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Fulminant hepatic failure post liver transplantation: clinical syndromes, correlations and outcomes

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Abstract This paper reports the clinical syndrome of fulminant hepatic failure (FHF) following liver transplantation. FHF was defined as the sudden onset of liver failure [encephalopathy and prolonged International Normalised Ratio (INR)] without arterial thrombosis in the setting of a liver allograft. FHf post-transplant was seen in 8/154 (5.2 %) adult patients undergoing transplantation. These eight patients developed a clinical syndrome characterised by : (a) a rapid rise in ALT levels to above 1000 U/l (mean maximum 1600 U/l), (b) a sudden increase in the INR to above 5 (mean maximum 5.6), (c) the development of high fever, (d) the persistence of thrombocytopenia (mean nadir 40×10^9/dl), (e) a progressive rise in the bilirubin (mean maximum 400 μmol/l) and (f) the development of hepatic encephalopathy. In seven cases this syndrome occurred following good initial graft function at day 6 post (mean)-transplant. In one case the above syndrome developed immediately after liver transplantation. Four of the eight patients developed multiorgan failure associated with systemic acidosis (mean pH 6.84). All of these patients died (mean day 11). Four patients developed systemic alkalosis. Two of these four patients underwent successful retransplantation (on days 12 and 13) and remain alive at a mean of 11 months post-transplant. Six of the eight patients received OKT3 therapy without any apparent affect on clinical outcome. Compared to a control group of patients (n = 28), 2/8 versus 2/28 had a positive cross-match with donor lymphocytes (P = NS), 1/8 versus 7/28 were ABO-non-identical (P = NS), 3/8 versus 10/21 had total MHC mismatches (P = NS) and 5/7 versus 6/16 had UW ischemic times above 10 h (P = NS). No patients had main hepatic artery thrombosis on angiography although four patients had evidence of intrahepatic microthrombi or arterial necrosis at autopsy. In all cases the histology showed massive haemorrhagic necrosis. Three cases had evidence of veno-occlusive lesions whilst foam cell arteriopathy was seen in two cases. Immunofluorescence was performed in three cases. In two cases there was evidence of immunoglobulin, complement and fibrin deposition in blood vessels. In conclusion, we describe an uncommon clinical syndrome occurring post liver transplant. This syndrome represents humorally mediated allograft rejection but there seems to be no relationship with tissue matching (antibody, ABO, MHC) or donor ischaemic times. If recognised earlier in the absence of multiorgan failure, urgent retransplantation seems to be the only effective therapy.

Key words Liver transplantation, hepatic failure · Hepatic failure, liver transplantation

Introduction

The sudden loss of a human liver allograft is an uncommon event and is usually related to hepatic arterial thrombosis or failure of the transplanted organ to begin to function (so-called primary nonfunction) [3, 11]. Although some grafts are lost to uncontrolled acute rejection, this is unusual as rejection readily responds to standard increases in immunosuppressive therapy [9]. However, it is recognized that some grafts may fail suddenly for unexplained reasons. Hubscher et al. described 6 patients out of 85 transplant recipients who suffered acute graft loss and had the pathological features of massive haemorrhagic necrosis [8]. The pathological features in these patients also included foam cell arteriopathy and veno-occlusive lesions, suggesting a vascular aetiology perhaps related to a delayed "hyperacute" rejection syndrome. Clinical descriptions and correlations were not extensively examined in that report. In this paper we describe a similar syndrome in 8 of 154 adults undergoing liver transplantation and examine clinical features, correlations and outcomes.

Patients, materials and methods

The records of 154 adults who underwent orthotopic liver transplantation at our institution between January 1986 and December 1992 were reviewed. Our protocols for liver transplantation have been previously published and include routine immunosuppression with cyclosporin, azathioprine and prednisone [10]. There was no anticoagulation used in any of our patients apart from intra-operative, low-dose heparin to maintain veno-venous bypass. Control patients were selected by choosing four patients (two either side) closest to an index case. The syndrome of fulminant hepatic failure (FHF) was defined as the onset of liver failure (encephalopathy and a prolonged prothrombin ratio) without evidence of a major arterial thrombosis following human liver transplantation.

Eight patients fulfilled the criteria defined above. There were six males and two females with an average age of 44 years (range 31–56 years). The underlying original diseases were: primary sclerosing cholangitis (PSC; $n = 2$), alcoholic liver disease ($n = 2$), Wilson's disease ($n = 1$), autoimmune chronic active hepatitis ($n = 1$), chronic hepatitis B ($n = 1$) and FHF secondary to drug reaction ($n = 1$). For each of these eight patients, four control patients with transplants either side of the index case where chosen for the study. Due to the occurrence of the syndrome in two successive patients, only 28 control subjects were able to be selected.

Results

Clinical features

Seven of the eight patients had good initial graft function with dark bile production (in non-PSC patients), falling serum bilirubin, falling liver transaminases and improving prothrombin index. At a mean day 6 post-transplant, however, there was a rapid rise in ALT levels to above 1000 U/l, a significant prolongation of the International Normalised Ratio (INR) and a falling platelet count (as opposed to increasing count by day 7 in controls). The serum bilirubin level, which had begun to increase in these patients at day 4, continued to rise. The biochemical features were associated with high fever, abdominal discomfort and tachycardia in all patients. There was no difference between controls and index patients with regard to the pattern of the peripheral white blood cell response at the onset of the illness. Within 24–48 h there was evidence of clinical encephalopathy, persisting hyperbilirubinaemia, persistent transaminitis (> 1000 U/l), thrombocytopaenia and abnormal coagulation studies (Fig. 1). In one patient the above syndrome developed progressively starting on day 1 post-transplant.

Table 1

Case no.	Maximum systemic ph disturbance	Day of occurrence	Multiorgan failure
1	7.45	12	–
2	7.53	12	–
3	7.5	6	–
4	7.49	7	+
5	6.97	8	+
6	6.87	11	+
7	6.92	15	+
8	6.27	7	+

Table 2 Summary of pathology

Case no.	Massive haemorrhagic necrosis	Arterial micro-thrombi	Veno-occlusive changes	Bile duct necrosis	Cell rejection
1	+	+[a]	+	–	+
2	+	–[a]	–	–	+
3	+	–	–	–	–
4	+	+	+	–	+
5	+	+	–	–	–
6	+	+	–	+	–
7	+	–	–	–	–
8	+	–	+	–	–

[a] Arterial foam cell arteriopathy

Table 3 Radiological findings and outcomes

Case no.	Hepatic arteriography	Outcome	Time to death or ret x (days)
1	Normal	Retransplantation	13
2	Normal	Retransplantation	12
3	Sluggish flow	Died	8
4	Normal	Died	7
5	Not done	Died	10
6	Sluggish flow	Died	14
7	Sluggish flow	Died	14
8	Normal	Died	10

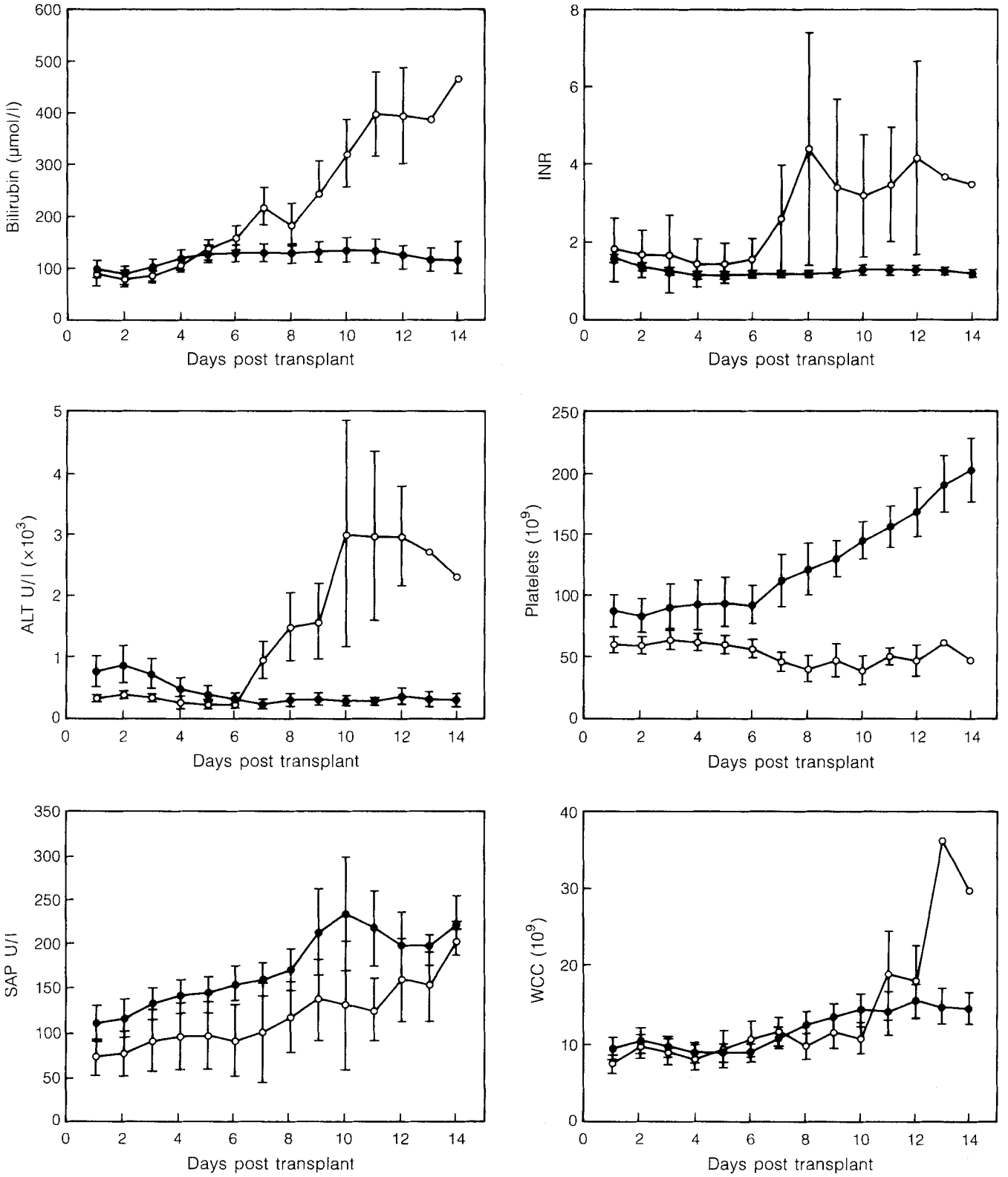

Fig. 1 Biochemical and haematological parameters in 8 patients with fulminant hepatic failure (*) and 28 control patients (●). Results are expressed as means + SD

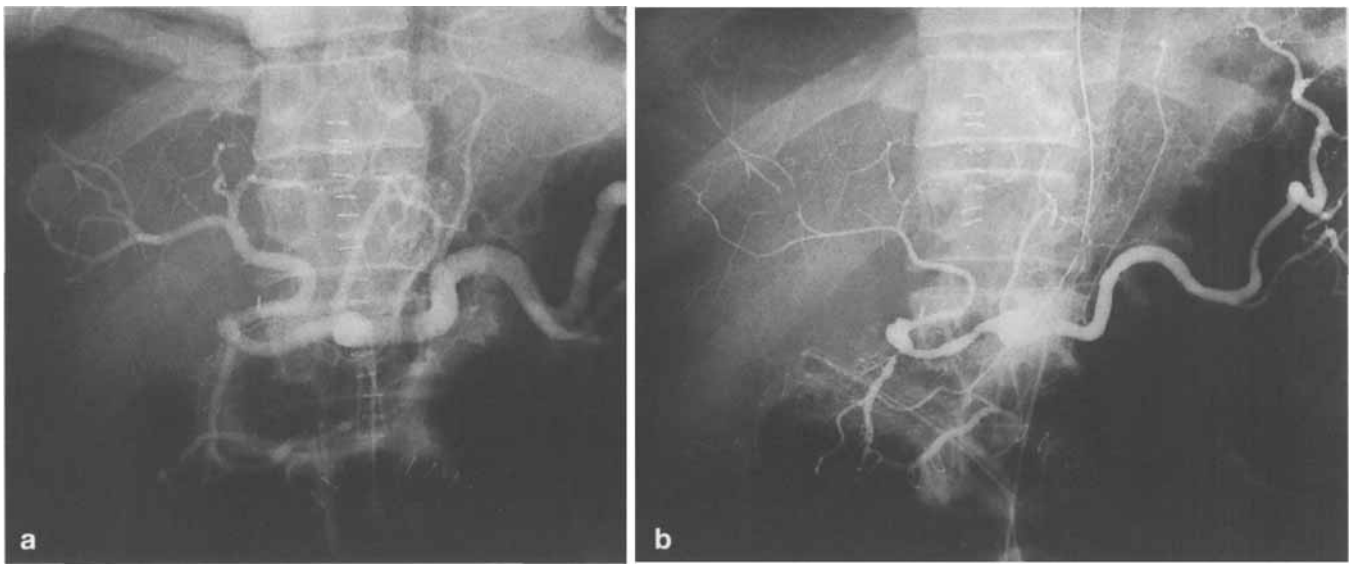

Fig. 2 a, b Hepatic angiogram of patient 7: **a** at the onset of hepatic function and **b** 48 h later, showing the development of diffuse arterial narrowing and segmental obstruction with low hepatic blood flow

The acid-base disturbances of these patients were of interest. Case numbers 1–8 refer to the same cases in Tables 1–3. Therefore, it is possible to crosscorrelate acid-base balance, pathology, radiological findings and outcomes. As seen in Table 1, four patients (case nos. 1–4) developed systemic alkalosis while four others (case nos. 5–8) rapidly developed systemic acidosis associated with multiorgan failure (renal, lung, heart). Only one of the four patients with systemic alkalosis developed multiorgan failure; this was the patient who developed the clinical syndrome immediately after transplantation (case 4).

Radiological investigations

Hepatic angiography was performed on seven patients. The hepatic artery was completely patent in seven patients but in three of these there was sluggish flow with the allograft. Sluggish flow occurred in 2/4 patients with systemic acidosis and 1/4 with systemic alkalosis. In one patient (case 7), the hepatic arteriogram showed normal blood flow with a patent hepatic artery at the onset of liver dysfunction. However, 72 h later, the hepatic angiogram was repeated. This showed multiple intrahepatic strictures with very sluggish flow within the allograft but no major arterial thrombosis (Fig. 2).

Outcomes

Six of the above patients died (mean day 11 post-transplant) while two underwent successful retransplantation. Four deaths were associated with multiple organ failure, one with cerebral oedema and one with cerebral haemorrhage. The two survivors had systemic alkalosis and no evidence of multiorgan failure. All patients received pulses of methylprednisolone and six patients received at least one dose of OKT3 therapy during the course of their illness.

Pathology

The pathological features of each case are summarized in Table 2 and examples are seen in Fig. 3. All cases had evidence of massive haemorrhagic necrosis of hepatocytes. In all cases the main hepatic artery was patent. There were, however, thrombi with fibrin deposition within segmental intrahepatic arteries in three cases. Two cases had evidence of foam cell arteriopathy (both had systemic alkalosis and normal angiography). The bile duct anastomoses in all patients were intact, although at autopsy there was evidence of microscopic bile duct necrosis in two patients. Veno-occlusive lesions were seen in three patients (all with normal angiography). There was evidence of portal tract inflammation consistent with mild acute cellular rejection in three patients. All of these patients had systemic alkalosis and two of them were the only ones to undergo retransplantation and survive. Immunofluorescent studies were performed in only three cases (case nos. 5.7). In two cases (cases 5.7) there was evidence of immunoglobulin (IgG and IgM), fibrin and complement deposition (C3 component only) in hepat-

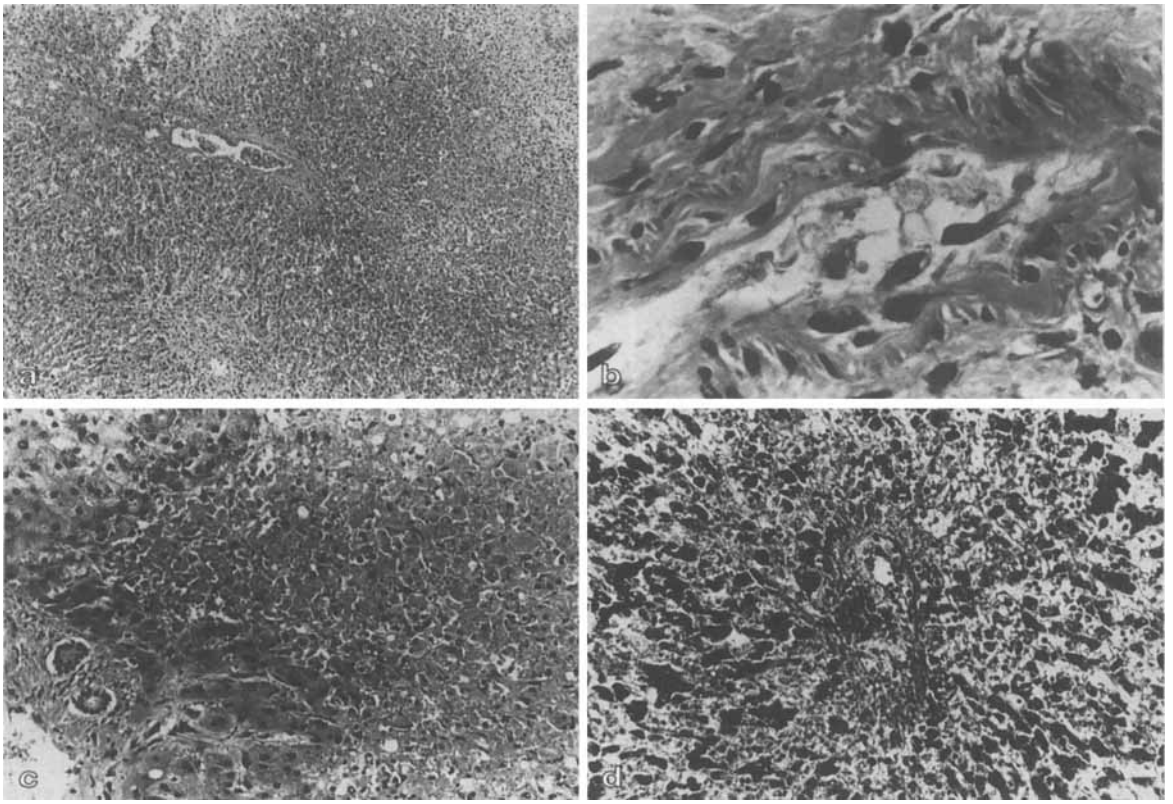

Fig. 3 a–d Representative examples of pathology fulminant hepatic failure in post liver transplantation: **a** low-power view of massive haemorrhagic necrosis (patient 5). H & E, x200; **b** high-power view of segmented artery in portal tract showing initimal hyperplasia and early foam cell formation suggestive of arterial rejection (patient 1). H & E, x2000; **c** higher power view of graft necrosis (patient 8) with preservation of periportal hepatocytes. No inflammatory cells are seen in the adjacent portal tract. H & E, x500; **d** veno-occlusive lesion seen in patient 8 showing almost total occlusion of cental vein. Vein wall outlined by Masson stain, x500

ic arterial vessel walls and sinusoids. At autopsy, evidence of related sepsis was only seen in one patient (case 8), who had evidence of aspergillus bronchopneumonia.

Correlations

An analysis was undertaken to look for correlations between ABO blood group or MHC matching, lymphocytoxic antibody crossmatch and donor ischemic time in the 8 index cases compared to the 28 controls. This analysis is shown in Table 4. As can be seen, there were no significant differences in ABO blood group identity, percentage lymphocytoxic cross-match, MHC mismatches at any locus and donor ischemic time between controls and index patients.

Discussion

The clinical syndrome we have described is almost identical to that of the six patients described by Hubscher et al. [8]. Clinically, there was an explosive onset of acute liver failure. This usually occurred in a patient otherwise doing well at the end of the 1st week following liver transplantation in the absence of major hepatic/arterial thrombosis. The clinical course progressed rapidly. Unlike the six patients described by Hubscher et al., not all of our patients died. The two patients who did not develop multiorgan failure or systemic acidosis were able to undergo successful retransplantation. In our experience and that of Hubscher, increased immunosuppressive therapy failed to alter the progressive deterioration.

The pathology in our eight patients was also almost identical to that described by Hubscher et al. [8] and distinctly different from the features of acute cellular rejection. Massive hepatic necrosis was the predominant feature. We found evidence of veno-occlusive lesions in three patients versus four out of six in the Hubscher study. Foam cell arteriopathy was similar in both studies (2/8 vs 2/6).

Hubscher et al. claimed that the clinical-pathological picture described above seemed to comprise a specific "post-transplant syndrome" [8]. However, our descriptions do not really help in defining the aetiology of the

Table 4 Analysis of variables

Variable	Index cases	Controls
ABO-Identical	7/8	21/28
ABO-Non-Identical	1/8	7/28
ABO-Incompatible	–	–
Positive lymphocytotoxic AB crossmatch with donor cells	2/8	2/28
Total MHC mismatch	3/8	10/21
Total class II mismatch	5/8	12/21
Total class I mismatch	5/8	17/21
Total class II match	0/8	1/21
Any class II match	3/8	9/21
Donor ischaemic times > 10 H in UW solution	5/7	6/16
Mean donor ischaemic time (hours) in non-UW solution	4.41	4.52
Mean donor ischaemic time (hours) in UW solution	9.45	9.26

graft injury. We believe that the syndrome is likely to represent predominantly humorally mediated graft rejection and is in agreement with the speculation by Hubscher. Immunoglobulin and complement deposition was seen in two of our three cases studied. This is intriguing and also supports a humorally mediated graft injury. It is possible that these antibodies are directed against endothelial antigens, as described by Cerilli et al. [2]. There are certain similarities between graft loss in our study and graft loss secondary to ABO incompatibility or positive lymphocytoxic antibody crossmatches [4, 5]. In the study by Demetris et al. massive hepatic necrosis with the deposition of antibody and complement were predominant pathological findings in grafts that were lost to ABO incompatibility [4]. Massive hepatic necrosis was also a feature of graft loss in patients with more than 50% lymphocytoxic antibody donor crossmatches [5]. The focal bile duct necrosis and intrahepatic arterial microthrombi seen in our patients were also seen in a minority of patients. In our series there were no cases involving ABO incompatibility but two patients did have strongly positive crossmatches with donor cells. No lymphocytoxic crossmatches were seen in the patients reported by Hubscher et al., although there was one case of ABO incompatibility. Isolated case reports of humorally mediated or "hyperacute" liver allograft rejection have been reported with similar pathology to our cases and to those reported by Hubscher [1, 7, 12]. These reports supplement the hypothesis that the clinical-pathological syndrome reported here represents humorally mediated graft rejection.

The role of sepsis as a complicating or precipitating factor in at least one of the cases, however, needs to be addressed. Sepsis may occur secondarily in this acute situation or, alternatively, it is possible that it may be the underlying pathogenic mechanism as it may present as FHF [6]. This possibility makes the diagnosis of hyperacute rejection even more difficult. It is clear in this clinical situation, particularly if there is systemic acidosis and multiorgan failure, that sepsis needs to be actively investigated and treated.

The relationship of the above syndrome to acute cellular rejection needs to be examined. In two of our patients, the above syndrome developed rapidly following the diagnosis of acute cellular rejection compared to in three out of six of Hubscher's patients. However, there was only a mild cellular infiltrate in these cases. In our other six patients, the first sign of graft dysfunction was associated with the rapidly developing clinical features described above. The data seem to imply that there may be an overlap between severe, unresponsive and progressive acute cellular rejection and the syndrome.

Everything described above is consistent with an antibody – mediated pathogenic mechanism resulting in graft loss. Once the clinical picture described above arises, there seems little place for routine increases in immunosuppressive drugs. Emergency retransplantation is the only effective therapy. However, if antibody is the predominant effector mechanism, then the role of urgent plasmapheresis needs to be explored, either as primary or bridging therapy to retransplantation.

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