We herein report on a challenging and unprecedented occurrence of malignant perivascular epithelioid cell neoplasm (PEComa) of the thoracic parietal pleura, featuring a mass-forming protrusion into the serous cavity as documented by means of chest imaging and biopsy samples by means of immunohistochemistry and fluorescence in situ hybridization analysis. PEComas make up a heterogeneous family of ubiquitous mesenchymal neoplasms ranging from indolent to highly malignant lesions, which variably feature spindle, epithelioid, or other mesenchymal cell appearance.1-3 The hallmark of all PEComas is the hybrid expression of myo-melanocytic markers,1-3 with the most consistent and sensitive one being the human melanoma black-45 (HMB-45) antibody4 that identifies the premelanosome-associated glycoprotein Pmel17/gp100.5 In the thorax, PEComa has been described in the lung and mediastinum as lymphangioleiomyomatosis, clear cell tumor, diffuse PEComatosis, malignant PEComa, or angiomyolipoma3,6-10; but localization in the thoracic parietal pleura of a malignant epithelioid PEComa forming a dominant mass inside the serous cavity has not been documented. Firm minimal criteria for malignancy have not been formally settled for PEComas, but necrosis, mitotic activity, marked nuclear atypia, pleomorphism, epithelioid appearance, and invasive pattern of growth have been equated to fully fledged sarcomas with aggressive clinical behavior.1,2 Most thoracic PEComas are sporadic, but some tuberous sclerosis complex (TSC)-associated instances are also on record,11 with transcription factor binding to IGHM enhancer 3 (TFE3) gene rearrangements and TSC complex subunit 1 (TSC1) and subunit 2 (TSC2) gene mutations being the most frequent and mutually exclusive molecular alterations.2,3

A 76-year-old Caucasian male, nonsmoker, suffering from arterial hypertension, chronic ischemic cardiomyopathy with stenting, and permanent atrial fibrillation was admitted to a hospital for progressive asthenia of a few months' duration. The patient had been a truck driver and had asbestos exposure, bilateral pleural fibrous plaques, and a clinical history of cholecystectomy and left inguinal herniectomy. Chest X-ray and computed tomography scan examination performed at the beginning of July 2018 showed a 12.6-cm tumor extensively involving the costal parietal pleura with a mass-forming protrusion into the serous cavity and homolateral pleural effusion but no mediastinal lymph node involvement (Fig. 1A and B). An fluorodeoxyglucose positron emission tomography-computed tomography scan showed intense metabolic uptake in the thoracic wall lesion but no distant lesions (Fig. 1C). Small-sized core biopsy featured a spindle cell tumor with five mitoses per 2 mm², collagenous stroma, and hemangiopericytoma-like branching vascular pattern along with CD99 decoration, which was interpreted as malignant solitary fibrous tumor (SFT) in July 2018 (Fig. 2A and inset). HMB-45 immunostaining was negative, and so were smooth muscle actin, desmin, S100 protein, CD117,
epithelial membrane antigen, CD31, CD34, ERG (ETS-related gene family transcription factor), WT1 (Wilms tumor 1 protein), and calretinin. Fluorescence in situ hybridization analysis for SYT/SS18 (synovial sarcoma) translocation and MDM2 (mouse double minute 2 homolog) amplification (dedifferentiated liposarcoma) was unremarkable, whereas a homozygous deletion of CDKN2A (p16) gene was found in 83% tumor cells, which also missed p16 labeling (Fig. 2B). Because resection attempt failed because of either life-threatening blood loss during operation or local infiltration requiring thoracectomy and right pneumonectomy, a 2.7-cm open biopsy was performed to confirm diagnosis at the beginning of October 2018. Histologic examination showed spindle to epithelioid mesenchymal tumor cells organized in fascicles and nests (Fig. 2C) that featured abundant eosinophilic and granular cytoplasm, round nuclei, prominent nucleoli, thin-walled vascular channels, some place with a hemangiopericytoma-like pattern (Fig. 2C and D), and nine mitoses per 2 mm², even atypical (Fig. 2E). Reactivity for HMB-45 and microphthalmia-associated transcription factor was focal (Fig. 2F and inset), and positivity was observed for smooth muscle actin (Fig. 2G) and calponin (Fig. 2H) in HMB-45-negative tumor areas. Cytoplasmic granularity of tumor cells was ascribable to abundant mitochondria content (Fig. 2I), which differed from the diffuse filamentous decoration for vimentin (Fig. 2I and inset). Staining for CD99 was observed in many tumor cells (Fig. 2J), whereas TFE3 was focal (Fig. 2K) in keeping with the absence of TFE3 translocation (Fig. 2L). These findings were consistent with the diagnosis of malignant primary epithelioid PEComa of the thoracic parietal pleura. The patient underwent first course chemotherapy with gemcitabine, but his clinical conditions rapidly worsened because of sudden glycemic decompensation and worsening asthenia. He died of progressive disease 6 months later in January 2019.

Differential diagnosis of pleural PEComa included metastatic carcinoma, malignant epithelioid to sarcomatous mesothelioma, SFT, synovial sarcoma, malignant hemangioendothelioma, epithelioid variants of diverse sarcomas, and metastatic melanoma owing to its bewildering capability of simulating diverse tumor types. Once malignant mesothelioma was excluded (past exposure to asbestos), malignant SFT diagnosis

Figure 1. Chest X-ray (A) and computed tomography scan (B) examinations revealed a large neoplastic mass of solid type in the right costal pleura, with huge protrusion into serous cavity. Double imaging through 18F-fluorodeoxyglucose positron emission tomography-computed tomography showed an intense uptake of tracer being limited to the thoracic wall (C), thus supporting a primary tumor (C, inset).
was considered because of clinical presentation, collagenous background (about 15% of PEComas belong to the sclerosing variant), and prominent hemangiopericytoma-like vascular pattern. However, reappraisal of the previous core biopsy by means of signal transducer and activator of transcription 6 immunostaining, a highly sensitive and specific marker for SFT that was not available in our laboratory at that time, turned out to be unreactive. Coexistence of HMB-45 and smooth muscle markers is the main diagnostic clue to PEComa, even though their erratic distribution could result in challenges on small-sized biopsies. Original and previously unreported findings of PEComas we herein document include the richness in mitochondria and \textit{CDKN2A} homozygous deletion. The former could account for either granular cytoplasm

\textbf{Figure 2.} In core biopsy, a spindle cell tumor with hemangiopericytoma-like branching vascular pattern (A) and collagenous background (A, inset) was observed, along with \textit{CDKN2A} (p16) deletion on FISH as highlighted by missing red signals (B). In open biopsy, spindle and epithelioid tumor cells were intermingled with each other alongside focal hemangiopericytoma-like vascular pattern (C, white asterisk). Epithelioid tumor cells presented with abundant granular cytoplasm, roundish nuclei, prominent nucleoli, thin-walled vascular channels (D, white arrows), and mitotic figures, even atypical (E, white dashed circle). The hallmark of perivascular epithelioid cell neoplasm was human melanoma black-45 immunoreactivity (F), which paralleled microphthalmia-associated transcription factor nuclear labeling (F, inset). Muscular cell markers were represented by smooth muscle actin (G) and calponin (H) in tumor areas missing human melanoma black-45 immunoreactivity. Cytoplasmic granularity was due to plentiful mitochondria (I), whereas vimentin decoration was intense and diffuse (I, inset). CD99 was not negligible in tumor cells (J). IGHM enhancer 3 was observed in a fraction of tumor cells (K), which was in keeping with the absence of IGHM enhancer 3 translocation on dual-color, break-apart fluorescence in situ hybridization showing only fusion yellow signals (L).
of epithelioid cells or huge $^{18}$F-fluorodeoxyglucose uptake of positron emission tomography imaging $^{14}$; the latter could be considered a new malignancy criterion in keeping with its frequent occurrence in many aggressive somatic cancer tissues. $^{15}$

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**References**


