



EMERGING SUPER BUG- A CASE OF MULTIDRUG RESISTANT COMPLICATED SALMONELLOSIS

Medicine

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ABSTRACT

Typhoid fever, a common infectious disease may present with only a febrile illness or with various life threatening intestinal as well as extraintestinal complications. Resistance to multiple antibiotics including 3rd generation cephalosporins is emerging and posing serious health problems.

We report a case of Typhoid fever who presented with high grade fever, thrombocytopenia, hepatitis, myocarditis and milliary nodules in the lung. Salmonella Typhi isolated from bone marrow showed resistance to multiple drugs.

KEYWORDS

Typhoid, Complications, Bone Marrow Culture, Drug Resistance

INTRODUCTION

Typhoid fever, a disease of the tropical and subtropical region is caused by consuming food and water contaminated with gram negative bacterium *Salmonella typhi*¹. *Salmonella* serotypes exert huge health and economic impacts due to their virulence or carriage of antibiotic resistance traits.

Typhoid fever usually presents with high grade fever and abdominal complaints. Patients can develop intestinal as well as various systemic complications. Diagnosis is by isolation of the organism from blood, bone marrow, urine and stool. Third generation cephalosporins are now the drug of choice but resistance to these drugs is also emerging

CASE REPORT

A 27 year old male patient presented to casualty with high grade fever for 5 days. There was history of dull aching diffuse abdominal pain, vomiting and dry cough for 3 days. There was no history of rash, altered bowel habits, bleeding manifestations, altered sensorium or seizures.

On examination he was febrile and icteric, his pulse was 120 beats/min irregular and blood pressure was 100/60 mmHg. Systemic examination was unremarkable.

Lab investigations showed Hemoglobin of 14 gms % ,total WBC count of 2700/cmm with 56% neutrophils and 44% lymphocytes. Platelet count was 30,000/cmm. Liver function tests showed a high bilirubin 4.7mg% (direct 3mg%) and raised liver enzymes; SGPT 252 U/L and SGOT 140 U/L. Alkaline phosphatase was 542 U/L. Prothrombin time and INR were normal. Urine examination and renal function tests were normal. Chest Xray was normal. CT thorax showed multiple milliary nodules. His sputum was negative for AFB and CBNAAT was negative. ECG at admission showed generalised ST-T changes with few nodal and atrial ectopics. Subsequent ECG's showed QRS widening with prolonged QTc interval of .6 sec. Cardiac enzymes showed raised CPK-MB 33ng/ml (normal 0-25ng/ml). Troponin I was weakly positive. Echocardiography was normal and showed an ejection fraction of 58%. Blood Widal showed titres of S. Typhi O antigen more than 1/320 and S. Typhi H Antigen more than 1/320. Repeat Widal after 1 week showed same titres. Tests for malaria, dengue, leptospirosis, viral hepatitis, KFD, rickettsia were negative. ANA was negative.

His blood, urine and stool cultures were sterile. However his bone marrow culture showed growth of *Salmonella typhi* which was resistant to nalidixic acid, ciprofloxacin, ceftriaxone, cefepime, cefoperazone/sulbactam, aminoglycosides, piperacillin/tazobactam. Low sensitivity was present to first line drugs like ampicillin,

amoxycillin and cotrimoxazole. Sensitivity to Meropenem and imipenem was very good. Patient was initially started on iv Ceftriaxone, however he did not respond. Upon receiving the reports of sensitivity, he was shifted to meropenem. He responded to meropenem and became afebrile. His pulse regularised, his LFT's normalised, platelet count became normal and chest findings cleared.

DISCUSSION

Typhoid fever is endemic in India. Typhoid spreads through contaminated food and water. Poor sanitation still remains the most important risk factor for enteric fever, especially in developing countries. *Salmonella* enter the body through the mouth and penetrate the lymphoid tissue of the GIT

Haematological dissemination then takes place and the organism reaches the reticuloendothelial cells of liver, spleen, bone marrow and other organs¹. The incubation period is around 10 – 14 days. Main symptom is high grade fever which can continue upto 4 weeks. Other symptoms include headache, cough, myalgia, nausea, vomiting, diarrhea and abdominal pain. About 10-15% patients develop severe disease with intestinal or extra intestinal complications. This depends on strain virulence, inoculum, host factors like immunosuppression, previous exposure and carrier state¹. Intestinal complications like gastrointestinal bleeding and intestinal perforation which occur in the third week and fourth week result from ulceration of Peyer's patches.^{1,2} Extraintestinal complications include hemophagocytic syndrome, hepatitis, pancreatitis, myocarditis, endocarditis, glomerulonephritis, splenic abscesses, pneumonias, arthritis, osteomyelitis, meningitis. Thrombocytopenia which was observed in our patient is not commonly seen in typhoid fever. Leucopenia and anemia are more commonly observed. In a case of typhoid fever reported by Shiv Charan et al³ the patient presented with a low platelet count of <10,000/cmm and bleeding gums.

Thrombocytopenia in typhoid fever may be associated with hemophagocytic histiocytosis in bone marrow³, bone marrow suppression or may be associated with subclinical DIC³.

Myocarditis refers to inflammation and damage of heart muscles. It occurs in 1-5% of cases of typhoid fever.² Cases of enteric fever with myocarditis have been reported by Pankaj Sahu et al² and Partha Pratham et al⁴. Patients present with arrhythmias, hypotension, shock and features of heart failure². ECG's show ST-T changes with bundle branch blocks, QTc prolongation and arrhythmias.^{2,4} Cardiac enzymes rise may be seen. Echocardiography shows hypokinesia of myocardium and decreased left ventricular function.

Pulmonary features occur in 1% patients⁵. Earliest symptom is dry cough. Patients may develop bronchitis, pneumonia, lung abscess

ARDS. Non specific chest X'ray abnormalities are seen in 25% of patients with pulmonary symptoms. 5 Pneumonia and diffuse pulmonary infiltrates on Chest Xray were seen in patients of enteric fever reported by by Adarsh M Sharma et al. 5. Our patient's CT scan of the thorax showed millitary nodules (1-4 mm opacities) scattered throughout the lung fields which resolved after treatment. These are not commonly seen in typhoid fever.

Hepatic involvement in Salmonella is known to occur. Mechanisms involved include direct invasion by salmonella, endotoxic damage to hepatocytes and immune mediated damage. 6. In a study conducted by Najam Arif et al in patients with typhoid hepatitis no specific clinical features were found and liver function tests were variable 6.

Diagnosis of typhoid fever is by isolation of organism from blood, stool, urine, bone marrow, intestinal secretions or other sterile sites. Blood culture -sensitivity is 90% during the first week and decreases to 50% by third week. 1. Low yield may be due to low number of organisms or recent antibiotic treatment. 1.

Stool cultures are positive throughout the course of the disease. Bone marrow culture is valuable and is positive even when blood cultures are negative. It remains positive even after 5 days of antibiotic treatment. 1.

In a study conducted by Guerra-Caceres et al 7. Salmonella typhi was recovered from marrow cultures in 95% of patients and blood cultures were positive in only 43.3%. Agglutination tests were positive in 56.7%. They noted that if diagnostic workup for salmonella is limited to blood cultures and agglutination test diagnosis would be missed in 21.7% cases 7.

Serological tests like Widal test measures the presence of O and H agglutinins for typhoid and paratyphoid in the patients serum. Agglutinins appear at the end of first week and the titre increases till the third or fourth week and then decreases. Prior disease, inapparent infection and immunisation can cause titre to be high but no rise in titre will be seen when the test is repeated.

For the treatment of typhoid fever antibiotics like chloramphenicol, ampicillin and cotrimoxazole were used as first line drugs till the mid 80's. 1. With the emergence of resistance to these drugs fluoroquinolones became the drug of choice. However resistance to fluoroquinolones also developed in the 1990's in the Indian subcontinent, in South Asia and SubSaharan Africa. Third generation cephalosporins like ceftriaxone, cefotaxime and oral cefixime were then found effective and are still extensively used 1. Some cases of cephalosporin resistance have been reported and higher antibiotics like imipenem and meropenem are being used in these resistant cases.

Multidrug-resistant strains of *Salmonella* (resistant to 3 or more different groups of antibiotics) are now encountered frequently worldwide and the rates of multidrug-resistance have increased considerably in recent years. In a study conducted by Shesh Raj Patel et al 9 nalidixic acid was found to face the highest resistance 76.6%, followed by amoxicillin 38.3%, ciprofloxacin 25.5%, ceftriaxone 23.4%, azithromycin 21.3%, co-trimoxazole 19.1%, imipenem 8.5%. Multi drug resistance was seen in 26.6% of patients 9. MA Rahman et al 8 concluded in their study that none of the isolates of *Salmonella* were sensitive to all the antimicrobials against *Salmonella*. The resistance rates were 77.14% for ciprofloxacin and 68.57% for ceftriaxone, 95.29% for azithromycin. Increased sensitivity was noted for imipenem 88.57% highlighting the fact that we are at a verge of facing a superbug version of a very common disease in our country. Multidrug resistant *Salmonella* typhi is a focus of concern.

CONCLUSION

In patients with suspected Typhoid fever with systemic complications and negative blood cultures it is advisable to do a bone marrow culture before considering an alternate diagnosis. Multidrug resistant strains of *Salmonella* Typhi pose serious therapeutic challenges and hence reliable and efficient identification and sensitivity testing is required for proper treatment. Large studies need to be conducted to study the local antimicrobial susceptibility and resistant patterns of this organism.

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