Imported Melioidosis in South Korea: A Case Series with a Literature Review

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KEYWORDS: Burkholderia pseudomallei, diabetes complications, melioidosis

Abstract

Objectives: Melioidosis is a potentially fatal infectious disease caused by the environmental anaerobic Gram-negative bacillus Burkholderia pseudomallei. Melioidosis is endemic to areas of northern Australia and Southeast Asia. With increasing international travel and migration, imported cases of melioidosis are being reported regularly. Here, we summarize the 11 cases of melioidosis reported in South Korea from 2003 to 2014.

Methods: Tracing epidemiological investigations were performed on every patient reported to the National Surveillance System since 2011. A systematic literature search was performed to identify melioidosis cases that occurred prior to 2011.

Results: The overall fatality rate was 36.4%. All the patients had visited Southeast Asia where melioidosis is endemic. The stay in the endemic region ranged from 4 days to 20 years. Of the seven patients who developed initial symptoms after returning to South Korea, the time interval between returning to South Korea and symptom onset ranged from 1 day to 3 years. The remaining four patients developed symptoms during their stay in the endemic region and were diagnosed with melioidosis in South Korea. Seven (63.6%) patients possessed at least one risk factor, all of whom were diabetic. Pneumonia was the most frequent clinical manifestation, but the patients showed a wide spectrum of clinical features, including internal organ abscesses, a mycotic aneurysm of the aorta, and coinfection with tuberculosis.

Conclusion: An early diagnosis and initiation of the appropriate antibiotics can reduce the mortality of melioidosis. Consequently, increased awareness of the risk factors and clinical features of melioidosis is required.
2.2. Epidemiological and clinical data

2.1. Case series

Melioidosis was designated as a national notifiable infectious disease on December 30, 2010. Since then, a national melioidosis surveillance system has been established, and medical institutions are responsible for reporting all melioidosis cases to that system. Five cases of melioidosis have been reported to the system since 2011. However, little was known about melioidosis prior to establishment of the National Surveillance System. Thus, a systematic literature search was performed using PubMed and the Korean Medical Database, with the following keywords “melioidosis” and “Burkholderia pseudomallei” to identify melioidosis cases that occurred before 2011. As a result, six cases were found.

2.2. Epidemiological and clinical data

Tracing epidemiological investigations were performed on every patient reported to the National Surveillance System since 2011. The epidemiological investigations were performed by Epidemic Intelligence Service officers via patient interviews and retrospective review of medical records. The standard questionnaire included the following variables: basic demographic characteristics (age, sex, address, and occupation), clinical features (presenting symptoms, date of onset, mortality, and laboratory and imaging results), melioidosis risk factors (underlying diseases and alcohol consumption), history of visiting other countries, and suspected exposure (presence of skin wounds, a history of inhaling dust, ingesting infected water, or contact with a patient with melioidosis). We collected data on cases that occurred prior to 2011 by reviewing earlier reports.
Table 1. Clinical features and results of evaluations of melioidosis patients in South Korea, 2003 to 2014.

| Characteristics                        | Seok et al [4] | Lee et al [5] | Lee et al [6] | Son et al [7] | Park et al [8] | Hong et al [9] | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|----------------------------------------|----------------|---------------|---------------|---------------|---------------|---------------|--------|--------|--------|--------|--------|
| Year                                   | 2003           | 2004          | 2008          | 2008          | 2010          | 2010          | 2011   | 2013   | 2013   | 2014   | 2014   |
| Age (y)                                | 47             | 50            | 32            | 47            | 55            | 48            | 60     | 47     | 66     | 61     | 62     |
| Sex                                    | Male           | Male          | Male          | Male          | Male          | Male          | Male   | Male   | Male   | Male   | Male   |
| Country visited                        | Malaysia       | Indonesia     | Thailand      | Cambodia      | Malaysia      | Malaysia      | Thailand| Cambodia| Vietnam| Thailand|
| Occupation                             | Engineer       | Businessman   | Driver        | Welder        | Construction  | Construction  | Actor  | Businessman| Businessman| Businessman|
| Length of stay                         | 1 year         | 20 years      | 30 years      | 4 days        | 2 years       | 4 months      | 8 months| 7 days  | 1 months| 9 years| 1 month|
| Return to onset                        | During stay    | 6 weeks       | During stay   | 1 month       | During stay   | 9 months      | 1 day   | 50 days| 2 months| During stay|
| Risk factors                           | Diabetes       | None          | Diabetes      | Diabetes      | None          | Diabetes      | Diabetes,| Diabetes,| Diabetes,| Diabetes,| None   |
| Acute/chronic                          | Acute          | Chronic       | Acute         | Acute         | Acute         | Chronic       | Acute   | Acute   | Acute   | Acute   | Chronic |
| Presenting symptoms                   | Fever          | Fever, cough,| Dyspnea       | Dyspnea       | Facial swelling,| Cough         | Acute   | Fever, | Acute   | Acute   | Fever, |
|                                        |                | malgilia      |               |               | dysuria, fever|              |        | dysuria|        |        | dysuria |
| Clinical manifestation                 | Pneumonia      | Pneumonia     | Pneumonia     | Pneumonia     | Soft tissue   | GU infection  | Pneumonia| GU infection| Pneumonia| GU infection|
| Shock on admission                     | Absent         | Absent        | Present       | Present       | Absent        | Absent        | Absent  | Absent  | Absent  | Absent  | Absent  |
| CXR/chest CT                           | Multiple nodules| Multiple nodules| Multiple nodules| Ill-defined | Normal        | Patchy       | Mass-like consolidation| GGO | GGO | Consolidation, lung cancer| Multiple nodules|
| Other findings                         | Spleen/liver abscess | Head/neck opacities | Prostate abscess | Head/neck | Prostate abscess | Prostate abscess | Hand swelling | Prostate abscess | aortic aneurysm |
| Diagnosis                              | Blood culture  | Bronchoscopic washing culture | Blood culture | Blood culture | Blood culture | Blood culture | Tissue (lung) & sputum culture | Blood culture | Blood culture | Tissue (aorta) & blood culture |
| Bacteremia                             | Present        | Absent        | Present       | Present       | Present       | Absent        | Present  | Present  | Present  | Present  | Present  |
| Outcome                                | Survived       | Survived      | Died          | Died          | Died          | Survived      | Survived | Survived | Survived | Survived | Survived |

CKD = chronic kidney disease; CT = computed tomography; CXR = chest x-ray; GGO = ground-glass opacity; GU = genitourinary.
4. Discussion

Here, we summarized the reported cases of melioidosis in South Korea. A total of 11 cases of melioidosis were reported during the past 12 years, and the overall fatality rate was 36.4%. All the patients had visited Southeast Asia, where melioidosis is endemic. Most of the cases stayed in the endemic area for months to years, and developed symptoms before returning to South Korea or within a few months after the return. However, some cases stayed in the endemic region for as little as a few days, and one case developed symptoms 3 years after returning to South Korea. Pneumonia was the most frequent clinical manifestation, but the patients showed a wide spectrum of clinical features, including a mycotic aneurysm of the aorta and coinfection with tuberculosis. An early diagnosis and initiation of the appropriate antibiotics can reduce mortality. Consequently, increased awareness of the risk factors and clinical features of melioidosis is required.

Most melioidosis cases result from recent exposure, as the majority of melioidosis cases in the endemic region occur during the rainy season. The incubation period of melioidosis ranges from days to months [10]. A previous study calculated an incubation period of 1–21 days between the inoculating event and symptom onset [11]. However, B. pseudomallei can reactivate after an initial asymptomatic infection with extremely prolonged latency. There are reports of melioidosis becoming symptomatic more than 20 years after the suspected exposure [12,13]. In this report, incubation periods could not be determined clearly, as most of the patients failed to recall the actual event of inhalation or inoculation. Therefore, the time period between returning to South Korea and the onset of symptoms was recorded as an indirect measure of the minimum incubation period. More than half of the cases developed symptoms during their stay in the endemic region or within 1 month after returning to South Korea. However, the initial symptoms developed more than 1 month after returning to South Korea in five cases, and the interval between return and symptom manifestation was as long as 3 years in one case [4]. Although poorly understood, the prolonged latency of B. pseudomallei is thought to be associated with its facultative anaerobic nature, ability to persist without nutrients, and ability to endure antibiotic pressure by assuming filamentous forms [14]. It is important that physicians should not rule out melioidosis simply because the duration from the suspected exposure to symptom onset is longer than a month.

Risk factors for melioidosis include diabetes mellitus, heavy alcohol consumption, chronic lung disease, chronic renal disease, malignancy, and immunosuppressive treatment [3]. Patients with these risk factors are predisposed to melioidosis, and previous studies showed that 80–87% of melioidosis patients had at least one risk factor [3,15,16]. Of the risk factors, diabetes mellitus is most important. Diabetes has been reported in 38–60% of melioidosis patients [17–20], and the calculated risk of melioidosis in diabetics is as high as 21.2 (95% confidence interval 17.1–26.3) times the risk in nondiabetics [16]. The presence of risk factors is associated not only with susceptibility to the disease, but also with its severity and clinical manifestations. The chronic form of melioidosis was less common in diabetic patients and more commonly observed in patients without risk factors. In addition, patients without risk factors tended to have lower rates of bacteremia, septic shock, and mortality [3]. In the present series, seven (64%) patients had at least one risk factor, all of whom were diabetic. Of the four patients without risk factors, chronic infection was observed in three (75%) and two (50%) had bacteremia. By contrast, none of the seven patients with at least one risk factor developed a chronic infection and all of them were bacteremic.

Previous reports showed that male sex is an independent risk factor for melioidosis [16,21]. High occupational exposure to soil and water is a significant risk factor for melioidosis [22], and the association between male sex and melioidosis is suggested to reflect an increased exposure to B. pseudomallei [16]. In the present series, all the cases were male, and this may also be associated with high environmental exposure. Cases with higher occupational exposure to soil and a prolonged duration of stay in an endemic area have a higher chance of exposure to B. pseudomallei. Under the current social circumstances of South Korea, men are more likely to work in foreign countries for a long period, and
this may explain the reason that all the patients are male. In fact, only three cases in the present series were tourists, and the remaining eight cases were those who stayed in Southeast Asia for occupational purpose for months to years.

The fatality rate of melioidosis ranges from 14% to 49% [3,17,18] and was reported to be as high as 65% in bacteremic patients [19]. Old age (≥50 years), the presence of risk factors (diabetes, heavy alcohol use, and chronic lung or renal disease), and markers of organ dysfunction (leukopenia; raised liver enzyme, urea, and creatinine levels; and acidosis) on admission are thought to be associated with mortality [3,23,24]. In the present series, four patients, three with diabetes and one elderly patient, died from melioidosis. Two patients had septic shock with evidence of organ dysfunction on admission. The overall fatality rate was 36.4%. Despite its considerable fatality rate, a recent study suggested that survival is improving. In the Darwin study, the fatality rate from melioidosis decreased from 30% to 9% over the past 20 years, and this was attributed to an early diagnosis, early treatment with the appropriate antibiotics (ceftazidime or meropenem), and access to intensive care management [3]. Similarly, the mortality of melioidosis in South Korea may be reduced by an early diagnosis and initiation of the proper antibiotics. Empirical antibiotic treatment often does not cover \textit{B. pseudomallei}, so an early suspicion of melioidosis is essential.

Pneumonia is the most common presenting feature of melioidosis, followed by genitourinary infection and soft tissue infection [1,3]. Similarly, in this study, seven (63.6%) patients presented with pneumonia, three (27.3%) patients presented with genitourinary infection, and one (9.1%) patient presented with soft tissue infection. Abscesses were found in the prostate, spleen, and liver, which are well-recognized sites of abscess formation [3]. A mycotic aneurysm of the aorta was observed in Case 5. Although very uncommon, mycotic aneurysms due to melioidosis have been reported, and are thought to be associated with high mortality and relapse rates [25]. Therefore, melioidosis should be suspected when patients with risk factors for melioidosis present with a mycotic aneurysm. Moreover, although pain is seen in the majority of patients, the presenting symptoms of a mycotic aneurysm are often nonspecific [25]. The patient in Case 5 denied any pain on admission, and the mycotic aneurysm was detected incidentally in the process of evaluation of the fever focus. Therefore, a mycotic aneurysm should be included in the sites for further evaluation in melioidosis patients whose primary infection focus is obscure.

Case 1 had a coinfection with pulmonary tuberculosis and melioidosis. The patient was initially diagnosed with pulmonary tuberculosis, but showed a poor response to antitubercular treatment and was finally diagnosed with melioidosis. Melioidosis might manifest as a chronic pulmonary infection that mimics pulmonary tuberculosis and could be misdiagnosed as tuberculosis, especially in areas endemic for tuberculosis, but not for melioidosis [26]. Moreover, as in this case, a coinfection of melioidosis and pulmonary tuberculosis can occur [27], leading to considerable confusion in the treatment process. Although not well established, previous case reports suggested that mycobacterial infection is a risk factor for melioidosis, reflecting host susceptibility to intracellular pathogens [1]. The patient of Case 1 might have had underlying pulmonary tuberculosis, and this might have acted as a risk factor for melioidosis. Increased suspicion for melioidosis is required when patients with a history of visiting endemic regions present with chronic pneumonia.

In summary, we presented the detailed epidemiological and clinical features of the reported cases of melioidosis from 2003 to 2014.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**References**

1. Cheng AC, Currie BJ. Melioidosis: epidemiology, pathophysiology, and management. Clin Microbiol Rev 2005 Apr;18(2):383–416.
2. Wiersinga WJ, Currie BJ, Peacock SJ. Melioidosis. N Engl J Med 2012 Sep;367(11):1035–44.
3. Currie BJ, Ward L, Cheng AC. The epidemiology and clinical spectrum of melioidosis: 540 cases from the 20 year Darwin prospective study. PLoS Negl Trop Dis 2010;4(11):e900.
4. Seok HJ, Kim JI, Lee JH, et al. A case of septicemia and septic pneumonia due to \textit{Burkholderia pseudomallei}. Infect Chemother 2004;36(2):114–7.
5. Lee SW, Yi J, Joo SI, et al. A case of melioidosis presenting as migrating pulmonary infiltration: the first case in Korea. J Korean Med Sci 2005 Feb;20(1):139–42.
6. Lee HM, Choi SH, Chung JW, et al. A case of disseminated melioidosis in a migrant worker from Thailand. Korean J Lab Med 2009 Apr;29(2):140–4.
7. Son JY, Kwon KT, Choi EJ, et al. Fatal melioidosis in a tourist returning from Cambodia. Korean J Med 2009;77(2):246–50.
8. Park SY, Kang C, Joo E, et al. Septicemic melioidosis presenting as head and neck abscesses. Infect Chemother 2012;44(4):315–8.
9. Hong YM, Kim BS, Park SM, et al. A case of prostatic abscess due to \textit{Burkholderia pseudomallei}. Korean J Med 2011;81(4):526–32.
10. Leelarasamee A, Bovornkitti S. Melioidosis: review and update. Rev Infect Dis 1989 May–Jun;11(3):413–25.
11. Currie BJ, Fisher DA, Howard DM, et al. The epidemiology of melioidosis in Australia and Papua New Guinea. Acta Trop 2000 Feb;74(2–3):121–7.
12. Kingston CW. Chronic or latent melioidosis. Med J Aust 1971 Sep;2(12):618–21.
13. Mays EE, Ricketts EA. Melioidosis: recrudescence associated with bronchogenic carcinoma twenty-six years following initial geographic exposure. Chest 1975 Aug;68(2):261–3.
14. Gan YH. Interaction between \textit{Burkholderia pseudomallei} and the host immune response: sleeping with the enemy? J Infect Dis 2005 Nov;192(10):1845–50.
15. Currie BJ, Fisher DA, Howard DM, et al. Endemic melioidosis in tropical northern Australia: a 10-year prospective study and review of the literature. Clin Infect Dis 2000 Oct;31(4):981–6.
Currie BJ, Jacups SP, Cheng AC, et al. Melioidosis epidemiology and risk factors from a prospective whole-population study in northern Australia. Trop Med Int Health 2004 Nov;9(11):1167–74.

Limmathurotsakul D, Chaowagul W, Chierakul W, et al. Risk factors for recurrent melioidosis in northeast Thailand. Clin Infect Dis 2006 Oct;43(8):979–86.

Malczewski AB, Oman KM, Norton RE, et al. Clinical presentation of melioidosis in Queensland, Australia. Trans R Soc Trop Med Hyg 2005 Nov;99(11):856–60.

Puthucheary SD, Parasakthi N, Lee MK. Septicaemic melioidosis: a review of 50 cases from Malaysia. Trans R Soc Trop Med Hyg 1992 Nov–Dec;86(6):683–5.

Shih HI, Chuang YC, Cheung BM, et al. Sporadic and outbreak cases of melioidosis in southern Taiwan: clinical features and antimicrobial susceptibility. Infection 2009 Feb;37(1):9–15.

Limmathurotsakul D, Wongratanacheewin S, Teerawattanasook N, et al. Increasing incidence of human melioidosis in Northeast Thailand. Am J Trop Med Hyg 2010 Jun;82(6):1113–7.

Suputtamongkol Y, Chaowagul W, Chetchotisakd P, et al. Risk factors for melioidosis and bacteremic melioidosis. Clin Infect Dis 1999 Aug;29(2):408–13.

Chaowagul W, White NJ, Dance DA, et al. Melioidosis: a major cause of community-acquired septicemia in northeastern Thailand. J Infect Dis 1989 May;159(5):890–9.

Cheng AC, Jacups SP, Anstey NM, et al. A proposed scoring system for predicting mortality in melioidosis. Trans R Soc Trop Med Hyg 2003 Sep–Oct;97(5):577–81.

Low JG, Quek AM, Sin YK, et al. Mycotic aneurysm due to *Burkholderia pseudomallei* infection: case reports and literature review. Clin Infect Dis 2005 Jan;40(1):193–8.

Vidyalakshmi K, Chakrapani M, Shrikala B, et al. Tuberculosis mimicked by melioidosis. Int J Tuberc Lung Dis 2008 Oct;12(10):1209–15.

Shetty AK, Boloor R, Sharma V, et al. Melioidosis and pulmonary tuberculosis co-infection in a diabetic. Ann Thorac Med 2010 Apr;5(2):113–5.