Development of Ceftazidime Resistance in *Burkhoderia pseudomallei* in a Patient Experiencing Melioidosis with Mediastinal Lymphadenitis

Dear Editor

Melioidosis caused by *Burkholderia pseudomallei* is endemic to Southeast Asia and Northern Australia.[1,2] Melioidosis was nicknamed the "greater mimicker" because of its diverse clinical manifestations. We report a case of melioidosis manifested as mediastinal lymphadenitis and ceftazidime-susceptible *B. pseudomallei* bacteremia. After treatment with ceftazidime, the *B. pseudomallei* that subsequently grew from the patient's lymphatic tissue was found to be resistant to ceftazidime. The patient was successfully treated with imipenem and surgical intervention. Literature was additionally reviewed.

Case Report

A 48-year-old male construction worker was hospitalised because of fever, malaise, vomiting and body weight loss for 3 weeks. He was an alcoholic, and did not have a travel history outside Taiwan. Upon admission, his body temperature was 39.2°C and blood pressure 131/71 mmHg. Physical examination was unremarkable. His peripheral leukocyte count was 1520/μl (normal, 3900 to 10,600/μl) and C-reactive protein level was 271.2 mg/l (normal, <5mg/l). His chest radiography showed a widening mediastinum, and chest computed tomography (CT) revealed enlargedmediastinal lymph nodes. After sampling blood for culture, parenteral ceftriaxone (2g/day) was empirically started. Blood culture grew *B. pseudomallei*, which was identified by ID GN 32 System (Biomérieux Vitek Inc., Hazewood, MO, USA) and confirmed by Centers for Disease Control (CDC), Taiwan. Susceptibility tests with Vitek (BiomérieuxVitek Inc.) using GNS-131 cards performed in accordance with the manufacturer's instructions disclosed that the *B. pseudomallei* isolated from blood culture was susceptible to ceftazidime (MIC, <8μg/ml). The administered antibiotic was then switched to ceftazidime (2g/8 hours) on day 5. Serial chest CT revealed progressive necrotic change of lymph nodes in the mediastinum that subsequently invaded the upper lobe of the right lung (Fig.1). Minimal pericardial effusion was echocardiographically detected. Thoracotomy for wedge resection of the upper lobe of the right lung and debridement as well as drainage of the mediastinal abscess were performed on day 29. The excised necrotic lymphatic tissue from the mediastinum histopathologically showed suppurative necrosis and granulomatous inflammation. Gram-staining and acid-fast staining of the pus and necrotic tissue were negative. Culture of the excised necrotic lymphatic tissue and pleural effusion all grew *B. pseudomallei* that were resistant to ceftazidime (MIC, 48μg/ml by the Etest test [AB Biodisk, Solna, Sweden]). Ceftazidime was switched

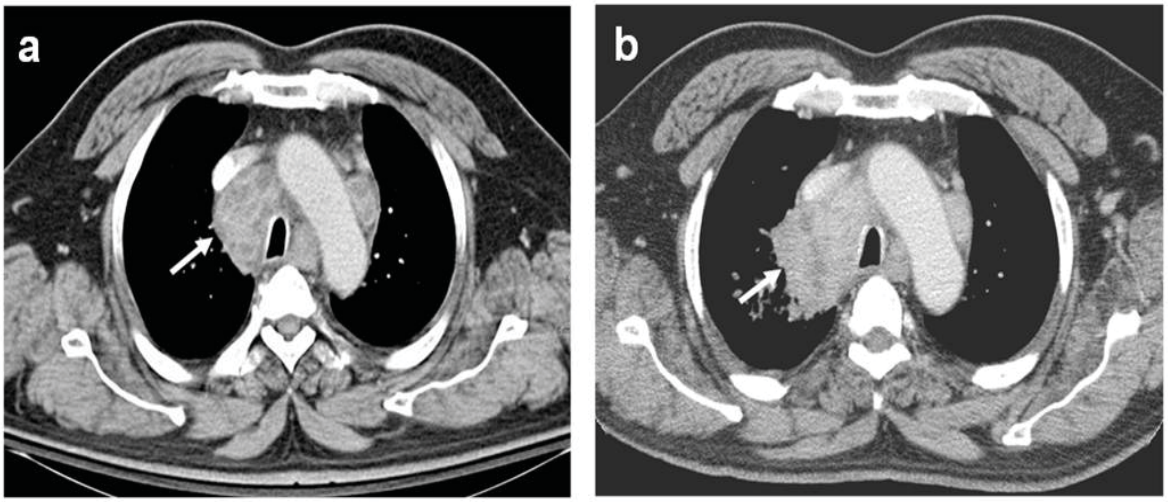

Fig. 1. Serial computed tomography shows progressive change (see arrows) of lymph nodes in the mediastinum: (a) multiple enlarged lymph nodes in the mediastinum upon patient's admission, and (b) progressive necrotic change of lymph nodes with invasion of the upper lobe of the right lung on day 25.

to imipenem (1g/6 hours) on day 36. The patient's course was uneventful thereafter. The patient was released from the hospital on day 45, and he continued to take trimethoprim/sulphamethoxazole (80/400mg) 3 tablets twice per day for 3 months. He was clinically well and his chest radiography was normal when he was last seen one year later.

Literature Review and Discussion

From PubMed search, a total of 6 reported cases of melioidosis with detailed description of mediastinal lymphadenitis were found;[3-6] these cases involved 4 men and 2 women (median age, 54 years; range, 38 to 71 years), with diabetes mellitus/alcoholism being the major underlying disease/condition, and fever of unknown origin and/or tuberculous lymphadenitis being the tentative diagnosis. Of note, Currie et al[2] reported in a series that of 252 patients with melioidosis in Northern Australia, 6 were found to have mediastinal masses presumably caused by *B. pseudomallei*. Unfortunately, the authors did not provide detailed clinical information of their affected patients. As tuberculosis is more prevalent than melioidosis in tropical countries, it is no wonder that tuberculous lymphadenitis always takes priority to melioidosis with mediastinal lymphadenitis when it comes to differential diagnosis.[3-6]

In vitro study discloses that after invading a phagocytic cell, *B. pseudomallei* has the ability to induce cell fusion and multinucleated giant cell formation, which enables the microbe to evade the host defense system during acute infection and to construct a protected niche to multiply. These findings may explain how *B. pseudomallei* establishes latent foci that become niduses for delayed opportunistic reactivation.[7] The histopathology of human melioidosis is not tissue-specific, and varies from acute to chronic granulomatous inflammation, which is consistent with the protean clinical manifestations of melioidosis.[8] *B. pseudomallei* is hardly visualised in Gram-stained biopsied tissues,[8] highlighting the importance of tissue culture.

Remarkably, in the present case, ceftazidime resistance was found in the *B. pseudomallei* isolate recovered from the necrotic lymphatic tissue in the mediastinum 24 days after starting ceftazidime therapy for melioidosis with *B. pseudomallei* bacteremia. Although molecular differentiation was not performed, it is logical to speculate that it was one clonal *B. pseudomallei* being responsible for melioidosis in the affected patient, and the subsequent emergence of ceftazidime resistance in the *B. pseudomallei* isolate from the mediastinal necrotic lymphatic tissue resulted from the microbe's prior prolonged exposureto the suboptimal concentrations of ceftazidime in the lymphatic niche.[9]

One recent reported case of melioidosis involving a diabetic patient with pneumonia under treatment with ceftazidime clearly delineated 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.[10] Mutations in Ambler class A β-lactamase leading to ceftazidime resistance in *B. pseudomallei* was well documented,[10,11] while other β-lactamases present in the genome and the putative efflux pumps of *B. pseudomallei* have not yet been conclusively associated with β-lactamase resistance.[10]

The development of resistance to ceftazidime, the drug of choice for melioidosis, in *B. pseudomallei* isolate during therapy with this antibiotic is worrisome given the fact that a mortality rate of approximately 35% was reported in patients with melioidosis treated with ceftazidime to which the culprit pathogens were susceptible.[12]

Conclusion

In summary, to secure a timely diagnosis of melioidosis in geographic areas where this infectious disease is endemic, lymphatic biopsy for bacterial culture should be considered necessary in patients with prolonged fever coupled with unexplained mediastinal lymphadenopathy. The emergence of ceftazidime resistance in *B. pseudomallei* compounds the problem in terms of antibiotic therapy. Susceptibility testing on *B. pseudomallei* isolates grew from serial culture for providing guidance to antibiotic treatment of melioidosis may be clinically important.

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