FATAL SEPTICEMIC MELIOIDOSIS IN A YOUNG MILITARY PERSON POSSIBLY CO-INFECTED WITH *LEPTOSPIRA INTERROGANS* AND *ORIENTIA TSUTSUGAMUSHI*

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Concurrent melioidosis, leptospirosis, and scrub typhus after rural activities is rarely reported. A 19-year-old previously healthy man had fever onset after 2 weeks of military training. Pneumonia became evident on the fifth day of fever under intravenous penicillin and oral minocycline therapy. Acute respiratory failure developed the next day with shock and acute renal and liver function deterioration, which resulted in death. Blood cultures on the third and fifth days grew *Burkholderia pseudomallei.* Serology revealed leptospirosis and scrub typhus. The emergence of melioidosis in Taiwan and this death without antibiotic treatment for melioidosis alert us that *B. pseudomallei* should be included as a possible pathogen of pneumonia and sepsis, especially after rural activities.

Key Words: melioidosis, scrub typhus, leptospirosis
(*Kaohsiung J Med Sci* 2005;21:173–8)

Fever onset after recent rural activities, both recreational and occupational, including hiking, farming, and military training, should raise the possibility of endemic pathogens acquired from soil, water, or insects. In southern Taiwan, infectious diseases that reportedly related to rural activities include scrub typhus, murine typhus, Q fever [1], leptospirosis [2], melioidosis [3], dengue fever, and Hanta virus infection [4]. However, an early differential diagnosis based on the symptoms of these diseases is difficult and challenges the clinician to choose the critically important empirical therapy for potentially rapidly fatal diseases [1]. We report a fatal case of melioidosis, leptospirosis, and scrub typhus after military training and briefly review previous reports about these endemic diseases in Taiwan.

Received: October 4, 2004 Accepted: January 24, 2005
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CASE PRESENTATION

A 19-year-old male military school student had fever and chills associated with a sore throat and cough from July 19, 2004. This previously healthy man had attended an intensive battlefield training course that included crawling on hands and knees and lessons in a swimming pool at a military school in Kaohsiung County, Taiwan, 2 weeks before his illness. Because myalgia and abdominal pain developed and his fever did not subside after primary treatment at the school clinic, he was brought to a military medical center on July 20, 2004. Physical examination revealed normal breathing sounds. Laboratory examination at admission showed leukocytosis with a white blood cell (WBC) count of 16.8×10^9/L, hemoglobin at 151 g/L, and a platelet count of 191×10^9/L. The differential leukocyte count showed predominant polymorphonuclear cells (segmented, 84.1%; lymphocytes, 7.1%; monocytes, 8.4%; basophils, 0.3%; eosinophils, 0.1%). Other laboratory results were abnormal liver function as shown by an aspartate transaminase (AST) level of 108 U/L, an alanine transaminase (ALT) level of 88 U/L, a high C-reactive protein (CRP) concentration

(118 mg/L), and a high creatine phosphokinase (CPK) level (353 U/L; normal, 12–167 U/L). Other laboratory values were normal: blood urea nitrogen (BUN), 90 mg/L; creatinine, 88.4 μmol/L; and lactate dehydrogenase (LDH), 212 U/L (normal, 180–460 U/L). Chest radiograph on arrival at the military hospital was normal.

The fever did not subside after 2 days of intravenous penicillin G and oral minocycline treatment. Progressive dyspnea developed on the third day after admission (July 23, 2004). Follow-up chest radiograph revealed bilateral infiltration. The WBC count dropped to 1.9×10^9/L and his differential leukocyte count had changed (segmented, 11%; band, 30%; metamyelocytes, 38%; myelocytes, 11%; lymphocytes, 8%; monocytes, 2%). His hemoglobin was 143 g/L and platelet count was 156×10^9/L. Arterial blood gas analysis when the patient was using a non-rebreathing mask with oxygen usage of 15 L/min had a pH of 7.36, a partial pressure of carbon dioxide (pCO_2) of 25 mmHg, a partial pressure of oxygen (pO_2) of 66 mmHg, and a bicarbonate (HCO_3) concentration of 14.6 mmol/L. His prothrombin time (PT) and activated partial thromboplastin time (APTT) were prolonged (20.4/11.1 and 70.1/31.4 seconds, case/control, respectively). He was sent to another medical center where physical examination revealed tachypnea, conjunctival suffusion, and crackling breathing sounds at night on July 23, 2004. His blood pressure was 109/48 mmHg, heart rate was 113/bpm, and respiratory rate was 26/min without an inotropic agent. Two chest radiographs 8 hours apart showed progressively increasing bilateral infiltration (Figures 1 and 2). His WBC count increased to 2.83×10^9/L but platelet count dropped to 19×10^9/L. Laboratory results illustrated deteriorated liver and renal function: (AST), 502 U/L; ALT, 224 U/L; BUN, 140 mg/L; and creatinine, 145 μmol/L. Other laboratory results indicating deteriorated condition were: CRP, 166 mg/L; LDH, 1,310 U/L; and CPK, 945 U/L. Impending respiratory failure was shown by arterial blood gas analysis: pH, 7.395; pCO_2, 26.4 mmHg; pO_2, 64.5 mmHg; and HCO_3, 15.8 mmol/L. After supportive care for 8 hours and antimicrobial therapy with intravenous ceftriaxone and oral azithromycin and doxycycline, his condition continued to deteriorate with aggravated dyspnea that necessitated ventilator use. His blood pressure could not be maintained over 90/60 mmHg with the inotropic agents dopamine and norepinephrine. Worsening laboratory results were also noticed: BUN, 240 mg/L; creatinine, 292 μmol/L; bilirubin (Total/Direct), 71.5/30.78 μmol/L. His PT and APTT were more prolonged: 23/11.6 and 98.2/30.2 seconds (case/control, respectively). A D-dimer level of 170.2 mg/L,

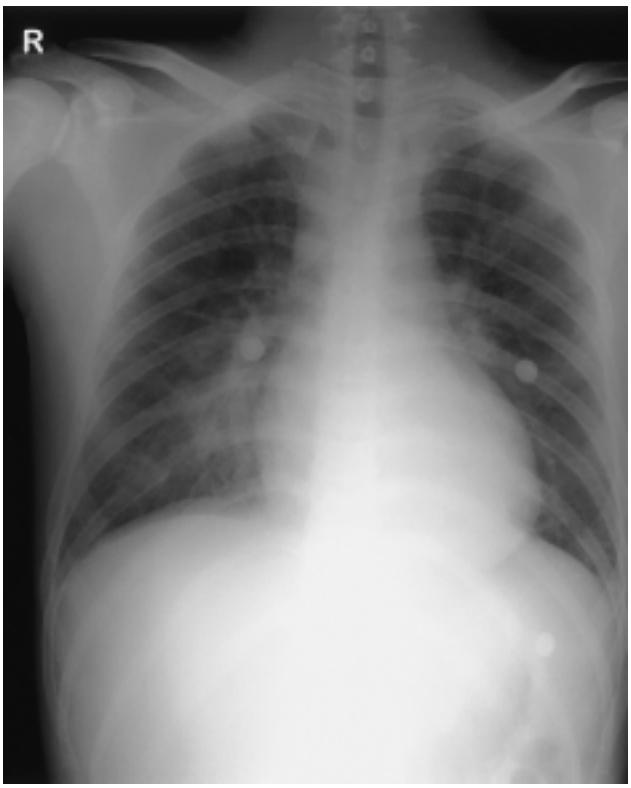

Figure 1. *Chest radiograph at night on the fifth day after fever onset.*

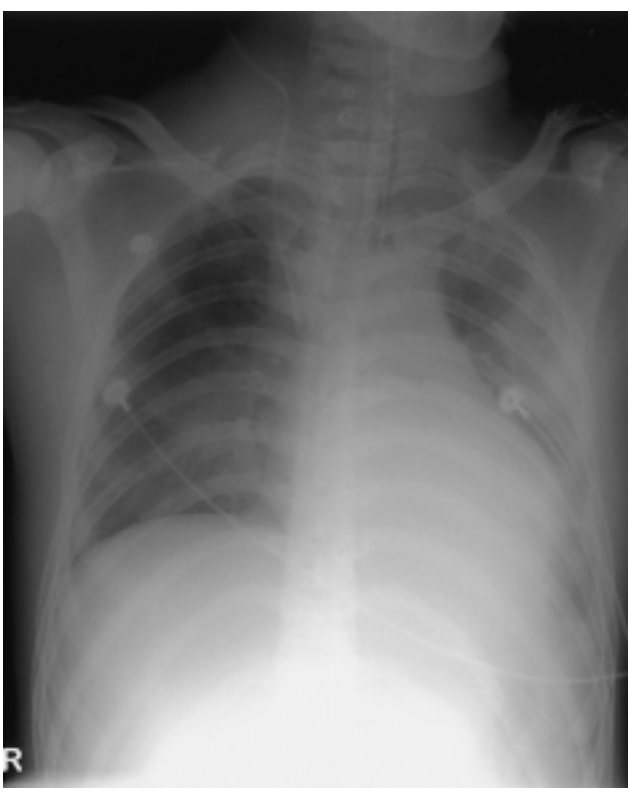

Figure 2. *Chest radiograph 8 hours after that in Figure 1.*

fibrinogen split product of 1:40, and fibrinogen of 5.49 μmol/L indicated disseminated intravascular coagulation. He died 13 hours after transfer to the referral center, on the fifth day after fever onset.

Blood cultures on admission to both hospitals revealed an oxidase-positive, Gram-negative bacillus that was resistant to polymyxin. It was identified as *Burkholderia pseudomallei* by conventional biochemistry tests and the ID32 GN test (bioMerieux, Marcy I'Etoile, France). The disc diffusion method [5] revealed susceptibility to amoxicillin/clavulanate, ceftazidime, ceftriaxone, and meropenem, but resistance to gentamicin, amikacin, cefmetazole, and cefepime. Polymerase chain reaction (PCR) tests for *B. pseudomallei* with primers for the 16S RNA gene (forward primer CGGCAGCRCGGGCTTCGG and reverse primers TGTGGCTGGTCGTCCTCTC and CACTCCGGGTATTAGCCAGA) and the flagella gene (forward primer CTGTCGTCGACGGCCGTG and reverse primer ATTGTTGACCGTCGCGAG) [6,7] were positive.

Two serology studies were also positive. A test for scrub typhus using an immunofluorescence antibody (IFA) [8] on one serum sample taken at the acute stage revealed a high immunoglobulin (Ig) M titer of 1:80 and an IgG titer of 1:40 to *Orientia tsutsugamushi*. A microscopic agglutination test (MAT) [9,10] showed a fourfold increase in the antibody titer of *Leptospirosis interrogans* sensu lato serovar *shermani* (1:100 to 1:800, from July 21 to July 24). Other serology studies for murine typhus, Q fever, dengue virus, Japanese encephalitis virus, and Hanta virus were negative. PCR testing for influenza virus and severe acute respiratory syndrome coronavirus were all negative. These tests were performed in the laboratory of the Center for Disease Control, Taiwan. Serologic studies of acute-phase blood samples were negative for *Chlamydia* and *Mycoplasma*.

Discussion

Melioidosis is caused by *B. pseudomallei*, an aerobic Gram-negative bacillus found in moist soil and water in endemic areas. Since infection is through inoculation or inhalation, and this organism has been found in rice fields in southern Taiwan [6], our patient might have acquired melioidosis from heavy exposure to soil through military training exercises. This case is different from those previously reported in Taiwan because of the young age of the patient and his evident occupational exposure. The previous 16 cases were aged 40–76 years and none had occupational exposure [11].

Scrub typhus, a mite-transmitted disease caused by *O. tsutsugamushi*, may cause serious complications including acute respiratory failure, acute renal failure, and septic shock [12], all of which were present in this case. *Leptospira* is excreted in the urine of infected animals and may survive for days to months in fresh water, soil, or mud [13]. Our patient had similar symptoms to most recognized cases, presenting with a febrile illness of sudden onset and symptoms including chills, headache, myalgia, abdominal pain, and conjunctival suffusion [9]. The jaundice and acute renal failure in this case could be due to shock from fulminant septicemia. It is also possible that the patient had severe leptospirosis, called Weil's disease. Co-infection with *Leptospira* and *O. tsutsugamushi* has been reported in Thailand [14], but simultaneous infection with these three organisms is rare.

Though the three diseases were diagnosed using current standard and specific methods of laboratory diagnosis (MAT for leptospirosis, IFA for scrub typhus [9,15], and culture for *B. pseudomallei*), the nature of serology testing makes a false-positive result possible. However, to the best of our knowledge, there is no report of a cross-reaction between either MAT for leptospirosis and melioidosis or IFA for scrub typhus and melioidosis. In addition, seropositivity for both leptospirosis and scrub typhus is regarded as co-infection in literature and not as cross reactivity [14]. Since the peak *Leptospira* MAT titer in the acute phase ranges from 1:200 to 1:12,800 and a more than fourfold increase less than 2 weeks apart is common [16], our patient may have had a rapid increase in *Leptospira* titer.

Penicillin G is used for community-acquired pneumonia and tetracycline for *Rickettsia* diseases or leptospirosis. Whether the initial 3-day regimen of penicillin G and minocycline had an antagonistic effect similar to that of the combination of penicillin and chlortetracycline, resulting in a poorer outcome for pneumococcal meningitis [17] and influencing leptospirosis treatment, has not been demonstrated in the literature. However, it is noteworthy that there are no reports suggesting the use of both penicillin G and tetracycline for leptospirosis.

B. pseudomallei is frequently resistant to many antibiotics, including aminoglycosides and first- or second-generation cephalosporins [11,18]. Since other third-generation cephalosporins such as ceftriaxone were less active than ceftazidime in previous studies [19,20] and among Taiwanese strains [11], ceftazidime is the treatment of choice [18,21]. The Taiwan pneumonia guidelines suggest third-generation cephalosporins as one possible treatment for severe community-acquired pneumonia without mentioning the

various third-generation cephalosporins [22]. In areas where melioidosis is endemic, empirical regimens that contain cefotaxime or ceftriaxone to treat severe community-acquired pneumonia or septicemia may not be appropriate [11], especially when caring for patients exposed to melioidosis. Melioidosis should be suspected in diseases unresponsive to standard antibiotic therapy.

Although scrub typhus and leptospirosis have been known to be endemic in Taiwan for more than 30 years, an indigenous case of melioidosis was first diagnosed only in 1994 [3]. Scrub typhus has been known to cause infection in military personnel in Taiwan for 25 years [23]. Though leptospirosis and melioidosis were both formerly considered occupational diseases of military personnel [21,24], there has been no previous report of melioidosis in Taiwan military personnel after training. In southern Taiwan, including Kaohsiung and Pingtung Counties, there were 79 cases of scrub typhus, 72 of Q fever, 41 of endemic typhus, 23 of leptospirosis, and 12 of melioidosis from 2002 to June 2004 (unpublished data from the Center for Disease Control, Taiwan). The recent emergence of melioidosis and its rarity result in a lack of familiarity with the culture characteristics of *B. pseudomallei* [25] and clinical alertness for melioidosis. This will cause delays in recognition, identification, diagnosis, and treatment. The incidence of melioidosis, known as a great mimicker for its wide spectrum of clinical manifestations [26], could be underestimated due to a lack of awareness of the disease and relatively inaccessible and insufficiently rapid diagnostics in Taiwan, as indicated by the history of melioidosis in Thailand [25].

Our patient received minocycline because the clinician was alert to the possibility of rickettsial infection and was aware that it is effective for scrub typhus and leptospirosis. However, the fact that empirical treatment for melioidosis was not initiated early led to persistent septicemia and subsequent multiple organ failure. The appearance of pneumonia on the third day of septicemia indicated that the lung infection was secondary to hematogenous spread. The continuous bacteremia and the isolation of *B. pseudomallei* 12 hours before death indicated that the rapid fatality was attributable to septicemia. Mortality for scrub typhus with extensive pneumonitis and cyanosis unrelieved by oxygen is 22% in Taiwan [27]. The fatality rates for severe leptospirosis range from 5% to 40% [28]. In view of these high mortality rates, the concurrent scrub typhus and leptospirosis may have contributed to the fatal outcome in this patient.

Many kinds of infections can be acquired after recreational activities [29] or occupational exposure [21,24]. Mixed infections after rural activities are possible and our case is an example. Confirmation of diagnosis of infections related to rural exposure is frequently delayed. However, early treatment is important to prevent death. Melioidosis causes death in 40% of treated cases in northeastern Thailand, and physicians managing patients in Taiwan should be alert to the possibility that *B. pseudomallei* might cause community-acquired pneumonia and sepsis. In view of the benefit of appropriate antimicrobial therapy: ceftazidime use is associated with a 50% lower overall mortality [21].

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一年輕軍人因類鼻疽菌血症並可能合併鉤端螺旋體病及恙蟲病之致死病例

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在野外活動後合併感染類鼻疽病、鉤端螺旋體病及恙蟲病為罕見病例報告。一位 19 歲健康男性在二週軍事訓練後因發燒入院，在接受 penicillin 及 minocycline 治療下，於發燒第五天出現肺炎症狀，次日隨即進入急性呼吸衰竭合併有休克、急性腎臟及肝功能惡化而死亡。在發病第三天及第五天之血液培養結果顯示 *Burkholderia pseudomallei* 菌血症，血清學檢驗顯示合併有感染鉤端螺旋體病及恙蟲病。類鼻疽病近年在台灣陸續有本土病例報告以及此死亡病例未接受類鼻疽病之抗生素經驗療法顯示醫師在病人患有肺炎併敗血症時，尤其是在患者有最近之野外活動時，應小心 *B. pseudomallei* 為可能的致病菌。

關鍵詞：類鼻疽，鉤端螺旋體病，恙蟲病

（高雄醫誌 2005;21:173–8）

收文日期：93 年 10 月 4 日

接受刊載：94 年 1 月 24

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