RELAPSE OF THE BUG AT A DIFFERENT SITE- A CASE OF MULTIDRUG RESISTANT MELIOIDOSIS

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PRESENTATION OF CASE

A 60-year-old farmer who is diabetic for five years presented with pyrexia of unknown origin for one month. Fever was high grade associated with chills, dysuria and increased frequency of micturition, dull aching diffuse abdominal pain and weight loss. There was no history of rash, vomiting, altered bowel habits, cough, bleeding manifestations, altered sensorium and seizures. Patient denied history of recent travel, consumption of raw milk and contact with tuberculosis.

Melioidosis, an emerging underdiagnosed infectious disease is caused by *Burkholderia pseudomallei*, a Gram negative bacillus commonly found in the soil of tropical countries. It is important to consider melioidosis as a differential diagnosis amongst pyrexia of unknown origin cases even in non-endemic areas for an early antibiotic treatment and prevention of relapse.^[1] Almost all *B. pseudomallei* strains are susceptible to the first line antibiotic Ceftazidime. We report a case of culture proven melioidosis primarily resistant to ceftazidime who developed relapse at different sites in the eradication phase of treatment despite adequate course of in vitro sensitive antibiotics.

DIFFERENTIAL DIAGNOSES

- Complicated urinary tract infection.
- Tuberculosis.
- Abdominal abscess.
- Occult abdominal malignancy.

CLINICAL DIAGNOSIS

On examination, patient's vital parameters were stable. There was pallor, icterus, diffuse abdominal tenderness and mild hepatosplenomegaly. The examination of other systems was unremarkable. Laboratory investigations revealed anaemia, leukocytosis with total counts of 20000/mm³ with neutrophilic predominance (Haemoglobin- 9.3 gm%, neutrophil count- 90%, platelet count- 4 lakh/mm³). Serum creatinine was 1.5 mg/dL and there was also a rise in bilirubin (Total bilirubin 4.4 mg/dL, direct bilirubin 2 mg/dL) with normal liver enzymes. Urine routine microscopy revealed 60 to 80 pus cells. Tests for malaria, leptospirosis, enteric fever,

urine culture, IgM Brucella, HIV Elisa and Mantoux test were found to be negative. Chest x-ray and echocardiography was normal. Abdominal ultrasound revealed hepatosplenomegaly with internal echoes in the bladder. Patient was empirically started on ceftriaxone in view of urinary tract infection. On the fourth day of admission, patient developed spontaneous thrombophlebitis of the left cephalic vein. Doppler revealed complete thrombosis of left cephalic vein extending into subclavian vein. CT scan of thorax and abdomen revealed multiple small hypodense areas in liver (Figure 1), spleen and prostate (Figure 2) showing peripheral enhancement suggestive of microabscesses and bilateral bulky echogenic kidneys with minimal perinephric fluid. Primary BACTEC blood culture revealed significant growth of *Burkholderia pseudomallei*.

Figure 1. CT Abdomen showing Multiple Hypoechoic Lesions in the Liver and Spleen suggestive of Abscesses

Figure 2. CT Abdomen showing Multiple Hypoechoic Lesions suggestive of Prostatic Abscesses

MANAGEMENT

Patient was empirically started on ceftazidime, but he did not respond even after eight days of ceftazidime and continued to have high-grade fever with high total leucocyte counts. *B. pseudomallei* were in vitro strongly sensitive to piperacillin and tazobactam, but resistant to ceftazidime. Forty eight hours after initiation of piperacillin and tazobactam, patient became afebrile and total counts improved to 12000/mm³.

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He received IV antibiotics for four weeks. Oral trimethoprim-sulphamethoxazole (TMP-SMX) was prescribed for 12 weeks at discharge. Patient was afebrile with total counts of 6000/mm³ and serum creatinine of 1.4 mg/dL at the time of discharge with good urine output. Repeat ultrasound abdomen showed resolving microabscesses and blood culture was sterile. Seven weeks after discharge patient developed acute left arm abscess with fever, breathlessness and septic shock in spite of TMP-SMX during the eradication phase. Complete haemogram revealed haemoglobin of 7.3 gm% with total leucocyte counts of 25000/mm³ and serum creatinine of 2.5 mg/dL. Echocardiography was suggestive of pericardial effusion with partial right ventricular collapse. The left arm abscess was drained and patient was empirically started on meropenem. But he developed cardiorespiratory arrest on the same day and in spite of vigorous resuscitative and ionotropic measures, he could not be revived. Post mortem pericardial fluid was negative for tuberculosis. Blood culture sent at admission revealed significant *B. pseudomallei* resistant to piperacillin-tazobactam, ceftazidime and meropenem indicating relapse of disseminated melioidosis resistant to multiple antibiotics.

DISCUSSION

Melioidosis predominantly affects adults with risk factors such as farming, diabetes mellitus and chronic renal and liver disease.^[1] It has a tendency for abscess formation in multiple organs such as lung, musculoskeletal system, liver, spleen and prostate. There are also case reports of melioidosis presenting as isolated brain abscess, chest wall abscess and osteomyelitis.^{[1],[2]} Melioidosis with cardiac involvement in the form of pericardial effusion is rare and is often combined with septicaemia, for which the mortality rate is 20% - 60%.^{[2],[3]} Our patient presented as UTI and left subclavian thrombosis with dissemination to liver, spleen, prostate and relapsed at a different site as arm abscess with pericardial effusion which is a rare clinical phenomenon.

Melioidosis is treated by an intensive two weeks course of ceftazidime or a carbapenem followed by at least 12 weeks of oral trimethoprim-sulphamethoxazole to eradicate the organism and prevent relapse. The median time of resolution of fever is nine days. In patients with abscesses, the resolution can take more than a month.

The studies on recurrent melioidosis have shown it to be either a relapse or a reinfection. A relapse is defined as a new presentation with an acute culture confirmed melioidosis after the resolution of the symptoms and the completion of at least the intensive intravenous phase of the antibiotic therapy for the initial melioidosis presentation.^[4] A multifocal infection, disseminated melioidosis during the primary episode and duration and compliance of the therapy have been found to be risk factors for relapse.^[5] According to Limmathurotsakul et al, the site of relapse is usually the same as that of the primary episode due to the presence of a quiescent infective nidus and granulomas.^[6] Such cases were

associated with 4% antibiotic resistance rates. However, our case proved to be contrary to this theory.

Reports of ceftazidime resistance due to its regular use for melioidosis are increasingly emerging from endemic areas such as Malaysia, Australia, Thailand, Singapore and India.^{[7],[8]} It is becoming an important cause of treatment failure and relapse, probably due to the expression of β -lactamase and efflux pumps. There are also reports of pan drug-resistant *B. pseudomallei* from southern Karnataka.^[9] The rate of primary resistance to ceftazidime in recurrent melioidosis is higher, but is still uncommon.^[10] Hence, it is advisable that empirical ceftazidime still remain an acceptable first choice in melioidosis prior to in vitro antibiotic sensitivity results.

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