Pathology of liver tumours

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Abstract

Histopathological assessment of liver tissue is essential for the management of patients with a whole range of liver tumours. Biopsies are often helpful in establishing the initial diagnosis of a lesion. Intraoperative frozen sections can provide the surgeon with valuable information regarding the nature of a liver lesion and/or the clearance of surgical margins. Examination of tissue from resection and transplant operations is important in confirming the preoperative diagnosis and for providing additional prognostic information. This review outlines the pathway for the processing of liver tumour tissue in the histopathology laboratory, before discussing the pathological features of the more commonly encountered benign and malignant liver tumours. Included within this discussion are epithelial tumours of both hepatocellular and biliary derivation, mesenchymal lesions and metastatic liver lesions. The age of the patient and the presence or absence of background liver disease are major determinants of the likely differential diagnosis of a liver lesion. The review also summarizes the key data items included in a histopathology report for surgical excision specimens.

Keywords Cholangiocarcinoma; focal nodular hyperplasia; hepatocellular adenoma; hepatocellular carcinoma; liver pathology

Pathological assessment of liver tumours

Liver tumours may be encountered by the pathologist in whole livers removed during transplantation ('explant livers'), surgical resection specimens and as core biopsies. The aim of pathological assessment of biopsy material is generally restricted to establishing a diagnosis. For surgical excisions of malignant lesions the pathologist is able to provide additional prognostic and staging information and to evaluate the completeness of the excision. Pathologists may also receive fresh specimens for intraoperative diagnosis ('frozen sections') and are also increasingly involved in sampling material for tissue banking and research projects, such as the 100,000 genome project.

Specimens are usually submitted to pathology immersed in formalin. The purpose of formalin fixation is to prevent tissue degradation by forming cross-links between proteins. Formalin penetration of tissues is slow (approximately 1 mm per hour). After examination of the specimen for integrity of the liver capsule, excision specimens may be serially sliced through the capsule leaving the hilum and/or parenchymal resection margins intact. This increases the surface area of the specimen which facilitates fixation. It is generally recommended the volume of formalin used to fix a specimen is ten times the volume of the specimen.

Formalin fixation causes degradation of nuclear material through formation of cross-links with DNA-protein complexes such as histones. If tissue is required for research purposes (currently molecular testing is not part of the routine work-up of liver tumours) it is best sampled fresh. Once this has been performed the remaining specimen can be left to fix in formalin for routine pathological assessment.

After adequate fixation specimens are dissected and examined. The specimens are weighed and measured. The presence, size and appearance of the tumour is documented. In liver resection specimens the distance between the tumour and the hepatic resection margin is measured. Large-calibre vessels are examined for evidence of tumour involvement (i.e. tumour thrombus). It is helpful to photograph specimens at this point for future discussion at the multidisciplinary team meeting.

Small pieces of tissue (approximately 20 × 15 × 3 mm) are sampled for histological analysis. Although the number of blocks taken varies depending on the nature of the case, sampling will usually include: tumour with the nearest hepatic resection margin, tumour with adjacent liver (this is helpful to look for vascular invasion under the microscope), tumour with liver capsule, hilar structures (if present) and background liver.

Specimens are then dehydrated, embedded in paraffin, thinly sectioned and stained with haematoxylin and eosin (H&E). After examination of the H&E slide, it may be necessary for more sections to be cut from the paraffin blocks for immunohistochemistry or other histochemical stains. The glass slides and the paraffin blocks are stored for several decades after reporting. The non-sampled tissue is destroyed soon after the pathology report has been authorized.

Specimens submitted for intraoperative diagnosis are received fresh. After examination and dissection the tissue is frozen, sectioned and stained, allowing the pathologist to provide a verbal report to the clinicians within 15–20 minutes of the sample having been received. Although very rapid, the sections produced from this procedure are more difficult to interpret than standard H&E sections due to the inferior staining properties and increased tendency to artefacts inherent to frozen tissue.

Classification and pathological features of liver tumours

There are 45 separate entities listed in the most recent World Health Organization (WHO) classification of tumours of the liver and intrahepatic bile ducts. Broadly these tumours can be divided into epithelial tumours of hepatocellular and biliary derivation, mesenchymal tumours, germ cell tumours, lymphomas and secondary (metastatic) tumours. This review will discuss some of the more commonly encountered lesions (Box 1). Although hepatectomy may be performed for perihilar cholangiocarcinoma (a term which encompasses the classical Klatskin hilar cholangiocarcinoma), this is considered a tumour of the extrahepatic bile ducts rather than the liver, and is therefore not discussed in this review.

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Selected tumours of the liver and intrahepatic bile ducts

- Epithelial tumours: hepatocellular
  - Benign
    - Hepatocellular adenoma
    - Focal nodular hyperplasia
    - Large regenerative nodule
  - Premalignant
    - High-grade dysplastic nodule
  - Malignant
    - Hepatocellular carcinoma
    - Hepatoblastoma
- Epithelial tumours: biliary
  - Benign
    - Solitary bile duct cyst
    - Biliary microhamartoma (von Meyenburg complex)
    - Bile duct adenoma
  - Premalignant
    - Mucinous cystic neoplasm
    - Intraductal papillary neoplasm
  - Malignant
    - Intrahepatic cholangiocarcinoma
- Mesenchymal tumours
  - Benign
    - Cavernous haemangioma
    - Paediatric vascular lesions*
    - Angiomyolipoma
    - Inflammatory pseudotumour
    - Mesenchymal hamartoma
  - Malignant
    - Epithelioid haemangioendothelioma
    - Angiosarcoma
- Metastatic tumours

*Comprising hepatic infantile haemangioma (GLUT-1 positive) and congenital haemangioma (GLUT-1 negative).

Box 1

Hepatocellular adenoma (HCA)

HCA is a benign tumour of hepatocytes arising, by definition, on the background of a non-cirrhotic liver. It most commonly affects younger women. It is associated with use of the oral contraceptive pill, and the risk of HCA increases with the duration of use of the pill. HCA is also associated with a history of obesity, diabetes mellitus, glycogen storage diseases, familial adenomatous polyposis, and anabolic steroid use. It generally presents incidentally or as an abdominal mass, although larger lesions can present acutely following significant haemorrhage into the peritoneal cavity.

Macroscopically HCA has a variable appearance: it may be tan, fatty or haemorrhagic (Figure 1). Microscopically the tumour is composed of neoplastic hepatocytes closely resembling the cells of the background liver, although the lesional cells tend to be slightly smaller. Large vessels may be prominent and arterioles unaccompanied by bile ducts are characteristic. Normal portal tracts are absent. Molecular studies have been used to subclassify HCA into three groups: HNF1α inactivated, β-catenin activated and inflammatory. These groups have characteristic clinical, morphological and immunohistochemical features. The β-catenin activated subgroup has the highest risk of progression to hepatocellular carcinoma. Approximately 10% of HCAs have no known mutation and fall outside this classification.

Diagnosis of HCA may be made from either biopsy material or following surgical excision. In some instances distinction from a well-differentiated hepatocellular carcinoma may be impossible in biopsy material. In such cases the biopsy is reported as a well-differentiated hepatocellular neoplasm, with the definitive diagnosis being deferred to the excision specimen.

HCA is not diagnosed in the context of a cirrhotic liver, where the differentials for a macroscopically distinct nodule lie between large regenerative nodule/dysplastic nodule and well-differentiated hepatocellular carcinoma (see below).

Focal nodular hyperplasia (FNH)

FNH is a hyperplastic response of hepatocytes, probably to alterations in blood flow, and usually occurs in the context of a non-cirrhotic liver. It most commonly affects young women, but a higher proportion (5–15%) occurs in men compared with hepatocellular adenoma. It usually presents incidentally but may occasionally present with pain.

Macroscopically FNH is nodular and has a characteristic central scar (Figure 1). Microscopically it is composed of normal-looking hepatocytes with an intact reticulin framework, arranged in nodules separated by fibrous tissue containing multiple small bile ductules and thick walled arteries. Normal portal tracts are not present. On immunohistochemistry FNH shows a characteristic 'map-like' pattern of glutamine synthetase staining.

There is no convincing evidence that FNH is pre-neoplastic. It may be biopsied or excised in order to exclude more sinister pathology. In biopsy material it may be difficult to distinguish FNH from inflammatory HCA and from non-lesional cirrhotic liver.

Hepatocellular carcinoma (HCC)

Classical HCC: HCC is a malignant tumour of hepatocytes and is the main type of primary liver cancer. It is the second commonest cause of cancer-related death worldwide, with the highest incidence seen in East Asia. Most HCCs arise on a background of chronic liver disease and cirrhosis. In East Asia viral hepatitis is the commonest underlying disease, whereas in Northern Europe and Northern America alcohol-related and non-alcohol-related fatty liver diseases are relatively more common. Hepatitis B and C viral infection and genetic haemochromatosis are risk factors for HCC, even in the absence of cirrhosis. HCC can be reliably diagnosed radiologically and international guidelines now advocate performing a biopsy to establish the diagnosis only in cases where the imaging is equivocal or an alternative pathology is considered.

Macroscopically HCCs have a variable appearance (Figure 2). They may be single or multiple nodules. They may be tan, green

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