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A Cutaneous Myoepithelial Carcinoma Arising in a Papillary Eccrine Adenoma

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Cutaneous myoepithelial neoplasms and papillary eccrine adenomas (PEA) are rare conditions. Malignant tumors within a PEA are even rarer, with only one case reported to date. Herein, we present an extremely rare case of a cutaneous myoepithelial carcinoma arising in a PEA in a 70-year-old man presenting a solid mass in the left buttock. Histopathologically, most of the resected tumor revealed features consistent with the diagnosis of PEA. Some small nests and nodules were intermixed with the PEA and were present adjacent to the PEA. The tumor cells of nests and nodules showed ovoid to spindle shaped nuclei and slightly eosinophilic cytoplasm. Immunohistochemically, they were positive for both epithelial and myogenic markers, consistent with myoepithelioma. An inguinal lymph node with a metastatic lesion showed the same findings of myoepithelioma despite inconspicuous atypia. Our case showed malignant transformation of the myoepithelial cells at the outermost layers of the PEA.

Key Words: Skin; Myoepithelial carcinoma; Papillary eccrine adenoma

Benign and malignant neoplasm of myoepithelial cells comprise a rare but well-characterized group of tumors in the salivary glands,[1] breasts,[2] and soft tissues.[3] Histopathologically, myoepitheliomas show solid, reticular, trabecular architecture and myxoid or hyaline stroma, and are composed of round/epithelioid or spindle cells. The tumor cells of myoepitheliomas possess the capacity for epithelial and myoid differentiation and, as a consequence, immunohistochemical reactivity is variable, showing combinations of immunoexpression for cytokeratin, epithelial membrane antigen (EMA), S-100 protein, α-smooth muscle actin (α-SMA), calponin, and glial fibrillary acidic protein (GFAP).[4] In normal skin, myoepithelial cells are present as spindle-shaped cells arranged as a discontinuous peripheral layer around eccrine and apocrine glands; their contractions aid delivery of the secretory products of these glands.[5] Only recently have neoplasms been shown to compose only myoepithelial cells that occur primarily in the skin.[6-11] Because fewer than 50 such cases have been published to date, limited data are available regarding the morphological spectrum and immunophenotype of these cells. Moreover, the criteria for differentiating benign form from malignant myoepithelioma have not been fully clarified.

The papillary eccrine adenoma (PEA) was first described by Rulon and Helwig[12] in 1977; it is a rare, benign, slow-growing tumor. Clinically, the tumor presents as a solitary dermal nodule and is most commonly located on the extremities.[12] Histopathologically, the tumor is composed of multiple, dilated tubular structures lined by two or more layers of epithelial cells. However, malignant change of a PEA is extremely rare, with only one case reported to date.[13]

Here, we report an extremely rare case of cutaneous myoepithelial carcinoma arising in a PEA with lymph node metastasis. To the best of our knowledge, this is the fifth case of a myoepithelial carcinoma and the second case of malignant change of a PEA reported in the medical literature.

CASE REPORT

A 70-year-old man was referred to our hospital with a 1-year history of a continuously growing mass in the left buttock. In addition, he underwent an excisional biopsy of the inguinal mass

at a local clinic. The initial diagnosis was metastatic basal cell carcinoma involving the inguinal lymph node. The physical examination of the buttock revealed a non-tender, protruding, and dark-red colored subcutaneous mass, approximately 6.0 cm in diameter (Fig. 1). The patient underwent a wide surgical excision of the lesion. Although he was not treated with any postoperative radiotherapy or chemotherapy, he was well for the next eight months.

The excised specimen was composed of an ellipse of skin, measuring 8.0×6.5 cm, partly containing subcutaneous fat. A large, dark red solid mass, measuring 6.0×1.5 cm, was present. On the histopathological examination, most of the tumor revealed features consistent with the diagnosis of a PEA. It was composed of numerous dilated epithelium-lined tubular structures of various sizes surrounded by fibrous stroma (Fig. 2A). The tubules were lined by two or more rows of epithelial cells: a single row of flattened cells comprised the outermost layer, while the inner layer cells were cuboidal or columnar, and often

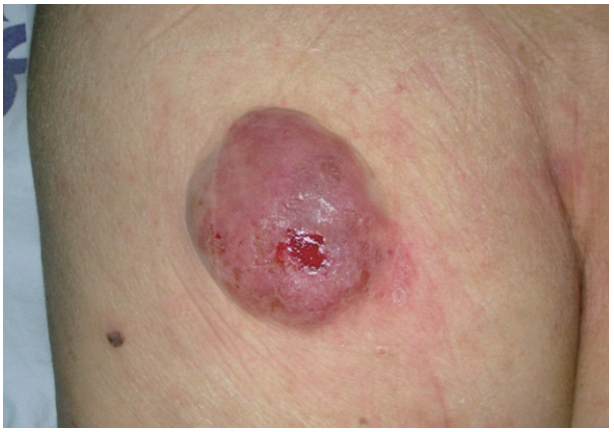

Fig. 1. Clinical apperance of the tumor. A non-tender, protruding, and dark-red colored subcutaneous mass is seen on the buttock.

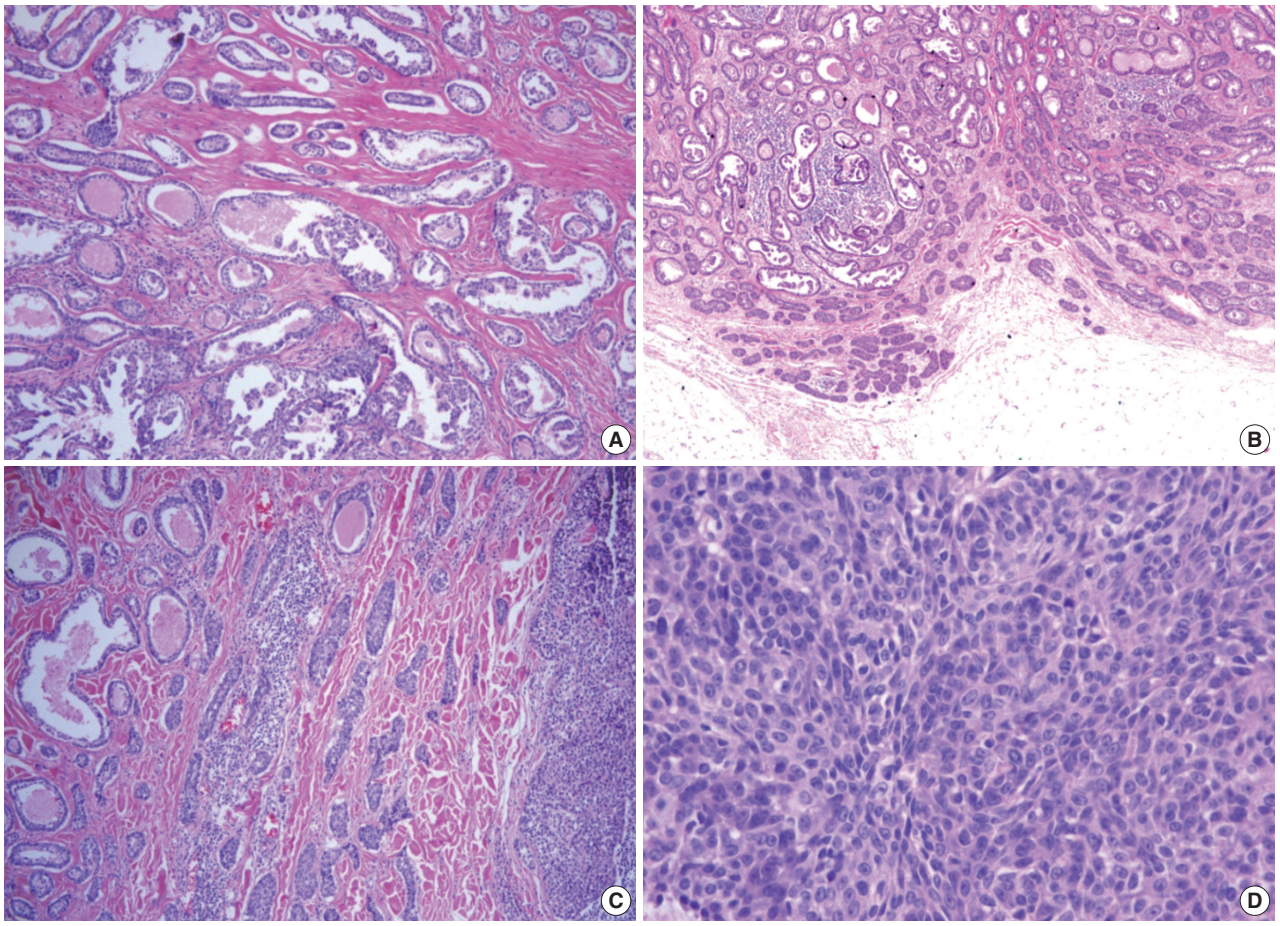

Fig. 2. (A) Photomicrograph of papillary eccrine adenoma demonstrates several eccrine tubules with papillary projections and surrounded by a collagenous stroma. (B) Low-power photomicrograph shows myoepithelioma is intermixed with papillary eccrine adenoma and infiltrates into the subcutaneous fat tissue. (C) Photomicrograph of a feature papillary eccrine adenoma (left) merging into myoepithelioma (right). (D) High-power photomicrograph of tumor cells of myoepithelioma shows ovoid to spindle shaped nuclei, slightly eosinophilic cytoplasm, and small conspicuous nucleoli.

formed papillary projections into the lumen. However, decapitation secretion was not observed. The lumen either appeared empty or was filled with an acellular and granular eosinophilic secretion material. Cell necrosis, mitosis, and nuclear pleomorphism were absent. The epidermis overlying the tumor presented irregular acanthosis and showed an eroded surface in the center. Connection of the tubules to the epidermis was observed. Some small nests and nodules without glandular structures were intermixed with PEA component and were present adjacent to the PEA component (Fig. 2B, C). Moreover, the small nests infiltrated into the subcutaneous tissue (Fig. 2B). The tumor cells of the small nests and nodules showed ovoid to spindle shaped nuclei, slightly eosinophilic cytoplasm, and small conspicuous nucleoli (Fig. 2D). Nuclear atypism was not prominent and mitotic figures were generally infrequent. No ductal and/or tubular differentiation was evident. The results of the immunohistochemical analysis of the buttock mass are summarized in Table 1. Briefly, cudoidal or columnar cells in the inner layers of the PEA were positive for cytokeratin and carcinoembryonic antigen (Fig. 3A). However, the flattened cells of the outermost layer of the PEA were positive for vimentin, α-SMA and p63 (Fig. 3B). This finding suggested that the outermost layer cells of the PEA were composed of myoepithelial cells. The tumor cells of the small nests were diffusely positive for EMA, 34βE12, α-SMA, S-100 protein, and p63, which was consistent with the diagnosis of a myoepithelial neoplasm (Fig. 3B).

Table 1. Results of immunohistochemical staining

Antibody	Papillary eccrine adenoma		Myoepithelioma
	Inner layer	Outermost layer	
Cytokeratin	+	-	-
34βE12	+	+	+
CEA	+	-	-
EMA	+	+	+
Vimentin	-	+	+/-
α-Smooth muscle actin	-	+	+
Muscle-specific actin	-	-	-
p63	-	+	+
S-100 protein	-	+/-	+
Desmin	-	-	-
GFAP	-	-	-

CEA, carcinoembryonic antigen; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; +, positive; -, negative; +/-, focally positive.

We also reviewed the previously excised inguinal lymph node. The metastatic tumor was entirely composed of strands and nests of myoepithelial cells and lacked a definite epithelial component (Fig. 4A). The stroma showed a more myxoid appearance than that of the buttock mass. Immunohistochemical stains of the lymph node showed diffuse positivity for p63 and focal positivity for S-100 protein (Fig. 4B). However, the remaining immunohistochemical markers were negative. The final diagnosis was a metastatic myoepithelial carcinoma.

DISCUSSION

Normal eccrine glands are composed of three segments: intraepidermal duct, intradermal duct, and secretory portion. The secretory portion is a convoluted tube composed of three cell types: clear cells, dark cells, and myoepithelial cells.[14] Myoepithelial cells originate embryologically from the ectoderm but show bidirectional differentiation, displaying both epithelial and mesenchymal features.[6] Therefore proliferating myoepithe-

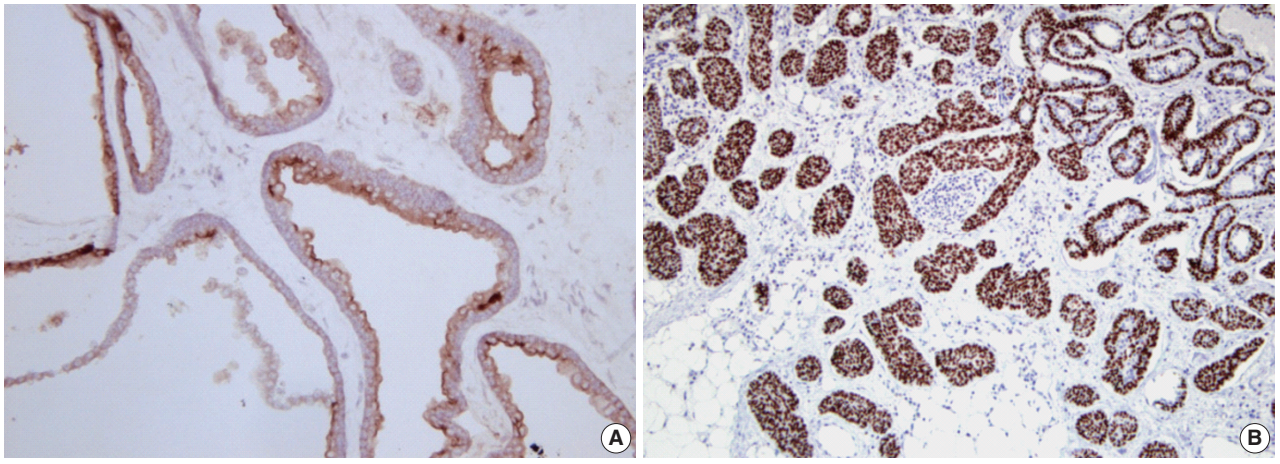

Fig. 3. (A) Immunohistochemical stain for carcinoembryonic antigen shows diffuse positive reaction in columnar cells in the inner layers of papillary eccrine adenoma. (B) Immunohistochemical stain for p63 shows positive reaction in outer myoepithelial cell layers of papillary eccrine adenoma (right) and in myoepithelioma (left).

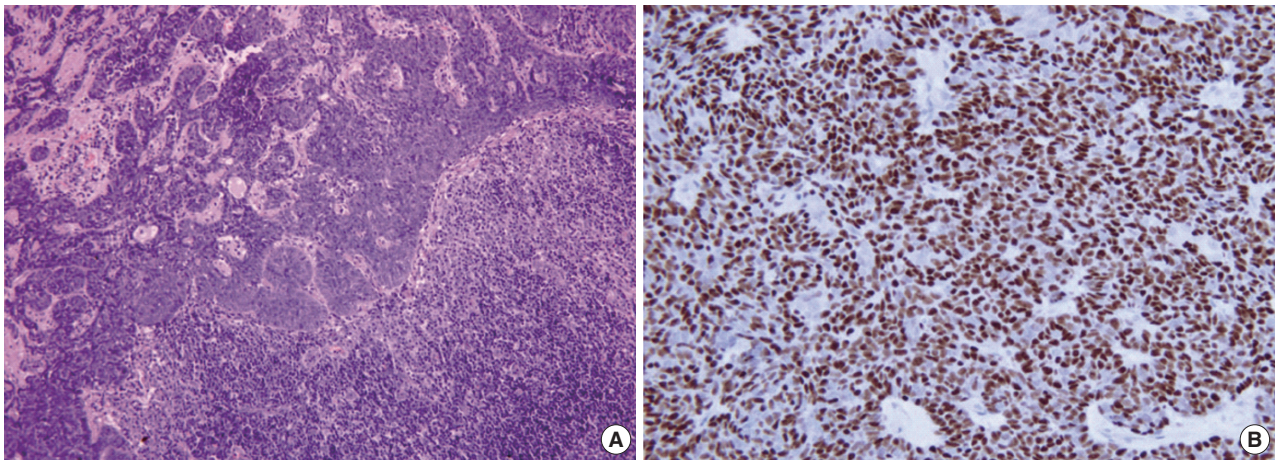

Fig. 4. (A) Photomicrograph of lymph node demonstrates presence of metastatic myoepithelioma. (B) Immunohistochemical stain for p63 shows diffuse positive reaction in metastatic myoepithelioma.

lial cells in a neoplasm may express a variety of histological patterns, including the presence of ducts, nests, and cords of spindle-shaped, ovoid, plasmacytoid or epithelioid cells with clear cytoplasm or even squamous differentiation within a hyalinized to chondromyxoid stroma.[8]

For the skin, the term myoepithelioma was originally used by Lever[15] in 1948 to describe "myoepithelial tumors," a neoplasm that was later referred to as clear cell hidradenoma. Recently, Kilpatrick *et al.*[16] following the study of 19 patients with mixed tumors and myoepithelioma of the soft tissue, redefined the term "myoepithelioma" of the skin and subcutis to refer to a neoplasm with predominantly myoepithelial differentiation. However, cutaneous myoepithelial neoplasms are extremely rare; only 44 cases have been reported to date.[6-11] The reported cases, including the present case, have a wide age range (3 to 93 years; mean age, 44 years), a male predominance (male : female = 2.2 : 1), and are most commonly identified on the extremities, in contrast to mixed tumors of the skin, that are commonly found in the head and neck region. Histopathologically, myoepitheliomas may display considerable variation in the morphological features observed under the microscope. The histopathological criteria for a myoepithelioma proposed by Kutzner *et al.*[8] includes: 1) a well-circumscribed dermal nodule with no epidermal connection; 2) a solid appearance of the neoplasm, with cluster-like aggregation of neoplastic cells and, less often, small sheets or strands of cells; 3) monomorphous neoplastic cells with ovoid nuclei and pale eosinophilic cytoplasm; and 4) hyalinzed or myxoid stroma. Because the tumor cells are shown to react positively for both epithelial and myogenic markers in the immunohistochemical analysis, immunoreactivity for S-100 protein and smooth muscle actin appears to be the most constant immunophenotype, whereas immunoexpression for cytokeratin, EMA, and GFAP are more variable. Our case showed solid nodules composed of monomorphic neoplastic cells with ovoid to spindle shaped nuclei, without evidence of ductal differentiation. Immunohistochemically, our case was diffusely positive for EMA, 34βE12, α-SMA, S-100 protein, and p63. These findings were consistent with myoepithelioma. Although the buttock mass showed no evidence of hyalinized to myxoid stroma, the tumor of the lymph node was entirely composed of strands and nests of myoepithelial cells and showed myxoid stroma. Moreover, the immunohistochemical stains of the lymph node showed diffuse positivity for p63, which was known as a myoepithelial marker. This result suggests that the tumor of the lymph node was a metastatic lesion from the myoepithelial carcinoma of the buttock.

PEA is a rare cutaneous neoplasm with a histopathological appearance that is diagnostic. It was first described by Rulon and Helwig[12] in 1977 who reported 14 cases. Clinically, PEA appears as a solitary, firm, raised mass and is located on the distal extremities of middle-aged patients.[12,17] Morphologically, PEA is distinctive in that the proliferating tubules are composed of two different types of cells; an outermost layer of flattened cells, and inner cuboidal-to-columnar cells that demonstrate prominent intraluminal papillary projections. In the cell morphology of the lining of tubules, the absence of decapitation secretion indicates eccrine differentiation. Immunohistochemically, our case showed positive responses to carcinoembryonic antigen and EMA in an inner layer of PEA. Additionally, an outermost layer of PEA was positive for not only α-SMA but also p63, which has recently been reported to be a basal/myoepithelial marker of sweat glands.[18]

Malignant tumors within a PEA are extremely rare, with only one case having been reported thus far.[13] Galadari *et al.*[13] reported a nodular lesion present for more than 10 years on the upper lip of a 59-year-old man; the tumor showed that most parts had a mixture of histological patterns of the PEA and tubular type of eccrine adenocarcinoma. Unlike the above case, in our case, the myoepithelial cells at the outermost layers of the PEA formed a myoepithelioma, and they infiltrated the subcutaneous fat tissue, and then metastasized to the inguinal lymph node, although the tumor cells showed inconspicuous atypia and low mitotic figures.

Due to the rarity of cutaneous myoepithelial neoplasms, there are no definite histological criteria for differentiating benign from malignant myoepitheliomas. As for myoepithelial tumors of the salivary gland, in the absence of frankly malignant cytomorphology, such as nuclear atypia and a high mitotic rate, infiltration of the surrounding salivary gland or normal tissue has been proposed as the features suggestive of a malignancy.[1] For myoepithelial tumors of soft tissue, Kilpatrick *et al.*[16] reported that infiltration by neoplastic cells at the tumor/soft tissue interface was associated with metastasis and proposed the application of similar rules to those used for salivary gland neoplasms to predict the clinical behavior of the neoplasm. However, Hornick and Fletcher[3] showed that infiltrative borders and the mitotic rate did not correlate with aggressive behavior; the only histological feature significantly associated with recurrence or metastasis was the presence of moderate to severe cytological atypia.

Among the published cutaneous myoepithelial neoplasms reported to date, four cases were initially diagnosed as malignant.[9-11] Three of these showed cytologically malignant features, such as coarse chromatin, prominent large nucleoli, and a high mitotic rate. However, there was no sign of local recurrence or metastasis after complete excision.[9,10] The fourth case was diagnosed as a myoepithelial carcinoma because of lymph node metastasis at the time of the diagnosis despite benign cytological morphology, similar to the present case study.[11] However, among the cytologically benign cutaneous myoepitheliomas with follow-up available, six cases recurred; one of these also metastasized to the lymph nodes after several years.[10] Moreover, in one of these cases, the patient developed pulmonary metastasis and died due to the tumor.[7] Due to the extreme difficulty in predicting the behavior of cutaneous myoepithelial neoplasms, Tanahashi *et al.*[11] suggested it might be better to avoid using the definitive term 'benign' until further studies establish the true long-term behavior of such lesions.

In conclusion, we report an extremely rare case of a cutaneous myoepithelial carcinoma arising in a PEA with lymph node metastasis at the time of the initial diagnosis. However, the criteria for malignancy in cutaneous myoepithelial neoplasms are not yet established, and clinical behavior may be difficult to predict from the morphology of the tumor alone. Therefore, further studies are required to establish definite criteria for the differentiation between benign and malignant myoepitheliomas of the skin. The complete excision with a clear-cut margin and appropriate clinical follow-up are recommended for the management of these neoplasms.

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