Case Report

Late-stage Use of Low-dose Corticosteroids Aid Recovery of Severe H1N1 Viral Pneumonia

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The role of corticosteroids in the management of severely ill patients with influenza A (H1N1) viral infection is unclear and controversial. Two critically ill cases with influenza A (H1N1) infections complicated with organizing pneumonia (OP) in 2011 successfully treated with low dose corticosteroids were reported here. After initial clinical improvement, the condition of both patients aggravated 20-23 days after the onset of illness. Chest X-ray and computed tomographies (CT) showed an increment of lung infiltrates. Cultures of blood, pleural fluid and transbronchial aspirate were negative for bacteria and fungi. Organizing pneumonia was diagnosed clinically and both patients were successfully treated with low-dose corticosteroids. Low-dose corticosteroids initiated during convalescence may be beneficial for severe swine-origin influenza A H1N1 pandemic 2009 virus (S-OIV) infections.

Key words: H1N1; Pneumonia; Corticosteroids

During the last flu season in Beijing, China, swine-origin influenza A H1N1 pandemic 2009 virus (S-OIV) came back and became the predominant subtype of influenza. Total of 83 laboratory confirmed influenza cases were hospitalized in our hospital between December 2010 and March 2011, including 69 cases infected with S-OIV (83.1%) and 14 cases with H3N2 (16.9%). Among the 69 laboratory confirmed hospitalized S-OIV infections, 60.5% had pneumonia and 20% developed to acute respiratory distress syndrome (ARDS). We described here two severe S-OIV pneumonia cases with ARDS who improved initially but deteriorated again 20-23 days after the onset of illness. Organizing pneumonia (OP) was diagnosed clinically and both of them responded to prednisone 0.3-0.5 mg·kg⁻¹·d⁻¹ dramatically. Physicians should be aware of OP which may complicate the recovery of patients infected with S-OIV.

CASE PRESENTATION

Case 1

A 39-year-old man, smoker (30 packages per year),

BMI 27.2 kg/m² was admitted to the ward of infectious diseases with a history of high fever, myalgia, fatigue for 10 days and 3 days of dry cough, dyspnea and hemoptysis.

On physical examination, respiratory rates 32 per minute, blood pressure 120/80 mm Hg, heart rate 89 per minute, moist rales were heard on bases of both lungs. Real-time PCR for swine influenza A (H1N1) was positive following the protocol recommended by WHO.¹ Chest X-ray and computed tomographies (CT) showed extensive ground glass opacities with areas of peripheral and peribronchovascular lobular consolidations (Figure 1A, Figure 1B). Arterial blood gas (ABG) analysis revealed severe hypoxemia (PaO₂/FiO₂ as 108). Most relevant laboratory findings at admission were WBC 2 350/ml, platelets 175 000/ml, CRP 1.85 mg/L, procalcitonin 0.05 ng/ml, and LDH 430 U/L. Ceftriaxone (2 g, Qd) and oseltamivir (150 mg, Bid) were initiated and methylmethosone (80 mg, Bid) was added. Noninvasive positive pressure ventilation (NPPV) with IPAP 10 cm H₂O, EPAP 6 cm H₂O and FiO₂ 50%-60% was given. Four days after hospitalization, sputum culture was positive for *Klebsiella pneumoniae* (ESBL negative, non K1 or K2 capsular polysaccharide synthesis (cps) genotyped by PCR). Ceftriaxone was changed to imipenem (1 g, Q8h) and methylmethosone was stopped. Voriconazole was added for prophylactic purpose

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Figure 1. Chest X-ray and computed tomographies of case 1.

Notes: Chest X-ray (1A, on admission) and CT (1B, 5 days before admission) showed extensive ground grass opacities with areas of peripheral and peribronchovascular lobular consolidations. Chest X-ray (1C, 9 days after hospitalization) revealed progression of consolidation in left lower and right lower lobes. Chest CT (1D, 30 days after hospitalization) showed decrease of ground grass opacities and consolidations.

though both sputum fungi culture and blood fungi antigen detection were negative. The patient improved progressively with normal temperature, antibiotic was suspended and NPPV was returned to oxygen inhalation with venturi mask (FiO_2 50%). ABG also showed that $\text{PaO}_2/\text{FiO}_2$ increased to 215. Thirteen days after hospitalization, his oxygen exchange deteriorated again to $\text{PaO}_2/\text{FiO}_2$ as 115. Chest X-ray revealed progression of consolidation in left lower and right lower lobes (Figure 1C). In addition, high fever, increased respiratory rate were observed with normal WBC (6 970/ml) and procalcitonin (0.08 ng/ml). Imipenem and voriconazole were administered again. NPPV was tried out but failed because of pneumothorax of the right lung. Thoracic close drainage and mechanical ventilation was given with FiO_2 80%, PEEP 8 cm H_2O . Cultures of blood, pleural fluid, and transbronchial aspirate were negative for bacteria and fungi. Organizing pneumonia was suspected clinically, but open lung biopsy was not performed. Methylmethosone 40 mg/d was given and significant improvement was observed. He was successfully weaned of mechanical ventilation after 8 days incubation and later discharged from hospital in good conditions. On discharge, his $\text{PaO}_2/\text{FiO}_2$ was 250, chest CT showed partial resolution of lung infiltrate (Figure 1D).

Case 2

A 51-year-old woman, obese (BMI 35.2 kg/m^2), with 3-year hypertension, was admitted to the ward of infectious diseases with a history of high fever, dry cough, myalgias for 7 days, and dyspnea and hemoptysis for 5 days. On physical examination, respiratory rates was 26 per minute and moist rales were heard on bases of both lungs. Real-time PCR detection for swine influenza A (H1N1) got positive results. Chest X-ray and CT showed diffused ground grass opacities and air space consolidations (Figure 2A, Figure 2B). ABG revealed severe hypoxemia ($\text{PaO}_2/\text{FiO}_2$ as 146). Most relevant laboratory findings at admission were WBC 3 590/ml, platelets 160 000/ml, CRP 15.1 mg/L, procalcitonin 0.23 ng/ml and LDH 587 U/L. Cefuroxime and oseltamivir (150 mg, Bid) were initiated. Noninvasive positive pressure ventilation (NPPV) with IPAP 10 cm H_2O and EPAP 8 cm H_2O , FiO_2 50%-60% was given. Six days after hospitalization, sputum culture was positive for *Klebsiella pneumoniae* (ESBL positive, non K1 or K2 cps genotyped by PCR). And then ceftriaxone was changed to cefoperazone/sulbactam. The patient improved progressively with normal temperature, so antibiotic was suspended and NPPV was returned to oxygen mask (FiO_2 50%). Fourteen days after hospitalization, chest X-ray and CT revealed new

Figure 2. Chest X-ray and computed tomographies of case 2.

Notes: Chest X-ray (2A) and CT (2B) on admission showed diffused ground grass opacities and air space consolidations. Chest X-ray (2C, 11 days after hospitalization) and CT (2D, 15 days after hospitalization) revealed new infiltrates with consolidations. Chest CT (2E, 22 days after hospitalization) showed decrease of ground grass opacities and consolidations.

Figure 3. Respiratory rate and oxygen exchange of case 2.

Notes: A: Decrease of respiratory rate; B: Improvement of oxygen exchange. d1, d3, d5, d7 refers to the first day, third day, fifth day and seventh day of initiation of prednisone, respectively.

infiltrates with consolidations (Figures 2C, 2D). Organizing pneumonia was suspected clinically, but open lung biopsy was not performed. Prednisone (30 mg/d) was given and significant decrease of respiratory rates and improvement of oxygen exchange were observed (Figure 3). One week after initiation of prednisone, she was discharged in good

conditions. On discharge, her PaO₂/FiO₂ was 280, chest X-ray and CT showed decrease of ground grass opacities and consolidations (Figure 2E).

DISCUSSION

The role of corticosteroids in the management of

severely ill patients with S-OIV infection is unclear and controversial.²⁻⁶ We agree with Martin-Loeches et al⁴ and Brun-Buisson et al⁵ that early use of corticosteroids may do harm to patients with S-OIV infection for excessive ICU-acquired superinfection. But 2-3 weeks after S-OIV acute infection when viral titer drops⁷ and inflammation becomes predominant in some subtypes, corticosteroids may be helpful, even life-saving at some time.

Organizing pneumonia (OP) is a pulmonary inflammatory condition that may occur after bacterial or viral respiratory infection.⁸ Recently, Cornejo et al reported two cases that developed to OP associated with S-OIV. After initial clinical improvement, both patients presented fever and aggravated in oxygen exchange during their second week of ICU stay (10-14 days after onset of illness). Chest X-rays and CT showed an increment on lung infiltrates, given by areas of consolidation and ground glass opacification. In both cases, an open lung biopsy was performed, and histopathological examination of the specimen was compatible with OP. Both patients were successfully treated with high-dose corticoids.⁹ Gómez-Gómez et al also reported two patients with confirmed S-OIV pulmonary infection who developed into peripheral opacities during convalescence, for whom tissue diagnosis was confirmed as OP.¹⁰ Again, both patients were treated with corticosteroids (1 mg/kg) for 1 month followed by 0.5 mg/kg for 6 weeks, with symptom and radiographic resolution.

OP remains a diagnosis of exclusion. In most cases, the disease was diagnosed based on clinical-radiologic context, with transbronchial biopsy or open lung biopsy confirmation in a minority of patients. Roberts et al reported a subtype of patients with respiratory failure following H1N1 (n = 2) or RSV (n = 1) pneumonia in whom high dose steroids were initiated during convalescent period and had a dramatic effect on outcome.¹¹ But no lung biopsy were performed. They called them steroid-sensitive post-viral inflammatory pneumonitis (PVIP) which might be OP pathologically.

In Cornejo's series, the incidence of OP after S-OIV infection was higher than 10% (2 out of 19 patients).⁹ In our series during 2009-2010, we found 13.8% patients with pneumonia caused by S-OIV infection had progressive dyspnea after resolution of fever, which was one of the two independent risk factors for death (relative risk, 5.852; 95% CI, 1.395-24.541; $P = 0.016$). When the paper was

published in Chest last year, we could not explain the findings.¹² Now we believe that OP may develop during convalescence which may lead to adverse outcome without corticosteroid intervention.

OP and corticosteroids intervention timing is an interesting point in these cases. In Cornejo's series, the diagnosis was confirmed 10-14 days after onset of S-OIV infection.⁹ Gómez-Gómez et al made OP diagnosis 3 weeks after S-OIV infection,¹⁰ and Roberts et al made the diagnosis of PVIP on day 24 to day 41.¹¹ In our series, we made the diagnosis 20-23 days after onset of illness. We thought the initiation of corticosteroids depends on clinical suspicions of OP. Dose of corticosteroids is another interesting point. We agree with Flowers et al who showed good results by only prednisone 0.5 mg·kg⁻¹·d⁻¹ to treat OP.¹³ In our series, both patients responded dramatically to equivalent prednisone 0.3-0.5 mg·kg⁻¹·d⁻¹.

In conclusion, low-dose corticosteroids initiation during convalescence may be beneficial for severe S-OIV infection. More case-controlled studies and placebo-controlled trials are needed to validate the optimal dose, timing and duration of corticosteroid therapy for S-OIV infected patients.

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Potential conflicts of interest

All authors declare that they have no conflicts.

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