CME Article

Clinical mimicry of hepatocellular carcinoma: imaging-pathological correlation

Y F A Chung, C H Thng, H F Lui, K Mancer, P K H Chow, Y M Tan, P C Cheow, L L P J Ooi

ABSTRACT

This pictorial essay aims to show the clinical mimicry of hepatocellular carcinoma (HCC) and its diagnostic difficulty, and to create awareness among clinicians and radiologists of potential diagnostic pitfalls. A selected consecutive series of hepatectomies with proven HCC over a three-year period, identifying clinical presentation, blood results and imaging of patients with difficult preoperative diagnosis, was reviewed. The imaging of the focal liver lesions is presented pictorially with pathological correlation.

Six patients out of 34 cases of resected HCC were diagnosed to have benign (three liver abscesses) and neoplastic (one Klatskin tumour, one colorectal liver metastasis, one gallbladder cancer) conditions. Compared to the rest in the series, all six patients had normal serum alpha fetoprotein levels. On computed tomography, the mosaic appearance of HCC mimicked locules of liver abscess while HCC with pseudocapsule (rim enhancement) was misdiagnosed as unilocular abscess or metastatic lesion. Arterial enhancement on contrast-enhanced triphasic computed tomography was useful in diagnosis of HCC.

In summary, HCC can mimic benign and neoplastic clinical syndromes. The diagnosis of liver abscess can delay subsequent diagnosis of HCC and potentially complicate the treatment plan. Contrast-enhanced triphasic computed tomography or magnetic resonance imaging is useful to resolve difficult diagnosis, especially when the serum alpha fetoprotein level is not raised.

Keywords: alpha fetoprotein, diagnostic imaging, hepatocellular carcinoma, liver abscess, liver tumour

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INTRODUCTION

The best chance of cure for patients with hepatocellular carcinoma (HCC) is surgery, with stage at surgery being an independent predictor of survival[1]. Early diagnosis is therefore important. This is especially so in an endemic Hepatitis B population like Singapore since Hepatitis B is a strong aetiological factor for HCC[2,3]. However, HCC may present as innocuous clinical syndromes that may delay its diagnosis and hence, treatment at a later stage. Occasionally, it may also mimic other forms of liver lesion. A search of the medical literature did not yield any report confirming this suspicion. In order to highlight such potential diagnostic pitfalls that may delay or change treatment plan, we reviewed surgical cases of proven HCC to determine their preoperative presentation and diagnosis. This pictorial essay will also help clinicians and radiologists alike to be cognizant of possible clinical scenarios that might be misleading in the diagnosis of resectable HCC.

CLINICAL MATERIAL

Between 2001 and 2003, 34 consecutive hepatectomies with histologically-proven HCC performed by single surgeon (CYFA) were reviewed. There were 29 men and 5 women, with a median age of 69.5 years (range 48-84 years). Eighteen (52.9%) patients were known chronic hepatitis carrier (16 hepatitis B, 2 hepatitis C). The serum alpha fetoprotein (αfp) (normal range 1-10 ng/L) was elevated in only 19 (55.9%) patients, with only 12 (35.3%) having levels above the diagnostic 400 ng/L. The majority (22) of patients had minor hepatectomy defined as three or fewer segmental resections, while 12 (35.3%) patients underwent major hepatectomy. The median size of the resected tumours was 4.8cm (range: 2.3-20cm). Eleven (32.4%) patients had macroscopic cirrhosis at time of surgery.

The diagnosis of HCC was not made preoperatively or additional imaging was required to make a diagnosis of HCC in six patients. Diagnosis was difficult if the preoperative serum αfp was not raised, even with the aid of initial imaging. All the six "misdiagnosed" cases had normal serum αfp. Among the smaller tumours (<4.8cm), five (29.4%) patients had difficult diagnosis compared to only one (5.9%) patient with larger tumour size ≥4.8cm. The clinical mimicry of

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Table 1. Details of the patients with resected HCC mimicking clinical syndromes of benign and neoplastic conditions.

Patient	Age/sex	Clinical presentation	Blood investigation	Imaging	Clinical diagnosis	Operative findings	Pathological findings	Outcome
Benign								
1	63/male	Acute epigastric pain previous biliary colic	TW 12 x 10^9/L↑, neutrophils 94%↑, hepatitis B+ve, C-ve	CT(Fig. 1a)	Cholecystitis with unilocular liver abscess	Ductal stone & solid segment V lesion on IOUS	2.5cm encapsulated grade I HCC (Fig. 1b)	Alive
2	67/ female	Right hypochondrium pain Known diabetes mellitus Previous biliary stones treated with endoscopy	No leucocytosis, hepatitis B-ve, C-ve	CT(Figs. 2a-b) Repeat CT 2 weeks later CT- guided bx†	Multiloculated liver abscess *	Gallstones	7cm non-encapsulated grade IV HCC with vascular invasion & satellite foci	Died with disease (10 mths)
3	76/male	Right hypochondrium pain Previous surgery for perforated diverticulitis	TW 19 x 10^9/L↑, neutrophils 81%↑, hepatitis B-ve, C-ve	CT(Fig. 3a) Repeat CT 2 weeks later (Figs. 3b-c)	Multiloculated liver abscess *	Gallstones & colonic diverticuli	4cm nodular grade II HCC (Fig. 3d)	Alive
Neoplastic								
4	63/male	Painless obstructive jaundice	CA 19-9 2,213 U/ml↑, bilirubin 201 μmol/L↑, ♂-GT 1,091 U/L↑, hepatitis B+ve, C-ve	CT (Fig. 4a) MRI (Fig. 4b-c)	Klatskin tumour Type IIIB (Bismuth)	Tumour extends to right secondary hepatic ducts	4cm non-encapsulated grade II HCC with major hepatic ducts invasion (Fig 4d)	Alive
5	69/male	Right hypochondrium pain Colon cancer Duke's B resected 2 years ago	CEA normal, hepatitis B+ve, C-ve	CT(Figs. 5a-c)	Cholecystitis & solitary colorectal liver metastasis	Gallstones	2.5cm non-encapsulated grade II HCC	Alive
6	72/male	Unilateral deep vein thrombosis of the leg	CEA/ CA 19-9 normal, hepatitis B-ve, C-ve	CT(Fig. 6)	Gallbladder cancer	Gallbladder normal	3.6cm non-encapsulated grade II HCC abutting gallbladder	Deceased No HCC (22 mths)

Key : TW: total white blood cell count, CEA: carcinoembryonic antigen, CA 19-9: carbohydrate antigen, ♂-GT: gamma-glutamyl transferase, IOUS: intraoperative ultrasonography.

* These patients had dedicated triphasic liver CT scans 2 weeks later following a course of antibiotics, confirming the diagnosis of HCC preoperatively.

† Patient 2 initially refused surgery and had CT- guided percutaneous biopsy (+ve for HCC) at another hospital.

Grade of tumour is according to Edmonson classification, where I, II-III and IV are well-, moderately- and poorly- differentiated, respectively.

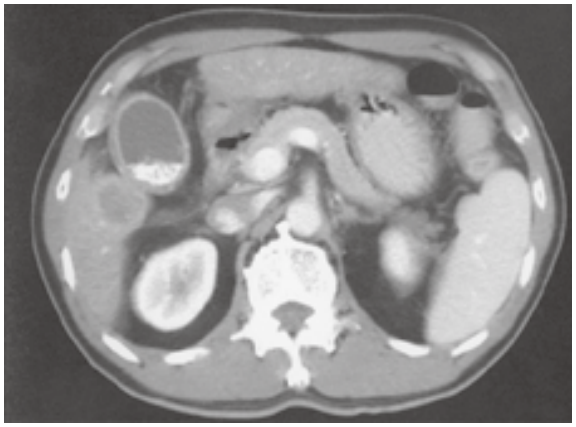


Fig. 1a Patient 1. Enhanced portal venous phase CT image shows thickened gallbladder with biliary calculi and an adjacent rim-enhancing hypodense lesion mimicking a unilocular liver abscess.

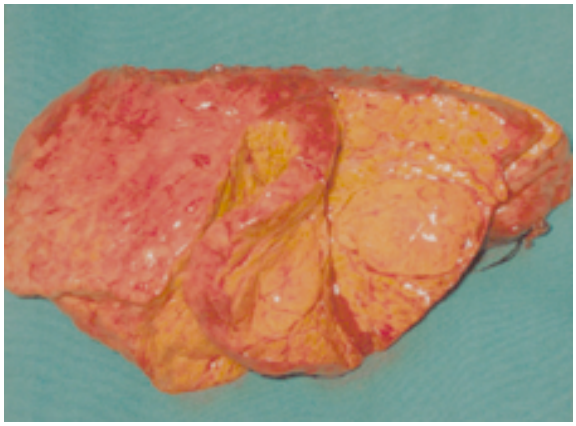


Fig. 1b Patient 1. Photograph of the resected specimen shows a mildly-cirrhotic liver with a well-circumscribed, homogeneously solid lesion of well-differentiated HCC with fatty change (note the yellow hue of the tumour). Fatty metamorphosis is well documented in early HCC as part of hepato-carcinogenesis and demonstrates hypodensity on CT.

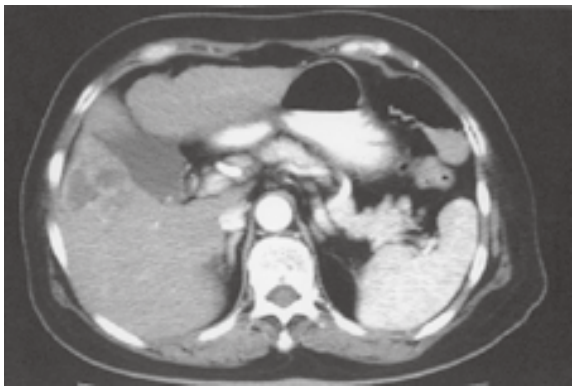


Fig. 2a Patient 2. Enhanced arterial phase CT image of the liver shows a lesion in segment V adjacent to the gallbladder with early rim and internal septal enhancement.

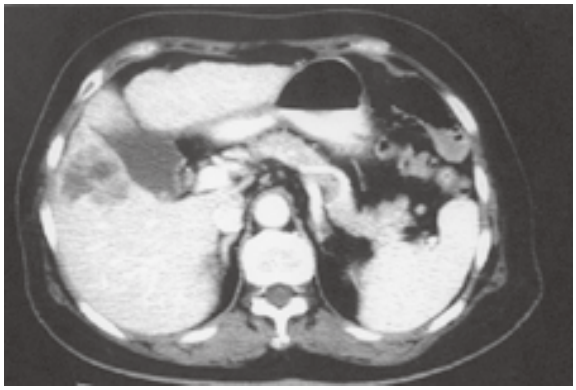


Fig. 2b Patient 2. Corresponding enhanced portal venous phase CT image shows the relatively more hypodense lesion with "wash-out" of the contrast.

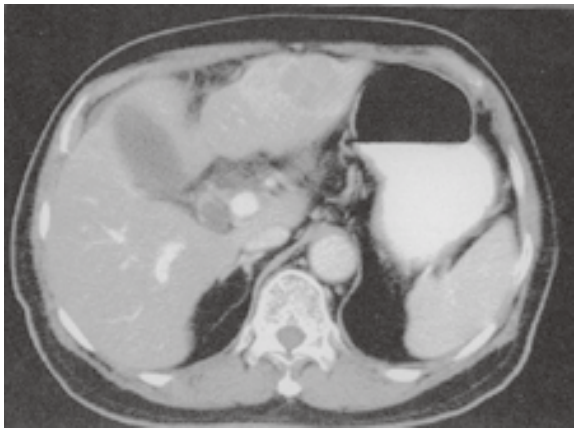


Fig. 3a Patient 3. Initial enhanced portal venous phase CT image shows a rim-enhancing lesion with septa, mimicking a multiloculated abscess.

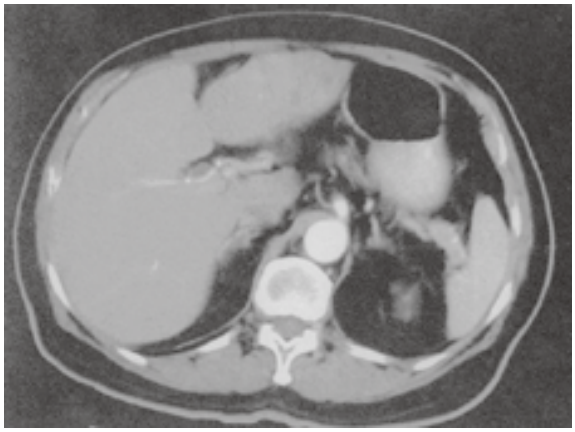


Fig. 3b Patient 3. Repeat enhanced arterial phase CT image shows the lesion with a nodular area of early enhancement.

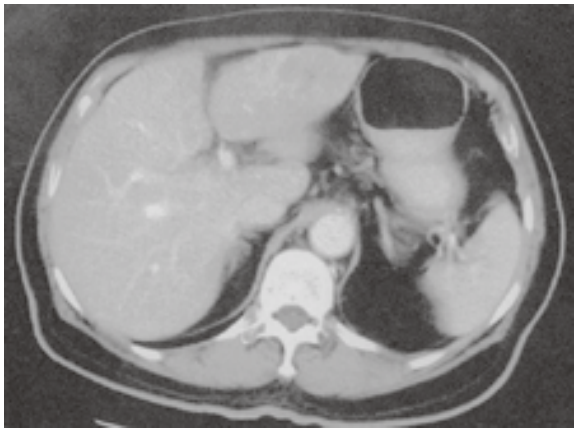


Fig. 3c Patient 3. Repeat enhanced portal venous phase CT image subsequently shows the nodule becoming hypodense with a rim-enhancing pseudocapsule and mosaic pattern. These are characteristic features in dynamic CT scanning of HCC.

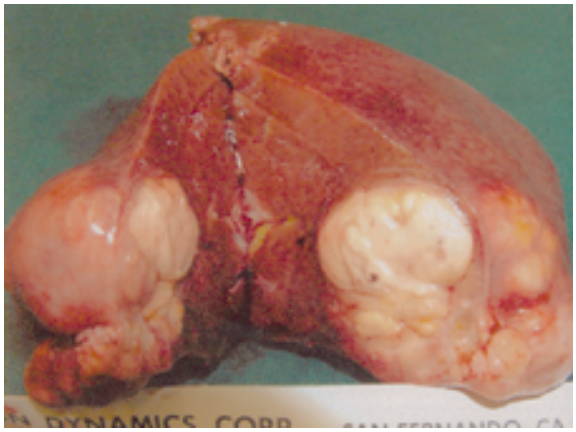


Fig. 3d Patient 3. The bisected specimen shows lobules of tumour cells with fatty change separated by intertwining bands of fibrosis. (which represent septa seen on CT)

HCC can be categorised into two broad groups of clinical significance, namely: benign and neoplastic (Table I). The radiological images are presented, with hindsight knowledge and clinical-pathological correlation, with the aim of creating an awareness of the mimicry of HCC and to improve future diagnostic acumen.

BENIGN MIMICS

The clinical mimicry of HCC in the benign group has greater clinical implications. It can masquerade as a uni- or multiloculated liver abscess in the background of coexisting biliary stone disease. While clinical features of fever, pain and leucocytosis was suggestive of an infective process in these cases in

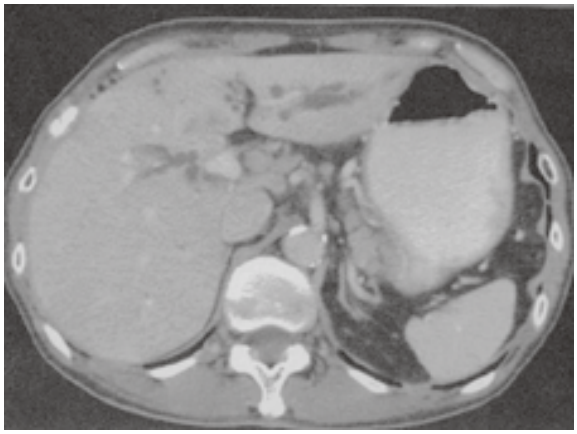


Fig. 4a Patient 4. Enhanced portal venous phase CT image shows a hypodense lesion at the hilum with bilobar biliary dilatation.

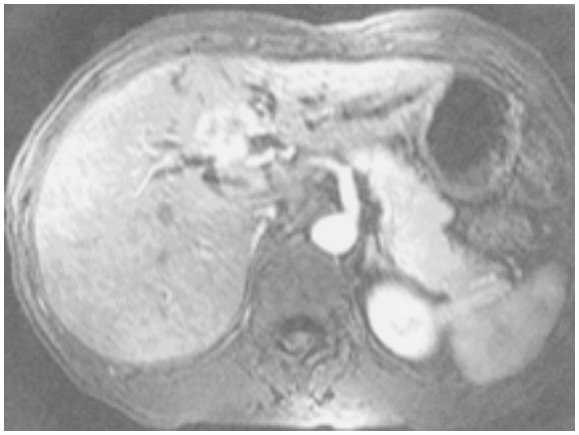


Fig. 4b Patient 4. Enhanced arterial phase T1-W MR image shows a lesion with a thick enhancing rim.

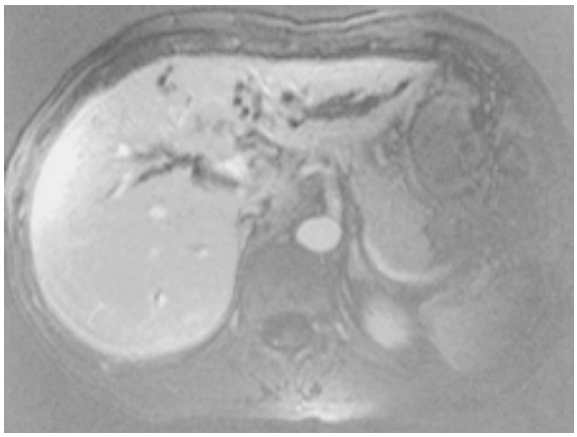


Fig. 4c Patient 4. Corresponding enhanced portal venous phase T1-W MR image show that the enhancement fades off into a thin pseudocapsule.

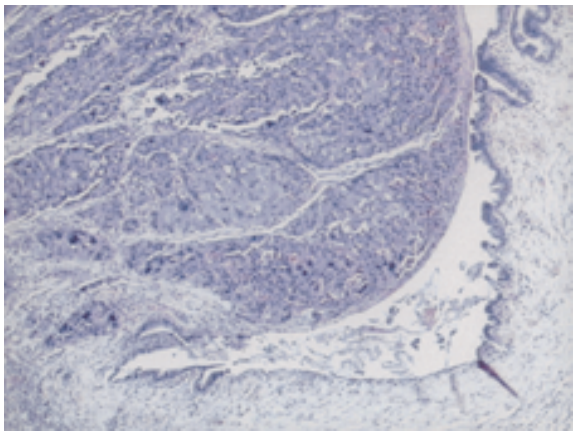


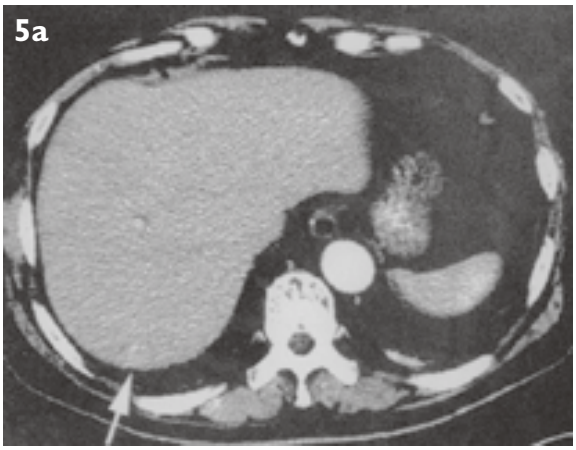
Fig. 4d Patient 4. Photomicrograph of the resected specimen shows enlarged, bizarre HCC cells with hyperchromatic nuclei breaching through the main bile duct epithelium (Haematoxylin & eosin, x 200)

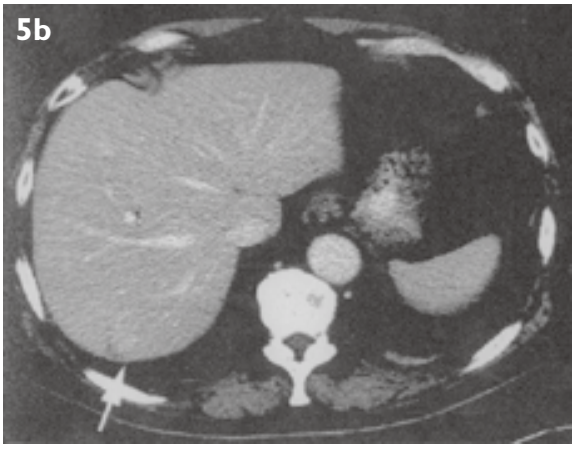
the series, the computed tomography (CT) features of HCC was also misleading for abscess, especially when only a single portal venous scan was assessed. The variegated "mosaic" appearance mimics the multiple locules of liver abscess separated by internal septa. Small HCC with pseudocapsule seen commonly on the portal venous phase of CT can be misinterpreted as a unilocular abscess. The diagnosis of liver abscess can potentially lead to a late diagnosis of HCC if there is no heightened suspicion to follow-up this lesion closely with repeat imaging. If drainage of the misdiagnosed lesion is undertaken, tumour spillage and seeding can occur with the percutaneous needle or at surgery. As such, a misdiagnosis of liver abscess can potentially complicate treatment of HCC. Repeating a dedicated triphasic CT or magnetic resonance (MR) imaging of the liver helps to characterise the lesion better.

NEOPLASTIC MIMICS

A diagnosis of other primary hepatic neoplasms in HCC mimicry does not change the surgical intent if the lesion is resectable. HCC mimics gallbladder neoplasm because of the latter's close anatomical relationship. Obstructive icteric HCC is a distinct, though rare entity, comprising only 2-3% of all HCCs and it can mimic Klatskin tumour[4]. In the local population where HCC is prevalent, this type of tumour is a differential diagnosis in patient with hilar obstructive jaundice. The differentiation from cholangiocarcinoma is difficult but cholangiography by MR imaging or endoscopy helps with diagnosis and staging for intervention[5,6]. In patient 4, the arterial hypervascularity seen on MR imaging was not typical for cholangicarcinoma but because of its hilar location, this was misdiagnosed as such. Nevertheless, surgery is aggressive, not unlike in cholangiocarcinoma, as the prognosis is similar to resectable HCC with no jaundice, stage for stage[4].

HCC mimicry as a metastatic liver lesion in patients with history of previous malignancy can be misleading. Other than colorectal liver and sarcoma metasectomy[7,8], which has convincing long-term





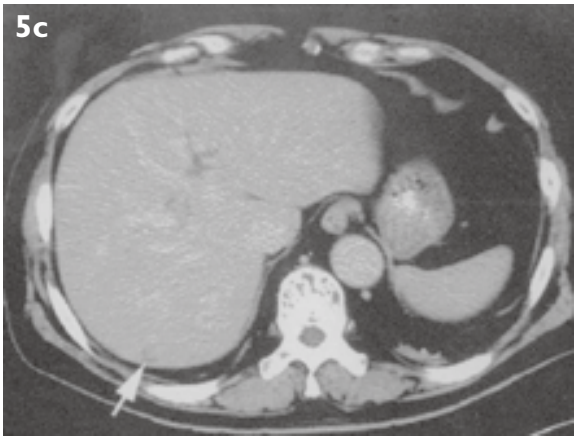


Fig. 5 Patient 5. Isodense lesion in segment VII (arrow) which is hardly discernible on the (a) enhanced arterial phase CT image, fading off with a pseudo-capsule on the (b) portal venous phase CT image, and becoming hypodense during the (c) delayed phase (detected readily). A pre-contrast CT image will help to better characterise the lesion (arterial enhancement is observed when the lesion changes from hypodense (pre-contrast) to isodense (arterial phase) relative to surrounding parenchyma).

results, hepatectomy for other types of malignancy is controversial. Thus, these patients with previously-treated malignancy and who subsequently present with focal liver lesions may be labelled as metastatic liver disease (Fig. 7). There is a need to differentiate these metastatic lesions from HCC. In selected cases of resectable multifocal HCC, aggressive surgery is of benefit[9].

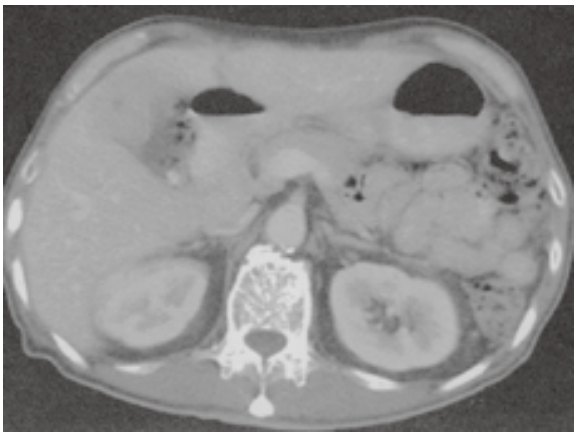
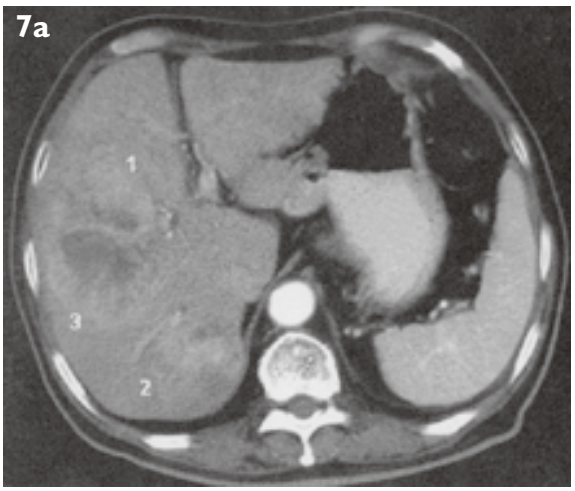


Fig. 6 Patient 6. Enhanced portal venous CT image shows a non-enhancing lesion at the gallbladder fossa forming eccentric fundal thickening of the gallbladder. MR imaging would be useful to enhance the soft-tissue contrast between the 2 structures. However, in this situation, further imaging will not change the surgical intent.



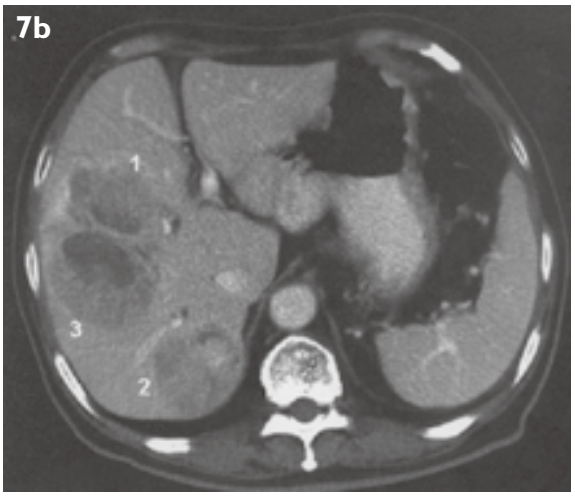


Fig. 7 76-year-old man with past history of resected gastric carcinoma was diagnosed to have multiple hepatic metastases on follow-up CT, until a dedicated triphasic CT was done. The serum αfp and CEA were normal. He was offered surgery after these scans, but he refused. He passed away 2 years later (the repeat αfp and CEA were 16, 456 and 2.3 ng/L, respectively) (a) Enhanced arterial phase CT image shows 2 lesions in the right lobe with solid nodules of early enhancement (1 & 2) and a thick early enhancing rim (3). (b) Enhanced portal venous phase CT image shows fading away of enhancement, leaving areas of hypodensity (1 & 2) and thin pseudo-capsule (3), characteristic of mosaic pattern of HCC.

DIAGNOSTIC TECHNIQUES

The diagnosis of HCC relies heavily on a raised αfp. In this series of resected HCC, only 56% had elevated serum αfp, with 35% above the diagnostic level of 400 ng/L[10]. This is similar to other large Asian series[4]. All the presented cases that had diagnostic difficulties did not have a raised serum αfp level. It is apparent that imaging plays an important role in the diagnosis of HCC, especially in those with normal αfp. It is notable that three of these patients (patients 1, 5 & 6) had lesions incidentally- detected on imaging, and would otherwise required dedicated or follow-up scans for proper evaluation.

Accurate diagnosis of HCC comes from advances in imaging technique and better image interpretation. CT and MR imaging of HCC are characterised by the timing and pattern of contrast enhancement. The tumour is typically hypervascular, feeding off the hepatic artery. As the tumour enlarges, there is degeneration of normal hepatic arterioles and portal venules in combination with neoplastic arterial formation[11]. This gives rise to peak enhancement at the arterial phase CT in the form of homogeneous hyperdensity, heterogeneous hyperdensity or isodensity. This arterial hypervascularity has very high positive predictive value for HCC, especially in cirrhotics[12]. The contrast material washes out quickly, leaving behind pseudocapsules or septa in a typically variegated "mosaic" appearance in the portal venous phase[13-15].

The triple phase CT of arterial, portal venous and delayed phase is sufficient for most HCC diagnosis[16], though pre-contrast or unenhanced images help to characterise them better in selected cases[17]. In hindsight, it is evident that the diagnosis of HCC could be made in patients who had multiphasic scans as depicted in the figures. MR imaging is complementary to CT with the added value of chemical shift ability, better soft tissue contrast and cholangiographical examination[15,18]. It is superior to CT in detecting and characterising HCC[19]. However, because of cost and limited availability, MR imaging should be reserved for use in selected cases.

The knowledge of tumour characterisation lags behind for each new imaging modality. Hence, it is important for clinicians and radiologists to be cognizant of potential diagnostic pitfalls in HCC mimicry. Clinicoradiological conference allows for interactive discussion and learning. As Sir William Osler aptly puts it[20], *"to study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all"*. It is therefore important then for all involved in the care of patients to be in that boat at sea together.

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

Multiple Choice Questions (Code SMJ 200501A)

	True	False
Question 1. Hepatocellular carcinoma (HCC):		
(a) Can mimic liver abscess.	❑	❑
(b) Never presents with obstructive jaundice.	❑	❑
(c) Can develop in patients with previously treated malignancy.	❑	❑
(d) May be detected incidentally on imaging and merits further dedicated scans to characterise it.	❑	❑
Question 2. Regarding the pathogenesis of HCC:		
(a) As the tumour enlarges, there is degeneration of the normal hepatic arterioles.	❑	❑
(b) As the tumour enlarges, there is increase in neoplastic vessels.	❑	❑
(c) It is hypervascular in the hepatic arterial phase and appears bright on CT.	❑	❑
(d) Fatty change (deposition) can occur during HCC formation.	❑	❑
Question 3. In the presence of focal liver lesion, the diagnosis of HCC is:		
(a) Excluded if the serum alpha fetoprotein (αfp) is normal.	❑	❑
(b) Highly probable when serum αfp is ≥400 ng/L.	❑	❑
(c) Always associated with a positive serology of chronic viral hepatitis infection.	❑	❑
(d) Comparatively more difficult if the lesion is small.	❑	❑
Question 4. Regarding diagnostic imaging of HCC on CT and MR imaging:		
(a) The CT features of HCC can be misleading for abscess when read on a single portal venous scan.	❑	❑
(b) HCC demonstrates a "mosaic" or variegated pattern in the portal venous phase.	❑	❑
(c) Dedicated triple phase CT scan is sufficient for most HCC diagnosis.	❑	❑
(d) MR imaging is cheap but inferior to CT scan in detecting HCC.	❑	❑
Question 5. Regarding the treatment of HCC:		
(a) The best chance for cure is surgery with clear margins.	❑	❑
(b) It should not include inadvertent puncture or "drainage" of lesion as it may spill tumour cells.	❑	❑
(c) Resectable obstructive icteric HCC has poorer prognosis compared to similar stage non-icteric HCC.	❑	❑
(d) There is a role for curative surgery in selected multifocal disease.	❑	❑

Doctor's particulars:

Name in full: _____

MCR number: _____ Specialty: _____

Email address: _____

Submission instructions:

A. Using this answer form

1. Photocopy this answer form.
2. Indicate your responses by marking the "True" or "False" box ☑
3. Fill in your professional particulars.
4. Either post the answer form to the SMJ at 2 College Road, Singapore 169850 OR fax to SMJ at (65) 6224 7827.

B. Electronic submission

1. Log on at the SMJ website: URL http://www.sma.org.sg/cme/smj
2. Either download the answer form and submit to smj.cme@sma.org.sg OR download and print out the answer form for this article and follow steps A. 2-4 (above) OR complete and submit the answer form online.

Deadline for submission: (January 2005 SMJ 3B CME programme): 12 noon, 25 February 2005

Results:

1. Answers will be published in the SMJ March 2005 issue.
2. The MCR numbers of successful candidates will be posted online at http://www.sma.org.sg/cme/smj by 20 March 2005.
3. Passing mark is 60%. No mark will be deducted for incorrect answers.
4. The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council.