**CASE REPORT**

Pandemic (H1N1) 2009-Associated ARDS Rescued by Neuraminidase Inhibitors with Emergency Use of Extracorporeal Membrane Oxygenation

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**Abstract**

A 36-year-old man with underlying systemic lupus erythematosus complicated by autoimmune hemolytic anemia underwent immunosuppressive treatment. After showing a low-grade fever for two days, his fever spiked. He was confirmed to have pandemic (H1N1) 2009 by real-time reverse transcription polymerase chain reaction (PCR). His condition deteriorated to acute respiratory distress syndrome (ARDS), and mechanical ventilation became necessary. The lowest PaO₂/FIO₂ ratio was 77, and he was placed on extracorporeal membrane oxygenation (ECMO). Based on our observation, the emergency use of ECMO in addition to peramivir might be useful. A noteworthy point is that once ARDS deteriorates due to pandemic (H1N1) 2009, intensive supportive care should be started.

**Key words:** influenza, pandemic (H1N1) 2009, acute respiratory distress syndrome


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**Introduction**

The 2009 pandemic H1N1 influenza virus causes severe respiratory disease. From July 28, 2009 to March 23, 2010, the total number of hospitalized cases reached 17,583, and fatal cases totaled 198 (1). Recently in an interesting case, Nakajima et al reported an autopsy case who died of respiratory failure (2). Severe pulmonary edema and diffuse alveolar damage were revealed, and proliferation of the influenza virus was detected in alveolar epithelial cells. They also showed the elevation of several inflammatory cytokines not only in the serum but also in the lung tissues. Takiyama et al also reported a death case without underlying disease due to acute respiratory distress syndrome (ARDS) which progressed rapidly in less than 24 hours (3). It is likely that an immunocompromised patient is at a higher risk of influenza. A patient was reported with human immunodeficiency viral infection who developed lethal respiratory failure due to pandemic (H1N1) 2009 (4). In the present report, we describe a patient with ARDS due to pandemic (H1N1) 2009. He underwent immunosuppressive treatment for an underlying disease. Based on this case report, we discuss the therapeutic management of ARDS due to pandemic (H1N1) 2009.

**Case Report**

At the beginning of January 2010, a 36-year-old man was admitted to our department due to the recurrence of autoimmune hemolytic anemia (AIHA). He had previously been diagnosed with AIHA at the age of 9 years old, and developed nephritic syndrome at age 27 years old. Anti-nucleic antibodies were positive, and renal biopsy specimens were compatible with lupus glomerulonephritis, diagnosed as systemic lupus erythematosus (SLE). Steroid pulse therapy remitted the disease activity. He had been receiving maintenance therapy combined with prednisolone at 20 mg/day and cyclosporine A at 150 mg/day. On admission, his blood pressure was 140/90 mmHg, pulse was regular at 82/min,
Figure 1. High-resolution chest CT scans show no abnormal infiltration in the lungs prior to influenza infection (A). After a low-grade fever persisted for 48 hours, patchy infiltration appeared in the bilateral lung fields on chest X-ray (B). High-resolution chest CT scans showed ill-defined ground-glass opacities in the upper, middle, and lower lobes of both lungs (C). Three days later, X-ray demonstrated severe bilateral air-space disease with a massive loss of normal aerated lung tissue (D). After the introduction of extracorporeal membrane oxygenation, the lung fields improved, with residual areas of fibrotic strias (E).

The respiration rate was 24/min, and temperature was 36.4°C. Physical examination of the chest was normal. Auscultation and palpation of the abdomen were also normal. Laboratory tests showed a peripheral leukocyte count of 18,300/μL with 83% neutrophils, platelet count of 554×10^3/μL, hematocrit of 20%, hemoglobin level of 6.9 g/dL, reticulocytes at 24.9%, total bilirubin level of 4.2 mg/dL, unconjugated bilirubin level of 3.0 mg/dL, aspartate transaminase level of 26 U/L, alanine transaminase level of 26 U/L, lactate dehydrogenase level of 541 U/L, alkaline phosphatase level of 362 U/L, serum creatinine level of 0.6 mg/dL, and post prandial serum glucose level of 131 mg/dL. Both direct and indirect Coombs were positive, anti-nucleic acid was 320x, and the serum haptoglobin level was undetectable. The next day, the hemoglobin level had decreased to 4.8 g/dL. Steroid pulse therapy consisting of intravenous methylprednisolone (500 mg/day) was performed for three days, followed by the oral administration of prednisolone (1 mg/kg/day). Two weeks later, the hemoglobin level increased to 12.9 g/dL, and the dose of prednisolone was tapered to 0.8 mg/kg over 2 weeks. On chest X-ray, there was no infiltration. At the end of January 2010, he underwent a CT scan of the lungs to check for any side effects of the immunosuppressant (Fig. 1A), showing neither abnormal interstitial change nor intralobular infiltration. The next day, he was given permission to leave the hospital temporarily and took a walk downtown for five hours. The next morning, he had a low-grade fever with a maximum of 37.6°C, lasting 2 days. On the third day, his body temperature was elevated to 39.5°C. He experienced a mild cough, but no other symptom was observed. Physical examination showed a pulse of 88/min, respiration rate of 12/min without respiratory distress, and blood pressure of 116/62 mmHg. His oxygen saturation using a pulse oxymeter (SaO2) was 97-99% in room air. Intravenous meropenem was empirically started. Later, the results of urine and blood cultures were negative. The high fever persisted the next day, when nasopharyngeal swab specimen was positive for influenza virus type A antigen using the rapid test (ESPLINE® Influenza A & B Kit; Fujirebio, Tokyo, Japan). Consequently, oseltamivir (150 mg 2x/d) was started. On the 2nd day of oseltamivir treatment, he experienced slight respiratory distress. Physical examination showed decreased breath sounds at bases, a pulse of 108 beats/min, blood pressure of 114/64 mmHg, and respiration rate of 40/min. His SaO2 decreased to 89% in room air at rest. A chest X-ray showed bilateral infiltration (Fig. 1B). High-resolution chest CT scans revealed ground-glass opacities on both sides of the lobes (Fig. 1C). Oxygen was started via a nasopharyngeal catheter at 5 L/min to keep the SaO2 above 90%. The leukocyte count suddenly decreased to 1,700/μL, and the platelet count also decreased to 76×10^3/μL, while the hemoglobin level was maintained at 12.0 g/dL. CRP elevated to 5.28 mg/dL. Based on coagulation tests, he was not complicated with disseminated intravascular coagulation (DIC). Serum complement levels were within normal ranges with C3c at 82.5 mg/dL, C4 at 28.6 mg/dL, and CH50 at 39.8. Anti-double-stranded DNA was 80.5. Based on these results, the activity of SLE was low. The elevation of serum KL-6 of 515 U/L revealed the complication of interstitial lung inflammation. Meropenem was switched to intravenous ciprofloxacin (300 mg every 12 hours). Over the next 24 hours, the SaO2 value decreased to below 90% despite increasing the oxygen supply to 15 L/min. To avoid SLE aggravation and cytokine-
induced alveolar damage, steroid pulse therapy consisting of intravenous methylprednisolone (1,000 mg/day) was administered for three days, followed by tapering. However, a chest X-ray showed an expansion of the ground-glass opacity in both lungs. He then required mechanical ventilation to maintain the SaO2 above 90%. At this point, the patient met the criteria for ARDS (5), showing an acute onset, ratio of PaO2/FIO2 of 145 torr, and bilateral lung infiltration without heart failure. Aspiration cytology from bronchial washings revealed the destruction of ciliated columnar epithelium, some of which showed squamous metaplasia with cytologic atypia typical of diffuse alveolar damage. Thoracentesis showed transudative fluid negative for acid-fast bacilli, bacteria, and fungi. Both the cytomegalovirus pp65 antigenemia test and Aspergillus galactomannan antigen were negative. A nasopharyngeal swab specimen was taken at this time, yielding a positive result for pandemic (H1N1) 2009 by real-time reverse transcription-polymerase chain reaction (PCR). Based on this finding, the interstitial pneumonia was caused by influenza. So, he was started on peramivir hydrate intravenously at a dose of 600 mg per day for five consecutive days. A protective ventilatory strategy with a tidal volume of 6 mL/kg and positive end expiratory pressure (PEEP) of 10 cmH2O was instituted. He was started on the continuous infusion of sivelestat at a dose of 0.20 mg/kg/h and the rapid infusion of ulinastatin at a dose of 100 thousand units every 8 hours. However, he required FiO2 above 0.8 to maintain the SaO2 value above 90%. He showed a modified acute lung injury score of 2.7 using the FiO2 and PEEP, calculated as reported (6). On the 2nd day of intubation, an X-ray showed bilateral air-space infiltration with massive loss of the normal aerated lung tissue (Fig. 1D). The SaO2 value was constantly below 90% despite the FiO2 being increased to 1.0. The PaO2 value was 70 mmHg and the PaCO2 value was 45.3 mmHg. The modified acute lung injury score was estimated to be 4.0 (Fig. 2). Then, we decided to emergently administer extracorporeal membrane oxygenation (ECMO) with continuous veno-venous hemodiafiltration. He was admitted to the intensive care unit (ICU). ECMO was started with a blood flow of 0.8 L/min and gas flow of 2 L/min of 100% oxygen. Following the initiation of ECMO, the P/F ratio markedly decreased. The patient’s hemodynamic condition was well maintained with a blood flow of 2.4 L/min, and then the blood flow decreased to 0.7 L/min over 3 days while monitoring the improvement of the air-space opacity on chest X-ray. The modified acute lung injury score gradually decreased to 2.0 (Fig. 2). On the third day after the start of ECMO, subcuta-
neous bleeding was noted. We could not increase the blood flow to 0.5 L/min. Once ECMO was stopped, the P/F ratio was maintained 167. So, ECMO was discontinued. Two days later, he underwent successful extubation. A post-extubation chest X-ray showed a marked decrease in infiltrates (Fig. 1E). Oxygen was delivered via a nasopharyngeal catheter at 2 L/min and the SaO2 value remained above 96%. The daily dose of prednisolone was decreased to 20 mg/day. A CT scan showed a partial resolution (Fig. 1F). Pulmonary function tests showed a moderate restrictive pattern: vital capacity at 52.3% of that predicted, and a forced expiratory volume in 1 second at 117.6% of that predicted. Two weeks later, he started rehabilitation for daily activities free off oxygen supplier and then was discharged from the hospital at the end of March.

Discussion

It is important to note the preceding asymptomatic period with only a mild fever. Systemic symptoms such as myalgia, fatigue, and arthralgia were all absent. As for treatment, he started oseltamivir within 24 hours after the onset of the high fever. On the assumption that the preceding low-grade fever was caused by influenza, the delay in therapy was estimated to be 72 hours. The cytokine response associated with acute influenza infection might have been decreased due to the use of corticosteroids for underlying disease. In fact, asymptomatic influenza infection has been reported, and the disease onset is often uncertain in hematopoietic cell transplant recipients (7). Although he did not show respiratory symptoms early in the course, the CT findings revealed lung infiltration. The characteristic CT findings have been described as well-defined ground-glass opacity (8), usually bilateral, and sometimes a predominantly sub-pleural distribution (9). Based on the CT findings, it is reasonable to suppose that the lungs in the present case deteriorated into the exudative stage of diffuse alveolar damage, as previously reported (2), so we started treatment against ARDS.

Peramivir is a highly selective inhibitor of neuraminidase, and has a more marked potency than either zanamivir or oseltamivir carboxylate in vitro (10). Peramivir is a potent anti-viral agent that could be administered intravenously and be kept at high plasma concentrations to the sites of infection. The availability of an intravenous neuraminidase inhibitor may be important in treating severe and potentially life-threatening patients, in whom the plasma concentrations may be unstable with currently available oral or inhaled neuraminidase inhibitors (11). In the present case, virus shedding was prolonged and detected after three days of treatment with oseltamivir. In addition, his state was so deteriorated that he was incapable of taking oral medication. Thus, we started to administer peramivir. The fact that the pulmonary infiltration gradually improved after peramivir treatment suggests the effectiveness of peramivir. Indeed, the preceding oseltamivir might be also effective on the assumption that the oral medication could be continued. It may be presumed that rapid and reliable drug delivery is likely important in a severe patient. As a result, the present patient was administered neuraminidase inhibitors (oseltamivir or peramivir) for a total of 8 days. As for patients with hematological malignancies, an initial course of treatment is proposed to last 10 days if the patient remains asymptomatic (12). The results of this report might be useful regarding the efficacy and duration of administration of neuraminidase inhibitors. The present patient developed severe respiratory failure that was unresponsive to conventional therapeutic intervention. ECMO was the core device for salvage from the critical stage until recovery of the respiratory function. We would be unable to report on the possible outcome of our patient if ECMO had not been used. However, a poor prognosis could be made on the grounds that the higher PEEP level, FiO2 level of 100%, and lower PaO2 level could induce oxidative stress and mechanical damage of alveolar tissue. Recently, a multicenter study on the use of ECMO for pandemic (H1N1) 2009-associated ARDS was reported (13). In that report, ECMO was utilized in 53 patients confirmed to have 2009 influenza A (H1N1) complicated with ARDS, and 42 patients recovered. In another report, four out of six patients with extracorporeal lung support survived (14). The examination of more data is required to clarify the indication of ECMO for ARDS due to pandemic (H1N1).

Another issue to discuss here is the treatment for ARDS, we administered sivelestat just after the appearance of the bilateral grand-glass opacity. Neutrophil elastase is an enzyme that causes endothelial damage and increases permeability in ARDS (15). Sivelestat is a neutrophil elastase inhibitor, but its efficacy remains controversial (16, 17). We also introduced ulinastatin (UTI), which is one of the Kunitz-type protease inhibitors (18). It is generally believed that UTI has the ability to control a series of proinflammatory mediators and cytokines (19). In the light of the present clinical course, the effect of these drugs was not significant. The efficacy of sivelestat and UTI against pandemic (N1H1) 2009 should be further evaluated. The use of steroids for the treatment of ARDS has also been discussed. The fact that the present patient developed a high fever followed by abrupt neutropenia and thrombocytopenia suggests the production of higher levels of inflammatory cytokines as indicated (20). Just after the introduction of steroid pulse therapy, the high fever and cytopenia resolved. So, the therapy might be able to suppress the production of inflammatory cytokines. However, we were unable to conclude whether or not it facilitated the patient’s recovery from ARDS. According to a meta-analysis, the use of a low-dose corticosteroid (methylprednisolone: 1-2 mg/kg/day for 7-28 days) might be associated with improved mortality in ARDS (21). In a randomized study, methylprednisolone (2 mg/kg) was useful for recovery from ARDS and the discontinuation of ventilator use (22). There is another study indicating that the prolonged administration of hydrocortisone (300 mg/day) is associated with the improvement of lung injury due to H1N1...
influenza (23). In addition, the current evidence indicates that high dose steroid pulse therapy is not effective for ARDS (24). The clinical course of the present case calls on us to reflect on our administration of a higher dose of methylprednisolone. Further studies are needed to confirm the usefulness of steroids for ARDS due to pandemic (H1N1).

In summary, we emphasize the importance of the early diagnosis and treatment of influenza in compromised hosts, although lacking typical symptoms. Routes of neuraminidase inhibitor administration and the treatment duration might be significant for severe patients. Once a patient deteriorates to ARDS due to pandemic (H1N1) 2009, intensive supportive care should be actively employed, as this report demonstrated the potential to recover from severe respiratory failure.

References