First documented co-infection case of cat-scratch disease and melioidosis in Malaysia: A cause of undifferentiated prolonged febrile illness

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SUMMARY

Cat-scratch disease is a zoonotic infection of worldwide prevalence that is endemic in tropical or subtropical countries. Likewise, melioidosis is one of the major endemic health problems in Malaysia. Epidemiologically, mixed infections of cat-scratch disease and melioidosis are possible because similar environmental conditions are needed for the transmission of both infections. Still, their co-infection is rarely reported in medical literature. History of contact with plantation soil or contaminated water is important in raising the suspicion of the disease. Cat-scratch disease has increased as many children are in close proximity to cats. Here, we report a case of cat-scratch disease and melioidosis co-infection in a two-year-old boy who presented with prolonged fever and painless cervical lymphadenitis and had serological testing results positive for *Bartonella henselae* and *Burkholderia pseudomallei*. A history of travelling around Malaysia during school holidays and being exposed to cat and contaminated environment are clues to diagnosis.

INTRODUCTION

Cat-scratch disease (CSD) is an emerging infectious diseases caused by the gram-negative bacteria *Bartonella henselae* and transmitted by cats. This zoonotic infection is spread by cat's saliva through direct contact with broken skin or mucosal surfaces such as an open wound or cat's bites or scratches. The disease was first described in 1931, but the causative organism was detected about 50 years later in 1983.[1] CSD is now recognised as one of the most common causes of fever of unknown origin (FUO) with unilateral lymphadenopathy.[2] Melioidosis is one of the world's most neglected tropical diseases. It is caused by *Burkholderia pseudomallei*, a gram-negative saprophyte that lives in moist soil and water in endemic areas of Southeast Asia and Northern Australia. *B. pseudomallei* was discovered in 1911 and first described as *Bacillus pseudomallei* associated with 'glanders-like' disease among morphine addicts in Myanmar.[3] This bacterium was proven to cause melioidosis in 1932 and was renamed B. pseudomallei in 1992.[3] There is no pathognomonic feature specific to melioidosis. In endemic areas, physicians need to consider melioidosis in clinical scenarios of prolonged fever, progressive pneumonia, or sepsis.

CSD and melioidosis are considered in patients with prolonged febrile illness of unclear origin.[2-5] Though co-infections of many zoonotic and tropical diseases have been described, reports on CSD and melioidosis co-infection are limited.

CASE REPORT

A two-year-old Malay boy presented with prolonged fever for three weeks. The fever was described as relapsing intermittent high grade with the highest recorded temperature of 39 degrees Celcius, but not associated with chills or rigors. Despite completing two courses of antibiotics (amoxicillin-clavulanic acid and cefuroxime), his fever persisted. He was still active during the febrile illness without other significantly associated symptoms such as cough, vomiting, or diarrhoea. There was a significant weight loss of 1.2 kg over a three-week-period. One week prior to the illness, he had history of visiting various places in Malaysia including multiple outdoor and water activities in a plantation. He also had contact with domesticated animals, particularly cats but denied being scratched or bitten by them. He had completed immunisation with no significant past medical history.

Clinically, he was active but febrile with a temperature of 39.5°C. His weight on admission was 10.7 kg at the 5th percentile for age. Physical examination was unremarkable except for a few painless palpable lymph nodes over the bilateral cervical regions with the largest lymph node measuring 2 × 2 cm in diameter. He had no hepatosplenomegaly. Preliminary blood investigations showed increased inflammatory markers; erythrocyte sedimentation rate of 105 mm/hr (reference range 0–15 mm/hr) and C-reactive protein of 5.4 mg/dL (reference range < 0.3 mg/dL) were reported.

He continued to be febrile despite empirical therapy with high dose intravenous ceftriaxone. His blood, urine and stool cultures, anti-nuclear antibody, complement proteins C3 and C4, tuberculin skin test, and chest radiographs were all negative. The *B. henselae* IgM and IgG by indirect fluorescence assay (IFA) revealed positive results with titres of 1:24 and 1:256, respectively. His serum was also positive for *B. pseudomallei* with IgM titre of 1:320. A final diagnosis of CSD and melioidosis co-infection was made.

Ultrasonography of the abdomen showed a septated right subdiaphragmatic collection measuring 2.8 × 1.1 × 3.8 cm (see Figure 1). His condition improved remarkably after the

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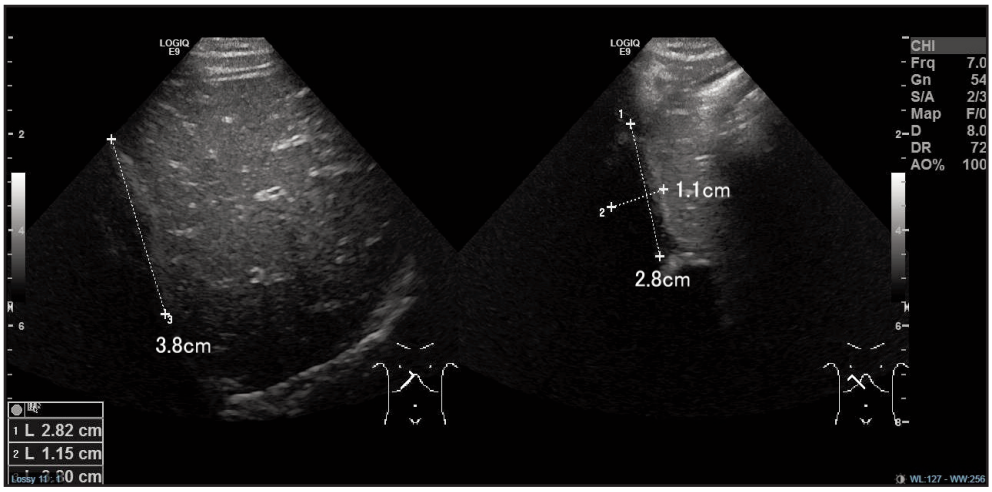

Fig. 1: Septated right subdiaphragmatic hypoechoic collection on ultrasound of the abdomen.

antibiotic treatment was changed to intravenous ceftazidime (50 mg/kg four times a day) for a total of four weeks, and completed oral azithromycin for five days (10mg/kg daily on day one then 5mg/kg daily on day two to five. He was discharged well and completed 20 weeks of oral amoxicillin-clavulanate 20 mg/kg tds at home. Unfortunately, the repeat serologies for both *B. henselae* and *B. pseudomallei* were not done at four weeks of illness due to patient/parent refusal for blood taking in view of recurrent intravenous catheter insertion.

Clinic follow-up revealed clinical improvement consistent with four-fold titre resolution; *B. henselae* IgM became negative (<1:12) and IgG decreased from 1:256 to 1:64 after two months, and *B. pseudomallei* IgM decreased from 1:320 to 1:80 within five months. A repeat abdominal ultrasonography after two months showed resolution of the right subdiaphragmatic collection.

DISCUSSION

To our knowledge, this is the first documented case of co-infection of CSD and melioidosis in Malaysia, which was confirmed by serological tests for both organisms. Clinically, symptoms of melioidosis and CSD often are nonspecific and may mimic each other.

In CSD, the typical history of being scratched, licked, and/or bitten by an infected cat may not be apparent in 25% of cases as illustrated in our patient; hence, any history of exposure is equally important.4 The infection usually begins with formation of an erythematous papule 3–10 days after exposure, followed by regional lymphadenopathy that appears 1–3 weeks post-inoculation, often non-tender, and frequently occurs in the axilla and epitrochlear (45%), head and neck (26%), and groin (17.5%) regions.[4,5] Systemic illness is usually mild, but 5–10% of CSD can develop various complications such as prolonged fever of unknown origin, pneumonia and/or pleural effusion, hepatosplenic manifestations, encephalopathy, osteomyelitis, and ocular disease.[5] Serological analysis for *B. henselae* is the mainstay of laboratory diagnostic tool of CSD. Sera with anti-*B. henselae* immunoglobulin G (IgG) titres of ≥1:256 or IgM titres of ≥1:20 are regarded as positive and indicate current or recent infection.[4,5]

The most common clinical presentation of melioidosis is pneumonia with or without septicaemia. Some *B. pseudomallei* infection can be latent and may present as chronic disease such as tuberculosis; hence, melioidosis is often referred to as the 'great mimicker'.[6] Apart from prolonged fever, localised lymphadenopathy, and subtle weight loss, our patient did not have other symptoms and signs to suggest systemic involvement of CSD or melioidosis. Undifferentiated fever, with no overt focus of infection, is another important manifestation, occurring in over 28% of children with melioidosis in Malaysia.[7] Patient's travel history during December school holidays, which is known as the raining season in certain parts of Malaysia, should raise the suspicion of melioidosis.

Confirmation of melioidosis is established by positive culture from blood, sputum, cerebrospinal fluid, or other specimens.8 Seroconversion or single high antibody titres (e.g. >160) by indirect haemagglutination assay (IHA) or enzyme-linked immunosorbent assay (ELISA) with consistent clinical features are also supportive for diagnosis of melioidosis.[8] In our case, there was a four-fold decrement of IgG and IgM titres after completion of antibiotics with clinical and radiological resolution, which supports the diagnosis. The additional finding of right subdiaphragmatic abscess in this case denotes the importance of ultrasonographic surveillance once there is evidence of melioidosis.

The typical course of CSD is usually benign and self-limiting in most cases.[4] Oral azithromycin is recommended for the treatment of mild to moderate disease for five days (10 mg/kg/dose on day 1, and 5 mg/kg/dose on days 2 to 5 as a single daily dose).[4] The use of azithromycin led to a more rapid resolution of lymphadenopathy.[9] The treatment for melioidosis consists of an intensive and eradication phase. During intensive phase, intravenous ceftazidime or carbapenem is given for 14 days followed by trimethoprim or amoxicillin-clavulanate for 20 weeks during the eradication phase.[10] It is fortunate that despite having fever and a subdiaphragmatic collection, our patient had a relatively mild disease as compared to adults, whereby the rate of severe sepsis and mortality is high due to presence of predisposing factors such as type-2 diabetes mellitus and chronic heart disease.

CONCLUSION

Our patient presented with undifferentiated prolonged febrile illness, significant travel history to a plantation situated in a melioidosis endemic area, and exposure to cats a week prior to developing symptoms. He had elevated immunoglobulin titres for both *B. henselae* and *B. pseudomallei* few weeks after admission. This case illustrates the importance of obtaining a detailed history and the need to have a high index of suspicion for cases with travel history to melioidosis endemic area and contact with cats. Imaging studies may suggest the diagnosis, and specific serology may confirm it, perhaps avoiding the need for biopsy.

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CONFLICT OF INTEREST

None to be declared by the authors.

CONSENT

Permission obtained from parent for this case report (see attached consent form).

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