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Case Report: Fatal Co-Infection–Melioidosis and Leptospirosis

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Abstract. Co-infection of melioidosis and leptospirosis is uncommon. We report here four such cases, confirmed by blood culture for melioidosis and blood polymerase-chain reaction for leptospirosis, which occurred among rescuers involved in a search and rescue operation for a young man who was suspected to have drowned in Lubuk Yu, a recreational forest in Pahang, Malaysia. Despite treatment, three of the patients died from the co-infection.

INTRODUCTION

Melioidosis caused by the gram-negative bacillus, *Burkholderia pseudomallei*, is a common infection in the tropical and subtropical regions, especially in tropical Australia[1] and in Southeast Asian countries, particularly Malaysia,[2,3] Thailand,[4] and Singapore.[5] Leptospirosis is another common tropical infectious disease. Both diseases are zoonotic and the organisms can be found in soil and water. Confirmed co-infection of melioidosis and leptospirosis was not previously reported except for a possible case in Taiwan in which the diagnosis of leptospirosis was based on serology.[6]

On June 26, 2010, a young man was suspected to have drowned at Lubuk Yu, a natural recreational forest with river and waterfall in Pahang, Malaysia. A team composed of more than 150 members from the police, army, divers, firemen, and volunteers from a nearby village were involved in the search and rescue operation. There was heavy downpour on the first 2 days. Part of the slope near the river bank eroded, bringing down the soil, rubbish, and debris into the river. As the river water level receded later, multiple puddles were formed. During the operation, some of the rescuers swam in the river, although many just walked along the river bank searching for the victim. All the rescuers used water from the river particularly the stagnant part to wash their hands, legs, and faces. The operation ended after his body was recovered at about 10 km downstream 5 days later.

Following this rescue, at least 20 people presented with an acute illness and 10 were confirmed melioidosis by bacteriological culture. Among them, four were positive for leptospirosis by a blood polymerase chain reaction (PCR) test. We describe the clinical presentation, management, and outcome of these four patients with melioidosis and leptospirosis co-infections.

CASE 1

The patient was a 50-year-old fireman who was recently diagnosed with type 2 diabetes mellitus. He was admitted to Jengka Hospital (JH), a district hospital on July 3, 2010 after complaining of high-grade fever associated with generalized myalgia, arthralgia, and headache a day after the search and rescue operation ended. He also complained of watery diarrhea, nausea, and vomiting for 2 days. He denied any cough or shortness of breath. Physical examination found him to be febrile, hemodynamically stable, and having bibasal coarse crepitations. Blood investigations showed a leukocyte count of 13.6×10^6/L (92% neutrophils), platelet count of 102×10^9/L, mildly elevated liver transaminases (alanine transaminase [ALT] 121 U/L, aspartate aminotransferase [AST] 133 U/L), and normal renal function. Blood films for malarial parasites and dengue rapid test were negative. Chest radiograph showed infiltrates in both lower zones. He was initially treated for community-acquired pneumonia with intravenous (IV) Augmentin 1.2 g tds and oral Erythromycin 500 mg qid, but when his fever persisted after 5 days of treatment, he was referred to Sultan Ahmad Shah Hospital (HoSHAS), a general hospital for further management.

Upon arrival at the Emergency Department (ED) of HoSHAS, he was febrile at 38°C with a blood pressure of 121/84 mmHg and heart rate of 102/min. He was not tachypneic and appeared to be in discomfort caused by severe generalized myalgia. He was pink and mildly icteric and had a three fingerbreadth non-tender hepatomegaly but no splenomegaly or ascites. Auscultation of the lungs revealed similar findings to the previous examination. His antibiotics were changed to IV Ceftriaxone 2 gm daily and oral Doxycycline 100 mg bd. Later, blood culture confirmed *B. pseudomallei* and blood PCR for leptospira was positive. The antibiotic IV Ceftriaxone was changed to IV Ceftazidime 2 g tds and IV Penicillin 1.5 mega unit qid was added.

After a week in the hospital, he remained stable apart from an unsettling fever and uncontrolled hyperglycemia. Ultrasonographic examination did not reveal any hepatic or splenic abscesses. Physical examination revealed right knee effusion. Right knee joint aspiration was performed under local anesthesia and 20 mL of pus was drained. This was followed by right knee arthrotomy and washout under general anesthesia, which drained out 50 mL of frank pus that grew *B. pseudomallei.*

Post-surgery, he developed hypotension that required vasopressor support. He was then ventilated in the high dependency ward (HDW). The antibiotic IV Ceftazidime was changed to IV Meropenem 1 g tds in view of general deterioration of his condition. His condition improved and fever settled. He was extubated and vasopressor support was stopped a week after surgery. Unfortunately, he arrested 2 days later in the ward. There was no electrocardiogram (ECG) monitoring and postmortem was declined.

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CASE 2

This 29-year-old Chinese farmer was an active smoker and diagnosed with type 2 diabetes mellitus, hypertension, and obesity for the past 2 years. He had a history of a right gluteal abscess a few months ago that was surgically drained without any complication. He presented with symptoms of high-grade fever associated with generalized myalgia, watery diarrhea, and vomiting that began 3 days after the search and rescue operation. There was no history of cough or bleeding tendencies. He was initially diagnosed to have viral fever and was treated as an outpatient. However, his symptoms worsened and he was admitted to JH 2 days later. The next day, he developed sudden onset of breathlessness and was transferred to HoSHAS for further management.

Upon arrival at the ED of HoSHAS, he was found to be tachypneic with a respiratory rate of 60 breaths/min and his arterial blood gas analysis showed severe type 1 respiratory failure (pH 7.409, pCO_2 18.8 mm of Hg, pO_2 47.9 mm of Hg, HCO_3 12.0 mmol/L) despite being put onto a high flow mask with 15 L/min oxygen. Chest radiograph was suggestive of acute respiratory distress syndrome. He was intubated and ventilated. He developed cardiopulmonary arrest post-intubation and was successfully resuscitated. His blood pressure was supported by IV noradrenalin infusion and IV Cefepime 1 g tds and IV Azithromycin 500 mg daily were started. He was then ventilated in the HDW. Blood investigations showed a serum creatinine of 85 μmol/L, sodium of 113 mmol/L, platelet count of 86×10^9/L with normal leukocyte count, and hemoglobin. Blood culture and blood for leptospira PCR were sent. Unfortunately, he developed cardiopulmonary arrest again and could not be revived. Blood culture later returned positive for *B. pseudomallei* and PCR for leptospira was also positive. Post-mortem was not performed.

CASE 3

The patient was a 55-year-old Chinese mechanic, an ex-smoker, who had type 2 diabetes mellitus and hypertension for the past 10 years. He had also undergone coronary artery bypass surgery 6 years ago. He presented to JH on July 6, 2010 complaining of a non-productive cough that started 2 days after the search and rescue operation, which was associated with nausea, vomiting, myalgia, and watery diarrhea. Physical examination was unremarkable and his vital signs were stable. He was admitted to the hospital because of poor oral intake and was started on oral co-amoxiclav 625 mg twice daily.

The next day, he developed abrupt-onset breathlessness and hypotension that failed to respond to fluid resuscitation. There was no chest pain, fever, or hemoptysis. He was started on IV noradrenalin infusion. His oxygen saturation was 98% under 3 L/min oxygen by nasal cannula. Auscultation of his lungs revealed bibasal coarse crepitations. Blood assays revealed a platelet count of 126×10^9/L, normal leukocyte count (8.9×10^6/L), and hemoglobin level (14.1 g/dL). Blood urea was 6.5 mmol/L, serum creatinine was 87 μmol/L, potassium was 3.1 mmol/L, and sodium was 127 mmol/L. His ECG did not show any acute ischemic changes. Chest radiograph showed bilateral patchy consolidation. He was subsequently referred to HoSHAS for further management.

Upon arrival in HoSHAS, the patient was dependent on IV noradrenalin and IV dobutamine infusions. His blood pressure was 107/65 mm of Hg on arrival to the ED. Blood gas analysis showed pH 7.405, pO_2 67.0 mm of Hg, pCO_2 18.4 mm of Hg, HCO_3 11.6 mmol/L. Repeat blood tests at the ED revealed mild renal impairment (urea 10.0 mmol/L, creatinine 152 μmol/L) with worsening thrombocytopenia (platelet count 56×10^9/L) and leukopenia (1.6×10^6/L). Sinus tachycardia was noted on the ECG and the chest radiograph showed a worsening pneumonia. Blood culture was taken immediately.

He was intubated and ventilated because of worsening respiratory failure. He was treated for community acquired pneumonia and started on IV Ceftriaxone 2 g daily and IV Azithromycin 500 mg daily. His condition did not improve over the next 2 days. He developed atrial fibrillation with rapid ventricular response on Day 3 of admission that was rate- controlled with IV Digoxin. Oral oseltamivir was added for suspected influenza H1N1 co-infection. He developed oliguric acute renal failure secondary to septicemic shock that required hemodialysis. Unfortunately, he died on Day 4 of admission despite intensive monitoring and treatment. After he died, blood culture confirmed *B. pseudomallei* and blood PCR for leptospira was positive.

CASE 4

This 60-year-old farmer, an active smoker had type 2 diabetes mellitus for the past 12 years. He presented to JH on July 7, 2010 complaining of fever, generalized myalgia, arthralgia, nausea, and watery diarrhea that began 3 days after the search and rescue operation. Apart from high-grade fever and hyperglycemia, he was hemodynamically stable and physical examination was unremarkable. Blood investigations showed mild leukocytosis (11.4×10^6/L), normal hemoglobin level (12.7 g/dL), and platelet count (198×10^9/L). Liver profile revealed mildly elevated transaminases (ALT 98 U/L, AST 112 U/L). As the outbreak was already recognized at that time (even though bacteriology was still pending), he was transferred to HoSHAS the following day for further management.

On arrival to the ED of HoSHAS, he was found to be pink, dehydrated, but not tachypneic. He had a temperature of 39°C, an admitting blood pressure of 120/84 mm of Hg, and a good-volume pulse of 90/min. Pulse oximetry recorded an oxygen saturation of 100% under venturi mask 40% oxygen. There was no jaundice or conjunctivitis noted. He did however have non-tender hepatomegaly of two fingerbreadths below his right subcostal margin. There was no splenomegaly or ascites appreciated. His heart and breath sounds were normal on auscultation. His major muscle groups of all limbs were tender, especially his right thigh, which was severely tender. There was no regional lymphadenopathy. Further blood assays showed hyponatremia (125 mmol/L) but otherwise normal renal function. Hb_{A1C} was 9.9%.

He was initially started on IV Ceftriaxone 2 g daily and oral Doxycycline 100 mg bd at JH. He was also vigorously rehydrated with 0.9% saline infusion. Additional blood culture and serology were also ordered. After confirming the outbreak of melioidosis and leptospirosis, IV Ceftriaxone was switched to high-dose IV Ceftazidime 2 g tds and IV crystalline Penicillin 1.5 mega unit 6 hourly was added. Oral Doxycycline was stopped.

His condition continued to improve clinically over the next few days. Blood culture confirmed *B. pseudomallei* and blood

TABLE 1
Summary of patients with confirmed melioidosis and leptospirosis

No.	Age	Occupation	Possible incubation period (days)	Co-morbid	Date of onset	Date and place of admission	Initial symptoms	Date of positive tests	Complications date and time of death
1	50	Fireman	1–5	NIDDM smoker	1/7/10	JH: 3/7/10 HoSHAS: 8/7/10	Fever, myalgia, arthralgia, headache, diarrhea, vomiting	Blood C&S: positive-B pseudomallei 10/7/10 leptospirosis PCR:POSITIVE-10/7/10	Right knee septic arthritis hypotension 27/7/10 @ 0311H
2	29	Farmer	3–7	NIDDM HPT obesity smoker	3/7/10	JH: 5/7/10 HoSHAS: 8/7/10	Fever, myalgia, diarrhea, vomiting	Blood C&S: positive-B pseudomallei 8/7/10 leptospirosis PCR:POSITIVE-8/7/10	ARDS 8/7/10 @ 1410H
3	55	Farmer	3–7	NIDDM HPT IHD Ex-smoker	3/7/10	JH: 6/7/10 HoSHAS: 7/7/10	Cough, vomiting, myalgia, diarrhea.	Blood C&S: positive-B pseudomallei 8/7/10 leptospirosis PCR:POSITIVE-8/7/10	ARDS Acute renal failure hypotension atrial fibrillation 9/7/10 @ 0140H
4	60	Fireman	2–6	NIDDM smoker	2/7/10	JH: 7/7/10 HoSHAS: 8/7/10	Fever, myalgia, arthralgia, diarrhea	Blood C&S: positive-B pseudomallei 10/7/10 leptospirosis PCR:POSITIVE-10/7/10	Unstable angina alive

Date of rescue operation: 26–30 June 2010.
NIDDM = non-insulin-dependent diabetes mellitus; HPT = hypertension; IHD = ischemic heart disease; JH = Jengka Hospital; ARDS = adult respiratory distress syndrome; HoSHAS = Sultan Haji Ahmad Shah Hospital.
Dates are in DD/MM/YY.

PCR for *Leptospira* was positive. Abdominal ultrasonography did not show any hepatic or splenic abscesses. Nevertheless, he still had high-grade spiking temperatures. A week later, he developed angina pectoris with dynamic ST-T changes on his ECG. His cardiac enzymes were not elevated. Consequently, he was diagnosed with unstable angina and treated promptly with antiplatelets and low-molecular-weight heparin. There were no immediate complications arising from his acute coronary syndrome.

His fever completely settled 10 days later and his glycemic control improved. He was discharged home 2 weeks later with oral Doxycycline 100 mg bd and oral co-trimoxazole 960 mg bd for 5 months. No follow-up leptospirosis serology was performed. Summaries of all four patients are in Table 1.

DISCUSSION

Melioidosis is endemic in Pahang, Malaysia with an incidence of 6.02/100, 000 populations/year.[3] It commonly occurs during the rainy season.[1,3,4] Outbreak of melioidosis is uncommon and a few clusters or outbreaks were reported in the literature. The outbreak in Taiwan was following a typhoon and in Western Australia, it was caused by contaminated water supply.[6,7] Our outbreak was noted on July 8, 2010 when at least 20 patients presented with acute febrile illness after being involved in the search and rescue operation. Ten patients had blood culture confirmed melioidosis and four of them had concomitant leptospirosis based on blood PCR (the details of the outbreak will be reported separately). Both *B. pseudomallei* and *Leptospira interrogans* are present in the fresh water and soil; therefore, co-infection is possible as shown in our cases. Furthermore, we have isolated *B. pseudomallei* in the soil and stagnant water at Lubuk Yu. Several water samples from this site were positive for leptospira PCR.

All four patients had diabetes mellitus, which is the most common predisposing factor for melioidosis in Pahang.[3] The mode of transmission of melioidosis in this outbreak is likely to be caused by inhalation rather than cutaneous contact as none of our patients had obvious wounds, cuts, or significant skin lesions. Another evidence of inhalation as the likely mode of transmission was the heavy rainfall and flooding a day earlier that could have stirred up the organisms from the soil. Together with strong wind that was present during the period of the rescue operation, infected aerosolized particles could have been spread as it happened in the outbreak of melioidosis following a typhoon in Taiwan.[8] Furthermore, these four patients did not swim, bathe in the river, walk bare-footed, or come into contact with the soil but they did use water from the river to wash their hands and faces. This predisposed them to leptospirosis, as the portal of entry of leptospira is by the conjunctiva, in addition to abraded skin and mucous membrane. There were divers and other rescuers who swam in the river but none fell ill.

In leptospirosis, more than 75% of patients present with fever, myalgia, and headache and almost half may have nausea, vomiting, and diarrhea.[9] These symptoms were present in all our patients and because of these non-specific symptoms, some of our patients were treated as viral infections initially. These symptoms were likely caused by leptospirosis rather than melioidosis. Myalgia, which is a characteristic feature in leptospirosis but not melioidosis, was seen in all our patients and at least two of them had severe myalgia. The classical appearance of pulmonary hemorrhage, which is a rare complication of leptospirosis, was not seen in our patients but at least two of them had fulminant pneumonia that may be caused by melioidosis rather than leptospirosis. Other than pneumonia, abscesses in the liver, spleen, prostate, brain, and other organs are characteristics of melioidosis, which were not seen in these four patients.[1–3] However, one patient had septic arthritis, which is a common presentation of melioidosis but not leptospirosis.

The diagnosis of leptospirosis was made by blood PCR testing. Polymerase chain reaction was carried out using G1/G2 primers, as described by Fonseca Cde and others.[10]

This PCR technique only amplified the conserved sequences of *L. interrogans* and therefore was unable to differentiate the serovars of leptospirosis. The information on serovar is indeed helpful for epidemiological purposes but rapid diagnosis of the infection was of utmost priority in this event. Serology tests for leptospirosis were done on three patients only and were negative. There were no repeated serology tests as these patients died within 8 weeks of admission.

Mortality caused by melioidosis is extremely high especially in the bacteremic form. A study by Puthucheary and others[2] showed that the mortality was 65% in patients with bacteremic melioidosis. In Pahang, the overall mortality was 54% as compared with 19–44% in Australia, Singapore, and Thailand.[1,3–5] Mortality of leptospirosis was between 5% and 54% in hospitalized patients.[9] Co-infection of both infections may cause higher mortality even though the number presented in this report may be too small to draw this conclusion.

In conclusion, melioidosis and leptospirosis co-infection is possible and may cause misleading non-specific clinical presentation and lead to high mortality. We should consider co-infection in patients who have fresh water and soil exposures, especially in those with underlying immune-compromised illnesses.

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