Acute liver failure: a message found under the skin

M Meier, A Woywodt, M M Hoeper, A Schneider, M P Manns, C P Strassburg

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Acute liver failure is a rare syndrome with rapid progression and high mortality. It is characterised by the onset of coma and coagulopathy usually within six weeks but can occur up to six months after the onset of illness. Viral hepatitis, idiosyncratic drug induced liver injury, and acetaminophen ingestion are common causes. This report describes the case of a 35 year old man who presented with acute liver failure shortly after binge drinking. Repeated history taking disclosed a gluteal disulfiram implant that the patient had received to treat his alcohol dependence. The patient recovered with maximum supportive care after surgical removal but without liver transplantation. This case illustrates that only meticulous history taking will disclose the sometimes bewildering causes of acute liver failure.

Acute liver failure is characterised by liver cell dysfunction leading to coagulopathy and hepatic encephalopathy, mainly attributable to viral, acetaminophen, or drug induced liver injury. Fulminant hepatitis is a rare but potentially fatal adverse reaction that may occur after the use of disulfiram, a drug used to treat alcoholism. We report a case of a 35 year old man who experienced acute liver failure associated with a gluteal disulfiram implant and alcohol misuse.

CASE REPORT

A 35 year old man first presented to a primary hospital in April 2003 with fatigue, vomiting, and vague abdominal complaints. His medical history included ongoing alcohol misuse despite various attempts of treatment. An alcohol binge had occurred three days before admission. On examination by the admitting physicians, he was jaundiced and drowsy. Initial laboratory studies showed increased aspartate aminotransferase (24012 U/l), total bilirubin (150 μmol/l), and blood alcohol (7.7 mmol/l). Transfer to our medical intensive care unit was arranged with a tentative diagnosis of alcohol induced liver failure.

On admission, the patient appeared acutely ill with pronounced jaundice, hepatic foetor, and hepatomegaly. Auscultation and percussion of heart and lungs were normal and the patient had no clinical signs of liver cirrhosis or portal hypertension. A 2 cm scar in his left lateral gluteal region was noted. Laboratory studies in our hospital on admission confirmed a massive increase in aspartate aminotransferase (60 620 U/l), alanine aminotransferase (16726 U/l), lactate dehydrogenase (38180 U/l), glutamate dehydrogenase (12211 U/l) total bilirubin (179 μmol/l), and lactate (5.2 mmol/l). Severe coagulopathy with thromocytopenia was present (INR 8.29; factor V 12%; 16 000/μl platelets), which precluded liver biopsy. Abdominal ultrasound showed hepatic oedema and excluded cirrhosis. The portal vein, hepatic artery, and hepatic veins were all patent. In view of progressive encephalopathy the patient was sedated and intubated. Cerebral oedema and haemorrhage were excluded by cranial computed tomography. Fluid refractory hypotension ensued, vasopressor support was begun, and anuric renal failure prompted continuous veno-venous haemodialysis. Fresh frozen plasma, platelets, packed red cells, factor XIII, and fibrinogen were given. Further laboratory tests excluded common causes of acute live failure like viral hepatitis A-C, Wilson's, and liver autoimmune diseases as

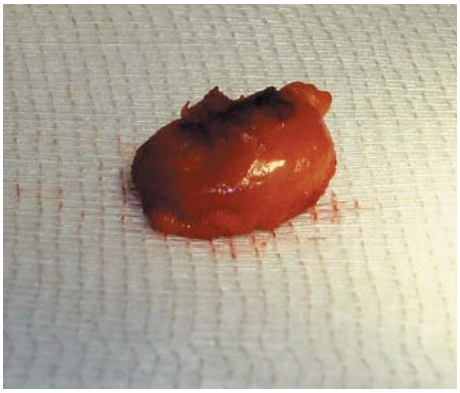

Figure 1 Disulfiram implant excised from the left gluteal region.

judged by the absence of autoantibodies (ANA, SMA, LKM, SLA). A comprehensive drug screen was negative. High urgency orthotopic cadaveric liver transplantation was considered but declined on the basis of ongoing alcohol misuse in accordance with policies of German organ transplant legislation and Eurotransplant.

The medical history was scrutinised again to shed light on the aetiology of the liver failure. The patient was not receiving any medication and denied recreational or occasional exposure to drugs or toxic substances. It transpired that our patient had received a subcutaneous implantation of the oral drug disulfiram (Esperal) in his left buttock in Poland three months previously to "get rid of the drinking". The implant was then immediately excised (fig 1). After surgical removal and under further supportive treatment the patient made an uneventful recovery after six days in the intensive care unit during which hepatic synthesis and detoxification normalised. He was then discharged to the referring hospital without neurological sequelae.

DISCUSSION

The main differential diagnosis in a 35 year old patient with acute liver failure would include alcohol induced liver disease, acetaminophen intoxication, viral hepatitis (predominantly HBV) as well as drug reactions and other rare diagnoses such as autoimmune hepatitis, Wilson's disease, and Budd-Chiari syndrome.[1]

Disulfiram has been in use for adjunctive treatment of severe alcoholism since 1948.[2] A thiuram derivative, it inhibits the second step of ethanol metabolism by inhibition of acetaldehyde dehydrogenase.[3] This leads to immediate accumulation of acetic aldehyde and results in nausea, flushing, and vertigo. By virtue of this action it exerts a penalising effect on alcohol consumption.[2 3] However, disulfiram has been widely abandoned because of its unfavourable safety profile. Inadvertent ingestion of alcohol may cause severe acetic aldehyde reaction requiring medical assistance.[4] Fulminant hepatitis after the use of disulfiram usually occurs within the first two months after disulfiram treatment, with symptoms suggestive of acute hepatitis including fatigue, malaise, anorexia, nausea, vomiting, abdominal pain, jaundice, fever, rash, and pruritus.[5] The pathophysiology, however, has not been elucidated.[5] Both accumulation of toxic metabolites such as carbon disulfide, an end product of the disulfiram metabolism, and immunological mechanisms have been suggested.[5 6] Forns *et al* concluded that disulfiram hepatotoxicity is mainly produced by the accumulation of toxic metabolites,[6] whereas many case reports are consistent with a hypersensitivity reaction and include clinical findings such as eosinophilic infiltrates, arthralgia, fever, rash, and pruritus.[5] Depot preparations of disulfiram have been described in the literature albeit without proper evaluation of their benefit-hazard ratio.[7] Notably, concomitant alcohol misuse opens the possibility of aggravated reactions to drugs.[5] Based on the literature, we believe that an idiosyncratic adverse drug reaction of disulfiram is the most probable pathophysiological mechanism, which is compatible with the course of the disease.

Learning points

- Acute liver failure is a rare syndrome with rapid progression and high mortality.
- Acetaminophen ingestions, viral hepatitis and idiosyncratic drug toxicity are common causes.
- Idiosyncratic drug induced hepatitis attributable to disulfiram is a rare but well described cause.
- History taking in liver failure should include occupational exposure to toxins, alternative therapies, and herb ingestion.
- Several sets of criteria have been proposed to identify patients who will only survive with liver transplantation.

CONCLUSION

Our patient experienced liver failure associated with a gluteal disulfiram implant and alcohol misuse. This case illustrates that acute liver failure can have a bewildering aetiology while concomitant alcohol misuse opens the possibility of aggravated reactions to drugs such as disulfiram induced toxic hepatitis. Maximum supportive care was started only after the implant had been discovered and appreciated as a potentially reversible cause of hepatotoxicity.

Authors' affiliations

M Meier, A Woywodt, Division of Nephrology, Hanover Medical School, Germany
A Schneider, M P Manns, C P Strassburg, Division of Gastroenterology, Hepatology and Endocrinology, Hanover Medical School
M M Hoeper, Division of Respiratory Medicine, Hanover Medical School

Correspondence to: Dr M P Manns, Department of Gastroenterology, Hepatology and Endocrinology, Hanover Medical School, Carl-Neuberg-Strasse 1, D-30625 Hanover, Germany; mpmanns@aol.com

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