Pathology of liver tumours

Christopher OC Bellamy

Abstract

The liver is an important site for both primary and metastatic tumours. In non-cirrhotic patients, the most common hepatic presentation of malignant disease is metastasis from other sites, most commonly the colon, lung, stomach, pancreas and breast. In patients with cirrhosis, hepatocellular carcinoma is the most likely cause of hepatic malignancy, and is a major cause of cancer death worldwide. The malignant cells of hepatocellular carcinoma show differentiation resembling hepatocytes. There is a strong link with chronic viral hepatitis and cirrhosis of any cause, although an unusual slow growing variant of hepatocellular carcinoma called fibrolamellar carcinoma does not show these associations. Cholangiocarcinoma is adenocarcinoma arising in a bile duct, and is usually of unknown cause although some cases are linked with chronic biliary inflammation or infection. Intrahepatic cholangiocarcinoma is increasingly diagnosed, although definitive diagnosis requires clinical exclusion of a metastasis from elsewhere. There is a variety of benign liver tumours, often manifesting incidentally during investigations. Some have a risk of malignant progression (dysplastic nodules in cirrhotic liver, some hepatocellular adenomas), while others are notable mainly for mimicking more serious disease than for great intrinsic significance.

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

This chapter describes the pathology and practical issues relating to diagnosis of tumours or tumour-like lesions arising in the liver. Metastases to the liver will not be covered. The presentation and management of liver tumours are dealt with elsewhere in this issue (Malignant liver tumours on pages 655–660 and Benign liver lesions on pages 648–654), so will not be fully repeated here. Nevertheless, it is important to emphasize that definitive evaluation and management of a primary liver tumour will usually need to be carried out in specialist hepatobiliary units with a multidisciplinary approach (hepatobiliary surgeon, hepatologist, interventional radiologist, medical oncologist, specialist pathologist) and a full range of diagnostic and therapeutic options.

Handling of tissue specimens

Tissue sent for pathological diagnosis may take the form of a targeted needle biopsy (one or more passes into the lesion, sometimes with a pass into non-lesional tissue for comparison), an open biopsy (occasionally with tissue sent for provisional frozen section diagnosis), or may be the resection specimen itself (possibly after some form of ablative treatment or chemotherapy has already been administered). Each of these specimen types offers its own challenges to diagnosis.

Christopher O C Bellamy *PhD FRCPath is a Reader in Pathology at Edinburgh University and an Honorary Consultant at the Royal Infirmary of Edinburgh, Scotland, UK. Conflicts of interest: none declared.*

Histologic diagnosis relies on examination of high-quality tissue sections stained with haematoxylin and eosin, supplemented with other histochemical stains as necessary, and with immunohistochemistry to demonstrate particular target proteins of diagnostic, therapeutic or prognostic significance. Molecular-cytogenetic testing is beginning to play a role in some situations but is not yet routine. However the use and range of immunohistochemistry for diagnosis is increasing all the time.

Proper fixation of the tissue is essential to provide the high-quality sections needed for diagnosis, and buffered formalin is the usual fixative of choice. Formalin penetrates tissue relatively slowly (about 1 mm per hour), which is not a problem for needle biopsies. However, sizeable resection specimens must have formalin introduced into the specimen to allow timely fixation before the tissue degrades, which requires the pathologist to perfuse or thinly slice the unfixed specimen as soon as possible. Hence resection specimens are generally best submitted fresh direct to pathology at the end of the procedure, rather than placed in small amounts of formalin and left to the vagaries of the local specimen pickup. If the operation is completed late at night, the specimen can be placed in a bag on ice and left overnight in the fridge for prompt transport direct to pathology the next morning. This will give a better result than leaving it at room temperature unsliced in formalin.

Epithelial tumours and tumour-like lesions

Hepatocellular lesions

Focal nodular hyperplasia

Definition – a hyperplastic tumour-like growth of hepatocytes, typically lobulated with radiating fibrous septae carrying abnormal arterial vessels, and often with a central scar (Figure 1). The lesion is characterized by abnormal arterial hyperperfusion and lack of portal venous perfusion of the affected liver parenchyma, thought to be the root cause of the localized hyperplasia.

Clinical features – these occur in otherwise normal liver. They most often affect adult women, who are usually asymptomatic or sometimes have abdominal discomfort.

Similar arterialized hyperplastic lesions are described in a variety of abnormal liver settings, including after chemotherapy for colorectal carcinoma (where the lesion may give rise to concern for a metastasis), in cirrhosis and in hereditary haemorrhagic telangiectasia. By convention, lesions in such pathologic settings are described as arterialized large regenerative nodules rather than focal nodular hyperplasia (see below).

Pathology – most are under 5 cm diameter, although can be much larger. There may be multiple lesions in the affected liver, or the focal nodular hyperplasia may itself be incidental to another lesion such as liver cell adenoma. The histology on a needle biopsy can resemble a biliary cirrhosis unless the pathologist is alert to this being a focal lesion, but is generally distinctive enough, with thickened vessels in fibrous septa with marginal ductules the septa delineating regions of bland-appearing hepatocytes without portal tracts. Immunohistochemistry for glutamine synthetase usually shows a characteristic so-called 'map-like' anastomosing staining pattern of groups of hepatocytes that helps discrimination from liver cell adenoma. A differential diagnosis on targeted needle biopsies that have only sampled the edge of a localized

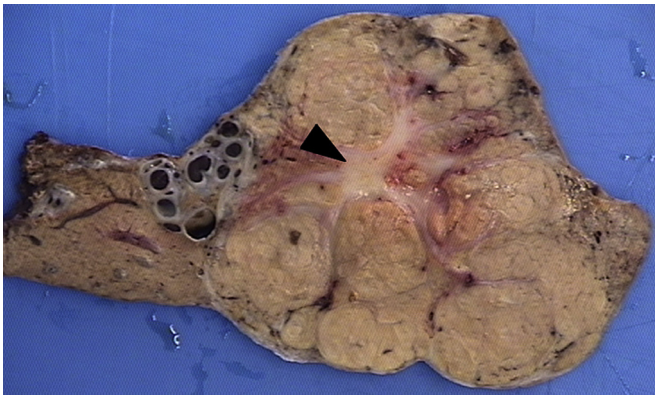

Figure 1 Resection specimen showing a focal nodular hyperplasia within non-cirrhotic liver. Note the slightly off-centre scar (arrowhead) with radiating white septae that delineate a vaguely lobular appearance to the lesion.

abnormality is of peri-tumoural hyperplasia, which is a hyperplastic response in the rim of liver surrounding a metastasis (or occasionally a primary carcinoma).

Liver cell (hepatocellular) adenoma

Definition — a rare benign neoplasm of liver cells that arises in non-cirrhotic liver and can be solitary or multiple.

Clinical features — hepatocellular adenomas most often affect women of reproductive age (about 90%) and are associated with oral contraceptive usage, but can also arise in particular disease settings where men are more often affected, including inherited glycogen storage diseases, familial diabetes mellitus, exposure to non-contraceptive oestrogens (e.g. Danazol) and anabolic steroids. Diagnosis is often by chance, but patients may present with abdominal discomfort, or sometimes acutely due to intraperitoneal haemorrhage. Small adenomas may remain stable after stopping the oral contraceptive, while a few may regress. Patients with an adenoma may also have a focal nodular hyperplasia or haemangioma elsewhere in the liver (possibly a greater than chance association), and so the nature of each additional lesion in the liver has to be considered independently. There is no particular clinical value in categorizing patients according to whether they have one or multiple adenomas, and it is the clinical setting, gender and lesion size that are important.

Pathology — adenomas are circumscribed tumours in non-cirrhotic liver. They may be as large as 20 cm or more, but are more typically several cm diameter. Where there is more than one adenoma (as many as one-third of patients), the additional lesions may range down to 1 cm or even smaller (called 'microadenomas'). Adenomas larger than 4–5 cm often have areas of haemorrhage and sometimes necrosis. Those with haemorrhage identified on imaging at presentation may have arterial embolization/ligation as a temporary control measure in the months preceding resection. In such cases, the haematoma and sometimes the resected adenoma itself can have shrunk substantially from the size at presentation.

On microscopy, there are sheets of bland-looking hepatocytes with mildly thickened liver plates and prominent small vessels, but no true portal tracts with bile ducts. Distinction from a well-differentiated hepatocellular carcinoma on a needle biopsy can be very difficult or impossible.

There has been considerable recent progress in identifying clinically relevant molecular subgroups of adenomas, although a minority remains unclassified. These subgroups tend to have characteristic appearances on routine histology, which can usually be validated with immunohistochemistry, even if molecular analytic techniques are unavailable. Adenomas with extensive fatty change (detectable with imaging) are often HNF1α-mutated (inactivated), seem to be stable with a low risk of malignant progression, and are more often associated with other microadenomas in the liver. Immunohistochemistry for loss of liver fatty acid binding protein expression from the tumour cells is diagnostic. Adenomas expressing inflammatory proteins on immunohistochemistry ('inflammatory adenomas') often have characteristic inflammation and vascular changes on histology (sometimes also called telangiectatic adenomas). The patients may also have a biochemical inflammatory syndrome, and there are associations with high alcohol intake, obesity and fatty liver disease (Figure 2). Molecular analysis shows these adenomas to have mutations activating inflammatory signal transduction pathways, most often mutant gp130 that constitutively activates STAT3. A small minority show malignant progression.

Complications — haemorrhage is the most common complication. The risk of malignant progression within the adenoma to hepatocellular carcinoma is increased in larger adenomas (>5 cm) and adenomas showing β-catenin-activation, which can sometimes be detected with immunohistochemistry. However malignant progression is sufficiently more likely in men that adenomas of any size in males may be considered at risk. Identification of the malignant areas is generally only possible in the resected specimen, so the clinical management of adenomas is dictated by risk factors rather than direct identification of malignancy with imaging or biopsy.

Dysplastic nodule

Definition — a benign nodule of neoplastic hepatocytes in cirrhotic liver, with increased potential to develop hepatocellular carcinoma.

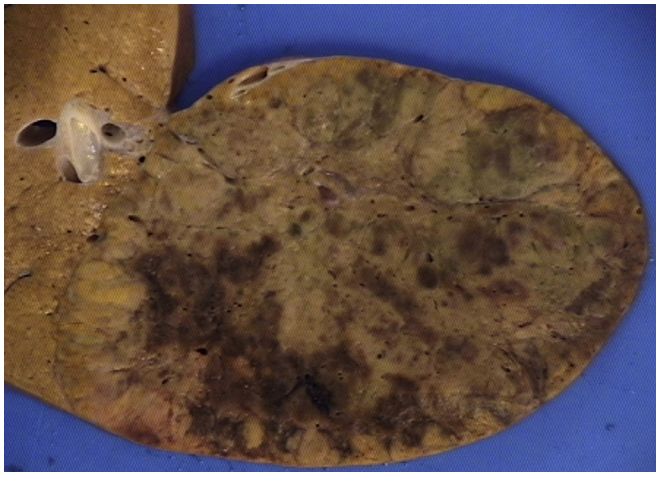

Figure 2 Resection specimen showing a 91 mm adenoma arising in non-cirrhotic liver in a morbidly obese patient. On microscopy, the adenoma was of telangiectatic (inflammatory) type, and the surrounding liver showed steatohepatitis.