

Brief Original Article

Melioidosis In Suspected Recurrent Tuberculosis: A disease in disguise

Rahul Garg¹, Tushar Shaw¹, Kalwaje E Vandana¹, Rahul Magazine², Chiranjay Mukhopadhyay^{1,3}

¹ Department of Microbiology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India - 576104

² Department of Pulmonary Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India – 576104

³ Center for Emerging and Tropical Diseases, Manipal Academy of Higher Education, Manipal, Karnataka, India – 576104

Abstract

Introduction: Melioidosis, caused by the soil saprophyte *B. pseudomallei*, is a ‘neglected’ infectious disease in many Asian countries. It remained undiagnosed or misdiagnosed in India for long due to a lack of awareness and facilities to diagnose the disease; however, it is slowly gaining the status of an emerging disease recently. The disease is well known as a great mimicker, as the presentations are very similar to many other tropical diseases, and more importantly, to tuberculosis.

Methodology: A prospective observational study was conducted from January 2016 – December 2018 to find the occurrence of melioidosis in patients with ‘recurrent’ tuberculosis infection in a tertiary health care hospital from southern India. All suspected cases of recurrent tuberculosis were simultaneously tested for the presence of *B. pseudomallei*, and basic demographics and clinical details were documented.

Result: Among 11,138 patients admitted with suspected tuberculosis infection, 586 (5.2%) patients were confirmed. There was recurrent *Mycobacterium tuberculosis* infection in 11/586 (1.8%) cases, and 7/586 (1.2%) had growth of *B. pseudomallei* in culture. Patients with melioidosis had either pulmonary involvement, or bone and joint infections and deep abscesses. Uncontrolled diabetes mellitus was the major risk factor.

Conclusion: The study foreshadows the need for prompt and accurate microbiological diagnosis along with a high index of suspicion from the clinicians in countries which are endemic for both melioidosis and tuberculosis, thus ameliorating the irrational anti-tuberculosis treatment.

Key words: Melioidosis; tuberculosis; *Burkholderia pseudomallei*; tropical infection; recurrence; India

J Infect Dev Ctries 2020; 14(3):312-316. doi:10.3855/jidc.12051

(Received 25 September 2019 – Accepted 06 February 2020)

Copyright © 2020 Garg *et al.* This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Melioidosis is caused by *Burkholderia pseudomallei*, which is a Gram-negative, oxidase-positive, non-lactose fermenting, arginine dihydrolysing soil saprophyte. It can infect individuals in endemic regions through inhalation, inoculation or ingestion. Acquiring an infection greatly depends on two factors - environmental exposures and the host susceptibility, especially with comorbidities like uncontrolled diabetes mellitus, chronic kidney diseases, etc. [1]. It manifests as acute community acquired pneumonia with or without septicaemia and multi-organ failure leading to high mortality, or as localized chronic infection to the skin and other deep organs mimicking tuberculosis (TB). The case-fatality rate is quite high (10–50%) in acute cases, even when appropriately treated.

The estimated incidence of TB in India is 211 per 100,000 populations (<http://www.who.int/tb/country>

[data/profiles/en/](http://www.who.int/tb/country)). It is one of the major causes of high mortality and morbidity in the country. The annual incidence rates of melioidosis range from 4 to 41.7 cases per 100,000 populations in the endemic countries [2] with the majority of cases being reported during the monsoon. Melioidosis is endemic in tropical south Asian countries with India predicted to have the highest burden of the disease [3]. Unfortunately, the true burden of melioidosis in India still remains elusive, even after 30 years of the first melioidosis case being detected [4]. A recent review from India documented 583 cases of melioidosis reported from different parts of the country [5], with the highest number of cases reported from Karnataka and Tamil Nadu.

Culture remains the gold standard method for the diagnosis of melioidosis. Blood, throat, and urine cultures can be performed in patients with suspected melioidosis, regardless of their symptoms [6]. Specimens from localized disease, such as sputum,

tissues, pus and aspirates need to be collected. Standard laboratory media (e.g. 5% sheep blood and MacConkey agar) support the growth of *B. pseudomallei*. However, the use of selective media like Ashdown's agar is recommended for specimens like tissues or respiratory secretions where contamination with normal flora is expected [6]. After 24-48 hours incubation at 37°C, isolated bacterial colonies may produce a characteristic metallic sheen which eventually turn dry and wrinkled after 3-4 days of incubation. The bacterium is susceptible to amoxicillin-clavulanic acid and resistant to colistin and gentamicin, which helps in differentiating it from other Burkholderia species. PCR based molecular assays and rapid antigen detection tests can be useful in early diagnosis of cases [7,8].

The treatment regimen for melioidosis requires an intensive phase of meropenem or ceftazidime for 10-14 days followed by the eradication phase with cotrimoxazole for 12-14 weeks [9]. The eradication phase of treatment might be challenging, in view of long term follow-up and failure of compliance leading

to relapse [10]. Hence, early diagnosis and prompt management are essential requisites for better patient outcomes.

Although the clinical features of chronic melioidosis are similar to active TB, and latent forms of both melioidosis and TB have similar host susceptibility and immune response, the co-occurrence of TB and melioidosis is quite low [11]. It poses a serious challenge to the treating physicians to have a preliminary clinical diagnosis. With a high burden of TB in India, it is very well possible that melioidosis might be misdiagnosed as TB, especially in patients with a past history of active TB infection. Keeping this background in mind, we performed an observational study to document the occurrence of melioidosis cases in patients suspected with recurrent TB infection.

Methodology

A prospective observational study was conducted at a tertiary health care hospital in south India from January 2016 to December 2018. Patients with a known

Table 1. Details of melioidosis cases in suspected recurrent tuberculosis.

Case No.	Age	Gender	Occupation	History of soil exposure	Comorbidities	Sample	Radiological findings	Antitubercular treatment	Treatment	Outcome
1	51	M	Farmer	Yes	DM, COPD	BAL	CT- cavity lesion	Ongoing	Meropenem, Cotrimoxazole	Cured
2	42	M	Teacher	No	HIV infection	Pus from Splenic abscess	X-ray- Pleural effusion USG- Hypoechoic lesion in the spleen	Completed	Meropenem, Cotrimoxazole	Cured
3	45	M	Farmer	Yes	DM	Blood	X-ray- Right lower lobe consolidation	Completed	Meropenem	Expired
4	53	M	Fisherman	No	DM	Pus from a splenic abscess and ankle joint	USG- Hypoechoic lesions in the spleen	Completed	Ceftazidime, Cotrimoxazole	Cured
5	63	M	Driver	Yes	DM	Synovial fluid	MRI of right knee - Multifocal involvement, suggestive of TB	Completed	Ceftazidime, Cotrimoxazole	Cured
6	55	M	Doctor	No	DM, alcoholism	Pus from a gluteal abscess and hip joint	-	Ongoing	Meropenem, Cotrimoxazole	Cured
7	42	M	Farmer	Yes	DM	Blood	X-ray- Bilateral haziness	Completed	-	Expired

DM: Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disorder; BAL: Broncho-Alveolar Lavage; HIV: Human Immunodeficiency Virus.

Table 2. Clinical presentations and site of involvement in melioidosis cases.

Cases	Fever	Respiratory Symptoms	Bone and joint involvement	Cutaneous ulcers	Hepatomegaly
Case 1	Yes	Cough	Absent	Absent	Yes
Case 2	Yes	Cough and breathlessness	Absent	Absent	Yes
Case 3	Yes	Cough	Absent	Absent	Yes
Case 4	Yes	Absent	Ankle (Right)	Absent	Yes
Case 5	No	Absent	Knee (Right)	Absent	No
Case 6	Yes	Absent	Hip (Right)	Present	No
Case 7	Yes	Cough and Breathlessness	Absent	Present	Yes

history of TB and having suspected recurrence of infection were recruited in the study. Recurrence of TB was confirmed by smear microscopy, culture and/or Xpert MTB/RIF (Cepheid Inc. USA) [12]; the samples were simultaneously screened for the presence of *B. pseudomallei* on enrichment culture and by TTSS1 PCR [7].

Basic demographics, clinical features and the outcome of the confirmed cases of recurrent TB and melioidosis were documented (Table 1 and Table 2). The association of the risk factors such as diabetes mellitus, renal dysfunction, chronic alcoholism, etc. was compared in patients with melioidosis and recurrent TB. The data was analyzed using SPSS ver. 16 (IBM). Descriptive statistical tools were used to determine the frequencies of categorical study variables. Pearson's Chi-square test and Fisher's exact test were used in determining the presence of any significant association. P-value <0.05 was considered significant. The study was approved by the Institutional Ethical Committee.

Results

Among 11,138 patients admitted to the hospital during the study period with suspected TB, 586 (5.2%) cases were confirmed by laboratory methods. Among them, recurrent TB was documented in 11/586 (1.8%) cases. Seven (1.2%) patients suspected as recurrent TB but with negative result had shown the growth of *B. pseudomallei* in culture. Out of them, 4 patients had pulmonary involvement and 3 had bone and joint infection (2 cases osteomyelitis and 1 case of septic arthritis).

A comparison of recurrent TB with that of melioidosis revealed that patients with bone and joint involvement with or without hepatomegaly had an association with melioidosis. Deranged liver functions and higher blood glucose levels, suggesting uncontrolled or poorly controlled diabetes mellitus, were significantly associated with melioidosis (Table 3). Among the melioidosis patients, 5 (71.4%) had a suggestive history of soil exposure.

Discussion

Melioidosis is an emerging and 'killer' infectious disease in South Asia, especially in India, which remained as an underestimated public health problem for decades. The bacterium is ubiquitously distributed in the environmental niches of tropical countries like India, where there is a gradual escalation of the number of cases from various parts of the country in the last few years [5].

Among the cases with past TB infection, 11 (1.8%) was readmitted with recurrence and 7 (1.2%) with melioidosis. Patients with chronic pulmonary melioidosis may present with signs, symptoms and chest radiology similar to TB, which may lead to misdiagnosis and inappropriate treatment [13]. India has the highest burden of both TB including multidrug-resistant (MDR) TB based on estimates reported in the Global TB Report (https://www.who.int/tb/publications/global_report/en/). The country has lately achieved the dubious distinction of being the 'diabetes capital', with 41 million Indians having diabetes [14]. Diabetes mellitus is a proven risk factor for both melioidosis and TB. Diagnosing a neglected disease like melioidosis with a similar clinical presentation like TB in this milieu is challenging for the treating physicians. Patients with a past history of TB are usually diagnosed as recurrence based on suggestive clinical presentations, indicative radiological findings and other non-confirmatory laboratory parameters (ADA profile, high ESR), rather by laboratory confirmation [15,16] and treated with anti-tubercular antibiotics. This may be considered as one of the major causes of misdiagnosis of melioidosis, as it is reflected in our observation of seven cases of melioidosis, who were suspected to have recurrent TB at primary health care settings. It shows the lack of awareness and expertise to detect melioidosis and the dearth of laboratory facilities at the first point of contact. Even the possibility of co-infection of melioidosis and TB was not suspected. *B. pseudomallei* is well known to cause latent infection [17], although it is not documented that whether the anti-tubercular treatment has any effect in suppressing the bacteria

which might get activated from latent foci at a later stage.

Bone and joint involvements like septic arthritis and osteomyelitis are very well-documented clinical presentations in melioidosis [18], whereas pulmonary involvement was more commonly observed in TB. The extra-pulmonary involvement is more common in melioidosis than TB and less challenging in diagnosis, still it is missed most often [19, 20]. Deranged liver function tests along with hepatomegaly is another entity in this case, which is more common in melioidosis than TB [21]. The higher blood glucose level among the melioidosis infected individuals is an indicator of uncontrolled diabetes, which is a well-established risk factor for both the diseases. However, these laboratory findings should be evaluated further in a large cohort for any significant correlation. Overall, the study highlights the importance of appropriate microbiological investigations in diagnosing melioidosis in patients with suspected recurrent TB infection. Differentiating melioidosis from TB is an essential requisite in our setting, as both the diseases have different management protocols and antibiotic treatment regimens. We propose that patients with suggestive signs of TB may also be looked for

melioidosis in endemic areas, preferably using routine culture media, enrichment broth and/or molecular assays, depending on the availability of the tests in the laboratory. Smear-negative sputum samples from suspected TB cases should further be checked for melioidosis. This will help provide correct diagnosis and prescribe appropriate antimicrobial treatment for melioidosis, and thereby, prevent further morbidity and mortality [22]. It will also reduce the over-use of anti-tuberculosis drugs, which can lead to adverse drug reactions and evolution of drug-resistant TB.

Conclusion

This is the first study estimating the occurrence of melioidosis among patients presenting with recurrent TB in India. The study foreshadows the need for timely and accurate diagnostic testing for melioidosis in patients with suspected TB, and also among cases with recurrent infection in highly endemic areas of LMICs. Further, clinical awareness among clinicians and public health personnel is a requisite for early suspicion of melioidosis, which may lead to rational and targeted empirical treatment.

Table 3. Factors associated with melioidosis as compared to recurrent TB infection.

	Recurrent tuberculosis N = 11 n(%)	Melioidosis N = 7 n(%)	P value
Demographics			
Age (yrs)	54 (43-64)	51 (27-55)	0.42
Gender (male)	9 (82)	7 (100)	0.23
Clinical presentation			
Fever	5 (45)	6 (86)	0.12
Pulmonary symptoms	10 (90)	4 (57)	0.02
Bone and joint involvement	1 (9)	3 (43)	0.02
Hepatomegaly	1 (9)	5 (71)	0.02
Cutaneous ulcer	1 (9)	2 (29)	0.18
Comorbidities			
Diabetes mellitus	4 (36)	5 (71)	0.20
Chronic kidney disease	1 (9)	0 (0)	0.38
Chronic lung disease	2 (18)	1 (14)	0.36
Hypertension	1 (9)	1 (14)	0.33
Laboratory findings			
Total WBC count	9.5×10 ³ (7.5-12.5×10 ³)	12×10 ³ (7-19.2×10 ³)	0.19
Neutrophils,%	74.2 (63.9-81.5)	77.6 (52.5-84.5)	0.87
Monocytes,%	7.8 (5.6-12.2)	7.2 (4.3-9.5)	0.59
AST, mg/dL	19 (15-28)	40 (19.2-82)	0.04
ALT, mg/dL	18.5 (9.7-26.2)	18.5 (11.5-61.5)	0.49
ALP, mg/dL	90.5 (67.5-122.5)	144 (99.5-587.5)	0.04
Total bilirubin, mg/dL	0.4 (0.2-0.7)	0.4 (0.2-0.6)	0.81
Creatinine, mg/dL	0.8 (0.7-1.1)	1 (0.7-1.4)	0.28
Urea, mg/dL	22 (15-26)	21 (13.5-36.2)	0.88
Random blood glucose	106 (98-132)	235 (123-364)	0.01

References

- Cheng AC, Currie BJ (2005) Melioidosis: epidemiology, pathophysiology, and management. *Clin Microbiol Rev* 18: 383-416.
- Currie BJ, Dance DA, Cheng AC (2008) The global distribution of *Burkholderia pseudomallei* and melioidosis: an update. *Trans R Soc Trop Med Hyg* 102 Suppl 1: 1-4.
- Limmathurotsakul D, Golding N, Dance DA, Messina JP, Pigott DM, Moyes CL, Rolim DB, Bertherat E, Day NP, Peacock SJ, Hay SI (2016) Predicted global distribution of *Burkholderia pseudomallei* and burden of melioidosis. *Nat Microbiol* 1: 15008.
- Raghavan K, Shenoi R, Zaer F, Aiyer R, Ramamoorthy P, Mehta M. (1991) Melioidosis in India. *Indian Pediatr* 28: 184-188.
- Mukhopadhyay C, Shaw T, Varghese G, Dance D (2018) Melioidosis in South Asia (India, Nepal, Pakistan, Bhutan and Afghanistan). *Trop Med Infect Dis* 3: 51.
- Hoffmaster AR, AuCoin D, Baccam P, Baggett HC, Baird R, Bhengri S, Blaney DD, Brett PJ, Brooks TJ, Brown KA, Chantratita N (2015) Melioidosis diagnostic workshop, 2013. *Emerg Infect Dis* 21: e141045.
- Tellapragada C, Shaw T, D'Souza, Eshwara VK, Mukhopadhyay C (2017) Improved detection of *Burkholderia pseudomallei* from non-blood clinical specimens using enrichment culture and PCR: narrowing diagnostic gap in resource-constrained settings. *Trop Med Int Health* 22: 866-870.
- Shaw T, Tellapragada C, Vandana KE, AuCoin DP, Mukhopadhyay C (2018) Performance evaluation of Active Melioidosis Detect-Lateral Flow Assay (AMD-LFA) for diagnosis of melioidosis in endemic settings with limited resources. *PLoS One* 13: e0194595.
- Dance D (2014) Treatment and prophylaxis of melioidosis. *Int J Antimicrob Agents* 43: 310-318.
- Halim I, Shaw T, Tellapragada C, Vandana K, Mukhopadhyay C (2017) Melioidosis: Reinfection going incognito as relapse. *Indian J Med Microbiol* 35: 593-596
- Sriwijitalai W, Wiwanitkit V (2019) Concurrent melioidosis and tuberculosis: An expected incidence in endemic tropical country. *Int J Mycobacteriol* 8: 412.
- Chaudhuri AD (2017) Recent changes in technical and operational guidelines for tuberculosis control programme in India-2016: A paradigm shift in tuberculosis control. *J Assoc Chest Physicians* 5: 1-9.
- Jayakumar E, Barani R, Mani M, Seshan V, Kothandaramanujam SM, Balakrishnan R, Srikanth P (2016) Molecular evidence of melioidosis among patients suspected for tuberculosis. *Int J Infect Dis* 45: 34.
- Joshi SR, Parikh RM. (2017) India; the diabetes capital of the world: Now heading towards hypertension. *J Assoc Physicians India* 55: 323-324.
- Linguissi LS, Vouvongui CJ, Poulain P, Essassa GB, Kwedi S, Ntouni F (2015) Diagnosis of smear-negative pulmonary tuberculosis based on clinical signs in the Republic of Congo. *BMC Res Notes* 8: 1-7.
- Collazos J, Espana P, Mayo J, Martiénez E, Izquierdo F (1988) Sequential evaluation of serum adenosine deaminase in patients treated for tuberculosis. *Chest* 114: 432-435.
- Shaaban H, Hallit R, Slim J, Sree A, Sensakovic JW (2014) Reactivation of latent melioidosis presenting with acute pyelonephritis and bacteremia. *Avicenna J Med* 4: 20-21.
- Zueter AM, Abumarzouq M, Yusof MI, Wan Ismail WF, Harun A (2017) Osteoarticular and soft-tissue melioidosis in Malaysia: clinical characteristics and molecular typing of the causative agent. *J Infect Dev Ctries* 11: 28-33. doi: 10.3855/jidc.7612.
- Di Nuzzo M, Trentini A, Grilli A, Massoli L, Biagi E, Maritati M, Contini C (2018) Extrapulmonary tuberculosis among immigrants in a low-TB burden and high immigrant receiving city of northern Italy. *J Infect Dev Ctries* 12: 73-79. doi: 10.3855/jidc.10167
- Vidyalakshmi K, Chakrapani M, Shrikala B, Damodar S, Lipika S, Vishal S (2008) Tuberculosis mimicked by melioidosis. *Int J Tuberc Lung D* 12: 1209-1215.
- Tyagi P, Shah V, Sharma P, Bansal N, Singla V, Kumar A, Arora A (2014) Melioidosis presenting as Fever and jaundice: a rare presentation. *J Clin Exp Hepatol* 4: 172-174.
- Deris ZZ, Hasan H, Siti Suraiya MN (2010) Clinical characteristics and outcomes of bacteraemic melioidosis in a teaching hospital in a northeastern state of Malaysia: a five-year review. *J Infect Dev Ctries* 4: 430-435. doi: 10.3855/jidc.491.

Corresponding author

Chiranjay Mukhopadhyay
 Department of Microbiology
 Kasturba Medical College
 Manipal Academy of Higher Education
 Madhavanagar
 Manipal, Karnataka 576104, India
 Tel: +91 0820 2922717
 Fax: +91 0820 2571927
 Email: chiranjay.m@manipal.edu; chiranjay@gmail.com

Conflict of interests: No conflict of interests is declared.