Epidemiological and Clinical Features of Melioidosis: A Report of Seven Cases from Southern Inland China

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Abstract. Some subtropical regions with similar climatic conditions to melioidosis-endemic areas, such as southern Guangxi, may be new endemic zones for melioidosis. We retrospectively reviewed seven culture-proven melioidosis patients from October 2006 to March 2015. Their clinical characteristics, diagnosis, and treatment, and the geographical and environmental factors were analyzed. Seven male patients lived at latitudes of 21–23°N in Beihai, Nanning, Chongzuo City of the Guangxi Province. Symptom onset occurred during the rainy season. All patients had pneumonia, six patients had diabetes, five patients had a history of wounds or exposure to soil or water, and two patients had liver and spleen abscesses. Most patients were misdiagnosed before the confirmatory laboratory testing. The final diagnosis was confirmed as melioidosis by isolation of *Burkholderia pseudomallei* in a culture of blood or pus. The 6- to 17-month treatment included carbapenems, ceftazidime, or other antibiotics active against the organism in vitro. All patients initially appeared cured, but two subsequently had recurrent melioidosis. In non-highly endemic areas, there is often a lack of awareness of melioidosis, and this leads to misdiagnoses. Other subtropical regions with climatic conditions similar to the highly melioidosis-endemic areas such as southern Guangxi may also be melioidosis endemic.

INTRODUCTION

Melioidosis, caused by *Burkholderia pseudomallei*, was first described in Yalong in 1912.¹ Incidence rates of *B. pseudomallei* are increasing in regions of Southeast Asia and Northern Australia to which it is highly endemic. In mainland China, only sporadic cases have been reported, largely because it is an underrecognized and underreported disease. Guangxi, located in southern China at a latitude of 20–26°N, has a subtropical monsoon climate. Melioidosis is a very rare but emerging disease in Guangxi. We encountered seven cases of septicemia due to melioidosis in Guangxi. This study aimed to retrospectively analyze these seven cases and to discuss the epidemiology, clinical characteristics, diagnosis, and treatment of melioidosis.

MATERIALS AND METHODS

Study subjects. The study included seven patients with melioidosis admitted to Guangxi Medical University from October 2006 to March 2015. They were identified by repeated culture of blood, bone marrow, or pus cultures. This study was approved by the Faculty of Medicine, First Affiliated Hospital of Guangxi Medical University Ethics Committee. The identities of patients and their data remained anonymous.

Diagnosis. Bacterial identification and bacterial antimicrobial susceptibility testing were recommended by the Clinical and Laboratory Standards Institute guidelines. Blood culture bottles were cultured in the Bact/ALERT 3D 240 automatic blood culture machine (BioMerieux, Marcy-l'Étoile, France). Bacteria were isolated with a MacConkey and blood agar plate. A VITEK-32 Compact automated identification system (BioMerieux) was used for bacterial identification and bacterial antimicrobial susceptibility testing. Pneumonia was diagnosed based on the clinical symptoms and signs (e.g.,

fever, cough, sputum production, shortness of breath, or pleuritic chest pain) and an abnormal chest computed tomography scan. The abscesses were diagnosed when the abdominal ultrasonogram revealed a large, well-defined hypoechoic mass lesion in the liver or spleen.

RESULTS

Epidemiology. All patients were admitted during the rainy season from August to October. All patients lived in latitudes of 21–23°N within Beihai, Nanning, Hechi, Chongzuo City in the Guangxi Province, where the rainy season is from April to October. During the rainy season, the temperatures range from 20.0 to 33.3°C, humidity ranges from 76% to 81%, average rainfall rates are > 800 mm, and altitudes range from 12 to 177 m (Figure 1).

Clinical manifestations. All seven male patients were Guangxi natives and their ages ranged from 36 to 63 years. The infection of *B. pseudomallei* for all patients manifested as sepsis, with initial symptoms of chills and a high-grade fever. All patients had pneumonia, five patients had bone infection, four patients had skin and soft tissue infection, two patients had liver and spleen abscesses, and one patient developed septic shock. Three patients were known to be diabetic previously. The other three patients satisfied the international criteria for the diagnosis of diabetes. Case 4 had an increased fasting blood glucose level; however, after completing all the treatments, the blood glucose level reached normal limits (Table 1).

Results of the blood culture and antibiotic susceptibility testing. All patients in our study underwent a blood culture within the first 1–3 hours of admission. Of the seven patients, five were blood culture positive, three were pus culture positive, one was bone marrow culture positive, and two were both blood and pus culture positive for *B. pseudomallei*. All *B. pseudomallei* isolates were sensitive to trimethoprim-sulfamethoxazole, levofloxacin, carbapenem, and β -lactam + β -lactamase inhibitors and they were resistant to gentamicin, amikacin, and aztreonam.

Treatment and outcome. All patients had a high-grade fever, and the empirical treatment comprised imipenem, meropenem, vancomycin, ceftazidime, cefoperazone/sulbactam, or

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FIGURE 1. Map of Guangxi, China, showing the geographical distribution of the seven cases of melioidosis. This figure appears in color at www.ajtmh.org.

piperacillin–tazobactam. Treatment of melioidosis included intravenous and oral therapy. Carbapenems (either meropenem or imipenem), ceftazidime, cefoperazone/sulbactam, or levofloxacin was used based on the results of the antibiotic susceptibility tests. The duration of intravenous antimicrobial treatment, until the clinical effects were observed, ranged from 28 to 34 days. Once the patients showed no fever for 48 hours and had a negative repeat blood culture for seven consecutive days, intravenous therapy was changed to oral therapy. Trimethoprim–sulfamethoxazole was commonly used as oral therapy, either alone or in combination with amoxicillin/clavulanic acid. The duration of oral therapy ranged from 5 to 10 months (average, 6 months). All patients were given intensive insulin therapy and four patients underwent surgical drainage of abscesses. The total duration of treatment was 6–17 months (average, 7 months), and all patients initially recovered clinically. The longest treatment course in our group was 17 months because of the patient's serious condition, premature withdrawal of drugs, and poor glucose control. Patients were generally reviewed at monthly infectious disease outpatient visits until completion of eradication therapy. However, two patients had subsequent culture-positive recurrence; they presented with chills, fever, and skin and soft tissue abscesses due to the premature withdrawal of drugs after hospital discharge. After reinitiating the same antimicrobial treatment, these two patients were cured. All patients were followed after discharge, and there has been no further recurrence till date (Table 2).

DISCUSSION

Melioidosis is endemic in the tropical areas of the world.² Melioidosis-endemic regions have tropical monsoon climates and abundant rainfall. During the rainy season, the average rainfall rates range from 800 to 1,712.7 mm, temperatures range from 26.3 to 39.2°C, humidity ranges from 77.3% to

88.5%, and average altitudes range from 12 to 177 m.^{2–4} In endemic areas, melioidosis mainly occurs in the wet season. *Burkholderia pseudomallei* thrive in soil, surface water, or other natural environments and are distributed in the environment during rainfall.⁵ Guangxi is located in southern China and has a subtropical monsoon climate. Fifteen years ago, in Nanning, Beihai, Chongzuo, and other cities at latitudes of 21–23°N within the southern Guangxi province, a number of epidemiological studies showed that *B. pseudomallei* was isolated from animals and soils, and antibodies to *B. pseudomallei* were detected in humans, indicating that natural *B. pseudomallei* strains were present in Guangxi.⁶ However, it was not until 2010 that cases of melioidosis in humans were reported.⁷ The seven patients in our study lived at latitudes of 21–23°N in Beihai, Chongzuo, and Nanning City in the Guangxi Province. They had never traveled outside of Guangxi, so the infections were considered to have been acquired locally. The geography, climate, environment, rainfall, soil, and other factors from the municipalities are similar to those of areas where melioidosis is endemic.^{8,9}

Melioidosis is usually acquired through skin abrasions or wounds, or inhalation, but zoonotic and person-to-person spread is uncommon.¹⁰ Melioidosis is more common in men; the susceptible population includes farmers, fishermen, and outdoor workers, especially those with diabetes, chronic lung disease, chronic kidney disease, long-term steroids use, and people older than 50 years.¹¹ Among these known risk factors of melioidosis, diabetes is the most significant.^{12–16} All patients in our study were men and two patients were ≥ 50 years; in addition, most of them were farmers or fishermen, had a history of wounds or exposure to soil or water, and had type 2 diabetes mellitus or other underlying diseases. Thus, the seven patients from the subtropical region of southern Guangxi presented with similar onset seasons, risk factors, and possible infection routes as cases in other melioidosis-endemic regions.

TABLE 1
Clinical data of the seven patients

Case no.	Age (year)	Gender	Occupation	Month of occurrence	Duration of symptoms (day)	Clinical symptoms and signs	Sites of infection	Type of exposure	Risk factors
1	52	Male	Farmer	September	28	Sepsis and pneumonia	Lung, right lower leg, and ankle	Stabbed by a fish bone in the right calf and contact with soil and water	Type 2 diabetes mellitus (new diagnosis)
2	48	Male	Worker	August	28	Sepsis and pneumonia	Lung, left knee and ankle, and right knee	Skin and soft tissue contusion of the left ankle and contact with soil	Type 2 diabetes mellitus
3	36	Male	Fisherman	September	30	Sepsis, pneumonia, liver and splenic abscess, and lymphadenitis	Lung, liver, spleen, pancreas, lymph node, and right upper mediastinum	Stabbed by a fish and contact with water	Kidney calculi and type 2 diabetes mellitus
4	43	Male	Farmer	October	34	Sepsis and pneumonia	Lung, right temporal fossa, parotid gland, nasopharynx, right parietal wall, sphenoid, ethmoid, right facial area, and right lower extremity	Contact with soil and water	No risk factors
5	63	Male	Unemployed	October	30	Sepsis and pneumonia	Lung and left ankle joint	Unknown	Age $\geq$ 50 years, type 2 diabetes mellitus (new diagnosis), and kidney calculi
6	47	Male	Government staff member	October	30	Sepsis, pneumonia, liver and splenic abscess, and urinary tract infections	Lung, liver, spleen, and right ankle joint	Unknown	Type 2 diabetes mellitus
7	45	Male	Farmer	September	30	Sepsis, pneumonia, and lymphadenitis	Lung, lymph node, right arm, and upper tibia	Contact with soil and water	Type 2 diabetes mellitus (new diagnosis)

Melioidosis is readily misdiagnosed in non-highly endemic areas because of a lack of familiarity with its clinical features. The highly variable manifestations of melioidosis make the diagnosis impossible without confirmatory laboratory testing.

In our study, six patients were misdiagnosed. Only one patient was diagnosed as having melioidosis, as he was blood culture positive for *B. pseudomallei* and treated at Beihai People's Hospital before being transferred to our hospital. Their clinical

TABLE 2
Treatment of the seven patients

Case no.	Primary diagnosis	Initial treatment	Time to diagnosis of melioidosis	Intravenous treatment and time	Oral treatment and time	Time to recurrence
1	Sepsis, pneumonia, and septic shock	Meropenem plus vancomycin	5 days after admission	Imipenem for 14 days and ceftazidime for 14 days	Trimethoprim-sulfamethoxazole for 6 months	None
2	Soft tissue infection of the right lower extremity and type 2 diabetes mellitus	Cefoperazone/sulbactam plus clindamycin	6 days after admission	Imipenem for 28 days	Trimethoprim-sulfamethoxazole for 5 months	None
3	Pulmonary tuberculosis	Ceftazidime plus clindamycin	9 days after admission	Ceftazidime for 30 days	Trimethoprim-sulfamethoxazole for 1 month	2 months after withdrawal of drugs
4	Encephalitis	Ceftazidime plus clindamycin	17 days after admission	Cefoperazone/sulbactam plus levofloxacin for 34 days	Trimethoprim-sulfamethoxazole for 6 months	None
5	Pneumonia and type 2 diabetes mellitus	Vancomycin plus piperacillin/tazobactam	14 days after admission	Ceftazidime for 30 days	Trimethoprim-sulfamethoxazole for 6 months	None
6	Septicemic melioidosis, pneumonia, and type 2 diabetes mellitus	Imipenem plus ceftazidime	The day of admission	Imipenem plus ceftazidime for 30 days	Trimethoprim-sulfamethoxazole plus amoxicillin/clavulanic acid for 6 months	None
7	Severe pneumonia, sepsis, type 1 respiratory failure, and type 2 diabetes mellitus	Meropenem plus vancomycin	5 days after admission	Meropenem plus ceftazidime for 30 days	Trimethoprim-sulfamethoxazole plus for 2 months	2 months after withdrawal of drugs

manifestations of anemia, weight loss, a severe systemic inflammatory response, and multisite abscess formation are characteristic of septicemic melioidosis. Abscesses were also identified in the bones, joints, pancreas, parotid gland, and other organs; we also noticed that the pus had a distinctive earthy and musty odor, which is uncommon in other pathogenic infections.

Current international treatment guidelines for melioidosis are usually divided into two phases: intravenous therapy is given for 10–14 days and oral therapy is administered for 3–6 months. Ceftazidime or a carbapenem (either imipenem or meropenem) is the first-line intravenous therapy; trimethoprim/sulfamethoxazole and co-amoxiclav are preferred for oral therapy.^{17,18} We note that some antimicrobial prescriptions such as a combination of cefoperazone/sulbactam plus levofloxacin (case no. 4) and a combination of ceftazidime plus carbapenem (case nos. 6 and 7) were not recommended as antimicrobial regimens for melioidosis, and there is no evidence to support such prescriptions. In addition, studies reported in the literature have recommended that early generation β -lactams, aminoglycosides, macrolides, and fluoroquinolones should not be used for treating melioidosis because of the high failure rate.^{18,19} Information and standard guidelines for the management of melioidosis need to be provided to all health-care workers in China and nonendemic areas for melioidosis. However, patients treated according to these guidelines still have high mortality and relapse rates, particularly in those with poor drug adherence.^{13–16} Extended periods of treatment may be needed to achieve cure and prevent recurrent infection. The median duration of intravenous therapy for patients in Northern Australia is now approximately 4 weeks and this may need to be extended to 8 weeks followed by 6 months of oral therapy for severe infections.²⁰ The durations of intravenous and oral therapy in our study were longer than those recommended in the current international guidelines. Compared with the high mortality in Thailand, Australia, Singapore, and Malaysia,^{13–16} our study had a low mortality (0%; 7/7). This could be due to the small sample size, along with the facts that all patients had subacute presentations (duration of symptoms before presentation > 7 days), only one patient had septic shock on clinical presentation, and durations of intravenous and oral therapy were longer.

In summary, in nonendemic areas, there is often a lack of awareness about melioidosis. This leads to misdiagnoses, which can have fatal consequences. In our study, the epidemiology and clinical characteristics of melioidosis observed from the Guangxi region of southern China, a subtropical region, are very important for raising awareness of melioidosis. The pathogenic features, clinical characteristics, drug sensitivity results, and the geography, climate, environment, soil, rainfall, and other factors associated with melioidosis in Guangxi are very similar to those of known endemic regions. Some other subtropical regions with similar climatic conditions to melioidosis-endemic areas such as southern Guangxi may be melioidosis endemic.

Received February 18, 2017. Accepted for publication January 25, 2018.

Published online April 2, 2018.

Acknowledgments: We thank Zhenbo Feng, Professor of Pathology, Department of Pathology, First Affiliated Hospital of Guangxi Medical University.

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