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Outpatient liver biopsy: a prospective evaluation of 500 cases

Percutaneous core liver biopsy plays an important role in the management of parenchymal liver disease in establishing diagnosis, evaluating prognosis and monitoring the effect of therapy. Despite the first biopsy been carried out over 100 years ago, debate surrounds best practice.

Day case liver biopsy has become increasingly popular and has not been shown to be associated with increased complications.[1 2] Under most day case regimens, patients are observed for up to six hours post biopsy but the majority of complications occur within the first hour post procedure and studies have suggested that the observation period may be reduced from the standard 4–6 h.[3–5]

Our study prospectively evaluated short stay (1 hour observation) liver biopsy over a 3 year period. Patients referred for non-focal core ultrasound guided liver biopsy were recruited. Patients were excluded if platelet counts were $<50\ 000/mm^3$ or prothrombin time >3 s and also if they suffered from severe ascites or intrahepatic biliary dilatation. Patients were required to have a responsible adult to accompany them for the first 24 hours after the procedure. Ultrasound guided biopsies (Bardâ Biopty-Cutâ 18G cutting needle) were usually taken from the right lobe of the liver using an intercostal approach.

Patients were observed for 1 h within the ultrasound department, receiving analgesia as required. The radiologist who had performed the procedure reassessed the patient prior to discharge. No other departments within our hospital were involved in the management of the patient.

In total, 500 patients (291 males and 209 females) underwent core liver biopsy. Mean patient age was 43 years (range 18–76). In 495 (99%) patients, a definitive or indicative pathological diagnosis was obtained from the biopsy.

A total of 110 (22%) patients experienced pain at the time of or within 1 h of the procedure and of these, 15 (3%) required analgesia; 496 patients were discharged after 1 h of observation. Three patients were kept under observation for a further 1 h due to pain. One patient (0.2%) required admission for a haemorrhagic complication. There were no recorded delayed complications or deaths at follow up.

Our study has shown that outpatient percutaneous liver biopsy may be performed within a 2 h total time period and that almost all patients are safely discharged within 1 h of observation following the procedure. Most guidelines for day case percutaneous liver biopsy recommend an observation period of 4–6 h.[3] This is based primarily on studies showing that only 60% of complications occur within 2 h of the procedure but we feel that our study, together with recent investigations, suggest that this observation period is too long and that most patients can safely be discharged within 1 h.[4–7]

In patients who have the procedure carried out with ultrasound, the reported complication rate is low, generally significantly less than 1% for major complications.[8 9] However, in a review of clinical practice among physicians in the USA, only 76% used ultrasound.[10] We believe that the low complication rate that we recorded was related to the use of ultrasound during the procedure and that short stay liver biopsy should always be coupled with imaging guidance. In many institutions, a day ward is used for procedures such as liver biopsies. By performing the procedure on an outpatient (short observation) basis, significant cost savings may be accrued.

In conclusion outpatient liver biopsy is safe when performed on carefully selected patients in a setting that provides close observation for 1 h after biopsy. Major complications after outpatient liver biopsy are rare and manifest early. We propose that short stay liver biopsy is a safe and feasible technique.

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Inflammatory syndrome with liver adenomatosis: the beneficial effects of surgical management

We report a case of a patient with an inflammatory syndrome cured after resection of an adenoma. A 33-year-old woman was admitted to the department of internal medicine in May 2004 for invalidating pain in the spinal cord in the context of an inflammatory syndrome. The patient had been on oral contraceptives (Adepal) for the past 16 years. The inflammatory syndrome involved fever (37.4–38°C), anaemia, C reactive protein 90 mg/l, fibrinogen 7 g/l, sedimentation rate 106 mm and haptoblobin 2.9 g/l. Investigations for infectious, viral, systemic, hormonal and haematological disorders were all negative.

Liver function tests showed abnormally high levels of alkaline phosphatase (×3N), γ-glutamyltransferase (×2N), and alanine aminotransferase (×1.5N). Liver ultrasound scan showed two nodules in the right lobe (12 and 4 cm across), which was confirmed by magnetic resonance imaging (MRI), and three additional 1-cm-nodules in the same lobe. A right hepatectomy was performed in November 2004. In March 2005, the inflammatory syndrome had normalised: the red blood cell count was 4.4 T/l, haemoglobin 12.7 g/dl, hematocrite 39.2%, mean globular volume 93 μm^3, C reactive protein 3 mg/l, sedimentation rate 6 mm, and liver tests had returned to normal

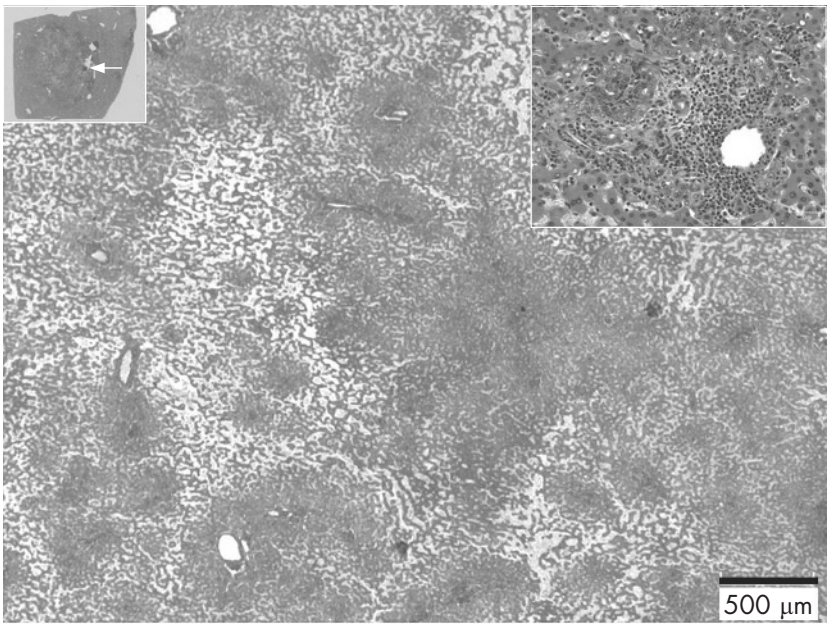

Figure 1 Small nodule with telangiectatic features. This nodule is shown at a low power (upper left corner), with the white arrow indicating the border with the non-tumoral tissue. In the upper right corner is a closer view showing pseudo portal tracts with inflammatory cells and a mild ductular reaction.

values. MRI performed in August 2005 was normal.

Three major nodules (9×8 cm, 4.5×2.5 cm and 1.5×1.5 cm) and numerous smaller ones (<1 cm across) were identified macroscopically. The main nodules were non-encapsulated, poorly delimited, with soft, pink, red and yellowish areas. Some of the larger nodules had the typical aspect of inflammatory/telangiectatic adenoma as described previously (fig 1).[1] Most of the smaller nodules were steatotic. The non-tumoral liver was generally normal, except for the presence of some isolated or grouped lobules that were either entirely steatotic or with slightly dilated sinusoids.

Hepatocyte cytoplasm was strongly immunostained for AA amyloid (serum amyloid A) in all nodules, whether steatotic or telangiectatic; there was a clear demarcation with the adjacent liver (fig 2). We identified a germline HNF1α gene variant A→T at codon 1573 leading to a T525S amino acid substitution in the frozen liver tissue and blood lymphocytes. No additional somatic mutation was found in the tumour, and mRNA of both HNF1α alleles was detected.[2] No activating β-catenin mutation was found in the tumour.

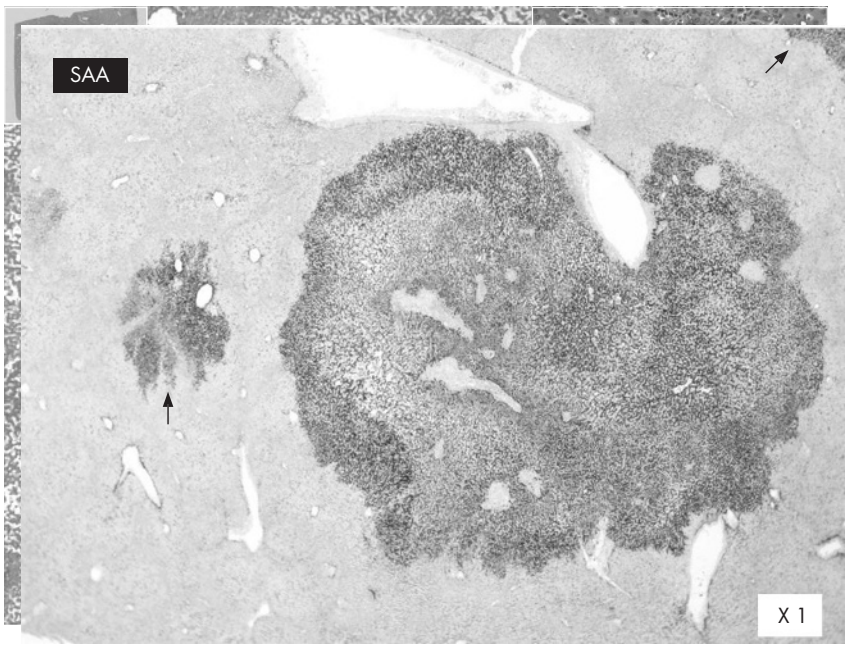

Figure 2 Serum amyloid A immunostaining (telangiectatic nodule) with sharp boundary. Only hepatocytes are labelled. Note the additional positive foci (arrows) in the surrounding liver.

We recently described a new four-group classification of adenomas on the basis of genotype/phenotype correlation[3]: adenomas with mutation of the HNF1α gene, adenomas with mutation of the β-catenin gene and adenomas without either mutation, constituted with and without inflammatory lesions. The group with inflammatory features is comparable to the entity previously called ''telangiectatic focal nodular hyperplasia''.[1]

We have reported a case of a morphologically typical multiple inflammatory adenoma (so called adenomatosis because of the large number of nodules), although different aspects were observed in different areas of the same tumour and in different nodules. There have been several reports of an inflammatory syndrome with systemic or renal amyloidosis in patients with liver adenomas, which was cured by hepatic resection or adenoma regression.[4–10] Fibrillar deposits were described in the liver, in the Disse space or in vessels, or in both. Our case strengthens the idea of the existence of inflammatory adenomas. In contradiction with previous reports,[4–10] we did not detect any extracellular deposit of serum amyloid A in the liver, but there was a strong labelling of tumoral hepatocytes. The reason for this is unclear. Whatever the explanation, the mechanism of the inflammatory process is unknown.

All HNF1α mutations identified from nearly 50% of hepatocellular adenomas were inactivating and biallelic.[2] Consequently, the role, if any, of the germline HNF1α variant A→T at codon 1573 leading to a T525S amino acid substitution is unknown. Indeed, this T525S variant has not been described previously in the general population; it may be a rare polymorphism because the threonine to serine substitution is conservative and the patient does not have diabetes.

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Wnt pathway may not be implicated in all routes to colorectal cancer

Schneikert and Behrens (*Gut*. Published Online First: 13 July 2006. doi: 10.1136/gut.2006.093310) have produced a comprehensive and instructive overview of the Wnt signalling pathway and its role in colorectal tumorigenesis. They have emphasised that dysregulation of the Wnt pathway is a prerequisite for the initiation of colorectal neoplasia, and is also sufficient for explaining the early growth of neoplasms. They also state that aberrant activation of the Wnt signalling pathway occurs almost exclusively through the mutation of the two key regulators: adenomatous polyposis coli (APC) and β-catenin. However, if these premises are to be accepted, then it should be possible to show the mutation of either APC or β-catenin in virtually all primary colorectal cancers. Standard texts indeed state that approximately 80% of colorectal cancers (CRCs) have APC mutations and that β-catenin mutations occur in around 50% of the remaining CRCs.[1] Similarly, Schneikert and Behrens suggest that up to 80% of CRCs have APC mutations, whereas 10% of CRCs have β-catenin mutation (sources not given).

Given the crucial importance of oncogene and tumour suppressor gene mutation in explaining tumorigenesis, and the availability of technology to detect mutations, spanning two decades, we would have imagined that the frequency of APC and β-catenin mutations in CRC would be well and truly settled by now and that estimates in standard texts should be reliable. Some of these mutational data are derived from cancer cell lines, but such data may be unreliable because of the inevitable selection that occurs in the generation of cell lines. Overall, APC mutations are found in approximately 60% of primary CRCs.[2–9] It could be argued that detection of mutations is not 100% reliable and that APC mutations will be present even if they cannot be detected. However, this suggestion has similarities with the tale of the Emperor's new clothes! If it were true, CRCs lacking APC mutations should be distributed with equal frequency throughout the colorectum. In fact, CRCs with APC mutations become increasingly frequent in a proximal to distal direction.[8]

Schneikert and Behrens state correctly that CRCs with DNA microsatellite instability (MSI) are less likely to have APC mutations (and are more likely to occur proximally). Could this be the subset with β-catenin mutation? Although, in general, β-catenin mutations seem to be rare in CRC,[10] they have been well documented in some CRC cell lines with MSI,[11] and also in some early-onset CRCs with MSI.[12] However, β-catenin mutations are not found in the larger subset of sporadic CRCs with MSI,[6 13] and these reliable data are fully consistent with immunohistochemical expression patterns.[14 15] Mutation of β-catenin is restricted to CRCs occurring in the context of Lynch syndrome and was found in only 18% of Lynch syndrome CRCs in a well-characterised series.[13] If approximately 2% of CRCs occur in the setting of Lynch syndrome, then the overall frequency of β-catenin mutations in CRC may be as low as 0.4%. Clearly, β-catenin mutations cannot fill the 40% gap comprising CRCs without APC mutations.

Given the accumulating evidence that CRC is a multipathway disease, there is neither scientific rationale nor any supporting data for perpetuating the dogma that implicates dysregulation of the Wnt pathway in the early development of the vast majority of CRCs. The alternative or serrated pathway implicates BRAF or KRAS mutations, coupled with extensive DNA methylation as early genetic events and encompasses sporadic CRCs with MSI.[16] APC may itself be methylated in around 18% of CRCs,[17] and it has been suggested that this epigenetic mechanism could bridge the mutational gap.[18] However, APC methylation is not associated with either MSI or with methylation of other genes.[17] Furthermore, Schneikert and Behrens[19] have shown previously that at least one APC allele must be retained in a truncated form to drive proliferation and tumorigenesis. This indicates that bi-allelic methylation of APC (leading to complete silencing) may not provide an important growth advantage to explain its selection as a genetic change in the alternative pathway.

Progress in studies of causation as well as clinical management of CRC depends absolutely on moving away from the ''canonical'' orthodoxy of the one-pathway model. In other words, instead of postulating on the existence of the Emperor's new clothes, we must accept the existence of several emperors, each with a different wardrobe.

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Author's reply

The comment by Jass stating that aberrant activation of the Wnt pathway might not be responsible for the development of all cases of colorectal cancer and that other pathways may be important is well taken. This does not challenge the view that mutation of APC is a key oncogenic event, which was the basis of our review. It is of interest that we found the expression of the Wnt specific target gene conductin/axin2 to be elevated in approximately 70% of colorectal carcinomas compared with normal mucosae.[1 2] This indicates that Wnt signalling is activated in a high proportion