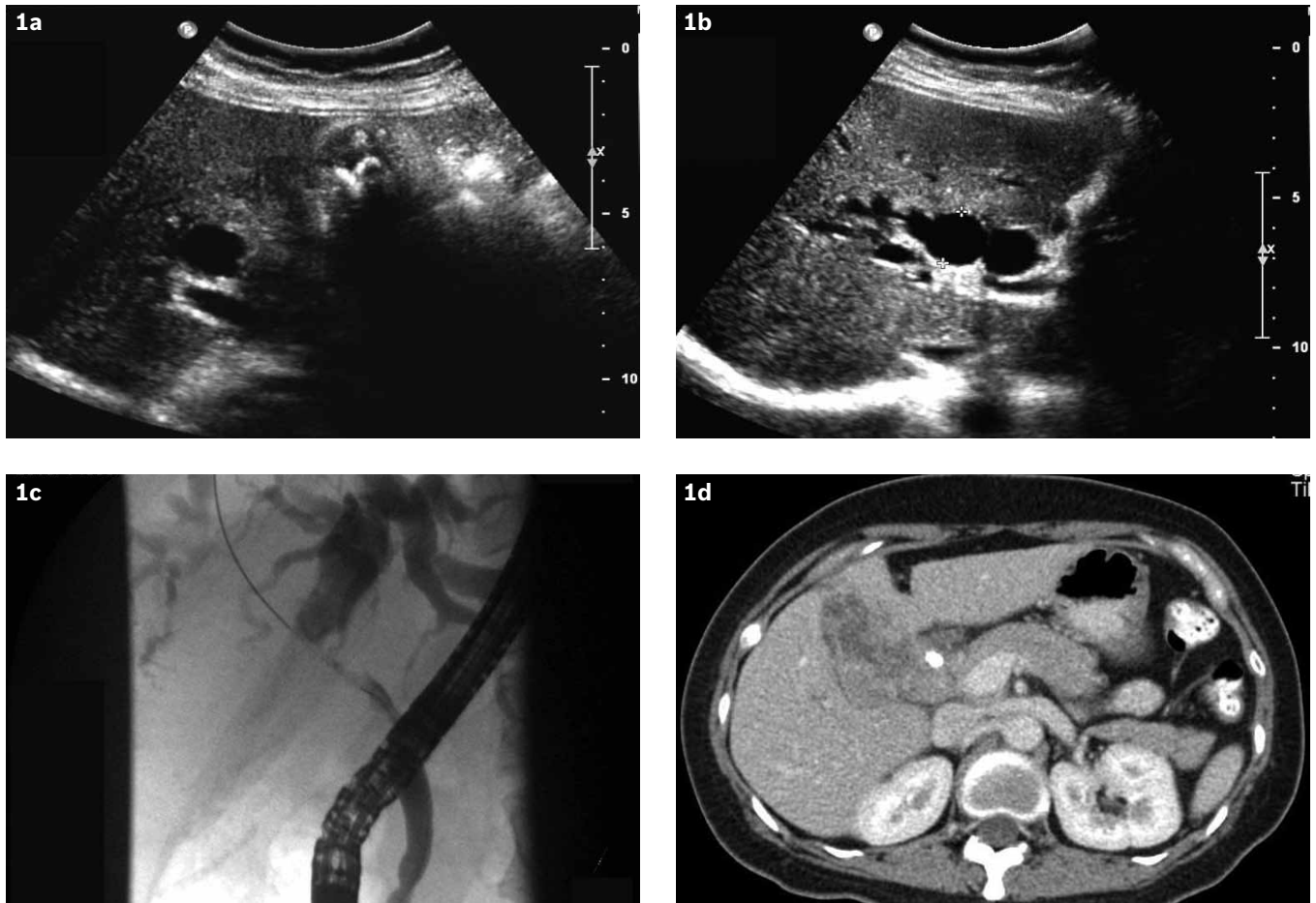


## CMEARTICLE

## Clinics in diagnostic imaging (137)

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**Fig. 1** Greyscale US images of the liver show (a) the gallbladder fossa; and (b) the common bile duct. (c) ERCP image performed one day later and (d) axial CT image obtained during portal venous phase.

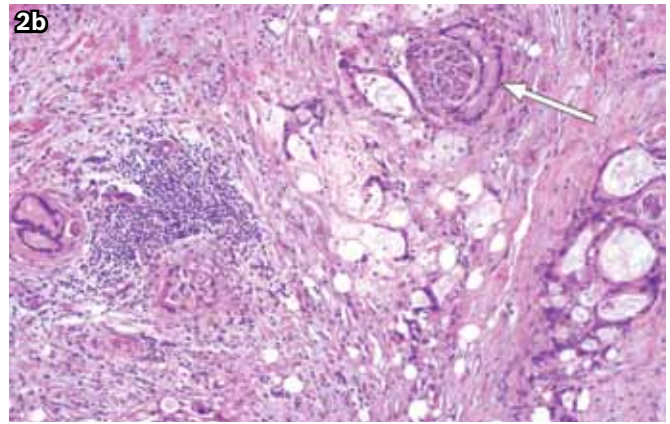
## CASE PRESENTATION

A 45-year-old woman with no significant past medical history presented to her general practitioner with a six-day history of generalised body itch, dark-coloured urine and pale stools. She also complained of loss of appetite and recent weight loss. The patient was subsequently referred to the Emergency Department, as she was noted to have jaundice. On physical examination, the abdomen was soft, with no focal tenderness or palpable mass. Her blood tests revealed an elevated serum bilirubin level of 118 (normal range [NR] 5–22)  $\mu\text{mol/L}$ . Liver

enzymes were deranged: aspartate aminotransferase (AST) 298 (NR 10–30) U/L; alanine aminotransferase (ALT) 578 (NR 10–36) U/L; alkaline phosphatase (ALP) 346 (NR 22–104) U/L; and gamma glutamyl transpeptidase 407 (NR 7–32) U/L. Full blood count, renal function test and coagulation profile were all unremarkable. Ultrasonography (US) of the liver was performed, followed by endoscopic retrograde cholangiopancreatography (ERCP) and contrast-enhanced computed tomography (CT) of the abdomen and pelvis (Figs. 1a–d). What do these images show? What is the diagnosis?

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**Fig. 2** (a) Photograph of the excised gallbladder tumour shows complete obliteration of the lumen by the tumour, with infiltration of the adjacent liver (arrow). (b) Photomicrograph of the resected gallbladder shows tumour cells with abundant fibrous tissues. Perineural involvement is also seen (arrow) (Haematoxylin & eosin, x 100).

### IMAGE INTERPRETATION

Transabdominal US of the liver showed a heterogeneous irregular lesion in the gallbladder fossa, which contained several echogenic foci (Fig. 1a). The lesion was inseparable from the liver. The adjacent liver parenchyma appeared to be more hypoechoic compared to the rest of the liver. Marked dilatation of the intrahepatic and extrahepatic bile ducts was also demonstrated, with the proximal common bile duct measuring 1.8 cm in diameter (Fig. 1b). ERCP (Fig. 1c) revealed severe dilatation of the intrahepatic ducts in both lobes. A 3-cm stricture involving the common hepatic and proximal common bile ducts was seen. The opacified distal common bile was of normal calibre. Intravenous contrast-enhanced CT image of the upper abdomen showed a heterogeneously enhancing mass in the gallbladder fossa, replacing the entire gallbladder. Infiltration of the adjacent liver parenchyma in segment 4B was observed (Fig. 1d). Biliary tree dilatation was due to common bile duct invasion at the porta hepatis. A stent was present within the common bile duct.

### DIAGNOSIS

Locally advanced gallbladder carcinoma.

### CLINICAL COURSE

The patient underwent laparotomy and excision of the gallbladder mass. Operative findings revealed a hard gallbladder mass (Fig. 2a) invading into Segments 4B and 5 of the liver, as well as the right branch of the portal vein, the right hepatic duct and the lateral wall of the duodenum. Extended right hemihepatectomy, Whipple procedure, portal vein resection and reconstruction were performed.

Histopathological examination of the resected gallbladder specimen revealed diffusely infiltrating adenocarcinoma of the gallbladder (Fig. 2b). Postoperatively, the patient's hospital stay was complicated by sepsis and intra-abdominal abscess collection, which were treated with intravenous antibiotics and percutaneous drainage. She made a satisfactory recovery subsequently and was discharged one month after the surgery.

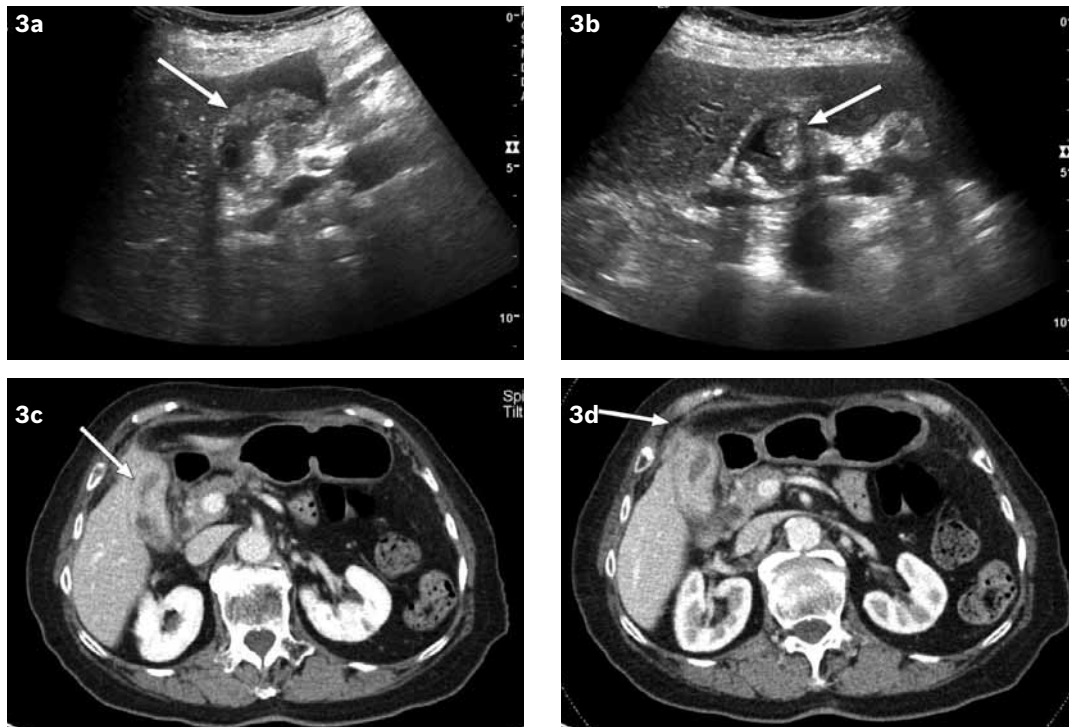
### DISCUSSION

Although its overall prevalence is low, primary carcinoma of the gallbladder is the most common malignant tumour of the biliary tract.<sup>(1,2)</sup> It is three times more common in women than men, and the frequency of diagnosis increases with age.<sup>(1-3)</sup> Predisposing risk factors include cholelithiasis, chronic biliary infections (e.g. chronic *Salmonella* Typhi infection), primary sclerosing cholangitis, porcelain gallbladder, congenital dilation of the common bile duct and abnormal connections between pancreatobiliary ducts, and low cystic duct insertion.<sup>(2-4)</sup> Common histologic types of gallbladder carcinoma include adenocarcinoma, adenosquamous carcinoma, squamous cell carcinoma and oat cell carcinoma. Adenocarcinoma is by far the most common subtype and accounts for 90% of all gallbladder carcinomas.<sup>(3,5)</sup>

The prognosis for primary gallbladder carcinoma is poor, with the five-year survival rates reported to be 5%–13%.<sup>(5,6)</sup> Diagnosis is often unsuspected and delayed due to vague and nonspecific symptoms, leading to advanced staging and dismal prognosis at the time of diagnosis. Early-stage carcinoma is typically diagnosed incidentally when the patient presents with inflammatory symptoms related to coexistent cholelithiasis or cholecystitis.<sup>(3)</sup> Some of the more common presenting complaints include chronic abdominal pain, anorexia, jaundice and weight loss. Jaundice is more often a sequela of biliary tree invasion and obstruction rather than hepatic metastasis or obstructing stones.<sup>(7)</sup>

Imaging plays an important role in the diagnosis, staging and post-treatment follow-up of gallbladder carcinoma. Radiography of the abdomen is usually the initial radiological examination performed in patients presenting with upper abdominal pain. It may show calcified gallstones or a porcelain gallbladder. Aerobilia or abnormal collection of gas in the right upper quadrant may be visible when there is formation of a choledochenteric fistula or an invasion of the adjacent bowel by an advanced gallbladder carcinoma. Diagnosis of gallbladder carcinoma cannot be made based solely on radiographic findings.

On US, three patterns of sonographic findings have been described.<sup>(1-3)</sup> The most common finding is a mass occupying or replacing the gallbladder, presenting in 40%–65% of all cases of



**Fig. 3** An 83-year-old woman with histologically proven adenocarcinoma of the gallbladder. (a & b) Greyscale US images show diffuse, asymmetric nodular thickening of the gallbladder wall (arrows), with near complete obliteration of the lumen. Contrast-enhanced CT images show (c) diffused thickening of the gallbladder wall (arrow) with increased enhancement and (d) extension of the tumour from the gallbladder fundus to the perihepatic space (arrow).

gallbladder carcinoma at initial presentation.<sup>(3)</sup> The mass appears as a heterogeneous mass in the gallbladder fossa, with the absence of a normal-looking gallbladder. The mass itself is usually diffusely hypoechoic, but central hyperechoic areas are not uncommon due to the presence of coexisting gallstones, gallbladder or tumoural calcification and intraluminal air or necrotic debris.<sup>(1,3)</sup> Direct invasion of the adjacent liver and biliary tree may result in ill-defined hypoechoic changes in the affecting liver parenchymal and biliary tree dilatation distal to the stricture.

Another common US finding in gallbladder carcinoma is a thickening of the gallbladder wall, which may be either diffuse or focal. This is seen in 20%–30% of gallbladder carcinoma cases.<sup>(1-3)</sup> The appearance of the gallbladder wall often poses a diagnostic challenge, as it mimics the appearance of the more common acute or chronic inflammatory conditions of the gallbladder. However, the presence of diffuse wall thickening (> 1.0 cm), mural irregularity and marked asymmetry of the thickened gallbladder wall should raise concerns for malignancy.<sup>(3,8,9)</sup> An example of such an appearance in a histologically proven adenocarcinoma of the gallbladder is shown in Fig. 3.

Thirdly, an intraluminal mass within the gallbladder is a less common appearance of gallbladder carcinoma, occurring in 15%–25% of cases.<sup>(3)</sup> The diagnostic challenge is to differentiate malignancy from benign conditions that may give rise to similar sonographic appearance, e.g. adenomatous or hyperplastic cholesterol polyps. An intraluminal mass with irregular border is highly suspicious of malignancy. Malignant lesions should also be considered when polypoid lesions are more than 2 cm in diameter, solitary, sessile or have a thickened implantation base or associated

with gallstones.<sup>(4,9)</sup> In recent years, contrast-enhanced US has been gaining popularity in the workup of hepatobiliary lesions. The two studies by Hattori et al, using Levovist (Nippon Schering, Tokyo, Japan) and Sonazoid (Daichi-Sankyo, Tokyo, Japan), have shown the usefulness of contrast-enhanced US in differentiating benign and malignant polypoidal gallbladder tumours.<sup>(10,11)</sup>

The sonographic findings of gallbladder carcinoma described above can also be applied to CT studies.<sup>(1-4)</sup> The changes of a mass replacing the gallbladder, gallbladder wall-thickening and polypoidal mass in the gallbladder can all be clearly demonstrated with the latest multidetector-row CT (MDCT). The diagnostic accuracy, sensitivity and specificity of MDCT in cases of gallbladder cancer have been proven.<sup>(12)</sup> Primary gallbladder carcinoma is usually hypodense on unenhanced CT. Hypervascular foci of enhancement equal to or greater than that of the liver have been observed after administration of intravenous contrast.<sup>(2)</sup> The degree of contrast washout in the portal venous and delayed phases is less (remain hyperdense) than that of hepatocellular carcinoma due to the presence of fibrous stromal components of gallbladder carcinoma.<sup>(2)</sup> This is helpful in differentiating it from large central hepatocellular carcinoma with involvement of the gallbladder. CT is also widely used to determine the local extent and staging of primary gallbladder carcinoma, with a high level of accuracy reported.<sup>(12)</sup> Associated lymphadenopathy, tumour extension into the liver, involvement of the biliary tree and evidence of haematogenous metastasis are readily diagnosable on contrast-enhanced CT.

Magnetic resonance (MR) imaging is a sensitive modality for detection and evaluation of gallbladder carcinoma and its local



extent.<sup>(1)</sup> However, due to the issues of cost and availability, MR imaging is usually not the imaging modality of choice in the initial evaluation of the gallbladder. It is helpful in cases of focal or diffuse mural thickening to distinguish gallbladder carcinoma from benign conditions such as adenomyomatosis and chronic cholecystitis.<sup>(3,13)</sup> In addition, the T1 signal intensity contrast between the tumour and surrounding tissues provides valuable information in the detection of direct tumour invasion when US and CT findings are inconclusive.<sup>(1)</sup> For example, the presence of a normal fat signal intensity between the gallbladder and duodenum would exclude invasion of the duodenum. In general, gallbladder tumour is hypointense on T1-weighted images and hyperintense on T2-weighted images relative to the liver parenchyma.<sup>(1)</sup> Enhancement characteristics are similar to those of contrast-enhanced CT (early enhancement in arterial phase with slow contrast washout in the subsequent phases).

Positron-emission tomography with fluorodeoxyglucose (FDG-PET) is useful in the follow-up of gallbladder carcinoma for detection of disease recurrence as well as occult nodal disease or distant metastasis. A common clinical setting in which PET is particularly helpful is when there is clinical or laboratory evidence of disease progression but inconclusive evidence in other imaging studies. Disease recurrence or distant metastases appear as foci of increased FDG uptake. PET is less useful in the initial diagnosis of gallbladder carcinoma, as it lacks specificity in distinguishing primary gallbladder carcinoma from other malignant lesions. Benign condition such as xanthogranulomatous cholecystitis may give rise to false positive result as well.<sup>(14)</sup>

Surgery provides the best hope of cure in patients with localised disease. Depending on the extent of local disease, surgical options range from simple cholecystectomy to radical cholecystectomy, including variable degrees of hepatic resection and regional lymph nodes dissection. With regard to post-surgical adjuvant chemotherapy and radiotherapy, existing data for their effectiveness in preventing local disease recurrence and improving overall survival shows mixed results, and treatment preference seems to differ from centre to centre.<sup>(15)</sup> In patients with non-resectable disease, palliative care is offered. The goal of palliation is to relieve pain, jaundice and bowel obstruction. Significant symptomatic benefit can often be achieved by relieving biliary obstruction, which can be done via percutaneous transhepatic radiologic catheter bypass or endoscopically placed stents. Chemotherapy and radiation therapy are other potential options for regional palliation in reducing tumour size and the associated mass effect. However, there is again insufficient data to fully justify either of the treatment options as standard care.<sup>(15)</sup>

In summary, gallbladder carcinoma is a rare but aggressive tumour with poor prognosis. Various cross-sectional imaging modalities have a vital role in making the diagnosis and guiding the treatment path. Although early disease is curable, diagnosis is often delayed due to vague symptoms and various benign conditions that can mimic early gallbladder carcinoma. Knowledge of the various appearances of gallbladder carcinoma on imaging is important

for the reporting radiologist in making the diagnosis or raising the suspicion of possible malignancy, although detection of early disease remains a challenge.

**ABSTRACT** A 45-year-old woman presented with generalised body itch, dark-coloured urine and pale stools for six day. Ultrasonography, endoscopic retrograde cholangiopancreatography and computed tomography revealed dilated intrahepatic ducts with stricture at the proximal common bile duct. The gallbladder was replaced by a large heterogenous mass invading the liver and common bile duct. She underwent gallbladder resection, right hemihepatectomy, Whipple procedure, portal vein resection and reconstruction. Histopathology revealed diffusely infiltrating adenocarcinoma of the gallbladder. The patient made satisfactory postoperative recovery. The imaging features of gallbladder carcinoma are discussed.

*Keywords:* computed tomography, gallbladder carcinoma, magnetic resonance imaging, positron emission tomography, ultrasonography  
*Singapore Med J 2012; 53(1): 70-74*

## ACKNOWLEDGEMENT

The authors thank Dr. Elizabeth Fe Dacanay, Pathology Department, Khoo Teck Puat Hospital for providing Figs. 2a & b.

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## SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

(Code SMJ 201201B)

**Question 1.** Concerning gallbladder carcinoma:

- (a) It is usually diagnosed early.
- (b) It is prevalent among adolescence and young adults.
- (c) Women are more commonly affected.
- (d) Adenocarcinoma is the least common histologic subtype.

**Question 2.** Predisposing risk factors of gallbladder carcinoma include:

- (a) Porcelain gallbladder.
- (b) Chronic biliary infection.
- (c) Primary sclerosing cholangitis.
- (d) Cholelithiasis.

**Question 3.** Concerning imaging of gallbladder carcinoma:

- (a) Diagnosis can be made on plain abdominal radiograph.
- (b) Gallbladder mass is poorly visualised by computed tomography.
- (c) Mural irregularity and asymmetric wall thickening on ultrasonography images indicate benign aetiology.
- (d) Gallbladder carcinoma shows less contrast washout in the portal venous and delayed phases compared to hepatocellular carcinoma.

**Question 4.** The following are common patterns of sonographic findings in gallbladder carcinoma:

- (a) An extra-luminal mass.
- (b) Comet tail artefacts arising from the gallbladder wall.
- (c) A mass occupying or replacing the gallbladder.
- (d) Focal or diffuse thickening of the gallbladder wall.

**Question 5.** Concerning magnetic resonance (MR) imaging and positron emission tomography (PET) in the workup of gallbladder carcinoma:

- (a) MR imaging is the modality of choice in the initial workup of patients with suspected gallbladder carcinoma.
- (b) MR imaging is useful in determining local extend of gallbladder carcinoma.
- (c) Gallbladder tumours are usually hypointense relative to the liver parenchyma in both T1- and T2-weighted images.
- (d) PET is highly specific in differentiating gallbladder carcinoma from benign inflammation involving the gallbladder.

True False

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