Cases with Life-Threatening Respiratory Failure due to Influenza A (H1N1) Virus Infection in Intensive Care Unit

Yoğun Bakım Ünitesinde İnfluenza A (H1N1) Virüs Enfeksiyonuna Bağlı Hayatı Tehdit Edici Solunum Yetmezliği Olan Vakalar

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ABSTRACT We present four cases in critical condition diagnosed as influenza A (H1N1) infection with significant risk factors and severe hypoxemia. Their chest X-rays showed bilateral extensive infiltrative lesions. The ratio of partial arterial oxygen pressure to inspired fraction of oxygen (PaO2/FiO2) of the patients was below 200. Three of the patients were given oseltamivir before laboratory confirmation of diagnosis. Influenza A virus infections were confirmed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test from nasopharyngeal swabs. Lung protective invasive ventilation and positive end-expiratory pressure (PEEP) titration were performed in early period. Three patients were ventilated 5-7 days and discharged to ward uneventfully. In conclusion, we want to emphasize that antiviral treatment, intensive care and invasive mechanical ventilation in early period can decrease mortality and intensive care unit stay in patients with severe hypoxemia.

Key Words: Intensive care units; influenza A virus, H1N1 subtype; respiratory insufficiency; respiratory distress syndrome, adult

ÖZET Biz önemli risk faktörleri ve ciddi hipoksemisi olup A gribi (H1N1) tanısı konan dört kritik hastayı sunmaktayız. Akciğer filmlerinde bilateral geniş infiltratif lezyonlar saptandı. Parsiyel arteryel oksijen basıncının inspire edilen oksijen fraksiyonuna oranı (PaO2/FiO2) 200'ün altında idi. Hastaların üçüne laboratuvar tanısı beklenmeden oseltamivir başlandı. Influenza A virüsü enfeksiyonu nazofarengeal sürüntüden yapılan gerçek zamanlı ters transkriptaz-polimeraz zincir reaksiyonu (RT-PCR) testi ile teyit edildi. Akciğer koruyucu invazif ventilasyon ve pozitif ekspirasyon sonu basıncı (PEEP) titrasyonu erken dönemde yapıldı. Üç hasta 5-7 gün ventile edildi ve olaysız şekilde taburcu edildi. Sonuç olarak, erken dönemde antiviral tedavi, yoğun bakım ve invaziv mekanik ventilasyonun, ağır hipoksemili hastalarda mortaliteyi ve yoğun bakımda kalışı azaltabileceğini vurgulamak istiyoruz.

Anahtar Kelimeler: Yoğun bakım üniteleri; influenza A virüsü, H1N1 alttip; solunum yetmezliği; solunum sıkıntısı sendromu, yetişkin

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In April 2009, the first two cases with a novel influenza A (H1N1) virus were reported in the United States.[1] The virus has spread throughout the world and caused an influenza pandemic.[2] In November 2009, the highest level of pneumonia and influenza-related mortality was 8.1% in the United States.[3] In a study that was held in Mexico, critical illness occured in 58 of 899 patients admitted to the hospital with H1N1 Influenza A infection. Fifty-four patients received mechanical ventilation for severe hypoxemia.[4] In this article, we aimed to present our approach to critically ill

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patients with influenza A (H1N1) virus infection who had significant risk factors. The written informed consents were obtained from four patients.

CASE REPORTS

CASE 1

A 29-year-old male patient with history of familial cardiomyopathy who worked in the same hospital as a janitor was hospitalized after his admission to emergency service with the complaints of fatigue, fever, cough, nausea and vomiting, and night sweating. An empirical antibiotic treatment with ampicilline-sulbactam and claritromicine was given. The legionella antigen was searched in urine to investigate atypical pneumonia and the result was negative. The patient's body mass index (BMI) was 20 kg m^{-2}. He was taken to the intensive care unit (ICU) on the fourth day of his hospitalization since he had symptoms of dyspnea, tachypnea, cyanosis and tachycardia. He was diagnosed as type 1 respiratory failure. His arterial blood gas parameters were as follows: pH: 7.32, partial pressure of arterial oxygen (PaO_2): 19.3 mm Hg, partial pressure of arterial carbon dioxide ($PaCO_2$): 31 mm Hg, bicarbonate (HCO_3^-): 15.8 mmol/L, base excess (BE):-10.2 mmol/L. He was intubated and ventilated in SIMV (syncronized intermittentt mandatory ventilation) mode. His total blood count and biochemical parameters were as follows: White blood cells (WBCs): 11300 cells/μL, platelets (PLT): 151000/μL, activated partial thromboplastin time (APTT): 78.2 secs (interquartile range [IQR], 26-36 secs), glucose: 421 mg/dL, blood urea nitrogen (BUN): 21 mg/dL, creatinine: 1mg/dL, aspartate transaminase (AST): 140 IU/L, alanine transaminase (ALT): 83 IU/L, albumin: 1.9 g/dL, lactate dehydrogenase (LDH): 1341 IU/L, creatine kinase (CK): 941 IU/L, CK-MB: 183 IU/L, D-dimer: 6.500 ng/mL (IQR, 0-150 ng/mL). His chest X-ray showed bilateral extensive infiltrative lesions and the ratio of PaO_2/FiO_2 was 30 mm Hg (Figure 1). Sedation, paralysis and positive end-expiratory pressure (PEEP) titration were performed. The hemodynamic parameters deteriorated when PEEP was 16 cm H20 so PEEP was adjusted as 14 cm H2O. During ventilation, the parameters were as follows: Tidal volume (Vt): 5 mL/kg, plateau pressure (P_{pl}): 30 cm H_2O, compliance: 10 L/cm H_2O. Permissive hypercapnia was allowed. The patient was receiving dopamine (15-20 μg/kg/min) and dobutamine (10-20 μg/kg/min) infusions for hypotension, but due to unresponsiveness he was, administered epinephrine (0.1 μg/kg/min) infusion for resistant hypotension. His sequential organ failure assessment score on admission was 10 points. At the first hour of admission to the ICU, the patient died. The same day it was confirmed that he was H1N1 influenza A virus positive.

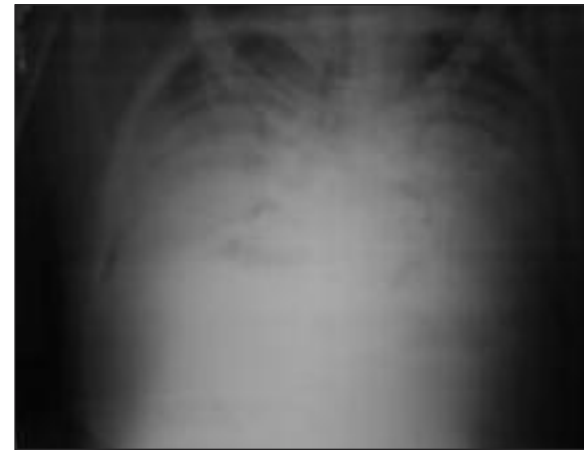

FIGURE 1: Chest X-ray of case 1.

CASE 2

A 68-year-old female patient with history of chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), non-insulin-dependent diabetes mellitus (NIDDM) and hypertension was admitted to emergency service with the complaints of cough, difficulty in breathing, palpitation and fever. Her chest X-ray showed bilateral infiltrative lesions (Figure 2). She was diagnosed as type 2 respiratory failure. Her BMI was 34 kg m^{-2} and ejection fraction was 54%. On the fourth day of her hospitalization, she was taken to the ICU since she had symptoms of dyspnea, lethargy, tachycardia and hypertension. Her arterial blood gas parameters were as follows while keeping FiO2 constant at 30%: pH: 7.17, PaO_2: 46 mm Hg, $PaCO_2$: 73 mm Hg, HCO_3^-: 27 mmol/L, BE: +2 mmol/L. The patient was intubated and ventilated in SIMV mode.

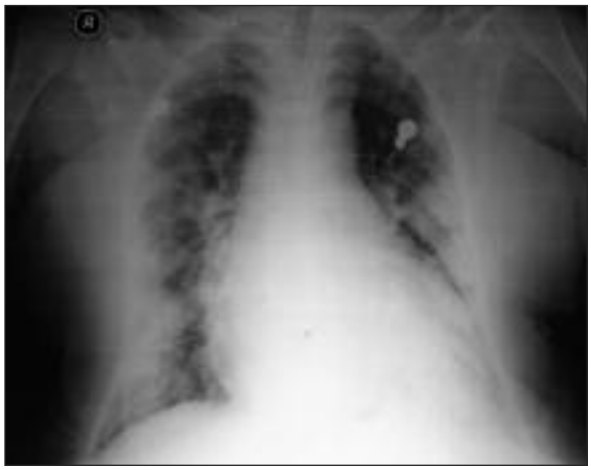

FIGURE 2: Chest X-ray of case 2.

Her total blood count and biochemical parameters were as follows: WBCs: 18000 cells/μL, Glucose: 212 mg/dL, BUN: 40 mg/dL, Creatinine: 1.6 mg/dL, AST: 136 IU/L, ALT: 74 IU/L, Albumin: 2.8 g/dL, LDH: 485 IU/L, CK: 87 IU/L, D-dimer: 550 ng/mL. PaO_2/FiO_2: 150 mm Hg, P_{pl}: 10 cm H_2O and compliance was measured as 40 L/cm H_2O. Tidal volume was applied at 6-8 mL/kg. PEEP titration was performed and optimal PEEP was adjusted as 8 cm H2O. On her third day in the ICU, her transaminases increased (AST 207 IU/L, ALT 335 IU/L) but returned to the normal ranges during the follow-up. Her APACHE II score was 18 and $SOFA_1$ score was 4 points. Empiric antibiotic treatment with levofloxacilline had been given when she was first hospitalized. On the sixth day, *Klebsiella pneumoniae* was isolated in urine and tracheal aspirate, therefore imipenem was given. On the second day, oseltamivir was given 75 mg twice daily for five days because H1N1 influenza A virus was found to be positive. She was invasively ventilated for seven days. She made a good recovery after nine days and was discharged to the ward.

CASE 3

A 22-year-old female patient with history of major depression and smoking was admitted to the emergency service with the complaints of dispnea, fatigue, nausea and vomiting and was hospitalized with the diagnosis of pneumonia. Nasopharyngeal swab was taken to search for influenza A (H1N1) virus. Oseltamivir and levofloxacilline were given empirically. Her BMI was 27 kg m^{-2}. On the second day of her hospitalization she was taken to the ICU since she had symptoms of headache, fatigue, dyspnea, tachypnea, tachycardia. Her chest X-ray showed extensive bilateral infiltrative lesions (Figure 3). She was diagnosed as type 1 respiratory failure. Her arterial blood gas parameters were as follows: pH: 7.42, PaO_2: 47.4 mm Hg, $PaCO_2$: 37.3 mm Hg, HCO_3^-: 24 mmol/L, BE:0 mmol/L. She was intubated and ventilated in SIMV mode. Sedation and paralysis were performed for two days to provide consistency for ventilation. Her total blood count and biochemical parameters were as follows when she was admitted to the ICU: WBCs: 2300 cells/μL (lymphopenia: 400/μL), AST: 102 IU/L, ALT: 43 IU/L, Albumin: 2.9 g/dL, LDH: 743 IU/L, CK: 173 IU/L, D-dimer: 1.283 ng/mL. PaO_2/FiO_2 ratio was 88 mm Hg and compliance was 20 L/cm H2O. We diagnosed her with acute respiratory distress syndrome (ARDS). Tidal volume was applied at 6-8 mL/kg. It was aimed to hold the $P_{pl} \leq 30$ cm H_2O. PEEP titration was performed and optimal PEEP was adjusted as 18 cm H2O. SpO_2 was aimed to be above 90%. Oseltamivir was given 75 mg twice daily for five days since influenza A (H1N1) virus was positive. She had neurological symptoms including twitches on hands, feet, and eyelids and irritability following oseltamivir treatment. Since she had fe-

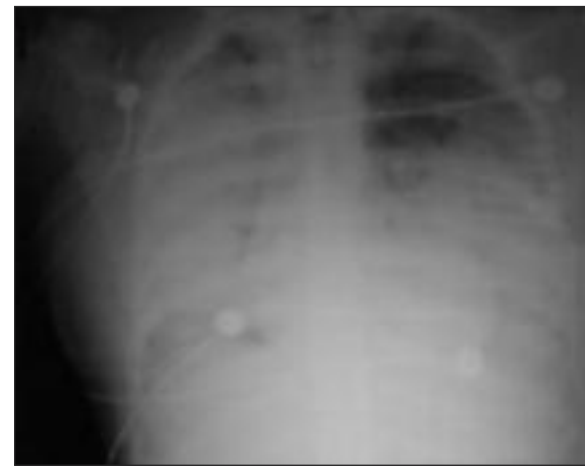

FIGURE 3: Chest X-ray of case 3.

ver on fifth day imipenem was given. Her APACHE score was 12 points and $SOFA_1$ score was 8 points. She was invasively ventilated for seven days. She made a good recovery after ten days and discharged to the ward.

CASE 4

A 21-year-old female patient was presented to the emergency department with difficulty in breathing. She gave a history of premature membrane rupture on 18th gestational week and therapeutic curettage was performed. Cefazolin sodium was given to her. One week after the curettage her flu-like symptoms began. Two weeks later she deteriorated and had difficulty in breathing. Her pelvic ultrasonographic findings were normal. BMI was 25 kg m^{-2}. After her admission to emergency department, she was taken to the ICU since she had symptoms of dyspnea, tachypnea, cyanosis and tachycardia. Her chest X-ray showed bilateral extensive infiltrative lesions (Figure 4). She was diagnosed as type 1 respiratory failure. Arterial blood gas parameters were as follows: pH: 7.33, PaO_2: 15.7 mm Hg, $PaCO_2$: 34 mm Hg, HCO_3^-: 21 mmol/L, BE:-3 mmol/L. She was intubated and ventilated in SIMV mode. Sedation and paralysis were performed for two days to provide consistency for ventilation. When she was admitted to the ICU her labarotory parameters were as follows: Hb: 10.4 g/dL, Htc: 31%, WBCs: 7600 cells/µl, AST: 60 IU/L, ALT: 66 IU/L, Albumin: 2.2 g/dL, LDH: 253 IU/L, CK: 144 IU/L, D-dimer: 579 ng/mL. $Pa-O_2/FiO_2$ ratio was 80 mm Hg and compliance was 22 L/cm H_2O. Since, her hypoxemia worsened we diagnosed her with ARDS. Tidal volume was applied at 6-8 mL/kg. It was aimed to hold the $P_{pl} \leq 30$ cm H_2O. PEEP titration was performed and optimal PEEP was adjusted as 18 cm H2O. SpO_2 was aimed to be above 90%. Oseltamivir was given on her first and linezolid on her third day in the ICU. However the result of nasopharyngeal swabs and bronchial aspirates did not confirm H1N1. The result was considered as false negative. She received oseltamivir 150 mg daily for five days. Her APACHE score was 17 and $SOFA_1$ score was 10 points. She was invasively ventilated five days. She made a good recovery after eight days and discharged to the ward.

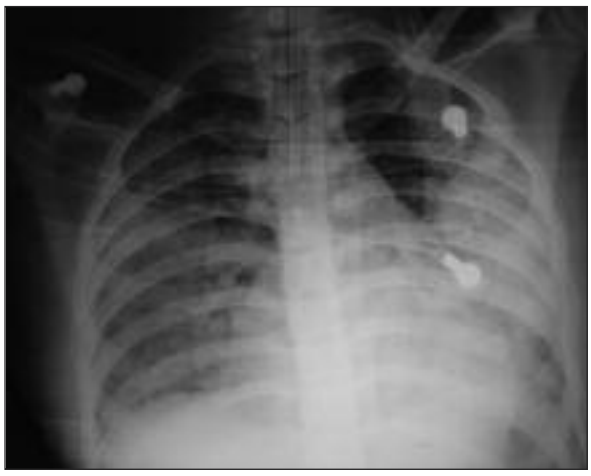

FIGURE 4: Chest X-ray of case 4.

DISCUSSION

We present three cases of influenza A (H1N1) confirmed by RT-PCR test. One of the patients (case 4) was considered to be infected by H1N1 influenza A virus according to her history and clinical course despite H1N1 was negative in the nasopharyngeal swabs and bronchial aspirates with RT-PCR. Negative results of immunoflouresence or viral culture were reported for influenza A (H1N1) virus.[5] In a trial held in China on respiratory samples from 587 patients diagnosed with influenza A (H1N1) virus infection, comparison of laboratory diagnostics showed viral culture and RT-PCR gave comparable results with overall sensitivities of 93.9% and 98.1% respectively.[6]

Three of the patients had underlying conditions associated with a higher risk for influenza A (H1N1). One patient had undergone therapeutic abortus one week ago, one had hypertension, COPD, CAD, NIDDM, one had cardiomyopathy, and history of being a janitor in hospital. However, rapidly progressive lower respiratory tract disease resulting in respiratory failure associated with novel influenza A (H1N1) virus infection has occured among persons who did not have these conditions and were previously healthy.[7]

One of the patients (case 4) experienced her clinical course just after the therapeutic curettage

performed at 18th gestational week. Maternal respiratory changes occur in pregnancy. In addition, immune system is affected by decreased cytotoxic lymphocytic activity in pregnancy. With these physiologic changes, the pregnant patients lose their activity to compansate for and resist against viral respiratory infections. The most common observed infection is influenza infection.[8] In a study, it was reported that 10% of the H1N1 cases followed in the intensive care unit with life threatening respiratory failure were pregnant or in the postpartum period.[9]

One of the patients (case 3) had major depression and did not have any other comorbid diseases. We belive that major depression is a probable comorbid condition. Trials indicated that T cells with their neuroprotective and anti inflammatory effect might play an important role in development of depression. Impaired T cell function contribute to the development of depression.[10]

The high prevalance of obesity in some trials is striking. Obese patients have a higher prevalance of comorbid conditions that confer higher risk for influenza complications, including chronic heart, lung, liver, and metabolic diseases.[9,5] One of the patient's (case 2) BMI was 34 kg m^{-2} and she had comorbid conditions.

Data on H1N1 influenza A infections in Mexico demonstrated that patients were between 13 and 47 years of age.[7] Three of the patients were between 21 and 29 years of age. In a study that was held in Mexico, there was proportionately lower morbidity among persons who were 60 years of age or older.[11] One of the patients was 68 years of age (case 2). Despite comorbid conditions, her clinical condition was better compared to the other patients. Her clinical condition was limited with pneumonia, and acute respiratory distress syndrome did not develop in that patient.

One of the patients (case 3) had leukopenia and lymphopenia. In a trial that was held in Mexico, 61% of patients had lymphopenia.[7] *Klebsiella pneumoniae* was isolated in one of the patients tracheal secretion. In a trial, clinical evidence of secondary bacterial pneumonia following ICU admission was found in 24.4% all of the patients.[12] Another common feature of the Mexico and Michigan trial is that all patients had raised transaminases, LDH, D-dimer levels when they were admitted to the ICU.[5,7]

Antiviral treatment was given to the patients on the 2nd-6th days of the symptoms. We used oseltamivir 75 mg twice daily for 5 days. Oseltamivir is a neuraminidase inhibitor and it is well absorbed from gastrointestinal tract and has an active metabolite. Treatment is most effective when administered within 30-36 hours after onset of illness.[13]

One of the cases (case 3) had neuropsychiatric symptoms such as difficulty in sleeping, twitches in eyelids, hands and feet. She had a history of major depression but her antidepressant therapy was not completed. This condition might have aggrevated her neuropshyciatric symptoms.

ARDS may occur as a result of primary viral pneumonia.[5] Possible mechanisms of damage include direct injury to the respiratory epithelium with a secondary cytokine storm.[14] We diagnosed ARDS according to the American-European Consensus Conference (1994) criteria.[15] Lung protective ventilation and PEEP titration were performed in the immediate period. Patients were ventilated with a mean Vt of 6-8 mL/kg ideal body weight. It was aimed to hold the $P_{pl} \leq 30$ cm H_2O. In a study by Thompson et al.,[16] volume-asist control ventilation was applied to 58% of the patients who have $PaO_2 / FiO_2 \leq 200$ and SIMV or SIMV plus pressure support was applied to 23% of the patients who have $PaO_2 / FiO_2 \leq 200$. The patients were ventilated in SIMV mode (SIMV plus pressure support). When the sedation and the paralysis were performed on the patients, lung-protective volume-controlled ventilation was made. When we stopped sedation and paralysis, by decreasing the mandatory breaths, the spontaneous breathing was permitted. None of the patients had any complications releated to ventilation.

A study of 168 critically ill patients with 2009 influenza A (H1N1) infection in Canada, mean $SOFA_1$ was 6.8 and mortality rate of 28 days was 14.3%.[12] Higher SOFA scores were associated with

increased mortality. The mean $SOFA_1$ score of patients was 8. One of the patients (case 1) with an admission SOFA score of 10 points, oxygenation could not be improved and the patient died in the first hour in ICU.

CONCLUSIONS

We presented four critically ill patients admitted to the ICU with severe hypoxemia. Since young patients can compensate progressive hypoxemia in the early period, the time between initiation of symptoms and admission to ICU can be longer. We wanted to emphasize that antiviral treatment, intensive care and invasive mechanical ventilation in early period can decrease mortality and shorten ICU stay in patients with severe hypoxemia.

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