Abdominal Pain and Abnormal Liver Tests After Orthotopic Liver Transplantation

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THE CASE

A 53-year-old man is seen in clinic 4 months after receiving an orthotopic liver transplant (OLT) for two small (<3 cm in diameter) hepatomas which were discovered incidentally. The patient had a history of heavy alcohol use in his twenties and thirties, but has not used alcohol for over 10 years. Liver histology on the resected organ revealed early micronodular cirrhosis with the two tumor nodules localized to the right lobe. He has been well since leaving the hospital. His T-tube was removed 2 weeks prior to the clinic visit and subsequent endoscopic retrograde cholangiopancreatography (ERCP) (Figure 1). The patient experienced immediate severe discomfort when the tube was withdrawn and he was admitted to hospital for over-night observation and narcotic analgesia. The pain improved by the next day, when an abdominal ultrasound examination was performed; this showed no obvious fluid collection(s) that might suggest a bile leak. His pain persisted for about 1 week, and was managed with oral analgesia. Liver function tests (LFTs) carried out during the overnight hospitalization revealed mildly elevated serum bilirubin at 1.7 mg/dl (normal <1 mg/dl) with aspartate and alanine aminotransferases (AST and ALT) of 180 IU/l and 220IU/l, respectively (both mildly elevated). Alkaline phosphatase was also elevated, at 310 IU/l. Cytomegalo-virus (CMV) serology was positive (a conversion from negative before the transplant).

As the abnormal LFT values have persisted, the patient has been sent with a request for ERCP to define his biliary anatomy. Figure 1 shows one view of his cholangiogram. The very distal part of the common bile duct (CBD) is obscured by the endoscope; there is also a pool of contrast in the duodenal bulb. Other views of the distal CBD show no evidence of obstruction. Bile appeared to drain freely from the papilla.

MODERATOR'S QUESTIONS

Based on the history provided, I would like to ask Dr Muñoz-Navas for his comments on the case. Was the ERCP indicated? How do you interpret the cholangiogram? Are any therapeutic interventions indicated? And what does the literature say about the utility of ERCP for evaluating abnormal liver serology following liver transplantation?

GUEST DISCUSSANT'S REPLY

Thank you very much for the invitation to review this interesting case. The patient is a 53-year-old man who received an orthotopic liver transplant (OLT) in the setting of cirrhosis (probably alcoholic) with two small hepatocellular carcinomas (HCCs) of diameter <3 cm. This is a good indication for liver transplantation, because most hepatologists favor OLT for managing HCCs rather than liver resection, especially when the tumors are single and <5 cm in diameter, or when there are three or fewer nodules each <3 cm in diameter, without extrahepatic lesions. The reported 5-year survival of OLT in this setting is around 70% [1]. This patient made an uneventful recovery from his OLT and was able to leave the hospital for convalescence.

At 4 months after getting his new liver, the patient experienced severe abdominal discomfort that was clearly related to the act of removing the T-tube. This episode required overnight hospital admission and narcotic analgesia. His laboratory tests showed elevations in serum bilirubin, ASL and ALT, and alkaline phosphatase. His CMV serology was noted to have converted from negative pre-operatively to positive. The abdominal pain slowly diminished but the patient needed oral analgesia for a week, and his LFT abnormalities persisted. For these reasons, ERCP was requested. The clinical data suggested a bile leak. We would have expected to visualize an abdominal fluid collection by ultrasound examination if the leak was of any magnitude. However, as the old saying goes, "absence of evidence is not evidence of absence": the leak may have been small and short-lived, with no significant accumulation of fluid. A repeat abdominal ultrasound examination would have been useful before proceeding with more invasive studies [2], to look for delayed accumulation of a "bilioma". Additional techniques for evaluating possible bile leaks include competed tomography scan, radionuclide (e. g. ^{99m}Tc HIDA) scanning, and magnetic resonance cholangiography. The ERCP showed dilatation of the native (CBD) with a persistent T-tube track. There is a possible stricture at the duct-to-duct anastomosis with no dilatation above (i.e. of the donor bile duct). The dilatation of the native CBD is almost certainly the result of denervation secondary to surgery. Since the apparent "stricture" of the anastomosis does not cause dilatation above it, I do not consider it to be functionally important. Most small bile-duct leaks heal spontaneously [3]. However, it may be appropriate, in the setting of a suspected recent leak, to place a biliary stent or nasobiliary drain, or to perforen biliary sphincterotomy at the time of ERCP. In this particular case, I would have been tempted to place a 10-Fr straight biliary stent through the papilla without prior sphincterotomy. This is less troublesome for the patient than a nasobiliary drain and less likely to cause complications than a sphincterotomy. If biliary stones or sludge had been seen, we would have a good excuse for performing sphincterotomy.

Inadvertent early removal of T-tubes is a well known cause of bile peritonitis. However, routine delay of T-tube removal (2-5 months) in transplant patients has not decreased the incidence of bile leakage [3]. This is because the maturation of the T-tube track in immunosuppressed liver-transplant patients takes much longer than in nonimmunosuppressed patients. For this reason, many centers have abandoned the routine use of T-tubes, with encouraging results [4,5].

ERCP is useful following OLT in patients with suspected biliary fistula or bile-duct obstruction. Endoscopic methods have been used to treat biliary leaks, strictures, stones/casts, and papillary stenosis related to transplantation [6]. Abnormal LFTs after

OLT can be caused by a wide range of problems, not just bile leaks; other causes, such as hepatic arterial occlusion, allograft rejection, and viral infection have to be considered [3]. Liver biopsy may be helpful, especially when the diagnosis is rejection or viral (CMV) infection, the latter being encouraged by marked suppression of cell-mediated immunity, which is also an independent risk factor for opportunistic and fungal infection [7]. Identified risk factors for post-OLT infection include the type of biliary anastomosis, transfusion requirement at surgery, surgical complications, duration of the surgery duration of post-operative ventilation, serologic status of the donor and recipient, steroid use, anti-lymphocyte serum use to treat rejection, and pre-transplant and post-transplant antibiotic use [8]. The three potential sources of CMV are the donor liver, cellular blood products, and reactivation of endogenous (latent) virus, which has a prevalence of around 75% in OLT recipients. Most of the clinical CMV syndromes occur in liver-transplant patients between the 3rd and 16th week after transplantation [9]. Clinically, it is very important to make the distinction between CMV disease and CMV infection. CMV disease is defined as an invasive CMV infection with either histologic evidence (pathognomonic CMV-infected cells with their characteristic inclusions or positive immunochemistry using in situ hybridization), or a positive CMV culture from deep tissue specimens (e. g. liver biopsy, endoscopic mucosal biopsy or brushings, etc), or demonstrated viremia in the setting of clinical manifestation [9]. In this patient, the change from seronegative to seropositive for CMV and the abnormal liver tests strongly suggest the possibility of graft dysfunction due to CMV disease. Patients with CMV disease are treated with a reduction, if possible, of the immunosuppressive treatment and (in particular) tapering of the steroid dose, plus specific antiviral therapy with ganciclovir.

MODERATOR'S COMMENTS

Dr Muñoz-Navas is correct in stating that the biliary anatomy is probably irrelevant to the patient's current problem with persistently abnormal liver serology (LFTs). The cholangiogram shows a persistent fistulous track at the site where the T-tube had been, and a narrowing at the site of the donor-to-recipient bile-duct anastomosis. It is not uncommon for there to be a mismatch between the donor and the recipient bile-duct diameter, causing the appearance of a possible stricture at the anastomosis. As our expert notes, the lack of dilatation above (proximal to) the "stricture" militates against significant mechanical obstruction. In fact, a small balloon was pulled through this site without resistance at the time of ERCP. The apparent fistula at the site where the T-tube had been has a blind ending, suggesting that it has sealed off. It is likely that the patient's acute pain attack was the result of a small bile leak at the time of the T-tube removal. The lack of a bile collection (biloma) on ultrasound scanning does not exclude this possibility. In this patient's case, the problem appears to have been self-limiting. As the patient's pain had all but resolved at the time of our ERCP, and we could not demonstrate a collection beyond the fistula, we felt that the abnormal LFTs were most likely due to parenchymal disease. However, the hepatologist managing the patient disagreed and requested that we place a stent to assess the effect. A 7-Fr straight stent was placed with the tip above the pseudostricture. The following day the liver tests were worse, with a bilirubin up to 3.3 mg/dl and equivalent rises in transaminases and alkaline phosphatase. The patient re-ported an increase in abdominal discomfort. Although the liver tests progressively returned to their pre-ERCP and stent-placement

levels, we elected to remove the stent at day 5, considering it unlikely that further stenting would benefit this patient. A subsequent liver biopsy showed changes consistent with CMV infection of the graft. This was treated aggressively, as outlined above. This case serves to demonstrate that not every cholangiographic abnormality is indicative of active pathology. To paraphrase the famous saying, even if it walks like a duck, and quacks like a duck, in the post-transplant patient it may be a platypus! Many thanks to Dr Muñoz-Navas for his excellent evaluation of this case.

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Figure 1. Cholangiogram obtained at endoscopic retrograde cholangiopancreatography (ERCP) in a 53-year-old man who previously had an orthotopic liver transplant (see text for details).