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Case report

Possible respiratory syncytial virus infection presenting as diffuse alveolar hemorrhage in an elderly treated with systemic corticosteroid: A case report

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ABSTRACT

Introduction: Respiratory syncytial virus infection is gaining interest in the elderly due to its growing morbidity and mortality. We present a Case of respiratory syncytial virus infection presenting as diffuse alveolar hemorrhage that was highly responsive to systemic corticosteroid in an elderly patient.

Case presentation: An 82-year old man was admitted to the intensive care unit with worsening hypoxic respiratory failure. Chest radiograph showed non-homogeneous air space opacities. Bronchoalveolar lavage showed a finding of alveolar hemorrhage. The diagnosis of diffuse alveolar hemorrhage was made and high-dose systemic corticosteroid was given. However, concomitant respiratory syncytial virus infection was later confirmed. Therefore, ribavirin and human immunoglobulin were added. During the course of his treatment, the steroid was stopped and restarted. Interestingly, the clinical course was highly responsive to systemic corticosteroid.

Conclusion: It appears that diffuse alveolar hemorrhage in this patient may have been due to an immunological process caused by respiratory syncytial virus. Therefore, corticosteroid therapy was highly effective in improving the patient's hemoptysis and hypoxic respiratory failure. We suggest that further studies are required on the use of steroid in this subset of patients with respiratory syncytial virus lower respiratory tract infection.

Introduction

Respiratory syncytial virus (RSV) is a common pathogen that causes respiratory illness in all ages. In the past, severe RVS infections developed mostly in infants and young children, and therefore, it was not recognized as a significant pathogen in the elderly [1]. However, with the increasing number of elderlies and immunocompromised adults, severe RSV infections are now prevalent in these populations [2,3]. Falsey et al. reported in a 2005 study that RSV was the second most commonly identified cause of hospitalization in the elderly, developing annually between 3% and 7% with a the mortality of 8% [4].

Diffuse alveolar hemorrhage (DAH) is a clinicopathologic syndrome that can cause respiratory failure. A spectrum of disorders can cause DAH, and pulmonary infections are one of the known causes [5]. However, DAH caused by RSV infection is rarely reported and most of them are published in pediatric journals [6–8]. We encountered an RSV infection presenting as DAH in an elderly patient, which was successfully treated with systemic corticosteroid treatment.

Case presentation

An 82-year old man with atrial flutter, coronary artery disease on clopidogrel, and high degree atrioventricular block with a permanent pacemaker was admitted to hospital with a diagnosis of pneumonia. His symptoms of cough and rusty sputum began seven days before admission. On the third day of hospitalization, he was transferred to the medical intensive care unit (MICU) for worsening hypoxic respiratory failure.

When the patient was transferred to the MICU, he was febrile to 39.2 °C with a respiratory rate of 29 breaths per minute. On physical examination, a bilateral coarse breathing sound was heard. There was no rash, joint swelling, jugular venous distension, or pitting edema of the lower extremities. The laboratory test showed no leukocytosis with a near-normal platelet count and coagulation. Cardiac enzymes were within normal limits (Table 1). Bedside echocardiography showed normal ejection fraction without wall motion abnormality. The chest radiography showed non-homogeneous air space opacities (Fig. 1-a) and the initial blood gas analysis showed an arterial partial pressure of

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Table 1
Laboratory findings on the day of transfer to medical intensive care unit.

Hematology		Coagulation		Immunology	
WBC	8500/μL	PT	12.1 sec	CRP	4.56 mg/dL
Neutrophil	83.0%	PT (INR)	1.07	MPO-ANCA	<3.5 IU/mL
Lymphocyte	11.0%	aPTT	31.6	PR3-ANCA	<2.0 IU/mL
Monocyte	5.6%	**Urine analysis**		anti-GBM Ab	<1.0 U/mL
Basophil	0.2%	RBC	0-2/HPF	ANA titer	<1:40
Eosinophil	0.2%	WBC	0-2/HPF	Anti-CL Ab	negative
Hemoglobin	14.7 g/dL	Albumin	++	Anti-B2GP	negative
Platelet	142 $x10^3$/μL	Glucose	++	RF	<10.6 IU/mL
				Anti-CCP Ab	<5.0 U/mL
Biochemistry		**ABGA**	(on 6 L/min NP)	C3	112.0 mg/dL
Na	135 mmol/L	PH	7.39	C4	23.1 mg/dL
K	4.4 mmol/L	$PaCO_2$	35.4 mmHg	CH50	79.4 U/ml
Cl	98 mmol/L	PaO_2	66.2 mmHg	HIV Ag & Ab	negative
BUN	15 mg/dL	HCO_3	22.0 mmEq/L	HCV Ab	negative
Cr	0.98 mg/dL			HB_sAg	negative
BNP	393 pg/mL	**BAL fluid**	(Second bottle)	Anti-HB_s Ab	negative
Protein	7.3 g/dL	RBC	11300/μL		
Albumin	3.9 g/dL	WBC	242/μL		
AST	31 IU/L	Neutrophil	54%		
ALT	33 IU/L	Lymphocyte	10%		
LDH	240 IU/L	Histiocyte	36%		

WBC: white blood cells, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, Cre: creatinine, BNP: brain natriuretic peptide, CRP: C-reactive protein, Antineutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane (GBM) antibodies, antinuclear antibodies (ANA), anti-double stranded DNA antibodies (anti-dsDNA), anticardiolipin antibodies, anti-beta-2-glycoprotein, complement levels (C3, C4, or CH50), rheumatoid factor, and anti-cyclic citrullinated peptide antibodies were all negative.

oxygen (PaO2) of 66.2 mmHg while the patient was receiving 6 L/min of oxygen via nasal cannula (P/F ratio: 146). The empiric antibiotics were switched from ceftriaxone to piperacillin-tazobactam and levofloxacin.

Due to the finding of the chest X-ray, fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) was performed with the successive instillation and retrieval of 30 mL, 30 mL, and 40 mL of saline. The BAL fluid aliquots were progressively bloodier, suggesting DAH (Fig. 2). Therefore, the diagnosis of diffuse alveolar hemorrhage was made based on the symptom of rusty sputum, chest radiographic finding of non-homogeneous air space opacities, and progressive hemorrhage in the BAL sample. With this diagnosis, clopidogrel was stopped and methylprednisolone 1 mg/kg (total of 65mg) was started. For the treatment of severe hypoxia, 100% fraction of inspired oxygen (FiO2) was delivered through a high-flow nasal cannula with a flow of 40 L/min. The subsequent gas analysis showed PaO2 of 150.1 mm Hg.

Laboratory tests for vasculitis and connective tissue disease were added to investigate the etiology of the DAH. All the following results were negative: antineutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibodies, antinuclear antibodies, anti-cardiolipin antibodies, anti-beta-2-glycoprotein, complement levels, rheumatoid factor, and anti-cyclic citrullinated peptide antibodies (Table 1). In addition, reverse transcription polymerase chain reaction (RT-PCR) and cultures were negative for the following pathogens; Mycoplasma pneumonia, Chlamydophila pneumonia, *Legionella pneumophila*, Pneumocystis jirovecii, *Mycobacterium tuberculosis*, influenza virus, parainfluenza virus, adenovirus, and cytomegalovirus.

On the second day of MICU admission, his hemoptysis and dyspnea improved. The FiO2 requirement decreased to 25%. The chest radiograph showed an improvement in diffuse ground-glass opacity (Fig. 1-b). However, the laboratory confirmed a positive result for RSV B in both BAL fluid and the nasopharyngeal swab. Additional history taking revealed that his granddaughter had an upper respiratory infection when she visited him a few weeks ago. Because all blood tests for vasculitis and connective tissue diseases were negative and RSV infection was confirmed, the steroid was discontinued after the first dose. This was because studies have shown worse outcomes with high-dose steroid use in viral pneumonia. Instead, intravenous ribavirin and human immunoglobulin were started from the second day of MICU stay.

However, over the four consecutive days without steroid, his hemoptysis symptom reappeared and the FiO2 requirement gradually increased to 65%. The lowest P/F ratio was found to be 131 during this period. The chest X-ray on day 5 of MICU stay showed worsening of the opacities (Fig. 1-c). Therefore, we decided to restart the steroid with a lower dose (methylprednisolone 0.5mg/kg) in addition to ribavirin and immunoglobulin. Surprisingly, a significant improvement was observed over the course of 48 hours. His FiO2 requirement decreased to 30% and the opacities on the chest radiograph resolved significantly (Fig. 1-d).

Since the patient did not present any symptoms and did not show signs of respiratory distress, he was transferred to the general ward on the eighth day of his stay in the MICU. He was continued on the same dose of steroid for the next six days. The patient was discharged home with an oral form of steroid and it was tapered off over the three weeks as an outpatient. Clopidogrel was restarted when the steroid was completely discontinued. There was no recurrence of cough or hemoptysis. The patient had monthly follow-up visits for six months, but no signs or symptoms of autoimmune diseases were observed. Follow-up labs were performed for vasculitis and connective tissue disease, but all results were negative.

Discussion

To our knowledge, this is the first reported Case of DAH caused by RSV infection in an elderly patient which was successfully treated with systemic corticosteroid. Coughs with rusty sputum, diffuse ground-glass opacities on chest radiograph, and bronchoscopic finding showed a typical representation of DAH. RSV infection was diagnosed by positive RT-PCR from both nasal swab and BAL. The history that his symptoms developed after the visit of his granddaughter, who had an upper respiratory infection, supports the causality of this case.

RSV was first discovered in 1957 as a causative pathogen of infant bronchiolitis and has been identified as the leading cause of hospitalization for respiratory tract illness in infants and young children [1]. Before the 1980s, RSV was considered a virus of no importance to adults. However, with the aging population, RSV is increasingly recognized as a significant pathogen in the elderly and immunocompromised adults [2]. In the US, RSV was found to be the second leading cause of viral pneumonia in the elderly after the influenza virus [9]. The clinical findings of RSV infection in adults are more diverse and less distinctive than in children, and clinicians may often not suspect RSV to be the cause of infection [1].

The clinical presentation of RSV infection is considered to be affected by both viral activity and host inflammatory response [10]. Studies have found that RSV infection can cause changes in the host's immune system

and create extensive inflammation in the lower respiratory tract [11–13]. In a study by Jozwik et al. bronchial biopsies from healthy volunteers after experimental RSV infection showed extensive macroscopic inflammation and infiltration of $CD8^+$ T cells in association with RSV antigen [14]. The mechanism of DAH associated with RSV infection cannot be fully explained, but there may be a possibility that inflammation in the lower respiratory tract plays an important role.

As the inflammation process is part of the pathology of RSV infection, the use of steroid had been extensively investigated. However, multiple randomized control studies were not able to find a clinical benefit of steroid in RSV lower respiratory tract infection [15–17]. Furthermore, in other viral outbreaks, the use of steroid resulted in worse outcomes such as delayed clearance of the virus and increased mortality due to secondary infections [18]. Therefore, we were cautious of using steroid in our patient and it was used as a salvage therapy to avoid invasive mechanical ventilation.

However, there may be a subset of viral lower respiratory tract infection that steroid would be beneficial. Roberts et al. published a Case series introducing an interesting concept. They called this group of patients as "steroid-sensitive post-viral inflammatory pneumonitis" [19] They reported three cases of viral pneumonias (H1N1 and RSV) in which high-dose steroids had a dramatical effect on the outcome. The article argues that there is a subset of patients with viral lower respiratory infection who may need treatment with systemic steroids. They also argue that these patients could be vaguly diagnosed as ARDS and that steroid would not be used. Similarly, we would have diagnosed our patient as ARDS if it was not for the early bronchoscopic evaluation. Without the detection of DAH and RSV, steroid and antiviral therapy would not have been used, resulting in worse outcome.

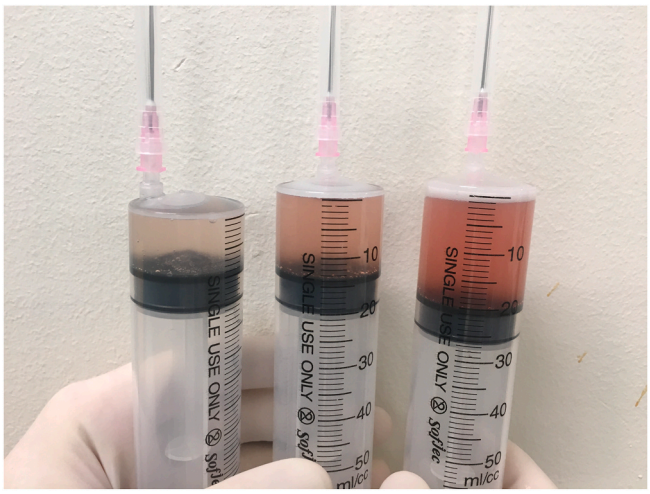

Fig. 2. Sequential sampling of bronchoalveolar lavage (BAL) fluid showing progressive hemorrhagic return.

The following are the limitations of this Case report. There is a possibility that the patient had an undetected cause of DAH. Since there are various causes of DAH that can respond to corticosteroid, RSV infection might not have been the only cause of DAH in this patient. However, the negative results of repeated blood tests and the absence of recurrence of DAH during the six months of follow-up reduce this

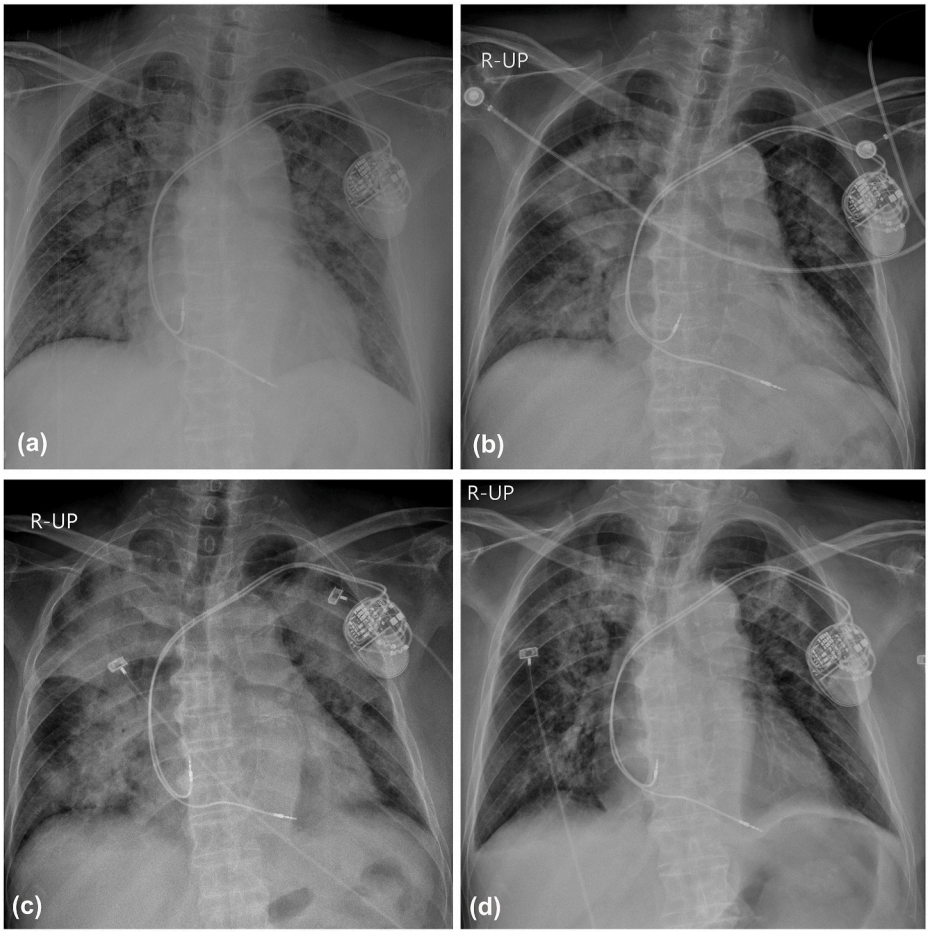

Fig. 1. Serial chest radiography: diffuse bilateral ground glass opacities on the day of admission (a); improvement of opacities after first dose of steroid (b); worsening opacities after four days without steroid (c); and improvement of opacities on the second day after restarting steroid (d).

possibility. Before the MICU transfer, clopidogrel was being used and this may have contributed to the development of DAH. However, his clinical course worsened even after clopidogrel was discontinued and there was no recurrence of DAH after resuming this medication. Finally, the absence of histological confirmation of inflammation of the lower respiratory tract limits the explanation of our hypothesis.

Conclusion

We report a Case of RSV infection that presented as DAH in an adult patient. In this case, the RSV infection may have caused extensive inflammation of the lower respiratory tract, resulting steroid-responsive DAH. We suggest that a case series is needed to further discuss use of steroid in this subset of patients with RSV lower respiratory tract infection.

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Declaration of competing interest

None.

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