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CORRESPONDENCE

Metastatic PEComa to the brain

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Neoplasms of perivascular epithelioid cells (PEComas) have in common the co-expression of melanocytic and muscle immunohistochemical markers. While most reported PEComas have behaved in a benign fashion, malignant PEComas have occasionally been documented [3–5]. We present a case of malignant PEComa, which was first diagnosed as a brain metastasis; this represents the first documentation of brain involvement by PEComa.

A 53-year-old woman presented with malaise. Computerized tomography (CT) of the chest and abdomen revealed multiple lung lesions bilaterally, as well as a solitary mass in the left adrenal gland. The largest lung lesion was located in the right upper lobe and measured 5.4 × 3.5 × 3.4 cm, while the adrenal mass measured 4.8 × 3.2 × 2.9 cm. Fine needle aspiration of one of the lung lesions was interpreted as indeterminate for malignancy. The liver, pancreas, spleen and kidneys were normal by abdominal imaging.

Several months later, she presented with headache, nausea and vomiting. She had difficulty with naming. A CT scan of her head revealed a mass in the left posterior temporal lobe, which was mostly solid with cystic components (Fig. 1). The patient underwent a temporal craniotomy and resection of the brain tumor. Postoperatively, neuroimaging showed no evidence of residual tumor. The patient's headache improved and she was discharged home.

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Pathologic examination of resected tumor tissue showed cells arranged in sheets and nests, invested with a prominent capillary vasculature (Fig. 2a). The interface between tumor and uninvolved brain was sharp and several foci of necrosis were present. The neoplastic cells were epithelioid, with abundant cytoplasm that varied from eosinophilic and granular to clear (Fig. 2b). The nuclei were round with moderate pleomorphism and they often contained conspicuous nucleoli; mitoses were rare. Periodic acid–Schiff (PAS) staining, with and without diastase digestion, demonstrated intracytoplasmic glycogen (Fig. 2c). The biopsied lung lesion was morphologically similar to the brain tumor, although there was greater nuclear pleomorphism and more prominent nucleoli in the latter.

Immunohistochemistry showed strong positivity within tumor cells for HMB45, Melan-A and caldesmon, while desmin was focally positive (Fig. 3a, b). The neoplastic cells failed to stain with antibodies against S100, tyrosinase, epithelial membrane antigen (EMA), vimentin, cytokeratin (AE1/AE3, 8/18, 7/20, 34BE12), inhibin, actin (smooth muscle and muscle specific), smooth muscle myosin, neuron specific enolase (NSE), synaptophysin, chromogranin, neurofilament, glial fibrillary acidic protein (GFAP), CD10, CD99, CD117, CD34, carcinoma embryonic antigen (mono and polyclonal), calretinin, heppar1 and placental alkaline phosphatase. Ultrastructural examination of glutaraldehyde-fixed tissue revealed intracytoplasmic glycogen and lipid. Premelanosomes and desmosomes were absent.

The WHO has recently offered formal recognition to a group of neoplasms with perivascular epithelioid cell differentiation. This group of tumors have in common the presence of epithelioid to spindle cells with

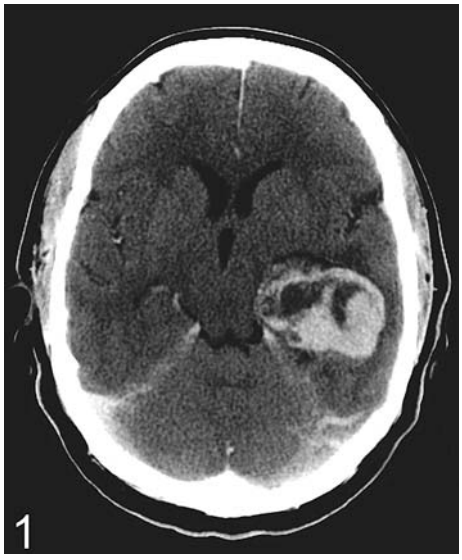

Fig. 1 A CT scan showed a variably solid and cystic mass in the left posterior temporal lobe

eosinophilic to clear cytoplasm that demonstrate positive immunostaining for markers of both melanocytic (HMB45, Melan-A, tyrosinase, microphthalmia transcription factor) and myoid (smooth muscle actin, desmin, caldesmon, calponin) differentiation. Tumors within this family have been documented at an increasing number of anatomical sites and the term "PEComa" has become the umbrella term for these lesions [4].

Folpe et al. [4] recently reviewed all reported cases of PEComa up to 2005 (61 cases). In their review, 100% were HMB45 positive, 41% were Melan-A positive, 59% were smooth muscle actin positive, 11% were S100 positive, 31% were desmin positive, 0% were cytokeratin positive and 33% were CD117 positive. The present case illustrates the usefulness of caldesmon immunohistochemistry for identifying smooth muscle differentiation in cases that are immunonegative for smooth muscle actin. Fukunaga [5] also reported a case of uterine PEComa that expressed

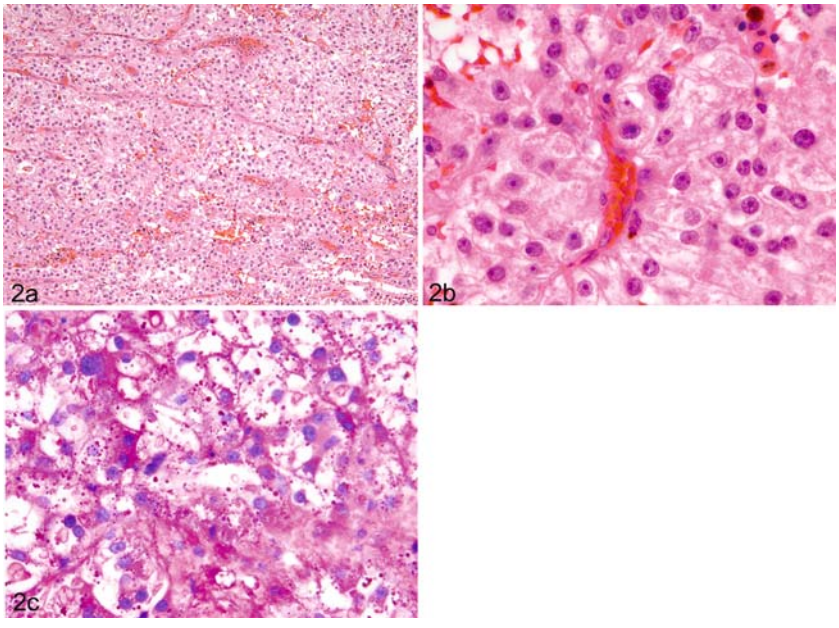

Fig. 2 **a** Neoplastic cells were arranged in nests, with a rich capillary vasculature (HE ×100). **b**, **c** Tumor cells were epithelioid with eosinophilic, granular cytoplasm (**b** HE ×600), containing glycogen (**c** PAS ×400)

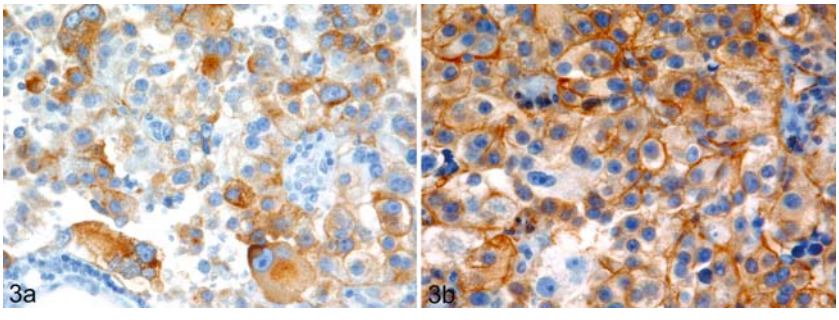

Fig. 3 **a**, **b** Tumor cells were positive for Melan-A (**a** Melan-A ×400) and caldesmon (**b** caldesmon ×400)

HMB45 and caldesmon, but failed to express smooth muscle actin. Caldesmon is a cytoskeleton-associated protein present in smooth muscle cells, functioning by binding calmodulin and calcium, and is involved in regulating cellular contraction [2]. Other studies have confirmed caldesmon as a highly sensitive and specific marker for smooth muscle differentiation [2].

In the present case, it is difficult to be absolutely certain about the site of the primary tumor. While the clinical impression was of a primary lung tumor with metastases to the contralateral lung, adrenal gland and brain, the largest lung tumor and adrenal tumor were of similar size and both were discovered coincidentally on imaging. Further, as genetic analysis to demonstrate shared chromosomal aberrations between each of these foci of PEComa was not performed, the possibility of multiple primaries cannot be absolutely ruled out.

The main differential diagnosis included metastatic melanoma and carcinoma (especially from kidney or adrenal gland). The presence of intracytoplasmic glycogen and caldesmon expression, coupled with the lack of immunoexpression for S100 protein argues against the diagnosis of melanoma. The presence of HMB45 expression, coupled with the lack of immunoreactivity for cytokeratin and vimentin argues against the diagnosis of either renal cell or adrenocortical carcinoma. Primary brain tumors that could show similar morphology include anaplastic oligodendroglioma, clear cell ependymoma, clear cell meningioma and hemangioblastoma. However, none of these tumors would be expected to express melanocytic or muscle markers, the lack of GFAP expression helps to rule out gliomas and the lack of immunostaining for EMA and NSE helps to exclude meningioma and hemangioblastoma, respectively.

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