Clinical aspects of influenza A (H1N1) in HIV-infected individuals in São Paulo during the pandemic of 2009

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ABSTRACT

Objective: To describe the clinical aspects of H1N1 among HIV coinfected patients seen at a reference center for AIDS treatment in São Paulo, Brazil. **Design:** Observational and prospective cohort study. **Methods**: Descriptive study of clinical and laboratory investigation of HIV-infected patients with confirmed diagnosis of influenza A (H1N1) in 2009. We analyzed patients monitored in CRT/DST/AIDS, a specialized service for people living with HIV, located in São Paulo, Brazil. **Results**: 108 individuals presented with symptoms of H1N1 infection at the CRT DST/AIDS in 2009. Eighteen patients (16.7%) had confirmation of the diagnosis of influenza A. Among the confirmed cases, ten (55.6%) were hospitalized and eight (44.4%) were outpatients. Dyspnea was present in nine patients (50%), hemoptysis in three (16%). Six patients (60%) required therapy with supplemental oxygen. All patients had good clinical outcomes and none died. **Conclusions**: In our hospital, the symptoms that led patients to seek medical care were similar to the common flu. Hospital admission and the early introduction of antibiotics associated with oseltamivir may have been the cause of the favorable outcome of our cases.

Keywords: influenza A virus, H1N1 subtype; HIV; acquired immunodeficiency syndrome.

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INTRODUCTION

In April 2009, a new viral subtype of influenza virus was identified in Mexico, United States and Canada.[1,2] In July 2009 the first cases of sustained transmission of influenza A (H1N1) were confirmed in Brazil.[1,3] Cases of severe acute respiratory syndrome associated with influenza A started to be described in all regions of Brazil. Many patients presented pulmonary complications, especially children, pregnant women, obese and people with comorbidities, such as diabetes, hypertension, cardiovascular disease, immunodeficiencies and malignancies.

Sustained transmission of H1N1 virus in Brazil had already been declared.[1,3] In this new epidemic scenario, the Health Ministry in Brazil started to give priority to the investigation and treatment of patients with severe acute respiratory syndrome (SARS) and those who were at risk for complications, as patients with chronic diseases.

Initially, even patients with mild symptoms were hospitalized, considering the possibility of an evolution with greater severity in this group of patients. Later, with more data on H1N1 and on disease outcome, only cases with more severe symptoms were hospitalized.

Until July 29, 2009, among 543 confirmed cases of SARS in Brazil, 56 patients died, which corresponds to a lethality rate of 10.3%.[3]

In São Paulo, by the end of July, there were 2,078 suspected cases reported, 894 confirmed cases and 27 deaths, representing 48.2% of total deaths due to H1N1 infection in Brazil.[2]

It is known that the H1N1 infection in HIV patients is potentially more serious,[5,6] but despite the increasingly emerging information about the pathogenesis and clinical course of the infection caused by H1N1, there are still little data available on the course of infection in HIV patients. Considering the scarcity of data in the literature on H1N1 infection in HIV patients, we decided to conduct an analysis of patients with confirmed influenza A who received care in our service.

Our study aimed to describe the main clinical, laboratory and radiological findings in HIV-infected patients with confirmed influenza A (H1N1) infection at the Center for Reference and Training in STD / AIDS of Health Secretariat of São Paulo (CRT DST/AIDS), a highly specialized health care center for people living with HIV, located in São Paulo city, Brazil.

METHODOLOGY

A descriptive clinical and laboratorial study was conducted with all cases with confirmed diagnosis of influenza A (H1N1) among HIV-infected individuals attended at CRT/STD/AIDS. Confirmed cases of influenza A were defined as patients with a positive PCR (real-time reverse transcriptase polymerase chain reaction assay) for influenza A (H1N1).

The PCR test at nasopharyngeal secretions was collected at admission to the service among those with symptoms suggestive of influenza, such as high fever, cough, myalgia, sore throat and respiratory distress. The samples were sent to Adolfo Lutz Institute (ALI), the reference laboratory for diagnosis of influenza A (H1N1) in São Paulo, for analysis. Data was prospectively collected. A protocol with patient information as identification, epidemiological history of exposure to H1N1, data related to the HIV infection (including use of antiretroviral and adherence to them, history of immunization against seasonal influenza in the past year, tobacco use, comorbidities, signs of influenza and related symptoms) were collected. Results of radiological and laboratory tests of each patient were also included. These questionnaires were completed by infectious disease specialists who were providing care to patients. We used the same instrument for inpatients and outpatients evaluation. The questionnaires were reviewed by the principal investigator and when important data were missing, it was retrieved from the medical records.

Body mass index (BMI) of all patients were calculated to determine if there was obesity or not. In this study, any patient with a BMI greater than 30 kg/m^2 was considered obese.

The case definition of pneumonia was the presence of acute pulmonary infiltrate associated with the presence of one or more of the following signs or symptoms: dyspnea, fever, hypoxemia, cough and chest pain.

RESULTS

Our study was conducted from July 22 to October 30, 2009. During this period 108 samples of nasopharyngeal swabs were tested for H1N1 infection in HIV-infected individuals. Eighteen HIV-infected tested positive for H1N1 (first positive test result at 22nd July 2009. Last positive result at 23rd September 2009).

The obtained convenience sample of eighteen patients with positive PCR were followed-up. No pregnant patient was included in our study.

Among the eighteen confirmed patients with H1N1 infection, ten (55.6%) were hospitalized and eight (44.4%) were treated as outpatients. Thirteen (73%) were male and five female (27%). The mean age was 41.3 years (ranging from 12 to 59 years) and body mass index (BMI) ranged from 16.7 to 31.5 (mean 24). Seventeen patients (94%) were on antiretroviral therapy (Table 1).

Table 1. Clinical and laboratorial findings of HIV-infected patients with confirmed H1N1 infection in CRT/DST /AIDS, São Paulo, Brazil

	n = 18 patients (100%)
Gender	
Male	13 (73%)
Female	5 (23%)
Use of antiretroviral drugs	
Yes	17 (94%)
No	1 (6%)
CD4 count	
> 200 cels/mm^3	15 (84%)
< 200 cels/mm^3	3 (16%)
HIV viral load (HIV RNA quantitative)	
< 50	14 (77%)
> 50	4 (23%)
History of seasonal influenza vaccine	
Yes	9 (50%)
No	9 (50%)
Comorbidities	
Obesity	1 (5%)
Hypertension	5 (27%)
Diabetes	2 (11%)
Depression	3 (16%)
Pulmonary tuberculosis	2 (11%)
Smoking	2 (11%)
Asthma	1 (5%)

CD4 count ranged from 271,149 cells/mm^3, with an average of 600 cells/mm^3. Only three patients (16%) had CD4 counts below 200 cells/mm^3. HIV viral load was undetectable in fourteen patients (77%). The mean length of HIV infection was thirteen years. Only nine patients (50%) had received seasonal influenza vaccine in the previous year.

For other comorbidities, five (27%) had hypertension, two (11%) had diabetes, three (16%) had depression and two (11%) had a history of pulmonary tuberculosis. One case (5%) had been diagnosed of asthma and two (11%) were smokers.

Regarding symptoms, sixteen patients (88%) had fever over 38°C that lasted up to twelve days when they were diagnosed with influenza A. Myalgia was present in nine patients (50%), arthralgia in only one case (5%). Cough was reported by all patients (100%). Dyspnea was present in nine patients (50%), hemoptysis in three cases (16%). Chest x-rays were available for sixteen patients. Four patients (25%)

had diffuse interstitial infiltrates, one case (6%) showed bilateral alveolar infiltrate, one showed an opacity in the right base, and ten of sixteen (62.5%) patients had normal chest radiology. Hypoxemia (pO_2 < 70 mmHg), and pneumonia were detected in six patients. Six patients (33%) required therapy with supplemental oxygen through a Venturi mask and one also needed CPAP. There was no need for mechanical ventilation in any patient. In the group of ten inpatients, increased LDH was found in three patients (30%). Only one patient had thrombocytopenia (10%). Three patients had increased CPK (30%).

The average hospital stay was 5.3 days. Sixteen patients (88%) received treatment with oseltamivir for five days and in twelve cases (66%) it was necessary to combine treatment with antibiotics. No patient received treatment with corticosteroids.

DISCUSSION

Considering the scarcity of data in the literature on H1N1 infection in HIV patients, we decided to perform an analysis of patients with confirmed influenza A in our service. A total of 108 samples of nasopharyngeal swabs were tested for H1N1 infection, but only eighteen turned out positive. In consequence, the number of patients evaluated was small, and this limitation should be borne in mind.

Another study of hospitalized HIV-infected patients with H1N1 in the United States showed that most of them with immunosuppression and preexisting conditions, had developed more severe H1N1 infection.[4,6] However, in our service, all confirmed cases of influenza A had satisfactory outcomes. The vast majority of patients had high CD4 (above 500 cells/mm^3) and undetectable HIV RNA quantitative, which may have contributed to this favorable development. However, it is noteworthy that even those who had low CD4 progressed well. Antiviral therapy (Oseltamivir 150 mg/day) was initiated early on and the majority of patients presented with normal chest x-ray, in contrast with other studies that observed greater pulmonary involvement.[8] Only one patient in our study was considered obese.

Associated bacterial infections were common in our study, especially pneumonia, otitis and sinusitis with negative blood cultures. Many patients had to receive both antibiotics and Oseltamivir. Complications observed were: pneumonia (six patients, 33%), sinusitis (one patient, 5%), pancreatitis (one case, 5%) and otitis (two patients 11%).

In an autopsy study performed in 77 patients with death attributed to H1N1 infection, 22 had histopathological and immunohistochemical evidence of concomitant bacterial lung infection.[9]

The association between bacterial pneumonia and influenza has been well documented through experience gained in other influenza epidemics.[10] These data point to the fact that concomitant bacterial infections may contribute to mortality in patients with H1N1.

Many of our inpatients were treated with antibiotics early on. Two patients who did not receive antibiotics returned later with important bacterial complications. One had severe pneumonia within thirty days of treatment with Oseltamivir, requiring hospitalization, intravenous antibiotic therapy and use of supplemental oxygen. Another patient presented with otitis media with suppuration few days after initiation of treatment for H1N1 with Oseltamivir.

In addition to pneumonia and otitis, sinusitis was also found. We believe that in HIV-infected patients, antibiotics should be strongly considered because of the possibility of unfavorable outcomes in these cases.

One patient tested positive for H1N1 twelve days after onset of symptoms. This patient presented with more severe symptoms. This finding is consistent with the data shown by a study conducted in Mexico that evaluated HIV-infected patients with H1N1.This study showed that duration of disease was higher in HIV-infected compared to HIV-negative patients.[10]

Finally, some patients in our study persisted with positive H1N1 (RT-PCR) samples even after full treatment with Oseltamivir (five days). This should be valued, since persistence of viral replication after treatment with antiviral drugs may be related to the emergence of resistant strains. The same finding was described in the aforementioned study.[10]

CONCLUSION

The presence of OIs or bacterial infection suggests a more complicated course of the disease and may mask the influenza symptoms and signs, resulting in delayed treatment with a consequent increased risk for a more severe disease and death.

HIV-infected patients should be routinely screened for influenza in the context of an outbreak and OIs, and should have early antiviral treatment and early indication of flu vaccine.[7,11-13]

Admission to the hospital and early introduction of antibiotics associated with Oseltamivir may explain the favorable outcomes of our cases.

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