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A Case of Coexistent Angiosarcoma and Follicular Carcinoma of the Thyroid

Angiosarcoma of the thyroid has long been a controversial entity, and it is histologically defined as cleft-like anastosmosing spaces lined by large, atypical cells of endothelial lineage. However, clear-cut separation between the angiosarcoma and anaplastic carcinoma of the thyroid is difficult because they yield nearly the same clinical prognosis and overlapping histologic findings. We report a case of thyroid neoplasm composed of minimally invasive well differentiated follicular carcinoma and angiosarcoma with intervening transitional area. Immunohistochemically, the angiosarcomatous portion showed focal immunoreactivity for endothelial markers such as CD31, CD34, *Ulex europaeus* 1 lectin, factor VIII-related antigen, and immunonegativity for epithelial markers including pancytokeratin, epithelial membrane antigen and thyroglobulin, whereas the reverse was demonstrated in the minimally invasive follicular carcinomatous portion. The follicular carcinoma portion was positive for thyroid transcription factor-1 (TTF-1). Each component showed ultrastructural findings of epithelial and endothelial differentiation, respectively. The present case was unique in that angiosarcoma of the thyroid was confirmed by immunohistochemistry and electron microscopy, as well as light microscopy, and also coexisted with a minimally invasive well differentiated follicular carcinoma in the same mass. This combination has never been described in the literature. Although restricted to a single case, the present case further supports that angiosarcoma is a true existent entity rather than a variant of anaplastic carcinoma.

Key Words : *Hemangiosarcoma; Adenocarcinoma, Follicular; Thyroid Gland*

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INTRODUCTION

High-grade neoplasms of the thyroid with an angiomatoid appearance by light microscopy have been debated for about 100 yr (1), and have not yet been included into the latest World Health Organization (WHO) classification of the thyroid (2). Several authors have described such tumors that display both anaplastic carcinoma and pseudoangiosarcomatous appearance, making difficult the inclusion of these tumors in either the anaplastic carcinoma of the thyroid or conventional angiosarcoma groups of the WHO classification. However, angiosarcoma generally represents a rare connective tissue tumor of the thyroid, and has been designated as malignant hemangioendothelioma by many authors (3, 4), and rarely occurs in that organ. We described a case of an angiosarcoma and well differentiated follicular carcinoma with intervening transitional area. The present report will provide an additional evidence that angiosarcoma of the thyroid is a specific condition of endothelial origin, which is different from angiosarcoma-like anaplastic carcinoma. Here, to confirm the nature of the present tumor, immunohistochemistry and ultrastructural examination were done.

CASE REPORT

A 64-yr-old-man was admitted due to a painless mass in the anterior region of the neck that had been rapidly growing for several months. ^{99m}Tc thyroid scan showed a cold defect in the right lobe of the thyroid. The results of thyroid function tests were within the normal ranges. He has a history of right pneumonectomy for tuberculosis about 20 yr ago. Fine needle aspiration cytology of the thyroid showed atypical cells showing nuclear pleomorphism and anaplasia, which were suggestive of anaplastic carcinoma. Careful examinations using radiologic methods as well as nuclear medicine did not disclose any metastatic or primary foci, and the tumor was confined within the thyroid region. The patient underwent total thyroidectomy. Two months later, slight dyspnea developed. Skull radiography showed multinodular osteolytic lesions and chest computed tomography showed multifocal bilateral scattered nodules, implying metastatic tumor nodules. He refused further evaluation. Chemotherapy and local radiation therapy were scheduled, but he was lost to follow-up.

Grossly, the right lobe and left lobe measured 8×5×3 cm, and 6×3×2 cm. Each weighed 56 g and 20 g. The external

surface of each lobe was smooth, glistening with beefy red appearance. The cut surface showed a bulging solid hemorrhagic dark red mass, measuring 4.8×3.2×2.5 cm, at the lower pole of the right lobe (Fig. 1). It was confined within the thyroid gland. During operation, a frozen diagnosis was required and a poorly differentiated malignant tumor was diagnosed. The specimen was fixed in 10% neutral formalin, and then embedded in paraffin. Immunohistochemistry was done by an avidin-biotin-peroxidase complex method. Antibodies against the following antigens were used: pancytokeratin (AE1/AE3, Dako, Glostrup, Denmark, 1:80 dilution), epithelial membrane antigen (E29, Dako, 1:50 dilution), thyroglobulin (DAK-Tg6, Dako, 1:80 dilution), thyroid transcription factor-1 (TTF-1, 8G7G3/1, Dako, 1:50 dilution), calcitonin (Cal3-F5, Dako, 1:1,200 dilution), vimentin (Dako, 1:80 dilution), CD31 (JC/70A, Dako, 1:20 dilution), CD34 (QBEnd 10, Dako, 1:100 dilution), *Ulex europaeus* 1 lectin (Ventana, prediluted), factor VIII-related antigen (BioGenesis, Poole, U.K., 1:150 dilution). Microscopically, the tumor was composed of microfollicles with extensive hemorrhage in the center of the tumor. These follicular carcinomatous portion was composed predominantly of a solid microfollicular growth pattern with capsular invasion (Fig. 2A, B), and the tumor cells were relatively uniform sized nuclei that were slightly hyperchromatic. In other area of the mass, there were anastomosing channels lined by atypical neoplastic cells of a high nuclear-cytoplasmic ratio with occasional multinucleated bizarre morphology (Fig. 2C). Atypical mitoses were also found in up to 3 per 10 consecutive ×400 magnification. These areas resembled epithelioid angiosarcoma, and capsular invasion of angiosarcomatous components were also found (Fig. 2D).

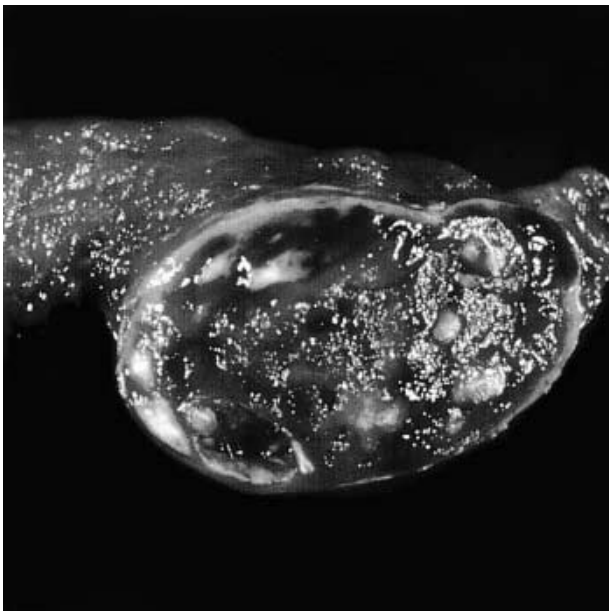

Fig. 1. The cut surface of the thyroid shows a well demarcated bulging, variegated and hemorrhagic dark red lesion.

At the mixed areas between the two, extensive hemorrhage with stromal hyalinization was found (Fig. 2E). Immunohistochemically, tumor cells of microfollicles were reactive for pancytokeratin, TTF-1 (Fig. 3A) and thyroglobulin. Colloid accumulation of follicular lumen was reactive for thyroglobulin, while they were negative for calcitonin or vimentin. Angiosarcomatous portion showed immunoreactivities for *Ulex europaeus* 1 lectin, CD31 (Fig. 3B), CD34, and total negativities for pancytokeratin, TTF-1, or thyroglobulin. Less than 1% of tumor cells of the angiosarcomatous area were positive for factor VIII-related antigen. Both follicular carcinomatous and angiosarcomatous areas of paraffin block were taken for ultrastructural examination. They were deparaffinated and fixed in 2.5% glutaraldehyde, followed by 1% osmium with propylene dioxide and finally embedded in Epok 812 (Oken Shoji Ltd., Tokyo, Japan). The thick sections (1 μm) were stained with toluidine blue and Azure B solution to ascertain that the desired cells were in the block. Thin sections were poststained with uranyl acetate and lead citrate and examined with a transmission scanning electron microscope (H-7100, Hitachi High-Technologies, Tokyo, Japan) at an accelerating voltage of 75 kv. Electron microscopy revealed that oval tumor cells in the follicular carcinomatous and angiosarcomatous components were outlined by basal lamina (Fig. 4A). The tumor cells had follicular lumina with microvillous processes, rounded nuclei, lysosomal dense bodies in the cytoplasm and well-formed desmosomes. Those findings were compatible with follicular epithelial glandular differentiation. In contrast, portions microdissected from angiosarcomatous and undifferentiated areas in the intervening transitional zone showed endothelial differentiation, i.e. frequent basal laminae, junctional complexes of the zonula adherens type between tumor cells. The cytoplasm contained moderate amounts of pinocytotic vesicles (Fig. 4B), usually oriented along the plasma membrane and microfilaments were also seen (Fig. 4C). Weibel-Palade bodies were not found in the tumor cells. The diagnosis was coexistent angiosarcoma and minimally invasive follicular carcinoma.

DISCUSSION

Angiosarcoma of the thyroid is rare and is composed of cleft-like anastomosing spaces lined by large, atypical endothelial cells. The differential diagnosis includes pseudoangiosarcomatous carcinoma of the thyroid, which shows artifactual spaces made in acantholytic/adenomatoid squamous carcinoma, i.e. accumulation of hyaluonic acid in the stroma of the tumors leading to the formation of the spaces (5). Pseudoangiosarcomatous carcinomas share light microscopic features with angiosarcoma, but lack of immunoreactivity for endothelial markers or ultrastructural evidence of endothelial differentiation can distinguish the former from true angiosarcoma. Ultrastructural endothelial differentiation has been said to be diag-

nostic for angiosarcoma; the presence of dilated cisternae of endoplasmic reticulum, pinocytotic vesicles, Weibel-Palade bodies and basal lamina (6). However, the concept of angiosarcoma in the thyroid has long been a matter of debate because some authors believe that most, if not all, angiosarcomas are in fact "angiomatoid" anaplastic carcinomas. In Alpine region of Central Europe, where adenomatous goiter is prevalent ranging up to 16% of all thyroid lesions (7), vascular or pseudovascular thyroid neoplasm is also common (2). Although both anaplastic carcinoma and angiosarcoma take nearly the same grave prognosis, and their distinction and investigation of their origin is even regarded as an academic interest, the concept of angiosarcoma of the thyroid has changed and is still changing (4). Some authors proposed that the origin of angiosarcoma of the thyroid be as endothelial lineage (8), and others regarded it as poorly differentiated epithelial malignancies for divergent endothelial differentiation (9, 10). Advances in immunohistochemistry has brought more confusion to this controversial entity. Pfaltz et al. (11) categorized angiomatoid neoplasms into three groups; classic angiosarcomas, borderline tumors

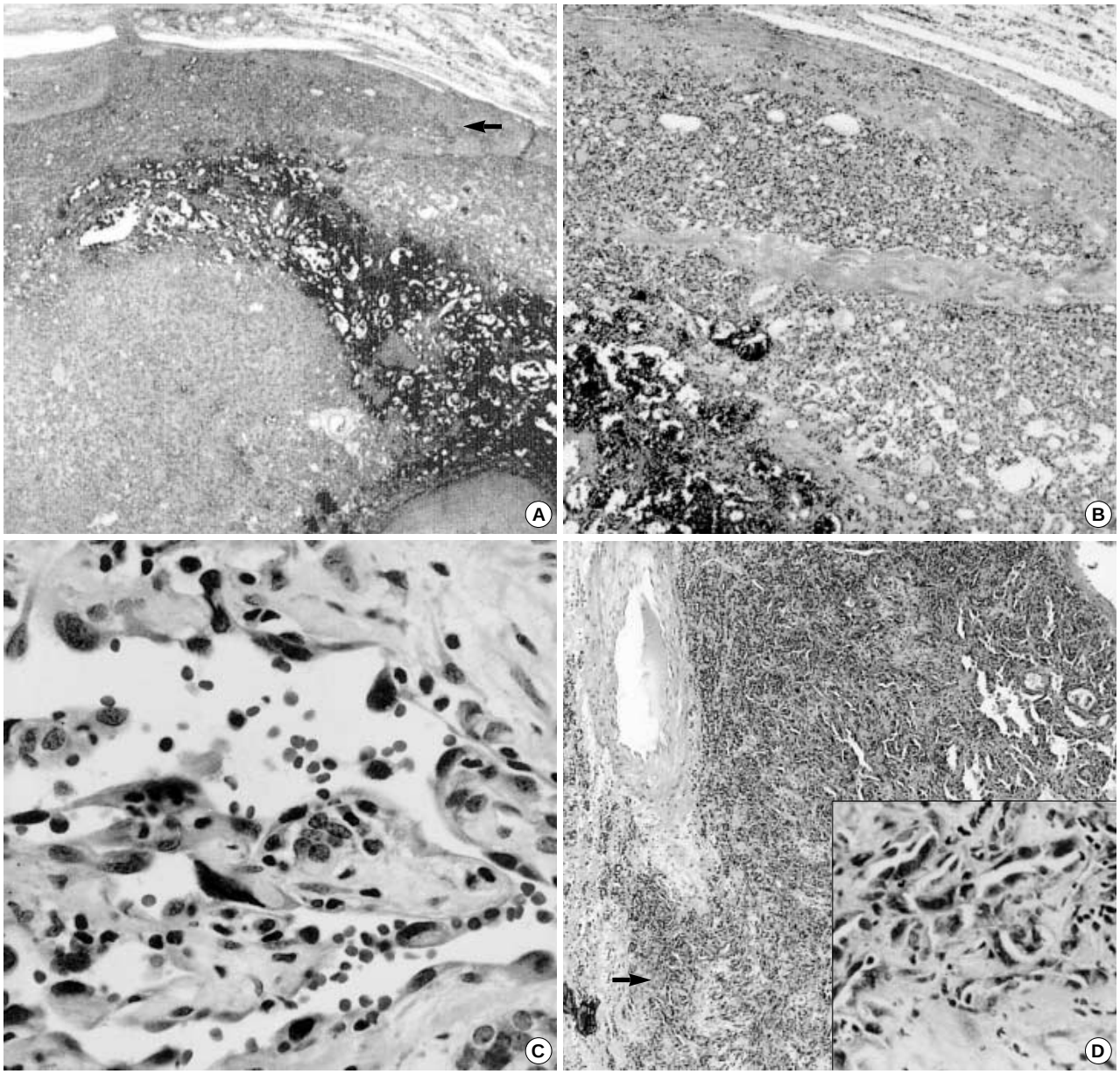

Fig. 2. (A) Follicular neoplasmic portion is composed of small, closely packed follicles of benign cytoarchitecture. Arrow indicates capsular invasion (H&E stain, ×40). (B) High magnification of capsular invasion (H&E stain, ×100). (C) Anastomosing racemoce-like vascular channels lined by atypical endothelial cells showing occasional multinucleated cells are present in angiosarcomatous portion (H&E stain, ×200). (D) Capsular invasion of angiosarcomatous components (arrow, inset) is also found (H&E stain, ×100). *(Fig. 2 continued next)*

showing angiosarcoma and anaplastic carcinoma, anaplastic carcinoma with an angiosarcoma like growth pattern. Immunoreactivity for endothelial markers as factor VIII-related antigen was 60%, 21%, and 0%, respectively. They explained that some borderline cases with a positivity for *Ulex europaeus* 1 lectin and a negativity for factor VIII-related antigen seem to be a sign of dedifferentiation and may cause a decrease in the production of factor VIII-related antigen. These immunohistochemical results well corresponded to the sensitive marker of *Ulex europaeus* 1 lectin and specific marker of factor VIII-related antigen (12, 13). However, considering immunohistochemical heterogeneity of angiosarcomatoid neoplasm of the thyroid, these immunohistochemical findings simply document the phenotype of the tumor, and does not equate with the definition of the cellular origin (9, 14, 15). In our opinion, it is more reasonable that the mass should be diagnosed as angiosarcoma admixed with well differentiated follicular carcinoma rather than anaplastic carcinoma or sarcomatoid carcinoma with angiosarcomatous differentiation, because there was neither histological anaplasia in follicular carcinoma portion nor cytokeratin-reactivity in angiosarcoma portion.

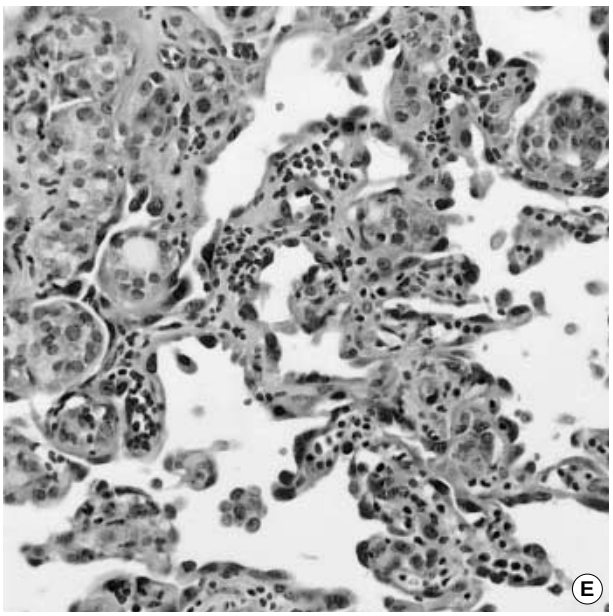

Fig. 2. *(Continued from the previous page)* (E) Mixed area shows scattered microfollicles of the follicular carcinoma (left), which are mixed with angiosarcoma (right, H&E stain, ×200).

The concept of angiomatoid thyroid neoplasm including angiosarcoma have shared histologic findings with ordinary anaplastic carcinomas (16); cleft-like spaces lined by malignant cells showing nuclear atypia and mitotic activity can be found in the latter. Other findings include some portions showing stromal papillae with hyalinized cores and extensive stromal hemorrhage and erythrophagocytosis. Necrosis and stromal hemosiderins are typical in angiomatoid thyroid neoplasm. Occasionally, angiomatous foci merge with a solid sheet like growth pattern, or spindle cell areas simulating those seen in pure spindle cell anaplastic carcinomas or a small focus of well differentiated typical papillary carcinoma adjacent to the high-grade component, as is often the case with ordinary anaplastic carcinomas (17). Mills et al. (18) proposed that many of the tumors diagnosed as angiosarcoma of the thyroid may

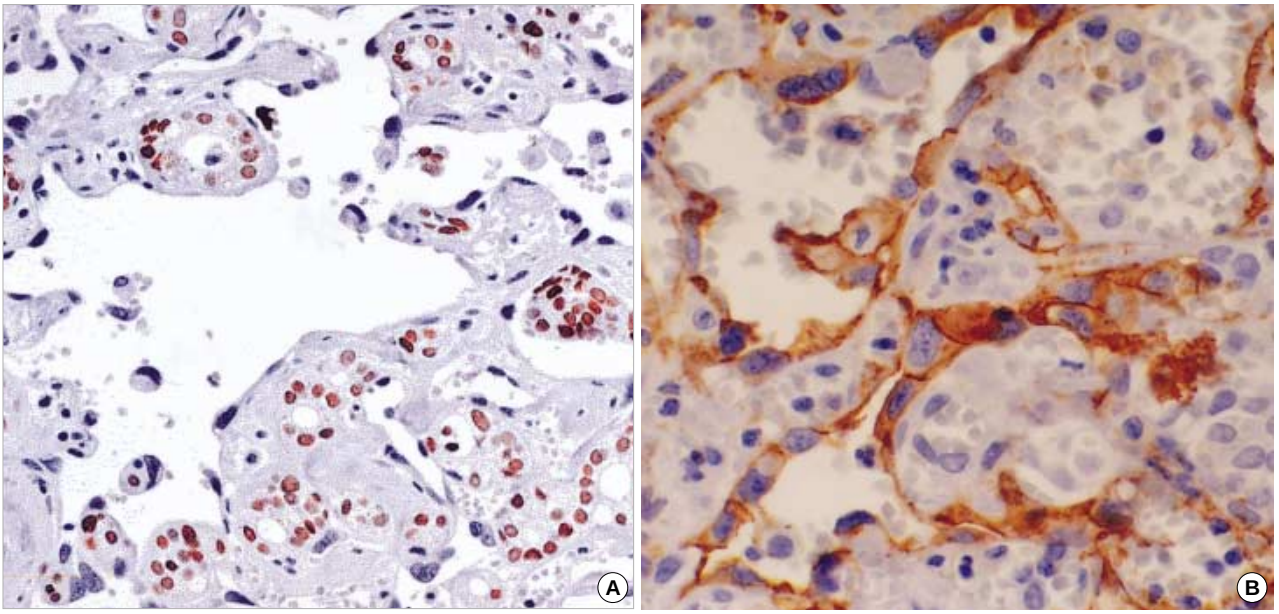

Fig. 3. (A) Well differentiated follicular carcinoma portion shows nuclear and cytoplasmic immunoreactivity for TTF-1. Note totally negative reaction of intervening angiosarcoma at the transitional area (TTF-1 immunostain, ×400). (B) Bizarre lining cells of angiosarcoma portion are strongly positive for CD31 (CD31 immunostain, ×400).

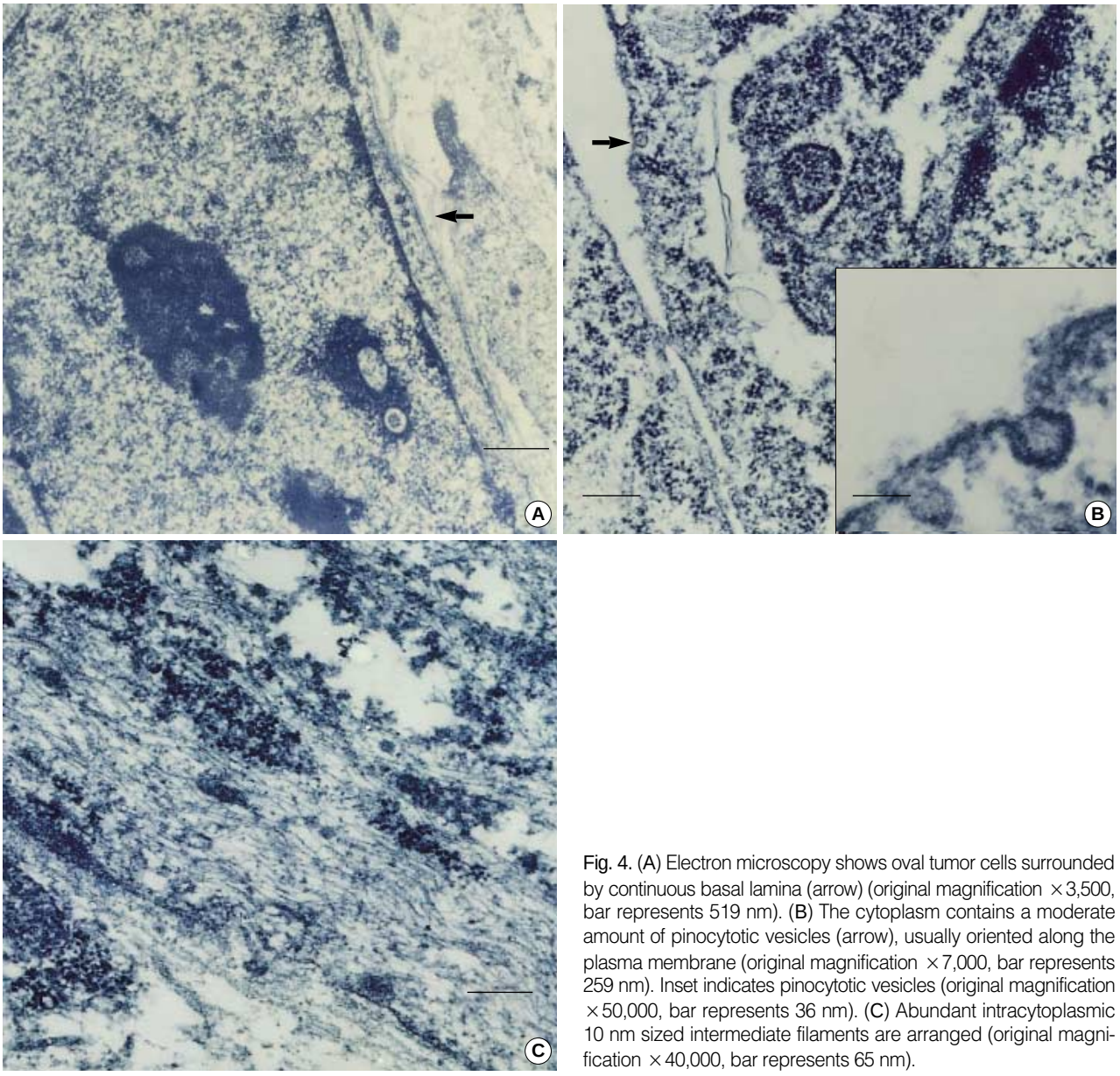

Fig. 4. (A) Electron microscopy shows oval tumor cells surrounded by continuous basal lamina (arrow) (original magnification ×3,500, bar represents 519 nm). (B) The cytoplasm contains a moderate amount of pinocytotic vesicles (arrow), usually oriented along the plasma membrane (original magnification ×7,000, bar represents 259 nm). Inset indicates pinocytotic vesicles (original magnification ×50,000, bar represents 36 nm). (C) Abundant intracytoplasmic 10 nm sized intermediate filaments are arranged (original magnification ×40,000, bar represents 65 nm).

be pseudoangiosarcomatous carcinomas even in cases expressing focal immunoreactivity for endothelial markers because the uptake of antigen-rich serum by tumor cells may cause immunoreactivity for factor VIII-related antigen. In such circumstances, angiosarcoma can be distinguished from it by recent molecular techniques and immunohistochemistry for TTF-1; a weak signal for thyroglobulin mRNA was present in all anaplastic carcinoma but not in angiosarcoma of the thyroid, confirming that anaplastic carcinoma and angiosarcoma of the thyroid are unrelated malignant tumors (8, 19). Immunohistochemical staining for TTF-1 has been used to identify pulmonary non-small cell carcinomas or well differentiated follicular and papillary carcinomas of the thyroid (20). The present case differs from the aberrant expression of endothelial markers in that the spaces are lined by neoplastic cells showing true endothelial differentiation, supported by positive reaction for more specific endothelial markers, i.e. CD31 and CD34 as well as ultrastructural evidence of endothelial lineage. In the viewpoint of cellular origin, our case showed that only follicular carcinomatous portion exhibited nuclear and cytoplasmic expression for TTF-1, suggesting that angiosarcoma of the thyroid is an independent tumor different from pseudosarcomatous or anaplastic carcinoma or follicular carcinoma. However, on the pathogenesis, there still remains remote possibility that the two tumors have originated from common progenitor cells, bidirectionally differentiating into endothelial and follicular epithelial lineage. Several supporting facts are as follows; first, rare aberrant expression of cytokeratin

in angiosarcoma in other organs has occasionally been reported because embryonic endothelial cells may express keratin (2, 21, 22). Second, the light microscopic presence of areas of well differentiated cells is observed in close vicinity to anaplastic cells, i.e. so-called "transforming areas" (23).

The present case postulates that angiosarcoma of the thyroid is a distinctive entity, not same as anaplastic carcinoma or angiomatoid thyroid neoplasm.

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