1 THE FOCAL LIVER LESION: GENERAL CONSIDERATIONS

INTRODUCTION

The liver is the largest and one of the most complex organs in the human body with a multitude of functions that range from a synthetic and secretory nature to detoxification and surveillance. There is dual blood supply from the portal vein and hepatic artery (Fig. 1.1). The liver is also part of the monocyte–macrophage system. Hence, it is affected not only by primary hepatic pathologies but by extrahepatic/systemic diseases as well. A kaleidoscope of morphologic patterns exists. To add to this complexity is the fact that one generic pattern can be caused by more than one etiology and vice versa. Therein lies the challenge of attempting to render a definitive diagnosis. Pattern recognition is more of an art than an exact science.

Tumors and tumor-like lesions manifest as solitary or multiple, cystic or solid nodules and may occur in livers that already harbor developmental, metabolic, or chronic inflammatory disorders. Two major diagnostic challenges are posed by focal liver lesions. First, the liver itself often develops cirrhosis, from which a spectrum of well-differentiated hepatocellular nodular lesions of variable biologic status can evolve. These nodules have to be distinguished from hepatocellular carcinoma (HCC), which is the most important therapeutically and prognostically. Second, the liver is a common depository for metastases from all parts of the body. Some of these histologic entities, such as neuroendocrine tumors, can arise in the liver whilst others can mimic the two most important primary liver cancers, namely HCC and intrahepatic cholangiocarcinoma (ICC).
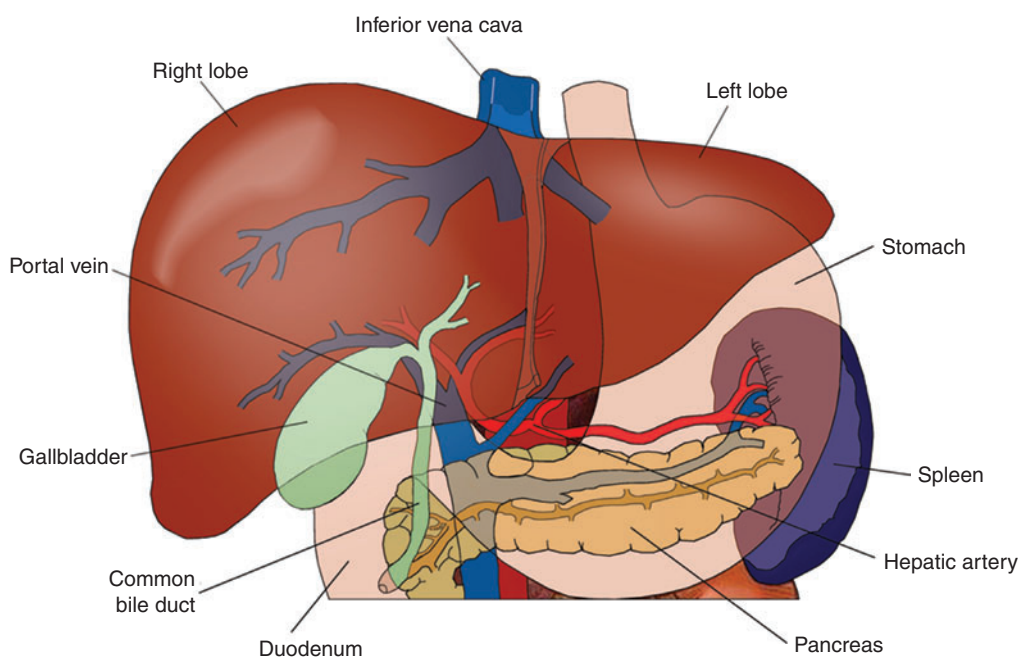

Figure 1.1 Liver and gallbladder with biliary tract.
The liver is situated in the right upper quadrant of the abdominal cavity. It has a dual blood supply from the portal vein draining the gastrointestinal tract and from the hepatic artery. Blood leaves the organ via the hepatic veins into the inferior vena cava. The biliary tract drains into the duodenum at the ampulla of Vater. Note the neighboring organs and structures.

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Of note is that metastases tend to bypass cirrhotic livers, possibly due to the non-receptive milieu.

Small tissue samples can be procured by fine needle aspiration biopsy (FNAB) or core needle biopsy (CNB) under radiologic guidance for cytohistologic assessment, often with the aid of ancillary tests. The diagnostic expertise of the radiologist contributes greatly to the overall diagnostic yield and accuracy. Both pathologic and radiologic assessments are complementary rather than competitive diagnostic tools in a given clinical setting. A working knowledge of the imaging principles and parameters on which specific radiologic diagnoses are arrived at is of great help to the cytopathologist in deciding whether a sample is representative or not. It is emphasized that all three components – clinical, radiologic, and pathologic perspectives – are equally relevant but for the purpose of this monograph, the focus is on the pathologic aspect.

THE FOCAL NODULAR LESION

The generic term seems understandable enough. However, do radiologists, clinicians, and pathologists use the term in a similar fashion? What basic parameters define the term and what does it encompass? Are there any inherent diagnostic, prognostic, or therapeutic implications with usage of this term?

Radiologic perspective

Tumors and tumor-like lesions in the liver may manifest as space-occupying lesions or with mass effect on intrahepatic bile ducts and vessels. Focal liver lesions are usually first detected and designated as such on imaging. A focal lesion is an area or region of abnormal or altered echogenicity on ultrasound, abnormal density on computerized tomography (CT), or abnormal signal intensity on magnetic resonance imaging (MRI). A focal nodular lesion is usually round or oval, in contrast to segmental wedge-shaped changes that conform to vascular supply. Nodules >1 cm are easier to detect whereas those <1 cm may require specialized techniques and intravenous contrast agents. Solid nodules <1 cm are usually followed up as many of them cannot be characterized accurately and are also difficult to biopsy. Most of the nodules that are 1–2 cm in size may be accurately characterized with contrast-enhanced ultrasound, CT, and MRI but may need biopsy confirmation when atypical features are present. Nodules >2 cm can be accurately diagnosed with clinical information, laboratory tests, and imaging characteristics and only uncommonly require tissue confirmation. Liver cysts are also a very common finding and easily diagnosed by their characteristic appearances and stability during follow-up imaging. Cysts that are not unilocular and those with solid contents/debris, thick enhancing walls, or nodular thickening (complex cysts) are suspicious and subjected to further evaluation. In general, solid nodular lesions that are >1 cm in size with atypical imaging characteristics and complex cystic lesions are typical candidates for biopsy. Solid enhancing lesions always need to be evaluated to rule out malignancy.

Pathologic perspective

Pathologically, any localized focus comprising a distinct group of neoplastic or nonneoplastic cells that are aberrant in composition, distribution, or location in the liver constitutes a focal lesion. Generally, focal nodular lesions are seen as space-occupying solid or cystic masses, distinct from surrounding parenchyma. Solid lesions tend to exhibit a variety of macroscopic features, such as distinct delineation with/without capsule; variable color, texture, and consistency with bulging cut surface, hemorrhage, and necrosis; invasive borders and secondary mass effects on neighboring parenchyma (Fig. 1.2). Cystic lesions may exhibit loculation and septation with excrescences or solid areas on the inner surfaces. Cyst contents range from serous fluid, mucin, and pus to necrotic debris.
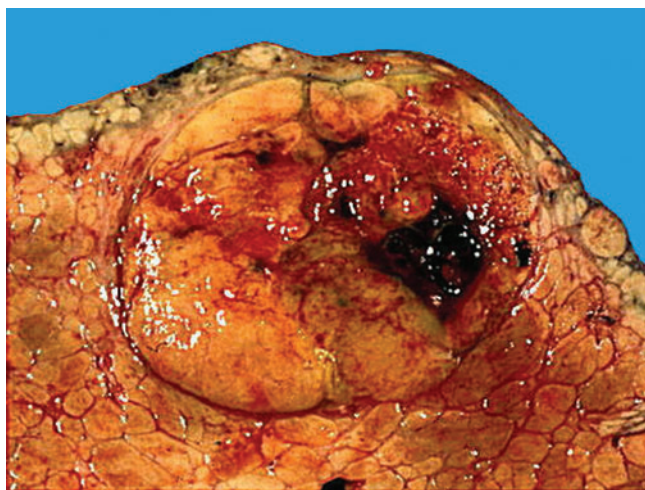

Figure 1.2 Hepatocellular carcinoma in hepatitis B-associated cirrhosis; resection of liver.
Cirrhotic liver containing a 4-cm-diameter circumscribed solid tan nodule showing a bulging cut surface with hemorrhage.

Focal liver lesions may also be microscopic and disseminated, for example granulomas, microabscesses, and von Meyenburg complexes. A significant example is a dysplastic focus (by definition, <1 mm in size) of large cell or small cell change in cirrhosis. These examples beg the question of what is the minimum cut-off size for focal liver lesions. For the purpose of this book, the cut-off is when they are below radiologic detection. The exception is small subcentimeter subcapsular liver lesions seen under direct vision during laparotomy or laparoscopy.

Clinical perspective

The outcome of patients with focal liver lesions is dependent on the overall clinical assessment. Advances in dynamic imaging modalities have enhanced the accuracy of radiologic diagnosis. Large size, solid nature, rapid enlargement, and symptomatology expedite prompt action. However, the index of suspicion is heightened when small nodules are detected in cirrhotic patients. Incidental lesions that can be established radiologically to have low or no suspicion of malignancy are followed up conservatively. Others considered indeterminate in nature are subjected to FNAB or CNB. In essence, although size generally determines the index of suspicion for malignancy, size is after all only a relative intuitive factor.

THE APPROACHES

Factors that can influence the optimum small tissue sample

Awareness of the factors that may determine the outcome of small tissue samples greatly impacts one's confidence in signing out a case. Understanding the process may permit improvements to be made. The factors are as follows:

- *Size of lesion*: Size is a major determinant for sample adequacy and diagnostic yield. Subcentimeter lesions require much procurer skill and patient cooperation; often missing the target. Sampling errors are also experienced in "nodule-in-nodule" lesions where the malignant subnodule is likely to be bypassed for the larger parent nodule.
- *Location of lesion*: This determines the accessibility to sampling. For nodules that are small and deep-seated in the left lobe or near the hilum, endoscopic

ultrasound-guided FNA (EUS-FNA) is far superior to the percutaneous route.

- *Choice of technique, radiologic guidance, and needle bore size*: The most popular route is percutaneous (transabdominal) FNAB or CNB performed under ultrasound or CT guidance. Biopsies can be performed under direct vision at laparoscopy/laparotomy. EUS-FNA requires a trained gastroenterologist. The needle bore caliber ranges from 18 gauge for CNB to 20 to 24 gauge for FNAB. The smaller the bore, the more flexible is the needle. The choice is largely dependent on the suspected likely diagnosis, size, accessibility of the lesion, proximity to vital structures, patient suitability, risk of complications, and procurer preference. The sensitivity and specificity of FNAB and CNB should also be considered when choosing the optimal technique.
- *Skill of procurer*: With a skilled procurer, the number of FNAB passes can be kept to a minimum and the diagnostic yield and accuracy greatly improved. The risk of complications is also reduced.
- *Patient cooperation*: This is essential for accurate intranodular placement of the needle.
- *Rapid on-site evaluation* (*ROSE*): This is also referred to as immediate cytologic evaluation (ICE). An on-cytology service with trained personnel allows for rapid assessment of sample adequacy and triage of specimens for microbiologic studies, flow cytometry, and molecular analysis, if necessary. Smears are of better quality and touch imprints and retrieval of particulate tissue for cell blocks can be performed.
- *Specimen handling, preparation, processing and staining*: The preferred choice of preparation for liver aspirates is still by conventional cytology. The cost of liquid-based preparations and the diagnostic challenges posed by such specimens currently outweigh the advantages. Crush artifacts and thick, over-stained smears can obscure/obliterate cytologic details. Availability of representative histologic material is useful for special stains and immunohistochemistry.
- *Nature of the lesion*: In aspirates, the cellularity and patterns of spread are determined by the nature of the lesion; degree of cell cohesion; reticulin framework; vascular complexity; and presence of fibrosis, necrosis, and calcification. The integrity of aberrant tissue in tissue cores is determined largely by the same factors. Fragmentation of cores can also be related to the procedure/needle caliber.

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Table 1.1 Criteria for adequate and representative small tissue samples of focal liver lesions

Minimum criteria for optimum aspirates	Minimum criteria for optimum core biopsies
• Cellular smears composed entirely of aberrant cell population/s with no associated parenchyma	• Abnormal pattern/s with no associated parenchyma
• Cellular smears composed of aberrant cell population/s with associated parenchyma (hepatic/extrahepatic)	• Abnormal "replacement or effacement pattern" with associated parenchyma (hepatic/extrahepatic)
• Cellular smears composed of minimally aberrant hepatocellular population with or without normal/diffusely aberrant hepatic parenchyma	• Well-differentiated hepatocellular nodular lesion with or without normal/diffusely aberrant hepatic parenchyma
• Cellular smears composed of abscess contents or other types of inflammatory cells	• Evidence of abscess wall and contents or other types of inflammatory tissue
• Variably cellular smears composed of cyst contents with specialized lining cells	• Evidence of specialized cyst lining with/without cyst contents

(a)
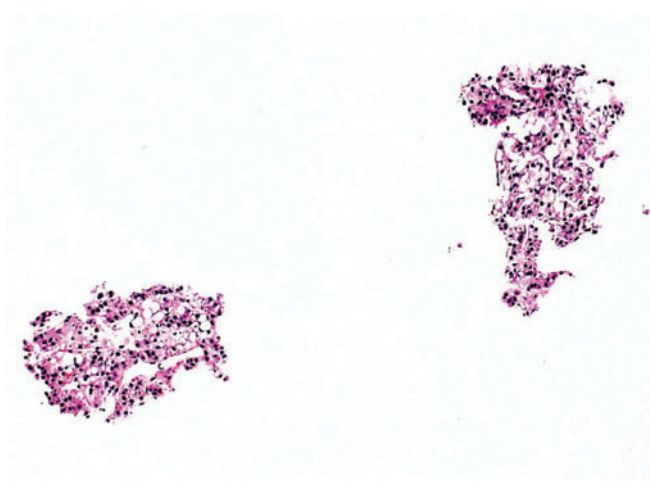
(b)
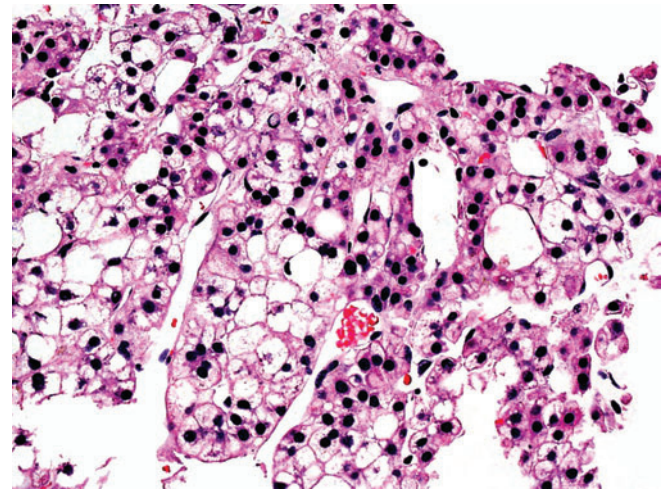
Figure 1.3 Hepatocellular carcinoma with fatty change; core biopsy of liver.
(a) Two tiny fragments of aberrant tissue. H&E, ×40.
(b) Although scanty, deeper levels reveal a classic trabecular–sinusoidal pattern with broad cords of malignant hepatocytes exhibiting fatty change; obviating any need for immunohistochemistry. H&E, ×200.

Assessment for adequacy

Assessment of adequacy and representative sampling of the purportedly labeled lesion is integral to FNAB or CNB interpretation because it conveys the degree of certainty with which one can rely on the result. Normal hepatic parenchyma consists of a polymorphous cell population composed predominantly of hepatobiliary cells with few Kupffer cells and endothelial cells. The normal architecture consists of portal tracts and central veins distributed at regular intervals. The liver can undergo cirrhosis with possible evolution of precancerous lesions thereafter. Consideration of focal liver lesions must always take into account the likely incorporation of background aberrant parenchyma. Rarely, an extrahepatic lesion may be mistaken radiologically for a hepatic problem. Both the quality and quantity of the small tissue sample contribute to the ideal diagnostic material.

Representative samples

The minimum criteria for optimum aspirates and core biopsies (Fig. 1.3) are listed in Table 1.1.

Unsatisfactory samples

- Inadequate: Too few cells, atypical or otherwise, preclude optimal assessment. Sclerotic tumors, for example ICC and some metastases, are prone to "dry" aspirates.
- Blood: A traumatic aspiration not withstanding, it could also be from a hemangioma.
- Cellular aspirates with preservation, processing, or staining artifacts: Air-drying, crush/smearing artifact, thick smears, and over-staining preclude optimal assessment. Nuclear streaks are common in small round cell tumors.

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■ Tissue cores with fragmentation and crush artifacts: Samples of necrotic/fibrotic/calcified tissue and cirrhotic tissue are prone to fragmentation, making assessment of architecture and spatial relationships difficult. Crush artifacts pose the same diagnostic problems as in smears.

Nondiagnostic or nonrepresentative samples

1. **Intrahepatic constituents**
   - ■ Normal liver background: In core biopsies, cirrhotic fragments and well-differentiated hepatocellular nodular lesions may resemble "normal" liver.
   - ■ Aberrant liver background:
     - Fatty liver disease: Pitfalls include focal fatty change and hepatocellular nodular lesions with fatty change.
     - Cholestasis: Reactive hepatocytes producing bile may mimic a bile-secreting hepatocellular neoplasm.
     - Hemochromatosis: A siderotic nodule may be diagnosed without realizing that there is diffuse iron overload.
     - Cirrhosis: Similar restoration features are seen in large regenerative nodule and focal nodular hyperplasia.
     - Nodular regenerative hyperplasia: This may be mistaken for normal or cirrhotic liver, or hepato-cellular nodular lesions, such as hepatocellular adenoma and liver adenomatosis.
   - ■ Surrounding hepatic parenchyma with secondary mass effect (Fig. 1.4).
   - ■ Large portal tracts or hilar structures.
   - ■ Liver capsule.
2. **Extrahepatic constituents**
   - ■ Mesothelial cells (Fig. 1.5a, b).
   - ■ Gallbladder and extrahepatic biliary tract.
   - ■ Gastrointestinal contaminants (EUS-FNA): Glandular epithelium may mimic adenocarcinoma (Fig. 1.5c, d).
   - ■ Kidney (Fig. 1.5e, f).
   - ■ Adrenal gland: Adrenocortical cells may mimic hepatocellular nodular lesions.
   - ■ Lung.
3. **Necrotic debris only**
   - ■ Coagulative necrosis: This is common in colorectal metastases ("dirty necrosis"), HCC with/without post-ablation therapy, and neuroendocrine tumors. Infarction may extend to adjacent liver due to locoregional ablation therapies. Therapy-
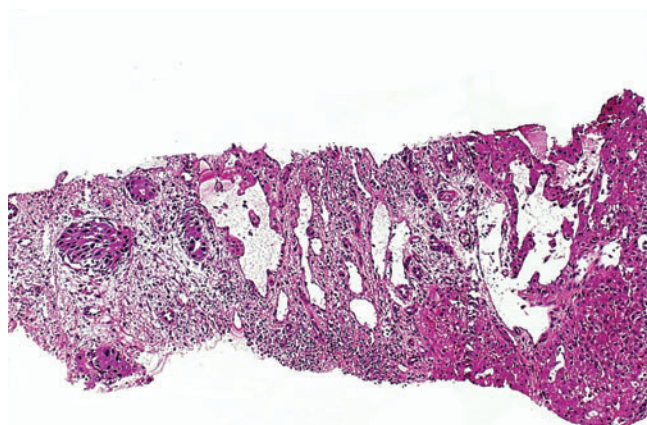

Figure 1.4 Secondary mass effect; core biopsy of liver.
The hepatic parenchyma in the vicinity of an adenocarcinoma shows marked irregular sinusoidal dilatation. This may be misdiagnosed as a vascular lesion if the biopsy falls short of the tumor (left). H&E, ×40.

   induced cytologic atypia can occur in adjacent hepatobiliary cells (beware of their inclusion in necrotic debris).
   - ■ Caseous necrosis: Tuberculous granulomas have to be considered.
   - ■ Liquefactive necrosis: Amebic abscess is a possibility.
   - ■ Suppurative necrosis: Pyogenic, fungal, and parasitic causes have to be considered.
4. **Cyst contents only**
   - ■ Serous/proteinaceous fluid: Look for parasitic parts and specialized epithelial cells (true cysts).
   - ■ Mucin: This is pathologic if contamination from gastrointestinal tract during EUS-FNA is not an issue. Absence of specialized lining cells precludes definitive diagnosis of mucinous neoplasms.

Morphologic approach

An initial blinded pattern recognition approach with cell profiling is advocated for the microscopic assessment of smears and histologic sections to avoid bias (Chapter 2). Any cytohistologic material should be correlated. The volume, nature, and color of cyst contents; and the length, fragmentation, and color of tissue cores are recorded. The first step is low power scanning assessment of the slides for adequacy and representative sampling. In aspirates, the appearance of the spread of the cells is a useful clue. In tissue cores, the extent and confines of the lesion are appraised. The next step is pattern recognition with
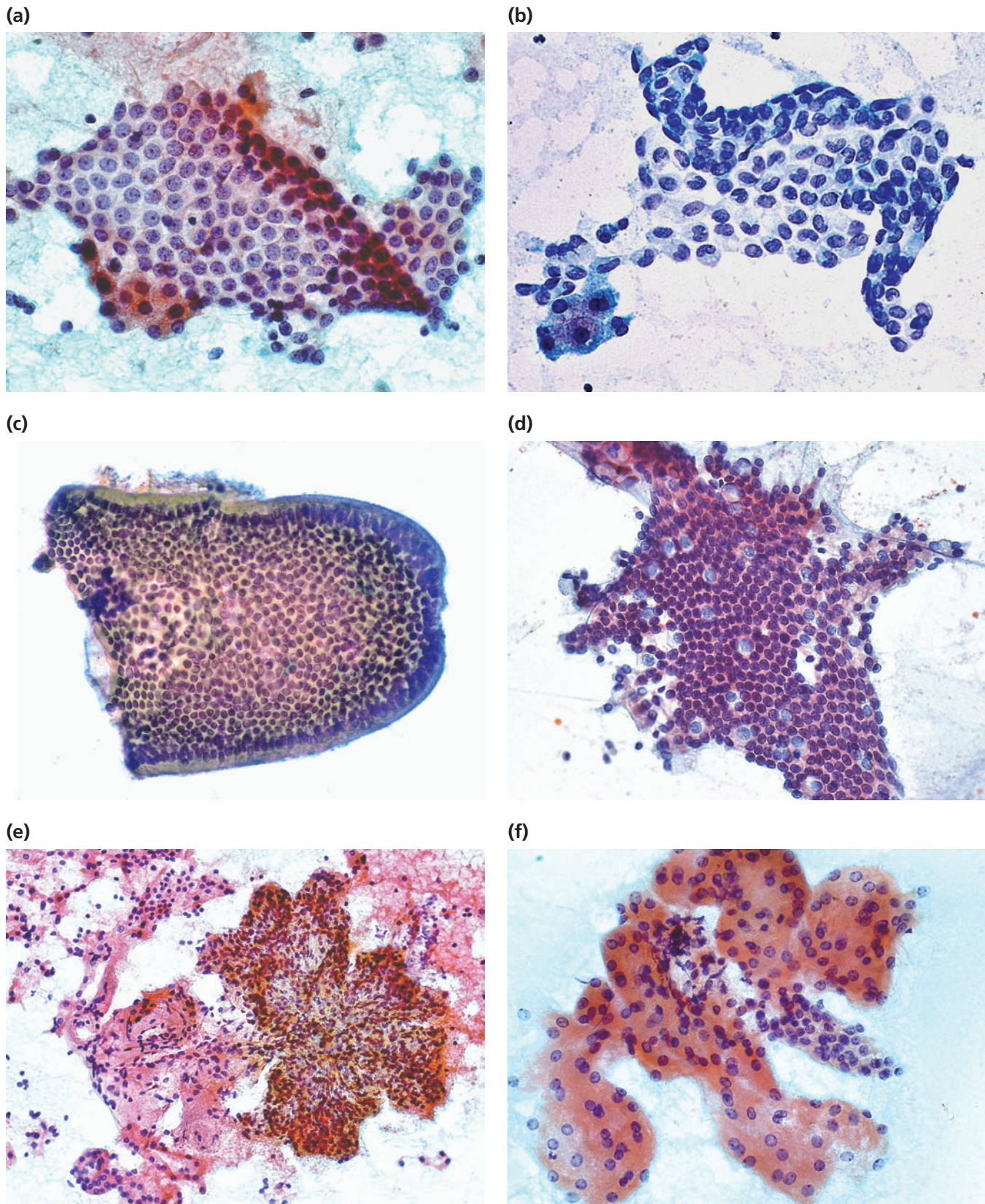
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(a)

(b)

(c)

(d)

(e)

(f)

Figure 1.5 **Extrahepatic constituents; FNABs of liver.**

Cytopathology report

Clinical summary
55 yr, Chinese male. Serum AFP 1000 μg/L. Hepatitis C with cirrhosis.
CT abdomen showed cirrhosis with a solitary 4.0 cm mass in the left hepatic lobe. Radiologic features were indeterminate.

Method
EUS-FNA of mass

Material
1st pass: 2 air-dried and 2 alcohol-fixed smears
          2 May–Grünwald–Giemsa (MGG) and 2 Papanicolaou-stained smears
Cell block: Available

Rapid on-site evaluation (ROSE)
Sample adequacy: Yes
Provisional diagnosis: Malignant cell yield. Favor hepatocellular carcinoma.
Comments: Nil

Microscopic description
Hypercellular smears showed granular trails of irregular tumor aggregates composed predominantly of arborizing tongues of malignant cells exhibiting hepatocytic features. Transgressing and peripheral endothelium were evident. The tumor cells displayed pleomorphism with high nuclear–cytoplasmic ratio, nuclear contour irregularities, prominent nucleolus, and coarse granular chromatin. Bare atypical nuclei were present in the background.

Cell block: Malignant hepatocytes were arranged in trabecular–sinusoidal pattern. Cords appeared more than 3 cells thick.

Immunohistochemistry (performed on cell block): There was tumor positivity for AFP with diffuse CD34 sinusoidal capillarization.

Diagnosis
Liver, focal lesion; EUS-FNA biopsy:
 •   **Hepatocellular carcinoma**
 •   **History of hepatitis C-associated cirrhosis**

Comments
Nil.

Figure 1.6 Sample of a cytopathology report for a focal liver lesion. AFP, α-fetoprotein.

cell profiling to establish the solid or cystic nature, the nonneoplastic or neoplastic (benign or malignant) status, and the cell lineage of the lesion. In most instances, a definitive diagnosis can be rendered at this stage without ancillary studies.

Diagnostic algorithm

The five-step diagnostic algorithm shows the reader how to: (i) "*clinically assign*" patients into classic settings, (ii) "*radiologically outline*" the focal liver lesions,

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Caption for Figure 1.5 (*cont.***)**
Mesothelium:
(a) Folded monolayered sheet of uniformly spaced, flat quiescent cells with ample pale cytoplasm, bland nuclei, and small nucleolus. Papanicolaou, ×200;
(b) Folded monolayered sheet of reactive cells exhibiting bean-shaped, vesicular nuclei that appear eccentric with ample cytoplasm. Note normal hepatocytes in left lower quadrant. Papanicolaou, ×200.
Gastrointestinal contaminants, EUS-FNA:
(c) A 3-dimensional sheet of gastric foveolar epithelium showing uniform picket-fence alignment of columnar epithelium with supranuclear mucin secretion. Papanicolaou, ×200;
(d) A flat honeycomb sheet of intestinal epithelium with distributed goblet cells. Papanicolaou, ×200.
Kidney:
(e) A normal glomerulus resembling a cauliflower-like vascular tuft with paler proximal tubular cells. Papanicolaou, ×40;
(f) A convolution of polygonal proximal tubular cells with pale cytoplasm and bland central nuclei next to a collecting duct exhibiting smaller crowded denser cells. Papanicolaou, ×200.

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Histopathology report

Clinical summary
45 yr, Chinese male. Hepatitis B with cirrhosis on regular cancer surveillance. Serum AFP 10 μg/L.
CT abdomen showed cirrhosis. There were three nodules measuring 1.9, 1.5, and 1.0 cm in size and involving both lobes.
There was no contrast enhancement.

Method
CT-guided core biopsy (18G) of largest nodule

Material
Received in formalin a core of tan-colored tissue measuring 0.8 cm in length.

Microscopic description
The core showed mainly cirrhotic parenchyma. Part of a well-differentiated hepatocellular nodular lesion with ill-defined margins was identified at the tip. The lesion was composed of hepatocytes arranged in 2-cell-thick cords and exhibiting small cell change.
The monotonous aberrant cells showed dense eosinophilic cytoplasm, increased nuclear–cytoplasmic ratio, and increased nuclear density. The reticulin framework was not deficient.

Immunohistochemistry: The tumor was negative for glypican-3, glutamine synthetase, and heat shock protein 70. CD34 showed focal sinusoidal capillarization. CK19 performed to delineate intranodular and extranodular ductular reaction was noncontributory due to lack of aberrant tissue.

Diagnosis
Liver, focal lesion; CT-guided core biopsy:
- **Well-differentiated hepatocellular nodular lesion with small cell change; cannot differentiate between high-grade dysplastic nodule and early hepatocellular carcinoma**
- **History of hepatitis B-associated cirrhosis**

Comments
Close follow-up with repeat biopsy if clinically warranted.

Figure 1.7 Sample of a histopathology report for a focal liver lesion.

(iii) "*microscopically streamline*" the aberrant cells/tissue into generic patterns and cell profiles, (iv) "*immuno-histochemically define*" the exact histogenesis and site of origin, and (v) "*integratively refine*" the final diagnosis based on review of all available data (Chapter 3). The reader is recommended to walk through the morphologic assessment algorithms (Chapter 2). Then match the probable morphologic diagnosis with the clinical setting to which the patient has been assigned. This dual exercise underpins the rationale for the clinically oriented chapters in this book.

REPORTING OF SMALL TISSUE SAMPLES

The rendering of a cytohistologic report should be treated as patient (material) consultation and not another machine-churned-out laboratory result. The report is a means of communication to assist in further patient management; hence, it should be worded accordingly. Furthermore, it is an archival record of the morphologic findings should the slides fade or be misplaced and no digital archival library is available. This is especially so for medicolegal reasons when sent-in consultation material are to be returned. A description of the features often helps one to refine the diagnosis. Avoid "negative for malignancy" phrases as the *sole* diagnostic statement. This does not educate the procurer in improving their technique. Neither does it train the reader to account for the findings or the lack of.

A cytopathology/histopathology report should provide the following information (Figs. 1.6, 1.7):

(i) Clinical summary (optional)
(ii) Method of tissue procurement
(iii) Materials received
(iv) ROSE findings/provisional diagnosis (if any)

(v) Microscopic description:
- Assessment of adequacy
- Description of pattern/architecture and cell profiles
- Mention of background material, artifacts, if any
- Results of ancillary studies

(vi) Final diagnosis

(vii) Comments:
- Reference to other relevant cytohistopathology reports
- Suggestions for further investigations, if clinically warranted

(viii) Photomicrographs (optional).

CLINICAL VIGNETTES

Focal liver lesions are first identified on imaging. Despite recent advances and state-of-the-art imaging technology, there still remains a group of indeterminate nodules that require tissue characterization. Vignette 1.1 illustrates the role of tissue sampling to confirm the radiologic findings. It also emphasizes the problems of choice of biopsy site, the advantages of complementary sampling techniques, and that cytohistopathology reporting is a three-way consultative process. However, at times one sampling technique is superior to the other. The core biopsy in Vignette 1.2 facilitates the analysis and comparison of aberrant and residual tissues.

Clinical Vignette 1.1

A 14-year-old boy presented with fever and abdominal pain. CT abdomen was performed (Fig. 1.8). An abscess was deemed more likely than a neoplasm. First CT-guided core biopsy showed hepatic tissue with coagulative necrosis and visible reticulin framework but no inflammation (Fig. 1.9). FNAB performed one week later showed benign

Figure 1.8 Hepatocellular adenoma with infarction; CT abdomen. Contrast-enhanced CT image of the liver shows an irregular exophytic multilocular lesion measuring 14 × 12 cm. It is thick-walled, peripherally enhancing, and contains air pockets (arrow).
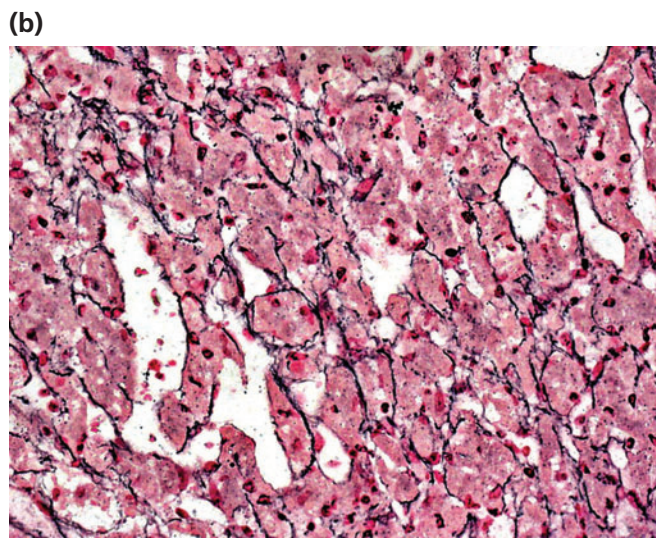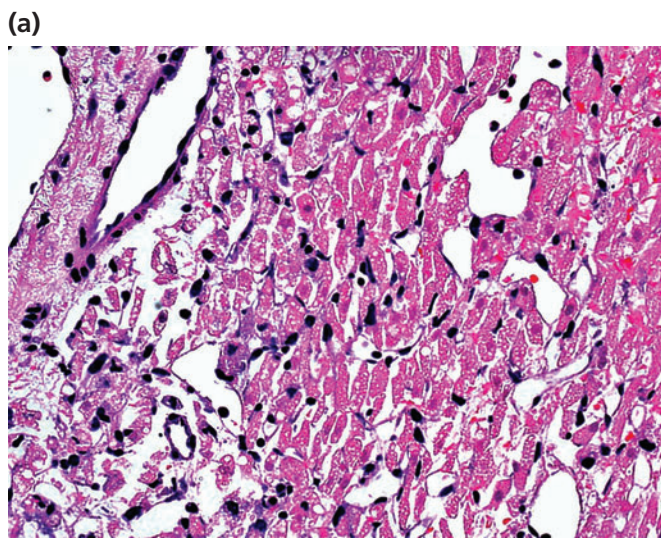
(a) **(b)**

Figure 1.9 Hepatocellular adenoma with infarction; core biopsy of liver.
(a) The hepatocytes show total infarction. Note irregular sinusoidal dilatation and unpaired arterioles. H&E, ×200.
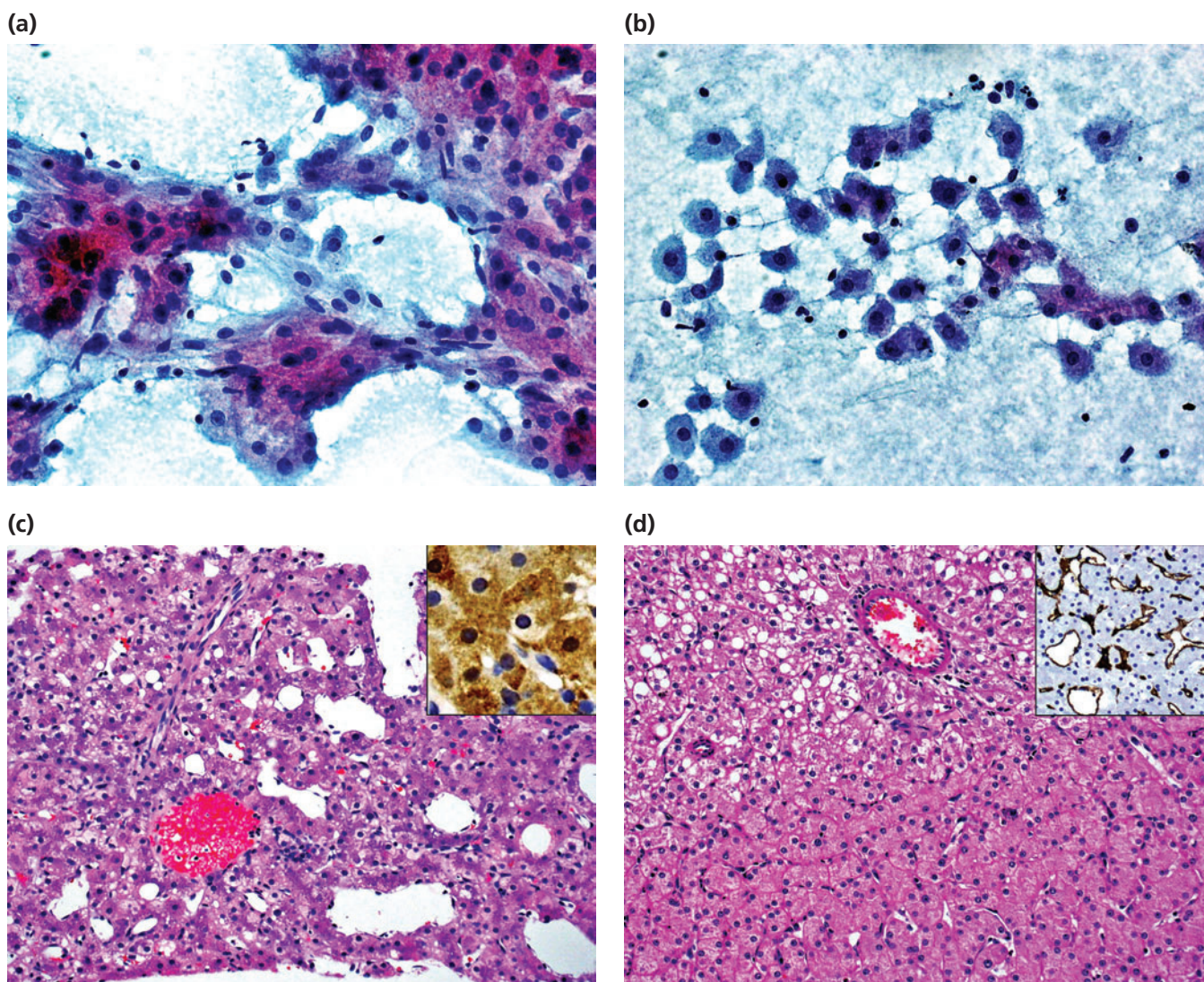(b) The reticulin framework shows cords of 1 to 2 cells thick. Gomori, ×200.

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Figure 1.10 Hepatocellular adenoma; (a, b) FNAB, (c) core biopsy, and (d) resection of liver.
(a) Well-differentiated hepatocytes with normal nuclear-cytoplasmic ratio and transgressing endothelium. Papanicolaou, ×200.
(b) Some dissociated aberrant hepatocytes. Papanicolaou, ×200.
(c) Expanse of well-differentiated hepatocytes arranged in 1- to 2-cell-thick cords with irregular sinusoidal dilatation and unpaired arteries but no portal tracts. H&E, ×100.
Inset: Diffuse tumor positivity for glutamine synthetase. Immunostain, ×200.
(d) The tumor is composed of well-differentiated hepatocytes arranged in 1- to 2-cell-thick cords with unpaired arterioles. H&E, ×100. Inset: CD34 highlighted diffuse sinusoidal capillarization and arterialization. Immunostain, ×100.

hepatocytes with transgressing endothelium, loosely lying endothelial cells, and sparse ductal clusters (Fig. 1.10a, b). The repeat core showed a benign well-differentiated hepatocellular nodular lesion exhibiting unpaired vessels, sinusoidal dilatation, and extramedullary hematopoiesis but no portal tracts (Fig. 1.10c). Immunohistochemistry revealed diffuse CD34 sinusoidal capillarization and diffuse glutamine synthetase positivity. Glypican-3 and CK19 were negative. It transpired that the patient was on anticonvulsant therapy (phenytoin) for epilepsy.

Discussion

This lesion exhibits a hepatocellular pattern with benign neoplastic features. Wide expanses of benign-looking hepatocytes forming twin-cell plates accompanied by unpaired vessels and diffuse CD34 sinusoidal capillarization, in the absence of portal tracts, are features pathognomonic for hepatocellular adenoma (HCA). Had clinical, radiologic, and histologic correlation been made *ab initio*, the diagnosis of a necrotic well-differentiated hepatocellular nodular lesion favoring HCA might have been alluded to from the beginning. Infarction is