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Pulmonary melioidosis: an experience over years from a tertiary care hospital from southwest India

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Abstract

Background: Melioidosis is endemic in northern Australia, South and South East Asia. Infection usually follows percutaneous inoculation or inhalation of the causative bacterium, Burkholderia pseudomallei, which is present in soil and surface water in the endemic region. Our aim was to study the clinical, radiological and laboratory presentations of pulmonary melioidosis and compare them with other sporadic cases reported from India.

Method: This prospective, hospital based study was conducted during 2007 to 2015 in a tertiary care hospital situated in southern India. Diagnosis of melioidosis was confirmed by isolation of B. pseudomallei from any of the sterile or unsterile sites. Patients' details like baseline demography, possible risk factors, clinical and radiological presentations, laboratory features, treatment and outcome were documented.

Results: A total of 65 (65/148, 43.9%) culture confirmed cases of pulmonary melioidosis were diagnosed in eight years, most of which (80%) were acute. Majority of the patients were male (85%). Most of the patients presented with fever (91%) and productive cough (78.4%). The most common radiological feature was consolidation of the upper lobe (26.3%). There were 2 cases of co-infection with pulmonary tuberculosis, which were subsequently treated for dual infection. The most common drug of choice was ceftazidime (49%). Overall mortality rate was 21%, significantly associated with sepsis, septic shock, organ dysfunction and bacteraemia.

Conclusion: Acute pulmonary melioidosis should be kept in mind by clinicians whenever a patient of acute clinical deterioration presents with symptoms and radiological diagnosis similar to tuberculosis.

Keywords: Community acquired pneumonia (CAP), Burkholderia pseudomallei and pulmonary tuberculosis.

Introduction

Melioidosis is a life threatening infectious disease caused by Tier 1 Select Agent Burkholderia pseudomallei, a Gram negative soil saprophyte [1]. Melioidosis is highly endemic in northern Australia where it is the commonest cause of fatal community-acquired pneumonia and/or bacteraemia [2]. In northeast Thailand, it is the third most common deadly disease after HIV and tuberculosis [3]. Moreover, in recent past, cases of melioidosis is also increasingly reported from many countries such as India, Sri Lanka, Bangladesh, regions of south and central America, some countries in Africa including Nigeria, Gambia, Kenya and Uganda [1]. Common modes of transmission include inoculation [4] followed by inhalation during extreme weather [5] and ingestion of contaminated water [7]. The disease most frequently affects the lungs. Lungs may be the primary focus of infection or may be part of the multi-organ dissemination in patients with septicemia. The clinical spectrum of pulmonary melioidosis ranges from silent sub-acute or chronic illness to acute fulminant septicemia. While the acute form may manifest as localized suppurative infection, acute pneumonia with or without dissemination and septicemia with high mortality, chronic melioidosis may mimic as tuberculosis clinically and radiologically [8 – 10]. Although there has been adequate literature on pulmonary Melioidosis from endemic places like Thailand and northern Australia, but there has not been sufficient data, except few case reports from Indian sub-continent. Recent report has predicted India to have the highest burden of Melioidosis [11]. However, the occurrence, distribution and frequency have been unknown in India for long. Here we report the sixty-five microbiologically confirmed cases of pulmonary melioidosis in eight years from our tertiary care hospital describing varied clinical and radiological presentations and compare them with other sporadic cases reported from other parts of India.

MATERIALS AND

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Table 1: Basic demography, clinical presentations, comorbidities, treatment and outcome of 65 diagnosed cases of pulmonary melioidosis.

Variables (N = 65)	No. of patients, n (%)
Age groups	
<30	07 (10.8)
30-60	46 (70.8)
>60	12 (18.4)
Gender	
Male	55 (84.6)
Female	10 (15.4)
Occupation	
Agriculturist	04 (6.2)
Professional	26 (40)
Home Maker	06 (9.2)
Skilled	06 (9.2)
Unskilled	14 (21.5)
Unknown	09 (13.8)
Clinical presentations	
Fever	59 (90.8)
Cough	51 (78.5)
Breathlessness	36 (55.4)
Bacteremia	35(53.8)
Sepsis	31(47.7)
Organ dysfunction	25(38.5)
Septic shock	17(26.2)
Respiratory failure	14 (21.5)
Chest pain	08 (12.3)
Chest X-ray findings	
Consolidation	17 (29.3)
Nodules	16 (27.6)
Effusion	09 (15.5)
Infiltration	08 (13.8)
Cavity	04 (6.9)
Infiltration & effusion	02 (3.4)
Consolidation & cavity	01 (1.7)
Consolidation & effusion	01 (1.7)

Variables (N = 65)	No. of patients, n (%)
Co-morbidities	
Diabetes mellitus	45 (69.2)
Chronic alcoholism	38 (58.5)
Chronic kidney disease	19 (29.2)
Hypertension	17 (26.2)
Immunosuppression	03 (4.6)
Malignancy	03 (4.6)
Seasonal pattern	
Rainy season	38 (58.5)
Others	27 (41.5)
TreatmentIntensive phase	
Ceftazidime + Cotrimoxazole	19 (29.3)
Meropenem + Cotrimoxazole	10 (15.4)
Only Ceftazidime	06 (9.3)
Only Meropenem	07 (10.8)
Others	23 (35.4)
Eradication Phase	
Cotrimoxazole	32(49.2)
Doxycycline	10(15.4)
Others	23(35.4)
Outcome	
Improved	52 (80)
Expired	13 (20)

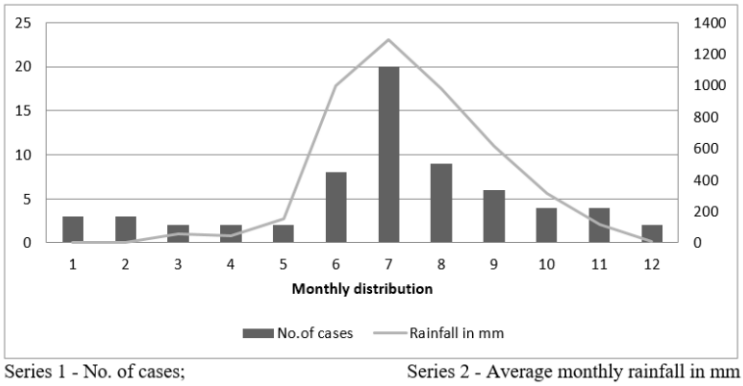

Figure 1: Average monthly rainfall compared with pulmonary melioidosis cases from 2007 to 2015.

Table 2: Comparison between survivors and non-survivors with regard to clinical presentations and co-morbidities.

Variables	Survivors n = 52	Non-survivors n=13	p value, risk ratios (95% Confidence interval)
Clinical presentations			
Sepsis	18	13	0.002, 4.6 (1.4-14.6)
Septic shock	6	11	<0.001, 6.9 (2.5-18.8)
Organ dysfunction	12	13	<0.001, 6.7 (2.1-21.3)
Bacteremia	23	12	0.05, 2.5 (0.9-7.1)
Co-morbidities			
Diabetes mellitus	36	9	0.17, 0.51 (0.2-1.3)
Chronic alcoholism	15	1	0.17, 0.28 (0.03-2.13)
Chronic kidney disease	9	10	0.02, 3.6 (1.5-8.4)
Hypertension	13	4	0.91, 0.93 (0.28-3.03)

METHOD:

Selection of Patients, data collection and laboratory processing:

The present prospective, hospital based study was conducted during 2007 to 2015 in a tertiary care hospital situated in southern Karnataka, India. This study was approved by institutional ethical committee. Cases of pulmonary melioidosis were recruited on the basis of previously described definition [12]. Definitive diagnosis was made by isolation of B. pseudomallei from any of the sterile or non-sterile sites with significant pulmonary and radiological findings. Details of individual cases like baseline demography, clinical presentations, biochemical, haematological, radiological and microbiological investigations, treatment and outcome were recorded after taking an informed consent. Possible risk factors for melioidosis like diabetes mellitus, chronic alcoholism, chronic renal disorder, other underline disorders and occupational exposure were identified. Microbiological processing included routine culture of respiratory specimens on 5% sheep blood agar and MacConkey agar along with enrichment culture using CVC 50 broth and Ashdown agar were performed [13]. Blood cultures were done using BacT/Alert system (BioMérieux). Suspected colonies of B. pseudomallei which showed oxidase positive, non-glucose fermentative, resistant to polymyxin B and colistin were confirmed by latex agglutination assay (Mahidol University) [14] and TTS1 based PCR [15].

Data analysis:

The data was entered and analysed using SPSS software version 22.0. The Pearson chi-squared test or Fisher exact tests were employed to compare different variables; p values ≤ 0.05 were considered significant and risk ratios for mortality at 95% confidence intervals were then calculated.

RESULT:

During the eight years of study period, a total of 148 culture confirmed cases of melioidosis were diagnosed. Out of these 148, 65 (43.9%) cases were identified with pulmonary melioidosis. Patients were equally distributed into age groups < 50 years (33, 51%) and > 50 years, (32, 49%), the majority of the patients were male 55 (85%). Most of the cases 52 (80%) were acute, with <2 months of presenting symptoms.

Table 1 describes the basic demographic features, clinical presentations, comorbidities, treatment and outcome of 65 diagnosed cases of pulmonary melioidosis. Fever (59/65, 91%) was the most common presentation along with productive cough (51/65, 78.4%) and breathlessness (36/65, 55.4%). Chest x-ray was available for 58 (89.2%) patients. The most common finding was consolidation of the upper lobe 17 (26.3%) and multiple small pulmonary nodules 16 (27.6%), mostly seen in the septicemic patients. Although pleural effusion is uncommon in melioidosis, there were 9 cases (13.8%) with effusion. There were 8 cases (6.1%) with multilobar infiltrates, usually starting from the upper

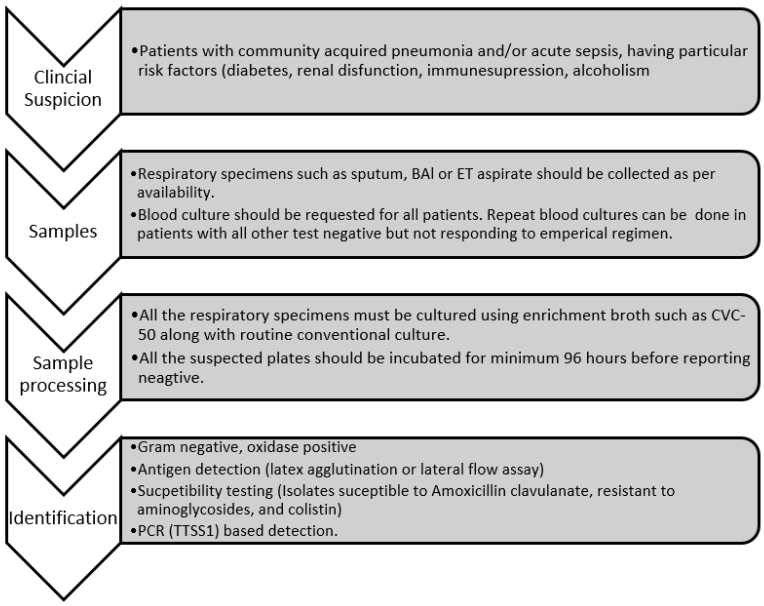

Figure 2: The algorithm for detection and diagnosis of pulmonary melioidosis.

lobe. Cavitary lesion on chest x-ray was seen in 4 patients (6.1%), they were initially suspected as tuberculosis. There were 2 cases of co-infection with pulmonary tuberculosis, which were subsequently treated for dual infection. Figure: 1 elaborates the seasonal pattern of cases of pulmonary melioidosis which showed rainy season (June-October) had a major stake of cases 48 (74%) compared to dry season 17 (26%).

Among these 65 cases, 51 (78.5%) patients had received disease specific treatment. Ceftazidime was the most common drug of choice 25 (49%) followed by meropenem 19 (38.8%). Overall mortality rate was 21% (13/65), of these 11(84.6%) were associated with bacteraemia. Mortality was significantly associated with sepsis (p = 0.002), septic shock (p <0.001), organ dysfunction (p <0.001) and bacteraemia (p = 0.02). Mortality was significantly higher in those with chronic kidney disease (p = 0.02). Although no other individual risk factor, including diabetes, was predictive of mortality, the absence of any risk factors was strongly predictive of survival (Table 2).

DISCUSSION:

Melioidosis was first reported from India in 1991 [19] since then there are few reports being documented in the current literature. Cases of Pulmonary melioidosis among these reports are very few. The clinical presentations documented were varied from acute fulminant pneumonia [20], to chronic encysted pleural effusion progressing to osteomyelitis of the rib [28]. In majority of the reports, it was observed that pulmonary melioidosis presented with acute pneumonia spreading to the blood leading to adverse outcome. Co-infection of melioidosis with tuberculosis has also been reported [21]. The varied clinical manifestations of Pulmonary melioidosis are remarkable but the less reports signify the under diagnosis of the disease in the nation.

In our study, the overall rate of pulmonary melioidosis among the culture confirmed cases was 43.9% (65/148), this is comparable to the rate of cases reported from other parts of the world [2, 8]. Previously reported study from India described pulmonary melioidosis as the most common clinical presentation (34.7%) among the total cohort of culture confirmed cases [22]. Other studies conducted in southern India also reported pulmonary manifestation among 48% and 42.8% of the total patients diagnosed with melioidosis [23-24]. In this study, most of the blood culture from patients with CAP had grown B. pseudomallei (35; 53.8%). Mortality rate was significantly higher (11/13, 84.6%) in patients with sepsis. Similar finding was also observed in another study from India, where bacteraemia was observed among 57.5% (19/33) with overall mortality being highest among patients with bacteremic pneumonia [22]. CAP with B. pseudomallei contributes in increasing the rate of bacteraemia in patients, as it is evident in a study from Northern Australia [8]. Blood culture always had an upper hand in the diagnosis of pulmonary melioidosis as compared to the respiratory samples. Sputum sample was found to be less sensitive for direct isolation of B. pseudomallei but use of enrichment culture has showed better efficacy for isolation from non-sterile samples. Blood culture has diagnosed 53.8% of the overall pulmonary cases, this could be due to the high sensitivity of automated blood culture system or a higher rate of dissemination among late referred patients to the tertiary care settings. Since bacteraemia was one of the associated risk factors (p=0.05, 2.5 0.9-7.1) for mortality in the study population hence there is a requisite for early diagnosis and prompt treatment of pulmonary melioidosis to avoid its systemic dissemination.

Dissemination is more commonly observed among pulmonary melioidosis in comparison to other form of the disease, which is proved by an experimental study in mice model that demonstrated an early spread of B.pseudomallei from lungs to other organs (27). Unknown bacterial virulence or host factors might also be accountable for such events demanding a further investigation of the same. Pulmonary symptoms in melioidosis may be secondary due to spread of pathogen from other primary foci. In our study 10% patients had confirmed radiological findings and symptoms of pulmonary melioidosis but culture positivity was observed from other sites such as synovial fluid and aspirates from lung and spleen. Such cases might be indication for dissemination of B.pseudomallei from these sites to the lungs or vice versa. Pulmonary melioidosis manifesting as isolated pleural effusion is rare, but occurred in 12.2% of the total 162 cases reported between 1996 and 2002 in study conducted in Thailand (25) which is concordant to our study (15.5%). Unilobar or bilobar infiltrates are mainly associated with acute form of the disease whereas cavitory lesions are suggestive of chronic condition. In the present study 6.9% cases presented with cavity. Such type of cases might go misdiagnosed as tuberculosis due to the similar clinical and radiological presentation.

In our study, chronic kidney disease was an associated risk factor with mortality in patients diagnosed with pulmonary melioidosis. Abnormality in the reactive oxygen species (ROS) pathway leads to the impairment of bacterial killing by the phagocytic cells in CKD patients which could be a major factor for the link of high mortality with the disease [26]. The choice of treatment for B.pseudomallei is limited due to its inherent resistance to a wide group of antibiotics. Meropenem or ceftazidime are the recommended drugs for intensive therapy. In our study population ceftazidime with or without cotrimoxazole was the most common drug administered for treatment. There has been lack of clinical trials with evidence of improved outcomes when cotrimoxazole was added to the recommended intensive therapy, but it is certainly worth considering a combination therapy for patients with worsening ailment. Despite of resistance been reported elsewhere, ceftazidime still remains as an antibiotic of choice in our setting due to unaffordability of patients to carbapenems at several instances. Cotrimoxazole was the most common drug employed for eradication therapy followed by doxycycline. Overall the choice of antibiotic did not show any difference in the outcome of patients.

A confirmatory diagnosis of melioidosis requires awareness of the clinical presentation and a laboratory capable of isolating and identifying B. pseudomallei from clinical specimens. Despite being predicted as the country with highest burden of melioidosis lack of diagnostic facilities and awareness among the clinicians could be the reasons for under diagnosis of the disease in the Indian sub-continent. In India potential default

witnessed with failure in diagnosis of pulmonary melioidosis is the high endemicity of tuberculosis and low microbiological capacity at primary health care settings. In melioidosis, patients may have presentations mimicking tuberculosis, with fever, weight loss, productive cough, upper lobe infiltrates with or without cavitation on chest radiograph [11], at such instances misdiagnosing melioidosis as TB may not be uncommon. Studies have been strongly suggested that melioidosis needs to be ruled out in all cases of CAP and AFB smear negative cases of tuberculosis [12, 13]. One possibility could also be co-infection of TB with melioidosis, till date many cases of pulmonary melioidosis have been reported, which were initially suspected as case of pulmonary tuberculosis [16, 17] earlier reports are suggestive that melioidosis can cause cavity or can infect a previously present tubercular cavity [21]. In conclusion, our study findings suggest that acute pulmonary melioidosis should be kept in mind by radiologists and clinicians whenever a patient of acute clinical deterioration presents with symptoms and radiological diagnosis similar to tuberculosis.

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