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Primary Perivascular Epithelioid Cell Tumor (PEComa) of the Liver – A Case Report and Review of the Literature –

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Perivascular epithelioid cell tumor (PEComa) is a mesenchymal tumor consisting of distinctive perivascular epithelioid cells, and is commonly detected in the uterus. The liver is an uncommon site for primary PEComa. In this study, we report a case of primary hepatic PEComa in a 36-year-old woman. Upon gross examination, the tumor was a well-defined, brownish solid mass, measuring 6.5×5.2×4.5 cm. Microscopically, the tumor consisted largely of epithelioid cells and some spindle cells with a clear to eosinophilic cytoplasm and a rich network of delicate capillaries in the stroma. With the exception of their relatively large size and microscopically sinusoidal infiltrative growth pattern, all other histopathologic features of the tumor were consistent with their being benign. The tumor cells were positive for human melanoma black-45 and smooth muscle actin, and negative for cytokeratin-cocktail and c-kit.

Key Words: Perivascular epithelioid cell neoplasms; Liver

Perivascular epithelioid cells (PECs) were initially proposed, by Bonetti *et al.*[1] in 1992, to describe an "unusual atypical cell type" of epithelioid shape and harboring a clear to eosinophilic cytoplasm with perivascular distribution in both renal angiomyolipoma (AML) and clear cell sugar tumor (CCST) of the lung. This perception gradually became accepted and led to the concept of perivascular epithelioid cell tumors (PEComas). The PEComa family now embraces AML, CCST, lymphangiomyomatosis (LAM), and neoplasms composed predominantly of PECs have been designated by a variety of names, including clear cell myomelanocytic tumor (CCMMT), monotypic epithelioid AML, etc.[2-4] Non-AML, non-LAM PEComa, a neoplasm composed solely of PECs, most commonly occurs in the uterus, but is relatively rarely detected in the liver.[3-6] In this study, we describe a case of primary PEComa occurring in the liver.

CASE REPORT

A 36-year-old woman presented with a palpable right upper quadrant mass, which was incidentally discovered. A computerized tomography scan showed a 7.0×5.6 cm-sized, well-demarcated, heterogeneous mass in the left lateral segment of the liver (Fig. 1A). Hepatocellular adenoma or a malignancy such as hepatocellular carcinoma was suspected. The remaining liver parenchyma had a 2 cm-sized, delayed enhancing nodule, which was considered to be a hemangioma, in segment VIII, and multiple tiny cysts in both lobes. Both kidneys were unremarkable. A lateral segmentectomy was done to excise the largest main mass.

Gross examination revealed a relatively well-demarcated, oval-shaped, soft mass, measuring 6.5×5.2×4.5 cm beneath the hepatic capsule. The cut surface of the mass showed a nodular with perinodular expansion-like pattern of the hepatocellular carcinoma and a brown color with extensive hemorrhagic areas (Fig. 1B). Microscopically, the tumor was unencapsulated and had infiltrated into the adjacent parenchymal liver tissue. The tumor was composed largely of polygonal epithelioid cells with sheets or a vague trabecular pattern separated by a rich sinusoidal vascular network (Fig. 2A). In some areas, spindle-shaped cells were admixed with epithelioid cells. The epithelioid tumor cells had clear to eosinophilic granular cytoplasms with distinct cell borders. Nuclei were round to oval-shaped with prominent nucleoli, but no cellular pleomorphism was noted. Mitosis was rare. No necrosis or venous invasion was present. No multinucleated giant cells were identified. Dark or light brown pigments were noted within some epithelioid cells. Some

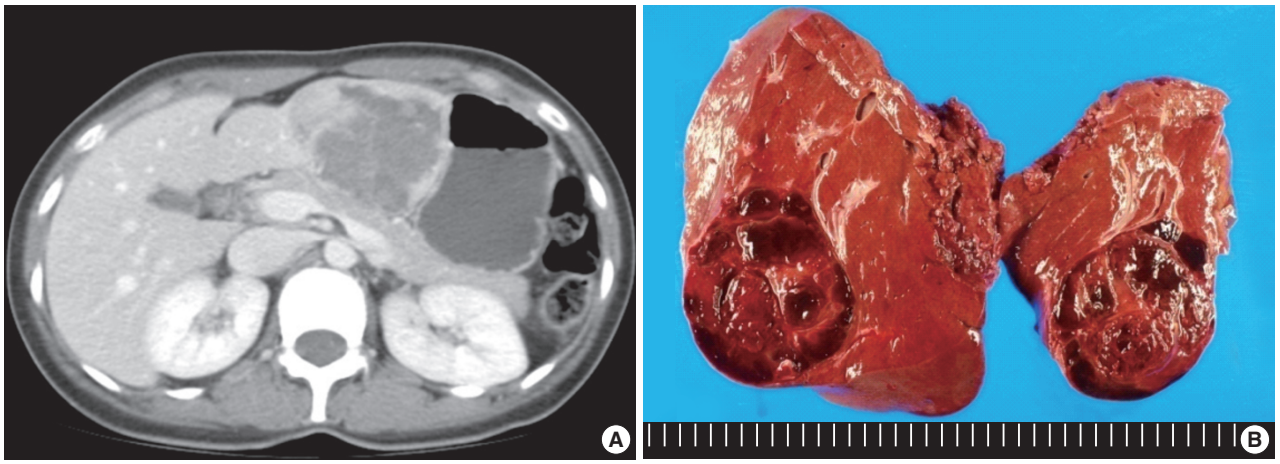

Fig. 1. (A) Computerized tomography reveals a well-defined mass with heterogeneous signal intensity in the liver. (B) The tumor is well-demarcated and soft with a brownish cut surface upon gross examination.

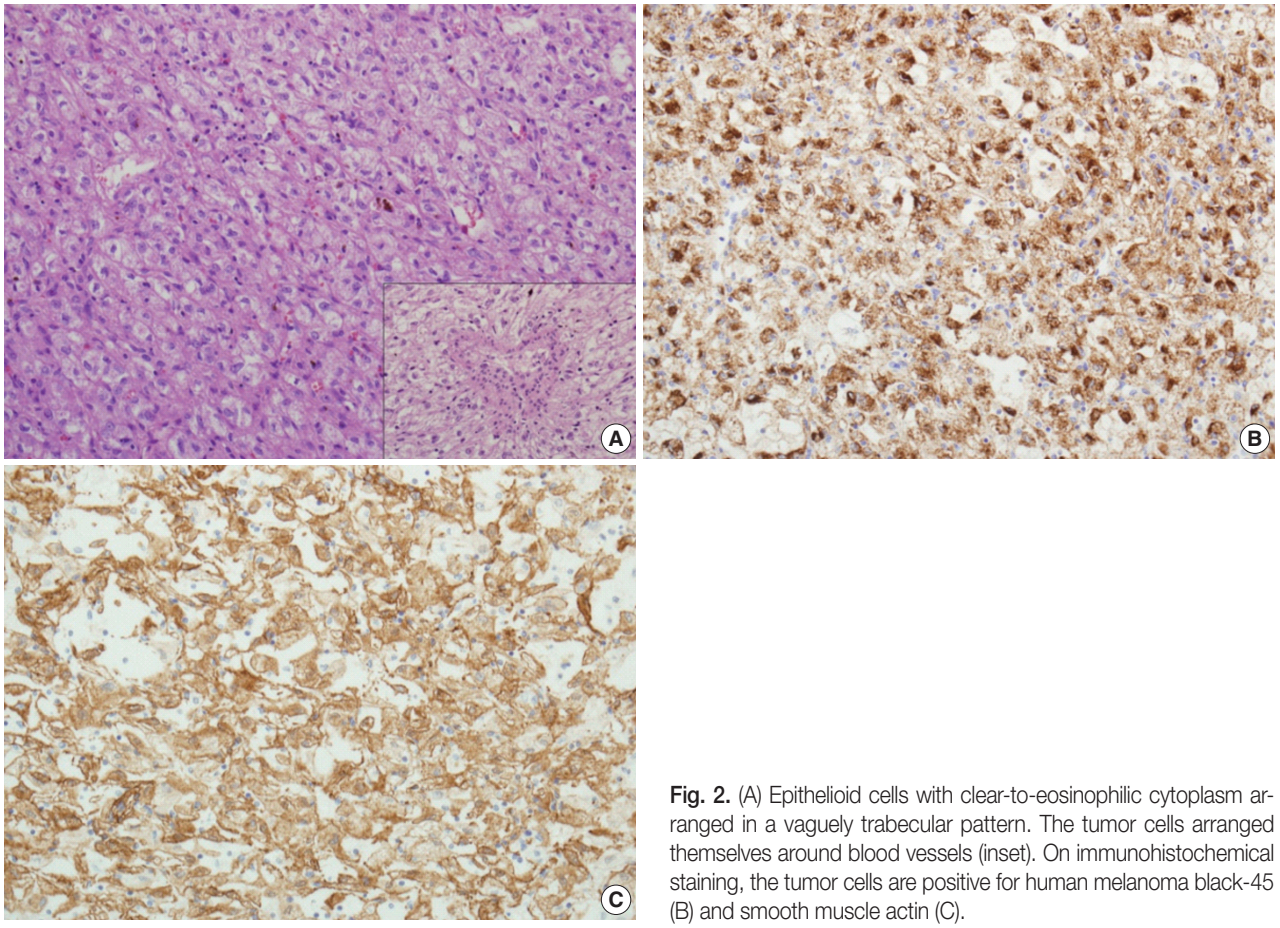

Fig. 2. (A) Epithelioid cells with clear-to-eosinophilic cytoplasm arranged in a vaguely trabecular pattern. The tumor cells arranged themselves around blood vessels (inset). On immunohistochemical staining, the tumor cells are positive for human melanoma black-45 (B) and smooth muscle actin (C).

of these pigments were stained with Fontana-Masson, and others were stained with Prussian blue. No adipocyte, smooth muscle, or thick-walled, torturous vessels were present. Upon immunohistochemistry, the epithelioid cells were diffusely positive for human melanoma black-45 (HMB-45) and smooth muscle actin, and weakly reactive for S-100 protein (Fig. 2B, C). Tests for cytokeratin-cocktail, CD34, and c-kit were negative. The epithelioid cells were positive for Melan-A, but the spindle cells were Melan-A-negative. The Ki-67 proliferation index of tumor cells was approximately 1%. Upon periodic acid-Schiff

(PAS) staining, PAS-positive and diastase-susceptive granules were detected in the cytoplasm of the epithelioid cells.

Three months after surgery, the patient remains in good health with no evidence of local recurrence or metastasis.

DISCUSSION

PEComa comprise a family of mesenchymal tumors composed of histologically and immunohistochemically distinctive PECs.[2] The members of this family include AML, LAM, pulmonary CCST, and non-AML, non-LAM PEComa, as different stages of modulation.[7] Due to their rarity, relatively little is known regarding PEComa, excluding AML, LAM, and pulmonary CCST. Zamboni *et al.*[8] suggested the name PEComa for neoplasms composed solely of PECs in his 1996 report, in which he described the first case of a pancreatic tumor that was identical to a CCST. However, no standard names were used for these neoplasms until the World Health Organization (WHO) provided a formal designation of PEComa, which included monotypic epithelioid AML, primary extrapulmonary sugar tumor, CCMMT, and abdominopelvic sarcoma of perivascular epithelioid cells.[3,4] We initially diagnosed our case as a monotypic epithelioid variant of AML.

PEComa of non-AML, LAM, or pulmonary CCST types are most commonly detected in the uterus, and have been reported in the falciform ligaments, prostate, kidney, pancreas, skull, pelvic wall, and heart.[2] The tumor is more common in females, with a broad age range. In a few cases, the condition has been associated with the tuberous sclerosis complex.[2-5] Histologically, the tumor was composed of epithelioid and spindle cells with variable rates arranged in sheet, nest, and fascicular patterns. The tumor cells had clear to granular, lightly eosinophilic cytoplasm. The majority of these tumors had nuclear features of low-grade, small, normochromatic, round- to oval-shaped nuclei, although in some cases high-grade nuclei were detected. There was an elaborate vascular network, reminiscent of that observed in renal cell carcinoma.[5,7,9,10] Upon careful examination, these tumor cells have been observed to arrange themselves around blood vessels.[9] Immunohistochemically, the tumor cells were positive for melanocytic markers, including HMB-45, Melan-A, and microphthalmia transcription factor, and in most cases, these tumor cells were positive for myocytic markers, including smooth muscle actin and muscle-specific antigen.[3,5,7,9]

PEComa in the liver, not related to the falciform ligament, is relatively uncommon.[10] Tsui *et al.*[11] previously described 5 cases of AML composed predominantly of epithelioid cells without adipocytes in a study of 30 cases of hepatic AML and unusual morphologic variants. However, these tumors differed from PEComa in that a few abnormal vessels were noted.[7,12] We identified 11 cases of hepatic PEComa, composed solely of PECs, that were reported in the relevant English language literature (Table 1).[6,10,12-19] In 12 cases, including the present case, the clinicopathologic and microscopic findings were similar to the findings of PEComas in other sites.[2-6,10,12-19] These 12 cases arose in 10 women and 2 men, with a mean patient age of 47 years (range, 25 to 70 years). In 7 cases, no association with the tuberous sclerosis complex was found. The remaining 5 cases had no self-reported history of tuberous sclerosis complex involvement. All cases were positive for melanocytic (HMB-45 and/or Melan-A) and myogenic markers, except for one case that was positive only for melanocytic markers.[6,10,12-19]

Table 1. Summary of 12 cases of PEComa in the liver

Reference	Diagnosis	Age (yr)	Sex	Size (cm)	Follow up (mo)	Event
Yamasaki *et al.*[12]	MEAML	30	F	3.2×3.0	12	No
Dalle *et al.*[13]	Malignant AML	70	F	26.0	7	Recurrence and metastasis (omentum)
Parfitt *et al.*[14]	PEComa	60	F	14.0×11.0	108	Multiple metastasis (trapezius muscle, lung, pancreas, and bladder wall)
Larbcharoensub *et al.*[15]	CCMMT	31	F	1.8×1.6×1.5	6	No
Fang *et al.*[6]	PEComa	56	F	5.1×4.2	24	No
		63	F	-	12	No
Paiva *et al.*[16]	PEComa	51	F	0.8×0.6	-	-
Zimmermann *et al.*[10]	PEComa	53	M	8.0	17	No
Akitake *et al.*[17]	PEComa	36	F	3.5	18	No
Strzelczyk *et al.*[18]	PEComa	57	F	17.0	53	No
Wen *et al.*[19]	MEAML	25	M	5.5×4.0×4.0	-	-
Present case	MEAML	36	F	6.5×5.2×4.5	3	No

PEComa, perivascular epithelioid cell tumor; MEAML, monotypic epithelioid angiomyolipoma; F, female; AML, angiomyolipoma; CCMMT, clear cell myomelanocytic tumor; M, male.

Clear criteria for malignancy have yet to be established for PEComa. Folpe *et al.*[5] proposed unique criteria for malignant PEComas, and it appears that Folpe's criteria are the best approach at this time, even though they have yet to be completed.[7] The features suggestive of malignancy were tumor size more than 5 cm, infiltration into surrounding normal tissue, high nuclear grade and cellularity, mitotic index of more than 1 per 50 high-power fields, necrosis, and vascular invasion. Tumors with two or more of these features were classified as malignant. Tumors with nuclear pleomorphism or multinucleated giant cells only or size more than 5 cm only were considered as neoplasms of uncertain malignant potential.[5] Only two cases of malignant PEComa with metastasis were reported in liver.[13,14] One case fulfilled criteria for malignancy, with large size, necrosis and venous invasion.[13] However, the other case showed multiple metastases after 9 years, even though microscopic findings were consistent with a benign status except for size more than 5 cm.[14] Four of 11 published cases were thought to have uncertain or more malignant potential according to Folpe's criteria, but did not exhibit recurrence or metastasis.[10,12,18,19] This might be attributable to the fact that the follow-up durations in these cases were relatively short. The prognosis of PEComa remains unpredictable, and long-term follow-up appears to be necessary in every case of hepatic PEComa.[14,18] In our specific case, the patient exhibited two features that favored malignancy: tumor size and an infiltrative growth pattern.

The histogenesis of PEComa remains a matter of some controversy. Some have suggested the possibility of myoblastic origin with acquired melanogenesis, pericytic origin, or undifferentiated neural crest cell origin with the ability to differentiate into myocytes and melanocytes.[7] However, more studies will be required to determine accurately the origin of PEComas.

In summary, we present herein a case of PEComa in the liver. This case is, to the best of our knowledge, the first report of hepatic PEComa in Korea. Hepatic PEComa is similar to PEComa arising from other sites in terms of the salient clinical, histologic, and immunohistochemical findings. Since the behavior of hepatic PEComa is unpredictable and some cases of late metastasis have been reported, long-term follow-up durations are recommended in cases of hepatic PEComa.

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