Sclerosing variant of PEComa: report of a case and review of the literature

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Summary. Tumours of perivascular epithelioid cells (PEComas) are a heterogeneous group of uncommon mesenchymal neoplasms which exhibit a peculiar immunohistochemical co-expression of muscle and melanocytic markers. PEComas occur at various visceral and soft tissue sites, generally with a benign clinical course. Nevertheless, there has been evidence of cases having an unfavourable outcome, thus prompting investigation of pathological criteria for malignancy.

A sclerosing variant of PEComa, more frequently encountered in the retroperitoneum of middle-aged women, has been reported. Prognosis has generally been regarded as favourable and complete surgical excision appears to be adequate treatment. To the best of our knowledge, only two cases of sclerosing PEComa displayed high-grade malignant morphology and were associated with adverse outcome.

An additional case of retroperitoneal sclerosing PEComa with a two-year follow-up and indolent behaviour is herein described. Light and electron microscopy were performed, along with immunohisto-chemical analysis.

Further studies are needed to clarify the histogenesis and to predict the biological behaviour of this uncommon entity.

Key words: Sclerosing PEComa, PEComa, Retro-peritoneal tumours

Introduction

In 1992 Bonetti and colleagues proposed the descriptive term "PEComa" for those mesenchymal neoplasms containing a distinctive perivascular epithelioid cell (PEC) component (Bonetti et al., 1992).

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PECs are typically arranged around blood vessel walls and show immunophenotypic features of both smooth muscle and melanocytic differentiation. PECs also show ultrastructural distinctive features including abundant cytoplasmic glycogen, thin filaments with electron dense condensation, poorly formed intercellular junctions, numerous mitochondria and membrane-bound dense granules (Weeks et al., 1991; Bonetti et al., 1993; Folpe et al., 2000; Tanaka et al., 2000; Tazelaar et al., 2001; Martignoni et al., 2008). No known normal cellular counterpart has been demonstrated for the PEC (Bonetti et al., 1992; Hornick and Fletcher, 2008).

According to the current World Health Organization Classification of Soft Tissue Tumours (Folpe, 2002), the PEComa family comprises angiomyolipoma (AML) of the kidney, clear cell "sugar" tumour of the lung (CCST), lymphangioleiomyomatosis (LAM) and other soft tissue and visceral neoplasms mostly developing in the abdominopelvic or retroperitoneal cavities (Folpe, 2002; Hornick and Fletcher, 2008). Despite the large number of anatomic sites within which they may arise ("ubiquitous tumours" Martignoni et al., 2008) PEComas other than AML, CCST or LAM are extraordinarily rare (Folpe, 2002).

PEComas are more commonly found in women than in men, over a wide age range (Folpe, 2002). A subset of PEComas (i.e. AML, LAM, and more rarely, CCST) may be associated with tuberous sclerosis, although all of these tumours can also occur sporadically (Folpe, 2002). Loss of heterozygosity (LOH) of TSC1 or TSC2 genes has been documented in certain PEComas, whether or not associated with tuberous sclerosis (Pan et al., 2006; Martignoni et al., 2008). It is still poorly understood whether cyclin D1 has a role in the genesis of PEComas (Weinreb et al., 2007), although Soucek and colleagues have shown cyclin D1 abnormalities correlated with the loss of the TSC2 gene (Soucek et al., 1997).

Reports of PEComas behaving in a malignant fashion are on the increase, highlihting the importance of early diagnosis and management (Bonetti et al., 2001;

Dimmler et al., 2003; Pan et al., 2003; Fink et al., 2004; Harris et al., 2004; Lehman, 2004; Evert et al., 2005; Folpe et al., 2005; Mai and Belanger, 2006; Parfitt et al., 2006; Huang et al., 2007). An infiltrative pattern of growth, hypercellularity, nuclear pleomorphism/enlargement, hyperchromasia and the presence of clearly sarcomatous areas may indicate an aggressive clinical course (Folpe, 2002). In recent years, Folpe and colleagues have suggested that a diameter greater than 8 cm, mitotic activity of >1/50 High Power Fields (HPF) and necrosis were associated with poor prognosis (Folpe et al., 2005). Furthermore, they have suggested the identification of benign, uncertain malignant potential, and malignant PEComas according to pathological parameters (Folpe et al., 2005).

Hornick and Fletcher have described a peculiar variant of PEComa ("sclerosing PEComa") with predominant sclerotic and hyalinized stroma (Hornick and Fletcher, 2008). Although rarely encountered, the incidence of this variant should not be underestimated, especially when the retroperitoneum is involved and the patient is a middle-aged woman. To the best of our knowledge, only two of the reported cases of sclerosing PEComa showed an aggressive clinical course and both cases were histologically characterized by a high-grade malignant phenotype (Hornick and Fletcher, 2008; Ramaiah et al., 2009).

We herein present an additional case of benign sclerosing PEComa of the retroperitoneum with a review of the related literature.

Materials and methods

A retroperitoneal mass was incidentally diagnosed in a 66-year-old woman. Past medical history was unremarkable and the patient did not present any clinical features of tuberous sclerosis. Radiological investigations disclosed an ill-defined solid mass in the retroperitoneum, contiguous with the right kidney and measuring 8.5 cm in greatest diameter (Fig. 1). Radiological differential diagnosis included renal, adrenal and retroperitoneal tumours. A surgical excision was carried out with complete resection of the tumour. The surgical specimen containing the tumour was fixed in 4% buffered neutral formalin and then sampled and processed for conventional histology. Serial 3- to 4-μm-thick sections were prepared from paraffin-embedded tissue and stained with haematoxylin and eosin.

Immunohistochemical stains were performed on 4-μm thick paraffin-embedded sections using BenchMark® XT automated staining system (Ventana Medical Systems, Tucson, AZ). The following panel of prediluted Ventana antibodies was employed: monoclonal anti-cytokeratin (Pan) (Clone AE1/AE3 & PCK26); monoclonal anti-low molecular weight cytokeratin (Clone CAM5.2); monoclonal anti-EMA (Clone E29); monoclonal anti-melanosome (Clone HMB45); polyclonal anti-S100 protein; monoclonal anti-MART-1/Melan A (Clone A103); monoclonal anti-chromogranin A (Clone LK2H10); monoclonal anti-

CD31 (Clone JC70); monoclonal anti-CD34 (Clone QBEnd/10); polyclonal anti-FVIII; monoclonal anti-CD99 (Clone O13); monoclonal anti-α-smooth muscle actin (Clone 1A4) and monoclonal Ki-67 (Clone 30-9). For antigen retrieval, slides were heated with Cell Conditioning Solution 1 (CC1) followed by peroxidase blocking dispenser included in the same ultraView kit. All primary prediluted antibodies were applied for 32 minutes at 37°C in BenchMark® XT autostainer and the primary antibody-HRP labelled antibody complex was visualized using DAB, resulting in a brown/black target signal. After the staining run was complete, the slides were removed from the autostainer, counterstained with haematoxylin, dehydrated and mounted with permanent mounting medium. Appropriate positive experiments for all antibodies were performed, with negative controls substituting each primary antibody with a Ventana dispenser filled with non-immune serum at the same concentration as the primary antibody. Immunostaining with each antibody in at least 10% of neoplastic cells was defined as a positive reaction.

Transmission electron microscopy was conducted in a routine fashion with retrieval of tissue from the paraffin block. Fragments of tumour tissue were post-fixed in osmium tetroxide, sequentially dehydrated through increasing concentrations of alcohol, and embedded in epoxy resin. Ultra-thin sections of tumour were stained with silver acetate and lead citrate and examined under a 100 kV transmission electron microscope.

Results

At gross examination, the surgical specimen consisted of a well-circumscribed mass, measuring 8.5 cm in size. There was no evidence of vascular invasion,
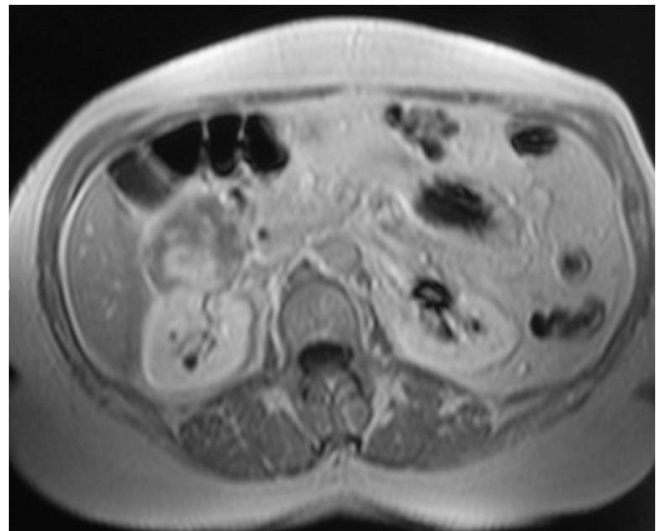

Fig. 1. Radiological image documenting an ill-defined retroperitoneal mass, contiguous to the right kidney and the inferior border of the liver. Focal areas of hypodensity and calcium deposits are also seen.

infiltrating growth into the surrounding soft tissue, abdominal or pelvic lesions or nodal enlargement. The cut surface of the tumour was yellowish to whitish in colour. Histologically, an abundant sclerotic stroma separated small nests and tiny bundles of medium-sized epithelioid cells (Fig. 2A,B). More cellulated areas co-existed with areas of prevalent hyalinized stroma. Neoplastic cells were monomorphous, with a small amount of clear to faintly eosinophilic cytoplasm and nuclear atypia was not detected. At times, the tumour cells had a perivascular arrangement. The tumour did not contain adipose tissue. Neither necrosis nor mitotic figures were seen.

Neoplastic cells exhibited immunoreactivity for HMB-45 and α-smooth-muscle-actin, whereas they did not stain with the other antibodies employed (Fig. 3A,B). The estimated proliferation fraction, based on Ki-67 immunostaining, was less than 1%.

Ultrastructural findings included the presence of cytoplasmic granules of varying electron density, which

Table 1. Clinico-pathological features of previously reported sclerosing PEComas.

	Age/Sex	Site	Size (cm)	Clinical signs/symptoms	TS	Recurrence	Metastasis	Status
1	43/F	R	9	NA	No	NA	NA	NA
1	36/F	AW	8	NA	No	NA	NA	NA
1	46/F	R	4.5	Incidental	No	None	None	ANED, 64 mo
1	50/F	R	11.5	Incidental	No	None	None	ANED, 51 mo
1	51/F	R	22	Back pain	No	None	None	ANED, 22 mo
1	50/F	P	13	Diarrhea, weight loss, abdominal pain	No	None	Lung, liver, abdominal wall, 39 mo	Alive with metastases, 46mo
1	59/F	R	NA	NA	No	None	None	ANED, 39 mo
1	53/F	R	4.5	Incidental	No	NA	NA	Died, UNK, 15 mo
1	34/F	U	10	Uterine rupture	No	None	None	ANED, 33 mo
1	73/F	R	9	Abdominal pain	No	None	None	ANED, 23 mo
1	47/F	R	28	NA	No	None	None	ANED, 10 mo
1	49/F	R	6.1	NA	Yes	NA	NA	NA
1	48/F	R	19	Pressure sensation	No	-	-	Recent case
2	56/F	K	2	Incidental	No	None	None	ANED, 10 mo
2	44/F	R	13	Lower abdominal disconfort	No	NA	NA	NA
3	63/F	UA	15	Incidental	No	None	Lung, liver	Died, 4 mo after surgery
4	66/F	R	8.5	Incidental	No	None	None	ANED, 24 mo

An additional case is herein detailed by the Authors. 1: Hornick and Fletcher, 2008; 2: Matsuyama et al. 2008; 3: Ramaiah et al., 2009; 4: Present case; R: retroperitoneum; AW: abdominal wall; U: uterus; P: pelvis; K: kidney; UA: uterine adnexa; TS: tuberous sclerosis; NA: not available; mo: months; ANED: alive with no evidence of disease; UNK: disease status unknown.
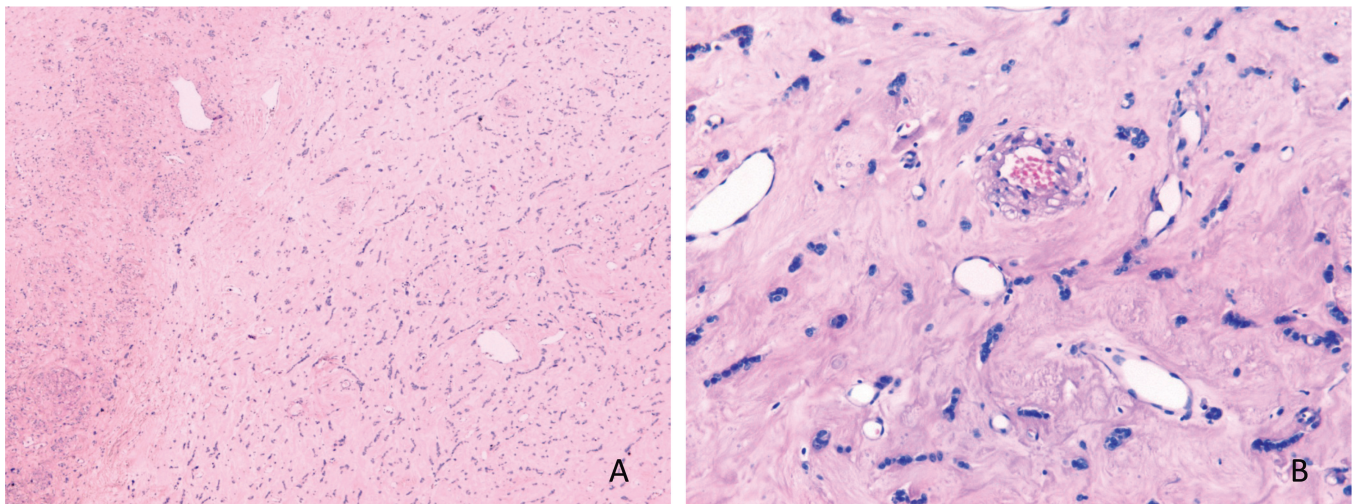

Fig. 2. Histological appearance of a sclerosing PEComa arising in the retroperitoneum of a 66-year-old woman. The tumour consists of a population of relatively monomorphous epithelioid or short spindle cells forming cords and trabeculae surrounded by an abundant hyalinized stroma. H/E. A, x 10; B, x 20

were interpreted as secondary lysosomes, pools of glycogen particles, and bundles of thin filaments at the periphery of the cytoplasm (Fig. 4). Neither melanosomes nor pre-melanosomes were identified.

On the basis of the morphological features and immunohistochemical studies, the diagnosis of PEComa was rendered. Postoperative course was uneventful and 24 months after surgery the patient is well, without evidence of tumour recurrence or distal metastasis.

Discussion

Sclerosing PEComa is a rare histological variant of PEComa recently described by Hornick and Fletcher (Hornick and Fletcher, 2008). In their original paper, out of 70 cases of PEComa observed over a period of 10 years, they identified 13 cases with a markedly sclerotic stroma (Hornick and Fletcher, 2008). To the best of our knowledge, only 3 further cases of sclerosing PEComa were reported after its first description (Table 1) (Hornick and Fletcher, 2008; Matsuyama et al., 2008; Ramaiah et al., 2009).

The patient we observed was a 66-year-old woman, presenting with a retroperitoneal mass, at pararenal site. This seems to be the typical clinical presentation of sclerosing PEComa, as previously reported by Hornick and Fletcher, who found a remarkable predilection for pararenal retroperitoneum of middle-aged women in their series (Hornick and Fletcher, 2008). In a subsequent study, Matsuyama and colleagues reported two other epithelioid angiomyolipomas with significant sclerosis of the stroma occurring in middle-aged women. One of the cases was located in the retroperitoneum, whereas the other was an intracortical, renal lesion (Matsuyama et al., 2008). A sclerosing PEComa arising in the uterine adnexa has recently been described in a 63-year-old woman (Ramaiah et al., 2009).

The retroperitoneal PEComa herein described was found in a patient with no clinical features of tuberous sclerosis. In contrast with AML and LAM, extra-renal PEComas are only rarely associated with tuberous sclerosis. Among the 16 patients with sclerosing PEComa previously reported in the literature, only one had tuberous sclerosis (Hornick and Fletcher, 2008).
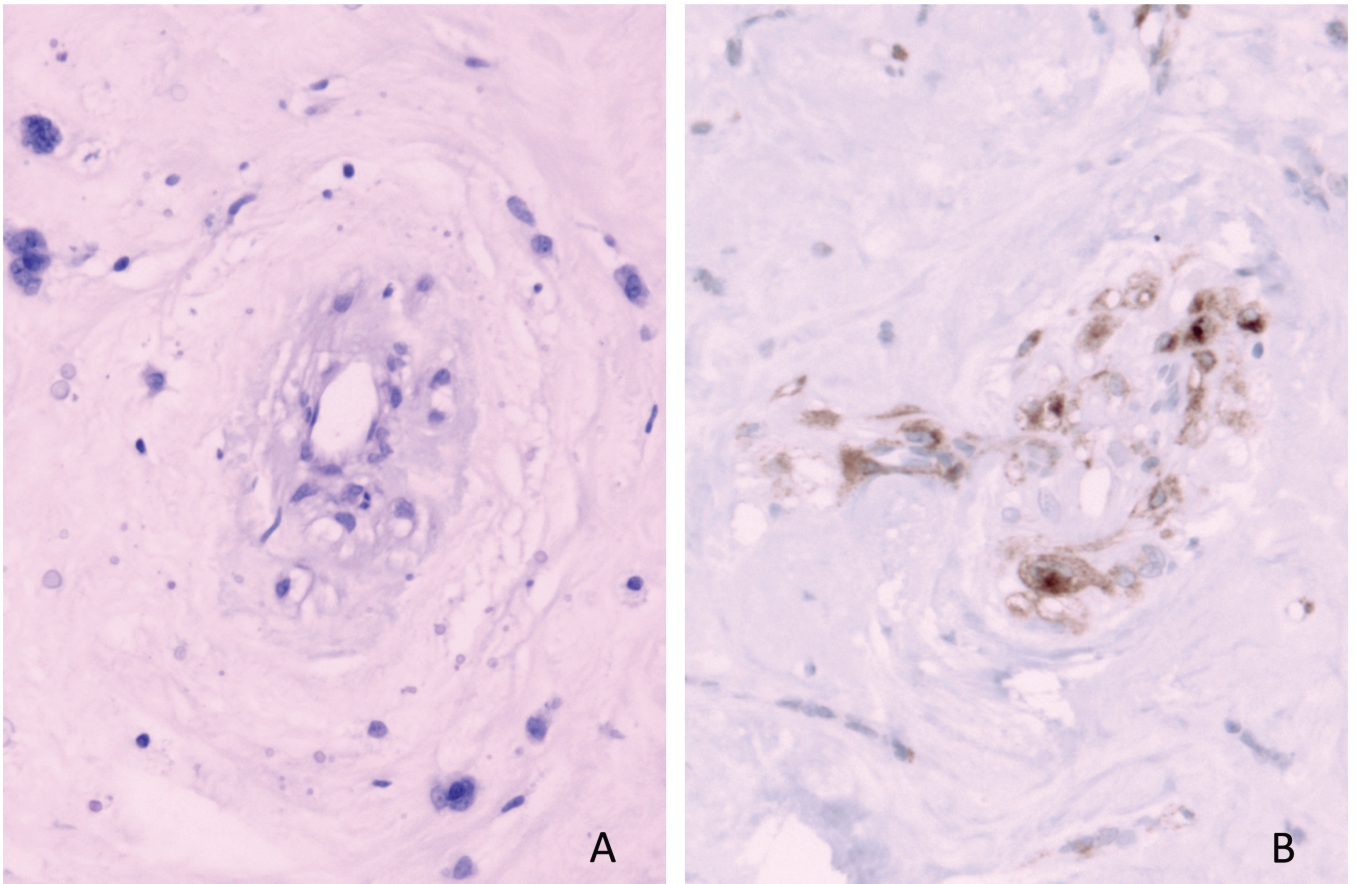

Fig. 3. Neoplastic cells are focally orientated around blood vessel walls (**A**, H/E) and exhibit HMB-45 immunoreactivity (**B**). A, x 40, B, x 20

Histologically, sclerosing PEComa consists of cords and trabeculae of cytologically monomorphous epithelioid cells showing clear to palely eosinophilic cytoplasm and round nuclei with small nucleoli, embedded in an abundant sclerotic stroma. Tumour cells may focally be arranged around blood vessels. Unlike conventional PEComas, the sclerosing variant lacks the typical alveolar or nested architecture and shows a prominent delicate vasculature. Spindle cell and sheet-like areas may also be observed (Folpe, 2002; Hornick and Fletcher, 2008).

None of the tumours in the series observed by Hornick and Fletcher contained a lipomatous component typical of other PEComas (Hornick and Fletcher, 2008), however one of the two neoplasms described by Matsuyama and colleagues displayed small areas of mature fat tissue (Matsuyama et al., 2008). Such a case suggests that the presence of fat does not preclude the diagnosis of sclerosing PEComa, since this entity seems to be a lesion with sclerosing features along a morphological continuum of the PEComa family of tumours comprising trilineage (vascular, smooth muscle and lipidic), epithelioid and monotypic epithelioid AML (Matsuyama et al., 2008).

Neoplastic cells show a distinctive immuno-phenotype with positivity for both melanocytic and smooth muscle markers. Nevertheless, in contrast with conventional PEComas, sclerosing PEComas usually exhibit a more diffuse positive staining for smooth muscle markers (including smooth muscle actin, desmin and caldesmon) and a more limited immunoreactivity for HMB-45 (Folpe, 2002). Microphthalmia transcription factor (MiTF) is also a useful marker of sclerosing PEComa, being present in 92 % of cases (Hornick and Fletcher, 2008).

In the case we observed, electron microscopic examination revealed the presence of abundant dense granules in a subpopulation of neoplastic cells, but these lacked periodic filaments or the lattice-like structure of typical melanosomes. With few exceptions, most ultrastructural studies have failed to demonstrate the presence of premelanosomes and/or melanosomes in PEComas. It has been suggested that granules found in PEComas may be atypical melanosomes in which small amounts of melanin are masked by other electron dense constituents, or alternatively, there are only a few typical melanosomes which may escape detection by electron microscopy (Banerjee et al., 2001).

The PEComa family of tumours derives its name from the perivascular epithelioid cells (PECs) characteristic of these neoplasms. The debate on the nature of PECs still continues. Connections between PECs and melanocytes, muscle cells, pericytes and neuroendocrine cells have been investigated, without definitively assessing the origin and direction of differentiation of this intriguing type of cell for which no known normal counterpart has been identified (Weinreb et al., 2007; Folpe and Kwiatkowski, 2010). Although new instances have been put forward, what Bonetti and colleagues asserted several years ago still holds, i.e. epithelioid cells with perivascular distribution, showing clear-eosinophilic cytoplasm and immunoreactivity for melanocyte markers are present at various anatomic sites and pertain to tumours and tumour-like conditions with
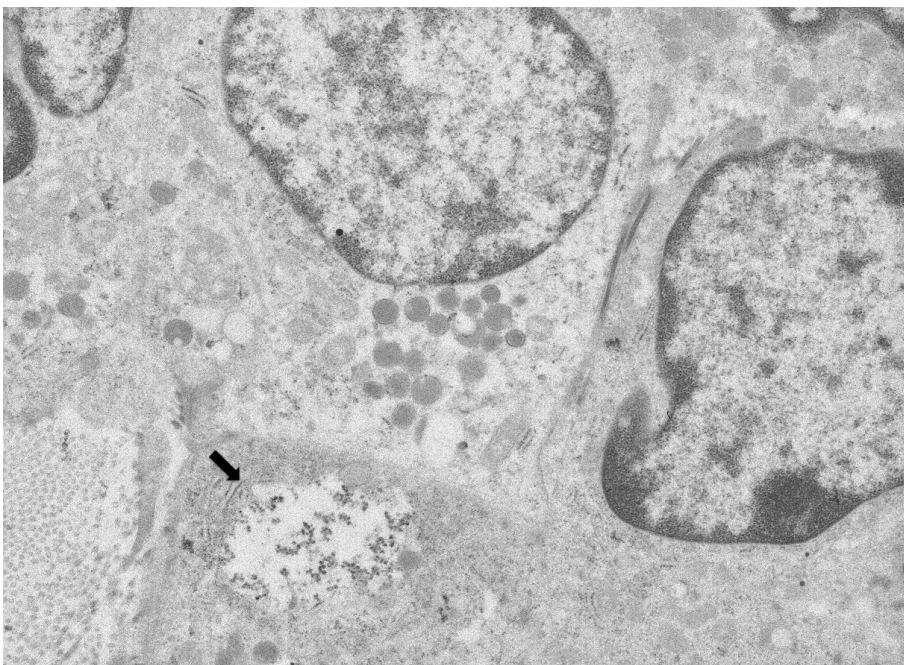

Fig. 4. At the ultrastructural level, the cytoplasm of neoplastic cells contained secondary lysosomes, pools of glycogen (arrow), and few rough endoplasmic reticulum cisternae. x 4,400

prominent vascular proliferation (Bonetti et al., 1992). Martignoni and colleagues suggested that PECs can modulate their morphology and immunophenotype displaying features of muscle differentiation (with the development of a spindle shape and a more diffuse positivity for actin than for HMB-45), epithelioid features (with intense reactivity for HMB-45 and weaker staining for actin), or else become vacuolated mimicking adipocytes (Martignoni et al., 2008).

Sclerosing PEComas may histologically overlap with many entities including round cell/epithelioid variants of both gastrointestinal stromal and smooth-muscle tumours, desmoplastic small round cell tumours, clear cell sarcomas, paragangliomas, malignant melanomas, metastatic carcinomas and epithelioid haemangioendothelioma of soft tissues (Hornick and Fletcher, 2008; Matsuyama et al., 2008). Nevertheless, the peculiar immunohistochemical profile of PEComas, together with clinicopathological correlations, usually allows distinction among these neoplastic entities.

Based on the small number of reported cases with available follow-up, sclerosing PEComas are regarded as benign tumours. Prognostic factors are still under investigation and until now only the concomitant presence of a striking histologically high-grade malignant component has been associated with metastatic disease (Hornick and Fletcher, 2008; Ramaiah et al., 2009). It is noteworthy that the two reported cases of sclerosing PEComa with aggressive clinical course arose in the pelvic cavity (Hornick and Fletcher, 2008) and in the uterine adnexa (Ramaiah et al., 2009), whereas most sclerosing PEComas, including the case herein described, were located in the retroperitoneum and showed a benign nature, giving rise to the hypothesis that the anatomical site of origin could influence the behaviour of sclerosing PEComas.

Although conventional AML of the kidney, still considered the prototype of PEComas, shows an invariably benign clinical behaviour, its rare epithelioid variant (EAML) has been reported in association with local recurrence and distant metastases. On reviewing a large series of AMLs, Aydin and colleagues argued that malignant EAMLs have prevalent epithelioid morphology with cytological pleomorphism, whereas other troublesome pathological features (i.e. coagulative tumour necrosis, nuclear atypia, mitosis and atypical mitotic figures) do not predict an unfavourable outcome (Aydin et al., 2009). Moreover, Nese and co-authors have recently observed that approximately half of the patients affected by pure epithelioid PEComas of the kidney showed progression of disease (Nese et al., 2011). In this series, association with tuberous sclerosis complex (TSC) or concurrent AML, necrosis, size > 7 cm, extrarenal extension and/or renal vein involvement and carcinoma-like growth pattern were indicative of aggressive biology. With the exception of TSC and concurrent AML, these criteria are similar to those put forward by Folpe and colleagues for prognostic stratification of PEComas at other sites (Folpe et al.,

2005). Further studies with long-term follow up of PEComas, whether from the kidney or other sites, are needed in order to improve prognostication in this biologically intriguing neoplastic entity.

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