Egyptian Liver Journal

CASE REPORT

Open Access

Late acute cellular rejection after switch to everolimus monotherapy at 11 months following liver transplantation

Chantelli Iamblaudiot Razafindrazoto[1*], Noémie Trystram[2], Gustavo Miranda Martins[3], Christiane Stern[2], Frédéric Charlotte[4] and Pascal Lebray[2]

Abstract

Background: Acute cellular rejection beyond the 6th month posttransplant is an uncommon complication after liver transplantation. The inadequate immunosuppression (IS) remains the main risk factor. We report a case of acute cellular rejection after a switch to everolimus monotherapy at 11 months following liver transplantation.

Case presentation: This was a 69-year-old man who underwent liver transplantation after hepatocellular carcinoma. The initial immunosuppression was a combination of three immunosuppressive drugs (corticosteroids + tacrolimus + mycophenolate mofetil). The corticosteroid therapy was stopped at the 4th month posttransplant. Serious side effects of the immunosuppressive drugs (agranulocytosis and renal dysfunction), which occurred 4 months after transplantation, required a reduction and then a discontinuation of tacrolimus and mycophenolate mofetil. Everolimus was introduced as a replacement. The patient was consulted at 11 months after liver transplantation, 1 month after stopping the two immunosuppressive drugs, for liver function test abnormalities such as cytolysis and anicteric cholestasis. A moderate late acute cellular rejection was confirmed by a liver biopsy. A satisfactory biological evolution was observed following corticosteroid boluses and optimization of basic immunosuppressive drugs.

Conclusion: Late acute cellular rejection remains an uncommon complication, observed mostly in the first year after liver transplantation. The main risk factor is usually the decrease of immunosuppression.

Keywords: Liver transplantation, Immunosuppression, Complications, Graft rejection, Case report

Background

Late liver function test abnormalities are common following liver transplantation (LT) and can be caused by a wide range of pathology. Systematic investigation, including a detailed pretransplant, posttransplant, and donor history, is critical in the effective identification of the underlying etiology [1]. Late acute cellular rejection (LAR) was one cause of abnormal liver function tests and source of morbidity with graft loss [2, 3]. LAR varied from 7 to 40% [3–6]. Inadequate immunosuppression (IS) is the main risk factor for LAR [1–6]. Diagnosis is based on liver biopsy, which remains the gold standard [2–4]. The severity of rejection can be assessed histologically by the Banff classification [2, 7, 8]. Standard management of acute rejection involves optimization of basic IS such as tacrolimus or cyclosporine associated in case of severe rejection with corticosteroid boluses [2–8]. We report a case of acute cellular rejection after a switch to everolimus monotherapy at 11 months following liver transplantation.

*Correspondence: iamblaudiotchantelli@yahoo.com
[1] Department of Gastroenterology, University Hospital Joseph Raseta Befelatanana, 101 Antananarivo, Madagascar
Full list of author information is available at the end of the article

Case presentation

A 69-year-old man was hospitalized on November 16, 2018, for liver function test abnormalities occurring 11 months after a liver transplantation. He did not have a history of alcohol abuse.

Patient history was the following: metabolic syndrome (hypertension, hypercholesterolemia, insulin-requiring type 2 diabetes), ischemic heart disease with coronary angioplasty placement in 2010, prostate adenocarcinoma treated with radiation therapy in 2017, and nonalcoholic steatohepatitis cirrhosis complicated by hepatocellular carcinoma (HCC). HCC was treated with two sessions of chemoembolization (July and August 2017).

The patient had benefited from a LT on December 2017. He had no history of renal dysfunction before LT. The operative report reported a biliary to biliary anastomosis without biliary drain and a cold ischemia time of 06h 44mn. Examination of the explant showed a micronodular cirrhosis, a well-differentiated 5-mm HCC, non-encapsulated, no emboli, or satellite nodule. Cytomegalovirus (CMV) polymerase chain reaction (PCR) was negative in both donor and recipient. The patient was initially treated with a combination of three immunosuppressive drugs including tacrolimus (Prograf 4mg × 2/day), mycophenolate mofetil (Cellcept 1g × 2/day), and corticosteroid (Cortancyl 20mg/day). The corticosteroid was maintained at 20 mg/day for the first 3 months and then gradually decreased until the 4th month. The postoperative follow-up was simple. Radiological follow-up in March 2018 did not report any graft abnormality. Hepatic Doppler ultrasound (March 2018) was normal. Chest, abdominal, and pelvic CT scans (March 2018) reported no evidence of neoplastic progression and no graft abnormality. Magnetic resonance cholangiopancreatography (MRCP) (March 2018) showed good visibility of the intrahepatic and extrahepatic bile ducts, with no dilatation and no anastomotic stenosis.

The patient had presented on April 23, 2018, at 4 months of Cellcept introduction, a severe leukopenia at 2300/mm^3 (normal range 4000–10,000/mm^3) with agranulocytosis at 287/mm^3 (normal range 2000–7500/mm^3). Cellcept was halved on April 24, 2018, and then stopped on June 13, 2018, in the face of persistent neutropenia at 2200/mm and agranulocytosis at 440/mm^3 (Table 1). The patient also presented at 3 months posttransplant (07/03/18) a renal dysfunction at 115 µmol/L of serum creatinine, of progressive aggravation with an elevation of serum creatinine to 170 µmol/L 6 months later, obliging to decrease Prograf to 3mg/day (residual level 7.7 ng/mL) and to introduce Certican at 7 mg/day on September 11, 2018. Prograf was stopped on October 9, 2018, due to worsening renal dysfunction at 178 µmol/L. Only Certican was maintained as monotherapy from October 9, 2018, i.e., at 10 months of TH. The evolution of abnormal liver function tests (ALFTs) and the stages of stopping immunosuppressive drugs are reported in Table 1.

On November 16, 2018, the patient was admitted to emergency for ALFTs. Biological investigations showed major cytolysis with alanine aminotransferase at 200 U/L (normal range, 9.0–52.0 U/L), aspartate aminotransferase at 91 U/L (normal range, 14.0–36.0 U/L) associated with anicteric cholestasis with alkaline phosphatases at 801 U/L (normal range, 53–128 U/L), γ-glutamyl-transpeptidase at 305 U/L (normal range, 7–32 U/L), but total bilirubin at 16 mol/L (normal range, 3.0–22.0 mol/L). Residual everolimus level

Table 1 Evolution of ALFTs, stages of stopping immunosuppressive drugs, and in-hospital outcomes

Laboratory tests (2018)	Jan 23	Mar 07	April 24	Jun 13	Sept 11	Oct 09	Oct 22	Nov 16	Dec 02	Dec 13
ALT (NR 0–55 U/L)	43	14	10	12	11	13	11	**200 (H)**	25	11
AST (NR 5–34 U/L)	15	12	14	15	14	18	17	**91**	24	18
ALP (NR 42–98 U/L)	117	57	62	71	89	82	69	**801**	90	86
γ-GT (NR 9–36 U/L)	134	23	12	28	11	11	10	**305**	30	11
Total bilirubin (NR 0–20 µmol/L)	10	9	5	7	5	5	3	16	18	7
Leukocytes (NR 4000–10,000 cells/mm^3)	6900	5400	**2300 (A)**	**2200 (B)**	**1800**	**1800**	**1700**	4970	6.2	5.70
PMN (NR 1300–7500 cells/mm^3)	-	-	**287**	**440**	**455**	**369**	**643**	3280	4.02	3.90
Creatinine level (NR 49–90 µmol/L)	91	**115**	**133**	**160 (C)**	**170 (D)**	**178 (F)**	**166**	**171**	**145**	**138**
Hemoglobin (NR12–16 g/dL)	11.4	11	10	10	9	9.4	8.6	7.8	12.5	10
Residual tacrolimus level (objective 6–10 ng/mL)	9.2	8.6	6	7.7	4.6	3.6	-	-	9.3	8.9
Residual everolimus level (objective 5–10 ng/mL)	-	-	-	-	**(E)**	6.4 **(G)**	5.7	4.5	5	5.7

ALFTs abnormal liver function tests, *NR* normal range, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphate, *γ-GT* γ-glutamyl-transpeptidase, *PMN* polymorphonuclear neutrophil, *Jan* January, *Sept* September, *Oct* October, *Nov* November

A: decrease Cellcept 500mg × 2/day, B: stop Cellcept, C: decrease Prograf 1.5mg × 2/day, D: decrease Prograf 1.5mg × 2/day; E: start everolimus (Certican®); F: stop Prograf; G: Certican® monotherapy; H: corticosteroid bolus + optimization of immunosuppression

was 4.5 ng/mL (therapeutic range, 5–10ng/mL). Renal dysfunction was observed with a serum creatinine level of 170 mol/L (Table 1). PCR for viral hepatitis (A, B, C, and E), cytomegalovirus (CMV), and herpes simplex virus (HSV) were negative. PCR for Epstein-Barr virus was weakly positive but not significant. Antinuclear, anti-smooth muscle, anti-liver-kidney microsome 1 (anti-LKM1), anti-soluble liver antigen (anti-SLA), and anti-mitochondrial M2 antibodies were negative. Abdominal and pelvic Doppler ultrasound showed permeable hepatic vessels with resistance indexes of the left and right hepatic arteries between 0.71 and 0.73, an absence of intrahepatic and extrahepatic bile duct dilation, and an absence of uro-nephrological abnormalities. MRCP reported an absence of bile duct dilatation and no biliary anastomotic stenosis. Transjugular liver biopsy showed portal venous endothelial inflammation (a), lymphocytic cholangitis (b), dystrophic ducts (c), and portal infiltration by lymphocytes, macrophages, and eosinophils, without plasma cells or interface hepatitis (d) (Fig. 1). The Banff score was 6. These histologic features were suggestive of moderate acute cellular rejection. The diagnosis of moderate LAR at 11 months after liver transplantation was retained. A bolus of methylprednisolone associated with an optimization of the basic immunosuppressive regimens was proposed with reintroduction of Prograf 2mg/day and Cellcept 1g/day and an increase of Certican to 8mg/day.

The intra-hospital outcome was favorable with normalization of liver function tests and a stabilization of the moderate renal dysfunction (Table 1). The patient was closely and regularly under biological monitoring. The last evolution (2021) showed normal liver function tests.

Discussion

Acute cellular rejection, although common, is a rare cause of graft loss and liver retransplantation [1, 2]. LAR remains a histological diagnosis, usually occurring within 3 to 6 months after transplantation [7–9]. A systematic review including 9 studies reported that the incidence of LAR varied from 7 to 40%; however, only one study-related incidence was greater at 25% [3]. This prevalence has decreased in recent years due to the new ISs [2–9].

Risk factors for LAR include inadequate IS, younger donor age, previous early acute rejection, previous graft failure, seronegative hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis prior to transplantation, while transplantation for viral disease seems to be protective [1, 10, 11]. D'Antiga et al. [12] reported that underlying liver disease, decreased immunosuppression, and poor compliance were the main factors predisposing patients to develop LAR. A US study found a high rate of LAR in female and young recipients and in patients with primary diagnoses of autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis [13]. A recent study showed that younger recipients, primary

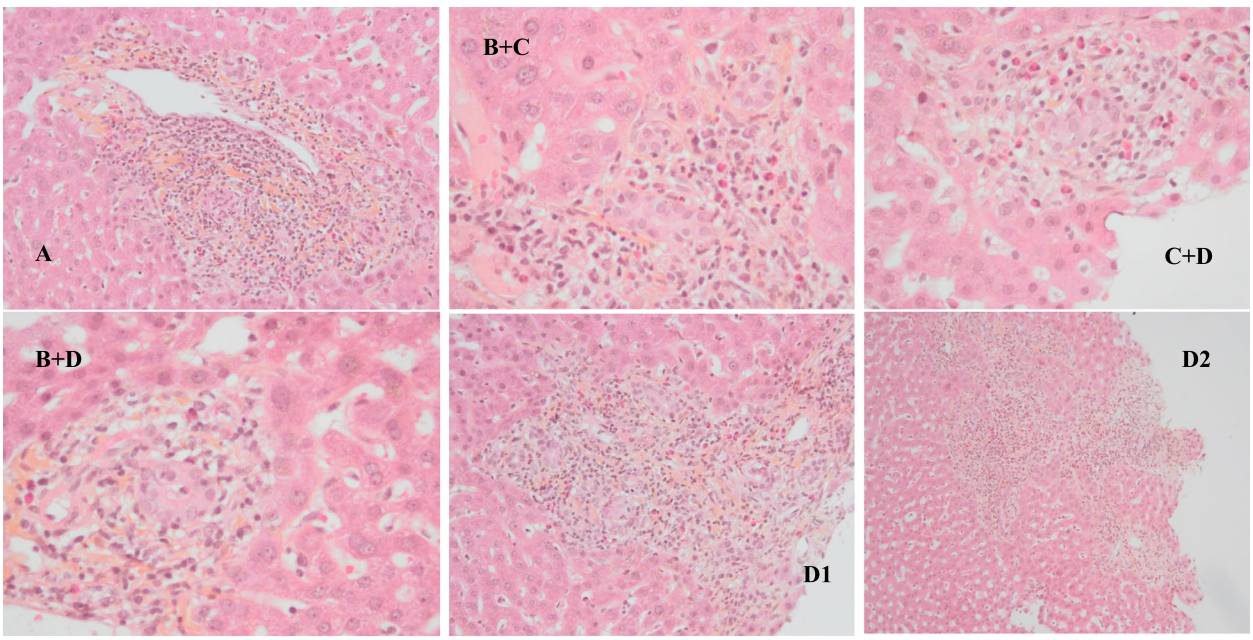

Fig. 1 Histopathological appearance of the liver showing portal venous endothelial inflammation (**a**), lymphocytic cholangitis (**b**), dystrophic duct (**c**), and portal infiltrations by lymphocytes, macrophages, polynuclear eosinophilic, without plasma cells, without interface hepatitis (**d**) (magnifications: D2 ×20, others ×200)

biliary cirrhosis, and previous graft loss were significant independent predictors of LAR ($P < 0.001$) [11]. Inadequate IS due to a significant decrease in SI was the only risk factor for LAR found in our observation. This decrease in SI was the result of a gradual discontinuation of immunosuppressive drugs following hematological and renal side effects. Therefore, any reduction in SI should be closely monitored within 6 months of any dose change [11].

The diagnosis of LAR is more difficult to make than that of early acute rejection, as histological abnormalities are less classic and differential diagnosis is broader [1, 7–9], hence the need for a systematic investigation as described in our case report, including a detailed pretransplant, pertransplant, posttransplant, and donor history [1]. Our case, LAR, was discovered following ALFTs with a predominance cholestasis, which was consistent with the literature review [2]. Jung et al. [14] observed a predictive increase in transaminase levels prior to routine biopsies in patients with histologic evidence of late acute rejections. However, LAR can be clinically asymptomatic and incidentally discovered during a routine liver biopsy. Hence, the systematic search for LAR during posttransplant follow-up even in the absence of ALFTs requires at least one systematic liver biopsy during the first 12 months posttransplant [2]. Histology remains fundamental for the diagnosis of acute rejection and the evaluation of its severity in order to adapt the management. We have retained the diagnosis of LAR for our patient on biochemical, radiological, and histological arguments, associating ALFTs with histological lesions compatible with acute rejection. The severity of the rejection is assessed histologically by the Banff criteria and classified into 3 categories: mild (0–3), moderate (4–6), and severe (>6) [2, 7, 8]. In our case, the score was 6, classifying it as moderate. The moderate form remains the most common. Moderate LAR accounted for more than half of the patients (63%) with LAR in an English study [11].

LAR is a potentially serious complication with a risk of graft loss (*HR* 1.71; 95% *CI* 1.23–2.37; $P = 0.001$), progression to chronic rejection (3–28% of cases), and decreased patient survival (*HR* 1.89; 95% *CI* 1.35–2.65; P=0.001) [1, 2, 5, 7]. According to Thurairajah et al. [11], the rate of developing chronic rejection after a single episode of LAR was 28%, with an overall rate of graft failure of 6%. The causes of mortality included end-stage liver failure from chronic rejection, sepsis, malignancy, recurrent of primary disease, hepatic artery thrombosis, and cardiovascular deaths, hence the need for urgent, prompt, and adequate management. According to the literature, acute rejection usually responds to corticosteroid boluses. Rejection resistant to corticosteroids is rare [2, 11]. However, Nakanishi et al. [15] had already reported a case of steroid-resistant LAR, but rescue therapy with deoxyspergualin was used successfully. One study showed that as few as 51% of treated LAR patients completely respond to high-dose steroids [16]. In an English study, in which the majority of patients with rejection were treated with high-dose pulsed corticosteroids (prednisolone 200 mg/day for 3 days), a complete normalization of serum transaminase levels in 23 (22%) cases, a partial response in 42 (40%) cases, and no response in 18 (17%) cases were reported [11]. The management of acute rejection depends on the degree of liver injury and histological grading. Optimization of basic immunosuppressive drugs is sufficient for mild acute rejection, while moderate and moderately severe acute rejection requires corticosteroid, boluses combined with intensification of the basic IS [2]. Our patient had moderate LAR and responded well to corticosteroid bolus combined with intensification of the basic IS.

Conclusion

LAR remains an uncommon complication, observed mostly in the first year after liver transplantation. The main risk factor is usually an inadequate IS. LAR can have deleterious effects with an associated long-term risk of chronic rejection, graft loss, and reduced survival. Beyond the first year, LAR is often due to poor patient compliance with IS therapy or unfavorable drug interactions. In case of resistance to an increase of the IS therapy, histology is then mandatory for the diagnosis and the evaluation of the severity and to decide on corticosteroid bolus.

Authors' contributions

Conceptualization: CIR, NT, and PL. Data curation: CIR. Methodology: CIR, NT, GMM, CS, FC, and PL. Visualization: CIR, NT, GMM, CS, FC, and PL. Writing the original draft: CIR. Writing, review, and editing: CIR, NT, GMM, CS, FC, and PL. The authors read and approved the final manuscript.

Funding

This research was not supported by any specific grants from the public, commercial, or nonprofit funding agencies.

Availability of data and materials

Data are available upon request from the authors. Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Informed consent was obtained from the patient. A signed consent form authorizing the publication is available and included in the patient's chart.

Competing interests

The authors declare that they have no competing interests.

Author details
[1]Department of Gastroenterology, University Hospital Joseph Raseta Befelatanana, 101 Antananarivo, Madagascar. [2]Department of Hepato-Gastroenterology and Liver Transplantation, University Hospital Pitié Salpêtrière, APHP, Paris, France. [3]Department of Hepato-Gastroenterology and Liver Transplantation, Hospital Felicio Rocho, Belo Horizonte, Brazil. [4]Department of Pathology, University Hospital Pitié Salpêtrière, APHP, Paris, France.

Received: 23 November 2021 Accepted: 2 January 2022
Published online: 07 January 2022

References

1. Mitchell O, Cosar AM, Malik MU, Gurakar A (2015) Late liver function test abnormalities post-adult liver transplantation: a review of the etiology, investigation, and management. Hepatol Int 10(1):106–114
2. Charlton M, Levitsky J, Agel B, O'Grady J, Hemibach J, Rinella M et al (2018) International Liver Transplantation Society consensus statement on immunosuppression in liver transplant recipients. Transplantation 102(5):727–743
3. Nacif LS, Pinheiro RS, de Arruda Pécora RA, Ducatti L, Rocha-Sntos V, Andraus W, D'Albuquerque LC (2015) Late acute rejection in liver transplantation: a systematic review. ABCD Arq Bras Cir Dig 28(3):212–215
4. European Association for the Study of the Liver (2016) EASL clinical practice guidelines: liver transplantation. J Hepatol 64:433–485
5. Jadlowiec CC, Morgan PE, Nehra AK, Hathcock MA, Kremers WK, Heimbach JK, Wiesner RH, Taner T (2019) Not all cellular rejections are the same: differences in early and late hepatic allograft rejection. Liver Transpl 25(3):425–443
6. O'Grady J (2011) The immunoreactive patient: rejection and autoimmune disease. Liver transplantation 17(S3):S29–S33
7. Demetris A, Adams D, Bellamy C, Blakolmer K, Clouston A, Dhillon AP et al (2000) Update of the International Banff Schema for Liver Allograft Rejection: working recommendations for the histopathologic staging and reporting of chronic rejection. An International Panel. Hepatology 31(3):792–799
8. Banff Working G, Demetris AJ, Adeyi O, Bellamy CO, Clouston A, Charlotte F et al (2006) Liver biopsy interpretation for causes of late liver allograft dysfunction. Hepatology 44(2):489–501
9. Lucey, M.R., N.A. Terrault, L. Ojo, J.E. Hay, J. Neuberger, E. Blumberg, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by AASLD and the American Society of Transplantation, AASLD, Editor. 2012.
10. Ramji A, Yoshida EM, Bain VG, Kneteman NM, Scudamore CH, Ma MM et al (2002) Late acute rejection after liver transplantation: the Western Canada experience. Liver Transpl 8(10):945–951
11. Thurairajah PH, Carbone M, Bridgestock H, Thomas P, Hebbar S, Gunson BK et al (2013) Late acute liver allograft rejection; a study of its natural history and graft survival in the current era. Transplantation 95(7):955–959
12. D'Antiga L, Dhawab A, Portmann B, Francavilla R, Rela M, Heaton N et al (2002) Late cellular rejection in paediatric liver transplantation: aetiology and outcome. Transplantation 73:80–84
13. Uemura T, Ikegami T, Sanchez EQ, Jennings LW, Narasimhan G, McKenna GJ et al (2008) Late acute rejection after liver transplantation impacts patient survival. Clin Transplant 22:316–323
14. Jung G, Tullius SG, Klitzing V, Schewior L, Pratschke J, Radke C et al (2005) The influence of late acute rejection episodes on long-term graft outcome after liver transplantation. Transplant Proc 37:1716–1717
15. Nakanishi C, Kawagishi N, Sekiguchi S, Akamatsu Y, Sato K, Miyagi S et al (2007) Steroid resistant late acute rejection after a living donor liver transplantation: case report and review of the literature. Tohoku J Exp Med 211(2):195–200
16. Anand AC, Hubscher SG, Gunson BK, McMaster P, Neubergerr JM (1995) Timing, significance, and prognosis of late acute liver allograft rejection. Transplantation 60:1098–1103

Publisher's Note