Case Report

Fatal 2009 pandemic influenza A (H1N1) in a bone marrow transplant recipient

Anselmo Abdo[1], Carlos Alfonso[2], Guillermo Diaz[1], Mario Wilford[3], Maykel Rocha[1], Niurka Verdecia[4]

[1]*Intensive Care Unit, Center for Medical and Surgical Research (CIMEQ), Havana, Cuba*
[2]*Pathology Department, Center for Medical and Surgical Research (CIMEQ), Havana, Cuba*
[3]*Haematology Unit, Center for Medical and Surgical Research (CIMEQ), Havana, Cuba*
[4]*Microbiology Department, Center for Medical and Surgical Research (CIMEQ), Havana, Cuba*

Abstract

Conditions characterized by immunosuppression have been recently reported as risk factors for severe novel swine-origin influenza A (H1N1) virus (S-OIV) infection during the current 2009 pandemic. We report clinical and virological findings, antiviral therapy, and post-mortem study of S-OIV in an adult bone marrow transplant recipient. The viral genome was amplified by real time reverse transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal swab specimen. The patient developed acute respiratory distress syndrome, septic shock, and eventually succumbed with a severe pulmonary haemorrhage. To the best of our knowledge, the entire clinical/therapy management and pathological examination in a transplant recipient infected with the S-OIV has not been previously documented. The fatal ending in this bone marrow transplant recipient supports recommendations that call for education measures, S-OIV vaccination, early diagnosis and aggressive treatment in the transplant population.

Key words: H1N1; influenza; bone marrow transplant; necropsy; immunosuppression; oseltamivir

J Infect Dev Ctries 2010; 5(2):132-137.

(Received 01 April 2010 – Accepted 04 July 2010)

Introduction

The 2009 pandemic caused by the novel swine-origin influenza A (H1N1) virus (S-OIV) emerged in Mexico in March 2009 during the influenza season in the northern hemisphere. In June 2009, the World Health Organization (WHO) raised its pandemic alert to the highest level, phase 6, indicating widespread community transmission on at least two continents. By 25 January 2010, infection with S-OIV had been identified in 138 countries and had caused over 15,000 deaths. On 12 May 2009, the first confirmed S-OIV case was reported in Cuba and by 19 January 2010, fifty-three deaths related to this virus infection had been recorded [1].

The clinical features of this illness and the risk factors for severity are not completely understood. Recent reports indicate most hospitalizations and severe cases occur among young and middle-aged people, and among patients with underlying conditions that include asthma, diabetes, heart disease, chronic obstructive pulmonary disease, neurologic disease, and pregnancy [2-6]. Conditions characterized by immunosuppression such as HIV infection, cancer, congenital immunodeficiency, and transplantation [2,6-11] have also been reported as risk factors.

Lung tissue studies from fatal S-OIV cases have been performed in Mexico [12], the United States [2] and Brazil [5]. However, the comprehensive clinical findings, management, and *post-mortem* studies in a fatal transplant recipient infected with S-OIV have not been reported.

This study indicates that immunosuppressed transplant recipients may have a higher risk of severe S-OIV disease despite early and aggressive anti-viral therapy hence S-OIV should be included among the potential pathogens in the transplant population.

Case Report

We report a 56-year-old male with a personal history of chronic myeloid leukaemia diagnosed three years ago. Eighteen months previous to the present admission, the patient underwent hematopoietic stem cell transplant surgery. Subsequently, a graft-versus-host disease and renal dysfunction were diagnosed.

Anticalcineurinic therapy was changed to prednisone (50 mg daily) due to the renal dysfunction.

Three days previous to his admission in the intensive care unit at the Center for Medical and Surgical Research (CIMEQ) in Havana, the patient complained of cough, fever, dyspnea and weakness. The physical examination revealed wet rales in both lung bases, tachypnea of 30 per minute and 87% oxygen saturation using pulse oximetry (SpO2). The first chest radiograph showed inflammatory-like haziness of the lung fields with greater density in the pulmonary hilum and lung bases (Figure 1 A). The presumptive diagnosis was influenza viral pneumonia caused by S-OIV. Oseltamivir treatment was prescribed 150 mg twice a day during ten days in association with antibacterial therapy (1 gr ceftriaxone twice a day, 10 mg/Kg amikacin and 500 mg azithromycin per day).

Two days after hospitalization the patient required intubation and mechanical ventilation as a result of acute respiratory distress syndrome (ARDS) with the need of high O2 concentration (up to 100%) and positive end expiratory pressure (PEEP) (up to 20 mmHg). The same day, following recommended international guidelines for real time reverse transcriptase polymerase chain reaction (RT-PCR) [13], the S-OIV genome was amplified from a nasopharyngeal swab sample that had been taken 24 hours after admission.

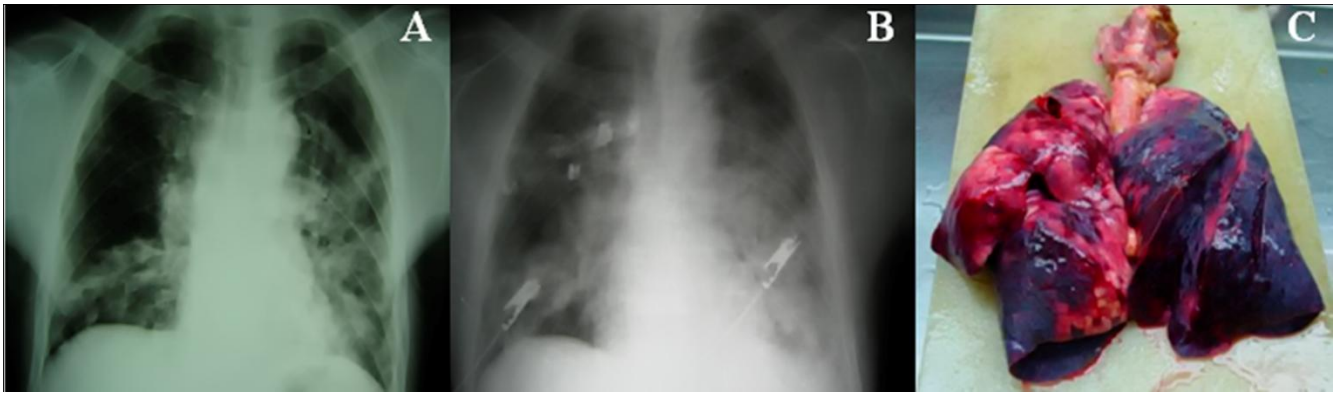
Blood cell counts on admission were normal; however, during hospitalization mild anaemia, thrombocytopenia (from 90 to 130 x109/L in the last three days) and leukopenia were found. During the illness's evolution, white blood cells decreased from 4.50 X109/L when the patient was admitted to 1.20 X109/L on the sixth day. Transaminases were also slightly elevated during the disease.

On the fifth day, septic shock with acute renal failure developed; therefore, norepinefrine infusion and continuous venovenous hemodiafiltration were started. During the sixth day of hospitalization there was mild recovery in hemodynamic, oxygenation and renal function; however, a sudden and severe pulmonary haemorrhage associated with cardiac arrest eventually precipitated the patient's death.

No bacterial presence was demonstrated in blood cultures (Oxoid SIGNAL Blood Culture System Medium) performed at admission and in the fifth day of hospitalization. A multiplex PCR, which detects five different herpes viruses, including HSV, varicella-zoster virus, cytomegalovirus (CMV), human herpes virus 6 and Epstein-Barr virus [12]) was performed on a blood specimen obtained three days after admission and CMV genome amplification was demonstrated.

The necropsy macroscopic examination showed edematous lungs with increased weight (right lung with 1,140 g and left lung with 900 g; normal 450 g) and severe haemorrhage in the bases and posterior regions (Figure 1 C). In addition, pulmonary tissue sections evaluated by hematoxylin-eosin stain revealed severe diffuse alveolar damage, extensive intraalveolar haemorrhage, formation of hyaline membranes, and cytopathic effect in alveolar epithelial cells that was comprised of hyperplasia of pneumocytes and viral-like intranuclear inclusion bodies (Figure 2 C, D).

Figure 1. (A) First chest radiograph on admission revealing inflammatory-like haziness of the lung fields with greater density in the hila and lung bases and **(B)** progressive worsening on the third day of hospitalization. **(C)** Necropsy macroscopic examination showing edematous lungs with severe haemorrhage in the bases and posterior regions.



No inflammatory response by immune cells or bacterial presence was observed in the lung tissue sections examined. On the other hand, bone marrow and peripheral lymphatic nodes were hypocellular. In the latter, the B and T cell areas were affected. Signs of osmotic nephrosis were observed in the kidney tissue. There was no leukaemia cell infiltration in bone marrow and liver tissue. In the cardiac, hepatic, and brain tissues sections examined no further histopathological abnormalities were found.

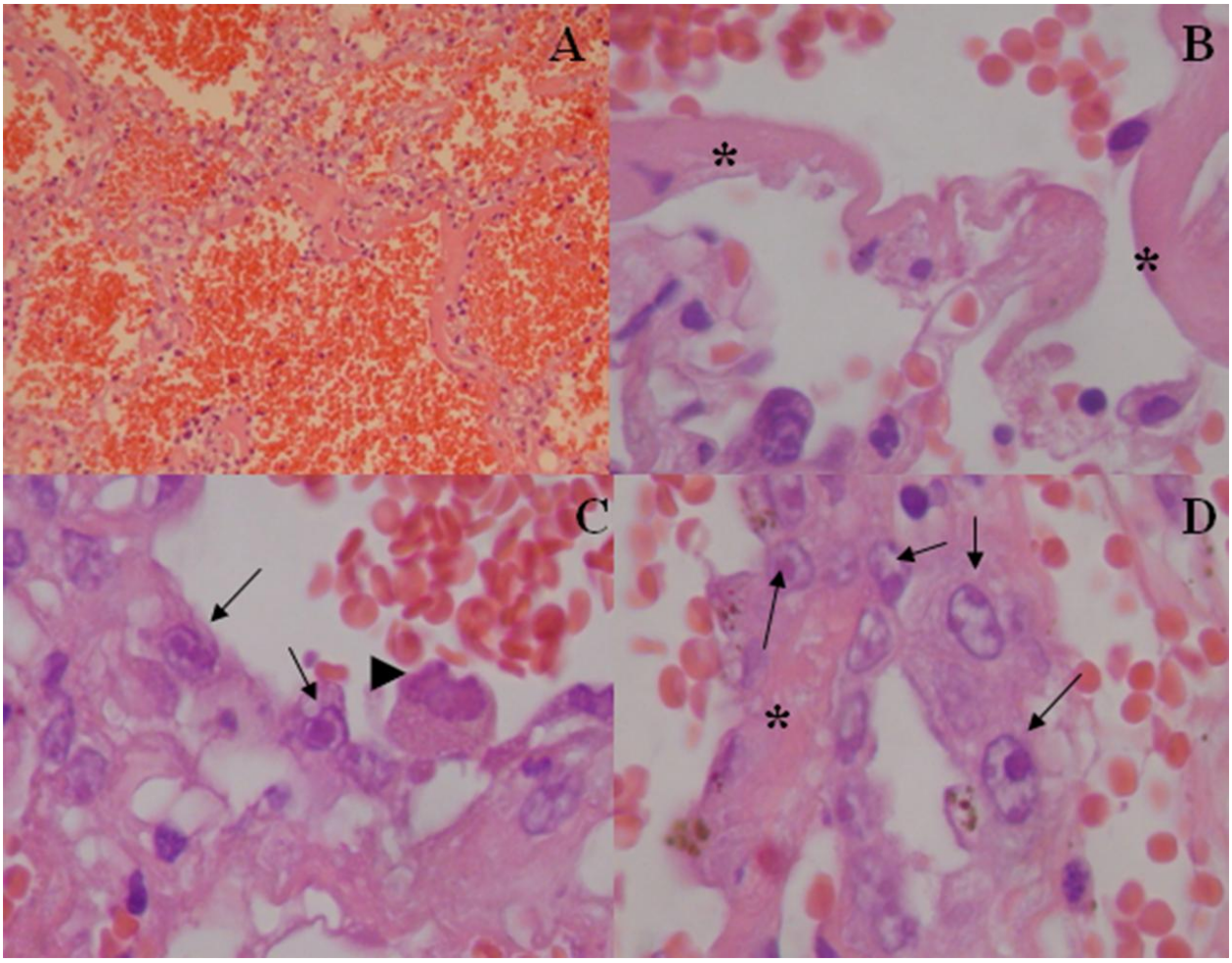
The patient was not an obese subject considering the body-mass index of 24.5 (the weight in kilograms divided by the square of the height in meters) when obesity is defined as a body-mass index greater than 30 in adults.

Discussion

A number of viruses cause increased morbidity and mortality in transplant patients [14-17]; for example, we recently described the first report of herpes simplex virus and Norwegian scabies in a fatal renal transplant recipient [18]. To protect transplant patients, the American Society of Transplantation (AST) Infectious Diseases Community of Practice and the Transplant Infectious Diseases section of The Transplantation Society (TTS) developed a guidance document for S-OIV in solid organ transplantation recipients [19].

S-OIV infection has been reported in recipients of allogeneic hematopoietic cells [9-11], in addition to those who have undergone lung [20], kidney [21], heart [22,23] and liver transplantation [8].

Figure 2. (A) Lung tissue sections examined with hematoxylin-eosin staining that demonstrate extensive intraalveolar haemorrhage, magnification 200X, and **(B)** presence of hyaline membranes (asterisks), magnification 1000X. **(C) (D)** Micrograph showing cytopathic effect comprising the presence of hyperplasia in an alveolar epithelial cell (arrowhead), and viral-like intranuclear inclusion bodies in pneumocytes (arrows). Large hyaline membrane (asterisk) is also showed, magnification 1000X.



Transplantation was included in the immunosuppressive conditions associated with S-OIV infection in fatal outcomes from California [6] and two fatal cases in Brazil [5]. More recently, the clinical course of the first fatal allogeneic hematopoietic stem cell transplant recipient infected with S-OIV was documented [10]. However, as far as we know, the clinical and necropsy findings in a fatal transplant recipient caused by S-OIV have not been previously reported.

Very recently, the lung pathology of 21 confirmed S-OIV fatal cases from Brazil were documented. The histopathological findings included mainly diffuse alveolar damage as well as necrotizing bronchiolitis and extensive haemorrhage. In addition, an abnormal lung immune response producing enhanced inflammation and characterized by the marked expression of Toll-like receptor-3 and IFN-gamma and a great number of CD8+ T and granzyme B+ cells was found [5]. The study goes on to describe that in the two transplant recipients (kidney and bone marrow transplant), the exudative diffuse alveolar damage with intense alveolar haemorrhage were the essential findings. Hyaline membranes in the alveolar walls were also present; however, cytopathic effect was not demonstrated [5].

In contrast, an autopsy study in lungs from five Mexican fatal cases infected with S-OIV showed hyaline membranes, alveolar septal edema, hyperplasia of type II pneumocytes, fibrin thrombus in the vascular lumen, necrosis of the bronchiolar walls, inflammatory infiltrate below the endothelium, and pneumonia foci with intraalveolar exudates without evidence of bacterial colonies [12]. Lung tissue sections observed in our study also exhibited severe diffuse alveolar damage, extensive intraalveolar haemorrhage, and hyaline membranes. However, rather than immune cell infiltrates and pneumonia foci in the pulmonary tissues, viral-like intranuclear inclusion bodies in pneumocytes were found.

To the best of our knowledge, inclusion bodies in pulmonary cells have not been reported in transplant recipients with seasonal influenza viral pneumonia. Intranuclear inclusion bodies were not found in the lung sections of 21 fatal cases infected with S-OIV but influenza-like particles within the cytoplasm were detected by electron microscopy [5]. Characteristic viral inclusion bodies in the respiratory tract have been reported previously in transplant patients with CMV [24] or adenovirus infection [25]. In the present case, a CMV infection was demonstrated by molecular identification in a blood specimen and it may be involved in the severe septic complications; however, the intranuclear inclusion bodies observed were not distinctive of CMV disease, taking into account that characteristic large CMV cells with owl's eye inclusion bodies were not detected (Figure 2 C, D) [24]. On the other hand, adenoviral infection was not tested in the lung tissue and we cannot exclude completely the likely contribution of adenovirus in viral intranuclear inclusion development in this subject [25].

In contrast to the aberrant lung immunopathology found in the Brazilian study [5] and inflammatory infiltrates documented in the Mexican report [12] of recent fatal S-OIV cases, it is very likely immune cell infiltrates were absent in our evaluated pulmonary tissue as a result of immunosuppression. The immunosuppressive condition was also shown in the small amount of immune cells in the peripheral lymphatic nodules as well as the significant decrease in circulating white blood cells. Leukopenia has been reported previously in severe H1N1 patients who were not particularly suffering from immunosuppressive conditions [7]. However, our studied case had a personal history of bone marrow transplantation because of chronic myeloid leukaemia and he was on a prednisone regime. Interestingly, leukopenia has also been documented in CMV infections in transplant recipients [16] and it is probable that the presence of this opportunistic virus is associated with the white blood cell picture detected in the patient described here. Therefore, the altered antiviral immune response found in this immunosuppressed individual might be involved in the evolution of the septic complications and fatal outcome.

In the present case, the previous haematological disorder, associated with the hypocellular bone marrow demonstrated in the pathological study, along with the sepsis, may be related to the anaemia and thrombocytopenia developed during the hospitalization [26]. In addition, the thrombocytopenia, diffusal alveolar damage, and mechanical ventilation with elevated PEEP may be related to the severe pulmonary hemorrhage found in the patient.

Most fatalities caused by influenza A virus occurred concurrently with bacterial pneumonia [27]. Recent studies show bacterial coinfections of 15% to 38% in patients infected with S-OIV [2,5,6]. However, we did not identify bacterial infection in the lung tissue sections examined. In addition,

bacteremia was not detected during hospitalization and empirical antibacterial therapy was given. Nevertheless, we cannot exclude completely the contribution of bacterial coinfection to the death of this transplant recipient.

A number of respiratory viruses can infect hematopoietic cell transplant recipients [28] and emergent respiratory virus infection caused by human metapneumovirus [29], severe acute respiratory syndrome virus [30], and more recently by human coronavirus NL63 [31] has been documented in bone marrow transplant recipients. However, this is the first time that clinical findings, therapeutic measures, and a post-mortem examination from a transplant recipient with fatal outcome caused by the pandemic S-OIV infection is documented.

A number of studies have suggested that obesity may be a risk factor for severe S-OIV disease [6,7,32]. Yet our studied fatal case was not obese.

The WHO has recommended oseltamivir treatment of 75 mg twice a day in S-OIV infection [33]. However, taking into consideration the haematological malignancy, chronic myeloid leukaemia, the immunosuppressive therapy contributing to a clearly deficient antiviral immune control, and the late respiratory illness recognition (more than 48 hours after illness onset) in the present S-OIV infected case, the oseltamivir treatment was increased to 150 mg twice a day for ten days. Similarly, another transplant recipient infected with S-OIV, ventilated because of a type 2 respiratory failure, died despite treatment with a ten-day course of oseltamivir [8] and two hematopoietic stem cell transplant recipients infected with S-OIV acquired oseltamivir-resistance after prolonged oseltamivir therapy [11].

In summary, we report for the first time the clinical characteristics, treatment and pathological studies from a fatal transplant recipient caused by S-OIV. This report highlights the potential higher risk of a fatal outcome in transplant recipients with immunosuppressive therapy despite early antiviral treatment and propose that preventive education, S-OIV vaccine, early diagnosis and aggressive treatment in this high-risk population is needed.

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Corresponding author

Professor Anselmo Abdo, MD, PhD
Head of the Intensive Care Unit
Center for Medical and Surgical Research (CIMEQ),
216 Avenue, entre 11 y 13, Siboney, Playa, Havana, Cuba.
Tel: 537 8581511
Fax: 537 8581511
Email: aaabdo@infomed.sld.cu

Conflict of interests: No conflict of interests is declared.