Introduction.
Primary tumors of the liver are divided into benign and malignant epithelial and non-epithelial neoplasms. The epithelial neoplasms are the most common, and fall predominantly into the hepatocellular and bile-ductular types. However, in addition, other nonneoplastic, tumor-like lesions of various types can be of significance as well. The World Health Organization’s classification scheme which includes both neoplasms and tumor-like lesions is listed in Table 1.

Reporting of tumor resection specimens.
The verification of tumor type and status as a primary or metastatic neoplasm versus a nonneoplastic tumor are the most important considerations in the diagnosis. The descriptive comments should focus on information important for tumor staging such as tumor size (smaller or larger than 2 cm), number of lesions (single or multiple), which lobes (or segments) are involved, local extension of the lesion outside of the liver, and the presence or absence of gross vascular invasion, especially noting which of the major vessels (portal or hepatic vein) are involved. Microscopic evaluation of a mass should have adequate numbers of sections relative to tumor size in order to evaluate for vascular invasion or extension outside of Glisson's capsule, since these factors which are associated with decreased survival. Sections near the edge of the tumor are generally recommended to identify vascular invasion if gross invasion is not noted. Any gross observation of possible large vessel invasion should be documented microscopically. A section of nonneoplastic liver should also be included in order to identify any significant pathology.

Generally, it is recommended that the surgical margins of the resection should be inked prior to sectioning the tumor in order to more definitively evaluate the distance from the margin to the tumor, and the status of the resection margins should be included in the report. Some studies have suggested that a tumor-free margin of at least 1cm may be directly related to a better prognosis for some malignant tumor types. Other studies have shown that more extensive resections of hepatocellular carcinomas are preferable to limited excisions when the lesion is small. Thus, the distance from tumor to the closest margin of resection should be documented.

Biopsy samples- special considerations
Both small core and fine needle aspiration biopsy (FNAB) are often utilized successfully for the diagnosis of specific tumor types. However, it is important to remember that the accuracy of the FNAB can be enhanced by utilizing extra tissue preparations such as cell buttons in order to evaluate the microhistology of paraffin embedded sections of the sample collected from the FNAB material. Utilization of such methodology is especially helpful in the evaluation of well-differentiated lesions of hepatocellular type, in which subtle cytologic features such as the cell size, crowding of nuclei, and increased nuclear:cytoplasmic ratio or architectural features such as the formation of trabeculae or the width of the cell plates may be difficult to assess on smears alone. In these instances, the use of histologic sections in combination with well-prepared smears are highly successful in differentiating the well-
differentiated hepatocellular carcinoma from other lesions such as adenoma, focal nodular hyperplasia, large regenerative nodules, or dysplastic nodules. In addition, preparation of the cell button in cases of poorly differentiated neoplasms or in tumors with unusual morphology can result in more accurate diagnoses by the application of immunoperoxidase techniques to these samples.

Since the biopsy material is often quite limited in amount, it is recommended that slides of unstained material also be cut when the block is initially sectioned in order to insure that sufficient material will be available if it becomes necessary to evaluate additional level sections or other stains. It is also advised that the usual panel of stains (which often include trichrome, reticulin, PASD, and iron stains) should not be ordered automatically at the time of gross examination as this excess sectioning (before examination of the H&E morphology) often depletes the block of the diagnostic material so that sufficient tissue may not be available for other more diagnostic stains.

References
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<thead>
<tr>
<th>Epithelial tumors or tumor-like lesions</th>
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<tbody>
<tr>
<td><strong>Benign</strong></td>
<td></td>
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<tr>
<td>Large regenerative nodule</td>
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<tr>
<td>Low-grade dysplastic nodule</td>
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<td>High-grade (borderline) dysplastic nodule</td>
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<td>Hepatocellular adenoma</td>
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<td>Focal nodular hyperplasia</td>
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<td>Bile duct adenoma</td>
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<td>Bile duct hamartoma</td>
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<td>Biliary cystadenoma</td>
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<td>Intraductal biliary papillomatosis</td>
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<td>Congenital biliary cysts</td>
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<td>Focal fatty change</td>
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<tr>
<td><strong>Malignant</strong></td>
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<tr>
<td>Hepatocellular carcinoma, including fibrolamellar variant</td>
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<tr>
<td>Combined hepatocellular and cholangiolar carcinoma</td>
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<tr>
<td>Cholangiocarcinoma, peripheral, hilar, and extrahepatic type</td>
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<td>Biliary cystadenocarcinoma</td>
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<td>Intraductal papillary adenocarcinoma</td>
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<th>Nonepithelial tumors or tumor-like lesions</th>
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<td>Hemangioma</td>
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<td>Angiomyolipoma</td>
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<td>Infantile hemangioendothelioma</td>
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<td>Mesenchymal hamartoma</td>
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<td>Localized fibrous tumor</td>
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<td>Solitary necrotic nodule</td>
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<td>Inflammatory pseudotumor</td>
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<td>Infectious cysts</td>
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<td>Other rare benign tumors</td>
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<tr>
<td><strong>Malignant</strong></td>
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<tr>
<td>Epithelioid hemangioendothelioma</td>
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<tr>
<td>Angiosarcoma</td>
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<td>Undifferentiated sarcoma (embryonal sarcoma)</td>
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<tr>
<td>Lymphoma and other hematopoietic tumors</td>
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<tr>
<td>Kaposi’s sarcoma</td>
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<td>Other malignant tumors</td>
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CASES 1 AND 2- LESIONS IN NONCIRRHOTIC LIVERS

CASE 1

Clinical history and operative findings: 41 year old man who was undergoing a total proctocolectomy for rectal cancer was found at surgery to have a liver mass. The mass measured 6 cm and was nodular. The surrounding liver was unremarkable.

Pathologic findings: The cut surface of the lesion was nodular and tan. The lesion was not encapsulated but was well demarcated from the surrounding liver. Sections show nodular parenchyma with bands of fibrosis. No significant hepatocellular atypia is seen. The fibrotic areas contain chronic inflammation and proliferating bile ductules at the interface.

Diagnosis- FOCAL NODULAR HYPERPLASIA (FNH)

Comment

Clinical features. Focal nodular hyperplasia (FNH) is a benign, nonneoplastic lesion, which is most commonly seen in young women. A significant number of these lesions can still be seen in men. FNHs are usually solitary lesions, but can be multifocal in a 20-30% of the cases. Classic FNH often is noted as an incidental finding, but may also present with complications due to large size (only rarely due to hemorrhage or with complaints of upper abdominal pain). Nodules similar to FNH have been described adjacent to hemangiomas. Some patients with the so-called multiple FNH syndrome have at least two FNH lesions associated with one or more lesions such as hepatic hemangioma, arterial structural defects, vascular malformations, meningioma, and astrocytoma. A rare variant of FNH, the telangiectatic type, is commonly associated with the multiple FNH syndrome.

Pathogenetic features. FNH is not thought to develop due to the use of oral contraceptives, but many speculate that this lesion may increase in size with their use or regress with their cessation. The currently favored hypothesis for the development of FNH is that it represents a hyperplastic and altered growth response to changes in bloodflow in the parenchyma surrounding a preexisting arterial malformation. The presence of numerous abnormal muscular vessels within the lesion and the fact that some of these lesions or similar hyperplastic foci have been noted in association with hemangiomas and the Budd-Chiari syndrome lend support to this theory. (The International Working Party has recommended that FNH-like lesions associated with the Budd-Chiari syndrome and Osler-Weber-Rendu disease not be designated as FNH, but rather referred to as regenerative nodule). FNH has no known malignant potential and, in spite of its rare association with fibrolamellar hepatocellular carcinoma, most feel that the lesion itself does not progress to carcinoma. Instead, it is speculated that the association of FNH with fibrolamellar hepatocellular carcinoma may represent a hyperplastic response in the adjacent parenchyma to the increased vascularity of the carcinoma. Some have proposed that FNH may have clonal features to the nodules, but this is still controversial.

Gross features. FNH has a nodular appearance (which can suggest the appearance of macronodular cirrhosis), and tends to be lighter brown than the adjacent liver. These lesions are often located near the capsule of the liver, which can cause the surface of the liver to have a nodular appearance mimicking cirrhosis, and occasionally, the lesions can be pedunculated. The edges of FNH appear demarcated from the adjacent normal parenchyma because of the nodularity, but no fibrous capsule is present. The lesions may vary considerably in size. Most of these lesions have a "central fibrous scar," which consists of fibrovascular tissue (usually not
dense scar tissue), but this central focus of connective tissue may be absent. A rare variant of this lesion, the telangiectatic type, does not have the central fibrous zone, but rather has a gross appearance of either the hepatic adenoma or a vascular lesion such as hemangioma or peliosis hepatitis.

**Microscopic features.** The classic type of FNH is composed of mostly normal-appearing hepatocytes arranged in incomplete nodules that are partially separated by fibrous tissue, which tends to extend from the central fibrous zone when it is present. An important feature is the variable numbers of bile ductular structures present within the fibrous stroma and at the edge of the nodules. The cell plate architecture with an intact reticulin framework is similar to that in normal liver, but the cell plates are usually wider (2-3 cells thick) as in a regenerative nodule. The hepatocytes in the lesion can demonstrate increased glycogen in the cytoplasm, as well as other findings such as focal fatty change, bile stasis, lipofuscin, iron pigment, copper-associated protein, and Mallory bodies. Some foci of atypical hepatocytes with larger nuclei and mild hyperchromasia, with or without conspicuous nucleoli, can be present. Another important diagnostic feature is the presence of medium to large, thick-walled muscular vessels, which often exhibit myointimal myxoid or fibromuscular hyperplastic changes. These vessels are not a component of a portal tract as there is no large duct of similar caliber or portal vein associated with them. In fact, usually no normal portal tracts are present within the lesion, although a bile duct of intermediate or large caliber can be found in the central fibrous zone in rare cases. Sinusoids can be somewhat dilated, and Kupffer cells can be present. Inflammatory cell infiltrates are relatively common, and generally consist of lymphocytes, although neutrophils and eosinophils can be noted, especially around the bile ductular structures. Rarely, granulomas may be seen.

The telangiectatic variant contains dilated blood-filled vascular spaces instead of a central fibrous zone, so the gross appearance may be more typical of adenoma, hemangioma or peliosis hepatitis. The arteries in this variant are smaller and more numerous than in typical FNH, and the fibrous septa are less prominent.

Other, relatively rare, nonclassical forms can be present, including forms that lack the central fibrous zone, with the macroscopic and microscopic appearance mimicking adenoma and the telangiectatic form. The thick walled vessels are present at least in part of these lesions, and bile ductular proliferation is always present, although this latter feature may be very focal and subtle.

**Special studies.** FNH will stain positively for the usual hepatocellular markers including the cytokeratin marker CAM5.2 and the canalicular marker polyclonal CEA. In addition, CD34 will often be positive on the endothelial cells lining the cell plates, so this marker cannot be used to distinguish this lesion from adenoma or hepatocellular carcinoma (HCC). Alpha-fetoprotein is also negative in these lesions.

**Differential diagnosis.** FNH resembles hepatic adenoma or normal liver on small biopsy samples. One of the most important distinguishing feature for FNH are the bile ductular structures (see Table 2). Due to the relative paucity of the bile ductular findings, a large sample of core needle biopsy or a wedge biopsy is likely to be necessary to make this diagnosis. The finding of the large vessels with abnormal hyperplastic features surrounded by connective tissue may also be very helpful, as the larger vessels in adenoma tend to have a more normal configuration and lack significant perivascular connective tissue stroma.
CASE 2

Clinical history and operative findings: 30 year old woman with chest pain and RUQ pain for 6-9 months. Abdominal U/S demonstrated a liver mass that was confirmed with abdominal CT and MRI. The tumor was 8 cm and hemorrhagic while the adjacent liver appeared normal.

Pathologic findings: The tumor was hemorrhagic and tan with a smooth cut surface. Sections show a proliferation of hepatocytes with areas containing fibrin and hemorrhage. No portal areas are seen, but there are thin walled vessels. The hepatocytes are arranged in two-cell-thick liver plates with intact reticulin framework.

Diagnosis- HEPATOCELLULAR ADENOMA (HA)

Comment

Clinical features. Hepatic adenomas (HA) are rare tumors that are seen almost exclusively in young women during their reproductive years and are only rarely found in men or children. HA can be single or multifocal; the latter condition known as multiple hepatocellular adenomatosis. These tumors occur in a liver that is histologically normal or nearly normal. The clinical presentation is generally that of an abdominal mass, but some patients also have complaints of abdominal pain, discomfort, or nausea, and a significant number present with hemoperitoneum. Serum alkaline phosphatase may be elevated, but serum AFP levels are generally normal or minimally elevated. Radiographically, the lesions show an increased vascular pattern.

Pathogenetic features. Many HAs are thought to result from the use of oral contraceptives or anabolic steroids. However, with the low-dose pills now widely used, the incidence may be decreasing. Some of the HAs associated with oral contraceptives appear to regress after cessation of the drugs, but others do not. Other risk factors for the development of adenomas include metabolic disorders, especially the carbohydrate metabolic disorders such as the glycogen storage diseases I and IV, galactosemia, and familial diabetes mellitus, as well as tyrosinemia. The consensus opinion of the International Working Party is that the diagnosis of adenoma should not be made for a lesion arising in a cirrhotic liver unless there is evidence of regression when the stimulus is removed or one of the above risk factors is present. Rarely, hepatocellular carcinomas have been found arising within HA.

Gross features. HAs are round tumors that tend to bulge on cut section, are soft, and are typically somewhat lighter in color than the surrounding liver, but the appearance may vary if necrosis or hemorrhage are present. HA generally lacks significant evidence of fibrosis or nodularity, but rarely, such features may be present. Usually, a capsule is not present. Rarely, adenoma may have a slate gray to black color due to the presence of large amounts of lipofuscin pigment, the so-called “black adenoma”.

Microscopic features. HAs are composed of a relatively uniform population of hepatocytes arranged in cell plates which are one to three cells thick. The cell plates are usually more irregular and nonlinear than in the normal liver. A key feature is that the reticulin framework of the cell plates is intact or only focally decreased. The tumor cells are usually about the same size as in the normal liver, but they can also be slightly smaller or larger compared to normal hepatocytes. Even if the size of the cells vary, however, the nuclear:cytoplasmic ratio remains about the same as in normal liver. The cytoplasm of the tumor cells may be eosinophilic, clear, or contain fat droplets, and bile stasis, lipofuscin pigment, or
Mallory hyaline may be noted. Other variations in cellular morphology such as multinucleated hepatocytic tumor cells and focally atypical or pleomorphic hepatocytes may also be present. Regardless of the cellular morphology, mitotic figures are absent or extremely rare. Variations in the architecture such as the formation of acini (pseudoglands, or gland-like structures composed of hepatocytes) are relatively common findings; such acinar structures can contain bile. Alterations in the sinusoids can also be present; they may appear compressed, resulting in a somewhat uniform, solid appearance to the tumor, or alternatively, sinusoidal dilation and peliosis hepatitis may be present. Large vessels are often quite prominent. Kupffer cells may be seen but tend to be fewer in number than in the normal liver. HAs may or may not be encapsulated, and if a capsule is present, it is often only partially complete, with foci of tumor cells merging with the adjacent parenchyma at sites where the capsule is absent. Adenomas associated with anabolic steroids are more likely to show nuclear atypia, peliosis hepatitis, or a prominent acinar (pseudoglandular) pattern. No portal zones are present. Areas of infarction and hemorrhage are relatively frequent findings.

**Special studies.** HA will stain positively for the usual hepatocellular markers including the cytokeratin marker CAM5.2 and the canalicular marker polyclonal CEA. As will often show CD34 positivity on the endothelial cells lining the cell plates, similar to that seen in hepatocellular carcinoma, so this marker cannot be used to distinguish the two lesions. Alpha-fetoprotein is negative in these lesions.

**Differential diagnosis.** Diagnostic problems most often arise in the differentiation of HA from FNH (Table 2) or well-differentiated hepatocellular carcinoma (HCC) (Table 3). For HA, the relatively uniform cell population resembling normal liver and lacking mitotic activity, lack of cell plates greater than three cells thick, and an intact reticulin framework lining the cell plates help to distinguish the lesion from well-differentiated HCC. For differentiation from focal nodular hyperplasia, the lack of nodularity, fibrous bands or central fibrous zone, and proliferating bile ductules are the most helpful features. However, one must be careful not to confuse acinar formation seen in HA for bile ductules. The distinction among these lesions may be difficult, especially on small samples. Immunohistochemistry does not appear to be helpful in distinguishing HA from either of these two lesions.

**References**


<table>
<thead>
<tr>
<th></th>
<th>Adenoma</th>
<th>Focal Nodular Hyperplasia</th>
<th>Nodular Regenerative Hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>3rd-4th decade, OCP, usually women, acute abdominal pain</td>
<td>3rd-4th decade, some OCP, women &gt; men asymptomatic</td>
<td>5th-7th decade, women=men, portal hypertension, connective tissue disorder</td>
</tr>
<tr>
<td><strong>Gross</strong></td>
<td>Usually single, tan-hemorrhagic</td>
<td>Usually single, tan nodular</td>
<td>Multiple, tan</td>
</tr>
<tr>
<td><strong>Hepatocytes</strong></td>
<td>Usually normal, cytoplasmic glycogen or fat may be present</td>
<td>Usually normal, cytoplasmic glycogen or fat may be present</td>
<td>Usually normal</td>
</tr>
<tr>
<td><strong>Architecture</strong></td>
<td>1-2 cells wide, reticulin normal</td>
<td>1-2 cells wide, but wider may be present, plates can be compressed to give impression of solid growth</td>
<td>1-2 cells wide, reticulin intact</td>
</tr>
<tr>
<td><strong>Bile ducts</strong></td>
<td>None present</td>
<td>Present in fibrovascular zone, edge of hepatocytic nodules</td>
<td>Portal tracts present</td>
</tr>
<tr>
<td><strong>Vessels</strong></td>
<td>Peliosis hepatis and sinusoidal dilation can be seen; some large vessels, intranodular arteries common</td>
<td>Abnormal large muscular vessels generally surrounded by a zone of connective tissue stroma</td>
<td>Rare intranodular arteries (nontriadal)</td>
</tr>
<tr>
<td><strong>Connective tissue</strong></td>
<td>Occasional fibrous septa, encapsulation discontinuous</td>
<td>Fibrovascular central zone, not encapsulated, chronic inflammatory infiltrates may be present.</td>
<td>Compressed parenchyma and regenerative nodules without fibrosis</td>
</tr>
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CASE 3- LESIONS IN A CIRRHOTIC LIVERS

Clinical history: 45 year old man with cirrhosis who underwent a liver transplant. In his explant, a 1.5 cm nodule was found in the background of a cirrhotic liver.

Pathologic findings: Cut section of the liver showed a cirrhotic liver with a 1.5 cm dominant nodule that was poorly circumscribed from the surrounding liver. Microscopic sections showed atypical hepatocytes with an increased nuclear to cytoplasmic ratio. The cell plates were thickened and some areas showed cell plates greater than 2-3 cells thick, while others showed complete loss of the reticulin framework.

Diagnosis- SMALL HEPATOCELLULAR CARCINOMA

Comment
A brief overview of the currently recommended terminology used for the cytologic changes is necessary as a prelude to the discussion of nodules within the cirrhotic liver. The cirrhotic nodule very frequently contains scattered enlarged hepatocytes with abundant cytoplasm and atypical, enlarged nuclei, but the ratio of nucleus to cytoplasm is relatively normal. This cytologic feature was designated as “large cell dysplasia” in the past, but now the International Working Party has recommended the terminology of large cell change for this finding as there is a consensus that this lesion is likely to not be truly dysplastic in nature, and this cellular change is too frequently present to be assumed to be a premalignant process. Similarly, cirrhotic nodules may also contain hepatocytes smaller than normal with normal, slightly smaller, or slightly larger nuclei and scant cytoplasm that results in an overall increase in the nuclear/cytoplasmic ratio. This cytologic feature was previously designated as “small cell dysplasia”, but the International Working Party has recommended the terminology of small cell change for this process. Again, there is currently a consensus that small cell features in cirrhotic livers could be regenerative rather than dysplastic, and may only be preneoplastic in certain instances when the cells are arranged in clusters within a cirrhotic nodule. These clusters of small cells can be present in any nodule in the cirrhotic liver, may be a focus of no more than 1-2 mm in diameter, and appear like a nodule within a nodule. This type of change has been designated a “dysplastic focus” without further grading into low or high grade by the International Working Party, and has been noted to have a high prevalence in diseases such as chronic hepatitis B and C, alpha-one-antitrypsin deficiency, and tyrosinemia. Dysplastic foci may also contain cells with enlarged nuclei with hyperchromasia, with the spectrum of nuclear atypia varying from minimal to severe. Cytoplasmic fat or glycogen may differ in content from the surrounding liver. The same International Working Party also recommended that the term “dysplasia” be used only in the description of nodules or the above described “dysplastic foci” rather than for more generalized cytologic changes within the liver.

Large Regenerative Nodule (Macoregenerative nodule) and Low-Grade Dysplastic Nodule

Nomenclature. In the cirrhotic liver, benign nodules that are larger than the typical cirrhotic nodule have been referred to by various names including large regenerative nodule, macoregenerative nodule, or adenomatous hyperplasia. For similar nodules in the noncirrhotic liver, the International Working Party has recommended that they be designated as multiacinar regenerative nodules or adenomatous hyperplasia. These latter nodules tend to occur in the setting of Budd-Chiari syndrome, portal vein thrombosis, or as a sequelae of necrosis with
regeneration. These large regenerative nodules and multiaicinar regenerative nodules are thought to be a reactive process rather than a clonal, preneoplastic lesion.

In contrast, the low-grade dysplastic nodule in the cirrhotic liver is thought to represent a clonal proliferation of hepatocytes, although the gross and standard microscopic features can be indistinguishable from the large regenerative nodule. For this reason, the remainder of the descriptions generally apply to both lesions, and in practice, many do not try to distinguish these as clonality studies may be the only mechanism to do so. Rather, in practice, the terms are almost used interchangeably to represent a nodule that lacks the cytologic or architectural abnormalities seen in the high-grade dysplastic nodule.

**Clinical Features.** Large regenerative nodules/low-grade dysplastic nodules occur in the setting of cirrhosis, with a few exceptions when they are noted in the setting of chronic liver disease without fully developed cirrhosis. They are often found as incidental findings at autopsy or at the time of transplantation, but can also be noted on radiographic studies. Serum AFP is normal or within the same range as the underlying chronic liver disease/cirrhosis.

**Pathogenetic Features.** These nodules are generally considered benign lesions and either may represent regenerative foci or presumed clonal proliferations in a liver with chronic disease. Nodules with this benign histologic pattern have been associated with an increased incidence of hepatocellular carcinoma, and in some instances may be predisposed to the development of hepatocellular carcinoma. However, it is important to point out that since almost all of the past studies of these nodules have not attempted to define the lesions as regenerative or clonal, but have rather defined the nodules by routine histologic examination as lacking features of high-grade dysplastic nodules or hepatocellular carcinoma, one cannot definitively state at this time whether the regenerative nodules and the clonal nodules have similar risks for the association with hepatocellular carcinoma. Such nodules are more typically seen in cirrhosis due to HBV, HCV, alcohol, and hemochromatosis, but unlikely to be seen in primary biliary cirrhosis, so the risk factors tend to be the same as for hepatocellular carcinoma.

**Gross features.** Large regenerative nodules/low-grade dysplastic nodules are larger than other cirrhotic nodules. The lower limit for size is generally accepted as between 0.8 and 1 cm in diameter, and these lesions are almost always less than 3 cm in greatest diameter. These nodules may tend to bulge on cut section, the edges of the nodules are rounded and sharply circumscribed, and they may be more bile stained or paler yellow to tan than the other cirrhotic nodules.

**Microscopic features.** These nodules histologically resemble cirrhotic nodules. They have an intact reticulin framework similar to normal liver, and the cell plates are 1-2 cells in thickness. The hepatocytes typically have unremarkable cytology, although some focal variations in cell size, especially scattered large cell change similar to that seen in the other cirrhotic nodules, can be present in the large regenerative nodule. The low-grade dysplastic nodule would probably be expected to have a more uniform population of hepatocytes due to its clonal nature, but many of the specific features of this type of clonal nodule have not been definitively established. Findings such as Mallory bodies, bile stasis, clear cell cytoplasmic change, iron or copper deposits, a slight decrease in cell size [Ferrell, 1993 #101], and focal or diffuse fatty change may be present. Portal tracts are usually present within the nodule and bile ductular proliferation may be prominent, but fibrous septa without the complete triad of duct, vein, and artery may also be present [Ferrell, 1994 #365].

**Special studies.** Studies of the vascularity of these lesions have shown that they tend to have an increased number of arteries that lack the other components of a portal zone, the so-
called “unpaired artery”. However, staining for vascular markers such as CD34 or CD31 as a marker for sinusoidal capillarization is essentially the same as that seen in cirrhotic nodules, which consists of some peripheral staining at the edges of the nodule. The nodules are negative for alpha-fetoprotein, and otherwise show the similar staining patterns expected in normal liver for cytokeratin and polyclonal CEA.

**Differential diagnosis.** The size of this nodule differentiates it from other cirrhotic nodules. Rarely, a nodule with this pattern of histology may lack portal zones, but this does not warrant a diagnosis of adenoma in the cirrhotic liver unless one of the risk factors discussed above is present. The features differentiating it from high-grade dysplastic nodules and small, well-differentiated HCC are outlined in Table 3.

### High-Grade Dysplastic (Borderline) Nodules

**Clinical features.** The high-grade dysplastic nodule, also known as borderline nodule, type II macroregenerative nodule, atypical adenomatous hyperplasia, and atypical macoregenerative nodule almost always occurs in a cirrhotic liver. Serum AFP is normal or in the range seen with the underlying chronic liver disease/cirrhosis. Most recommend that these lesions should be excised or ablated since they are considered to be a premalignant process.

**Pathogenetic features.** This type of nodule typically occurs in the setting of cirrhosis and is considered to be a premalignant change on the pathway to the development of hepatocellular carcinoma.

**Gross features.** These nodules have essentially the same gross features of the large regenerative /low-grade dysplastic nodules with the exception that some of them may appear to be less well circumscribed or have irregular edges.

**Microscopic features.** When the dysplastic changes are noted uniformly throughout the nodule, then the nodule is designated as a high-grade dysplastic nodule. Alternatively, a nodule containing one of more dysplastic foci is also designated as a dysplastic nodule. The atypical features seen are not overtly diagnostic for HCC but are more atypical than expected in the usual cirrhotic nodule. The nodule is often recognized by zones of small cell change with increased nuclear:cytoplasmic ratio, also designated as increased nuclear density, which is defined as the estimated number of hepatocyte nuclei per microscopic field compared to the normal liver. Large cell change is rarely a feature of high-grade dysplastic nodules, but if it is, the focus must be a discrete zone of atypical cells rather than enlarged nuclei scattered singly throughout a nodule. Other common features are the focal zones of cell plates up to three cells thick, focal decrease in the reticulin framework, and mild dilation of sinusoids. These nodules can also contain foci of Mallory bodies, fat, clear cell change, cytoplasmic basophilia, bile, and portal tracts. Iron deposits may be present, but the high-grade dysplastic lesions tend to lack iron deposits in contrast to the low-grade nodules, where iron deposits are more common. The edges of the nodule may be irregular, and focal acini (pseudoacini) may be present.

**Differential diagnosis.** This lesion is differentiated from overt HCC by features as described in Table 3. Features that are probably most helpful for the diagnosis of HCC are the presence of mitotic figures in moderate numbers, trabeculae, cell plates greater than 3 cells thick, nuclear density greater than 2 times normal, marked reduction in reticulin framework, numerous unpaired arteries, and absence of portal zones.

### Hepatocellular Carcinoma
Clinical features. Hepatocellular carcinoma (HCC) is the most common malignant primary tumor in the liver, and is usually seen in the setting of cirrhosis (noted in approximately 85% of cases). Lesions less than 1.5 cm generally do not enhance on radiographic angiography, and HCC may be more or less echogenic than the adjacent liver. A high serum AFP level (>1000ng/ml) is seen in almost two-thirds of the cases of the larger tumors; tumors less than 2-3 cm in size are unlikely to have an elevated serum AFP. Elevations of serum AFP of less than 500 ng/ml can be seen in many liver disorders and levels between 500 and 1000 ng/ml are suspicious for HCC but not as reliably specific. Prognosis is typically correlated with staging for lymph node and distant metastases as well as histologic features that can be evaluated routinely on resection samples, such as vascular invasion, adequacy of surgical resection margins (with at least 1 cm typically recommended), number and location of lesions, and size of tumor. The relationship of histologic tumor grade or subtype of HCC to prognosis is considered by most to be not as important as the factors noted above, except when the histology is that of fibrolamellar HCC (see below). Liver transplantation has now been shown to be an effective form of therapy for HCCs less than 5 cm in greatest diameter and without evidence of large vessel invasion. Alternative therapies such as cryoablation, percutaneous ethanol injection, and transarterial chemoembolization have also been used, predominantly in inoperable cases, to improve length of survival.

Pathogenetic features. The major etiologic association for HCC is cirrhosis, but hepatitis B or C viral infections are also predisposing factors. Patients with cirrhosis due to hemochromatosis and alpha-1-antitrypsin disease may also have an increased risk of HCC over patients with cirrhosis due to other causes (excluding HBV and HCV). Other risk factors include exposure to thorotrast (thorium dioxide), aflatoxins, and estrogenic steroids.

Gross findings. Most HCCs arise in the cirrhotic liver. HCC may be more bile-stained or paler than the adjacent liver, and can have irregular borders or even satellite nodules. Large vein invasion and a fibrous capsule may be noted associated with the larger tumors. Small HCC is generally defined as HCC measuring less than 2 cm in diameter; these small tumors usually lack gross vascular invasion, necrosis or hemorrhagic zones.

Microscopic findings. Several typical histologic patterns of HCC have been described by the World Health Organization. The most common is the trabecular pattern, also known as the sinusoidal pattern. In this variant, the tumor morphology mimics the cell-plate architecture of normal liver, but with important differences. First, the cell plates in trabecular HCC are three cells thick or greater in comparison to the plates of normal or regenerative liver, which are only one to two cells thick. The tumor cell plates are lined by endothelial cells similar to normal liver, but with reticulin stain, the framework is often absent or may be markedly decreased or distorted, with irregular or absent staining of the edges of the trabeculae. The tumor cells often have features of small cell change. Large cell change can also be noted, but is probably less frequently seen except in the higher grade tumors. Often, foci of small or large cell change are admixed. Kupffer cells are typically absent.

The acinar, pseudoglandular, or adenoid pattern of HCC is less common than the trabecular type. The defining feature in this variant is gland-like spaces, or acini, lined by the hepatocytic tumor cells. These acinar structures are formed by the dilation or expansion of bile canaliculi and they often contain bile. Less frequently, the spaces are a result of central necrosis of the trabeculae and so may instead contain protein, cellular debris, or macrophages. Due to the formation of these gland-like spaces, one must not mistake this lesion for adenocarcinoma. The acinar pattern is frequently admixed with the trabecular pattern.
The solid, or compact, pattern of HCC is a relatively uncommon variant characterized by dense aggregates of tumor cells that may seem to lack the endothelial-cell-lined trabeculae or cell plates; however, careful examination with endothelial cell markers will often reveal the presence of compressed trabeculae. Loss of the reticulin framework is typically seen in the solid, crowded zones as well.

The final pattern is the scirrhous pattern, which contains focal to diffuse, prominent areas of fibrosis that can be associated with any of the patterns above. Occasionally, the tumor cell plates (or trabeculae), may be separated by increased amounts of connective tissue instead of by the endothelial-cell-lined sinusoidal spaces. In these instances, reticulin staining is usually increased in the bands of connective tissue rather than decreased as described above for the trabecular pattern of HCC. The thickened cell plates, which are separated by this prominent reticulin framework in these cases, often have a linear or ribbon-like arrangement. This pattern could be subclassified as a form of scirrhous HCC as well, although the overall amount of fibrous tissue may not be as prominent as typically described.

The cytologic features of HCC within any of these patterns also tends to resemble normal hepatocytes. The tumor cells often maintain a polygonal shape and have round vesicular nuclei and prominent nucleoli, typical features of hepatocytic differentiation. Intracellular vacuoles (composed of cytoplasmic invaginations) and glycogenation of nuclei (another feature seen in normal liver) are fairly common findings. Small cell change (as described above) is probably the most common cytologic change, but large cell change and giant and/or pleomorphic cells may be present as either a diffuse or focal finding. The amount of cytoplasm may vary, and is often slightly more basophilic than in seen in normal hepatocytes. The cytoplasm may also have a granular appearance, or be exceptionally oxyphilic due to the presence of large numbers of mitochondria. Cytoplasmic inclusions such as Mallory bodies or globular acidophilic bodies composed of proteins including albumin, fibrinogen, alpha-1-antitrypsin, or ferritin may be present. Fat, glycogen, or even water can be prominent as well, giving the cells a “clear cell” appearance, which has been described as the clear cell variant of HCC. If the entire tumor shows this type of clear cell change and occurs in the noncirrhotic liver, it may be difficult to differentiate HCC from other clear cell tumors such as metastatic renal cell carcinoma. Other cytoplasmic changes that are seen much less frequently include the pale bodies (which are round to oval, lightly eosinophilic or clear cytoplasmic structures most frequently seen in the fibrolamellar variant of HCC, see below), ground glass cells containing HBsAg that are present in some patients with HBV infections, and dark-brown to black pigment like that seen in the Dubin-Johnson syndrome. Very rare forms of HCC with a prominent spindle cell component and a small cell type have been described.

Histologic grading of HCC. The grading of HCC has traditionally been based on three or four grades, based on the system developed by Edmondson and Steiner in 1954. They originally defined four grades as distinguished by proportional increases in nuclear:cytoplasmic ratio, variability in nuclear shape, hyperchromasia, and loss of cell plate architecture from low to high grade tumors. These grades are basically still used with some modifications, mostly in the low grade classifications. Some of Edmondson/Steiner’s Grade I tumors with minimal cytologic atypia and architectural distortion were only recognized as malignant by their association with admixture of other higher grades of HCC or by the presence of metastatic lesions. With the current criteria now available as established by the International Working Party, stricter definition for Grade I lesions can possibly separate out some of these as dysplastic nodules. Grade II tumors are still well-differentiated, and still have a typical trabecular pattern but with
increased nuclear size as compared to Grade I tumors. Grade II lesions can also contain acinar structures and bile. Grade III tumors are moderately differentiated, and have more cytologic and architectural variability than the Grade II lesions. Multinucleated and giant cells are often seen focally, and in contrast to grade II lesions, bile is often not present. When trabeculae are present, they are typically wider and/or more variable in structure than those in Grade II tumors. Grade IV consists of poorly differentiated tumors, or anaplastic lesions for which classification as HCC is difficult without the appropriate clinical setting such as cirrhosis or significantly elevated serum AFP. Grade IV lesions can include spindle cell and small cell components as well. An alternate three grade system is often used, with Grade I representing well-differentiated lesions (Grade I and II above combined); Grade II, the moderately differentiated lesions; and Grade III, the poorly differentiated and anaplastic lesions.

**Differential diagnosis.** Immunoperoxidase studies are not helpful to differentiate benign from malignant hepatocellular tumors; however, they can help to distinguish HCC from other tumors in the liver. Most of the diagnostic problems arise in differentiating the benign hepatocellular tumors such as adenoma or focal nodular hyperplasia from well-differentiated hepatocellular carcinoma, or poorly differentiated HCC from other primary or metastatic neoplasms. Well-differentiated HCC can be differentiated from large regenerative/low-grade dysplastic nodules and high-grade dysplastic nodules by features noted in Table 3.

**Fibrolamellar Variant of HCC**

**Clinical features.** The fibrolamellar variant of HCC (FLHCC) occurs in the noncirrhotic liver in young adults (mean age 26 years, females>males) and, with this strict definition (as is generally accepted), has a better prognosis than typical HCC of similar size. Lesions with similar morphology have been noted in the cirrhotic liver, but these HCCs should not be diagnosed as FLHCC by convention due to their much more variable outcome. Presentation may be accompanied by complaints such as abdominal pain or swelling, anorexia, weight loss, jaundice, and rarely, hemoperitoneum. No definitive risk factors have been identified. Nodular hyperplastic changes have been noted adjacent to FLHCC, but most concur that this is a secondary affect due to vascular changes within the liver adjacent to the tumor rather than suggesting that FLHCC arises in association with FNH. Serum AFP levels are usually normal; only rarely have high levels have been reported. Complete excision of the involved lobe is the current therapy of choice. When the tumor location precludes resection, liver transplantation has been done, but the outcome is not as favorable.

**Gross features.** FLHCC is a well-circumscribed, nodular, yellow to brown tumor with fibrosis. Rarely, a prominent central, fibrous zone similar to that of FNH can be present. The larger tumors can shows foci of hemorrhage and necrosis; satellite lesions are rare.

**Microscopic features.** The cellular component of FLHCC consists of small to large clusters or sheets of tumor cells separated by dense bands of lamellar fibrous tissue. The tumor cells tend to have a polygonal shape, and they routinely have eosinophilic and granular cytoplasm. Nuclei are large with prominent nucleoli easily identified. Other cytoplasmic features include the "pale body," which may contain fibrinogen and/or albumin and PASD-positive bodies, which probably represent various glycoprotein secretions. Other focal features that can be noted are acinar structures, bile, multinucleated tumor cells, copper, fat, epithelioid granulomas, and peliosis hepatitis. Glandular differentiation with mucin secretion as well as zones of trabecular HCC have also been noted; it is not clear whether these variations result in poorer prognosis.
**Combined Hepatocellular-Cholangiolar Carcinoma**

**Clinical features.** Combined (or mixed) hepatocellular-cholangiolar carcinoma (HCC/CC) may account for up to 5% of all primary carcinomas of the liver. The risk factors are essentially the same as for HCC alone.

**Diagnostic features.** Combined HCC/CC contains a mixture of hepatocellular and ductular elements scattered throughout the tumor. Collision tumors, where each element is separated or side by side, are not considered to fall into this combined category by the World Health Organization classification.

**Special studies.** Cytoplasmic mucin and/or immunoperoxidase stains for keratin types such as AE1/AE3, cytokeratins 19 or 20 (as seen in ductular tumors) can be used to identify the cholangiocarcinoma component. CK7 also identifies ductular components, but this can also stain cells within HCC as well so caution should be used in interpretation of CK 7 alone. Bile production by tumor cells, or immunoperoxidase positivity for markers specific for hepatocytes such as AFP, polyclonal CEA, and hepatocyte antibody can help to identify the hepatocellular component.

**Sclerosing Hepatic Carcinoma**

This term has been used to refer to a mixture of hepatocellular, cholangiolar, or combined hepatocellular-cholangiolar carcinomas with tubular neoplastic structures embedded in a fibrous stroma that are typically associated with hypercalcemia.

**References**


Table 3: Nodules in a Cirrhotic Liver

<table>
<thead>
<tr>
<th></th>
<th>Macrogeneative Nodule</th>
<th>Low Grade Dysplastic Nodule</th>
<th>High Grade Dysplastic (Borderline) Nodule</th>
<th>Well-Differentiated Hepatocellular Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocyte</td>
<td>Similar to cirrhotic nodules</td>
<td>A uniform population of hepatocytes suggesting a clonal proliferation</td>
<td>Variable, usually similar to normal size or slightly smaller</td>
<td>Smaller or larger cells, diffuse type changes most common</td>
</tr>
<tr>
<td>Small cell change</td>
<td>Absent or only scattered cells</td>
<td>Absent or only scattered cells</td>
<td>Occasional small foci, but nuclear density &lt;2x normal, can be diffuse or prominent; dysplastic focus may have appearance of a nodule within the larger nodule</td>
<td>Small foci to large zones commonly present</td>
</tr>
<tr>
<td>Cell plate architecture</td>
<td>Less than 2-3 cells thick, reticulin intact</td>
<td>Less than 2-3 cells thick, reticulin intact</td>
<td>May see some plates &gt; 3 cells thick, but no zones of trabeculae present, focal loss of reticulin</td>
<td>Trabeculae commonly seen, zones of reticulin loss</td>
</tr>
<tr>
<td>Increased iron deposits</td>
<td>Sometimes present</td>
<td>Unknown</td>
<td>May be present</td>
<td>Almost always absent even in the setting of a siderotic liver</td>
</tr>
<tr>
<td>Periphery of nodule</td>
<td>Well-circumscribed</td>
<td>Well-circumscribed</td>
<td>Some with irregular edge</td>
<td>Common to see infiltrative or irregular edge</td>
</tr>
<tr>
<td>Portal zones or fibrous tissue zones</td>
<td>Almost always present, focal bile ductular proliferation may be present</td>
<td>Probably present</td>
<td>Normal portal zones often seen within the larger dysplastic nodules</td>
<td>No intact portal zones present unless entrapped near edge of tumor</td>
</tr>
</tbody>
</table>
CASES 4 AND 5- DIFFERENTIATION OF HCC FROM OTHER TUMORS

Case 4
Clinical history: 62 year old man with history of colon cancer, presented with 2 month history of shoulder and epigastric pain. Abdominal MRI showed a 5 cm tumor in the lateral segment of the left hepatic lobe.

Pathologic findings: The surface of the mass was irregular and the cut surface was tan-yellow and nodular. Microscopic sections showed hepatocytes arranged in a pseudoglandular pattern with some areas showing cells with clear cytoplasm.

Diagnosis: HEPATOCELLULAR CARCINOMA, PSEUGLANDULAR AND CLEAR CELL PATTERN

Case 5
Clinical history: 53 year old man who was found to have a 3 cm mass in his liver on an abdominal CT scan.

Pathologic findings: The mass appeared yellow and hemorrhagic. The surrounding liver was normal. Sections show tumor composed of cells with clear cytoplasm.

Diagnosis: METASTATIC RENAL CELL CARCINOMA

Comment
In most cases, the clinical history will be the most helpful feature in distinguishing tumors. H&E useful features seen more commonly with HCC include cirrhotic liver or chronic hepatitis. Features seen more frequently with metastatic lesions include multiple masses in a non-cirrhotic liver.

Special stains
1. Mucin: Most HCC are negative but combined HCC-cholangiocarcinomas can be positive.
2. Reticulin: Helpful in distinguishing benign from malignant hepatocellular tumors.

Immunoperoxidase stains
1. Alpha-fetoprotein (AFP): AFP is a reasonably specific marker for hepatocellular carcinoma; however, the staining tends to be patchy and completely absent in more than half of the HCCs, and particularly has been noted to be absent in small, well-differentiated HCCs. AFP is useful when positive for HCC.
2. Polyclonal CEA: pCEA highlights the bile canaliculi, and is relatively specific for hepatocellular differentiation, but only tends to stain the well to moderately-differentiated HCC’s. This stain will also delineate outer cellular membranes in adenocarcinomas, which can potentially mimic a canalicular pattern on tangential sectioning. The interpretation of pCEA is hindered by confusion in determining staining pattern in some cases – luminal with pseudoglandular HCC, membranous vs canalicular in some adenocarcinomas.
3. Other adenocarcinoma markers (MOC-31, Ber-Epi-4, Leu-M1, etc): Negative in most HCC and positive in most adenocarcinomas.
4. Cytokeratins: Hepatocytes express the low molecular weight cytokeratins including 8 and 18, CAM5.2; while most adenocarcinomas express both low and high molecular weight cytokeratins. Cytokeratin AE1/3 is positive in adenocarcinomas and negative in many HCC. CAM5.2 cannot be used in isolation since cytokeratin CAM5.2 and AE1/3 will stain most adenocarcinomas. Cytokeratin 7 is negative in most HCC, but will focally stain smaller ductular-like hepatocytes or some acinar structures within HCC in our experience. Cytokeratin 7 is positive in many adenocarcinomas. Cytokeratin 20 is negative in HCC and positive some adenocarcinomas primarily colorectal. Cholangiocarcinoma are Cytokeratin 7+ and Cytokeratin 20+ or – and so are similar to many metastatic adenocarcinomas. Cytokeratin stains are useful for site of origin in some cases of metastatic adenocarcinoma

5. HepPar1, Hepatocyte: A newer hepatocyte antibody (Hep Par 1) is relatively specific for hepatocellular differentiation and only rarely stains adenocarcinomas. This antibody stains in a granular pattern within the cytoplasm to a varying degree within tumors with hepatocytic differentiation, but as with the polyclonal CEA, tends to be less sensitive for the poorly differentiated HCCs. Hepatoid adenocarcinomas reported positive

6. CD10: Pattern of staining is similar to pCEA in HCC and negative in most adenocarcinomas. Advantage over pCEA – less confusion with determining pattern; disadvantage over pCEA – less sensitive.

7. CD34: CD34 typically stains the endothelial-lined trabeculae in HCC and highlights the increased vascularity.

8. ER/PR: Most HCC are negative. Be careful with determining site of origin of tumor. Up to 20% of adenocarcinomas can be positive and some metastatic breast carcinomas are negative.

9. Her2-Neu: HCC are negative, while some adenocarcinomas are positive.

**Differential between other tumors and HCC:**

*Distinction from adenocarcinoma.* Monoclonal CEA is often diffusely positive in some types of adenocarcinomas, and usually does not stain hepatocellular tumors. Polyclonal CEA stains adenocarcinomas (membranous and cytoplasmic) in a different pattern from HCC (canalicular). Leu-M1, MOC31, B-72.3, and Le\(^\alpha\) tend to be positive in adenocarcinomas and negative HCC and when used in combination with CEA and perhaps the hepatocyte antibody (see above) can be helpful to distinguish poorly differentiated adenocarcinomas from HCC. Routine histochemical stains for the epithelial mucins such as mucicarmine or periodic acid-Schiff with digestion (PASD) are often helpful as mucins should not be present in HCC except in combined HCC-cholangiocarcinoma and in some cases of fibrolamellar variant of HCC (FLHCC). One must take some care in the interpretation of the PASD stain, however, since this method also reacts with many cytoplasmic glycoproteins produced by hepatocytes, resulting in a possible false positive interpretation. A combination of CK7, 19, and 20 profiles can be helpful as these tend to be positive in cholangiocarcinoma (CK19 is essentially always positive in cholangiocarcinoma) or metastatic carcinoma and negative in hepatocellular carcinoma.

Suggested panel for HCC vs adenocarcinoma (metastatic or cholangiocarcinoma):

**Hepatocyte, pCEA, MOC-31.** In our experience, this panel correctly classified 99% of tumors.

Add to help determine site of origin if necessary:

Cytokeratin 7 and 20.
**Distinction from neuroendocrine tumors.** HCC can also be difficult to distinguish from a neuroendocrine neoplasm as both can form acinar or trabecular-like structures, and can be composed of relatively large tumor cells with abundant eosinophilic cytoplasm and round nuclei. Features that favor a neuroendocrine tumor in such cases are a prominent vascular or capillary network, and/or stromal hyalinization. These neuroendocrine tumors can rarely arise as a primary lesion in the liver, but otherwise, are almost always metastatic. Focal neuroendocrine differentiation has been noted in HCC, including the fibrolamellar variant, as well as in hepatoblastoma, using various markers such as neuron specific enolase (NSE), protein gene product 9.5 (PGP 9.5), vasoactive intestinal peptide (VIP), calcitonin, and S-100 but diffuse staining with a marker such as chromogranin or synaptophysin would strongly support a neuroendocrine tumor.

**Distinction from other tumor types.** Clear cell carcinomas in the liver can pose a diagnostic challenge to distinguish the clear cell variant of HCC from clear cell renal cell carcinoma metastatic to the liver. In a cirrhotic liver, the diagnosis of clear cell variant of HCC can be made with enough certainty that stains would not be necessary. However, for lesions in a noncirrhotic liver without significant AFP elevation, the likelihood of a metastatic lesion makes differentiation more critical. Keratin profiles are not helpful as both of these tumors typically show similar staining (positive for CAM5.2, negative for CK7 and 20). However, HCC of these clear cell types will often demonstrate polyclonal CEA canalicular staining, while renal cell carcinomas show no canalicular pattern. Other useful markers are EMA, which tends to be positive in RCC and negative in HCC, and the hepatocyte antibody (see above) that does not stain RCC.

Melanomas can also mimic HCCs, but S-100 and HMB-45 are usually, but not always, negative in hepatocellular tumors. Rarely, an adrenal cortical tumor may need to be distinguished from a primary hepatocellular tumor. In these instances, positive staining for inhibin A, which has a high percentage of positivity in adrenal tumors but not in hepatocytic lesions may be helpful in addition to the hepatocyte markers previously discussed such as polyclonal CEA and hepatocyte antibody. The use of immunohistochemistry in the differentiation of HCC from primary mesenchymal tumors will be discussed below.

**References**


Table 4: The distinction of tumors in the liver with immunohistochemical markers

<table>
<thead>
<tr>
<th></th>
<th>HCC</th>
<th>Adenocarcinoma</th>
<th>RCC</th>
<th>NET</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>+/-</td>
<td>-*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hepatocyte</td>
<td>+</td>
<td>-*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pCEA</td>
<td>+ (canalicular)</td>
<td>+ (cytoplasmic/membranous)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMWCK (8,18)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Ck7</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ck20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD10</td>
<td>+/- (canalicular)</td>
<td>-**</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MOC31</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>EMA</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Vimentin</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

* Positive in hepatoid variant, ** Rarely positive in the cytoplasm
CASE 6 and 7- BENIGN DUCTULAR LESIONS

Case 6

Clinical history: 40 year old man with cirrhosis who underwent a liver transplantation. The explant liver contained a 1 cm tan firm nodule in that appeared different from the surrounding nodules.

Pathologic findings: Cirrhotic liver with a nodular proliferation of ducts in a fibrotic area. Ductular structures with a tubular appearance and no cytologic atypia in a fibrotic stroma with some surrounding lymphocytes.

Diagnosis- BILE DUCT ADENOMA

Comment

Bile Duct Adenoma

Clinical features. Bile duct adenoma (BDA) is a less common lesion than biliary hamartoma. The designation of “adenoma” may be a misnomer as most feel this lesion does not represent a true neoplasm, but rather represents a localized ductular proliferation at a site of previous injury or a form of peribiliary gland hamartoma. The lesions are usually discovered as incidental findings, and may be biopsied at time of surgery (often for frozen section) to exclude metastatic disease.

Gross features. BDAs are small lesions, usually less than 2 cm in diameter, firm, white to grey-tan, and well-circumscribed. Typically, they are noted in a subcapsular location, but they can be located deep in the parenchyma. BDAs can be single or multifocal.

Microscopic features. The ductules in BDA are more uniform in size without the appearance of dilatation and with less intervening fibrous stroma than the ductules in hamartomas. Although the fibrous stroma is typically not as pronounced as that in hamartoma, the amount of collagenization may vary considerably, and focal zones of dense collagen can be present. The ductules tend to have tubular or curvilinear shapes and are lined by cuboidal epithelium with bland round to oval nuclei without mitotic activity. Mucinous metaplasia of the epithelium, alpha-one-antitrypsin droplets, and neuroendocrine differentiation may be seen in the tubular lining cells. Typically, residual portal tracts are often preserved within or near the edge of the lesion and small aggregates of lymphocytes are present at the periphery.

Biliary Hamartoma

Clinical features. Biliary hamartoma (BH), or the von Meyenburg complex, is thought to represent a ductal plate malformation, and so these lesions are often seen as part of the spectrum of polycystic disease in the liver and other organs.

Gross features. BH is a small (usually less than 0.5 cm), grey to white, irregularly shaped lesion; multifocality is common.

Microscopic features. BH consists of numerous small to medium-sized ductules, which are typically more dilated than normal ducts, and are separated by dense collagen. They typically are located within and at the edge of a portal zone. The ductules are lined by small,
cuboidal to flattened epithelium with round to oval nuclei, are also more irregularly shaped than normal ducts, and may contain eosinophilic debris or inspissated bile.

Case 7-Cystic biliary lesions

Case 7

Clinical history: 32 year old asymptomatic woman with a large palpable non-tender mass in her RUQ found on physical exam. CT scan showed a mass in the liver. The mass was cystic and measured 8 cm.

Pathologic findings: Multilocular cyst partially denuded with a focal epithelial lining. Mucinous epithelium with basally oriented nuclei and an underlying “ovarian type” stroma.

Diagnosis- BILIARY CYSTADENOMA

Comment

Hepatobiliary (biliary) cystadenoma (and cystadenocarcinoma)

Clinical features. Hepatobiliary, or biliary, cystadenomas are rare lesions, with a higher incidence in women and histological counterparts in the pancreas and ovary. These cystic tumors are typically associated with an ovarian type of stroma when they occur in women, but not in men. The lesion can also be associated with the development of cystadenocarcinoma, which tends to be a low-grade adenocarcinoma in the women, but has greater malignant potential in men.

Gross features. Hepatobiliary cystadenomas are almost always multilocular with a smooth or somewhat trabeculated inner surface to the cyst walls. The cysts contain fluid of variable appearance, including serous, mucinous, gelatinous, occasionally hemorrhagic, or even purulent. There is no communication between the cysts and the biliary tree. Large polypoid projections from or dense masses in the wall of a cyst often indicate zones of malignant transformation.

Microscopic features. The cysts are lined by a single layer of epithelial cells, usually of a mucinous type. The cells can vary from flattened to cuboidal to columnar shapes, and small papillary tufts may be present along the surface. The epithelial nuclei are bland and basally located without mitotic activity. The underlying stroma often has an appearance similar to ovarian stroma (when the lesion occurs in a woman), but this stroma may not be uniformly present. A more densely, hyalinized stroma often separates the ovarian-like stroma from the adjacent liver. The cyst walls may also be lined focally by macrophages, calcification, or scar-like tissue.

Cystadenocarcinomas arising in this lesion often have a tubulopapillary type of histology. Features such as marked nuclear pleomorphism, loss of polarity, mitotic figures, and multilayering of the epithelium all could suggest the possibility of transformation to malignancy, and be designated as in situ cystadenocarcinoma, but invasion of the tumor into the stroma is the best evidence for the presence of carcinoma.

Simple cyst

Clinical features. Simple biliary cysts are generally an incidental finding. When multiple cysts are present, they often represent a component of polycystic disease and are often
accompanied by von Meyenburg complexes (biliary hamartomas). Simple cysts have no or only slight premalignant potential.

Gross features. Simple cysts are usually found in a subcapsular location, but some can occur deeper in the parenchyma. They typically contain a clear, light-yellow fluid.

Microscopic features. Simple cysts are lined by a cuboidal to low columnar epithelium with a fibrous wall. The epithelium may be disrupted or may be flattened, and the wall may be thickened. Evidence for reactive changes such as recent or remote hemorrhage in the cyst wall may be present.

CASE 8 - MALIGNANT DUCTULAR LESIONS

Case 8

Clinical history: 54 year old woman with cirrhosis and a history of ulcerative colitis. She presented for pre-liver transplant evaluation and abdominal CT demonstrated marked hepatomegaly and severe dilation of biliary tree, suggestive of obstruction of the common hepatic duct. At gross examination, multiple ducts were found to contain papillary excrescences.

Pathologic findings: Intraductular papillary proliferation of columnar epithelium within the liver, low power. Severely dysplastic columnar epithelium (carcinoma in-situ), high power.

Diagnosis - INTRADUCTAL CHOLANGIOCARCINOMA (BILIARY PAPILLOMATOSIS)

Comment

Cholangiocarcinoma

Clinical features. Cholangiocarcinoma typically occurs in the elderly, with both sexes affected equally. There is no association with cirrhosis in general, although patients with primary sclerosing cholangitis do have a significantly increased risk for developing this tumor. The tumor is most prevalent in Southeast Asia, where liver fluke infestation with Clonorchis and Opisthorchis is high. Other possible risk factors include congenital anomalies of the biliary tree such as von Meyenberg complexes, choledochal cyst, Caroli’s disease, and anomalous arrangements of the pancreatic and common bile ducts; hepatolithiasis, and thorotrast. The presenting systems depend on the location of the tumor, with four locations often designated separately as peripheral (intrahepatic), hilar, extrahepatic, or intraductal. The peripheral type usually remains asymptomatic until the tumor is in a late stage; the hilar, extrahepatic, and intraductal types present with signs of obstruction. Prognosis for the peripheral, hilar, and extrahepatic types is dismal, usually because the disease has reached an advanced stage by the time it is diagnosed rendering surgical removal difficult if not impossible; however, the length of survival may be increased when tumor-free surgical margins can be attained.

The intraductal papillary type, also known as intraductal papillomatosis, biliary papillomatosis, or intraductal papillary tumor generally involves extensive areas of the intrahepatic and/or the extrahepatic bile ducts, with preference for the latter. Men are more affected than woman at about a 2.4 to 1 ratio, and patients are usually middle to older age (mean age 60). Although histologically benign in most cases, the lesion is generally considered in the clinical setting as a borderline or low grade malignant tumor due to its tendency to recur, its multicentricity, its ability to undergo malignant transformation and metastasize (although only rarely), and its significant morbidity and mortality due to its intraductal growth pattern and subsequent complications such as recurrent bouts of cholangitis and obstructive jaundice, as well
as episodes of sepsis and hemobilia. Even with invasion present, the incidence of metastases is still much less than the other forms of cholangiocarcinoma. In spite of the fact that most of these intraductal papillary tumors may not become invasive or metastasize, due to the multicentric nature of the lesions, the possibility of a cure is unlikely without liver transplantation. Even then, the lesion may possibly recur in the extrahepatic ducts.

**Gross features.** The peripheral, hilar, and extrahepatic variants of cholangiocarcinoma are usually firm, white-tan lesions due to dense fibrous stroma within the lesions. In contrast, the intraductal papillomatous variants are soft, polypoid or cauliflower-like lesions that protrude into the large ducts and cause ductal dilatation; these lesions are typically multifocal.

**Microscopic features.** The peripheral, hilar, and extrahepatic variants are adenocarcinomas that typically have a significant component of dense fibrous stroma. The tumors often are well-differentiated, with tubular gland formation and minimal cytologic changes; however, foci of atypia with increased nuclear:cytoplasmic ratios, prominent nucleoli, variation in nuclear size, and loss of polarity will often be seen. Features that have been noted to support the diagnosis of carcinoma over a benign hyperplastic or reactive process include the formation of intracytoplasmic lumina or a focal cribriform pattern. In addition, multilayering of nuclei and intraluminal cellular debris can also be helpful features to suggest the possibility of malignancy.

Intraductal papillomatosis, or biliary papillomatosis (and its invasive form, papillary adenocarcinoma) grows into the duct lumina as a multifocal, papillary lesion. The architecture consists of papillae lined by columnar epithelial cells supported by a delicate fibrovascular stroma. The nuclei are round to oval, and basally located, without significant multilayering. The cytoplasm is generally abundant and mucinous, but clear, or oncocytic differentiation as well as intestinal metaplasia with goblet cell change can also be present. Mitotic figures are infrequent. Frank invasion of the stalk and underlying periductular tissues must be seen for a diagnosis of adenocarcinoma.

**Special studies.** Immunoperoxidase and mucin staining can be used to differentiate cholangiocarcinoma from HCC as described previously (see above). However, differentiation from metastatic adenocarcinoma can be very problematic if there is no known primary at another site. An adenocarcinoma composed of tall columnar cells with an adenomatous pattern, focal cribriform pattern, lack of intraepithelial mucin, and luminal necrotic debris is more suggestive of metastatic colonic carcinoma than primary cholangiocarcinoma. The latter usually shows more intraepithelial mucinous differentiation or is composed of glands lined by low-columnar to cuboidal cells. Cytokeratin profiles for types 7, 19, and 20 have also shown to be helpful in differentiating primary from metastatic lesions. The cholangiocarcinoma is generally CK7 and 19 positive, 20 negative, while metastatic colorectal adenocarcinoma is CK7 negative in about 90% of cases, but usually positive for either 19 or 20. 30,31 Another marker that could be helpful is Le, which often shows cytoplasmic and membranous reactivity in cholangiocarcinoma but only cytoplasmic reactivity in metastatic carcinoma. In contrast, Leu-M1 and B72.3 are more likely to show the opposite pattern with cytoplasmic staining in cholangiocarcinoma and cytoplasmic and membranous staining in metastatic adenocarcinoma.

**References**
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BDA=bile duct adenoma, VMC=von Meyenberg’s complex, BDP=bile duct proliferation
CASE 9 AND 10- MESENCHYMAL TUMORS

Case 9
Clinical findings: 50 year old man presented with 2 week history of hematemesis and epigastric pain, and EGD and CT demonstrated a large gastric mass. At surgery he was found to also have a 5 cm liver mass.

Pathologic findings: Cellular epithelioid and spindled cell tumor in the liver. There are occasional mitotic figures and cytologic atypia.

Diagnosis-METASTATIC GASTROINTESTINAL STROMAL SARCOMA

Comments

Metastatic Sarcoma

Clinical features. History of sarcoma. Sarcomas that metastasize to the liver include gastrointestinal stromal sarcomas and soft tissue sarcomas. Patients generally present with mass effect or nonspecific symptoms and elevated liver function tests.

Gross features. May present with multiple lesions.

Microscopic features. Reflects the histology of the primary tumor.

Differential diagnosis. Sarcomatoid carcinomas including HCC can mimic a sarcoma. Primary soft tissue sarcomas have been reported to occur in the liver. Liposarcoma, malignant fibrous histiocytoma, dendritic reticulin sarcoma, fibrosarcoma, among others have all been reported in the liver.

Special studies. Immunohistochemical studies are very useful the help identify the tumor. Useful stains include cytokeratins, vimentin, CD117 (C-kit), CD34, S-100, and SMA.

Spindle cell tumors: Low molecular weight cytokeratins may help identify a carcinoma. Do not forget about metastatic sarcomas most commonly gastrointestinal stromal tumor (CD34+, C-kit+, Bcl-2+, SMA-, S-100-). Vascular tumors should be immunoreactive with CD31 and CD34.

CASE 10-Benign and malignant primary mesenchymal lesions

Case 10
Clinical findings: 36 year old woman with one tumor in the right lobe and other small nodules in the left lobe. The tumors had white-tan and firm surfaces.

Pathologic findings: Nests of atypical cells embedded in a myxohyaline matrix, low power. Nests and single atypical round cells with a rare intracytoplasmic vacuole containing erythrocytes.CD31 immunoreactivity in the atypical cells and lack of staining in admixed benign bile ducts.

Diagnosis- EPITHELIOID HEMANGIOENDOTHELIOMA

Comment

Malignant Mesenchymal Lesions

Epithelioid Hemangioendothelioma
Clinical features. Epithelioid hemangioendothelioma (EHE) is a rare, low-grade malignancy that occurs in adults of any age, but tends to be more common in women. Many lesions are discovered as an incidental finding, but presenting symptoms can include upper abdominal mass or discomfort. Serum alkaline phosphatase levels may be elevated. Liver transplantation can be a reasonable means of treatment in unresectable cases, showing a survival similar to hepatocellular carcinoma of the same stage. Overall, the prognosis is better than that of angiosarcoma, even if excision is incomplete or extrahepatic metastases are present.

Gross findings. EHE is a firm, white to yellow tumor that often has an ill-defined border. The tumor is often multifocal with involvement of both right and left liver lobes. Focal calcification can be present, and cause a somewhat gritty consistency.

Microscopic findings. The cells comprising this tumor can be dendritic or epithelioid in appearance. The former are irregularly-shaped, elongated, or stellate cells with branching processes. The cell cytoplasm may contain a vacuole which represents an intracellular “capillary” luminal space. The epithelioid tumor cells are rounder with more abundant cytoplasm than the dendritic cells. These cells often form small papillations or tufts within thin-walled vascular spaces. Both cell types are surrounded by a myxoid to fibrous stroma. Calcification of the more dense type of stroma may be present. The tumor tends to grow around and leave intact the preexisting structures such as the portal zones and residual hepatocytes or bile ducts can be present within the tumor, especially near the periphery of the lesion. The tumor also has a marked predilection for invading vascular structures such as portal and central veins, which can mimic the histologic appearance of vascular thrombosis. Scattered inflammatory cells such as lymphocytes and neutrophils are often seen.

Special studies. Histologic differentiation of this lesion from adenocarcinoma (including cholangiocarcinoma) or HCC can be problematic on routine staining. However, immunohistochemical staining for the endothelial markers such as CD34, CD31, and/or Factor VIII on the tumor cells will confirm the diagnosis of EHE. Care must be taken, however, not to mistake focal keratin positivity in this tumor due to either entrapped hepatocytes or ducts and possibly also in tumor cells for carcinoma. Another diagnostic problem can be the differentiation of EHE from venous thrombosis/veno-occlusive disease as the tumor growth within large vessels can mimic an organizing thrombus.

Angiosarcoma

Clinical features. Angiosarcoma is a rare primary malignant tumor that usually occurs in middle-aged adults, but has also been noted rarely in children, some in the setting of infantile hemangioendothelioma. Other definitive associations include thorotrast and vinyl chloride exposure, but many of these tumors have no apparent etiologic factor. Presenting signs include hepatomegaly, ascites, jaundice, thrombocytopenia, hemoperitoneum, and liver failure. The mean survival after diagnosis is six months.

Gross findings. Angiosarcomas are often large hemorrhagic tumors with indistinct borders and variable solid or cystic areas, the latter usually containing blood. Satellite nodules can be present.

Microscopic findings. The tumor typically has a mixed pattern of histology, with sinusoidal, solid, papillary, and cavernous types of growth. The sinusoidal pattern is the most distinctive growth pattern in the liver. In this pattern, the endothelial cells line both sides of the hepatic cell plates in a scaffold-like arrangement that dissects the plates, and often results in sinusoidal dilation. The tumor cells lining the cell plates are more numerous, more
hyperchromatic, and larger than normal endothelial cells. This sinusoidal pattern is more likely to be noted at the periphery of the tumor, and so may represent an early outgrowth of the tumor, which then later transforms into the solid or papillary forms. The solid pattern may have a fascicular or whorled appearance, or may resemble fibrosarcoma. The papillary pattern consists of nodules of stroma lined by tumor cells that protrude into a lumina. The cavernous pattern consists of large blood-filled spaces, and is commonly seen with any of the other patterns.

**Special studies.** Endothelial markers such as Factor VIII, CD 31, and CD34 will typically be positive on the tumor cells, but not all tumor cells may stain. FVIII is the most sensitive and specific marker for the tumor.

**Kaposi's Sarcoma**

**Clinical features.** Kaposi's sarcoma (KS) most often occurs in the liver in the setting of the acquired immune deficiency syndrome (AIDS) usually only after the tumor is known to be present at other sites.

**Gross findings.** Most of the findings of KS in the liver are similar to those seen at other sites. The tumor can have a fibrous to hemorrhagic, multifocal appearance, often centering around portal triads.

**Microscopic findings.** The tumor consists of spindled cell proliferation that forms slit-like spaces or, in larger lesions, a more solid, fibrosarcomatous-like pattern. As at other sites, cellular pleomorphism and mitotic activity are minimal, and extravasation of erythrocytes, hemosiderin deposits, and small eosinophilic globules are typically present. One pattern that is typically seen only in the liver is the growth of the spindled tumor cells into and along the sinusoidal spaces, usually at the periphery of the tumor nodules. This pattern of growth results in dilated channels that contain erythrocytes that replace the normal sinusoids, findings that have a peliotic appearance. The tumor also tends to surround or infiltrate the portal zone, often leaving the hepatic artery and interlobular bile duct intact.

**Special studies.** The tumor cells are positive for endothelial markers including CD31 and CD34, which can be useful to help differentiate KS from fibroblastic proliferations.

**Benign Mesenchymal Lesions**

**Hemangioma**

**Clinical features.** Hemangioma is the most common primary tumor of the liver. This benign vascular neoplasm is usually noted as an incidental findings at surgery or autopsy, but may come to surgical excision due to hemorrhage or its large size. It has been suggested that estrogen therapy may lead to enlargement of the tumors. Rarely, thrombotic events within a large hemangioma may be associated with thrombocytopenia. These tumors can occasionally be multiple in the liver, and also can be associated with hemangiomas at other sites as part of Von Hippel-Lindau disease or skeletal/systemic hemangiomatosis syndrome.

**Gross features.** Hemangiomas are well circumscribed, red to red-brown tumors. They almost always have a spongy texture or honeycombed surface that represents the cavernous vascular component, and many will also have undergone thrombosis and sclerosis, which results in a firm, white to white tan appearance.

**Microscopic features.** The hallmark of this tumor is the cavernous vascular channels. The walls of these channels consist of fibrous stromal bands, which are lined by a single layer of flattened endothelial cells without cytologic atypia or mitotic activity. Sclerotic zones can be present and can be quite extensive. Thrombosed channels can also be seen. Extensively
sclerotic hemangiomas may only have a few remaining vascular channels, and so can mimic a localized scar.

**Angiomyolipoma**

**Clinical features.** Angiomyolipomas (AML) are only rarely noted in the liver. The tumor often presents in the 30 to 40-year-old age group in men or women of varying ages. Some of these tumors occur in the setting of tuberous sclerosis, but many do not. The tumor is thought to arise from the perivascular epithelioid cell, and related lesions in other organs include the clear cell “sugar” tumor and lymphangioleiomyomatosis of the lung.

**Gross findings.** AML can present as a large, variably colored tumor due to fat, necrosis, and hemorrhage.

**Microscopic findings.** This lesion usually is composed of various elements including smooth muscle-like cells, blood vessels, fat, and hematopoietic tissues. The smooth muscle-like differentiation is often the most prominent in liver AML, and consists of either epithelioid or spindled cells which often surround the vessels. The epithelioid cells have a rounded or polygonal shape with abundant eosinophilic cytoplasm. The nuclei are typically large and round with prominent nucleoli, but their appearance can vary. The cytoplasmic contents may be oncocytic, and may be condensed around the nucleus with a clear zone near the cell membrane, giving the appearance of a “spider-web”. The spindled cells have eosinophilic cytoplasm and small oval nuclei. Trabeculae, usually composed mostly of the epithelioid type of cells have also been noted. Either the epithelioid or spindle cell component may predominate to the exclusion of the other. The vascular component is typically made up of thick-walled arterial or venous-like channels admixed with thin-walled venous-like spaces. The fatty tissue consists of mature fat cells scattered throughout the tumor as single, clusters, or sheets of cells; however, in the liver variants of this lesion, the fat component can be scant or absent. Foam cells containing fine-droplets of lipid can also often be seen. Peliotic spaces closely associated with areas of hemorrhage can be present. These paces mostly lacked an endothelial lining. Prominent dense lymphoid aggregates composed of a mixture of T and B cells can be noted as well. Rarely, the inflammatory cells can be associated with the stromal spindle cell component of the tumor, mimicking inflammatory pseudotumor. Rarely, hemosiderin and melanin pigments can be present. Variable numbers of hematopoietic elements including megakaryocytes, erythroid and myeloid precursors are often present.

**Special studies.** Most of the diagnostic problems arise when the epithelioid smooth muscle-like cells predominate within the tumor as the large round nuclei with prominent nucleoli and abundant eosinophilic cytoplasm mimics HCC or hepatic adenoma. In addition, any formation of trabeculae containing the epithelioid cells closely mimics HCC. Immunohistochemistry can thus be very helpful to identify the tumor as angiomyolipoma rather than HCC or adenoma by demonstrating positivity for HMB-45 and smooth muscle actin (SMA) in the smooth-muscle-like cells. The spindle cells often stain stronger for the SMA while the epithelioid cells for the HMB-45. Desmin positivity has been noted in the spindle cells as well. Stains for keratin are negative. S-100 has been noted to be focally positive in angiomyolipoma as well, generally staining the epithelioid and fat cells. The combination of spindled and epithelioid cells can also mimic metastatic melanoma, so the HMB-45 positivity of AML can add to the confusion.

**Inflammatory Pseudotumor**
Clinical features. Inflammatory pseudotumor (IPT) is a rare, inflammatory and fibrosing lesion that can be found in other organs besides the liver. Patients may present with abdominal pain, fever, chills, jaundice, vomiting, and weight loss. The lesions have also been reported associated with chronic cholangitis. The lesion can be mistaken clinically for cholangiocarcinoma if the lesion is in the hilar region. Evidence for Epstein-Barr virus has been noted in tumors from various sites, including the liver. Some have also suggested the possibility of an association with the proliferation of the follicular dendritic reticulum cells.

Gross features. The appearance can vary considerably, especially in the larger lesions, with foci of fibrosis, hemorrhage, and necrosis present. The tumor can vary considerably in size, may be solitary or multiple, and may arise either in the porta hepatic or elsewhere in the liver parenchyma.

Microscopic features. IPT consists of a mixture of inflammatory and fibrous tissue, but the relative degree of these components can be variable. The inflammatory component of the lesion usually contains a polyclonal population of plasma cells, but neutrophils, eosinophils, lymphocytes (predominantly T cells), and macrophages (often xanthomatous) are also often present to some degree. The spindle cell component is made up of fibroblasts, and sclerotic foci are common. Mitotic figures may be seen but should not be numerous, and abnormal mitotic figures should not be seen. Occasionally, granulomas or phlebitis (or varying degrees of venous obstruction) may also be present.

Special studies. The IPT should be differentiated from other sarcomas such as angiosarcoma or metastatic gastrointestinal stromal tumor. In these sarcomas, cellular atypia, frequent mitotic figures should be noted, and the sarcomas typically lack numerous inflammatory cells. Immunohistochemistry can be helpful as well, as angiosarcomas stain positively for Factor VIII and other vascular endothelial markers and metastatic gastrointestinal tumors react with CD117 and CD34. The differentiation from follicular dendritic cell (FDC) tumor may be more difficult, but the absence of plasma cells and the presence of pleomorphic tumor cells in FDC as well as specific markers for FDC such as CD21, CD35, and R4/23 should help distinguish the two lesions.

References
CASES 11 AND 12- PEDIATRIC NEOPLASMS

Case 11

Clinical findings: A 22-month-old boy with Down’s syndrome presented with failure to thrive and a large abdominal mass. Abdominal CT scan showed a large hepatic mass.

Pathologic findings: Irregular lobules of atypical cells with increased nuclear to cytoplasmic ratio with collagenous septae. There are foci of extramedullary hematopoiesis within the sinusoids of the tumor.

Diagnosis- HEPATOBLASTOMA

Comments

Hepatoblastoma

Clinical features. Hepatoblastoma (HB) is the most common malignant liver tumor in children, with about 66% occurring under the age of 2 years and 90% under the age of 5. This tumor can occasionally arise in older children and, very rarely, adults. The lesion has a surprising male preponderance of almost two to one. Associations with other congenital conditions such as Beckwith-Weidemann syndrome, cleft palate, diaphragmatic hernia, Down’s syndrome, familial polyposis coli, hemihypertrophy, renal malformations, and other chromosomal abnormalities can be noted in as many as one-third of reported cases. Presenting symptoms such as an abdominal mass, failure to thrive, and loss of weight are relatively common. Less common are features such as vomiting, diarrhea, or jaundice. A patient may rarely present with signs of precocious puberty such as virilization, which is associated with production of human chorionic gonadotropin (HCG) by the tumor. Serum AFP is nearly always elevated, and has proven to be a useful marker for tumor recurrence or metastasis after therapy. Prognosis is directly related to complete surgical excision and tumor stage. The treatment of choice is thus complete surgical resection, but chemotherapy is often used preoperatively to reduce tumor size, as well as for residual tumor, and for non-resectable tumors. Some histology subtypes (see below), such as the pure fetal types, are thought by some to have a better prognosis after complete resection than the fetal/embryonal or mixed patterns. Other subtypes, such as the small cell and macrotrabecular types, may worsen the prognosis. Tumor-free margins are thought to be important for prognosis, but vascular invasion probably does not have a significant effect on outcome. Other factors thought to be associated with a more adverse outcome are age of presentation under one year, large tumor size, and involvement of vital structures.

Gross features. HB occurs in the noncirrhotic liver, typically as a large, single mass. The gross appearance can be variable, but the tumor is often multinodular with foci of hemorrhage and necrosis present. Since grossly different nodules or zones within the tumor can represent different histologic components, which in turn, may correlate with prognosis, adequate sections of these various areas must be taken. After chemotherapy, tumors may be very necrotic and their mesenchymal components, especially the osteoid, often remain prominent.

Microscopic features. The two subtypes of differentiation most commonly seen in HB are the epithelial and the mixed epithelial-mesenchymal types. The epithelial type presents typically as a combination of two histologic forms, the embryonal and fetal patterns, but rarely, a
pure fetal subtype can occur. The mixed epithelial-mesenchymal subtype is usually composed of the two epithelial patterns admixed with a spindle-cell mesenchyme; osteoid is also a common finding.

Within the epithelial subtype, the embryonal pattern is the more “immature” form, and consists of small tumor cells with fairly round to oval nuclei and scant basophilic cytoplasm which tend to form tubular, acinar, or ribbon-like arrangements. The fetal pattern is the other, more “mature” form that more closely resembles fetal liver, including tumor cell arrangement in plates or cords. The tumor cells in the fetal pattern are typically smaller than normal hepatocytes, but are slightly larger than the tumor cells in the embryonal pattern and show cytoplasmic changes of hepatocellular differentiation. The tumor cells in the fetal pattern also have moderate amounts of eosinophilic and/or clear cytoplasm, with the clear cell change due to the presence of lipids and/or glycogen. Both eosinophilic and clear cytoplasmic features often occur in the same tumor and result in an alternating pink and white appearance that is quite distinctive. Nuclei in the fetal pattern are typically small and round similar to normal fetal liver cells. For both patterns, mitotic figures are rare. Extramedullary hematopoiesis is often present, usually associated with the fetal component.

Less commonly seen subtypes of HB include the small cell undifferentiated type, macrotrabecular type, and mixed type with teratoid features. The small cell type consists of sheets of tumor cells without evidence of hepatocellular differentiation. These cells have very scant cytoplasm similar to that of neuroblastoma, so one of the other typical patterns of HB must be present in order to exclude this possibility. The macrotrabecular type forms wide trabeculae that must be greater than 10 cells thick. Fetal and/or embryonal type tumor cells typically make up these trabeculae, but a less common pattern of larger cells with more cytoplasm can rarely been seen, which can histologically mimic HCC. Again, the presence of other patterns of HB and the occurrence in a noncirrhotic liver can help to distinguish this variant of macrotrabecular HB from HCC arising in a child. A tumor with limited macrotrabecular component should probably be classified according to the other predominant patterns. The mixed type HB with teratoid features contains both epithelial and mesenchymal components as well as foci of other tissue types such as intestinal-type glandular elements, squamous epithelium, melanin pigment, other mesenchymal elements such as cartilage or skeletal muscle, or neural tissue.

**Special Studies.** HB stains positively for AFP in the embryonal component, and hepatocyte antibody as well as polyclonal CEA will stain the epithelial component, especially the fetal component, of this tumor. Focal neuroendocrine staining with chromogranin A has been reported in the embryonal, fetal, and osteoid components.

**Differential diagnosis.** Pure fetal HBs can be histologically similar to adenoma; the tumor cells tend to be smaller in HB than in adenoma and the alternating pink and white cytoplasmic staining pattern of HB is typically not present in adenoma. However, the lesions are conventionally separated by clinical parameters as well. For example, hepatic adenoma essentially does not occur before age five except in association with a metabolic disorder such as glycogen storage disease and serum AFP should not be elevated in adenoma. Clinical parameters also play an important role in distinguishing the macrotrabecular variant of HB and HCC, as the latter essentially only occur in this young age group in the presence of a preexisting liver disease or metabolic disorder, usually in the setting of cirrhosis.
CASE 12-PEDIATRIC MESENCHYMAL LESIONS

Clinical findings: 23 year old woman presented with 40 lb unintentional weight loss, abdominal fullness, and non-specific abdominal pain. Abdominal CT demonstrated a hepatic neoplasm, and at surgery, a greater than 10 cm hemorrhagic and necrotic mass was found.

Pathologic findings: Proliferation of spindled and stellate cells, low power. Spindled and stellate cells with ill-defined cell borders and rare multinucleated giant cell, high power. Epithelioid atypical cells containing hyaline globules within the cytoplasm and stroma, PAS stain with diastase, high power.

Diagnosis- EMBRYONAL SARCOMA

Comments

Undifferentiated (Embryonal) sarcoma

Clinical Features. Embryonal sarcoma is a rare tumor that typically occurs in children between the ages of 6 and 10, with some occurring in a slightly older age group (under the age of 20). The presenting features are often that of a mass or of abdominal pain. Complete surgical excision generally offers the best outcome.

Gross findings. Embryonal sarcomas are usually large, soft tumors, with a variably cystic and solid areas and a white, shiny or gelatinous or mucoid surface. Additional areas of necrosis and hemorrhage are often present.

Microscopic findings. These tumors contain a mixture of spindled and stellate cells embedded in a myxoid stroma. The tumor cells have a granular to bubbly, light pink cytoplasm, and many contain cytoplasmic globules of various sizes which are PAS-digest-positive. These globules may also be noted in the stroma. Other cellular features include the presence of other large atypical tumor cells with hyperchromatic nuclei as well as multinucleated tumor cells. The surrounding stroma is usually myxoid but some dense collagen deposits can be present. Mitotic figures are usually numerous. Hematopoeisis is often noted and entrapped hepatocytes and/or ductules can be present at the tumor’s periphery.

Special studies. The tumor cells of the lesion have been shown to immunohistochemically stain for vimentin, alpha-1 antitrypsin, alpha-1 antichymotrypsin.

Mesenchymal Hamartoma

Clinical features. Mesenchymal hamartoma (MH) is a benign tumor which occurs primarily in young children, predominantly presenting at less than 2 years of age. It is the third most common tumor of the liver in this age group (following hepatoblastoma and infantile hemangioendothelioma). The patient often presents with such clinical symptoms as a palpable liver mass, abdominal enlargement, or respiratory distress due to compression by the tumor. No risk for malignant transformation has been noted.

Gross findings. The tumor can be solid or cystic, with the solid areas of this tumor typically a tan color. When cysts are present, they contain a translucent fluid or a gelatinous material. These cysts may form due to the degeneration of the loose mesenchymal tissue of the tumor, and it is thought that the tumor probably enlarges by continued accumulation of fluid into these cysts.

Microscopic features. MH has epithelial and stromal components. The former consistent of relatively normal-appearing hepatocytes and bile ducts, both which are surrounded by varying
amounts of myxoid to fibrous stroma. The hepatocytes are cytologically unremarkable and are arranged for the most part either in small clusters or in larger groups with retention of the cell plate architecture as in the normal liver. The bile duct structures are typically arranged in a branching pattern, and often are associated with an acute inflammatory infiltrate in the duct walls or adjacent to it. The cystic spaces, when present, may be lined by flattened to cuboidal epithelial cells, which are surrounded by a loose to dense fibrous tissue. Cysts may also lack any lining cells. The stroma generally contains increased numbers of small vascular structures (but the cysts are not lined by endothelial cells), spindle cells, and inflammatory cells. No normal portal zones are present. Extramedullary hematopoiesis is often noted.

Infantile Hemangioendothelioma

Clinical features. The infantile hemangioendothelioma (IHE) is the second most common tumor in children under three years of age, second only to hepatoblastoma, and almost all the reported cases have occurred in infants less than six months old. The tumor is almost twice as common in girls than in boys. The tumors are often multifocal within the liver and about 10% of the patients also have hemangiomas present in other organs. The tumors may also be associated with other congenital anomalies, such as bilateral renal agenesis, Beckwith-Wiedemann syndrome, hemihypertrophy, and meningocele. The clinical presentation may be an abdominal mass or distention (with hepatomegaly), jaundice, diarrhea, constipation, vomiting, congestive heart failure, or failure to thrive. Other less common findings can include thrombocytopenia due to sequestration of platelets within the tumor(s) or rupture with hemoperitoneum. These tumors are generally benign histologically, but because of their multifocality and/or large size, the patients have a high mortality rate due to cardiac or hepatic failure. The tumors can regress, but therapy such as resection, embolization, hepatic arterial ligation, or chemo/radiation is often necessary for patient survival. Angiosarcoma may rarely arise in this lesion.

Gross findings. IHE is often a poorly circumscribed lesion, and can be solid and cystic, with variable hemorrhagic foci. These foci typically alternate with the fibrotic (solid) zones. The tumors are multifocal.

Microscopic findings. Two histologic subtypes have been described for this lesion, although practically speaking, distinguishing the two can be difficult. Type 1 is defined by a mixture of large numbers of small vascular channels and fewer, large, irregularly shaped spaces with a cavernous appearance, with both types of vascular channels lined by a single layer of endothelial cells. The vascular spaces are separated by a poorly-developed stroma with only scattered collagen or reticulin fibers. Small bile ducts and well as hepatocytes can be seen in the stroma as well, often near the periphery of the tumor. Focal necrosis, hemorrhage, fibrosis, and calcification are often present. Type 2 lesions contains endothelial cells with more atypical cytologic features, with mitotic activity and hyperchromasia, and arranged in a more complex budding or branching pattern [Craig, 1989 #396] than noted in type 1 lesions.

Special studies. The endothelial cells of the tumor will stain with CD34, CD31, and Factor VIII. The stromal cells underlying the basement membrane of the capillary structures are alpha-smooth muscle actin and HHF35 positive, desmin negative, a profile consistent with pericytes.
References