Case Report

The role of Granulocyte Colony-Stimulating Factor and carbapenem therapy in severe melioidosis: A case report from Malaysia

Arwa Mohamed Amin Mostafa and Chee Ping Chong*

Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia (USM), 11800 Minden, Penang, Malaysia

Abstract. Melioidosis is a fatal disease endemic in Southeast Asia and Australia. Type 2 diabetes mellitus is one of the main risk factors for acquiring this infectious disease. We described a case of severe melioidosis in a 31-year-old female patient with multiple hepatosplenic abscesses and underlying type 2 diabetes mellitus. The blood culture showed positive results to *Burkholderia pseudomallei* only after one month of on and off fever experienced by the patient. A splenectomy was done to prevent the development of peritonitis. The use of granulocyte colony-stimulating Factor (G-CSF) in addition to shifting from ceftazidime to meropenem therapy played an effective role in the recovery of the patient. In this case report we reviewed the literature on the impaired immunity in type 2 diabetic patient that put the patient on risk of acquiring melioidosis and the suggested role of G-CSF and carbapenem therapy.

Key words: Melioidosis, granulocyte colony-stimulating factor, carbapenem, hepatosplenic abscess

1. Introduction

Melioidosis is an infectious disease which can affect humans and animals (1-3). It is caused by the gram negative bacterium *Burkholderia pseudomallei* (1,4). This bacterium is soil-borne where water and soil are the major reservoirs. Therefore, it is highly prevalent in the tropical areas of South East Asia and Northern Australia (4,5). The disease can be acquired by direct contact with the bacteria in humid soil, and by inhalation or aspiration of contaminated water in the aforementioned areas (1,3-5). In Malaysia, the disease was reported in both humans and animals and in various areas like Johor, Pahang, Kedah, Kelantan and Kuala Lumpur (2,4,6). Although it is evidenced that the rainy season is strongly correlated to the cases of melioidosis in global endemic areas, the available data in Malaysia showed variable degrees of correlations between high rain fall and melioidosis cases (4,6-8). There are several risk factors that can increase the susceptibility of acquiring the disease, such as, diabetes mellitus, thalassemia, kidney disease, alcohol drinking and soil contact occupations (4,9,10). Nevertheless, a retrospective study conducted in Kelantan, Malaysia observed no relation between melioidosis and soil contact occupations (4). The clinical presentation and symptoms may vary from asymptomatic cases to complicated focal lesions affecting several organs (4,5,11). The pneumonic presentation is highly prevalent in Malaysia, while brain, liver and spleen abscess are among the low to rare presentations (4,6).

The effective treatment of melioidosis is hindered by the high antibiotics resistance of *Burkholderia pseudomallei* and the host comorbid conditions that reduce the patient immunity (5,10,12). Ceftazidime (with or without trimethoprim/sulphamethoxazole) or meropenem are the antibiotic of choice to treat melioidosis (12-14). However, meropenem had been reported to be more effective than ceftazidime in severely septic patients (15). Recent studies suggested that impaired immunity were found among septic patients irrespective of the co-morbidity (16,17). Whereas, low immunity were also noticed among

*Correspondence: Chee Ping Chong PhD.
Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia (USM), 11800 Minden, Penang, Malaysia
TeL: +6 012 534 2685
Fax: +6 04 657 0017
E-mail: jjueping@gmail.com
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patients with underlying type 2 diabetes mellitus (10,18). Hence, the granulocyte stimulating factor (G-CSF) may play a substantial role in the management of sepsis secondary to melioidosis particularly for those with co-morbidity of diabetes mellitus (19-21).

Here, we describe a case of a patient with underlying type 2 diabetes mellitus who was having severe hepatosplenic abscess and septicaemia secondary to melioidosis. Besides splenectomy, the patient recovered after the adjunctive treatment with G-CSF in addition to the shifting of ceftazidime to meropenem regimen.

2. Case report

A 31-year-old, Malay woman was referred to intensive care unit (ICU) after her diagnosis with septicaemia secondary to melioidosis. The patient was initially admitted to medical ward because of fever and abdominal pain. Before she was referred to ICU, she had two blood cultures and one computed tomography (CT) scan. Her first blood culture was done on the first day of her hospital admission which showed no bacterial growth. Her CT scan was performed on the second day of her admission which showed multiple hepatic and splenic abscess and splenic infarct with splenic vein thrombosis. The diagnosis of melioidosis was suspected. However, the diagnosis of melioidosis was confirmed on the third day of hospital admission after the second blood culture which indicated the bacterial growth of *Burkholderia pseudomallei*. The bacteria were sensitive to ceftazidime, imipenem, tetracycline and amoxicillin clavulanate, while it were resistant to trimethoprim/sulphamethoxazole.

The patient had been diagnosed with type 2 diabetes mellitus since 3 years ago. She was unable to remember the name of her oral hypoglycaemic drug and was not taking it on regular bases. She had history of bronchial asthma but was currently not on any medication. She is a house wife with 3 children and she denied any history of soil contact. One month ago, she had hospital admission due to fever and cough. All her blood cultures showed no growth and hence she was treated empirically with Tazocin® (piperacillin/tazobactam) 4.5 g every 6 hourly for one week. She was discharged from the hospital after the improvement in her condition. However, she continued to have on and off fever for about three weeks after the discharge from hospital.

On day 5 of the current hospital admission, the patient was referred to ICU due to respiratory failure. Upon the admission to the ICU, the patient was alert, conscious but feverish. Her abdomen was not distended, nevertheless of her abdominal pain. Her body temperature was 38.5°C, blood pressure was 115/58 mmHg and pulse rate was 85 per minutes. She was intubated and ventilated with respiratory rate of 18 per minutes after the ventilation support. Her blood profile showed white blood cells count of 5.1 x 10^3/µL, neutrophils count of 70.6%, hematocrit of 22.1%, haemoglobin of 6.8 g/dL and platelet count of 78 x10^3/µL. The patient's kidney function was constantly normal during her admission with the calculated creatinine clearance of between 92.1 ml/min to 156.7 ml/min. Her liver profile was normal except for low total protein (62 g/L), albumin 14 g/L and total bilirubin 48 g/L. Her fasting blood sugar was 16.0 mmol/L. The patient's random blood sugar level was subsequently controlled at 5.8 mmol/L to 8.9 mmol/L via insulin therapy throughout her ICU admission.

The patient was initially treated with intravenous (i.v.) Tazocin® (piperacillin/tazobactam) 4.5 g every 6 hourly for the first two days of her admission in medical ward. When the second blood culture showed *B. pseudomallei* infection on day 3 of hospital admission, the therapy was switched to i.v. meropenem 1 g every 8 hourly. On day 6 of her hospital admission (day 2 of ICU admission), the third blood culture was obtained and the result was again positive with *B. pseudomallei* infection. At this point, the antibiotic therapy was subsequently changed to i.v. ceftazidime 2 g every 8 hourly for 14 days. In addition to the antimicrobial treatment, she was given i.v. Neupogen® (Filgrastim – a human G-CSF produced by recombinant DNA technology) 300 µg once daily for 10 days, starting from the first day of her ICU admission. During the G-CSF treatment, the patients' neutrophil count rose gradually from 70.6 % to 80.0 % and her white blood cells increased from 5.1 x 10^3/µL to 10.6 x 10^3/µL. The fourth blood culture result on day 8 of her ICU admission showed that there was no bacterial growth. However, along the ceftazidime therapy, she continued to have fever and her body temperature was in the range of 38.0 to 40.5°C. On day 10 of ICU admission, due to the spiking fever and MRSA endemic in the ICU, she was empirically given i.v. vancomycin 1 g every 12 hourly for 2 days. Concurrently, i.v. ampicillin/sulbactam 1.5 g every 6 hourly was given for 2 days in addition to the ceftazidime therapy in order to give a broader empirical coverage of beta-lactamase producing strain of

gram positive, gram negative and anaerobic bacteria.

On day 12 of ICU admission, the patient had splenectomy and drainage of the liver abscess. The surgery report indicated that the patient had right large liver lobe abscess and enlarged spleen with multiple abscesses. On day 15 of ICU admission, ceftazidime therapy was stopped and replaced by i.v. meropenem 1 g every 8 hourly for 10 days. The change in antibiotic therapy was because of the patient's unresolved febrile condition throughout the ceftazidime treatment. The patient's body temperature and physical status continued to improve since the initiation of meropenem therapy. On day 26 of ICU admission, she was discharged to the medical ward for further eradication treatment.

3. Discussion

Melioidosis is an endemic disease in South East Asia and North Australia (1,9). It has high fatality rate globally, and the reported mortality rate in Malaysia is 30-65% (4,6,9). The main challenge to the diagnosis of melioidosis is the broaden clinical symptoms and presentations (9). The common clinical presentations range from fever to septicaemic, pneumonic, osteomyelitic, hepatic and splenic focal development (4,6,9,22). The pulmonary involvement is the commonest in the endemic areas including Malaysia (4,6,11). Meanwhile, liver and splenic cases with different outcomes have been reported in Thailand, Taiwan and India (23-27). A retrospective review in Singapore had found that melioidosis is the common cause of hepatosplenic abscess where diabetes was a co-factor (28). In fact, as the *B. pseudomallei* bacteria behaves like opportunistic infections, predisposing conditions such as type 2 diabetes mellitus, renal impairment, thalassemia, liver cirrhosis, alcoholic and other immuno-compromising conditions are considered as the main risk factors for the disease development and mortality (4,6,22).

The type 2 diabetes mellitus has been reported to be the highest patient underlying condition in melioidosis (4-6,8). In fact, this might be due to the altered immunity functions and inflammatory response in diabetic patients (10,18,29). Recent studies have evidenced that the anti microbial activity of the polymorphonuclear neutrophils (PMNs) is defected in diabetic patients (10,18,30). These PMNs has a vital immunity and inflammatory role in host defence response against microbial infections by bacterial killing, phagocytosis, migration and apoptosis (10,30). A recent study suggested that the defect in PMNs function may trigger a disoriented compensatory inflammatory response in diabetic patient infected by *B. pseudomallei* regardless of the bacterial load (18). Additionally, the positive effect of glycaemic control in regulating this inflammatory response was also observed in the same study (18). Another study found that melioidosis with underlying type 2 diabetes patients who priory treated with glyburide, an oral hypoglycaemic drug with anti-inflammatory properties, had more survival than those who were not on prior treatment with the same drug (31). In the present case, the patient has poorly controlled diabetes due to her low compliance to medication. This increased her susceptibility to acquire the melioidosis infection and the subsequent complications.

The aforementioned findings in concern of host immunity have help in conceptualizing the effective role of G-CSF in increasing the survival and reducing the mortality of severe septic melioidosis (19,21). Neupogen® (Filgrastim – G-CSF), which is a synthesized recombinant protein form of the endogenous G-CSF has been extensively studied and used in the treatment of chemotherapy induced neutropenia in cancer patients (32). G-CSF exerts its immunity boosting effect by stimulating the proliferation, differentiation and defence function of PMNs (18,19,32). In regards of G-CSF use in melioidosis management, studies revealed a vital role of its use in septicaemic melioidosis. A study in Australia, indicated a 10 % to 95 % reduction in mortality rate in melioidosis patients treated with i.v. G-CSF (300 µg once daily for at least 10 days) compared to the non treated group (19). Besides, a randomized controlled trial conducted in Thailand showed an increase in survival time of melioidosis patients treated with i.v. G-CSF 263 µg once daily for 3 days (21). In this study, the median survival of G-CSF group (34 hours) was significantly longer than the non-G-CSF group (19 hours) with the hazard ratio of 0.56 (21). Although the Thailand study has failed to imply significant mortality benefit as compared to the Australian study, we can infer that some factors may contribute to this difference, such as the G-CSF dose variation and the difference in ICU supportive resources (21). Therefore, we can assume that the extensive glycaemic control in addition to the G-CSF use in this patient have helped to increase her survival time and her recovery.

The primary choice of antibiotic to treat melioidosis is ceftazidime (with or without trimethoprim/sulphamethoxazole) or carbapenem (preferably meropenem) (12). However, the choice of ceftazidime has recently reported to fail

in some cases, especially in patients with splenic abscess (26,27,33). Carbapenem is preferred to ceftazidime due to its post antibiotic effect, decreased endotoxin release (34,35), and its faster bactericidal time (36). Indeed, Cheng and colleagues had concluded in a retrospective study that meropenem might be associated with better outcome in septicaemic melioidosis patients than the ceftazidime therapy (15). Meropenem has better neuro-profile as compared to imipenem. As this patient has normal kidney function and was free of intracerebral infection, the risk of seizure development induced by carbapenem was low (15,37). Previous case reports have showed different outcomes in the melioidosis patients with liver and/or splenic complication (23-27,38). However, it can be implied that the use of meropenem as the antibiotic of choice in addition to the drainage of the abscess and splenectomy had substantial roles in preventing the development of peritonitis and the relapse of the disease as shown in the present case.

4. Conclusion

The use of G-CSF therapy to overcome the impairment of immunity induced by diabetes mellitus and septic melioidosis has played a preeminent role in the remission from melioidosis in this patient. However, the drainage of liver abscess and splenectomy was imperative intervention for the full recovery of the patient. Besides, meropenem is an effective antibiotic of choice for melioidosis patient with hepatosplenic involvement.

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