The Cytology of Metastatic Angiosarcoma in Pleural Fluid
- A Case Report -

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Received: February 5, 2009
Accepted: May 20, 2009

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Angiosarcoma is a malignant tumor of endothelial cells, and it is one of the rarest forms of soft tissue neoplasms with an incidence of 1 to 2% of all soft tissue tumors. It originates from the endothelial cells of the blood vessels, and it can affect a variety of organs, including the retroperitoneum, skeletal muscle, subcutis, liver, heart and breast. The head and neck region is one of the common sites for angiosarcomas, but angiosarcoma of the scalp is a very rare disease. Metastases to the lung, pleura or chest wall are common. However, there are few reports in the medical literature on the exfoliative or aspiration cytological findings of metastatic angiosarcomas, and the cytologic features of this tumor have not currently been fully elucidated.

We describe here the cytologic findings of the pleural fluid in a case of metastatic angiosarcoma, along with how to make the cytologic differential diagnosis.

CASE REPORT

A 74-year-old Korean woman presented with an abrupt onset of dyspnea that she had experienced for a week. She had been suffering from cutaneous nodules in the scalp for a year. Thoracentesis of the pleural fluid was performed. The Papanicolaou-stained smears, Thin prep and cell block preparations revealed clusters of oval-shaped cells concentrically layered about amorphous acellular cores, i.e., there was microacinar lumen formation as well as singly scattered atypical cells. The cells occasionally demonstrated intracytoplasmic vacuoles and hemosiderin deposits. Those cells stained for CD31 and they were negative for pancytokeratin. Punch biopsy from the scalp nodules revealed angiosarcoma. There are currently few reported cases of angiosarcoma in an exfoliative pleural effusion. Angiosarcoma has diverse, heterogeneous cytologic features. Making the cytologic diagnosis of metastatic angiosarcoma in pleural fluid is a challenge for pathologists. Knowledge of the clinical history is of great help for diagnosing this tumor when it appears in rare sites. Immunopanels with CD31, pan-keratin and TTF-1 are helpful for making the differential diagnosis. The pathologists should look for clues suggesting the presence of vascular differentiation in the exfoliative cytologic materials when a diagnosis of angiosarcoma is suspected.

Key Words: Pleural effusion, Malignant; Angiosarcoma; Exfoliative cytology; Scalp
block were also obtained. The exfoliated tumor cells in the pleural fluid occurred singly, in irregular clusters and in sheets with a focal gland-like arrangement, i.e., microacinar lumen formation. They showed ill-defined, pale wispy cytoplasm and fairly regular round-to-oval nuclei with irregular chromatin patterns (Fig. 1A, B). The nuclear features were an irregular chromatin pattern, an irregularly thickened nuclear membrane and eosinophilic prominent nucleoli. The cells occasionally demonstrated intracytoplasmic hemosiderin deposits (Fig. 1C). Intracytoplasmic erythrophagocytosis was also found within the intracellular lumens. Many macrophages were seen in the background. Mitotic figures were rarely found.

The above cytologic findings prompted us to suggest the diagnosis of metastatic angiosarcoma in the pleural fluid. Immunohistochemically, the tumor cells in the cell block were positive for CD31 (JC70A; DAKO, Glostrup, Denmark, 1:40, Fig. 1D),

Fig. 1. (A) Loosely cohesive atypical cells are arranged in microacinar architecture (H & E). (B) The tumor cells show hyperchromatic nuclei and intracytoplasmic vacuoles (arrow). Inset indicates amorphous acellular core (H & E). (C) The tumor cells have intracytoplasmic hemosiderin pigments (H & E). (D) Immunocytochemistry for CD31 shows the membranous staining of the tumor cells (Immunocytochemistry).
vimentin (V9; DAKO, prediluted) and vWF (factor VIII-related antigen, DAKO, prediluted). The tumor cells were negative for CK7 (OV-T1; DAKO, 1:100), CK20 ( ks20-8; DAKO, 1:50), thyroid transcription factor-1 (8G7G; DAKO, 1:50) and pan- cytokeratin (AE1/AE3, DAKO, prediluted). Bleaching with using the Papanicolaou-stained cytology slides was done with 1% hydrochloric acid, and then immunohistochemical stainings for CD31 and CD68 (PG-M1; DAKO, prediluted) were performed. The majority of the vacuolated cells were CD68-positive macrophages, and some of them were CD31 positive tumor cells.

A punch biopsy from the scalp revealed oval to round-shaped epithelioid cells arranged in solid sheets and nests. In some areas, the tumor cells formed anastomosing vascular spaces (Fig. 2A). These cells had large, round to oval eccentrically placed nuclei. The nucleus showed a vesicular chromatin pattern and it often contained a prominent, round eosinophilic nucleolus. The cytoplasm was moderately abundant with a granular to dense character. Immunohistochemically, the tumor cells were positive for CD31, CD34 (QBEnd10; DAKO, prediluted), vimentin and vWF (Fig. 2B), and they were negative for pancytokeratin.

**DISCUSSION**

Angiosarcoma is a rare neoplasm. The variable histological appearance of angiosarcoma also makes the cytologic appearance variable and diverse. Therefore, recognizing angiosarcoma in a cytopathologic specimen is difficult, but making the definitive cytologic diagnosis of angiosarcoma often has to be done in the absence of an ancillary method unlike tissue section.

Few cases concerned with the exfoliative cytology of angiosarcoma have currently been reported.\(^2\) We compared the cytologic findings in our present study with those of the studies by Chu et al.,\(^8\) Liu and Layfield,\(^9\) and Boucher et al.\(^3\) The cellularity of angiosarcoma varies from hypocellular smears to cellular smears.\(^3\)\(^8\)\(^9\) Chu et al.\(^8\) described that the hypocellular, hemorrhagic pleural fluid showed highly pleomorphic oval or spindle-shaped tumor cells that were singly scattered or grouped in loose groups, in knitted syncytial aggregates and in an acinar pattern. In Chu et al.’s study, almost all the tumor cells showed variable sized intracytoplasmic vacuoles and their nuclei were sometimes crescentic due to a huge vacuole. Occasional binucleated tumor cells and mitotic figures were present. Erythropagocytosis, cellular debris and streaky materials were identified. Boucher et al.\(^3\) noticed the unique vasoformative features such as microacinar structures, arborizing microtissue fragments, intracytoplasmic vacuoles or lumens, signet ring-like cells and rare erythropagocytosis. The cells were oval, round or spindled, with eccentric, round to spindle-shaped nuclei and scanty to abundant amounts of pale blue-gray, vacuolated cytoplasm. The nuclear features varied from hyperchromatic to euchromatic nuclei with coarse chromatin, and prominent nucleoli may be seen. Sin-
gly scattered atypical cells were also seen. These single tumor cells in the effusion cytology should be distinguished from scattered macrophages, which have finely vacuolated cytoplasm and peripheral, spherical or kidney-shaped nuclei. The immunohistochemistry for CD68 and endothelial markers such as CD31, CD34 or vWF using unstained or bleached slides may be needed in confusing cases.

The tumor cellular morphology of angiosarcoma, i.e., spindle and/or epithelioid, broadly encompasses melanoma, carcinoma and sarcoma. Malignant spindle cells may be seen in spindle cell sarcomas such as fibrosarcoma and monophasic spindle-cell synovial sarcoma. Synovial sarcoma is generally highly cellular with both single cells and groups of cells with a monotonous spindle-shape morphology. Fibrosarcoma may be highly cellular and it demonstrates a predominance of single cells and small cell clusters with only small rims of cytoplasm in a filamentous to myxoid granular background. A vasoformative arrangement is seen only in angiosarcoma, but its presence is variable. Those findings render diagnostic clues, but they are not pathognomonic. In the absence of this pattern, angiosarcomas tend to be diagnosed as poorly differentiated carcinomas. Intracytoplasmic hemosiderin deposits are important in diagnosing angiosarcoma with using a cytology specimen, although they can also be identified in Kaposi’s sarcoma and dermatofibrosarcoma protubers. However, significant cytologic pleomorphism is not seen in Kaposi’s sarcoma and dermatofibrosarcoma protubers, and the morphology of the main atypical cells in those tumors is a spindle appearance. Intracytoplasmic vacuoles and a microcinar structure with a central acellular core are features that angiosarcoma shares with poorly differentiated carcinoma, and especially adenocarcinoma. Other high grade sarcomas such as epithelioid sarcoma, liposarcoma and malignant fibrous histiocytoma should be included in the cytologic differential diagnosis. Necrosis is occasionally seen in angiosarcoma, and it is one of characteristic features of epithelioid sarcoma. Intracytoplasmic vacuoles may occasionally mimic a multivacuolated lipoblast that is uni- or multivacuolated with scalloped nuclei. However, the cytomorphologic features of liposarcoma include a network of anastomizing capillary vessels and slightly atypical lipoblasts. The cytologic background of liposarcoma is brownish and mucoid in nature, whereas that of angiosarcoma is inflammatory and serosanguinous in nature. Malignant fibrous histiocytoma yields significantly great cellularity and markedly pleomorphic cells. Wispy cytoplasm and intracytoplasmic vacuolation without nuclear hyperchromasia or prominent macronuclei are features of radiation-associated changes.

Among those features, the most important cytologic feature is the identification of intracytoplasmic hemosiderin deposits and singly scattered oval or spindle-shaped pleomorphic cells on the exfoliative cytology. Differentiation of malignant melanoma from angiosarcoma can occasionally be difficult because the color of those pigments can have a similar appearance. The melanin pigments of malignant melanoma are finer than the hemosiderin of angiosarcoma, and intranuclear inclusions are helpful for making the diagnosis of malignant melanoma.

To overcome the diverse cytologic findings of angiosarcoma as described above, immunohistochemistry for the endothelial markers (CD31, CD34, and vWF), cytokeratin and B72.3 is a proven confirmatory diagnostic tool. Among them, CD31 is more sensitive and it is the most reliable marker of endothelial differentiation in the cytology and histology specimens. However, caution is often needed because cytokeratin and B72.3 may be positive in some angiosarcomas and poorly differentiated epithelial neoplasms.

We report here on a rare case of metastatic angiosarcoma in pleural fluid with its cytologic differential diagnosis. On diagnosing the exfoliative cytology of angiosarcoma in pleural fluid, the patient’s clinical history and immunohistochemical findings are important because angiosarcoma shares cytological features with other neoplasms in addition to the tumor’s rarity and heterogeneity.

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