International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

A Case of Fever of Unknown Origin -? Melioidosis Presenting as Severe Sepsis and Multiple Organ Dysfunction Syndrome

Sharon Wilson[1], Tintu Thomas[2], Dr. Elizabeth James[3], Aromal Kannan Madhu[4]

[1,2]PharmD Intern, Nazareth College of Pharmacy, Thiruvalla, Kerala
[3]Associate Professor, Department of Medicine, Believer's Church Medical College, Thiruvalla, Kerala
[4]PharmD Intern, Karnataka College of Pharmacy, Bengaluru, Karnataka

Abstract
Melioidosis is an emerging infection in India[1], well known for its protean clinical manifestations. We report a case of probable disseminated Melioidosis with hyperferritinemic septic shock and multi organ dysfunction syndrome. She presented as a case of PUO- with high fever- 1week, loose stools, headache and shortness of breath, to our hospital. She had a turbulent course in hospital, with fever not responding despite 2 weeks of hospitalization. Her respiratory system showed bilateral crackles. Per Abdomen examination revealed tenderness in right iliac fossa, suprapubic region and left iliac fossa, bowel sounds were sluggish. CECT chest and Abdomen showed right basal pneumonia, hydro-ureteronephrosis, with ureter showing narrowing at the region of right adnexa, PID, subcentrimetric , mesentric , and perirectal lymph nodes; rectal wall showing inflammatory changes with inflammation of mesorectal fascia . She responded well and fully recovered with injection Meropenem for 8 weeks; followed by oral Trimethoprim-Sulfamethoxazole for 3 months.

Keywords: Pyrexia of Unknown Origin, Multiple abscesses, Septic shock, MODS, Burkholderia Pseudomallei

Introduction

Melioidosis, also known as Whitmore's disease, is a zoonotic disease caused by non-fermentative bacteria, Burkholderia pseudomallei. Transmission is from animals such as sheep, goats, pigs, cows and horses humans, through inhalation of contaminated dust or water droplets. Diabetes mellitus, pre-existing renal diseases, Thalassemia, and occupational exposure were confirmed to be significant risk factors for Melioidosis; while only Diabetes mellitus was found to be a significant risk factor for bacteraemic Melioidosis[2]. The pathogen, Pseudomonas pseudomallei/ Bacillus pseudomallei is intrinsically resistant to beta lactam antibiotics, first and second generation Cephalosporins, Aminoglycosides, and Polymyxin B, a feature which not only aids in laboratory identification, but also in the choice of treatment.

Case Report

A 44 years old female patient presented with h/o high spiking fever, headache, greenish loose-stools and

shortness of breath of 7 days duration. She had h/o contact with contaminated water multiple times, as a part of work- related exposure. She was initially taken to a Government Hospital where she developed multiple episodes of vomiting followed by abdominal distention and developed oliguric AKI (Blood Urea 66mg%, Creatinine 1.7 mg/dl) and was referred to our tertiary care and admitted in Medical ICU, for initiation of SLED.

On general examination, the patient was conscious and obeying commands. Her temperature was 100.2F, Blood pressure- 100/80 mm/Hg; Pulse rate 128/min, Respiratory rate 30 breaths/min, SpO2 95% on NIV. On systemic examination; Respiratory system showed bilateral crackles. Per Abdomen examination revealed tenderness in right iliac fossa, suprapubic region and left iliac fossa and bowel sounds were sluggish.

Her initial investigations were as given in Table 1. It showed a normal blood sugar, leucocytosis, thrombocytopenia; normal triglycerides, raised inflammatory markers and transaminitis. Her Procalcitonin, Ferritin and CRP were elevated. ECG showed nonspecific ST-T Changes. The Cardiac Biomarkers were strongly positive. Renal Function Tests were deranged with urine showing 5-10 pus cells. The chest x-ray showed bilateral non homogenous opacities (Fig:1), (R > L), and bilateral pleural effusions (R >L). USG Abdomen, HRCT thorax (Fig: 2) showed collapse consolidation of Right lung with bilateral pleural effusion (R>L) – her condition was reported as likely to be of infective aetiology. CT abdomen also showed Right Pyelonephritis, cystitis, mild prominent appendix with perinephric stranding.

Thus, a preliminary diagnosis of Urosepsis with MODS was made; and injection Meropenem, as per eGFR along with Doxycycline to cover for any tropical fever in view of deranged LFT and thrombocytopenia, was initiated for 2weeks and course completed. Her general condition and vitals improved and she started taking oral feeds with this regimen, and so she was shifted out of ICU care, and mobilized. However, on stopping antibiotics, within 2 days, again high spiking fevers reappeared. She was further subjected to various investigations, and our diagnosis needed a revision.

Her Mantoux Test, sputum CB NAAT and IGRA test, Bone Marrow Aspiration / Cytology / Culture; Blood, urine and sputum cultures, Scrub IgG/IgM and Leptospira IgG / IgM were negative. In view of persistent fever, a WIDAL, Weil Felix and Smear for MP were done, including viral markers; all these were negative. RA Factor and ANA by IFA were also negative. A Gynaecological check-up ordered was inconclusive. An Ultrasound guided Pleural fluid tap was attempted – but unsuccessful. A Transthoracic and Trans oesophageal 2D Echo test was also normal. Repeated Blood, Urine and sputum cultures were negative. As she continued to spike with fever, a diagnosis of Melioidosis was considered in absentia. She could not afford a PET CT with FDG tracer and hence it wasn't done.

She was restarted with IV Meropenem empirically, dose calculated according to the creatinine clearance. Her fever responded within 3 days and renal and other lab parameters improved with drug therapy and hydration. She was observed for a total of 4 more weeks in the ward, during which she remained asymptomatic, and subsequently discharged on oral Trimethoprim-Sulfamethoxazole for 3 months. She was asymptomatic on follow up.

Lab values (Table -1)

WBC = 25700 cells/cubic millimetre^2 (NR 4000 – 11000 cells/cubic millimetre^2)

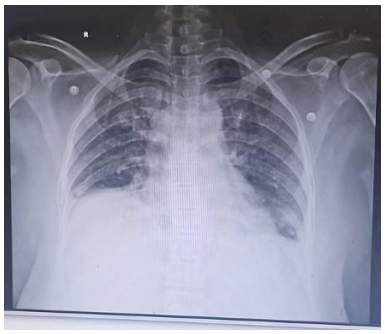
Platelets = 1.02 lakhs/micro L (NR 1.5-3.5 lakhs/micro L)

ESR = 70 mm/ hr (NR 0-35 mm/ hr)

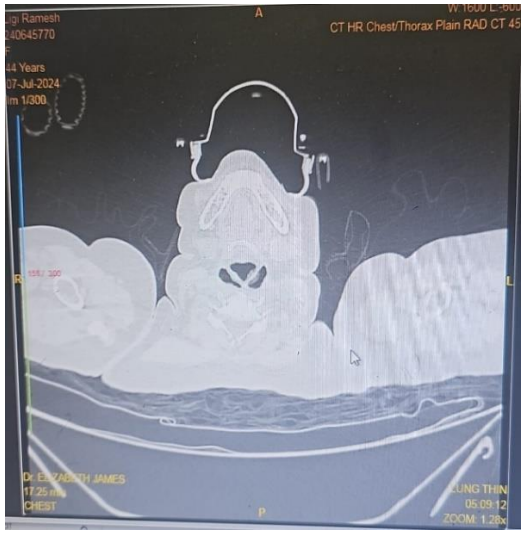
Trop I = 2.2 ng/micro L (NR 0–0.04 ng/ml)

CRP =628 mg/ L (NR 0-5 mg/L)
Ferritin =434.2ng/ml (NR 40–300 ng/mL or µg/L)
Triglyceride- 92mg% (NR 60-100 mg%)
AST= 136 IU /L (NR 0-40 IU/L)
ALT= 83 IU/L (NR 0-40 IU/L)
LFT- Total Bilirubin / Total Protein and Serum Alkaline Phosphatase – normal values- INR-1
HbA1c- 5.5% (NR – 4.5% -5.6%)
Urea=130.9 mg% (NR 0-40 mg%)
Creatinine=2.30 mg/dl (NR 0- 2 mg%)
Procalcitonin >10,000 (NR 0- 0.10 ng/mL)
D-Dimer > 10,000 (NR 0 - 0.50 mg/L)
TSH 1.5 mU/L (NR 0.4- 4 mU /L)
ANA Profile / Anti CCP Ab test / RA Factor – Negative
Urine Culture, Blood culture, Sputum culture, Sputum AFB, negative; IgG, IgM for Scrub typhus and Leptospira, Weil Felix and Widal Test =negative
Viral Markers- HIV1,2, HbsAg, HCV = non -reactive
Bone Marrow Aspiration Biopsy - Cytology and Culture was normal – No features of hemophagocytic lympho-histiocytosis [HLH]; any granuloma or malignancy.

Chest XRAY (Fig.1)



CT CHEST (Fig 2)



Discussion

Melioidosis, or Whitmore disease, is spread by contact with contaminated water or soil. It is caused by the gram-negative saprophyte *Burkholderia pseudomallei*, and is a disease of public health importance in Southeast Asia and northern Australia that is associated with high case-fatality.[3, 4] Melioidosis has been known as a remarkable imitator, because it can mimic tuberculosis, pyogenic bacterial infection or gram-negative sepsis. It can present as abscesses in various organs with or without septicaemia. One of five global deaths are attributable to sepsis. Patients presenting with hyperferritinemic sepsis-induced multiple-organ dysfunction syndrome, are associated with high mortality. [3, 4]

Infections still lead the cause of PUO, with tuberculosis topping the list (28%), particularly in Southeast Asian countries.[4,5,6] Once tuberculosis is excluded by a thorough workup of PUO, physicians often find themselves in a tight predicament trying to pin-point other causes of PUO. [7]

Pneumonia is the most common clinical presentation in most of the case series, the patient can also present as internal abscesses of various sites such as soft tissue, bone and joint, liver, spleen, skin, prostate, and parotid.[8] Other manifestations include, lymphadenopathy, encephalomyelitis and rarely, pericardial and ocular involvements. In Australian patients with Melioidosis, prostatic abscess has been reported in as high as 20% of cases. In India, Prostatic Abscess has been reported from Kerala, Karnataka, Tamil Nadu, West Bengal and Bihar[9,10,11,12].

Several features of Melioidosis are similar to that of tuberculosis, which is very common in our country, especially among diabetic patients[13]. It can mimic pulmonary as well as musculoskeletal tuberculosis. The lymph node biopsies in Melioidosis can show granulomas. Radiological manifestations of Melioidosis presenting with spondylitis and psoas abscess are also similar to those with tuberculous spondylitis[14]. In most of these cases, bacterial cultures will clinch the diagnosis.

Our patient had disseminated "septicaemic Fever of Unknown Origin"-? Melioidosis with MODS (ARDS, AKI, deranged LFT, thrombocytopenia, hypotension, and metabolic acidosis). Initiation of early appropriate antibiotic therapy saved our patient. The mortality rate of uncomplicated Melioidosis is 10%, while it is 80%, for severe sepsis with bacteraemia and hypotension[13].

Treatment for Melioidosis requires prolonged antibiotics in two phases. Intravenous antibiotics like ceftazidime, meropenem, or imipenem are administered during the intensive phase for two to eight weeks. Ceftazidime is usually dosed at 50 mg/kg up to 2 g every 6-8 h. After completion of the intensive phase, oral antibiotics such as co-trimoxazole, doxycycline, or amoxicillin-clavulanate are administered for 3-6 months during the eradication phase, with co-trimoxazole preferred at 320 mg of trimethoprim twice daily for adults over 60 kg. Challenges include prolonged treatment, adherence, follow-up, and risks of relapse and reinfection. Prevention involves avoiding direct soil and water contact and minimizing outdoor activities, especially during the rainy season. Currently, no vaccines are available.[8,15]

Conclusion

Melioidosis should be kept in the differential diagnosis of febrile illness in India. Imaging to look for internal abscesses is important when patients do not respond to antibiotic therapy, as these abscesses may need drainage for proper response. A high index of suspicion by the physician along with the help of a clinical microbiologist, will help in timely diagnosis and save lives.[4,5]

Abbreviations:

SLED -Sustained low-efficiency dialysis, WBC- White Blood Cells, RBS- Random Blood Sugar, ESR-

Erythrocyte Sedimentation Rate, CRP- C Reactive Proteins, AST- Aspartate Amino Transferase, ALT-Alanine Amino Transferase, ALP-Alkaline Phosphatase, MODS-Multiple Organ Dysfunction Syndrome

References

1. Mohapatra PR, Mishra B., "Burden of melioidosis in India and South Asia: Challenges and ways forward", The Lancet Regional Health-Southeast Asia. 2022 Jul 1;2.
2. Suputtamongkol Y, Chaowagul W, Chetchotisakd P, et al., " Risk Factors for Melioidosis and Bacteremic Melioidosis", Clin Infect Dis 1999; 29 (2): 408-413. doi: 10.1086/520223
3. Mohan A, Paranchothy M, Segaran S, et al., "Fatal Pediatric Melioidosis and the Role of Hyperferritinemic Sepsis-Induced Multiple-Organ Dysfunction Syndrome", Am J Trop Med Hyg. 2022 Jun 20;107(2):393-396. doi: 10.4269/ajtmh.22-0051. PMID: 35895426; PMCID: PMC9393471.
4. Fan Z, Kernan KF, Qin Y, et al., " Hyperferritinemic sepsis, macrophage activation syndrome, and mortality in a paediatric research network: a causal inference analysis", Crit Care. 2023 Sep 6;27(1):347. doi: 10.1186/s13054- 023-04628-x. PMID: 37674218; PMCID: PMC10481565.
5. Krishna MSV, Lakshmanan S, Rajendran V, et al, Pyrexia of Unknown Origin in a Young Male: Unmasking Melioidosis in a Tuberculosis-Endemic Setting. Cureus. 2024 Jul 7; 16(7):e64024. doi: 10.7759/cureus.64024. PMID: 39109095; PMCID: PMC11302954.
6. David A, Quinlan JD. "Fever of Unknown Origin in Adults. Am Fam Physician", 2022 Feb 1;105(2):137-143. PMID: 35166499.
7. Pannu AK, Golla R, Kumari S, et al., " Aetiology of pyrexia of unknown origin in north India"Trop Doct. 2021 Jan;51(1):34-40. doi: 10.1177/0049475520947907, Epub 2020 Aug 17. PMID: 32807027.
8. Cheng AC, Currie BJ., " Melioidosis: epidemiology, pathophysiology, and management", Clin Microbiol Rev. 2005 Apr;18 (2):383-416. doi: 10.1128/CMR.18.2.383-416.2005. Erratum in: Clin Microbiol Rev. 2007 Jul;20 (3):533. Dosage error in article text. PMID: 15831829; PMCID: PMC1082802.
9. Abdel RZ, Chan YY, Mahmoud A, et al., " The epidemiology and clinical spectrum of Melioidosis in a teaching hospital in a North Eastern state of Malaysia: a fifteen-year review" , BMC Infect. Dis. 2016; 16:333
10. Morse LP1, Moller CC, Harvey E, et al., " Prostatic abscess due to Burkholderia pseudomallei: 81 cases from a 19-year prospective melioidosis study".J Urol. 2009 Aug;182(2):542-7;
11. Currie BJ, Ward L, Cheng AC., " The epidemiology and clinical spectrum of Melioidosis: 540 cases from the 20 year Darwin prospective study", PloS Negl Trop Dis. 4(11): e900.
12. Ng TH, How SH, Amran AR, et al., " Melioidotic prostatic abscess in Pahang" ,Singapore Med J. 2009 Apr.50(4):385-9.
13. Vidyalakshmi K, Lipika S, Vishal S, et al., " Emerging clinico-epidemiological trends in melioidosis: analysis of 95 cases from western coastal India", Int J Infect Dis. 2012 Jul;16(7):e491-7. doi: 10.1016/j.ijid.2012.02.012, Epub 2012 Apr 16, PMID: 22512851.
14. Aphinives C, Pacheerat K, Chaiyakum J, et al., " Prostatic abscess: Radiographic fndings and treatment", J Med Assoc Thai 2004; 87:810-5.
15. Lipsitz R, Garges S, Aurigemma R, et al., " Workshop on treatment of and postexposure prophylaxis for Burkholderia pseudomallei and B. mallei Infection, 2010", Emerg Infect Dis. 2012 Dec; 18(12):e2. doi: 10.3201/eid1812.120638. PMID: 23171644; PMCID: PMC3557896.