ORIGINAL ARTICLE

Severe Novel H1N1 Influenza A Infection in the Immediate Postoperative Period of a Liver Transplant Patient

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In 2009, the World Health Organization recognized the novel H1N1 influenza A virus as a pandemic infection. Since April 2009, thousands of cases of novel H1N1 influenza A infection have been reported worldwide, and they have resulted in thousands of deaths. South American countries were affected by this infection during their winter season, and Chile presented one of the highest incidence rates. We have recently managed a liver transplant patient who presented with a severe novel H1N1 influenza A infection in the early postoperative period and required prolonged mechanical ventilation. The early suspicion of this infection during the current pandemic influenza in Chile made possible a timely treatment with oseltamivir. We decided to report this case because no other cases of liver transplant patients affected by H1N1 influenza A have been reported so far. We intend to alert clinicians about this potentially devastating viral infection in view of the current pandemic scenario, and here we review some of the recommendations for its prevention, diagnosis, therapy, and possible complications. ***Liver Transpl 16:447-452, 2010.*** © **2010 AASLD.**

Received October 19, 2009; accepted December 17, 2009.

Since the detection in mid-April 2009 of the first few cases of human infection with novel H1N1 influenza A virus in the United States and Mexico, the World Health Organization has been notified of more than 375,000 cumulative cases of laboratory-confirmed human cases and 4500 deaths in 170 countries (data as of October 4, 2009).[1]

This new influenza virus (influenza A/2009/H1N1/swl), carrying genetic material from swine, human, and avian viruses, belongs to the influenza A species and has unusual surface hemagglutinin and neuraminidase antigens of subtypes H1 and N1 that allow human infection with nearly universal susceptibility.[2] All respiratory secretions of H1N1 influenza A cases should be considered potentially infectious. Its estimated incubation period is unknown and could range from 3 to 7 days. The definitive diagnosis of novel H1N1 influenza A can be made only by nucleic acid testing using influenza A and H1N1 influenza A/2009/swl–specific primers and polymerase chain reaction (PCR).

In response to the increasing number of people infected worldwide, the World Health Organization raised the world pandemic alert level to phase 6 by mid-June 2009. Most cases and deaths have been reported from the Americas (146,016 cases and 3292 deaths).[1] Countries in the southern part of South America, including Chile, recorded a rapid increase in cases of pandemic influenza early in the winter season. Chile (with an estimated population of 15,805,000 people) has been considered among the countries with the highest incidence rates of novel H1N1 influenza A, with 12,252 PCR-confirmed cases and 134 deaths reported as of October 6, 2009.[3] Because of the advanced stage of the pandemic, the Ministry of Health of Chile adopted during the

Abbreviations: ICU, intensive care unit; LT, liver transplantation; OLT, orthotopic liver transplantation; OPTN, Organ Procurement and Transplantation Network; PCR, polymerase chain reaction.

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DOI 10.1002/lt.22013
Published online in Wiley InterScience (www.interscience.wiley.com).

outbreak (as many other countries did) the strategy of considering the diagnosis of novel H1N1 influenza A in any patient having the typical respiratory symptoms without any laboratory confirmation (syndromic surveillance of influenza-like illness). With this definition, 367,041 cases of novel H1N1 influenza have been reported in our country (as of October 6, 2009).[3] Of the 12,252 confirmed cases, 1585 (12.9%) presented with a severe respiratory syndrome requiring hospitalization (the mean age was 33 years, and 55% were women), with 46% of them having underlying medical conditions considered to be high-risk for complications of seasonal influenza (chronic lung disease, heart disease, kidney disease, immunosuppression, and pregnancy).[3,4] More recently, influenza activity has clearly declined in our country as we have moved away from winter.

We recently treated a patient who had undergone liver transplantation (LT) and presented with a severe novel H1N1 influenza A infection in the immediate postoperative period. We decided to report this case because no other cases of LT patients affected by novel H1N1 influenza A have been reported so far, and this clinical situation may soon become frequent in LT programs across all countries. We intend to alert clinicians about this potentially devastating viral infection in view of the current pandemic, and we review some of the recommendations for its prevention, diagnosis, treatment, and potential complications.

CLINICAL CASE

A 49-year-old Chilean man who weighed 70 kg underwent orthotopic liver transplantation (OLT) for end-stage liver cirrhosis due to hepatitis C on July 13, 2009. The patient had moderate hepatopulmonary syndrome (orthodeoxia, minimal dyspnea on exertion, an increased alveolar-arterial oxygen gradient, a normal spirometry test, and confirmation of a right-to-left shunt on a contrast transthoracic echocardiogram), with arterial gases showing a resting partial pressure of oxygen of 61 mm Hg. The donor was a 19-year-old man weighing 80 kg who died of head trauma. The piggyback technique was used with end-to-end portal and arterial anastomosis. The cold ischemia time was 4 hours, and the warm ischemia time was 50 minutes. Induction immunosuppression included 1 g of methylprednisolone, and this was followed by 50 mg of methylprednisolone every 6 hours during the first postoperative day; the dose was tapered according to protocol. In the intensive care unit (ICU), the patient was extubated 12 hours after LT without incident. Oral immunosuppression was started with oral cyclosporine (Neoral, Novartis, Chile; 4 mg/kg, 300 mg every 12 hours) and mycophenolic acid (Myfortic, Novartis; 720 mg every 12 hours).

At the same time, the ICU had 2 other patients with novel H1N1 influenza A on mechanical ventilation, but our LT patient had always been in an isolated room since admission. During this outbreak of influenza, healthcare providers followed strict infection prevention strategies, including handwashing or hand hygiene (alcohol-based hand gels) before and after patient care, the use of N95 masks during aspiration of tracheal secretions during intubation, and the mandatory use of masks during close contact with any patient whether he was intubated or not. The same strict measures were applied to relatives visiting the patients.[5] During this period, there were no certified cases of influenza between the healthcare personnel.

On day 6 post-LT, the patient presented with a fever of 38°C, which was accompanied by disorientation, agitation, and oxygen desaturation. His oxygen requirements rose to 100%. Orotracheal reintubation and mechanical ventilation were needed. A chest radiograph showed a lower left lobe consolidation. Intravenous vancomycin (500 mg every 6 hours) and piperacillin-tazobactam (4.5 g every 6 hours) were then started empirically. Sputum cultures of the patient were taken as well as indirect immunofluorescence and PCR for H1N1 influenza A. On the 7th postoperative day, oseltamivir (75 mg every 12 hours) was added empirically because of the epidemiological situation in Chile (a severe outbreak of novel H1N1 influenza A) and in the ICU. Mycophenolic acid was discontinued, and the cyclosporine dose was decreased. On day 7, a chest computed tomography scan showed bilateral pneumonia with multiple condensations (Fig. 1). Voriconazole (400 mg every 12 hours intravenously) was also added empirically. On day 9, PCR positive for novel H1N1 influenza A was confirmed. All other bacterial and fungal cultures were negative. Antigen PP-65 for cytomegalovirus was also negative.

After 48 hours of treatment with oseltamivir, the patient defervesced (his temperature decreased from 39°C to 37°C), and this coincided with a slight improvement in his respiratory condition. After 5 days of treatment with oseltamivir (postoperative day 12), an improvement of the respiratory status was noted, and this made extubation and noninvasive mechanical ventilation possible. We decided to maintain oseltamivir for a total of 10 days because of the recent transplant with immunosuppression and the severity of the disease. He evolved with progressive improvement of his respiratory status and decreasing oxygen requirements. On day 23 post-LT, a chest computed tomography scan showed a marked reduction of the pulmonary condensations (Fig. 2). Antibiotics were administered empirically for 14 days. On day 26 post-OLT, the patient was weaned from mechanical ventilation. The patient persisted after weaning, with a tendency to hypoxemia, and required oxygen (O_2: 30%-35% mask) to obtain adequate oxygen saturation levels (>90%). A contrast echocardiogram confirmed the presence of a significant right-to-left shunt with an intravenously injected, agitated saline solution. A new computed

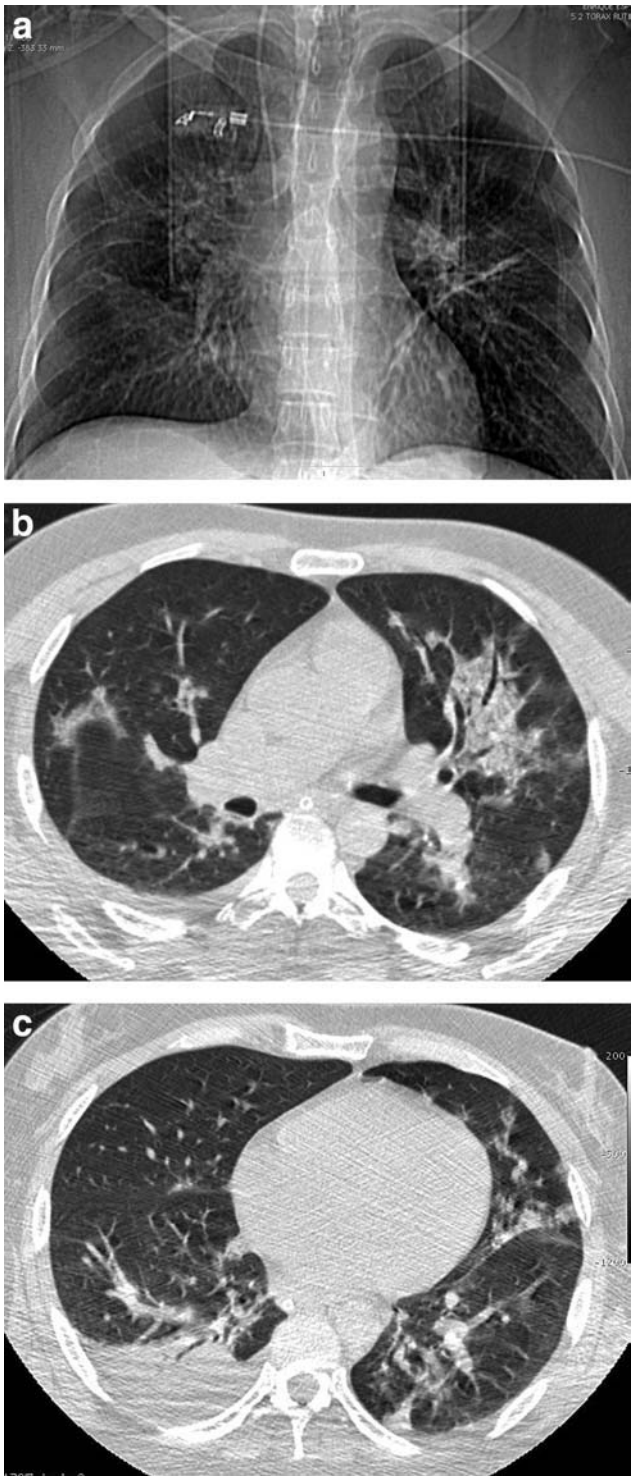

Figure 1. Postoperative day 7: perihilar bilateral condensations and small cylindrical bronchiectasis of left predominance, a small right basal pleural effusion with basal atelectasis, and some foci of alveolar filling.

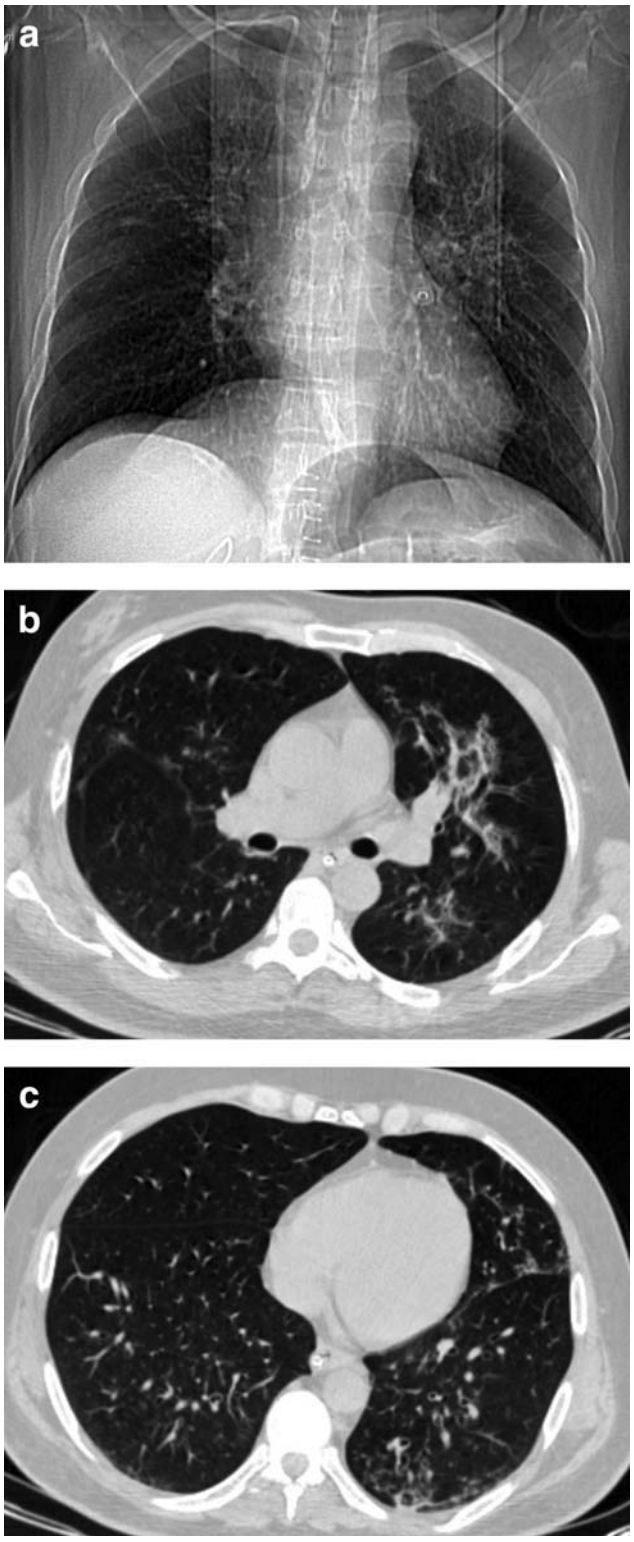

Figure 2. Postoperative day 23: regression of condensations, small foci of bilateral perihilar alveolar filling (predominantly left), and the same bronchiectasis already described in the previous images. The pattern is consistent with atypical pneumonia.

tomography scan of the thorax on day 35 showed a marked improvement of the previous pulmonary abnormalities (Fig. 3).

The patient was discharged home on day 40 with 2 L of oxygen for the management of hepatopulmonary

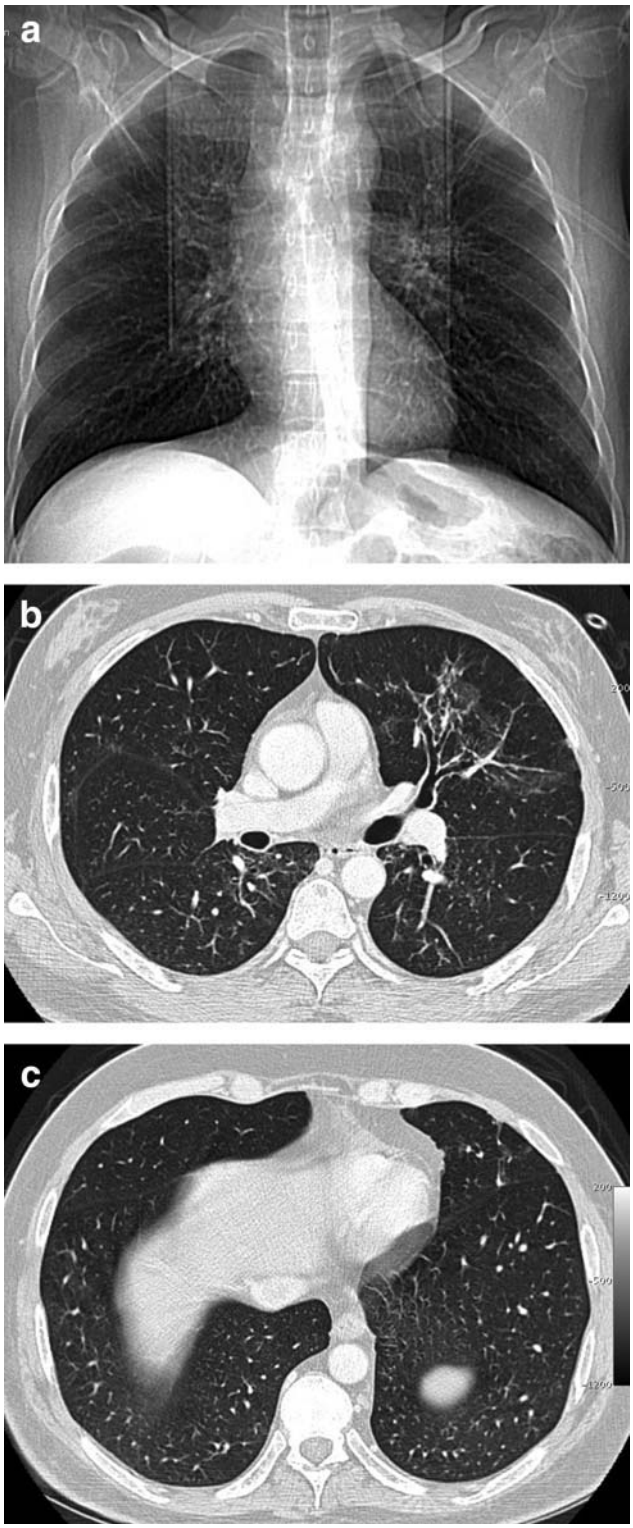

Figure 3. Postoperative day 35: marked regression of the perihilar and pulmonary infiltrates.

syndrome, which was improving. The patient was in good clinical condition with normal liver enzymes while on triple immunosuppression (prednisone, cyclosporine, and mycophenolic acid).

DISCUSSION

The clinical spectrum of 2009 pandemic novel H1N1 influenza A virus infections is broad; it ranges from mild upper respiratory symptoms with or without fever and occasional gastrointestinal symptoms to severe complications such as pneumonia resulting in respiratory failure (as in our patient), acute respiratory distress syndrome, and eventually multiorgan failure and death.[2]

Recipients of solid-organ transplants have a higher risk for severe infections because of their lifelong immunosuppression. Despite emerging evidence that vaccinations are safe and relatively effective in LT patients, most vaccines are still underused.[5] Recommended vaccination in LT patients should include influenza, tetanus-diphtheria, hepatitis A and B, antipneumococcal, and *Haemophilus influenzae* type b vaccines.[4,6] Both the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and *H. influenzae* vaccination may thus prevent secondary pneumonia during the current outbreak of novel H1N1 influenza A. Our patient did not receive the seasonal influenza or pneumococcal vaccine because the national vaccination program considers only individuals over 60 years of age or those with a chronic disease (chronic liver diseases are not clearly considered in the program, although they probably should be). During the influenza pandemic, vaccination strategies should also include the vaccination of household contacts and healthcare workers at transplant centers, unless this is contraindicated. The composition of the influenza vaccine changes each year on the basis of new virus features.

Data for adult LT recipients are controversial, but overall, they suggest that the postvaccination antibody titers for influenza are lower than those in healthy controls.[7–9] Also, recipients of solid-organ transplants are known to be at higher risk of developing a severe infection from influenza in comparison with the general population because of a poor immune response to infections.[8] Thus, they are considered a vulnerable group and at higher risk for severe influenza. On May 1, 2009, the Organ Procurement and Transplantation Network (OPTN) posted the following statement on the United Network for Organ Sharing/OPTN Web site: "The OPTN shares the worldwide concern over the public health risk posed by the newly discovered H1N1 influenza strain. At this point, we are not aware that this flu strain has affected any transplant candidates or recipients. However, we urge all transplant professionals, as well as transplant candidates, recipients and family members, to take prudent precautions to minimize the risk of infection and transmission."

As we know, the seasonal influenza vaccine did not protect against this new H1N1 influenza A virus. However, a new vaccine against novel H1N1 influenza A has been recently introduced. The Food and Drug Administration has licensed 4 new monovalent vaccines for the prevention of respiratory

illness caused by the novel H1N1 influenza A virus.[10] The novel H1N1 influenza A vaccine is not intended to replace the seasonal influenza vaccine. It is intended to be used alongside the seasonal influenza vaccine.

The pandemic novel H1N1 influenza A strain is typically susceptible to oseltamivir and resistant to amantadine, unlike the 2008-2009 seasonal H1N1 influenza A. Different international societies have also recommended the immediate use of neuraminidase inhibitors (oseltamivir or zanamivir) as the antiviral agents of choice for this viral infection, especially for patients with risk factors for severe disease, including older individuals (>65 years old), pregnant women, patients with chronic diseases or immunosuppression, and young children.

Immunosuppressed patients with influenza virus infections have been shown to shed the virus for prolonged periods of time, and this increases the possibility of developing drug resistance.[11–13] In August 2009, the Centers for Disease Control and Prevention reported the first 2 cases of resistance to oseltamivir in severely immunosuppressed patients (leukemia patients) infected with the novel H1N1 influenza A virus.[14] In both patients, the virus was initially susceptible to oseltamivir, and resistance developed subsequently (because of mutation H275Y) while the patients were being treated with the drug. Undoubtedly, this recent report from the Centers for Disease Control and Prevention highlights the importance of close monitoring for antiviral drug resistance in this subset of patients receiving antiviral treatment. More recently, up to 21 such virus isolates carrying the H2275Y mutation have been described around the world, with resistance conferred to oseltamivir but not to zanamivir.[1] Of these 21 cases, 12 have been associated with postexposure prophylaxis, and 4 have been associated with long-term oseltamivir therapy in immunosuppressed patients.

In the clinical case that we have described here, concurrently with the presence of 2 H1N1 influenza A cases in the same ICU and despite the isolation measures implemented, our LT patient acquired the infection very early after surgery. Whether the patient acquired the infection before or after OLT cannot be clearly defined because of the incubation period (3-7 days). During the current pandemic with the peak incidence of contagious respiratory diseases, our patient, who had recently undergone LT and was presenting with fever (>37.5°C) and acute respiratory symptoms, immediately raised the suspicion of novel H1N1 influenza A infection. In this setting, concurrently with the search for other infectious etiologies, we initiated an empirical antiviral treatment with oseltamivir (while waiting for confirmation). Once the diagnosis of H1N1 influenza A was confirmed, the antiviral treatment was administered for 10 days because of the immunosuppression of our patient. The optimal duration of therapy for influenza in this setting has not been well established, and courses longer than the currently approved 5 days may be needed and individualized as they are in immunosuppressed patients.[5]

Chemoprophylaxis with oseltamivir can be a valid measure in immunocompromised individuals (eg, transplant recipients), especially during an outbreak of influenza, because immunization will provide only limited protection. A recent randomized controlled trial using oseltamivir versus placebo in 477 transplant patients exposed to community influenza (solid-organ transplant recipients or allogeneic hematopoietic stem cell transplant recipients)[15,16] showed that oseltamivir prophylaxis significantly reduced the incidence of seasonal influenza infection in this setting; it had a protective efficacy of 75% and was well tolerated, and there were no cases of resistance. Considering this information, in the next 2 LT patients in our unit and after the case reported here, we decided to use 75 mg of oseltamivir daily (10 days) because of the possibility of new nosocomial infections in recently transplanted patients in the middle of the epidemic outbreak in Chile. This strategy has been changed more recently because we are in springtime and away from the outbreak, and only a few isolated cases have been reported during the last few weeks. As we know, there might be another outbreak during the following few months, as occurred in Mexico.

To the best of our knowledge, this is the first reported case of novel H1N1 influenza during the postoperative period after LT, and this may soon become all too familiar to transplant programs with the widespread transmission of novel H1N1 influenza A. This article should alert clinicians about the prevention, diagnosis, and treatment of this potentially devastating infection during the current influenza pandemic.

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