BMJ Case Reports

Learning from errors

Incidence of CMV-HCV coinfection in renal transplant recipient

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Summary

The authors report a case of a 47-year-old cytomegalovirus (CMV) immunoglobulin G (IgG) seropositive male patient with end stage renal disease who received a live renal transplant from a CMV IgG seropositive donor. Six months post-transplantation, the patient presented with reduced renal allograft function associated with fever, severe breathlessness, new onset jaundice and pancytopenia. His CMV DNA PCR came positive. Hepatitis C virus (HCV) RNA PCR also came positive (genotype I) though anti-HCV test performed before and after transplantation was negative. The patient was treated with oral valganciclovir and showed improvement of his clinical condition and was subsequently discharged under supervised therapy. However, the patient could not be treated for HCV because of risk of renal allograft rejection. The authors suggest oral valganciclovir for management of CMV infection and proper detection and eradication of HCV before renal transplantation to avoid future complications and prolongation of allograft survival.

BACKGROUND

The success of renal transplantation depends on the prevention or early diagnosis and prompt successful treatment of infections which may even lead to potentially life-threatening complications due to long-term immunosuppressive therapy. The potential sources of infection may be due to impaired immune responses which makes the individual easily accessible to infective agents or reactivation of latent pathogens particularly viruses due to immunesuppression. Post-transplantation, cytomegalovirus (CMV) is a potential threat to renal transplant recipients and is a significant cause of morbidity and mortality.[1–6]

The CMV serostatus of the donor (D) and the recipient (R) before transplantation is a very important factor for post-transplantation CMV complications. In the post-transplant setting, CMV infection facilitates renal allograft rejection and may result in a varied spectrum of diseases ranging from respiratory tract to gastrointestinal diseases, retinitis, myelosuppression and neurological involvement. Among the complicacies, CMV pneumonitis in renal transplant patients is a well-known complication with high mortality and morbidity rates.[7 8]

CMV also plays very important role in immune suppression and aggravates other viral diseases. CMV is associated to enhance hepatitis C virus (HCV) pathogenesis by preventing the normal mechanisms responsible for HCV clearance, thus playing vital role in HCV persistence and pathogenicity.[9] HCV infected renal transplant patients suffer from reduced survival rates.[10] The anti-HCV test performed for HCV detection often gives false negative results if HCV antigen is present in low concentrations.[11] The most sensitive test is the HCV RNA PCR test- but is rarely performed. However, no treatment can be offered for HCV post-transplantation because of risk of renal allograft rejection.[12–17]

Thus, the purpose of this study is to generate awareness that proper detection of HCV and eradication (in case of HCV positive cases) before renal transplantation and CMV prophylactic therapy to the renal transplant recipients for the first 6 months after transplantation is essential to avoid these viral-related post-transplant complicacies thereby increasing chances of graft and patient survival.

CASE PRESENTATION

We report case of a 47-year-old male non-diabetic patient diagnosed as end stage renal disease (ESRD) of unknown aetiology who had been on haemodialysis for 9 months before he received renal transplant from a live unrelated immunoglobulin G (IgG) CMV seropositive donor in the Department of Nephrology in SSKM Hospital, Kolkata, India. He was also found to be CMV IgG seropositive. He had received induction therapy with daclizumab (50 mg intravenously on day 0 and day 14 of transplantation) followed by tacrolimus (0.1 mg/kg), azathioprine (75 mg once daily) and prednisolone(30 mg once daily). His baseline creatinin post-transplantation was 1.7 mg/dl blood and urea-46 mg/dl. As he was unable to afford oral valganciclovir, CMV prophylaxis was not undertaken (the cost of CMV prophylactic treatment is very high).

About 6 months post-transplant, the patient developed new onset diabetes mellitus for which patient was started on oral hypoglycaemics with which his blood sugar was adequately controlled. The patient presented with pancytopenia – that is, along with preexisting anaemia (Hb-6.3 g/dl) (of chronic renal disease) the patient developed a new onset bicytopenia – Leucopenia: total leucocyte count (TLC)-1600 mg/dl and thrombocytopenia- platelet count-56000 mg/dl with increased creatinine-4.1 mg/dl and urea-70 mg/dl. Urine output was gradually decreasing and patient's general condition was deteriorating.

Considering a possibility of azathioprine induced myelosupression, it was stopped and granulocyte-macrophage colony stimulating factor was started but bicytopenia did not improve despite therapy. After 28 days, the patient presented with a new onset jaundice and rapidly progressing anasarca (body weight – baseline+8 kg).

Meanwhile the patient was also having moderate grade, continuous fever for 30 days which was not responding to broad-spectrum antibiotic therapy. The patient had severe breathlessness even at rest with orthopenea and non-productive cough. His respiratory rate was 28/min, pulse-112/min, blood pressure-154/94 mm Hg. The patient was using all the accessory muscles of respiration but there was no palpable lymphadenopathy. Abdominal examination revealed tender hepatomegaly. There was no evidence of coagulopathy or any flapping tremor. The patient was alert, conscious and orientated. Plantar response was flexor. But, fluid thrill and shifting dullness was present. Creatinine level increased to 5.1 mg/dl and urea-82 mg/dl. Diagnostic paracentesis from ascitic fluid revealed the following findings-physical appearance-clear, straw coloured, cells – 233/mm^3, predominantly mesothelial cells, few occasional lymphocytes, protein-2.3, albumin-1.5. This was indicative of transudative ascites. Haematological parameters revealed the following findings- Hb%-9.2 g%, TLC-1400, platelet-44000/mm^3, erythrocyte sedimentation rate-68. Liver function test-bilrubin-total 5.2, unconjugated-2.0, conjugated-3.2, total protein-6.6, serum albumin-2.2, globulin-4.4, serum glutamate pyruvate transaminase-76, serum glutamate oxaloacetate transaminase-64, alkaline phosphatase-178, P time-15 s (normal). HBsAg and Anti-HCV assay were repeated but were negative. HCV RNA PCR came positive with 1140 IU/ml and genotyping showed genotype-1. In order to determine the source of HCV infection, the donor also underwent HCV RNA PCR which came out as negative. Chest x-ray was normal. High resolution CT thorax showed patchy bilateral foci of ground glass opacities and air-space consolidationin both the lung fields with relative sparing of basal segments of both lower lobes. No evidence of bronchiectasis was noted (bilateral patchy pneumonitic changes in both lungs). Bronchoscopy with broncho alveolar lavage and lung biopsy were planned for cytological and histopathological confirmation of the causative agent of pneumonitis. But due to respiratory distress the patient did not co-operate for bronchoscopy and also did not consent for a lung biopsy. So these investigations could be performed. Sputum for acid-fast bacillus smear and culture were negative. CMV PCR was done in view of CMV pneumonitis which turned out to be positive with 4.5×10^6 copies of CMV DNA/ml of serum. His transforming growth factor (TGF) β1, IL6 and C reactive protein levels were also detected to be 43.34 ng/ml, 36.5 pg/ml and 24.2 mg/l respectively.

TREATMENT

The patient was then started on tablet valganciclovir 450 mg once daily as maintenance therapy along with diuretic therapy for combating anasarca. However, no treatment could be offered for HCV infection in anticipation of renal allograft rejection.

OUTCOME AND FOLLOW-UP

So this is a case of CMV pneumonitis co-infection with HCV in a postrenal transplant patient. With initiation of therapy, the patient showed improvement of his clinical condition. He became afebrile and relief from breathlessness and gradual increase in urine output. He was subsequently discharged with tapering of diuretic therapy and is under supervised therapy. He is under regular bimonthly thorough clinical follow-up and is doing well. His treatment with valganciclovir is being continued for 6 months to prevent any chance of recurrence of CMV associated complications.

DISCUSSION

CMV is one of the commonest opportunistic infections in solid organ transplant recipients. CMV belongs to the family of herpes viruses and is also known as Human Herpes Virus 5 (HHV-5). 50–80% of people develop CMV antibodies at some time during their lives.[18] Symptomatic CMV infection occurs in 20 to 60% of all transplant recipients and is a significant cause of increased morbidity and mortality in this population.[1 19]

CMV infection can initiate endothelial cell activation and vascular injury that may facilitate acute rejection, chronic rejection, atherosclerosis, transplant glomerulopathy or thrombotic microangiopathy.[4] Thus, active CMV infection in renal transplant recipients is often associated with episodes of allograft rejection. Among systemic involvements, pulmonary involvement is a common organ system involved and CMV pneumonitis is a well-known complication. Previous studies report a high death rate of 48% associated with CMV pneumonitis among renal transplant patients.[8] In ventilator assisted cases, the death rate may go even over 90%.[9] Thus proper prophylactic therapy for CMV post-transplantation is mandatory for patients at risk. Valganciclovir is a drug commonly used in the management of CMV infection. However, the only restraint is high cost for which it is not being used in a regular basis as it is unaffordable for many sections of the society particularly in a developing country like India. Hence, the need for reimbursement of the drug becomes extremely crucial in these circumstances. Lack of reimbursement may lead to non-compliance of even starting or maintaining the drug in the required dose for the necessary duration (depending on the severity of infection). It may thereby result in the development of several CMV related complicacies including rejection of the renal allograft and lack of prolongation of graft survival.

CMV D+/R– patient group are at the highest risk for CMV related complications post-transplant within the first 6 months, predominantly within first 3 months of transplantation.[20] However, different studies reveal that during the first 3 years of postrenal transplantation, D+/R+ group of patients have the worst graft and patient survival.[21 22] The cause behind this may be attributed to vascular injuries such as transplant glomerulopathy.[23] Allograft rejection is further enhanced by CMV by activating the transcriptional factor NF-κB which stimulates several genes with wide range of inflammatory responses. CMV stimulates NF-κB by enhancing the expression of major histocompatibility complex (MHC) class I and class II antigens.[18 24] CMV is also associated with increasing

BMJ Case Reports 2012; doi:10.1136/bcr.12.2011.5314

serum levels of IL6 and TGF β1 which play extensive roles in renal failure.[25 26]

CMV in renal transplant patients is also associated with leucopenia which further suppresses the cell-mediated immunity and decrease the T-helper/T-supressor cell ratio and modulation of non-HLA-restricted cells that kill CMV. This includes- natural killer cells and macrophages.[27]

This cell-mediated immune suppression by CMV in addition to immunesupressive induction therapy thereby accelerates the reactivation of other viruses which might have remained latent in the host.[9 27] Moreover, it triggers the production of tumour necrosis factor-α,[28 29] a key mediator in the pathogenesis of HCV.[29 30] HCV reactivation in renal transplant patients particularly increases the death rates.[31–33] Studies suggested that decompensated liver disease contributed to increased death rates in HCV positive kidney recipients.[34] Within the first 5 years of transplantation, 40% of the HCV positive renal transplant recipients develop progressive hepatic fibrosis and further liver-related complications are very common particularly in cases with advanced fibrosis.[35]

The different treatments in offer including IFN monotherapy or IFN plus ribavirin combination therapy have raised concerns as several studies have shown high rates of graft failure.[12 16 17 23 26 27]

IFN γ plays a pivotal role in promoting the influx of macrophages into the graft and their subsequent activation into more destructive cells by developing a delayed-type hypersensitivity response. Thus, as the allograft reaction begins, localised production of IFN γ in the graft induces endothelial cells and monocytes to express class II MHC molecules making these cells target for T lymphocyte attack.[36]

Proper detection and treatment of HCV before renal transplantation can avoid future complicacies. Anti-HCV tests often give false negative results if HCV antigen is present in low concentrations. The third generation immunoassay (enzyme immunoassay-3) provides better results with a high positive predictive value.[37 38] However, in suspected HCV infected patients having negative antibody test result despite showing an elevated serum aminotransferase levels, an HCV RNA assay with a detection limit ≤50 IU/ml is recommended to evaluate for HCV infection. This method can no doubt restrict the rates of false negative cases to a significant extent as this is the most sensitive test for HCV detection.[39] Previous studies reveal that false negative serology for HCV infection among haemodialysis patients is not uncommon. A study by Schneeberger *et al* revealed that out of a total of 2576 anti-HCV negative dialysis patients of the Netherlands, six contained HCV RNA as has been confirmed by HCV RNA PCR.[40] Me´ndez-Sa´nchez *et al* demonstrated that 3 out of 149 (2%) haemodialysis patients at a tertiary-care hospital in Mexico City, Mexico who were anti-HCV negative had detectable HCV RNA.[41] A study conducted by Hinrichsen *et al* reported a higher percentage of false negative cases to HCV antibody among the haemodialysis patients. They found that 24 of 111 HCV RNA positive patients (21.6%) were negative for anti-HCV assays.[37]

Literature studies reveal a reduction in the rates of HCV-associated renal dysfunction after transplantation if the HCV infected ESRD patient are properly for HCV before transplantation achieves sustained virological response (SVR).[28 42] The standard treatment protocols in offer include: pegylated and non-pegylated IFN and combination therapy with non-pegylated IFN plus low dosage weight based oral ribavirin. Two meta analysis of data from 25 published studies comprising of 482 HCV infected ESRD patients who have undergone IFN monotherapy pretransplantation, had SVR rates of 33 to 39%. Genotype 1 HCV infected patients show lesser SVR rates of 26 to 30.6% on IFN monotherapy.[28 42]

In this article we report one D+/R+ renal transplant recipient who had developed CMV complications leading to reduced renal function and CMV pneumonitis. Furthur, the patient also developed complications from HCV infection in the form of jaundice, ascites and transaminitis. On treatment with oral valgancyclovir, improvement in his clinical condition was observed. However, no treatment could be offered for HCV infection in anticipation to renal allograft rejection. This case thus demonstrates that proper prophylactic therapy for CMV post-transplantation for patients at risk and proper HCV detection and eradication before renal transplantation is of utmost importance as there exists no optimal treatment procedure for post-transplant HCV infection.

Learning points

- HCV and CMV infection and co-infection increases the chances of renal allograft rejection and initiates further complications.
- HCV detection with highly sensitive HCV RNA assay before renal transplantation must be done.
- For HCV positive patients, proper treatment and complete eradication of HCV must be done before renal transplantation.
- CMV prophylaxis (by treating with oral valgangiclovir) for the first 6 months post-transplantation, is recommended to all the D+/R+, D+/R− and D−/R+ renal recipients.

Acknowledgements This work was supported by intramural funds received from Indian Council of Medical Research, Government of India.

Competing interests None.

Patient consent Obtained.

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