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Acute Disseminated Melioidosis Resulting in Septic Shock, Pneumonia, Acute Kidney Injury, Metabolic Acidosis, Myocarditis and ARDS in A Soldier with Open Fracture of Femur and Tibia Due to Mine Injury: A Case Report

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CASE SUMMARY

A-29-year-old soldier had multiple open fracture of both legs; fracture femur on right side and fracture tibia on left side due to mine injury. He developed multiorgan failure: wound sepsis, septicaemia, septic shock, metabolic acidosis, acute kidney injury, myocarditis, heart failure and ARDS. *Burkholderia pseudomallei* was grown in the wound and he was successfully treated with meropenum, ceftazidime. He recovered after three months intensive treatment with multidisciplinary team.

Key words; melioidosis, open fracture, wound sepsis, *Burkholderia pseudomallei*, multi-organ failure, meropenum, ceftazidime

INTRODUCTION

Melioidosis, an infection caused by the gram-negative bacillus *Burkholderia pseudomallei*, distributed in soil and surface water. It is endemic in Southeast Asia and Northern Australia. Cases were reported from Taiwan, Singapore, China (Cheng & Currie, 2005), India and Syri Lanka. Those coming back from these endemic area also contracted melioidosis (Alhatmi et al., 2020); moreover, the cause of death in soldiers coming back from Vietnam were due to acute melioidosis (Patterson et al., 1967). The common mode of transmission is through contact with contaminated water or soil. In Myanmar, sporadic cases of melioidosis have been diagnosed since 1911(Whitmore., 1913); and, nearly 300 cases were reported till now(Aung & Mar, 2008) (Zaw-Than-Htun et al.,2013) (M. M. Win et al., 2018), but none of them was related to mine injury or open fracture. In addition, their reported cases were not coming from northern part of Myanmar, Myanmar-China border, the soil survey for *Burkholderia pseudomallei* in different sites of Myanmar was not included (T. T. Win et al., 2019)(M. M. Win et al., 2018b).

The incubation period may be as short as 1day and as long as several months or years; most of the affected are asymptomatic if the host is immune-competent. The disease has two clinical spectrum: acute and chronic. If acute disease predominates, pneumonia is the most frequent mode of presentation (Barman et al., 2011) (Currie, 2003).

The affected may have other organ involvement: genitourinary infection (QUE et al., 1991) (Rahim et al., 2018) (Wijewickrama & Weerakoon, 2017); hepato-biliary infection (Mohamad et al., 2012); skin infection (Barman et al., 2011); soft tissue abscesses (Miralles et al., 2004) (Chen et al., 2018); bone and joint infection (Karunarathna et al., 2018) (Raja & Scarsbrook, 2016) including septic arthritis (Lee et al., 2015) (Parija et al., 2020); cardiovascular infection- endocarditis, myocarditis, pericarditis (Velusamy & Muhi, 2020), mycotic aneurysm (Low et al., 2005); and, central nervous system infection- encephalomyelitis (Amarasena et al., 2019). Chronic form can imitate tuberculosis (Antony S et al., 2017) and malignancy (Saravu et al., 2012).

The mortality rate is very high 20-50% depending on early diagnosis, complications, significant co-morbidities and facilities for health care (Chakravorty & Heath et al., 2019). *Burkholderia pseudomallei*is notorious for multi-drug resistance; therefore, the choice of antimicrobial therapy is not easy for treating physician especially in the era of antimicrobial resistance. Furthermore, the duration of treatment is long to get complete eradication; 2-6 months.

We report a rare presentation of melioidosis in a previously healthy, young soldier with mine injury causing open fracture of femur and tibia giving rise to septic shock, pneumonia, acute kidney injury, metabolic acidosis, myocarditis and ARDS leading to management problem.

CASE PRESENTATION

A 29 year old soldier hadland-mine injury in Ta Naing front line, near Myanmar-China border, and he was transferred to our hospital. It resulted in open fracture femur on right side with foul-smelling yellowish-brown discharge and cellulitis. He also had open fracture tibia on left side with foul-smelling, brownish discharge too; he was very ill and toxic. (Figure 1 & 2) His blood pressure was 70/50 mmHg and pulse rate was120/min. Temperature was 104ºF and SaO_2 on air was 92%. His respiratory rate was 22/min and lungs were clear on auscultation. His urine output was reduced (200 cc/24 hour) and serum creatinine was raised (2mg%). He had metabolic acidosis as his arterial pH was 7.3 and HCO_3 was 15 IU/L. He was put on parenteral antibiotics (metronidazole, cefepime, meropenem), fluid & electrolyte replacement and inotropes (noradrenaline). He was on oxygen with nasal bag and haemodialysis was initiated for acute kidney injury. His haemoglobin was 8 gm% and total WBC count was 14.0 $X10^9$/L (neutrophil leucocytosis).

Figure (1). *Very ill patient on arrival, during wound dressing*

Figure (2). *External traction after wound dressing to open fracture femur on right side*

Over next 24-48 hour, his condition was deteriorated; he became more tachypnoeic (respiratory rate 28/min) although he was on oxygen. Lungs became full of crackles. CXR showed patchy consolidation in middle and lower zone. (Figure 3) Blood for complete picture revealed further rise in total WBC count (20 $x10^9$/l) and falling haemoglobin (6 gm%) possibly due to septicaemia and intravascular haemolysis. Therefore, his anaemia was corrected with blood transfusion.

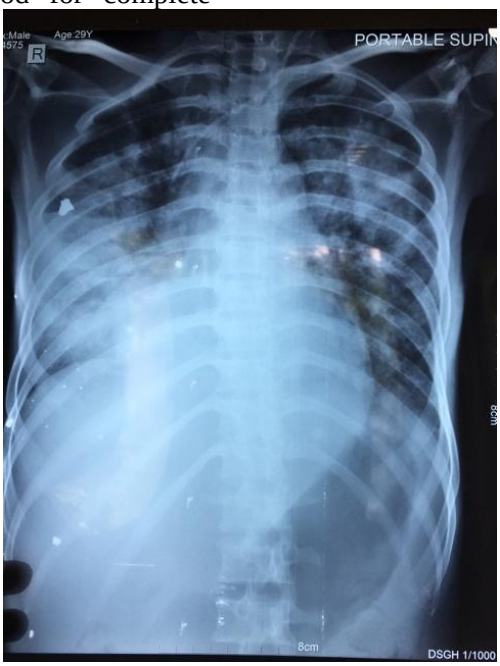

Figure (3). *CXR with cardiomegaly and consolidation right middle & lower zone and left middle zone*

On third day, his clinical condition was desperate:more tachypnoeic (respiratory rate 36/min) and SaO_2 was falling (80% on 15L O_2 therapy). The features were suggestive of ARDS; therefore, theintensive care physician team decided to put him on ventilator. The orthopedic team was doing wound debridement twice a day and external traction was applied to both legs.

End of first week, the wounds becameclean and their smell was better i.e.,no more foul smelling. The results of both blood culture and the culture of wound swab from the site of open fracture femur showed the growth of *Burkholderiapseudomallei*; and, it was sensitive to ceftazidime, meropenum and imipenum. Thus, we switched to ceftazidime and increased the dose of meropenem which was initially prescribed on the day of arrival to our hospital. Recheck CXR was improving. (Figure 4) Two weeks later, the wounds were better. (Figure 5& 6)

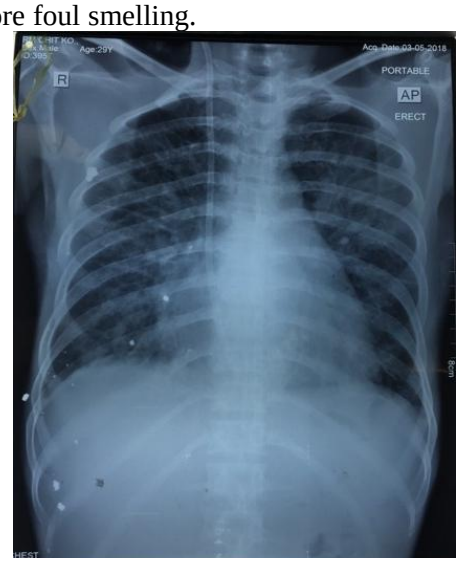

Figure (4). *CXR with central line, consolidation resolved 3.6.18*

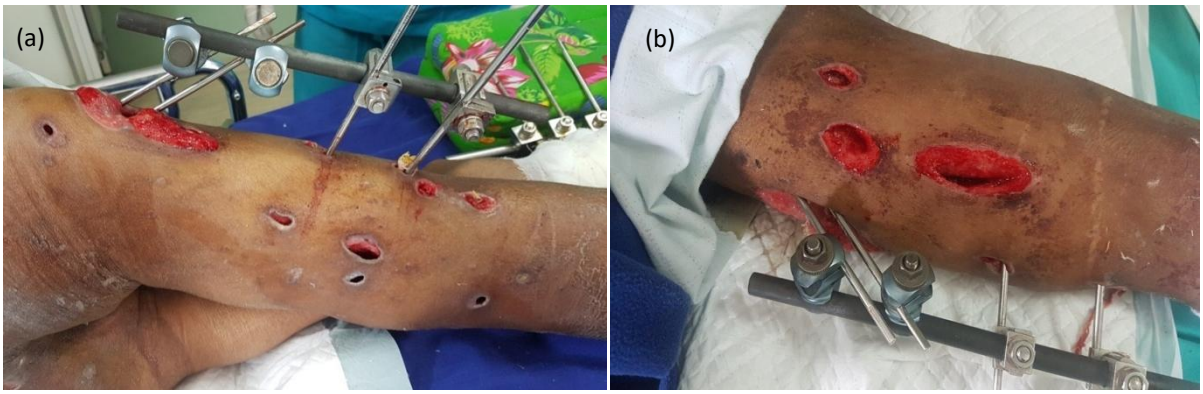

Figure (5). *Open fracture femur (right) with external splint and multiple splinters wound*

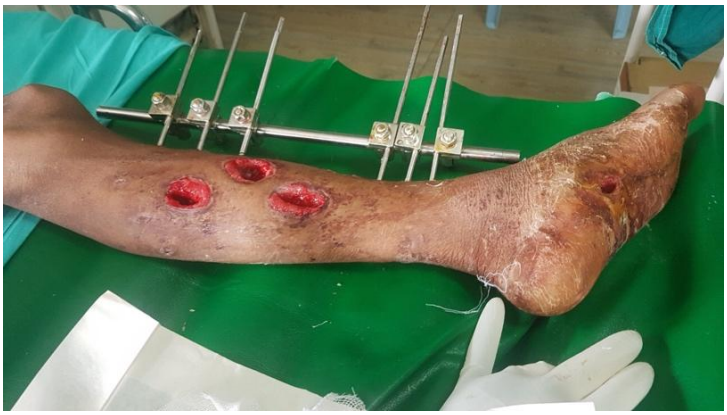

Figure (6). *Open fracture Tibia (left) with external splint and multiple splinters wound*

By third week,his temperature touched normal. The wounds were cleaner thanthat of second week. Blood pressure became stable; 120/80 mmHg without inotropes. He was eating well; his appetite was great. His anaemia was corrected with blood transfusion. His renal function was better; serum creatinine was 1.5 mg% with haemodialysis three times a week. His oxygen requirement was decreased; his SaO_2 was stable at 94% with 4L of oxygen. However, he had undue tachycardia; heart rate was 120/min with normal temperature and without inotropes. ECG showed sinus tachycardia. CXR revealed huge cardiomegaly and lung fields were clearer than before. (Figure 7) Global hypokinesia was seen in echocardiogram and it was consistent with myocarditis. His blood for CK MB was raised five times normal too. ASO titre was normal (<200). Cardiologist put him on diuretics, beta blocker and thiamine.

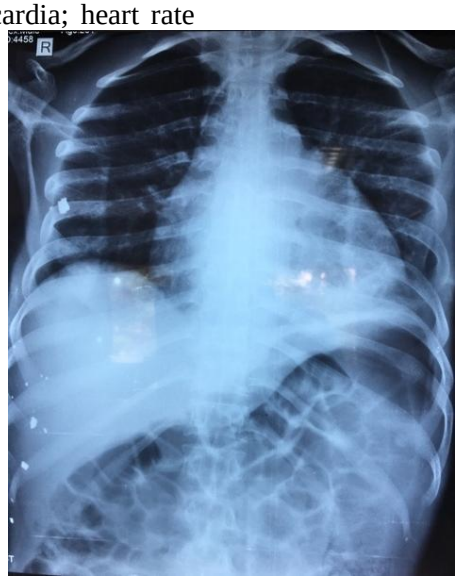

Figure (7). *CXR showing gross cardiomegaly, increased hepatic shadow and dilated intestine*

One month later, temperature was normal; no fever spike. His SaO_2gradually rose to 96% with 2L of oxygen. His heart rate responded to carvedilol and repeat CXR showed improvement in cardiomegaly. (Figure 8) Improvement in both lung field and heart were more pronounced in repeat CXR. (Figure 9)

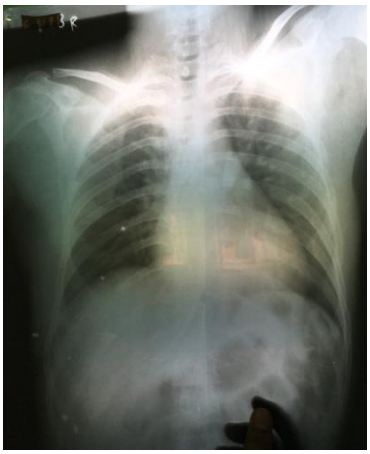

Figure (8). *CXR showing moderate cardiomegaly*

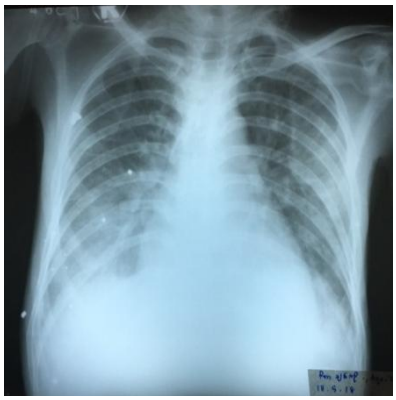

Figure (9). *CXR showing moderate cardiomegaly and patchy opacities in both middle and lower zone*

Two months later, he regained normal renal function without the need for dialysis. He recovered after intensive multidisciplinary treatment for three months. (Figure10) After 5 months, he was doing physiotherapy and ambulating with wheel-chair. (Figure 11) He got complete union of both bones by 6 months. (Figure 12 & 13)

Figure (10). *Patient on recovery with POP left leg (3 months)*

Figure (11). *Patient on recovery with POP left leg (5 months)*

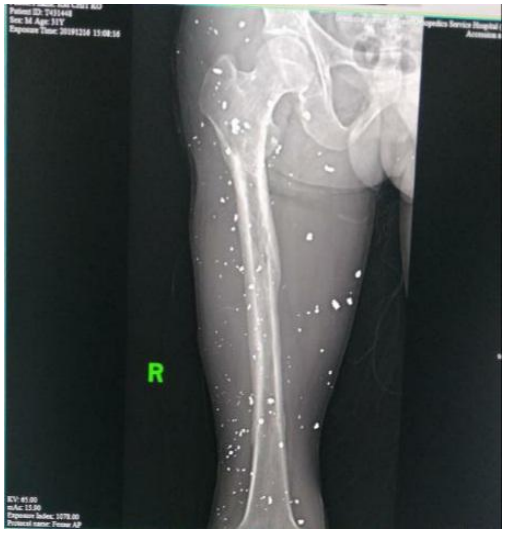

Figure (12). *Healed fracture femur with multiple splinters*

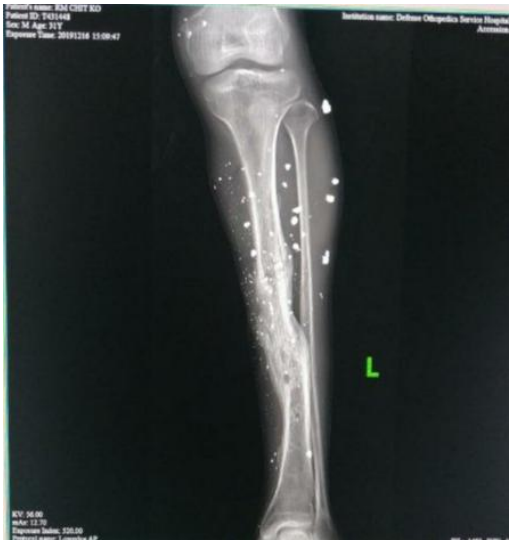

Figure (13). *Healed fracture Tibia with multiple splinters*

DISCUSSION

Burkholderia pseudomallei is notorious for multi-drug resistance and inherently resistant to empiric antibiotic regimens used to treat pneumonia or sepsis; the mortality rate in melioidosis was very high (Chakravorty & Heath, 2019). Thus, early diagnosis and appropriate antibiotics are essential.

Our patient was a previously healthy, young soldier who got open fracture of two long bone in both legs with multiple splinter wounds following mine injury. As the wounds were heavily contaminated with soil in the battle field, his presentation was in state of septic shock and metabolic acidosis. It was again complicated by acute kidney injury. Later, he developed pneumonia in both lungs. An inadequate response to empiric antimicrobial therapy initially and the development of bilateral pneumonia with heavily contaminated wound urged us to consider possibility of very virulent organism in the wound and then, septicaemia and septic shock. In the past, there were reports on war wounds having melioidosis (Patterson et al., 1967) (Ngauy et al., 2005); and, such kind of wound are rare at present. This is the first reason for reporting rare case in 21st century.

This patient got mine injury while he was performing military duties in Ta Naing which is close to Myanmar-China border. Although the study for "soil sample from the different site of Myanmar for melioidosis" did not include Myanmar-China border (T T Win et al., 2019) (M M Win et al., 2018), we can conclude that the chances of soil in Myanmar-China border area having *Burkholderia pseudomallei* is probable. It again signifies epidemiological importance of this case. It also pointed out the case reports from China (Cheng & Currie, 2005).

Regarding the incubation period, it may be as short as one day or may be too long for several years. The shortest incubation period was seen in cases with drowning and the survivors from psunarmi (Chierakul et al., 2005) and they presented with acute melioidosis; severe pneumonia and multi-organ failure. In this case, the incubation period was very short; and he developed fever 20 hours after land-mine injury. He was very rare case of acute melioidosis too.

Burkholderia pseudomallei was grown in the blood culture and wound swab from the site of open fracture femur and it was sensitive to ceftazidime, meropenum and imipenum. As we got the culture result for *Burkholderia pseudomallei* from wound by Vitek test and haemagglutination test, we increased the dose of meropenum; and, ceftazidime was initiated. Shortly after initiation of ceftazidime and the high dosage of meropenum, the improvement in clinical response was more pronounced particularly the temperature, the degree of wound contamination, colour and smell, and blood pressure. These clinical changes provided the evidence to Gunasekaran Ket al.(2018); they suggested that "if melioidosis presents with multisystem involvement with disseminated abscess, standard dosing of meropenem may not be sufficient in achieving therapeutic levels and therapeutic dose monitoring with increased dosing in these critically ill patients will improve outcome".

Treatment of melioidosis consists of two phases; intensive phase and oral eradication therapy phase. The antibiotics recommended in the intensive phase are intravenous meropenem or ceftazidime. Four to eight weeks of therapy is recommended in critically ill patients with severe pulmonary disease or deep-seated abscesses. Therefore, in our patient, initial intensive therapy was continued for 3 months was in line with the recommendations. The recommended drugs to be used for oral eradication are TMP–SMX, doxycycline or amoxicillin–clavulanate, all to be continued for 3 months. In our patient, we continued amoxicillin–clavulanate for one month for the oral eradication. Thus, total duration of therapy was 4 months in our patient.

Though metabolic acidosis and septic shock commonly provoke acute kidney injury, the duration of renal replacement therapy (haemodialysis) in this patient was long ie three months. We presumed that the mechanism of acute kidney injury was more than pre-renal ie shock; and he most probably had acute tubular necrosis though we did not prove by renal biopsy.

Several studies have reported varying degree of mortality depending on the presence of complications as follows. According to Prabhu et al. (2021), the chances of having acute kidney disease in melioidosis was 35% and the mortality increases with increasing degree of renal impairment. Furthermore, the study by

Chakravorty & Heath. (2019) revealed that the mortality rate was more than 50% in acute melioidosis in resource-poor settings with limited access to modern diagnostic and intensive care unit (ICU) facilities, particularly in people who have significant comorbidities. In Australian study which involved nearly 300 patients over 10 years revealed that "mortality rate was 86% if acute melioidosis had septic shock" (Bart J. Currie et al., 2000). Our patient recovered very luckilyas the mortality rate was nearly 90% with his presentation. It signifies another importance of this case.

Velusamy & Muhi. (2020) found that the mortality was high if there was myocarditis. The patient was also diagnosed to have myocarditis presumptively based on the undue tachycardia, global hypokinesia in echocardiogram and gross cardiomegaly on CXR with raised CK MB and normal ASO titre. Two weeks later, the improvement of all features was supportive for the above diagnosis.

The presence of *Burkholderia pseudomallei*in open fracture was seen in only one report from Malaysia;and, it was mentioned that "11 year old boy had open fracture ulnar following fall into a water-filled drain and the wound was contaminated with *Burkholderia pseudomallei* (Laila Maisarah AR et al.,2010). From hot orthopedic point of view, it highlights the rarity of this case.

This case was extremely challenging as it had multi-organ failure, multi-drug resistant organism and open fracture of two long bones on both legs. According to the guidelines for management of open fracture, thorough wound debridement, appropriate antibiotics and external fixation were applied and the fracture were healed well. Giving appropriate antibiotics for adequate duration is parenteral ceftazidime and meropenum high dose for three months, followed by one month course of amoxicillin-clavulinic acid for *Burkholderia pseudomallei*; and timely diagnosis and treatment of complications- septic shock, pneumonia, metabolic acidosis, acute kidney injury, ARDS, myocarditis and heart failure were challenging for all team members.

This case demonstrates atypical presentation of acute melioidosis giving rise to multi-organ failure in immune-competent soldier with multiple open fracture in both legs- femur and tibia due to land-mine injury. This points out the importance of having a high clinical suspicion to avoid diagnostic delay of melioidosis even in patient withopen fracture.

Although the patient was immune-competent, he developed multiorgan failure; wound sepsis, septicaemia, septic shock, metabolic acidosis, acute kidney injury, myocarditis, heart failure and ARDS. It also confirmed the finding by Zainal Abidin et al. (2017) –"In endemic area, melioidosis can occur in immunocompetent youths with no recognisable risk factors".

And the patient recovered finally because of intensive treatment by multi-disciplinary team.

CONCLUSION

In endemic area, melioidosis can occur in immunocompetent youth- soldier with land-mine injury. Acute disseminated melioidosis giving rise to septic shock, pneumonia, acute kidney injury, metabolic acidosis, myocarditis, heart failure and ARDS pose significant challenges to the medical team because it has high rate of morbidity and mortality. Multidisciplinary team managementsave the life of patient as well as his legs- open fracture of femur and tibia.

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