Acute Respiratory Failure in Melioidosis

S D Puthucheary, J Vadivelu, K T Wong, G S Y Ong

ABSTRACT

Background: In melioidosis caused by *Burkholderia pseudomallei*, although every organ in the body may be involved, the highest mortality of 73% occurs when the respiratory system is affected. These patients invariably die of acute respiratory failure. Most of them also have underlying predisposing factors like diabetes mellitus.

Aim of Study: A retrospective study of six such cases was carried out in order to elicit the possible causes and mechanisms of acute respiratory failure in patients with melioidosis.

Method: Patients' records were reviewed for demographic, clinical, laboratory, radiological and histopathological data.

Results: The rapidity of onset of respiratory failure was remarkable and was accompanied by relentless hypoxaemia that was refractory to treatment despite the application of high positive end expiratory pressure and other supportive measures. All had bilateral opacities on frontal chest radiographs, focal and diffuse necrotizing pneumonia and presence of hyaline membranes in lung tissues seen histologically, supporting the accepted criteria for ALI/ARDS.

Conclusion: Patients with sepsis due to *B. pseudomallei* develop ALI/ARDS very rapidly resulting in high mortality rates. Possible mechanisms involved are discussed. Awareness of the disease in endemic areas, the development of rapid diagnostic methods and appropriate management procedures are urgently needed for the prevention of ARDS and subsequent reduction in mortality in such cases.

Keywords: melioidosis, acute lung injury, acute respiratory syndrome

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INTRODUCTION

Melioidosis, a potentially serious infection caused by a gram negative bacillus *Burkholderia pseudomallei* is endemic in Southeast Asia and Tropical Australia. The clinical manifestations demonstrate a wide spectrum of symptoms and signs and every organ in the body may be involved. In Malaysia 46% of 50 septicaemic patients with melioidosis had "pneumonia"[1] and the mortality rate was 73% in these patients compared to an overall mortality of 60%. All these patients with pulmonary involvement died of acute respiratory failure.

The clinical syndrome of acute respiratory failure due to non-cardiogenic pulmonary oedema can result from a host of insults, such as the sepsis syndrome, pulmonary aspiration, disseminated vascular coagulation, severe pneumonia, bacteraemia, long bone or pelvic fractures, hyper transfusions and others[2]. The acute changes seen may include abnormal water or solute accumulation in the air spaces, cellular damage and necrosis in the lung parenchyma thus giving rise to abnormal pulmonary gas exchange and ventilation. In addition, with increasing lung injury there will be an increasing severity of abnormality with the development of progressive hypoxaemia refractory to treatment. The clinical manifestation of this late stage is the Acute Respiratory Distress Syndrome (ARDS) whilst the early stage is generally recognised as Acute Lung Injury (ALI), but a clinical continuum is usually recognised between the early and late stages[3].

The most lethal and most common cause of ARDS is the sepsis syndrome and the time frame for its development can be as little as six hours and in most patients studied, was within 24 hours[4]. Overall mortality from ARDS is reported to be greater than 50%, with most deaths resulting from the underlying predisposing illness, sepsis or multi-organ dysfunction[2]. ARDS can be defined as a triad consisting of radiologic bilateral pulmonary infiltrates, hypoxaemia and decreased compliance. More recently, the American-European Consensus Conference[5] established the definition of ARDS as consisting of (a) Oxygenation: $Pa0_2/ Fi0_2 \leq 200$ mmHg (regardless of positive end-expiratory pressure level); (b) Chest radiograph: bilateral infiltration seen on frontal radiograph; and (c) Pulmonary artery occlusion pressure: ≤ 18 mmHg when measured or no clinical evidence of atrial

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Table I. Summary of findings in 6 fatal cases of melioidosis with acute respiratory failure.

Case No	Age/ Sex	Clinical Presentation	Past History	Chest X-ray *P/F ratio	Lung Pathology
1	61F	Fever, chills 3d; Delirium ld. Progressive dysphagia and weight loss 2mths	Diabetes mellitus	Bilateral opacities	R lung = 600g L lung = 430g
		Temp. 39°C Pulse 160/min BP l00/60 mmHg Respiratory rate 40/min TWBC 2500/ml		P/F - NA	Multiple areas of consolidation.
		Remained hypoxic with pneumonia. Died 12hrs after admission			Extensive, focal necrotising pneumonia No hyaline membranes. Focal granulomatous inflammation
2	68M	Breathlessness ld.	Epididymo-orchitis 2mths ago.	Gross bilateral opacities	R lung= l000g L lung = 1060g
		Temp 38°C Pulse 105/min BP 103/84 mmHg TWBC 37,200/ml	Cotri-moxazole 6wks.	P/F - NA	Patchy consolidation, oedema and congestion.
		Confused, developed skin rashes with blisters. Became hypoxic Died 17hrs after admission.	Right hemipareisis (meningioma)		Focal and diffuse necrotising pneumonia. No hyaline membranes
3	39M	Fever, cough 4d. Breathlessness ld. Temp 37.5°C Pulse 119/min B/P 112/59 TWBC 8,700/ml	Alcoholic, cigarette smoker	Bilateral opacities P/F - 50	R lung = 580g L lung = 1460g Consolidation with severe congestion
		Hypoxic, collapsed and resuscitated PCWP 17mmHg Died l0hrs after admission			Focal and diffuse necrotising pneumonia Only a focus of hyaline membrane present in the non-involved lung area.
4	18F	Fever and joint pains 3wks	Nil	Bilateral opacities	R lung = 580g L lung = 330g
		Temp 39°C Pulse 90/min BP 120/80mmHg TWBC 10,000/ml		P/F - 106	Patchy consolidation and abscesses
		Acutely ill, delirious. Developed pneumonia. Died 30hrs after admission			Diffuse necrotising pneumonia. Mild evidence of diffuse alveolar damage with scattered hyaline membranes.
5	36M	Fever, chills and rigors 4d. Breathlessness ld. Temp 37°C Pulse 120/min BP 106/70mmHg TWBC 18,000/ml Acute respiratory distress, hypoxic Died 6hrs after admission	Diabetes mellitus Abscess in R chest wall, wound not healing despite incision & drainage and ampicillin and gentamicin	Bilateral opacities P/F - 110	R lung = 1350g L lung= 1200g. Multiple yellowish "miliary" nodules and abscesses. Extensive focal necrotising pneumonia, no hyaline membranes noted.
6	l9F	Fever lwk Septic arthritis ld. Temp 39.6°C Pulse 100/min BP 100/60mmHg TWBC 16,000/ml	Diabetes mellitus llyrs	Bilateral opacities P/F - 50	R lung = 920g L lung = 800g. Several nodular areas of consolidation and oedema. Extensive "miliary" abscesses, necrotising pneumonia. Extensive hyaline membranes and fibrin thrombi.
		Developed acute renal failure, refractory hypoxia. Multiple organ dysfunction. Died 30hrs post- ventilation and 72hrs after admission.			

*P/F = $Pa0_2/Fi0_2$ = Ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen
NA = not available

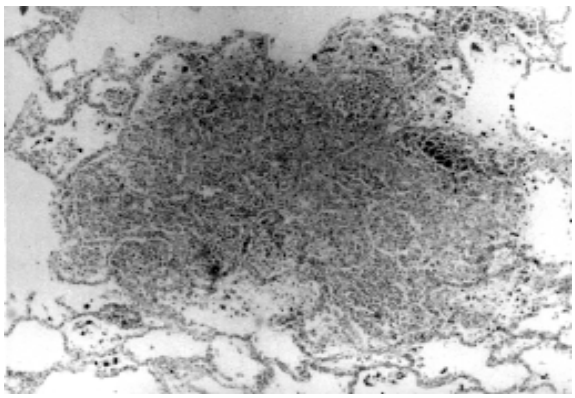

Fig. 1 Focal necrotising inflammation in the lung. (H&E, X40 magnification).

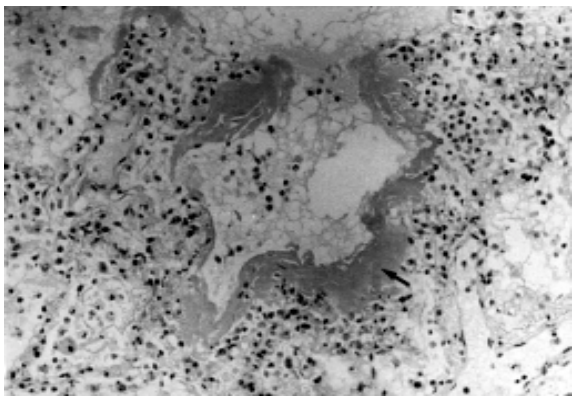

Fig. 2 Hyaline membrane formation (arrowed) in inflamed lung. (case # 6. H&E, X200 magnification).

hypertension. The criteria for acute lung injury is similar except that the $Pa0_2$ / $Fi0_2$ ratio is equal to or less than 300 mmHg.

This report is a retrospective study of six melioidosis patients who died of acute respiratory failure and were autopsied. Patients' records were reviewed for demographic, clinical, laboratory, radiological and histopathological data in order to elicit the possible causes and mechanisms of acute respiratory failure in patients with melioidosis.

CASE HISTORIES

Table I summarises the relevant data of the six cases with blood cultures taken ante-mortem being positive for *B. pseudomallei*, thereby confirming the diagnosis of septicaemic melioidosis. There were three males and three females with two being young patients in the 2nd decade, two in the 4th and two in the 7th decades of life.

Fever, chills and signs and symptoms relevant to the respiratory system were the predominant presenting features. The most common physical findings were pyrexia, tachypnoea and tachycardia. All were given ventilatory support and nursed in the intensive care unit. All six patients were given empirical antibiotic therapy and only one patient (case # 2) was given specific anti-melioidosis therapy as the diagnosis here was known before death. Sudden cardiac arrest with hypoxia occurred in four patients in the ward and in one at the emergency unit. The hypoxaemia was refractory to treatment, despite the application of high positive end expiratory pressure.

Four patients died within six and 17 hours of admission to hospital. Patient number # 4 passed away 30 hours after hospitalisation and although patient number # 6 had been in the ward for three days, *B. pseudomallei* was identified from the blood cultures only after the patient passed away.

At autopsy, multiple organ involvement was observed in all six cases, the most common being the lungs, liver and spleen where acute necrotising inflammation was generally observed. *B. pseudomallei* was demonstrated both intra- and extracellularly by gram stain and by immunohistochemistry[6,7]. Discrete granulomas were found in the lungs only in case # 2 as described previously[6]. Evidence of hyaline membranes in the lungs were found in three of these cases (Table I: cases # 3, # 4, # 6), the most unequivocal case of ARDS being case # 6 in which hyaline membranes were found extensively (Fig. 1 & 2). The following is a more detailed report of cases # 4 and # 6.

Case # 4.

An 18-year-old Indian female was admitted on 27th September 1990 with a one month history of fever and joint pains. The fever was continuous and associated with a headache. The joint pains initially involved the left wrist and both knees and subsequently the small joints were affected but there was no swelling or hyperaemia. At the same time, she also developed a dry and unproductive cough.

Previously, she had been admitted to a district hospital and a diagnosis of rheumatoid arthritis was made as the rheumatoid factor was positive with an ESR of 94mm/hr. Aspirin therapy had relieved her symptoms and she was discharged after 10 days. The fever and joint pains recurred within a few days and she sought admission to the University Hospital. Clinically, she was febrile with a temperature of 40°C. Crepitations were heard over the infrascapular region of the right lung and X-ray revealed a consolidation of the right lower zone. Crystalline penicillin was administered to which she responded and became afebrile after 24 hours. But then she complained of severe epigastric pain associated with diarrhoea. The abdomen was soft on palpation with mild tenderness over the epigastrium. Pulse and blood pressure were normal. But two hours later she suffered a sudden cardiopulmonary arrest and resuscitation was instituted immediately. Arterial blood gas analysis revealed severe metabolic acidosis. $Pa0_2$ was 106 mmHg, $PaC0_2$

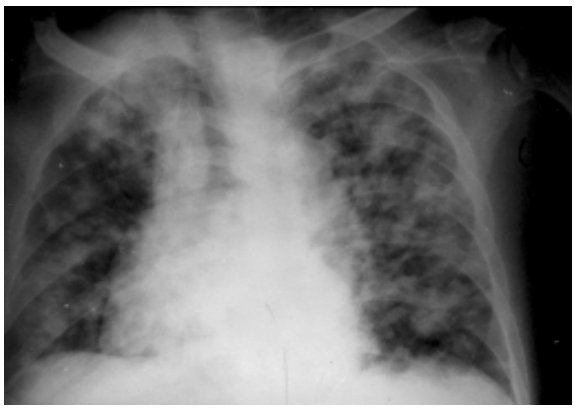

Fig. 3 Chest radiograph showing extensive bilateral opacities in case # 6.

33 mmHg on an inspired oxygen concentration of 100%. Serum potassium was 4.1 mmol/L, sodium 134 mmol/L and urea 6.7 mmol/L. An electrocardiograph taken during resuscitation showed small complexes with no changes suggestive of a pulmonary embolus. An effective cardiac output could not be obtained and she was declared dead after an hour of resuscitation.

Ante-mortem blood cultures were identified as positive only after the patient passed away, as were post-mortem cultures of the spleen and the lungs. The autopsy revealed bilateral pleural effusion and mild ascites. The right lung showed patchy consolidation. Abscesses were found in the lungs, liver and spleen. All other organs including the kidneys, adrenals and intestines were uninvolved.

Case # 6

A 19-year-old girl was admitted to the hospital on 17th January 1996 with a one week history of fever and pain over the right knee. She had a medical history of diabetes mellitus for 11 years and was on oral hypoglycaemics. On examination, she was febrile, temperature of 39.6°C and the right knee was tender with a firm rounded mass over the anterolateral aspect. X-ray revealed a soft tissue mass over the lateral condyle and a diagnosis of septic arthritis was made. A septic workup was performed and she was given cefuroxime 750 mg tds but continued to be febrile.

On the third day of hospitalisation she complained of chest discomfort and subsequently became acutely breathless and cyanosed with a pulse oximetry reading of 50%. Crepitations were heard over both lungs and X-ray showed bilateral opacifications (Fig. 3). Investigations revealed severe hypoxaemia and hypocarbia. Serum creatinine 380 mmol/L, urea 26.1 mmol/L, serum sodium 123 mmol/L and serum potassium was 3.6 mmol/L.

She was transferred to the intensive care unit where ventilatory support was given for acute respiratory failure with a high oxygen concentration and application of high positive end expiratory pressure. An electrocardiogram showed sinus tachycardia and echocardiography revealed impaired left ventricular function. Right heart chambers were not dilated. There was no evidence of pulmonary embolism. Cardiac impairment was consistent with severe septicaemia. Ionotropic circulatory support was instituted and cefuroxime was replaced with ceftazidime and cloxacillin. The next day pustules appeared over the right knee, she became hypotensive (BP 70/30 mmHg), pulse rate of 137/min and renal impairment was also noted. Air entry was equal over both lungs but the volume was greatly reduced. She remained hypoxaemic which was followed by bradycardia. She then went into asystole and could not be resuscitated.

Blood cultures and tracheal secretions were identified as positive only after the patient passed away. Swabs of lung abscess taken at post-mortem were also positive. At autopsy tiny skin pustules were noted over the chest and abdomen. There were small nodular abscesses on the external and cut surfaces of the lungs. In the abdominal cavity there was evidence of ascites and the liver and spleen were enlarged although no nodular abscesses were seen macroscopically. All other organs were normal.

DISCUSSION

Pathophysiologically ALI/ARDS can be described as "acute non-cardiogenic oedematous lung injury"[8]. The pathogenesis of ALI/ARDS is probably multifactorial but neutrophil priming and recruitment by the activation of the alternate complement pathway as well as the release of various cytokines may play an important role in causing lung damage. The release of chemotactic agents such as C5a, a by-product of complement and leukotriene B_4 (LTB_4) from the lung cells themselves or from cells in other remote sites, may be stimulated by bacterial endotoxins and exotoxins as well as by other endogenous chemical mediators[9,10]. These include various cytokines such as tumour necrosis factor (TNF), IL-1, IL-6, IL-8 and adhesion molecules such as ICAM-1[11]. All these factors may lead to the release of oxygen radicals and elastase by activated neutrophils which produce damage and fluid leakage in the lungs; thus, playing a role in the pathophysiology of acute respiratory failure especially in gram-negative sepsis.

However, this does not explain the rapidity of the onset and progression of respiratory failure in patients with melioidosis. *B. pseudomallei* is known to be an intracellular organism that can give rise to latent or dormant infection[12]. Any immunosuppressive predisposing factor, especially undiagnosed or uncontrolled diabetes mellitus may trigger the rapid multiplication of these intracellular organisms giving rise to fulminant sepsis. Further, it is not possible to

diagnose melioidosis clinically and hence appropriate empirical antibiotic therapy may not have been administered, thus leading to fulminant sepsis. This triggers off a series of immunological events which give rise to the release of neutrophil, resulting in endothelial dysfunction and its sequalae of acute respiratory failure.

From a pathological perspective, all the six cases presented here appeared to have lung changes which could account for acute respiratory failure. All of them had histological evidence of either focal and/or diffuse pneumonia which appeared to have affected the lungs to such an extent as to interfere with gaseous exchange resulting in acute respiratory failure. Over and above this, in one case (# 6) there appeared to be pathological evidence of a full blown ARDS as well (Fig. 2). The lungs showed extensive hyaline membrane formation and the lung weights were increased. In two other cases (# 3 and # 4), scattered hyaline membranes were found which may suggest early ARDS but the pathological evidence is less certain particularly in the absence of lung weight increase bilaterally.

In cases # 1 and # 2, although the PF ratio was unavailable, radiologically there were bilateral opacities as well as histological evidence of consolidation and extensive necrotising pneumonia in case # 1 and focal and diffuse necrotising pneumonia in case # 2 together with hypoxaemia suggesting acute lung injury. Case # 5 was similar to cases # 1 and # 2 but in addition had a PF ratio of 110 which suggested the possibility of early ARDS. The absence of hyaline membranes does not exclude a diagnosis of ARDS as these membranes have been reported to appear several days after the appearance of the protein rich oedema[13]. In addition, based on both clinical presentation and pathophysiologic changes, all our six cases fulfilled the criteria used in clinical trials in ARDS[14]. All six patients had multi-organ involvement with evidence of necrotising inflammation and although all died of acute respiratory failure, the contribution of multiorgan failure as a determinant of the ultimate outcome must not be underestimated[13].

It has been well established that ARDS can occur as a secondary outcome of bacterial sepsis. However, in our experience, it has been found that patients with sepsis due to *Burkholderia pseudomallei* develop ALI/ ARDS more rapidly than in patients with sepsis caused by other known bacteria. It may be hypothesised that this rapidity of onset of acute respiratory failure may possibly be due to the sequestration and activation of the infected polymorphonuclear leucocytes in the lungs, with the release of the bacteria together with toxic oxygen radicals and other cellular products leading to massive endothelial damage and lung injury. Hence, this substantiates the need for, increased awareness of melioidosis in endemic areas, rapid diagnostic procedures and a well-designed management approach in order to reduce the development of ARDS and subsequent death in patients with melioidosis.

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