Current Neurobiology 2010; 1 (2): 91-94

Case Report

A case of low-grade malignant eccrine spiradenoma with massive necrosis among multiple benign nodules: an immunohistochemical study

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Abstract

Multiple eccrine spiradenomas (ES) including benign and malignant lesions in a single patient are extremely rare. In the present study, a detailed investigation of multiple nodular ESs is reported in a Japanese woman in her late sixties. A tumor extirpated from the back consisted microscopically of more than 10 separate micronodules, each less than 7mm in size. Each of the small nodules was clearly a benign ES, but the largest one, which was 7mm in diameter, exhibited massive necrosis and hemorrhage. In addition, a microinvasive pattern was also detected, as well as mitotic figures and disordered arrangement of tumor cells. In particular, many CD1a-positive Langerhans cells were detected not only in the largest one, including areas of necrosis in it, but also in the multiple benign ESs. This largest necrotic nodule, associated with multiple nodular benign ESs, was considered a low-grade malignancy, although no metastasis or recurrence of it has thus far been detected. Although ESs are usually benign, low-grade malignant or malignant ESs do exist, some of which exhibit or are associated with necrosis or metastatic foci.

Key words: Multiple eccrine spiradenoma, Low-grade malignancy, Necrosis, CD1a, Histopathology, Immunohistochemistry

Accepted June 11 2010

Introduction

Eccrine spiradenoma (ES), a benign skin appendage tumor, is usually solitary, and patients with multiple and/or malignant ES are rare [1-12]. The diagnosis of malignancy of ES is usually made based on distant organ metastases[2.8] or lymph node metastases [3,4,5,11]. However, histopathologically, necrosis [4,7.9,12], vascular invasion[7], mitotic figures in tumor cells, disordered arrangement of two types of tumor cells, cellular atypia, and other findings [4,12] are useful as evidence of malignancy in differentiating malignant from benign ES. Indeed, in the malignant cases reported, both benign and malignant lesions were rarely detected simultaneously in the same patient [3,4,8,12]. Many Langerhans cells (LCs) are also found in ESs [13,14] as well as other types of skin appendage tumors, such as cylindromas[15] and trichoepitheliomas [16], some of which exhibit Birbeck granules in LCs ultrastructurally [13,14,16]. The reason for and significance of their presence have yet to be clearly determined.

In the present study, detailed immunohistochemical investigation was performed, particularly in the large, low-grade malignant, necrotic nodule present among multiple benign ESs, with special reference to the presence of CD1a-positive LCs in ESs.

Case report

The patient was a Japanese woman in her late sixties who underwent macroscopic resection of two tumors in her back. These tumors, which were grossly 10mm and 3mm in size, each exhibited more than ten separate micronodules microscopically (Fig. 1A), and were examined immunohistochemically. The extirpated elastic-soft tumors were fixed in 10% formalin solution and embedded in paraffin. The dewaxed sections were Hematoxylin-Eosin (HE)- & Azan-stained. Immunohistochemical staining was performed as reported [14,17], employing labeled streptoavidin-biotin (LSAB)2 kit/HRP (DakoCytomation, Kyoto, Japan) with diaminobenzidine as the substrate for horseradish peroxidase, with the following antibodies:

AE1/AE3 (1:400, pronase-pretreated (P), Boehringer-Mannheim, Germany), CAM5.2 (1:20, P, Becton-Dickinson, USA), CD1a (prediluted, no-pretreatment (NP), Immunotech, France), CD10 (prediluted, autoclaved (AC), Novocastra), p63 (1:50, AC, Dako, Japan), CD4 (1:15, AC, Novocastra), CD8 (1:30, AC, Dako, Japan), CK5/6 (1:50, AC, Dako, Japan), EMA (1:50, Microwave, Dako, Japan), S-100 protein (1:100, NP, Dako, Japan), α-smooth muscle actin (ASMA)(1:100, NP, Dako, Japan), p53 (1:50, AC, Dako, Japan), Collagen type IV (1:50, P, Dako, Japan), estrogen receptor (ER) (1:50, AC, Dako, Japan), progesterone receptor (PGR) (1:800, AC, Dako, Japan), and MIB-1 (1:50, AC, Dako, Japan).

The patient provided written informed consent, and the identity of the patient has been protected.

Clinicopathological findings

The multiple tumors on the back, less than 1 cm in diameter each microscopically, were located in the dermis without connection to the epidermis and each ~~well~~ surrounded well by a thick and dense fibrous capsule (Fig. 1A). Except for the largest nodule (Fig.1A, arrow), they were composed of large and small tumor cells in solid nests (Figs. 1B,C). The large cells often formed small glandular spaces (Fig.1C, arrow), in association with dark small

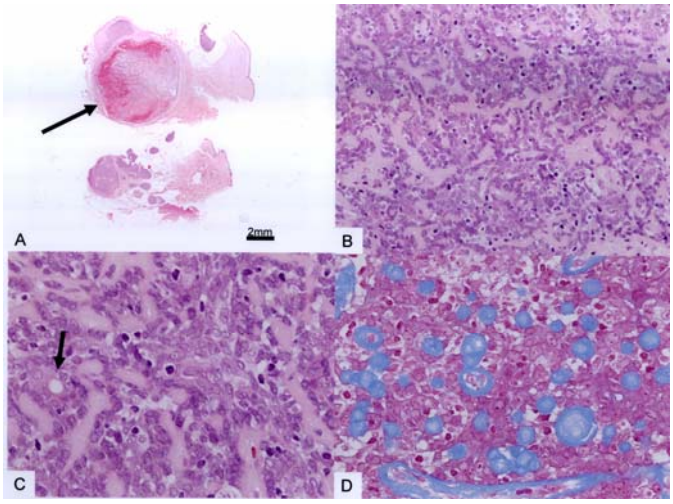

Figure 1. *A: A general view of the micronodular benign tumors, including a necrotic one(arrow).*
B: Tumor cells are arranged in a trabecular pattern, with intervening collagenous stroma.
C: Higher magnification of the tumor cells, disclosing both large and small tumor cells and revealing glandular structures (arrow).
D: Cylindromatous pattern of tumor, exhibiting stromal collagen as bluish bodies.
A, B, C: HE stain, D: Azan stain, B:X200, C,D: X400.

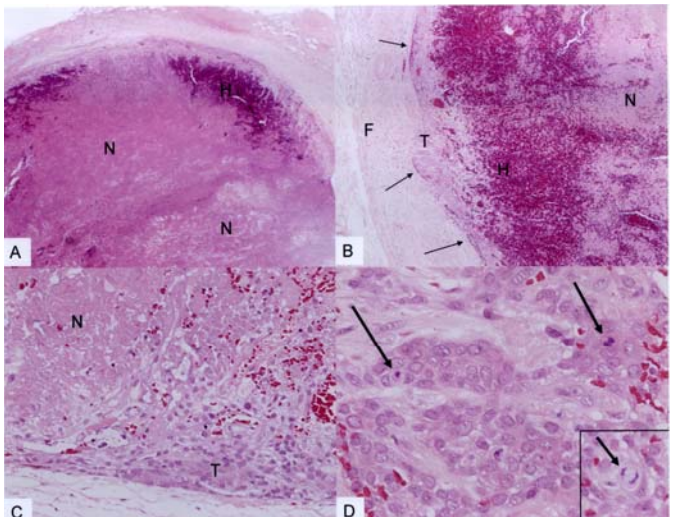

Figure 2. *A: A general view of the necrotic nodule exhibiting massive hemorrhage and necrosis.*
B: The tumor tissue survived at the periphery of the tumor (arrows). Note fibrous capsule (F).
C: At the periphery, necrosis and remaining tumor are obvious.
D: Higher magnification of the invasive pattern, including mitotic figures (arrows), of tumor cells.
H: hemorrhage, N: necrosis, T, tumor tissue. A-D: HE stain, A: X2, B,C: X100, D: X400.

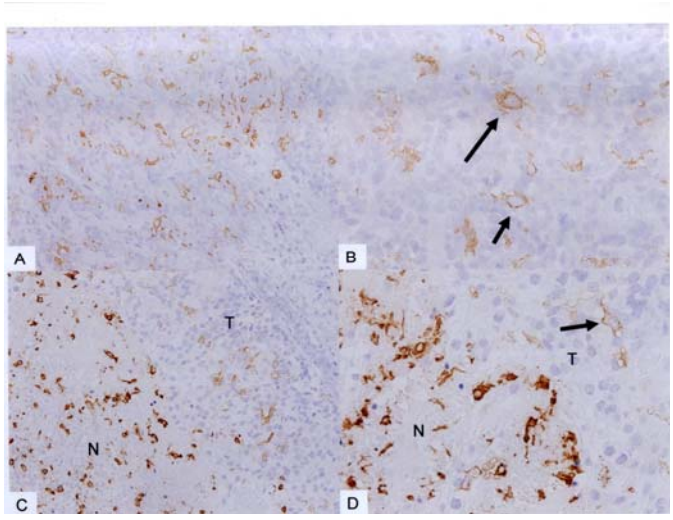

Figure 3*.A: Scattered CD1a-positive LCs in benign ES.*
B: LCs in dendritic form at higher magnification (arrows).
C: CD1a-positive LCs in the necrotic area and remaining tumor tissue in the largest necrotic nodule. D: Strong positive reaction on staining of LCs in both necrotic area and remaining tumor tissue at higher magnification.
N: necrosis, T, tumor tissue. A-D: CD1a immunostain, A,C: X200, B,D: X400.

cells, which had proliferated in nests (Fig. 1C) with no mitotic figures or necrotic areas. In some parts of the tu-

mors, small cells were arranged in palisading patterns at the periphery of the large nests. Small numbers of lymphocytes had infiltrated the stroma. On Azan stain, round collagen fibers were surrounded by tumors, exhibiting a cylindromatous pattern in benign ESs in parts (Fig.1D). These findings were those of benign ES.

The largest nodule, 7mm in diameter, was generally demarcated clearly by fibrous capsule on sections (Fig. 1A, arrow), though massive necrosis and hemorrhage were found inside of the tumor, with tumor tissue remaining at the periphery of the nodule (Fig. 2A,B). The necrosis was coagulative in type, with nests of cells and trabecular structures in the necrotic areas. In the remaining tumor, two types of cells, large epithelial and small round cells, were arranged irregularly (Fig. 2C) with small numbers of mitotic figures (Fig. 2D, arrows), and a stromal invasive pattern was detected in some regions (Fig. 2D).

Staining with antibodies to AE1/AE3 and CK5/6 was diffusely positive in all tumor cells including large and small ones, while with anti-CAM5.2 antibody strongly positive tumor cells were observed in some regions, exhibiting glandular differentiation. In sharp contrast, staining with p63 antibody was positive in small round tumor cells arranged in the periphery. CD8-positive lymphocytes had infiltrated to a much greater extent than CD4-positive ones in ESs. These staining patterns were not detected in the non-necrotic area of the largest nodule. Staining for MIB-1 was much more strongly positive in some parts of the largest nodule than in the small nodules. The labeling index for MIB-1 stain was far less than 1 % even in the largest nodule. Staining for CD10 was negative, as well as that for ASMA and p53. Staining for both ER and PGR was negative in tumor cells.

Infiltrating CD1a-positive LCs harboring interdigitating nuclei were easily detected at the light-microscopic level (Figs. 3A-D). Many LCs were detected in both micronodules of benign ESs (Figs. 3A,B) and the large necrotic nodule (Figs. 3C,D), and were dendritic in form (Fig. 3B, arrow). The numbers of these LCs were roughly equal in benign and necrotic tumors. Many LCs were detected even in necrotic areas, and in larger number than in benign regions. Staining with anti-EMA antibody was positive only on the surface of glandular or intracytoplasmic lumina in vacuole-like structures. Staining with S-100 protein antibody was positive in both the nuclei and cytoplasm of LCs. At 10 months after surgical extirpation, there is no evidence of recurrence or metastasis in this patient.

Based on these findings, including those of immunohistochemistry, the largest necrotic nodule was considered a low-grade malignant ES associated with multiple benign micronodular ESs in the same patient.

Discussion

The presence of distant metastases to the lung, liver, lymph nodes, and other organs is clear evidence of malignant ES[1-12]. In the case of low-grade malignancy, it is difficult to determine histopathologically whether distant metastasis has occurred[7,12]. Nuclear atypia, mitotic figures, vascular invasion[4,7], pleomorphism, hyperchromasia, and disordered arrangement of two types of tumor cells[4] are features of malignancy on histopathologic examination. There has been reported malignant cases, without no metastasis, because of the presence of necrosis and high mitotic rate in the literature[4,7,12]. In the present case, among multiple clearly benign ESs, only the one largest nodule exhibited an necrosis, hemorrhage, and mitotic figures in parts, without metastasis. Recurrent[12,18], long-standing[2,10,18] and/or rapidly growing[18]tumors may be malignant . In fact, in the present case, the largest nodule enlarged rapidly, resulting in massive necrosis and hemorrhage within it. Although this case is not clearly malignant, it can be considered an intermediate malignancy, i. e. a low-grade malignancy[7], because of the massive necrosis and mitotic figures in tumor cells associated with apparently benign micronodules.

Immunohistochemically, many CD1a-positive dendritic cells were detected not only in necrotic areas but also the benign lesions. These dendritic cells appeared to be Langerhans cells, because of their positive staining for CD1a. Although no fine-structural study was performed in this case, both benign and malignant nodules were detected, and many CD1a-positive dendritic cells were found in both the benign and low-grade malignant lesions. Some cylindromatous findings were also found in this case in benign areas. In a previous study of multiple ESs, Birbeck granules were detected in LCs on fine-structural study[13,14,16]. ES, cylindroma, and trichoepithelioma have each been reported to contain many LCs[13-16]. However, the reason for and significance of these LCs remain unclear.

Our examination of the malignant ES revealed that tumor cells clearly exhibited differentiation to eccrine glandular cells, which were positive for AE1/3, CAM5.2, and p63, with intermingled indeterminate small cells, which were positive for staining with p63 antibody, with no evidence for apocrine differentiation.

Immunohistochemically, staining with antibodies to cytokeratins AE1/AE3, CAM5.2, and CK5/6 was diffusely positive in all tumor cells, though not in intermingled LCs, which harbored interdigitated nuclei. The cytoplasm of LCs was positive for S-100 protein and CD1a, and the nuclei of these cells were also occasionally positive for S-100 protein. Staining for EMA was positive on the surfaces of both intracytoplasmic and true glandular lumina.

Interestingly, many CD1a-positive LCs were also detected in the necrotic foci. The MIB-1 index was less than 1% in the larger ES.

In these microscopic examinations of multinodular ESs, one of the largest nodules appeared to be a low-grade malignancy due to the presence of massive necrosis and occasional mitotic figures in tumor cells, features not possessed by the benign micronodular ESs. CD1a-positive LCs were distinctly detected in both the low-grade malignant nodule, including necrotic areas, and the benign nodules of ESs, as revealed by CD1a-immunostaining. Determination of the significance of these many LCs in ESs will require further investigation of a larger number of cases.

Acknowledgement

The authors are grateful for the technical assistance of Mr. T. Watanabe and Mrs. M. Izumimoto, and for the secretarial assistance of Ms. K. Yamamoto and Ms. K. Takasuka.

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