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Isoniazid-related fulminant hepatic failure in a child: assessment of the native liver's early regeneration after auxiliary partial orthotopic liver transplantation

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Abstract We report the first case of auxiliary partial orthotopic liver transplantation (APOLT) in a patient with isoniazid (INH)-related fulminant hepatic failure (FHF) with the aim to determine the ability of the native liver (NL) to recover after this particular toxic event. A 10-year-old boy with INH-related FHF underwent APOLT after left hepatectomy on the NL. Neurological status and liver function rapidly improved, but, on postoperative day 22, urgent re-transplantation was needed for graft–hepatic artery thrombosis (HAT) and the NL's incapacity to sustain adequate liver function. Histological examination of the NL showed signs evident of its regeneration, however. In conclusion, though we faced the clinical failure of the NL functionally to sustain the patient in the presence of the graft HAT 3, weeks after APOLT, such a failure may be interpreted as time related. In fact, the histological picture in this particular case may suggest the potential for NL recovery after INH-related FHF.

Keywords Isoniazid · Fulminant hepatic failure · Auxiliary orthotopic liver transplantation · Liver regeneration · Function recovery

Introduction

Approximately 2 billion people, nearly one-third of the world population, are thought to be infected with *Mycobacterium* tuberculosis. In addition to the people with active TB, many others are asymptomatic carriers (latent TB) and may develop active TB at some time in their lives [1, 2]. Isoniazid (INH) is widely used as the first-line anti-microbial treatment for both latent and active TB infection, but its most important side effect is liver toxicity [2]. Liver function test (LFT) abnormalities are relatively common, occurring in 10%–20% of people taking the drug, and symptomatic hepatitis (defined as both clinical signs and liver transaminase levels more than five times the upper limit of normal) develops in 1%–2% of patients [3]. The severity of presentation varies from acute hepatitis that responds to INH withdrawal to fulminant hepatic failure (FHF) that needs transplantation. Before the transplantation era most patients with FHF died; a few (15%–20%) recovered,

however, and their liver function was usually fully restored [4].

Orthotopic liver transplantation (OLT) is currently considered an effective treatment for FHF, with a 1-year patient survival rate of approximately 60%–70% [5], but it implies the removal of a native liver that might have recovered, as well as the need for long-term immunosuppression. Auxiliary partial orthotopic liver transplantation (APOLT), a procedure in which part of the native liver (NL) is left in situ, represents an attractive alternative to total transplantation because the orthotopically implanted partial graft may rapidly correct acute liver failure while offering the NL a chance to recover, thereby subsequently enabling the withdrawal of immunosuppressive treatment. The likelihood of NL regeneration depends critically on FHF aetiology, however [5, 6, 7]. Whether INH-related FHF has the potential for recovery has yet to be established. We report on a case of APOLT in this setting, with a view to assessing the NL's ability to recover from INH-related hepatic toxicity.

Case report

In April 2001, an otherwise healthy 10-year-old boy of Moroccan origin, weighing 27 kg, displayed a positive tuberculin skin test after prolonged contact with his TB-positive mother and was placed on prophylactic doses of INH (300 mg/day orally). This treatment was discontinued in July 2001, immediately after the child was found to have jaundice and abnormal LFT values (Table 1). On the 5th day after admission he developed lethargy, so he was transferred to our Paediatric Department with a suspected diagnosis of INH-related FHF. Laboratory tests excluded viral and autoimmune hepatitis, Wilson's disease, α-1 anti-trypsin deficiency and haemochromatosis, leading us to the conclusion that he had INH-related FHF. On the 20th day after admission, because his condition was rapidly deteriorating in both LFT abnormalities (Table 1) and neurological status (grade III encephalopathy requiring mechanical ventilation), the patient was listed for emergency OLT.

Table 1 LFT abnormalities. APOLT had been performed on day 21. *AST*aspartate aminotransferase, *ALT* alanine aminotransferase, *PT* prothrombin time, *INR* international normalized ratio

LFT	Day of admission	At 20 days	At 25 days	At 42 days
AST (U/l)	1,485	3,640	75	2,071
ALT (U/l)	1,400	2,945	201	1,706
Total bilirubin (μmol/l)	172	275	110	184
Lactic acid (μmol/l)	1.2	1.8	0.8	2
PT (%)/INR	71/1.34	51/1.74	70/1.33	36/1.87

On the 21st day after admission, a left lateral adult hepatic graft weighing 230 g (small for size), harvested by the split-liver in situ technique, became available, so an APOLT was performed after left hepatectomy on the NL. The NL's left hepatic vein was anastomosed with the graft's left hepatic vein, and the portal reconstruction was performed by an end-to-side anastomosis between the left portal vein of the graft and the recipient's portal trunk. An arterial graft was interposed between the infrarenal aorta and the hepatic artery of the graft. Histological examination of the native left liver showed massive multi-acinar hepatocellular necrosis, with a few residual islands of hepatocytes. Only portal tracts were spared, and there was no fibrosis (Fig. 1a); this picture was consistent with a toxic injury. Immunosuppression was based on tacrolimus and prednisolone, as previously described [8]. The child regained consciousness, along

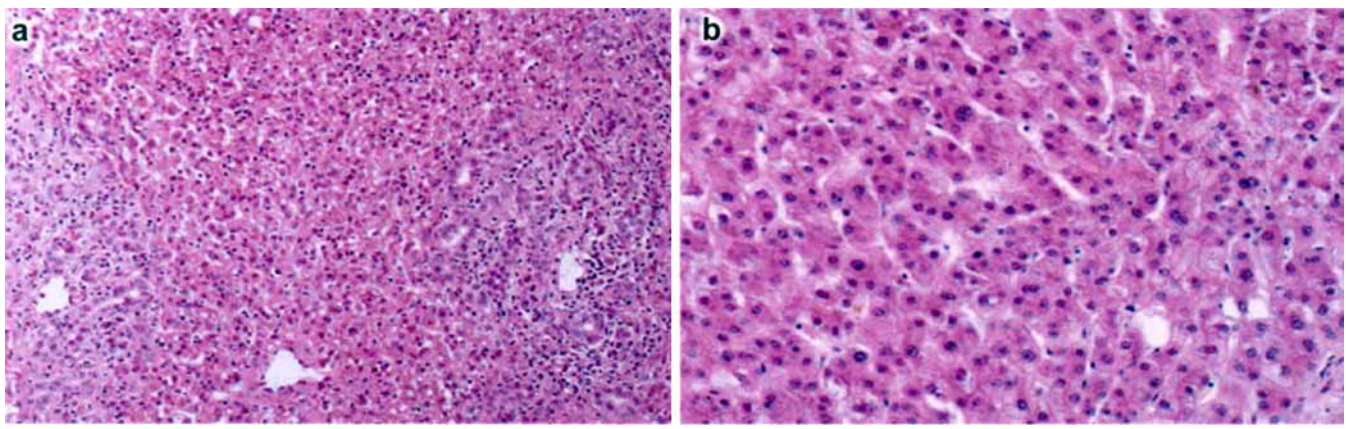

Fig. 1 **a** Acute massive hepatocellular necrosis. Spared portal tracts are evident (*right*) with marginal ductular proliferation and mild inflammation. Haematoxylin & eosin, original magnification ×40. **b** Native liver after total hepatectomy. Large areas of viable, often bi-nucleated hepatocytes are evident and account for approximately 1/5 of the entire liver. Haematoxylin & eosin, original magnification ×40)

with the improvement of liver function, in the early postoperative period (Table 1).

However, on post-transplant day 22 the graft failed because of hepatic artery kinking and thrombosis following graft regeneration and enlargement. The patient's clinical condition (grade III encephalopathy requiring mechanical ventilation) and LFT (Table 1) rapidly deteriorated again. Urgent re-transplantation was needed, and, after total hepatectomy, histology showed diffuse ischaemic necrosis of the graft. Large areas of viable hepatocytes were evident in the NL, with signs of regeneration (several bi-nucleated hepatocytes and diffuse ductular proliferation) (Fig. 1b). Those areas accounted for approximately 1/5 of the entire liver. The postoperative course was complicated by an episode of acute rejection (Banff's score 5), which was successfully treated with steroids, and upper GI bleeding due to a duodenal ulcer, controlled with medical therapy. Two months after OLT the child developed pulmonary tuberculosis, which was successfully treated with streptomycin, ciprofloxacin, amoxicillin, rifampicin and a reduction in the immunosuppression. Currently (24 months after APOLT), the patient is healthy, with normal LFT.

Discussion

The risk of INH-related liver injury increases in older age, female gender and Oriental ethnicity [3], but our case of INH-related FHF developed in a 10-year-old Caucasian boy. Isoniazid rarely causes FHF, but, given the extensive use of the drug worldwide, a better understanding of this dramatic adverse event is warranted. For instance, one of the key points seems to be whether to consider this form of FHF in the group of FHFs with a better prognosis (viral or paracetamol-related) or, on the contrary, in the almost invariably irreversible group. Such a distinction has obvious implications in the treatment strategy choice (OLT, APOLT, bio-artificial bridging procedures, medical therapy) when this type of FHF occurs. Several cases of successful OLT for INH-related FHF have been described in the past decade [9], but, to the best of our knowledge, we report here on the first case of APOLT for INH-related FHF.

There are several general and particular considerations in favour of APOLT:

1. The major advantage of APOLT over OLT lies in its potential for NL regeneration [6]. In addition, the APOLT procedure itself has an intrinsic positive effect on NL recovery, since surgical hepatectomy is possibly the most significant hepatic regeneration inducer currently available and immunosuppressive drugs (cyclosporine and tacrolimus) have also been found to stimulate liver regeneration [10].
2. Several authors have shown that patient and graft survival rates after APOLT do not differ significantly from the values for OLT in cases of FHF, while 65% of survivors are free of immunosuppression 1 year after APOLT [5].
3. The chance of withdrawal of immunosuppression is particularly interesting in the case of INH-related FHF because it could reduce the risk of the onset or recurrence of tuberculosis after transplantation [3].
4. An age <40 years, potentially reversible hepatitis (viral or caused by paracetamol overdose) and an interval between the onset of jaundice and encephalopathy <7 days (hyperacute FHF), are all recognized indicators of a relatively favourable outcome in patients with FHF, in whom a high rate of complete NL regeneration after APOLT has been observed [6].

In this particular clinical case there were two indicators in favour of a potential complete NL regeneration, i.e. age <40 and hyperacute FHF, whereas how the aetiology of the child's disease might influence NL outcome is still not known. More generally speaking, APOLT is a procedure that is capable of increasing the chances of transplantation when a donor liver is urgently needed (in FHF patients, any delay can result in the onset of severe infectious complications or permanent neurological damage [6], especially in the case of a medium-sized recipient (approximately 30 kg) for whom a split left lateral lobe might be too small while a right lobe might be too large, prolonging the waiting time. In this sense, APOLT was performed as an acceptable life-saving bridging procedure in our case, irrespective of any NL recovery.

As for the issue of NL recovery, deprivation of arterial blood supply, which occurred 3 weeks after APOLT due to HAT, resulted in the NL's not yet being capable of sustaining the patient's metabolic and biosynthetic needs, a situation confirmed by the patient's rapid neurological and bio-humoral deterioration. Clear signs of regeneration (Fig. 1b) were found at histology of the NL explanted 3 weeks after APOLT, however. This finding is consistent to some degree with reports showing that NL regeneration is only partial 2 weeks after APOLT and may be complete after 3–4 weeks [6]. We considered a potential for a toxic negative impact on the NL by the necrotic graft after HAT. However, at the time of HAT diagnosis we had insufficient clinical evidence to sustain a simple graft removal without re-transplantation, from the view of a potential risk of inadequate metabolic activity of the NL alone in an already compromised patient. At that point, we considered unacceptable the risk of further hepatic insufficiency.

The histological picture of the NL 3 weeks after APOLT, therefore, suggests that liver recovery may take

longer after INH-related injury than is seen for other aetiologies. The inconclusive pattern of the present case strongly suggests that—for INH-related FHF—APOLT is a technical procedure that needs further testing to ascertain the liver's potential for recovery after such a toxic injury. In conclusion, although we faced the clinical failure of the NL to sustain the patient metabolically in the presence of the graft HAT 3 weeks after APOLT, such a failure may be interpreted as time related. In fact, the histological picture in this particular case may suggest the potential for NL recovery after INH-related FHF. On these bases, although further experiences are needed before definitive conclusions can be drawn concerning the role of APOLT in INH-related FHF, attempts to rescue the native liver by this technique in this setting seem to be justified.

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