferenza," San Giovanni Rotondo, Italy; ¶Dermatohistopathologische Gemeinschaftspraxis, Friedrichshafen, Germany; #Unit of Dermatopathology, Department of Dermatology, St. Barbara Hospital, Duisburg, Germany; **Clinical Department of Dermatology and Venereology, Medical University Innsbruck, Innsbruck, Austria; ††Department of Pathology, Haartman Institute, University of Helsinki, Finland; ‡‡Department of Dermatology, University of Lübeck, Lübeck, Germany; §§Department of Pathology, Jikei 3rd Hospital, Tokyo, Japan; ‖‖Department of Histopathology, Royal Devon and Exeter Hospital, Exeter, UK; ¶¶Department of Pathology, Health Science Center, Peking University, Beijing, China; ##Division of Dermatopathology, Albany Medical College, Albany, NY; ***Department of Pathology, Arcispedale "S. Maria Nuova," Reggio Emilia, Italy; †††Department of Dermatology, Hospital do Desterro, Lisbon, Portugal; and ‡‡‡Department of Dermatology, Charles University, Medical Faculty Hospital, Pilsen, Czech Republic.

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Reprints: Michal Michal, MD, Sikl's Department of Pathology, Charles University, Medical Faculty Hospital, Alej Svobody 80, 304 60 Pilsen, Czech Republic (e-mail: michal@medima.cz).



Primary mucinous (colloid) carcinoma of the skin is a rare neoplasm. The most common histopathologic description of the tumor in standard textbooks of dermatopathology and surgical pathology is that of "nests of epithelial cells floating in lakes of extracellular mucin." However, a careful analysis of the reports suggests considerable microscopic heterogeneity, similar to mammary mucinous lesions. In the breast, at least two types of mucinous carcinoma are delineated on morphologic grounds, pure and mixed; the clinical behavior of each is also different. Pure mucinous carcinomas are composed of mucinous areas that comprise more than 90% of the neoplasm; an in situ component may be present but is rarely seen. Mixed mucinous carcinomas manifest an invasive ductal component of usual type in addition to the mucinous pattern. Less

common mucin-producing mammary neoplasms include mucinous cystadenocarcinoma, columnar cell mucinous carcinoma, and signet-ring cell carcinoma.[41] Mucocele-like tumors are a further group of lesions characterized by accumulation of large extracellular pools of mucin, and these constitute a morphologic continuum, ranging from benign lesions to low-grade mucinous carcinomas.[15,33,36,46]

In the skin, approximately 140 cases have been reported and most describe pure mucinous carcinoma without an in situ component, but closer examination of the literature reveals a broader spectrum. We have found rare descriptions and/or illustrations of in situ lesions (in the form of ductal hyperplasia or low-grade carcinoma in situ),[32] mucocele-like lesions,[3,24,29] mixed mucinous carcinomas,[50,51] lesions with neuroendocrine differentiation,[17] cases resembling a solid papillary carcinoma of the breast.[12] Some primary cutaneous mucinous carcinomas reported to occur in the vulva have most likely originated from anogenital mammary-like glands.[8,53] These cases and the surprisingly diverse morphology indicate a degree of homology between mammary and cutaneous mucinous neoplasms, although so far no systemic study has ever been performed to support this view.

Therefore, our study aimed to collect a sufficient number of cases of primary cutaneous mucinous carcinomas so as fully to characterize the clinicopathologic spectrum and compare it with that seen in the breast. Second, we wanted to reevaluate differential diagnostic criteria for distinguishing primary mucinous carcinomas from those involving the skin secondarily. Third, it has recently been shown in the breast that pure mucinous carcinomas demonstrate immunohistochemically and ultrastructurally so-called inverse cell polarity, where tumor cells facing the stroma acquire apical secretory properties, and this may account for their peculiar histopathologic presentation and indolent behavior.[1] Rosai suggested that these tumors may not be invasive as traditionally held but come into being as a result of progression from an in situ neoplasm.[34,35] We aimed to study this aspect in cutaneous mucinous carcinomas.

## MATERIALS AND METHODS

### Case Selection

Within the consultation, personal, and routine files of all the authors, 78 cases were found of cutaneous mucinous carcinoma, primary and secondarily involving the skin. Histologic sections were reexamined by two of the authors (D.V.K. and M.M.), and the histopathologic findings were retrospectively correlated, with clinical workup and follow-up information kindly provided by the referring clinicians or pathologists. The extent of clinical investigation and available information varied from case to case but was usually comprehensive enough reliably to establish or confirm the primary site. This included a medical history with a complete or partial review of systems (often including breast, rectal and pelvic examination), chest, neck, lymph node, abdomen, or bone x-ray or CT or ultrasound investigations, and laboratory analysis. In some cases, endoscopy (ileocolonoscopy, esophagogastroscopy), scintigraphy of the skeleton, and magnetic resonance imaging were performed. All women were subjected to breast physical examination, a majority also to mammography, with or without a subsequent fine needle biopsy. Some patients were clinically evaluated a second time.

One case of primary cutaneous mucinous carcinoma had previously been published[7] but was included in this study since the follow-up was updated and new investigations had since been performed.

### Inclusion/Exclusion Criteria

Microscopically, we considered all mucinous carcinomas as such, if a tumor featured a mucinous pattern, even as a minor component. A neoplasm with appropriate histopathologic features was considered a primary cutaneous carcinoma if it met one or both of the following criteria: 1) there was no history or clinical evidence of any internal tumor; 2) the presence of an in situ component adherent to the duct wall with an intact peripheral myoepithelial layer demonstrable both microscopically and immunohistochemically in a tumor from any location except the skin overlying the breast.

If a patient had a history of an internal malignancy or an extracutaneous tumor was found during clinical investigation, the histologic specimens were compared. If the histopathologic evidence indicated clearly that the tumors were part of the same process, the cutaneous ones were considered metastatic or to represent direct invasion of the skin, provided the temporal relationship and anatomic location were appropriate. Cases that were devoid of an in situ component microscopically and lacked adequate clinical investigation (or information was not available) were excluded from the study.

### Histopathologic Assessment

Available paraffin blocks were cut into 5-μm-thick sections and stained with hematoxylin and eosin, mucicarmine, Alcian blue, and PAS with and without diastase treatment. Histopathologically, using an analogy to the breast, our cases were classified into pure mucinous carcinomas and mixed mucinous carcinomas (tumors in which the mucinous pattern was admixed with an ordinary invasive ductal component). For the purpose of the study, we used the terminology used in mammary pathology and, following Rosai's suggestion,[34,35] we did not consider the mucinous component as invasive. When an in situ (intraductal) component was detected and was abnormal, the changes were estimated as to whether they represented ductal hyperplasia (DH), atypical ductal hyperplasia (ADH), or ductal carcinoma in situ (DCIS). To this end, we used the criteria listed by Rosai.[35]

We also assessed the mucinous component with a three-grade system on the basis of cytologic criteria. Although such a grading of the mucinous component is not a common practice in breast pathology, it was performed to compare the grades of the intraductal and the mucinous components. Grade 1 was defined as small, uniform cells with oval to round nuclei, with no or only rare subtle pleomorphism; there were no atypical mitoses (Fig. 1A). Grade 2 referred to small- to medium-sized cells with round to oval nuclei and a haphazard arrangement within an epithelial island; some cells had prominent nuclei. Pleomorphism was moderate, and there were atypical mitoses (Fig. 1B). Grade 3 denoted cells that showed

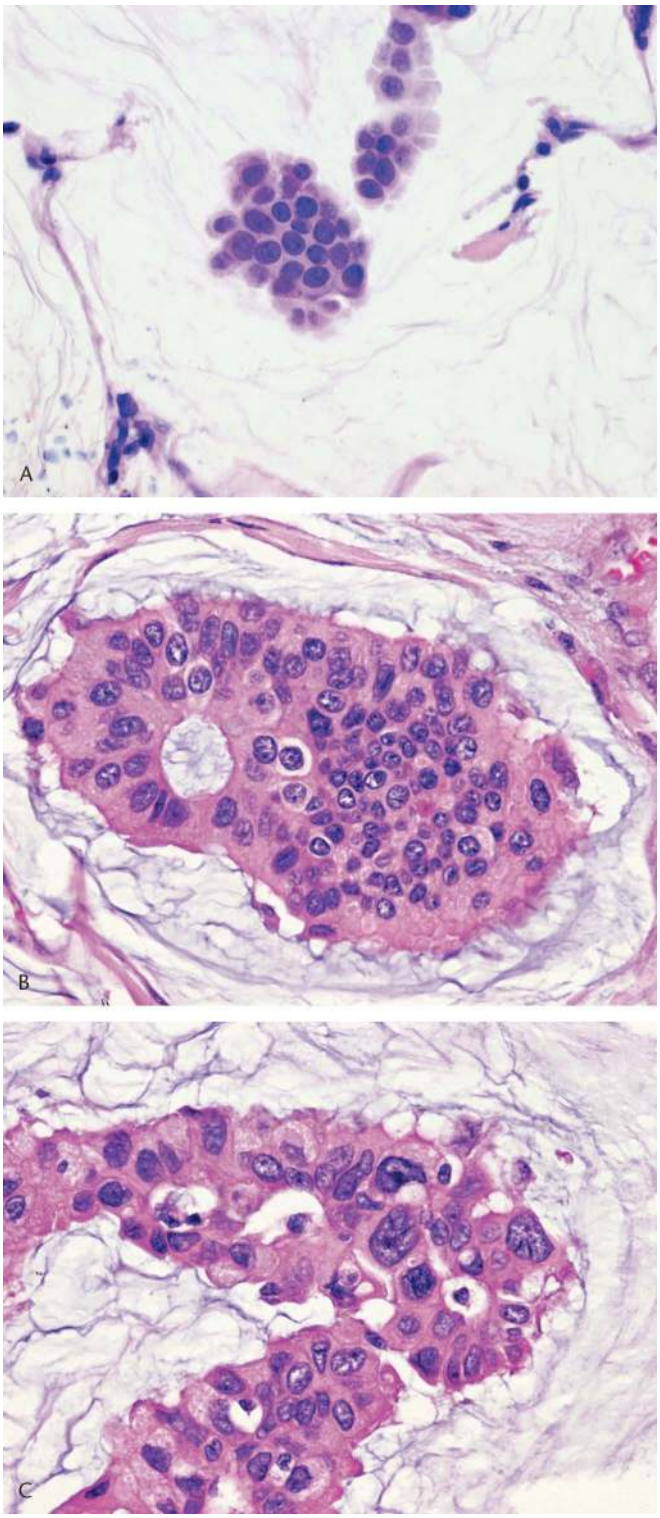


**FIGURE 1.** Cytologic grades of the mucinous component. A, Grade 1. Cells are small, uniform, with oval to round nuclei. B, Grade 2. Cells are small to medium-sized, round to oval with a haphazard arrangement within a single island; some cells have prominent nuclei. Pleomorphism is moderate. C, Grade 3. Cells show substantial pleomorphism; some are large, with irregular cloven nuclei.

substantial pleomorphism; some were large, with irregular cloven nuclei or they had a blastic appearance. Atypical mitoses were frequent (Fig. 1C). In neoplasms with an ordinary invasive ductal component, the latter was graded on a cytologic basis with the same three-grade system.

For mucinous carcinomas secondarily involving the skin, cytologic grading was not performed. Grading for all lesions was independently performed by two of us (D.V.K., M.M.). In 4 cases, a disagreement between the observers was settled by reviewing the cases together.

### Immunohistochemical, Cytogenetic, and Electron Microscopic Studies

In those cases with available blocks or unstained sections, immunohistochemical studies with a panel of primary antibodies depicted in Table 1 were performed. Immunostaining was carried out according to standard protocols using an alkaline phosphatase-anti-alkaline phosphatase method or avidin-biotin complex labeled with peroxidase or alkaline phosphatase. Appropriate positive and negative controls were applied. The immunostaining was scored as negative (<5% of cells positive), focally positive 1+ (5%–25% cells positive), 2+ (26%–50% cells positive), or 3+ (>50% cells positive), with the assessment of a typical reaction pattern for each antibody. HER2/*neu* (*c-erb*B-2) protein expression was interpreted following the criteria by DAKO for the HercepTest published elsewhere (negative 0, 1+, weakly positive 2+, strongly positive 3+).[38,39] In selected cases, fluorescence in situ hybridization for HER-2/*neu* gene amplification was performed using the PathVysion HER-2/*neu* DNA probe kit (VYSIS/ABBOTT, Downers Grove, IL) as previously described.[38] Ultrastructural studies were performed on the formalin-fixed, paraffin-embedded tissue obtained from 2 cases. The tissues were deparaffinized in xylene and further processed as reported by Widehn and Kindblom with some modifications.[48] Specimens were examined with a Philips (Eindhoven, The Netherlands) EM 208S electron microscope.

## RESULTS

### Classification

Thirty-seven cases were classified as primary cutaneous mucinous carcinoma and 24 cases as mucinous carcinoma secondarily involving the skin. The latter included 11 lesions from the breast, 11 from the intestine, and 1 each from the gallbladder and lung. In 1 case, cutaneous and lung neoplasms were found simultaneously, and it was not possible to decide clearly about the origin. Also, it was not possible to establish with certainty the origin (skin vs breast) in 1 woman with a neoplasm showing an in situ component involving the skin overlying the breast. Excluded from the study were 10 cases of mucinous carcinoma that lacked adequate clinical information and microscopic evidence of an in situ component. Also excluded from the study were 4 cases of cutaneous mucin-producing carcinomas other than mucinous carcinoma. One was histopathologically similar to the case reported by Santa Cruz et al[37]; the second was a recurrent adnexal carcinoma, not otherwise specified (NOS), featuring a mucinous-papillary

**TABLE 1.** Antibodies Used for Immunohistochemical Study

| Antibody Specificity | Clone | Dilution | Source |
|---|---|---|---|
| CK1-8, 10, 14-16, 19 | AE1-AE3 | 1:200 | Boehringer, Mannheim |
| CK7 | OV-TL 12/30 | 1:200 | DakoCytomation, Glostrup |
| CK20 | $K_s$20.8 | 1:300 | DakoCytomation, Glostrup |
| EMA | E29 | 1:700 | DakoCytomation, Glostrup |
| CEA | Poly | 1:300 | DakoCytomation, Glostrup |
| Serotonin | 5HT-H209 | 1:100 | DakoCytomation, Glostrup |
| Chromogranin A | DAK-A3 | 1:200 | DakoCytomation, Glostrup |
| GCDFP-15 | BRST-2 | 1:1000 | Signet Laboratories, Dedham |
| Lysozyme | Poly | 1:200 | DakoCytomation, Glostrup |
| MUC1 | Ma695 | 1:200 | Novocastra, Newcastle |
| MUC2 | Ccp58 | 1:400 | Novocastra, Newcastle |
| MUC5AC | CLH2 | 1:400 | Novocastra, Newcastle |
| MUC6 | CLH5 | 1:400 | Novocastra, Newcastle |
| CDX-2 | CDX2-88 | 1:150 | Biogenex, San Ramon |
| Surfactant protein B* | SPB01 | 1:50 | Neomarkers, Westinghouse |
| TTF-1* | 8G7G3/1 | 1:100 | DakoCytomation, Carpinteria |
| Ki-67 | MIB-1 | Prediluted | DakoCytomation, Carpinteria |
| ER | ER1D5 | 1:1000 | Immunotech, Marseille |
| PR | 1A6 | 1:50 | Immunotech, Marseille |
| c-*erb*B-2 | 10A7 | 1:500 | Novocastra, Newcastle |
| E-cadherin | SC-8426 | 1:500 | Santa Cruz, Wiena |
| CD10 | 56C6 | 1:100 | Novocastra, Newcastle |
| CD15 | LeuM-1 | 1:400 | Becton Dickinson, Mountain view |
| p53 | DO-7 | 1:50 | DakoCytomation, Glostrup |
| p63 | 4A4 | 1:500 | Biotex, Westinghouse |
| Calponin | CALP | 1:1000 | DakoCytomation, Carpinteria |
| Collagen IV | CIV22 | 1:50 | DakoCytomation, Carpinteria |
| PSA† | Poly | 1:12800 | DakoCytomation, Carpinteria |
| PSAP† | PASE/4LJ | 1:200 | DakoCytomation, Glostrup |

CK, cytokeratin; EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen; GCDFP-15, gross cystic disease fluid protein-15; TTF-1, thyroid transcription factor 1; ER, estrogen receptor; PR, progesterone receptor; PSA, prostate specific antigen; PSAP, prostate-specific acid phosphatase.

*Tested in individual cases.

†Tested in male patients only.

architecture similar to the case described by Geraci et al[13]; the third was a recurrent lesion with micropapillary arrangement and only a relatively small amount mucin (original biopsy signed out as mucinous carcinoma was not available for examination); and the last case was a poorly differentiated carcinoma (porocarcinoma) with abundant stromal mucin. One case of mucinous carcinoma with 8 recurrences over 10 years and regional lymph node metastasis (lymph node slides were available) was also excluded because no specimen was available from the cutaneous primary.

## Primary Cutaneous Mucinous Carcinoma

### Clinical Features, Treatment, and Follow-up

The main clinical features are presented in Table 2. There was a female predominance (24:13). The age ranged from 31 to 89 years (mean, 65.2 years; median, 67 years). Locations included the scalp (n = 15), face other than eyelids (n = 9), eyelid (n = 6), ear (n = 3), medial canthus of the eye (n = 1), vulva (n = 1), earlobe (n = 1), and hand (n = 1). All but 1 patient presented with a solitary nodule or a cyst-like lesion ranging in size from 0.5 to 7 cm (mean, 2.1 cm; median, 1.5 cm) (Fig. 2). One patient presented with clinically obvious bilateral involvement of the eyelids, and although 1 lesion microscopically showed only mucin, it is likely that this represented part of a mucinous carcinoma; bilaterality has previously been reported.[5] Only in 1 case was mucinous carcinoma suspected clinically. The duration of symptoms was recorded in 9 cases and ranged from 1 to 3 years (mean, 2.1 years; median, 2 years). Six patients described lesions as long-standing or present for years, and 3 patients reported fast growth of the tumor and a short history (1 to several months). A clinical workup was negative in 25 cases, and in 1 patient (case no. A21) a noninvasive papillary DCIS without a mucinous component was found in the breast, but this woman's skin biopsy displayed an in situ component. One patient (case no. A25) had previously had invasive mammary ductal carcinoma, NOS, pT1c pN0 M0 diagnosed 14 years prior to the occurrence of the cutaneous neoplasm. We examined numerous slides from the breast tumor and found no mucinous component whatsoever, whereas the skin biopsy showed a definite in situ component.

The treatment of all skin neoplasms was surgical excision. The surgical margins were involved in 7 cases, and these

**TABLE 2.** Primary Cutaneous Mucinous Carcinoma of Pure (Case Nos. A1–A31) and Mixed (Case Nos. A32–27) Type: Main Clinicopathologic Features

| Case No. | Sex/Age (yr) | Location | Clinical Features | Treatment |
|---|---|---|---|---|
| A1 | M/52 | Face (chin) | 1-cm solitary nodule | Excision, reexcision |
| A2* | M/63 | Face (zygomatic area) | 2-cm solitary nodule | Excisions |
| A3 | F/54 | Scalp (nonspecified) | Solitary nodule | Excisions |
| A4 | M/65 | Face (zygomatic area, right) | Solitary nodule | Excision, 2 reexcisions |
| A5 | M/73 | Scalp (temple, right) | Atheroma? | Excision, reexcision |
| A6 | F/46 | Scalp (nonspecified) | 0.5-cm solitary nodule. Cyst? Atheroma? | Excision |
| A7 | F/74 | Scalp (temple, right) | Solitary lesion | Excision, reexcision |
| A8 | F/78 | Scalp (nonspecified) | 3.5 × 3-cm solitary nodule | Excision |
| A9 | M/60 | Hand, right, dorsal aspect | 1.5-cm pinkish nodule | Excision |
| A10 | M/67 | Face (cheek) | Solitary nodule | Excision |
| A11 | M/76 | Eyelid, lower, right | Cyst? | Excision |
| A12 | F/69 | Eyebrow, right | 1 × 2 × 1-cm solitary nodule | Excision |
| A13 | F/31 | Scalp | 3 × 2 × 1-cm solitary ulcerated nodule | Excision |
| A14 | F/54 | Earlobe, right | Solitary nodule | Excision |
| A15 | M/76 | Eyelid, right, lower | 0.5-cm pearly nodule, BCC | Excision, reexcision |
| A16 | M/57 | Face (periorbital area, left) | Solitary nodule | Excision |
| A17 | M/61 | Medial canthus, left eye | 1 × 2-cm solitary nodule | Excision |
| A18 | F/79 | Eyelid, left, lower | Solitary lesion | Excision |
| A19 | F/65 | Face (cheek, right) | Translucent sessile domeshaped papule. BCC? MEC? | Excision |
| A20* | M/54 | Face (cheek) | Solitary nodule | Excision |
| A21 | M/46 | Face (nasolabial fold) | Deep-seated nodule. Tricholemmal cyst? | Excision |
| A22 | F/64 | Eyelid, upper | 1 × 0.5-cm solitary nodule | Excision |
| A23 | F/70 | Scalp (temple, right) | Cystic tumor with gelatinous content | Excision |
| A24 | F/68 | Eyelid | 1 × 0.8-cm fast growing nodule | Excision |
| A25 | F/38 | Ear, left, helix | Solitary bluish nodule | Excision, reexcision |
| A26 | F/75 | Ear. left | Solitary nodule | Excision |
| A27 | F/68 | Scalp (occipital area) | Solitary nodule, BCC? | Excision |
| A28 | F/89 | Scalp (nonspecified) | Epidermoid cyst | Excision |
| A29 | F/80 | Both lower eyelids | Left eyelid mucin only, right tumor | Excision |
| A30 | F/61 | Scalp (nonspecified) | 0.9-cm solitary nodule | Excision |
| A31 | F/66 | Scalp (temple, right) | 2-cm solitary nodule | Excision |
| A32 | M/46 | Face (cheek, left) | 0.7-cm hard nodule | Excision, reexcision |
| A33 | F/76 | Scalp (temple, left) | Solitary nodule | Excision? |
| A34 | F/73 | Scalp (retroauricular area, right) | 3.5 × 3 × 1.0-cm tumor | Excision |
| A35 | F/85 | Vulva, labium | 5 × 7 cm tumor | Excision |
| A36 | F/74 | Scalp (parietooccipital area) | 5 × 5-cm hyperkeratotic crusted tumor, occipital lymphadenopathy | Excision |
| A37 | F/74 | Scalp (nonspecified) | Solitary tumor | Excision |

| Case No. | Follow-Up | In Situ Component | Mucinous Component | Invasive Component |
|---|---|---|---|---|
| A1 | NED, 5 yrs | No | Grade 1 | No |
| A2* | Recurrences in 5.5 yrs and in 9 yrs, NED at 12 yrs | No<br>No | Grade 1<br>Grade 1 | No<br>No |
| A3 | Recurrence in 25 mos, NED at 3 yrs | No | Grade 1 | No |
| A4 | NED, 3 yrs | No | Grade 1 | No |

(*continued on next page*)

**TABLE 2.** (*continued*) Primary Cutaneous Mucinous Carcinoma of Pure (Case Nos. A1–A31) and Mixed (Case Nos. A32–27) Type: Main Clinicopathologic Features

| Case No. | Follow-Up | In Situ Component | Mucinous Component | Invasive Component |
|---|---|---|---|---|
| A5 | DUC, 2 yrs later | No | Grade 1 | No |
| A6 | NED, 4 yrs | No | Grade 1, 2 | No |
| A7 | NED, 3 yrs | No | Grade 2 | No |
| A8 | NED, 2 yrs | No | Grade 2 | No |
| A9 | NA | No | Grade 1,2,3 | No |
| A10 | NED, 6.5 yrs | No | Grade 2 | No |
| A11 | NA | No | Grade 1 | No |
| A12 | NED, 5 yrs | No | Grade 1 | No |
| A13 | NED, 5 yrs | No | Grade 2 | No |
| A14 | NA | DH | Grade 1 | No |
| A15 | NA | DH | Grade 1,2 | No |
| A16 | NA | ADH | Grade 1 | No |
| A17 | NED, 6 mos | ADH | Grade 1 | No |
| A18 | NA | ADH | Grade 1 | No |
| A19 | NA | ADH | Grade 1 | No |
| A20* | Recurrence in 2 yrs, NED at 6 yrs | ADH | Grade 1 | No |
| A21 | NED, 11 yrs | DH, ADH, DCIS 1 | Grade 1 | No |
| A22 | NED, 2 yrs | DH, ADH, DCIS 2 | Grade 2 | No |
| A23 | NA | DH, ADH, DCIS 1 | Grade 2 | No |
| A24 | NED, 16 mos | DH, ADH, DCIS 2 | Grade 2 | No |
| A25 | NED, 11 mos | DH, ADH, DCIS 1 | Grade 1 | No |
| A26 | NA | DH, ADH, DCIS 1 | Grade 1 | No |
| A27 | NED, 2 yrs | DCIS 1 | Grade 2 | No |
| A28 | NED, 3 yrs | DCIS 1 | Grade 2 | No |
| A29 | NA | DCIS 2 | Grade 2 | No |
| A30 | NED, 4 yrs | DCIS 2 | Grade 2 | No |
| A31 | Recurrence in 3 yrs NED at 11 yrs | DCIS 2 | Grade 3 | No |
| A32 | NED, 4 yrs | DCIS 2 | Grade 2 | Grade 2 |
| A33 | NA | DCIS 3 | Grade 3 | Grade 3 |
| A34 | NED, 4 yrs | DCIS 3 | Grade 3 | Grade 3 |
| A35 | Recent case | DCIS 3 | Grade 3 | Grade 3 |
| A36 | Recurrence in 1 mo, then NA | DH<br>No | Grade 1<br>Grade 2 | Grade 1<br>Grade 2 |
| A37 | Recent case | No | Grade 2 | Grade 2 |

*Only recurrent lesions were available for review.
NED, no evidence of disease; DUC, death of unrelated cause; NA, not available; BCC, basal cell carcinoma; MEC, mucinous eccrine carcinoma.

patients underwent reexcision. Follow-up information was available in 24 patients, with a duration of 6 months to 12 years (mean, 4.4 years; median, 4 years). Eighteen patients had an uneventful clinical course with no recurrence or metastasis or evidence of an internal neoplasm. Five patients had recurrences (persistence), and in 1 of them the tumor recurred twice. One patient died of an unrelated cause. In 1 patient with a negative clinical workup at presentation (case no. A12), invasive ductal carcinoma, NOS (without mucus), was found in the breast 4 years after the surgery for the skin neoplasm.

## Gross Features

An adequate macroscopic description was available in 8 cases. The lesions were described as soft, having a gelatinous or mucinous appearance, nonencapsulated and often poorly circumscribed, and without lobulation. Rare cases showed focal hemorrhage.

## Histopathologic Findings

Thirty-one of the 37 cases were pure mucinous carcinomas, with or without an in situ component (case nos. A1–A31) and the remaining 6 tumors were of mixed type,

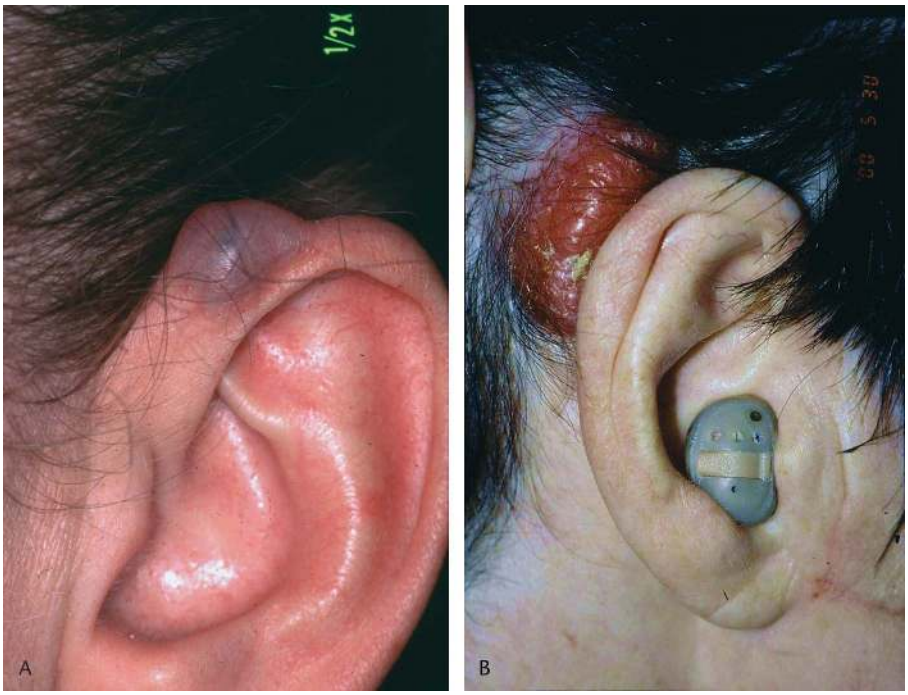


**FIGURE 2.** A, A cyst-like bluish lesion on the helix of the left ear. Histopathologically, this tumor represented a pure mucinous carcinoma with abundant mucinous component. B, Hard, poorly circumscribed, crusted nodule in the retroauricular areas. Microscopically, this neoplasm was the mixed type of mucinous carcinoma.

demonstrating an additional invasive ductal component (case nos. A32–A37) (Table 2). Of the former, 13 neoplasms demonstrated the mucinous pattern only (Fig. 3); whereas in the other 18, there was an additional in situ component. In general, any in situ lesion was only a minor part of the neoplasm and required a search to detect it, but in contrast, in a few cases it was obvious that the mucinous component had arisen as a result of a disrupted in situ lesion (Fig. 4). In situ lesions comprised DCIS alone in 5 cases, ADH in 5 cases, DH in 2 cases, and a whole spectrum of changes ranging from an unremarkable epithelium through DH to ADH to DCIS in 6 cases (Figs. 5, 6). Thus, of the 31 cases, DCIS was detected in 11 cases and was estimated as grade 1 in 6 cases and grade 2 in 5. Architecturally, the most common patterns of DCIS were cribriform, solid, or micropapillary, or a combination of the three (Fig. 7). Trabecular bars or Roman bridges were seen rarely. In 2 cases with a combined solid/cribriform DCIS, there were also papillae with fibrovascular cores (Fig. 7B). In 1 case, the DCIS contained dimorphic cells with clear cytoplasm (Fig. 7A), such as are often present in intraductal (intracystic) papillary carcinoma of the breast.[23] These cells simulating myoepithelial cells are sometimes called "globoid cells" in the breast.[35]

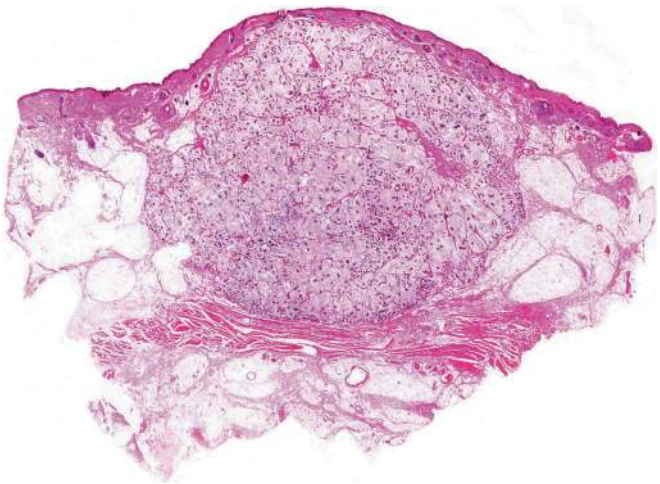

**FIGURE 3.** A whole-mounted view of a pure mucinous carcinoma. Small cellular nests lie in pools of extracellular mucin that are separated by fibrous septae. The tumor abuts the underlying skeletal muscle, but there is no muscular involvement.

In many cases containing in situ lesions, there was evidence of cell detachment into the lumen from the underlying neoplastic cells or myoepithelial cells or basal membrane (Fig. 4B). These detached cells then became free-floating nests and in some cases maintained the form of the in situ lesion (cribriform, streaming pattern, papillae, micropapillae). Otherwise and most often, the cells in the mucinous areas were arranged in variably sized, roundish, oval or irregular nests, strips or solitary units. Secondary microlumina were present constantly, especially in larger nests. While a majority of lesions were subdivided by variably thin fibrous septa, in rare neoplasms there were few or no septae at all. Grading of the mucinous component in these 31 cases of pure mucinous carcinoma was as follows: grade 1, 17 cases; grade 2, 10 cases; grade 3, 1 case (Fig. 1). In a further tumor, cytologic features ranged within a single lesion from grade 2 to grade 3, and in the 2 other cases both grade 1 and grade 2 cells were present simultaneously. In 10 lesions, the grade of the mucinous component was higher than that of the in situ lesion. In 4 cases with an in situ component represented by DH or ADH, it was difficult to classify the epithelium in the mucinous part as grade 1 or "normal" because epithelium in the mucinous parts

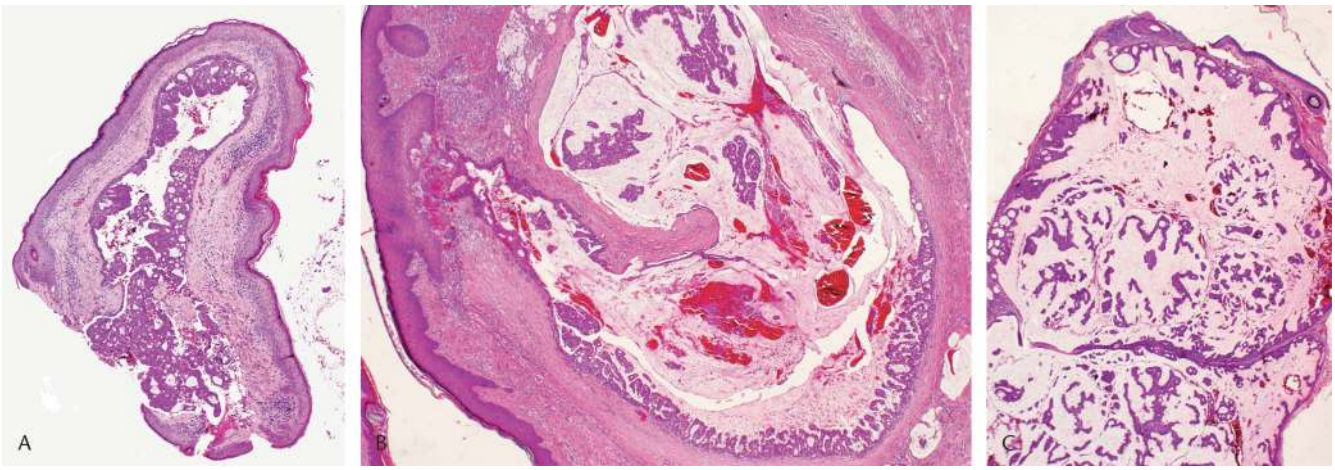


**FIGURE 4.** This figure demonstrates suggested progression of pure mucinous carcinoma from an in situ lesion. A, The neoplasm is almost entirely intraductal carcinoma. Floating cells with incipient detachment are seen within this in situ cribriform carcinoma. Part of the mucinous component was squeezed out of the lesion during tissue processing and is seen nearby. B, The in situ lesion is represented by a micropapillary carcinoma. Extruded intradermal mucin contains islands of cells, some of which maintain the architectural form of the in situ carcinoma. C, This lesion is represented by a ductal carcinoma with a cystic configuration. The mucinous component is almost entirely intraductal. The wall of the lesions is focally disrupted.

looked uniform. In some lesions, there was a clear correlation between the size and shape of the nests and their grade in the sense that larger aggregations tended to be of a higher grade and often demonstrated a more complex arrangement. Albeit not the rule, there was some correlation between the presence and the thickness of septae and grade, namely, low-grade lesions were more often associated with delicate septae.

Microcalcifications were seen in 8 cases, and in 2 of them psammoma bodies were apparent. Microcalcifications were mostly present in the mucinous component, but also in the DCIS in 1 tumor. In 8 cases, stromal escape of mucin investing small epithelial islands simulated lymphatic invasion, and in some of these cases it was evident that the extrusion of mucin into the dermis occurred as a result of a disrupted in situ lesion (Fig. 8). Decapitation secretion was seen in 16 cases (Fig. 7B) and focal intratumoral hemorrhage in 13 neoplasms. Perilesional fibrosis or a desmoplastic reaction was detected in 9 and 4 cases, respectively. Other changes recognized included hair follicle induction (n = 3), a close approximation of neoplastic nests to skeletal muscle (n = 3) (Fig. 3) or to infundibular epithelium (n = 3), oxyphilic metaplasia (n = 1), aggregates of foamy macrophages in epithelial nests (n = 1), and columnar metaplasia (n = 1). Comparison of the primary and recurrent lesions revealed no differences, except that recurrent lesions tended to have a sharper demarcation.

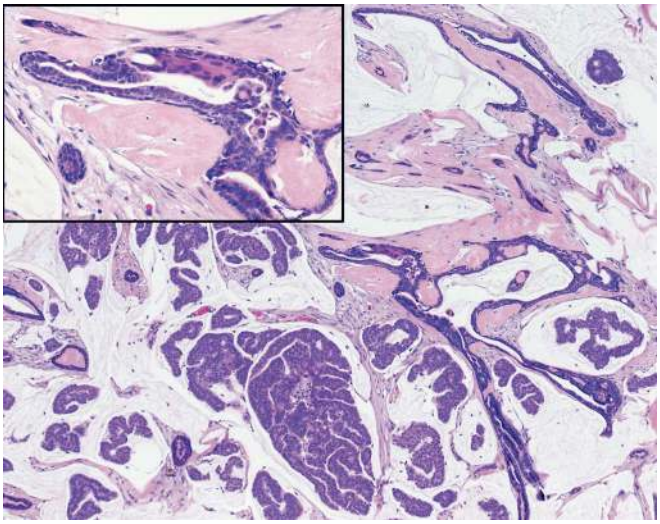

**FIGURE 5.** The in situ component of this tumor ranges from normal epithelium to ADH. A close-up view of incipient ADH (inset).

One case (case no. A27) was unusual in that the neoplasm was almost entirely composed of signet-ring cells floating in large extracellular pools of mucus, while an in situ component was represented by a low-grade cribriform DCIS composed of non–signet-ring cells (Fig. 9). Apart from this case, scarce signet-ring cells were noted focally in 2 otherwise typical cases of pure mucinous carcinoma.

Of the 6 cases with an invasive ductal component (mixed carcinomas), 4 (case nos. A32–A35) were similar in their microscopic appearance in that the invasive ductal component (grade 2 or 3) predominated over a minor mucinous component (grade 2 or 3), and an intraductal lesion was represented by DCIS (grade 2 or 3). Architecturally, the invasive ductal component was solid, cribriform, or NOS in 2 cases, and in addition comedocarcinoma was seen in 2 examples (Fig. 10A). Microinvasion from an in situ component was seen in 1 case (Fig. 10B). Microcalcifications were seen in 2 cases, and in 1 case there were psammoma bodies. In 2 cases, there was stromal extrusion of mucin-carrying small epithelial nests. In 1 case (case no. A36), there was a minor in situ component characterized by DH and an equal proportion of a mucinous and invasive carcinoma, with the latter appearing as small nests and cords/strands of neoplastic epithelial cells spilling

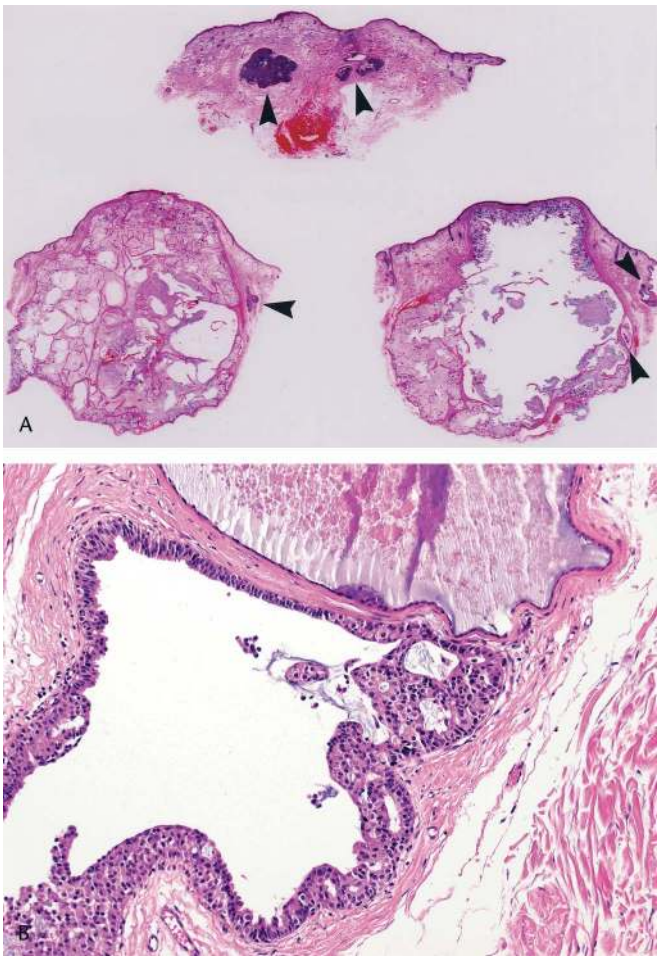


**FIGURE 6.** A, This tumor was sampled in three blocks. In one specimen (the upper lesion), there is no mucinous component; while elsewhere, mucinous components dominate. Arrows point to in situ lesions. B, A closer view of in situ changes ranging from normal epithelium to overlying dysplastic epithelium.

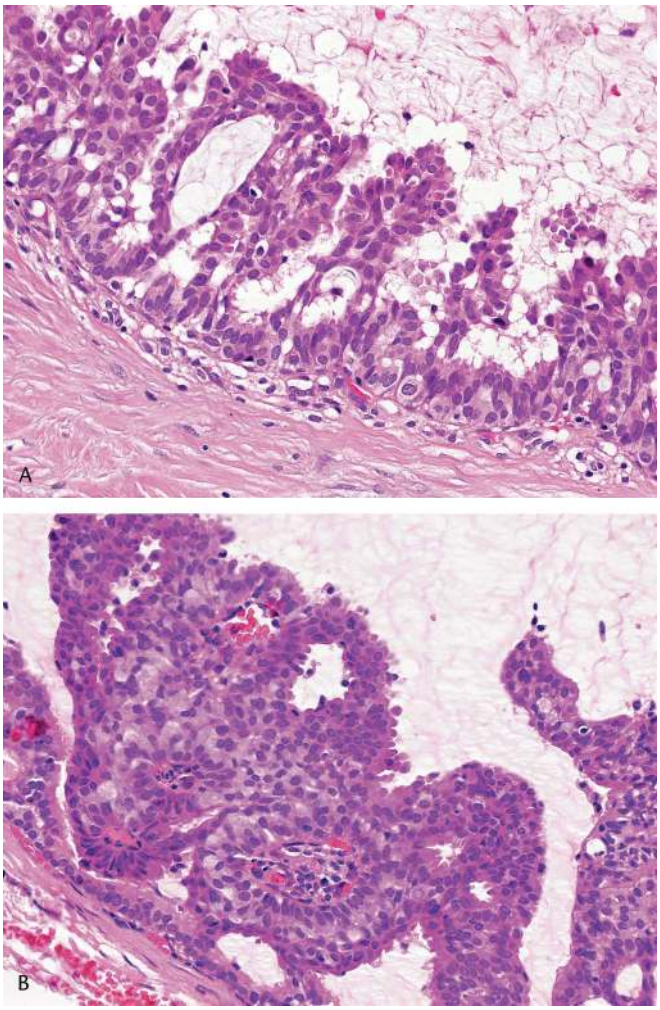


**FIGURE 7.** A, Micropapillary carcinoma in situ. Micropapillae have no fibrovascular cores. Note dimorphic round cells with a clear cytoplasm. B, This carcinoma in situ contains papillae with fibrovascular cores. Note decapitation secretion. This part of the lesion was sampled for electron microscopic study.

into the adjacent collagenous stroma. This tumor recurred 1 month later, and microscopically it then displayed a more prominent invasive component of a higher cytologic grade, as well as extensive geographic necrosis; no in situ component was detected in the recurrent lesion. In the last case (case no. 37), the neoplasm manifested no in situ lesions, while mucinous and invasive ductal components were equally represented. There was extensive tumor cell necrosis in the mucinous part of the neoplasm.

In none of the 37 cases was there a salivary or lacrimal gland present in the specimens.

## Clinicopathologic Correlation

No obvious correlation between the type of the tumor (pure mucinous vs mixed) and the clinical data such as age, sex, location, and behavior was evident. Pure forms were more likely to be described clinically as cyst-like lesions, whereas mixed tumors were always nodular or tumorous lesions (Fig. 2). In addition, mixed carcinomas tended to have a larger size at presentation and often were of a higher grade in comparison to pure forms.

## Immunohistochemical Findings

The results are summarized in Table 3. In all cases with an in situ component, the latter was demonstrated with p63 and calponin, which stained a continuous layer of myoepithelial cells. In all but 4 cases, there was evidence of a basal membrane (immunopositive for collagen IV) around an in situ component. There were differences in the pattern of MUC1 and MUC2 staining in cases of pure mucinous carcinoma and mixed mucinous carcinoma with an invasive ductal component (Fig. 11). In the former, the following pattern was seen: 1) MUC1 stained the luminal aspect of the cells comprising an in situ component (if present), the lowermost portions of the detaching cellular nests from an in situ component, secondary microlumina, and the whole periphery of free-floating epithelial nests (stroma-facing surface); only rarely was

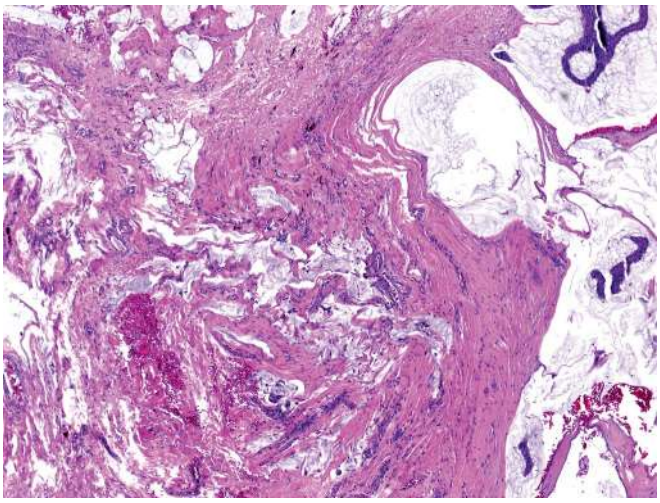

**FIGURE 8.** Pools of mucin in the dermis dissecting the dermal collagen bundles and containing small epithelial nests, simulating focally intralymphatic invasion. Note the similarity of the picture to pseudomyxoma ovarii.

intracytoplasmic labeling seen and, if so, then it was focal. 2) MUC2 demonstrated an intracytoplasmic reaction in a majority of cells. In the carcinomas with an invasive ductal component, the mucinous parts stained similarly to those seen in pure mucinous tumors, but in the invasive ductal component, labeling with MUC1 was diffuse and intracytoplasmic, and MUC2 decorated only a minority of cells. Diffuse staining with MUC1 in the mucinous component was seen only in the case with signet-ring cells. This case showed CK7−/CK20− immunophenotype, whereas all the others were CK7+/CK20−. All 26 cases tested were negative for MUC5AC, and the majority of the cases were negative for MUC6 (Table 3).

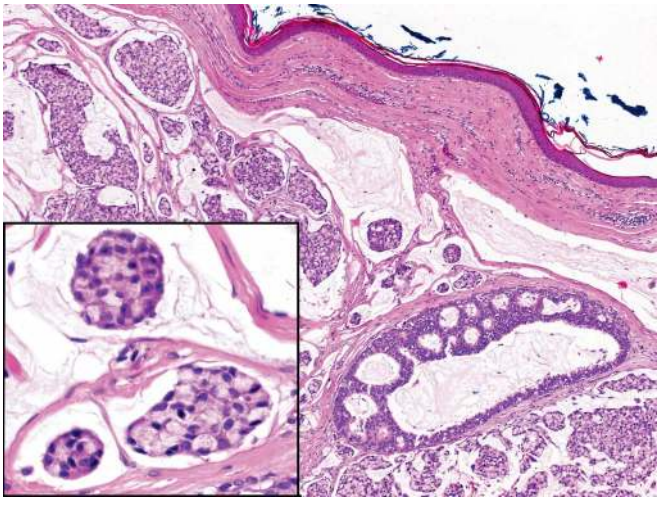

**FIGURE 9.** The neoplasm is composed almost entirely of signet-ring cells floating in large extracellular pools of mucus. Only an in situ component represented by a low-grade cribriform DCIS is composed of non–signet-ring cells. Floating signet-ring cells (inset). Because of this unusual cytomorphology, the patient underwent meticulous clinical investigation twice to exclude a metastasis from the gastrointestinal tract (case no. A25).

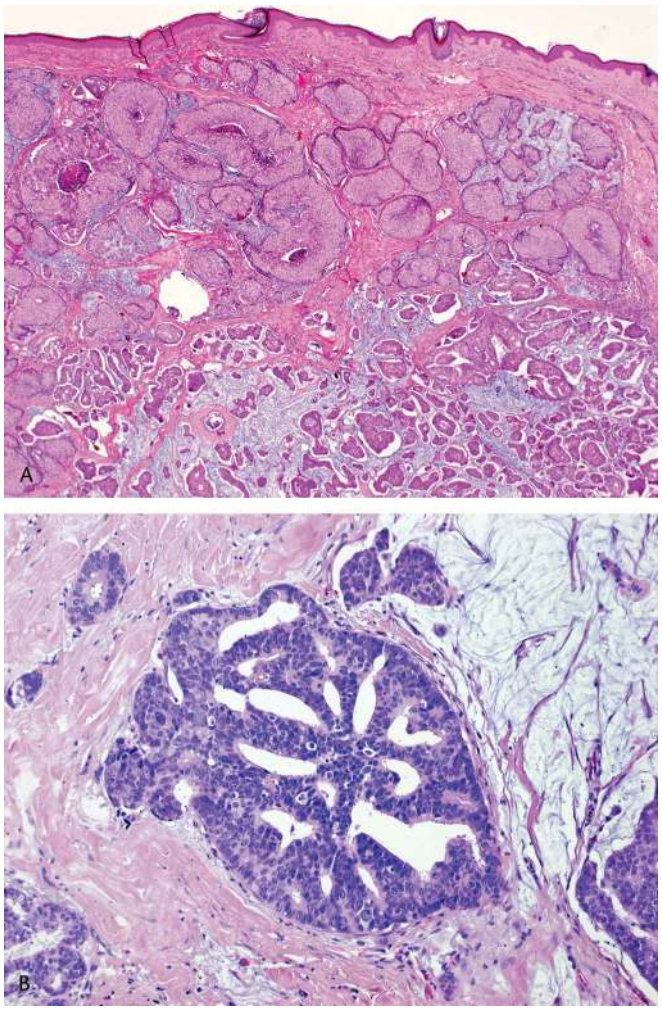


**FIGURE 10.** A, Mixed type of mucinous carcinoma: the mucinous part is accompanied by a widely invasive ductal component of solid type with features of comedocarcinoma. B, Microinvasion from an in situ component is visible in a mixed type of mucinous carcinoma.

## Her2/*neu* Fluorescence In Situ Hybridization Analysis

The Her2/*neu* gene was not amplified in 4 cases tested (Table 4).

## Ultrastructural Findings

Free-floating epithelial nests were sampled in 1 case and part of DCIS in another. Nuclear and organelle characteristics were mainly in accordance with the previously published studies.[18,28,51] There was a condensation of mucigen granules in the ectoplasm adjacent to the mucinous matrix (Fig. 12A). Microvilli were evident on the cell surface adjacent to the extracellular mucin, in intercellular spaces and in secondary microlumina (Fig. 12). Extrusion of the mucus from the cells into the extracellular or intercellular space was often seen, sometimes resembling the so-called apical caps (Fig. 12B). The correlation of the sampled areas with hematoxylin and eosin-stained slides indicated that these caps may indeed represent an

 

**TABLE 3.** Results of Immunohistochemical Study of Primary and Secondary Mucinous Carcinoma of the Skin

| Origin | Skin | | | | Breast | | | | Intestine | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Score | − | 1+ | 2+ | 3+ | − | 1+ | 2+ | 3+ | − | 1+ | 2+ | 3+ |
| AE1-AE3 | 0 | 0 | 0 | 26 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 4 |
| CK7 | 1 | 2 | 0 | 22 | 0 | 0 | 0 | 7 | 6 | 0 | 0 | 0 |
| CK20 | 26 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 | 1 | 0 | 5 |
| EMA | 0 | 0 | 1 | 24 | 0 | 0 | 0 | 7 | 0 | 1 | 0 | 4 |
| CEA | 15 | 2 | 4 | 0 | 4 | 1 | 0 | 2 | 0 | 0 | 0 | 5 |
| Serotonin | 25 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 5 | 0 | 0 | 0 |
| Chromogranin | 23 | 2 | 0 | 0 | 7 | 0 | 0 | 0 | 5 | 0 | 0 | 0 |
| GCDFP-15 | 10 | 6 | 6 | 3 | 0 | 0 | 3 | 2 | 5 | 0 | 0 | 0 |
| Lysozyme | 13 | 4 | 3 | 5 | 2 | 0 | 0 | 3 | | | Not done | |
| MUC1 | 0 | 0 | 0 | 27 | 0 | 0 | 0 | 8 | 7 | 0 | 0 | 0 |
| MUC2 | 0 | 0 | 2 | 25 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 7 |
| MUC5AC | 26 | 0 | 0 | 0 | 6 | 1 | 1 | 0 | 1 | 1 | 0 | 5 |
| MUC6 | 16 | 2 | 1 | 1 | 3 | 1 | 1 | 2 | 4 | 0 | 0 | 2 |
| CDX-2 | 1 | 0 | 0 | 1 | | | Not done | | 0 | 0 | 0 | 4 |
| Ki-67 | 9 | 16 | 1 | 0 | 2 | 2 | 2 | 1 | 0 | 0 | 2 | 3 |
| ER | 0 | 0 | 0 | 25 | 1 | 0 | 0 | 6 | | | Not done | |
| PR | 1 | 0 | 0 | 24 | 0 | 0 | 0 | 7 | | | Not done | |
| c-*erb*B-2 | 22 | 5 | 0 | 0 | 4 | 0 | 1 | 3 | 0 | 2 | 0 | 0 |
| E-cadherin | 1 | 0 | 1 | 25 | 1 | 0 | 0 | 6 | 0 | 0 | 0 | 6 |
| CD10 | 24 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 5 | 0 | 0 | 0 |
| Leu-M1 | 24 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 5 | 0 | 0 | 0 |
| p53 | 27 | 0 | 0 | 0 | 5 | 1 | 1 | 0 | 5 | 0 | 0 | 0 |
| PSA | 7 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| PSAP | 7 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |

apocrine type of secretion (Fig. 7B). In the sample with DCIS, cells with well apparent ultrastructural features of myoepithelium were present.

## Mammary Mucinous Carcinoma Involving the Skin

### Clinical Features, Treatment, and Follow-up

There were 10 women ranging in age from 44 to 90 years (mean, 70.5 years; median, 76.5 years) and a 68-year-old white man (Table 5). All but 1 patient presented with a solitary lesion. Considering the locations (chest wall, breast, axilla), it appears that all cases represented either direct cutaneous involvement by an underlying mammary carcinoma or its recurrence (persistence) after previous removal. An underlying breast malignancy was found in 4 patients during clinical investigation. Notably, in 2 cases (case nos. B7 and B9), mammography failed to disclose the mammary carcinoma, and the latter was found only at surgery, which was performed because of a high suspicion rate for a primary in the breast. The other 5 patients had a history of mucinous carcinoma detected 1 to 4 years earlier (mean, 2.4 years; median 2.1 years). The skin lesions were treated by surgical excision alone in 7 patients, and in 4 patients a combination of surgery with chemotherapy or radiotherapy was used. Eight cases with follow-up included 4 patients with no evidence of disease at 1, 4, 8, and 9 years, respectively, 2 patients who died with widespread cutaneous and internal metastases 1 and 3 years after the development of the skin tumor, and 2 patients who died of an unrelated cause.

### Histopathologic Features

Cutaneous specimens from 5 patients demonstrated pure mucinous carcinoma, and in 6 patients the tumors showed an additional invasive ductal component (solid or cribriform or NOS). Pure mucinous carcinoma was typified by small, variably shaped nests of neoplastic cells lying in mucin pools. Fibrous septae subdividing the lesions were thick, delicate, or both; in 2 of these cases, occasional infiltrating strands of neoplastic cells were noted between collagen bundles. The neoplastic cells were pleomorphic in all cases, sometimes with a "blastic" appearance and intracytoplasmic and intranuclear vacuoles. Mitotic figures, including abnormal ones, were readily seen. Other findings included transepidermal elimination of neoplastic cells through a follicular epithelium (n = 2), prominent decapitation secretion (n = 2), epidermal ulceration (n = 1), and hair follicle induction (n = 1). There was no "dirty" necrosis or in situ component. In 6 cases, it was possible to review the original breast carcinoma: both mammary and cutaneous neoplasms looked identical in that the original breast tumors, whether pure mucinous or invasive ductal carcinomas with a mucinous component, retained their morphology in the skin.

### Immunohistochemical Findings

These are shown in Table 3. Similarly to primary cutaneous tumors, the stroma-facing aspects of the cells in the mucinous areas stained for MUC1, and the cytoplasmic reaction with MUC2 was prominent. The areas corresponding to an invasive ductal component stained diffusely for MUC1, and MUC2 reacted focally in these areas. MUC5AC reacted

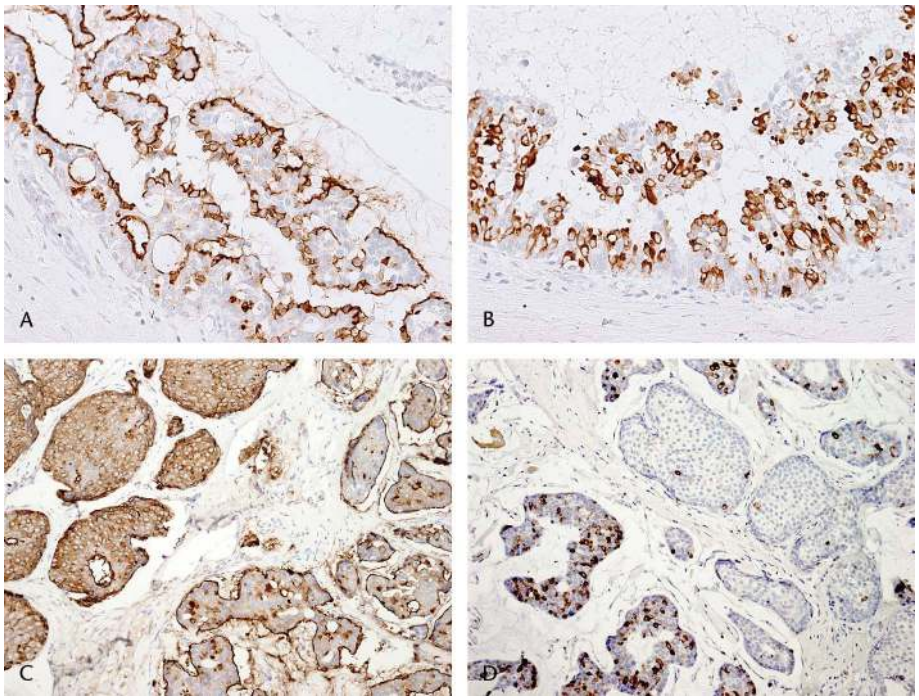


**FIGURE 11.** Comparison of MUC1 and MUC2 expression in pure and mixed types of mucinous carcinoma. A, Pure type: MUC1 stains the luminal aspect of cells comprising an in situ component, the lowermost portions of the detaching nests, secondary microlumina, and the whole periphery of free-floating nests. B, Pure type: MUC2 demonstrates an intracytoplasmic reaction in a majority of cells. C, Mixed type: MUC1 stains an invasive ductal component; labeling with MUC1 is diffuse and intracytoplasmic. The pattern of staining in the mucinous areas is similar to that in pure type. D, MUC2 stains cells in the mucinous parts and only rare cells are decorated in areas representing invasive ductal component.

negatively in all but 2 cases tested. Staining for MUC6 was variable. All 7 tumors tested manifested CK7+/CK20− immunophenotype.

## Intestine Mucinous Carcinoma Involving the Skin

### Clinical Features, Treatment, and Follow-up

The patients included 5 women and 6 men ranging in age from 59 to 89 years (mean, 69.2 years; median 67 years) (Table 6). All patients had a prior history of a malignant intestinal mucinous neoplasm located in the rectum (n = 5), right ascending colon (n = 2), descending colon (n = 1), cecum (n = 1), appendix (n = 1), or anus (n = 1). In 4 patients, the internal tumor was confined to the intestine, whereas in the other 7 patients it involved the adjacent tissues and/or lymph nodes. Skin lesions, multiple in 4 cases and solitary in 7, appeared 4 months to 7 years (mean, 2.5 years; median, 2 years) after the removal of the internal malignancy. One patient presented with pseudomyxoma peritonei that invaded the skin (Fig. 13A). The skin lesions were surgically removed in all patients. Seven patients with follow-up included 4 patients who died of disease, 2 with no evidence of disease, and 1 with a skin recurrence.

**TABLE 4.** Results of Her2/*neu* FISH Analysis and Correlation With Immunohistochemistry

| Case No. | ICH | FISH | Interpretation |
|---|---|---|---|
| A4 | 0 | 1.32 | Nonamplified |
| A5 | 0 | 1.12 | Nonamplified |
| A7 | 1+ | 1.4 | Nonamplified |
| A21 | 1+ | 1.45 | Nonamplified |

### Histopathologic Features

Architecturally, 2 tumors showed the pattern of pure mucinous carcinoma with small epithelial nests floating in plentiful extracellular mucus, and in the other 9, similar mucinous areas were accompanied by the intradermal proliferation of variably sized and shaped glandular and cystic structures embedded in a desmoplastic stroma that contained plentiful neutrophilic granulocytes (Figs. 13B, 14A). The epithelial cells in these glandular structures often showed the cytologic features of a colorectal epithelium (Fig. 14A). In larger lumina and cysts, the neoplastic cells were often attenuated, disrupted, and mainly arranged in a single layer, while in smaller ones there was disorderly multilayering. Of the 11 lesions, 9 demonstrated highly pleomorphic nuclei and plentiful mitoses. In 1 of the 2 pure mucinous carcinomas, the predominant cell population comprised signet-ring cells. In 10 of the 11 tumors (the exception being the carcinoma composed of signet-ring cells), there were zones of "dirty" necrosis (eosinophilic necrotic foci containing nuclear debris)[21] (Fig. 14B). These areas with "dirty" necrosis qualitatively ranged from discrete collections of neutrophils in the vicinity of the neoplastic glandular structures with only few pyknotic epithelial cells, to necrosis of a whole glandular structure or an epithelial nest; no extensive geographic necrosis was observed. Epidermal involvement was seen in 4 cases, in 3 of which glandular carcinomatous structures were seen growing into the epidermis, whereas the other displayed pagetoid spread of the neoplastic cells. In 2 tumors, there was pseudoepitheliomatous hyperplasia of the epidermis, and in 1 there was prominent induction of hair follicles. Perineural invasion was seen in 3 of the 11 cases.

### Immunohistochemical Findings

The results are summarized in Table 3. All tested neoplasms were CK7−/CK20+. Neoplastic cells were invariably

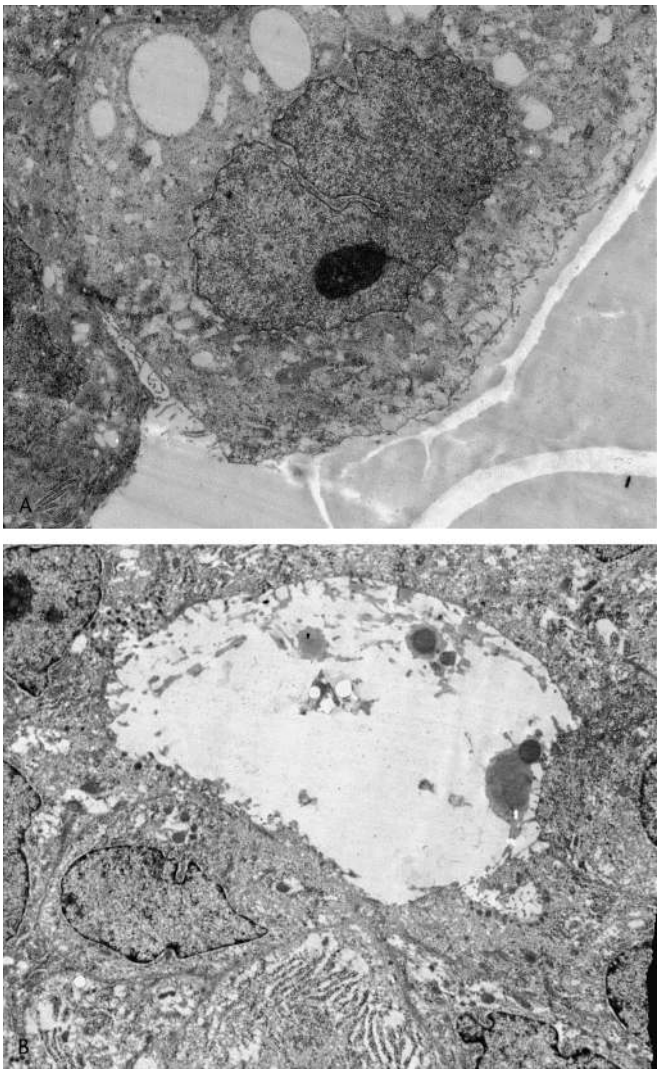

**FIGURE 12.** Electron microscopic study. A, The peripheral parts of a free-floating fragment in the mucus. There are microvilli and a condensation of lucent mucigen granules at the apical surface. Microvilli are also visible in the intercellular space. B, Secondary lumen in a DCIS. Focal apical condensation of granules and microvilli. Mucin secretion resembling an apical apocrine cap. This part corresponds to the areas depicted in Figure 7B.

positive for MUC2 and CDX-2 and variably positive for MUC5AC. MUC6 reacted negatively in 4 of 6 cases tested.

## Mucinous Carcinoma From Other Sites Involving the Skin

### Case No. D1

A 74-year-old man presented with a hematoma-like lesion on the left upper arm that allegedly appeared after a minor trauma (Table 7). It was excised and diagnosed microscopically as cutaneous mucinous carcinoma; no clinical investigation was performed initially. The patient had a history of nonmucinous adenocarcinoma in the colon (slides were not available for examination). He returned 1 month later with multiple lesions on the trunk and extremities, and a well-differentiated mucinous adenocarcinoma in the right lung was found. The skin biopsy showed a well-circumscribed nonencapsulated tumor with substantial hemorrhage composed predominantly of large cellular aggregates and pure mucinous areas. The neoplastic cells were relatively uniform, small in size, with little cytoplasm and intensely basophilic nuclei. There was no "dirty" necrosis. Immunohistochemically, the neoplastic cells were diffusely and strongly positive for AE1-AE3, CK7, E-cadherin, and surfactant protein B and were negative for CK20, CDX-2, EMA, CEA, MUC1, MUC2, MUC5AC, MUC6, GCDFP-15, serotonin, chromogranin A, c-*erb*B-2, ER, and PR.

### Case No. D2

A skin biopsy from the abdomen of a 68-year-old woman revealed a well-differentiated mucinous adenocarcinoma with an identical appearance to a previously excised gallbladder tumor: the neoplasm was composed of numerous wide ducts lined by a single layer of relatively uniform cells; however, in rare lumina, slight pleomorphism of the adjacent cells was noted. Most lumina were disrupted by an abundant amount of mucin that spilled into the paucicellular stroma. Intralymphatic invasion was noted focally. There was no "dirty" necrosis. The neoplastic cells were diffusely and strongly positive for AE1-AE3, EMA, CEA, lysozyme, CK7, MUC2, MUC5AC, and E-cadherin and were negative for MUC1, MUC6, CD10, CD15, GCDFP-15, serotonin, chromogranin A, p53, p63, calponin, CK20, c-*erb*B-2, ER, and PR. It is most probable that this carcinoma represents an incidental implant of the gallbladder tumor during its surgical removal.

## Mucinous Carcinoma With an Unknown Origin

### Case No. E1

A 63-year-old woman had a solitary 2-cm diameter nodule on the scalp that was excised. Clinical investigation disclosed a 1-cm nodule in the upper lobe of the left lung, which was removed by a left upper lobectomy. The skin and lung neoplasms proved to be pure mucinous carcinomas, with no in situ component demonstrable in either site; several removed bronchial lymph nodes were not involved. Immunohistochemically, both neoplasms were positive for CK7, MUC1, MUC2, and E-cadherin (weak) and were negative for TTF-1, surfactant protein B, CK20, MUC5AB, MUC6, chromogranin, serotonin, p63, and HER2/*neu*. The skin tumor was negative for CDX-2, while focal positivity for this marker was seen in the pulmonary lesion. Three years later, the patient was found to have multiple bilateral lung nodules, ranging in size from 2 mm to 4 cm; no biopsy was performed. Chemotherapy was administered 7 years later. At last admission, 13 years after the diagnosis, the patient is alive with evidence of lung involvement.

### Case No. E2

A 60-year-old woman presented with a cutaneous mass on her breast, but investigation revealed no primary lesion within the breast itself. Histologically, the tumor was a mucinous carcinoma with DCIS, grade 2, and microinvasion. There was prominent epidermotropism of the neoplastic cells and induction of hair follicles. No follow-up was available.

**TABLE 5.** Mammary Mucinous Carcinoma Involving the Skin: Main Clinical Features, Treatment, and Follow-Up of the Patients

| Case No. | Sex/Age (yr) | Skin Location | Clinical Presentation |
|---|---|---|---|
| B1 | F/53 | Left chest wall underneath breast | 2-cm irregular plaque |
| B2 | F/61 | Right chest wall | Solitary lesion in scar. Dermatitis? Resistant to corticosteroids for 2 mo. |
| B3 | F/75 | Axilla | Solitary nodule |
| B4 | F/90 | Breast | 2-cm solitary nodule |
| B5 | F/44 | Left chest wall | Deep-seated nodule |
| B6 | F/52 | Right chest wall | Solitary nodule; recurrence of CA? |
| B7 | F/79 | Left axilla | Multiple 0.5–2-cm nodules; ipsilateral lymphadenopathy |
| B8 | F/83 | Left breast | 4-cm solitary nodule |
| B9 | F/78 | Left breast, and inframmary fold | Inflammatory plaque |
| B10 | F/90 | Left breast, near the nipple | 4.5-cm ulcerated tumor |
| B11 | M/68 | Right chest wall underneath nipple | Corymbiform dense infiltration of 2 week duration, gynecomastia |

| Case No. | Breast Neoplasm | | | Temporal Relation | Course/Follow-Up |
|---|---|---|---|---|---|
| | Histologic Diagnosis | Extension | Treatment | | |
| B1 | Invasive ductal carcinoma with a focal mucinous component* | 3/17 axillary LN | Modified radical mastectomy with axillary dissection | B→S 2 yrs | NA |
| B2 | Adenocarcinoma | Skin only | Ablation with axillary dissection + RT | B→S 1 yr | Recurrence in 1 yr with multiple skin lesions on upper limbs and trunk + pleura involvement DOD 26 mos later |
| B3 | Mucinous carcinoma | Skin only (14 LN negative); pT1cpN0M0R0G1 | Modified radical mastectomy | S = B | NED, 9 yrs |
| B4 | Invasive ductal carcinoma with a focal mucinous component* | Unknown | Unknown | S = B | NA |
| B5 | Pure mucinous carcinoma, 2.2 cm in size* | pT2 pN0–G1 + Leser-Trelat sign (18 LN negative) | Radical mastectomy with axillary dissection | B→S 3 yrs | NED, 8 yrs |
| B6 | Pure mucinous carcinoma, 3.5 cm in size* | pT4 pN1–G2 (7/7 LN positive) | Radical mastectomy with axillary dissection | B→S 26 mos | NED, 1 yrs |
| B7 | Moderately differentiated breast carcinoma of mucinous type | pT2, pN1biv (1/4), R0, G2 | Radical mastectomy with axillary dissection | S = B | NED, 4 yrs |
| B8 | Pure mucinous carcinoma* | pT2pN0M0, 3 LN negative | Segmentectomy with axillary dissection + RT | B→S 50 mos | Recurrence in 4 yr, DUC at 5 yr |
| B9 | Mixed mucinous carcinoma | T1N1M1 stage IV | Modified radical mastectomy with axillary dissection + CT | S = B | DUC 7 mos later |
| B10 | Mixed mucinous carcinoma* | 4/4 LN positive | Radical mastectomy with axillary dissection | S = B | DOD at 3 yrs with generalized Mt |
| B11 | Moderately differentiated micropapillary DCIS | Skin only | Mastectomy with axillary dissection | S = B | Recent case |

B→S, breast neoplasm diagnosed before skin involvement; S = B, skin tumor and internal neoplasm diagnosed simultaneously (during workup); LN, lymph node; RT, radiotherapy; CT, chemotherapy; NED, no evidence of disease; DOD, death of disease; NA, not available; DUC, death of unrelated cause.
*Slides from original mammary neoplasm were available for examination.

Owing to the location and the deep biopsy, it is not possible totally to exclude a mammary origin (an intradermal lactiferous duct).

## DISCUSSION

Our study demonstrates that primary cutaneous mucinous carcinomas show a morphologic spectrum analogous to that in the breast. At its "benign" extreme are lesions with an in situ component in the form of DH, whereas the "malignant" part of the spectrum is represented by mucinous carcinomas with DCIS. That this is a continuum is validated by lesions with a simultaneous in situ component of DH, ADH, and DCIS (Figs. 5, 6). Some cutaneous mucinous carcinomas display a mucocele-like configuration. In the breast, intraductal carcinoma has been found in 50% of the "malignant mucocele-like lesions."[15] Apart from these pure mucinous

**TABLE 6.** Intestinal Mucinous Carcinoma Involving the Skin: Main Clinical Features, Treatment, and Follow-Up of the Patients

| Case No. | Sex/Age (yr) | Skin Location | Clinical Presentation | Site |
|---|---|---|---|---|
| C1 | F/59 | Right labium majus | Multiple nodules | Anus |
| C2 | F/60 | Perianal skin | Small multiple nodules | Rectum |
| C3 | F/67 | Perineum | Solitary nodule | Rectum |
| C4 | M/64 | Right buttock, previous skin involvement 13 mo earlier in perineum | Mass | Rectum |
| C5 | F/89 | Navel | A solitary nodule of several mo duration, then in 6 mo multiple lesions over the trunk | Rectum |
| C6 | M/84 | Perineum | Multiple nodules. Granuloma? Mt? Prolapsus? | Rectum |
| C7 | M/63 | Abdomen | Erythematous nodule | Right ascending colon |
| C8 | M/71 | Right leg | Small nodule | Right ascending colon |
| C9 | F/69 | Abdomen | Mass | Appendix |
| C10 | M/75 | Perianal | 5 × 5 × 4-cm mass | Descending colon |
| C11 | M/60 | Abdomen | Solitary nodule in postoperative scar | Cecum |

| | Intestinal Neoplasm | | | Temporal | |
|---|---|---|---|---|---|
| Case No. | Histologic Diagnosis | Extension | Treatment | Relation | Follow-Up |
| C1 | Mucinous carcinoma | pT0N×M0R0, MGI/II | Rectum amputation with extirpation of perianal tumor | I→S 6 yrs | NED, 1 yr |
| C2 | Invasive mucin-secreting AC* | Confined to rectum | Abdominoperineal resection | I→S 1 yr | DOD with multiple Mt to lungs and liver |
| C3 | Invasive AC with focal mucinous component* | Mts to regional LN | Abdominoperineal resection | I→S 3 yrs | DOD, 16 mos |
| C4 | Mucinous carcinoma | Prostate, posterior wall of urinary bladder, tissue around orifices of left and right ureter, left seminal vesicle | Abdominoperineal resection | I→S 7 yrs | NA |
| C5 | Moderately differentiated invasive mucinous AC in tubulovillous adenoma | LN and liver metastases G2pT3, pN2, pM1, stage IV | Abdominoperineal resection | I→S 4 yrs | DOD with multiple Mt to lung, liver, peritoneum 1 yr later |
| C6 | Mucinous AC* | Confined to rectum | Abdominoperineal resection + RT | I→S 10 mos | AWD (skin recurrence), 8 mos |
| C7 | Moderately differentiated AC with prominent mucinous areas* | Pericolonic fat, 3/15 pericolonic LN positive for tumor | Right hemicolectomy | I→S 1 yr | DOD with multiple Mt 1 year later |
| C8 | Well-differentiated mucin-secreting AC, Dukes C | Pericolonic fat, 5/12 pericolonic LN positive for tumor | Right hemicolectomy | I→S 2 yrs | NA |
| C9 | Mucinous cystadenocarcinoma* | Ascending colon, both ovaries, omentum; recurrence in 4 mo with peritoneum and skin involvement | Right hemicolectomy, bilateral oophorectomy, omentectomy; recurrent lesions: excision | I→S 4 mos | NED, 7 mos |
| C10 | Mucinous AC | Confined to descending colon | Left hemicolectomy | I→S 2 yrs | Recent case |
| C11 | Well-differentiated mucinous AC | Cecum, ileum, and sigmoid | Right hemicolectomy with resection of ileal loop and sigmoid | I→S 10 mos | NA |

AC, adenocarcinoma; I→S, intestinal neoplasm diagnosed before skin involvement; LN, lymph node; RT, radiotherapy; NED, no evidence of disease; DOD, death of disease; AWD, alive with disease; NA, not available.

*Slides from original intestinal neoplasm were available for examination.

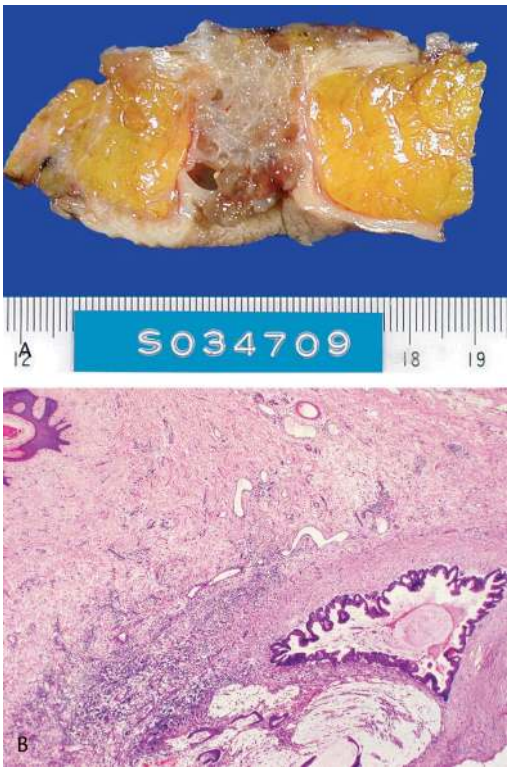


**FIGURE 13.** Pseudomyxoma peritonei involving the skin. A, Grossly, the lesion is seen as multicystic structures containing mucus. B, Histologically, intradermal mucin and cyst-like structures lined by a layer of epithelial cells resembling goblet and absorptive cells are seen.

carcinomas, which seem to predominate in the skin, there are neoplasms that also contain an invasive ductal component, most commonly of a high grade (Fig. 10). Such lesions in the breast (mixed carcinomas) have a more aggressive behavior than pure mucinous carcinomas, but this correlation cannot be confirmed from our study, as the number of mixed cases is too small. Besides, as often happens in the skin, these tumors may well follow an indolent course due to the superficial location and relatively poor accessibility to the underlying lymphatics. Future reports on these cases with a long follow-up would be helpful in determining their clinical course and correlation with the clinical setting.

We reviewed the literature on primary cutaneous mucinous carcinoma focusing on the cases with rapid progression, regional and distant metastases, and fatal outcome to find out whether these tumors correspond to this mixed type.[2,4,24,25,28,30,40,44,47,49,52,53] Unfortunately, some microscopic descriptions are poor or there are no histologic illustrations, but those reports adequately documented neither illustrate nor mention any invasive ductal component. Interestingly, 6 of those aggressive cases occurred in the axilla or vulva, which are unusual sites for primary cutaneous mucinous carcinoma, and this raises the question whether a closer proximity to lymph nodes in comparison to the skin elsewhere may account for the aggressive behavior.

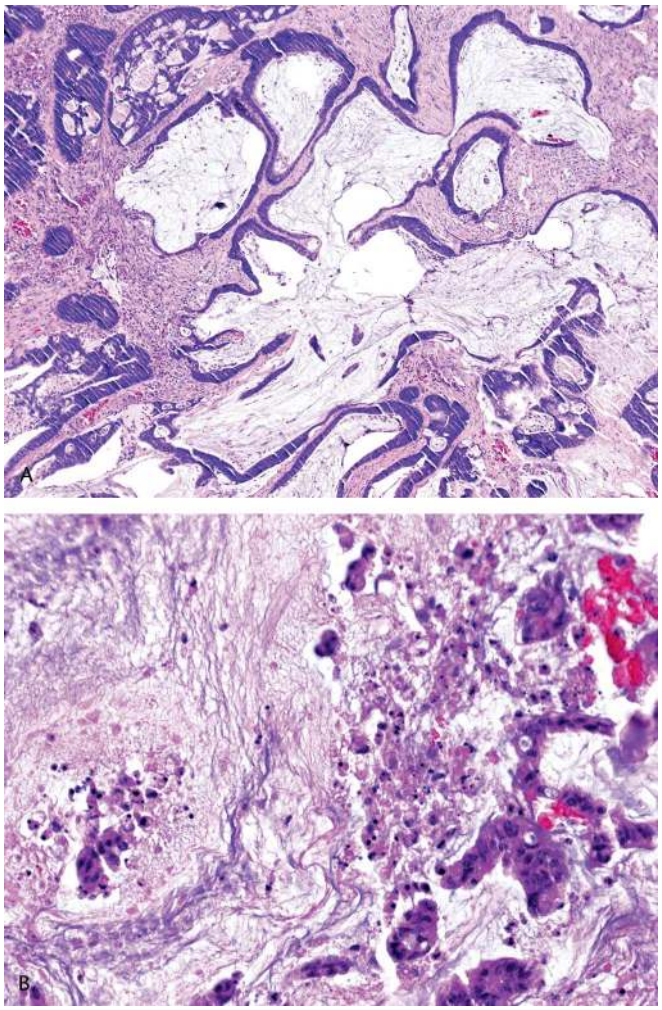


**FIGURE 14.** Involvement of the skin by a colorectal mucinous carcinoma. A, Epithelial elements are lined by a columnar colorectal epithelium and are surrounded by mucinous areas and desmoplastic stroma. B, Derangement of cells resulting in cellular debris forming foci of ''dirty'' necrosis. ''Dirty'' necrosis was a typical finding in the skin in colorectal mucinous carcinomas involving the organ.

Our study suggests that a majority of pure mucinous carcinomas in the skin may in fact derive from in situ lesions lacking invasive properties (Fig. 4). When an in situ component was present, it was often clearly apparent that detached epithelial nests appeared as a result of separation from the proliferating ductal epithelium. An indirect proof for an in situ lesion as a precursor also includes the fact that these free-floating nests sometimes retained the form (cribriform, streaming, micropapillary pattern) of the "parent" in situ lesion and positive reaction for E-cadherin, considered to be an indicator of a ductal origin in mammary pathology. The higher incidence of an in situ component found in cutaneous tumors as compared with mammary neoplasms may be further support for this view: cutaneous tumors are very likely to be removed earlier, when an in situ component is still detectable while many of these mammary lesions are still clinically occult. As

**TABLE 7.** Mucinous Carcinoma from Other Sites Involving the Skin: Main Clinicopathologic Features

| Case No. | Sex/Age (yr) | Skin Location | Clinical Presentation | Origin |
|---|---|---|---|---|
| D1 | M/74 | Left upper arm first; later trunk and limbs | Solitary 1-cm hematoma-like, later multiple lesions | Right lung, lower lobe, segment 10 |
| D2 | F/68 | Abdomen | Deep-seated subcutaneous nodule in postoperative scar; Schloffler nodule? | Gallbladder |

| | Internal Neoplasm | | | Temporal | |
|---|---|---|---|---|---|
| Case No. | Histologic Diagnosis | Extension | Treatment | Relation | Follow-Up |
| D1 | Well-differentiated mucinous AC (transthoracic biopsy) | Pleura, upper lobe of right lung, mediastinum T3N2M1 Stage IV | None (refused by patient) | S→I 1 mo | Recent case |
| D2 | Well-differentiated mucinous AC with lymphatic invasion; gangrene of gallbladder | Confined to gallbladder | Cholecystectomy | I→S 2 yrs | NED, 6 mos |

AC, adenocarcinoma; I→S, internal neoplasm diagnosed before skin involvement; S→I, skin tumor diagnosed before internal neoplasm; NED, no evidence of disease.

a tumor progresses, an excessive production and accumulation of mucin may lead to the distention of the ducts and subsequent disruption of the myoepithelial layer, its misplacement and, finally, complete disappearance. The resulting picture is a pure mucinous carcinoma with no identifiable in situ component. Rare "transition" ("half-way") forms appear to represent an in situ lesion gradually blending with the mucinous portions. A concept suggesting that pure mucinous carcinomas of the breast are in fact clusters of noninvasive in situ cells floating in the overproduced mucus has been first proposed by Rosai.[34] The progression of mixed tumors seems to be associated with the growth of a ductal invasive component, although the small number of cases means that firm conclusions cannot be drawn.

We compared the grades of the intraductal and the mucinous components of primary cutaneous mucinous carcinomas. Although it seems that grades and growth patterns of the in situ lesion have no prognostic implication, it is notable that in a majority of our cases the cells in the mucinous component were of a higher grade to the concurrent in situ lesion. This phenomenon may have two different explanations. First, the detached cells could have a higher rate of proliferation than those in the in situ component, but this seems unlikely as MUC2 produced invariably and often in large quantities by these lesions has been shown to act as a tumor suppressor factor.[45] Alternatively, a more likely explanation is that the more dysplastic cells are more prone to detach from the underlying cells than less dysplastic cells. A similar phenomenon is well known in urinary bladder pathology, where in situ carcinoma cells often virtually all desquamate into the urine, giving the appearance of a denuded lamina propria ("denuding cystitis").[27] In contrast, nondysplastic urothelial epithelium of the urinary bladder practically never detaches spontaneously from the stroma. Therefore, it is possible that exuberant mucin secretion disrupt ducts, detaches the epithelium from the underlying stroma (and myoepithelial layer), breaks it up into typical nests of epithelial cells, and engulfs it. In addition, it is also evident that the pools of mucin dissect the stroma of the dermis and carry small nests of epithelial cells so that the resulting picture often resembles dissecting infiltration of the ovarian stroma in cases of pseudomyxoma peritonei caused by mucin-producing tumors of the appendix. The picture may be so similar to "pseudomyxoma ovarii" (Fig. 8)[54] that one wonders whether the term "pseudomyxoma cutis" could be used here for this distinctive pattern in the skin. In any case, we think that this pattern does not serve as evidence of infiltrative properties of primary mucinous carcinomas of the skin. Nevertheless, these areas of "pseudomyxoma cutis" containing viable neoplastic cells and situated in some cases at a distance from the main bulk of the lesion may account for the known propensity to recurrence (persistence) of cutaneous mucinous carcinoma. A similar phenomenon is observed with aggressive angiomyxoma of the pelvic-perineal region, a soft tissue lesion with frequent recurrences and "aggressive behavior" that may also be explained by the poor circumscription due to the mucinous quality of the lesion, limiting possibilities for complete resection.[11]

Our study of mucinous skin carcinoma shows that the phenomenon of inverse cell polarity is likely to be relevant to the skin, thus linking the pathogenesis of cutaneous and mammary mucinous carcinoma. Routine fixation and limited material did not allow us to confirm the absence of a basal membrane in combination with microvilli formation at the stroma-facing surface as shown in breast mucinous carcinomas.[1] However, condensation of mucigen granules in the ectoplasm adjacent to the mucinous matrix and plentiful microvilli at the cell surface adjacent to the abundant extracellular mucin may well reflect the inverse cell polarity. As this ultrastructural feature seems to strongly correlate with MUC1 staining, the identification of this marker on the cell surface facing the myoepithelial cells and basal membrane of an in situ component is further support for this view (Fig. 14A). Previous electron microscopic studies identified dark and light cells and concluded that cutaneous mucinous carcinoma is an eccrine neoplasm, as lipid-containing dark cells had a strong similarity to the dark cell of the eccrine secretory coil.[18,28,51] We also noted the dark cell-light cell phenomenon in our cases, but in our experience and that of others, it has no implication,

 

as it is a common finding in various normal and pathologic tissues.[14] Although speculation on the eccrine versus apocrine nature of cutaneous mucinous carcinoma is beyond the scope of this study, the detection of decapitation secretion in many cases in our series rather points to apocrine differentiation, as suggested by others beforehand.[32] Further support is the detection of apocrine cap-like features on ultrastructural examination because these areas clearly corresponded to decapitation secretion seen by light microscopy.

Assuming cutaneous mucinous carcinoma originates from an in situ lesion, it still remains unresolved whether it arises from the ducts or the secretory portions of sweat glands. It is known that normal eccrine and apocrine ducts, in contradistinction to their secretory parts, have no myoepithelial cells, and the transition between the secretory part and the excretory duct in both gland types is abrupt.[9,43] Yet, we have seen mucinous carcinomas containing in situ lesions with a preserved myoepithelial layer, and these in situ components were situated at the level up in the dermis where no secretory parts are normally present. This finding is rather in accordance with the observations of Hamperl who noted that the transition between the secretory parts and excretory ducts is not abrupt and that the ducts of sweat glands do indeed contain myoepithelial cells, although they are somewhat different morphologically and functionally from those in the secretory parts.[16] It may be that the basal cells of the ducts (cells in the outer layer) may do indeed represent modified myoepithelial cells, as they have been found to express myoepithelial markers.[42] An alternative explanation is that the outer cells of the ducts of sweat glands acquire myoepithelial features under abnormal conditions such as hyperplasia or neoplasia. An analogy well known in the prostate where the peripheral layer of normal acini invariably lacks the ultrastructural and immunohistochemical properties of the myoepithelial cells, but in conditions such as sclerosing adenosis, well-formed myoepithelial cells can clearly be demonstrated.[20]

Although intestinal mucinous carcinomas often manifest a signet-ring cytomorphology, such tumors in the breast are now thought to represent variants of infiltrating lobular carcinoma, different from mucinous carcinoma.[35] In the skin, signet-ring cells have been reported in mucinous carcinomas, but this population represented only a minor component of the lesion.[44] Our case no. A27 is unique in that the tumor showed both intracellular and extracellular accumulation of mucin: free-floating nests were exclusively composed of signet-ring cells and an in situ component was predominantly composed of "ordinary" cells, with only rare mucin-rich signet-ring cells (Fig. 9). Moreover, the tumor cells were positive for E-cadherin, which, in mammary pathology, would be consistent with an intraductal origin. To the best of our knowledge, only 1 example of mammary mucinous carcinoma composed of signet-ring cells has been reported.[6]

The occurrence of mucinous carcinoma in the skin often requires the exclusion of a metastasis or direct invasion from an underlying neoplasm. Several criteria have been proposed to discriminate between primary and secondary mucinous carcinomas, among which the thickness of fibrous septae, epithelial-mucin ratio, pattern of CK7/CK20 expression (for exclusion of colorectal origin), and presence of an in situ component have been suggested to be most useful.[10,29,32] In our opinion, measurement of the thickness of the septae is often subjective, as is the assessment of the epithelium-to-mucin ratio, which our cases demonstrated may vary even within the same lesion (Fig. 6A). We think that the most logical criterion is the presence of an in situ component, which denotes that a tumor arose primarily in the skin. A metastatic carcinoma from a distant site simply cannot contain an in situ component, and direct spread of an underlying malignancy is very unlikely to incorporate an in situ component either, although it is theoretically possible that a mammary tumor originating from an intradermal lactiferous duct could be indistinguishable. In contrast, the absence of an in situ component does not automatically imply an extracutaneous origin, as disrupted myoepithelial cells may no longer be observable. For such cases, full clinical investigation remains the gold-standard approach to establish the origin, but as evident from our series there remain rare instances in which the origin will remain unknown, even after full clinical and histopathologic assessment.

As evident from our series and previous publications, the location of the tumor could also be of help in the differential diagnosis, as mammary neoplasms show a strong predilection for the chest, breast, and axilla.[19,22,26] A large series showed that the overlying skin is involved by underlying mammary pure or mixed mucinous carcinomas in 9% and 19%, respectively.[31] The histopathologic clue to an intestinal origin of mucinous carcinoma is the combination of "dirty" necrosis (even incipient) and the presence of epithelial cells with absorptive/goblet cell differentiation. We have seen at least small foci of "dirty" necrosis in all but 1 case with a colorectal origin. Such a distinctive, although not entirely specific, type of necrosis is most often seen in the colonic metastases in the ovaries.[21] These features seem to be so distinctive that they will allow one to suspect a colorectal origin of mucinous carcinomas even on hematoxylin and eosin-stained slides.

In summary, primary cutaneous mucinous lesions span a morphologic spectrum compatible to their mammary counterparts. Most lesions seem to originate from intraductal lesions that may represent DH, ADH, or DCIS, or a combination of the three. Inverse cell polarity appears to facilitate the progression of the changes similar to lesions in the breast. The presence of an in situ component defines the neoplasm as primary cutaneous, but its absence does not exclude the diagnosis, although for such neoplasms full clinical assessment is essential.

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