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Ceftazidime resistance in *Burkholderia pseudomallei*: First report from India

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ABSTRACT

Melioidosis, a disease of public health importance in Southeast Asia and Northern Australia, of late has shown an increasing trend in India, particularly Southern India. We describe a case of a 39-year-old diabetic patient with left elbow septic arthritis, multiple liver, splenic abscesses, pneumonia, pleural effusion, followed by sepsis syndrome. Blood cultures and culture of the joint aspirate yielded pure growth of *Burkholderia pseudomallei (B. pesudomallei)*, sensitive to carbapenem, co-trimoxazole and resistant to ceftazidime. The patient was successfully treated with imipenem- cilastin.He was discharged on co-trimoxazole to complete the 24 weeks course and follow-up has continued to date. The patient continues to remain asymptomatic. The case re-emphasizes the need to monitor the trend of *B. pseudomallei* in India, particularly the development of ceftazidime resistance, which incidentally is the drug of choice.

1. Introduction

Melioidosis, a disease of public health importance in Southeast Asia and Northern Australia, of late has shown an increasing trend in India, particularly Southern India. The causative microorganism, *Burkholderia pseudomallei* (*B. pseudomallei*), infects individuals with predisposing factors like diabetes mellitus and alcoholism. Therapeutic approaches consist of the clinical resolution of acute infection (acute phase) followed by the eradication of residual intracellular infection to prevent relapse (maintenance phase). In India, the first-line regimen in the acute phase is intravenous ceftazidime. We report a case of ceftazidime resistant *B. pseudomallei*, successfully treated by imipenem. This case of disseminated melioidosis re-emphasizes the need to monitor the trend of *B. pseudomallei* in India, particularly the development of ceftazidime resistance as well as a possible role of carbapenem in treating melioidosis in developing countries.

2. Case report

A 39 year old male from Rajamundry, a coastal village of Andhra Pradesh, India was referred to our hospital with a history of jaundice of 2 days, abdominal pain and vomiting for 10 days. He had history of recurrent, remittent type of fever, loss of appetite and weight loss in last 8 months which was treated outside with antimalarials and multiple oral antibiotics whose precise dosage and duration could not be known. He also had pain and swelling of the left elbow joint for last 1 month. His prior history included a recently diagnosed (4 months back) non-insulin dependent diabetes mellitus with irregular treatment. On admission, physical examination revealed a temperature of 39 ℃, a blood pressure of 100/70 mmHg, respiratory rate of 24/min. He was icteric and dehydrated. His vitals were stable. General examination revealed extensive oropahryngeal thrush and swelling and tenderness over the medical epicondyle of the left elbow joint. Examination of the abdomen revealed hepatosplenomegaly. Initial laboratory investigations revealed elevated TLC (28 900/mm^3 with 90% polymorphs, elevated C reactive protein (315 mg/L) and elevated transaminases: aspartate aminotransferase 144 IU/L and alanine aminotransferase 68 IU/L. Despite the absence of respiratory symptoms and a normal initial chest X-ray on the day of admission, the patient developed respiratory distress requiring O_2 support, the following day, due to severe bilateral abscess-forming pneumonia and was started on IV imipenem-cilastin (500 mg /6 hours). An X-ray and a computed tomography of chest at 36 hours after admission showed bilateral infiltrates with nodular lesions probably corresponding to micro-abscesses, along

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with moderate pleural effusion. Ultrasound scans of the abdomen and pelvis revealed hepatosplenomegaly with multiple hepatic and splenic abscesses. Ultrasound scan of the left elbow joint revealed well-defined thick, collection measuring about 3.9 cm × 2.6 cm. US guided aspirate was sent for culture. Gram negative rods were isolated from blood culture as well as joint aspirate after 24 hours of incubation. On sheep blood agar, small, smooth, circular, non-haemolytic colonies were obtained after 24 hours of incubation, which subsequently changed over to large, flat, dry, and wrinkled with central umbonation after 96 hours of incubation. MacConkey agar showed non-lactose fermenting colonies. Microscopy from culture revealed Gram negative, medium sized, straight and motile bacilli. The isolate was subsequently identified as *B. pseudomallei* (MicroScan Walkaway 40) and was resistant to ceftazidime (MIC>16 μg/mL) and sensitive to imipenem (MIC<4 μg/mL) and co-trimoxazole (MIC<2/38 μg/mL). Over the next week, the patient steadily improved clinically on imipenem and was discharged on TMP-SMX to complete the 24-week course. 1 double strength tablet every 12 h was given for 6 months. At this time, he continues to be asymptomatic and his chest radiography and ultra sonography abdomen and pelvis are normal.

3. Discussion

Melioidosis has shown an increasing trend in Southern India in recent years[1]. Saravu *et al* analyzed the epidemiological and clinical profile of melioidosis in southern India over a period of six years, which documented a 6-fold increase in the number of cases in 2006 and 2007 as compared to 2001[1]. Diabetes mellitus was the major predisposing factor in 68% of cases[1]. Disseminated melioidosis was the most common (68%) presentation, followed by the septicaemic (28%) and localized cutaneous abscesses (16%)[1]. In our report, uncontrolled diabetes mellitus was the only predisposing factor. The patient was a government service person by occupation and had no relevant history of occupational/recreational exposure.

Several previous randomized, controlled trials have examined intensive phase interventions in severe melioidosis and were the basis of ceftazidime-based regimens[2,3]. Ceftazidime has benefit in the treatment of this disease in a sequential open-label randomized trial of ceftazidime against chloramphenicol-doxycycline-trimethoprim-sulfamethoxazole (known as conventional therapy) in severe disease[2].

Resistance to ceftazidime in the present isolate is noteworthy as till date all the *B. pseudomallei* isolates reported from India retained sensitivity to third generation cephalosporins, particularly ceftazidime[1]. The development of resistance to ceftazidime, the drug of choice for melioidosis, in a *B. pseudomallei* isolate during therapy with this antibiotic was recently reported by Chia Te Kung *et al* in a case of mediastinitis[4]. The authors speculated the subsequent emergence of ceftazidime resistance (MIC, 48 μg/mL) in the *B. pseudomallei* isolate [the original isolate recovered from blood culture was susceptible to ceftazidime (MIC, <8 μg/mL)] from the mediastinal necrotic lymphatic tissue might have resulted from the microbe's prior prolonged exposure to the suboptimal concentrations of ceftazidime in the lymphatic niche[4]. A single clonal population of the culprit *B. pseudomallei* evolving into subpopulations with differing ceftazidime susceptibilities (*i.e.* coexistence of ceftazidime-susceptible, ceftazidime-intermediate and ceftazidime-resistant subpopulations) as a result antibiotic selective pressure was also reported recently in a diabetic patient with pulmonary melioidosis under ceftazidime treatment[5]. This together with the report of high mortality rate (35%) of patients with melioidosis treated with ceftazidime, to which the *B. pseudomallei* isolates were susceptible, highlights a possible role of carbapenem in the treatment of melioidosis in developing countries[6,7]. Carbapenems have some benefits over ceftazidime for the treatment of melioidosis given that they are more active *in vitro*, display a post-antibiotic effect and have association with decreased endotoxin release[8,9].

The diagnosis of melioidosis requires clinical vigilance and an intensive microbiological workup. To our knowledge, this is perhaps the first report of ceftazidime resistant *B. pseudomallei* from the Indian sub-continent. This together with the increasing incidence of melioidosis in Southern India raises the alarm for a suspicion of melioidosis in the differential diagnosis of sepsis in diabetic patients in this area. In conclusion, we suggest that all *B. pseudomallei* isolates should carefully be evaluated for their sensitivity to ceftazidime, as traditionally it has been the treatment of choice in the acute/intensive phase.

Conflict of interest statement

We declare that we have no conflict of interest.

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