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Colonization or spontaneous resolution: Expanding the role for *Burkholderia pseudomallei*

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ABSTRACT

A 19-year-old Asian Indian female presented with productive cough since the past one month and low grade fever since the past two weeks. She was diagnosed with pulmonary tuberculosis and treated with antitubercular drugs. Subsequently, delayed cultures of bronchoalveolar lavage fluid grew *Burkholderia pseudomallei (B. pseudomallei)*. On follow up the patient reported significant subjective improvement and ESR progressively returned to normal. In summary, this case report raises two distinct and equally intriguing roles for *B. pseudomallei*, *i.e.* respiratory colonization and spontaneously resolving pulmonary infection. The pathogenic potential of *B. pseudomallei*, the etiologic agent of melioidosis, is well known. Confirmation of either colonization or spontaneous resolution, would potentially spare many patients unnecessary and expensive therapy with broad-spectrum antibiotics, and contribute to more rational usage of antibiotics, especially in co-infection with *Mycobacterium tuberculosis* and *B. pseudomallei*-two bacterial diseases with closely similar clinical, radiologic and histopathologic features.

1. Introduction

Melioidosis is a disease that results from infection with *Burkholderia pseudomallei* (*B. pseudomallei*) - a gram negative, non-sporing aerobic bacillus[1] and can pursue either an acute suppurative or a chronic granulomatous course. The pathogenic potential of *B. pseudomallei*, a soil saprophyte, has been well established on the basis of numerous large-scale studies[2], conducted principally in the Northern Territory of Australia and in Thailand, where the disease is endemic. Clinically and radiologically, melioidosis can mimic tuberculosis, another granulomatous infection endemic to South-East Asia. Needless to say, isolation of *B. pseudomallei* from sputum or bronchoscopically obtained sampling in the presence of suggestive radiological evidence is considered as conclusive of pulmonary melioidosis. This case report raises the possible role of *B. pseudomallei* as a respiratory colonizer against the equally intriguing prospect of spontaneously resolving pulmonary infection with *B. pseudomallei*.

2. Case report

A 19-year-old Asian Indian female with no significant past medical history, presented with productive cough since the past one month and low grade fever with evening rise of temperature since the past two weeks. She denied recent contact with any known case of pulmonary tuberculosis. There was no history of substance abuse. General physical examination showed mild pallor. Respiratory examination revealed fine crepitations in the left supraclavicular, axillary and suprascapular areas. Review of routine laboratory parameters was notable for anemia (Hb: 9.5 g/dL), leukocytosis (16 000 cells/μL), elevated ESR (98 mm/hr),

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hypoalbuminemia (3.0 g/dL) and increased serum globulins (4.5 g/dL). Chest X-ray revealed an upper zone cavitory lesion in the left lung field (Figure 1, panel A). Sputum samples were however persistently negative for acid-fast bacilli. Mantoux skin test was also negative. In pursuit of a conclusive diagnosis, a flexible bronchoscopy was performed next, and broncho-alveolar lavage (BAL) fluid obtained for microbiological analysis. As the overall clinical and radiological picture was strongly suggestive of tuberculosis, the patient was initiated on anti-tubercular therapy (ATT) with isoniazid, rifampicin, ethambutol and pyrazinamide, pending microbiological reports and subsequently discharged.

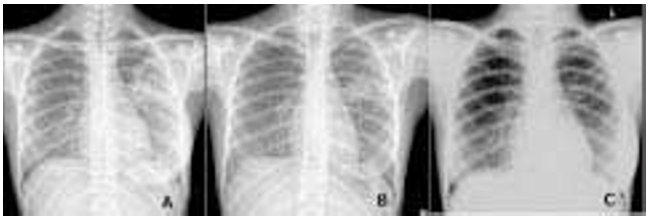

Figure 1. Initial chest X-ray showing an upper zone cavitory lesion in the left lung field (panel A). Serial chest X-rays on follow-up showing complete resolution of the lesion (panels B, C).

Ziehl-Neelson staining of BAL fluid was subsequently negative for acid fast bacilli, but delayed bacterial culture yielded a growth of dry, wrinkled pink-colored colonies after 14 days of incubation. The isolate was biochemically identified as *B. pseudomallei*, which was further confirmed by API-GN (Biomerieux, France). On follow up the patient reported significant subjective improvement and ESR progressively returned to normal, eventually reaching 7 mm/hr. Serial chest X-rays also demonstrated complete resolution of the cavitory lesion (Figure 1, panels B, C).

In view of the excellent clinical and radiological response to ATT, it was decided to continue the same line of management, despite the absence of microbiological evidence for infection with *Mycobacterium tuberculosis (M. tuberculosis)*. Antibiotic therapy for *B. pseudomallei* was also withheld. The patient continued to improve nevertheless, and remains asymptomatic and well on follow-up one year after the index illness, and six months after completion of ATT.

3. Discussion

Co-infection with *M. tuberculosis* and *B. pseudomallei* have been reported in a number of case reports[3,4]; in all these cases, isolation of *B. pseudomallei* was taken as prima facie evidence of pathogenecity. The principal obstacle of course, to such an approach is the very nature of these infections, and the close clinical, radiological and histopathologic characteristics they share. Indeed, had *B. pseudomallei* been isolated early in the course of hospital stay, our patient too would probably have received chemotherapy for melioidosis in addition to, or in lieu of ATT. It was only the excellent response to ATT that prompted withholding of chemotherapy for melioidosis.

B. pseudomallei has now been recognized as a potential colonizer in patients with cystic fibrosis and bronchiectasis[1]. Colonization of tuberculous lungs by *B. pseudomallei*, as postulated in our case report, is a reasonable extension of the same phenomenon. The complete and durable recovery of the patient with ATT would suggest that in this instance, *B. pseudomallei* was in fact just a colonizer and not a true pathogen.

Serendipitous impact of ATT on pathogenic *B. pseudomallei*, resulting in clearance of the organism and subsequent recovery was also considered. A careful review of literature yielded no studies on the in vivo efficacy of rifampicin against *B. pseudomallei* in human subjects. An animal model[5] with mice showed modest susceptibility but only with massive dosing on the scale of 170 to 550 mg per kg per day. The same study demonstrated a mean in vitro MIC of 35.7 μg/mL for rifampicin and *B. pseudomallei*. Another study by Alexander and Williams[6] was also corroboratory with the majority of strains displaying MICs greater than 25 μg/mL. A pharmacokinetic study by Goutelle *et al*[7] with 600 mg single dosing of rifampicin showed maximal serum concentrations of less than 14 μg/mL with correspondingly lower concentrations in epithelial lining fluid and alveolar cells, all well below the MIC for most strains of *B. pseudomallei*. Moreover, as a consequence of its relatively short half-life as well as its property of auto-induction of its own metabolism, rifampicin achieves its peak serum and fluid concentrations for only a brief period of time, followed by a rapid decline; such a pharmacokinetic profile appears unsuitable for a hardy organism like *B. pseudomallei*, where sustained exposure to killing concentrations of antibiotic would probably yield superior efficacy. There is no available evidence of activity for the other antitubercular drugs administered in our patient. In conclusion, a brisk response of *B. pseudomallei* to ATT would seem remote.

A rapid review of previous case reports of tuberculosis

and meliodosis co-infection[3,4] reveals similar diagnostic dilemmas. In each case the patient presented with a clinical picture compatible with tubercular mono-infection; simultaneous isolation of *B. pseudomallei* was used to justify co-infection. Indeed, in one case repeated isolation of the organism was specifically invoked to discount the possibility of colonization; it would be pertinent to note that repeated isolation can rule out contamination, but not colonization. Moreover, patients in these case reports received simultaneous therapy with ATT and antibiotics for *B. pseudomallei*, making it impossible to determine whether the patient responded to the ATT alone or the combined therapy of ATT and antibiotic.

A major point of difference between our case and the older reports is of course, the consistent absence in our case, of definitive microbiological evidence of tuberculous infection. This pattern would support *B. pseudomallei* as the likely underlying organism. Given the improbability of a robust response of melioidosis to ATT, the only other explanation would then be spontaneous resolution of pulmonary melioidosis in the absence of specific chemotherapy. Spontaneous clearance has been reported previously for cutaneous melioidosis[8,9] – a mild form of the disease, but never before for pulmonary melioidosis. Interestingly, self-limited and spontaneously resolving forms of melioidosis, as well as asymptomatic carriage have been suggested as an explanation for seropositivity in endemic areas in individuals with no history of melioidosis[8]. Either of these states could account for the findings in our patient; neither of these states has been reported heretofore in association with pulmonary melioidosis.

In summary, this case report raises two distinct and equally intriguing roles for *B. pseudomallei*, *i.e.* respiratory colonization and spontaneously resolving pulmonary disease. Perhaps, a more conservative strategy of initiating ATT first in patients with concomitant pulmonary melioidosis and gauging the clinical and radiological response before treatment with antibiotics could clarify the role of *B. pseudomallei* in such situations. Confirmation of either colonization or spontaneous resolution, would potentially spare many patients unnecessary and expensive therapy with broad-spectrum antibiotics, and contribute to more rational usage of antibiotics.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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