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CASE REPORT

Fever of unknown origin: An atypical presentation of typhoid in a child with glucose-6-phosphate dehydrogenase (G6PD) deficiency

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ABSTRACT

Typhoid is an acute febrile illness primarily caused by *Salmonella* enterica serotype typhi (*S.* Typhi) which could be challenging to diagnose in children, owing to its non-specific clinical signs and symptoms which may resemble other febrile illnesses. Here, we present a case of typhoid which was atypically presented as fever of unknown origin (FUO) in a two-year-old boy with underlying glucose-6-phosphate dehydrogenase (G6PD) deficiency. This child was initially diagnosed and managed as acute tonsillopharyngitis, however remained febrile despite medications. A series of investigations were performed and *S.* Typhi was isolated from the bone marrow culture after almost a month of admission. The antibiotic was started based on antibiotic susceptibility testing and he recovered well. Our case underscores the challenges of diagnosis establishment and clinical management of typhoid in paediatric patients who has underlying disease and emphasizes the importance of having high index of clinical suspicion to ascertain timely and proper diagnosis.

Keywords: Typhoid; fever of unknown origin (FUO); *Salmonella* typhi; children; Malaysia.

INTRODUCTION

Typhoid is a potentially fatal multisystemic infection, primarily caused by *Salmonella enterica* serotype Typhi (*S.* Typhi). It manifests in a variety of ways ranging from sepsis to low grade fever, abdominal pain and diarrhoea. In typhoid, blood and stool cultures may not yield any growth, hence without appropriate targeted antibiotic therapy, the fever would be prolonged and may be regarded as fever of unknown origin (FUO).

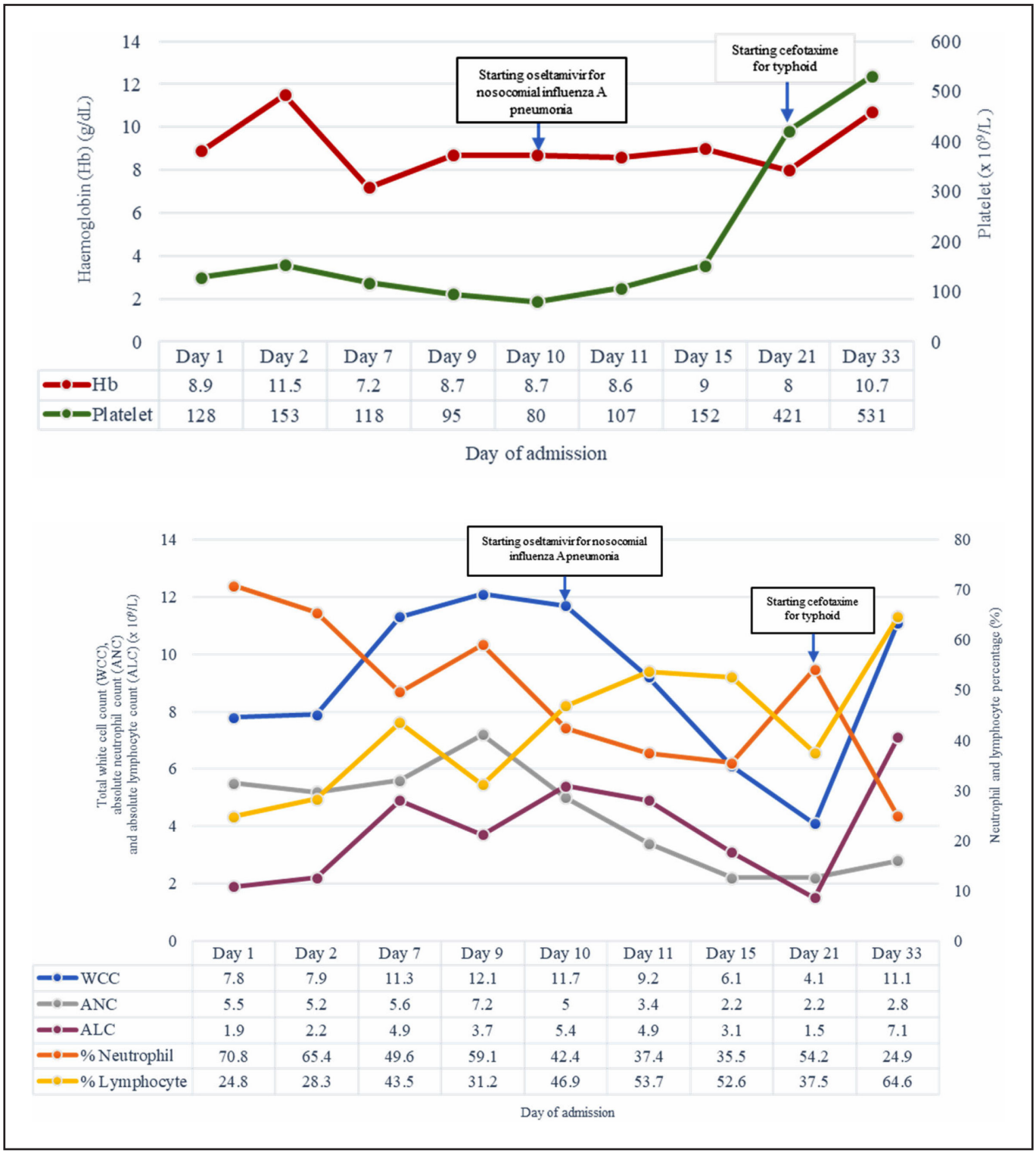
CASE REPORT

A two-year-old boy with G6PD deficiency presented with fever and reduced oral intake for six days associated with four episodes of loose stool (Bristol type 7) over two days. The child was born at term, his expected developmental milestones were achieved, and his immunizations were up to date according to the Malaysian schedule. He had moderate Class III G6PD deficiency (level of residual G6PD enzyme activity 32.31%) with no episode of acute haemolytic anaemia previously and this was his first hospitalization. Based on his current symptoms, he was initially diagnosed as having acute tonsillopharyngitis by a general practitioner. Syrup amoxicillin 30mg/kg BD and paracetamol 15mg/kg QID were prescribed for three days; however, his symptoms were not improved despite medications.

He was brought to the emergency department and physical examination revealed that he appeared pink with no jaundice, had warm peripheries, moist mucosa, with no sunken eyes. His capillary refilling was less than two seconds with body temperature of 40.2°C. He was having tachycardia (145 beats per minute) with normotensive blood pressure (93/66 mmHg). He had a regular respiration rate (27 breaths/minute) with no intercostal recession. His oxygen saturation was 98% at room air. His throat was inflamed with enlarged tonsil without exudative discharge. Abdominal examination revealed normal findings with no evidence of organomegaly. Review of other systems was unremarkable. Initial blood tests showed anaemia (haemoglobin: 8.9 g/dL), thrombocytopaenia (platelet: 128 x 10^9/L) with normal total white cell count for his age (TWC: 7.8 x 10^9/L) as well as elevated level of c-reactive protein (CRP: 71.8 mg/L). Deranged renal profile with hyponatremia (sodium: 122 mmol/L) and hypokalaemia (potassium: 2.7 mmol/L) was also noted while liver function test was not done initially. Based on the clinical history, physical examination and initial laboratory findings, a preliminary diagnosis of acute tonsillopharyngitis with parenteral diarrhoea was made. Intravenous fluid rehydration and C-Penicillin 50000unit/kg stat then QID were commenced.

In the ward, he had been having persistent fever despite the treatment given. His clinical course was further complicated with worsening anaemia and the lowest haemoglobin was 7.2 g/dL on day 7 of admission (Figure 1). He received 20ml/kg packed cell transfusion and serial peripheral blood films revealed normochromic, normocytic anaemia and occasional blister cells suggestive of oxidative haemolysis, true thrombocytopaenia, and neutrophilia with toxic granulation and reactive lymphocytes consistent with underlying infection or inflammation. The lactate dehydrogenase (LDH) which is a sensitive but non-specific marker for haemolysis was high at 509 u/L and antiglobulin (Coombs) test was negative. The impression based on the findings was acute haemolytic anaemia secondary to G6PD deficiency with underlying ongoing infection.

During the second week of his in-patient stay, he had a new onset of cough and rhinorrhoea, therefore nasopharyngeal aspirate was sent for respiratory virus antigen screening and resulted positive for Influenza A. This child was then treated for nosocomial influenza A pneumonia with syrup oseltamivir 30mg BD for ten days. Notably, his total white cell count was reducing in trend and there was a shift to lymphocyte predominance during this episode (Figure 1). Even so, the incessant spiking fever episodes continued despite



	Day 1	Day 2	Day 7	Day 9	Day 10	Day 11	Day 15	Day 21	Day 33
Hb	8.9	11.5	7.2	8.7	8.7	8.6	9	8	10.7
Platelet	128	153	118	95	80	107	152	421	531

	Day 1	Day 2	Day 7	Day 9	Day 10	Day 11	Day 15	Day 21	Day 33
WCC	7.8	7.9	11.3	12.1	11.7	9.2	6.1	4.1	11.1
ANC	5.5	5.2	5.6	7.2	5	3.4	2.2	2.2	2.8
ALC	1.9	2.2	4.9	3.7	5.4	4.9	3.1	1.5	7.1
% Neutrophil	70.8	65.4	49.6	59.1	42.4	37.4	35.5	54.2	24.9
% Lymphocyte	24.8	28.3	43.5	31.2	46.9	53.7	52.6	37.5	64.6

Figure 1. Trend of full blood count.

prescription of antiviral and multiple courses of antibiotics (Table 1). Moreover, his liver function test was deranged with raised alanine transaminase (ALT:196 u/L) and aspartate aminotransferase (AST:169 u/L), implicating of transaminitis. Abdominal ultrasound was done and showed homogenous, normal size liver for age with smooth outline and no evidence of intra-abdominal focal lesion or collection. Echocardiogram was performed twice and revealed normal cardiac structure and function without vegetation. Extensive investigations including infective screening were also performed to elucidate the cause of FUO (Table 2).

The high-grade fever persisted until the fourth week of admission hence a bone marrow aspirate (BMA) was collected to elicit the cause of FUO. The BMA was sent for histopathological examination and culture and sensitivity (C&S) test. The histopathological examination of the BMA showed hypocellular marrow with an increase in erythropoiesis possibly secondary to peripheral destruction such as haemolysis. There was an increase in megakaryopoiesis which was likely due to underlying reactive causes such as infection. While C&S of the BMA revealed a gram-negative bacilli and non-lactose fermenter organism. This organism was identified as *S.* Typhi after 18 hours of incubation, by matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF Bruker MS Biomerieux). The isolate was confirmed as *Salmonella* (ser Typhi) by Bacteriology Unit Laboratory, Institutes for Medical Research, National Institutes of Health, Malaysia. Antimicrobial susceptibility testing showed susceptibility towards ceftriaxone, ciprofloxacin, trimethoprim-sulfamethoxazole and ampicillin.

After the microbiology result was available, further contact history was taken from the parent and caretaker. There was a history that the patient's elder brother was diagnosed as having typhoid two years prior to this patient's admission. Furthermore, it was eventually discovered that the patient had attended a family gathering two months prior to admission. Two other family members who were also in attendance, consecutively were diagnosed with typhoid. Following this, the parent and caretaker were screened for typhoid and the results were all negative. A final diagnosis of typhoid was made after considering his clinical presentation, contact

Table 1. Summary of prescribed antimicrobial therapies during admission

Antimicrobial	Indication	Duration	Week 1	Week 2	Week 3	Week 4	Week 5
IV C-Penicillin 50000unit/kg/dose QID	Empirical: Acute tonsillopharyngitis	6 days					
IV Cefuroxime 100mg/kg/day	Empirical: Cover for pneumonia	7 days					
Syrup Oseltamivir 30mg BD	Nosocomial Influenza A pneumonia	10 days					
Syrup Cloxacillin 50mg/kg/day	Empirical: Thrombophlebitis	3 days					
IV Augmentin 30mg/kg/dose TDS	Empirical: Cover for secondary bacterial infection	7 days					
IV Cefotaxime 50mg/kg/dose TDS	*Salmonella* Typhi (Typhoid fever)	14 days					

Abbreviation: IV, intravenous; BD, twice a day; TDS, three times a day; QID, four times a day.

Table 2. Summary of investigations

Test	Result
Blood culture (2 pairs collected in separate time)	No growth
Bone marrow culture	*Salmonella* Typhi
Urine culture	No growth
Urine FEME	Protein 1+/Leucocyte negative/Nitrite negative
Stool for rota virus and adenovirus	Negative
NPA for Respiratory Viruses	Influenza A
Epstein-Barr virus IgM	Negative
Parvovirus IgM	Negative
Leptospira IgM	Negative
Mycoplasma antibody	Negative
Rickettsia IIP IgM/IgG	No evidence of infection
Infective screening (HIV/HBV/HCV)	Not reactive
TB Workout: Gastric lavage AFB x3	No acid fast bacilli seen
Gene Xpert MTB	Not detected
Mantoux	No induration
Immunoglobulin	IgG: 15.23g/L (Normal value: 3.17-9.97) IgA: 2.0g/L (Normal value: 0.2-1.0) IgM: 1.52g/L (Normal value: 0.19-1.46)
C3/C4	C3: 1.15g/L (Normal value: 0.90-1.80) C4: 0.4g/L (Normal value: 0.10-0.40)
Echocardiogram	Normal cardiac structure and function, no vegetation and minimal pericardial effusion noted
Ultrasound Abdomen	No sonographic evidence of intrabdominal focal lesion or collection.

Abbreviations: AFB, acid fast bacilli; FEME, full examination and microscopic examination; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IIP, Indirect immunoperoxidase; NPA, nasopharyngeal aspirate; TB, tuberculosis.

history and the laboratory investigation results. The cefotaxime 50mg/kg TDS was administered intravenously for two weeks. His fever subsided with stable haemoglobin level, normalized platelet count, and normal liver and renal function. The child was well upon discharge.

DISCUSSION

Typhoid is predominantly endemic in low and middle-income countries with incidence varies substantially between countries. Based on the World Health Organization (WHO) estimation, the highest incidence occurred in South-East Asian (306 cases per 100,000 persons), followed by Eastern Mediterranean and African regions (Hancuh *et al*., 2023). In endemic countries, typhoid is more frequent in infants, preschool age and school age children than in adults (Owais *et al*., 2010). In Malaysia, even though the annual incidence rate has been decreasing, typhoid remains endemic (Health Informatics Centre, 2024). Living in an endemic country with age falls into the susceptible group, making our patient at high risk of acquiring typhoid.

Typhoid is caused primarily by *Salmonella enterica* serotype Typhi (*S.* Typhi), gram-negative, facultatively anaerobic bacilli belonging to the family Enterobacterales. They are host-restricted to humans and there is no known zoonotic reservoir. The transmission of *S.* Typhi is predominantly through faecal-oral route with human transmission occurs when the bacteria enter the digestive tract via contaminated water or food. In our case, a short-cycle transmission is more likely to have occurred, contributed by faecal shedding in the immediate environment of the patient. The shedding probably originated from the patient's elder brother or other family members who attended the recent gatherings. The faecal shedding may contaminate a common source of water or food in which the transmission would be further facilitated and sustained through poor hygiene and sanitation practices.

Typhoid is characterised by an incubation period of one week or more, with prodromal symptoms including abdominal pain, constipation or diarrhoea, followed by the onset of fever (Eng *et al.*, 2015). A study in 112 children, reported that typhoid commonly presented with fever more than five days (98.2%), gastrointestinal symptoms such as vomiting (39.3%), diarrhoea (26.8%) and abdominal pain (21.43%) as well as hepatomegaly (16.1%). Laboratory findings that have been reported in children with typhoid are including anaemia (42.86%), thrombocytopaenia (14.3%), hyponatraemia (12.5%), hypokalaemia (8.9%) and transaminitis (30.4%) (Behera *et al*., 2021). Thrombocytopaenia is a relatively common finding in typhoid either as a presenting symptom or as a complication. The mechanism is not entirely understood but it has been proposed to be due to bone marrow suppression, peripheral destruction of thrombocytes by the reticuloendothelial system, autoimmune-induced destruction, and *Salmonella* endotoxin-induced thrombocytopaenia (Al Reesi *et al*., 2016). Fever, abdominal pain, diarrhoea, deranged renal and liver functions and bicytopaenia were exhibited in this case. These were non-specific findings and may overlap considerably with other causes of acute febrile illnesses leading to low index of suspicion for typhoid.

G6PD deficiency is the most prevalent X-linked recessive inherited genetic enzymopathy worldwide and G6PD enzyme is essential in preventing cellular damage from reactive oxygen species mainly in erythrocytes and for immune system function particularly in key phagocytes effector function. G6PD deficiency may have impact on susceptibility to infection and increased risk for bacteraemia and sepsis. This has been reported among G6PD-deficient patients for intracellular pathogens including *S.* Typhi as well as *Rickettsia* sp. and *Toxoplasma gondii* (Shah *et al*., 2024). Infection is also known as the most commonly reported causes of acute haemolytic anaemia in patients with G6PD deficiency, attributed to an increased production of reactive oxygen species through the inflammatory response. The interplay between G6PD deficiency as a risk factor for the patient to be susceptible to typhoid coupled with faecal shedding that facilitate the transmission and retain the source of infection establishes the pathogenesis of infection in the present case.

Moreover, our patient was presented with persistent fever during admission which meets the criteria for FUO. To date, FUO is defined as a body temperature above 38.3°C, at least once a day, for more than eight days in a child evaluated by the paediatrician with inconclusive history, physical examination, and first-level investigations (Trapani *et al*., 2024). There is no standard process to investigate the aetiology of FUO, neither in adults nor in paediatric. Nonetheless, the four-stage investigative protocol may be utilised as a framework to identify the aetiology as demonstrated in this case. Stage 1 incorporates careful history taking, physical examination and screening tests, stage 2 consists of reviewing the history, repeating physical examination, perform specific diagnostic tests and non-invasive investigations, stage 3 requires performing the indicated invasive tests including bone marrow assessment and stage 4 involves the prescription of therapeutic trials (Dockrell *et al*., 2019). A study in paediatric patients with FUO, revealed that the causes were identified in 45.6%, 35.4%, 16.5% and 2.5% in stage 3, 2, 4 and 1 respectively using the four-stage investigative protocol (Chien *et al*., 2017). Other studies have shown that the most common causes of paediatric FUO are infectious diseases followed by connective tissue diseases and malignancies. Typhoid has been reported as one of the common infectious aetiologies for FUO in children in addition to tuberculosis, leptospirosis, and rickettsial diseases (Hassan *et al*., 2014; Chien *et al*., 2017).

Isolation of *S.* Typhi from culture (blood, bone marrow or other sterile sites) is the gold standard for diagnosis of typhoid. Bone marrow aspirates culture have been established to be more sensitive than peripheral blood culture, as demonstrated by this case. It has been suggested that the proportion of *S.* Typhi intracellularly in the bone marrow is ten times higher than in the peripheral blood. Therefore, a significantly larger volume of blood for culture would be needed to match the positivity rate of a smaller volume of bone marrow aspirate (Mogasale *et al*., 2016). Furthermore, the viable *S.* Typhi counts in the bone marrow were considerably less affected by antimicrobial consumption and may remain positive for up to five days or longer after starting antibiotic treatment (Crump *et al*., 2015). A study by Jha *et al.,* (2009) revealed that of 57 FUO cases, *S.* Typhi was the most frequently isolated organism from bone marrow comparing to its paired blood cultures. However, in view of bone marrow aspiration invasive sampling, its culture is not routinely performed for initial evaluation. Another common non-invasive test is stool culture, which relatively demonstrated reduced sensitivity (31.3%) but high specificity (91.5%) (Mawazo *et al*., 2019).

In Malaysia, ceftriaxone or ciprofloxacin for five to seven days are recommended for treatment of uncomplicated typhoid, in view of quinolone resistance in our local setting (Ministry of Health, 2024). However, in this patient, cefotaxime was used owing to his low serum albumin. As ceftriaxone is a highly protein-bound antibiotic, low serum albumin will increase the unbound fraction of the drug. These would reduce the antibacterial exposures that might compromise the pharmacodynamic targets (Ulldemolins *et al*., 2011).

CONCLUSION

Typhoid is an important treatable cause that must be excluded in children with FUO. A four-stage protocol is recommended for evaluation of children with FUO to ensure achievement of timely and appropriate diagnosis.

Disclosure statement

The authors declared no conflicts of interest.

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