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BRIEF REPORT

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

Seung Woo Kim [a], Geun-Yong Kwon [b], Bongyoung Kim [a], Donghyok Kwon [a], Jaeseung Shin [a], Geun-Ryang Bae [a,*]

[a]*Division of Epidemic Intelligence Service, Korea Centers for Disease Control and Prevention, Cheongju, Korea.*
[b]*Division of HIV and Tuberculosis Control, Korea Centers for Disease Control and Prevention, Cheongju, Korea.*

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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.

*Corresponding author.
E-mail: bgr824@naver.com (G.-R. Bae).

1. Introduction

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, including Thailand, Malaysia, Cambodia, Laos, and Vietnam [1]. *B. pseudomallei* dwells in soil and water, and is transmitted via percutaneous inoculation, inhalation, or the ingestion of infected food or water. Consequently, individuals in regular contact with soil and water are frequently affected [2]. Melioidosis shows a wide range of clinical manifestations with varying severity. Pneumonia is the most frequent presenting feature, followed by genitourinary infection, skin infection, septic arthritis, and osteomyelitis [3]. Disseminated abscess formation in the internal organs is the hallmark of melioidosis. With increasing international travel and migration, cases of melioidosis imported from endemic regions are being reported regularly, and it is important that physicians should be more aware of melioidosis. In South Korea, there were 11 known cases of melioidosis from 2003 to 2014, and the first six of these cases had been reported previously [4–9]. Here, we summarize the epidemiological and clinical manifestations of the imported melioidosis in South Korea.

2. Materials and methods

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.

3. Results

3.1. Demographic features

Since the first report in 2003, 11 cases of imported melioidosis have been reported in South Korea. The mean age of the patients was 52.3 years, ranging from 32 years to 66 years. Ten patients (90.9%) were older than 45 years, and all patients were male. With regard to their occupations, the patients included businessmen (36.3%), construction workers (18.2%), welders (18.2%), engineers (9.1%), drivers (9.1%), and actors (9.1%). The demographic, epidemiologic, and clinical features of the patients are summarized in Table 1.

3.2. Epidemiologic features

All the patients had visited Southeast Asia, which is a traditional endemic region for melioidosis. The countries from which melioidosis were imported included Malaysia (27.3%), Thailand (27.3%), Cambodia (18.2%), Philippines (9.1%), Indonesia (9.1%), and Vietnam (9.1%). Domestic cases of melioidosis have never been reported in South Korea, based on previous epidemiological investigations, and so all cases are thought to be imported. Nine patients had stayed in the endemic region for >1 month. However, two patients developed melioidosis after a few days of travel to the endemic region. Four patients developed symptoms during their stay in the endemic region and were diagnosed with melioidosis after returning to South Korea. The remaining seven patients developed initial symptoms after returning to South Korea. Of these patients, the interval between returning to South Korea and symptom onset ranged from 1 day to 3 years. Seven patients had at least one risk factor for melioidosis. Diabetes mellitus was the most frequent risk factor (63.6%), followed by lung cancer (9.1%) and chronic kidney disease (9.1%).

3.3. Clinical manifestations

Eight patients had acute infections (symptom duration of <2 months) and three had chronic infection (symptoms for > 2 months). Of these 11 patients seven (63.6%) presented with pneumonia, three (27.3%) with genitourinary infection, and one (9.1%) with soft tissue infection. Abscess formation was observed in the prostate in three patients, and in the spleen and liver in one patient. Three patients had septic shock on admission with

Table 1. Clinical features and results of evaluations of melioidosis patients in South Korea, 2003 to 2014.

	Case										
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	Philippines	Thailand	Cambodia	Vietnam	Thailand
Occupation	Engineer	Businessman	Driver	Welder	Construction worker	Construction worker	Welder	Businessman	Actor	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	3 years	During stay	6 weeks	1 month	During stay	During stay	9 months	1 day	50 days	2 months	During stay
Risk factors	Diabetes	None	Diabetes	Diabetes	None	Diabetes	None	Diabetes, CKD	Diabetes	Diabetes, cancer	None
Acute/chronic	Acute	Chronic	Acute	Acute	Acute	Acute	Chronic	Acute	Acute	Acute	Chronic
Presenting symptoms	Fever	Fever, cough, myalgia	Dyspnea	Dyspnea	Facial swelling, fever	Dysuria, fever	Cough	Fever	Fever, dysuria	Fever, cough	Fever, dysuria
Clinical manifestation	Pneumonia	Pneumonia	Pneumonia	Pneumonia	Soft tissue infection	GU infection	Pneumonia	Pneumonia	GU infection	Pneumonia	GU infection
Shock on admission	Absent	Absent	Present	Present	Absent	Absent	Absent	Absent	Present	Absent	Absent
CXR/chest CT	Multiple nodules	Multiple nodules	Multiple nodules	Ill-defined opacity	Normal	Patchy opacities	Mass-like consolidation	GGO	GGO	Consolidation, lung cancer	Multiple nodules
Other findings			Spleen/liver abscess		Head/neck abscess	Prostate abscess			Prostate abscess	Hand swelling	Prostate abscess, aortic aneurysm
Diagnosis	Blood culture	Bronchoscopic washing culture	Blood culture	Blood culture	Blood & abscess culture	Blood & abscess culture	Tissue (lung) & sputum culture	Blood culture	Blood culture	Blood culture	Tissue (aorta) & blood culture
Bacteremia	Present	Absent	Present	Present	Present	Present	Absent	Present	Present	Present	Present
Outcome	Survived	Survived	Died	Died	Died	Survived	Survived	Survived	Died	Survived	Survived

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

evidence of organ dysfunction, all of whom underwent rapid progression of the disease and died. Nine patients were bacteremic. In the remaining two patients, *B. pseudomallei* grew in bronchoscopic washing and surgical specimen obtained by pulmonary lobectomy. Four patients died and seven patients survived without relapse.

Of the five patients reported since 2011, two patients showed unusual clinical manifestation. Case 1 had a coinfection with pulmonary tuberculosis and melioidosis. The patient initially presented with chronic cough, and *Mycobacterium tuberculosis* was cultured in a lung biopsy. The patient underwent antitubercular therapy. However, the cough persisted, and the patient underwent a left upper lobectomy more than a year after returning from the endemic region. The surgical specimen grew *B. pseudomallei*. Case 5 was the first melioidosis patient in South Korea presented with a mycotic aneurysm of the aorta. The patient initially developed dysuria and was diagnosed with a prostate abscess. Although fever subsided after the treatment, fever recurred about 50 days after its onset. The subsequent diagnostic workup revealed a mycotic aneurysm of the aorta. The patient underwent surgical treatment of the aneurysm, and blood and the surgical specimen grew *B. pseudomallei*.

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 *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.

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