

Case report

Hepatocellular adenoma: diagnostic difficulties and novel imaging techniques

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Abstract. We report the case of a 30-year-old eastern European female who presented with right upper quadrant pain. Clinical examination was unremarkable and liver function tests were normal. CT identified a 5 cm lesion in segment V of the liver, which was of homogeneous low density with no calcification or significant enhancement. MRI showed the lesion to be hypointense to liver on T_1 weighted sequences and isointense on T_2 weighted sequences. Rapid arterial enhancement with gadolinium-DTPA faded without leaving a definite central scar. Ultrasound showed the lesion to be echogenic with minimal vascularity. Administration of a liver-specific microbubble contrast agent showed low uptake relative to the surrounding liver. Phosphorus-31 MR spectroscopy, localized to the lesion itself, revealed a markedly increased phosphomonoester resonance with a decreased phosphodiester resonance, compatible with increased cell turnover. Biopsy confirmed the lesion to be a hepatocellular adenoma. The diagnosis of a hepatic adenoma is difficult with tissue diagnosis the gold standard, but it may be suggested by a combination of imaging modalities. We have described two new imaging techniques not previously described in characterization of hepatic adenomata, namely ultrasound with contrast agent and MR spectroscopy.

Hepatocellular adenomas (HCAs) are benign hepatic neoplasms, which have a tendency to haemorrhage and, very rarely, a propensity to undergo malignant transformation [1, 2]. The non-invasive differentiation of HCA from other benign or malignant neoplasms has remained challenging with no satisfactory test apart from histological examination of a liver biopsy sample. MR, CT, ultrasound and nuclear medicine characteristics of HCA have been described, but it is rare for one lesion to be characterized on all modalities. We describe characteristics of a biopsy-proven HCA on MRI and MR spectroscopy (MRS), ultrasound with microbubble contrast and multiphasic CT. The imaging appearances of HCA on MRS and microbubble ultrasound have not been previously described.

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Case report

A 30-year-old eastern European female presented with right upper quadrant pain. She had a medical history of polycystic ovaries, Type II diabetes mellitus and a euthyroid goitre. She had also been on antidepressants and had taken oral contraceptives for a number of years. Clinical examination was unremarkable and liver function tests were normal: α -fetoprotein (AFP) 1.8 u l^{-1} (normal range $0\text{--}6 \text{ u l}^{-1}$); alanine transaminase 9 u l^{-1} (normal range $0\text{--}40 \text{ u l}^{-1}$); γ glutamyl transpeptidase 8 u l^{-1} (normal range $11\text{--}50 \text{ u l}^{-1}$). Ultrasound of the liver revealed a 5 cm echogenic mass adjacent to the upper pole of the right kidney.

CT identified a 5 cm lesion in segment V of the liver, which was of homogeneous low density with no calcification. There was no significant enhancement in the arterial phase, but minor peripheral enhancement was seen in the portal phase (Figure 1). MRI showed the lesion to be hypointense to liver on T_1 weighted sequences and isointense on T_2 weighted sequences with fat saturation. There was rapid blush on arterial

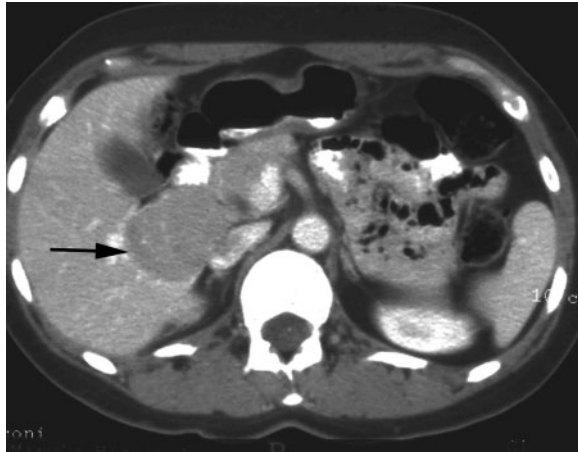


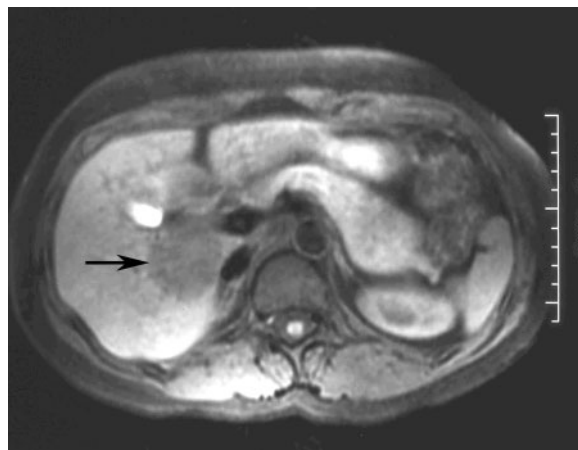
Figure 1. Post-contrast (portal phase) axial CT image shows the non-enhancing lesion in segment V (arrow).

enhancement with gadolinium-DTPA, which faded without leaving a definite central scar (Figure 2). The latter finding made focal nodular hyperplasia (FNH) unlikely and the possibility of an unusual

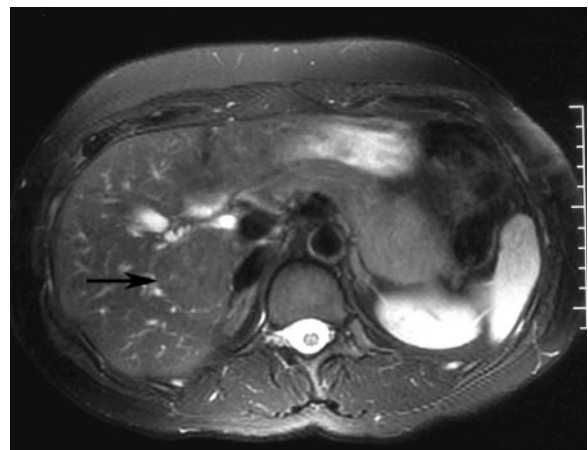
HCA or hepatocellular carcinoma (HCC) was raised.

Further ultrasound was performed with contrast enhancement, using the microbubble agent Levovist (Schering AG, Berlin, Germany). These agents have a blood-pool phase that may be used to assess blood volume, and a delayed liver-specific phase for assessment of liver parenchymal uptake/activity [3, 4]. The initial scan showed the echogenic lesion in segment V, but also revealed another similar 7 mm lesion in segment II. On the vascular phase, after iv bolus injection of 2 g of Levovist, relatively little enhancement was seen. On the liver-specific phase, 5 min post-injection, using a new and sensitive microbubble specific mode (ADI; Acuson Inc., Mountain View, CA), the lesion showed relatively low uptake in comparison with the surrounding liver (Figure 3).

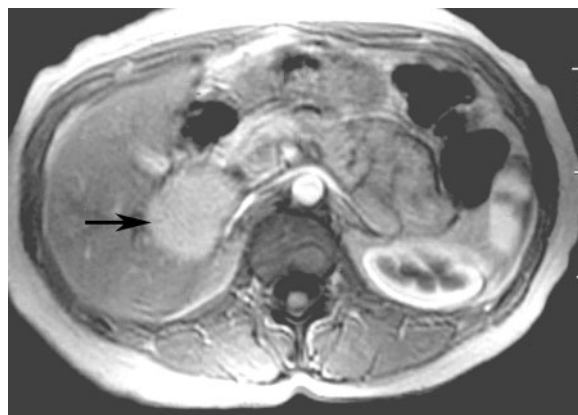
The smaller lesion, which was only seen on ultrasound with contrast medium, remains indeterminate but is probably benign. It is being followed with serial measurements on follow-up ultrasound every 3–6 months. Thus far, there has been no



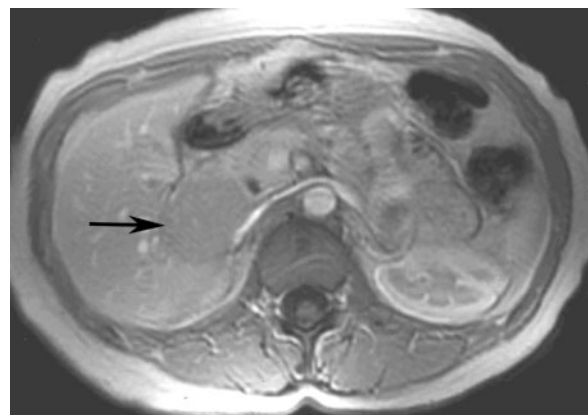
(a)



(b)

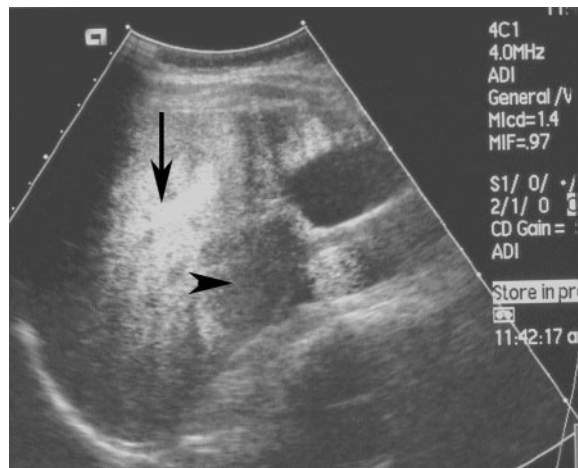


(c)



(d)

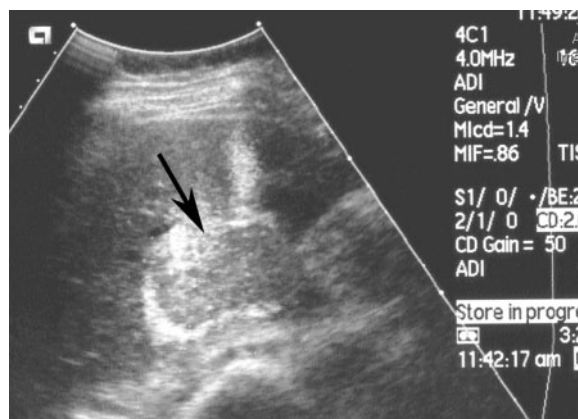
Figure 2. (a) Low signal lesion in segment V depicted on T_1 weighted MR image with fat saturation (arrow) (TR/TE: 400/17 ms). (b) The lesion appears isointense on fat saturated, T_2 weighted MR sequences (arrow) (TR/TE: 6666/74.5 ms). (c) The lesion enhances rapidly post-iv enhancement with gadolinium-DTPA. The MR images were obtained immediately post-infusion of contrast medium (arrow) (TR/TE: 130/4.2 ms). (d) In the delayed phase, post-contrast administration, the lesion fades and becomes isointense to the rest of the liver parenchyma (arrow) (TR/TE: 130/4.2 ms).



(a)



(b)



(c)

Figure 3. (a) The lesion in segment V appeared echogenic. (b) After administration of Levovist (Schering AG, Berlin, Germany), using a microbubble specific mode (ADI; Acuson Inc., Mountain View, CA), minimal activity is shown on ultrasound within the segment V lesion (arrowhead). Note the “bright” normal liver parenchyma, which demonstrates uptake of microbubble contrast agent (arrow). (c) Transverse ultrasound image of the lesion post-contrast, again demonstrating minimal activity using ADI mode (arrow).

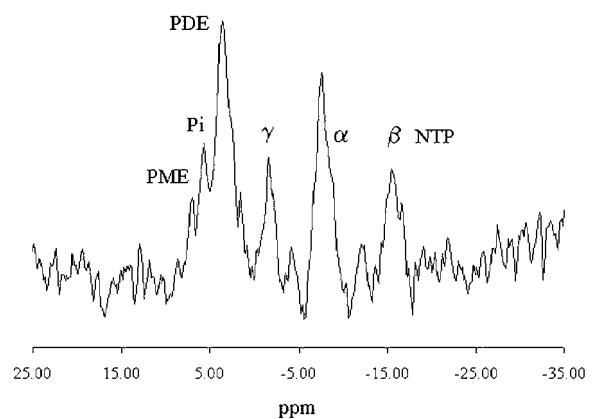
change in the appearance or size of this smaller lesion on repeat ultrasound scanning with contrast.

Phosphorus-31 (^{31}P) MRS, localized to the lesion itself, revealed a markedly increased phosphomonoester (PME) resonance and a decreased phosphodiester (PDE) resonance, which would be compatible with increased cell turnover. This pattern of abnormality has been reported in a variety of hepatic tumours and in cirrhosis [5]. However, MR spectra from the uninvolved liver were entirely normal (Figure 4).

Diagnosis, based on the clinical and imaging findings, lay between a HCA and a well-differentiated HCC. However, the patient was reluctant to undergo surgical intervention and so a histological sample of the lesion was obtained under ultrasound guidance, confirming a non-malignant lesion with characteristic features compatible with a HCA. At this size, surgical removal is advocated [2, 6], but the patient has declined surgery and is considering radio-ablation of this lesion [7].

Discussion

HCAs are tumours composed mostly of hepatocytes with varying numbers of Kupffer cells and no



	Normal Spectra	Abnormal Spectra
PME/PDE	0.097	0.757 (elevated)

Figure 4. MR spectrum revealing normal metabolite ratios in the unaffected liver and an increased phosphomonoester (PME): phosphodiester (PDE) ratio within the lesion. Pi, inorganic phosphate; γ -, α - and β -NTP, γ -, α - and β -nucleoside triphosphate; ppm, parts per million.

biliary ducts [8]. They are encapsulated and are solitary in 80% of cases [2]. These tumours have seen an increase in incidence since the advent of the contraceptive pill and are associated with underlying metabolic diseases, such as type I glycogen storage disease and diabetes mellitus [1, 2, 8]. The diagnosis of this benign tumour is important as they can rupture, leading to life threatening haemorrhage. They also have a small propensity to transform into HCCs [1, 2, 6]. Approximately 50% of tumours demonstrate intratumoural haemorrhage and can present with haemoperitoneum and resultant hypotension and shock [2]. Imaging characteristics are therefore based on lipid content, extent of intratumoural haemorrhage and vascularity of the adenoma. These features are discernible on the various cross-sectional modalities, but are not specific for a HCA.

Levovist, an ultrasound microbubble contrast agent, has been shown to have a liver-specific phase, optimally visualized between 5 min and 10 min [4]. Early experience of focal hepatic lesion characterization using Levovist demonstrated strong late-phase activity similar to normal adjacent liver parenchyma in benign lesions, such as FNH and some haemangiomas. This is in contradistinction to malignant lesions such as HCCs or metastases that demonstrate no uptake and appear as focal defects [9]. We demonstrated that our HCA lesion showed uptake in the liver-specific phase, although this was relatively low. This characteristic would have been atypical for FNH or a haemangioma as these lesions show higher uptake of contrast agent. However, while it is reassuring to demonstrate uptake within a lesion, a few well differentiated HCCs have demonstrated minimal activity [9]. The characteristics of HCA after microbubble administration have not been described previously, but our finding of minimal uptake is similar to those documented for liver-specific agents in MR and nuclear scintigraphy. HCAs have been shown to demonstrate a variable degree of uptake of these contrast agents, the mechanism of which is thought to be related to Kupffer cell activity [8, 9]. However, this has yet to be proven for Levovist. Microbubble enhanced ultrasound, although not 100% specific in differentiating benign from malignant hepatic lesions, could prove a more reliable discriminatory tool than other imaging modalities. Further investigation is therefore warranted.

³¹P MRS of the liver is not clinically available to characterize liver lesions. However, information on a number of phosphorus-containing compounds can be obtained, including a handle on cell turnover, by measuring the PME resonance, which contains information on cell membrane

precursors, and the PDE resonance, which contains information on cell membrane degradation products [5, 10]. Cox et al [5] observed an increase in the PME:PDE ratio in 17 patients with primary or secondary hepatic tumours. This was either related to an increase in PME or, in some cases, a reduction in PDE and would be compatible with increased cell turnover. The MR spectra, however, did not show aetiological specification. Other studies have shown similar findings in non-malignant conditions such as cirrhosis, but in the cirrhotic liver this spectroscopic abnormality is generalized through the liver rather than being focal [10]. We report a similar finding in our case of HCA, but with normal spectra in the uninvolved liver parenchyma.

The diagnosis of a HCA can be suggested by a combination of imaging modalities, but owing to the non-specificity of imaging findings, tissue diagnosis is a necessity. Histological confirmation can also be difficult as low grade HCCs can look similar to HCAs. Correlation with imaging findings are helpful in this situation. Other criteria, such as interval change and elevated serum AFP, would favour a HCC. Ultimately, large (>5 cm) HCAs should be surgically removed owing to potential haemorrhage and the small possibility of malignant transformation [1, 2, 6].

We have described two new imaging techniques, which have not been previously described in characterization of HCAs, namely ultrasound with contrast agent and MR spectroscopy. Confirmatory studies on more patients need to be performed in order to further delineate the characteristics we have described. These techniques hold promise in the difficult task of differentiating HCAs from other benign and malignant hepatic lesions.

References

1. Gordon SC, Reddy KR, Livingston AS, Jeffers LJ, Schiff ER. Resolution of a contraceptive steroid induced hepatic adenoma with subsequent evolution into hepatocellular adenocarcinoma. *Ann Intern Med* 1986;105:547-9.
2. Leese T, Farges O, Bismuth H. Liver cell adenomas: a 12 year surgical experience from a specialist hepato-biliary unit. *Ann Surg* 1988;208:558-64.
3. Blomley MJ, Albrecht T, Cosgrove DO, et al. Improved imaging of liver metastases using stimulated acoustic emission in the late enhancement phase of the ultrasound contrast agent Levovist, early experience. *Radiology* 1999;210:409-16.
4. Blomley MJ, Albrecht T, Cosgrove DO, et al. The use of stimulated acoustic emission to image a late liver and spleen-specific phase of Levovist: an investigation in normal volunteers and in patients without liver disease. *Ultrasound Med Biol* 1999;25:1341-52.

5. Cox IJ, Menon DK, Sargentoni J, et al. Phosphorus-31 magnetic resonance spectroscopy of the human liver using chemical shift imaging techniques. *J Hepatol* 1992;14:265–75.
6. Terkivatan T, de Wilt JH, de Man RA, van Rijn RR, Zondervan PE, Tilanus HW, et al. Indications and long-term outcome of treatment for benign hepatic tumors: a critical appraisal. *Arch Surg* 2001;136:1033–8.
7. de Jode MG, Lamb GM, Thomas HC, Taylor-Robinson SD, Gedroyc WM. MRI guidance of infra-red laser liver tumour ablations, utilising an open MRI configuration system: technique and early progress. *J Hepatol* 1999;31:347–53.
8. Goodman ZD, Mikel UV, Lubbers PR, Ros PR, Langloss JM, Ishak KG. Kupffer cells in hepatocellular adenomas. *Am J Surg Pathol* 1987;11:191–6.
9. Blomley MJK, Sidhu PS, Cosgrove DO, et al. Do different types of liver lesions differ in their uptake of the microbubble SHU 508A in its late liver phase: early experience. *Radiology* 2001;220:661–7.
10. Taylor-Robinson SD, Sargentoni J, Bell JD, et al. *In vivo* and *in vitro* ³¹P magnetic resonance spectroscopy and electron microscopy of the cirrhotic liver. *Liver* 1997;17:198–209.