Recurrence of autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis after liver transplantation

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Liver transplantation (LT) is the standard therapeutic approach for the treatment of end-stage acute and chronic autoimmune liver disease as autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

Results of liver transplantation in these indications are good with a patient survival after LT at 5 years of 85%.

However several series have reported a possible recurrence of primary autoimmune liver disease after liver transplantation. Concerning all these three autoimmune liver diseases, recurrence of the disease on the graft may have multiple clinical, biochemical, histological and radiological expression influenced by different factors as the diagnostic methods used, the degree of immunosuppression and the genetic background of the recipient.

We would like with this overview to describe the different pattern of recurrence of these autoimmune liver disease, their potential influence on the liver graft and their therapeutic management.

Recurrence of autoimmune hepatitis after liver transplantation

The first case of recurrence of AIH after LT was reported by Neuberger *et al.* (1). The authors described 18 months after LT a recurrent disease with high level of transaminases and autoantibodies titers ; moreover, liver graft biopsy revealed a mononuclear cell infiltrate, piecemeal necrosis and bridging collapse (1). Remission was successful with an increase in immunosuppressive therapy. Since this first demonstration of autoimmune disease on the graft, several studies have demonstrated a recurrence of the liver disease on the graft. The main studies are detailed in table 1.

The frequency of recurrent AIH after LT is highly variable with an incidence ranging from 17% to 82% (2-7), as reports are different concerning time of follow-up and use different definitions, based on biochemical abnormalities, autoantibody titers, histologic lesions and/or steroid dependency. The main problem to establish recurrence of AIH is the lack of a single diagnostic marker and we will focus on these different diagnostic parameters to assess or not the diagnosis of recurrence of AIH.

Concerning biochemical abnormalities

In the majority of cases, increased serum transaminases are a feature of recurrent of AIH on the liver graft. However this feature lacks of specificity and sensibility. We and other groups have demonstrated that several patients who underwent systematic liver biopsies have histological features of recurrent autoimmune disease (6,7).

Concerning serum autoantibodies levels

Autoantibodies are markers of autoimmune hepatitis. Concerning recurrence, the interest of this marker is more discussed ; however, in most studies, when recurrence occur, autoantibodies level have persisted or the level is higher than before liver transplantation (4,6,7).

Concerning the type of antibodies, interestingly, in our recent study anti-SLA antibodies, which are specific markers of autoimmune hepatitis, were detected in 2 of the 7 patients who had recurrence but not in the patients who remained free of recurrence (7). Moreover, in one case, it was the sole antibody detected. However, these results concern a small number of patients, and further investigations are necessary before recommending routine anti-SLA antibody screening for suspected recurrence.

Histological findings

Histological features with the presence of numerous plasma cells and prominent interface hepatitis have been described in the cases of recurrence. However various degree of these features may be present because of the different type of immunosuppression (8).

Some of these histological features are not specific and may be present in cases of HCV, HBV infection or rejection.

In our recent study, histological recurrence was diagnosed in 7 of the 17 patients with a mean of 2.5 years after LT. In 4 of these 7 patients, histologic signs of recurrence were found on protocol biopsies between 1

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Table 1. — **The main reports of recurrence of AIH after liver transplantation**

Authors	Number of patients	Lenghth of follow-up (months)	Incidence	Delay of incidence (months)	Evolutio	Risk
Prados *et al.*	2	44 (8-	9/27	30 (8-	Complete remission with immunosuppressive therapy in 50% of case	Type 1 vs type 2
Milkiewicz *et al.*	4	5	13/47 (28%	29 (6-	3 lost	–
Gotz *et al.*	2	4	18/22 (82%	–		–
Reich *et al.*	3	27 (6-	6/24	15 (12-	4 lost	Chronic hepatitis versus fulminant hepatiti
Ayata *et al.*	1	67 (12-	5/12	4 (1-	2 patients become chirrhoti	severe histological features before OL
Gonzalez-Koch *et al.* 200	4	7	7/41	5	good response to immuno-suppressive therapy	HLA DR3/DR4 of the
Duclos-Vallee *et al.* 200	1	>	7/17	28 (7-	3 lost	–

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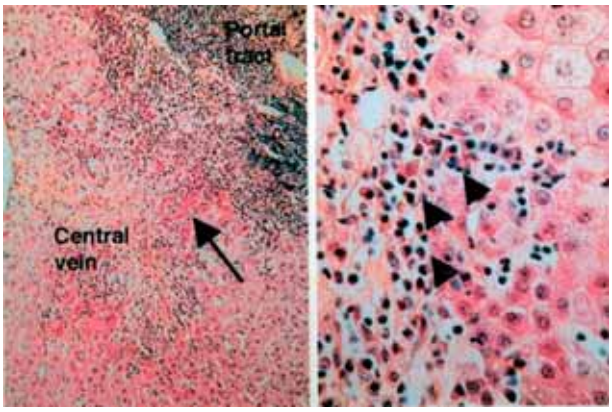

Fig. 1. — A typical example of histologic recurrence 2 years after LT with presence of interface hepatitis (black arrow) and numerous plasma cells in the periportal tract.

and 5 years after LT (mean, 2.5 years). The histological features consisted of portal plasmocytic infiltration in 4/4 patients (moderate or severe in 3 and mild in 1) ; piecemeal necrosis in 3/4 patients ; lobular activity in 4/4 patients ; and fibrosis in 4/4 patients (severe in 1, moderate in 2 and mild in 1) (7). Figure 1 shows a typical example of histologic recurrence 2 years after LT with presence of interface hepatitis and numerous plasma cells.

Risk factors

Several studies have focused that recurrent disease was more frequent in cases of HLA-DR3-positive recipients of HLA-DR3 negative grafts (2,6,9). However, these results were not confirmed by other studies including ours. The small number of the patients studies represent a good reason for these discrepant findings. Of course differences in the genetic profile of the donor and recipient populations in different centers may also be involved. Interestingly in our recent study, two of our patients who developed severe clinical recurrences were HLA DR3, and one of these was A1B8DR3 ; the other patient was A1B8DR4 and her donor was A1B8DR3 (7).

It also has been suggested that type II AIH recur more often than type I (3,7,9). Pehraps this fact is related that type II is a more aggressive disease (10) ; moreover, it has been recently suggested that a severe activity detected on the native liver was found to be a predictor of recurrent AIH (5).

Outcome

In most of cases, reascension of immunosuppressive therapy permit a remission of the recurrent disease. However, we suggest that immunosuppressive therapy may be decreased very slowly (7). However, in some cases the disease progress to a severe form, necessitating a change immunosuppressive therapy and eventually a retransplantation. In cases of retransplantation a high incidence of recurrence, rapidly after transplantation has been observed (4).

To avoid these issues, we have suggested that recurrence may be treated the more earlier as possible (7). We have recently underlined the importance of late protocol biopsies because normal biochemical liver tests, gamma globulin levels and the absence of anti-tissue autoantibodies may mask the recurrence of autoimmune disease (7).

In few patients, biological and histological recurrence may occur more than 10 years after OLT. Two severe cases in our series occurred 10 and 14 years after OLT (7,11). These late recurrences observed suggest that immunosuppressive therapy should be pursued for more than 10 years and that any dose reduction should only be undertaken with care (7,11,12).

De-novo autoimmune hepatitis

De-novo autoimmune hepatitis concern the appearance of autoimmune patients transplanted for another

Table 2. — **Description of the main series describing *de novo* autoimmune hepatitis**

Authors	Recipient	Incidence	Delay post LT (months)	Time of follow-up after diagnosis (months)	Outcome
Kerkar *et al.* *Lancet*, 1998	Children	7/180 (3.8%)	24 (6-45)	9 (4-24)	Good response to immunosuppressive therapy
Gupta *et al.* *Transplantation*, 2001	Children	5/155 (2.5%)	61 (18-108)	–	Good response to immunosuppressive therapy
Hernandez *et al.* 1997	Children	6/115 (5.2%)	–	–	Two lost graft
Heneghan *et al.* *Hepatology*, 2001	Adult	7/1000 (0.7%)	52 (4-86)	–	Two lost graft
Salcedo *et al.* *Hepatology*, 2002	Adult	12/350 (3.4%)	28 (6-97)	48 (3-65)	Lost graft in all untreated patients (n = 5), well outcome in patients treated with immunosuppressive therapy (n = 7)

liver disease than autoimmune or viral disease disease (13-18, table 2). The features consist of the apparition of autoantibodies and histological features suggestive of autoimmune liver disese. This syndrome was first described in children in whom indication for LT included extrahepatic biliary atreasia, drug-induced liver failure, alpha1-antitrypsin deficiency. The response to increased immunosuppression was good and the patients remained in remission. However, a study published by Heneghan *et al.* reported two cases among seven allograft recipients with *de-novo* autoimmune hepatitis who developed graft failure despite an increased immunosuppression.

De-novo autoimmune hepatitis represent a syndrom of "graft dysfunction mimicking AIH" or another model of self intolerance probably due to similar pathogenic mechanism than AIH.

Recurrence of primary biliary cirrhosis after liver transplantation

Description and rate of recurrence

The first cases of recurrence of PBC were reported by Neuberger *et al.* in 1982 (18). All three patients developed after LT cholestasis, reascension of antimitochondrial antibodies (AMA). Biopsies revealed portal inflammation, lymphoid aggregates, granulomas, bile duct injury, and ductopenia. (19).

Since this preliminary report, several studies have reported recurrence after OLT.

Polson *et al.* reported an incidence of 90% of recurrence of PBC after LT (20). Moreover few patients developed extrahepatic manifestations. Liver biopsies at time of recurrence were very suggestive of recurrence with presence of ductular proliferation, breaks in the bile duct membrane, lymphocytic aggregates within portal tracts, and granulomas.

In the study by Hübscher *et al.* 13/83 patients (16%) had signs suggestive of recurrence on liver biopsy (21). The characteristic portal tract lesions included mononuclear infiltrate, lymphoid aggregates, epithelioid granulomas and bile duct damage. Interestingly, twelve of these thirteen patients, were asymptomatic.

Balan *et al.* studied 60 patients with PBC for at least 1 year of follow-up. Florid duct lesions (granulomatous cholangitis) were seen in 5 of 60 (8%) PBC patients 2 to 6 years post OLT (22).

Our group studied 69 patients transplanted for PBC and 53 patients transplanted for other conditions (23). Six (8.7%) of the patients had signs of histological recurrence with inflammatory infiltrate, nonsuppurative destructive cholangitis, and ductopenia suggestive of recurrent disease. In another study, of our group, which studied 16 patients transplanted for PBC and who were followed at least 4 years after LT (24), antimitochondrial antibody titers had normalized 1 year after transplantation in 7 patients, declined in seven others and remained unchanged in two. Routine liver biopsies performed on a yearly basis did not disclose any pattern suggestive of primary biliary cirrhosis recurrence. AMA persist after LT, whether or not there is histological evidence of PBC recurrence. So, AMA do not appear themselves to be pathogenetic. Van de Water *et al.* who used a monoclonal antibody reacting with the inner lipoyl domain of PDC-E2) found that all sections from patients grafted for PBC showed a pattern of staining identical to that seen in the native PBC liver, whether or not there was evidence of disease recurrence (25).

A recent study by the Mayo Clinic used strict histologic criteria for recurrent PBC , on the histologic presence of a florid duct lesion which was identified in 14 of 100 patient of the PBC group (26). Three of the 14 florid duct lesions were identified after 7.2 years post-LT. Collectively, strict criteria for histologic recurrence of PBC were met in 17 of 100 patients (17%) of PBC study group. Fourteen of the 17 duct lesions meeting strict diagnostic criteria for recurrent PBC were identified in protocol biopsies. At the time of the first diagnostic lesions of recurrent disease, the alkaline phosphatases

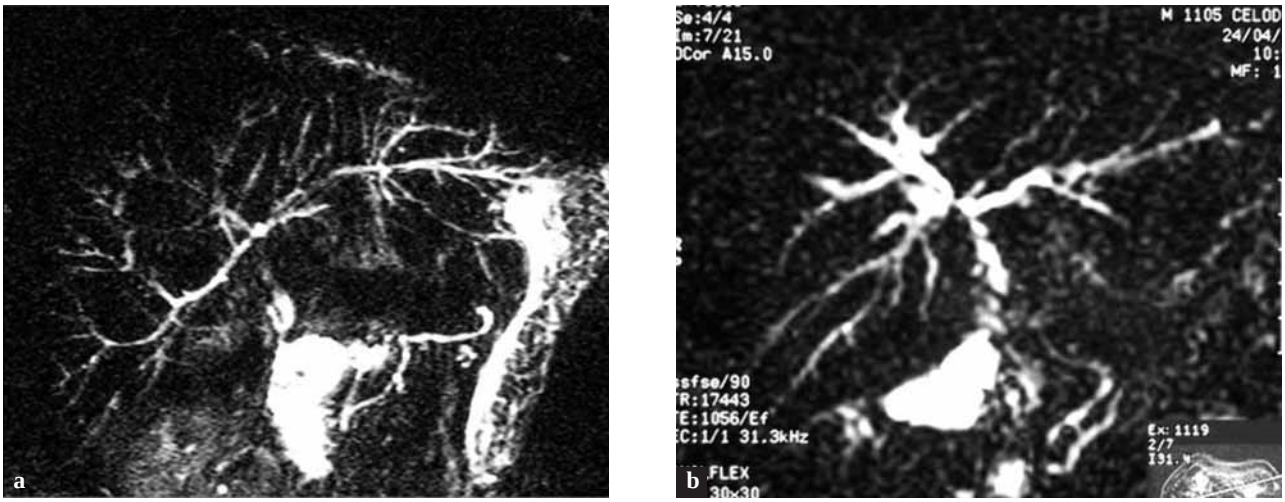

Fig. 2 a,b. — Radiologic features of recurrence with magnetic resonance cholangiography showing focal dilatation of intrahepatic biliary tract and irregular aspects of the walls of the intrahepatic bile ducts.

was known to be elevated in 8 of these patients (57%). Of the 17 patients diagnosed with recurrent PBC based on strict histologic criteria, 13 patients had detectable AMA at some time postoperatively. Serum AMA titers do not predict histologic recurrence of PBC. During the study period, only 2 of 17 patients with recurrent PBC based on strict histologic criteria showed histologic progression to septal fibrosis (stage 3) (26).

Risk factors

Recipient age, cold ischaemia and immunosuppression have been defined as risk factors in the Pittsburg study (27). Neuberger *et al.* showed that donor and recipient age, treatment with tacrolimus (compared with ciclosporin) and warm ischaemic time were the only significant risk factors for recurrence (28).

Outcome

Among the 400 patients in the Birmingham series, one patient required retransplantation after 8 years and one patient progressed to cirrhois 3 years afte the recurrent diagnosis. No statistical difference was observed in graft and patient survival between the group with or without recurrence (28). At the present time, the role of ursodeoxycholic acid in the treatment of recurrence must be demonstrated.

Recurrence of primary sclerosing cholangitis after liver transplantation

Description and rate of recurrence

PSC is a chronic cholestatic liver disease of unknown origin and follows a highly variable but virtually progressive course. The treatment of choice for PSC in patients with end-stage disease is liver transplantation. PSC accounts for 10% of all liver transplantations in North America, in Europe for 4% (29).

Most centers report post-transplantation survival rates which are comparable with those achieved in patients with other autoimmune liver diseases with one year patient survival exceeding 90% in recently published series (29-33). However, long-term patient survival was initially reported to be inferior as compared to patient survival rates in e.g. recipients of a liver allograft due to PBC. Recent studies have show a slightly retransplantation rate but not decreased long-term patient survival ; this increase retransplantation rate has been demonstrate to be related in particular to biliary strictures (34).

Studies from several centers have indicated that as many as 20-40% of PSC patients receiving a liver allograft will experience recurrent disease (35-41,44,45,47-49) (Table 3).

Recurrence of PSC, which was first suggested by Lerut *et al.* (42) in 1988 transplantation is difficult to diagnose and exclusion of other conditions commonly associated with intrahepatic and extrahepatic biliary strictures is necessary. Hepatic arterial occlusion and preservation injury can produce ischemic strictures which may mimic PSC features. Several mechanisms may be responsible for biliary strictures in PSC patients after LT ; I) hepatic artery stenosis or thrombosis, ii) graft preservation injury, iii), chronic rejection, iv) blood type ABO-incompatibility, possibly v) ascending infections from the choledochojejunostomy constructed during OLT, and vi) recurrent PSC.

McDonald *et al.* reported that three of the 6 patients who developed peripheral non-anastomotic were transplanted for PSC (43).

In a Birmingham study, the authors concluded that fibrous cholangitis was more common in transplant recipients with a diagnosis of PSC. Fibroobletrative lesions werte only seen in PSC recipients (44).

Table 3. — **Description of the main series describing recurrence of PSC after transplantation**

Reference	n	% of recurrence	Cholangio-graphy	Hist.
Harrison *et al.* 1994	22	14	–	+
Narumi *et al.* 1995	33	12.5	+	+
Sheng *et al.* 1996	32	25	+	–
Jeyarah *et al.* 1998	100	16	+	+
Goss *et al.* 1997	127	9	+	+
Kubota *et al.* 1999	53	6	+	+
Graziadei *et al.* 1999	120	20	+	+
Liden *et al.* 2000	47	9	+	–
Yusoff *et al.* 2002	12	17	+	+
Vera *et al.* 2002	152	37	+	+
Kugelmas *et al.* 2003	71	21	+	+
Khettry *et al.* 2003	42	14	+	+

The Mayo Clinic has defined recurrence of PSC following liver transplantation as : confirmed diagnosis of PSC prior to OLT and intrahepatic and/or extrahepatic biliary stricturing, beading and irregularities more than 90 days post OLT or fibrous cholangitis and/or fibro-obliterative lesions with or without ductopenia, biliary fibrosis, or cirrhosis-without hepatic artery thrombosis or stenosis, ABO incompatibility, chronic ductopenic rejection, early biliary strictures and anastomotic strictures (44).

It is obvious that MR cholangiography will be enable to diagnose and characterize PSC recurrence very precisely in the near future (46).

Concerning Risk factors

Cytomegalovirus infection and donor recipient gender mismatch have been proposed as risk factors of PSC recurrence. Pre-transplantation colectomy has been claimed to be associated with a lower rate of recurrence (39). With a multivariate analysis, Vera *et al.* showed that being a male and an intact colon before transplantation were associated with recurrence (47).

Outcome

In most cases, patients with recurrence of PSC are asymptomatic ; moreover medium term patient and graft survival does not appear to be affected. Of course several therapies as balloon dilation with or without placement of stents, surgical revision, or retransplantation are therapeutic options for biliary strictures of PSC recurrence (45,48,49).

Conclusions

Autoimmune liver diseases may recur after transplantation. However diagnosis of recurrence could be difficult and well-defined clinical, biochemical, serologic, histologic and radiologic criteria are required. A particular survey of these patients is justified particularly to have a very early diagnosis of recurrence which could justify changing the protocol survey and the immunosuppressive therapeutic approach.

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