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Case Series

Internal Medicine Section

Variable Presentations of Enteric Fever, beyond Fever and Pain Abdomen: A Case Series

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ABSTRACT

Enteric Fever (Typhoid and Paratyphoid fever) is an illness that presents with marked pyrexia, abdominal pain and other gastrointestinal symptoms. Symptoms and complications primarily involve gut. But sometimes it involves other organ systems like heart, and brain. It thus poses a great diagnostic challenge in diagnosing these extraintestinal manifestations. The three cases depicted in this case series had unusual presentations in the form of dilated cardiomyopathy, non haemophagocytic lymphohistiocytosis (HLH) dyslipidaemia and encephalopathy. The first case is a case of reversible cardiomyopathy in a 26-year-old male presenting with fever for seven days with headache, loose motions and vomiting with audible S3 and bibasal crepitations without oedema. The patient responded to ceftriaxone and azithromycin. On echocardiography dilated cardiomyopathy was diagnosed after which treatment with ramipril and metoprolol was started. The second case was of a 30-year-old female presenting with fever, vomiting, and abdominal pain. There was hypertriglyceridaemia with normal ferritin levels. The patient responded to ceftriaxone. High Density Lipoprotein (HDL) level was low. Statin and fenofibrates were added after which the triglyceride levels came down. This was an interesting case of non-HLH dyslipidaemia which responded to therapy. The third case was of a 40-year-old female presenting with fever for six days with impairment of consciousness. Bilateral plantar responses were extensor and there was no papilledema or any cranial nerve palsy. Magnetic Resonance Imaging (MRI) Brain and Cerebrospinal Fluid (CSF) study were normal. The patient responded to ceftriaxone and dexamethasone proving beneficial effects of steroids in enteric encephalopathy. The purpose of the case series was to make clinicians aware of these uncommon presentations of a common disease so that early diagnosis and treatment with Anti *Salmonella* antibiotics can be initiated quickly to prevent complications.

Keywords: Dilated cardiomyopathy, Dyslipidaemia, Encephalopathy, Non haemophagocytic lymphohistiocytosis, Reversible cardiomyopathy

INTRODUCTION

Enteric fever (Typhoid and Paratyphoid fever) are systemic febrile illness caused by bacteria *Salmonella enterica* serotype- Typhi and Paratyphi A, B, C [1]. It commonly presents with marked fever, abdominal pain, diarrhoea and altered bowel habits. The highest incidence of enteric fever is found in South Central and South East Asia. It is transmitted by feco-oral routes and is endemic in those countries with poor public health and low socio-economic indices [2]. The clinical diagnosis is difficult due to vague presentations. Gold standard for diagnosis of enteric fever is isolation of *Salmonella* from a patient commonly by blood culture [3]. The commonly used serological test is Widal test. Widal test has various limitations. Various rapid dot blot test like Typhi dot test are gaining popularity now-a-days for rapid detection of enteric fever [3].

Typhoid fever presents with various uncommon features like encephalopathy, HLH, myocarditis, cardiomyopathy which have been discussed here. Apart from that it may present as bilateral parotid enlargement with epididymoorchitis [4]. The prevalence of uncommon presentations usually occur in Multidrug Resistance (MDR) typhoid fever. Parotid may be enlarged in enteric fever in Human Immunodeficiency Virus (HIV) patients, but is uncommon in immunocompetent patients [5,6]. Atypical features include severe headache mimicking meningitis, acute pneumonia, arthralgia. Sometimes in India and Africa, it may present as delirium, parkinsonism or Acute Demyelinating Polyneuropathy (AIDP). Pancreatitis osteomyelitis, orchitis, meningitis and abscesses may also be the uncommon manifestations [7,8]. The associated typical clinical features with the positive blood culture tests and IgM antibody tests help to explain and correlate the uncommon manifestations which help to initiate appropriate and timely treatment to prevent complications.

CASE SERIES

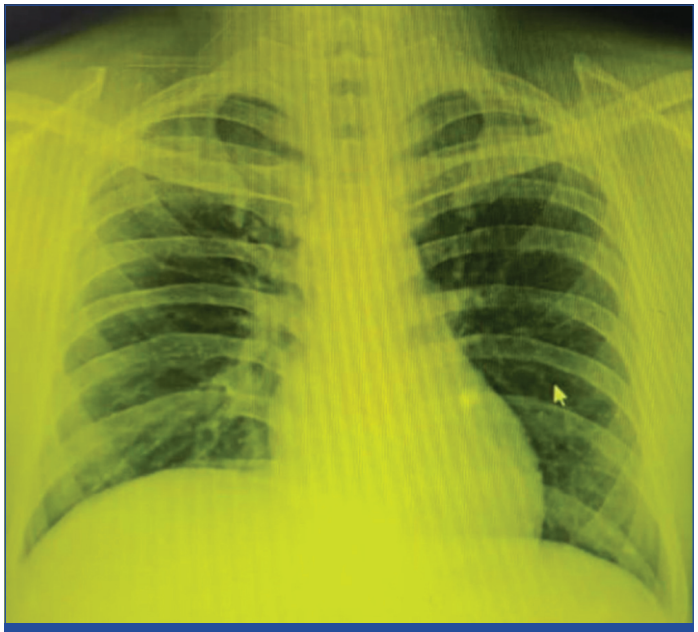
Case 1

A 26-year-old male presented with fever for seven days with chill and rigor relieved with sweating associated with headache with history of intermittent loose motions and history of vomiting. There was no history of skin rash, joint symptoms or any history of burning sensation during micturition, nor any history of pain abdomen. On examination the patient was alert, conscious and co-operative. He had fever of 101.0° F with mild headache but there were no signs of meningeal irritation. Pulse was 102 bpm with Blood Pressure (BP) of 110/70 mm of Hg. There was mild pallor without any icterus, lymphadenopathy, clubbing, skin rash. There was bilateral vesicular breath sounds with S1, S2, S3 was also audible at the apex with bibasal crepitations without any pedal oedema. Malaria and typhoid fever were the differential diagnosis.

Treatment was started with intravenous fluids normal saline:Ringer lactate (1:1) iv 8 hourly with paracetamol, injection Proton Pump Inhibitors (PPI), injection ondansetron with injection ceftriaxone 2 gm iv twice a day (after skin test) with azithromycin 500 mg one tablet twice a day with probiotic supplementation.

Blood samples were drawn to test for Malaria Parasite (MP) with dual antigen, Typhi Dot M, IgG and IgM Dengue Antibody (Ab), Scrub typhus IgM Antibody (Ab), urine for routine examination and culture sensitivity. Typhi Dot M came positive. Other tests of fever profile were negative and the urine report was unremarkable. Complete Blood Count (CBC) revealed mild normocytic normochromic anaemia with normal White Blood Cells (WBC) and platelet counts with Erythrocyte Sedimentation Rate (ESR) of 30 mm in 1st hour. Urea and creatinine were mildly raised. There was mild hyponatraemia and hypokalaemia. Magnesium level was normal. Arterial Blood Gas (ABG) and chest x ray were normal [Table/Fig-1], and echocardiography revealed global Left Ventricle (LV) hypokinesia with Ejection Fraction (EF) of 45% with

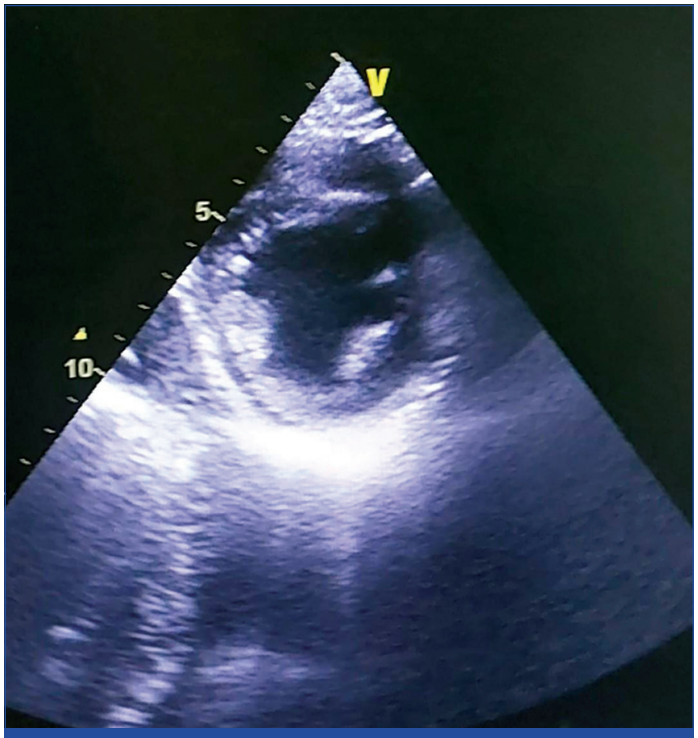
systolic dysfunction although the cardiac bio markers were normal. Ultrasound (USG) whole abdomen revealed mild hepatosplenomegaly and serology was unremarkable. Liver Function Test (LFT) revealed mild transaminitis (SGOT>SGPT) with normal bilirubin, albumin, globulin and Alkaline Phosphatase (ALP) levels. COVID-19 Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) was negative Blood culture-sensitivity was positive for *Salmonella* typhi. Cardiac MRI could not be done as it was not available in the institute.



[Table/Fig-1]: Chest X Ray of case 1 with recovered enteric cardiomyopathy.

Patient started improving from 2nd day of ceftriaxone and azithromycin administration and fever subsided on day 5 of admission. The iv fluid was stopped on day 5 of admission. Sodium and potassium supplementation were given to correct dyselectrolytaemia. The patient was started on ramipril 1.25 mg od with metoprolol XL 12.5 mg od as a diagnosis of typhoid cardiomyopathy was done.

Repeat echocardiography done after seven days of the first echocardiography revealed LVEF of 55-60% with normalisation of systolic abnormality [Table/Fig-2]. Urea and creatinine levels were also normalised. The patient was diagnosed as reversible cardiomyopathy due to enteric fever. The patient was discharged and advised to attend cardiology Outpatient Department (OPD).



[Table/Fig-2]: Echocardiography of patient with recovered enteric cardiomyopathy.

Case 2

A 30-year-old female presented with fever with chill and rigor for three days associated with vomiting, headache with pain abdomen for the same duration. There was no history of joint symptoms, skin rash or any bladder bowel complaints. The pain abdomen was localised in the right upper quadrant. There was no travel history and menstrual history was unremarkable. On examination, the patient was febrile with mild pallor without any icterus and was haemodynamically stable. There was mild hepatomegaly with tenderness in the right upper quadrant of the abdomen with mild splenomegaly. On examination of the cardiovascular and respiratory and neurological system, no abnormalities were detected. A differential diagnosis of enteric, malaria and urinary tract infection were considered. Investigations conducted were CBC, Fasting Blood Sugar (FBS), urea, creatinine, RFT, MP slide and dual antigen, NS1 antigen, Typhi Dot M, urine for examination and culture. Blood for culture/sensitivity aerobic single hand, LFT.

The patient was treated with iv fluids, injection PPI, ondansetron, paracetamol and injection ceftriaxone 2 gm iv bd (APST) was started. Typhi Dot M came positive and other reports of fever profile were negative. A diagnosis of typhoid fever was made. RFT were normal with LFT showing mild transaminitis (SGOT>SGPT) with normal levels of albumin, globulin and ALP. CBC revealed mild normocytic normochromic anaemia with leukopenia Total Leukocyte Count (TLC)-3900/mm^3) and normal platelet counts. COVID-19 RT-PCR was negative. Ferritin and triglycerides were sent of which ferritin was normal, but triglycerides were elevated with levels of 485 mg/dL. HDL levels were low (30 mg/dL). Considering HLH, bone marrow was advised which the patient refused. USG revealed mild hepatosplenomegaly with acalculous cholecystitis but chest radiograph and echocardiography were normal. Blood cultures revealed *Salmonella* typhi. The thyroid profile tests were normal.

As triglycerides were elevated statin and fenofibrates were added. Antibiotics were continued for seven days. She started improving with therapy, triglycerides decreased to 200 mg/dL after five days and transaminitis also subsided. The patient was discharged after eight days from day of admission. She was requested for follow-up visit after seven days.

Case 3

A 40-year-old female presented with fever for six days with chill and rigor with mild impairment of consciousness. There was no history of vomiting, loose motions, pain abdomen, nor were there any joint symptoms, skin rash or bladder bowel complaints. She had headache for the last five days without any localising signs. Last menstrual period was 20 days earlier than usual. There was no history of weakness of any side of the body, nor involuntary movements. Travel history, vaccination history were unremarkable and she was not on any medicines.

On examination, the patient was drowsy with disorientation and fever. Neck was supple and there were no signs of meningeal irritation. No false localising signs depicting bilateral 6th cranial nerve palsies were detected. Tone and reflexes were normal, but plantar responses were extensor bilaterally. Ophthalmoscopy was unremarkable and examination of other systems did not reveal any abnormality except mild hepatosplenomegaly.

A differential of fever with encephalopathy was made with possibilities of septic or metabolic encephalopathy. CBC showed neutrophilic leukocytosis (12,300/mm^3) with 75% neutrophils. Haemoglobin and platelet counts were normal with mildly raised ESR. FBS, RFT, LFT, International Normalised Ratio (INR) were normal. MP slide and dual antigen, NS1 antigen were negative, but Typhi DOT M was positive. COVID-19 RT-PCR, urine analysis did not reveal any abnormality. Chest x ray, echocardiography were normal and USG revealed mild hepatosplenomegaly. MRI brain, CSF study, CPK,

Creatine phosphokinase-MB (CPK-MB) were normal. EEG revealed encephalopathy. A diagnosis of enteric encephalopathy was made.

The patient was admitted in the ICU with Ryle's tube and catheterisation was done. Intravenous fluids was started with injection PPI, injection ceftriaxone 2 gm iv bd (APST), injection ondansetron and paracetamol and injection doxycycline 100 mg iv bd (APST) and dexamethasone were also started.

She started to recover after 16 hours and intensity of fever decreased from 102° F to 100° F. The patient was conscious and oriented from 3rd day after starting antibiotics after which catheter and Ryle's tube were removed. Blood culture-sensitivitywas positive for Salmonella typhi. Steroids were tapered within seven days by reducing thrice daily dose to twice daily and then once daily. The patient was discharged on day 15 of admission. The patient came for follow-up after 10 days of discharge and was doing well.

DISCUSSION

Myocarditis is an unusual complication of Typhoid fever with only few reported cases. A case study of typhoid cardiomyopathy by Majid A et al., reported a young male presented with incompletely treated typhoid fever with raised cardiac enzymes and features of dilated Cardiomyopathy on Echocardiography. The condition gradually improved with adequate treatment [9]. Similarly, Shah S and Dubrey SW reported a case of young male presented with myocarditis and chest pain mimicking myocardial infarction was found to be associated with typhoid fever in a traveller returning to United Kingdom (UK). The fever and other symptoms completely subsided with treatment with third generation cephalosporin for 2 weeks [10].

The patients here were fruit sellers and students staying in slums. They had poor hand hygiene and sanitation habits. This could be the predisposing reason for increased infection. The first patient was a young male of reversible cardiomyopathy. He was febrile so all relevant investigations were done. The result was only positive for Tyhoid fever (Typhi dot M). The common causes of cardiac dysfunctions (hypertension, diabetes, electrolyte disturbances) were also ruled out. Finally, a diagnosis typhoid cardiomyopathy was made.

The second case was a young female patient with fever, vomiting, and abdominal pain. Investigation was positive for Typhi dot M, blood culture was positive for *Salmonella* typhi. The laboratory reports revealed normocytic normochromic anaemia with leukopenia and normal platelet count but liver enzymes and triglyceride level were raised though ferritin levels were normal.

A suspicion of typhoid associated HLH was thought of but none of the other criteria (hyper ferritinemia, hypofibrinogenemia etc) were present. Moreover, the patient responded very well to treatment with antibiotics. Fever subsided, the triglyceride and liver enzyme levels gradually approached baseline levels with treatment with antibiotics alone.

There are various studies which established a correlation between enteric fever and abnormal lipid profile (raised triglyceride levels). Tissue dyslipidaemia was studied in *Salmonella*- infected rats [11]. Tissue dyslipidaemia was studied in various studies in human and animal model like *Salmonella*- infected rats [11]. Estimation of serum lipid levels typhoid patients was studied by Shafiq A et al., where there was elevated triglycerides and reduced HDL levels due to lipid peroxidation [12]. Assessment of lipid profile and enteric fever was also studied by Ifoema CI et al., [13].

Studies also showed various haematological abnormalities associated with enteric fever infections and it explains the atypical findings present in the case. In the study by Uplaonkar SV et al., 20 (34.48%) patients had anaemia, 13 (22.41%) had leukocytosis, 23 (39.65%) had neutrophilia, and 10 (17.24%) had thrombocytopenia [14]. Typhoid-induced HLH is extremely rare. All patients had pancytopenia in the study by Sánchez-Moreno P and half of the patients were children [15]. However, in the present case series where the first patient presented with anaemia without significant haematological findings and all were adult patients.

The third case is a middle aged female patient who presented with fever and impaired consciousness. There was headache but no neck rigidity and all neurological examinations were normal except bilateral upgoing plantar reflex. All other causes of febrile encephalopathy were ruled out. Based on positive Typhi dot M test, a diagnosis of Typhoid encephalopathy was made. The patient responded very well to treatment with susceptible antibiotics and steroids.

Typhoid fever is associated with various neurological findings like spasticity, clonus, seizures, ataxia, ophthalmoplegia, cerebellar dysfunctions, neuro-psychiatric manifestations Typhoid encephalopathy poses a diagnostic dilemma among various other aetiologies that causes acute febrile neurological illness [16]. Though reversible, typhoid encephalopathy is a well-known entity lack of clinical suspicion makes the diagnosis difficult. Typhoid presents with various unusual manifestations.

Cardiovascular System (CVS) manifestations were seen in approximately 4.6% of patients in a study by Singh S and Singhi S [17]. Myocarditis was the most common, but pericarditis and endocarditis may occur rarely (exact incidence is unknown). Venous thrombosis (0.83%) and arterial thrombosis (only case reports available) were also reported [17]. Long-term follow-up is needed in these patients for monitoring of cardiovascular function and to detect any adverse outcomes in future [17,18]. It is also important to detect any genetic predisposition in the development of enteric cardiomyopathy.

The second case with non-HLH dyslipidaemia is a rare presentation with probable impact on lipid absorption in enteric fever. Though the hypertriglyceridaemia was reversible in the patient, but long-term follow-up is needed to determine its impact on cardiovascular morbidity and mortality. Moreover, more studies should be done to determine the incidence and impact of enteric dyslipidaemia. According to Rotimi So et al., *Salmonella* altered the metabolism of lipids in rats in different organs. There may be down regulation or up regulation of various lipids. Hepatic HMG CoA reductase activity was upregulated due to Salmonella and its treatment. HDL cholesterol levels may be decreased due to impairment of apolipoprotein induced cholesterol removal as was evident in this case [19].

Enteric encephalopathy responds to steroids and antibiotics. Antibiotics with high dose of dexamethasone reduces morbidity and mortality in patients of typhoid fever with encephalopathy [20]. If the steroid is not initiated promptly, there is increase in mortality and relapse [21,22]. Enteric encephalopathy may occur within 7-9 days as mentioned in an Indonesian study [23]. Steroids act by reducing the generation of free oxygen species and prostaglandins by macrophages induced by typhoid endotoxin [20].

CONCLUSION

Enteric fever presents with various atypical manifestations beyond fever and pain abdomen. It may affect multiple systems of the body and poses a diagnostic challenge. The cases presented here had atypical manifestations in the form of reversible cardiomyopathy, non HLH dyslipidaemia and reversible encephalopathy responding to antibiotics and steroids. The importance of the case series lies in the fact that high index of clinical suspicion is needed for early diagnosis and initiation of appropriate antibiotics to treat these reversible complications and also further studies are required for long-term impact of these reversible complications.

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