Infect Dis Trop Med 2023;9: e1060

Hyperinflammatory syndrome with enteric fever: a diagnostic challenge in the post COVID-19 era

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ABSTRACT:

— ***Background:*** *Despite the availability of effective vaccines, enteric fever continues to impart considerable morbidity in developing countries, especially among children. Coronavirus disease-2019 (COVID-19) has changed the approach to acute febrile illness in children since the onset of the pandemic. The similarities of complicated enteric fever and the multisystem inflammatory consequence of COVID-19 warrant discussion as elucidated in the case report here.*

— ***Case presentation:*** A previously healthy 11-year-old girl was referred to our centre with enteric fever with mucosal inflammation followed by encephalopathy, cytopenia, elevated inflammatory markers, rhabdomyolysis. Although she was not vaccinated, she had antibodies against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). She responded to intravenous ceftriaxone and intravenous immunoglobulin infusion.

— ***Conclusions:*** *The clinical overlap among infection-associated hemophagocytic lymphohistiocytosis, multisystem inflammatory syndrome in children and Kawasaki disease represented a diagnostic challenge. Knowledge of these entities and their complications is essential to aid in early diagnosis and appropriate timely management.*

— ***Keywords:*** *Enteric fever, Hemophagocytic lymphohistiocytosis, Multisystem inflammatory syndrome, Kawasaki disease, Intravenous immunoglobulin.*

INTRODUCTION

Enteric fever comprises typhoid fever caused by *Salmonella typhi* and paratyphoid caused by *Salmonella paratyphi A* and *B*, transmitted by the ingestion of contaminated food or water. The illness presents with fever, vomiting, diarrhea, abdominal pain, anorexia, hepatosplenomegaly and cytopenias. Effective antibiotic therapy is available to treat the disease. However, in some instances, children develop complications of enteric fever like shock, encephalopathy or infection associated hemophagocytic lymphohistiocytosis (HLH). Coronavirus disease-2019 (COVID-19) is caused by a respiratory virus named "severe acute respiratory syndrome coronavirus-2" (SARS-CoV-2). It causes respiratory illness of varying severity in children. Common clinical features noted during the acute phase of COVID-19 in children include fever, cough, sore throat, fatigue, headache, myalgia, loss of smell or taste, wheeze, breathing difficulty, abdominal pain, vomiting and diarrhea. The post-infectious complication which follows the acute phase of COVID-19 by a few weeks, termed multisystem inflammatory syndrome in children (MIS-C) shares several common features with HLH secondary to many infections, including enteric fever. A good understanding of the clinical features and prompt management of these illnesses are essential.

CASE PRESENTATION

A 11-year-old girl presented to our hospital, MGM Healthcare, located in Chennai city, in the southern part of India, on the 9th day of her illness. She had developed

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redness of eyes and mouth which lasted until day 3 of her illness and then faded. On the first day of her illness, she passed loose stools thrice, but the stool consistency was normal from the next day. By day 4, she had high grade, intermittent fever combined with poorly localized moderately severe abdominal pain and occasional dry cough. She experienced severe pain all over her body including in all her joints by day 6, which progressively worsened to the extent of requiring assistance to move around within her home. There was no history of joint swelling. The next day, she developed mood changes causing decreased interaction and lethargy interspersed with episodes of aggressive behavior. Her speech was eventually incoherent and irrelevant. She was managed symptomatically (paracetamol for fever and body pain, antihistamine for cough, and intravenous fluids due to poor oral intake) for a day before being referred to us. She had not been vaccinated for SARS-CoV-2. On examination in our Hospital, she was well nourished with weight and height between 50th-75th centiles for age. No rash or bleeds were demonstrable. She was well hydrated, hemodynamically stable, her respiratory parameters were normal and abdominal examination did not reveal organomegaly. She was drowsy and responded to queries predominantly by nods and gestures and rarely by appropriate single words. Pupils were bilaterally 4 mm in size and reacted well. Although no focal deficits were apparent, lower limbs were mildly hypertonic and plantar reflex response was extensor. On insertion of Foley's catheter, urine was witnessed to be high colored.

Considering her clinical background, dengue, multi-system inflammatory syndrome in children (MIS-C), other tropical infections like enteric fever or scrub typhus, severe sepsis with meningitis and incomplete Kawasaki disease (KD) were considered as possible diagnosis. After collecting blood samples for cultures, she was started on intravenous ceftriaxone (100 mg/kg/day), apart from supportive care. She was on continuous monitoring in high dependency unit. Preliminary investigations revealed leukopenia, thrombocytopenia, elevated C-reactive protein (CRP), mildly elevated liver enzymes (alanine transaminase: 211 U/l, aspartate transaminase: 48 U/l), normal renal functions, electrolytes and coagulation profile. Typhoid IgM antibody and dengue NS1 antigen and IgM antibody, all processed by ELISA (Abbott Laboratories, IL, USA), were reported negative. Brain MRI with contrast performed on the same day revealed no evidence of meningeal enhancement or focal lesions. Routine urine analysis tested positive for blood by dipstick, which was not confirmed by microscopic examination. Serum creatine kinase (679 U/l; range: 34-145), triglycerides (282.6 mg/dl; range: <200 mg/dl), D-dimer (10,455 ng/ml; range: <250 ng/ml) and ferritin levels were elevated, whereas fibrinogen level (170 mg/dl; range: 238-498) was low. Leptospirosis, scrub typhus, *brucella* and mycoplasma serologies turned out to be negative. Echocardiography showed normal diameter of coronary arteries and optimal functioning of both the ventricles, and normal serum level of pro brain natriuretic peptide (pro-BNP) was registered. Ultrasound abdomen revealed splenomegaly, but spleen was not clinically palpable. Although no prior history of coronavirus disease-2019 (COVID-19) was referred, the patient presented to our attention six weeks after the Omicron variant local peak. Further, anti-SARS-CoV-2 IgG antibodies in blood were reported positive, while reverse transcriptase polymerase chain reaction test in nasopharyngeal and throat swabs for COVID-19 was reported negative. The constellation of clinical and biochemical findings made it imperative to consider a diagnosis of MIS-C. Progressive thrombocytopenia was noted eventually. Her encephalopathy continued to worsen by the second day of hospitalization. Owing to normal brain MRI and progressive thrombocytopenia, lumbar puncture was deferred. She was treated with intravenous immunoglobulin infusion on day 2 at a dose of 1.5 g/kg over 12 hours considering MIS-C as a strong possibility. She responded well to that, with improvement in her sensorium and interaction. On day 3 of hospital stay, *Salmonella typhi* was isolated from her blood culture (automated Bact/Alert with drug sensitivity analysis performed by disc diffusion method), and it was sensitive to cephalosporins and resistant to fluoroquinolones. With continuation of ceftriaxone, by the fourth day in the Hospital, she turned afebrile, was well oriented and able to ambulate for short distances. Repeat blood investigations showed increasing leucocyte and platelet counts with fall in serum ferritin and CRP levels. Bone marrow analysis was deferred due to this improvement. Her activity, oral intake and mobility improved, and she was discharged home on the sixth day. She was advised to take oral cefixime in the appropriate dose (1,200 mg/day in two divided doses) to target *Salmonella typhi*. Follow-up blood investigations confirmed progressive increase in platelet count with fall in CRP and ferritin levels (Table 1). Repeat echocardiography at 4 weeks after discharge was confirmed normal and she was administered typhoid conjugate vaccine at 6 weeks after discharge. She had no further recurrences of any symptoms during her follow-up for 3 months (Table 1).

DISCUSSION

This child's case scenario provided a unique insight into the clinical dilemma in the post COVID-19 era, especially in tropical countries where various infections continue to be endemic. The diagnosis in this child proved to be a challenge because of the overlapping features of several different entities. The presence of enteric fever was certain, as the same was proven in blood culture, which is the gold standard for establishing the diagnosis. A severe presentation of enteric fever could account for most of the features in this child. A co-existent complication of infection associated hemophagocytic lymphohistiocytosis (HLH) was considered due to the cytopenia (most prominent being thrombocytopenia, but there was evidence of leukopenia and anemia, although their severity did not conform to the diagnostic criteria), splenomegaly noted in ultrasound, hyper ferritinemia, hypertriglyceridemia and hypofibrinogenemia. As bone marrow examination was not performed in this child,

Table I. Serial investigation reports counted from the day of hospitalization (which was the ninth day of the illness) demonstrating the changes in blood cell counts and inflammatory parameters. Intravenous antibiotic was started on day 1 and immunoglobulin infusion was administered on day 2 for this child who presented to us with an acute febrile illness with red eyes and encephalopathy.

Test	Day 1	Day 2	Day 3	Day 4	Day 5	Day 15	Day 30
Hb (g/dl)	10.4	10.7	10.4	9.7	10.5	10.5	11.1
WBC (x 1,000/µl)	2.37 (N83 L15)	4.12 (N80 L16)	2.59 (N64 L30)	3.58 (N56 L40)	10.18 (N34 L61)	9.0 (N30 L60)	9.69 (N42 L51)
Platelets (x 1,000/µl)	90	67	56	65	105	344	536
CRP (mg/l)	167.5	133.7	59.20	57.9	48.7	15.43	8.59
Ferritin (ng/ml)		33790	18595		7495	1005	285.8

Hb: Haemoglobin, WBC: White blood cell count, N: Percentage of neutrophils, L: Percentage of lymphocytes, CRP: C-reactive protein, Lab range of CRP: <5 mg/l, Lab range of Serum ferritin: 13-150 ng/ml.

definitive evidence of haemophagocytosis could not be demonstrated. Soluble CD25 and natural killer cell activity were not evaluated in this child. HLH has been reported[1,2] to occur due to a wide variety of viral, bacterial, protozoal and fungal infections apart from inflammatory disorders and malignancies. At least 7 cases of HLH in children secondary to *Salmonella typhi* infection have been reported[1,2] in literature. While antibiotic therapy is sufficient in some children, there is a need for immunomodulatory agents like intravenous immunoglobulin (IvIg), steroid or chemotherapeutic agents in others. A close differential diagnosis in this child was MIS-C (or its Kawasaki variant) considering the timing of presentation (about 6 weeks following the peak transmission of Omicron variant of COVID-19) and presence of antibody against SARS-CoV-2 in the blood. Presence of conjunctival congestion, oral erythema, prolonged fever, thrombocytopenia, low absolute lymphocyte count, encephalopathy, gastrointestinal symptoms at disease onset were in favor of this hypothesis[3]. Although thrombocytosis is characteristic of Kawasaki Disease (KD), thrombocytopenia can occur in the first 2 weeks of the illness and might be a harbinger of disseminated intravascular coagulation and coronary artery abnormalities, both of which were fortunately not described in this case[4]. HLH and KD are considered to be manifestations of cytokine storm triggered by various stimuli, including infection. It might be difficult to differentiate between HLH and KD on a clinical basis. However, a higher ratio of interferon gamma to tumor necrosis factor would more likely suggest HLH[5]. In the presence of a clinical diagnostic dilemma among HLH, MIS-C and KD, when an infectious etiology is yet to be definitively ruled out, but the clinical condition (like worsening encephalopathy) warrants a timely intervention for immunomodulation, it is prudent to consider a safer option like intravenous immunoglobulin rather than steroids or chemotherapeutic agents. The latter may result in immunosuppression and exacerbation of the infection.

Urine testing positive for blood by dipstick but not confirmed by microscopy, along with severe myalgia and moderate elevation of creatine kinase pointed towards a possible rhabdomyolysis, which has been described with enteric fever before. The proposed mechanism for rhabdomyolysis is tissue hypoxia secondary to sepsis, toxemia, direct bacterial invasion of muscle and altered muscle metabolic capacity[6]. A combination of typhoid, HLH and rhabdomyolysis has also been reported[7] in an adult. Neurological manifestations, although well described with typhoid encephalopathy, have also been described in MIS-C due to neuroinflammation resulting from post-infectious immune dysregulation or secondary injury from systemic inflammation. Altered consciousness and fatigue noted in this child have been among the commonly noted neurological abnormalities in MIS-C[8].

CONCLUSIONS

Although enteric fever is a common tropical infection, complications of the disease might mimic other pathologies. Clinicians should consider MIS-C, KD and HLH as differential diagnosis in a child presenting in the COVID-19 era with mucosal inflammation, prolonged fever, multisystem involvement, cytopenia and hyperinflammation blood markers. When there is insufficient time to wait for a confirmed diagnosis, intravenous immunoglobulin might serve as a safe and useful choice. A close follow-up to look for possible complications, especially the dilatation of coronary arteries, is necessary. Immunization against enteric fever is essential to ensure sustained long-term protection from recurrence.

Informed Consent:

An informed consent was obtained from the parents of the described child.

Ethics Approval:

The case report article was approved by the Hospital Ethics Committee for publication.

Acknowledgements:

The authors acknowledge the co-operation of the child and her parents throughout their difficult times, the contribution of the nurses and other healthcare staff who played a vital role in the care of this child and the specialists (paediatric cardiologist, paediatric hemato-oncologist and pathologist) involved in her care.

Funding:
No funding was received from any organizations for this research work.

Authors' Contributions:
AS and NMN were involved in the day-to-day care of the child and follow-up. AS conceived the report and compiled the first draft while NMN performed the literature search and proof-read the article.

Conflict of Interest:
None.

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