Anatomic Pathology of Hepatocellular Carcinoma

Histopathology Using Classic and New Diagnostic Tools

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KEYWORDS

- Hepatocellular carcinoma • Liver biopsy • Dysplastic nodule
- Immunohistochemistry • Glypican-3 • Glutamine synthetase • Arginase-1
- Biphenotypic

KEY POINTS

- The diagnosis of hepatocellular carcinoma requires careful evaluation of architecture and cytology on the H&E stained slide.
- Ancillary stains are helpful when applied in a systematic manner.
- High-grade dysplastic nodules are precursors to hepatocellular carcinoma, but a definitive diagnosis may not be possible by needle biopsy alone.

INTRODUCTION

The liver biopsy for a clinical concern of hepatocellular carcinoma (HCC) can be very straightforward for the pathologist or can present one of the more challenging specimens in surgical pathology, even for specialists. Despite ever-improving imaging techniques, such studies cannot always address the origin or the malignant potential of a hepatic lesion and thus a biopsy is performed. A concurrent biopsy of nonlesional liver for comparison is helpful when provided. This article is a guide through liver biopsy evaluation from the perspective of pathologists using routine stains available in most laboratories. The understanding is that such a biopsy is only carried out under highly specialized circumstances.[1]

CLINICAL DATA

Patient demographics and clinical history are important when reviewing a mass-directed biopsy. Specifically, patient gender and age provide the first breakpoints in

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Clin Liver Dis 19 (2015) 239–259
http://dx.doi.org/10.1016/j.cld.2015.01.003 **liver.theclinics.com**
1089-3261/15/$ – see front matter

the diagnostic algorithm for a differential diagnosis.[2] Men are at 3-fold risk for developing HCC in the United States, and risk for most adult liver carcinomas increases with age. Pediatric liver malignancies are separate considerations, not further discussed in this article. Knowledge of possible underlying chronic liver disease (CLD) is the next step in the decision tree. In a patient with known CLD or cirrhosis, the working diagnosis of a new nodule favors primary liver carcinoma over either metastatic liver disease or benign tumor of the liver because up to 90% of HCC cases occur in patients with underlying CLD[3] and benign liver tumors are very unusual in cirrhosis.

It is important for the pathologist to correlate histologic features with imaging studies (see elsewhere in this issue by Anis for further discussion). The most useful tool for a pathologist remains the routine hematoxylin-eosin (H&E) stain and, in most cases, it is the careful study of the H&E that will lead to the diagnosis or guide additional work-up.

HEMATOXYLIN-EOSIN STAIN EVALUATION OF THE DIRECTED BIOPSY FOR HEPATOCELLULAR CARCINOMA

Liver Biopsy in Hepatocellular Carcinoma: Yes or No?

Unlike other solid organs, consideration of biopsy for malignancy in the cirrhotic liver continues to be controversial. The most recent iteration of the controversy[4] highlights the use of the newer targeted molecular therapies in many other organs, which require tumor tissue analysis but do not yet exist for HCC. Pathologists have responded to these arguments in the past and will continue because several important considerations in the discussion remain.[5]

For cirrhotic patients, current practice guidelines[1] dictate that when imaging findings of a 1 to 2 cm lesion are atypical, the lesion should be biopsied (see later discussion).

Architecture

The initial assessment determines the presence of the lesion in the biopsy tissue, which begins with overall evaluation of parenchymal architecture. Unaccompanied arteries and lack of complete portal tracts indicate that lesional tissue is present (**Fig. 1**). The hepatocyte and cord growth patterns also highlight the lesion. Some HCCs have sheet-like compact growth, others have a pseudoglandular pattern with a dilated canaliculus in the center (**Fig. 2**), and others recapitulate the trabecular formations of hepatic cords or plates.

A well-differentiated HCC may initially appear, on low-power microscopy, to be normal hepatic parenchyma and, in this case, loss of the normal liver cell plates from 1 to 2 cell nuclei across (normal) to 3 or more nuclei in a single cord (neoplastic) is a feature of malignancy. Whereas normal liver should have narrow cords of hepatocytes running in parallel, even well-differentiated HCC tissue has a somewhat disorganized pattern secondary to the increased thickness of the hepatocyte cords (**Fig. 3**). These altered patterns of growth are an indication of lesional tissue. A reticulin stain may be an additional aid in these types of cases.

Cytology

Although architecture is often the most helpful tool in recognizing the presence of an HCC, cytologic clues are present in HCC as well. One may appreciate 2 different populations of cells, and the neoplastic population may take various appearances. Up to one-third of HCCs are steatotic and the presence of a fatty nodule in a background of nonfatty liver is suggestive of a lesion. In fact, HCC may show any cytologic or nuclear features of its benign counterparts, including steatosis, steatohepatitis, Mallory-Denk bodies, hyaline globules, and intranuclear inclusions.