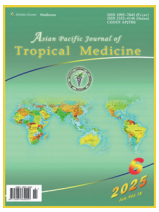

Case Report

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Uncommon presentations of enteric fever: A report of three cases

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ABSTRACT

Rationale: Enteric fever is a major public health problem in developing and underdeveloped counties. Extraintestinal manifestations in typhoid are estimated in 27% cases and are associated with severe and complicated diseases.

Patients concerns: We report three cases of enteric fever with rare extra intestinal manifestations.

Diagnoses: Enteric fever with acute motor-sensory axonal neuropathy, enteric fever with myocarditis, and enteric fever with splenic vein thrombosis.

Interventions: All patients were treated with antibiotics. Additionally, Patient 1 was treated with Ⅳ immunoglobulin; Patient 2 was treated with vasopressors and anti-cardiac remodeling drugs like ramipril and metoprolol; Patient 3 was treated with anticoagulation with low molecular weight heparin.

Outcomes: All patients improved clinically and were followed up on outpatient.

Lessons: The diagnosis of enteric fever is challenging and there is an urgent need for prompt-targeted management for better outcomes. Especially in endemic zones and in non-endemic zones as a disease of emporiatric significance.

KEYWORDS: Enteric; Acute motor-sensory axonal neuropathy; Myocarditis; Thrombosis; Splenic vein

1. Introduction

Enteric fever, interchangeably known as typhoid fever is a systemic bacterial infection with multisystem involvement. It is associated with potentially fatal outcomes in severe complicated forms. It was estimated that around 9 million people were infected with typhoid globally and 110 000 people die from it every year. Typhoid is prevalent in low income, under developed, and developing countries and an example of "infectious divide". In 2019, 44 countries with a high estimated typhoid burden (⩾100 cases/100 000 persons/year) are identified by the global burden of disease study. The most common presenting complaints are fever and headache, and other symptoms included anorexia, abdominal pain, chills, and cough. Diarrhea was more common than constipation[1]. Severe diseases and complications usually manifest in the second or third week of illness with prolonged fever, increasing weakness, anaemia, weight loss, persistent vomiting, or a clouded mental state called coma vigil. Severity of the disease was found to be associated with delayed treatment, the virulence of the bacterial strain, and host factors. Enteric fever related extraintestinal manifestations are uncommon. However, disseminated bacteraemia may involve almost every organ system. The central nervous system, cardiovascular system, pulmonary system, bones and joints, hepatobiliary system, genitourinary system, soft tissues, skin, and hematologic systems are among the common extra-intestinal sites of involvement. Three rare complications of enteric fever are discussed in detail hereunder.

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2. Case 1: Enteric fever with acute motor–sensory axonal neuropathy (AMSAN)

A 35-year female without any known comorbidities presented with complaints of fever for 15 days ranging from 38.3 ℃ to 40 ℃ associated with chills and rigors improving transiently with medication. She also complained of malaise and vague abdominal pain for which she was being treated on outpatient basis by a local physician. On examination, she was febrile, with pulse rate of 76 bpm, respiratory rate of 14 cycles/minute, blood pressure of 140/72 mm/Hg without postural drop, saturation of 99% at room air, conscious, oriented. There was no abdominal distention, with tenderness over epigastric region, without any guarding and rigidity. Bowel sounds were 5 times/min, without hepatosplenomegaly. On lab analysis hemogram was normal and all biochemical tests were in normal range. However, IgM typhi-dot ELISA was positive, Widal test was positive with O and H titres >1/160. Ultrasound whole abdomen showed mild hepatosplenomegaly. Blood, urine cultures and viral infections serological tests were negative. A diagnosis of enteric fever was made and she was started on empirical therapy with intravenous ceftriaxone 2 g/day and oral azithromycin 1 g/day. Defervescence of fever was observed by day 4 of admission. On day 5, she had 3 episodes of syncope lasting for a few seconds precipitated on standing up associated with sweating and improving on lying down. On examination, her blood pressure in supine position was 140/80 mm/Hg and 80/60 mm/Hg on standing up after 3 mins. Within a few hours, she started experiencing weakness of both lower limbs with Medical Research Council power grade 4/5 on examination. The weakness progressed involving all 4 limbs and was complete within the next 24 hours measuring 3/5 by Medical Research Council power grade. All the deep tendon reflexes were absent, orthostatic hypotension was present, without any bowel and bladder involvement. On sensory examination, fine touch, pain, vibration, temperature, and joint position senses were reduced. Cerebrospinal fluid (CSF) analysis was done to evaluate further, which revealed protein 250 mg/dL (normal CSF protein levels <50 mg/dL), albumin 230 mg/dL, total cell counts of 20 cells/mm^3 with 90% of lymphocytes and 10% neutrophils (normal CSF white blood cell count: <5 per μL in adults and children while RBC count is nil), sugar 72 mg/dL (normal sugar levels in CSF: 50-80 mg/dL or greater than two-thirds of the blood sugar level), evident of albumin-cytological dissociation. On nerve conduction studies, motor nerve conduction studies showed reduced amplitudes with prolonged distal latencies in bilateral ulnar, median, and peroneal nerves and decreased motor nerve conduction velocities. Compound muscle action potential amplitude was depressed in bilateral peroneal and tibial nerves. Sensory nerve conduction studies and *F* waves were not recordable in the above tested nerves suggesting axonal sensory motor polyneuropathy (Supplementary Table 1). Fundus examination was normal. Magnetic resonance imaging of the brain was normal except for age related atrophic changes. Magnetic resonance imaging of spine was suggestive of mild reduced height of L5 and S1 vertebrae. Serum creatinine phosphokinase, angiotensin-converting enzyme, perinuclear antineutrophil cytoplasmic antibody, cytoplasmic antineutrophil cytoplasmic antibody, antinuclear antibody, thyroid profile, serum phosphate, were normal. Glycated haemoglobin was 5.3%, electrocardiography (ECG) and echocardiography were within normal limits. Based on all the clinical, laboratory, and electrophysiological evidence a diagnosis of Guillain Barre syndrome variant, AMSAN had been made. The patient was immediately started on intravenous immunoglobulin (IVIg) 2 g/kg body weight for 5 days and was monitored in critical care setting for next 8 days, following improvement in symptoms, she was discharged after 23 days of admission with a final diagnosis of enteric fever with AMSAN with minimal residual weakness and was advised to follow up.

3. Case 2: Enteric fever related myocarditis

A 21-year-old male was brought to the emergency room with a history of high-grade fever for 15 days associated with chills and rigors for which he was being treated by a local practitioner without significant improvement. He also complained of vague abdominal pain, dull aching, not radiating and present throughout the day for same duration. He then developed fatigue for 10 days which worsened gradually, he then experienced shortness of breath for past 7 days, initially on exertion which later progressed to difficulty in breathing even at rest and worsened on lying down over past 3 days. He had no history of similar complaints in the past, no history of coronary artery disease risk factors, he was not on any medications and had no allergies. There was no history of alcohol, tobacco, or illicit drug use. He had no history of convulsions or recent contact with animals or anyone with a febrile illness. There is no family history of sudden cardiac death or heart diseases. At presentation he was sick looking, dyspnoeic, with blood pressure of 88/60 mm/Hg, pulse rate was 114 beats per minute, saturation was 89% on room air, oral temperature of 38.9 ℃, but the extremities were cold and

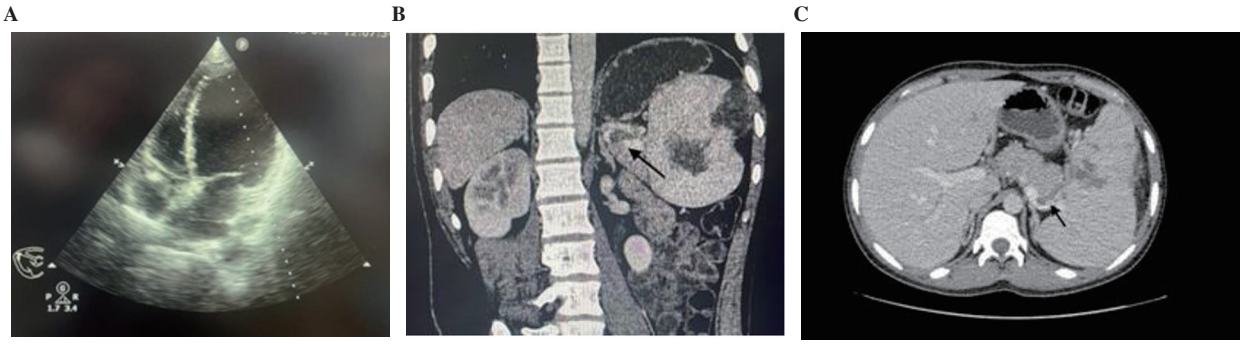

Figure 1. 2D echo of a 21-year-old male (Patient 2) on admission suggestive of global left ventricular hypokinesia and ejection fraction of 20% (A). CT abdomen coronal section showing splenic vein thrombus (arrow) as well as hypodense areas suggestive of infarct (B), and sagittal section showing splenic vein thrombus (arrow) extending up to segmental branches (C) in a 19-year-old male (Patient 3) diagnosed with enteric fever with multiple splenic infarcts secondary to splenic vein thrombosis.

clammy. On general examination, he was somnolent with Glasgow Coma Scale of 15, with normal pupillary reflexes and no signs of meningismus or meningeal irritation. The Jugular venous pressure was elevated and measured 6 cm above sternal angle and no visible pulsations were observed. Upon auscultation of chest bilateral end inspiratory crepitations up to the mid-scapular region were appreciated, both heart sounds S1, S2 were muffled and S3 gallop rhythm were heard. Bedside ECG showed sinus tachycardia, mild QT prolongation, and T-wave inversions in the anterior leads. On X-ray chest, perihilar vascular congestion suggestive of pulmonary congestion with no apparent cardiomegaly was noted. Arterial blood gas analysis showed mixed acidosis with pH 7.188, partial pressure of carbon dioxide (pCO_2) 44.1 mmHg, partial pressure of oxygen (pO_2) 68.2 mmHg, bicarbonate (HCO_3) 14.7 mmol/L, and lactate 3.8. Routine laboratory investigations were suggestive of mild anemia with hemoglobin of 10g/dL, total leukocyte count was 11.2×10^9/ L (neutrophils 57.7%, lymphocytes 30%, monocytes 1.2%) and platelet count of 40×10^9/L. Erythrocyte sediment ratio was 38 mm/hour in the first hour. Liver enzymes were raised with AST 1 800 U/L, ALT 700 U/L, alkaline phosphatase 600 U/L, suggestive of congestive hepatitis. Renal function tests are deranged with serum creatinine of 2.1 mg/dL, blood urea nitrogen (BUN) of 56 mg/dL with BUN: creatinine ratio of 26:1 suggestive of prerenal acute kidney injury. His cardiac biomarkers were elevated with Troponin Ⅰ of 3.24 of ng/mL (normal: 0 to 0.39 U/L) and *N*-terminal pro-B-type natriuretic peptide (NT pro-BNP) of more than 40 000 pg/mL. NS1Ag and MPQBC were negative. Prothrombin time (PT), APTT, *D*-dimer, and INR were within normal limit. Blood culture was negative, urine culture was negative, and stool culture sensitivity were negative. HBsAg, HCV, and HIV were non-reactive. However, IgM typhi dot was reactive. He was admitted in the intensive-care unit administered supplemental oxygen, started on vasopressors along with adequate fluid resuscitation, and broad-spectrum antibiotics. His primary echocardiography showed global left ventricular hypokinesia and reduced ejection fraction of 25%-30%, with normal valve morphology, without any evidence of vegetations, clot, or effusion (Figure 1A). A provisional diagnosis of acute decompensated heart failure secondary to myocarditis was made. A cardiac magnetic resonance imaging (MRI) was also performed, which was also suggestive of myocarditis as per Lake-Louise criteria. He was weaned off the vasopressor support over the next three days. He was discharged on oral ramipril 1.25 mg once daily and metoprolol 12.5 mg once daily and followed up on outpatient basis. Given the clinical picture and laboratory evidence of enteric fever, he was diagnosed as a case of typhoid related myocarditis with reversible cardiomyopathy.

4. Case 3: Enteric fever causing splenic infarction secondary to splenic vein thrombosis

A 19-year-old male with no other comorbidities presented with high-grade fever for 18 days associated with chills and rigors, which subsides temporarily on antipyretic drugs prescribed by a local practitioner. He also complained of sudden onset severe left upper quadrant abdominal pain for 1 day, radiating to the left shoulder. The pain is described as dull and constant, occasionally sharp, and worsens with deep breaths or movement associated with nausea and intermittent vomiting over the past 2 hours, along

with a sensation of fullness and mild bloating, especially after meals. There was no history of similar complaints nor altered bowl movements, gastrointestinal bleeding, liver disease, recent history of acute pancreatitis or trauma. There is no history of hematuria or passage of high coloured urine. On examination, the patient appears mildly distressed, well oriented to time place and person with oral temperature of 38.3 ℃, pulse rate of 106 beats per minute, blood pressure of 110/68 mm/Hg. On abdominal examination, there is no abdominal distension, visible scars, sinuses, or dilated veins. There is tenderness in left hypochondrium, without any guarding and rigidity, spleen was palpable 2.5 cm below the left subcostal margin of grade 2 of Hackett's grading of splenomegaly and was tender on palpation. Bowel sounds were present. Other systemic examination is within normal limit. On laboratory investigations, hemoglobin was 10.4 g/dL and general blood picture showed mild normocytic normochromic anemia with no evidence of sickling, platelet count was 1.13×10^9/L, and total leukocyte count was 9.3×10^9/L with neutrophil fraction suggestive of 38%, lymphocytes 54%, eosinophil 6%. C reactive protein was elevated measuring 108 g/dL. Liver enzymes were elevated with AST 220 U/L, ALT 122 U/L, total bilirubin of 2.1 mg/dL with direct bilirubin of 1.5 mg/dL, and indirect bilirubin of 0.6 mg/dL. Serum electrolytes, renal function test, and pancreatic enzymes were within normal limits. IgM typhi dot was reactive, Widal test was positive with *Salmonella typhi* at titres of 1:180 on the 2nd day and 1:320 on the 10th day of admission, respectively. NS1Ag and MPQBC were negative. Prothrombin time (PT), APTT, D-dimer, and INR were within normal limit. HBsAg, HCV, and HIV were non-reactive. Blood culture confirmed *Salmonella typhi* A, sensitive to ceftriaxone, piperacillin-tazobactam, imipenem, chloramphenicol, and ciprofloxacin. Urine and stool cultures were negative. ECG, 2D echocardiogram, antinuclear antibody, antiphospholipid antibody panel, urine routine and microscopy were within normal limits. Ultrasonography was suggestive of splenomegaly of 16 cm with ill-defined hypoechoic lesions in the splenic parenchyma, inferior vena cava measured 0.8 cm in diameter. Contrast-enhanced computed tomography of the abdomen showed hepatomegaly of 18 cm and splenomegaly with multiple wedge shaped peripherally located hypodense confluent areas of infarction, hypodense lesion at one pole suggestive of abscess breaching the capsule, adjacent sub-diaphragmatic collection, and thrombus in splenic vein extending up to segmental branches (Figures 1B and 1C). The patient was treated with intravenous fluids to correct dehydration, intravenous ceftriaxone (2.0 g/day) for fourteen days and azithromycin 500 mg twice a day for a week, along with anticoagulation with low molecular weight heparin at doses of 1 mg/kg subcutaneously every 12 hours aiming for an INR of 2.0-3.0. He then was switched to oral warfarin 5 mg and discharged with continued on anticoagulation for six months with regular coagulation monitoring. In the follow-up, the patient gradually improved with evidence of resolution of thrombus size in the follow-up colour Doppler imaging. Based on the clinical picture, laboratory evidence, and radiological results, the above case is diagnosed as a case of enteric fever with multiple splenic infarcts secondary to splenic vein thrombosis.

5. Discussion

Enteric fever, primarily caused by the bacterium *Salmonella enterica* serotype typhi, presents significant public health challenges due to its complications. Other serotypes, such as Para typhi A, B, and C, also contribute to this disease. It is a gram-negative bacillus associated with severe complications in approximately 27% of cases, including gastrointestinal bleeding, nephritis, and encephalopathy. Notably, neurological disturbances occur in about 35% of patients, often manifesting as delirium and acute psychosis[3]. Additional complications can include cholecystitis (1%-26% of cases), respiratory issues (1%-6%), cardiovascular problems (1%-5%), and rare conditions like renal abscesses and osteomyelitis[4]. This report focuses on three cases of enteric fever that underscore unusual extraintestinal manifestations and the need for updated clinical practice guidelines.

In the first case, a patient developed AMSAN, a severe variant of Guillain-Barré syndrome, which presents with progressive and symmetrical muscle weakness. Diagnosis is often confirmed through CSF analysis showing albumin-cytological dissociation. AMSAN is more common in Asia and South America, progresses rapidly, and has a poor prognosis. Characterized by axonal injury while preserving the myelin sheath, symptoms typically occur one to three weeks post-infection and correlate with autoantibodies targeting gangliosides (GM1 and GD1a)[5]. The patient initially showed classic enteric fever symptoms, followed by neurological complications confirmed by CSF analysis. The use of intravenous immunoglobulin led to significant clinical improvement. Although AMSAN cases are rare, literature supports the association between AMSAN and enteric fever, stressing the need for prompt diagnosis and intervention[6].

The second case involved patient diagnosed as myocarditis, recognized as a complication in approximately 1%-5% of enteric

fever patients. Myocarditis can result in severe issues like arrhythmias, heart block, and myocardial infarction-like symptoms, including chest pain and fatigue[7]. Symptoms typically emerge during the second week of illness, and postmortem studies often reveal inflammatory changes in intramural vessels and modifications in cardiomyocytes[8]. Our patient, serologically confirmed with enteric fever, exhibited myocarditis symptoms corroborated by an ECG showing sinus tachycardia and cardiac MRI findings. Notably, the patient's condition improved following antibiotic therapy, strengthening the diagnosis without the need for invasive procedures such as endomyocardial biopsy. This was similarly reported in a recent article by Rizwan Ullah *et al*[7].

The third case presented multiple splenic infarcts secondary to splenic vein thrombosis, which is relatively uncommon[9]. The patient primarily complained of abdominal pain, with gastrointestinal bleeding and nausea reported less frequently. The mechanism of splenic infarction in infectious diseases is not fully understood, but potential explanations include a transient hypercoagulable state, vascular occlusion from increased immune complexes and cellular stacking, and an imbalance between blood supply and the demand of an enlarged spleen[9]. In our case, the patient improved with antibiotic treatment and anticoagulation, as shown by subsequent color Doppler scan also documented in some previous studies[9].

The primary method for diagnosing enteric fever is a positive blood culture, which has a sensitivity of only 40% to 80%. This low rate may result from factors like low bacterial counts in the early disease stage, prior antimicrobial use, and culture conditions. A modified test, the Typhidot-M, provides better specificity in early diagnosis by targeting IgM, with sensitivities from 68% to 95% and specificities from 75% to 95%. Its high negative predictive value makes it suitable for areas with high endemicity, potentially making it a better option than the Widal test[10].

These cases emphasize the need for clinical practice guidelines to evolve. Current guidelines mainly focus on gastrointestinal symptoms and hematological irregularities, neglecting cardiac and neurological evaluations. Our observations suggest including recommendations for cardiac and neurological assessments in endemic regions, particularly for patients presenting beyond the first week of illness. Suggested measures include baseline ECG and neurological screenings, alongside the use of non-invasive imaging techniques like cardiac MRI and color Doppler as viable alternatives to invasive diagnostic tests. This patient-centered approach aims to ensure diagnostic accuracy.

Our cases suggest that *Salmonella enterica* infection leads to systemic immune dysregulation, causing inflammatory and thrombotic complications like AMSAN, myocarditis, and splenic vein thrombosis through molecular mimicry and endothelial dysfunction. This can be investigated through prospective studies measuring serum cytokines, autoantibodies (*e.g.*, anti-GM1/GD1a for AMSAN), and endothelial activation markers in enteric fever patients with and without complications. Animal models could further clarify mechanisms of thrombi formation and nerve damage, informing targeted therapies or prophylactic measures.

This case series highlights various rare extraintestinal manifestations associated with enteric fever, underscoring the necessity for clinicians to maintain a high index of suspicion. Timely diagnosis and management, including appropriate use of antibiotics and anticoagulation when needed, can lead to improved patient outcomes.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Patients' consents for publication

Written informed consents were obtained from the three patients for publication of this case report and any accompanying images.

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Authors' contributions

RK, SR, SQ, KK developed the theoretical formalism, performed the analytic calculations and performed the numerical simulations. RK, SR, SQ, KK contributed to the final version of the manuscript. SQ supervised the project.

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Publisher's note

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Supplementary table 1. Nerve conduction study results.

Test	Stimulation Site	Lat, ms	Ampl, mV	Dur, ms	Dist, mm	Vel, m/s
MOTOR CV	right, Median wrist	15.65	1	15.6	80	6.3
	elbow	16.01	1	20.5	220	7.8
MOTOR CV	left, Median wrist	8.9	1.5	15.7	80	6.5
	elbow	12.63	1.5	21.4	220	7.4
MOTOR CV	right, Ulnar wrist	14.7	0.9	16.8	80	6,2
	elbow	13.02	1	22.7	220	6.8
MOTOR CV	left, Ulnar wrist	13	2.3	15.1	80	7.1
	elbow	43.5	1.6	23.5	220	7.2
MOTOR CV	right, Peroneal head of fibula	6.90	0.8	12.21	350	40
MOTOR CV	left, Peroneal sole of foot	8.92	0.8	14.29	350	41
	head of fibula	18.35	0.7	14.56	330	40
MOTOR CV	right, Tibial medial malleolus	5.25	2.3	12.21	370	42
	popliteal fossa	4.35	0.7	12.94	370	40
MOTOR CV	left, Tibial medial malleolus	5.5	0.5	14.8	70	41
	popliteal fossa	7.8	0.5	21.8	350	40
SENSORY CV	right, Median wrist	NR				
SENSORY CV	left, Median wrist	NR				

SENSORY CV	right, Ulnar wrist	NR				
SENSORY CV	left, Ulnar wrist	NR				
SENSORY CV	right, Sural	NR				
SENSORY CV	left, Sural	NR				
F-Wave	right, Median	NR				
F-Wave	left, Median	NR				
F-Wave	right, Ulnar	NR				
F-Wave	left, Ulnar	NR				
F-Wave	left, Peroneal	NR				
F-Wave	right, Tibial	NR				
F-Wave	left, Tibial	NR				