Legionella pneumonia associated with severe acute respiratory distress syndrome and diffuse alveolar hemorrhage - A rare association

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ABSTRACT

Legionella pneumophila is a common, usually underreported and undiagnosed cause of community acquired pneumonia which can lead to significant morbidity and mortality. Diffuse alveolar hemorrhage rarely have been associated with legionella infection. We present a 61-year-old man with hypertension, diabetes mellitus and obesity admitted with severe acute respiratory distress syndrome. He was found to have Legionella pneumonia with associated diffuse alveolar hemorrhage diagnosed with bronchoscopic sequential bronchoalveolar lavage. He was successfully managed with antibiotics, lung protective strategies and intravenous pulse dose steroids. This patient highlights the unusual association of Legionella infection and diffuse alveolar hemorrhage. Additionally, the case re-enforces the need for early and aggressive evaluation and management of patients presenting with pneumonia and progressive hypoxia despite adequate treatment.

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1. Introduction

Legionella pneumophila, an aerobic gram-negative intracellular bacillus is a common cause of community acquired pneumonia (CAP) that can cause mild illness in 2–6% of cases [1]. Incidence of severe legionella infection leading to hospitalization is increasing in United States [2]. Eight to 20% of cases requires admission to the intensive care unit (ICU) with a case fatality rate of 5–25% in immunocompetent patients [3]. Legionella pneumophila triggers an immune-mediated reaction that can lead to severe CAP and acute respiratory distress syndrome (ARDS). Diffuse alveolar damage (DAH) in ARDS leading to direct leakage of red blood cells into alveolar spaces results in DAH which is a potentially life-threatening condition. Disorders associated with DAH are broadly divided into immune mediated and non-immune mediated. Pulmonary infections are an uncommon cause of non-immune-mediated DAH. In immunocompromised patients, the main infectious diseases associated with DAH are cytomegalovirus, adenovirus, invasive aspergillosis, mycoplasma, and strongyloides. In immunocompetent patients, Influenza A, dengue, leptospirosis, malaria, and Staphylococcus aureus are the most frequently reported infections associated with DAH [4].

2. Case presentation

A 61-year-old male was admitted to the ICU with three-day of progressive dyspnea associated with acute cough, productive of yellowish sputum and fever. He denied constitutional or gastrointestinal symptoms, chest pain, hemoptysis, exposure to birds, recent travel or sick contacts. His medical history was significant for hypertension, dyslipidemia, diabetes mellitus type 2, and obesity. Medications included olmesartan, amlodipine, hydrochlorothiazide, glyburide-metformin, pioglitazone and simvastatin. He had no surgeries and was a retired military officer. He denied smoking, use of illicit drugs and drank alcohol socially.

On presentation, the patient was in moderate to severe respiratory distress. He was febrile to 102.7 F, tachycardic with a pulse rate of 123 per/minute, tachypneic with a respiratory rate of 25 per/minute, and blood pressure of 154/74 mmHg. He was hypoxic with

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oxygen saturation of 80% on ambient air which improved to 96% with noninvasive positive pressure ventilation and FIO_2 of 0.7. Exam was significant for use of accessory respiratory muscles and bibasilar crackles. Cardiac, abdominal, neurological and skin examination were unrevealing. Initial laboratory showed leukocytosis, acute kidney injury, hyponatremia and rhabdomyolysis (See Table 1).

Initial chest radiograph (CXR) and computed tomography (CT) of the chest showed extensive left lower lobe alveolar infiltrates (Figs. 1 and 2).

Patient's clinical condition continued to deteriorate, he required intubation and mechanical ventilation on day 6 for severe ARDS (PAO_2/FIO_2 of 84). Piperacillin-tazobactim, vancomycin and azithromycin were started on admission, and Levofloxacin was added on day 5 when result for urine legionella antigen was positive. Blood and urine cultures, mycoplasma antibody and urine streptococcus pneumonia antigen were negative. He received ventilator management based on ARDSnet protocol and fluid restriction [5]. Fiberoptic bronchoscopy (FFB) with bronchoalveolar lavage (BAL) was performed to evaluate for associated infections or non-infectious process; lavage became progressively hemorrhagic, with no evidence of local bleeding. A rising RBC count in sequential BAL aliquots from same location was consistent with DAH (Fig. 3).

BAL cultures were negative for viral, mycobacterial and fungal infections, cell counts were predominant neutrophils, and cytology was negative for malignant cells. Evaluation for common causes of DAH including connective tissue diseases were performed (Table 2).

Considering severity of illness and presence of DAH, pulse steroid with one-gram methylprednisolone for three days followed by prednisone 1 mg/kg were given. Patient conditions steadily improved, with no evidence of hemoptysis or severe drop in hemoglobin. A final diagnosis of Legionella pneumonia associated with DAH and severe ARDS was made. Patient was liberated for ventilator after 7 days, antibiotics were deescalated to Levofloxacin to complete 21 days, steroids were tapered off and he was discharged home after three weeks of hospitalization.

3. Discussion

Legionellosis refers to clinical syndromes caused by bacteria of the genus Legionella. Legionnaires' disease refers to the pneumonic form of legionellosis [6]. Globally, most cases relate to *Legionella pneumophila*, with serogroup 1 being the most virulent and most common cause of legionella disease [7]. The yearly incidence is associated with climate changes, most cases been sporadic and transmitted by inhalation of aerosols, micro aspiration of contaminated water or direct contact with surgical wounds. Presentation of Legionnaires' disease ranges from mild to severe and it is characterized by an incubation period of 2—14 days and multi-systemic manifestations. Presence of gastrointestinal and neurological symptoms in patients with pneumonia suggest Legionnaires'

disease. Risk factors include chronic lung disease, smoking, old age, use of glucocorticoids, malignancies and organ transplant recipients. Radiological findings are nonspecific, with unilateral or bilateral infiltrates commonly reported [8]. First-line diagnostic test is urinary antigen while culture of the lower respiratory tract remains the gold standard [9]. Direct nucleic acid amplification by polymerase chain reaction of Legionella using respiratory, urine and serum specimens is currently the diagnostic method of choice [10]. Treatment with macrolides-azithromycin or quinolones-levofloxacin is considered highly effective and most patients respond within three days of treatment [11].

Progression of infiltrates despite appropriate therapy is common as radiographic improvement lags days behind clinical improvement. However, worsening pulmonary involvement with clinical deterioration should raise the suspicion for complications of pneumonia, associated conditions or other diagnosis.

DAH is a life-threatening condition with a mortality rate of 20—50% [12]. It is characterized by a distinct clinic-pathologic syndrome of pulmonary hemorrhage that originates from the pulmonary microcirculation leading to a clinical constellation of hemoptysis, anemia, diffuse radiographic pulmonary infiltrates, and hypoxemic respiratory failure. Constitutional symptoms like fever, chest pain, cough, and dyspnea have been reported. Hemoptysis can be absent in one-third of the patients [13].

Etiology of DAH can be divided into immune and non-immune mediated causes. Immune mediated include antineutrophilic cytoplasm associated vasculitis, connective tissue diseases (i.e. systemic lupus erythematosus, rheumatoid arthritis, inflammatory myopathies), antiphospholipid antibody syndrome, Henoch-Schonlein purpura, cryoglobulinemic vasculitis, Behcet disease, lung transplant rejection, hypocomplementemic urticarial vasculitis, drug-induced vasculitis and bone marrow transplantation. Non immune mediated causes include cardiac etiologies, medications, ARDS, idiopathic pulmonary hemosiderosis, coagulopathy, radiation and occupational exposure, crack cocaine inhalation and infectious etiologies [14].

Infectious etiologies may affect immunocompetent or immunodeficient patients [4]. The most common infections associated with DAH in immunocompetent patients are influenza A, dengue, leptospirosis, malaria, and staphylococcus aureus infections. DAH associated with Legionella have been rarely reported [15]. Risk factors for legionella in our patient was age and diabetes.

Radiological findings in DAH are nonspecific, with bilateral consolidation, ground-glass opacity or septal thickening with occasional crazy-paving pattern been the most commonly described [16,17]. This features can be indistinguible from findings in pneumonic process. Radiological distribution and temporal evolution of hemorrhage with the radiologic manifestations of underlying pulmonary disease are key features to suspect DAH [16]. DAH must be distinguished from localized pulmonary hemorrhage with diffuse aspiration of blood due to tumors or localized infections [18]. Bronchoscopy with BAL allows early diagnosis of DAH, evaluation of hemoptysis, and assist in excluding infectious or non-infectious etiologies such as alveolar proteinosis, eosinophilic pneumonias among others [19—21]. Histopathology of DAH includes presence of intra-alveolar red blood cells and fibrin, with accumulation of hemosiderin-laden macrophages, which may take 2—3 days to accumulate. One of three histologic patterns, pulmonary capillaritis, bland pulmonary hemorrhage and diffuse alveolar damage are associated with DAH with pulmonary capillaritis been the most frequently described [22]. Diffuse alveolar damage in ARDS leading to direct leakage of red blood cells into alveolar spaces is the suggested reason for DAH in legionella infection [23].

Acute management of DAH involves respiratory support, identification and correction of coagulopathy, and diagnosis and

Table 1
Pertinent laboratory parameters.

Laboratory parameters	On Admission	Day 6	On Discharge
Hemoglobin (g/dl)	10.2	9	10.9
Hematocrit (%)	31.8	29.9	33.5
White Blood Cell (WBC/ul)	18	18.5	16.5
Platelet (per/ul)	179	310	161
Sodium (mEq/L)	132	138	137
Blood Urea Nitrogen (mg/dL)	40	37	22
Creatinine (mg/dL)	1.6	1.7	1
Creatinine kinase (unit/L)	462	79	
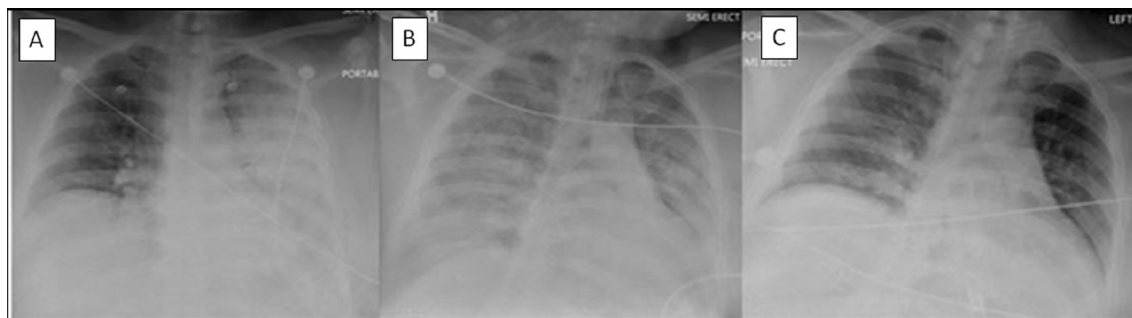
Fig. 1. Chest radiograph A/P view (A): On admission, showing left side dense infiltrate (B): Hospital day 4 showing worsening bilateral infiltrates (C): Hospital day 14 showing radiological resolution of infiltrates.
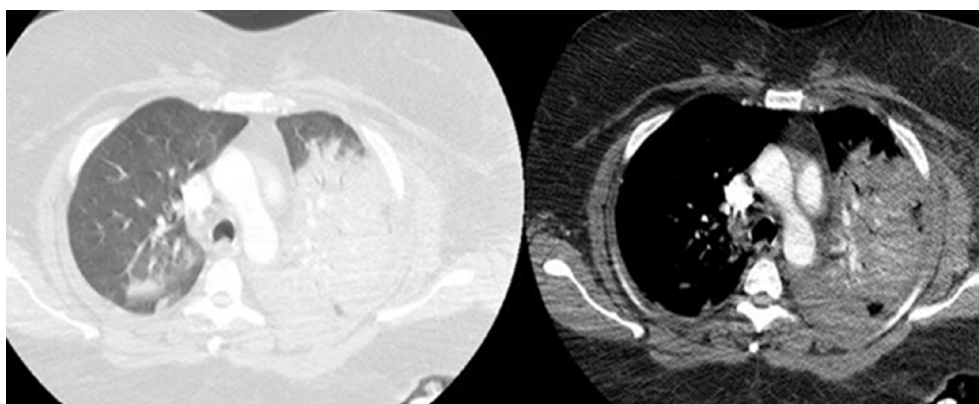
Fig. 2. Chest CT on admission showing dense consolidation in left side and mild infiltrate in right.
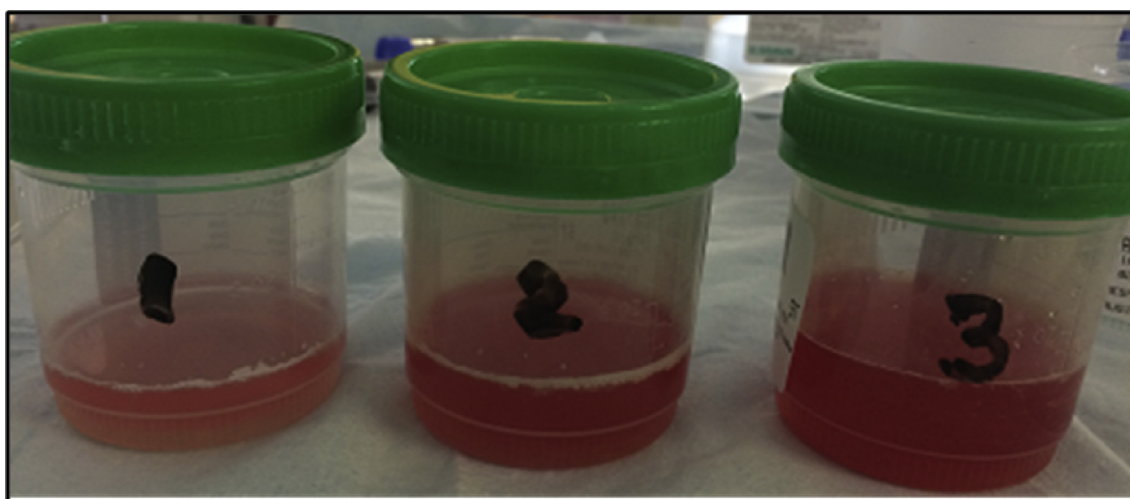
Fig. 3. FOB-BAL with sequential lavage showing progressively increasing hemorrhagic fluid.

treatment of underlying etiology. In immune-mediated cases, immunosuppressive therapy is paramount. Intravenous methyl-prednisolone up to 500 mg every 6 hours for 4−5 days is recommended by most experts, although lower doses seem to have similar efficacy, followed by a gradual taper to maintenance doses of oral steroids [24]. Based on the severity of the disease, underlying etiology and organ involvement, plasma exchange or other immunosuppressive drugs such as cyclophosphamide, azathio-prine, methotrexate, mycophenolate mofetil, etanercept may be indicated [25−27].

Treatment of non-immune mediated causes of DAH is targeted to management of the underlying etiology as immunosuppressive treatment could be deleterious [12]. Use of immunosuppressive therapy in patient with infections-related DAH should be individ-ualized and used mainly for patients receiving appropriate antibi-otics with deteriorating clinical course like our patient. We assumed that our patient developed pulmonary capillaritis due to infectious process, could not exclude infection−mediated immune

Table 2
Pertinent work up for Diffuse Alveolar Hemorrage.

Antinuclear antibody (ANA)	Negative
Anti Jo-1 antibody	Negative
Centromere antibody	Negative
Anti Ribosomal P antibody	Negative
Anti DNA antibody	Negative
Smooth muscle antibody	Negative
Anti Scleroderma 70 antibody	Negative
Myeloperoxidase	Negative
Proteinase 3 antibody	Negative
Cold Agglutinin antibody	Negative
Rheumatoid Factor	Weakly positive
Anti- Cyclic Citrullinated antibody	Negative
HIV	Negative
Mycoplasma Pneumonia antibody	Negative
Legionella antigen, urine	Positive
Blood, urine and respiratory culture	Negative
BAL cultures and acid fast bacilli stains	Negative

disorder and extrapolated data from treatment of immune-mediated DAH to offer steroid therapy.

Legionella pneumonia associated with DAH is rare, but should be considered in the diagnostic workup because of the obvious therapeutic implications. On review of the English literature, we found two cases reported of DAH due to legionella infection [15]. In our patient, we excluded other etiologies of DAH to a reasonable degree and he was treated successfully with high dose steroids and quinolones for legionella infection with favorable outcome. Immunosuppressive therapy for patients with DAH associated with infections is not well standardized and should be carefully individualized.

4. Conclusion

This case highlights the association of Legionella infection with DAH, both of which are potentially serious and occasionally fatal conditions. Clinicians caring for this patients should consider DAH in those patients with pneumonia with worsening clinic-radiological features especially if they develop anemia and or hemoptysis. Early diagnosis and intervention is vital as these patients might require high dose steroids in addition to the routine antibiotics management for favorable outcome.

Informed consent

Written consent was obtained from the next of kin for publication of this case report and accompanying images.

Competing interests

The author(s) of the manuscript declare that there is no conflict of interest regarding the publication of this paper.

Availability of data and materials

Not applicable.

Authors contributions

M K searched the literature and wrote the manuscript. GDF conceived and edited the manuscript. GDF supervised the patient treatment, critically revised and edited the manuscript. RP and BB were involved in patient care. All authors have made significant contributions to the manuscript and have reviewed it before submission. All authors have confirmed that the manuscript is not

under consideration for review at any other Journal. All authors have read and approved the final manuscript.

List of abbreviations

CAP   Community acquired pneumonia
ARDS   Acute respiratory distress syndrome
DAH   Diffuse alveolar hemorrhage
BAL   Bronchoalveolar lavage

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