J Korean Med Sci 1998; 13: 191-5
ISSN 1011-8934

Malignant Eccrine Spiradenoma with Florid Squamous Differentiation

Malignant eccrine spiradenoma (MES) is an exceedingly rare neoplasm of cutaneous adnexal origin. To date, 31 cases have been documented in the literature. We herein report an additional case of MES that arose in longstanding eccrine spiradenoma (ES). A 54-year-old woman was seen for a bluish nodular mass on the right flank that previously had been stable for 7 to 8 years and had recently increased in size and become tender. The excised mass (2.8×2.5×2.5 cm) had no attachment to the overlying epidermis. Microscopically, 2 to 3 sharply demarcated lobules were surrounded by a markedly thickened and hyalinized fibrous capsule. Of the lesion removed, approximately 20% of the tumor showed typical histologic features of benign ES. In the remaining malignant areas, the typical configuration of benign counterpart, consisting of peripheral rows of small dark basaloid cells and central layers of large pale cells partially forming lumina, was replaced with a massive solid proliferation of large pale cells showing nuclear pleomorphism, prominent nucleoli, increased mitotic activity (reaching 12/10 HPF) and loss of PAS-positive basement membrane. There were multiple foci of florid squamous differentiation in the malignant portion. Cytokeratin, focally S-100 and EMA were expressed in large pale cells, whereas alpha smooth muscle actin and S-100 were positive in small dark basaloid cells. Focal reactivity of CEA and EMA was found in the central lumina. P53 was not expressed in benign areas, whilst in malignant areas an occasional nuclear reaction was disclosed.

Key Words : *Acrospiroma, eccrine; Malignant eccrine spiradenoma; Cell differentiation; Immunohistochemistry*

Hyun Hee Lee, Kwang Gil Lee

Department of Pathology, Yonsei University College of Medicine, Seoul, Korea

Received : October 7, 1997
Accepted : November 26, 1997

Address for correspondence
Hyun Hee Lee, M.D.
Department of Pathology, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea
Tel : (02) 361-5240, Fax : (02) 362-0860

INTRODUCTION

Malignant eccrine spiradenoma is an exceedingly rare neoplasm of cutaneous adnexal origin. It apparently occurs within a longstanding solitary lesion of benign eccrine spiradenoma (ES). Since the original report by Dabska in 1971 (1), 31 examples have been documented in the literature to date (2-15). We herein report an additional case of malignant ES showing unusual florid squamous differentiation that arose in long-standing ES. Its histologic and immunohistochemical features are described.

CASE REPORT

A 54-year-old Korean woman was seen for an enlarging cutaneous nodule situated on the right flank that had grown very slowly for 7 to 8 years, recently increasing in size and becoming tender. It was well-circumscribed, firm, tender and was superficially covered with bluish discolored skin. The results of the rest of the physical and routine laboratory examinations were not contributory. The excised mass measured 2.8×2.5×2.5 cm and had no attachment to the overlying epidermis. Its cut surface consisted of reddish gray lobulated soft tissue with hemorrhage and myxoid change. Histologic examination revealed malignant transformation within an ES with negative margin. Follow-up 11 months later revealed no recurrence.

PATHOLOGIC FINDINGS

The specimen was fixed in a 10% neutral buffered formaldehyde solution and embedded in paraffin. Histologic sections were stained with hematoxylin-eosin and periodic acid-Schiff (PAS), and afterwards an immunohistochemical study was performed by the avidin-biotin complex (ABC) immunoperoxidase technique as previously described (16). The primary antibodies utilized in this study were cytokeratin (CK) (AE1/AE3, monoclonal, dilution

1/50, Zymed), epithelial membrane antigen (EMA) (monoclonal, dilution 1/100, Dako), carcinoembryonic antigen (CEA) (monoclonal, dilution 1/50, Dako), alpha smooth muscle actin (monoclonal, dilution 1/50, Dako), S-100 protein (polyclonal, dilution 1/1,500, Dako) and p53 protein (monoclonal, dilution 1/50, Novocastra).

Light microscopic findings

The tumor was surrounded by a thick hyalinized fibrous capsule and was composed of sharply demarcated lobules separated by fibrous septae (Fig. 1). Two distinct components, benign and malignant, were seen in the tumor (Fig. 2). Of the lesion removed, approximately 20 % of the tumor showed typical histologic features of benign ES, composed of two types of epithelial cells arranged in intertwining cords and partially forming lumina (Fig. 3). They were admixed with dilated vascular spaces and also contained cystic cavities filled with PAS-positive eosinophilic material. Cytologically, there were closely packed two cell populations. Cells of the first type which were located at the center of cellular aggregates were of large epithelial cells and possessed round to ovoid nuclei with evenly distributed pale chromatin and a scant rim of cytoplasm. They were arranged partially around small lumina, which contained small amounts of PAS and D-PAS positive finely granular eosinophilic material. Cells of the second type located at the periphery were small, dark and basaloid, and contained more hyperchromatic nuclei and inconspicuous basophilic cytoplasm. Hyaline material was focally present in the stroma that surrounded the cords of tumor cells. Focal lymphoedema were present within the tumor lobules accentuating the reticular pattern and formed several cystic spaces containing thin eosinophilic material. Only a mitotic figure is observed in this area. The remainder of the tumor, however, consisted of malignant neoplasm that transited from benign areas gradually or abruptly (Fig. 2). It showed confluent solid masses of a monomorphous large cell population. The nuclei were pleomorphic and had prominent nucleoli with vesicular chromatin pattern (Fig. 4). There were multiple foci of florid squamous differentiation of large pale cells frequently exhibiting squamous eddies with central luminal structures (Fig. 5). They occupied up to the half of the tumor. Mean numbers of mitotic figure was 9/10 HPF (high power fields) and increased up to 12/10 HPF (4/HPF). PAS stain outlined a partial loss or destruction of preserved hyaline meshwork between the cell nests and trabeculae (Fig. 6). No necrosis was identified.

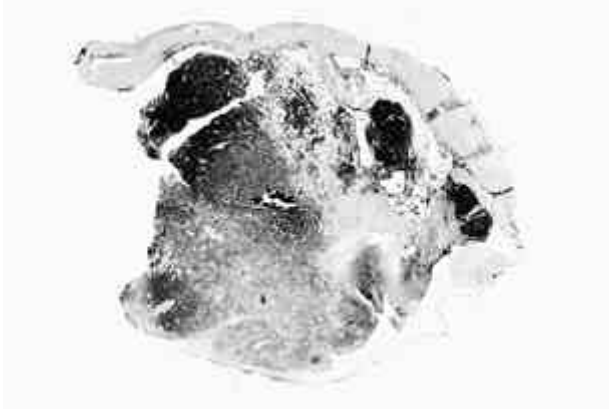

Fig. 1. Low power view demonstrates a well-demarcated tumor composed of lobules and surrounded by thick hyalinized fibrous capsule(H&E, ×5).

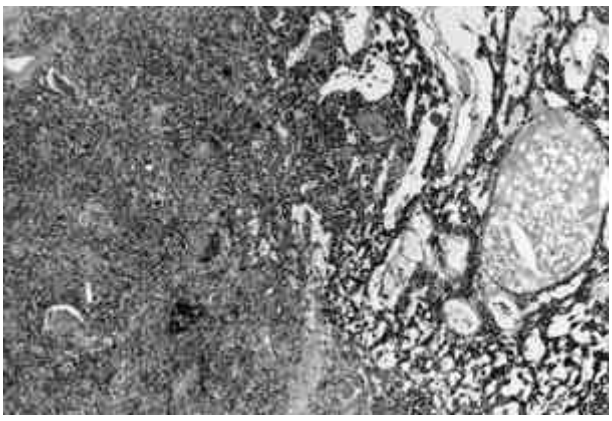

Fig. 2. The area of direct transition between the benign spiradenoma (on the right), presenting a typical reticulated pattern of growth, and the malignant counterpart (on the left) showing loss of the architectural features of spiradenoma and acquisition of cellular atypia (H&E, ×40).

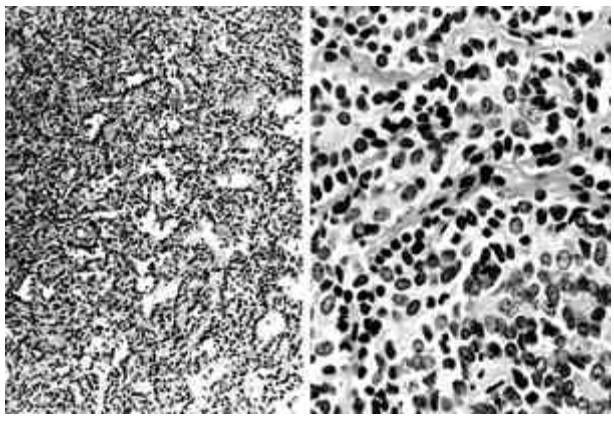

Fig. 3. Representative area showing a characteristic cellular pattern of benign eccrine spiradenoma. Higher magnification shows a dual population of small dark basaloid and larger pale cells partially forming lumina (H&E, ×100 & 400).

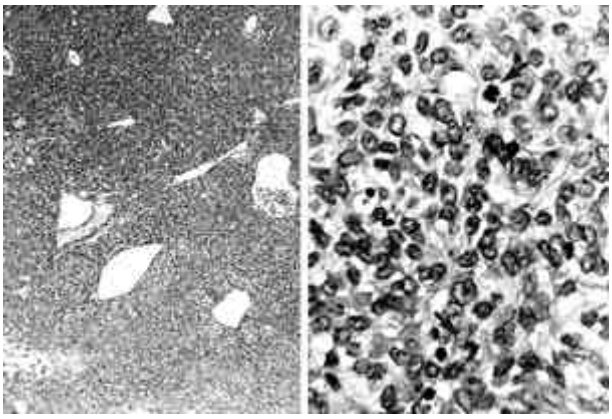

Fig. 4. Representative area from the malignant portion of the tumor shows solid proliferation of monomorphous large pale cells and absence of the dual cell population. Note the mitotic figures (arrow) (H&E, ×40 & 400).

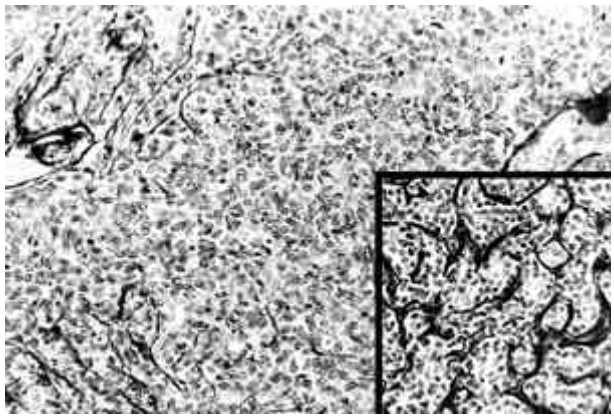

Fig. 6. PAS stain demonstrates partial loss of PAS-positive basement membrane in the malignant area. Note the well preserved networks in the benign area (inset) (PAS, ×200).

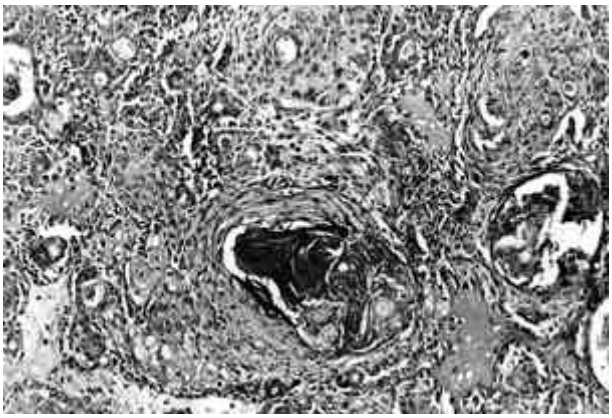

Fig. 5. Foci of florid squamous differentiation in the malignant portion (H&E, ×100).

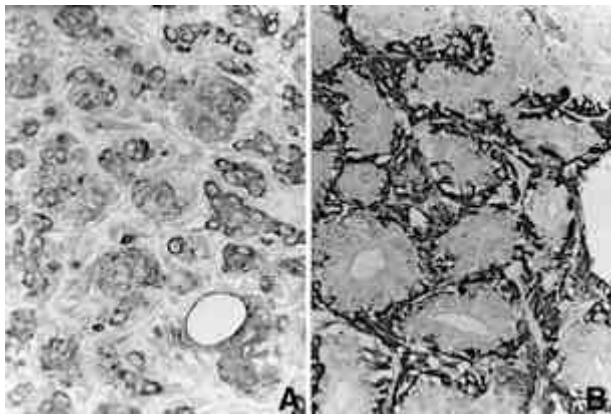

Fig. 7. Cytokeratin (AE1/AE3) is expressed in the central large cells (A), whereas alpha smooth muscle actin is exrpessed in the small basaloid cells (B) (×200).

Immunohistochemical findings

Cytokeratin (AE1/AE3) was strongly expressed in the central large, pale cells and luminal cells of the tubular structure (Fig. 7A), whereas alpha smooth muscle actin (Fig. 7B) and S-100 protein were positive in small dark basaloid cells (Fig. 8A). Focal reactivity of CEA and EMA was found in the central lumina. EMA was also expressed in a few cells around the lumina, especially of the squamoid areas. P53 was not expressed in benign areas, whilst in malignant areas an occasional nuclear reaction was disclosed. The phenotypes presented by benign and malignant components were consonant, although the S-100 protein was focally expressed in the large pale cells as well as small dark cells of the latter (Fig. 8B).

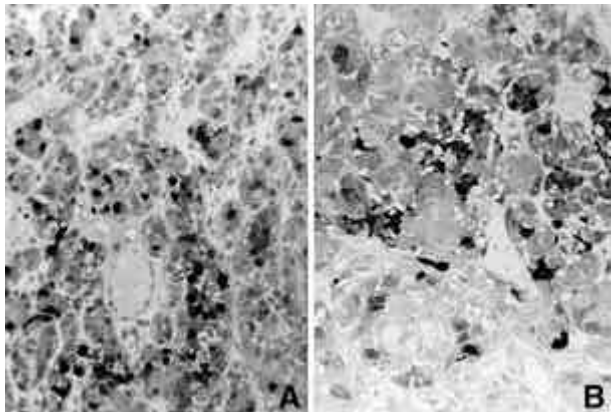

Fig. 8. S-100 protein immunoreactivity in the benign (A) and malignant portions (B). Note the focal reactivity in the large pale cells (B) (×200).

DISCUSSION

Eccrine spiradenoma is a well-defined benign adnexal neoplasm. Although most ES are benign, there have been

reports of occasional malignant transformation of this tumor. Most of the malignant eccrine sweat-gland tumors occur de novo in normal skin, but malignant ES never appears to arise de novo. Since the original report by Dabska in 1971, 30 cases have been documented in the English literature (2-14) and a case of malignant transformation diagnosed at recurrence has been reported in Korea (15).

Reviewing the reports of 32 cases including this case, it appeared that there was a typical history of a long-standing (often decades), unchanged lesion that suddenly became enlarged, ulcerated, tender, or changed in skin color. Our case gave such a typical history. The duration prior to diagnosis was from 0.1 to 70 years, although most lesions had been present for longer than 10 years. No sex predilection was noted. Age at presentation is variable ranging from 22 to 85 years. The trunk and extremities were most commonly affected. The size of the lesion varied from 0.21 to 10 cm. Six (19%) of the 32 patients had local recurrence. Ten (31%) had metastatic disease, five (16%) of which cases eventually died of metastasis. The method of spread appeared to be both lymphatics and hematogenous. Metastasis to lung, bone, brain and liver as well as regional lymph nodes had been described. The appropriate management of malignant ES appears to be wide local excision. The role of adjuvant radio- and chemotherapy is not yet well defined.

The histologic characteristics of this case were very similar to those previously documented. Areas of benign ES and carcinoma with transition confirmed the diagnosis of malignant transformation. Of the lesion removed, approximately 20% of the tumor showed typical histologic features of benign ES. In the remaining malignant areas, the typical configuration of benign counterpart, consisting of peripheral rows of small dark basaloid cells and central layers of pale large cells partially forming lumina, was replaced with massive solid proliferation of large cells showing nuclear pleomorphism, prominent nucleoli, increased mitotic activity and loss of PAS-positive basement membrane. There were multiple foci of florid squamous differentiation frequently exhibiting squamous eddies in the malignant portion. The epithelium of the eccrine sweat duct may undergo metaplastic changes, squamous or mucinous, under various stimuli. The eccrine duct cells, mostly of the superficial portion, can transform themselves into mature squamous cells with keratinization. The stimuli for squamous metaplasia are unknown. But, the local factors such as tissue ischemia and inflammation are considered (17). Although focal squamous differentiation had been described (5, 7, 10, 11) in ES, such florid squamous differentiation as this case had not ever been documented. It has been reported only in malignant form of ES. Therefore, the malignant ES should be ruled out, when the foci of squamous metaplasia are frequently observed in ES. Galadari et al. (7) suggested histologic indications of malignant transformation in ES. They included loss of characteristic histologic patterns, proliferation of solid masses of tumor epithelium, consisting of large cells with hyperchromatic nuclei and mitotic figures, loss of PAS-positive basement membrane and the hyaline sheath, peripheral invasion of the surrounding connective tissue, foci of squamous cell metaplasia and surrounding inflammatory cell reaction. Our case also shared those features.

As for mitotic figure, Cooper (18) evaluated mitotic rates in a series of sweat gland adenomas, providing baseline data that could be of value in estimating the importance of mitotic figure as a criterion of malignancy in sweat gland neoplasms. In ES, mean number of mitotic figures was 0.51/10 HPF. And mitotic figures were confined to basaloid cells and absent in cells lining well-formed ducts. In our case, only a mitotic figure is observed in whole benign areas, whereas frequent mitotic figures including atypical ones up to 12/10 HPF were found in malignant areas reaching the same conclusion as Cooper's. Mitotic figures, however, were not confined to the specific type of cells.

While the immunohistochemical profile of benign or malignant eccrine spiradenoma is not diagnostic of an eccrine neoplasm, it is helpful in elucidating the cellular differentiation and narrowing the differential diagnosis. Watanabe et al. (19) analysed cytokeratin expression of ES. In their study, the large pale cells expressed immunophenotypes similar to those of normal transitional portions between secretory segments and coiled ducts of eccrine glands. The small dark cells expressed immunophenotypes similar to those of basal cells in the transitional portion. The luminal cells of the tubular structures revealed an expression of CKs similar to that of large pale cells indicating differentiation into luminal cells in the transitional portion. CEA and EMA which were normally expressed on the inner surface of the lumina and the intercellular canaliculi in normal eccrine ducts and secretory components were expressed only on the inner surfaces of the luminal cells of tubular structures in ES. They, therefore, suggested that ES may differentiate towards the transitional portions and that some of the large, pale tumor epithelial cells were considered to differentiate towards tubular structures, forming a lumen lined with cuticle. On the other hand, Wiley et al. (20) demonstrated actin and/or S-100 protein positivity in basal epithelial cells in addition to cytokeratin expression in the central and luminal cells. They concluded that ES differentiated towards the secretory portion of the eccrine sweat gland. But, ultrastructural analyses showed a paucity of specialized differentia-

tion (6) or apparent differentiation toward ductal structures of eccrine gland (21). Our immunohistochemical studies were deficient for confirming the specialized differentiation. The results for CK, S-100 and actin seem to be supporting evidence for the differentiation of the eccrine secretory portion rather than ductal differentiation. But, EMA and CEA expressions as well as CK in the central lumina of tubular structure and squamoid areas, in association with frequent squamous differentiation in the large cells, may suggest differentiation into secretory and/or transitional portions.

The cause of malignant transformation remains unknown. Biernat et al. (22) demonstrated over-expression of p53 protein in malignant component within spiradenoma, but in the benign counterpart the immunostaining remained negative. Our same results for p53 staining supported their conclusion that the accumulation of p53 protein, which resulted from alterations in its turnover, accompanied the process of malignant transformation. These results also suggested the usefulness of p53 staining in the detection of malignant transformation.

In summary, malignant transformation of benign ES is rare and we describe an additional case showing florid squamous differentiation that had occurred in a long-standing lesion of benign ES. Presenting features include a change in character including size, color, bleeding and ulceration in a formerly present tumor. Its diagnosis requires the recognition of focal benign ES. Two distinct components are seen: typical benign ES and carcinoma, with areas of transition. Several histologic features suggesting the malignant transformation as previously described should be considered in its diagnosis. Because malignant changes can be focal in benign ES, the malignancy may be missed if the specimen is inadequately sampled. It is a high grade tumor with high recurrence, metastasis and mortality rates. Early diagnosis and adequate local surgical treatment are essential. Future studies of this tumor are needed to provide additional information on its specialized differentiation and clinicopathologic characteristics.

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