Pediatr Radiol (1999) 29: 53–55

Clara G. C. Ooi
Kwong L. Chan
Wilfred C. G. Peh
Htut Saing
Henry Ngan

Confluent hepatic fibrosis in monozygotic twins

Received: 14 November 1997
Accepted: 15 June 1998

C.G.C. Ooi · W.C.G. Peh · H. Ngan
Department of Diagnostic Radiology,
The University of Hong Kong,
Queen Mary Hospital, Hong Kong

K.L. Chan · H. Saing
Department of Surgery,
The University of Hong Kong,
Queen Mary Hospital, Hong Kong

C.G.C. Ooi (✉)
Department of Diagnostic Radiology,
The University of Hong Kong, Room 405,
Block K, Queen Mary Hospital,
Pokfulam Road, Hong Kong

Abstract The MRI and CT features of confluent hepatic fibrosis (CHF) are reported in two 6-year-old twins. This is the first case report in children of this little known entity, which may mimic mass lesions, and the first to describe an association of CHF with anti-tuberculous drugs.

Introduction

Previous reports of confluent hepatic fibrosis (CHF) have invariably had to do with adults with liver cirrhosis, with characteristic computed tomography (CT) and magnetic resonance (MR) imaging features [1, 2]. The etiology of this condition is unknown with no known associations with drugs. We report the CT and MT imaging findings of CHF occurring in monozygotic twins after anti-tuberculous therapy. This represents the first reported case of CHF in children and the first description of an association with anti-tuberculous drugs.

Case report

Two 6-year-old Filipino monozygotic twin boys presented simultaneously with jaundice 4 months after starting rifampicin and isoniazid 200 mg daily each for tuberculous contact. They had previously been treated with the same drugs for tuberculosis (TB) prophylaxis at 1 year of age without known complications. Both had completed the usual childhood course of vaccinations, including hepatitis B. There was no history of regular medication. Mild hepatomegaly was found on physical examination, with no other abnormal findings. Both twins had mildly elevated total bilirubin and alkaline phosphatase and markedly elevated transaminases. Haematological screening and α-fetoprotein levels were normal. Anti-TB drugs were stopped in view of the jaundice.

US showed abnormal heterogeneous areas in the left lobe of the liver in both twins. Helical dynamic contrast-enhanced CT of the liver (40 ml Omnipaque 300 mg/ml, 1.2 ml/s) with image acquisition after 25-s, 70-s and 10-min delays were performed. In twin 1, an atrophied medial segment of the left lobe of liver was seen, with capsular retraction and low-attenuation bands radiating to the liver hilum (Fig. 1 a). These bands became iso-attenuating after a 25-s delay but showed high attenuation during the second (70-s) phase (Fig. 1 b), with persisting enhancement on delayed images. On spin-echo (SE) T1-weighted (T1-W) and fast SE (FSE) T2-weighted (T2-W) MR images, the low-attenuation areas were hypo- and hyperintense, respectively (Fig. 2 a,b). These radiating band lesions were iso-intense on dynamic post-gadolinium-DTPA (Gd) fast spoiled gradient-echo (FSPGR) images acquired over 3.5 min but demonstrated marked enhancement on SE T1-W post-Gd images acquired after a 10-min delay (Fig. 2 c). The spleen and remainder of the liver were normal. In twin 2, the left lobe was markedly atrophied and consisted of a low-attenuation thin wedge of tissue with caudate lobe hypertrophy on unenhanced CT. This tissue also extended into the subcapsular area of the anterior segment of the right lobe (Fig. 3). The CT enhancement pattern and MR imaging characteristics were similar to those of twin 1.

The imaging features in both twins suggested a selective fibrotic process affecting the left lobe of the liver causing atrophy but did not correlate with known radiological descriptions of paediatric

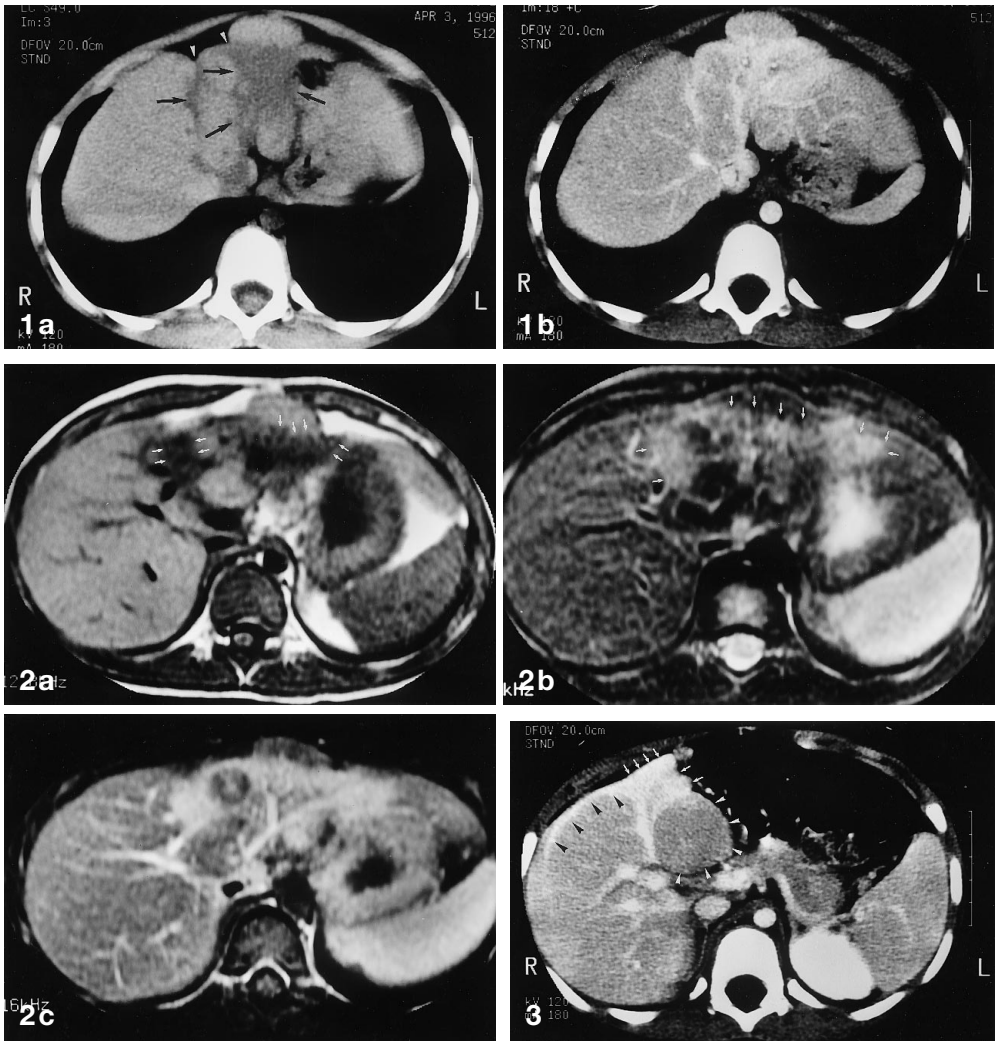

Fig. 1 **a** Unenhanced CT scan of twin 1 shows low-attenuation bands (*arrows*) radiating to the hilum in the medial segment of the left lobe. Note capsular retraction (*arrowheads*). **b** Postcontrast dynamic CT acquired 70 s after contrast administration. There is marked enhancement of these radiating bands

Fig. 2 **a** SE T1-W (TR/TE, 600/11) axial image in twin 1 demonstrates a lobulated medial segment of the left lobe, with hypointense bands (*arrows*) radiating to the hilum. **b** FSE T2-W (TR/TE, 2900/96) axial image shows that the radiating bands appear hyperintense (*arrows*). **c** SE T1-W (TR/TE, 580/24) axial image 10 min after Gd-DTPA administration shows intense enhancement of these band-like lesions

Fig. 3 Postcontrast dynamic CT of the liver of twin 2 acquired after a 70-s delay. There is marked left lobe atrophy, with intense enhancement of abnormal radiating band-like tissue (*small arrows*) extending into the subcapsular regions of the anterior segment of the right lobe (*black arrowheads*). Note the caudate lobe hypertrophy (*white arrowheads*)

neoplastic or inflammatory diseases. Confluent hepatic fibrosis (CHF) was considered the most likely radiological diagnosis, despite the lack of cirrhotic changes in the rest of the liver. Conservative management was adopted, and the twins' liver function returned to normal a few months after cessation of anti-TB therapy. A 6-mm core of liver tissue, obtained from a CT-guided liver biopsy performed on twin 1 12 months after initial presentation (automatic disposable 16-G, guillotine Temno needle, Bauer, Italy), confirmed portal fibrous septa traversing the specimen core and mild lymphocytic and neutrophilic subcapsular connective tissue infiltration. There was no evidence of steatosis, increased iron or copper deposition, α-antitrypsin body or cholestasis. The CT appearances of the liver are unchanged, and both twins remain well 2 years after presentation.

Discussion

Ohtomo et al. [1, 2] were the first to characterise CHF lesions by shape and location on MR and CT imaging into (a) wedge-shaped lesions radiating from the porta hepatis, (b) peripheral and band-shaped lesions remote from the porta hepatis and (c) total lobar or segmental involvement. The lesions in the twins would fall into the first and third classifications. The medial segment of the left lobe and anterior segment of the right lobe are most commonly involved by wedge-shaped lesions, while lobar or segmental involvement most commonly occur in the lateral segment of the left lobe [1]. Capsular retraction and volume loss are common associations [1, 2]. These lesions are low attenuation relative to normal liver tissue on unenhanced CT. However, on enhanced CT with image acquisition after a 40-s delay, most lesions are iso- to low attenuation, with a minority being high attenuation [1].

MR imaging characteristics are similar to fibrotic scars within liver tumours, being hypointense on T1-W and hyperintense on T2-W images [2–4]. As with CT, a variable MR enhancement pattern is seen, with lesions which were initially hypointense on the early phase of

dynamic scanning becoming iso-intense on the delayed images [2]. These findings suggest that CHF lesions have minimal or no enhancement in the early phases of contrast imaging, a fact which is substantiated by the present MR and CT findings. The lesions in both twins demonstrated intense enhancement on the second phase of dynamic CT scanning and on the post-contrast SE T1-W series. This enhancement pattern is also seen in intratumoral scars and post-hepatic necrosis [3–5] and may be due to pooling of contrast material within oedema and/or non-arterial vascular channels within the fibrotic lesions [2]. We believe that CHF encompasses a spectrum of hepatic fibrosis resulting from various chronic and subacute hepatic damage including post-necrotic scarring [1, 2, 5]. Although the initial description of CHF was in patients with cirrhosis undergoing liver transplantation, liver scarring per se can be seen without cirrhotic change [5, 6]. The mechanism of variable enhancement pattern is unknown but may be related to the degree of vascularity, collagen and inflammation present [3–5].

The cause of fibrosis in the twins is speculative because no underlying chronic liver diseases, congenital causes or viral hepatitis was evident in either patient. The most likely aetiology would be related to drug-induced hepatitis secondary to rifampicin and isoniazid. Isoniazid in particular induces hepatitis and cirrhosis in adults and children by the cytotoxic action of its toxic metabolite, hydrazine [7]. Rifampicin further induces hydrazine production if used in conjunction with isoniazid. By itself, rifampicin rarely results in hepatitis, causing only cholestatic injury by inhibition of hepatocyte bilirubin transport [7]. However, there has been no known link between CHF and these drugs. The reason for the apparent selective involvement of the left lobe and anterior segment of the right lobe in the twins is unclear, but preferential fibrotic involvement of the right lobe with sparing of the caudate lobe in cirrhotic livers has been observed [8]. This preferential susceptibility to toxicity may be related to differential vascular supply in the liver [8].

Although hepatocellular carcinoma and cholangiocarcinoma may show similar wedge-shaped lesions, the twins' youth would make these diagnoses highly improbable. The lack of early enhancement on contrast-enhanced CT and MR imaging is also uncharacteristic of hepatocellular carcinoma. Two other possible diagnoses are hepatic infarction and epithelioid haemangioendothelioma. Hepatic infarction is usually wedge-shaped and can be distinguished from CHF by rim enhancement on enhanced CT [1, 5]. The presence of normal hepatic vasculature and the absence of haematological diseases or other predisposing causes of vascular insufficiency should also help differentiate CHF from infarction. Epithelioid haemangioendothelioma is usually peripheral, low attenuation on unenhanced CT and associated with capsular retraction, features similar to those of CHF [9]. However, epithelioid haemangioendothelioma is almost exclusively found in adults and is usually multifocal and nodular and demonstrates peripheral enhancement on CT and MR imaging [9].

This report highlights the possible sequelae of chronic drug-induced hepatic damage associated with TB prophylaxis in infants and young children. However, a racial or genetic predisposition to drug-related injury may have been a factor in these twins. The presence of low-attenuation bands which radiate to the hepatic hilum on unenhanced CT with capsular retraction and/or lobar atrophy in the absence of other evidence of tumours or infarction in children should point to the possible diagnosis of CHF. Contrast imaging with either CT or MR imaging should further substantiate the diagnosis.

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