Case Report

A Rare Case of *Salmonella meningitis* and Hemophagocytic Lymphohistiocytosis

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Abstract

Enteric fever is a common infectious disease of the tropical world. Common age group involved is children aged between 5 and 10 years. In addition to diarrhea, it may lead to extraintestinal infections including aseptic meningitis, hepatitis, cholecystitis, acute abdomen, intestinal perforation, pneumonia, psychosis, and ataxia. Hematologic complications leading to hemophagocytosis have a prevalence of < 1%. *Salmonella meningitis* has an incidence of 6% with poor prognosis neurological sequelae. We report a rare case of enteric fever that presented with hemophagocytic syndrome and *S. meningitis*. Response to third-generation cephalosporins is dramatic, eventually giving good prognosis.

Keywords: Hemophagocytic lymphohistiocytosis, secondary hemophagocytic lymphohistiocytosis, *Salmonella meningitis*, enteric fever

Introduction

Typhoid fever is still a deadly disease in developing countries, particularly in India. The incidence of typhoid among children aged 2 and 5 years is 340.1 per 100,000 person-years in India.[1] Enteric fever can have complications involving systems such as central nervous system (CNS), cardiovascular system, pulmonary system, bone and joint, hepatobiliary, genitourinary, soft tissue infections, and hematologic. Hematologic complications, leading to hemophagocytosis, have a prevalence of <1%. The incidence of *Salmonella meningitis* has been reported to be about 6% of those with salmonellosis.[2] Neurological sequelae with *S. meningitis* are 85%, which include convulsion (69%), subdural effusion (31%), hydrocephalus (38%), empyema (23%), ventriculitis (15%), and intracranial hemorrhage and cerebral abscess (8%), with mortality being 18%.[3] Long-term neurological sequelae was seen with 47% of cases and relapse rate nil with favorable outcome in another study.[4] Here, we report a case of 5-year-old girl diagnosed with *Salmonella* infection which led to complications of hemophagocytic lymphohistiocytosis (HLH) and later bacterial meningitis.

Case Report

A 5-year-old girl presented to a tertiary care center with fever of moderate-to-high grade for 4 days and bleeding manifestations in the form of ecchymoses and bleeding gums for 2 days. There was associated history of generalized body ache along with nausea and decreased appetite. No history of abdominal pain, abdominal distention, vomiting, hematemesis, malena, hematochezia, or hematuria was provided. There was no history of any bone pains, drug intake, or recent travel. The child was immunized for age and developmentally normal. Birth history, family history, and past history were unremarkable. On examination, she was conscious, afebrile and ecchymotic patches seen over the elbow joint and legs with bleeding gums; severe pallor was present; however, no clubbing, cyanosis, lymphadenopathy, or bony tenderness was noted. Height was 114 cm (between 0 and +2 standard deviation [SD]) and weight was 22 kg (between +1 SD and +2 SD); body mass index was 17.05 (at + 1 SD). Abdominal examination revealed hepatomegaly 4 cm with liver span of 10 cm, and spleen of 3 cm below the left subcostal margin, and other systems were normal. On evaluation, her rapid tests of dengue, malaria, and leptospirosis were negative. Her complete blood count showed hemoglobin 8.1 gm/dL, platelet 15,000/cubic mm, and total leukocyte count 2300/cubic mm, with absolute neutrophil

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count 1380/cubic mm. Her blood culture showed no growth, chest X-ray normal, with liver enzymes SGOT - 17 U/L, SGPT - 20 U/L, serum bilirubin - 0.3 mg/dL and renal function with BUN - 16 mg/dL, and serum creatinine - 0.4 mg/dL. Prothrombin time was 14 seconds, with international normalized ratio of 1.0. Serial hemogram was suggestive of persistent cytopenia, involving all three cell lineages. Bone marrow examination revealed increased macrophage activation and hemophagocytic macrophages on histopathology [Figure 1]. On further evaluation, serum ferritin levels were 3247.73 ng/mL (normal range 7–140 ng/mL), serum triglycerides 360 mg/dL (150–200 mg/dL), and serum fibrinogen 327.6 mg/dL (150–350 mg/dL); hence, criteria for HLH were fulfilled. To rule out other causes of secondary HLH, Human immunodeficiency virus ELISA, hepatitis B surface antigen, and hepatitis C virus IgM/IgG antibody, Epstein–Barr virus DNA polymerase chain reaction (PCR), and parvovirus PCR tested negative. Flow cytometry for HLH revealed lymphocyte subpopulation of CD56 + NK cells, showing perforin expression of 98% (control - 86%) and CD107a expression of 33% (control - 24%). She was diagnosed with hemophagocytic syndrome with no family history of the same. She was empirically given ceftriaxone for 7 days, fever subsided on day 3 of admission, and after diagnosis of HLH, she was started on dexamethasone and etoposide. The patient was discharged and regularly followed up weekly as per the treatment protocol.

Fourteen days into this treatment, she presented with fever for 2 days and vomiting, headache, and neck stiffness for 1 day. On evaluation, activity was depressed , febrile (temperature – 39°), heart rate 160/min, regular, respiratory rate 30/min, peripheral pulses well felt, BP was 120/70 mm of Hg (more than 99th centile for age), with photophobia present. On CNS examination, higher mental functions, memory, and speech were intact with no cranial nerve deficit. No hypo or hypertonia was noted and power was 5/5, but deep tendon reflexes were brisk with flexion on plantar reflex. Kernig's sign and Brudzinski's sign were present along with neck rigidity. No cerebellar or sensory involvement was noticed. Her blood counts were 18,400/cubic mm (granulocyte - 73.3% and lymphocyte - 21.2%), hemoglobin - 9.2 gm/dL, and platelet – 325,000/cubic mm. Serum electrolytes were as follows: sodium - 146 mEq/L, potassium - 4.5 mEq/L, and chloride - 101 mEq/L. On fundus examination, possibility of papilledema was ruled out. Cerebrospinal fluid (CSF) examination was performed with a total of 150 cells seen showing 80% lymphocytes and 20% neutrophils with proteinaceous material, CSF protein - 172 mg/dL, sugar - 28 mg/dL, and corresponding random blood sugar - 90 g/dL; on Gram staining, it showed no organism. Computed tomography (CT) scan brain was suggestive of leptomeningeal enhancement and bilateral lateral ventricular dilatation with nonobstructive hydrocephalus [Figure 2].

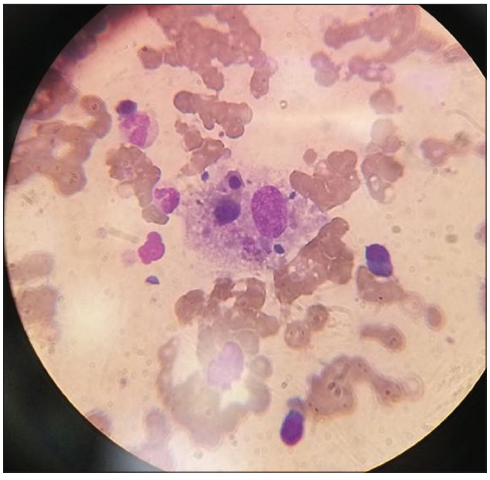

Figure 1: Bone marrow histopathology suggestive of hemophagocytosis

Anticerebral edema measures were undertaken with raised head-end, intravenous fluids and loaded with mannitol to reduce intracranial pressure. Empirical antibiotic therapy was started for meningitis with ceftriaxone (100 mg/kg/day in 2 divided doses) and dexamethasone. Complete tuberculosis workup was normal. CSF culture showed growth of *Salmonella typhi* sensitive to ampicillin, cotrimoxazole, chloramphenicol, ceftriaxone, and azithromycin. Widal test revealed antibody titer of 1:160 for O antigen and 1:320 for H antigen for *S. typhi*. On prolonged incubation, blood culture showed growth of *S. typhi* after 14 days of incubation, with no growth in urine and stool. Stool culture of family members was negative. Ceftriaxone was given for a total of 28 days, and the patient responded with the resolution of fever on the 3rd day of admission and meningeal signs on the 5th day of admission. Repeat CSF examination on day 14 showed no cells on microscopy and showed CSF protein - 25 mg/dL and CSF sugar - 75 mg/dL on routine examination. CSF culture did not grow any organism. On follow-up after 1 month, no focal neurological deficit or convulsion was noted. After 3 months, pure tone audiometry was normal and CT brain revealed complete resolution of previous changes.

Discussion

The pathophysiology of infection-associated hemophagocytosis is poorly understood, but it is suggested to be due to

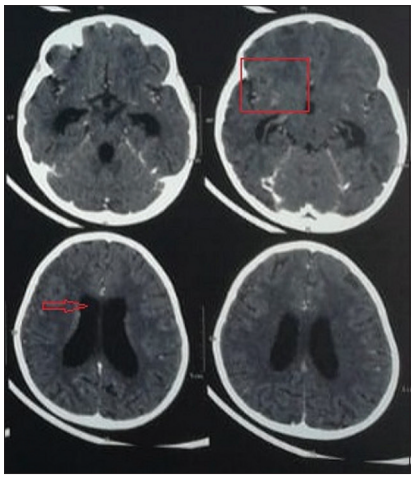

Figure 2: Computed tomography brain axial section. Box showing leptomeningeal enhancement. Arrow showing bilateral lateral ventricular dilatation

hypersecretion of the cytokines by persistently activated lymphocytes and histiocytes. Specific genetic polymorphisms in major histocompatibility complex class II and III genes have also been found in individuals with severe typhoid fever.[5] HLH is a disease with major diagnostic and therapeutic difficulties. HLH comprises two different conditions that may be difficult to distinguish from one another: a primary and a secondary form. Secondary HLH (sHLH) may develop due to strong immunological activation of the immune system, which may, for example, be caused by a severe infection [Table 1].[6]

Hemophagocytic syndrome associated with pyogenic bacteria can sometimes carry a better prognosis than virus-associated hemophagocytic syndrome. Infections with *Campylobacter*, *Fusobacterium*, *Mycoplasma*, *Chlamydia*, *Legionella*, *Rickettsia*, *Brucella*, *Ehrlichia*, etc., as well as typhoid and Lyme disease, have been identified in patients with hemophagocytic syndrome.[7,8] To the best of our knowledge, there are six cases of sHLH as a complication of typhoid fever by *S. typhi* reported in the pediatric population.[9] Thorough literature search did not reveal similar case with rare associations of this dual complication of meningitis and hemophagocytosis in the same patient. In our case, salmonellosis presented with HLH as a primary complication followed by meningitis later on. Risk factors for meningeal salmonellosis include corticosteroid therapy, malnutrition, infancy, old age, chemotherapy, and radiotherapy.[10] For successful treatment of salmonellosis, therapy with high dose of third-generation cephalosporins for 4 weeks should be given to prevent recurrence of infection. It has proven to reduce mortality rate to 6% and relapse rate to nil.[4]

Association of *S. meningitis* with infection-induced hemophagocytosis is a very rare entity. Detailed evaluation and thorough examination including bone marrow aspirate culture should be performed for early diagnosis. Early and accurate diagnosis of HLH is necessary for the administration of immunosuppressive drugs including steroids, cyclosporine, and etoposide for complete and early recovery. As specific treatment for each of these complications is completely different, a high index of suspicion and prompt diagnosis is mandatory.

Table 1: The diagnosis hemophagocytic lymphohistiocytosis can be established if one of either 1 or 2 below is fulfilled

A molecular diagnosis consistent with HLH
Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)
Initial diagnostic criteria (to be evaluated in all patients with HLH)
Fever
Splenomegaly
Cytopenia (affecting 2 of 3 lineages in the peripheral blood)
Hemoglobin <90 g/L (in infants <4 weeks: hemoglobin <100 g/L)
Platelets $<100\times10^9$/L
Neutrophils $<1.0\times10^9$/L
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides ≥3.0 mmol/L (i.e., ≥265 mg/dL)
Fibrinogen ≤1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes; no evidence of malignancy
New diagnostic criteria
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin ≥500 μg/L
Soluble CD25 (i.e., soluble IL-2 receptor) ≥2400 U/mL

HLH: Hemophagocytic lymphohistiocytosis, IL-2: Interleukin-2

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the guardian has given his consent for his daughter's images and other clinical information to be reported in the journal. The guardian understands that no names and initials will be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Research quality and ethics statement

The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines, notably the CARE guideline, during the conduct of this report.

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Conflicts of interest

There are no conflicts of interest.

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