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Rare pulmonary complications after transarterial chemoembolisation for hepatocellular carcinoma: two case reports

以肝動脈化療栓塞治療肝細胞癌後出現罕見的肺併發症：兩宗病例報告

We report two rare cases of acute pulmonary complication after transarterial chemoembolisation for inoperable hepatocellular carcinoma. Both cases involved a large tumour and hepatic vein invasion. The first patient, a 27-year-old man, died of pulmonary tumour embolism 4 days after transarterial chemoembolisation. Acute dyspnoea developed in the second patient, a 63-year-old man, following the procedure due to pulmonary oil embolisation and chemical pneumonitis. The chest condition of this patient improved, but he subsequently died of liver failure 3 weeks later. Our cases illustrate the point that if locoregional treatment is offered as a palliative treatment, patients with hepatic vein invasion should be warned of the possible complications of massive tumour embolism, pulmonary oil embolisation, and subsequent death.

我們報告兩宗罕見的病例，病人在接受肝動脈化療栓塞以治療不能手術切除的肝細胞癌後，出現急性肺部併發症。兩宗病例皆與大型腫瘤及肝靜脈侵襲有關。第一名病人是一名27歲男性，他在接受肝動脈化療栓塞四天後死於肺腫瘤栓塞。第二名病人為63歲的男性，因肺碘油栓塞及化學性肺炎在療法後出現急性呼吸困難。該名病人的胸部狀況有改善，但於三週後死於肝衰竭。我們的病例顯示利用局部性治療作為緩解性療法，應向患有肝靜脈侵襲的病人提醒可能出現的併發症，如大型腫瘤栓塞及肺碘油栓塞，以及因此引致死亡的可能性。

Key words:
Carcinoma, hepatocellular;
Chemoembolization, therapeutic;
Complications;
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關鍵詞：
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Introduction

Hepatocellular carcinoma (HCC) is common in Asia, and most cases are inoperable because of late presentation and underlying cirrhosis. Typical management of HCC is by transarterial chemoembolisation (TACE), which, for patients with large or advanced tumours, tumour may be palliative and can prolong survival. Hepatocellular carcinoma has a tendency to invade the portal and hepatic veins, and vascular invasion is a poor prognostic factor for survival. However, TACE may still be given in such cases, because tumour inside the veins may respond to treatment.[1-3]

Case reports

Case 1

A 27-year-old man presented to the Department of Medicine at the Queen Elizabeth Hospital in June 1999 with right upper quadrant pain and weight loss. He was a hepatitis B carrier. The α-fetoprotein level was 811 000 U/L, and ultrasonography revealed the presence of a 10-cm mass in the posterior segments of the right lobe. The right portal vein and the inferior vena cava (IVC) were compressed, and Doppler ultrasonography showed that they were patent; the hepatic veins were not visible, however, and definite tumour thrombus was absent

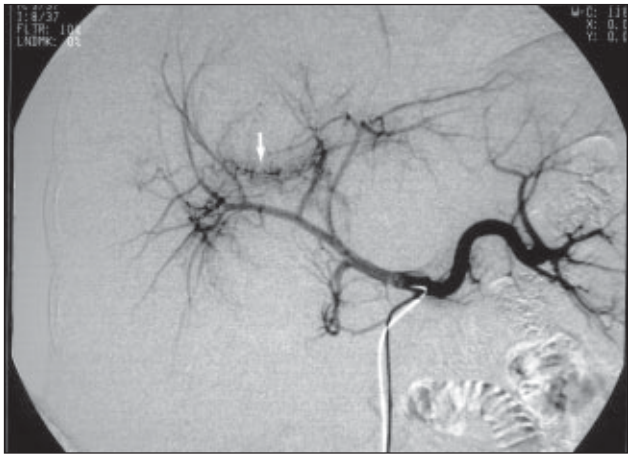

Fig 1. Coeliac angiogram in case 1 before transarterial chemoembolisation, showing arterio-hepatic venous shunt during the early phase and tumour in the right hepatic vein (arrow)

from the IVC. A 1.5-cm mass was also present in the left lateral segment. These clinical signs indicated that the patient had inoperable HCC; he had Child-Pugh class A cirrhosis and an Okuda stage II tumour. Thus, TACE was offered to the patient.

Angiography showed an arterio-hepatic venous shunt and tumour in the right hepatic vein (Fig 1). Multiple smaller masses were present in both lobes. The main portal vein and the left portal veins were patent. An emulsion of Cisplatin (Delta West Pty Ltd, Bentley, West Australia) [8 mg in 8 mL of normal saline] and 10 mL of lipiodol (Lipiodol Ultrafluide; Laboratoire Guerbet, Anlnay-sous-Bois, France) was prepared, and 22 mL of the mixture was administered intra-arterially to the right hepatic artery; 14 mL was also administered to the left hepatic artery, followed by Gelfoam (Johnson & Johnson Medical Ltd, Skipton, UK). The patient experienced right upper quadrant pain after TACE. Four days later, he experienced sudden cardiac arrest, but cardiopulmonary resuscitation failed. Postmortem examination showed a 1-cm necrotic tumour embolus in the right pulmonary artery; multiple small tumour emboli were also present in the right pulmonary arterial branches. Tumour invasion was evident in the right side of the IVC: at 1 cm in thickness, the tumour was fragile and partially necrotic. There was no intraperitoneal haemorrhage.

Case 2

A 63-year-old man, also a hepatitis B carrier, presented to the Department of Medicine at the Queen Elizabeth Hospital in September 2001 with right upper quadrant pain. The α-fetoprotein level was 7073 U/L. Computed tomography (CT) showed a 15-cm tumour mass involving both lobes of the liver. A tumour thrombus was present in the right portal vein and right hepatic vein (Fig 2a); however, the main portal vein and left portal vein were patent. A diagnosis of HCC was made, with Child-Pugh class A cirrhosis and an Okuda stage II tumour. Consequently, TACE was offered as a palliative treatment.

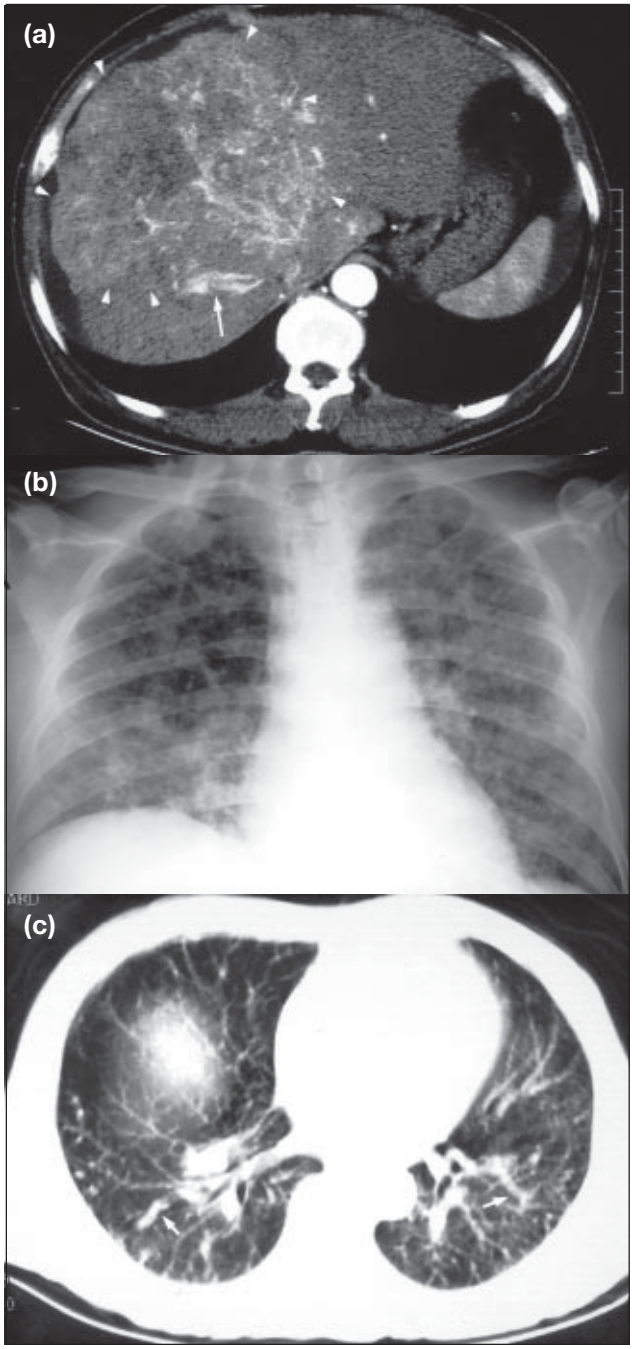

Fig 2. Computed tomography and X-ray findings in case 2
(a) Computed tomogram of the liver before embolisation treatment during the arterial predominant phase, showing a large tumour involving both lobes of the liver (arrowheads); arterial enhancement is present in the right hepatic vein (arrow), owing to tumour invasion. (b) Chest X-ray 1 day after embolisation treatment, showing increased reticular shadows in both lungs and increased involvement of the lower zones. (c) Computed tomogram of the lower thorax showing persistent bronchoalveolar thickening 2 weeks after embolisation treatment (arrows), most likely related to lipiodol-induced pneumonitis

There was no obvious arterio-hepatic venous shunt in the angiogram. A mixture of Cisplatin and lipiodol (30 mL, in the same composition as that used in case 1) was given. On the next day, acute dyspnoea developed. There was decrease in oxygen saturation (to 89%) and the chest X-ray

showed an increased reticular shadow in both lungs, especially in the lower zones (Fig 2b). Before TACE, the chest X-ray and CT scan of the lung base were normal. The clinical diagnosis was pulmonary oil embolisation causing pneumonitis. The patient's condition subsequently improved after 2 weeks and the X-ray findings gradually became normal. A set of CT scans was performed to assess the effect of treatment on the liver. However, a CT scan of the lung base still showed bronchoalveolar thickening (Fig 2c). The patient died of liver failure 1 week later. A postmortem examination was not performed.

Discussion

Transarterial chemoembolisation is widely used in the treatment of HCC, and treatment complications have been reported in the literature.[4-6] Apart from systemic complications, most other complications are confined to the abdomen and are related to the delivery of the chemotherapeutic drugs to the tumour or non-tumour area below the diaphragm. Pulmonary complications are uncommon. We encountered two rare pulmonary complications, which were probably associated with hepatic vein invasion by the primary tumour. In the first case, massive pulmonary embolus was due to a detached tumour after TACE, and in the second case, pulmonary oil embolisation occurred after injection of less than 20 mL of lipiodol.

Pulmonary tumour embolism from HCC is uncommon. The true incidence is unknown and it is usually not recognised until the postmortem examination. Most reported cases also involve death due to various malignancies.[7,8] In one study, of 79 deaths from HCC,[9] there were six (8%) cases of significant pulmonary tumour embolism; this was the primary cause of death in five (6%) cases. A further seven cases of HCC had progressed to invasion of the major hepatic vein and IVC, and significant pulmonary tumour embolism occurred in three (43%) of these cases. Reports of pulmonary tumour embolism after TACE are extremely rare. In one case in Japan,[10] the patient was suspected to have pulmonary emboli from necrotic hepatic vein and a tumour thrombus in the IVC, which occurred 20 days after TACE. The patient in our first case had a tumour thrombus in the hepatic vein; the IVC was compressed but patent. Although postmortem examination showed IVC invasion, this was not detectable during ultrasonography; the reason may be related to the plaque-like appearance of the tumour invasion and the large tumour size obscuring part of the view. Acute tumour embolism developed 4 days later, which was confirmed at the postmortem examination, and necrosis inside the tumour embolism suggested that the condition was related to TACE.

As for pulmonary complication and pulmonary oil embolisation after TACE, the first related incidence was reported in 1990 in a 75-year-old man,[11] who received 8 mL of lipiodol plus 40 mg of adriamycin. Because pulmonary oedema developed 30 minutes after the infusion, the authors concluded that the complication was due to a large amount of adriamycin flowing into the pulmonary artery via the arterio-venous shunt. In the subsequent study that reported specific pulmonary complications,[12] symptomatic pulmonary oil embolism developed in six of 336 patients receiving TACE; all six patients had received more than 20 mL of lipiodol. The symptoms were cough, haemoptysis, and dyspnoea, which developed 2 to 5 days after TACE; chest X-rays showed diffuse bilateral pulmonary parenchymal infiltration. Although there was no histological proof, the symptoms and signs, the radiological manifestation and the clinical course were similar to oil embolisation after lymphangiography, hysterosalpingography, and urethrography performed with administration of iodized oil. The authors concluded that massive pulmonary embolisation of iodized oil was the primary cause and recommended injection of less than 20 mL of lipiodol in subsequent procedures involving TACE.

Furthermore, in Japan,[13] three of 13 patients had perfusion defects detected in lung scans, but all three were asymptomatic. A similar effect was seen in four of 2300 patients undergoing TACE procedures[14]; three of the four patients were clinically insignificant cases and in the remaining patient, TACE was performed via the right inferior phrenic artery.

The patient in our second case was different from the previously reported cases in one aspect. He developed symptomatic pulmonary oil embolisation after receiving 30 mL of a mixture of Cisplatin and lipiodol—that is, approximately 17 mL of lipiodol, which is less than 20 mL recommended by Chung et al.[12] Our case involved hepatic vein invasion and, although we could not detect an obvious arterio-venous shunt, his condition may have had a higher chance of leakage of the agent into the hepatic vein and then into the pulmonary circulation, thus causing pulmonary oil embolisation.

One way to prevent excessive pulmonary oil embolisation is to calculate the degree of intrahepatic arteriovenous shunting with technetium Tc 99m–labelled macroaggregated albumin (99mTcMAA). This method is used during patient screening for intra-arterial injection of radioactive yttrium Y 90 microspheres in unresectable cases of HCC.[15,16] The 99mTcMAA is injected intra-arterially in the hepatic artery and the lung regions are then scanned for radioactivity. This protocol will exclude patients with excessive shunting of the yttrium-90 microspheres to the lung, which would cause lethal or debilitating irradiation pneumonitis. The same principle may be used if injection of a large dose of lipiodol is expected. However, this method may not be used for every patient receiving TACE, because this complication is rare and an additional investigation will incur extra cost. In selected cases, especially when there is hepatic vein invasion, this precautionary measure may prevent a severe complication.

The prognosis in HCC patients with vascular invasion is usually poor. Still, TACE may be offered to suitable patients in response to locoregional chemotherapy. Our cases illustrate the point that if locoregional treatment is offered as a palliative treatment, patients with hepatic vein invasion should be warned of the possible complications of massive tumour embolism, pulmonary oil embolisation, and subsequent death.

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