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CASE REPORT

Spontaneous Liver Rupture After Treatment With Drug-Eluting Beads

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Abstract Spontaneous rupture of hepatocellular carcinoma (HCC) after transcatheter arterial chemoembolization (TACE) is a rare and life-threatening complication. Pathophysiologic mechanisms are not yet fully known; it is suggested that rupture is preceded by reactive tissue edema and intratumerous bleeding, leading to a rapid expansion of tumour mass with risk of extrahepatic bleeding in the case of subcapsular localisation. This case report discusses a sudden, unexpected lethal complication in a 74 year-old male patient treated with TACE using DC Bead loaded with doxorubicin (DEBDOX) in a progressive multifocal HCC.

Keywords Interventional oncology · Chemoembolization/chemoembolisation · Embolization/embolisation/embolotherapy · Transarterial chemoembolization/embolisation (TACE) · Liver/hepatic · Hepatocellular carcinoma (HCC) · Tumor/tumour/neoplasm

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Introduction

Transcatheter arterial chemoembolization (TACE) of the liver is recommended by the Society of Interventional Radiology as a first-line treatment for inoperable hepatocellular carcinoma (HCC) in patients exceeding the Milan or University of California San Francisco criteria but still having well-preserved liver function [1]. Recent randomized trials have shown statistical survival benefits of TACE in patients with unresectable HCC compared with supportive care or systemic chemotherapy [2]. The combination of dearterialization of the tumour and selective delivery of chemotherapeutic agents to the tumor can be realized either by the use of iodized oil, chemotherapeutics, and bland particles or by use of drug-eluting microspheres. DC Bead (Biocompatibles, Farnham, Surrey, UK) microspheres are a new embolic material for TACE, in which the embolization particles are made from a unique drug-eluting bead (DEB) technology based on a polyvinyl alcohol hydrogel modified with sulfonate groups [3]. In HCC, DC Bead microspheres are often loaded with doxorubicin (DEBDOX), a chemotherapeutic anthracycline glycolide agent [4]. Delivery of the loaded beads into the feeding vessels of the target tumor usually leads to lumen occlusion and ischemia, and doxorubicin is gradually released locally, leading to tumor necrosis. Animal studies have shown that the characteristics of DEBDOX make it a highly suitable device for TACE because a single embolizing agent (i.e., loaded beads) achieves both local ischemia and increased local chemotherapeutic concentrations with fewer general side effects. As shown in the Precision V Study, TACE with DC Bead and doxorubicin is safe and effective in the treatment of intermediate-stage HCC and offers benefit to patients having more advanced disease [5]. We report a case of

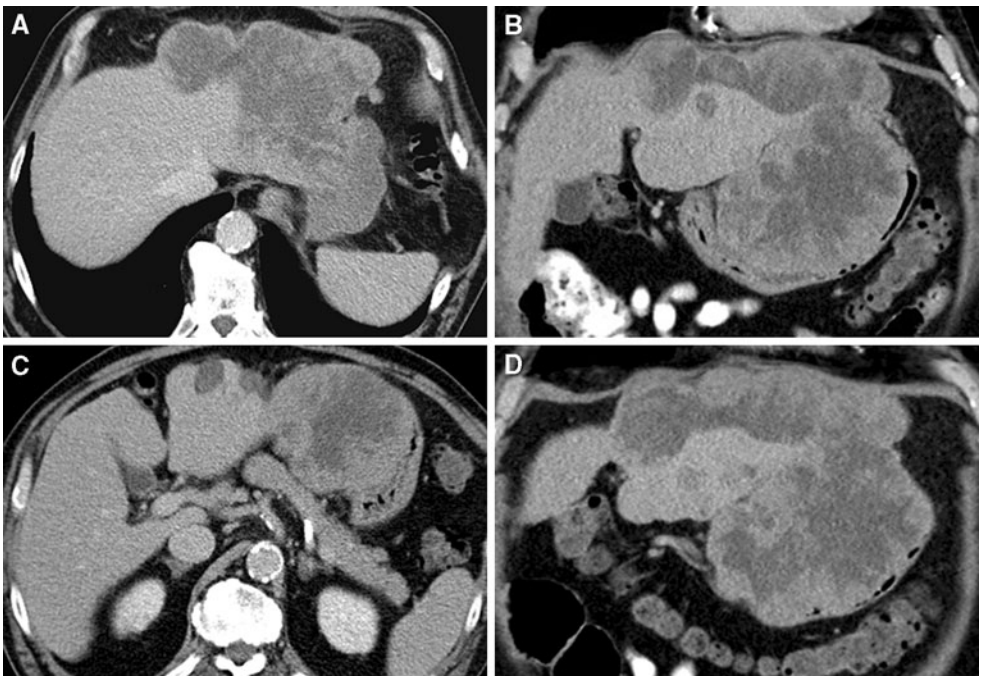

Fig. 1 (**A** and **C**) Axial and (**B** and **D**) coronal CT scan of the *upper* abdomen (portal–venous phase) showing a large tumour mass in the *left liver* lobe with partial central necrosis bulging the small curvature of the stomach

fatal complication after DEBDOX in a patient with progressive multifocal HCC.

Case Report

A 74-year-old male patient with alcoholic liver cirrhosis (Child-Pugh class A) suffering from multifocal, unilobar hepatocellular carcinoma (Barcelona Clinic Liver Cancer class B, Okuda stage 2, Eastern Cooperative Oncology Group status 0) was referred to our hospital for palliative treatment with TACE. After the first diagnosis of two HCC lesions 18 months previous, the patient had been successfully treated with radiofrequency ablation (RFA) in a different hospital. On a recent computed tomography (CT) scan, progressive HCC masses of segments III and IVb, measuring $\leq 16 \times 9 \times 7$ cm, were diagnosed (Fig. 1). The patient's further medical history showed peripheral artery disease (Fontaine group II b), hypertension, diabetes, chronic obstructive lung disease, and previous prostate cancer surgery. Laboratory results, including white blood cell count and neutrophils in addition to cholinesterase (3757/l [normal 5320 to 12920]), aspartate aminotransferase (88.6/l [normal $\leq$ 50]), gamma-glutamyl transferase (116/l [normal $\leq$ 60]), lactate dehydrogenase (410/l [normal $\leq$ 250]), haemoglobin (11.3 g/dl [normal 14 to 18]), and alpha fetoproteine (33305 µg/l [normal 0 to 7]), were normal.

Access for TACE was performed under sterile conditions, with the patient under local anaesthesia, by way of the right common femoral artery using a 5F sheath (Radifocus Introducer II; Terumo, Tokyo, Japan) in a retrograde fashion. After imaging the abdominal aorta with a 5F Soft-VU pigtail catheter (AngioDynamics, Latham, NY), the superior mesenteric artery was fathomed with a 5F Beacon Tip Torcon NB C1 Advantage catheter (Cook, Bloomington, IL). Indirect portography did not show signs of portal–venous thrombosis. With the same catheter, the celiac trunk was imaged, and the catheter was placed in the common hepatic artery using an angled hydrophilic 0.035 inch Radifocus guidewire (Terumo). With a 2.7F microcatheter system (Progreat; Terumo), the left hepatic artery was cannulated. High-pressure contrast injection showed many small feeding vessels of the capacious tumour burden in liver segments III and IVb (Fig. 2A). The presence of arteriovenous shunts or extrahepatic collateral vessels could be excluded. Before embolization a 5-HT3 inhibitor (8 mg ondansetron; a potent central antiemetic) as well as an opiod (200 mg tramadol; for pain relief during and after treatment) were administered intravenously. In addition, 50 mg pethidine was injected intra-arterially by way of the microcatheter to decrease local pain and discomfort owing to liver capsule tension during embolization. To minimize local tissue edema, we injected a glucocorticoid (20 mg dexamethasone) in advance. Before and after embolization, sufficient IV hydration was provided. The microcatheter was inserted to the level of segmental arteries III and IV followed by successive injection of two vials of 300–500 µm (4 ml) DC Bead (Biocompatibles, Surrey,

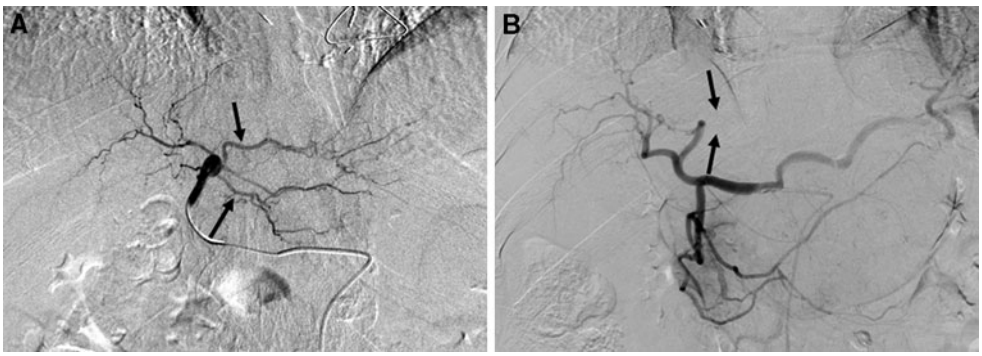

Fig. 2 (**A**) Selective angiography of the *left liver* lobe before chemoembolization indicating numerous feeder vessels. (**B**) Angiographic overview of the celiac trunk after chemoembolization revealing complete devascularization of the DEBDOX-treated *left liver* lobe and preservation of flow to the untreated *right liver* segments

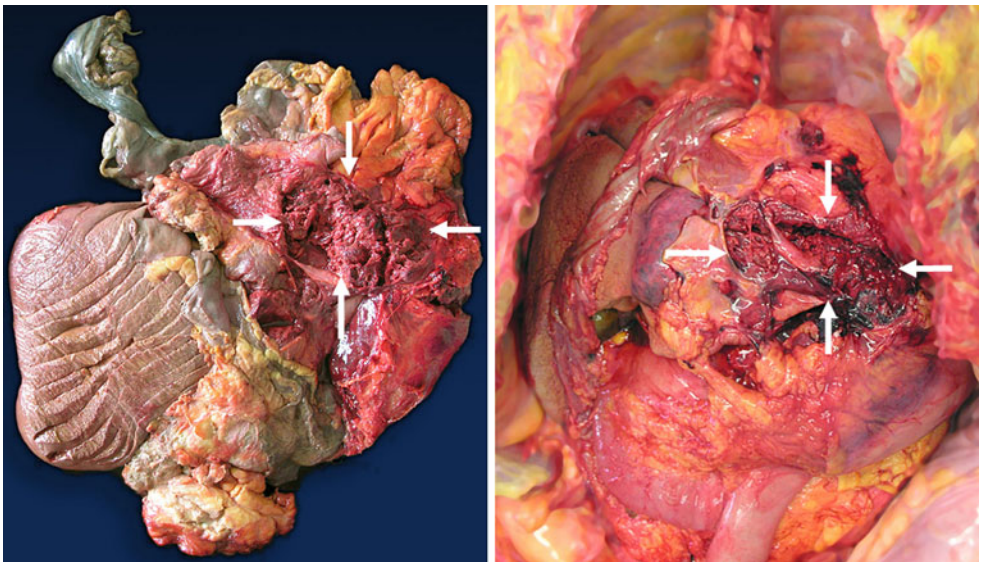

Fig. 3 Macroscopic images of the autopsy situs (*right*) and liver preparation (*left*). The bleeding source was located on the diagphragmatic side of the *left liver* lobe (segment III) where an extensive tumour rupture with concomitant perforation of the liver capsule was recognized (*white arrows*)

UK) loaded with 50 mg doxorubicin/vial mixed with non-ionic contrast medium (Imeron 300; Bracco-Altana, Konstanz, Germany). The procedure was terminated at the point of stop-flow within the main feeding vessels (Fig. 2B). Accession site was compressed manually for 15 min, after which a pressure dressing was applied for 24 h.

Approximately 14 h after treatment, the patient was found inanimate on the ward. After initially successful repeated cardiopulmonary resuscitation, the hemodynamically instable patient was transferred to the intensive care unit. There, an emergency ultrasound of the abdomen showed moderate fluid accumulation in the upper abdomen, but no bleeding source was found in the groin or in the small pelvis. Further CT imaging was not possible because the patient was too instable. A decrease in haemoglobin from 11.3 to 4.2 mg/dl and an increase of lactate out of range lead to death from circulatory shock within a few hours.

Autopsy showed a massive intraabdominal haemorrhage >2 l as well as numerous clots covering the greater omentum and intestinal loops. Accordingly, the internal organs were pale. The bleeding source was located on the diaphragmatic side of the left liver lobe, where an extensive tumor rupture with concomitant perforation of the liver capsule had occurred from a 16.0 × 9.0 × 7.0 cm focus of a multifocal, widely necrotic, moderately differentiated HCC (Fig. 3). In the liver arteries and the gallbladder (Fig. 4), as well as sparsely in the haemorrhage (Fig. 5) scattered detection of DC Bead was possible. According to the pathologist, the patient died from excessive intraabdominal bleeding due to a ruptured focus of the multifocal HCC after TACE with DEBDOX.

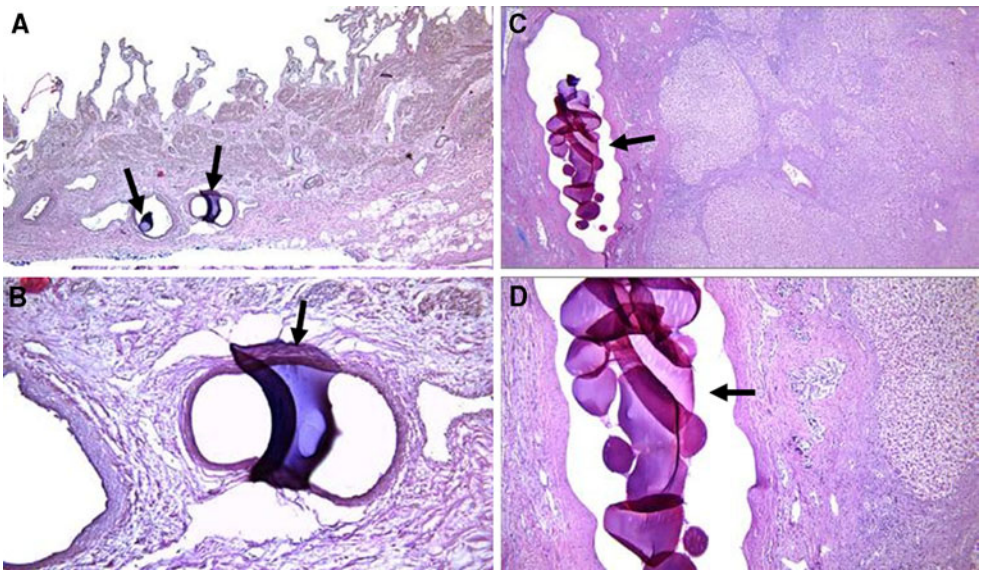

Fig. 4 (**A** and **B**) Microscopic images show particles of DC Bead (*black arrows*) in the wall of the gallbladder, indicating a minor backwash of particles, and (**C** and **D**) in the liver arteries of the *left liver* lobe

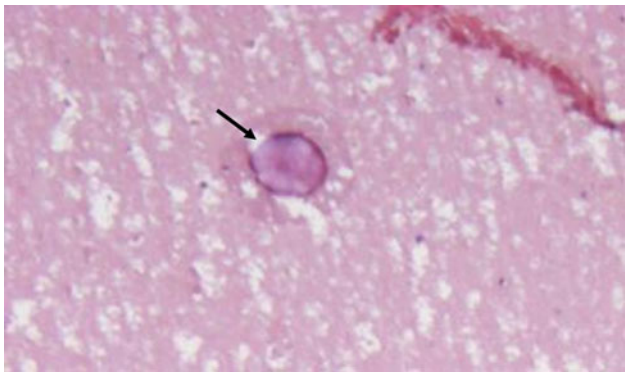

Fig. 5 Microscopic image (10 μm slice thickness) of an intra-abdominal haemorrhage sample with proof of a DC Bead particle (*black arrow*) supporting the diagnosis of free tumour rupture owing to DEBDOX therapy

Discussion

Oncologic embolotherapy of HCC with DEBDOX is a novel treatment technique. As palliative effect in patients with AngioDynamics, Latham unresectable HCC, TACE with DEB allows local tumour control in 15 to 60% of cases, and 5-year survival rates range from 8 to 43%. The potentially curative treatment option allows local tumor control from 18 to 63%. Among often-reported side effects of TACE with DEB is postembolization syndrome consisting of pain, fever, nausea, and a increase of liver enzymes (aspartate aminotransferase and alanine aminotransferase), whereas serum values >1,000 U/l are highly suggestive of liver failure and may require more intensive observation of the patient, thus incurring a prolonged hospital stay. Major complications, such as hepatic insufficiency or infarction, hepatic abscess, tumor rupture, bile duct injury, surgical cholecystitis, upper gastrointesinal bleeding, pulmonary embolism, splenic infarction or spinal embolization, are rare with a reported incidence of 3 to 4% and a 30-day mortality rate of 1 to 4% [6, 7]. Death due to tumor rupture after conventional TACE has been documented, usually in patients with large subcapsular tumours, with a reported incidence of <3% in Western countries [8, 9]. However, to the best of our knowledge, an acute fatal outcome after DEBDOX therapy, as in our patient, has not yet been reported. Increased intratumoural pressure, as a result of rapid edematic expansion due to tumor necrosis or vascular injury secondary to embolization, is thought to be the mechanism of late tumor rupture after conventional TACE [10]. Especially in cases of subcapsular lesions, there is a risk of intraperitoneal bleeding as well as peritoneal and mesenteric tumour cell spread. To minimize the risk of rupture, according to the Cardiovascular and Interventional Radiological Society of Europe *Clinical Practice Manual*, TACE should be avoided in patients with >50% tumor burden because there is evidence of a strong association with increased postprocedural morbidity and mortality. Although overall prognosis is poor, appropriate treatment of patients with ruptured HCC should consist of emergency transcutaneous arterial catheter embolization followed by emergency or staged hepatic resection if the lesion is technically resectable. As the first published data have shown show, DEB as a new drug-delivery system has proven to be extremely potent and safe by allowing large amounts of chemotherapeutic agent to concentrate within the tumor during a period of time, thereby maximizing the

cytotoxic effect, which also makes it attractive as an effective treatment for larger lesions. To our knowledge, no case of post-treatment liver rupture causing death after TACE with DEB has been reported until the present article. According to clinical literature, the matters of single treated tumour size and related potential of major complications have not yet been elucidated. In the published results of the Precision V Study, maximum lesion size was 9.4 cm ± 6.15 cm [5]. As a recent study showed, in the case of liver rupture typically there is no relationship between tumour size and severity of hemoperitoneum or tumour size and grade of cirrhosis [11]. It may be hypothesized that previous treatment with RFA might have potentiated the risk of rupture due to partially disrupted tumour tissue architecture.

In conclusion, with regard to the clinical scenario described herein, it may be worth critically considering whether DEBDOX treatment should be generally performed at all in patients with large tumour diameter and extrahepatic tumour growth to avoid any risk of acute liver failure or sudden tumour rupture. Interventional radiologists as well as clinicians should be aware of such an extraordinary and fatal course of DEBDOX therapy to provide effective patient management.

Conflicts of interest The authors declare that they have no conflict of interest

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