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Fine Needle Aspiration Cytologic Findings of Angiosarcoma – Report of Two Cases –

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Angiosarcoma is a rare malignant vascular neoplasm which can arise in any part of the body. Specific recognition of this neoplasm in cytological specimens is difficult in the absence of an ancillary method. Herein, we present the cytologic findings of two cases of angiosarcomas diagnosed on fine needle aspiration cytology. One case is a recurred angiosarcoma in the left chest wall and the other case is a lymphedema-associated angiosarcoma in the left lower leg. The cytologic findings of both cases are similar. Cytologic features that identified this neoplasm as an angiosarcoma included arborizing microtissue fragments, irregular anastomosing vascular spaces lined by atypical cells, microacini, intracytoplasmic lumen, and intracellular red blood cells, marked cell discohesiveness, spindle to ovoid, irregular, hyperchromatic nuclei, and elongated cytoplasmic processes with indistinct borders. This report emphasizes that when aspiration smears show vasoformative features in a bloody background, angiosarcoma should be included in the differential diagnosis.

Key Words: Angiosarcoma; Fine needle aspiration cytology

Angiosarcoma is a soft-tissue sarcoma and is an aggressive malignant tumor. Angiosarcomas are rare and account for less than 1% of all sarcomas.[1] They usually arise from the endothelial cell lining of the vascular channels and are frequently stained with endothelial markers such as CD31 and CD34. Angiosarcomas can arise in almost any part of the body, but most commonly arise in the skin of the head and neck region. Angiosarcomas are subdivided into cutaneous angiosarcoma, lymphedema-associated angiosarcoma, radiation-induced angiosarcoma, primary-breast angiosarcoma, and soft-tissue angiosarcoma, as well as some other types.[2] Histologically, angiosarcomas are divided into classical and epithelioid types.[3] The classical type can be well, moderately, or poorly differentiated. The cell population is usually mixed in classical angiosarcoma, and spindle cells are usually predominate. The epithelioid type of angiosarcoma is composed almost entirely of epithelioid cells.

The diagnosis of angiosarcoma in fine needle aspiration cytology (FNAC) is difficult due to its rarity and its variable cytologic findings. To the best of our knowledge, more than 100 cases of FNAC of angiosarcoma have been reported in the English literature,[3-11] including one case of lymphedema-associated angiosarcoma,[7] however only one case of FNAC of angiosarcoma and two cases of exfoliative cytology of angiosarcoma have been reported thus far in Korea.[12-14] The principal objective of this study was to emphasize the diagnostic FNA cytologic findings of angiosarcoma, showing vasoformative structures including arborizing microtissue fragments, microacinar lumen formation and intracytoplasmic vacuoles, with or without erythrocytes, especially in chronic lymphedema patients.

Herein, we present the cytologic findings of two cases of angiosarcomas diagnosed on FNAC. One case was a recurred angiosarcoma in the left chest wall and the other case was a lymphedema-associated angiosarcoma in the left lower leg.

CASE REPORTS

Clinical history

Case 1

A 49-year-old woman presented with a palpable mass in the left chest wall for 1 month. The woman had received modified radical mastectomy for high grade angiosarcoma 4 years ago. Ultrasonography revealed a tumor mass measuring 3.3×2.2×1.3 cm in the left chest wall. FNA was performed on the mass. Direct smears were stained with the Papanicolaou method and diagnosed as angiosarcoma. Radiation therapy was done after wide excision.

Case 2

A 78-year-old woman was referred to our hospital for a nodular mass in the left lower leg for 1 year. The woman had a history of radical hysterectomy for squamous cell carcinoma of the uterine cervix 13 years ago and received a total hip replacement arthroplasty in 2008. She had suffered from marked edema of the left leg after radical hysterectomy, and burning sensation for one year. Tibia magnetic resonance imaging revealed diffuse soft tissue edema of the left leg. FNA was performed and direct smears were stained with the Papanicolaou method. Subsequent wide excision was done.

FNAC findings

The cytologic findings were similar in both cases. The aspirates were highly cellular with abundant blood in the background. The patterns of cell arrangement were variable, showing thick, three-dimensional, multilayered aggregate, large irregular anastomosing microtissue fragments with prominent lining cells, papillary clusters, small loosely cohesive clusters and many discohesive, singly dispersed cells (Fig. 1A). The thick and three-dimensional aggregates showed thin, well-defined and arborizing vessels with a curved configuration. In case 1, thick and multilayered aggregates, microacini, and rosette-like appearance were more prevalent than in case 2 (Fig. 1B). The cells were intermediate to large in size and were monotonous in size and shape. The cells were round to oval epithelioid, or elongated and spindle-shaped. The spindle cells were more prevalent in case 1 and showed long cytoplasmic prolongations. The nuclei were round to oval and elongated with smooth contours and showed coarsely granular chromatin and indistinct nucleoli. Mitotic figures were frequently observed. The cytoplasm of tumor cells was moderate to abundant, wispy and delicate, with tail-like projections (Fig. 2A). In case 2, the tumor cells were predominantly epithelioid cells composed of moderately large round to ovoid cells admixed with polygonal cells, binucleated cells, and giant cells. The nuclei were round to oval in shape and showed vesicular or hyperchromatic nuclei, prominent single or multiple eosinophilic nucleoli, irregular contours and indistinct cytoplasmic borders (Fig. 3A). The cells of case 2 revealed more pleomorphism, less cytoplasm, frequent cytoplasmic vacuoles and single or multiple prominent nucleoli than cells seen in the case 1. Nuclear grooves and indentations were noted in both cases (Fig. 2B). Both cases revealed intracytoplasmic lumen, cytoplasmic vacuoles, and erythrophagocytosis (Fig. 3B). Intracytoplasmic hemosiderin deposits were identified in case 2, but

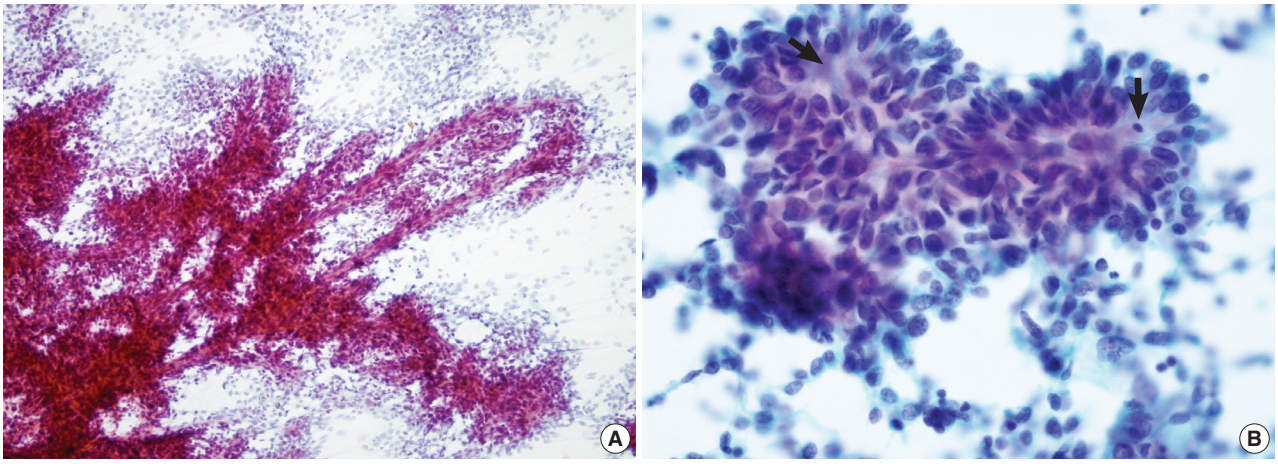

Fig. 1. (A) The aspirates are very cellular and composed of thick, three-dimensional, multilayered aggregate, large irregular anastomosing microtissue fragments with prominent lining cells, papillary clusters, small loosely cohesive clusters and many discohesive, singly dispersed cells in a bloody background. (B) Microacini and rosette-like appearance (arrows) are also seen.

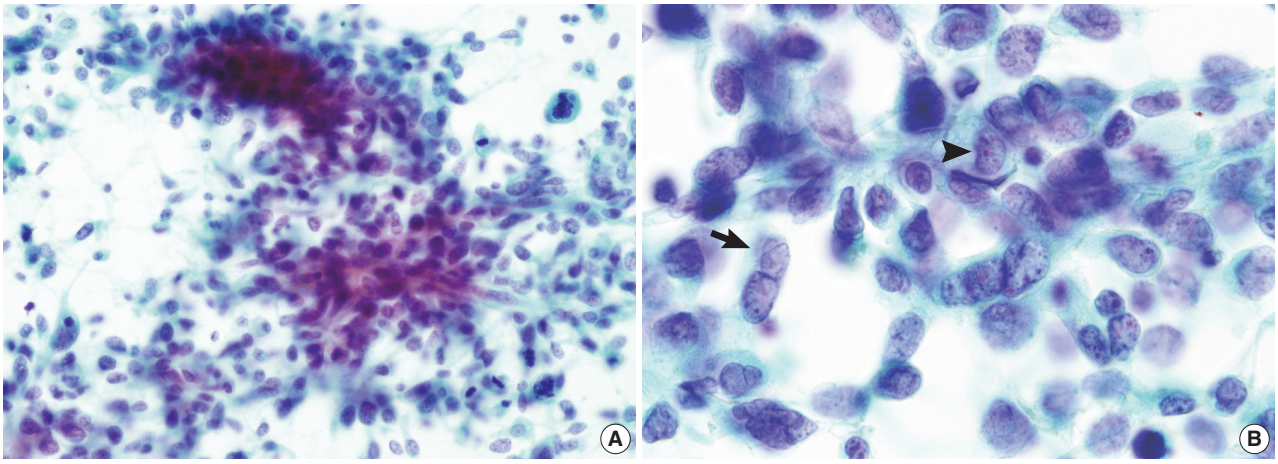

Fig. 2. (A) The cells are round to oval, epithelioid or spindle-shaped with ovoid, irregular, vesicular, or hyperchromatic nuclei, and tail-like cytoplasmic prolongations. Mitotic figures are observed. (B) Nuclear grooves (arrow) and indentations (arrowhead) are observed.

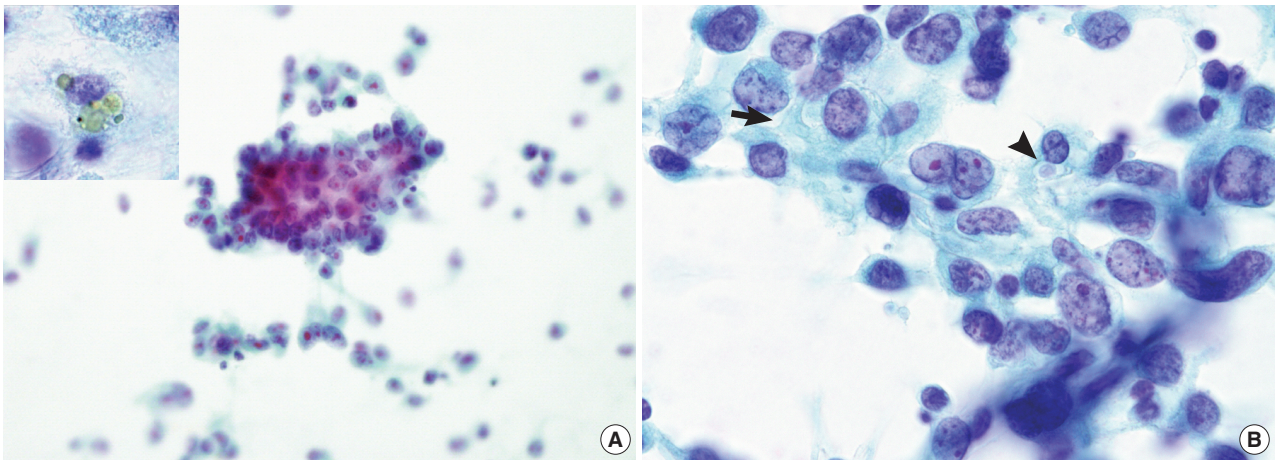

Fig. 3. (A) Predominantly epithelioid cells show round to oval, vesicular or hyperchromatic nuclei, prominent single or multiple eosinophilic nucleoli, irregular contours and indistinct cytoplasmic borders (inset, intracytoplasmic hemosiderin pigment). (B) Intracytoplasmic lumen, cytoplasmic vacuoles (arrow), and erythrophagocytosis (arrowhead) are noted.

not in case 1 (Fig. 3A inset).

Histologic findings

Histologically, the tumor of case 1 showed solid growth of mixed spindle and epithelioid cells with slit-like vascular channel and focal papillary appearance. The tumor cells were round to oval with elongated hyperchromatic nuclei, dense cytoplasm and frequent mitotic figures (Fig. 4A). Case 1 was diagnosed as poorly differentiated angiosarcoma. The tumor of case 2 was epithelioid angiosarcoma, showing a large area of necrosis and sheets of exclusively epithelioid cells with prominent papillary structures, mimicking carcinoma (Fig. 4B). Focal irregular anastomosing vascular channels were noted at the tumor periphery. The tumor cells of both cases are strongly reactive for CD31 and CD34 and negative for cytokeratin (Fig. 4A, B inset).

DISCUSSION

Angiosarcomas are rare malignant vascular neoplasm of blood vessel or lymphatic origin.[2] The breast is one of the most common sites for the development of angiosarcoma. Primary angiosarcomas of the breast are rare and account for 0.04% of all malignat breast tumors, and usually occur in young women between their second and fourth decades of life.[15] Secondary angiosarcomas usually occur in older women who have undergone breast conservation therapy with radiaton.[16] Our first case had

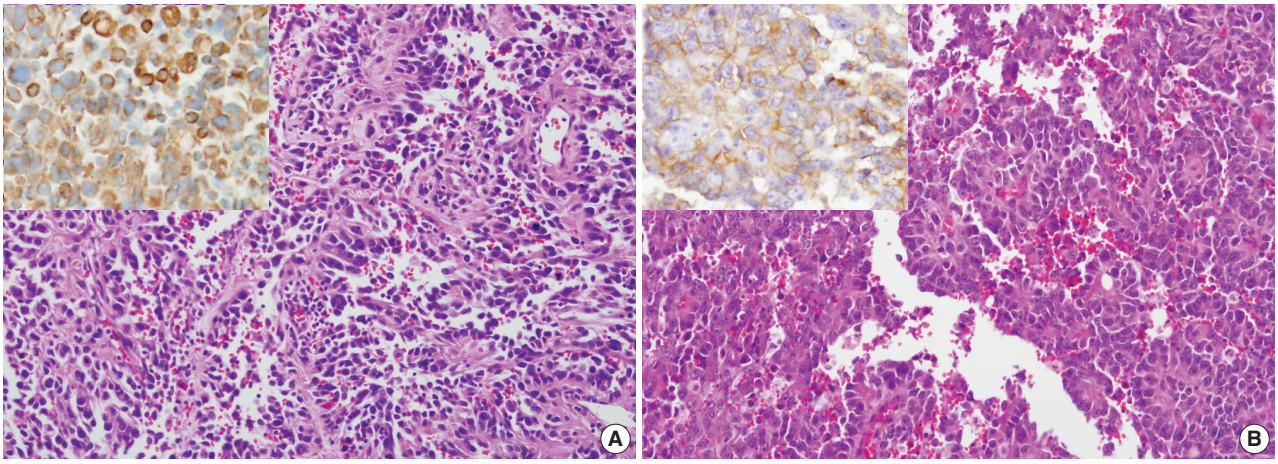

Fig. 4. (A) The tumor of case 1 shows solid growth of mixed spindle and epithelioid cells with slit-like vascular channel and focal papillary appearance (inset, The tumor cells are strongly reactive for CD31). (B) The tumor of case 2 shows sheets of epithelioid cells with papillary structures (inset, The tumor cells are strongly positive for CD31).

no history of breast carcinoma or radiation therapy and was diagnosed with recurrent primary angiosarcoma of the breast which was a high grade angiosarcoma according to Rosen's method for breast angiosarcoma grading.[17] On the contrary, our second case was secondary angiosarcoma, lymphedema-associated angiosarcoma (Stewart-Treves syndrome), occurring in the left lower leg after radical hysterectomy; this is extremely rare. Lymphedema-associated angiosarcoma was first described in 1948 by Stewart and Treves;[18] it develops on the lymphedematous limb and the chest wall after mastectomy and axillary lymph node dissection.

The FNA cytologic findings of angiosarcoma have been elucidated at different sites and in different organs.[3-11] The FNA cytologic diagnosis of angiosarcoma is difficult due to variable cytologic findings depending on tumor grade and subtype. Variable cellularity has been reported and the background is rich in blood.[5,19] The degree of nuclear atypia ranged from relatively bland to highly pleomorphic with spindle, epithelioid, or dual cell populations.[3-11] In contrast to the previous report of Liu and Layfield[4] where the smears showed hypocellularity, other reports[3,12-14] and our cases were highly cellular and showed vasoformative features consisting of arborizing microtissue fragments, microacinar structures, intracytoplasmic lumina, nuclear indentations, and rare erythrophagocytosis. Saleh and Tao[9] previously identified a mixture of spindle-shaped, ovoid-to-round and occasional bizarre cells with cytoplasmic hemosiderin pigment or erythrophagocytosis as typical FNA cytologic findings of angiosarcoma. Both of our cases showed erythrophagocytosis, but intracytoplasmic hemosiderin deposits were identified in case 2 and not in case 1. FNA cytologic findings of our second case revealed pseudopapillary structures with a more pleomorphic epithelioid appearance, prominent nucleoli and frequent cytoplasmic vacuoles, mimicking papillary adenocarcinoma. Pomplun *et al.*[7] reported that FNAC of the upper arm mass showing sheets and clusters of polygonal cells was misinterpreted as recurrent ductal carcinoma cells. Pohar-Marinsek and Lamovec[3] reported that the vasoformative structures may be helpful in classical angiosarcomas, but not in epithelioid angiosarcomas. However, our second case showed typical vasoformative features, although such features are not consistently found.[4,6] The diagnosis of epithelioid angiosarcoma in FNAC is more challenging due to less evidence of sarcomatous features. However, a tendency to form vasoformative or microacinar arrangement has been noted repeatedly in other reports. [3,4,8-11] Some authors have noted that postradiation angiosarcomas have poorly differentiated nuclei with vesicular nuclei, prominent nucleoli, and high mitotic activity,[20] although others detected no major morphologic differences between primary and postradiation angiosarcomas.[19] Thus far, there have been no reports regarding morphological differences between primary and lymphedema-associated angiosarcomas. The FNA cytologic findings of our two cases are relatively similar. When the cytologic findings of the present study were compared with those of the previously reported studies, features common to both studies were vasoformative structures, dispersed single atypical cells, and bloody background.

Those previous cytologic studies emphasize that cytologic findings are diverse and that the specific recognition of angiosarcomas in cytologic specimens is difficult due to their rarity and variable cytological features. The accuracy of FNAC diagnosis of angiosarcoma ranges between 15% to 37%.[3,6] The diagnostic accuracy of this method is lower for epithelioid angio-

sarcoma than for classical or mixed type angiosarcoma, primarily due to the morphological similarities of epithelioid angiosarcoma to carcinoma. The differential diagnoses of angiosarcoma broadly encompass benign spindle cell lesions, sarcoma, non-small cell carcinoma and melanoma. Classical, low-grade angiosarcoma can be mistaken for a benign lesion, particularly in smears with low cellularity. The bland spindle cells resemble fibroblasts and hyperplastic endothelial cells. When low cellularity is combined with an abundance of blood, hemangioma enters into the differential diagnosis.[4] FNAC of Kaposi's sarcoma and dermatofibrosarcoma protuberance typically reveals relatively bland spindle cells arranged in tight clusters, loose groups, and single cells, but the condition is sometimes indistinguishable from a low-grade angiosarcoma. In such cases, Kaposi's sarcoma can be diagnosed by demonstration of immunoreactivity for herpesvirus 8 on the smear. The majority of angiosarcoma showed greater cytologic atypia than anticipated in aspirates from Kaposi's sarcoma and dermatofibrosarcoma protuberance. High-grade classical angiosarcomas can be readily recognized as malignant and also as sarcoma. The differential diagnosis is spindle cell sarcoma including malignant peripheral nerve sheath tumor (MPNST), fibrosarcoma, leiomyosarcoma, synovial sarcoma, and malignant phyllodes tumors of the breast. FNAC of MPNST, fibrosarcoma, leiomyosarcoma, and malignant phyllodes tumors reveal tighter and more compact spindle cell clusters without vasoformative structures. Typical FNA cytologic findings of synovial sarcoma are small to medium-sized round or fusiform cells with round or oval nuclei, bland chromatin texture, and inconspicuous nucleoli. The lack of vasoformative features may assist in the differential diagnosis.[3] The differential diagnosis of epithelioid angiosarcoma on FNAC includes malignant melanoma, epithelioid sarcoma, epithelioid hemangioendothelioma, alveolar soft part sarcoma, all epithelioid variant of various sarcomas and poorly differentiated adenocarcinoma.

In FNAC of malignant melanoma, dispersed isolated cells, macronucleoli, intranuclear cytoplasmic inclusion and melanin pigment all represent helpful features in distinguishing it from angiosarcoma.[4] Aspirates from epithelioid sarcoma reveal large single cells and loosely cohesive cell clusters composed of round, polygonal, and elongated tumor cells with binucleation, inconspicuous to prominent nucleoli and cytoplasmic vacuoles.[3] In contrast, angiosarcomas tend to display more cytologic atypia than epithelioid sarcoma and occur primarily in older patients. Aspirates from epithelioid hemangioendothelioma are usually bloody and hypocellular with metachromatic material and are composed predominantly of single neoplastic cells with only occasional small loose clusters with no specific architectural arrangement. FNAC of alveolar soft part sarcoma reveals uniform clusters of large polygonal cells with round to oval vesicular nuclei, prominent nucleoli, and abundant cytoplasm. However, well-developed vasoformative structures are seen only in angiosarcoma.[10] Finally, the differential diagnosis includes poorly differentiated carcinoma based on the cytology of the aspirates. The loosely cohesive groups with acinar-like structures along with epithelioid morphology of the cells mimic the appearance of carcinoma in FNA specimens. Minimo *et al.*[5] noted that hemorrhagic background, fine vacuolization of the cytoplasm, and bi- and multinucleated cells are indicative of angiosarcoma but may be too subtle to discern at times. This finding constitutes a valuable diagnostic clue, but its presence is variable. Pohar-Marinsek and Lamovec[3] previously reported that vasoformative structures may be helpful in classical but not in epithelioid angiosarcoma, and differentiation between epithelioid angiosarcoma and certain carcinomas is not possible in FNAC. However, our case 2 of epithelioid angiosarcoma showed well-develped vasoformative structures. In the absence of vasoformative structures, epithelioid angiosarcomas may be diagnosed as poorly differentiated carcinomas. Accurate and reliable diagnosis of angiosarcoma requires evaluation and correlation of cytomorphologic and clinical findings, including the neoplasm site, pertinent clinical history, and immunocytochemical stains for CD31 and CD34.

In summary, we have described the FNA cytological features of a case of recurred angiosarcoma in the chest wall and a case of lymphedema-associated secondary angiosarcoma in the left lower leg. The cytologic findings of recurred angiosarcoma and lymphedema-associated angiosarcoma are similar. It is important to consider angiosarcoma in differential diagnosis in FNAC of skin or subcutaneous mass, showing cytoarchitectural features suggestive of endothelial differentiation, such as arborizing microtissue fragments, microacinar lumen formation, and intracytoplasmic vacuoles, with or without erythrocytes, particularly in chronic lymphedema patients. FNA cytologic findings of angiosarcomas are sufficiently distinctive to allow differentiation from other morphologically similar neoplasms, and can be confirmed with immunocytochemical staining.

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