CLINICAL MANIFESTATION OF PULMONARY MELIOIDOSIS IN ADULTS

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Abstract. Between 1996 and 2002, 162 cases of pulmonary melioidosis were reported from Srinagarind Hospital, Khon Kaen, northeast Thailand, 90 acute *vs* 72 subacute/chronic. Patients averaged 50 years of age and half worked as farmers. The male to female ratio was between 2 and 3 to 1 depending on the subgrouping. *Burkholderia pseudomallei* was confirmed by a culture or a four-fold rise in titer in the majority of cases, while the others were presumptive diagnoses based on response to treatment. Pulmonary melioidosis presented as either acute fulminant pneumonia or as an indolent disease. The common concurrent medical illness was diabetes mellitus. Mean incubation of the acute *vs* the subacute/chronic form was 8.7 *vs* 54.4 days, respectively. Leukocytosis was detected in 70% of cases. Sputum Gram's stain was not sensitive for diagnosis. Sputum culture and blood culture were diagnostic for 31.1 *vs* 22.2 and 40 *vs* 37.5% of the acute *vs* subacute/chronic forms, respectively. The common radiographic patterns for acute pneumonia were localized patchy alveolar infiltrate or hematogenous pattern. A bilateral diffuse patchy alveolar infiltration or multiple nodular lesions characterized the latter. Upper-lobe involvement with early cavitation and rapid progression were common. In the subacute/chronic forms, the radiographic pattern sometimes mimicked tuberculosis, with upper lobe involvement, patchy alveolar infiltrate with cavities or fibroreticular lesions. In ~30% of cases, liver and/or splenic abscess were common sites of extrapulmonary infection. Respiratory failure and septic shock from acute pulmonary melioidosis was 20% fatal. Early empirical antibiotic therapy should be given for severe pneumonia.

INTRODUCTION

Melioidosis is an infectious disease caused by the gram-negative bacterium, *Burkholderia pseudomallei*. It is endemic in northeast Thailand and contiguous areas (Punyagupta, 1983; Chaowagul *et al*, 1989; Maneechotesuwan, 1999). The clinical presentations range from localized infection to fulminant septicemia. The lung is the most common organ involved (~48% of cases) (Chaowagul *et al*, 1994). Patients with septicemic melioidosis often deteriorate rapidly, death occurring within days despite hospitalization. Rapid diagnosis and prompt treatment with appropriate antibiotics can reduce mortality by half (White *et al*, 1989). Clinical presentation of pulmonary melioidosis may be acute, subacute, or chronic. The acute form may mimic acute bacterial pneumonia, while the subacute/chronic form may mimic pulmonary tuberculosis, making differentiation difficult. The objective of this study was to define the clinical features, initial laboratory finding, and outcomes of pulmonary melioidosis.

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MATERIALS AND METHODS

A cross-sectional study was conducted between January 1, 1996 and December 31, 2002 at Srinagarind (university) Hospital, Khon Kaen University, Khon Kaen, northeast Thailand. Patients aged 15 years or older with pulmonary melioidosis were included. All of them had signs and symptoms of lower respiratory tract infection: fever, cough (with or without sputum production), dyspnea, pleuritic chest pain, and consolidation or crackles on physical examination. Chest radiographs showed new infiltrates or abnormal findings. Definitive diagnosis was achieved by isolation of the organism from blood, sputum, pleural fluid samples or sterile sites, or by a four-fold rise in melioid titer. Probable diagnosis was indicated by clinicals and chest radiographs and did not respond to conventional antimicrobial agents,

but did respond to high-dose ceftazidime ± cotrimoxazole.

Charts of patients diagnosed with melioidosis were retrieved and reviewed. Patients meeting the above criteria were included in the study, then categorized according to the duration of their symptoms to one of two major clinical forms; acute (≤14 days) or subacute/chronic (>14 days). Data collected included demographics, incubation period, underlying disease(s), severity of illness, complete blood count, result of sputum staining (Gram's), chest x-ray findings, results of sputum and blood cultures, abdominal ultrasound findings, serum melioid titer, clinical complications, morbidity and mortality, and length of hospitalization. Severe pneumonia was defined by the presence of either one of two major criteria (*ie* need for mechanical ventilation, or septic shock) or two of three minor criteria (*ie* systolic blood pressure <90 mmHg, multilobar involvement, or Pao_2/FIo_2<250).

Ethics

The Ethics Committee of the Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand approved the study protocols.

Statistical analysis

Descriptive statistics were used to describe the data. Means and standard deviations were calculated for the continuous data; number and percentage for the categorical data.

RESULTS

Over the seven-year study, 162 patients were diagnosed with pulmonary melioidosis and of these, 90 were acute and 72 were subacute/chronic. Definitive diagnosis of pulmonary melioidosis was made in 68 of 90 acute and 57 of 72 subacute/chronic cases. Probable pulmonary melioidosis was suspected in 22 acute, and 15 subacute/chronic, cases. The mean age of patients with the acute form was 54.3 (SD=13.4) years, the male**:**female ratio 3.1:1. The mean age of those suffering the subacute/chronic form was 52.2 (SD=10.7) years, the male**:**female ratio 2.3:1 The duration of symptoms before presentation was about one week *vs* two months for the acute *vs* subacute/chronic forms, respectively. Half the patients were farmers, and diabetes mellitus was the most common underlying disease (Table 1).

Table 1
Characteristics of patients with pulmonary melioidosis.

Characteristic	Acute N = 90	Subacute or chronic N = 72
Age, years (mean, SD)	54.3 (13.4)	52.2 (10.7)
Male:female ratio	3.1: 1	2.3: 1
Incubation, days (mean, SD)	8.7 (4.1)	54.4 (49.5)
Farmer occupation (%)	52.2	56.9
Underlying diseases (%)[a]		
Normal	31.1	43.1
Diabetes mellitus	44.4	47.2
Chronic renal failure or renal stone	12.2	5.6
Hematologic diseases	5.6	2.8
Connective tissue diseases	6.7	1.4
Chronic liver diseases	3.3	2.8
Old pulmonary tuberculosis	2.2	2.8
Nephrotic syndrome	1.1	1.4
HIV	1.1	0

[a]Some patients had more than one underlying disease

Table 2
Laboratory results.

Analysis	Acute N = 90	Subacute/ chronic N = 72
Complete blood count n (%)		
White blood cells >10,000 cells/mm^3	65 (72.2)	50 (69.4)
Polymorphonuclear cells >80%	49 (54.4)	35 (48.6)
Sputum Gram's stain n (%)		
Inadequate sputum	7 (7.8)	7 (9.7)
No organism	6 (6.7)	5 (6.9)
Gram-positive diplococci	10 (11.1)	4 (5.6)
Gram-positive cocci	4 (4.4)	1 (1.4)
Gram-negative bacilli	12 (13.3)	4 (5.6)
Gram-negative safety pin	1 (1.1)	2 (2.8)
Gram-negative cocci	2 (2.2)	1 (1.4)
Pleomorphic mixed organism	4 (4.4)	0 (0)
Positive sputum culture n (%)	28 (31.1)	16 (22.2)
Positive blood culture n (%)	36 (40.0)	27 (37.5)

Complete blood count, sputum Gram's stain, and chest radiographs comprised the initial laboratory investigations. Seventy percent of the pa-

Table 3
Chest x-ray.

Initial chest x-rays n (%)	Acute N = 90	Subacute/ chronic N = 72
Localized patchy alveolar infiltration	27 (30.0)	27 (37.5)
Upper lobe	8 (8.9)	14 (19.4)
Other location	19 (21.1)	13 (18.1)
Cavitary lesion	7 (7.8)	5 (6.9)
Atelectasis	0 (0)	4 (5.5)
Calcified node	0 (0)	1 (1.4)
Hilar adenopathy	0 (0)	4 (5.6)
Lobar infiltration	3 (3.3)	1 (1.4)
Multilobar infiltration	8 (8.9)	5 (6.9)
Fibroreticular infiltration	5 (5.6)	11 (15.3)
Localized	3 (3.3)	3 (4.2)
Both upper lobes	1 (1.1)	3 (4.2)
Diffuse	1 (1.1)	5 (6.9)
Bilateral diffuse patchy alveolar infiltration	15 (16.7)	5 (6.9)
Bilateral multiple nodular lesions	10 (11.1)	3 (4.2)
Other		
Lung abscess	2 (2.2)	5 (6.9)
Mass-like lesion or pulmonary nodule	1 (1.1)	6 (8.3)
Interstitial infiltration	4 (4.4)	3 (4.2)
Miliary pattern	1 (1.1)	1 (1.4)
Pleural effusion	11 (12.2)	11 (15.3)
Hydropneumothorax	1 (1.1)	2 (2.8)
Pneumothorax	0 (0)	1 (1.4)
Pericardial effusion	0 (0)	2 (2.8)

Table 4
Outcome of hospitalized patients.

Outcome	Acute N = 83	Subacute or chronic N = 64
Mortality rate, n (%)	18 (21.7)	5 (7.8)
Hospital stay, days (mean, SD)	17.5 (10.4)	18.6 (12.8)
Complication, n (%)		
Extrapulmonary infection	29 (34.9)	24 (37.5)
Septic shook	22 (26.5)	10 (15.6)
Respiratory failure	26 (31.3)	7 (10.9)
Acute renal failure	7 (8.4)	8 (12.5)
Parapneumonic effusion or empyema thorasis	9 (10.8)	8 (12.5)
Pneumothorax	1 (1.2)	1 (1.6)
SVC obstruction	0 (0)	1 (1.6)

tients had total white blood cell counts >10,000 cells/mm^3 (Table 2). Initial sputum could be collected for examination in 46 of 90 (51.1%) *vs* 24 of 72 (33.3%), acute *vs* subacute/chronic pneumonia patients, respectively. The gram-negative 'safety pin', the specific cue for diagnosis of melioidosis, was found in only one case *vs* two cases of the acute *vs* subacute/chronic forms, respectively. Gram-negative rods were found in 12 and 4 cases of the acute and subacute/chronic forms, respectively. Initial sputum examination had a high degree of variation (Table 2).

Results of the initial chest radiographs are presented in Table 3. In acute pneumonia, the prominent findings were localized patchy alveolar infiltrate (30%), commonly localized in the upper lobe (Fig 1). A quarter of such lesions had cavities. Bilateral diffuse patchy alveolar infiltration (Fig 2) or bilateral multiple nodular lesions (Fig 3), which favor blood-borne pneumonia, were the next most common finding. In some patients, the disease progressed within 24 to 48 hours, forming localized patchy infiltrate to bilateral diffuse patchy alveolar infiltrate.

In patients with subacute/chronic disease, localized patchy alveolar infiltrate was also a prominent finding (37.5%), commonly localized in the right upper lobe. Concomitant findings included cavities, atelectasis, hilar adenopathy, and calcified nodes. Fibroreticular infiltration was the next most common finding (Fig 4), distributed in the upper lobe or as diffuse lesions. Other patterns of chest radiographs in subacute/chronic forms included lung abscess, a mass-like lesion or pulmonary nodule, interstitial infiltration, and miliary pattern. Some patients who recovered from melioidosis had fibrotic lesions (Fig 5) or calcified nodes.

Isolate pleural effusion or minimal infiltrate with pleural effusion (Fig 6) occurred in 12.2 *vs* 15.3% of the acute *vs* subacute/chronic forms, respectively. Most had pleural effusion with neutrophilic exudative profile, especially in the acute form. Pericardial effusion was rare, but could occur in the subacute/chronic form.

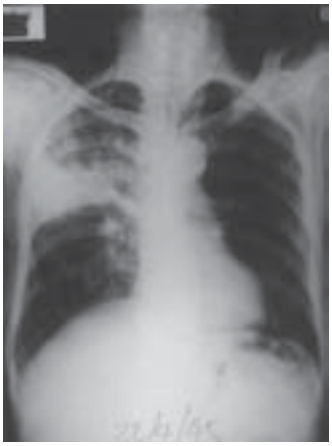


Fig 1–Localized patchy alveolar infiltration in the right upper lobe.

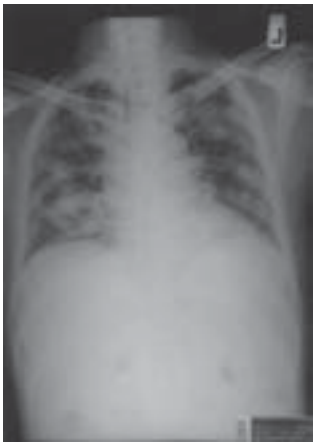


Fig 2–Bilateral diffuse patchy alveolar infiltration.

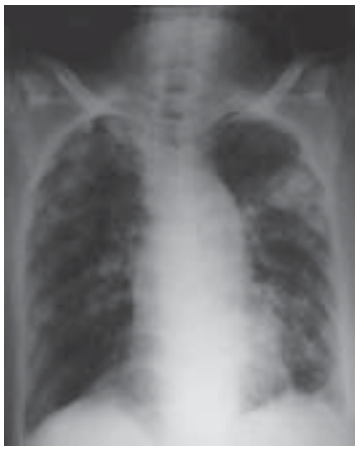


Fig 3–Bilateral multiple nodular lesions.

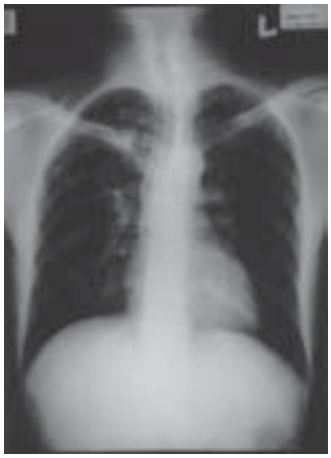


Fig 4–Fibroreticular infiltration in both upper lobes.

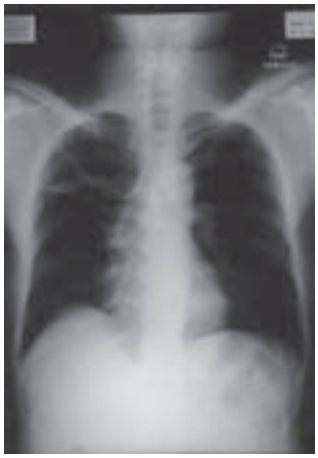
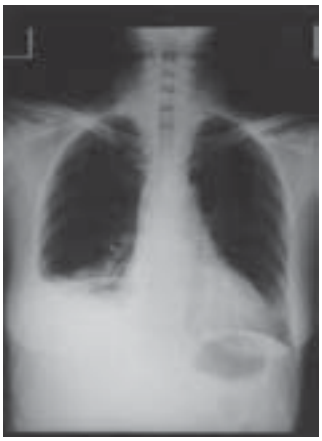


Fig 5–Fibrotic lesions in the right upper lobe.



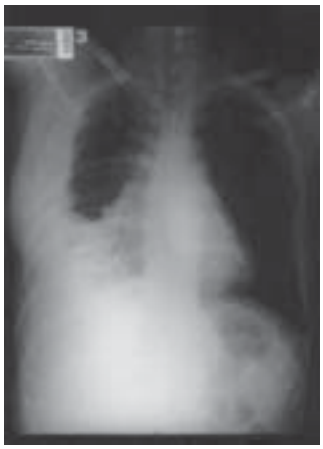


Fig 6–Patchy alveolar infiltration in the right lower lung with right pleural effusion. (CXR PA view and right lateral decubitus view).

The liver and spleen were common sites of extrapulmonary infection. Ultrasonography of the abdomen should be performed, especially for patients presenting with jaundice or having elevated levels of alkaline phosphates. In this study, liver and/or splenic abscess was found in 16 of 54 (29.6%) *vs* 17 of 48 (35.4%) acute *vs* subacute/chronic infections, respectively.

Single initial serology for melioidosis by indirect hemagglutination antibody (IHA), varied between 1:40 and 1:10,240. A high titer ≥1:160 was found in 33 of 90 (36.7%) *vs* 33 of 72 (45.8%) acute *vs* subacute/chronic pneumonias. A four-fold rise in the titer of paired sera should be used for diagnosis of melioidosis. Definitive diagnosis of melioidosis was made by isolation of *B. pseudomallei* from a variety of clinical specimens. In this study, 31.1% of patients with acute pneumonia had a positive sputum culture and 40% a positive blood culture, whereas 22.2% of patients with subacute/chronic pneumonia had a positive sputum

culture and 37.5% a positive blood culture (Table 2). Initial empirical antibiotics were recommended before definitive laboratory findings were available, especially in cases of acute, severe pneumonia. All isolates of *B. pseudomallei* were susceptible to ceftazidime, cotrimoxazole, chloramphenicol, and sulperazon.

Eighty-three of the patients with acute pneumonia, and 64 of those with subacute/chronic pneumonia were hospitalized. Mortality from acute infection was greater than the subacute/chronic form; 21.7 *vs* 7.8% for the acute *vs* the subacute/chronic forms (Table 4). More than 40% (36 of 83 cases) who presented with acute pneumonia met the criteria for severe pneumonia. The mean hospital stay for patients with acute *vs* subacute/chronic pneumonia was 17.5 *vs* 18.6 days, respectively. Rapid deterioration from a severe infection or prolonged hospitalization due to complications was common among sufferers of acute pneumonia. Septic shock and acute respiratory failure were major complications leading to morbidity and mortality. Extrapulmonary infection was found in one-third of these infections, occurring at the liver, spleen, joints, skin, central nervous system, and pericardium.

DISCUSSION

A specific diagnosis of melioidosis requires awareness of the clinical presentation and a laboratory capable of isolating *B. pseudomallei* from clinical specimens. The problem for clinicians is the wide spectrum of manifestation. The lung was involved in half of the cases (Chaowagul *et al*, 1994; Currie *et al*, 2000).

The mean age of the patients with pulmonary melioidosis was about fifty. Incidence in males was two to three times greater than females. Farming was by far the most common occupation (Leelarasamee *et al*, 1989) suggesting that frequent exposure to soil and water contaminated by *B. pseudomallei* was the primary risk factor (Vuddhakul et al, 1999). Nearly half of the patients had underlying diabetes mellitus, which was confirmed the significant factor for melioidosis and bacteremic melioidosis (Suputtamongkol *et al*, 1999).

Fifty-five percent (90/162) pulmonary melioidosis cases presented with acute pneumonia. The mortality rate in this group was high, especially in cases with rapid progression of disease or severe pneumonia at initial presentation. In this study, 40% of acute pneumonia cases from *B. pseudomallei* presented with severe pneumonia. Acute respiratory failure and septic shock were the two major complications needing intensive care (Puthucheary *et al*, 2001). Initial sputum Gram's stain was not sensitive for diagnosis. Leukocytosis was detected in 70% of patients. The chest radiographic appearances on admission were usually localized patchy alveolar infiltrate or a hematogenous pattern (Dhiensiri *et al*, 1988). Upper-lobe involvement with early cavitation and rapid progression were common. Bilateral diffuse patchy infiltration or multiple nodular lesion were the appearance of hematogenous pattern. The differentiation of blood-borne pneumonia from staphylococcal infection was a less frequent cause of pleural effusion, and no pneumatoceles were seen in melioidosis. Ultrasound of the abdomen in patients with jaundice or elevated alkaline phosphates aided diagnosis, if liver and/or splenic abscesses were present : multiple hypo-echoic or multi-loculated micro-abscess, bull's-eye, or cartwheel-like lesions.

The use of a single melioid titer for diagnosis had limitations because of mediocre sensitivity (70%) and specificity (69%) at the cut-off point 1:160 (Teparrugkul, 1997). However, a fourfold rise in paired sera suggested recent infection.

For subacute/chronic pulmonary melioidosis, mortality was not high, except for patients with septicemia. Most patients presented with indolent disease – the chest radiograph appeared as a patchy alveolar infiltrate or a fibroreticular lesion, commonly at the upper lobe. Tuberculosis-like lesions such as cavities, atelectasis, calcified hilar adenopathy or fibrotics may be concomitant (Ip *et al*, 1995), sometimes leading to ineffectual anti-tuberculosis treatment. In this study, eight patients with subacute/chronic pulmonary melioidosis had a previous history of definite diagnosis and complete treatment of pulmonary tuberculosis. On the other hand, four patients developed pulmonary tuberculosis after complete treatment of subacute/chronic pulmonary melioi-

dosis. It was interesting that all these patients had diabetes mellitus. Pleural effusion was not a common finding: the profile of this fluid was usually neutrophilic exudative pleural effusion.

In conclusion, pulmonary melioidosis should be suspected in endemic areas in patients with diabetes mellitus and/or those working in agriculture. Mortality from the acute form was high, so patients presenting with rapidly progressive pneumonia or severe pneumonia should receive the empirical treatment of 2 g ceftazidime intravenously every 8 hours. In the subacute/chronic form, the clinical presentation and chest radiographs may mimic tuberculosis. Definitive diagnosis is indicated by a positive culture from clinical specimens of sputum, blood, pleural fluid, or bronchoalveolar lavage. After the acute phase of treatment, patients should be treated for at least 3-6 months with a combination of oral doxycycline and cotrimoxazole.

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