

# Primary perivascular epithelioid cell tumor of the liver not related to hepatic ligaments: Hepatic PEComa as an emerging entity

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**Summary.** Primary perivascular epithelioid cell tumor (PEComa) of the liver is a very rare example of an emerging family of hepatic PEC tumors. Only few cases have been described so far. We report the case of a large but benign hepatic PEComa in a 53-year-old man without signs of tuberous sclerosis. In contrast to recently described PEC-derived liver tumors in children and young adults, this neoplasm was not related to the hepatic ligaments but had developed deeply within the liver substance. The neoplastic cells displayed the complete phenotype typical for PEComas, i.e. reactivity for several melanoma markers and for smooth muscle actin. The unique relationship of myoid tumor cells to the adventitia of blood vessels prompted us, in comparison with published findings obtained with angiomyolipomas, to comment on the possible origin of the still enigmatic perivascular epithelioid cells.

**Key words:** Perivascular epithelioid cell tumor, PEComa, Liver

## Introduction

The term, perivascular epithelioid cell (PEC), was coined in 1992 (Bonetti et al., 1992) to denote a distinct cell type that had originally been observed in renal angiomyolipomas (Apitz, 1944; Masson, 1956). PECs, which have no known normal cellular counterpart, are intimately related to blood vessels and are involved in a growing list of unusual tumors and tumor-like lesions sharing the expression of HMB45 and/or melan-A and smooth muscle cell markers. This tumor family currently includes angiomyolipoma and its several variants,

perivascular epithelioid cell tumors (PEComas), lymphangio(leio)myomatosis, pulmonary and extrapulmonary clear cell 'sugar' tumors, and abdominopelvic sarcoma of perivascular epithelioid cells (review: Hornick and Fletcher, 2006). Part of these lesions are associated with the tuberous sclerosis complex.

Recently, two groups reported a distinct variant of PEComa occurring in close spatial relationship to the hepatic falciform and/or round ligaments of the liver. These neoplasms, observed in children and young adults, were termed clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres (CCMMT; Folpe et al., 2000) and HMB-45/Melan-A and smooth muscle actin-positive clear-cell epithelioid tumor arising in the ligamentum teres hepatis (Tanaka et al., 2000), respectively. It has later been suggested that CCMMT falls within the morphologic spectrum of PEComa showing predominantly spindled cytomorphology (Hornick and Fletcher, 2006). Apart from these hepatic lesions, only five other reports described a PEComa of the hepatobiliary system, i.e. a perivascular epithelioid clear cell tumor of the common bile duct (Sadhegi et al., 2004), a malignant neoplasm of perivascular epithelioid cells of the liver (Parfitt et al., 2006), and hepatic PEComas in adult patients (Fang et al., 2007; Svajdler et al., 2007; Paiva et al., 2008). In the present communication, we report a large and expandingly growing PEComa arising within the liver substance of an adult patient, without relation to the hepatic ligaments, and comment on the possible cell of origin.

## Materials and methods

### Case history

A 53-year-old farmer in previously good physical health and particularly without signs of tuberous

sclerosis was hospitalized because of progressive abdominal pain over the last 24 hours. Physical examination revealed only mild hepatomegaly. Laboratory examinations showed normal liver function tests and a slight lymphocytopenia. Initial abdominal ultrasonography disclosed a spherical mass in the liver, measuring 8 cm in diameter. Subsequent CT and abdominal MRI confirmed this intrahepatic mass to be located in liver segments five and eight, without relation to the hepatic ligaments (Fig. 1A,B). Radiologic differential diagnosis included a large cavernous hemangioma with centrally thrombosed vessels, atypical hepatocellular carcinoma with central necrosis, and echinococcosis, these wide-spread propositions reflecting the unusual imaging morphology of the lesion. Owing to the deteriorating clinical situation and the ambiguous imaging findings, a right hemihepatectomy was performed, with complete resection of the tumor. 18F-FDG-PET imaging subsequent to the histologic diagnosis showed no other hepatic foci.

The follow-up 17 months after resection revealed that the patient is in excellent health, still fully working as a farmer, without evidence of disease. Recent control imaging disclosed compensatory hypertrophy of the contralateral liver lobe, normal portal and hepatic veins, and a completely normal liver parenchyma without focal changes.

#### Tissue sample, histology and immunohistochemistry

The specimen containing the tumor was fixed in 4% buffered neutral formalin and processed for histology by use of conventional methods. In addition to hematoxylin and eosin, special stains included reticulin stain, periodic acid-Schiff (PAS) with or without diastase predigestion, Van Gieson's stain, chromoaniline blue stain (CAB), Masson-Fontana stain, and Perls iron stain.

For immunohistochemistry, primary antibodies against the following antigens were used: CD34 (QBEnd/10), c-kit (polyclonal), desmin (D33), Ki-67 (MIB1), melan A (A103), melanoma antigen (PNL2), melanosome (HMB-45), myogenin (F5D), p53 protein (DO-7), S-100 protein (polyclonal), vimentin (Vim 3B4) (all from Dako, Glostrup, Denmark), beta-catenin (14), cytokeratin 8 (CAM 5.2) (both from BD Biosciences, San Jose, CA, USA), tyrosinase (T311) (Novocastra, Newcastle-upon-Tyne, UK), and  $\alpha$ -smooth muscle actin (1A4) (Sigma, St. Louis, MO, US).

Specific binding of primary antibodies was visualized using a streptavidin-biotin complex/alkaline phosphatase method (Dako, Glostrup, Denmark) with new fuchsin as the chromogen, as previously described (Zimmermann et al., 2002).

## Results

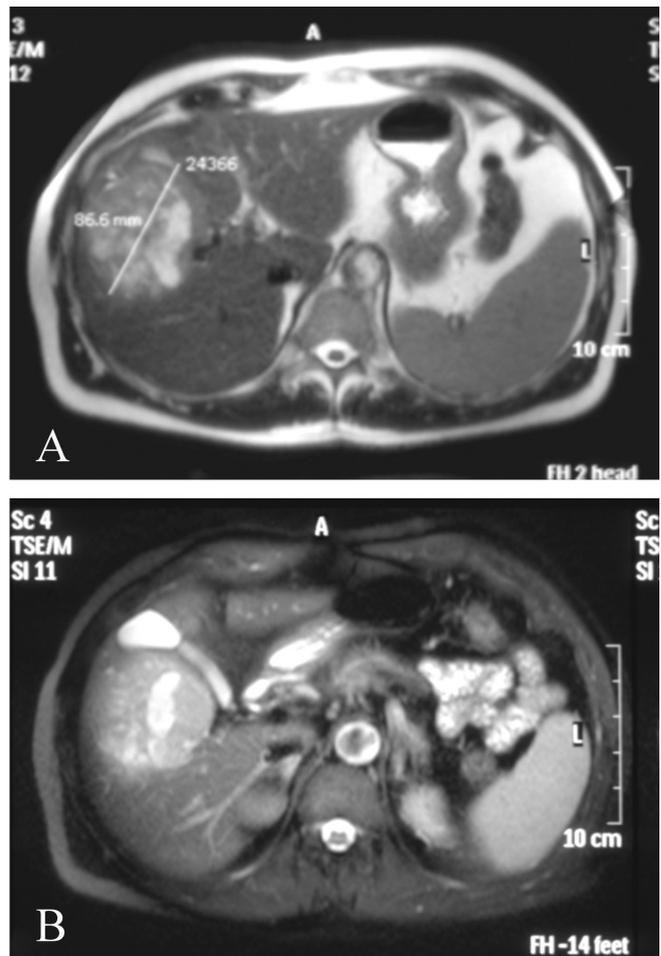
### Gross findings

Macroscopically, the right-sided hemihepatectomy

specimen contained a well circumscribed and expanding tumor mass measuring 7x6.5x6.5 cm. The neoplasm was clearly located deeply within the liver substance without relationship to the hepatic ligaments. Cut surfaces showed a yellow to tan and rather homogeneous mass that was friable in central parts (Fig. 2). The adjacent liver was macroscopically normal.

### Histologic and Immunohistochemical Findings

Histologically, the expanding growth of the tumor was confirmed, with some peritumoral atrophy of liver substance but no signs of invasive growth. The neoplasm consisted of several distinctive cell types: a) spindle cells with a pale to slightly eosinophilic cytoplasm and ovoid



**Fig. 1.** Both pictures depict the preoperative situation, with a mass located in liver segments five and eight. **A.** MRI – T2 emphasis. The liver tumor shows an inhomogeneous signal. The central region is hyperintense with small areas of liquid collection, whereas the periphery appears hypointense. **B.** MRI – contrast enhanced T1 emphasis. The lesion displays a heterogeneous intensity. It shows a strong contrast enhancement in the central part of the tumor. The mass appears relatively hypointense compared to the liver parenchyma.

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to elongated nuclei, forming bundles and at some places palisade-like structures (Fig. 3A); b) medium-sized clear cells arranged in bundles, nests or tiny nodules (Fig. 3B); c) epithelioid cells with a rich, eosinophilic and granular cytoplasm, growing in a more diffuse fashion (Fig. 3C); and large eosinophilic or pale cells with sometimes pleomorphic nuclei (Fig. 3D). At a few places, cells with a finely granular dark brown and iron-negative pigment were detected, suggesting a melanotic component. The Masson-Fontana stain showed a positive granular, black cytoplasmic staining in part of these cells. Mitotic figures were not recognized. Reticulin fibers predominated in the spindle cell components of the lesion. The tumor showed an elaborate vasculature with medium-sized vessels dividing the neoplasm into ill-defined compartments. There were central necroses and a focal lymphocytic and plasmacytic infiltration of the tumor. In numerous sections, no adipocyte-like cells were detected.

Immunohistochemically, the tumor cells were markedly reactive for HMB-45, epithelioid, clear and large cells more frequently and more strongly than elongated spindle cells (Fig. 4A), for Melan A (Fig. 4B), and for PNL2 (Fig. 4C). SMA reactivity was heterogeneous and chiefly involved the slender, myoid-looking spindle cells arranged in bundles (Fig. 4D). The palisading of part of the myoid cells was striking (Fig. 4E). Sometimes, SMA-reactive spindle cells were in close association with blood vessels, apparently engaging with the vessels' adventitia (Fig. 4F). At places where the periphery of the tumor was in close

association with large portal tracts, neoplastic cells markedly immunoreactive for SMA, but less so for HMB-45, Melan-A and PNL2, formed a tight interface with the outer contour of arteries and veins, sometimes completely encircling the vessels. Here, tumor cells were in part arranged in a radial fashion, spindled cells more frequently than epithelioid cells, and some cells had slender processes reaching into the outer vascular media. Reactivity for S-100 protein was not detected. Beta-catenin was expressed in a mixed, cytoplasmic and membranous pattern, cytoplasmic staining being more prominent in the epithelioid population. Interestingly, beta-catenin reactivity was more marked in tumor tissue near the tumor boundaries next to normal tissue (Fig. 5A,B). Based on Ki-67 immuno-staining, the estimated proliferation fraction was clearly less than 1%. No immunoreactivity of tumor cells was detected for tyrosinase, cytokeratin, vimentin, desmin, myogenin, CD34, c-kit, and p53 protein. The tumor contained relatively numerous c-kit-positive mast cells (not shown).

#### Discussion

Perivascular epithelioid cells (PEC) were first morphologically described in 1944 by Apitz in his seminal work on tumors and malformations of the renal cortex, specifically angiomyolipoma (Apitz, 1944). This author noted the presence, in close relationship to tumor vessels, of distinctive spindle cells that had either a myoid or an epithelioid aspect. This cell type was later



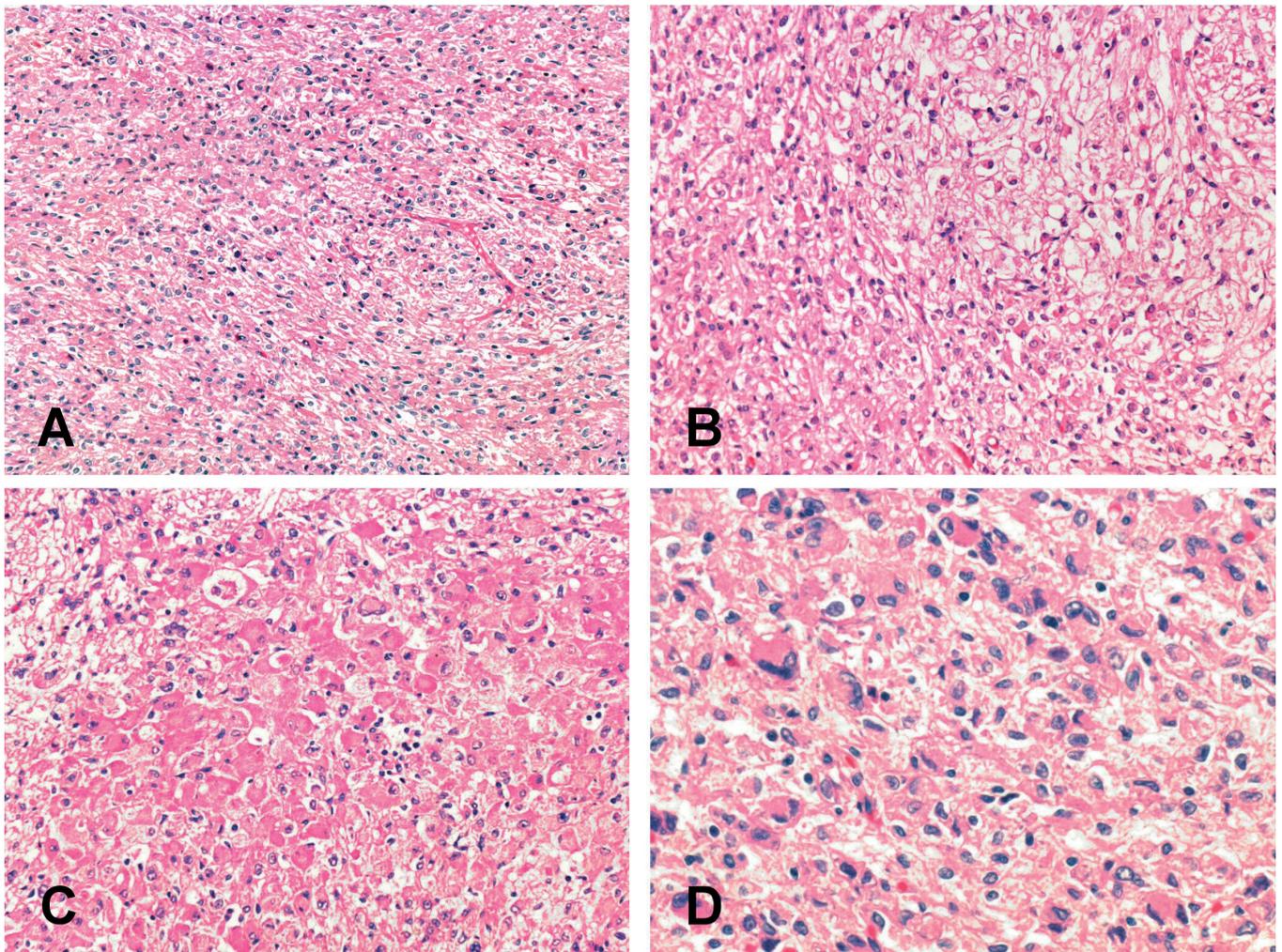
**Fig. 2.** Resection specimen. The cut surface shows a spherical, well demarcated tumor consisting of tan to yellowish tissue with focal hemorrhage. The lesion is situated within the liver substance and is not related to hepatic ligaments.

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recognized again in angiomyolipomas of the kidney, and the epithelioid feature of the cell was confirmed (Masson, 1956). Pea and coworkers, in 1991, stressed the similarities, both morphological and phenotypical, between angiomyolipoma of the kidney and clear cell 'sugar' tumor of the lung (Pea et al., 1991). One year later, the same group suggested the descriptive term, perivascular epithelioid cell (PEC), to identify this 'novel' cell type which seems to be the same cell described by Apitz as an 'abnormal myoblast' (Bonetti et al., 1992). This cell type has, so far, no normally identifiable counterpart, and its distinct immunophenotype, characterized by the sometimes synchronous expression of melanocyte markers and myoid markers, makes its histogenetic classification difficult (Bonetti et al., 1992; Hornick and Fletcher, 2006). In recent years it surfaced that the neoplastic offspring of PEC comprises

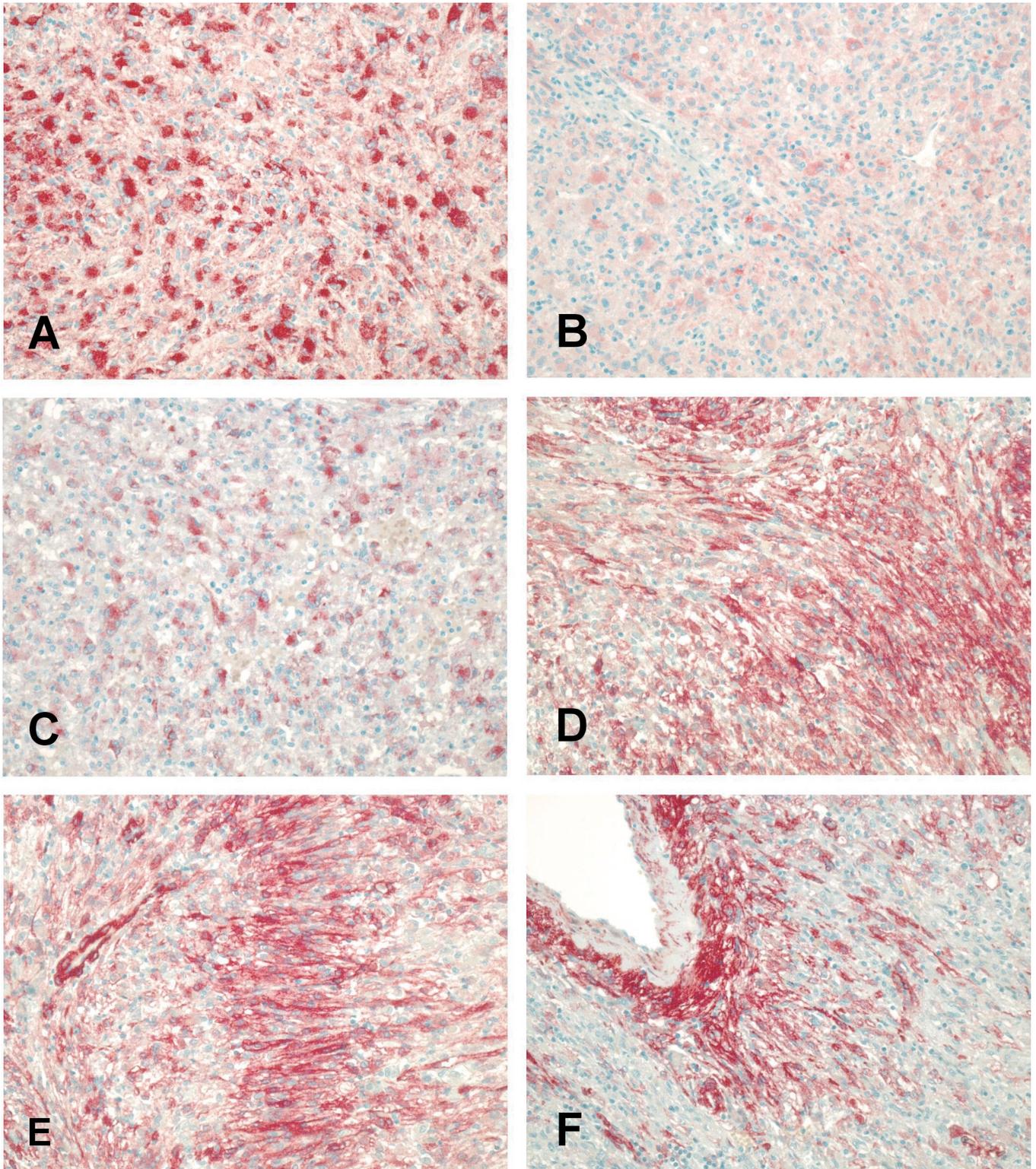
an entire family of lesions, including angiomyolipoma (AML) and its variants, monotypic epithelioid AML (renal epithelioid oxyphilic neoplasm; REON), renal microhamartomas (related to AML), renal capsular neoplasms (RCN; so-called capsulomas), perivascular epithelioid clear cell tumors (PEComas), the closely related or, as now suggested, identical clear-cell myomelanocytic tumors (CCMMT), pulmonary and extrapulmonary clear cell ('sugar') tumors, pulmonary clear cell nodules (CCN), abdominopelvic sarcoma of perivascular epithelioid cells, and lymphangio(leio)-myomatosis (Hornick and Fletcher, 2006).

PEComas have been reported to occur in several organs and tissues, including the gastrointestinal tract (Yanai et al., 2003; Birkhaeuser et al., 2004; Agaimy and Wunsch, 2006), the genitourinary tract including the kidneys (Vang and Kempson, 2002; Pan et al., 2003;



**Fig. 3.** **A.** Part of the tumor characterized by spindle cells with a slightly eosinophilic cytoplasm forming bundles. **B.** Medium-sized eosinophilic and clear cells arranged in bundles. Part of a nodular structure is seen at the bottom. **C.** In this tumor component, epithelioid cells with a rich, eosinophilic and slightly granular cytoplasm and growing in a diffuse pattern are shown. **D.** Apart from spindle cells and clear cells, this tumor part shows few large and atypical cells. H&E. A-C, x 200; D, x 400

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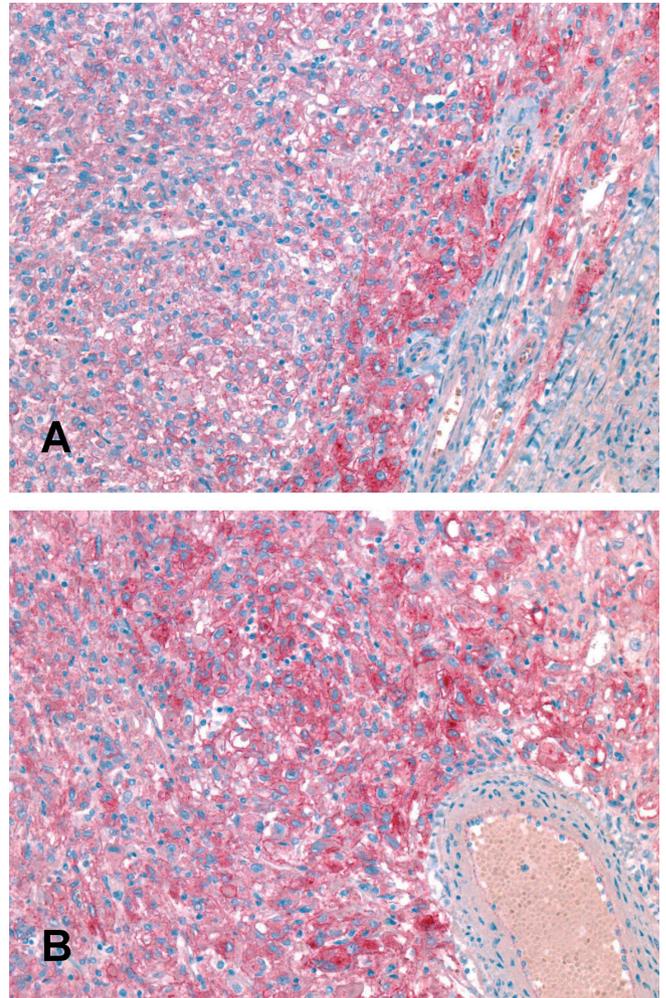
**Fig. 4.** **A.** Most of the epithelioid tumor cells are markedly immunoreactive for HMB-45, with a strong granular cytoplasmic staining (HMB-45 immunostain). **B.** In contrast to A, the density of tumor cells reactive for Melan A is less in this part of the tumor (Melan A immunostain). **C.** Predominantly cells with an epithelioid morphology are reactive for PNL2 (PNL2 immunostain). **D.** Marked reactivity for smooth muscle actin (SMA) in myoid spindle cells arranged in bundles (SMA immunostain). **E.** In this figure, SMA-reactive spindle cells exhibit striking palisade-like structures (SMA immunostain). **F.** Tumor in contact with an artery (top left). Note that SMA-reactive spindled tumor cells are in close association with the artery's adventitia, and seem to radiate from the outer vessel wall (SMA immunostain). x 200

Bhalla et al., 2004; Folpe et al., 2005), the abdominopelvic region (Evert et al., 2005), and soft tissues (Fukunaga, 2004; Folpe et al., 2005). Reported PEComas and related lesions occurring in the hepatobiliary tract so far comprise AML, CCMMT, a case of PEComa of the common bile duct (Sadhegi et al., 2004), a malignant neoplasm of perivascular epithelioid cells of the liver observed in a 60-year-old female patient (Parfitt et al., 2006), and hepatic PEComas reported in 2007 and 2008 (Fang et al., 2007; Svajdler et al., 2007; Paiva et al., 2008).

In 2000, Folpe and coworkers described seven cases (six females and one male) of a unique and previously unrecognized tumor of children and young adults, with ages ranging from 3 to 21 years (median, 11 years). All these tumors occurred in or immediately adjacent to the ligamentum teres and falciform ligament, and all grossly showed focal areas of hemorrhage and cystic change. The tumors had been culled from three institutions and had previously been allocated to other diagnoses, specifically leiomyosarcoma. These neoplasms consisted of clear to faintly eosinophilic spindled cells immunoreactive for HMB-45. In addition, part of the tumors were positive for smooth muscle actin, Melan-A and microphthalmia transcription factor, whereas no desmin and no tuberin were detectable. Follow-up of six of these patients disclosed five who were free of disease, whereas one had a radiographically presumed lung metastasis. The authors employed the term, clear cell myomelanocytic tumor (CCMMT) of the falciform ligament/ligamentum teres to denote this novel member of the PEComa group of tumors (Folpe et al., 2000). In the same year, Tanaka and coworkers described a similar lesion in the ligamentum teres hepatis of a 13-year-old Japanese girl without signs of tuberous sclerosis. In contrast to the tumors described by Folpe et al. (2000), this completely resected neoplasm did not show hemorrhage, and necrosis was not in evidence, but the histology and the immunophenotype were similar to those of the seven cases of the other group. The authors concluded that the neoplasm was consistent with clear cell 'sugar' tumor (i.e. a member of the PEComa family of lesions), but employed a rather complex term to denote this lesion (HMB-45/Melan-A and smooth muscle actin-positive clear-cell epithelioid tumor arising in the ligamentum teres hepatis; Tanaka et al., 2000). At the time of reporting, this patient had been well for 22 years. There is strong evidence that these tumors belong to a specific group of PEComas, also based on their striking association with the hepatic ligaments. Recently, it has however been suggested that CCMMT consisting predominantly of spindled cells may not form a distinct entity, but rather fall within the morphologic spectrum of PEComa showing predominantly spindled cytomorphology (Hornick and Fletcher, 2006).

The tumor described in the present report, observed in a 53-year-old male patient without stigmata of tuberous sclerosis, did not show a relationship to the hepatic ligaments, but was situated within the liver substance. Immunohistochemically, it showed the

phenotype typical for PEComas, including marked reactivity for HMB-45, Melan-A, PNL2, and smooth muscle actin, in the absence of reactivity for cytokeratin, vimentin and CD34. PNL2 is a novel monoclonal antibody directed against a fixative-resistant melanocyte antigen, labeling intradermal nevi and melanomas, but also angiomyolipoma and cells of lymphangio(leio)myomatosis (Rochaix et al., 2003). It is shown here that, in addition to the previously described reactivity for HMB-45 and Melan-A, PNL2 also clearly labels cells of a PEComa. Although there is some similarity to the epithelioid variant of hepatic AML (Dalle et al., 2000; Yamasaki et al., 2000), several features of the present tumor are different from AML. In hepatic AML, an early report (Goodman and Ishak, 1984) emphasized a resemblance to renal AML and highlighted the presence



**Fig. 5. A.** The tumor cells are reactive for beta-catenin. Note that cells adjacent to non-tumorous liver (to the right of the figure) show a more pronounced staining (beta-catenin immunostain). **B.** At higher magnification, the beta-catenin staining pattern is seen to be both membranous and cytoplasmic, the latter being more pronounced in large epithelioid cells (beta-catenin-immunostain). A, x 200; B, x 400

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of fat and sometimes prominent hematopoietic elements, both features lacking in our case. The amount of fat in hepatic AML varies considerably and is sometimes sparse (Yamasaki et al., 2000; Wang et al., 2006). Tsui and coworkers (Tsui et al., 1999) observed either tumors that were heavily fatty or tumors with absence of mature adipocytes but with fine fat droplets or large globules in sinusoids, what we did not detect in our case.

A novel finding for hepatic PEComa is the prominent immunoreactivity of beta-catenin in the neoplastic cells. In addition to membranous immunostaining, there was also marked staining of the cytoplasm, but particularly in large epithelioid cells. Conversely, nuclear beta-catenin staining was not found. A marked expression of beta-catenin in PEComa is of interest in the context of tuberous sclerosis (TSC) which is significantly associated with PEC tumors (Pan et al., 2006; Kenerson et al., 2007). It is now known that the TSC1/TSC2 complex associates with two members of the intracellular beta-catenin signaling pathway, i.e. glycogen synthase kinase 3 and axin, thus promoting beta-catenin degradation to inhibit Wnt-stimulated transcription. Specifically, it has been shown that beta-catenin and its effectors, cyclin D1 and connexin 43, are upregulated in TSC-related angiomyolipoma (AML) and lymphangioloio-myomatosis (LAM). In the Eker rat strain Tsc2 rodent model, spontaneous renal tumors in Tsc2 +/- rats expressed high levels of beta-catenin (Mak et al., 2003). In human AML and LAM tissues, expression of beta-catenin was elevated (Mak et al., 2005), suggesting that beta-catenin signaling plays a role in TSC pathogenesis. In the present tumor, beta-catenin staining was more pronounced near the tumor boundaries next to normal tissue, what has also been observed in both, renal tumors of Tsc2 heterozygous Eker rats and in TSC-related AML in humans (Mak et al., 2005).

The present tumor exhibited no immunoreactivity for S-100 protein. This is in contrast to part of hepatic angiomyolipomas, which showed positivity for S-100 protein in 7/9 cases analyzed (Yang et al., 2007). Negative results for S-100 protein expression have, however, been reported for PEComa of the liver (Svajdler et al., 2007) and colonic PEComa (Baek et al., 2007). Small foci of tumor cells with melanin-like pigment granules were recognized. A melanotic phenotype of PEComa family tumors has previously been reported, (sometimes with heavy pigmentation), including angiomyolipoma (Tsui et al., 1999), PEComa (Kalyanasundaram et al., 2005), CCMMT (Folpe et al., 2000; Kim et al. 2006), and clear cell epithelioid tumors of the kidney (Adachi et al., 2004; Yu et al., 2005). In part of these lesions, electron microscopy revealed the presence of premelanosomes (Kaiserling et al., 1994; Kim et al., 2006). The full spectrum of melanosome generation has also been observed in a further PEComa variant, clear cell tumor of the lung (Gaffey et al., 1991). The tumor contained relatively numerous c-kit-reactive mast cells, whereas the neoplastic cells were clearly negative. This is in contrast to reported hepatic

angiomyolipomas which were frequently c-kit-positive (67%: Makhlof et al., 2002; 78.9%: Zhang et al., 2004), and to renal angiomyolipoma, where almost half of the cases showed c-kit reactivity, predominantly in smooth muscle cells (Roma et al., 2007).

A striking feature of the present PEComa, not described in detail so far, was the distinct arrangement of markedly SMA-positive spindle cells ('myoid cells') within the lesion. Arteries located in the tumor itself and arteries of adjacent portal tracts in contact with the neoplasm were frequently encircled, sometimes in a radial fashion, by spindle cells that were more commonly SMA-reactive than reactive for HMB-45, Melan-A, or PNL2, while cells located more remotely with respect to arteries tended to show an epithelioid morphology associated with strong melanocyte marker reactivity. This predominance of a spindle and 'myoid' phenotype around blood vessels has already been observed in Apitz's original 1944 publication on renal angiomyolipomas (Apitz, 1944). In Figure 11 of Apitz's work, the author depicted periarterial spindle cell lesions that are almost the same now shown for the present PEComa, and argued that these myoid cells were not of angiomatous origin but rather got secondarily involved with the blood vessels. Apitz also found that angiomyolipomas with this specific feature were those with the most prominent growth behavior (Apitz, 1944). In a recent work on malignant PEComas, one case showed a continuous single layer of perivascular clear cells remote from the tumor, these cells being in direct contact with the abluminal surface of the basal lamina of capillaries ("pecosis"; Weinreb et al., 2007). One may, therefore, hypothesize that normal PEC are members of a still not well characterized vessel-associated cell lineage of unknown source. PEC share several features with neural crest-derived cells, including their capability to differentiate along a melanocyte-like pathway. In addition, PEC-derived angiomyolipomas express the neural stem cell markers, NG2 and L1 (Lim et al., 2007). It may be surmised that a neural crest-derived cell lineage is at the origin of PEC that may home to blood vessel walls. In fact, part of the neural crest is involved in cardio-and aortogenesis (Stoller and Epstein, 2005), and a phenotypically still not well defined subset of neural crest cells is a significant source of smooth muscle cells (Gittenberger-de Groot et al., 1999; Hirsch and Majesky, 2004), including those of blood vessel walls (Korn et al., 2002; Skowasch et al., 2003).

In conclusion, liver neoplasms derived from perivascular epithelioid cells form an emerging family of hepatic tumors with several distinct phenotypes, a complex clinical and radiological differential diagnosis, and a variable biology of disease.

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