Myoepitheliomas of the Skin and Soft Tissue
-A Clinicopathologic Study of Three Cases

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Myoepithelioma of the skin and soft tissue is a newly recognized entity with characteristic histopathologic and immunohistochemical features, which should be differentiated from a variety of tumors. Myoepitheliomas are in the same pathologic spectrum of mixed tumors and parachordomas. Tumors comprised mostly of myoepithelial cells without obvious epithelial differentiation are designated myoepitheliomas. Since the entity has not been well documented in Taiwan, the clinicopathologic features of three cases of cutaneous and soft tissue myoepitheliomas are reported. (Dermatol Sinica 27: 59-67, 2009)

Key words: Myoepithelioma, Soft tissue, Cutaneous neoplasms

INTRODUCTION

Neoplasms of myoepithelial cells can occur in a pure form as myoepitheliomas or in association with glandular structures as mixed tumors.1 Salivary gland myoepitheliomas are well known. Myoepitheliomas have also been described to occur in the breast, larynx, and retroperitoneum.2 Myoepitheliomas of the skin and soft tissue were recognized only 10 years ago.3 Since the entity has not been documented in Taiwan, we report the clinicopathologic features of three cases of cutaneous and soft tissue myoepitheliomas.

CLINICAL FEATURES

The clinical features of three cases of cutaneous and soft tissue myoepitheliomas are summarized in Table 1. There were one female and two male patients. Age at diagnosis ranged from 11 to 21 years. Two patients reported the development of painless and slowly growing mass. One patient (Case 2) was initially treated conservatively as growing pain by an orthopedic surgeon before the enlarged tumor was detectable on the left knee. The stated duration of symptom ranged from 6 months to 1 year. All neoplasms occurred in the extremities or limb girdle, and the sizes of the tumor ranged from 0.7-2.5 cm. In all cases, the clinical impression was an epidermal inclusion cyst. Two tumors (Cases 1 and 2) were not completely excised, and one of them (Case 2) received a wide re-excision. Clinical follow-up was available in all cases. One patient (Case 1) developed lo-
cal recurrence 6 months after the surgery. No recurrence occurred to the other two cases for 6 months and 3 months, respectively.

PATHOLOGIC AND IMMUNOHISTOCHEMICAL FEATURES

Microscopically, one tumor was located in dermis (Fig. 1A) and two tumors in subcutaneous soft tissue (Fig. 2A, 3A). Two cases (Case 1 and 3) were well circumscribed with a nodular growth pattern. The remaining case (Case 2) had an infiltrative growth pattern. Chondromyxoid or hyalinized stroma was seen in all tumors, and Case 1 tumor showed focal calcification. The tumor in Case 1 was composed of a mixed population of spindled, epithelioid, and plasmacytoid cells arranged around a central chondromyxoid stroma. Mild nuclear atypia (coarse chromatin and prominent nucleoli) was observed. It also contained 13 mitotic figures per 10 high power fields (Fig. 1B). The tumor in Case 2 was composed of dissociated small round cells in hyalinized stroma and scattered nests of epithelioid and plasmacytoid cells in fibrous stroma (Fig. 2B). The tumor in Case 3 was composed of two tumor nodules surrounded with a thick fibrous capsule. The tumor nodules were solid and comprised of a mixture of spindled cells and epithelioid cells in a fibrous stroma with focal chondroid or myxoid background. The larger epithelioid cells had clear cytoplasm and perinuclear granular eosinophilic cytoplasm (Fig. 3B). Occasional vacuolated nuclei were seen. No mitotic figures or tumor necrosis was observed in Case 2 or 3 tumors. The primary antibodies, clones, dilutions, pretreatment conditions, and sources of immunohistochemical stains are listed in Table 2. The staining procedure was performed in an automated NexES®, Ventana Medical Systems, Inc. The results of immunohistochemical stains in comparison with the two largest studies on cutaneous and soft tissue myoepitheliomas are summarized in Table 3. Briefly, all tumors were positive for vimentin. All showed some evidence of epithelial differentiation via immunoreactivity for cytokeratin (2 cases) or epithelial membrane antigen (EMA) (1 case). Two cases each were positive for S-100 protein, glial fibrillary acid protein (GFAP) and calponin. No immunoreactivity was seen for smooth muscle actin (SMA) (2 cases) or p63.
Table 2 Panel of Antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clone</th>
<th>Dilution</th>
<th>Antigen retrieval</th>
<th>Source</th>
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<tbody>
<tr>
<td>AE1/AE3</td>
<td>AE1/AE3</td>
<td>1:400</td>
<td>72 sec protease</td>
<td>Dako</td>
</tr>
<tr>
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<td>1:100</td>
<td>72 sec protease</td>
<td>Dako</td>
</tr>
<tr>
<td>Calponin</td>
<td>CALP</td>
<td>1:100</td>
<td>72 sec protease</td>
<td>Dako</td>
</tr>
<tr>
<td>SMA</td>
<td>1A4</td>
<td>1:200</td>
<td>None</td>
<td>Dako</td>
</tr>
<tr>
<td>GFAP</td>
<td>6F2</td>
<td>1:400</td>
<td>None</td>
<td>Dako</td>
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<td>Dako</td>
</tr>
<tr>
<td>p63</td>
<td>4A4</td>
<td>1:100</td>
<td>3 min pressure cooker in EDTA buffer</td>
<td>Dako</td>
</tr>
</tbody>
</table>

AE1/AE3, pancytokeratin; EMA, epithelial membrane antigen; SMA, smooth muscle actin; GFAP, glial fibrillary acidic protein; EDTA, ethylenediaminetetraacetic acid

(1 case).

DISCUSSION

Myoepithelial cells can exhibit dual epithelial and myoid differentiation. They may also show divergent metaplasia, including squamous, adipocytic, bone and cartilagenous differentiation. As a consequence, proliferating myoepithelial cells in neoplasms display a variety of histologic and immunohistochemical expression patterns.

In the recent World Health Organization classification of tumours of soft tissue, mixed tumors, myoepitheliomas, and parachordomas are considered to be in a pathologic spectrum. Mixed tumors are defined as well-circumscribed lesions displaying epithelial and/or myoepithelial elements in varying proportions within a hyalinized to chondromyxoid stroma. Tumors comprised mostly of myoepithelial cells and lacking obvious epithelial differentiation are designated myoepitheliomas. Parachordomas closely resemble mixed tumors, except that cytoplasmic vacuolation may be a prominent feature in the former.

It has been postulated that cutaneous myoepitheliomas are related to mixed tumors of skin and that soft tissue myoepitheliomas are derived from deeply located adnexal structures. Cutaneous myoepitheliomas of the head and neck may be derived from salivary gland tissue, as has been reported in two parotid gland myoepitheliomas presenting as infra-auricular subcutaneous masses. Therefore, the possibility of an underlying primary salivary gland neoplasm should be considered in myoepitheliomas presenting in the head and neck.

Kilpatrick et al., reported a study of 19 patients with mixed tumors and myoepitheliomas of soft tissue in 1997. Michal et al., reported 12 additional cases of myoepitheliomas of the skin and soft tissues in 1999. Recently, Hornick and Fletcher reported a series of 101 cases of soft tissue myoepitheliomas, et al.
Myoepitheliomas. The authors found that the tumors occur over a wide age range with peaks in the third to fifth decades, approximately equal distribution in gender, and are most common in the extremities and limb girdles. Later, Hornick and Fletcher\(^9\) conducted a study of 14 cutaneous myoepitheliomas. There were 11 males and 3 females. The study indicated that cutaneous myoepitheliomas occur with peaks in childhood (7 patients were between 10 and 20 years of age) and middle age and are most common in the extremities, in contrast to mixed tumors of the skin, which typically occur on the head and neck in middle-aged or elderly adults.

Similar to previously reported series, our cases occurred in children and young adults on the extremities and limb girdle. The clinical diagnosis considered in all of our cases was an epidermal inclusion cyst. Clinical diagnoses mentioned in the previous studies\(^9\) included dermatofibroma, neurofibroma, Kaposi’s sarcoma, keratoacanthoma, and cutaneous cyst. A continuous spectrum of cutaneous myoepithelial neoplasms ranges from benign mixed tumor of the skin to cutaneous myoepitheliomas and cutaneous myoepithelial carcinoma.\(^{10}\) The diagnosis of myoepithelioma is based on the combination of morphologic features with supportive im-

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**Fig. 1**
Histopathologic features of case 1.
(A) A nodular dermal tumor with chondroid-like changes and focal calcification (arrow). (H&E, original magnification x20)
(B) Spindled and epithelioid tumor cells with cytologic atypia and frequent mitotic figures (arrow). (H&E, original magnification x400)

**Fig. 2**
Histopathologic features of Case 2.
(A) The tumor is located in subcutis. The deeper part was not excised. (H&E, original magnification x40)
(B) Dissociated small round cells in hyalinized stroma. (H&E, original magnification x400)
munohistochemistry and/or ultrastructural features. Microscopically, the architecture of myoepitheliomas consists of lobulated, multinodular, reticular, solid, or mixed patterns without epithelial differentiation. Variably prominent chondromyxoid or hyalinized stroma can be found between cords or sheets of tumor cells. Tumor cells may be epithelioid (round or polygonal cells with variably abundant eosinophilic to pale cytoplasm), spindled (ovoid to elongated cells with predominantly eosinophilic cytoplasm and narrow, somewhat tapering nuclei), clear (clear cytoplasm with small nuclei), or plasmacytoid (plump cells with abundant, ec-}

**Fig. 3**
Histopathologic features of case 3.
(A) The tumor is well circumscribed and located in subcutis. (H&E, original magnification x40)
(B) Large epithelioid cells with clear and perinuclear granular eosinophilic cytoplasm. (H&E, original magnification x400)

**Fig. 4**
Immunohistochemical findings.
(A) Tumor cells are positive for pancytokeratin AE1/AE3. (Case 3, original magnification x400)
(B) Tumor cells are positive for calponin. (Case 2, original magnification x400)
(C) Tumor cells are positive for GFAP. (Case 3, original magnification x400)
(D) Tumor cells are positive for S-100 protein. (Case 1 original magnification x400)

centrally placed hyaline cytoplasmic inclusions). Squamous, adipocytic, osseous and cartilaginous metaplasia may be seen. Criteria for differentiating benign from malignant myoepitheliomas are not well established, although moderate to severe cytological atypia (prominent nucleoli, vesicular or coarse chromatin, nuclear pleomorphism) should warrant classification as myoepithelial carcinoma.

In all of our cases, the characteristic histologic features were found. A clue of chondromyxoid or hyalinized stroma with
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Myoepitheliomas

epithelioid and spindled cells led to our consideration of myoepithelioma. The tumors were limited to dermis in Case 1, and located in subcutaneous soft tissue in Cases 2 and 3. Only Case 1 demonstrated cytologic atypia with mitotic figures. A diagnosis of malignant myoepithelioma should be considered based on its cytologic atypia.

Once the diagnosis of cutaneous and soft tissue myoepitheliomas is considered, confirmatory immunohistochemical studies might be helpful. In salivary gland myoepitheliomas, tumor cells are generally positive for epithelial markers and S-100 protein with variable expression of GFAP and myogenic markers. Therefore, combinations of immunoreactivity for aforementioned markers are required for diagnosis of cutaneous and soft tissue myoepitheliomas. In our study, all of our cases showed histologic and immunohistochemical features of myoepithelioma. Stains for S100 protein, calponin, EMA, and cytokeratin AE1/3 appear to be the most sensitive markers (Table 3). However, as demonstrated in previous studies, the immunophenotype of myoepithelioma can be variable, and not all tumors have a consistent immunophenotype. Immunoreactivity for SMA, GFAP, and p63 may also be seen to variable degrees, and stains for these antigens may be good second line markers. Given the heterogeneity of tumor cell differentiation in myoepitheliomas, immunohistochemical results for the diagnosis of myoepitheliomas can only be interpreted in the proper morphologic context.

The differential diagnosis of cutaneous and soft tissue myoepitheliomas depends on the predominant histological pattern. Myoepitheliomas are differentiated from mixed tumors by the absence of epithelial structures. For myoepitheliomas with reticular architecture and myxoid stroma, which are most commonly encountered, the primary differential diagnoses are extraskeletal myxoid chondrosarcoma (EMC) and ossifying fibromyxoid tumor (OFMT). EMC typically shows a multinodular growth pattern with interlacing cords of cells in a myxoid matrix. The tumor cells in EMC are more spindled...

Table. 3 Results of Immunohistochemical Study and Comparison with the Two Largest Studies

<table>
<thead>
<tr>
<th>Case/Reference</th>
<th>AE1/AE3</th>
<th>EMA</th>
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<th>GFAP</th>
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<td>11/14</td>
<td>10/11</td>
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<td>(91%)</td>
<td>(57%)</td>
<td>(50%)</td>
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<td>51/66</td>
<td>52/83</td>
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AE1/AE3, pancytokeratin; EMA, epithelial membrane antigen; SMA, smooth muscle actin; GFAP, glial fibrillary acidic protein; ND, not done.
than those of myoepitheliomas. Immunohistochemical staining is required for diagnosis since the histologic differences between these two entities may be subtle. S-100 protein and epithelial markers are expressed in a minority of EMC and usually only focally, while both the markers are often extensively expressed in myoepitheliomas. OFMT is a lobulated tumor surrounded by a rim of metaplastic bone. The tumor cells are mostly pale-staining ovoid to round cells. Approximately 70% of OFMT show positivity for S-100 protein and vimentin and 50% of tumor cells are positive for desmin. The tumor cells in OFMT are rarely positive for epithelial markers and GFAP. Myoepitheliomas are generally negative for desmin, nearly half positive for GFAP, and nearly always show positivity for keratin and S-100 protein.

In myoepitheliomas with solid sheets of epithelioid, ovoid, or histiocytoid cells, the primary diagnostic considerations include epithelioid benign fibrous histiocytoma, melanocytic tumors, such as Spitz nevus, epithelioid sarcoma, and cellular neurothekeoma. Epithelioid benign fibrous histiocytoma usually shows a superficial dermal tumor with a well-developed epidermal collarette. Spitz nevus is characterized by a junctional component, nesting and maturation of tumor cells. In epithelioid sarcoma, multiple tumor nodules around central necrosis or even myxoid degeneration are often seen. More morphologic uniformity is observed in epithelioid sarcoma over myoepithelioma. Moreover, approximately 90% of epithelioid sarcoma are positive for vimentin, cytokeratin, and EMA, and around 60% are positive for CD34, but are generally negative for other markers typical of myoepithelial differentiation (S-100 protein, GFAP, myogenic markers). Cellular neurothekeoma consists of nesting of tumor cells, and are consistently S-100 negative.

Least commonly, myoepithelioma is composed of solid sheets of spindled cells. They should be differentiated from leiomyoma and Schwannoma. The nuclei of leiomyoma are broader cigar-shaped, and Schwannoma is characterized by alternating zones of cellularity and nuclear palisading. Characteristic clinical presentations, histologic features, and confirmatory immunostaining aid in the differential diagnosis as mentioned above.

The most important histologic feature predicting potentially aggressive behavior is the presence of cytologic atypia. Other clinicopathologic parameters, including patient age, status of excision margins, tumor depth, tumor size, infiltration into surrounding tissues, presence of tumor necrosis, and mitotic rate, are not statistically correlated with recurrence or metastasis. However, in 2 of the 3 locally recurred cutaneous myoepitheliomas reported by Hornick et al., the primary excision margins were either positive or marginal. In our Case 1, local recurrence 6 months after surgery can be attributed to incomplete excision and malignant nature of the tumor.

In conclusion, myoepitheliomas should be considered in the differential diagnosis of cutaneous and soft tissue tumors. Immunohistochemical study may aid in the diagnosis. Although most cutaneous and soft tissue myoepitheliomas behave in a benign fashion, there is a significant risk for local recurrence and a low metastatic potential. Wide excision with safe surgical margins and regular follow-up are crucial for the management of cutaneous and soft tissue myoepitheliomas. For myoepitheliomas located in the head and neck regions, further image studies are warranted to exclude primary salivary gland neoplasms.

ACKNOWLEDGEMENT

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REFERENCES

皮膚及軟組織肌上皮瘤
-三個病例之臨床病理研究

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皮膚及軟組織肌上皮瘤為近來被認定的腫瘤，具有特殊的組織病理和免疫組織化學染色，應與其他腫瘤鑑別診斷。肌上皮瘤和混合瘤、副脊索瘤在同一病理之範疇。肌上皮瘤的定義為由肌上皮細胞所組成，而缺乏明顯的表皮分化之腫瘤。皮膚及軟組織肌上皮瘤在台灣還未被詳加紀錄，我們在此報告三個病例，討論其臨床和病理表現。（中華皮誌：27: 59-67, 2009）