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Rare Cases of Enteric Fever-Associated Secondary Hemophagocytic Lymphohistiocytosis with Encephalopathy

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Keywords*Enteric fever**Typhoid fever**Salmonella Typhi**Endemic infection**Systemic infection***ABSTRACT**

Enteric fever, caused by *Salmonella Typhi*, primarily presents with systemic symptoms such as fever, gastrointestinal disturbances, and hematological abnormalities. However, neurological complications, including cytotoxic lesions of the corpus callosum, are rare. We report two cases of young adults diagnosed with typhoid fever, confirmed by positive blood cultures. The first case, a 24-year-old female, presented with fever, focal seizures, and progressive decreased responsiveness. Laboratory findings revealed significant thrombocytopenia, elevated serum ferritin, and a positive Widal test. The second case, a 27-year-old male, exhibited altered sensorium with features suggestive of meningeal involvement. MRI revealed a cytotoxic lesion of the corpus callosum, an unusual neurological manifestation in typhoid fever. Notably, in both cases, the presence of acute febrile illness, neurological symptoms and cytopenias warranted consideration of Hemophagocytic Lymphohistiocytosis alongside other causes particularly given the endemic nature of enteric fever in India. Both patients were initially treated with broad-spectrum antibiotics and later transitioned to targeted therapy based on antimicrobial susceptibility. They demonstrated significant clinical improvement and were discharged on oral antibiotics. These cases highlight the diverse and atypical neurological manifestations of typhoid fever, including cytotoxic lesions of the corpus callosum, which has been rarely reported. Comparisons with previously documented cases suggest that elevated inflammatory markers, particularly serum ferritin and D-dimer, may correlate with disease severity and neurological involvement. Early recognition of HLH and targeted antibiotic therapy led to favorable outcomes in both cases. This report underscores the need for heightened clinical awareness of neurological complications and secondary HLH in enteric fever. Further research is warranted to explore the mechanisms underlying neurological manifestations and HLH in typhoid fever and to establish standardized management strategies for such rare presentations.

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INTRODUCTION:

Typhoid fever and paratyphoid fever, collectively known as enteric fever, are clinically indistinguishable febrile multisystemic illnesses caused by *Salmonella enterica* subspecies *enterica* serovar/serotype Typhi and Paratyphi A, B, and C. Globally, enteric fever affects more than 9 million people, and results in around 110,000 deaths annually. [WHO. Typhoid Fact Sheet. 2023]. Enteric fever typically presents insidiously with the gradual onset of fever with fatigue, anorexia, headache, malaise, and abdominal symptoms after an incubation period of 10 to 14 days. If not treated promptly or effectively, it can lead to serious complications like meningitis, sepsis, or intestinal

perforation. Salmonellae are gram-negative bacilli that comprises 2 main species of which *Salmonella enterica* consist of 6 subspecies of which *S. enterica* subspecies *enterica* has the most serotypes and is the primary cause of human infections [1]. The ongoing burden of enteric fever in India is marked by changing clinical profiles and complications.

Pancytopenia is a complex hematologic disorder marked by a decrease in the counts of all three peripheral blood cell lineages. Diagnostic thresholds include a hemoglobin level below 12 g/dL in women and 13 g/dL in men, platelet count below 1,50,000 per μL , and leukocyte count below 4000 cells per μL (or absolute neutrophil count of less than 1800 cells per μL) [2]. Rather than being a distinct medical condition, pancytopenia serves as an indicator of an underlying problem, resulting in decreased blood cell production or increased destruction. The etiological workup should focus on ruling-out leukemia, autoimmune disorders and viral infections, before considering Hemophagocytic Lymphohistiocytosis (HLH) as a potential cause [3].

Though leukopenia with neutropenia are characteristic findings in enteric fever, the development of pancytopenia with severe

thrombocytopenia is uncommon (6.2 -8.3%) [4].

Case Presentation:

CASE 1: A 24-year-old female presented with a one-week history of continuous fever (100.1°F), accompanied by vomiting, loose stools, bilateral upper limb posturing, abnormal movements of the left lower limb suggestive of focal seizures, and progressive decreased responsiveness. Her vitals showed a pulse rate of 88/minute, respiratory rate of 16/minute, and blood pressure of 90/60 mmHg. Systemic examination of the cardiovascular, respiratory, and abdominal systems was unremarkable. Neurological assessment revealed a Glasgow Coma Scale (GCS) score of 12/15 (E1 V5 M6) and motor power of 4/5 in both upper and lower limbs.

The patient underwent a comprehensive hematological assessment daily from Day 1 to Day 6 and again on Day 11. This evaluation included hemoglobin (Hb) levels, red blood cell (RBC) count, total and differential leukocyte count, and platelet count. The table [Table 1] presents the hematological parameters measured in the patient (case 1) from Day 1 to Day 6 and again on Day 11.

Table 1: Hematological Parameters of Case 1 Assessed from Day 1 to Day 6 and Day 11

Parameter	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 11	Reference values
Hemoglobin (g/dl)	10.1	10.9	10	8.6	8.7	8.2	8.9	12-15
RBC (million/cu.mm)	3.32	3.72	3.39	3.11	3.03	2.88	3.16	3.8-4.8
Total Count (cells/cu.mm)	800	1130	960	1410	13130	10960	6340	4000-11000
Polymorphs (%)	26	37	8	72.4	65.1	61	60	45-70
Lymphocytes (%)	8	13	2	19.9	18.7	20	25	25-40
Eosinophils (%)	0	0	0	0	0	2	3	1-6
Monocytes (%)	0	0	0	3.5	2	2	4	2-10
Basophils (%)	0	0	0	0.7	0.4	0.5	0.8	0-1
Platelets (Lakhs/cu.mm)	0.36	0.29	0.31	0.2	0.73	0.59	1.62	1.5-4.5

The laboratory investigations which revealed normal renal function test (RFT) values with a blood urea nitrogen (BUN) of 5 mg/dL (biological reference interval: 6-20 mg/dL) and creatinine of 0.4 mg/dL (biological reference interval: 0.5-0.9 mg/dL). Serum electrolytes were found to be within normal biological reference range - sodium-136 mmol/L (biological reference interval: 136-145 mmol/L); potassium-4.2 mmol/L (biological reference interval: 3.5-5.1 mmol/L); chloride-104 mmol/L (biological reference interval: 98-107 mmol/L); bicarbonate-22 mmol/L (biological reference interval: 22-29 mmol/L). Liver function tests (LFT) showed elevated serum glutamate oxaloacetate transaminase (SGOT) at 159 IU/L (biological reference value: <32 IU/L) and serum glutamate pyruvate transaminase (SGPT) at 45 IU/L (biological reference value: <33 IU/L). Other biochemical parameters included a significantly elevated serum ferritin level of 2601 ng/mL (biological reference interval: 24-336 ng/mL),

serum lactate dehydrogenase (LDH) of 1145 U/L (1 in 10 dilution) (biological reference interval: 135-214 U/L), and fibrinogen levels of 274.4 mg/dL (biological reference interval: 250-520 mg/dL). Peripheral blood smear examination revealed normocytic normochromic anemia with thrombocytopenia and leukopenia. Abdominal ultrasonography (USG) showed mild hepatomegaly and borderline splenomegaly as shown in figure 1. CSF analysis showed glucose - 50 mg/dl; chloride-126 mmol/L; and cell count of one polymorphonuclear cell and one mononuclear cell. The dengue NS1 antigen assay (ELISA), ds DNA (IFA), *Clostridium difficile* toxin detection by LFA, and real-time qualitative PCR panel for HSV-1, HSV-2, EBV, and VZV in CSF were all negative. Serological tests for HIV, Hepatitis B, and Hepatitis C were also negative. Microbiological investigations showed no growth in urine and cerebrospinal fluid (CSF) cultures. However, on day-2, paired blood culture sets from both the left and right brachial

veins grew Salmonella Typhi susceptible to Ampicillin, Azithromycin, Cefixime, Ceftriaxone, Cephalexin, Chloramphenicol, Cotrimoxazole, Tetracycline and resistant to Ciprofloxacin. The Widal test results are as in Table 2.

Table 2: Case 1 Widal Test results

ANTIGEN	DILUTION	RESULT
TO	1:80	Positive
TH	1:160	Positive
AH	1:20	Negative
BH	1:20	Negative

These findings indicate an active Salmonella Typhi infection, associated with secondary HLH and enteric encephalitis.

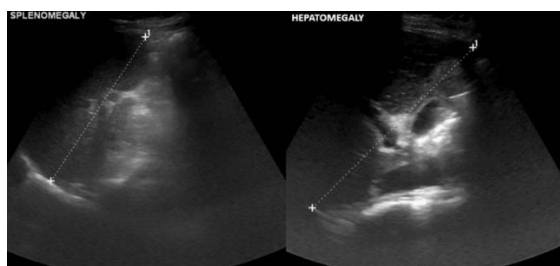


Figure 1: Ultrasound abdomen of case 1 showing borderline splenomegaly and mild hepatomegaly

The patient was empirically started on Inj.Acyclovir 500 mg iv TID for 4 days and anti-epileptics considering the neurological presentation, along with Inj.Meropenem 3g TID iv for 4 days for broad-spectrum bacterial coverage. Following the antibiotic susceptibility test (AST) results, therapy was de-escalated by switching to Inj.Ceftriaxone 2g iv OD for 5 days as the definitive treatment. Upon significant symptomatic improvement and achieving hemodynamic stability, the patient was

discharged with a step-down oral antibiotic regimen, consisting of Tab.Cefixime 200 mg P/O BD for 5 days and Tab.Azithromycin 500 mg P/O BD for 5 days along with Tab.Levetiracetam 500mg P/O BD. The patient was advised to complete the oral therapy as prescribed to ensure full recovery and prevent relapse.

CASE 2: A 27-year-old male presented with a history of fever 10 days ago, followed by loose stools 4-5 times/day for 3 days, 3 episodes of vomiting for 2 days, decreased food intake, generalized weakness for 3 days, and altered sensorium. On examination, he was drowsy but responsive to verbal commands, with a temperature of 99.5°F, pulse rate of 74/min, respiratory rate of 24/min, and blood pressure of 110/70 mmHg. A petechial rash was noted over the chest and tongue. CNS examination revealed a Glasgow Coma Scale (GCS) score of E4 V5 M6, bilateral reactive pupils, terminal neck stiffness, and muscle power of 4/5 in all limbs, suggesting possible meningeal involvement. However, Kernigs and Brudzinski signs were negative. Systemic examination of the cardiovascular, respiratory, and abdominal systems was unremarkable. Given the clinical presentation, possible neurological complications necessitated further evaluation with blood cultures, Widal test, and lumbar puncture to rule out meningitis or sepsis-related complications.

The table [Table 3] presents the hematological parameters measured in the patient (case 2) from Day 1 to Day 7.

Table 3: Hematological Parameters of Case 2 Assessed from Day 1 to Day 7

Parameter	Day 1	Day 2	Day 3	Day 4	Day 6	Day 7	Reference values
Hemoglobin (g/dl)	11.6	11.6	11.4	11.1	11.2	10.6	13-17
RBC (million/cu.mm)	3.92	3.96	3.99	3.74	3.95	4.05	4.5-5.5
Total Count (cells/cu.mm)	1110	1280	1420	1740	7600	8150	4000-11000
Polymorphs (%)	35	33	64.1	52.4	60.3	62	45-70
Lymphocytes (%)	15	17	30.3	42.5	33	34	25-40
Eosinophils (%)	0	0	0	0	0.4	0.9	1-6
Monocytes (%)	0	0	4.9	4	4.7	4	2-10
Basophils (%)	0	0	0	0	0.5	0.4	0-1
Platelets (Lakhs/cu.mm)	0.46	0.32	0.33	0.29	1.23	1.69	1.5-4.5

The patient underwent the advised laboratory investigation in which the renal function test (RFT) showed a BUN of 10 mg/dl (biological reference interval: 6-20 mg/dL) and creatinine of 0.7 mg/dl (biological reference interval: 0.5-0.9 mg/dL), both within normal limits. Serum electrolytes were found to be within normal biological reference range - sodium-123 mmol/L (biological reference interval: 136-145 mmol/L); potassium-3.6 mmol/L (biological reference interval: 3.5-5.1 mmol/L); chloride-94 mmol/L (biological reference interval: 98-107 mmol/L); bicarbonate-13 mmol/L

(biological reference interval: 22-29 mmol/L). Liver function tests (LFT) revealed elevated SGOT at 345 IU/L (biological reference value: <32 IU/L) and SGPT at 139 IU/L (biological reference value: <33 IU/L). Serum ferritin was significantly high at 22,485 ng/mL (biological reference interval: 24-336 ng/mL), while fibrinogen was low at 222.1 mg/dl (biological reference interval: 250-520 mg/dl). D-Dimer was elevated at 5.58 mg/L FEU (biological reference value <0.55 mg/L FEU), and triglycerides were high at 393 mg/dL (biological reference range-desirable: <150; borderline: 150-199; high: 200-

499; very high: >500). The peripheral blood smear showed normocytic normochromic anemia with thrombocytopenia and leukopenia. Ultrasound of the abdomen was unremarkable, and MRI of the brain revealed a small, well-defined ovoid lesion noted in splenium of corpus callosum which appeared T2/FLAIR hyperintense and showed diffuse restriction - likely cytotoxic lesion. The EEG was normal, while the lumbar puncture (LP) was a dry tap, and a repeat LP was not performed due to refusal of consent. The results of serological workup for tropical fever were as follows: Dengue NS1 antigen, IgM, and IgG (ELISA) were negative, as were Scrub typhus IgM (ELISA), Leptospira IgM (ELISA), and Malarial antigen (ICT). ANA (IF) was negative, and both C-ANCA and P-ANCA (ELISA) were negative. Serology for HIV, Hepatitis B, and Hepatitis C was negative. Bone marrow aspiration was not performed due to the patient's refusal of consent. Urine culture showed no growth, whereas, on day-2, paired blood culture sets from both the left and right brachial veins grew *Salmonella Typhi* (Figure 2), which was susceptible to all recommended antibiotics including Ampicillin, Azithromycin, Cefixime, Ceftriaxone, Cephalexin, Chloramphenicol, Ciprofloxacin, Cotrimoxazole, Tetracycline. The Widal test results are as in Table 4.

Table 4: Case 2 Widal Test results

ANTIGEN	DILUTION	RESULT
TO	1:40	Positive
TH	1:160	Positive
AH	1:20	Negative
BH	1:20	Negative



Figure 2: Isolation of *Salmonella Typhi* from case 2. Culture plates showing characteristic growth patterns: non-hemolytic grey moist colonies on blood and chocolate agar, and lactose non-fermenting colonies on MacConkey agar

These findings are consistent with a diagnosis of secondary HLH with septic encephalopathy due to *Salmonella Typhi*.

The patient was empirically treated with Inj.Acyclovir 500 mg iv three times a day (TID), Inj.Meropenem 3g iv three times a day (TID) for 2 days, and Tab.Azithromycin 1g P/O once a day (OD) for 2 days. Based on antibiotic susceptibility reports, the therapy was then de-escalated to Inj.Ceftriaxone 2g iv once a day (OD) for 7 days.

The patient showed signs of recovery and was subsequently discharged.

DISCUSSION:

Both cases involved young adults presenting with febrile illness, gastrointestinal symptoms, and neurological manifestations. Case 1, a 24-year-old female, exhibited fever, vomiting, diarrhoea, focal seizures, and progressive decreased responsiveness, while Case 2, a 27-year-old male, had fever followed by diarrhoea, vomiting, weakness, altered sensorium, and a petechial rash. Blood cultures confirmed *Salmonella Typhi* infection in both cases, with hematological findings of anemia, thrombocytopenia, leukopenia, and elevated inflammatory markers. Imaging in Case 2 revealed a cytotoxic brain lesion, indicating possible typhoid encephalopathy. Initial empirical therapy included Acyclovir and Meropenem, which was later modified to Ceftriaxone based on antibiotic susceptibility results. Case 1 was discharged with a step-down oral regimen of Cefixime and Azithromycin, while Case 2 completed a 7-day course of Ceftriaxone. Both patients showed significant recovery and were discharged in stable condition. While *Salmonella Typhi* commonly presents with gastrointestinal symptoms, severe cases may involve central nervous system (CNS) complications, including encephalopathy, seizures, and cytotoxic lesions in the corpus callosum [5]. Such neurological involvement, though uncommon, underscores the need for heightened clinical awareness.

These cases highlight unusual neurological manifestations of *Salmonella Typhi* infection, emphasizing the need for heightened clinical vigilance. Case 1 presented with focal seizures and progressive decreased responsiveness, while Case 2 exhibited altered sensorium with a rare cytotoxic lesion in the splenium of the corpus callosum, suggestive of typhoid encephalopathy. The significant elevation of inflammatory markers, including serum ferritin and D-dimer, raised concerns about an exaggerated immune response, potentially contributing to neurological involvement.

Additionally, the detection of *Salmonella Typhi* bacteremia in the absence of classical enteric symptoms underscores the importance of considering typhoid fever in atypical presentations. These cases reinforce the necessity of early blood culture testing, prompt initiation of appropriate antibiotics, and multidisciplinary management to address both systemic and neurological complications effectively.

Epinoza et al, reported that typhoid fever can result in various neurological complications, which can be

broadly classified into infectious or noninfectious sequelae [6]. Rodriguez et al in their study have concluded that among infectious manifestations, meningoencephalitis due to enteric fever is often associated with severe and immediate neurological complications, which includes subdural effusion/empyema, abscesses, ventriculitis, cerebritis, hydrocephalus, venous thrombosis, and infarcts [7]. Ichikawa et al have reported a wide spectrum of noninfectious neurological complications of enteric fever such as encephalopathy (seen in 3.7%-18% cases), neuropsychiatric disorder, cerebral edema, cerebellar ataxia, parkinsonism, acute disseminated encephalomyelitis, and encephalitis [6,8]. Pathologic findings in Salmonella Typhi-associated encephalopathy are nonspecific and can include cerebral edema, minimal ischemia, vasculitis, cellular infiltrates, and perivenous demyelination.

In addition, both our cases exhibited thrombocytopenia, leukopenia, and anemia, which align with hematological manifestations reported in enteric fever due to bone marrow suppression. Elevated serum ferritin, SGOT, and SGPT levels in both patients suggest a hyperinflammatory response, likely mediated by cytokine release during Salmonella Typhi bacteremia. The markedly high serum ferritin levels raise concerns about a possible macrophage activation syndrome (MAS), a severe inflammatory state that can occur in enteric fever.

Neurological manifestations, including focal seizures (Case 1) and altered sensorium with cytotoxic lesions in the corpus callosum (Case 2), are atypical but recognized complications of typhoid fever. Typhoid encephalopathy, often associated with a "typhoid state" (delirium, stupor, and confusion), occurs in approximately 10-15% of hospitalized patients with enteric fever [9]. The splenic lesion observed in Case 2, commonly referred to as a "reversible splenic lesion syndrome (RESLES)", has been linked to various infectious and inflammatory conditions. Similar lesions have been previously described in dengue, scrub typhus, and bacterial meningitis but are rarely documented in typhoid fever. The pathophysiology behind these lesions is thought to involve transient cytotoxic edema due to cytokine-induced endothelial dysfunction [10].

Chopra et al, reported a case of mild encephalopathy/encephalitis with reversible splenic lesion (MERS) as a rare neurological complication of Salmonella Typhi, characterized by transient MRI changes in the splenium of the corpus callosum. While some cases show diffuse hyperintense signals, others may have no abnormalities. MERS is associated with infections, metabolic disturbances,

and epilepsy, with a likely pathogenesis involving cytotoxic edema. It is more common in Asian children, but this case highlights its occurrence in an adult with typhoid encephalopathy. Treatment involves managing the underlying infection, with a good prognosis following appropriate antibiotic therapy [11].

Saha et al, reported two cases of typhoid fever with pancytopenia, linked to unhygienic food, and responded well to antibiotics. One case involved a septic abortion. Diagnosis was based on blood culture and Widal test. Bone marrow findings indicated active infection. Typhoid fever with pancytopenia is a rare clinical presentation. Reports from Asia and Africa in the late 20th century described cases, but in the past two decades, only a few cases have been documented. These include one case each from India, Pakistan, Nepal, Ghana, Malawi, Spain, Turkey, and the United States. Most cases involved hemophagocytic lymphohistiocytosis (HLH), with pediatric patients reported in Pakistan, Nepal, Malawi, Turkey, and Spain, while the others involved young adults. The U.S. case involved an Indian patient who had recently arrived in the country. Given the high prevalence of typhoid fever, the occurrence of typhoid-associated pancytopenia remains extremely rare [12].

Hemophagocytic lymphohistiocytosis (HLH) is a serious and relatively uncommon consequence of enteric fever, characterized by excessive cytokine release and histiocyte activation. This condition is also known as Hemophagocytic syndrome (HPS) and is characterized by a rapid progression of systemic inflammation, leading to cytopenia, a surge in cytokine production, and elevated serum ferritin levels. Patients with HLH often present with persistent fever, lymphadenopathy, organomegaly, and multiorgan failure including the liver, spleen, bone marrow, lungs, and central nervous system [13]. This condition is categorized as cytokine storm syndrome due to the significant cytokine production. HLH can manifest in both primary and secondary forms, with the primary form predominantly affecting children and attributed to genetic mutations. On the other hand, secondary or acquired HLH occurs in response to an underlying condition such as cancer, autoimmune disorder. Shekhar et al, reported a case with typhoid fever who developed HLH despite appropriate antibiotic therapy, showing worsening cytopenias, hepatitis, and ARDS. HLH was confirmed through lab findings and bone marrow aspiration. The patient improved with corticosteroids alongside antibiotics, highlighting the importance of early diagnosis and treatment. While many typhoid fever cases complicated by HLH can resolve with antibiotics

alone, some may require immunosuppression. This case underscores the need to consider HLH in patients with severe enteric fever, as it may often be missed due to overlapping clinical symptoms [14].

Case 1 and Case 2 were evaluated based on the 2009 modified criteria for Hemophagocytic Lymphohistiocytosis (HLH) [15]. The criteria are divided into essential features (at least three must be present) and additional features (at least one must be present). Both cases exhibit fever and thrombocytopenia. Case 1 also shows evidence of anemia, borderline splenomegaly and hepatitis, fulfilling the required three essential criteria. Both cases demonstrate elevated ferritin, meeting the additional criterion. Case 2, while lacking anemia, presents with hypertriglyceridemia, hypofibrinogenemia, and hyponatremia, which are supportive, though not strictly required, features. Neither case had bone marrow study for hemophagocytosis, soluble CD25 levels, absolute neutrophil count and NK cell activity were not performed. Ultimately, both cases appear to meet the diagnostic criteria for HLH as in Table 5.

Table 5: Case presentation based on modified 2009 HLH criteria

	CASE 1	CASE 2
AT LEAST THREE OF THE FOLLOWING		
Fever	YES	YES
Splenomegaly	YES	NO
Cytopenia in at least 2 cell lines:		
Haemoglobin <9gm%	YES	NO
Absolute neutrophil count <1000/cu.mm	Not done	Not done
Platelet <100000/cu.mm	YES	YES
Hepatitis	YES	YES
ATLEAST ONE OF THE FOLLOWING		
Ferritin elevation >500ng/ml	YES	YES
Elevated soluble CD25	Not done	Not done
Hemophagocytosis	Not done	Not done
Low/ absent NK cell activity	Not done	Not done
OTHER SUPPORTIVE FEATURES		
Hypertriglyceridemia (Fasting >265 mg/dl)	Not done	YES
Hypofibrinogenemia <1500 mg/dl	NO	YES
Hyponatremia	NO	YES

CONCLUSION:

These cases highlight the atypical neurological manifestations of Salmonella Typhi infection, including focal seizures and cytotoxic lesions of the corpus callosum (CLOCC), which are rarely reported in enteric fever. Early recognition, timely blood culture confirmation, and appropriate antibiotic therapy played a crucial role in achieving favorable clinical outcomes. The presence of markedly elevated inflammatory markers, such as serum ferritin and D-dimer, may serve as potential indicators of disease severity and neurological

involvement. While both patients responded well to targeted therapy, the underlying mechanisms of cytotoxic lesions of the corpus callosum in typhoid fever remain unclear.

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