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Case Report

New influenza A (H1N1/09) in three renal transplant patients

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Abstract

The pandemic new influenza A (H1N1/09) virus may be especially threatening for immunosuppressed renal transplant patients as they are at increased risk for complications, prolonged infection and mortality. This is the first case report of renal transplant patients with PCR-confirmed H1N1 respiratory tract infection. They showed a surprisingly mild clinical course despite respiratory fungal or viral co-infections in two cases. Treatment with oseltamivir in standard dosage was immediately started after diagnosis and proved to be rapidly beneficial with respect to clinical outcome and virus shedding without deteriorating renal transplant function.

Keywords: H1N1; oseltamivir; renal transplantation; respiratory

Background

A pandemic caused by the new influenza A (H1N1/09) virus resurged in March 2009. This new virus is a quadruple-reassortant influenza A virus composed of human, swine and avian strains. As evidenced previously, young adults and children are the subpopulations most affected [1]. Clinical disease generally appears mild, but complications can occur, especially in those with underlying disease, pregnancy or patients on immunosuppression [1,2]. Our aim was to evaluate the clinical course in renal transplant recipients, as they are at increased risk of more severe H1N1 infection and mortality [3].

The virus appears to have a predilection for infection of the lower respiratory tract [4], in some cases producing a severe pneumonia, acute respiratory distress syndrome or even multisystem organ failure. In Germany, no influenza (H1N1) strains circulating before December 2009 were reported to be resistant to neuraminidase inhibitors.

We describe here three renal transplant patients with proven H1N1 infection.

Case 1

A 48-year-old woman with her third renal transplantation in 2009 experienced severe surgical complications post-transplantation with an application of a colostomy and a split skin graft. She was under double immunosuppression with tacrolimus and prednisolone at the time of admission, presenting at reduced clinical condition with headache and dysuria. Creatinine was at 1.3 mg/dL (MDRD eGFR i.e. estimated GFR by utilizing the Modification of Diet in Renal Disease (MDRD) Study equation 45 mL/min). Antibiotic treatment was started and additional chest radiography on Day 2 after admission revealed an interstitial pneumonia, but simultaneous testing of H1N1 in nasopharyngeal swabs was negative. The bronchoalveolar lavage fluid (Day 4) revealed the presence of cytomegalovirus, and intravenous ganciclovir was initiated. Since Day 4, fever peaked to 39°C and C-reactive protein (CRP) to 4 mg/dL (Figure 1), and she developed a productive cough. Another swab H1N1 PCR (Day 7) proved positive. Oseltamivir (75 mg b.i.d.) led to a complete resolution of symptoms within 5 days. After discontinuation of oseltamivir, PCR testing revealed no H1N1. On Day 11, MDRD eGFR was at 37 mg/dL (creatinine 1.5 mg/dL). Tacrolimus dosage was stable. Antibiotic treatment was stopped, but ganciclovir was continued for 3 weeks after discharge.

Case 2

A 65-year-old woman transplanted in 2009, with triple immunosuppression with tacrolimus, prednisolone and mycophenolic acid [in reduced dosage (500 mg/b.i.d.) because of recurrent urinary tract infections] developed mild pulmonary symptoms with a non-productive cough 14 days prior to another urinary tract infection. She presented with dysuria and cough. Renal function was stable (creatinine 1.5 mg/dL, MDRD eGFR 36 mL/min). The initial chest X-ray was negative, but she was admitted to the hospital for intravenous therapy of the urinary *Pseudomonas* spp. infection. Another chest X-ray (Day 5) showed an infiltrate, while CRP peaked to 14.8 mg/dL (Figure 1). A bronchoalveolar lavage fluid revealed *Aspergillus* spp. and intravenous voriconazole was started. After positive nasopharyngeal swab H1N1 PCR (Day 6), oseltamivir (75 mg/b.i.d.) was initiated. Nine days later, following negative control H1N1 PCR, oseltamivir was discontinued. Tacrolimus dosage was adjusted due to elevated through

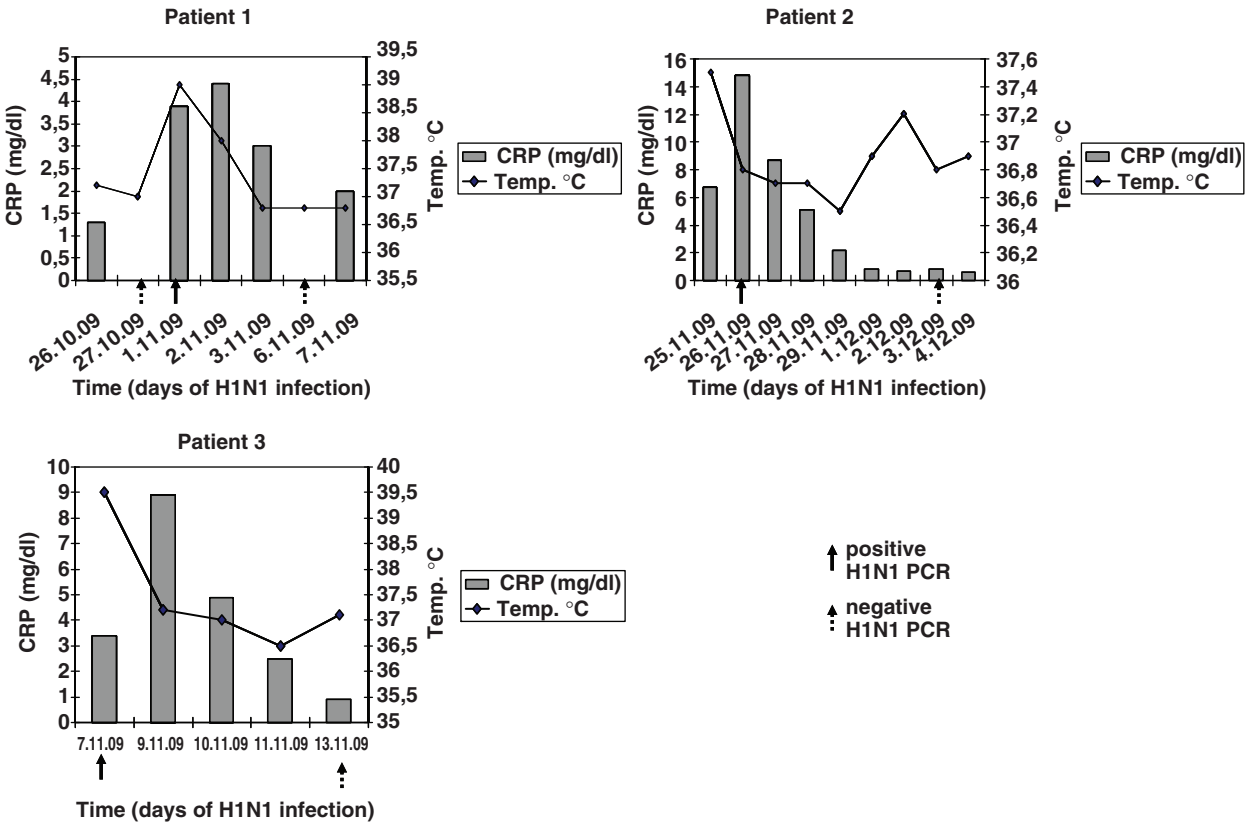

Fig. 1. Run of the curve of temperature and CRP measures of Patient 1, Patient 2 and Patient 3. Arrows indicate positive and negative H1N1 PCR results.

level. Creatinine increased to 1.8 mg/dL (MDRD eGFR 27 mL/min, Day 15). The patient received antifungal therapy for 3 weeks.

Case 3

A 61-year-old male, transplanted in 1999 and suffering from chronic hepatitis C infection, received double immunosuppression consisting of tacrolimus and prednisolone. In July 2009, he underwent nephrectomy of the left polycystic kidney due to a complicated cyst with ensuing multi-month hospital treatment because of postoperative complications with sepsis, an infected fistula of the pancreas and secondary wound healing with an application of a vacuum pump and consecutive antibiotic treatment (vancomycin, ciprofloxacin). In November, the patient, still under antibiotic treatment, showed stable clinical condition and transplant function (creatinine 2.4 mg/dL, MDRD eGFR 28 mL/min). Temperature then suddenly peaked to 39°C; CRP was at 3.4 mg/dL (Figure 1) as he developed respiratory symptoms with cough and rhinitis. The chest X-ray revealed no infiltration, but an H1N1 PCR from nasopharyngeal swab was positive. Antiviral therapy with oseltamivir 75 mg/b.i.d. led to a resolution of symptoms and a negative PCR control 1 week later (Figure 1). The renal function remained stable (creatinine 2.3 mg/dL, MDRD eGFR 29 mL/min), without tacrolimus adjustment. The patient was discharged 1 week later.

Discussion

Infection with influenza viruses can result in a wide spectrum of clinical disease manifestations. Influenza after solid organ transplantation appears to be more common among lung transplant recipients [5] but also causes significant morbidity among renal, liver and heart transplantation patients. Influenza has also been associated with allograft rejection [6]. To our knowledge, this is the first report on infections of renal transplant recipients with the new influenza A (H1N1/09) virus.

The three cases differ with respect to time after transplantation and to the immunosuppressive regimen. All three patients had concomitant infections. The first two cases are characterized by short time after grafting and reduced immunosuppression due to infectious complications. The third case had a longer time span after grafting with reduced immunosuppression and multiple infectious/surgical complications.

The patients had not been vaccinated against the new influenza A. They were treated with oseltamivir in a standard dosage (75 mg/b.i.d.) [7]. No adverse effects occurred.

Onset of respiratory symptoms was fulminant in Case 1, but antiviral treatment was delayed and led to a rapid resolution of symptoms and a negative PCR result 4 days later. Other authors report an overall percentage of 80% positive initial PCR [8]. The second case exhibited mild respiratory symptoms for nearly 20 days before H1N1 PCR testing and

antiviral therapy, which was effective within 1 week, despite fungal co-infection of the lung. Both cases underline the benefit of antiviral treatment in the immunocompromised patient even when started late after infection [9]. In the third case, onset of respiratory symptoms was acute. Antiviral treatment was rapidly effective.

Fast symptom relief with clearance of the virus after oseltamivir treatment is concordant with other reports [10], but this observation is noteworthy and reassuring in immunosuppressed patients. Overall, H1N1 infection showed an unexpectedly mild clinical course, similar to the general population.

Renal transplant function remained stable, while GFR decline in Case 3 was most probably induced by drug interactions.

Conclusion

The immunosuppressed renal transplant patient is prone to a severe H1N1 infection, but the cases described here showed a surprisingly mild clinical course despite respiratory co-infections. It is essential to test for influenza A (H1N1/09), as early administration of antiviral agents is recommended. Our cases show that early antiviral therapy contributes to a fast resolution of respiratory symptoms and clearance of the virus. In addition, in our three cases, even delayed therapy was associated with a fast symptom relief. Furthermore, oseltamivir in a standard dose proved effective without deteriorating transplant function or leading to adverse effects. Prospective studies in a larger collective are needed to confirm these positive findings.

Conflict of interest statement. None declared.

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