A rare case of primary hepatic solitary fibrous tumor associated with pregnancy

Gabriel Acosta-Gonzalez¹, Margaret Cho², Robert Rogers¹, Fernando Mariz³, Leon Pachter¹, Antonio Neto*¹

¹Department of Pathology, New York University School of Medicine, New York, United States
²Department of Pathology, Yale University School of Medicine, New Haven, United States
³Department of Obstetrics and Gynecology, The University of Toledo, Toledo, United States

Abstract

Purpose: To describe a case of histologically and immunohistochemically confirmed primary hepatic solitary fibrous tumor (SFT) associated with pregnancy.

Case report: A 40-year-old Caucasian woman G3P1021 with history of oral contraceptive use and no other known significant past medical history delivered via C-section in November of 2012. Two months post delivery, she noted that her abdomen did not decrease in size and sought medical attention. As part of the work-up, an abdominal MRI revealed a 15.9 cm mass centered in segment 4b of the liver with extension into segments 5 and 8 within the right lobe. In addition, an exophytic component extending inferiorly from the liver into the right mid abdomen was noted. The patient underwent an uncomplicated hepatic segmentectomy with cholecystectomy. Grossly, the tumor consisted of a firm tan-white well-circumscribed and partially encapsulated mass. Histologically, the tumor was composed of cytologically bland spindle cells with a patternless architecture with hypocellular and hypercellular areas embedded within a collagenous fibrous stroma with occasional dilated branching thin-walled blood vessels. The tumor showed no infiltrative margins or necrosis and a mitotic count of 1/10HPF. Tumor cells were strongly and diffusely positive for CD34, BCL-2, and vimentin; weakly positive for STAT6 (nuclear distribution); and focally positive for CD99 and β-Catenin. In addition, estrogen and progesterone receptors (ER and PR) were also performed and showed positive staining. The diagnosis of SFT was confirmed. To date, 36 months post-resection, our patient has been followed with imaging, showing no evidence of residual or recurrent disease.

Conclusions: Primary hepatic SFT is exceedingly rare and even more so in association with pregnancy. Positive immunohistochemical staining of tumor cells for progesterone and estrogen receptors may indicate hormonal stimulation as a driver of neoplastic cell proliferation.

Key Words: Solitary fibrous tumor, Hepatic solitary fibrous tumor, Liver, Pregnancy

1. Introduction

Solitary fibrous tumor (SFT) is a rare mesenchymal neoplasm that most commonly involves the pleura.¹¹ SFTs may also occur in the peritoneum, mesentery, pericardium, orbit, upper respiratory tract, and meninges.¹²⁻⁶ The liver is a rare primary site for SFTs with less than 50 cases reported in the English literature.⁷⁻¹⁷ Although most cases of SFTs are benign, there have been cases of SFTs with malignant features and metastasis.¹⁸,¹⁹ Both clinical and radiographic features are not entirely specific and cannot exclude malignancy. Sur-
gical resection with clean resection margins is the preferred therapeutic option.[20] Interestingly, only four cases of SFT associated with pregnancy have been reported, with one other case occurring in the liver.[21–24] We present a rare case of benign primary SFT occurring in the liver in association with pregnancy with ER and PR positive receptors.

2. CASE PRESENTATION

A 40-year-old Caucasian woman G3P1021 with history of oral contraceptive use until January 2011 with no other known significant past medical history delivered via C-section in November of 2012. Two months post delivery; the patient sought medical attention as she noted that her abdomen did not go down. Abdominal MRI revealed a 15.9 cm mass centered in segment 4b of the liver with extension into segments 5 and 8 within the right lobe. An exophytic component extended inferiorly from the liver into the right mid abdomen. The mass exhibited T1-hypointensity, T2-hyperintensity, intermediate ADC, and small arterial vessels coursing through the lesion without other evidence of arterial hypervascularity. The differential diagnosis of hepatocellular carcinoma, inflammatory adenoma, or SFT was raised radiographically. The patient was brought to surgery and an intraoperative frozen section was performed, which revealed a spindle cell lesion. The patient underwent an uncomplicated hepatic segmentectomy, with local aggressive resection of the tumor with clean surgical margins obtained, with cholecystectomy.

Gross examination revealed a 17.7 cm × 13 cm × 13 cm, partial hepatectomy specimen with a weight of 1,392 grams and intact smooth liver capsule. A tan-white well-circumscribed firm tumor (15.9 cm × 12.4 cm × 12.1 cm) was identified in the liver parenchyma and located 0.7 cm from the nearest resection margin. No hemorrhage, necrosis or cystic degeneration was grossly identified within the tumor. The uninvolved liver parenchyma showed no micro/macronodular cirrhosis or any other lesions. The intact gallbladder (7.6 cm in length and 4.3 cm in maximum diameter) had a 0.3 cm lymph node attached to the unremarkable cystic duct. The hepatic surface was rough. The peritoneal surface was smooth and glistening, and the mucosa was granular. The wall thickness averaged 0.2 cm with no other lesions seen.

Microscopically, the tumor showed patternless architecture with both hypocellular and hypercellular areas on a background of collagenized fibrous stroma. Tumoral cells were spindled and bland, without pleomorphism, bizarre mitotic figures or necrosis/apoptosis (see Figures 1-2). Some of the cells were grouped together forming intersecting fascicles, more so in the hypercellular areas. Vessels showed the so-called hemangiopericytoma-like thin-walled branching blood vessel in the center.

Figure 2. H&E 200×. Medium power view of the neoplasm showing cytologically bland spindle cells without atypia or pleomorphism, embedded within a collagenized stroma. There is no discernible mitotic activity. Note the characteristic hemangiopericytoma-like thin-walled branching blood vessel in the center.
dominantly hypocellular with a mitotic count of 1/10HPF, at most. The ki-67 showed very low proliferative index (< 10%). No lymphovascular, large vessel, or perineural invasion were identified. Surgical resection margins were negative.

The nonneoplastic liver parenchyma was predominantly unremarkable. The trichrome and reticulin stains showed no fibrosis or cirrhosis, and the iron and D-PAS stains were negative. The gallbladder was without significant abnormality.

Figure 3. Immunohistochemical stains showing tumor cells strong and diffusely positive for CD34 (A) and BCL-2 (B) and focally positive for PR (C) ER (D)

3. DISCUSSION

Solitary fibrous tumors, which were first described by Klemperer and Rabin in 1931,\cite{25} are defined by the WHO Classification as ubiquitous mesenchymal tumors of probable fibroblastic type, which show a prominent hemangiopericytoma-like branching vascular pattern.\cite{26} In the past, many SFTs were termed hemangiopericytomas, which are now classified as a variant of SFT by the WHO.\cite{27} SFTs are primarily thoracic cavity neoplasms, mainly occurring in the pleura. Extrapleural SFTs have been observed in middle-aged adults with a median age of 50 years, with no sex predilection.\cite{26} Clinical symptoms, including hypoglycemia, may occur secondary to production of insulin-like growth factor.\cite{28}

The liver is a rare primary site for SFTs with less than 50 cases reported in the English literature.\cite{7–19} Patient characteristics associated with hepatic SFTs include a mean age of 55 years at presentation, female sex predilection (2:1), and an average tumor size of 17 cm.\cite{7} Although the vast majority of hepatic SFTs behave in a benign fashion, their unpredictable behavior must be emphasized. Four of the reported cases in the literature displayed aggressive behavior with distant metastases, with one of the cases having a latency period of 6 years between initial diagnosis and advent of metastatic disease.\cite{7–12} Metastatic primary hepatic SFTs are associated with larger tumor size (median size of 28 cm) and higher mitotic activity.\cite{9} However not all large tumors behave aggressively and no relationship between morphologic features and poor behavior were identified.\cite{9} These findings underscore the importance of long-term follow-up
in all affected patients, due to the absence of reliable features that would allow for prognostic or risk stratification in this patient population.

**Figure 4.** Immunohistochemical stains showing tumor cells to be diffusely positive for Vimentin (A), focally positive for β-Catenin (B) with occasional nuclear staining, and a very low proliferation rate with ki-67 (C)

The association of SFTs with pregnancy is even rarer. Our literature search reveals only four cases of SFT associated with pregnancy occurring in the liver, adrenal gland, orbit, and retroperitoneum.[21–24] The role of pregnancy in the growth of tumors, in general, is not fully understood. However, it is known that hormonal conditions may favor the growth of soft tissue tumors.[22] Pregnancy has been associated with rapid growth of uterine leiomyomas during early gestation and increased incidence of abdominal wall desmoid tumors.[29, 30]

It is probable that the rise of sex steroids, along with a multitude of placental, fetal, and maternal hormones, play a collective role in the growth of tumors during gestation. This is supported by the reported cases of SFT of the orbit and adrenal gland associated with pregnancy. Both of these cases showed rapid tumor growth during the gestation, with the SFT of the adrenal gland increasing 3 cm in size during the last trimester of pregnancy.[22, 23] Of the four reported SFTs associated with pregnancy, immunohistochemistry for ER and PR was performed in only the adrenal gland specimen, which showed focal positive staining for PR while negative for ER.[22] Of note, one study evaluated the expression of steroid receptors (AR, ER, and PR) in thirty-two pleural SFTs. Eight out of thirty-two expressed PR (25%), while none expressed ER or AR, suggesting that progesterone may have a role in the growth of SFTs.[31] Our case demonstrated positive staining (focal) for ER and PR (see Figure 3), suggesting a role for hormonal stimulation as a driver of tumor cell proliferation in SFTs in keeping with what has been described in the literature.

Histologically, typical SFTs show a patternless architecture characterized by a combination of alternating hypocellular and hypercellular areas separated by thick bands of hyalinized, somewhat keloidal, collagen and branching hemangiopericytoma-like vessels. Myxoid change, areas of fibrosis and interstitial mast cells are commonly observed. Mitoses are generally scarce. SFTs may show morphologic features of malignancy, such as hypercellularity, cytological atypia, tumor necrosis, and numerous mitoses (> 4 mitoses per 10 high-power fields) along with infiltrative margins. Immunophenotype in SFTs include positivity for STAT6 (restricted nuclear expression), CD34 (90% to 95% of cases), and CD99 (70%). Recent studies, using whole exome sequencing, identified a recurrent and pathognomonic NAB2-STAT6 gene fusion in 100% of tested SFTs.[32] Immunohistochemistry for STAT6 has been shown to be an excellent surrogate marker for the fusion protein, with a recent study showing staining limited to the nucleus in 100% of SFTs tested (total of 49 cases).[33]

Our patient’s tumor showed no morphologic features of malignancy and to date, she has been followed with imaging; showing no evidence of residual or recurrent disease.

The differential diagnosis of SFT of the liver includes other mesenchymal neoplasms found in this location; including smooth muscle tumors, peripheral nerve sheath tumors, inflammatory myofibroblastic tumor, desmoid tumors, scleerosed, hemangioma, gastrointestinal stromal tumor, fibrosar-
coma, and dedifferentiated liposarcomas and synovial sarcomas. The histologic appearance of the tumor, along with the results of a comprehensive immunohistochemical panel (positive for STAT6, CD34, BCL-2, vimentin, CD99 and negative for SMA, CD117, ALK-1, S-100, AE1/AE3, β-Catenin, desmin) is key for the diagnosis of SFT and to rule out other diagnostic possibilities. Of note, although nuclear STAT6 immunoreactivity is considered a highly sensitive and specific marker of SFTs and can help clinch the diagnosis in difficult cases, 20% of cases can show heterogeneous staining with zonal attenuation. This probably reflects differences in tissue fixation and ischemia, and was most commonly seen in big resection specimens. Thus, pre-analytical variables can affect the performance of the STAT6 immunostain and tumor samples from large resection specimens should promptly be placed in fixative to ensure optimal results.

In summary, primary SFTs of the liver are rare and the association with pregnancy is even rarer. Awareness of the association of SFTs with pregnancy is important, as the hormonal milieu of gestation may promote or initiate their growth. SFTs must be differentiated from other entities with different biological behaviors and treatments. The prognosis of SFT is favorable; however aggressive surgical removal of the tumor with clear margins of resection is the mainstay of therapy. More studies are necessary to determine the association of this neoplasm with pregnancy, along with identification of molecular and clinical features that could better predict its biologic behavior. Until then, long-term follow-up of these patients is paramount, due to the unpredictable behavior of these neoplasms.

CONFLICTS OF INTEREST DISCLOSURE
The authors declare no conflict of interest.

REFERENCES


