Abdom Imaging 18:357–359 (1993)

Abdominal Imaging



# Fatal Liver Necrosis Following Percutaneous Ethanol Injection for Hepatocellular Carcinoma

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Received: 22 October 1992/Accepted: 29 November 1992

**Abstract.** A 76-year-old man underwent an injection of 5 ml of ethanol for the treatment of a hepatocellular carcinoma 3 cm in diameter. Shortly after the procedure, he had an attack of abdominal pain. His condition soon deteriorated and he died 5 days later. Massive hepatic necroses distant from the injection site and a myocardial infarction were found at autopsy. To our knowledge, this is the first fatality associated with percutaneous ethanol injection therapy.

**Key words:** Hepatocellular carcinoma, alcohol—Interventional procedures, complications—Liver, infarction—Liver neoplasms, therapy.

Percutaneous ethanol injection therapy (PEIT) is now widely used to treat malignant liver neoplasms. Common adverse reactions are transient pain at the site of the injection, fever, and alcohol intoxication [1]. The technique has been considered to be relatively safe with a 2.8% rate of major complications in a series of 289 procedures [2] and no major complications in another series of 2485 procedures [3]. As far as we know, no fatal complications have been reported. We present here a case of fatal hepatic necrosis following PEIT.

## Case Report

A 76-year-old diabetic war veteran had been suffering from upper abdominal pains for several years. Liver sonography (May 21, 1991) demonstrated an irregular, partly well-demarcated hypoechoic focus, which was relatively round in shape measuring 3 × 5 cm. This lesion was found in the lateral part of the right lobe. Two days later the lesion was verified by computed tomography (CT) (Fig. 1), which showed a hypodense focus measuring 2.5 cm in diameter. The patient was then moved to the University Central Hospital for further studies.

After two fine-needle aspiration biopsies and a large-needle biopsy (June 14, 1991) the lesion was verified to be hepatocellular carcinoma. A sonoguided ventral approach was used to guide the 0.8-mm (21 G) metallic needle (July 12, 1991) into the cancer focus. Five milliliters of ethanol were injected during a single inspiratory phase and the needle then removed. The patient had an acute attack of upper abdominal pain 2 h later. There was a transient rise of the systolic blood pressure to the level of 180–215 mmHg, 1.5–5 h after the procedure. Chest radiography showed minor basal plate atelectases, whereas plain abdominal films demonstrated gastric retention and dilated jejunal pattern with gas–fluid levels (July 14) indicating adynamic ileus. Systolic blood pressure fell to a level of 85–110 mmHg (from his normal level of 140–150 mmHg). The next day he became confused, tachypneic, and demonstrated flimmer rhythm in electrocardiogram. The patient was then intubated. His level of consciousness fell so that the patient reacted only to airway suction. Repeated ventricular tachyarrhythmias were noted and he was resuscitated once from a pulseless state by using 50–100 J DC shocks.

Upper abdominal ultrasound performed bedside on the day of treatment showed the usual focal echodensity of the injected tumor. Repeat examination on the next day showed widespread intrahepatic gas (Fig. 2). Mesenteric thrombosis with gas in the portal vein branches was suspected. Plain abdominal films showed paralytic ileus, and gas in the portal system was suspected in a penetrated hepatic radiograph. The patient remained hypotonic, anuric, and comatous. Acute heart infarct developed on July 16, 1991. Due to the hopeless situation, active treatment was finished and the patient died on July 17, 1991, 5 days after PEIT.

Because a complication of treatment could not be ruled out by clinical means, a medicolegal autopsy was carried out at the Department of Forensic Medicine. In addition to the acute myocardial infarction in the left ventricle, massive liver necroses both close to and distant from the injection site were found (Fig. 3). The mesenteric vessels, as well as the portal vein, were normally open and free of thrombi. The direct cause of death was most likely the large thrombosis in the right coronary artery and the consequent necrosis in the posterior wall of the left ventricle.

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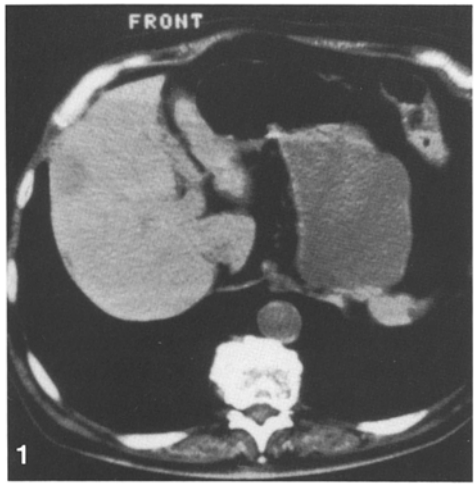
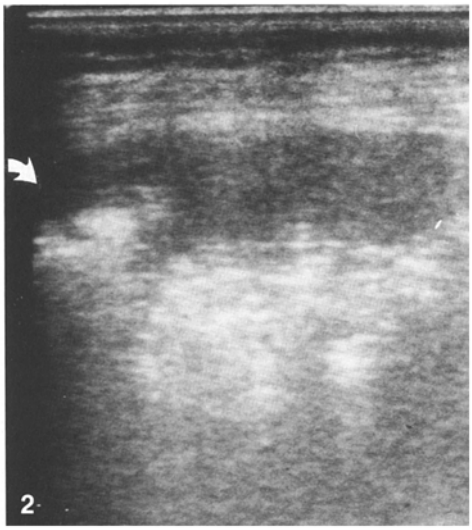
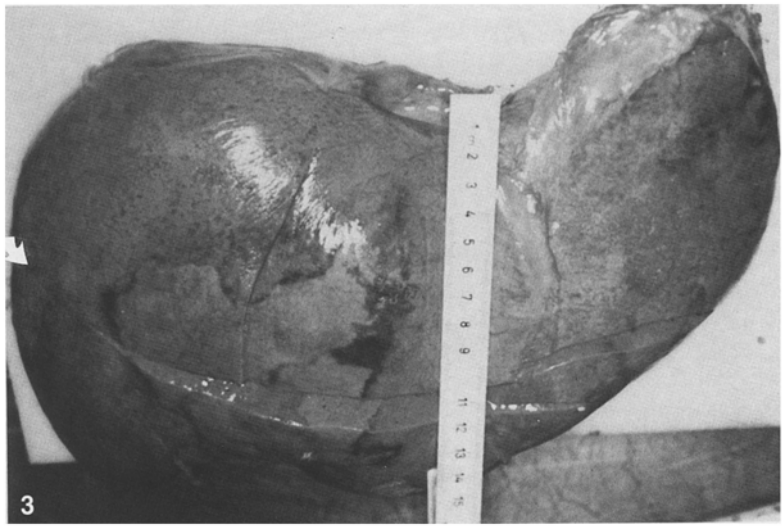



**Fig. 1.** A nonenhanced CT scan shows a hypodense tumor at the right margin of the liver.

**Fig. 2.** Close to the hyperechoic injection site (*arrowhead*) there is a large echodense area representing intrahepatic gas in the US scan.

**Fig. 3.** The postmortem liver with large necrotic areas in both lobes. The injection site is indicated (*arrowhead*).




## Discussion

There are no previous reports of deaths related to PEIT. Some recent papers, however, suggest the possibility of uncontrolled spread of ethanol following PEIT. Necrotic liver areas near tumors treated with clinical PEIT have been reported [4]. In an experiment with rabbits [5], high doses of ethanol (1–2 ml/kg body weight) induced necrotic lesions in the liver both near and remote from the site of injections due to an unpredictable intrahepatic diffusion. In another experimental work, an uncontrolled spread of ethanol occurred twice, when 48 ethanol doses of 0.5–2.0 ml were injected in the livers of normal pigs [6]. In addition to the fixative effect through deprivation of fluid from cells, ethanol may also cause indirect cell damage due to thrombus formation [7]. Could such thrombi send emboli into other parts of the liver? Decreased segmental portal blood flow is frequent after PEIT and the drainage of ethanol injected causes obstructive vasculitis [8].

The close temporal relationship of our patient's ethanol injection and the development of massive liver necroses strongly suggest a causative connection. Yet it is difficult to present a plausible explanation of the mechanism. The amount of ethanol—4 g—may be too small for direct massive toxic injury (0.06 ml/kg body weight). No intrahepatic escape of ethanol was noticed during the injection, and the sharp peritoneal reflux pain was of short duration as usual. The only local echodensity in the early hours after the acute attack was in the tumor. The location of the tumor in the right liver margin precludes intravascular spread of ethanol to the left liver lobe because it would have to flow a long distance against the bloodstream. The only system that could transport the ethanol is the biliary tract, but the gallbladder remained intact, and the ethanol would have to pene-

trate both the bile duct and the vascular wall in order to initiate intravascular coagulation.

If ethanol is seen to escape into blood vessels or bile ducts, the injection must be stopped at once. This may happen invisibly, however. Ethanol also might possibly diffuse through liver parenchyma into undesired areas. The mechanism of ethanol spread and the early pharmacokinetics of injected ethanol have been little studied so far.

Although PEIT could not completely be linked with the death of our patient at the time of autopsy 1 year ago, the current literature favors this view. There was no other alternative cause for the massive hepatic necroses. Liver necroses with associated pains probably led to cardiovascular imbalance and ultimately to acute myocardial infarct in our case.

Counting all the unpublished patients treated with PEIT, their number must be thousands. Because most of them have received more than one injection of ethanol, the total number of injections is most likely to be several thousands. Since this is the first published fatality, the occurrence of fatal complications seems to be very low, most likely less than 1/1000 injections. Regarding the complications, PEIT is therefore well-comparable with other kinds of treatments for hepatic malignancies and its use should be continued. Before the intrahepatic spread of ethanol following PEIT has been theoretically studied, there seems to be no way other than careful sonographic monitoring to try to hinder this kind of complication.

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