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Influenza A Pneumonia Associated with Diffuse Alveolar Hemorrhage. A Case Report and Literature Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Patient: Female, 80
Final Diagnosis: Diffuse alveolar hemorrhage in influenza A viral pneumonia
Symptoms: Generalized fatigue • shortness of breath
Medication: —
Clinical Procedure: —
Specialty: Critical Care Medicine

Objective: Rare co-existence of disease or pathology
Background: Diffuse alveolar hemorrhage (DAH) represents a life-threatening complication for many respiratory infections. We present a case of a patient with influenza A pneumonia associated with DAH.





Case Report: An 80-year-old female patient was admitted with lethargy, dyspnea, and chest pain. On examination, she was afebrile with bilateral basal inspiratory crackles. Her chest x-ray revealed retro-cardiac infiltrate. Her hospital course was complicated by respiratory failure and septic shock requiring intubation. Nasopharyngeal swabs, rapid testing was positive for influenza A. Bronchoscopy showed diffuse bleeding and bronchoalveolar lavage (BAL) of the left lower lobe showed progressively bloody returns, consistent with DAH. Methylprednisolone 250 mg daily was started, with improvement in oxygenation. Repeat bronchoscopy 2 days later revealed normal mucosa and no further bleeding. The patient's respiratory status and infiltrates improved, but her overall status continued to deteriorate, and she died 2 weeks after admission.

Conclusions: High fatality rates have been reported in patients with influenza A viral pneumonia complicated by DAH. Advanced age and the presence of significant co-morbidities might predispose a patient to the development of a more aggressive clinical manifestation of influenza A and also increases the risk of developing DAH. Therefore, clinicians managing patients with influenza A viral pneumonia with this predisposing history should also maintain a high suspicion for DAH. We suggest early BAL for diagnosis and for the evaluation of other infections etiologies. Aggressive supportive care and the use of antiviral agents is recommended. The role of steroids is unclear and can be considered in patients with fulminant disease but might have no outcome benefit.

MeSH Keywords: Hemorrhage • Influenza A virus • Pneumonia

Abbreviations: DAH – diffuse alveolar hemorrhage; BAL – bronchoalveolar lavage; ESRD – end-stage renal disease; COPD – chronic obstructive pulmonary disease; DAD – diffuse alveolar damage

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/913801>

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Background

Diffuse alveolar hemorrhage (DAH) is considered a life-threatening medical emergency with nonspecific signs, symptoms, and chest imaging that can lead to respiratory failure and death. Hemoptysis, anemia, and new lung infiltrates are the most common presentation; however, in one-third of cases, hemoptysis is absent. Hemorrhagic bronchoscopic bronchoalveolar lavage (BAL) on serial samples is confirmatory for DAH. Treatment is based on the etiology of the hemorrhage. Causes of DAH include vasculitis, which is the most common etiology, followed by thrombocytopenia, post-autologous stem cell transplantation, autoimmune disorders, coagulation disorders, drugs, and infections [1]. We present a case of an elderly immunocompetent patient with influenza A (H1N1) complicated with DAH presenting without hemoptysis and who was stabilized with antibiotics and steroids.

Case Report

An 80-year-old female was admitted to the intensive care unit during the winter season with a 4-day history of dyspnea, lethargy, and chest tightness. The patient denied cough, hemoptysis, fever, gastrointestinal symptoms, recent sick contacts, or traveling. Her medical history was significant for end-stage renal disease (ESRD) from long-standing hypertension on hemodialysis, severe pulmonary hypertension, and chronic obstructive pulmonary disease (COPD). She was a former smoker with 15-pack year history of cigarette use with no other toxic habits. The patient was not on any anti-coagulants, amiodarone, or chemotherapeutic agents, and had no recent nitrofurantoin use.

On examination, she was in acute respiratory distress with tachypnea and hypoxemia, oxygen saturation of 89% on room

air which improved to 95% on 2 liters of oxygen via nasal cannula. She was afebrile with a temperature of 36.7°C (98°F), a blood pressure of 89/55 mmHg, and a heart rate of 89 beats per minute. Lungs examination was normal. The patient was awake and alert, and the rest of her examination, including cardiac and abdomen examinations was normal. Her skin demonstrated no petechiae or bruising with no gingival bleeding on oral examination or oozing from sites of intravenous access. Laboratory investigations showed anemia with a hemoglobin level of 9.9 g/dL (noted to be 13.3 g/dL at 1 month prior), leukocytosis (white blood cell count was 13.0×10^3 cells/ μ L) with a left shift (neutrophil count was 10.8×10^3 cells/ μ L), a serum lactate of 3.7 mmol/L, and an arterial blood gas done on room air with a pH of 7.317, pCO₂ of 57.7 mmHg, and pO₂ of 40.2 mmHg. Coagulation profile reported an international normalized ratio (INR) of 1.1 with a prothrombin time (PT) of 13.5 seconds and a partial thromboplastin time (PTT) of 30.6 seconds. Urine and serum toxicology were negative. Chest x-ray showed retrocardiac infiltrates (Figure 1A). Nasopharyngeal swabs, rapid testing was positive for influenza A. The clinical status of the patient deteriorated rapidly with development of shock, for which she was intubated, and the patient was placed on mechanical ventilation and pressors. She was started on vancomycin, piperacillin-tazobactam, azithromycin, and oseltamivir for severe pneumonia. A chest computed tomography (CT) showed left lower and right upper lobe infiltrates, a right lower lobe nodule and no evidence of a pulmonary embolus (Figure 1B, 1C).

Fiberoptic bronchoscopy performed on day 2 of admission revealed airway erythema of the left and right bronchial trees and BAL performed in the left lower lobe showed progressive bloody returns consistent with DAH. BAL done in the right lower lobe also produced similar findings. Bronchoscopy and blood and urine cultures were negative. BAL cytology 4 1513 cells/mm³ for WBCs of which 54% were segmented neutrophils and 44%

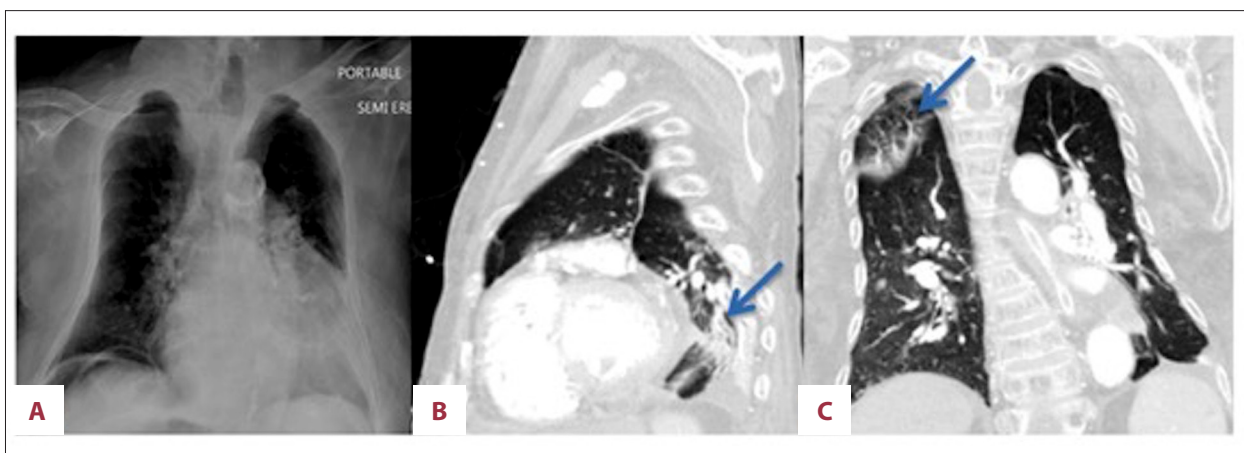


Figure 1. (A) Chest x-ray on admission demonstrating a retrocardiac infiltrate. (B) Computed tomography (CT) chest, sagittal plane demonstrating left lower lobe infiltrate. (C) CT chest, coronal plane demonstrating right upper lobe infiltrate.

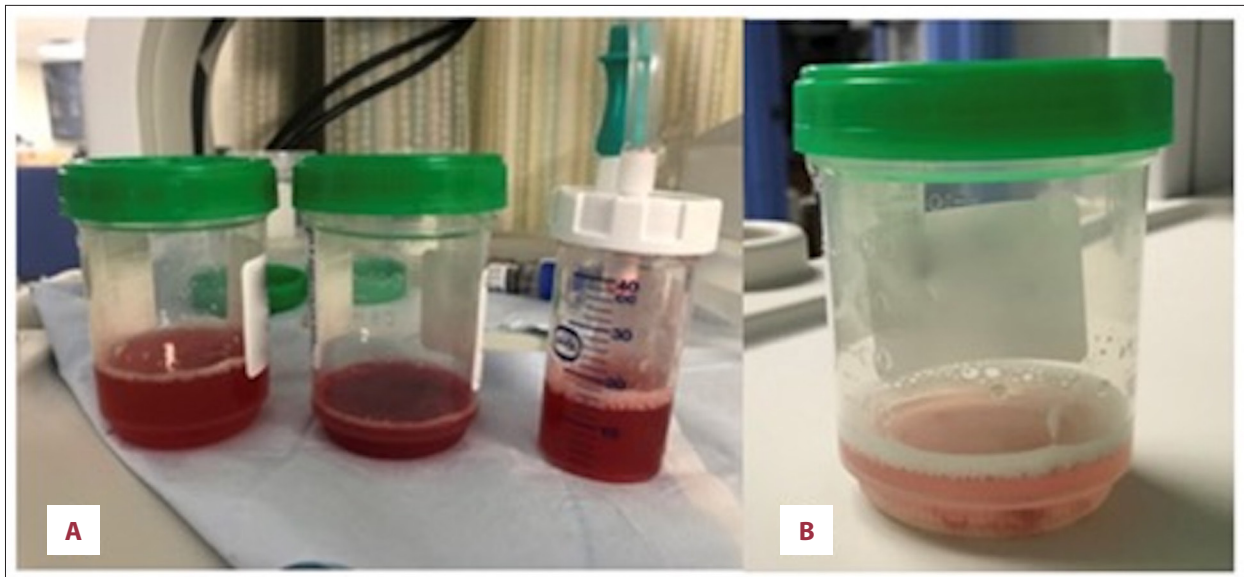


Figure 2. (A) Bronchoalveolar lavage (BAL) done with progressively bloody returns on day 2 of admission. (B) Repeat BAL done on day 5 of admission.

were lymphocytes. There were 111 250 million cells/mm³ of red blood cells. Autoimmune workup including antinuclear antibody, cytoplasmic and perinuclear antineutrophilic cytoplasmic autoantibodies, and rheumatoid factor were negative. Echocardiogram showed severe pulmonary hypertension with a pulmonary artery systolic pressure of 78 mmHg. The patient was hypoxic, with an arterial to inspired oxygen (PaO₂/FiO₂) ratio of 102 mmHg on a positive end expiratory pressure of 8 mmHg. On day 2 of admission in view of no improvement, intravenous methylprednisolone 250 mg/day was started with improvement in oxygenation by day 3 with an arterial to inspired PaO₂/FiO₂ ratio of 317 mmHg.

A repeated fiberoptic bronchoscopy done 3 days following the first revealed normal mucosa and progressively clear returns on BAL performed in the left lower lobe (Figure 2A, 2B). The patient's respiratory conditions improved with decreased oxygen requirement. She remained in septic shock and she died 2 weeks after admission.

Discussion

Diffuse alveolar hemorrhage (DAH) is a distinct syndrome of pulmonary hemorrhage resulting from disruption of the alveolar-capillary basement membrane from injury to the pulmonary microcirculation including the alveolar capillaries, arterioles, and venules [2]. It is considered a life-threatening condition with reported hospital mortality ranging from 20% to 100% [3]. A high degree of suspicion is necessary for early recognition and diagnosis, as prompt initiation of treatment is necessary for survival. DAH can present at any age, either associated

with an already established diagnosis or represent the initial presentation of a pre-existing or new systemic disease [1].

DAH is defined pathologically by the accumulation of red blood cells, fibrin, and/or hemosiderin-laden macrophages in the alveolar space on biopsy [4]. The etiology is typically divided into 3 main histologic patterns reflecting the nature of the underlying disease process. The 3 main histologic subtypes include pulmonary capillaritis, bland pulmonary hemorrhage, and diffuse alveolar damage (DAD). The causes of DAH can also be divided into infectious and non-infectious, with the later affecting immunocompetent or immunocompromised patients. In immunocompromised patients, the main infectious etiologies associated with DAH include cytomegalovirus, adenovirus, invasive aspergillosis, *Mycoplasma*, *Legionella*, and *Strongyloides*. In immunocompetent individuals, influenza A (H1N1), dengue, leptospirosis, malaria, and *Staphylococcus aureus* infection have been reported [5]. In general, pulmonary infections are rarely associated with DAH but should always be considered in the initial diagnostic workup due to high mortality associated with this condition if left untreated.

The diagnosis of DAH requires bronchoscopy with BAL showing progressively hemorrhagic returns; in addition, hemosiderin-laden macrophages can be found in the lavage [6]. Respiratory cultures provided from BAL can also be evaluated for potential infectious etiologies. Routine laboratory studies and serologic analysis for connective tissue diseases and systemic vasculitis is an essential part of the initial workup in patients diagnosed with DAH. Rarely, an open lung or surgical biopsy might be necessary if the history and laboratory investigations do not reveal a diagnosis [1]. In our case, we were presented with

an immunocompetent patient with acute hypoxic respiratory failure due to influenza A and associated DAH.

There are several diagnostic modalities that can be used for influenza A (H1N1), with real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) having the highest sensitivity and specificity [7]. Our patient was diagnosed with a Food and Drug Administration approved influenza A and B Rapid Influenza Diagnostic Test (RIDT). RIDTs are antigen-based tests used for the rapid diagnosis of influenza virus infections. These tests use monoclonal antibodies that target the viral nucleoprotein and employ either enzyme immunoassay or immunochromatographic (lateral flow) techniques. RIDTs have shown variable assay performance with sensitivities ranging between 10% to 70%, with up to 90% specificity compared to standard RT-PCR-based assays [8].

Presentations of influenza A virus infection vary from a mild upper respiratory illness to a fulminant pneumonia as was the case for our patient [9]. Clinical presentation includes an acute or subacute onset of cough, hemoptysis, and dyspnea, bilateral diffuse infiltrates of the lung, anemia, and acute respiratory failure. While hemoptysis is considered a hallmark presentation, it can be absent in up to one-third of the patients, as was the case for our patient described here. Extra-pulmonary manifestations are usually related to the underlying systemic disease. In the epidemiological data from the H1N1 2009 pandemic in the United Kingdom, several factors were associated with fulminant disease progression. These factors included age over 65 years, morbid obesity, cardiovascular disease, diabetes, chronic lung disease, metabolic disorders including diabetes mellitus, chronic renal or hepatic disease, immunosuppression, hemoglobinopathy, and a long history of smoking [10]. Our patient was 80 years old with ESRD and COPD with a 15-pack year history of smoking.

DAH represents a complication that has high mortality in patients developing influenza A viral pneumonia. In 2010, Gilbert et al. described a case of novel H1N1 influenza A viral infection associated with DAH in a patient who presented with fever and developed hemoptysis, with bilateral alveolar infiltrates on chest-x-ray [11]. As in our patient's case, this was a fatal case of influenza A (H1N1) infection despite aggressive management with mechanical ventilation, broad-spectrum antibiotics, and oseltamivir therapy. Mauad et al. reviewed the autopsy findings of 21 patients with confirmed novel human influenza A (H1N1) infection and found the presence of exudative DAD with intense alveolar hemorrhage in 5 patients of

the 21 patients. They also described an influenza virus-induced "cytokine storm" within the lungs and high circulating levels of tumor necrosis factor-alpha and interferon-gamma with viral overload leading to altered innate immune responses with a sustained increase in inflammation [12]. Another retrospective autopsy analysis of 15 fatal cases of influenza A (H1N1) infection also revealed DAD and DAD with hemorrhage [13].

Management of DAH involves aggressive supportive care and addressing the underlying systemic disease if any. In those patients with pulmonary capillaritis, the mainstay of treatment includes a combination of systemic glucocorticoids and immunosuppressive therapy, such as cyclophosphamide, rituximab, or plasmapheresis [2]. For patients with infection related DAD, treating the underlying infection is paramount. The role of steroids in the management of severe influenza A (H1N1) is less clearly defined. A meta-analysis conducted by Zhang et al. investigating the effect of steroids on hospital mortality in patients with severe influenza A (H1N1) infection suggested that corticosteroids has no beneficial effects in those patients [14]. In view of progressive respiratory deterioration, we decided to give systemic steroids to our patient with improvement in oxygenation and resolution of DAH following bronchoscopy. Several factors might have contributed to our patient's partial recovery including early administration of oseltamivir with aggressive supportive care and possibly the addition of steroids. This partial recovery was short-lived, however, as the patient succumbed to the significant burden of disease.

Conclusions

Influenza usually affects the elderly and those patients with significant co-morbidities; the same group of patients where the risk for DAH is increased. Influenza associated with DAH is a rare condition, and clinicians should maintain a high index of suspicion especially in patients with rapidly fulminant disease. We suggest early bronchoscopy with BAL as this will allow for diagnosis of DAH, as well as diagnosis of associated infections. Antiviral therapy with aggressive supportive care is paramount and could decrease mortality. The role for steroids in treating this condition is not well established, and likely has no impact on outcomes.

Conflict of interest

None.

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