CASE REPORT

# Acute hepatitis C infection in a renal transplant recipient: primacy of the liver or kidney?

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## SUMMARY

We present a case where a renal transplant recipient contracted chronic hepatitis C virus (HCV) infection post-transplantation. The disease progressed and deteriorated leading to fibrosing cholestatic hepatitis that mandated treatment. Treatment with pegylated interferon α-2a and ribavirin was successful in salvaging the liver and eradicating the virus but as a consequence lead to treatment-resistant acute rejection and loss of the renal allograft.

## BACKGROUND

Globally, the prevalence of chronic kidney disease (CKD) is on the rise.[1] Data from the National Health and Nutrition Examination Survey 2003–2006 database, with glomerular filtration rate estimated using the CKD epidemiology collaboration equation[2] showed that the overall prevalence of CKD stages 1 through 5 is 14.2%.[3] Given the shortage of organ donors and the ever expanding population of end-stage renal disease (ESRD) patients, one method of expanding the pool of donors is organ procurement from anti-hepatitis C virus (anti-HCV) positive donors. In one study among 38 270 patients awaiting transplantation, transplantation with such a kidney was significantly associated with improved survival as opposed to remaining on a transplant wait list.[4] In this case, the patient contracted HCV infection post-transplantation that led to fibrosing cholestatic hepatitis (FCH). We elected to treat aggressively, as a result the patient's liver was salvaged and her life was saved, but at the expense of her renal allograft.

## CASE PRESENTATION

We present the case of a 44-year-old woman who underwent pre-emptive, living non-related renal transplantation in China on October 2009; cause of renal failure prior to transplantation was undetermined. Prior to transplantation when she was followed up in the CKD clinic, she was informed of her progressive renal failure and the need for renal replacement therapy. She did not have a living-related donor, therefore, was given the option of peritoneal dialysis or haemodialysis while her transplant workup was ongoing in order to include her in the deceased-donor waiting list. She inquired about seeking a commercial transplant abroad as it is against the law here in Saudi Arabia. We explained that this approach was unethical and strongly advised against it. However, dreading a life dependant on dialysis, she managed to arrange a commercial transplant in China without our knowledge and returned to us with a functioning allograft. We were unable to obtain details of the institution where she was transplanted or donor characteristics. In a study conducted previously in our centre there was a rise in transplant tourism from 2001 to 2005 after which it had declined; this is consistent with the immense effort by the WHO and the declaration of Istanbul on organ trafficking in addition to the local efforts by the Saudi centre for organ transplantation in educating patients and preventing this occurrence.[5–7] This study also revealed that the rate of HCV seroconversion in transplant tourists was 7.5% compared with none in those transplanted at our institution.[5] Our patient had developed HCV infection post-transplantation with HCV genotype 4. Prior to transplantation she was HCV negative. History was negative for blood transfusions, intravenous drug abuse or alcohol ingestion. The source of HCV most probably may have been from the donor who is unknown as this was a commercial transplant.

## INVESTIGATIONS

Pre-transplant she had normal liver enzymes and synthetic function; aspartate aminotransferase (AST) was 16 U/L (10–45) and alanine aminotransferase (ALT) 26 U/L (10–45), serum albumin 41 g/L and a normal coagulation profile in August 2009. Post-transplantation on routine follow-up the patient had tested positive for HCV in January 2010, liver enzymes were elevated; AST 66 U/L and ALT 112 U/L. In this regard, mycophenolate mofetil was discontinued and her immunosuppression comprised of tacrolimus 1 mg twice daily and prednisone 5 mg once daily. She was immunised against hepatitis B virus. By January 2011 her AST was 128 U/L and ALT U/L 149 with a high HCV viral load by PCR; 1 246 451 IU/mL. To guide treatment decisions we elected for a liver biopsy. It revealed chronic hepatitis grade 1–2 of 4 and stage 1 of 4, and after review by the hepatology team, they opted not to treat at that point as the risk of transplant rejection with pegylated interferon α-2a treatment would outweigh benefit. At the same time her liver synthetic function was intact. In May 2012 during a routine scheduled outpatient visit, investigations revealed stable renal allograft function with a baseline creatinine of 72 μmol/L but the viral load had risen to 2 178 566 IU/mL with AST 168 U/L, ALT 190 U/L and γ-glutamyl transpeptidase 709 IU/L. She denied any changes in her

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medication or use of herbal medication. A decision was made to repeat the liver biopsy; it revealed chronic hepatitis grade 2 of 4 and stage 2–3 of 4 with macrovesicular steatosis 5%. On examination her vitals were stable, she was conscious, oriented and alert. Clinically, she had jaundice; her serum bilirubin level was 16.7 μmol/L (0.0–5.0). Abdominal examination revealed a tender right-upper quadrant with shifting dullness. The patient had developed fibrosing cholestatic hepatitis (FCH).

## TREATMENT

On the basis of current investigations we opted to initiate treatment in the form of pegylated interferon α-2a 135 μg once weekly and ribavarin 400 mg twice daily after potential risks and benefits of the proposed therapy was explained to the patient.

## OUTCOME AND FOLLOW-UP

On completing 2 months of treatment she presented with worsening fatigue, decreased urine output and nausea. She had a tender renal allograft in the right iliac fossa with +2 pitting oedema of both lower limbs. Investigations revealed doubling of her serum creatinine from 72 to 151 μmol/L; she underwent an urgent renal transplant biopsy. It revealed acute tubulointerstitial cellular rejection (acute T-cell-mediated rejection, Banff type IA), and was plasma rich (C4d negative). She was pulsed with intravenous methylprednisone followed by IVIG (intravenous immunoglobulin) but did not recover her renal function. Cause of rejection was most likely due to therapy with pegylated interferon α-2a treatment in an attempt to salvage the liver. Consequently, she underwent radical graft nephrectomy and was initiated on haemodialysis. She received a full course of combination therapy with pegylated interferon α-2a and ribavirin for a period of 48 weeks. She achieved sustained viral response (SVR) and sustained biochemical response (SBR).

## DISCUSSION

Treating chronic HCV infection is challenging in renal transplant recipients. FCH is characterised by progressive decline of liver function over weeks to months and is a potentially fatal disorder with a high mortality rate.[8] The 2008 Kidney Disease Improving Global Outcomes (KDIGO) guidelines for HCV infection in patients with CKD recommend monotherapy with interferon to be considered in renal transplant recipients who are HCV positive resulting in FCH and in those with life-threatening vasculitis.[9] Interferon α in addition to its antiviral activity has pleiotropic effects such as antiproliferative and immunomodulatory properties. It prompts cytokine gene expression, increased cell surface expression of human leucocyte antigens as well as heightened function of natural killer cells, cytotoxic T cells and monocytes.[10] Combination treatment with interferon α and ribavirin is associated with a 30% or greater risk of acute rejection that is refractory to corticosteroid therapy.[11 12] In one study using ultra low doses of interferon α in combination with ribavirin a significant proportion of patients did achieve sustained biochemical and virological response. However even with this dosing regimen three patients had to terminate treatment; two developed urosepsis and one developed acute rejection.[13] Furthermore, a recent prospective trial suggested that pegylated interferon α-2a in combination with ribavirin may be safe in renal transplant recipients infected with HCV at low risk for allograft rejection with modest efficacy rates.[14] We elected to treat our patient with combination therapy. There are life-threatening complications of HCV infection in which the benefits of treating with pegylated interferon α-2a therapy may justify the risk of possible renal allograft loss. For patients with CKD or ESRD who are HCV-positive transplant candidates—where possible, it is recommended to treat chronic HCV prior to transplantation. However, organ procurement from anti-HCV positive donors is permissible; a method by which the pool of organ donors can be expanded. Transplanted with such a kidney has also been shown to improve survival as opposed to remaining on the waiting list.[4] This case highlights the challenge a clinician may find oneself in; where efforts to save the liver can be detrimental to the renal allograft. Nevertheless, doing so saved the patient's life. Currently after completing treatment for HCV and successful eradication with both SVR and SBR, she is listed on the deceased-donor waiting list.

## Patient's perspective

I was informed on all possible options when I had advanced kidney failure. I felt helpless as I did not have a donor. I work as a teacher and could not see myself dependent on a machine for the rest of my life. I also knew that waiting on the list was something I could not handle. Therefore, I made the decision to seek a commercial transplant although I was advised against it. To my dismay, I had to deal with two failing organ systems. The risk of treatment for hepatitis C viral infection was explained to me and unfortunately after the treatment I lost my transplant. When I look back I realise that my doctors did what was best for me and I am grateful for that.

## Learning points

- Treatment of chronic or acute hepatitis C virus (HCV) infection in renal transplant recipients is challenging as the available therapeutic options may result in acute rejection.
- It is recommended to treat HCV infection in patients with end-stage renal disease prior to transplantation.
- Antiviral therapy may be considered if there is severe progressive liver disease such as fibrosing cholestatic hepatitis.

**Competing interests** None.

**Patient consent** Obtained.

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