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SUCCESSFUL LIVER TRANSPLANTATION FOR ISONIAZID-INDUCED HEPATIC FAILURE—A CASE REPORT[1]

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A 6–12-month course of isoniazid (INH)[*] has been recommended as prophylaxis against tuberculosis for individuals having an asymptomatic positive tuberculin skin test (1,2). Isoniazid is known to cause an elevation of liver enzymes (3-5), which usually improves after INH is discontinued. However, INH may sometimes cause fatal hepatic necrosis (6-9).

Liver transplantation has been reported to be effective for drug-induced hepatic failure of multiple etiologies (10-13). However, there have been no reports of liver transplantation for INH-induced hepatic failure. We describe here the case of a 16-year-old girl who developed hepatic failure following a 3-month course of INH use and was successfully treated with liver transplantation.

In September 1992, an otherwise healthy 16-year-old girl displayed a positive PPD skin test by routine examination, with a normal chest roentgenogram. She was placed on prophylactic doses of INH and pyridoxine. The INH was discontinued in late December, after she developed lethargy, weakness, and loss of appetite. In early January 1993, she was found to have scleral icterus, abnormal liver function tests, and coagulopathy (serum glutamic oxaloacetic transaminase 328 IUL, glutamic pyruvic transaminase 313 IUL, alkaline phosphatase 350 IUL, total bilirubin 10.4 mgldl, prothrombin time 20 sec, partial thromboplastin time 122 sec, ammonia 86 μmol/L). She was hospitalized and was started on lactulose, neomycin, cimetidine and vitamin K.

After 2 weeks, her total bilirubin decreased to 8.4 mg/dl, serum glutamic oxaloacetic transaminase decreased to 203 IUL, and ammonia decreased to 60 μmol/dl; however, her prothrombin time and partial thromboplastin time did not improve despite administration of fresh frozen plasma several times. She had not experienced episodes of bleeding or encephalopathy. She was transferred to our institution for possible liver transplantation. She had a firm liver without signs of portal hypertension. Computerized tomography scanning showed a diminished-size heterogeneous liver with calcified nodules (Fig. 1). There was no ascites or splenomegaly. Hepatitis A, B, C screens were negative. Serum alpha-1-antitrypsin, alpha-fetoprotein, copper, and ceruloplasmin levels were within normal ranges. Anti–smooth muscle, anti-DNA, anti-RNA, and antimicrosomal antibodies were negative.

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[*]Abbreviation: INH, isoniazid.

Cytomegalovirus and Epstein-Barr virus titers were negative. A chest roentgenogram was normal. Cultures from the sputa were negative.

In early February, she underwent orthotopic liver transplantation. Using the liver from a 10-year-old donor, the transplant was done with a transient portocaval shunt by the piggy-back method (14). An arterial graft was interposed between the infrarenal aorta and a small hepatic artery. The postoperative course was uneventful except for transient bleeding from a Roux-en-Y loop, which was treated with blood transfusion. Immunosuppression was with FK506 and steroids. Since her transplant, she has been on ethambutol and. pyrazinamide continuously as antituberculosis prophy-1axis. She had no episodes of rejection or infection and was discharged on the 13th postoperative day. She has had no respiratory symptoms and her chest roentgenogram has been normal during an 8-month follow-up.

The resected liver was 484.5 g and 16×6×7 cm in size (Fig. 2). It was red-brown, rubbery, firm, and shrunken, with massive areas of necrosis intermixed with yellowish nodules of intact liver tissue. Histologically, the liver had extensive necrosis mixed with areas of remaining islands of hepatocytes. There was extensive acute and chronic inflammation. There were some regenerating hepatocytes and many proliferating cholangioles. No significant fibrosis was seen.

Isoniazid hepatotoxicity is considered a hepatocellular hypersensitivity reaction that may cause diffuse hepatocellular necrosis (4). Initial elevation of transaminases occurs in 10–20% of patients undergoing INH therapy (15-17). Typically, this is remedied by discontinuation of INH. Although the mechanism of hepatic necrosis is unknown, once massive necrosis occurs the damage is irreversible and may be fatal. Mortality rates from hepatic failure are reported to be 23.2/100,000 or 57.9/100,000 (9,18). In the present case, the resected liver showed massive necrosis, which was considered to be irreversible and fatal without liver transplantation.

Isoniazid hepatotoxicity resembles viral hepatitis and is diagnosed by ruling out other possible etiologies. In the present case, hepatitis screens and autoantibodies were negative. Alpha-1-antitrypsin, Alpha-fetoprotein, copper, and ceruloplasmin levels were within normal ranges. The patient developed hepatic failure 3 months after the initiation of INH therapy.

Liver transplantation has been successful for drug-induced hepatic failure secondary to ketoconazole, paracetamol, fipexide, nonsteroidal antiinflammatory drugs, sulfasulfalamin, halothane, and salazopyrine (9-12). Severe irreversible cases of INH-induced hepatic failure reported previously did not undergo liver transplantation, although one patient died while waiting for transplantation (5). The present case is the first reported case of INH-induced hepatic failure to undergo successful liver transplantation.

It is important to differentiate an irreversible case from a reversible one. Coagulopathy and hyperammonemia, as well as elevated liver enzymes and bilirubin, which are resistant to medical therapy, should reflect irreversible hepatic necrosis requiring liver transplantation. Additionally, a small cirrhotic liver seen by computerized tomography scanning may reveal significant postnecrotic changes. Once these abnormalities occur, acute hepatic failure develops, with immediate need for transplantation.

After transplantation, prophylactic antituberculosis medication, exclusive of INH, was required in our patient who had not completed her initial course of therapy. Sinnott et al. (19) have recommended pyrazinamide for prophylaxis in the transplanted patient receiving cyclosporine-related immunosuppressives. We chose to treat our patient with a six-month course of the combination of pyrazinamide and ethambutol. The use of two second-line

antituberculosis medications was chosen to enhance the mycobactericidal activity in this immunosuppressed patient.

In conclusion, liver transplantation should be considered for severe irreversible INH-induced hepatic failure.

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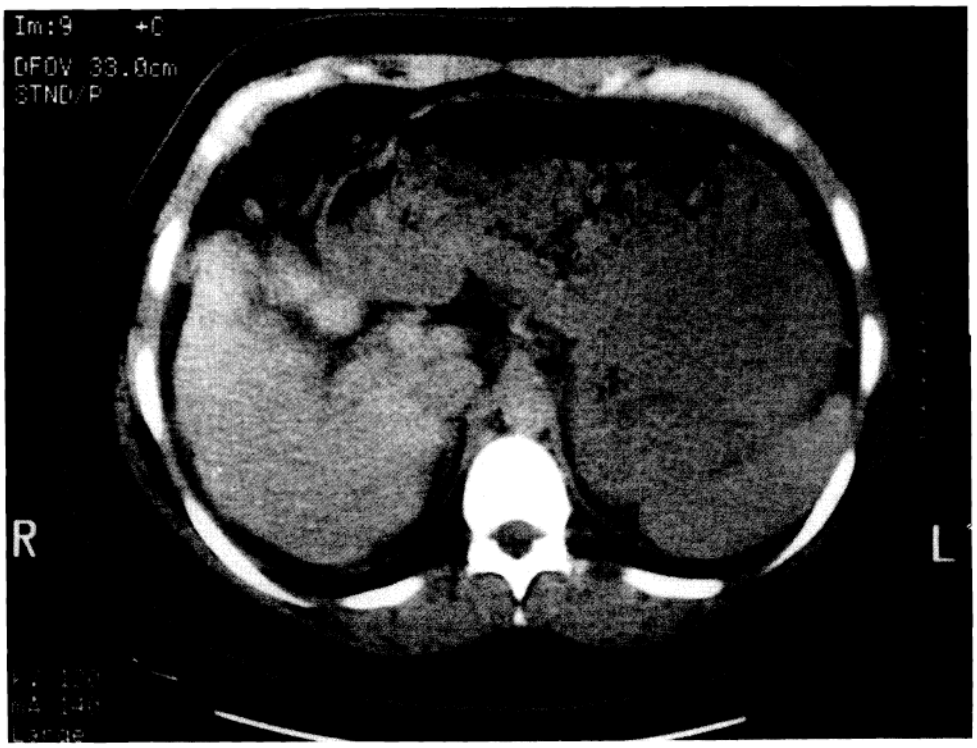

Figure 1.
Computerized tomography scan of the abdomen showing a diminished size heterogenous liver with calcified nodules.

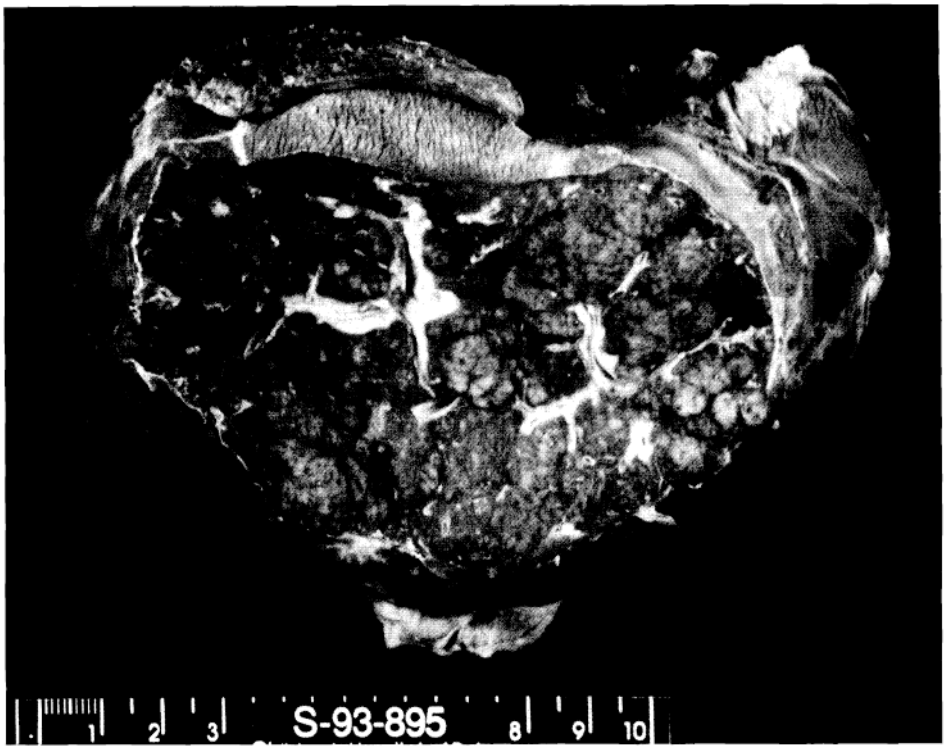

Figure 2.
The resected liver: weight: 484.5 g, size: 16×10×7 cm. The liver is rubbery, firm, and shrunken. There are massive areas of necrosis and small nodular areas of intact tissue.