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# A case of thoracic empyema due to suppurative melioidosis

# 化膿性類鼻疽引起的胸部積膿症病例

**Melioidosis is considered a rare disease in Hong Kong, and its diagnosis and treatment can be difficult. We report the case of a patient who presented with thoracic empyema. The material sampled from the empyema was initially labelled *Burkholderia cepacia*. The diagnosis of melioidosis due to *Burkholderia pseudomallei* could only be made after repeated cultures, and performing arginine dihydrolase and serological tests. The patient was initially treated with imipenem for 2 weeks, and then with ciprofloxacin as maintenance therapy. A resistant strain of the organism developed after 7 months of treatment. The patient was then given co-amoxiclav. Repeated courses of surgical drainage and debridement were also instituted. Subsequent computed tomographic scanning of the thorax showed gradual resolution of the empyema.**

在香港類鼻疽被認為是一種罕見的疾病，診斷和治療這種病是困難的。我們報告了一胸部積膿症患者的病例。從積膿抽取的樣本最初被認為是*Burkholderia cepacia*。而由*Burkholderia pseudomallei*引起的類鼻疽只可能在重覆培養，及進行精氨酸二聚水和血清學測試後診斷。患者最初用imipenem治療兩週，然後用ciprofloxacin作維持治療。在治療7個月後，生物體的抵抗趨緊。之後給患者服用co-amoxiclav，還反覆進行外科排膿和清創術，隨後，胸腔的電腦斷層掃描顯示了積膿症逐漸消失。

***Key words:***
*Burkholderia pseudomallei;*
*Melioidosis;*
*Pseudomonas pseudomallei;*
*Suppurative melioidosis;*
*Thoracic empyema*

***關鍵詞：***
*Burkholderia 假鼻疽杆菌；*
*類鼻疽；*
*假單胞菌屬假鼻疽杆菌；*
*化膿性類鼻疽；*
*胸部積膿症*

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## Introduction

Melioidosis includes all diseases caused by the bacterium *Pseudomonas pseudomallei*, subsequently renamed *Burkholderia pseudomallei*. Although recognised for more than 80 years, the disease remains poorly understood and is only lightly covered in most medical texts. The term is derived from the Greek word in which 'melis' means 'a distemper of asses'. It is an important infection, since the in-hospital mortality rate is 42%[1] and could be up to 80% if treatment was delayed in septicaemic patients.[2] The latent form of melioidosis causes considerable diagnostic and epidemiological problems. Melioidosis is endemic in Southeast Asia, with Thailand having the greatest number of reported cases. The incidence of the disease in northeast Thailand is 4.4 per 100 000 per year.[3] Sporadic cases are also reported in China, Hong Kong, India, Africa, the Middle East, and Central and South America. Outbreaks in non-endemic areas occur from time to time. The most recently reported outbreak occurred in India in 1994, involving 64 patients with acute lymphadenitis. Twelve of the 40 lymph node aspirates taken from these patients were positive for *B pseudomallei*.[4]

The first case of melioidosis in Hong Kong was reported in 1983, in a patient with systemic lupus erythematosis receiving steroid and

azathioprine treatment.[5] Fourteen percent of patients with underlying pulmonary disease in a tuberculosis sanatorium in Hong Kong were subsequently reported as positive for *B pseudomallei* on serological testing.[6] There have been few studies investigating melioidosis since this report in 1987, despite the fact that this disease may be endemic in Hong Kong. The following case report describes a patient who presented to Princess Margaret Hospital with suppurative melioidosis. Difficulties in diagnosis and treatment encountered during the course of management are discussed.

## Case report

The patient, a 51-year-old Nepalese man, had resided in Hong Kong for many years. He had a 5-year history of type II diabetes mellitus, with poor diabetic control prior to admission. The patient was admitted to Princess Margaret Hospital in early 1998, with a 2-week history of left-sided chest pain which increased on inspiration. He also reported fever and chills, but no cough, increased sputum production, or shortness of breath. The patient had not travelled outside Hong Kong for some time.

On physical examination, the patient was toxic, with a high oscillating fever which peaked at a temperature of 40°C. Pulse rate was 120 beats/min and respiratory rate was 24 breaths/min. The patient had intense tenderness over the left ribcage. Breath sounds over the left lower zone of the lung were decreased, with coarse crepitations heard on inspiration. Other systems examined were normal.

The patient's haemoglobin level was 120 g/L (normal range, 136-172 g/L) with normochromic and normocytic red cells. The white blood cell count was not elevated and the coagulation profile was normal. The erythrocyte sedimentation rate was 104 with a C-reactive protein level of 306 mg/L. The patient had inappropriate secretion of antidiuretic hormone with a serum sodium ion level of 128 mmol/L (normal range, 135-147 mmol/L), osmolarity of 269 mmol/L, and urine osmolarity of 620 mmol/L. Renal and liver function were normal initially, with the exception of a mild hypoalbuminaemia (35 g/L).

Chest X-ray showed pleural effusion over the left lower zone of the lung. Computed tomography (CT) scan of the thorax showed left lung empyema and multiple splenic abscesses (Fig 1). A large number of white blood cells were seen on microscopic examination of sputum, despite a negative culture. Further

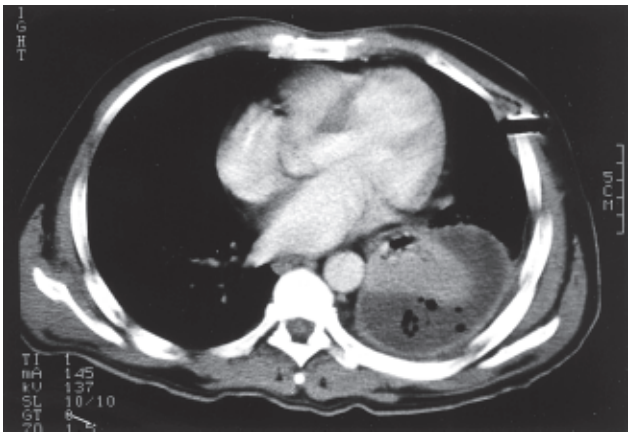

**Fig 1. Computed tomographic scan of the thorax on initial admission**

investigations for sepsis, including blood and urine cultures were negative. Thoracocentesis over the left lower zone yielded straw-coloured exudate. Microscopy and culture for acid-fast bacilli were negative. Gram stain of the fluid showed no organisms. Two weeks after admission, the initial bacterium isolated from the pleural fluid was identified as *B cepacia*—the colonial morphology of the organism on the agar plate was mucoid in nature, the organism showed weak susceptibility to aminoglycosides, and a negative reaction to arginine dihydrolase. The report was revised 2 weeks later and the organism identified as *B pseudomallei*, as all subsequent empyema aspirates showed positive reaction to arginine dihydrolase, and serological testing for *B pseudomallei* was strongly positive, with titres of 1:2560, the diagnosis of melioidosis was thus established. Antimicrobial susceptibility testing using the United States National Committee for Clinical Laboratory Standards method, revealed that the isolate was susceptible to ceftazidime, ciprofloxacin, imipenem, co-amoxiclav, piperacillin/tazobactam, tetracycline, and co-trimoxazole, but resistant to aminoglycosides.[7]

The patient was treated empirically with oral clarithromycin 500 mg twice a day for 9 days, and then with intravenous (IV) piperacillin/tazobactam 4.5 g every 8 hours for 1 week. No clinical improvement was noted, however, despite in vitro responsiveness. The patient had a continuing high fever and persistent chest symptoms. Repeated chest X-rays also showed no improvement. The patient was subsequently given IV imipenem (500 mg every 6 hours), and a chest tube was inserted to drain the empyema. Fever subsided after 2 days. Subsequent CT scans of the thorax showed resolving empyema and splenic abscesses (Fig 2). Imipenem was continued for 2 weeks, and oral ciprofloxacin 250 mg twice a day was then commenced as maintenance therapy. The patient

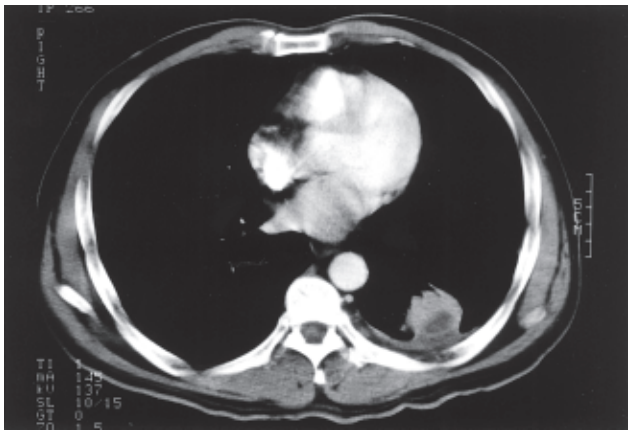

**Fig 2. Computed tomographic scan of the thorax after 12 months treatment**

remained well, and was discharged home after 2 months of hospitalisation, despite incomplete drainage of the empyema.

Subsequent repeated admissions to the Thoracosurgical Unit were needed, however, for debridement and drainage of the empyema. The exudate aspirated continued to grow *B pseudomallei* but the isolate was noted to be 'intermediate resistant' and then 'resistant' to ciprofloxacin over 7 months of treatment. Antibiotic therapy was changed to oral co-amoxiclav, 375 mg three times daily. Resistance might have similarly developed with this agent, since in vitro susceptibility testing showed 'intermediate resistance' to co-amoxiclav after 6 months of treatment, despite radiological and clinical improvement. The patient did not attend further follow-up however, and returned to Nepal.

## Discussion

The lung is reportedly the most common organ affected by melioidosis.[8] The disease can be acute, subacute, or chronic, and the incubation period as short as 2 days, or as long as 26 years.[2] It is likely that this patient was infected locally as *B pseudomallei* has been isolated from soil samples in the southern part of Hong Kong Island.[5] One cannot ignore the possibility of latent infection, however, since the patient had resided on a farm in Nepal for a lengthy period.

Melioidosis is difficult to diagnose clinically, due to its rarity in Hong Kong, and because it resembles other diseases, such as tuberculosis. A full account of a patient's travel and occupational histories can also be difficult to obtain. The current patient had worked as a farmer in Nepal. Although he did not work in the classic *B pseudomallei*–favoured site, the paddy field, close contact with the soil is itself a major risk factor. A further patient seen at Princess Margaret Hospital had worked in China as a horse-riding instructor. This patient developed the septicaemic form of melioidosis 1 month after an injury caused by falling from a horse. The accident occurred near a paddy field.

Other risk factors for melioidosis include an immunocompromised status and diabetes.[9] The current patient's poorly controlled diabetic state not only predisposed the patient to *B pseudomallei* infection, but also created problems in the treatment of his empyema. The first reported case of melioidosis in Hong Kong was in an immunocompromised patient with systemic lupus erythematosis receiving steroids and azathioprine.[5] With the increase in the number of patients infected with the human immunodeficiency virus (HIV), cases of melioidosis are expected to surge. This is particularly true in Thailand, where the number of HIV patients has risen substantially.

The microscopic or histological diagnosis of *B pseudomallei* may also be difficult. *Burkholderia cepacia* resembles *B pseudomallei* in many respects. Both show similar microscopic features and colonial morphology, although *B cepacia* may secrete a yellow pigment when grown on a Kligler's iron agar slant. Both *B cepacia* and *B pseudomallei* have a weak susceptibility to aminoglycosides. A positive biochemical reaction to cytochrome C oxidase and arginine dihydrolase is characteristic of *B pseudomallei*. This organism can also grow at 42°C, utilise citrate, oxidise glucose and maltose, accumulate β-hydroxybutyrate, and convert nitrate to gas.[10] Biochemical tests may fail to identify the bacterium, due to false negative results, and because it may not be possible to perform all relevant tests. Serological testing using haemagglutinating antibodies against *B pseudomallei* generates more reliable results, despite an inability to differentiate between acute and chronic infection, especially in an endemic area. A four-fold increase in serological titres 10 to 14 days apart may indicate acute infection.[2] The high titres seen in this patient, together with the clinical picture, indicate the diagnosis of acute melioidosis.

Management of melioidosis is expensive, as appropriate antibiotic therapy is relatively costly and the duration of therapy is prolonged. Treatment of severe melioidosis includes a minimum of 2 weeks of high-dose parenteral ceftazidime, imipenem or co-amoxiclav, followed by at least 20 weeks of maintenance therapy. The maintenance therapy includes oral co-amoxiclav and the conventional combination of chloramphenicol, doxycycline and cotrimoxazole.[5,11-13]

*Burkholderia pseudomallei* infections are well known for their ability to relapse, despite appropriate treatment. It is important to review the susceptibility of the bacterium to the antibiotic in use throughout the treatment period, since the emergence of an expanded spectrum of resistance has been reported.[5] The bacterium isolated from this patient was initially sensitive to several antibiotics, including ciprofloxacin and co-amoxiclav. Due to the subsequent development of resistance to ciprofloxacin and then co-amoxiclav, however, an alteration in the antibiotic regimen was required. The use of ciprofloxacin in the management of melioidosis overall appears limited.[8] The treatment failure rate for ciprofloxacin has been reported as 29%, with the median duration to failure 7 months.[14] Some clinicians still consider ciprofloxacin a useful maintenance drug, nonetheless, because of its long postantibiotic effect.[15]

Treatment of chronic suppurative melioidosis is difficult. This patient had already undergone more than eight episodes of surgical drainage and debridement. Rib resection may eventually become necessary in this case. A higher dosage of co-amoxiclav (60 mg/kg per day) has been suggested as appropriate in this clinical situation.[2] Parenteral co-amoxiclav dosing (160 mg/kg per day) has also been suggested for severe melioidosis, with a reported therapeutic effect comparable to parenteral ceftazidime.[12]

## Conclusions

Several key features of the diagnosis and treatment of melioidosis are illustrated in this case. Many clinicians in Hong Kong are unfamiliar with this disease. Melioidosis should, however, be included in the differential diagnoses for patients presenting with respiratory problems resembling tuberculosis. Clues to the diagnosis include pyrexia of unknown origin, with or without any obvious localising signs, immunocompromised status, a history of travel or residence in an endemic area (including the distant past), and close contact with soil or ground water in these areas. *Burkholderia pseudomallei* resembles *B cepacia* in many respects. Differentiating these two organisms requires clinical correlation and biochemical tests. The treatment of melioidosis, especially for suppurative conditions, is a challenging task for the clinician, since resistant strains readily develop over prolonged courses of treatment. Surgical drainage and debridement, along with adequate maintenance antibiotic therapy is essential. The controversy regarding the use of ciprofloxacin as maintenance therapy remains, but there is strong support for the use of co-amoxiclav in this clinical setting.

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