Editorial

Liver disease of uncertain cause

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When I began to study the clinical epidemiology of liver injury after myeloablative conditioning regimens and hematopoietic cell transplant, it was apparent that about 10–20% of patients who evinced liver dysfunction post transplant could not be readily classified as to etiology.^{1,2} For research purposes, I created a separate category for these patients, Liver Disease of Uncertain Cause.

The case reported by Favre *et al* in this issue is reminiscent of my experiences in dealing with diagnostic uncertainty when patients develop liver problems after transplant. Their patients developed elevated serum ALT at day 13 and mild hyperbilirubinemia and hepatomegaly at day 15 after a myeloblastic regimen containing cyclophosphamide, total body irradiation, and thioTEPA. When serum ALT levels exceeded 1000 U/l, the authors made a clinical diagnosis of acute hepatitis B because of the donor's HBV antibody status and the patient's pre-existing HBV infection. Treatment was started with horse antilymphocyte globulin and mycophenolate mofetil to blunt HBV-specific donor T-cell activity in the liver. Over the ensuing weeks, the patient's liver returned to normal and she ultimately seroconverted to anti-HBs.

When I reviewed this paper, I was skeptical that acute hepatitis B was the diagnosis, for the following reasons: (1) the patient had been started on lamivudine before the transplant (a highly effective strategy to prevent HBV-related liver damage after HCT) and there was insignificant viral replication after transplant, as judged by serum HBV DNA levels; (2) the patient's liver disease began before substantive engraftment of donor cells; (3) the sudden onset of hepatomegaly seemed out of proportion to the degree of viral replication, the paucity of donor T-cells, and ongoing immunosuppressive therapy; and (4) there was no proof that HBV-antigen-reactive donor T-cells were present in the patient.³ From my disadvantageous perch thousands of miles away from the bedside, my first hypothesis would have been that conditioning therapy had caused sinusoidal liver injury. Three liver-toxic drugs had been used in the conditioning regimen in high doses, and the somewhat later appearance of liver injury is typical of thioTEPA-related sinusoidal damage (sinusoidal obstruction syndrome, also known as venoocclusive disease of the liver).⁴ When we examined the causes of extreme elevation of serum ALT among 2136 consecutive patients who were post transplant, the leading cause was SOS, with peak ALT values at day 23 ± 9 .⁵ This patient's peak ALT occurred at day 16. The cause of elevated ALT in patients with SOS is likely ischemia, as embolized sinusoidal endothelial cells and extensive deposition of collagen within sinusoids compromise perfusion of hepatocytes in zone 3 of the liver acinus. Thus, my initial diagnosis of this patient's liver disease would have been SOS. The authors do not think that SOS

was likely because the published criteria for SOS were not met. As the author of the Seattle criteria for diagnosis of SOS, I can fairly point out that these criteria were established primarily for research purposes, that is, to have a high positive predictive value for toxic sinusoidal injury, as proven by liver histology. However, the spectrum of clinical signs and symptoms of sinusoidal injury is far wider, encompassing ALT elevations, isolated jaundice, isolated weight gain, gall bladder wall edema, and pain. When we examined autopsy liver tissue using a study design where the pathologist was blinded to clinical information, roughly half of the transplant patients whose liver dysfunction had been classified as Liver Disease of Uncertain Cause proved to have toxic sinusoidal injury – despite failing to meet the published criteria for the diagnosis of SOS.⁶

What should be done in such cases to remove uncertainty? Should anti-T-cell therapy have been instituted in this case without a clear diagnosis? Had I been at the bedside, I would have suggested a transvenous procedure that measured the wedged hepatic venous pressure gradient and obtained liver tissue for histology.^{7,8} These procedures can be done safely even in thrombocytopenic transplant patients and provide prompt diagnostic information.

The point here is that uncertainty in clinical diagnosis is relatively common in dealing with liver disease after transplant. Also, Occam's Razor may be disposable in the transplant setting – that is, more than one pathophysiological process may be present at the same time. I have never regretted measuring the hepatic venous pressure gradient and looking at liver history in order to resolve uncertainty. As it turned out, this patient's liver disease improved after the institution of anti-T-cell therapy. Whether this therapy was causal in the resolution of liver disease, or whether attribution of recovery to therapy was '*post hoc, ergo propter hoc*' reasoning, can never be known with certainty.

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