Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.1267

World J Gastroenterol 2009 March 14; 15(10): 1267-1272
World Journal of Gastroenterology ISSN 1007-9327

CASE REPORT

Liver cell adenoma showing sequential alteration of radiological findings suggestive of well-differentiated hepatocellular carcinoma

Takayuki Kogure, Yoshiyuki Ueno, Satoshi Sekiguchi, Kazuyuki Ishida, Takehiko Igarashi, Yuta Wakui, Takao Iwasaki, Tooru Shimosegawa

Takayuki Kogure, Yoshiyuki Ueno, Yuta Wakui, Takao Iwasaki, Tooru Shimosegawa, Division of Gastroenterology, Graduate School of Medicine, Tohoku University, Sendai 980-8574, Japan
Satoshi Sekiguchi, Division of Advanced Surgical Science and Technology, Graduate School of Medicine, Tohoku University, Sendai 980-8574, Japan
Kazuyuki Ishida, Department of Pathology, Tohoku University Hospital, Sendai 980-8574, Japan
Takehiko Igarashi, Division of Gastroenterology Osaki Citizen Hospital, Furukawa 989-6183, Japan
Author contributions: Kogure T, Ueno Y and Wakui Y participated in writing of the manuscript; Kogure T, Ueno Y, Iwasaki T, Shimosegawa T, Sekiguchi S, Ishida K, and Igarashi T participated in treatment of the patient.
Correspondence to: Yoshiyuki Ueno, MD, PhD, Division of Gastroenterology, Graduate School of Medicine, Tohoku University, 1-1 Seiryo, Aoba-ku, Sendai 980-8574, Japan. yueno@mail.tains.tohoku.ac.jp
Telephone: +81-22-7177171 Fax: +81-22-7177177
Received: September 25, 2008 Revised: November 1, 2008
Accepted: November 8, 2008
Published online: March 14, 2009

Abstract

A liver tumor 35 mm in diameter was found incidentally in a 40-year-old woman who had no history of liver diseases or the use of oral contraceptives. Radiological diagnostics showed the typical findings of liver cell adenoma (LCA). Dynamic computed tomography revealed that the tumor showed a homogenous enhancement in the arterial phase and almost the same enhancement as the surrounding liver parenchyma in the delayed phase. The tumor was found to contain fat on magnetic resonance imaging. A benign fat containing liver tumor was suggested. However, radiological findings altered, which caused us to suspect that a well-differentiated hepatocellular carcinoma (HCC) containing fat was becoming dedifferentiated. Partial hepatectomy was performed and the pathological findings showed the typical findings of LCA. This case was an extremely rare LCA, which had no background of risk for LCA and developed the sequential alteration of the radiological findings to suspect well-differentiated HCC.

Key words: Liver cell adenoma; Hepatocellular carcinoma; Diagnosis; Hepatectomy

Peer reviewers: Dr. Natalie J Torok, UC Davis Medical Center, Patient Support Services Building, 4150 V Street, Suite 3500, Sacramento, CA 95817, United States; Dr. Serdar Karakose, Professor, Department of Radiology, Meram Medical Faculty, Selcuk University, Konya 42080, Turkey

Kogure T, Ueno Y, Sekiguchi S, Ishida K, Igarashi T, Wakui Y, Iwasaki T, Shimosegawa T. Liver cell adenoma showing sequential alteration of radiological findings suggestive of well-differentiated hepatocellular carcinoma. *World J Gastroenterol* 2009; 15(10): 1267-1272 Available from: URL: http://www.wjgnet.com/1007-9327/15/1267.asp DOI: http://dx.doi.org/10.3748/wjg.15.1267

INTRODUCTION

Liver cell adenoma (LCA) is a benign tumor of the liver parenchyma that is associated with the use of oral contraceptives or with glycogen-storage disease[1]. The occurrence of LCA in patients without such backgrounds is extremely rare[2]. We report a case of LCA found in a 40-year-old woman without a history of oral contraceptive use in which the sequential alteration of the radiological findings suggested well-differentiated hepatocellular carcinoma (HCC).

CASE REPORT

In November 2006, a 40-year-old woman developed lower abdominal pain and was admitted to a hospital. The patient had no history of liver disease, alcohol consumption, oral contraceptive use, nor the use of any other medication. The family history of the patient was not noteworthy. The patient was diagnosed as having a left tubo-ovarian abscess and tubo-ovariectomy was performed. The resected ovary and oviduct showed the findings of endometriosis with bacterial infection, but there was no indication of neoplastic lesion. At this time, a space-occupying lesion (SOL) 35 mm in diameter was found in the liver by abdominal ultrasonography and computed tomography (CT). In the CT, the lesion in

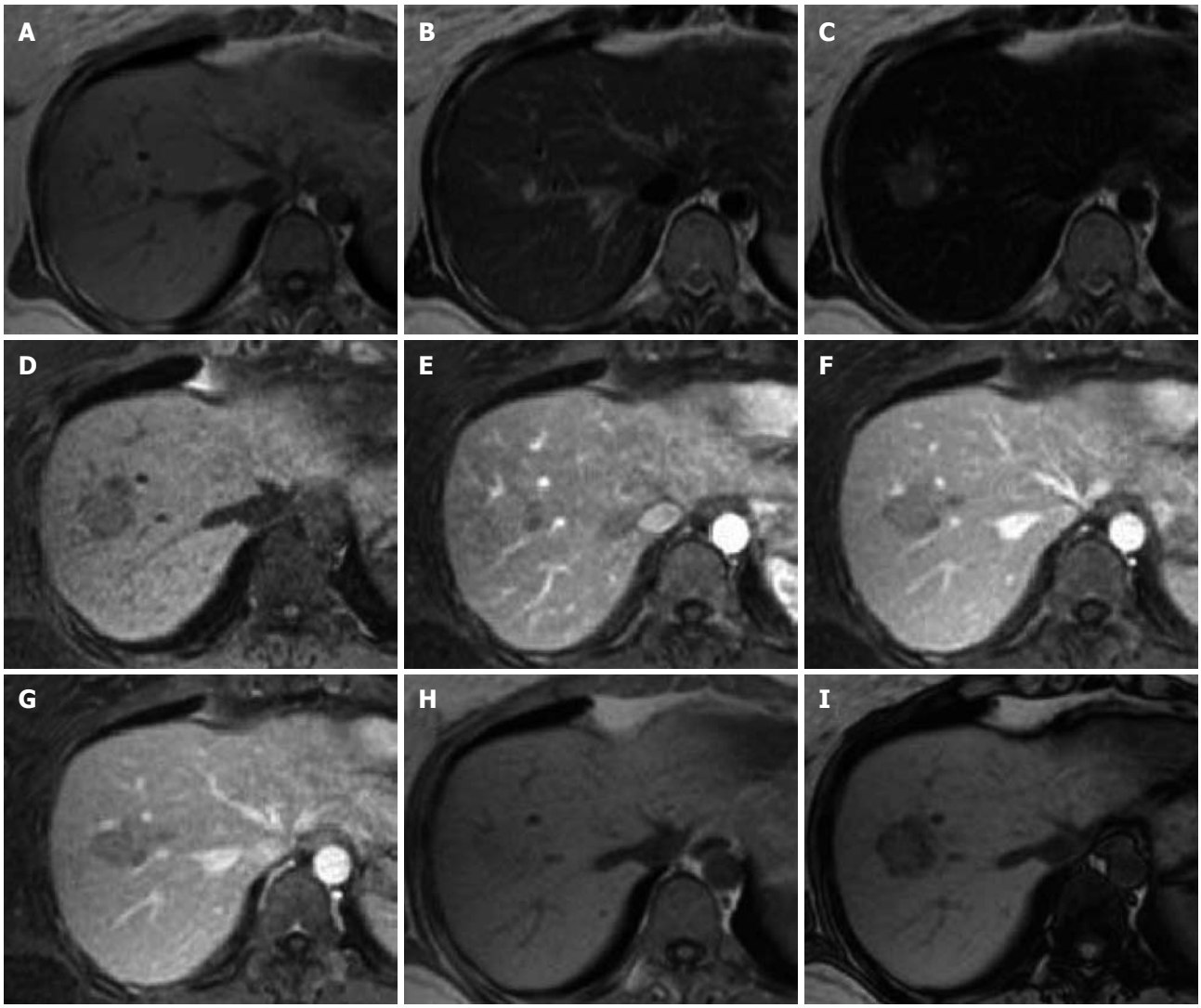

Figure 1 Magnetic resonance imaging (MRI). A: T1; B: T2; C: T2-SPIO; D: Plain; E: Arterial phase; F Portal phase; G: Delayed phase; H: T1 in phase; I: T1 opposed phase.

the liver (segment 8) showed slight low density by plain examination and an enhancing effect by the contrast agent. In the magnetic resonance imaging (MRI), the SOL showed almost isointensity on T1 and slightly high intensity on T2 (Figure 1A-B). Superparamagnetic iron-oxide (SPIO)-MRI indicated that the SOL did not show most of the SPIO uptake (Figure 1C). On the gadolinium-enhanced T1, the SOL indicated a slight homogenous enhancement in the arterial phase, and almost the same enhancement as the surrounding liver parenchyma in the delayed phase (Figure 1D-G). The SOL showed almost isointensity on the in-phase-T1 and slightly low intensity on the opposed-phase-T1, which indicated that the SOL contained a fat component (Figure 1-H, 1-I). A capsule or scars were not detected in the SOL. A benign, fat containing tumor was suggested. The dynamic CT in March 2007 showed that the SOL had not changed in size (Figure 2). The SOL indicated low density by plain examination, showed a slight homogenous enhancing effect in the arterial phase, and, an enhancing effect that was slightly lower than the surrounding liver in the delayed phase (Figure 2). In the dynamic CT after four months, the density of the SOL on plain examination was elevated and the enhancing effect in the arterial phase increased slightly, although the size and the form of the SOL did not show apparent changes (Figure 3). Because of the alteration of the findings in this CT, we suspected that the findings were suggestive of well-differentiated HCC. In August 2007, the patient was referred to our hospital for further examination and treatment. The physical examination of the patient showed no abnormal findings. The blood test indicated no abnormalities including liver related enzymes except slight iron deficiency anemia (Table 1). All the hepatitis virus markers were negative. There were no abnormal findings suggestive of autoimmune liver disease or metabolic liver disease including glycogen-storage disease. Hepatic arteriography was performed and the nodule presented with a slight tumor stain in the arterial phase and the hepatic parenchymal phase, and it did not show an apparent drainage vein (Figure 4). Positron emission tomography showed no difference in accumulation between the nodule and the surrounding hepatic parenchyma and no abnormal accumulation

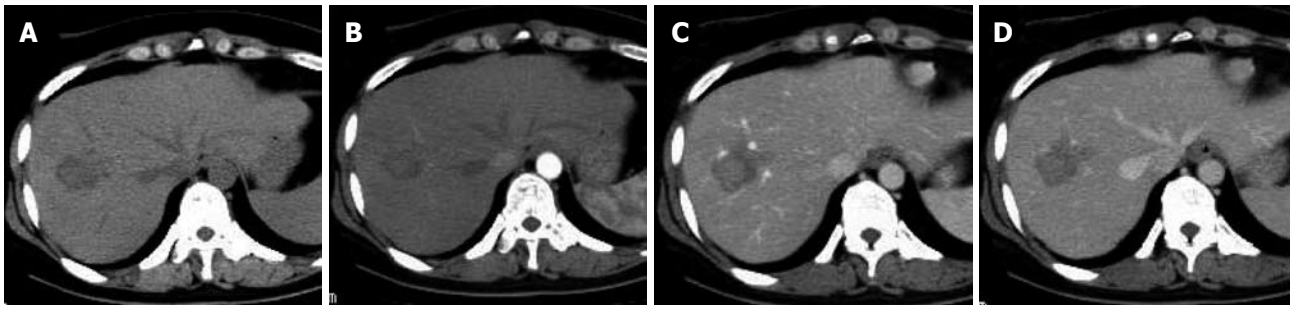

Figure 2 Computed tomography (CT) in March 2007. A: Plain; B: Arterial phase; C: Portal phase; D: Delayed phase.

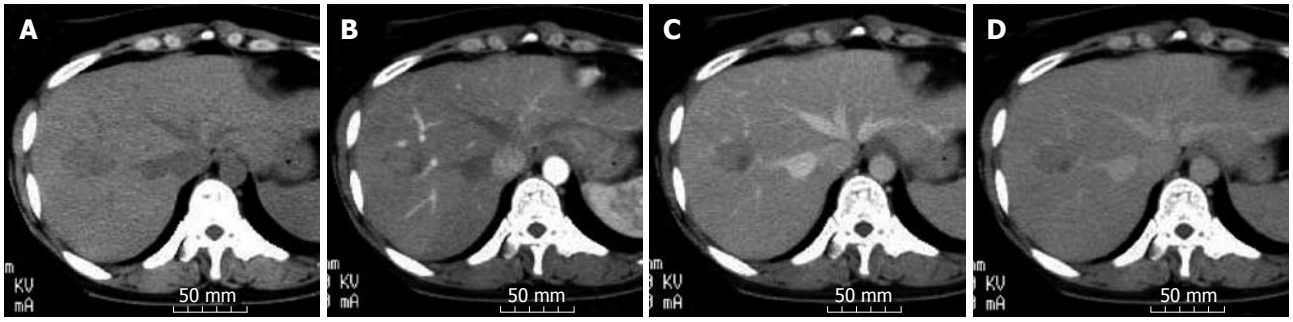

Figure 3 CT in July 2007. A: Plain; B: Arterial phase; C: Portal phase; D: Delayed phase.

Table 1 Laboratory data

Indicators	Value
White blood cell	3980/μL
Hemoglobin	9.8 g/dL
Platelet	232 × 10^3/μL
Prothrombin time	105%
Activated partial thromboplastin time	26.7 s
Aspartate aminotransferase	17 IU/L
Alanine aminotransferase	15 IU/L
Lactate dehydrogenase	146 IU/L
Alkaline phosphatase	175 IU/L
Gamma glutamyl transpeptidase	23 IU/L
Cholinesterase	257 IU/L
Total bilirubin	0.6 mg/dL
Direct bilirubin	0.1 mg/dL
Total protein	6.9 g/dL
Albumin	4.2 g/dL
Blood urea nitrogen	7.5 mg/dL
Creatinine	0.6 mg/dL
Uric acid	4.0 mg/dL
Na	142 mEq/L
K	4.2 mEq/L
Cl	106 mEq/L
Total cholesterol	202 mg/dL
Triglyceride	77 mg/dL
Glucose	101 mg/dL
C-reactive protein	0.03 mg/dL
IgG	1157 mg/dL
IgA	206 mg/dL
IgM	124 mg/dL
HBs-Ag	Negative
HBs-Ab	Negative
HCV-Ab	Negative
α-fetoprotein	5.1 ng/mL
Des-γ-carboxy prothrombin	34 mAU/mL
Anti-nuclear antibody	Negative
Anti-smooth muscle antibody	Negative
Anti-mitochondrial antibody	Negative

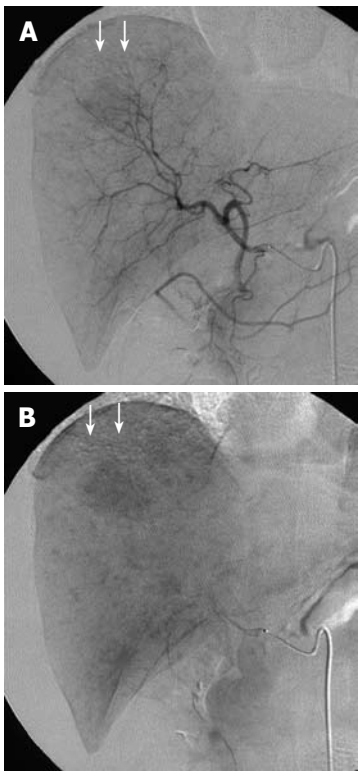

Figure 4 Digital subtraction angiography (DSA). A: Arterial phase; B: Liver parenchymal phase. Arrow: Tumor stain.

suspicious of malignant tumors in other organs. No abnormal findings were found suggesting a primary tumor in other organs in whole-body CT. Digestive tract endoscopy showed no abnormal findings. Taken together, the above-mentioned findings suggested the

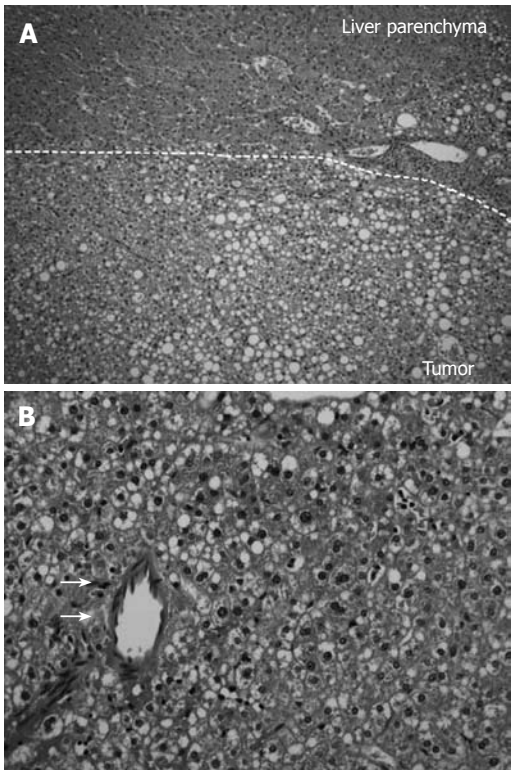

Figure 5 Pathological findings. A: Hematoxylin and eosin staining, original magnification, × 50; B: Hematoxylin and eosin staining, original magnification, × 200. Arrow: Myogenic artery.

possibility that the nodule was a well-differentiated HCC that was dedifferentiating. After receiving informed consent, partial hepatectomy was performed on August 28, 2007.

The pathological finding (Figure 5) revealed the following. Hepatocytes more lucent than that of the surrounding hepatic parenchyma had proliferated thickly in the nodule. Hepatocytes did not show severe cellular atypia. Exclusion of the surrounding hepatic parenchyma was apparent, but direct invasion to the surrounding was not seen. The nodule did not contain the portal tracts and bile ducts. Myogenic arteries, large lipid droplets, hemorrhage and degeneration were seen in the nodule. The surrounding hepatic parenchyma had no abnormal findings except fatty change with large lipid droplets around the nodule. Thus, we diagnosed the nodule as a LCA.

DISCUSSION

LCA is considered a rare benign tumor of the liver and is distinguished from solitary tumors and adenomatosis[3,4]. LCA was a very rare tumor until an association with oral contraceptives was reported. Before 1954, only two cases were detected among 5000 autopsies in 36 years[5]. The association with oral contraceptives was thoroughly described in the 1970s[6,7], and many cases of LCA have been reported since[8-10].

Due to the progress of diagnostic imaging techniques, the typical findings of LCA have been identified[4,11]. A typical LCA shows low density or isodensity on plain CT, presents a homogenous contrasting effect on arterial phase and does not show an apparent wash out on delayed phase. A typical LCA in MRI shows almost the same signal intensity as the surrounding parenchyma on T1 and T2 and shows high intensity on fat suppression T2. LCA may often present difficulties in a differential diagnosis with well-differentiated HCC and focal nodular hyperplasia[12-14]. The pathological findings of a typical LCA include the following[2,10,15-17]: (1) the tumor consists of hepatocytes with almost normal nuclei and cytoplasm presenting a homogenous increase, (2) and does not include the portal area and bile duct, (3) hepatocytes form hepatic cords, but sinusoids are pressed, and hepatic lobule structure is absent, (4) the tumor includes macrovesicular fatty changes, hemorrhage, degeneration, and myogenic arteries.

LCA can be divided into three categories: (1) LCA associated with oral administration of medicines including oral contraceptives and steroids[8-10], (2) LCA developing as a complication of glycogen-storage diseases[18-20], (3) adenomatosis[3,4,15]. Solitary LCAs are most frequently caused by oral contraceptives[7,21]. The occurrence of adenomatosis is unrelated to the use of oral contraceptives and the frequency of development is not related to sex[15]. It is reported that LCA occurs in patients of glycogen-storage disease type I [19]. In addition to oral contraceptives, oral administrations of such medications as clomiphene[22], barbituric acid[23] or androgen[24,25] are reported as risk factors for LCA. Also, it is reported that LCAs associated with oral contraceptives show regression after discontinuing the drug[26,27].

The main complications of LCA include tumor hemorrhage and malignant transformation. It is reported that hemorrhage is found in about one half of LCAs and can result in death[9,16,28]. Malignant transformation of LCA is considered to be rare. However, in several reported cases, LCA associated with glycogen-storage diseases and glucocorticosteroids developed HCC[29-32]. In another reported case, hepatocarcinogenesis occurred several years after discontinuation of oral contraceptives[32].

Although LCA is a benign liver tumor, treatment is often conducted to avoid hemorrhage and malignant transformation[3,4]. Surgical treatments such as lobectomy[21,33], enucleation[34] and liver transplantation[35] are performed for LCA. Percutaneous ethanol injection[20] and transcatheter arterial embolization[33] are established therapies for low invasive treatment of HCC, and were reported to be performed for LCA. However, precise pathological examination is not possible by these treatments. Since a definitive diagnosis of LCA by diagnostic imaging alone or by needle biopsy is difficult[11], tumor resection is often the most suitable approach. Our case was found by chance during treatment of the endometriosis complicated with bacterial infection. The patient did not have a history of using oral contraceptives or glucocorticosteroids which are known risk factors for LCA. Nor did the patient have metabolic liver disease including glycogen-storage

disease. By MRI, the tumor was found to contain fat. In dynamic studies, the tumor showed a homogenous enhancement in the arterial phase and almost the same enhancement as the surrounding liver parenchyma in the delayed phase. These findings were typical for LCA. However, the tumor showed an elevation of the density on plain CT and an increase of the early enhancement in the arterial phase, which caused us to suspect that well-differentiated HCC containing fat was becoming dedifferentiated. Accordingly, hepatic resection was performed.

In a prospective study of 48 LCA cases reported by van der Windt *et al*[27], serial observation was considered appropriate for tumors with the typical image findings of LCA if the diameter was less than 5 cm. Five of the 48 cases of LCA were resected because the radiological findings changed during serial observations and three of the five cases had well-differentiated HCC, while in the remaining two cases, it was difficult to distinguish between well-differentiated HCC and LCA pathologically. The present case showed the typical radiological findings for LCA and was 35 mm in diameter without an increasing tendency. However, diagnosis only by radiological findings is difficult in patients without a background supporting a diagnosis of LCA such as a history of receiving the above mentioned drugs or glycogen-storage disease. Resection of the tumor in the present case was therefore considered appropriate because of the risk of hemorrhage and possible malignant transformation.

REFERENCES

1 **Brophy CM**, Bock JF, West AB, McKhann CF. Liver cell adenoma: diagnosis and treatment of a rare hepatic neoplastic process. *Am J Gastroenterol* 1989; **84**: 429-432
2 **Kerlin P**, Davis GL, McGill DB, Weiland LH, Adson MA, Sheedy PF 2nd. Hepatic adenoma and focal nodular hyperplasia: clinical, pathologic, and radiologic features. *Gastroenterology* 1983; **84**: 994-1002
3 **Chiche L**, Dao T, Salamé E, Galais MP, Bouvard N, Schmutz G, Rousselot P, Bioulac-Sage P, Ségol P, Gignoux M. Liver adenomatosis: reappraisal, diagnosis, and surgical management: eight new cases and review of the literature. *Ann Surg* 2000; **231**: 74-81
4 **Grazioli L**, Federle MP, Ichikawa T, Balzano E, Nalesnik M, Madariaga J. Liver adenomatosis: clinical, histopathologic, and imaging findings in 15 patients. *Radiology* 2000; **216**: 395-402
5 **Edmondson HA**. Tumors of the liver and intrahepatic bile ducts. In: Atlas of tumor pathology. Washington DC: Armed Forces Institute of Pathology, 1958
6 **Baum JK**, Bookstein JJ, Holtz F, Klein EW. Possible association between benign hepatomas and oral contraceptives. *Lancet* 1973; **2**: 926-929
7 **Edmondson HA**, Henderson B, Benton B. Liver-cell adenomas associated with use of oral contraceptives. *N Engl J Med* 1976; **294**: 470-472
8 **Helling TS**, Wood WG. Oral contraceptives and cancer of the liver: a review with two additional cases. *Am J Gastroenterol* 1982; **77**: 504-508
9 **Meissner K**. Hemorrhage caused by ruptured liver cell adenoma following long-term oral contraceptives: a case report. *Hepatogastroenterology* 1998; **45**: 224-225
10 **Shortell CK**, Schwartz SI. Hepatic adenoma and focal nodular hyperplasia. *Surg Gynecol Obstet* 1991; **173**: 426-431
11 **Grazioli L**, Federle MP, Brancatelli G, Ichikawa T, Olivetti L, Blachar A. Hepatic adenomas: imaging and pathologic findings. *Radiographics* 2001; **21**: 877-892; discussion 892-984
12 **Charny CK**, Jarnagin WR, Schwartz LH, Frommeyer HS, DeMatteo RP, Fong Y, Blumgart LH. Management of 155 patients with benign liver tumours. *Br J Surg* 2001; **88**: 808-813
13 **Herman P**, Pugliese V, Machado MA, Montagnini AL, Salem MZ, Bacchella T, D'Albuquerque LA, Saad WA, Machado MC, Pinotti HW. Hepatic adenoma and focal nodular hyperplasia: differential diagnosis and treatment. *World J Surg* 2000; **24**: 372-376
14 **Cherqui D**, Rahmouni A, Charlotte F, Boulahdour H, Métreau JM, Meignan M, Fagniez PL, Zafrani ES, Mathieu D, Dhumeaux D. Management of focal nodular hyperplasia and hepatocellular adenoma in young women: a series of 41 patients with clinical, radiological, and pathological correlations. *Hepatology* 1995; **22**: 1674-1681
15 **Lewin M**, Handra-Luca A, Arrivé L, Wendum D, Paradis V, Bridel E, Fléjou JF, Belghiti J, Tubiana JM, Vilgrain V. Liver adenomatosis: classification of MR imaging features and comparison with pathologic findings. *Radiology* 2006; **241**: 433-440
16 **Erdogan D**, Busch OR, van Delden OM, Ten Kate FJ, Gouma DJ, van Gulik TM. Management of spontaneous haemorrhage and rupture of hepatocellular adenomas. A single centre experience. *Liver Int* 2006; **26**: 433-438
17 **Giusti S**, Donati F, Paolicchi A, Bartolozzi C. Hepatocellular adenoma: imaging findings and pathological correlation. *Dig Liver Dis* 2005; **37**: 200-205
18 **Fink AS**, Appelman HD, Thompson NW. Hemorrhage into a hepatic adenoma and type Ia glycogen storage disease: a case report and review of the literature. *Surgery* 1985; **97**: 117-124
19 **Parker P**, Burr I, Slonim A, Ghishan FK, Greene H. Regression of hepatic adenomas in type Ia glycogen storage disease with dietary therapy. *Gastroenterology* 1981; **81**: 534-536
20 **Yoshikawa M**, Fukui K, Kuriyama S, Tsujimoto T, Nakatani Y, Toyokawa Y, Kurematsu Y, Awata J, Shiroi A, Fukui H, Tsutsumi M. Hepatic adenomas treated with percutaneous ethanol injection in a patient with glycogen storage disease type Ia. *J Gastroenterol* 2001; **36**: 52-61
21 **Leese T**, Farges O, Bismuth H. Liver cell adenomas. A 12-year surgical experience from a specialist hepato-biliary unit. *Ann Surg* 1988; **208**: 558-564
22 **Carrasco D**, Barrachina M, Prieto M, Berenguer J. Clomiphene citrate and liver-cell adenoma. *N Engl J Med* 1984; **310**: 1120-1121
23 **Vázquez JJ**, Marigil MA. Liver-cell adenoma in an epileptic man on barbiturates. *Histol Histopathol* 1989; **4**: 301-303
24 **Carrasco D**, Pallardo L, Prieto M, Moll JL, Cruz JM, Berenguer J. Hepatic adenomata and androgen treatment. *Ann Intern Med* 1984; **100**: 316
25 **Dourakis SP**, Tolis G. Sex hormonal preparations and the liver. *Eur J Contracept Reprod Health Care* 1998; **3**: 7-16
26 **Kawakatsu M**, Vilgrain V, Erlinger S, Nahum H. Disappearance of liver cell adenoma: CT and MR imaging. *Abdom Imaging* 1997; **22**: 274-276
27 **van der Windt DJ**, Kok NF, Hussain SM, Zondervan PE, Alwayn IP, de Man RA, IJzermans JN. Case-orientated approach to the management of hepatocellular adenoma. *Br J Surg* 2006; **93**: 1495-1502
28 **Ameriks JA**, Thompson NW, Frey CF, Appelman HD, Walter JF. Hepatic cell adenomas, spontaneous liver rupture, and oral contraceptives. *Arch Surg* 1975; **110**: 548-557
29 **Burri E**, Steuerwald M, Cathomas G, Mentha G, Majno P, Rubbia-Brandt L, Meier R. Hepatocellular carcinoma in a liver-cell adenoma within a non-cirrhotic liver. *Eur J Gastroenterol Hepatol* 2006; **18**: 437-441

30 **Ito M**, Sasaki M, Wen CY, Nakashima M, Ueki T, Ishibashi H, Yano M, Kage M, Kojiro M. Liver cell adenoma with malignant transformation: a case report. *World J Gastroenterol* 2003; **9**: 2379-2381
31 **Uto H**, Shigehira M, Kawano T, Nagatomo H, Kuribayashi T, Taniguchi S, Koga K, Komada N, Kitamura T, Maruyama T, Tsubouchi H. Liver cell adenoma in a young man with elevated serum PIVKA-II level. *J Gastroenterol* 1996; **31**: 441-445
32 **Gordon SC**, Reddy KR, Livingstone AS, Jeffers LJ, Schiff ER. Resolution of a contraceptive-steroid-induced hepatic adenoma with subsequent evolution into hepatocellular carcinoma. *Ann Intern Med* 1986; **105**: 547-549
33 **Ribeiro A**, Burgart LJ, Nagorney DM, Gores GJ. Management of liver adenomatosis: results with a conservative surgical approach. *Liver Transpl Surg* 1998; **4**: 388-398
34 **Flejou JF**, Barge J, Menu Y, Degott C, Bismuth H, Potet F, Benhamou JP. Liver adenomatosis. An entity distinct from liver adenoma? *Gastroenterology* 1985; **89**: 1132-1138
35 **Mueller J**, Keeffe EB, Esquivel CO. Liver transplantation for treatment of giant hepatocellular adenomas. *Liver Transpl Surg* 1995; **1**: 99-102

S- Editor Cheng JX **L- Editor** O'Neill M **E- Editor** Yin DH