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Original Research Paper

Internal Medicine

# MEILIODOSIS - AN ENIGMA WITH VARYING ANTIBIOTIC RESPONSE

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**ABSTRACT** Melioidosis or Whitmore's disease is an infection of humans and animals caused by aerobic gram negative bacillus Burkholderia pseudomallei. This infection with a wide clinical spectrum is predominantly present in tropical climates, mainly Southeast Asia and Northern Australia. The clinical manifestations include pneumonia, skin ulcers or abscesses, osteomyelitis, prostatitis, encephalomyelitis and fulminant septic shock. The definitive diagnosis is made by a positive culture of Burkholderia pseudomallei. The bacteria is innately resistant to 6 classes of commonly used antibiotics. CDC recommends an intensive phase of intravenous antibiotics for 10 to 14 days followed by eradication therapy with oral antibiotics for 3 – 6 months. The intravenous agents effective against the bacteria are meropenem and ceftazidime. Trimethoprim sulfamethoxazole and amoxicillin/clavulanic acid are the oral antimicrobial agents used. Here we present two cases of Melioidosis, at opposite ends of the spectrum with varying antibiotic response. One patient is a young non immunocompromised female and the second an elderly immunocompromised (T2DM) male, both presented with skeletal melioidosis.

**KEYWORDS :** melioidosis,skeletal melioidosis

## CASE SUMMARY

### Case 1

A 74 year old male a known case of T2DM and systemic hypertension presented with history of fever for 1 week and persistent non productive cough with increased intensity during the night. Patient was initially treated with amoxicillin / clavulanate for suspected community acquired pneumonia. Blood investigations was normal except for hyponatremia which was attributed to diuretics that the patient was taking for hypertension. CT - Thorax showed two small thick walled cavities in the upper lobe of both lung and few mildly enlarged mediastinal lymph nodes. The patient was discharged with oral antibiotics (Amoxicillin / clavulanate). The patient was readmitted after 1 week with persisting cough and fever. Antibiotics were escalated to meropenem and vancomycin. Intravenous fluconazole was also initiated in view of candiduria. Whole body PET CT scan was done which showed necrotic mediastinal and left hilar lymphadenopathy and non FDG avid gastrosplenic ligament lymph node. The differential diagnosis considered were sarcoidosis or tuberculosis. Patient was initiated on empirical ATT. However the patient was readmitted after 1 week following ATT induced liver injury and the drugs were withheld temporarily. Endobronchial ultrasound was performed. Biopsy of the lymph node showed caseation with no acid fast bacilli. Tuberculosis culture was sent and patient was started on second line ATT. However the patient continued to have fever with chills. Samples for blood culture were obtained which showed Burkholderia pseudomallei growth[1]. Activity in PET scan is shown in Fig.1.As the patient was not clinically responding to ceftazidime after 7 days of therapy, meropenem with doxycycline was initiated. Patient also underwent fasciotomy and repeated wound debridement of the right lower limb cellulitis. In view of the subperiosteal involvement of tibia intravenous antibiotics were continued for 6 weeks along with cotrimoxazole. Patient is now on eradication therapy, at 3 months now.

### Case 2

27 year old female presented with history of high grade fever with chills for 1 week. Patient was treated with third generation cephalosporins for 7 days. At presentation patient was in septic shock and had >10 erythematous nodules shown in Fig.2. distributed over both lower limbs and upper limbs. Intravenous antibiotics were escalated to meropenem and clindamycin. The Febrile Agglutination test showed anamnestic reaction [2]and culture of the pus from the erythematous nodules[3] grew Burkholderia pseudomallei. In view of persisting fever PET CT scan was done on Day 16 to rule out visceral abscess. Right knee joint effusion was drained and intravenous ceftazidime dose was increased to 50 mg/kg sixth hourly. Patient had defervescence on day 5 of escalated dose. Since the patient had skeletal melioidosis, cotrimoxazole was started on the first week. Intravenous ceftazidime was continued for 6 weeks and the patient completed eradication therapy.

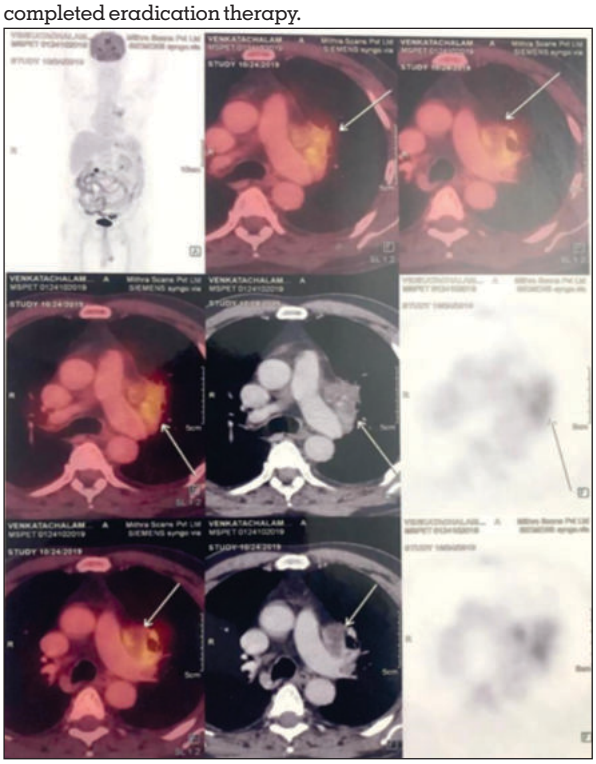

**Fig.1:**PET Scan Showing Disease Activity In Multiple Lymph Nodes

| FAT | | |
|---|---|---|
| WIDAL(Tube)-Salmonella Typhi "O" QUANTITATIVE / TUBE | 1:320 Significant | |
| WIDAL(Tube)-Salmonella Typhi " H " QUANTITATIVE / TUBE | 1:160 Significant | |
| WIDAL(Tube)-Salmonella Para Typhi "AH " QUANTITATIVE / TUBE | Negative 1:20 dilution | |
| WIDAL(Tube)-Salmonella Para Typhi " BH " QUANTITATIVE / TUBE | Negative 1:20 dilution | |
| Brucella abortus SEMI QUANTITATIVE / SLIDE | 1:320 Significant | NEGATIVE |
| Brucella Melintenis SEMI QUANTITATIVE / SLIDE | 1:320 Significant | NEGATIVE |
| I M Latex - SCREENING AGGLUTINATION | No agglutination | No agglutination |
| WEIL FELIX - OX - 19 SEMI QUANTITATIVE / SLIDE | 1:160 Significant | No agglutination |
| WEIL FELIX - OX - 2 SEMI QUANTITATIVE / SLIDE | 1:160 Significant | No agglutination |
| WEIL FELIX - OX - K SEMI QUANTITATIVE / SLIDE | 1:80 Insignificant | No agglutination |

**Fig.1** Anamnestic Response In Febrile Agglutination Test

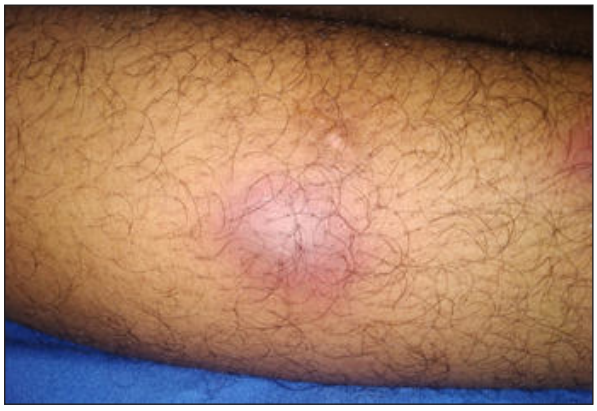

**Fig.2:** Erythematous nodules in lower limb

## DISCUSSION

Melioidosis or Whitmore's Disease is an infectious disease caused by a bacterium, Burkholderia pseudomallei. It is a gram negative facultative intracellular pathogen found in soil and surface water, and can infect human or animals. Route of entry is through skin by percutaneous inoculation, inhalation or ingestion. The most important risk factors for melioidosis are diabetes, alcoholism, renal disease, chronic lung disease and thalassemia. 20% of the cases do not have an underlying risk factor. The bacteria can invade and replicate inside various cells. The lipopolysaccharide which confers resistance to human serum and the ability of the bacilli to survive inside cells play a critical role in the pathogenesis. Following the entry of the bacterium into the human body, patient can develop sepsis, pneumonia or a latent infection. The host protective mechanisms include both cell mediated immunity and antibodies. The balance between pro inflammatory and anti inflammatory response determines the severity of the disease.

The clinical presentation of the infection is varied. It can range from skin lesions to pneumonia and sepsis[4]. Both our patients presented with history of fever. One patient had diabetes mellitus as an underlying risk factor, however the other did not have any comorbidities. Diabetic patients are predisposed to melioidosis due to impaired innate immune function such as defective macrophage phagocytosis, decreased lipopolysaccharide induced CD4 response and impaired TLR mediated primary response. Diabetes increases the relative risk of melioidosis to 20 fold. Diabetic patients are also have more propensity for sepsis due to decreased phosphorylation of NF□B , TNF□ and Interleukin 12.

Soft tissue abscess[5] was the most commonly reported clinical presentation of melioidosis followed by pneumonia as per Indian statistics. The case fatality rate of this infection varies from 7 to 35%. One of our cases presented with subcutaneous abscess involving all 4 limbs. The culture of pus obtained from these yielded B. pseudomallei. An anamnestic response to febrile agglutination test was also present. Case 1 was initially started on ATT as the PET CT scan and biopsy of the node was suggestive of tuberculosis. Diagnostic confusion with tuberculosis has been reported earlier in cases of melioidosis. However a subsequent blood culture showed B. pseudomallei growth. A positive culture of B. pseudomallei is the definitive diagnostic test.

Bone and joint involvement is well recognised entity in Melioidosis. Both our patients had skeletal melioidosis, where the eradication therapy should be started as soon as the diagnosis is made. B. pseudomallei have been found to be susceptible to various beta lactam antibiotics, especially ceftazidime, imipenem, meropenem etc with various degrees of bactericidal activity. Guidelines recommend an initial intensive therapy for 10 – 14 days followed by eradication therapy for minimum three months. But for deep seated infections like prostatic abscess, skeletal melioidosis, neuromelioidosis and complicated pneumonia intensive phase therapy should be given for 4 to 6 weeks. Both cases received intensive phase therapy for 6 weeks and is now under eradication therapy with TMP – SMX. Both the cases were susceptible to ceftazidime and meropenem[6] invitro, however the clinical response was different. Case 1 didn't respond to ceftazidime and case 2 didn't respond to meropenem which cannot be explained due to lack of genetic analysis of the bacterial genome at our centre. Ceftazidime resistance has been documented in India. Upregulation of *penA* transcription and deletion of the penicillin binding protein 3 is associated with high-level ceftazidime resistance. Amino acid substitutions in class A □-lactamase is responsible for ceftazidime and amoxicillin–clavulanic acid resistance. The development of antibiotic resistance during therapy is a cause for concern.

## CONCLUSION

Melioidosis is an emerging infection in India. This condition is however underdiagnosed due to low index of suspicion among clinicians and microbiologists. Knowledge about the antimicrobial resistance mechanisms and their implications for treatment is of increased significance now. More research in this area is needed to fill the gaps in our knowledge.

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