

# Cutaneous myoepithelial neoplasms: clinicopathologic and immunohistochemical study of 20 cases suggesting a continuous spectrum ranging from benign mixed tumor of the skin to cutaneous myoepithelioma and myoepithelial carcinoma

**Background:** Myoepithelial neoplasms, both benign and malignant, are rare but well-established clinicopathologic entities in the salivary glands, the breast, and the lung. Despite similarities between cutaneous sweat glands and glandular structures in the above-mentioned organs as well as the presence of regular myoepithelial cells around cutaneous eccrine/apocrine glands, the concept of cutaneous myoepithelial neoplasms is still debatable and not commonly accepted.

**Methods:** Twenty cutaneous myoepithelial neoplasms have been studied histologically and immunohistochemically.

**Results:** Nine neoplasms showed features of benign mixed tumor of the skin (chondroid syringoma) (five females and four males, age range 19–65 years, all cases arose in the head and neck region). Two cases represented the eccrine and seven the apocrine subtype. Interestingly, in three cases of the apocrine subtype, solid areas composed predominantly of myoepithelial cells were detected; these neoplasms were designated as benign mixed tumors with prominent myoepithelial cells. Nine cutaneous neoplasms were composed of spindled, epithelioid, and plasmocytoid cells without ductal differentiation and immunohistochemically stained variably positive for vimentin, epithelial and myogenic markers, S-100 protein, calponin, and glial fibrillary acidic protein (four females and five males, age range 3–71 years, four cases arose in the head and neck region and one case each on the finger, the thigh, the lower leg, the foot, and the breast, respectively); these neoplasms were designated as cutaneous myoepitheliomas. Two morphologically malignant neoplasms with cytologic and immunohistochemical features of myoepithelial cells arose on the face of a 70-year-old female and a 79-year-old male patient; these neoplasms were designated as malignant cutaneous myoepitheliomas (cutaneous myoepithelial carcinomas).

**Conclusions:** The study suggests a continuous spectrum of cutaneous myoepithelial neoplasms ranging from benign mixed tumor of the

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skin to cutaneous myoepithelioma and cutaneous myoepithelial carcinoma. Further studies with extended follow-up information are necessary to establish prognostic factors.

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Myoepithelial cells are characterized by their capacity for a bidirectional differentiation and show epithelial and myoid features on histologic, immunohistochemical, and ultrastructural levels.<sup>1,2</sup> In the skin, non-neoplastic myoepithelial cells are seen mainly around apocrine and eccrine glands. Morphologically, myoepithelial cells may show spindle, epithelioid, plasmocytoid and/or clear cell features, and also immunohistochemically a variable expression of vimentin, cytokeratins, epithelial membrane antigen (EMA), S-100 protein, muscle actins, glial fibrillary acidic protein (GFAP), and calponin is seen, whereas desmin is absent.<sup>3</sup> Benign and malignant myoepithelial neoplasms are rare but well-recognized in the salivary glands,<sup>4,5</sup> the breast,<sup>6</sup> and the lung.<sup>7</sup> Most recently, neoplasms of predominantly myoepithelial differentiation (myoepitheliomas) have been described in skin and soft tissues as well.<sup>8–10</sup> We report cases of benign cutaneous mixed tumors (chondroid syringomas) (apocrine and eccrine subtypes) including cases with prominent myoepithelial differentiation, cutaneous myoepitheliomas, and cutaneous myoepithelial carcinomas in order to demonstrate a continuous morphologic spectrum of myoepithelial neoplasms occurring in the skin.

## Materials and methods

Paraffin-embedded blocks and slides of nine benign mixed tumors of the skin, nine cutaneous myoepitheliomas, and two cutaneous myoepithelial carcinomas were retrieved from the routine files of the Dermatopathologische Gemeinschaftspraxis, Friedrichshafen, as well as from the personal files of the authors. Five out of nine cutaneous myoepitheliomas have been described in detail elsewhere.<sup>10</sup> Clinical information was obtained from the laboratory request forms and contributing clinicians and pathologists. In each case, tissue was fixed in 4% buffered formalin, routinely processed, and embedded in paraffin. Four-micron thick sections were stained with hematoxylin and eosin. In addition, sections in all cases were also stained immunohistochemically by the labeled streptavidin biotin technique, using commercially available

antibodies; antigen retrieval was used for all antibodies. Used antibodies, their sources, and dilutions are given in Table 1. Appropriate negative and positive controls were used in each case.

## Results

### Benign mixed tumor of the skin

Clinical features of nine cases of benign mixed tumor of the skin are summarized in Table 2. Briefly, all cases arose in the head and neck region of adult patients (five females and four males, age range 19–65 years), who presented with a soft, nodular lesion in most cases. The neoplasms were completely or marginally excised, and no sign of recurrence has been reported so far. Histologically, all neoplasms were restricted to the dermis, nodular, and well defined but not completely encapsulated. Seven cases (cases 1, 2, 3, 4, 6, 8, and 9) showed morphological features of the so-called apocrine subtype of benign mixed tumor of the skin with ducts and branching tubular structures lined by two layers of epithelial and myoepithelial cells (Fig. 1). These cells were cytologically uniform, without striking atypia and increased proliferative activity. The intercellular matrix showed prominent myxoid changes in cases 1, 3, 4, and 9 and rather myxohyaline changes in cases 2, 6, and 8. Chondroid areas were present in cases 1, 4, and 8, and focal adipocytic metaplasia was noted in cases 3, 4, 6, and 8. In cases 5 and 7, monomorphous small ductal structures, lined by a single layer of cuboid

Table 1. Immunohistochemical reagents used

Antibody	Clone	Dilution	Source
Desmin	D33	1:200	Dako, Glostrup, Denmark
S-100 protein	Polyclonal	1:4000	Dako, Glostrup, Denmark
ASMA	1A4	1:300	Dako, Glostrup, Denmark
Calponin	CALP	1:300	BioGenex, San Ramon, CA, USA
Vimentin	Vim3B4	1:150	Dako, Glostrup, Denmark
GFAP	GA-5	1:200	BioGenex, San Ramon, CA, USA
Pancytokeratin	MNF116	1:100	Dako, Glostrup, Denmark
EMA	E29	1:100	BioGenex, San Ramon, CA, USA

ASMA, alpha-smooth muscle actin; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein.

Table 2. Clinical findings in nine cases of benign mixed tumor of the skin

Case	Age (years)	Sex	Location
1	34	Male	Left cheek
2	19	Male	Forehead
3	70	Male	Head
4	39	Female	Right paranasal region
5	40	Female	Right temporal area
6	65	Male	Forehead
7	55	Female	Left temporal region
8	52	Female	Forehead
9	34	Male	Occipital scalp

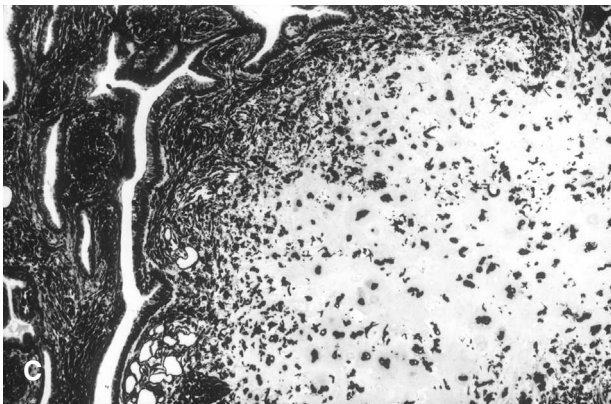
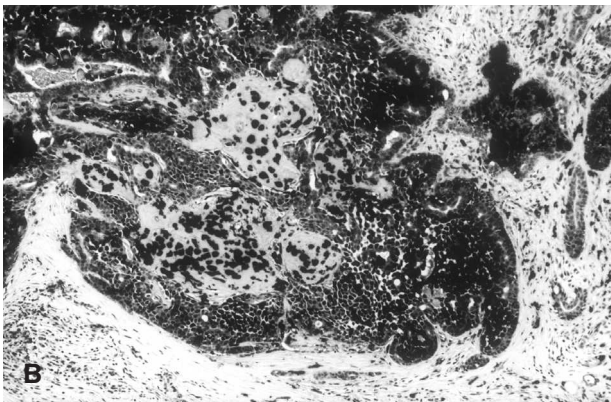


Fig. 1. Cases of benign mixed tumor of the skin are composed of tubular and ductal structures as well as solid appearing tumor areas set in a fibromyxoid stroma (A). Neoplastic cells in this case (case 4) stained positively for GFAP (B). Vimentin positive myoepithelial cells; note chondroid stromal changes on the right (C).

epithelial/myoepithelial cells and set in a myxoid as well as myxohyaline stroma consistent with the rare eccrine subtype of benign mixed tumor of the skin, were seen (Fig. 2). Interestingly, in cases 2, 4, and 9, solid areas without ductal differentiation were noted in addition to typical features of the apocrine subtype of benign mixed tumor of the skin. In these solid areas, epithelioid and/or plasmocytoid neoplastic cells were present (Fig. 3). Some of these cells in cases 2 and 9 contained enlarged and slightly irregular nuclei; however, the mitotic rate was not increased. These three neoplasms were designated as benign mixed tumors of the skin with prominent myoepithelial cells. Immunohistochemical results are summarized in Table 3. Epithelial tumor cells forming ducts and tubules stained positively for epithelial markers and were surrounded by myoepithelial cells, showing a coexpression of epithelial markers and vimentin. In addition, a variable positivity for S-100 protein, calponin, GFAP, and alpha-smooth muscle actin was noted (Fig. 2); none of the cases showed desmin expression. Tumor cells in mentioned solid areas of cases 2, 4, and 9 were characterized by stronger expression of myoepithelial markers.

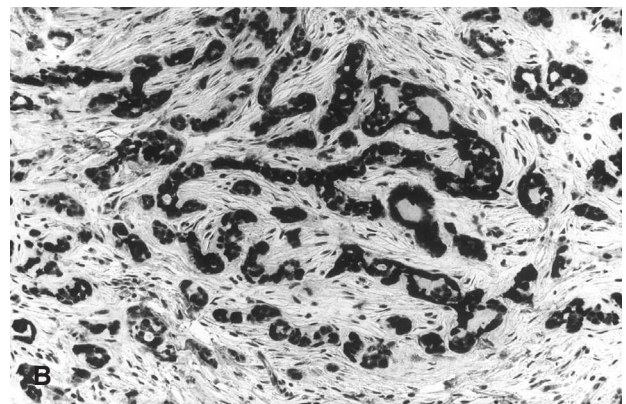
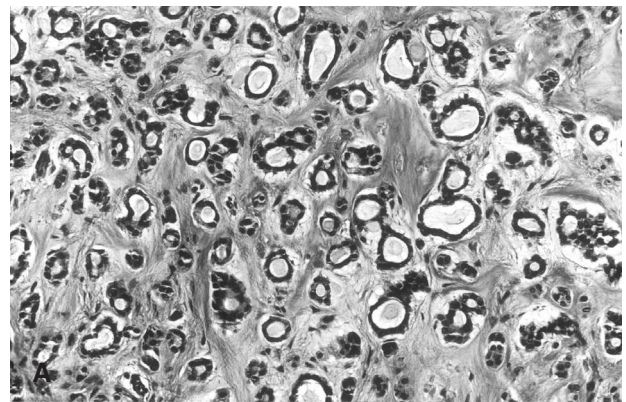


Fig. 2. Monomorphous ductal structures lined by cuboidal cells are typical for the eccrine subtype of benign mixed tumor of the skin (A). Tumor cells stained homogeneously positive for S-100 protein (B).

## Cutaneous myoepithelial neoplasms

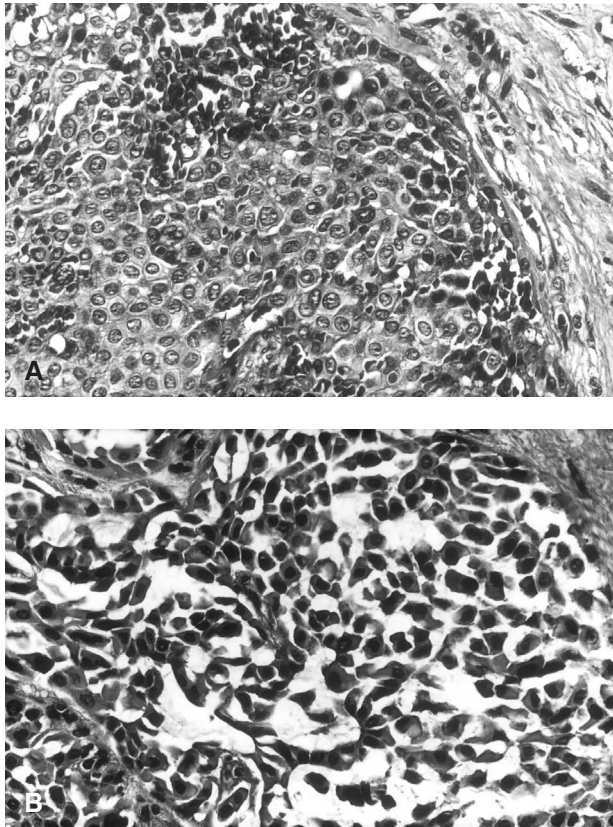


Fig. 3. Cases designated as benign mixed tumor of the skin with prominent myoepithelial cells contained solid areas without ductal differentiation (A) and/or areas composed of plasmocytoid cells (B).

### Cutaneous myoepithelioma

Nine cases (four females and five males, age range 3–71 years) were designated as cutaneous myoepithelioma and arose on the head (four cases), and one case each on the finger, the thigh, the lower leg, the foot, and the breast (Table 4). None of the cases recurred after complete excision. All cases were confined to the dermis, and only in case 7, expansion into superficial parts of the subcutis was present. Except cases 2 and 8 that showed focal extension into surrounding structures, neoplasms were nodular, solid, and well circumscribed. Histologically, a broad variation was seen. Whereas cases 3, 4, 5, and 6 were rather solid and composed of epithelioid cells admixed with

Table 4. Clinical findings in nine cases of cutaneous myoepithelioma

Case	Age (years)	Sex	Location
1	50	Male	Right ear
2	53	Male	Right middle finger
3	16	Male	Left thigh
4	3	Female	Right upper eyelid
5	38	Female	Left cheek
6	47	Male	Right cheek
7	71	Female	Left foot
8	40	Female	Right breast
9	26	Male	Left lower leg

plump and spindled neoplastic cells (Fig. 4), fusiform tumor cells arranged in bundles and fascicles predominated in cases 2, 8, and 9 (Fig. 5). Mainly plasmocytoid tumor cells were noted in case 1, and in case 7, epithelioid cells were admixed with plasmocytoid tumor cells (Fig. 6). By definition, no ductal and/or tubular differentiation was evident in these nine cases. The tumor stroma contained clusters of mature adipocytes in cases 2 and 8 (Fig. 5), and in cases 1, 2, 3, 4, 5, and 8, focal myxoid stromal changes were noted. Results of immunohistochemical stainings are summarized in Table 5. Briefly, all neoplasms stained positively for vimentin and at least one epithelial marker (cytokeratin and/or EMA) and showed a variable expression of S-100 protein, calponin, GFAP, and alpha-smooth muscle actin (Figs 5 and 6), whereas desmin was negative in all cases tested. Interestingly, spindled neoplastic cells in cases 2, 8, and 9 stained homogeneously positive for EMA, whereas pancytokeratin was absent in these three neoplasms.

### Malignant cutaneous myoepithelioma (cutaneous myoepithelial carcinoma)

The first case arose in a 70-year-old female patient, who developed an infiltrating dermal and subcutaneous neoplasm on her left cheek. The lesion measured 1.0 cm in greatest diameter and was not connected with the overlying epidermis and deeper located structures. Histologically, the cellular neoplasm was composed of atypical spindle-shaped tumor cells with enlarged and pleomorphic nuclei

Table 3. Immunohistochemical findings in nine cases of benign mixed tumor of the skin

Case	1	2	3	4	5	6	7	8	9
Vimentin	+	+	+	+	+	+	+	+	+
CK	+	+	+	+	+	+	+	+	+
EMA	+	(+)	-	+	(+)	(+)	ND	(+)	ND
S-100 protein	+	+	-	+	+	+	+	+	(+)
ASMA	(+)	-	(+)	-	(+)	(+)	-	(+)	-
Calponin	+	+	(+)	+	(+)	+	+	+	(+)
GFAP	+	(+)	(+)	(+)	+	+	+	+	-
Desmin	-	-	-	-	-	-	ND	-	ND

CK, pancytokeratin; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; +, positive; (+), focally/weak positive; -, negative; ND, not done.

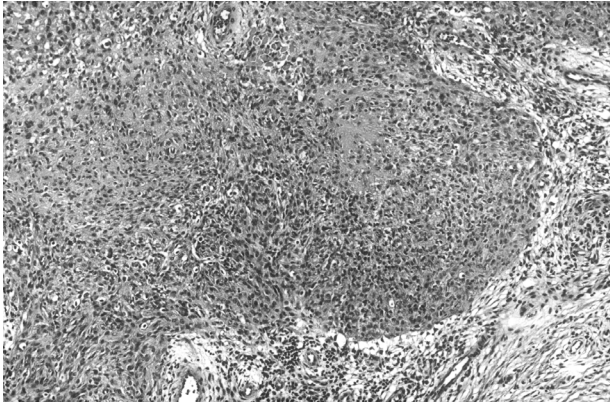


Fig. 4. This case of cutaneous myoepithelioma is composed of well-circumscribed solid tumor areas (without ductal/tubular differentiation).

containing occasionally prominent nucleoli (Fig. 7). Numerous mitoses (mean, eight mitoses/10 high power fields) and central tumor necrosis were found. Ductal structures and squamous or basaloid differentiation were not present. Immunohistochemically, neoplastic cells stained positively for vimentin, pancytokeratin, EMA, and alpha-smooth muscle actin (Fig. 7) as well as focally positive for calponin; S-100 protein, GFAP, and desmin were all negative.

The second case was that of a 79-year-old male patient, who developed a lesion, measuring 0.7 cm in largest diameter, in his left retroauricular region. Under an intact epidermis, a nodular dermal neoplasm with extension into subcutaneous tissue was seen (deeper located structures were not involved). The neoplasm was composed of plump, spindled, round, and stellated tumor cells set in a prominent myxoid matrix, with a tissue culture-like appearance in some areas (Fig. 8). Tumor cells contained an often well-delineated, pale eosinophilic cytoplasm, and enlarged pleomorphic nuclei with prominent nucleoli; scattered mono- and multinucleated tumor giant cells were noted. The mitotic rate was increased (mean, 16 mitoses/10 high power fields), and also atypical mitoses were found. Immunohistochemically, neoplastic cells stained homogeneously positive for vimentin, pancytokeratin, and alpha-smooth muscle actin, and a focal expression of S-100 protein and calponin was noted as well (Fig. 8); desmin and GFAP were negative.

In both cases, the diagnosis of malignant cutaneous myoepithelioma (cutaneous myoepithelial carcinoma) was established. There was no sign of local recurrence or metastasis 6 months as well as 2 years after complete excision.

## Discussion

Although relatively infrequent, benign and malignant myoepithelial neoplasms are well-established entities

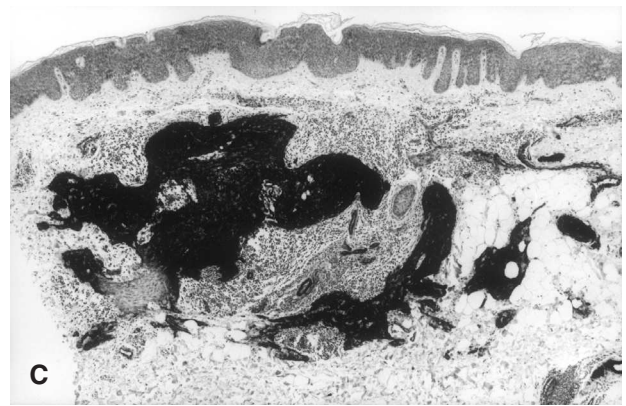
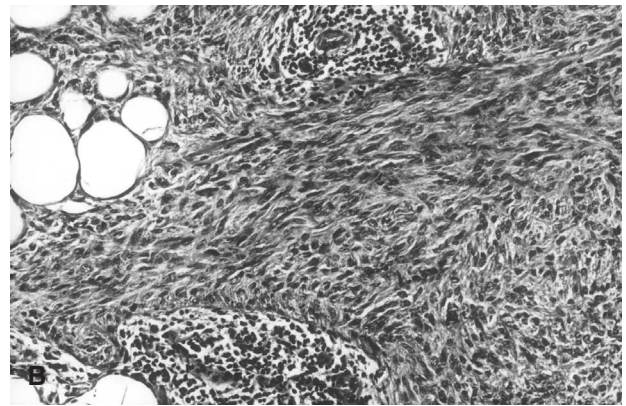
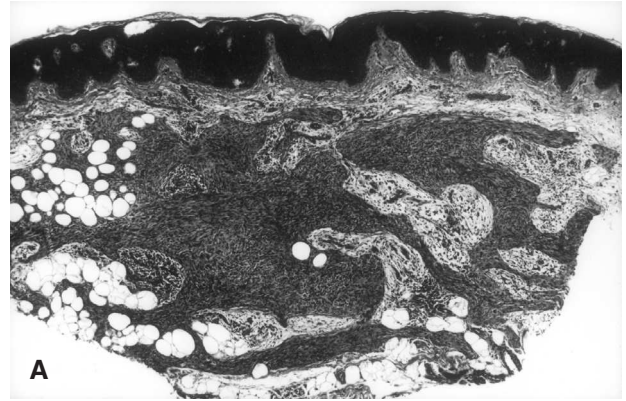


Fig. 5. Case 8 (spindle cell cutaneous myoepithelioma) is composed of spindle-shaped tumor cells set in a matrix with clusters of mature adipocytes (A, B). Neoplastic cells in this case stained positively for calponin (C).

in the salivary glands as well as in several organs such as the breast and the lung. In addition, it is now commonly accepted that neoplasms showing a myoepithelial line of differentiation may arise also in subcutaneous and deep soft tissues.<sup>8,9</sup> Despite embryologic and morphologic similarities between sweat glands, salivary glands, and mammary glands including their neoplasms<sup>11</sup> as well as the well-known presence of regular myoepithelial cells in the skin surrounding the secretory portion of apocrine and eccrine sweat glands, the concept of cutaneous

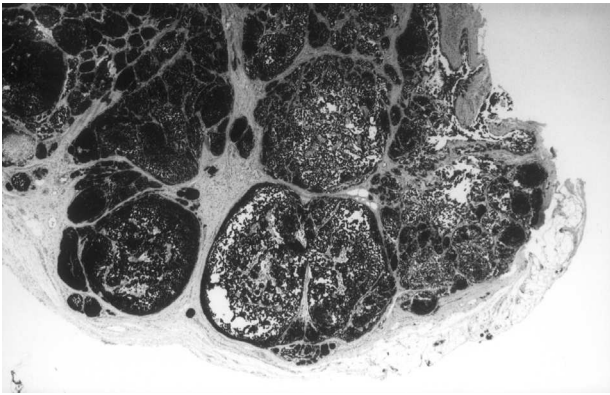


Fig. 6. Epithelioid and plasmocytoid tumor cells that stained positively for pancytokeratin were seen in this example of cutaneous myoepithelioma.

neoplasms composed partly or entirely of myoepithelial cells is not widely accepted, and cutaneous myoepithelial neoplasms represent under-recognized lesions.<sup>10</sup> On the other hand, it is well known that a number of epithelial cutaneous neoplasms may show also a myoepithelial differentiation, as for instance basal cell carcinoma.<sup>12,13</sup>

In 1948, Lever<sup>14</sup> described a group of neoplasms with clear cell differentiation, which he termed ‘myoepithelial sweat gland tumors’. However, later it has been recognized that these lesions actually represent hidradenomas (clear cell hidradenoma, nodular hidradenoma and solid-cystic hidradenoma).<sup>15</sup> The only one cutaneous neoplasm for which a varying myoepithelial differentiation has been accepted so far represents benign mixed tumor of the skin (chondroid syringoma), a lesion that closely resembles pleomorphic adenoma of the salivary glands on histological and immunohistochemical grounds.<sup>16,17</sup> Benign mixed tumor of the skin is characterized morphologically as a well-circumscribed lesion composed of nests and cords of epithelial cells, showing a tubuloalveolar and ductal differentiation set in a matrix, with myxoid and chondroid changes. In these neoplasms, epithelial cells are surrounded by vimentin-positive myoepithelial cells that show a variable expression of S-100

protein, muscle actin, calponin, and GFAP, whereas desmin is constantly negative.

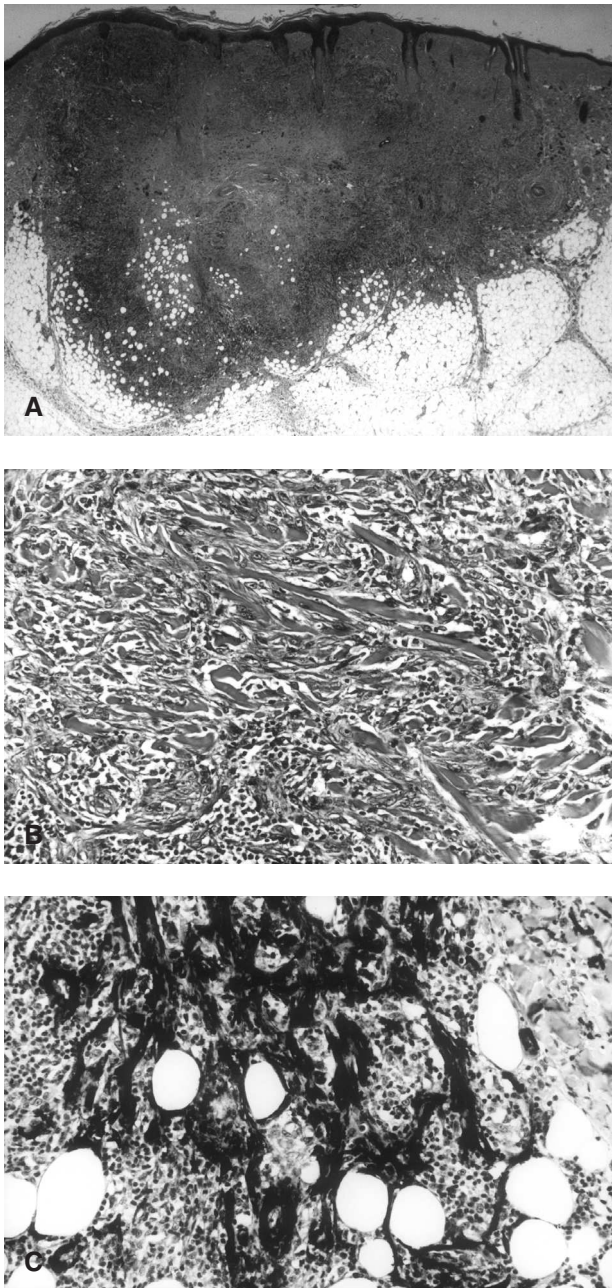
Most recently, a few examples of dermal neoplasms composed entirely of myoepithelial cells without tubuloalveolar and/or ductal differentiation have been documented,<sup>10,18</sup> and the presented series adds four examples. Although these neoplasms also occur frequently in the head and neck region, their anatomic distribution is wider than that of benign mixed tumor of the skin. Cutaneous myoepitheliomas are mainly well-circumscribed, but unencapsulated, nodular neoplasms, without connection to the overlying epidermis, composed of cytologically bland spindle, epithelioid, round, and/or plasmocytoid tumor cells containing a pale eosinophilic cytoplasm and ovoid or round nuclei without prominent nucleoli. Cutaneous myoepitheliomas show a variable admixture of the mentioned cellular components as well as show a variation in cellularity and in the amount of a myxoid and/or myxohyaline stroma, and focal adipocytic metaplasia is present in some cases. Immunohistochemically, the reported nine cases confirm these findings; neoplastic cells in cutaneous myoepithelioma show a variable expression of cytokeratin, EMA, S-100 protein, muscle actin, GFAP, and calponin, whereas desmin is not expressed. Neoplastic myoepithelial cells (especially spindle-shaped cells) are occasionally cytokeratin negative but show strong expression of EMA instead. The expression of EMA and the lack of desmin positivity, an immunohistochemical marker that is constantly negative in myoepithelial cells, are helpful in the distinction of spindle cell myoepithelial neoplasms from smooth muscle and myofibroblastic neoplasms of the skin.

As in subcutaneous and deep soft tissues<sup>8</sup> and also in the dermis, a morphological continuum of myoepithelial neoplasms ranging from predominantly ductal lesions (benign mixed tumor of the skin) to purely myoepithelioma of the skin (monophasic myoepithelial variant of benign mixed tumor of the skin) has been suggested tentatively.<sup>10</sup> The nine cases in the reported study designated as benign mixed tumor of the skin including lesions with prominent myoepithelial differentiation strongly support the

Table 5. Immunohistochemical findings in nine cases of cutaneous myoepithelioma

Case	1	2	3	4	5	6	7	8	9
Vimentin	ND	+	ND	ND	ND	ND	+	+	+
CK	+	-	+	+	+	+	+	-	-
EMA	(+)	+	+	+	+	+	-	+	+
S-100 protein	-	(+)	+	+	+	+	+	(+)	+
ASMA	+	+	+	+	+	+	-	+	-
Calponin	ND	+	ND	ND	ND	ND	(+)	+	(+)
GFAP	-	(+)	+	+	+	+	(+)	-	+
Desmin	ND	-	ND	ND	ND	ND	-	-	-

ASMA, alpha-smooth muscle actin; CK, pancytokeratin; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; +, positive; (+), focally/weak positive; -, negative; ND, not done.



**Fig. 7.** This example of malignant cutaneous myoepithelioma (cutaneous myoepithelial carcinoma) shows central tumor necrosis and diffuse infiltration of subcutaneous tissue (A). Atypical neoplastic cells contain enlarged, vesicular nuclei (B), and stain positively for alpha-smooth muscle actin (C).

hypothesis of a continuous morphologic spectrum. In addition to examples of the classic apocrine and eccrine variants, three cases showed overlapping features of benign mixed tumor of the skin and cutaneous myoepithelioma. These three cases contained areas of typical benign mixed tumor of the skin with ductal/tubular differentiation and solid areas without obvious ductal differentiation, composed of round and/or plasmocytoid myoepithelial tumor cells,

which also stained homogeneously positive for the so-called myoepithelial immunohistochemical markers (S-100 protein, calponin, GFAP, and alpha-smooth muscle actin).

Furthermore, two cases composed entirely of myoepithelial cells showing histologically overt features of malignancy are reported herein. In both neoplasms, an infiltration of superficial subcutaneous tissue was seen, and prominent cytologic atypia associated with increased proliferative activity and tumor necrosis in one case was present. The malignant counterpart of benign mixed tumor of the skin (malignant chondroid syringoma) is an exceedingly rare neoplasm.<sup>19</sup> These neoplasms arise frequently on the distal extremities of elderly patients and are characterized by a poor clinical course, with a high rate of metastases and mortality.<sup>20</sup> Another primary malignancy has to be excluded carefully in each case. Histologically, malignant chondroid syringomas are superficially located neoplasms and are composed of an epithelial and mesenchymal component. The epithelial component shows an infiltrative growth, prominent cellular pleomorphism and atypia, an increased proliferative activity, frequent tumor necrosis, and vascular/lymphatic invasion reflecting the malignant potential of these lesions; the benign mesenchymal stroma shows myxoid and chondroid features. Ideally, a benign precursor lesion should be identified, but this has been only very rarely reported.<sup>21</sup> In some reported cases, the majority of tumor tissue consisted of loosely arranged atypical spindle-shaped tumor cells set in a myxoid stroma (similar to features in case 2 of the cutaneous myoepithelial carcinoma reported herein) associated with small foci of squamous and tubular differentiation.<sup>21</sup>

In contrast to cases of malignant mixed tumor of the skin, the two cases reported showed no ductal/tubular differentiation but were characterized by a diffuse growth of atypical spindled/polygonal cells arranged in bundles and fascicles or rather patternless, showing marked atypia and increased proliferative activity. Cytologic and immunohistochemical findings with coexpression of vimentin, cytokeratin, EMA, S-100 protein, alpha-smooth muscle actin, calponin, and GFAP were in keeping with a myoepithelial line of differentiation. One could also argue that these two neoplasms actually represent dermal sarcomas, with coexpression of epithelial markers. However, cytokeratin/EMA coexpression in mesenchymal neoplasms is usually focal (i.e. synovial sarcoma and leiomyosarcoma) and also cytological features of our two cases were in keeping with a myoepithelial differentiation. These neoplasms were designated as malignant cutaneous myoepitheliomas (cutaneous myoepithelial carcinomas).

In summary, this study underlines that benign mixed tumor of the skin (chondroid syringoma)

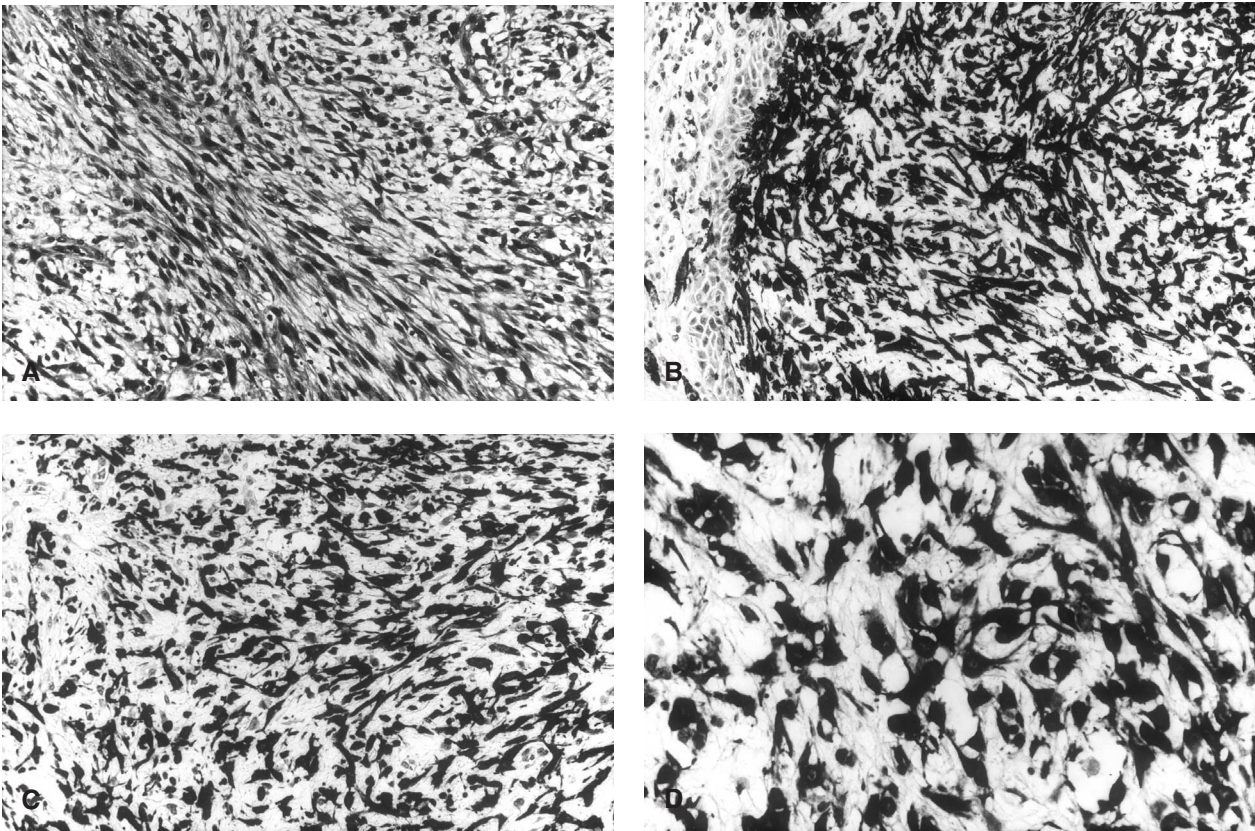


Fig. 8. The second case of malignant cutaneous myoepithelioma is composed of atypical spindled tumor cells set in a prominent myxoid matrix with a tissue culture-like appearance (A). Neoplastic cells showed a coexpression of alpha-smooth muscle actin (B), pancytokeratin (C), and calponin (D).

represents a dermal neoplasm of epithelial/myoepithelial differentiation. In addition, rare cases of cutaneous myoepithelioma without ductal differentiation and morphologically malignant neoplasms showing a myoepithelial line of differentiation are presented. The evidence of focal solid areas in benign mixed tumor of the skin composed predominantly of myoepithelial cells and resembling histologic features of cutaneous myoepithelioma, common stromal changes in cutaneous mixed tumor of the skin and cutaneous myoepithelioma (including myxoid changes as well as lipogenic and chondroid metaplasia) and overlapping immunohistochemical features strongly suggest the existence of a continuous spectrum of cutaneous myoepithelial neoplasms ranging from benign mixed tumor of the skin to cutaneous myoepithelioma and cutaneous myoepithelial carcinoma. Further studies with extended follow-up information are necessary to establish prognostic factors.

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