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Perivascular Epithelioid Tumor (Pecoma) of the Falciform / Broad Ligament

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PEComas localized in the region of falciform ligament and broad ligament are exceedingly rare. Most of them are built of spindle neoplastic cells. We report a case of epithelioid PEComa of the falciform ligament and/or broad ligament. There is only one report of such neoplasm in English-language literature. Histologically, the tumor was composed of nests of epithelioid clear cells stained positively for vimentin, HMB45, and SMA. Because of morphological features of the tumour (4 mitoses /20HPF, focal necrosis, and vascular invasion) we assess the neoplasm as potentially malignant.

Introduction

PEComas represent a family of myomelanocytic tumors, the best known members of which are angiomyolipoma (AML), clear cell tumor of the lung (CCST), and lymphangioleiomyomatosis (LAM). PEComas other than AML, CCST or LAM are exceedingly rare [5]. Among them is the clear cell myomelanocytic tumor of the falciform ligament (CCMMT), which differs somewhat from other PEComas in that it is almost exlusively a spindle cell lesion [4]. We report herein a case of epithelioid PEComa of the falciform / broad ligament. To our knowledge, there is only one report of such neoplasm in English-language literature [7].

Material and Methods

Clinical data

The patient was a 23-year-old previously healthy woman. She was operated on because of uterine bleeding. During laparotomy a huge tumor localized in the immediate vicinity of right ovary was found. Additionally, the satellite focus of neoplastic tissue was noticed in the uterosacral ligament. Total abdominal hysterectomy and ambilateral salpingo-oophorectomy were carried out with adjuvant radiotherapy. 11 months later a usg study revealed a multiple implants of the tumour in the pelvis. The recurrence was confirmed by fine needle aspiration.

Methods

Immunohistochemical studies were performed on the formalin-fixed, paraffin-embedded tissue sections using a panel of the following antibodies against: vimentin (V9, 1:200, Biogenex), gp100 protein (HMB45, 1:60, Novocastra), melan A (A103, 1:25, Novocastra), S100 protein (polyclonal, 1:200, Novocastra), α-smooth muscle antigen (αSM-1, 1:50, Novocastra), desmin (DER-11, 1:100, Novocastra), pancytokeratins (AE1/AE3, 1:20, Novocastra), EMA (GP 1.4, 1:200, Novocastra), inhibin (R1, 1:200, DAKO), calretinin (SP13, 1:100, LabVision), PLAP (8A9, 1:40, Novocastra), AFP (C3, 1:50, Novocastra), CD10 (56C6, prediluted, LabVision), CD34 (QBEnd, 1:400, LabVision), and Ki67 antigen (MiB1, 1:100, Dako). The Vysis EWSR1 translocation break apart probe pair (Abbott-Vysis- LSI EWSR1 Dual Color Breakapart Probe No 32-190059) was used for the detection of breaking in the *EWSR1* (22q12) gene according to the manufacturer's instructions.

Results

Macroscopically, a tumor measuring 14 x 9 x 8 cm was loosely connected with the right ovary and localized in the region of falciform and broad ligament. On cross-

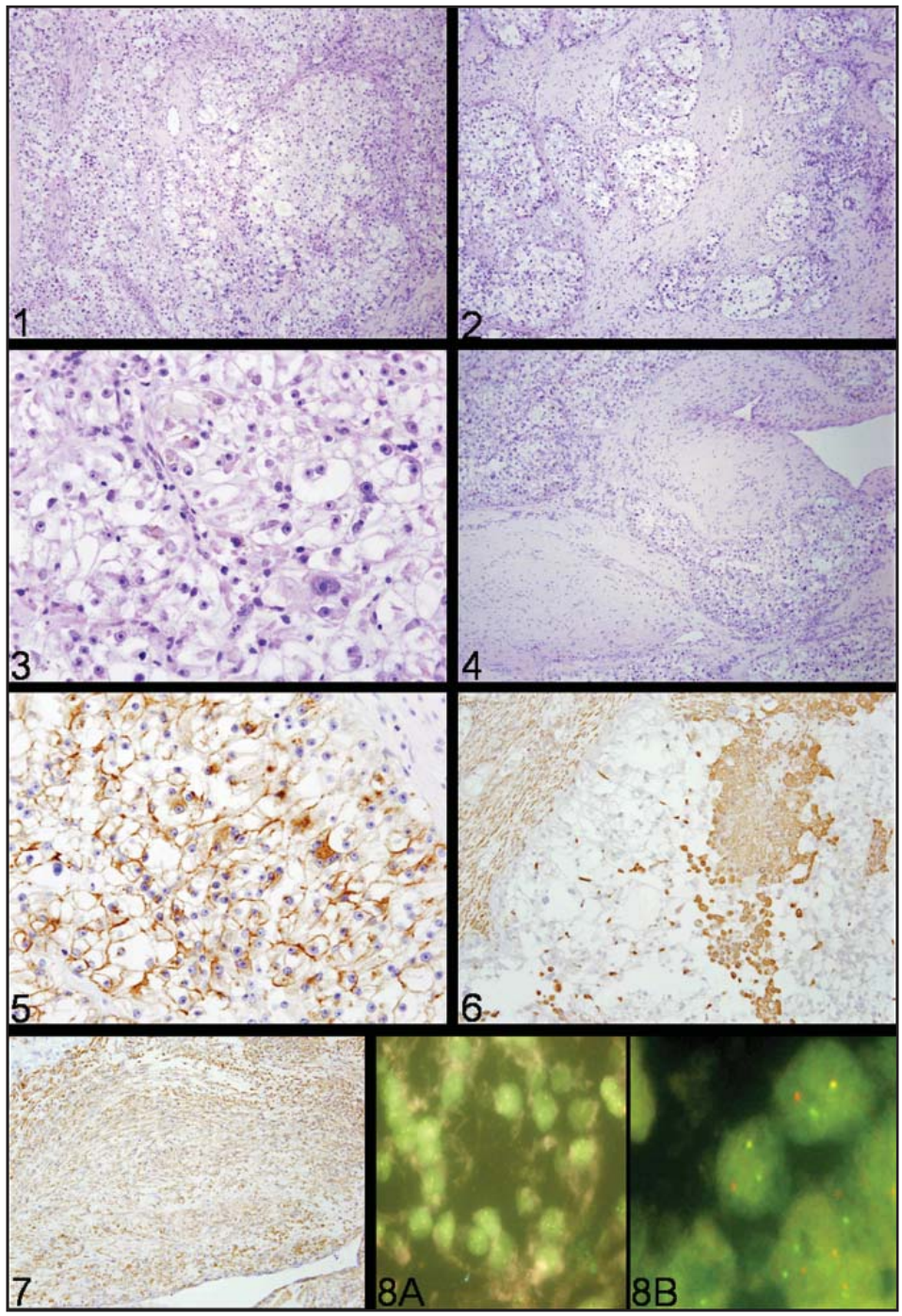

Fig. 1-2. Low power view of the tumor: the sheets and nests of epithelioid cells separated by reticular fibers and fibrous septa with prominent, both capillary-type and thick-walled blood vessels. Magn. 10x
Fig. 3. High power view of the tumor: the neoplastic cells are characterized by a moderate amounts of eosinophilic and clear cytoplasm, centrally located vesicular nuclei and prominent nucleoli. The cytoplasm of the several cells contained a melanin pigment. Magn. 40x
Fig. 4. The vessels' musculature passed directly into spindle cell fascicles forming a whirled texture. Magn. 10x
Fig. 5. Diffuse positive reaction with antibody against gp100 protein (HMB45) in the epithelioid neoplastic cells. Magn. 40x
Fig. 6. Both epithelioid neoplastic cells and stromal component of the tumor showing strong expression of vimentin. Magn. 20x
Fig. 7. Spindle cell fascicles were dyed with smooth muscle actin. Magn. 20x
Fig. 8. *EWSR1* gene break apart probe FISH images of PEComa studied (**A**) and a known case of clear cell sarcoma (**B)** as a positive control; the neoplastic cells of clear cell sarcoma present the one fusion, one orange and one green signal pattern indicative of rearrangement of one copy of the *EWSR1* gene.

sections the ovary was unchanged. The cut surface of the tumor was solid, partly reddish-tan and partly white-gray.

Histological analysis revealed the tumor composed of sheets and nests of epithelioid cells separated by reticular fibers and fibrous septa with prominent, both capillary-type and thick-walled, blood vessels (Fig. 1, 2). The neoplastic cells had moderate amounts of eosinophilic and clear cytoplasm, centrally located vesicular nuclei and prominent nucleoli. The cytoplasm of the several cells contained a melanin pigment (Fig. 3). Mitoses were frequent (4 figures /20 HPF). Focal areas of coagulation necrosis and angiolymphatic invasion were also visible. A striking feature of the tumor was the elaborate vasculature. Large vessels as well as small arching vessels subdivided the lesions into coarse packets. The vessels' musculature passed directly into spindle cell fascicles forming a whirled texture (Fig. 4).

Immunohistochemically, the epithelioid neoplastic cells are characterized by diffuse positive reaction with antibodies against HMB45 (Fig. 5) and vimentin (Fig. 6), whereas spindle cell fascicles were dyed with vimentin and smooth muscle actin (Fig. 7). The reactions against S100 protein, melan A, desmin, cytokeratins, EMA, inhibin, calretinin, PLAP, AFP, CD10 and CD34 gave negative results. Approximately 25% of neoplastic cells dyed positively with MiB-1 antibody.

The molecular search for the breaking of *EWSR1* (22q12) gene using dual color break apart probe gave a negative result. The simultaneous analysis of breaking in clear cell sarcoma presented the typical picture; the neoplastic cells showed the one fusion, one orange and one green signal pattern indicative of rearrangement of one copy of the *EWSR1* (22q12) gene (Fig. 8).

Discussion

The family of tumors built of "perivascular epithelioid cells" (PEComas) includes mainly renal angiomyolipoma (AML), clear cell tumor of the lung (CCST), and lymphangioleiomyomatosis (LAM) [4]. PEComas, other than AML, CCST, and LAM, appear to arise most commonly in the uterus [6] and gastrointestinal tract [1, 11]. They have also been described in pancreas [12], retroperitoneum [8], abdominal cavity and pelvis [2], skin [9] and somatic soft tissues [6]. Additionally, Folpe et al. [4] described a peculiar variant of PEComa which was built almost exclusively of uniform, moderate-sized spindle cells, with clear to faintly eosinophilic cytoplasm arranged in fascicles, nests, or even a storiform pattern. The authors named this unique tumor as clear cell myomelanocytic tumour of the falciform ligament (CCMMT). According to Folpe et al. CCMMTs usually occur in young girls, with a mean age at diagnosis of 11 years and are localized in falciform ligament and omentum [4].

The neoplasm described by us was also located in the falciform ligament area and it also concerned a young girl. But the histological texture of presented tumor was predominantly epithelioid. The tumor closely resembled the case of PEComa deriving from uterine broad ligament and described by Kim et al. [7] (Table 1) as well as PEComa of falciform ligament of the liver described by Tanaka [10].

Up till now, there have been ten well documented cases of PEComas or CCMMTs originating from and localized in the region of uterine falciform and broad ligaments (Table 1). Most of them were built of spindle cells (cases no 1-6 and 8-9), whereas only one (case no 10) presented the pure epithelioid pattern. Additionally, the case no 7 presented mixed, epithelioid and spindle cell texture [3]. All of these cases gave positive reaction with antibody to HMB45 and nearly all were negative for S100 protein. The reactions against smooth muscle actin and melan A gave positive results in 5/5 and 4/4 cases studied, respectively. Almost all (3/4) PEComas did not express desmin filaments (Table 2).

The results of the immunohistochemical studies fascilate the differential diagnosis of PEComas and CCMMTs which mainly includes metastatic melanoma, clear cell sarcoma, and metastatic renal cell carcinoma. These distinctions are arguably important because both PEComas and CCMMTs are less aggressive neoplasms than clear cell sarcoma, melanoma and metastatic renal cell carcinoma. Contrary to renal cell carcinoma, neither PEComas nor CCMMTs present the epithelial markers (cytokeratins or EMA) and CD10 antigen. The distinguishing between PEComas/CCMMTs and metastatic melanoma or clear cell sarcoma is much more difficult because all of these tumors present melanocytic markers. However, PEComa /CCMMT cells do not give positive reaction to S100 protein (typically expressed in melanoma), whereas clear cell sarcomas express both S100 protein and the melanocytic markers but do not express SMA. In difficult cases, the diagnosis of clear cell sarcoma can be excluded by cytogenetic or molecular genetic demonstration of the diagnostic translocation between chromosomes 12 and 22 [4]. Because we have at our disposal the paraffin material only, we could analyse the breaking in the *EWSR1* (22q12) gene using FISH method. This study gave a negative result. In our opinion this is an additional proof that our diagnosis was correct. Till now, no PEComa/CCMMT case presented the translocation t(12;22). One case of CCMMT studied cytogenetically disclosed a translocation t(3,10) [5].

TABLE 1
Clinicomorphological characteristics of PEComas of uterine falciform and broad ligament

No	sex	age	localization	size (cm)	histology	cell compo-nent	tumor border	mitotic activity	necrosis	follow-up	out -come	Author / year
1	M	29	falciform lig. / lig. teres	20	CCMMT	spindle	microscopically infiltrative *	< 1/20	(-)	12	DMI	Folpe (2000)
2	F	11	falciform lig. / lig. teres	9	CCMMT	spindle	microscopically infiltrative *	< 1/20	(-)	60	alive, NED	Folpe (2000)
3	F	21	falciform lig. / lig. teres	8.5	CCMMT	spindle	microscopically infiltrative *	< 1/20	(-)	24	alive, NED	Folpe (2000)
4	F	10	falciform lig. / lig. teres	5	CCMMT	spindle	microscopically infiltrative *	< 1/20	(-)		NED	Folpe (2000)
5	F	6	falciform lig. / lig. teres	5	CCMMT	spindle	microscopically infiltrative *	< 1/20	(-)	24	alive, NED	Folpe (2000)
6	F	3	falciform lig. / lig. teres	5.5	CCMMT	spindle	microscopically infiltrative *	< 1/20	(-)	10	alive, NED	Folpe (2000)
7	F	51	broad lig.	17	malignant PEComa	spindle + epithelioid	infiltrative	5/50	(+)	8	alive, NED	Fink (2004)
8	F	15	falciform lig. / lig. teres	4.5	spindled PEComa	spindle	no data	n/a	(+)	15	alive, NED	Folpe (2005)
9	F	16	broad lig.	4	spindled PEComa	spindle + giant cells	no data	0/50	(-)	35	alive, NED	Folpe (2005)
10	F	12	broad lig.	9	malignant CCMMT	epithelioid	circumscribed	4/10	(+)	18	alive, NED	Kim (2006)
11	F	23	falciform lig. / lig. teres	14	malignant PEComa	epithelioid	circumscribed	4/20	(+)	7	alive, NED	Rys (2008)

Legend
falciform lig./ lig. teres – falciform ligament/ligamentum teres, broad lig. – broad ligament, * macroscopically well demarcated microscopically infiltrative, follow-up – counting in months, NED – no evidence of disease, DMI – death because of myocardial infarction, n/a data not available

TABLE 2
Immunohistochemical characteristics of PEComas of uterine falciform and broad ligament

No	sex	age	cell component	HMB45	melan A	S100	SMA	desmin	Author (year)	citation no
1	M	29	spindle	(+)		(-)			Folpe (2000)	4
2	F	11	spindle	(+)		(-)			Folpe (2000)	4
3	F	21	spindle	(+)		(-)			Folpe (2000)	4
4	F	10	spindle	(+)		(-)			Folpe (2000)	4
5	F	6	spindle	(+)		(-)			Folpe (2000)	4
6	F	3	spindle	(+)		(-)			Folpe (2000)	4
				6 / 6	3 / 3	0 / 6	3 / 3	0 / 3	Folpe (2000)	4
7	F	51	spindle + epithelioid	(+)	(+)	(+)	(+)	(+)	Fink (2004)	3
8	F	15	spindle						Folpe (2005)	6
9	F	16	spindle + giant cells						Folpe (2005)	6
10	F	12	epithelioid	(+)		(-)	(+)		Kim (2006)	7
11	F	23	epithelioid	(+)	(-)	(-)	(+)	(-)	Rys (2008)	
				9 / 9	4 / 5	1 / 9	6 / 6	1 / 6		

Clear criteria for malignancy in PEComas have not been elaborated, owing to their rarity. However, most CCMMT cases to date appeared relatively benign [4]. Contrary, some PEComas built of epithelioid cells may exhibit aggressive behavior.

On the basis of selected prior reports, it appears that PEComas displaying any combination of infiltrative growth, high nuclear grade, high mitotic activity≥ 1/50 HPF, atypical mitotic figures, coagulative necrosis and vascular invasion should be regarded as malignant [5, 6]. Up till now no patient with PEComa of falciform and broad ligament region died even their neoplasms characterized by infiltrative growth (Table 1, case no 7) or presented bizarre (cases no 7 and 9) and mitotically active cells (case no 10) and foci of necrosis (case no 7, 8 and 10) [3, 6, 7]. However, except one case (case no 2) [4], the follow-up period of described patients was very short and ranged from 8 to 35 months. The tumor described by us was characterized by high mitotic activity, foci of coagulative necrosis, as well as lymphatic emboli. Because of these morphological features and the presence of satellite focus in the uterosacral ligament we estimate the neoplasm as potentially malignant. However, the real value of the morphological features of the tumor as well as clinical stage of disease in the estimation of the patient's risk of local recurrence or dissemination is still an open question and needs more multi-center studies, which will be able to collect the significant number of patients with PEComas.

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