Calcifying Nested Stromal-Epithelial Tumor of the Liver
An Update and Literature Review

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Calcifying nested stromal-epithelial tumor is a rare entity that has gone by a variety of names in the literature: ossifying malignant mixed epithelial and stromal tumor, ossifying stromal-epithelial tumor, and desmoplastic nested spindle cell tumor of the liver. To our knowledge, approximately 38 cases have been reported in the literature. The histogenesis is still largely unknown but histopathologically is characterized by nests of spindle and epithelioid cells in an organoid arrangement surrounded by a prominent dense myofibroblastic stroma with occasional psammomatous calcification and focal heterotopic ossification. Vascular invasion is rare and tumoral recurrence is uncommon with only a single reported case of metastasis leading to death. Treatment is mainly by surgical intervention with the role of chemotherapy seeming limited, but lack of data hinders a true recommendation. It is important to rule out other processes such as hepatoblastoma, calcified hemangioma, synovial sarcoma, metastatic ossifying stromal-epithelial tumor, and desmoplastic nest-like ossifying malignant mixed epithelial and stromal tumor, nonbiliary tumor of the liver with nests of epithelioid and spindle cells and an associated desmoplastic stroma. The average size is 12.6 cm with a range of 2.1 to 30 cm. CNSET may display irregular borders as well as multinodularity with the cut surface showing a homogeneous, tan, granular-appearing texture (Figure 1). The histologic features that characterize CNSET are well-circumscribed, macrolobulated masses, with enhancement and calcification. Areas of calcification appear hyperdense, whereas cystic or myxoid components within the tumor appear hypodense. On magnetic resonance imaging examination, there is a predominant T1 hypointensity and T2 hyperintensity. Based on the imaging characteristics of CNSET, the radiologic interpretation is likely to be a hepatoblastoma or a calcified hemangioma.

PATHOLOGIC FINDINGS
The gross examination of CNSET often reveals a well-circumscribed and lobulated mass with variable calcifications. The average size is 12.6 cm with a range of 2.1 to 30 cm. CNSET may display irregular borders as well as multinodularity with the cut surface showing a homogeneous, tan, granular-appearing texture (Figure 1). The histologic features that characterize CNSET are well-circumscribed nests of relatively bland-appearing cells surrounded by a variably cellular desmoplastic stroma. The cells comprising these nests are small, uniformly spindled to large eosinophilic epithelioid cells. The spindle cells within the nests are arranged in short fascicles at the periphery of the nest, while the epithelioid cells are more apparent in the

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| Source, y | Age, y/Sex | Clinical | Location | Size, cm | Follow-up |
|----------|------------|----------|----------|----------|-----------|
| Assmann et al,19 2012 | 16/Male | Palpable abdominal mass/Cushing-like body habitus | Right and left lobes | Unknown | Disease free/post liver transplant |
| | 3.1/Female | Obstructed | Left lobe | 6.5 | Disease free |
| Marin et al,28 2010 | 33/Male | Epigastric pain, pyrosis, regurgitations | Left lobe | 20 | Unknown |
| Teseen et al,29 2017 | 13/Female | Cushing syndrome/worsening abdominal pain | Right lobe | 17.3 | Disease free/post liver transplant |
| Weeda et al,9 2016 | 16/Male | Cushing syndrome/weight gain, distended abdomen | Spans right and left lobe | 19.5 | Disease free |
| Heywood et al,15 2002 | 28/Female | Incidental | Right lobe | 14.5 | Recurrence developed after 72 mo |
| Hill et al,20 2005 | 2/Male | Abdominal mass | Right lobe | 5.5 | Disease free |
| | 6/Female | Incidental | Right lobe | 2.8 | Disease free |
| | 6/Female | Incidental | Right lobe | 7.5 | Disease free |
| | 14/Female | Abdominal mass | Left lobe | 15 | Disease free |
| Heerema-Mckenney et al,4 2005 | 2/Male | Incidental | Left lobe | 12 | Disease free |
| | 11/Female | Cushing syndrome/abdominal mass | Left lobe | 12 | Disease free |
| | 12/Female | Cushing syndrome/abdominal mass | Right lobe | Unknown | Disease free |
| | 14/Female | Ileus | Unknown | 30 | Recurrence after 12 mo |
| Brodsky et al,2 2008 | 17.5/Female | Cushing syndrome | Left lobe | 22 | Recurrence after 12 mo |
| Meir et al,16 2009 | 2.5/Female | Incidental | Right lobe | 5.5 | Disease free |
| Grazzi et al,18 2010 | 25/Female | Diarrhea/abdominal pain | Right lobe | 17 | Disease free |
| Makhlouf et al,6 2009 | 14/Female | Incidental | Right lobe | 16 | Disease free |
| | 19/Male | Incidental | Right lobe | 10 | Recurrence after 168 mo |
| | 15/Female | Incidental | Right lobe | 12 | Unknown |
| | 18/Female | Incidental | Right lobe | 20 | Died at 40 mo/postoperative complications/no recurrence |
| Rod et al,17 2009 | 32/Female | Incidental | Right lobe | 11 | Disease free |
| | 16/Male | Cushing syndrome | Right lobe | 19 | Disease free |
| | 33/Female | Incidental | Right lobe | 10 | Disease free |
| | 2/Female | Incidental | Right lobe | 5.5 | Disease free |
| Oviedo Ramirez et al,22 2010 | 17/Female | Facial edema and acne | Left lobe | 13.2 | Disease free |
| | 33/Male | Abdominal pain/dyspepsia | Left lobe | 16 | Unknown |
| Wang et al,14 2011 | 34/Female | Incidental | Left lobe | 13 | Disease free |
| Procopio et al,2 2014 | 23/Female | Abdominal pain | Left lobe | 16 | Unknown |
| Schaffer et al,3 2016 | 14/Female | Abdominal distention (associated with Beckwith-Wiedemann syndrome) | Left lobe | 12 | Disease free |
| Khoshnam et al,2 2017 | 14/Female | Cushing syndrome/abdominal pain (associated with Beckwith-Wiedemann syndrome) | Right lobe | 12 | Disease free |
| Homann et al,22 2011 | 16/Female | Ileus | Left lobe | Unknown | Died after 37 mo/pulmonary metastasis |
| Ghodke et al,21 2012 | 9/Male | Abdominal pain, fever, jaundice | Unknown | 5 | Unknown |
| Malowany et al,8 2013 | 2/Female | Incidental (associated with Beckwith-Wiedemann syndrome) | Right lobe | 2.1 | Unknown |
| Geramizadeh et al,19 2012 | 8/Male | Weight gain, abdominal pain | Right lobe | 10 | Died after 10 d (status postsurgical intervention) |
| Samarghandi et al,13 2015 | 11/Female | Weight gain, abdominal pain | Right lobe | 20 | Unknown |
| Total | 38 Cases | | Right lobe: 20 | Average 12.6 cm | |
| | 27 Female | | Left lobe: 11 | | |
Calcifying nested stromal-epithelial tumors are of uncertain histogenesis with several hypotheses as to the cell of origin. One postulation is an epithelial origin with differentiation toward a mesenchymal phenotype. In contrast another study has speculated a mesenchymal origin with the expression of WT-1, which reflects a mesenchymal to epithelial phenotype. Additionally, Assmann et al investigated factors involved in mesenchymal-epithelial transition and demonstrated increased expression of the mesenchymal-epithelial transition factors SNAIL, SLUG, TWIST, c-Met, vimentin, and β-catenin. These findings indicate impaired mesenchymal-epithelial transition as a possible pathogenetic mechanism of this rare tumor. Heerema-McKenney et al noted the focal intimate association of bile ducts and cellular nests, which also shared expression of CD56, leading to the theory of a possible hepatic mesenchymal precursor cell with primitive differentiation along the bile duct lineage. Lending support to such a notion is the CD56 expression seen in proliferating bile ducts of obstructive liver disease but not in so-called resting bile ducts.

**HISTOGENESIS AND MOLECULAR CHARACTERISTICS**

Calcifying nested stromal-epithelial tumors are of uncertain histogenesis with several hypotheses as to the cell of origin.1 One postulation is an epithelial origin with differentiation toward a mesenchymal phenotype. In contrast another study has speculated a mesenchymal origin with the expression of WT-1, which reflects a mesenchymal to epithelial phenotype.4 Additionally, Assmann et al investigated factors involved in mesenchymal-epithelial transition and demonstrated increased expression of the mesenchymal-epithelial transition factors SNAIL, SLUG, TWIST, c-Met, vimentin, and β-catenin. These findings indicate impaired mesenchymal-epithelial transition as a possible pathogenetic mechanism of this rare tumor.19 Heerema-McKenney et al noted the focal intimate association of bile ducts and cellular nests, which also shared expression of CD56, leading to the theory of a possible hepatic mesenchymal precursor cell with primitive differentiation along the bile duct lineage. Lending support to such a notion is the CD56 expression seen in proliferating bile ducts of obstructive liver disease but not in so-called resting bile ducts.4

**CLINICAL BEHAVIOR AND ASSOCIATIONS**

Although there are only limited data on the clinical progression, or lack thereof, owing to the small number of cases reported, we may still draw some conclusions based on the available data. To date there is only 1 incidence of tumor metastasis.22 A 16-year-old female patient, who received a liver transplant, was found to have lung metastases 28 months postoperatively (biopsy-proven metastatic CNSET) and then later died (37 months post transplant).22 However, in most cases with follow-up data, disease-free survival after resection (or transplant) appears to be 71% (24 of 34) with no recurrence of disease after follow-up, although 12% (4 of 34) of patients experienced a recurrence of their disease (range, 12–168 months of follow-up) and 1 patient died 40 months after transplant.6 Interestingly, among 3 of the adult cases, the presence of a calcified mass since childhood was found, which again points to a seemingly benign and indolent clinical course.4 However, with the tumor’s recurrence potential, a more apt designation would be a tumor of low malignant potential until further cases with clinical follow-up are reported.

Interestingly, of the 38 reported cases of CNSET, 3 are in association with BWS. Beckwith-Wiedemann syndrome is characterized by an overgrowth syndrome with numerous signs and symptoms depending on the affected individual: omphalocole, other abdominal wall defects, macroGLOSSIA, visceromegaly, or hypoglycemia. Of the 3 reported associations, 2 cases of BWS are genetically confirmed. All the 3 cases show WT-1 positivity and none of them have a concurrent diagnosis of Wilms tumor, causing Khoshnam et al to postulate that there may be some cross-reaction between WT-1 and the BWS loci in the short arm of chromosome 11.

**DIFFERENTIAL DIAGNOSIS**

Calcifying nested stromal-epithelial tumor, having both an epithelial and mesenchymal component with variable calcification and ossification, lends itself to a myriad of differential diagnostic considerations. The differential diagnosis includes synovial sarcoma, hepatoblastoma, desmoplastic small round cell tumor, inflammatory myofibroblastic tumor, spindle cell carcinoma, metastatic gastrointestinal stromal tumor,
and finally, rhabdomyosarcoma.\textsuperscript{4,6,12,20} Hepatoblastomas, especially epithelial and mesenchymal hepatoblastomas, contain mesenchymal components such as fibroblastic stroma or osteoid, which makes them a very important differential diagnostic consideration in the setting of CNSET with osteoid formation.\textsuperscript{12} However, a distinguishing feature of hepatoblastoma is the presence of fetal or embryonal hepatocytes and the positivity of immunohistochemical staining for AFP or Hep Par 1. Additionally, extramedullary hematopoiesis is common in fetal and embryonal subtypes of hepatoblastoma. Small cell undifferentiated hepatoblastoma with its sheets of keratin-positive cells, oval hyperchromatic nuclei, variable nucleoli, and increased mitotic activity may also enter the differential diagnosis.\textsuperscript{23} The challenging aspect to this subtype is the lack of histology, recapitulating either the fetal liver or embryonal differentiation.\textsuperscript{23} Similar to CNSET, small cell undifferentiated hepatoblastomas are negative for AFP and Hep Par 1.\textsuperscript{23,24} However, the described translocation involving the long arm of chromosome 22 and loss of INI1 expression in a subset of small cell undifferentiated hepatoblastomas may aid in the differential with CNSET.\textsuperscript{24–27} Synovial sarcoma, the biphasic pattern, has spindle-shaped cells resembling synoviocytes and epithelial cells, which may form nests and cords. When there is doubt about the distinction on morphologic

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**Figure 2.** A, Low-power photomicrograph revealing a well-circumscribed tumor of the liver with an organoid proliferation of spindle or epithelioid cells and osteoid formation surrounded by prominent myofibroblastic stroma. B, High-power photomicrograph showing spindle and epithelioid cell nests with intermixed osteoid formation. C, Photomicrograph of β-catenin immunohistochemical stain showing cytoplasmic and nuclear staining pattern. D, Photomicrograph of WT-1 immunohistochemical stain showing cytoplasmic dotlike paranuclear staining pattern (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [B]; original magnification ×400 [C and D]).
grounds, one may also consider the usefulness of identifying the SYT-SSX1 and SYT-SSX2 translocations characteristic of synovial sarcoma by polymerase chain reaction. None of the CNSET cases are reported positive for the SYT-SSX rearrangement. Desmoplastic small round cell tumor is composed of small round blue cells in nests and anastomosing trabeculae surrounded by desmoplastic stroma. Like CNSET, desmoplastic small round cell tumors may also show areas of predominately spindle cell morphology and focal necrosis or cystic degeneration. Desmoplastic small round cell tumors are typically both positive for WT-1 stain and t(11;22) WT1-EWS translocation. However, WT-1-EWS translocation is lacking, although WT-1 nuclear or cytoplasmic dotlike paranuclear staining pattern can be seen in CNSET cases.\textsuperscript{5,6,20} Metastatic gastrointestinal stromal tumors usually have perinuclear vacuolization and often distinct nuclear palisading without desmoplastic stroma. The positive immunohistochemical stains for CD34, CD117, and DOG-1 in gastrointestinal stromal tumor are typically negative in CNSET. In the distinction of CNSET from neuroendocrine tumors, the positivity of CNSET for CD56 and neuron-specific enolase may cause confusion initially, but CNSETs are negative for synaptophysin and chromogranin A.

### TREATMENT CONSIDERATIONS

Treatment considerations for CNSET include wedge resections for smaller tumors and more substantial interventions in the form of partial hepatectomy or liver transplant for larger tumors.\textsuperscript{22,28,29} Chemotherapy using soft tissue sarcoma or hepatoblastoma protocol has been reported in the literature. However, it is unclear whether chemotherapy has any significant role in preventing tumor recurrence, as the complete resection of tumor has proved reported in the literature. However, it is unclear whether chemotherapy holds any benefit with the current data available.

### SUMMARY

Calyfing nested stromal-epithelial tumor is rare and is most commonly seen in young children with a female predominance. The histogenesis is still largely unknown but histopathologically is characterized by nests of spindled cells in an organoid arrangement with or without intermixed epithelioid cells surrounded by a prominent dense myofibroblastic stroma with occasional psammomatous calcification and focal heterotopic ossification. Vascular invasion is rare and tumoral recurrence is uncommon with only a single reported case of metastasis leading to death. Other patient deaths are the result of postoperative complications and not directly due to tumoral causes. Treatment is mainly by surgical intervention with the role of chemotherapy seeming limited but lack of data hinders a true recommendation. It is important to rule out other processes such as hepatoblastoma, calcified hemangioma, synovial sarcoma, metastatic gastrointestinal stromal tumor, desmoplastic small round cell tumor, among others, which appear similar radiographically and histologically.

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