Percutaneous ethanol ablation of hepatocellular carcinoma: Periprocedural onset alcohol toxicity and pancreatitis following conventional percutaneous ethanol ablation treatment

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A 73-year-old Asian man with hepatocellular carcinoma (HCC) was recently admitted to the multidisciplinary hepatobiliary service at the University of Toronto (Toronto, Ontario). In the summer of 2005, the patient received a renal sonogram to investigate suspected renal artery stenosis at which time a hypechoic hepatic lesion was discovered incidentally. The patient was further investigated with a contrast computed tomography (CT) abdominal scan in October 2005, which revealed a hypervascular hepatic mass 7 cm × 6 cm in size, consistent with HCC or a solitary metastasis (Figure 1). At that time, the patient was asymptomatic. Relevant medical history included a diagnosis of hepatitis B that was acquired by means unknown to the patient; otherwise, his medical history was unremarkable.

The patient was referred to our department, and due to the inability to resect the tumour because of its proximity to the porta hepatis, he received routine chemoembolization treatment of the lesion in December 2005. The patient was discharged home shortly thereafter with no complications. Immediately preceding the time of the most recent admission and subsequent to a three-month follow-up with the patient’s referring physician, three foci of HCC were identified with no portovenous shunting on selective catheterization angiogram (Figure 2). At the time of the most recent admission, the three HCC lesions were treated with percutaneous ethanol injection (PEI). By using continuous, real-time ultrasound (US) guidance with a 3.5 MHz convex probe, a 22-gauge, 20 cm needle (Ecoject, HS, Japan) was inserted into the deepest portion of each nodule and 95% sterile ethanol was slowly injected. Intranodular diffusion of the ethanol was assessed by the characteristically intense hypechogenicity induced by the alcohol, detected by real-time US scanning during the injection. The needle was then partially withdrawn and the more superficial parts of the nodules were injected. The needle was completely withdrawn thereafter and another puncture with a new needle was performed to inject other parts of the lesion that had not been perfused with ethanol. Multiple punctures were performed until the nodule appeared homogeneously hypechoic. Lesion 1 (primary lesion spanning segments 5 to 6) received 70 mL of ethanol, lesion 2 (segment 5) received 5 mL and lesion 3 (segment 8) received 15 mL. Laboratory data obtained two days postoperatively showed a serum total bilirubin level of 11 µmol/L (normal range 0 µmol/L to 18 µmol/L). No immediate clinical complications occurred and the patient was transferred to the postoperative acute care unit.

During the PEI procedure, the patient’s serum lactate level was recorded to be 5.30 mmol/L (normal range 0.50 mmol/L to 1.60 mmol/L) and the patient was acidic, with a serum pH of 7.26 (normal range 7.35 to 7.45) (Table 1). Within minutes after the procedure, the patient seemed to be intoxicated. Within three hours after the procedure, the patient’s serum lactate level had increased to 7.30 mmol/L, with a serum pH of 7.17. His serum lactate level peaked at 8.40 mmol/L 8 h postoperatively, and serum pH remained at the nadir of 7.17. At that time, the lactic acidosis was believed to be secondary to tissue injury as a result of the PEI procedure. His serum amylase level was 1694 U/L (normal range 35 U/L to 90 U/L) measured...
19 h postoperatively. During this time, the patient experienced acute epigastric pain that radiated posteriorly, was tachypneic, febrile, nauseous and hypotensive; consequently, he was transferred to the intensive care unit for further observation. The serum amylase level gradually decreased to within the normal range slightly more than three days postoperatively when he was discharged from the intensive care unit. His serum ethanol level 3 h postoperatively was 11 mmol/L (normal 0 mmol/L) and returned to normal levels within 24 h (the patient's body mass index was 23.8 kg/m²). Thereafter, the patient's acute pancreatitis resolved within just over three days and he was discharged home.

### DISCUSSION

To our knowledge, although periprocedural fatal acute pancreatitis has been reported as a result of intra-arterial PEI, periprocedural onset of acute pancreatitis after conventional PEI of an HCC mass has not been reported in the English medical literature (1).

HCC is one of the 10 most common solid tumours in the world, with an estimated annual incidence of one million patients (2). Surgical resection is often the first-line treatment option for primary and metastatic hepatic malignancies. However, only a minority of patients with HCC undergo potentially curative resection due to the presence of bilobar disease, in which resection would sacrifice too great a volume of hepatic parenchyma, or proximity of the tumour to important vascular or biliary structures (2). Ablative techniques have increasingly been offered to patients with unresectable cancers because these treatments are directed at tumour control and

### TABLE 1

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<th>Serum pancreatic amylase, lactate and pH</th>
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Normal ranges: Amylase 35 U/L to 90 U/L, Lactate 0.50 mmol/L to 1.60 mmol/L, pH 7.35 to 7.45
potential cure while minimizing injury to the surrounding functional hepatic parenchyma (2). These modalities have included PEI, radiofrequency ablation (RFA), transarterial chemoembolization, cryoablation, laser-induced interstitial thermotherapy and microwave coagulation (2). Although RFA is the preferred modality for local ablative therapy of HCC, US-guided PEI remains the most frequently used local ablative therapy for the treatment of HCC, globally, probably owing to its efficacy, simplicity, cost effectiveness and repeatability. This technique is well accepted because of its low cost, minimal technological requirements and good clinical outcomes (3). The mechanism of tumouricidal action is thought to be via cytoplasmic dehydration in addition to a vasculitis precipitated by disruption of endothelial cell integrity and platelet aggregation, with nonselective subsequent coagulation necrosis and fibrous reaction. The result is thrombosis of tumour microvasculature and tumour parenchyma ischemia (2,4).

Contraindications for PEI have included patients with more than three tumours, Child-Pugh class C cirrhosis, portal vein thrombosis and uncontrollable coagulopathy or severe ascites (5). Conversely, patients with HCCs larger than 5 cm in size have been excluded for PEI because complete tumour necrosis would require multiple injections and possibly leave viable tumour cells within the tumour area. Recently, however, a modified strategy of this procedure has been designed for patients with tumours larger than 3 cm in size, referred to as ‘single-session’ PEI whereby multiple injections of ethanol are administered in one session (6). This procedure can be performed under general anesthesia with approximately 60 mL to 150 mL of ethanol delivered via multiple injections over a 30 min span (7).

PEI has been reported to cause intra- and extrahepatic adverse effects. Serious complications have been rare, occurring in less than 5% of treated patients, and have included hepatic or peritoneal hemorrhage, hepatic or renal insufficiency or failure, hepatic infarction of the segment adjacent to the tumour, bile duct necrosis, biliary fistula, cardiovascular collapse, hypotension, stomach perforation and hyperbilirubinemia (2,8,9). Single-session treatment seems to be associated with higher morbidity and mortality including rupture of esophageal varices, rupture of subcapsular HCC and liver failure, and acute tubular necrosis (4,10). Extrahepatic complications have included transient renal insufficiency and a slowing of gastric myenteric activity without abdominal symptoms (11).

A recent review of the literature demonstrated that complete tumour necrosis can be achieved in 60% to 100% of patients treated with PEI, and a study of tumours with larger diameters (5 cm to 8 cm) revealed an ablation rate of approximately 60% after large-volume PEI (4,12). Furthermore, although RFA was considered superior to PEI with respect to long-term survival among HCC patients, a recent clinical trial (13) demonstrated that RFA with adjunct PEI increases long-term survival relative to RFA alone in HCC patients. Additionally, nonsurgical treatments such as PEI feature prominently in HCC treatment regimens because only 20% of HCCs are surgical candidates and even after treatment, HCC recurrence rates are high. These factors may encourage the increased use of PEI for HCC treatment. The largest reported HCC treated with single-session PEI had a diameter of up to 8.2 cm and the rate of major complications in this series of 108 large-HCC patients was 4.6% (14). Although reports (15) of hyperamylasemia occurring after hepatic resection have been published (the pathophysiology of this process remains unknown), and fatal acute pancreatitis has been reported in a number of studies using percutaneous intra-arterial ethanol injection (1,16), neither sequel has been reported as a complication of PEI. A possible hypothesis regarding the mechanism of acute pancreatitis in this setting includes a possible ethanol leak into the hepatic vasculature. Given our experience and the potential for increased use of PEI as a treatment modality for HCC, ethanol intoxication should be part of the differential diagnosis when acute pancreatitis occurs after PEI treatment of HCC.

REFERENCES