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Case Report

MERS CoV Infection in Two Renal Transplant Recipients: Case Report

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Middle East Respiratory Syndrome *Coronavirus* (MERS CoV) infection has recently emerged as a cause of severe potentially fatal pneumonia. The clinical presentation ranges from asymptomatic infection to severe pneumonia and acute renal failure. Data on the clinical presentation in solid organ transplant recipients are lacking. We report two cases of MERS CoV infections in two renal transplant recipients with variable clinical presentations and outcomes. The first patient presented with progressive respiratory symptoms, acute renal failure and died. While the second patient presented with respiratory tract symptoms, remained stable and had an excellent clinical recovery despite recent reception of thymoglobulin induction. This is a rare report of MERS CoV infection in renal transplant recipients. Further data are needed to gain better understanding of the impact of anti-rejection immunosuppressive therapy on the clinical presentation, severity and outcome of MERS CoV infections in solid organ transplant recipients.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CVVHD, continuous venovenous hemodialysis and hemofiltration; GCSF, granulocyte colony stimulating factor; MERS CoV, Middle East Respiratory Syndrome *Coronavirus*; RT-PCR, reverse transcription polymerase chain reaction

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Introduction

Coronaviruses are a frequent cause of self-limited community acquired upper respiratory tract infections (1). A novel coronavirus strain was discovered and reported in November 2012 and was subsequently called Middle East Respiratory Syndrome *Coronavirus* (MERS CoV) (2). Pneumonia caused by MERS CoV has been associated with severe morbidity and mortality in immunocompetent populations. However, clinical picture varies widely, it ranges from asymptomatic carrier state to severe rapidly fatal pneumonia (3). Certain risk factors for developing MERS CoV pneumonia and for having poor outcome such as end-stage renal disease have been identified (4). However, data on the clinical picture in solid organ transplant recipients and the effect of the anti-rejection immunosuppressive regimens on the clinical course of MERS CoV infection are lacking. There has only been one previously reported case of a renal transplant recipient with MERS CoV pneumonia (5). We report two cases of MERS CoV pneumonia in renal transplant recipients with variable clinical presentations and outcomes.

Case Summaries

Case 1

A 44-year-old gentleman, who underwent a live related renal transplant on September 13, 2004, due to hypertensive nephrosclerosis, presented to the emergency department on March 30, 2014, complaining of generalized fatigue of a 3-day duration. This was followed by sore throat and shortness of breath that started 1 day prior to presentation. He did not complain of cough, fever, diarrhea, abdominal pain or vomiting. There was no history of contact with similarly ill or febrile patients. On admission, he required 5–10 L/min of oxygen through facemask to maintain an oxygen saturation of 90%. Moreover, he had oliguria.

His laboratory testing revealed a white blood count 2.9×10^9/L, hemoglobin of 3.3 g/dL a platelet count 147×10^9/L, absolute neutrophil count 1.42×10^9/L, absolute lymphocyte count 0.14×10^9/L, lactate dehydrogenase 843 U/L, alanine aminotransferase 283 U/L, aspartate aminotransferase 238 U/L. The patient was found to have acute renal failure on admission where serum creatinine was 13.9 mg/dL, calculated creatinine clearance on admission was 7 mL/min. Chest X-ray revealed diffuse bilateral infiltrates (Figure 1). His anti-rejection regimen consisted of cyclosporine, azathioprine 50 mg once daily and prednisone 5 mg once daily. Continuous venovenous

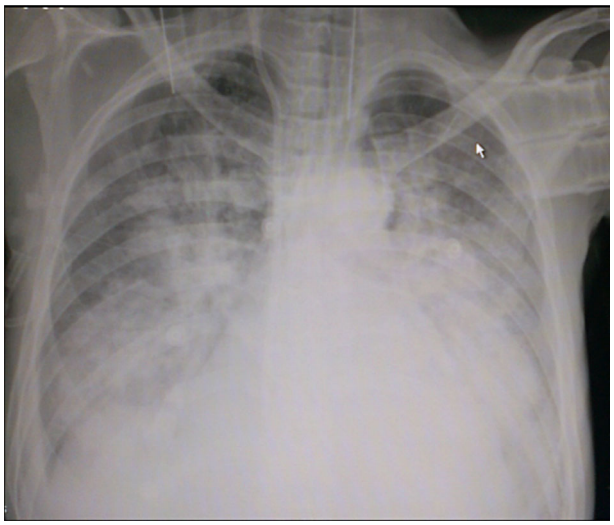

Figure 1: Chest X-ray of case 1 that shows bilateral diffuse airspace opacities with peribronchial cuffing.

hemodialysis and hemofiltration was promptly started. His low hemoglobin was attributed to upper gastrointestinal bleeding evidenced by a positive stool for occult blood test and an upper gastrointestinal scope that revealed gastric wall inflammation. The patient required a total of 12 units of packed red blood cells transfusion throughout the admission.

He initially received ceftriaxone and levofloxacin. Trimethoprim/sulfamethoxazole was initiated as empiric treatment for possible *Pneumocystis jirovecii* pneumonia, and oseltamivir for possible influenza H1N1 infection. Antimicrobial doses were adjusted to the patient's creatinine clearance. Given the patient's critical condition, a broader antibacterial coverage that consisted of imipenem, vancomycin in addition to trimethoprim/sulfamethoxazole was added a day later to replace ceftriaxone.

Two days after admission, the white blood count dropped to 0.98×10^9/L. Granulocyte colony stimulating factor was then initiated 300 mg subcutaneously once daily for 3 days and trimethoprim/sulfamethoxazole was discontinued. Viral pneumonia due to MERS CoV was suspected 6 days after admission. A nasopharyngeal swab as well as blood qualitative reverse transcription polymerase chain reaction assay (RT-PCR) for MERS CoV were both positive. The patient's clinical condition deteriorated necessitating endotracheal intubation.

When the results of MERS CoV PCR became available 2 days later; pegylated interferon α2a 180 μcg subcutaneously once weekly, in addition to ribavirin 400 mg loading dose followed by 200 mg orally twice daily were initiated. Bacterial cultures of sputum, blood and urine were all negative.

The patient's condition continued to worsen and he eventually succumbed to his infection and passed away 7 days after the diagnosis of MERS CoV pneumonia was made.

Case 2

A 30-year-old gentleman had a living related renal transplant on March 6, 2014, and received antithymocyte globulin induction therapy 100 mg intravenously (IV) once daily for 3 days prior to the date of transplant, followed by 50 mg (IV) once daily for 2 days posttransplant. Posttransplant course was complicated by hydronephrosis of the graft due to a lower ureteric stricture, which required a nephrostomy tube insertion on March 26, 2014, and the patient was discharged home on April 6, 2014.

His immunosuppressive regimen consisted of tacrolimus 2 mg orally twice daily, mycophenolate mofetil 1 gm twice daily, and prednisone 20 mg once daily. His antimicrobial prophylaxis consisted of trimethoprim/sulfamethoxazole and valganciclovir. He was admitted on April 21, 2014 with fatigue, shortness of breath and a productive cough of bloody sputum for 3 days. He had a temperature of 38.2°C during admission. Blood examination revealed a white blood cell count 4.44×10^9/L, absolute neutrophil count 4.25×10^9/L, absolute lymphocyte count 0.103×10^9/L, hemoglobin 10.5 g/dL, platelet count 209×10^9/L, lactate dehydrogenase 245 U/L, and serum creatinine 3 mg/dL. Tacrolimus level was 11.6. Chest X-ray on admission was normal (Figure 2). Nasopharyngeal swab on admission was positive for MERS CoV RT-PCR. Bacterial cultures for sputum and blood were both negative. Urine culture revealed *Enterobacter cloacae*. Antibacterial therapy with meropenem and levofloxacin was initiated. Mycophenolate

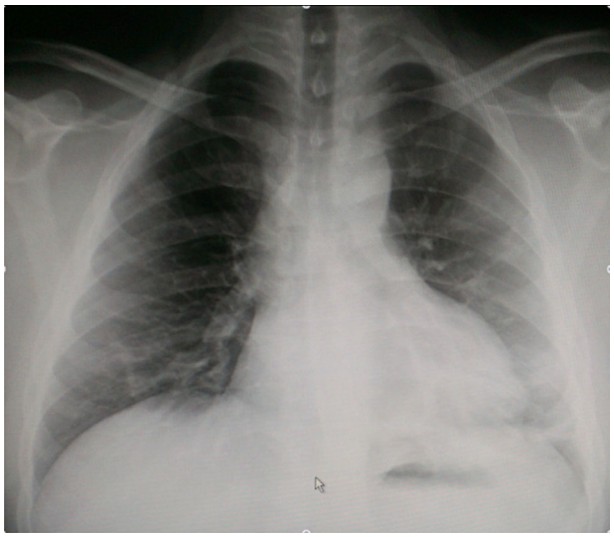

Figure 2: Chest X-ray of case 2 that shows prominent bronchovascular markings, no airspace opacities.

mofetil dose was reduced to 500 mg orally twice daily. The patient had a stable admission course, his symptoms improved and his fever resolved. He was discharged home on April 29, 2014.

Discussion

Pneumonia due to MERS CoV is associated with a high rate of mortality that reached 76% (4). Patients with comorbid conditions, particularly those with end-stage renal disease tend to have a worse outcome (4,6). Due to scarcity of data however, the clinical presentation as well as the effect of solid organ transplantation along with the immunosuppressive anti-rejection regimen on the severity and outcome of MERS CoV pneumonia remain unknown.

Here, we report two cases of MERS CoV infection in renal transplant recipients with variable clinical presentation. Diagnosis was confirmed using two qualitative real-time RT-PCR assays; one targets regions upstream of the E gene (upE) and the other targets the region within open reading frame 1b (7). The blood RT-PCR was done on plasma. No blood RT-PCR was done on case 2. It is difficult to make conclusions regarding the significance of positive blood RT-PCR in MERS CoV infections based on a single case. Whether blood MERS RT-PCR can be used as a prognostic indicator is worth investigating in large cohorts.

The number of patients is too small to be able to discern whether the natural history of MERS CoV infections is altered in transplant recipients. However, it appears that it may be similar to that of the nontransplant population based on the variable clinical presentation of these two cases. As the outcome was death in the patient who presented with severe pneumonia and multi-organ failure, while the young patient who had no pneumonia (evidenced by the normal chest X-ray) survived and recovered despite receiving antithymocyte globulin 40 days prior to admission with MERS infection.

It important to note that although fever is included in the World Health Organization and the Centers for Disease Control and Prevention MERS case definitions (8,9), it was absent in case 1. Therefore, absence of fever in transplant recipients should not preclude investigating for MERS infections in patients who otherwise fit the MERS infection definitions.

Poor outcome in the first patient may be related to the patient's acute renal failure, which is probably in part related to the significant volume depletion caused by his severe anemia. In addition, viral tropism to uroepithelial cells which has been implicated as a cause of the commonly observed acute renal failure in patients with MERS CoV pneumonia may have played a role in causing acute renal failure in this patient as well (10). In an attempt to treat the severe MERS CoV pneumonia, interferon α2a in combination with ribavirin was initiated based on a previous *in vitro* study where interferon α2b was found to lead to a dose dependent reduction in the number of genome copies of MERS CoV as well as a reduction in the cytopathic effect, which was magnified when combined with ribavirin in an *in vitro* model (11). This has led the authors to test this combination in an animal model (macaques) 8 h after they were inoculated with MERS CoV with favorable outcomes (12). The choice of interferon α2a instead of interferon α2b was due to the lack of interferon α2b availability. Failure of this regimen has been demonstrated in a case series that consisted of five patients with severe MERS CoV pneumonia, all of whom had a poor outcome (13). This combination was started late in both our cases and the case series by a minimum of 8 days post-admission with pneumonia. Whether the poor outcome in those cases is related to the delay in administration of treatment or due to lack of true *in vivo* efficacy in humans is difficult to conclude in the absence of controlled studies. Moreover, a more recent *in vitro* study demonstrated that interferon α2b has superior anti-MERS CoV activity compared to interferon α2a evidenced by a lower IC50 (14). Whether these factors have led to this patient's poor outcome, and whether other factors are involved is impossible to conclude based on the very limited data available.

It is interesting that despite the recent T-lymphocyte depletion with antithymocyte globulin prior to transplantation in the second case 6 weeks prior to his presentation with MERS CoV pneumonia, the patient had a relatively mild illness and an excellent clinical recovery. The positive outcome may be related in part to the patient's young age. Other factors may have had a positive impact on the outcome but this cannot be determined from a single case. None of the above patients had contact with similarly ill patients. However, the second patient started exhibiting symptoms 12 days after his discharge from the hospital. So his infection may have been from a nosocomial source, as nosocomial transmission has been a major obstacle in the control of MERS infections (15). Both patients were placed in isolation rooms once MERS diagnosis was suspected.

The transplant program, in response to the MERS CoV endemic, adopted a few changes. All solid organ transplant recipients, prior to their scheduled outpatient follow-up clinic visits, underwent initial screening in triage clinics to ensure absence of any symptoms or signs suggestive of MERS infection. In addition, transplant procedures were halted at the time of epidemic until this month.

In conclusion, we report MERS CoV pneumonia in two renal transplant recipients with poor outcome in one case and a favorable outcome in the other. More data are needed to gain better understanding of MERS CoV infections in solid organ transplant recipients.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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