Mesenchymal Tumors of the Liver: What’s New and Unusual (My Perspective)

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Introduction

Mesenchymal tumors of the liver are relatively uncommon (except cavernous hemangioma), so many pathologists are not as familiar with variations from the more typical appearances as described in many standard texts (See General References 1-4) and/or have not had significant experience with the rare variant types of mesenchymal lesions. Recently, there has been more focus on unusual and rare forms of mesenchymal tumors, especially within the spectrum of vascular lesions, so my personal perspective of these newly-described and unusual variants will be the focus of this presentation.

Cavernous Hemangioma, with Hemangioma-like Vessels in adjacent liver

Cavernous hemangioma (CH) is the most common form of mesenchymal/vascular tumor in the liver, but an under-recognized feature is the presence of multiple smaller clusters or foci of vascular structures in the liver adjacent to a large/giant CH; these have been designated as hemangioma-like vessels (HLV) (5,6). The structure of HLVs is identical to the architecture of the large vascular spaces seen in CH, with a predominantly collagenous wall with disorganized and somewhat scant smooth muscle and elastic fiber content. This wall is lined by cytologically bland/unremarkable endothelial cells with very low proliferative index (<2%). HLVs tend to be located in the periportal region, and may be single or multiple as a cluster.

Other unusual variants of CH have also been recently described (7) that include CHs involving >50% of the liver, multifocal forms within the liver, and those with HLVs extending into and around the structures of the hilum. In addition, rarely, CH may be associated with similar benign lesions in the lung, spleen, and omentum.

Small Vessel Hemangioma (SVH)

This type of hemangiomatous tumor is rare, and can be a diagnostic challenge, especially in the distinction from angiosarcoma. In our recent review of a small series of cases collected from an international group of pathologists (8), we found these lesions consist of small caliber vascular structures with an anastomosing pattern. The walls of the structures are thin, with only minimal collagenous framework, if visible at all, and are lined by small, usually rounded endothelial nuclei that are CD34 and CD31 positive. The cellularity of the endothelial lining is more than that of CH and the proliferative rate is also somewhat increased as compared to CH, with a rate of 4-10% as stained with Mib-1 (Ki-67). The edges of the lesions are typically irregular, with the small vascular structures percolating into the adjacent sinusoidal architecture which can mimic a pattern of scaffolding growth
typical of angiosarcoma. But in the case of this lesion, there is no significant cytologic atypia, the proliferative rate is lower than seen with angiosarcoma, and the extension along the sinusoids is less prominent. Of note, however, this pattern of growth can alter the background liver architecture to the extent that the hepatic plates can become distorted, with plates greater than 2-3 cells in thickness. This feature then mimics the widened trabeculae of well-differentiated hepatocellular carcinoma. (Similar plate changes can also be seen in vascular malformations of the liver, see below). Some features comparing angiosarcoma to this lesion are noted in the following table.

Table 1. Immunohistochemical findings in vascular tumors (8,9)

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>CD31</th>
<th>CD34</th>
<th>PS3</th>
<th>Mib1 (Ki-67) PI</th>
<th>GLUT-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVH (n=6)</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
<td>4% (0-10%), n=7</td>
<td>0%, n=5</td>
</tr>
<tr>
<td>CH (n=10)</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>EHE (n=8)</td>
<td>88%</td>
<td>88%</td>
<td>38%</td>
<td>6% (0-12%)</td>
<td>38%</td>
</tr>
<tr>
<td>AS (n=6 or7)</td>
<td>100%</td>
<td>80%</td>
<td>29%</td>
<td>32% (15-50%), n=7</td>
<td>50%, n=7</td>
</tr>
</tbody>
</table>

SVH= small vessel hemangioma, CH= Cavernous hemangioma, EHE= epithelioid hemangioendothelioma, AS= angiosarcoma, PI= Proliferative index, CD31, CD34, pS3, Mib1, and GLUT all represent immunohistochemistry findings.

Infantile Hemangioma

This tumor typically presents early in life with heart failure if the tumor is large. The structure of the vessels can be variable from zone to zone, both in size as well as components to the vascular walls. Degenerative and/or involutional changes, as well as intratumoral hemorrhage is common. Very large vessels can also be seen in these lesions (personal observation). Some of the small vascular structures can look much like the small vessel hemangioma described above, but other larger spaces with thicker walls have the appearance more like that of CH. The large zones of degenerative, myxoid to fibrous areas, with focal calcifications can make biopsy diagnosis somewhat difficult as these areas may completely lack a vascular pattern. The edge of the lesion can also be very unusual in appearance as the tumor also insinuates along the sinusoids to grow along the liver plates, causing abnormal clusters of hepatocytes. Ductular components are often seen entrapped within the tumor, and can be especially prominent at the periphery. These ductules may not be true bile ducts, but rather may represent a reactive metaplastic process when the hepatocytes, which are entrapped by the tumor as it grows along the sinusoids, transform to a more ductular phenotype. These ductular elements, as well as the hepatocytic changes at the edge of the lesion can mimic features of hepatoblastoma or maybe get confused with mesenchymal harmartoma on small samples, so it may be useful to remember this particular feature when examining biopsy specimens.

Epithelioid Hemangioendothelioma

This presentation will not spend any significant time to review this neoplasm, but it should be noted that in rare cases, cellular areas with less stromal component, nuclear atypia and a scaffolding pattern of growth like that of angiosarcoma can be rarely seen in these lesions; in such a case, it is possible that this may represent a more aggressive component (personal observation).
Angiosarcoma

The routine morphology of angiosarcoma (AS) has been well-described (1-4). There are some features that are actually somewhat common, though, that are worth reviewing in more detail, particularly those that mimic other less aggressive lesions already discussed above. One of these features is the scaffolding pattern of growth that can also be seen in many of the vascular lesions including the small vessel hemangioma, infantile hemangioma, and endothelial hemangioendothelioma. However, in AS, the proliferative rate is typically higher (see table 1 above) and cellular atypia is more pronounced. As in these other vascular lesions, AS also can alter the hepatic plate architecture as it spreads along the sinusoids, leading to entrapment of hepatocytes in plates and clusters. As the tumor progresses, these entrapped hepatocytes degenerate, resulting in a fibrous core lined by the tumor cells, and on sections, these remnants can appear as either as anastomosing vascular spaces, or as “papillary” structures as viewed on the glass slide.

Mimics of Vascular Neoplasms

Vascular malformations

Although these are not true neoplasms, the changes seen associated with these lesions, especially in larger lesions that are typical of Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Syndrome), may have many overlapping features with the other benign vascular neoplasms discussed above, as well as lead to significant hepatic plate architectural abnormalities as already described in the small vessel hemangioma (see above), and to nodular transformation of the liver in the form of focal nodular hyperplasia-like lesions (10, 11). The primary vascular abnormalities typically consist of highly irregular muscular vessels in increased numbers that are present within the connective tissue areas of the liver (portal and hilar areas), and the subsequent consequences of the abnormal blood flow through these lesions end up resulting in thrombosis and ectasias of these vessels. This, in turn, causes secondary changes in the liver that probably are primarily associated with vascular flow abnormalities and/or ischemic events. The ischemic complications can range from infarction of both lobular and portal structures as an acute serious complication of thrombosis, or may be more limited as a chronic effect such as periduct fibrosis. The flow abnormalities can lead to “capillarization” of the sinusoids (transformation to CD34 positivity), with formation of telangiectatic sinusoids that usually begins in the periportal regions. Over time, though, these telangiectasias can lead to a much larger vascular network of structures that resemble the morphology of cavernous hemangioma, or can also alter the hepatic plate architecture to the point that plates are widened as a mimic of the wide plates of HCC.

Undifferentiated (Embryonal) Sarcoma:

This presentation will not discuss this entity in detail, as this is well-described in many general texts (1-4). We would note, however, that this lesion lacks vascular markers, even though it can typically show focal positivity for alpha-1-antitrypsin, as well as a variety of other markers (12, 13). In addition, Glypican-3 can also be positive, and in our experience at UCSF, the giant cells may show this positive staining. The primary reason, however, to present this case as part of this presentation is to point out
that this tumor can also infiltrate the liver sinusoids in a similar pattern to that seen in the vascular neoplasms, and so mimic a scaffolding pattern of growth that could be mistaken for angiosarcoma. (In fact, this very feature has been recently misinterpreted in a case report as an embryonal sarcoma with both mesenchymal hamartomatous elements and angiosarcoma. Of note, I had reviewed this case as one of three expert consultants, none of the three consultants made this interpretation as reported, nor were any of the consultants mentioned in the report. I intentionally have not referenced this paper in this handout.)

**Angiomyolipoma**

An excellent review of the variants of AML was originally published by Tsui, et al (14), and additional texts also expand on these variants (15,16). The trabecular and inflammatory variants may represent the most diagnostically challenging, so one should be aware that these tumors can have a complex vascular or sinusoidal-like pattern, as well as an extremely prominent inflammatory component that could be mistaken for inflammatory pseudotumor or even a lymphoproliferative lesion.

**References from my personal perspective used for this presentation**

**General**


**Lesion-specific**


Mesenchymal Tumors

Focus on Vascular Tumors
- Benign and the “Probably Benign”
  - Newly-described and variant lesions
- Malignant
  - Distinction of benign/low grade lesions from Angiosarcoma
  - What is NOT Angiosarcoma

Focus on Angiomyolipoma: Problem variants that still lead to diagnostic errors
- Epithelioid, inflammatory, trabecular

Cavernous Hemangioma (CH)

- Not true arterial or venous architecture
- No organized muscle bundles
- No elastic laminae
- Not capillary-like
Cavernous Hemangioma (CH)

- Not true arterial or venous architecture
- No organized muscle bundles
- No elastic laminas
- Not capillary-like

Sclerosis within Cavernous Hemangioma

- Sclerosis of thrombosed, ischemic zones with scar formation.
- “Neo-vessels” Recanalized channels

Cavernous Hemangioma:
What is often “not seen”....

- Hemangioma-like vessels (HLV) in adjacent liver commonly seen with giant CH
  - Low mitotic/proliferative rate <5%
  - Present in almost 80% (16/19) of CH >5 cm
  - Retain composition of vascular walls in CH

Cavernous Hemangioma-like vessels in adjacent liver
Giant Cavernous Hemangioma

38 yr old woman, in liver failure.
- Explant, right lobe with giant hemangioma
- Left Lobe: Smaller, irregularly shaped CHs and transitional areas with HLVs admixed with liver, as well as smaller hemangiomas

Lesion extending into hilum around arteries, nerves and ducts

“Metastatic” and “Invasive” Cavernous Hemangioma

Cavernous Hemangioma Variant

Diagnoses: Giant Cavernous Hemangioma and Cavernous Hemangiomatosis
- CH-like vessels throughout liver
- Lung, spleen, omentum involved with CH-like lesions

“Metastatic” and “Invasive” Cavernous Hemangioma

Cavernous Hemangioma Variant

Diagnoses: Giant Cavernous Hemangioma and Cavernous Hemangiomatosis
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Vascular Malformations

- Hereditary Hemorrhagic Telangiectasia (HHT) arterial-venous malformations
  - also known as Osler-Weber-Rendu

- Other Arterial and Venous Malformations with similar features
  - (may or may not be HHT)

Spectrum:
Early or mild lesions can look much different than advanced or severe lesions probably primarily due to thrombosis and ischemic effects.

Vascular Malformations: Early Lesions or Mild Involvement

Contributors and co-authors of 2 abstracts:

Periportal fibrosis, Elastochrome stain

Periductal fibrosis (as early ischemic lesion)
### Vascular Malformations: More Severe or Advanced Lesions

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extension of lesions into sinusoids</td>
<td></td>
</tr>
<tr>
<td>Thrombosis within vessels and sinusoids</td>
<td></td>
</tr>
</tbody>
</table>

### Vascular Malformations: More Severe or Advanced Lesions

- Hemangioma-like changes, extensive sinusoidal dilation
- Cavernous hemangioma-like transformation

### Vascular Malformations: Severe sinusoidal changes

- Hemangioma-like changes, extensive sinusoidal dilation
- Cavernous hemangioma-like transformation

### Small Vessel Hemangioma

- Rare
- Newly described

- Small vascular channels with thin walls
- Bland endothelial cells with low proliferative rate <10% (CH <5%)
- Intermediate tumor cell density
- Irregular “infiltrative” growth pattern at border
- Abnormal liver architecture mimics HCC
- Scaffolding effect mimics angiosarcoma
Small Vessel Hemangioma

Small channels, thin walls, bland nuclei

Only focal fibrotic areas

Small Vessel Hemangioma

Small channels with thin walls, no organized muscle

Low Mib1 (Ki-67) rate

Small Vessel Hemangioma

Center of lesion, bland endothelial cells

Edge of lesion, with altered cell plate width

Small Vessel Hemangioma

Edge of lesion, trichrome

Edge of lesion, reticulin
Small Vessel Hemangioma

- Small vessel hepatic hemangioma (SVH): Exact outcome not definitive, so now recommending excision and followup.
- Differentiation from angiosarcoma: AS has higher proliferative rate (>15%) and subset + for P53 and GLUT1, but negative in small vessel hemangioma

References

Epithelioid Hemangioendothelioma

- Elastochrome stain: Central vein involvement by tumor
  - Elastochrome: trichrome plus EVG stain
  - Highlights vein wall elastic fibers
- Angiosarcoma-like pattern of scaffolding growth
Angiosarcoma

- Most aggressive form of vascular malignancy
- Highest proliferative rate
- Epithelioid or spindle cell forms
- Cystic and/or solid
- Known for the typical feature of “scaffolding” growth pattern

Angiosarcoma

Epithelioid pattern

High MiB1 (Ki-67) rate

Angiosarcoma

Scaffolding growth pattern along sinusoids

CD34 and expanded sinusoidal growth

Angiosarcoma

Cystic change (upper right)
Congestion
Necrosis
Sinusoidal growth
Angiosarcoma

Scaffolding pattern of growth surrounds hepatocytes

Sinusoidal growth results in anastomosing channels and pseudopapillary pattern

Angiosarcoma: Highlights

- High proliferative rate and cytologic atypia
- Early pattern of growth typically along sinusoids (scaffold-like); Atypical endothelial cells, dilated sinusoids
- Later pattern of growth can be pseudopapillary to solid; irregularly-shaped blood filled spaces
- Lacks the stromal prominence of epithelioid hemangioendothelioma, but overlapping cases may be seen
Undifferentiated (Embryonal) Sarcoma of the Liver

**What else is NOT angiosarcoma**

**Undifferentiated (Embryonal) Sarcoma**

- Typically younger patients; tumor of uncertain etiology
- Can be cystic due to necrosis/degeneration with irregular edges!! (Pattern similar to angiosarcoma scaffolding)
- Immunohistochemistry
  - Reactive with alpha-1-antitrypsin, alpha-1-antichymotrypsin, vimentin
  - Occasional cytokeratin positivity
  - Some CD10 and p53 positivity
  - Negative hepatocyte-Ab, muscle, S-100 and CD34
- Glypican-3 can be positive in giant cells (personal observation)

Undifferentiated sarcoma, tumor edge with growth along sinusoids

- PASD + globules
- Also Alpha-1-antitrypsin +

Undifferentiated Embryonal Sarcoma

Problem with Literature Search
- THIS IS NOT THE CORRECT DIAGNOSIS as per three expert consultants
- Authors got confused about peripheral growth

Angiomyolipoma

Problem variants
- Epithelioid, Trabecular, and Inflammatory

Problem Case
- 37-year-old woman
- 11 cm pedunculated mass
- No cirrhosis or other risk factors for HCC
- Mass noted during routine gynecologic exam, no symptoms
HCA, HCC?

Reticulin Stain: too much loss for HCA

Keratin and HMB-45

Angiomyolipoma, epithelioid variant

### Angiomyolipoma

**Classic features:**
- Fat
- Epithelioid
- Spindle cells

### Angiomyolipoma

<table>
<thead>
<tr>
<th>Epithelioid Cells</th>
<th>Spindle Cells</th>
</tr>
</thead>
</table>

### Angiomyolipoma

- HMB-45: stains stronger on epithelioid cells
- SMA: usually stains spindle cells

### Problem Case: Trabecular Angiomyolipoma
Problem Case: Trabecular Angiomyolipoma

Problem case: Inflammatory Angiomyolipoma

Focal dense to scattered diffuse T-cell infiltrate

Problem case: Angiomyolipoma, Inflammatory and Trabecular

Case with both inflammatory and “trabecular” background

Problem case: Angiomyolipoma, Inflammatory and Trabecular

HMB-45

SMA
Angiomyolipoma, Mixed variant

| Fatty areas | Trabecular areas |

Angiomyolipoma, Mixed variant

| Inflammatory areas, 10x |

Angiomyolipoma, Mixed variant

| HMB-45 |

Inflammatory foci with absent staining
(SMA only rare + cell, not shown)

THANKS FOR THE INVITATION TO PRESENT THIS TOPIC

AND SPECIAL THANKS TO ALL WHO HAVE CONTRIBUTED TO THE REFERENCED STUDIES:
WE WOULDN'T HAVE THIS DATA WITHOUT THESE COLLABORATION