The Korean Journal of Pathology 2010; 44: 554-7
DOI: 10.4132/KoreanJPathol.2010.44.5.554

Fine Needle Aspiration Cytology of Pulmonary Epithelioid Hemangioendothelioma with Prominent Hyaline Degeneration
– A Case Report –

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Received : April 1, 2010
Accepted : June 8, 2010

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Pulmonary epithelioid hemangioendothelioma (PEH) is a rare vascular tumor of low to intermediate malignant potential, and PEH can mimic other more common tumor entities pathologically as well as clinically. Compared to its well-recognized histological features, its cytological findings have been reported rarely to be plasmacytoid or epithelioid cells with abundant dense or finely granular cytoplasm, cytoplasmic vacuoles, round nuclei and prominent nucleoli. We report here on the fine needle aspiration cytologic findings of a 38-year-old woman with EH of the lung, that showed in addition to its classical cytomorphology, a somewhat peculiar cytologic finding such as big twig-like rosettoid structures with prominent hyalinized stroma. This tumor was histologically and immunohistochemically proven to be PEH by primary antibodies for CD31, CD34 and vimentin. We emphasize that the accuracy of making a cytologic diagnosis of this rare tumor can be increased by recognizing the peculiar cytologic finding that we report on here.

Key Words : Hemangioendothelioma, epithelioid; Lung; Biopsy, fine needle

Pulmonary epithelioid hemangioendothelioma (PEH) is a rare, low-grade, sclerosing angiosarcoma that typically presents with multiple pulmonary nodules in young women. Epithelioid hemangioendotheliomas are generally known to be the most aggressive form of hemangioendotheliomas and they have the potential for local recurrence and metastasis.[1] Although the hitologic features of PEH have been well described, there are very few reports on the fine needle aspiration (FNA) findings, with fewer than 10 case reports worldwide.[2-7] The cytologic findings reported to date can be summarized as follows: 1) loosely cohesive epithelioid cells that can be binucleated and multinucleated, 2) the nuclei are often eccentric, with slightly coarse granular chromatin and relatively prominent nucleoli and 3) the cytoplasms that are finely granular and contain variable-sized vacuoles. However, the big twig-like rosettoid arrangement of the epithelioid cells has not yet been reported in any cytologic report of PEH. We report here on the new cytologic finding in the FNA cytology of PEH, and it should help the interpretation and increase the diagnostic accuracy.

CASE REPORT

Clinical history

A 38-year-old woman visited Dankook University Hospital due to chronic cough and a recent onset of pain in the left upper abdomen and flank. Chest radiography revealed about a 2.5 × 2.0 cm-sized round mass in the left lower lung zone and additional chest computed tomography (CT) showed multiple bilateral pulmonary nodules at both lower lobes along with plaque-like pleural thickening. Abdominal CT also revealed a small hemangioma-like lesion at the segment V in the liver. The possibility of pulmonary tuberculosis or a certain metastatic lesion was clinically suspected. Fluoroscopy-guided percutaneous needle aspiration was done on the main mass in left lower lung. Two weeks later, the patient underwent a wedge-resection of the lung mass. Postoperatively, she received one cycle each of chemotherapy and radiotherapy, with the maintenance of pain control. However, 8 months later she admitted again with the chief complaint of aggravated pain in the chest and a newly ap-

peared abdominal wall mass. The mass was histologically confirmed by an excisional biopsy to be metastatic epithelioid hemangioendothelioma. Her clinical status was deteriorated despite symptomatic treatment, and she died about 7 months after the excision of the abdominal mass.

FNA cytology findings

FNA of the pulmonary lesion yielded a relatively abundant fibrin-rich exudative aspirate. The Papanicolaou stain showed a biphasic pattern throughout the area; a) loosely cohesive or discohesive cells and b) tightly cohesive cell clusters in the fibrinous inflammatory background (Fig. 1). The discohesive tumor cells were epithelioid and the nuclei were eccentric. Some cells exhibited bi- or multinucleation and intranuclear cytoplasmic inclusions were occasionally found. The nucleoli were small, but relatively prominent. The cytoplasm was dense and granular and intracytoplasmic vacuoles were occasionally observed (Fig. 2). Aggregated tumor cell clusters revealed the big elongated rosettoid arrangement with the central anuclear area and the peripheral rosettoid cellular rimming (Fig. 2). On higher magnification, mild nuclear pleomorphism was found, but there were no mitotic figures. Based on the above cytologic findings, adenocarcinoma and epithelioid hemangioendothelioma were considered as the main cytologic differential diagnoses.

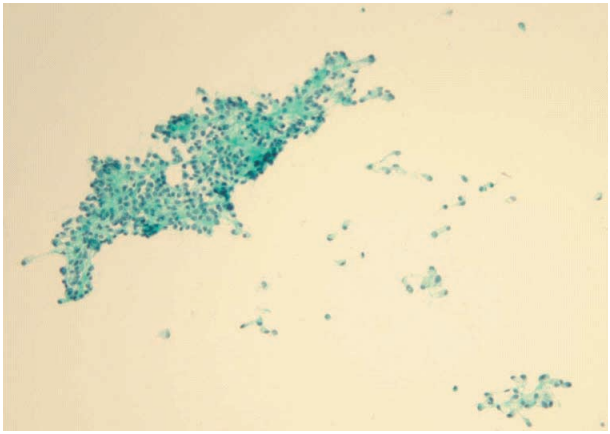

Fig. 1. A fine needle aspirate of the lung shows the biphasic pattern of a big cohesive cell cluster and some scattered discohesive epithelioid cells (Papanicolaou stain).

Histopathology

Grossly, the pulmonary mass was a well-demarcated, yellowish white, round, firm nodule that measured 1.8 × 1.7 × 1.6 cm. The cut surface was yellowish and solid with a grayish white myxoid peripheral rim.

On the low-power field of the light microscope, the tumor was usually well-demarcated, but focally poorly demarcated due to intraalveolar extension. The center of the tumor was predominantly composed of an exuberant eosinophilic hyaline matrix with necrotic cell shadows, but there were no calcified or ossified areas. Distinctively plump epithelioid cells were seen mainly at the peripheral rims, and these cells focally extended to the alveolar spaces. The tumor cells were usually arranged in an alveolar pattern along the scaffolds of interstitial connective tissue septa (Fig. 3). Among the tumor cells, multifocal spotty necrosis and chronic inflammatory cell infiltration were also found. On close examination, the plump epithelioid cells frequently showed variable-sized intracytoplasmic vacuoles, along

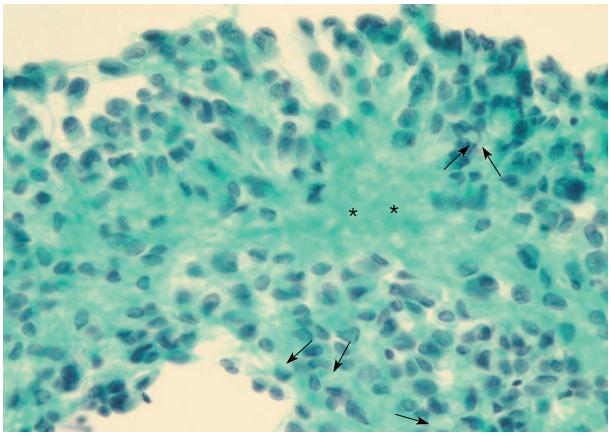

Fig. 2. The epithelioid tumor cells are arranged in a big rosettoid pattern (**), showing plump and occasionally vacuolated cytoplasms (arrows) and eccentric nuclei (Papanicolaou stain).

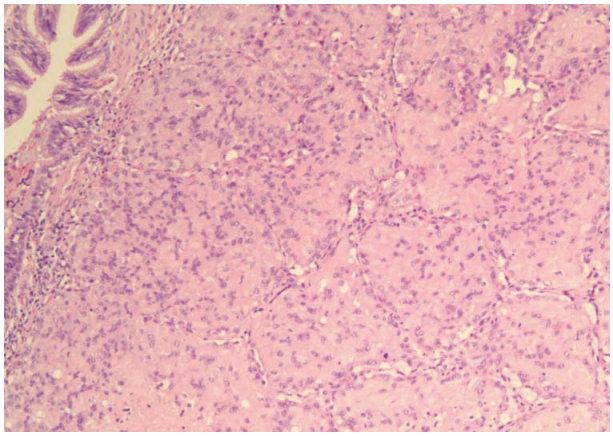

Fig. 3. The tumor cells are growing in nests along the alveolar spaces and characterized by the plump epithelioid cells with occasional intracytoplasmic vacuoles.

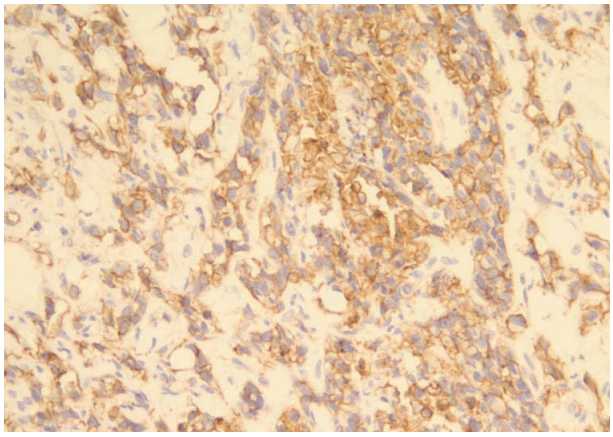

Fig. 4. Immunohistochemically, the tumor cells are diffusely reactive for CD31, an endothelial marker.

with occasional bi- or multinucleation. Immunohistochemically, the tumor cells were reactive for vimentin, CD31, CD34 and factor VIII and thery were negative for cytokeratin 7, carcinoembryonic antigen, epithelial membrane antigen, calretinin, S-100, smooth mucle actin and desmin (Fig. 4).

DISCUSSION

PEH is a rare vascular tumor of the lung of low to intermediate malignant potential, and this used to be described as "intravascular bronchioloalveolar tumor (IVBAT)" because it was believed to have an epithelial origin with adjacent vascular invasion.[8] In practice, it mimics epithelial cells or histiocytes histologically, but immunohistochemical and ultrastructural studies have demonstrated that it originates from endothelial cell rather than epithelial cells.[9-11] Despite considerable similarities to epithelioid hemangioendothelioma of other sites, PEH has a distinctive clinical nature. In most cases, PEH occurs predominantly in females with the mean age of 39 years (range, 12 to 61 years), with over half of them under the age of 30 years. It is generally identified incidentally as multiple bilateral nodules on chest CT because it is usually asymptomatic, although clinical symptoms are occasionally presented with chest pain, cough, sputum and on rare occasion alveolar hemorrhage. The present case was first diagnosed due to her back pain and cough of a long duration. Due to its multiple bilateral nodularity, it may be initially regarded as metastatic carcinoma or chronic granulomatous disease, as in our case.

Following a thorough review of the literature, including a Korean cytologic report,[12] we can summarize some distinctive cytological features of PEH as follows. The tumor cells are scattered singly or arranged in cords, nests or loosely cohesive clusters. The cells are epithelioid with dense granular cytoplasm. The nuclei are round to oval, eccentric (plasmacytoid) and often bi- or multinucleated. Each nucleus has a vesicular chromatin pattern and shows one or two small prominent nucleoli. Intranuclear inclusions may be sometimes observed. Cytoplasmic vacuolation is one of the most remarkable findings in PEH. Fragmented red blood cells are occasionally seen, which strongly supports that PEH is derived from a vascular origin.

In addition to the previously reported cytological features, we report here a somewhat peculiar cytologic finding, that is, the big twig-like rosettoid epithelioid cell clusters with hyalinized stromal cores. This cytologic finding has not yet been reported in any of the cytologic literature.

Many neoplastic conditions can share the common cytomorphology in that they have epithelioid cells with cytoplasmic vacuolation and prominent nucleoli.[6,7] First, primary adenocarcinoma should be initially included in the differential diagnosis because of its higher incidence. Adenocarcinoma has a female predominance and cytologic features of prominent intracytoplasmic vacuolation and often recognizable nucleoli. However, it lacks mesenchymal elements such as a hyalinized core. Second, the possibility of mesothelioma should be taken into account. While it is less frequent for the cytoplasms to be vacuolated, the vacuoles can be observed in mesothelioma cells. It can also show not only bi- or multinucleation but also a collagenous core. The only way to resolve this problem is to employ an immunohistochemical technique using mesothelial cell markers such as calretinin. Third, high-grade angiosarcoma should be considered due to endothelial differentiation. Epithelioid and discohesive features can be seen in some angiosarcomas. However, prominent cytoplasmic vacuolation is not commonly found in angiosarcoma. Additionally, other tumors should be excluded, including malignant melanoma, large cell lymphoma and anaplastic plasmacytoma. Thus, auxiliary immunohistochemical and ultrastructural studies are usually needed to arrive at a final diagnosis of PEH, in addition to the subtle morphological differential points.

In conclusion, the big rosettoid pattern with a central hyalinized core can be a key cytologic feature of PEH with prominent hyaline degeneration. Therefore, when one encounters multiple bilateral nodules on chest imaging, having an awareness of the cytologic feature that we stressed here may help to achieve a more accurate cytologic diagnosis for PEH.

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