NDT Plus (2008) 4: 241–243
doi: 10.1093/ndtplus/sfn027
Advance Access publication 5 April 2008

NDT PLUS
Nephrology Dialysis Transplantation

Case Report

Seronegative hepatitis C-related fibrosing cholestatic hepatitis after renal transplant: a case report and review of the literature

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Keywords: cholestasis; cirrhosis; hepatic fibrosis; hepatitis C; renal transplant

Case

Ms J is a 52-year-old female who underwent deceased donor renal transplant (RT) in May 2006 for membranous glomerulonephritis after 6 years on haemodialysis. She was initially treated post-transplant with alemtuzumab (Campath) secondary to delayed graft function and was subsequently discharged on tacrolimus, mycophenolate and prednisone for chronic immunosuppression. Ms J tested negative for anti-HCV in her first transplant consultation in 2004 and again just 12 days prior to surgery. Her bilirubin (0.5 mg/dL), alkaline phosphatase (ALP 94 IU/L), aspartate aminotransferase (AST 28 IU/L) and alanine aminotransferase (ALT 14 IU/L) were all within normal limits before transplant.

Subsequently, Ms J's alkaline phosphatase rose to 178 IU/L 7 days after procedure. Within 6 months her aminotransferases (AST 96 IU/L and ALT 78 IU/L) and bilirubin (1.5 mg/dL) became elevated as well, never returning normal. At that time tacrolimus was stopped in favor of cyclosporine, and computed tomography (CT) of the abdomen demonstrated cholelithiasis and small ascites. Despite this, an elective laparoscopic cholecystectomy did not result in improved liver chemistries and several repeat measurements of chronic anti-HCV/HBV antibody serologies remained negative. Testing for abnormal antinuclear antibodies (ANA), anti-smooth muscle antibody (ASMA), anti-mitochondial antibody (AMA) and quantitative immunoglobulins was also negative. Unfortunately, HCV RNA testing was not done. Over the next 7 months, Ms J became increasingly jaundiced with worsening, symptomatic ascites. This corresponded with declining renal graft function and uraemia.

A gastroenterology consult led to a transjugular liver biopsy 13 months after RT indicated cholestasis, periportal fibrosis and acute inflammation of the bile ducts with associated regeneration, and only mild lobular inflammation (figure 1). Features of HCV hepatitis were absent. A repeated anti-HCV assay at that time was negative, but HCV RNA by B-DNA was positive for 7.69×10^6 eq/mL of genotype 1a virus. Ms J was diagnosed with FCH C cirrhosis with renal allograft dysfunction from acute tubular necrosis and chronic rejection. She was felt to be unsuitable for HCV therapy and is currently exploring combined liver and RT.

Discussion

Only 14 cases of FCH in RT recipients secondary to HCV infection have been previously described. Prior to Zyldeberg *et al*.'s original report in 1995, FCH was an ominous complication of immunosuppressed liver transplant recipients infected with HBV and—less often—HCV [1–5]. Several other reports confirmed that a small subset of HCV-infected RT patients develop a rapidly progressive FCH, characterized by acute cholangiolitis, hepatocellular swelling and mild periportal fibrosis rather than the acidophilic hepatocyte necrosis, lobular inflammation or pericellular/sinusoidal fibrosis associated with HCV hepatitis [1,6–10].

Munoz *et al*. was the next to report FCH as a rare, but serious, complication in a cohort of known HCV-infected patients (4 out 259) status post-renal transplantation [11]. Like Ms J, these four patients were predominantly genotype 1, lacked the typical features of HCV hepatitis and had a rapid progression to severe liver dysfunction and/or death (Table 1). In Delladetsima *et al*.'s subsequent report of FCH in four seronegative HCV-infected RT recipients—despite abrupt immunosupression reduction in all four patients—only two patients seroconverted and had rapid improvement of their liver disease [7]. Similar to Ms J, three of the four patients were genotype 1, and all were on methylprednisone, azothiporine and

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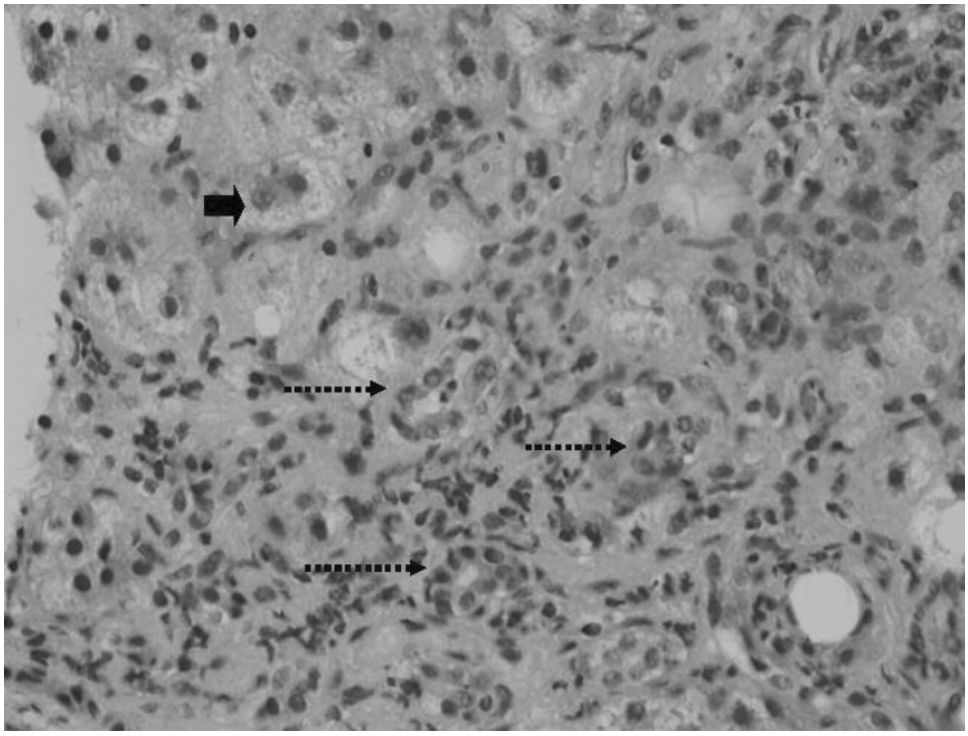

Fig. 1. Liver biopsy 13 months post-renal transplant. Acute cholangioliotis with neutrophil infiltration, hepatocyte ballooning (arrow) and disruption of the bile ductule (dashed arrows).

Table 1. Clinical characteristics of patients diagnosed with HCV-related FCH after RT

Study	No. of FCH cases	No. of genotype 1 cases	Cirrhosis/liver transplant/ deceased	+Anti-HCV pre-RT in FCH cases
Zylbeberg *et al*. [1]	1	1	1	1
Munoz *et al*. [11]	4 (of 259)	3	4	4
Delladetsima *et al*. [7]	4 (of 73)	3	2 (persistently anti-HCV negative)	0
Delladetsima *et al*. [6]	4 (of 17)	3	2	0
Hooda *et al*. [9]	1	1	1	1

FCH: fibrosing cholestatic hepatits; RT: renal transplant.

cyclosporine A. Also like Ms J, two persistently anti-HCV negative patients suffered progressively worsening liver function and end-stage liver disease within 18 months of RT. The authors propose this phenomenon may be secondary to peri-operative infection and aggressive post-transplant immunosupression.

Afollow-up retrospective analysis by the same group sought to clarify the effect that the timing of HCV infection had on the development of FCH in 17 RT recipients who were seronegative at the time of transplant, but who developed HCV RNA positive disease after surgery [6]. As in our case, this study observed a short mean time to new biochemical abnormalities in liver function (5.7 months) in the four patients diagnosed with FCH. Also, three patients with FCH at the time of the first biopsy (including the two who never seroconverted) were on triple immunosuppression and infected with HCV genotype 1. Finally, two persistently anti-HCV negative patients faired poorly, dying with advanced liver disease in a median of 6 years.

The factors influencing this rare complication remain unclear. Further study is indicated to determine if the FCH pattern of liver damage in RT patients is related to the timing of infection, aggressive early immunosuppression, patient-specific properties of immunity or HCV genotype as our case and previous reports suggest. Additionally, this case highlights the role of HCV RNA for screening in an immunosupressed population. While the false negative rate of anti-HCV testing for chronic HCV in high prevalence populations is 5%, multiple studies indicate a failure to form measured antibodies in up to 15% of haemodialysis and transplant patients [12–16]. Unfortunately, it was too long presumed that anti-HCV antibody alone was an adequate diagnostic tool in this case. Like Ms J, RT candidates would benefit from early HCV RNA testing for pre-surgical screening or to diagnose post-RT liver abnormalities. Finally, reversal of clinical liver disease in these patients has been reported with the discontinuation of immunosupression or the use of PEG interferon, but obviously the experience is limited [17]. A prospective trial is needed to confirm if pre- or post-transplant anti-HCV therapy will positively affect transplant outcomes.

Acknowledgements. Thanks is due to Dr. Emmett B. Keeffe, MD of Stanford University, USA for his assistance reviewing this work before publication.

Conflict of interest statement. None declared.

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Received for publication: 30.1.08
Accepted in revised form: 21.2.08