Virchows Arch (1999) 434:393–400

ORIGINAL ARTICLE

Michal Michal · Markku Miettinen

Myoepitheliomas of the skin and soft tissues

Report of 12 cases

Received: 6 July 1998 / Accepted: 5 December 1998

Abstract We describe 12 cutaneous and soft tissue myoepitheliomas, most of them in elderly patients. Morphologically the cutaneous and soft tissue myoepitheliomas revealed the same spectrum as their salivary gland counterparts. They were composed of a mixture of spindle, epithelioid and clear myoepithelial cells. Immunohistochemically they were positive to keratins and S-100 protein and reacted inconsistently with antibodies to smooth muscle actin. Morphologically they lacked any folliculo-sebaceous or apocrine differentiation. We believe that they are related to the eccrine type of cutaneous mixed tumours. Most cases had a benign behaviour, but 1 tumour metastasized, and the patient died of the tumour. Myoepitheliomas of soft tissues should be distinguished from other neoplasms with epithelial differentiation and from ossifying fibromyxoid tumour of soft parts, parachordoma and extraskeletal myxoid chondrosarcoma.

Key words Skin · Soft tissues · Myoepithelioma

Introduction

Myoepitheliomas of the salivary glands are rare, well-defined tumours composed of spindle, epithelioid or clear cells [5, 6, 13, 28, 29]. There is a relationship between myoepithelioma and pleomorphic adenoma, as both contain myoepithelial cells. However, pleomorphic adenoma also shows ductal differentiation with a sharp demarcation of the cellular cords from the myxoid, cellular stroma, while myoepithelioma lacks the chondroid differentiation typical of pleomorphic adenomas. The distinction is important because myoepitheliomas are characterized by more aggressive growth than pleomorphic adenoma and occasionally undergo malignant transformation [28]. In addition to the minor and major salivary glands, myoepitheliomas have been described in other locations, including the breast [9, 35] and lungs [34].

Myoepitheliomas of the skin and soft tissue have previously been described only once [17]. We present a series of cutaneous myoepitheliomas and compare their morphology with that of myoepitheliomas of the salivary glands.

M. Michal (✉)
Department of Pathological Anatomy, Medical Faculty,
Charles University, Dr. E. Beneše 13, 305 99 Pilsen,
Czech Republic
e-mail: michal@fnplzen.cz
Tel.: +420-19-272896, Fax: +420-19-273040

M. Miettinen
Department of Soft Tissue Pathology,
Armed Forces Institute of Pathology Washington, D.C., USA

Materials and methods

All cases were retrieved from the consultation files of the two authors. The tumour tissues were fixed in 4% formaldehyde, embedded in paraffin and routinely stained. For immunohistochemistry, the following primary antibodies were used (Table 1): cytokeratin (AE1-AE3: 1:500 Boehringer; CAM5.2: 1:50 Becton-Dickinson), S-100 protein (polyclonal: 1:1000: DAKO), synaptophysin (polyclonal: 1:1000 DAKO), chromogranin (monoclonal: 1:100 DAKO) and smooth muscle actin (1A4 1:1000 Sigma). Sections 4 µm thick were cut from the specimens and placed on slides coated with 3-aminopropyltriethoxy-silane (Sigma).

The sections were then deparaffinized and predigested with pepsin (0.05% in HCl acid, for 20 min). The binding of the primary antibodies was visualized using the supersensitive streptavi-

Table 1 Antibodies used in the study (*GFAP* glial fibrillary acidic protein, *EMA* epithelial membrane antigen, *SABC* streptavidin-biotin complex method)

Antibody specificity	Technique	Clone	Source
S-100 protein	SABC	Polyclonal	Dakopatts
Alpha-smooth muscle actin	SABC	1A4	Sigma
Cytokeratin	SABC	CAM 5.2	Becton-Dickinson
Cytokeratin	SABC	AE1-AE3	Boehringer
Chromogranin A	SABC	DAK-A3	Dakopatts
Synaptophysin	SABC	Polyclonal	Dakopatts

Table 2 Clinical features of the myoepitheliomas of the skin and soft tissue (*NED* no evidence of disease, *F* female, *M* male)

No.	Sex/age	Location	Size	Follow-up
1	F/75	Right auditory canal	1×1×1 cm	4 years, NED
2	M/19	Right calf	1×0.5×0.5 cm	3 years, NED
3	M/74	Back	3×4×3 cm	4 years, 2 recurrences
4	M/52	Face	3×4x3 cm	Lost to follow-up
5	M/57	Face	1×1×1 cm	Recent case, NED
6	M/93	Skin and soft tissues above the left scapula	12×16×18 cm	Recent case, NED
7	F/56	Umbilical skin and soft tissues	8×10×10 cm	2 years, 2 recurrences
8	M/74	Right thigh	2.5×2.5×3 cm	2 years, NED
9	F/52	Sole of the left foot	2.5 cm	Died of multiple pulmonary metastases in 1.5 years
10	M/73	Toe, laterality unspecified	2 cm?	Recent case, NED
11	M/26	Proximal thumb, laterality unspecified	1.5 cm	19 years, NED
12	M/52	Back	4 cm	Recent case, NED

din–biotin–peroxidase complex (Biogenex). Appropriate positive controls were used with each primary antibody. The colour was developed with diaminobenzidine, supplemented with hydrogen peroxide. The sections were lightly counterstained with Mayer's haematoxylin.

Results

The clinicopathological features of the myoepitheliomas of the skin and soft tissue are summarized in Table 2. The ages of the patients ranged from 19 to 93 years (median 58.5). Nine patients were men and three were women.

Of the 12 neoplasms, 4 arose in the skin and soft tissues of the trunk, 3 in the feet, 2 in the face, 2 in the extremities and 1 in the auditory canal; 4 tumours involved the dermis and superficial parts of the subcutis and 8 extended deep into the subcutaneous soft tissue. Clinical follow-up was available in 11 patients, and it ranged from 1 month to 19 years. There were 2 patients who each developed two local recurrences 1 year after the surgical excision; 8 patients, 4 of whom were recent cases, remained free of recurrences. One patient's tumour metastasized to the lungs, and the patient died of the disease 1.5 years later. The metastatic tumours in the lungs were not examined histologically. One patient was lost to follow-up.

Grossly, the tumours ranged from 1 cm to 18 cm in diameter and were well circumscribed, lobulated and off-white to grey colour. They were solid with an elastic consistency. None of them showed ossification.

Microscopically the tumours revealed epithelioid or spindle myoepithelial cells of variable morphology. They were composed of myoepithelial cells with variable appearances, ranging from spindle-shaped cells (Fig. 1) and epithelioid cells (Fig. 2) to clear myoepithelial cells (Fig. 3). Epithelioid myoepithelial cells in 2 cases revealed copious hyaline cytoplasm (Fig. 4) and had the appearance of the so-called hyaline cells in salivary gland tumours [20]. The transitions between the spindle and epithelioid myoepithelial cells were usually gradual, and in 3 cases the shape and arrangement of the myoepithelial cells resembled those seen in synovial sarcoma (Fig. 5). One tumour differed from the rest of the cases in its mixture of spindle and epithelioid myoepithelial cells, which lacked any transition and revealed a biphasic appearance (Fig. 6). Two tumours were distinctive in that they produced innumerable collagen crystalloids (Fig. 7). No ductal or syringomatous epithelial structures or cartilaginous areas were seen in any of the cases. None of the tumours produced any hair follicle, apocrine or sebaceous differentiation. In 3 cases there were minor foci of myxoid areas. Mitotic activity was typically scant, but 3 cases had up to 2 mitoses /10 high-power fields. Necrosis was not present in any of the tumours. The recurrences in cases 3 and 7 were histologically identical to the original tumours.

Immunohistochemically all cases stained positively with antibodies to S-100 protein and cytokeratins; in the case with biphasic spindle-epithelioid cell appearance, however, only the epithelioid component was cytokeratin positive (Fig. 8). Actin stained most of the cells in 3 cases (Fig. 9), and in 3 other cases the actin positivity was focal (Fig. 10). Six tumours were actin negative. Synaptophysin and chromogranin were uniformly negative in all cases.

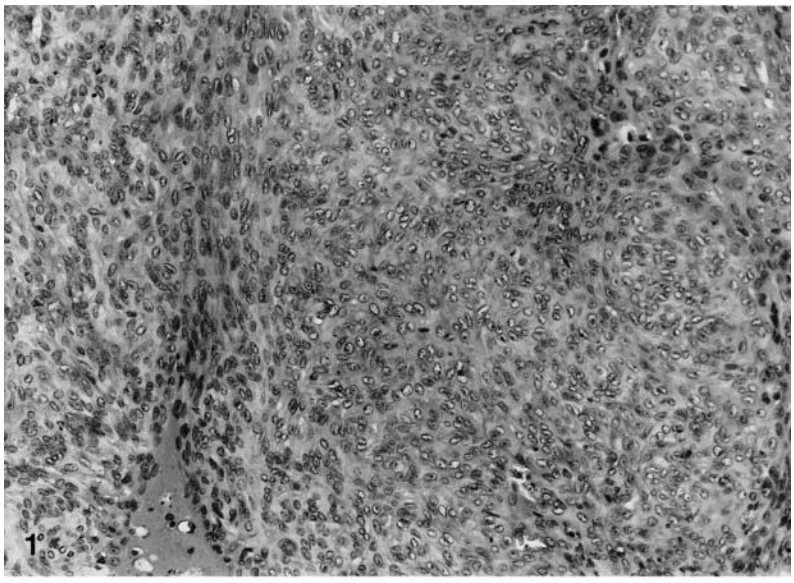
Discussion

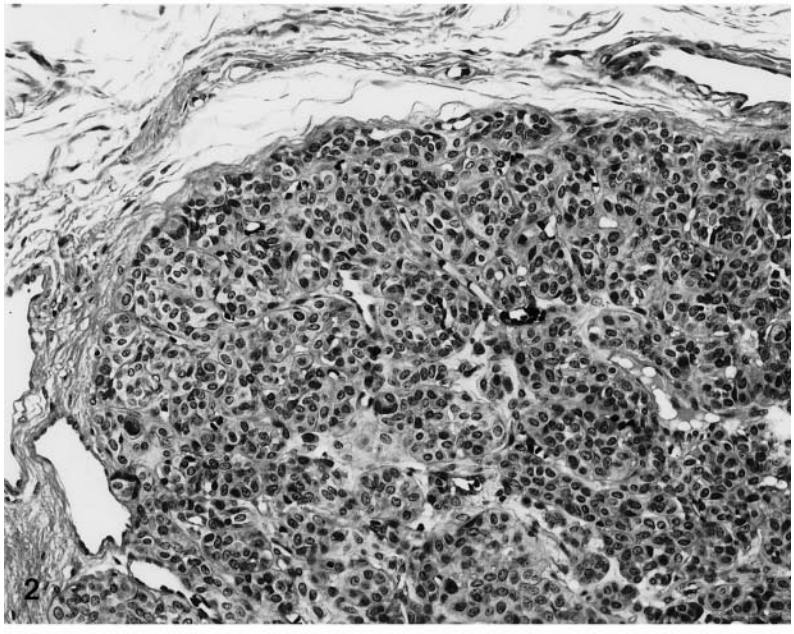
Myoepithelial cells are specialized basal epithelial cells that occur in complex epithelia in several organs, including salivary glands, respiratory tract and breast. In the skin, myoepithelial cells occur in the sweat glands. They have immunohistochemical and ultrastructural features of both epithelial and smooth muscle cells with reactivity to keratins and actins. These cells can give rise to rare tu-

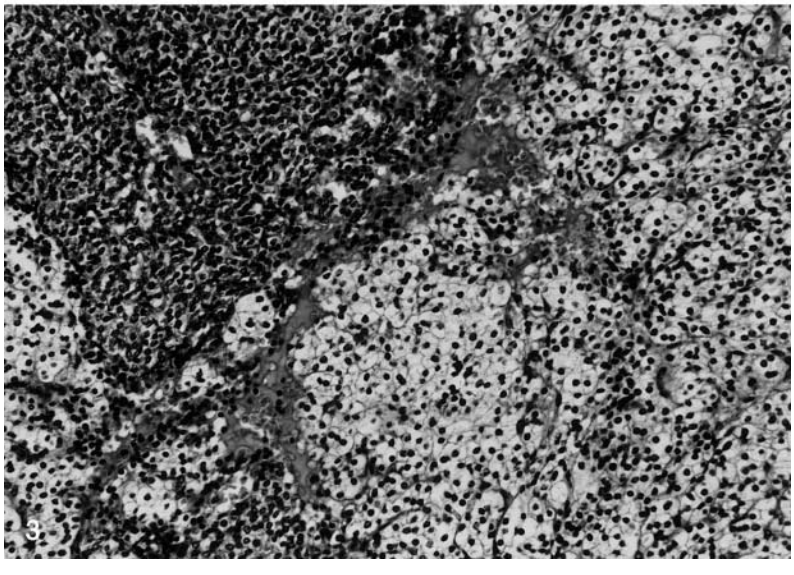
Fig. 1 A myoepithelioma composed of uniform spindle myoepithelial cells

Fig. 2 A myoepithelioma composed of round cell myoepithelial cells

Fig. 3 A myoepithelioma with clear cell foci







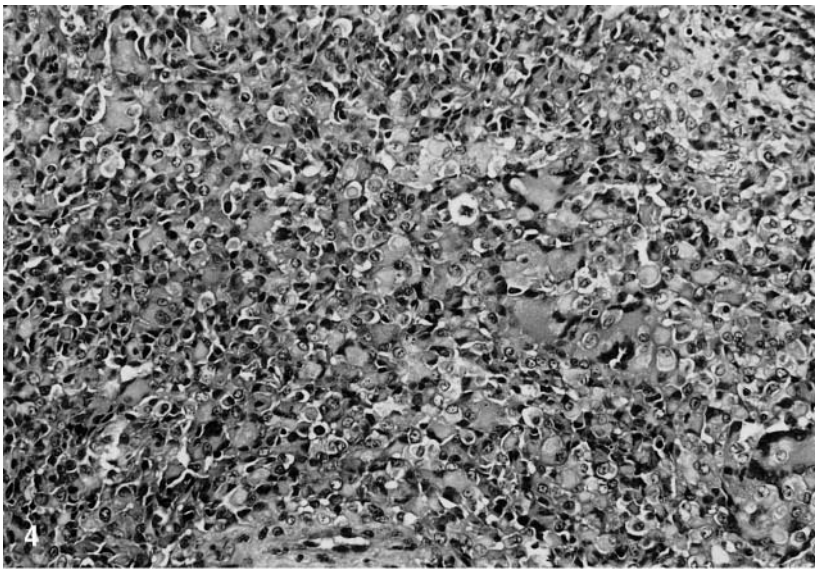


Fig. 4 Epithelioid myoepithelial cells revealing copious hyaline cytoplasm (found in 2 myoepitheliomas)

Fig. 5 Myoepithelial cells resembling those of synovial sarcoma in shape and arrangement (seen in 3 cases)

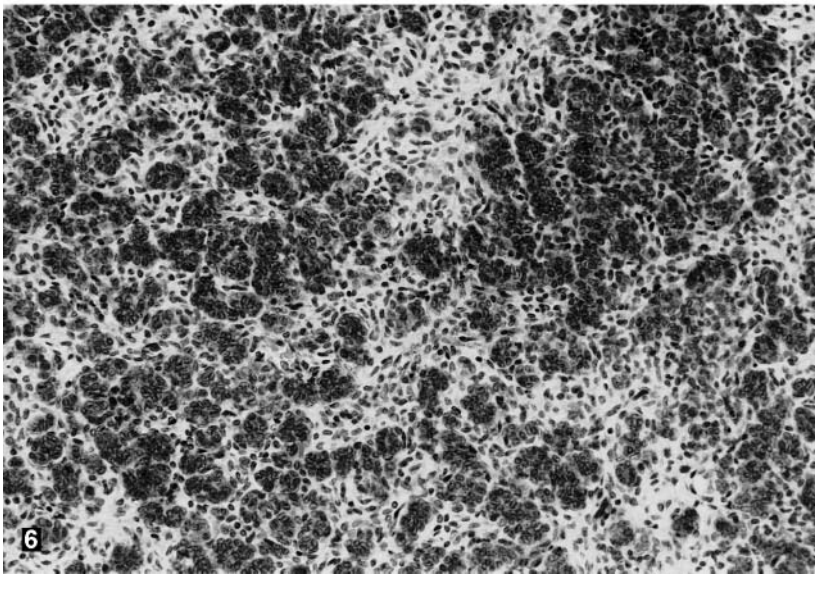


Fig. 6 One tumour differed from the rest of the cases in its mixture of spindle and epithelioid myoepithelial cells, which lacked any transition and revealed a biphasic appearance

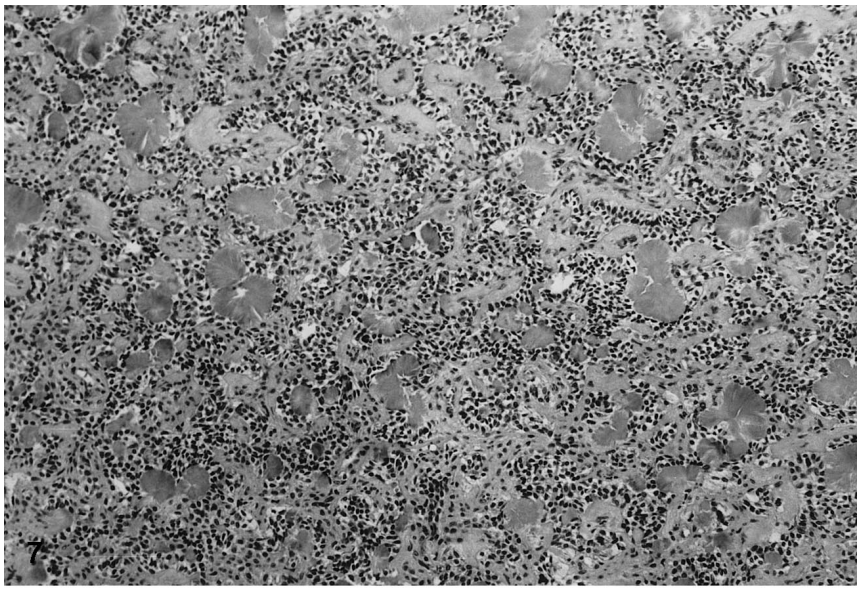


Fig. 7 Innumerable conspicuous collagen crystalloids produced by 2 myoepitheliomas and distinguishing them from the others

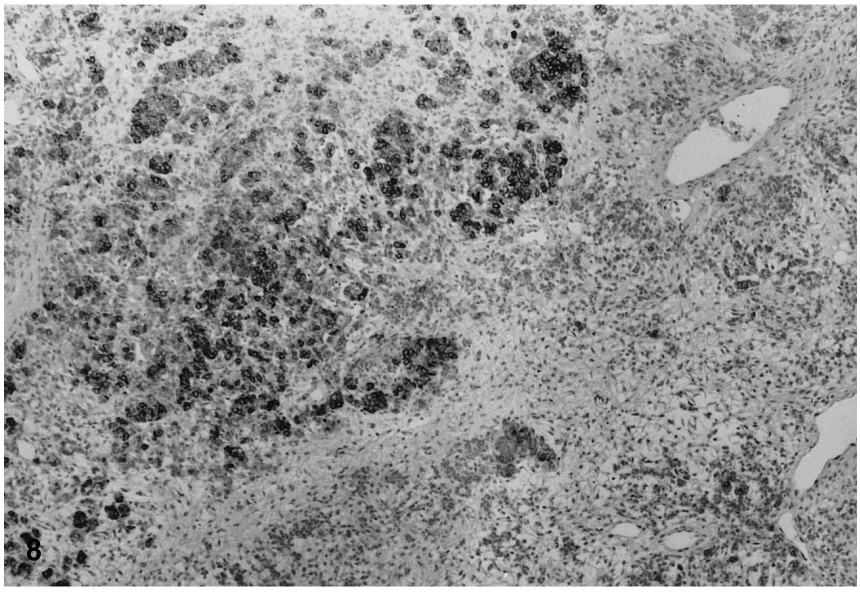


Fig. 8 Myoepithelioma with biphasic spindle-epithelioid cell appearance in which only the epithelioid component was cytokeratin positive

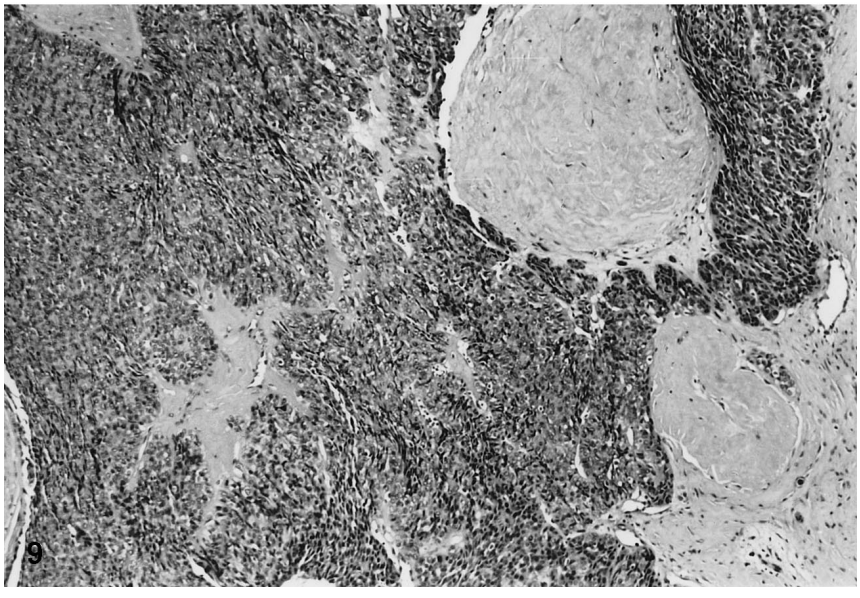


Fig. 9 Actin stained most of the cells in 1 case

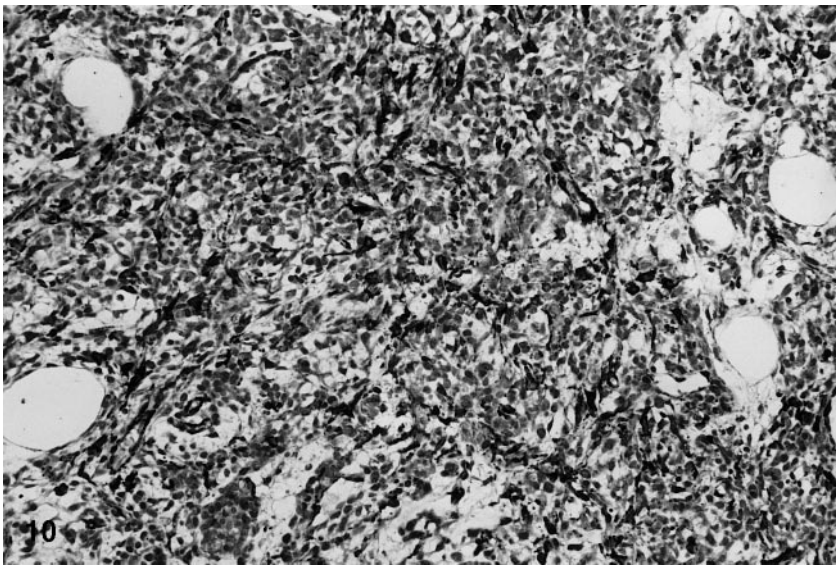


Fig. 10 In two cases actin positivity was focal

mours, myoepitheliomas, which are best defined in the salivary glands [5, 6, 13, 22, 28, 29]. Myoepitheliomas have also been described in the breast [9, 35] and in the lungs [34].

In 1952, Lever and Castleman described a series of clear cell myoepitheliomas of the skin [18]. However, the tumours in their series were later recognized as nodular (clear cell) hidradenomas, which lack myoepithelial differentiation [19]. With one notable exception [17], we are unaware of any publication describing a series of myoepitheliomas of the skin.

The 12 cases of myoepitheliomas of the skin and soft tissues in our series show that these tumours are similar in morphology and immunohistochemical profile to myoepitheliomas of the salivary glands [5, 6, 13, 28, 29]. These tumors are characterized by simultaneous cytokeratin and S-100 protein positivity and variable actin reactivity. However, even immunohistochemically actin-negative myoepitheliomas can retain the ability to produce myoid properties, including actin positivity in cell cultures [16].

Myoepitheliomas of skin and soft tissues usually behave in a benign fashion, despite high cellularity and moderate mitotic activity. However, in 1 of our cases, the patient developed pulmonary metastases and died of tumour disease.

The morphology of our cases varied in the proportions of spindle-shaped, epithelioid and clear cell myoepithelia. One of our cases revealed an unusual biphasic pattern, which consisted in epithelioid myoepithelial cells growing against a background of spindle-shaped myoepithelial cells (Fig. 6). We are aware of a report of a myoepithelioma of the parotid gland with a similar biphasic cellular arrangement [31].

Two of the myoepitheliomas in our series contained widespread collagenous crystalloids, which are well known to occur in mixed tumours and myoepitheliomas of the salivary glands [3, 21, 30, 32]. These crystalloids can be very helpful in the differential diagnosis of skin tumours. They are usually spherical structures measuring 20–100 µm, composed of radially arranged needle-shaped structures (Fig. 7) and displaying strong and homogeneous staining for type I collagen. Antibody to type III collagen stains peripheral parts of the collagenous crystalloids, but they usually lack immunohistochemical staining with antibody to laminin and type IV collagen [32]. They occur in 5% of the myoepitheliomas and mixed tumours of the salivary glands [3, 32], but have rarely been described in mixed tumours of the skin [1, 2]. These crystalloids are not specific for myoepithelioma and mixed tumours of the skin, having also been described in basal cell carcinomas of the skin [33, 37].

Myoepitheliomas of the salivary glands are generally recognized as being histogenetically close to the mixed tumours of the salivary glands. It is not, however, possible to draw a direct parallel between mixed tumours of the skin and of the salivary glands. Mixed tumours in the skin, sometimes called chondroid syringomas, are of two types; apocrine and eccrine [14, 15]. Apocrine mixed tumours, which account for over 80% of all mixed tumours of the skin, are characterized by branching tubular formations differing in size and shape and lined by two layers of epithelial cells. The luminal cells are columnar, with round nuclei at their bases and eosinophilic cytoplasm. These cells show evidence of decapitation secretion. It is probably not accurate to call these tumours apocrine; they very often reveal other signs of hair follicle differentiation, such as shadow cells, basophilic anagen hair bulb differentiation and sebaceous differentiation [25, 26, 36]. Very typical is the lipomatous metaplasia of the stroma seen in most of these tumours. The tumours are better referred to as mixed tumours with hair follicular differentiation to cover their folliculo-sebaceous-apocrine features. They should not be called chondroid syringomas, because the ductal system in syringomas forms complicated branching structures while no sy-

ringomatous structures are seen in these neoplasms. The tumours are unique to the skin, and we are unaware of identical neoplasms occurring in the salivary glands. Neither folliculo-sebaceous-apocrine structures nor lipomatous differentiation were seen in our cases.

Eccrine mixed tumours of the skin show a pattern consisting of small glands and ductlike structures lined by a single layer of cuboidal cells with pale eosinophilic cytoplasm and round nuclei. None of these glands show decapitation secretion. The stroma is usually chondroid or mucinous. The term chondroid syringoma is more appropriate to the eccrine than the apocrine type of cutaneous mixed tumour. It is our impression that the cutaneous myoepitheliomas are more closely related to the eccrine type of mixed tumour of the skin. We have seen chondroid syringomas (eccrine cutaneous mixed tumours) composed of sheets of myoepithelial cells giving a myxoid and cartilaginous matrix with ductlike differentiation without any folliculo-sebaceous-apocrine features [10]. Three of our cases of cutaneous myoepithelioma had minor areas of myxoid matrix similar to those seen in these mixed tumours.

Cutaneous myoepitheliomas should be distinguished from a number of soft tissue neoplasms with potentially similar features. Such tumours include extraskeletal myxoid chondrosarcoma, parachordoma, synovial and epithelioid sarcoma and metastatic carcinoma because of their epithelial differentiation.

Extraskeletal myxoid chondrosarcoma (ESMC) usually arises in deep soft tissues and shows cords of tumour cells in a mucoid matrix not observed in myoepithelioma. Only rarely do myoepitheliomas attain the large size usually observed in ESMC. Even if the neoplastic cells in ESMC show immunoreactivity for S-100 protein, expression of cytokeratin or actin is very unusual in this type of chondrosarcoma [12].

Parachordoma is an extremely rare soft tissue tumour, which has a typical lobular arrangement [4, 11, 24]. The parachordoma shares with myoepitheliomas an immunohistochemical reactivity for cytokeratin and S-100 protein [11]. In contrast to myoepitheliomas, the tumour cells of parachordoma typically have a vacuolated cytoplasm and form small nests of tumour cells in a myxoid background, somewhat similar to ESMC. Parachordoma is invariably actin negative immunohistochemically [11].

Ossifying fibromyxoid tumour of the soft parts shares the S-100 protein and occasionally even actin positivity with myoepitheliomas, but this tumour is nearly always cytokeratin negative. In contrast to myoepitheliomas, it forms characteristic lobules with septa, which often contain metaplastic ossification, especially in the periphery. The neoplastic cells are often arranged in thin cords, which are not seen in the myoepitheliomas [7, 8, 23, 27, 38].

Some forms of synovial sarcoma may be difficult to distinguish from myoepithelioma. However, synovial sarcomas typically arise in deep soft tissues in young adults, in contrast to the superficial location of myoepitheliomas and their preferential occurrence in an older population group. The characteristic hyalinization and calcification seen in synovial sarcoma do not occur in myoepithelioma. The imperceptible merging of the spindle-cell component into the epithelial component often seen in biphasic synovial sarcoma is hardly ever seen in myoepithelioma. The two tumours share cytokeratin reactivity, and some synovial sarcomas are S-100 protein positive. However, synovial sarcomas typically show keratin immunoreactivity in distinct subsets of tumour cells, as opposed to the global keratin reactivity seen in myoepithelioma. Furthermore, synovial sarcomas are actin negative.

Finally, epithelioid sarcoma and metastatic carcinomas share epithelial differentiation. The former lesion is clinicopathologically distinctive, with its primary occurrence in distal extremities in young persons, and histologically shows epithelioid (or spindle) cells with deeply eosinophilic cytoplasm. Metastatic carcinomas usually show definitive signs of malignancy, including mitotic activity and pleomorphism.

Our 12 cases of myoepithelioma of the skin and soft tissues had a generally benign clinical course with 1 exceptional metastatic case. Histological and immunohistochemical findings parallel those seen in myoepitheliomas of the salivary glands.

References

1. Argenyi YB, Balogh K (1991) Collagenous spherulosis in chondroid syringoma. Am J Dermatopathol 13:115–121
2. Banerjee SS, Harris M, Eyden BP, Howell S, Wells S, Mainwaring AR (1993) Chondroid syringoma with hyaline cell change. Histopathology 22:235–245
3. Campbell WG, Priest RE, Weathers DR (1985) Characterization of two types of crystalloids in pleomorphic adenomas of minor salivary glands. Am J Pathol 118:194–202
4. Dabska M (1977) Parachordoma. A new clinicopathologic entity. Cancer 40:1586–1592
5. Dardick I (1995) Myoepithelioma: definitions and diagnostic criteria. Ultrastruct Pathol 19:335–345
6. Ellis GL, Auclair PL (1996) Tumors of the salivary glands. (Atlas of tumor pathology, 3rd ser, fasc 17) Armed Forces Institute of Pathology, Washington DC, pp 57–68
7. Enzinger FM, Weiss SW (1995) Soft tissue tumors, 3rd edn. Mosby, St Louis, pp 1057–1059
8. Enzinger FM, Weiss SW, Liang CY (1989) Ossifying fibromyxoid tumor of soft parts. A clinicopathological analysis of 59 cases. Am J Surg Pathol 13:817–827
9. Erlandson RA, Rosen PP (1982) Infiltrating myoepithelioma of the breast. Am J Surg Pathol 6:785–793
10. Ferreiro JA, Nascimento AG (1995) Hyaline cell rich chondroid syringoma. Am J Surg Pathol 19:912–917
11. Fisher C, Miettinen M (1997) Parachordoma: a clinicopathologic and immunohistochemical study of four cases of an unusual soft tissue neoplasm. Ann Diagn Pathol 1:3–10
12. Fletcher CDM, Powell G, McKee PH (1986) Extraskeletal myxoid chondrosarcoma: a histochemical and immunohistochemical study. Histopathology 10:489–499
13. Hamperl H (1970) The myothelia (myoepithelial cells) Curr Top Pathol 53:161–213
14. Hassab-El-Naby HHM, Tam S, White WL, Ackerman AB (1989) Mixed tumors of the skin. Histological and immunohistochemical study. Am J Dermatopathol 11:413–428
15. Headington JT, Arbor A (1961) Mixed tumors of skin: eccrine and apocrine types. Arch Dermatol 84:989–996

16. Jaeger RG, de Oliveira PT, Jaeger MMM, de Araujo VC (1997) Expression of smooth-muscle actin in cultured cells from human plasmacytoid myoepithelioma. Oral Surg Oral Med Oral Pathol Radiol Endod 84:663–667
17. Kilpatrick SE, Hitchcock MG, Kraus MD, Calonje E, Fletcher CDM (1997) Mixed tumors and myoepitheliomas of soft tissue. A clinicopathologic study of 19 cases with a unifying concept. Am J Surg Pathol 21:13–22
18. Lever WF, Castleman B (1952) Clear cell myoepithelioma of the skin. Am J Pathol 28:691–699
19. Lever WF, Schaumburg-Lever G (1990) Histopathology of the skin, 7th edn. Lippincott, Philadelphia, pp 616–620
20. Lomax-Smith JD, Azzopardi JG (1978) The hyaline cell: a distinctive feature of "mixed" salivary tumours. Histopathology 2:77–92
21. Michal M, Skalova A (1990) Collagenous spherulosis. Pathol Res Pract 186:365–370
22. Michal M, Skalova A, Simpson RHW, Rychterova V, Leivo I (1996) Clear cell malignant myoepithelioma of the salivary glands. Histopathology 28:309–315
23. Miettinen M (1991) Ossifying fibromyxoid tumor of soft parts. Am J Clin Pathol 95:142–149
24. O'Hara BJ, Paetau A, Miettinen M (1998) Keratin and subsets and monoclonal antibody HBME-1 in chordoma: immunohistochemical differential diagnosis between tumors simulating chordoma. Hum Pathol 29:119–126
25. Rapini RP, Kennedy LJ, Golitz LE (1984) Hair matrix differentiation in chondroid syringoma. J Cutan Pathol 11:318–321
26. Requena L, Sanchez Yus E, Santa Cruz DJ (1992) Apocrine type of cutaneous mixed tumor with follicular and sebaceous differentiation. Am J Dermatopathol 14:186–194
27. Schofield JB, Krausz T, Stamp GWH, Fletcher CDM, Fisher C, Azzopardi JG (1993) Ossifying fibromyxoid tumour of soft parts: immunohistochemical and ultrastructural analysis. Histopathology 22:101–112
28. Seifert G, Sobin LH (1991) Histological typing of salivary gland tumours, 2nd edn. Springer, Berlin Heidelberg New York
29. Simpson RHW, Jones H, Beasley P (1995) Benign myoepithelioma of the salivary glands: a true entity? Histopathology 27: 1–9
30. Skalova A, Michal M (1994). Collagenous spherulosis and collagenous crystalloids. Am J Dermatopathol 16:640–642
31. Skalova A, Michal M (1994) Biphasic myoepithelioma of parotid gland with collagenous crystalloids. Histopathology 24: 583–586
32. Skalova A, Leivo I, Michal M, Saksela E (1992) Analysis of collagen isotypes in crystalloid structures of salivary gland tumors. Hum Pathol 23:748–754
33. Soyer HP, Kerl H (1997) What are these distinctive structures in a basal cell carcinoma. Dermatopathology [Pract Concept] 3:222–225
34. Strickler JG, Hegstrom J, Thomas MJ, Yousem SA (1987) Myoepithelioma of the lung. Arch Pathol Lab Med 111:1082–1085
35. Toth J (1977) Benign human mammary myoepithelioma. Virchows Arch [A] 374:263–269
36. Tsoitis G, Brisou B, Destombes P (1975) Mummified cutaneous mixed tumor. Arch Dermatol 111:194–196
37. Zamecnik M, Skalova A, Michal M (1996) Basal cell carcinoma with collagenous crystalloids. Arch Pathol Lab Med 120: 581–582
38. Zamecnik M, Michal M, Simpson RHW, Lamovec J, Hlavcak P, Kinkor Z, Mukensnabl P, Matejovsky Z, Betlach J (1997) Ossifying fibromyxoid tumor of soft parts: a report of seventeen cases with emphasis on unusual histological features. Annals of Diagnostic Pathology 1:73–81