Clinical manifestations and evolution of infection by influenza A (H1N1) in kidney transplant recipients

Manifestações clínicas e evolução da infecção pelo vírus da influenza A (H1N1) em receptores de transplante renal

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ABSTRACT

Introduction: The emergence of the pandemic outbreak of influenza A (H1N1) in April, 2009, represented a logistic challenge for public health. Although most infected patients presented clinical and evolutionary manifestations which were very similar to seasonal influenza, a significant number of individuals developed pneumonia and severe acute respiratory failure. The impact of influenza A (H1N1) in immunocompromised patients is not well established yet. **Method:** This study aimed to analyze the clinical presentations and evolution of influenza A (H1N1) in 19 kidney transplant recipients. Influenza A (H1N1) infection was confirmed by RT-PCR in all patients. Treatment included antiviral therapy with oseltamivir phosphate and antibiotics. **Results:** The studied population was compounded mostly of white people (63%), males (79%), at a mean age of 38.6 ± 17 years and patients with at least one comorbidity (53%). Influenza A (H1N1) infection was identified 41.6 ± 49.6 months after transplantation. Common symptoms included cough (100%), fever (84%), dyspnea (79%), and myalgia (42%). Acute allograft dysfunction was observed in 42% of the patients. Five patients (26%) were admitted to the Intensive Care Unit, two (10%) required invasive ventilation support, and two (10%) required vasoactive drugs. Mortality rate was 10%. **Conclusions:** Acute renal allograft dysfunction was a common finding. Clinical, laboratory, and evolutionary characteristics were comparable to those in the general population.

Keywords: respiratory tract infections, influenza A virus, H1N1 subtype, risk factors, kidney transplantation, immunosuppression.

RESUMO

Introdução: A emergência do surto pandêmico de *influenza* A, subtipo H1N1, em abril de 2009, representou um grande desafio para a logística de saúde pública. Embora a maioria dos pacientes infectados apresente manifestações clínicas e evolutivas muito semelhantes às observadas na *influenza* sazonal, um número significativo de indivíduos evolui com pneumonia e insuficiência respiratória aguda severa. O impacto da infecção pelo vírus *influenza* A, subtipo H1N1, em pacientes imunossuprimidos não é determinado. **Método:** Neste estudo, foram analisadas a apresentação clínica e a evolução da *influenza* A, subtipo H1N1, em 19 receptores de transplante renal. Os pacientes receberam confirmação diagnóstica pela técnica de RT-PCR. O manejo clínico incluiu terapêutica antiviral com fosfato de oseltamivir e antibióticos. **Resultados:** A população estudada foi predominantemente de indivíduos do sexo masculino (79%), brancos (63%), com idade média de 38,6 ± 17 anos e portadores de pelo menos uma comorbidade (53%). A infecção por *influenza* A, subtipo H1N1, foi diagnosticada em média 41,6 ± 49,6 meses após o transplante. Os sintomas mais comuns foram: tosse (100%), febre (84%), dispneia (79%) e mialgia (42%). Disfunção aguda do enxerto foi observada em 42% dos pacientes. Cinco pacientes (26%) foram admitidos em Unidade de Terapia Intensiva, dois (10%) necessitaram de suporte com ventilação invasiva e dois (10%) receberam drogas vasoativas. A mortalidade foi de 10%. **Conclusões:** A disfunção aguda do enxerto renal foi um achado frequente, e as características clínicas, laboratoriais e evolutivas foram comparáveis às da população geral.

Palavras-chave: infecções respiratórias, vírus da *influenza* A subtipo H1N1, fatores de risco, transplante de rim, imunosupressão.

Introduction

In April 2009, the World Health Organization (WHO) reported the infection caused by a new influenza A virus subtype (H1N1) in the Mexican population. This new subtype was the result of a genetic combination of influenza A virus strains, which are capable of infecting human, swine and bird organisms.[1]

The number of cases of influenza A H1N1 infection increased rapidly in Mexico and other countries, reaching pandemic proportions.[2]

Clinical presentation and the evolution of influenza A H1N1 infection are very similar to those of seasonal influenza. Less common signs and symptoms of seasonal influenza, such as vomit and diarrhea, are observed in a significantly larger number of patients.[3] Unfavorable clinical evolution, with pneumonia and severe respiratory failure, has been frequent and, as opposed to seasonal influenza, has affected mainly young patients and pregnant women.[4]

The impact of influenza A H1N1 infection in immunosuppressed patients is not well established. Knowing about the clinical impact of this virus in this population is essential to establish new policies to prevent and treat this important condition.

In this study, the clinical presentations and evolution of influenza A H1N1 were described, with a confirmed diagnosis by reverse transcriptase – polymerase chain reaction (RT-PCR), in 19 kidney transplant recipients followed up at *Hospital do Rim e Hipertensão*.

Methods

Study design and data collection

This study included 19 kidney transplant recipients, admitted at Hospital do Rim e Hipertensão from July 1st, 2009, to September 31st, 2009 for at least 24 hours, and with confirmed influenza A H1N1infection.

The analyzed data were gathered from medical files and investigation reports from Sistema de Informação de Agravos de Notificação da Secretaria Estadual de Saúde, state of São Paulo. The retrospective study considered demographic data, pneumococcal and influenza A vaccination history, associated comorbidities, clinical signs and symptoms, laboratory and radiological profile, and the aspects related to clinical evolution.

Clinical diagnosis

Diagnostic routine for influenza A H1N1 infection was performed in compliance with the Ministry of Health of São Paulo recommendations. Transplant patients with suspicion of infection by influenza[5] were considered to be eligible for hospital admission and empirical treatment with oseltamivir phosphate (Tamiflu®). From August 5, 2009 on, with the characterization of the pandemic outbreak of influenza A H1N1, ministry and state recommendations were revised, thus being considered for hospital admission only those patients with suspicion of acute respiratory infection by influenza and patients presenting with severe acute respiratory disease or alert signs and symptoms.[6]

Severe acute respiratory disease was characterized by fever higher than 100ºF, cough and dyspnea with or without laryngalgia or gastrointestinal symptoms. Alert signs and symptoms were mental confusion, tachypnea, systemic arterial hypotension (systolic blood pressure <90 mmHg and diastolic blood pressure <60 mmHg), and age superior to 65 years. Alert signs and symptoms for pediatric patients included flaring of the nostrils, intercostal retraction on inspiration, cyanosis, dehydration, lack of appetite, vomit, malaise, toxemia, and absence of family support.[5,6]

Laboratory diagnosis

Diagnostic screening by rapid QuickVue Influenza A+B test (Quidel, San Diego, CA, USA) was performed only at the beginning of the pandemic. After August 7, 2009, considering the transmission of influenza A H1N1 within the national territory and the low sensibility of the test, diagnostic screening was no longer recommended by the *Hospital do Rim e Hipertensão* Infection Control Commission.

The infection by influenza A H1N1 was confirmed by direct identification of the specific antigen for influenza by the RT-PCR technique, according to the protocol by the Center of Disease Control in USA and by WHO,[7] in a sample of respiratory secretion obtained from the nasopharynx or trachea. Molecular tests were performed at Instituto Adolfo Lutz, São Paulo.

Acute allograft dysfunction was defined as an increase of at least 20% in serum creatinine in comparison to basal value. Acute allograft dysfunction was classified as mild when serum creatinine elevations were between 20 and 50% of the basal value; as moderate, for values higher than 50%; and as severe when dialytic therapy was necessary.

Treatment

Patients received symptomatic and clinical support according to their need. Antiviral treatment with

oseltamivir phosphate was carried out in up to 24 hours after hospital admission, regardless of the time of symptoms onset. Treatment was predicted to last for five days. Complementary therapy with antibiotics was used according to clinical and laboratory judgment.

Statistical analysis

The variables were presented by means of statistical and descriptive parameters. Numerical variables were expressed as means and standard deviations, and categorical variables, as percentage frequencies. The program SPSS version 7.5.1 (SPSS Inc., Chicago, IL. USA, 1996) was used for statistical analysis.

Results

During the studied period, 44 patients were admitted to the hospital with flu symptoms and severe acute respiratory disease criteria. Rapid test for influenza A or B was performed in ten patients and was positive for influenza A in six of them (60%). Influenza A H1N1 infection was confirmed by molecular test in 14 patients. Five other patients who had been previously admitted for other indications (one due to acute allograft rejection and four due to infectious complications not related to the respiratory apparatus) had respiratory symptoms compatible with influenza, and then received diagnostic confirmation for influenza A H1N1 after the performance of molecular test. The 44 patients admitted with severe acute respiratory disease and the 19 diagnosed with influenza A H1N1 infection represented, respectively, 1.1 and 0.5% of the population of 4,091 recipients followed up in the institution during the same period. The 19 patients who had a confirmed diagnosis for influenza A H1N1 were predominantly adults (38.6 ± 17 years – 8-63), males (79%), white (63%), and presented at least one comorbidity (53%), as described in Table 1. Influenza A H1N1 infection was diagnosed 41.6 ± 49.6 (0-170) months after transplant. However, five patients (26%) had had a transplant less than three months earlier. Most patients (37%) received tacrolimus, prednisone and mycophelonate (sodium or mofetil) when being diagnosed for influenza A H1N1.

The most common symptoms were: cough (100%), fever (84%), dyspnea (79%) and myalgia (42%) (Table 2). Mean time between the onset of symptoms and hospital admission was 3.3 ± 2.4 (1-10) days. At hospital admission, eight patients (42%) presented with renal allograft dysfunction, and three (16%) had acute allograft dysfunction during admission. Five patients (26%) reported having previous contact with suspicious or confirmed cases of influenza A H1N1. Only one patient (5%) reported having received the seasonal flu vaccine, and two (10%) reported pneumococcal vaccine. The main radiologic finding was interstitial infiltrate (79%). Only one patient (5%) had a normal chest x-ray evaluation (Table 2).

Only one patient was not treated with oseltamivir phosphate because the viral infection diagnosis was

Table 1 General characteristics of kidney transplant recipients with influenza A subtype H1N1

Characteristic	n = 19
Age (years)	38.6 ± 17
Male	15 (78.9%)
Body Mass Index (kg/m^2)	22 ± 3.6
Ethnicity	
White	12 (63.0%)
Black	3 (16.0%)
Brown	4 (21.0%)
Previous comorbidities	10 (52.6%)
Diabetes mellitus	4 (21%)
Cardiopathy	1 (5.3%)
Pneumopathy	1 (5.3%)
Diabetes mellitus + cardiopathy	1 (5.3%)
Diabetes mellitus + cardiopathy + pneumopathy	1 (5.3%)
Others	2 (10.5%)
Previous seasonal flu vaccine	1 (5.3%)
Previous pneumococcal infection vaccine	2 (10.5%)
Time after the transplant (months)	41.6 ± 49.6
Type of donor	
Live	8 (42.1%)
Deceased	11 (57.9%)
immunosuppression*	
CI-MF-PRED	7 (36.80%)
CI -AZA-PRED	5 (26.3%)
MF-PRED	3 (15.8%)
CI -SRL-PRED	1 (5.3%)
CI-MF	1 (5.3%)
SRL-MF-PRED	1 (5.3%)
SRL-PRED	1 (5.3%)

*CI: calcineurin inhibitor; PRED: prednisone; AZA: azathioprine; MF: mycophelonate (sodium or mofetil); SRL: sirolimo.

Table 2 Clinical presentation and complementary evaluation of kidney transplant recipients with influenza A subtype H1N1

Variables	n = 19
Time between symptoms onset and admission (days)	3.3 ± 2.4
Signs and symptoms	
Cough	19 (100%)
Fever	16 (84.2%)
Dyspnea	15 (78.9%)
Myalgia	8 (42.1%)
Runny nose	7 (36.8%)
Migraine	5 (26.3%)
Chest pain	4 (21.1%)
Throat pain	4 (21.1%)
Diarrhea	3 (15.8%)
Arthralgia	2 (10.5%)
Hypoxemia	2 (10.5%)
Hypotension	2 (10.5%)
Nosocomial infection	5 (26.3%)
Previous contact with a suspicious or confirmed case	5 (26.3%)
Rapid test for *influenza* A or B	
Positive for *influenza* A	6 (31.6%)
Negative	4 (21.1%)
Not performed	9 (47.4%)
Findings in the chest x-ray	
No alterations	1 (5.3%)
Interstitial infiltrate	15 (78.9%)
Lobar infiltrate	1 (5.3%)
Mixed infiltrate	2 (10.5%)
Acute allograft dysfunction	
Mild	7 (53.8%)
Moderate	2 (15.4%)
Severe	2 (15.4%)

completed post-mortem, with RT-PCR performed with the respiratory tract secretion collected by the service of verification of death. This secretion collection to search for influenza A H1N1 was common at the time. Antimicrobial agents were used in 16 patients (84%) due to a suspicion of bacterial infection associated with viral infection. Third or fourth generation cephalosporins associated with macrolide antibiotics were the most used medicines (42% of the cases) (Table 3).

Table 3 Clinical evolution and treatment of kidney transplant recipients infected by influenza A H1N1

Variables	n = 19
Admission to Intensive Care Unit	5 (26.3%)
Need for mechanical ventilation	2 (10.5%)
Need for vasoactive drugs	2 (10.5%)
Antimicrobial treatment	16 (84.2%)
Cephalosporin + macrolide	8 (42.1%)
Cephalosporin + macrolide + glycopeptide	3 (15.8%)
Cephalosporin + glycopeptide	3 (15.8%)
Antipseudomonal penicillin + macrolide + glycopeptide	1 (5.3%)
Quinolone	1 (5.3%)
Hospital stay (days)	13 ± 12.4
Death	2 (10.5%)

Five patients (26%) were admitted to the Intensive Care Unit, two (10%) needed invasive ventilation support and two (10%) received vasoactive drugs. Two patients (10%) presented unfavorable evolution of the respiratory tract and died on the first and seventh days of follow-up. Mean hospital admittance time was 13 ± 12.4 days (Table 3).

Discussion

Clinical and epidemiological monitoring of influenza A H1N1 infection in our cohort of kidney transplant recipients showed demographic characteristics similar to the demographic profile of the general population in need of hospital admission and referred by other institutions.[8-10]

According to Oliveira et al., a high percentage of patients with severe forms of the disease in the general population are young adults with other associated comorbidities such as chronic respiratory diseases, metabolic and endocrine disorders, and pregnancy, as well as those who are immunosuppressed by diseases or medicines.[11] Patients in this study also presented with comorbidities, mainly chronic pulmonary disease, heart failure and diabetes mellitus. None of the patients was obese, although many transplant recipients present with significant weight gain in the post-operative period,[12] and even though this was a risk group in the general population.[11]

Mean transplant time during hospital admission was 41.6 months, and 26% of the patients had been followed-up for less than three months. Even though

52% of our patients received the combination of calcineurin, prednisone and azathioprine inhibitors[13] as initial immunosuppression agents, most studied patients (37%) received calcineurin, prednisone and mycophelonate inhibitors as immunosuppression.

Despite the fact that these data suggest high immunosuppression makes patients susceptible to the disease and its more severe forms, the information obtained in this study is not sufficient to make a conclusion about such association.

The most peculiar clinical presentation of H1N1 infection in the population of kidney transplant recipients studied here was the high incidence of renal dysfunction (58%), when compared to immunocompetent patients.[9,14,15] In spite of the description of the association between respiratory tract viral infections and the acute renal allograft rejection,[16,17] none of these events were attributed to acute rejection. In these patients, allograft dysfunction was attributed to volemic depletion, acute tubular necrosis secondary to sepsis, rhabdomyolysis, or calcineurin inhibitor nephrotoxicity, increased by the high blood levels resulting from the pharmacological interaction of these drugs with the antimicrobials agents used,[15] although many recipients present renal allograft dysfunction with no apparent etiology during systemic infections.[18,19] It is important to emphasize that 73% of the allograft dysfunction episodes were diagnosed at hospital admission, and 45% of the patients who presented acute allograft dysfunction did not receive simultaneous calcineurin inhibitor and macrolide antibiotics. At the end of the observation period, only one patient did not fully recover renal function.

Treatment with oseltamivir phosphate was administered even 48 hours after symptoms onset (minimum of one day and maximum of ten days after the first manifestation). Although there is no evidence of benefit for using the antiviral to treat the infection in healthy subjects 48 hours after the beginning of symptoms,[5,20] immunosuppressed patients present delay in the peak of viral replication activity, as well as increase in the length of time necessary to completely depurate the viral load, which indicates that the therapeutic benefit for this population might be superior.[21,22] The difficulty to define the diagnosis between viral and bacterial infection at the moment of admission, combined with the higher risk of association with bacterial pneumonia in patients infected by influenza, resulted in a high frequency (84%) of empirical treatment with antimicrobial agents associated with antiviral treatment.[23,24]

Infection by influenza A and B is associated with important morbidity and mortality in the population of organ transplant recipients, especially bone marrow and lung recipients.[16,25,26] In this study, admission in the Intensive Care Unit, the need for mechanical ventilation, and the use of vasoactive drugs and mortality were similar to the general population infected by H1N1.[9,14,15] Although the condition of the risk population for clinical complications has favored the admission of a higher number of patients with a less compromised health state, the present findings indicate that kidney transplant recipients did not have additional risk for unfavorable evolution of influenza A.

In conclusion, the population of kidney transplant recipients infected with influenza A H1N1 analyzed in this study presented a high rate of acute allograft dysfunction, but no differences in other clinical, laboratory and evolutionary findings when compared to the general population.

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