Solitary Fibrous Tumor/ Hemangiopericytoma of the Liver

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Abstract

Solitary fibrous tumors form a complex spectrum of neoplasms, at least part of which were previously related to perivascular cells and thus termed hemangiopericytomas. The classical solitary fibrous tumor, occurring in the form of several variants, typically develops in the pleuropulmonary compartment, but also exists in certain visceral organs, including the liver. Rare variants are those which contain components with hemangiopericytoma-like features. In addition to these lesions, there still exist so-called true hemangiopericytomas, neoplasms that typically occur in the meninges and the sinonasal space. In the liver, primary solitary fibrous presents as well-circumscribed and expanding lesions with fibroma-like features. Histologically, the neoplasms are cellular tumors composed of spindle cells looking different from fibroblasts and myofibroblasts. These cells are arranged in a storiform pattern or form dense sheaths surrounding slit-like vascular channels. The origin of the cells is not yet elucidated. Solitary fibrous tumors show recurrent breakpoints in 12q13, associated with frequent deletions affecting STAT6, caused by somatic fusions of two genes, NAB2 and STAT6.

ICD-O codes:

Solitary fibrous tumor	8815/1
Hemangiopericytoma including lipomatous hemangiopericytoma	9150/1

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Introduction

This group of tumors was previously thought to be derived from specialized cells supporting blood vessels, i.e., pericytes and glomus cells, leading to the term hemangiopericytoma. The lesion was first described in 1942 as a vascular tumor featuring Zimmermann's pericytes (Stout and Murray 1942). In 2002, the WHO tumor classification system reclassified soft tissue tumors known so far as hemangiopericytomas as a variant of solitary fibrous tumor. In particular, cellular solitary fibrous tumor is regarded as a synonym of hemangiopericytoma (Park and Araujo 2009). Solitary fibrous tumors represent a heterogeneous group of spindle cell neoplasms with a biological behavior varying between benign and low-grade malignant phenotypes. The term, solitary fibrous tumor (SFT), is now preferred to the former term, hemangiopericytoma, all the more so because the cell of origin is still disputed (Penel et al. 2012). In the WHO classification, solitary fibrous tumor is listed in the intermediate (rarely metastasizing) category, characterizing neoplasms that are often locally aggressive but may have the capability to give rise to distant metastases in some patients, the risk of such a metastatic phenotype being less than 2 % and not predictable from the histologic presentation. Solitary fibrous tumor has several subgroups, comprising fibrous, cellular, fat cell-containing, and giant cell variants. The cellular variant, showing a hypercellular component exceeding 90 % of the tumor, covers most of the "classical" hemangiopericytomas (Knösel et al. 2010). The fat cell-containing variant was previously termed lipomatous hemangiopericytoma, and the variant rich in giant cells is equivalent to giant cell angiofibroma.

Currently, a small spectrum of tumors with a hemangiopericytoma-like pattern may be considered (Table 1). However, recent molecular genetic findings suggest that the entire spectrum of lesions may be separated into two major groups, i.e., classic pleuropulmonary SFT showing the most common NAB2-STAT6 fusion variant, mainly occurring in older patients and having a more favorable course, and deep-seated hemangiopericytomas showing the second most common NAB2-STAT6 fusion variant, occurring in much younger patients, and having a more aggressive phenotype (Barthelmess et al. 2014).

Table 1 Tumors with a hemangiopericytoma-like pattern

Solitary fibrous tumor (classical pleuropulmonary SFT and several variants, in part in other visceral organs)
True hemangiopericytomas (meningeal hemangiopericytoma, deep-seated hemangiopericytomas, myopericytoma, glomangiopericytoma, and the sinonasal hemangiopericytoma group)
Tumors with occasional hemangiopericytoma-like features

Hemangiopericytoma was described in 1942 as a relatively uncommon distinctive vascular tumor thought to be derived from Zimmermann's pericapillary pericytes (Stout and Murray 1942). Pericytes, identified in 1873 already (Rouget 1873) and analyzed in detail in 1923 (Zimmermann 1923), are dendritic or arborizing cells with multilineage features, arranged along capillaries and venules. In addition to their cases, Stout and Murray cite one or possibly two cases of hemangiopericytoma in a group of vascular tumors described in 1937 (Schmidt 1937) which this author, following the suggestion of Orsos (1934), termed gemmangiomata (gemmangiomas). The features of this neoplasm were characterized in more detail in the following years (Stout 1949; 1956; McMaster et al. 1975; Enzinger and Smith 1976; Mentzel et al. 1994; Nappi et al. 1995; Spitz et al. 1998), also in context with related tumors and the question as to the true entity of hemangiopericytoma (Gengler and Guillou 2006; Park and Araujo 2009). Pericytes can differentiate along fibroblastoid, myoid, osseous, and adipocyte lineages, what is of importance for the understanding of tumors derived thereof, because some pericytomas can develop a myoid component or produce neoplastic adipocytes (lipomatous hemangiopericytomas) (fat-forming solitary fibrous tumors; Lee and Fletcher 2011). Related tumors comprise myofibromatosis and the so-called infantile hemangiopericytoma, glomangiopericytoma, myopericytoma, and perivascular myoma. As most of the hepatic primary manifestations of this tumor category were

described under the term hemangiopericytoma, this label will sometimes be used in addition to solitary fibrous tumor in the following paragraphs.

Epidemiology

Solitary fibrous tumor typically presents in adult individuals. Among 106 cases analyzed, the mean age at presentation was 45 years. The tumors were usually deep-seated lesions (Enzinger and Smith 1976). The tumors occupy clinically and biologically characteristic anatomical locations, including meningeal, cerebral, orbital, sinunasal, osseous, pulmonary, pleural, soft tissue, and visceral tumors. The tumors also occur in the pediatric age group (Fernandez-Pineda et al. 2011), including the entity of multicentric infantile hemangiopericytoma (Sulit et al. 2011). For hepatic SFT, the tumors develop more frequently in females, and the mean age at diagnosis was 55.8 years (Vennarecci et al. 2005). In an earlier study of nine patients, seven patients were female and two male, with an age range at presentation of 32–83 years (mean, 57.5 years; Moran et al. 1998). A recent review of 38 published cases listed 26 female and 12 male patients (Liu et al. 2013). In one investigation, hepatic hemangiopericytoma was associated with occupational exposure to vinyl chloride monomer (Hozo et al. 2000). Most reports concerning primary hepatic SFT described single cases or very small series of this neoplasm.

Selected References Kim and Damjanov 1983; Kottke-Marchant et al. 1989; Kasano et al. 1991; Bost et al. 1995; Barnoud et al. 1996; Chan 1997; Khalifa et al. 1997; Levine and Rose 1997; Lecesne et al. 1998; Guglielmi et al. 1998; Moran et al. 1998; Fuksbrumer et al. 2000; Vaswani et al. 2000; Yilmaz et al. 2000; Lin et al. 2001; Saint-Marc et al. 2002; Chithriki et al. 2004; Neeff et al. 2004; Vennarecci et al. 2005; Moser et al. 2005; Changku et al. 2006; Ji et al. 2006; Jia et al. 2006; Lehmann et al. 2006; Nath et al. 2006; Terkivatan et al. 2006; Kwak et al. 2007; Obuz et al. 2007; Weitz et al. 2007; Chen et al. 2008; El-Khouli et al. 2008; Kandpal et al. 2008; Korkolis et al. 2008; Perini et al. 2008; Novais et al. 2010; Huanca et al. 2011; Güray Durak et al. 2013; Liu et al. 2013.

Hemangiopericytoma/Solitary Fibrous Tumor of the Liver

Clinical Features

Primary SFTs exhibit a clinical presentation that is non-characteristic in most patients, but particularly in the case of large tumors, abdominal distension, right upper quadrant or periumbilical pain, nausea, weight loss, and abnormal liver tests may occur. Hepatic SFT is a rare lesion, and metastatic disease may be difficult to exclude in a given patient owing to the peculiar biology of these neoplasms (Balouet and Destombes 1967; Bergnach 1967; Weitzner 1970; Klein et al. 1971; Wyrick and Wren 1975; Roesler et al. 1985; Thapa et al. 1986; Sano et al. 1991; Zornig et al. 1992; Maeda and Nakaba 1995; Noda et al. 1995; Flores-Stadler et al. 1997; Campion et al. 1999; Hozo et al. 2000; Kruskal and Kane 2002; Ghiur et al. 2003; Plikat et al. 2003; Caruso et al. 2009; Bokshan et al. 2012). In one series, tumor size ranged from 2 to 32 cm in diameter, and the largest weight of a published tumor was 4725 g (Vennarecci et al. 2005). The tumors can grow to such a large size that resection is not feasible, even in the absence of remote disease (Bergnach 1967). Primary hepatic SFT/hemangiopericytoma can present as a multicentric tumor with cystic cavernoma-like areas (Klein et al. 1971).

Part of the hepatic lesions have been reported to show an aggressive course (malignant hemangiopericytoma; Thapa et al. 1986; Sano et al. 1991; Yilmaz et al. 2000; Ghiur et al. 2003; Plikat et al. 2003; Chan et al. 2007; Seijas et al. 2009; Peng et al. 2011; Jakob et al. 2013). These lesions exhibit an invasive phenotype, can traverse the liver capsule, infiltrate the abdominal wall, and give rise to metastasis either in the liver

or in extrahepatic sites. Frankly malignant variants may present with abdominal hemorrhage due to tumor rupture. In one patient SFT of the liver exhibited local recurrence 6 years after resection, and histologic examination of the recurrent tumor displayed features of an aggressive form of SFT (Brochard et al. 2010). In a given case, it is difficult to judge what the biologic course will probably be, although hypercellular parts with increased nuclear atypia and elevated proliferative activity have been observed, suggesting low-grade malignant transformation (Fuksbrumer et al. 2000).

Several observations document an association between SFT/hemangiopericytomas and sometimes severe hypoglycemia, a syndrome called non-islet cell tumor hypoglycemia (NICTH), tumor-associated hypoglycemia (TAH), and the Doege-Potter syndrome (Paullada et al. 1968; Wegmann et al. 1994; Adams et al. 1999), a phenomenon also known for primary SFT/hemangiopericytoma of the liver (Weitzner 1970; Guglielmi et al. 1998; Campion et al. 1999; Kruskal and Kane 2002; Plikat et al. 2003; Bokshan et al. 2012), related to the production of insulin-like growth factor II (ILGF-II) and caused by loss of imprinting of the respective gene (Sohda and Yun 1996; Grunenberger et al. 1999), or by ILGF-II- and ILGF-binding protein 6 (Hoekman et al. 1999), by these neoplasms. Tumor-associated hypoglycemia has also been detected in a patient with hepatic fibrosarcoma (Immerman et al. 1982).

Imaging Features

Hepatic solitary fibrous tumors/hemangiopericytomas are usually solitary lesions, but multicentricity has also been reported (Klein et al. 1971). Sonographically, a complex mass with hyper-isoechoic solid components and hypoechoic cystic areas was described (Caruso et al. 2009). Speckled calcifications may be found. Administration of contrast media in CT and MR imaging reflects the high vascularization of the lesions, showing early, intense, and prolonged enhancement (Caruso et al. 2009). Scintigraphically, large cold nodules in the liver have been reported in a patient with multifocal tumor (Klein et al. 1971). In MR pictures, solid tumor masses prevail, sometimes with a large central necrosis (Plikat et al. 2003).

Macroscopic Pathology

Similar to tumors in other locations, the neoplasms form well-circumscribed and expanding lesions and usually form solid masses of gray to reddish or tan color. The tissue is firm, similar to that of fibromas. The tumors often exhibit partial or apparently complete encapsulation, sometimes with a typically shiny capsule, or formation of a pseudocapsule with perifocal liver atrophy. The cut surface is lobulated. Part of the tumors exhibit whorled and fasciculated cut surface (Korkolis et al. 2008). Hemorrhages may occur, while gross necrosis is unusual, at least in primary tumors. However, very large tumors have shown extensive geographic and sometimes infarctoid central necrosis (Moran et al. 1998). Both gross necrosis and hemorrhage have been encountered (Guglielmi et al. 1998). Some primary hepatic tumors grow to large or huge size (Kottke-Marchant et al. 1989; Guglielmi et al. 1998; Fuksbrumer et al. 2000), and masses up to 22 cm in diameter have been seen (Weitzner 1970), with a weight exceeding 4 kg (Chan et al. 2007). Central cystic cavities have been reported (Barnoud et al. 1996), and the hepatic lesions rarely present as a cyst containing a hemorrhagic fluid and mural tumor nodules of varying size (Klein et al. 1971). SFT with a multiloculated cystic appearance has also been described (Güray Durak et al. 2013). An expanding growth mode prevails, with the adjacent liver showing marked compression atrophy and signs of vascular engorgement. Secondary vascular and/or bile duct compression is sometimes found, and local invasive growth can be encountered, including invasion of intrahepatic veins (Fuksbrumer et al. 2000). Rarely, a pedunculated growth pattern has been seen (Moran

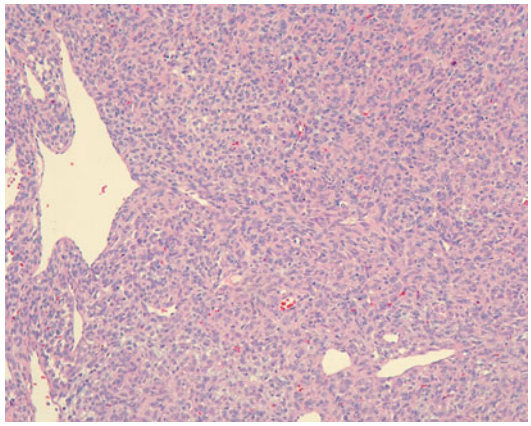

Fig. 1 Primary solitary fibrous tumor of the liver. Part of the tumor cells are associated with vascular spaces (hemangiopericytoma-like pattern; hematoxylin and eosin stain)

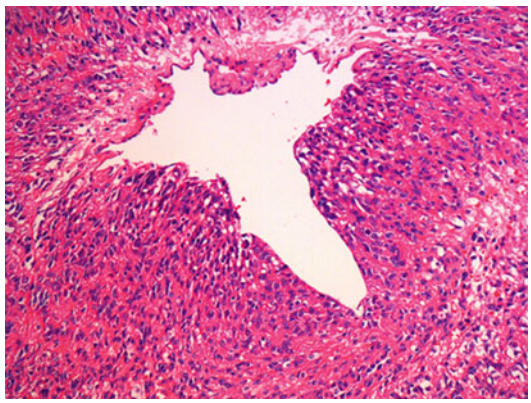

Fig. 2 Solitary fibrous tumor of the liver. The perivascular cellular cuff results in a pericytomatous pattern (hematoxylin and eosin stain)

et al. 1998; Park et al. 2011). Hepatic SFT belongs to the category of liver neoplasm causing capsular retraction (Blachar et al. 2009).

Histopathology

SFTs are often cellular tumors composed of spindle cells with a rather poorly developed and only slightly eosinophilic cytoplasm. These cells, which look different from both fibroblasts and myofibroblasts, either form a short storiform

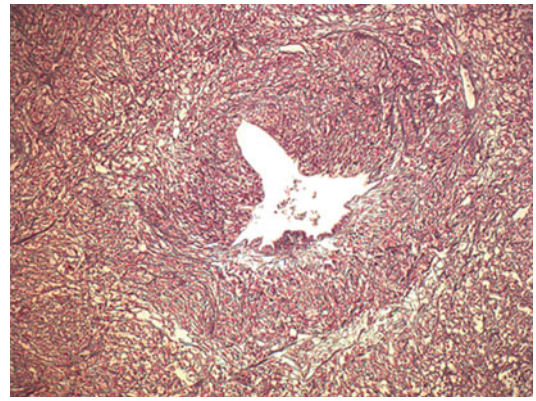

Fig. 3 Solitary fibrous tumor of the liver with a dense network of reticulin fibers (Gomori silver stain)

(so-called patternless) pattern or dense sheaths surrounding slit-like vascular channels (Figs. 1, 2, and 3). The latter pattern previously raised the suspicion that the cells might represent a pericyte or a pericyte-like cell. In most cells, the cytoplasm is not well delineated, and the nuclei are hyperchromatic and either spindled in shape or plump. Mitotic figures are usually rare, but one may find areas with 5–10 mitoses per ten high-power fields. The cellular lesions are traversed by a characteristic vascular ramifying tree showing a "staghorn" pattern. In silver stains, the tumor displays a very dense network of reticulin fibers, which encircle groups of spindle cells or even single cells, and is usually more dense in proximity of blood vessels (the pericapillary reticulin sheath; Stout 1949). In part of cases, an inflammatory response with lymphocytes and mast cells may be encountered. Focal myxoid change may occur (Korkolis et al. 2008), an alteration that can dominate SFT presentation in extrahepatic tumors (myxoid SFT; Lau et al. 2009).

Electron Microscopy

Electron microscopically, the tumor cells are closely apposed, but show poor development of cell-to-cell junctions. The organelle content of cells is highly variable and non-characteristic. Flocculent basement membrane material is

deposited linearly along the surface of many tumor cells (Flores-Stadler et al. 1997).

Immunohistochemistry

Immunohistochemically, the majority of the tumor cells are markedly reactive for vimentin, and staining for BCL-2, CD99, and alpha-1 antitrypsin is at least focally present (Patra et al. 2012; Liu et al. 2013). Endothelia of the intervening vessels and part of the spindle cells are CD34 positive (Fig. 4; Hanau and Miettinen 1995; Barnoud et al. 1996; Kwak et al. 2007; Korkolis et al. 2008; Peng et al. 2011). CD34 reactivity is considered characteristic for SFT (Brunnemann et al. 1999). Part of hepatic SFT expressed VEGF in a pattern resembling that of proliferating hemangiomas, and some of the cells were reactive for factor XIIIa, similar to the interstitial cells of cellular hemangiomas of infancy (Flores-Stadler et al. 1997). A subpopulation of factor XIIIa-positive cells was identified, similar to the "interstitial cells" of cellular hemangiomas of infancy (Flores-Stadler et al. 1997). At least part of the tumors exhibit nuclear reactivity for STAT6 (Doyle et al. 2013; Schweizer et al. 2013; Barthelmess et al. 2014), linked to NAB2-STAT6 fusion (see below). Immunoreactivity for cytokeratins, epithelial membrane antigen (EMA), desmosomal proteins, S-100 protein, smooth muscle actin, and desmin is usually lacking, although keratin positivity has been reported in one instance (Kim and Damjanov 1983).

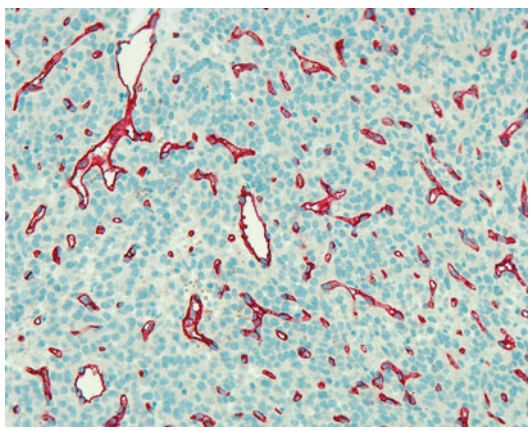

Fig. 4 Solitary fibrous tumor of the liver. The highly cellular neoplastic tissue is strongly vascularized (CD34 immunostain)

Solitary Fibrous Tumor/ Hemangiopericytoma of Hepatic Ligaments

Hemangiopericytoma/SFT rarely develops in the ligamentum teres of the liver (Majnarich and Stout 1960) and in the falciform ligament (Gidwani et al. 2004).

Differential Diagnosis

SFTs/hemangiopericytomas primary to diverse locations can extensively metastasize to the liver (van Assendelft et al. 1984; Chakravarty et al. 1991; Nakamura et al. 2005; Alberti et al. 2006; Balaji et al. 2008; Cheng et al. 2008; Zalinski et al. 2009; Balibrea et al. 2013). Among these neoplasms, meningeal hemangiopericytoma is particularly prone to metastasize to the liver (Buccauw et al. 2011). The metastases can cause paraneoplastic non-islet cell hypoglycemia due to production of IGF-II (Bell and Buist 1981; Sohda and Yun 1996; Lawson et al. 2009). Intra-abdominal SFT/hemangiopericytoma located close to the liver and/or extensively spreading may mimic hepatic localizations of this tumor, e.g., peritoneal spread (Prakash et al. 2009; Reicks and Wilkinson 2011).

Molecular Genetic Alterations

In SFT, chromosome banding and FSH showed recurrent breakpoints in 12q13, associated with frequent deletions affecting STAT6. This feature is associated with somatic fusions of the two genes, NGFI-A-binding protein 2 (NAB2) and STAT6, and nuclear expression of the C-terminal part of STAT6 (Chmielecki et al. 2013; Mohajeri et al. 2013; Robinson et al. 2013; Schweizer et al. 2013; Barthelmess et al. 2014; Koelsche

et al. 2014). In a series of 52 cases of SFT, 12 different NAB2-STAT6 fusion variants were detected in 92 % of cases. Immunohistochemically, all tumors showed strong and diffuse nuclear reactivity for STAT6 (Barthelmess et al. 2014). The NAB2-STAT6 fusion was also found in meningeal hemangiopericytomas (Schweizer et al. 2013). NAB2 is the transcriptional regulator NGFI-A-binding protein 2, a protein which functions in the nucleus to activate or repress transcription, in part through interaction with nucleosome remodeling and deacetylase complexes. NAB2 regulates and modulates the expression levels of the tumor necrosis factor (TNF) family member TNF-related apoptosis inducing ligand/TRAIL (Balzarolo et al. 2013). SFT also strongly expresses the GRIA2 gene (Vivero et al. 2014), encoding a protein of the ionotropic AMPA glutamate receptor.

Putative Cellular Origins

The cell of origin and the histogenesis of solitary fibrous tumors have not been elucidated so far, but putative mesothelial or primitive mesenchymal cells have been suggested. What is the evidence for the involvement of a mesenchymal progenitor cell? One argument is based on the finding of several lines of differentiation in solitary fibrous tumors: (1) fibrous variant, (2) cellular variant (more than 90 % cellularity), (3) adipocyte-forming variant (fat-forming SFT; lipomatous hemangiopericytoma), (4) giant cell-rich variant (giant cell angiofibroma with floret cells, including the vascular variant), (5) myxoid SFT, (6) synchronous pleuro-renal and renal solitary tumor, and (7) malignant solitary fibrous tumors. Based on electron microscopic investigations showing a mixture of mesenchymal cells and cells with features of mesothelia, a submesothelial origin of the tumor has been proposed (Kottke-Marchant et al. 1989; Barnoud et al. 1996). However, the convincing demonstration of SFTs at extrapleural sites strongly argues against its mesothelial or submesothelial origin. Parts of the cells are reactive for CD99 and CD34, and ultrastructurally the dominant cell population exhibits some degree of myofibroblastic differentiation, focal smooth muscle features, and undifferentiated cells in a perivascular location (Ide et al. 2005; Rodriguez-Gil et al. 2009). The involvement of a perivascular cell is also supported by the fact that solitary fibrous tumors may show transition to hemangiopericytomas (the hemangiopericytoma/solitary fibrous spectrum; Park and Araujo 2009). In fact, soft tissue with hemangiopericytoma-like growth patterns can now be divided into three categories, as summarized in the Table, and one of these categories is the solitary fibrous tumor group (Knösel et al. 2010). Therefore, a CD34-reactive fibroblastoid and vessel-associated progenitor cell may histogenetically be involved, but such a putative mesenchymal stem cell has not yet been identified in the normal liver. A common or characteristic cytogenetic anomaly has not been detected so far (Torabi et al. 2008; Torres-Olivera et al. 2009).

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