

Case Report

Prone Positioning in Influenza A Infection Following Lung Transplantation: A Case Report

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Abstract

Since 2009, influenza A infection represents a major concern for the scientific community; in the immediate postoperative of lung transplantation it is a rare event that may cause severe respiratory impairment. In case of refractory hypoxemia due to influenza infection, alternative strategies of oxygenation such as prone positioning have been efficiently used; however, no data exploring this issue were published. Herein, we describe the first case of refractory hypoxemia due to influenza A virus infection in the immediate postoperative of lung transplantation that was rescued with prone positioning. This case is an example of the potential harmful effects of influenza infection following lung transplantation and represents, to our knowledge, the first report of effective prone positioning in the immediate postoperative period of lung transplantation.

Keywords: Lung transplantation; Prone positioning; Virus A influenza; H2N3 Virus.

Abbreviation: WHO: World Health Organization; ECMO: Extracorporeal Membrane Oxygenation; ICU: Intensive Care Unit; FiO₂: Fraction of Inspired Oxygen; PCR: Polymerase Chain Reaction; BAL: Bronchoalveolar Lavage; PaO₂: Partial Pressure of Oxygen; PEEP: Positive End-Expiratory Pressure

Introduction

Respiratory infection is a frequent complication in the immediate postoperative period of lung transplantation, with a high attributable mortality [1,2]. Among respiratory infections, bacterial pneumonia is the most frequent complication [3]. Since the introduction of the prophylaxis with ganciclovir, viral pneumonitis is a rare complication in the immediate postoperative of lung transplant [4]. However, cases of influenza transmission through lung transplantation have been reported in the literature [5,6].

Since March 2009 influenza A H1N1 virus infection has spread worldwide, and on June 11th 2009 the World Health Organization (WHO) declared the state of pandemic, until August 2010 [7]. After the pandemic, other strains of influenza A virus such as H3N2 became predominant, although A H1N1 and B influenza virus continued to co-circulate [8]. Because of the high rate of previously healthy population that were severely affected and required hospitalization, influenza A infection became a main challenge for the scientific community. In the population of solid organ transplant recipients, influenza A H1N1 infection has been found

to be associated with higher mortality [9]. The most frequent cause of death from influenza A pneumonia was refractory hypoxemia due to acute respiratory distress syndrome [10,11] and strategies such as protective mechanical ventilation, prone positioning and extracorporeal membrane oxygenation (ECMO) were widely used [12,13]. Herein, we present a case of severe hypoxemia due to influenza A virus infection in the immediate postoperative period of bilateral lung transplantation that required prone positioning.

Case Report

Fifty-eight years old Caucasian woman diagnosed of pulmonary emphysema in 2003. Active smoker until 2003 with tobacco exposure of 90 packs/year, with a history of bronchial hyperresponsiveness and need of nearly one hospital-admission per year, due to exacerbations. She suffered chronic respiratory failure and received 24 hours/day of oxygen therapy. Her treatment was inhaled tiotropium, salmeterol and fluticasone, without needing of systemic steroid treatment. In November 2013 she received the annual influenza vaccination, active against A and B influenza strains.

In January 2014, after suitable organs became available, she underwent bilateral lung transplantation. Of note, prior to the intervention she was found to have some non-specific symptoms, including malaise, rhinorrhea and cough. Preoperative blood analysis was not suggestive of infection and the chest X-ray was similar to previous. The intervention was well tolerated and uneventful, without needing extracorporeal bypass. Graft ischemic time was five and seven hours for left and right lungs respectively.

At intensive care unit (ICU) admission, she was in hypovolemic shock and severe respiratory failure requiring norepinephrine and

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protective mechanical ventilation. The ratio of partial pressure arterial oxygen and fraction of inspired oxygen ($\text{PaO}_2/\text{F}_1\text{O}_2$) at admission was 58 mmHg. Blood test analysis showed mild leukocytosis, normal hepatic and renal function, no myocardial necrosis markers elevation. Chest X-ray showed bilateral interstitial infiltrate with left pleural effusion. Antimicrobial prophylaxis and immunosuppression were started at ICU admission with ceftazidime and amoxicillin-clavulanate, and methylprednisone plus tacrolimus, according to our protocol. Forty-eight hours after ICU admission her $\text{PaO}_2/\text{F}_1\text{O}_2$ ratio normalized, vasopressors were withdrawn and there was no new clinical complications. Furthermore, the chest X-ray bilateral interstitial infiltrates disappeared after negative fluid balance (Figure 1a). Thus, spontaneous breathing trials and weaning from mechanical ventilation were initiated.

However, 72 hours after the intervention she had hypoxemia requiring higher fraction of inspired oxygen (F_1O_2), controlled mechanical ventilation and deep sedation. Twenty-four hours later, a polymerase chain reaction (PCR) assay of the bronchoalveolar lavage (BAL) that was carried out immediately prior to the transplant turned positive for influenza A H3N2 virus, while the remaining microbiological cultures were negative. A BAL was repeated, a pulmonary biopsy was performed and oseltamivir 150 mg twice daily via nasogastric tube was empirically initiated. Again, PCR kept positive for influenza A virus, while the rest of cultures were negatives. Pulmonary biopsy showed acute nonspecific mild interstitial pneumonitis, without signs of rejection or bacterial infection. Same dose of methylprednisolone was continued, as indicated per protocol; tacrolimus was adjusted to maintain plasmatic levels of around 10 ng/mL; and mophetil mycophenolate was not initiated. Table 1 shows type and dose of the immunosuppressant and the days of delivery of oseltamivir.

Despite antiviral treatment, neuromuscular blockade, protective

mechanical ventilation and negative fluid balance, hypoxemia got worse during the following 48 hours; partial pressure of oxygen (PaO_2) was 72 mmHg with 0.8 of F_1O_2 and higher pressures (plateau pressure over 30 cmH_2O) were needed to clear the carbon dioxide. Chest X-ray showed a new bilateral interstitial infiltration (Figure 1b). Because of the persistent severe hypoxemia, patient was placed in prone position presenting a dramatic improvement in gas exchange: the $\text{PaO}_2/\text{F}_1\text{O}_2$ ratio after 18 hours of prone positioning was 264 mmHg, with 0.4 F_1O_2 . Compliance of the respiratory system also improved. The manoeuvre was not associated with any complication, and an optimal respiratory function was maintained after supine positioning. Ventilator weaning was restored and the patient was finally extubated on day 10th from the transplant.

After 10 days on oseltamivir a BAL was repeated: PCR for H2N3 influenza virus remained positive, thus, it was decided to keep antiviral treatment 5 more days. Finally, after 15 days of antiviral treatment, a third BAL showed a negative PCR for influenza A virus: oseltamivir was withdrawn and mophetil mycophenolate initiated.

As a complication, the patient developed severe post-critical myopathy requiring prolonged ICU admission, and she was finally transferred to the ward after 19 days of ICU admission without clinical changes or new complications. She was discharged home in a good condition after 2 month of hospitalization. At 3-month follow-up, the patient maintained good respiratory function and she is continuing her usual activities of daily living. She doesn't relate dyspnoea and has a clear chest X-ray (Figure 1c).

Discussion

This is the first published case of successful prone positioning in the immediate postoperative period of lung transplantation complicated with severe hypoxemia due to influenza A infection.

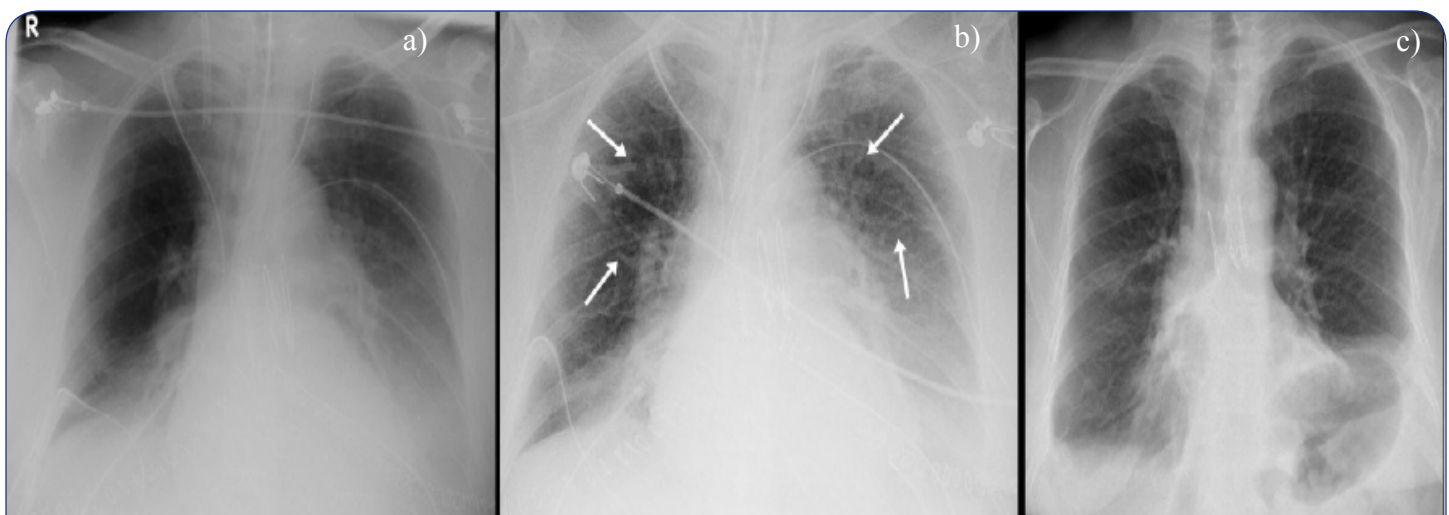


Figure 1: chest X-Ray before influenza A infection (1a); after diagnosis of influenza A virus pneumonitis (1b) and after full resolution (1c). Arrows in figure 1b show the new bilateral interstitial infiltration secondary to influenza A infection.

Table 1: Days of delivery and doses of immunosuppressant and oseltamivir

Days from transplantation	Tacrolimus: dose delivered	Tacrolimus: plasmatic levels [ng/ml]	Methylprednisone: dose delivered	Mophetil Mycophenolate: dose delivered	Oseltamivir: dose delivered
+1	3 mg/12 h	-	125 mg/8 h	-	-
+2	2 mg/12 h	26.2	30 mg/12 h	-	-
+3	1 mg/12 h	25.1	30 mg/12 h	-	-
+4	0 mg	26.2	30 mg/12 h	-	150 mg/12h
+5	0 mg	11.6	20 mg/12 h	-	150 mg/12h
+6	1 mg/12 h	6.4	20 mg/12 h	-	150 mg/12h
+7	2 mg/12 h	8.0	20 mg/12 h	-	150 mg/12h
+8	2 mg/12 h	13.5	20 mg/12 h	-	150 mg/12h
+9	2 mg/12 h	10.9	30 mg/24 h	-	150 mg/12h
+10	3 mg/12 h	10.4	30 mg/24 h	-	150 mg/12h
+11	2 mg/12 h	12.2	30 mg/24 h	-	150 mg/12h
+12	2 mg/12 h	13.1	30 mg/24 h	-	150 mg/12h
+13	2 mg/12 h	13.7	20 mg/24 h	-	150 mg/12h
+14	3 mg/12 h	11.6	20 mg/24 h	-	150 mg/12h
+15	4 mg/12 h	10.9	20 mg/24 h	-	150 mg/12h
+16	4 mg/12 h	8.6	20 mg/24 h	-	150 mg/12h
+17	4 mg/12 h	7.2	20 mg/24 h	-	150 mg/12h
+18	4 mg/12 h	8.0	20 mg/24 h	-	150 mg/12h
+19	4 mg/12 h	6.7	20 mg/24 h	500 mg/12h	-

In ICU patients with refractory hypoxemia due to influenza A infection, prone positioning is an effective rescue therapy for severe hypoxemia [14,15]. In this particular case, the recent chest-surgery was a relative contraindication for prone positioning, mainly due to the thorax instability secondary to the thoracotomy. Moreover, to date, no data are available in the literature supporting the use of prone positioning in the postoperative period of lung transplant that presents severe hypoxemia. In this population, the best standard of care does not differ from that of the non-transplanted patients. Protective mechanical ventilation is mandatory and positive end expiratory pressure (PEEP) may be individualized, taking into account the sutures. Neuromuscular blockade may be needed to improve compliance and reduce oxygen consumption. Nitric oxide may be useful to some patients with refractory hypoxemia especially in patients with associated pulmonary hypertension. Despite these procedures, hypoxemia may persist and non-conventional measures may be needed. The new devices used for the modern ECMO support may maintain oxygen delivery of some of these patients [16]; however, the technique is still associated with potential life-threatening complications and carries high costs [17]. Conversely, prone positioning is a rapid and inexpensive procedure that may significantly improve the gas exchange and the compliance

of the respiratory system. In our patient, the manoeuvre improved significantly the oxygenation and allowed to decrease pressures in the respiratory system to avoid further damage in the parenchyma and even in the sutures. The manoeuvre was carried out during 18 hours without any complication. In lung transplant recipients the risks of prone positioning are relatively high, mainly due to the recent heavy manipulation of heart and the lung structures; in this setting, any complication related to prone positioning could conduce to catastrophic sequels. Thus, the experience of the personnel on proning is mandatory. Although no data are available in the literature, according to our experience, the incidence of complications in prone positioning in the immediate postoperative period of lung transplantation is fairly low. The most frequent are: fail of thoracotomy closure or other wound complications such as bleeding or skin suture failure; pneumothorax due to the pinch of pleural drainage; accidental release of any medical device such central line, tracheal tube or tracheostomy, thoracic drainage or nasogastric tube.

Regarding the influenza A infection, prior to transplantation, the patient referred mild symptoms without clinical or radiographic signs of severity. Furthermore, the intervention was performed

in winter: during the seasonal flu epidemic and when the risk for exacerbation is the highest for patients with chronic respiratory failure. For these reasons, our patient was considered to be at low risk for influenza A pneumonitis and no further investigations were performed. Nevertheless, due to the low sensibility of the clinical presentation and the high risk of severe complications related to a not recognized influenza A infection [1], we consider that a generalized screening for influenza infection for patients undergoing lung transplantation is an unresolved issue that should be better investigated in future research.

Finally, another interesting issue is the management of immunosuppression during the influenza A infection. In the present case we stick to our institution protocol, the only differences were: maintaining the plasmatic level of tacrolimus in the lower therapeutic range (around 10 ng/mL); waiting the full resolution of the infection before initiating mycophenolate since its use has been shown to be associated with cytomegalovirus reactivation in solid organ transplantation [18,19]. However, there is no clinical evidence to support this measure, and every decision should be carefully taken and based on caution. Again, more investigation is needed and an important challenge in the next future is to increase the currently available evidence in this field.

In conclusion, we reported an unusual case of severe hypoxemia due to influenza A infection in the immediate postoperative of bilateral lung transplantation. The respiratory failure was treated with prone positioning manoeuvre, without observing related complications.

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