

Fine needle aspiration biopsy of malignant mass lesions in the liver: a revisit of diagnostic profiles and challenges

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Fine needle aspiration biopsy (FNAB) of the liver with 20-23 G needles under radiologic guidance has been shown to be a safe and efficacious tool for procuring small tissue samples from liver mass lesions (1-3). The advantages of percutaneous (transabdominal) FNAB are well documented. However, as with all small samples, there are limitations of sampling error and insufficient material for ancillary tests. Part of this shortfall can be overcome by multiple sampling (up to 4 passes) of different parts of large lesions. Of late, endoscopic ultrasound-guided FNA (EUS-FNA) has emerged as a superior technique to access the left lobe, hilar structures and small deep-seated lesions in the liver; thereby increasing the sensitivity and accuracy of radiologic detection and intrahepatic staging (4-6). Some hepatologists prefer 16-18 G core needle biopsies (CNB) whenever the situation permits (7,8). Although the histologic material allows for appreciation of architecture, spatial relationship and host tissue, and more material is available for performing ancillary tests, the wider bore needles are shorter and less flexible. Furthermore, there is a greater risk of bleeding amongst other contraindications/complications.

Complementary cytohistologic approach is strongly recommended. In fact, many radiologists perform FNAB and CNB at the same sitting nowadays. It is always advantageous to have rapid-on-site examination (ROSE) (9,10). This cytology service allows for rapid assessment of sample adequacy on air-dried Diff-Quik-stained smears prepared from aspirates/tissue core touchpreps; and triage of samples for microbiologic studies, flow cytometry and molecular tests. Cytologic specimens include conventional air-dried and alcohol-fixed smears stained with Giemsa and Papanicolaou stains, respectively, and cytospin smears from needle rinses. Histologic specimens can be prepared from core biopsies, microcores (from FNAB), and cell

blocks (from retrieving particulate matter from FNAB). Immunohistochemical panels are routinely performed (11-16). The role of liquid based cytology in the context of FNAB of liver mass lesions has yet to be fully explored (2).

The major indication for performing FNAB/CNB of focal liver lesions is to establish a malignant diagnosis in patients with clinically or radiologically suspected neoplasia or for staging in patients with known tumors at other sites (17). Nowadays, advances in imaging techniques have obviated the need for tissue confirmation in classic hepatocellular carcinoma (HCC) (18). Routine radiologic surveillance of high-risk patients, such as those with cirrhosis due to hepatitis B and C or alcohol, has enabled detection of increasingly smaller and smaller liver nodules of indeterminate status. Under other circumstances, FNAB is performed after locoregional ablative therapies for nodules that have shown partial/no response. However, with personalized targeted molecular therapy where intra- and extratumoral tissue are required for molecular signature studies, FNAB has a big role to play as point of care in the future management strategy of patients with liver tumors, especially HCC (19).

The diversity of focal liver lesions is due to the anatomical and functional complexity of the organ. Primary diffuse/focal hepatic pathologies as well as extrahepatic/systemic conditions affect the liver. A kaleidoscope of morphologic patterns exists. One generic pattern can be caused by more than one etiology and vice versa. Therein lies the diagnostic challenge in handling small tissue samples of liver mass lesions. There may be developmental or acquired, solitary or multiple, and cystic or solid nodules. The spectrum ranges from cysts, abscesses, regenerative nodules to tumors and tumor-like lesions.

Two major diagnostic challenges are posed by focal

lesions found in the liver (2,3). Firstly, the liver often undergoes cirrhosis - from which a spectrum of well-differentiated hepatocellular nodular lesions of variable biologic status can evolve, namely, large regenerative nodule, low- and high-grade dysplastic nodules, and HCC. Secondly, the organ is a common depository for metastases - some nonhepatobiliary neoplasms can originate in the liver whilst others can mimic the two most important primary liver cancers, namely, HCC and intrahepatic cholangiocarcinoma (ICC) (20,21).

The diagnostic issues encountered in the morphologic workup of liver mass lesions are as follows:

- To separate well-differentiated hepatocellular nodular lesions from reactive hepatocytes
- To differentiate between the various benign well-differentiated hepatocellular nodular lesions, namely, large regenerative nodule, low- and high-grade dysplastic nodules, focal nodule hyperplasia and hepatocellular adenoma (+/- fatty change)
- To distinguish early HCC from benign well-differentiated hepatocellular nodular lesions
- To identify the variants of HCC and distinguish them from benign/malignant mimics
- To differentiate intrahepatic cholangiocarcinoma (ICC) from metastatic adenocarcinomas
- To differentiate poorly differentiated HCC from poorly differentiated ICC
- To separate poorly differentiated primary liver carcinomas from metastases
- To recognize mixed hepatobiliary carcinomas and their permutations
- To establish histogenesis of benign/malignant nonhepatocellular tumors
- To determine primary site of origin of malignant nonhepatocellular tumors
- To distinguish benign from malignant cystic lesions
- To recognize inflammatory/infective lesions that may mimic tumors

Although the title states the cytopathologic diagnosis of liver mass lesions, the authors have focused their review on primary and metastatic malignancies occurring in the liver. This is in essence a brief overview of their literature search for articles pertaining to the key cytologic characteristics of malignant liver lesions, diagnostic utility of immunohistochemical markers, and pertinent molecular tests. They mention important differential diagnoses and highlight common diagnostic pitfalls. Tumors with suspected metastatic disease can be divided into three main groups: (I) Tumors in which likely tumor and primary site can be predicted with high level of confidence based on cytologic appearances, such as colonic adenocarcinoma,

breast carcinoma, small cell carcinoma of lung and renal cell carcinoma; (II) Tumors having characteristic cytologic pattern but without specific clues to primary site, such as adenocarcinomas, squamous cell carcinomas, neuroendocrine tumors, lymphomas and melanoma; and (III) Undifferentiated neoplasms.

Most of our comments pertain to practice in established centers with state-of-the-art facilities and dedicated trained personnel to handle such focal liver masses from start to finish. This is not the case in many institutions and regions of the world. Blind or US-guided FNAB may be the practice, often for advanced disease. Practising under such circumstances requires a high level of basic diagnostic skill without the crutch of fancy ancillary tests. A diagnostic algorithm based on generic pattern recognition cum cell profiling to map out the possible liver mass lesions, benign/malignant, solid/cystic, primary/secondary, would be of great help (20,21).

The authors stress the importance of integrative clinicopathologic and radiologic correlation for the final diagnosis of liver mass lesions. This review is suitable reading for general non-cytopathology community. It enlightens them on the similarities of some liver conditions and the difficulties faced by cytopathologists in addressing small tissue samples of mass lesion from an organ as complex and diverse as the liver. The diagnostic tribulations are accentuated in the absence of diagnostic aids, such as immunohistochemistry.

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