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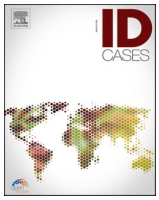

Case report

Acute non-immune hemolytic anemia in enteric fever due to nalidixic acid-resistant Salmonella enterica serotype Typhi: A case report

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ABSTRACT

Nalidixic acid-resistant Salmonella enterica serotype Typhi is a well-known cause of enteric fever, and its prevalence is increasing worldwide. However, the incidence of enteric fever complicated by non-immune hemolytic anemia without co-existing thalassemia or glucose-6-phosphate dehydrogenase deficiency is rare. In this case report, we present a case of acute non-immune hemolytic anemia in enteric fever caused by nalidixic acid-resistant Salmonella enterica serotype Typhi.

1. Introduction

Enteric fever is a systemic infection caused by *Salmonella enterica* serotype Typhi (formerly *S. typhi*) and *S. enterica* serotypes Paratyphi A, B, or C [1]. This disease usually spreads by taking food or water contaminated with urinary or fecal excretion of the disease carrier [2]. After an asymptomatic period of 7–14 days, patients develop fever, chills, coated tongue, and mainly abdominal features, such as diarrhea, vomiting, abdominal pain or discomfort, anorexia, constipation, rose spot, splenomegaly, hepatomegaly, hepatitis [2,3]. Other systems may also be involved, and a wide range of complications may occur. Patients may also develop headaches, relative bradycardia, shock, cough, pneumonia, seizures, delirium, meningitis, encephalopathy, anemia, and pancytopenia [2,3,4,5]. Disseminated intravascular coagulation (DIC), acute kidney injury, GI bleeding, and perforation can also occur [6,7]. However, the incidence of acute hemolytic anemia without co-existing thalassemia or glucose-6-phosphate dehydrogenase deficiency in enteric fever is rare [8,9]. Herein, we present a case of nalidixic acid-resistant Salmonella enterica serotype Typhi presenting as non-immune hemolytic anemia in enteric fever.

2. Clinical presentation

A 70-year-old male was admitted into our medicine inpatient department with complaints of high-grade intermittent fever for 7 days. He is a nonsmoker and nonalcoholic with no significant past medical history. He also had no recent travel history in the malaria endemic area of the country, mosquito bites, drug history, or contact with a sick person.

On clinical examination, the patient was febrile, tachycardic, mildly icteric, and moderately pale. Otherwise, the rest of the general examination findings were normal. Abdominal examination showed mild tenderness on the right upper abdomen, but no organomegaly was appreciated. Other systemic findings were unremarkable. The patient's temperature chart showed a typical stepladder pattern of fever.

Initial investigations revealed moderate normocytic normochromic anemia (hemoglobin 7 gm/dL; normal range: 13.5–17.5 gm/dL in male), leukopenia (leukocyte count 4000/mm^3; normal range: 4500–11,000/mm^3), high erythrocyte sedimentation rate (ESR) (124 mm/h in 1st hr; normal range: Male: 0–15 mm/h in 1st hr), elevated C-reactive protein (17 mg/dl, normal range: 0.3–1.0 mg/dL).

He had a high reticulocyte count (5.35 %; normal range: 0.5 %–1.5 %), low haptoglobin (14 mg/dL; normal range: 41–165 mg/dL), and high lactate dehydrogenase (LDH) level (770 U/L; normal range: 45–200 U/L). Peripheral blood smear showed normocytic normochromic red blood cells with moderate rouleaux formation, white blood cells (WBC) were mature, and platelets were adequate. Serum total bilirubin was also increased (2.9 mg/dL; normal range: 0.1–1.0 mg/dL) with predominantly indirect hyperbilirubinemia (indirect bilirubin 2 mg/dL; normal range: 0.2–0.8 mg/dL and direct bilirubin 0.9 mg/dL; normal

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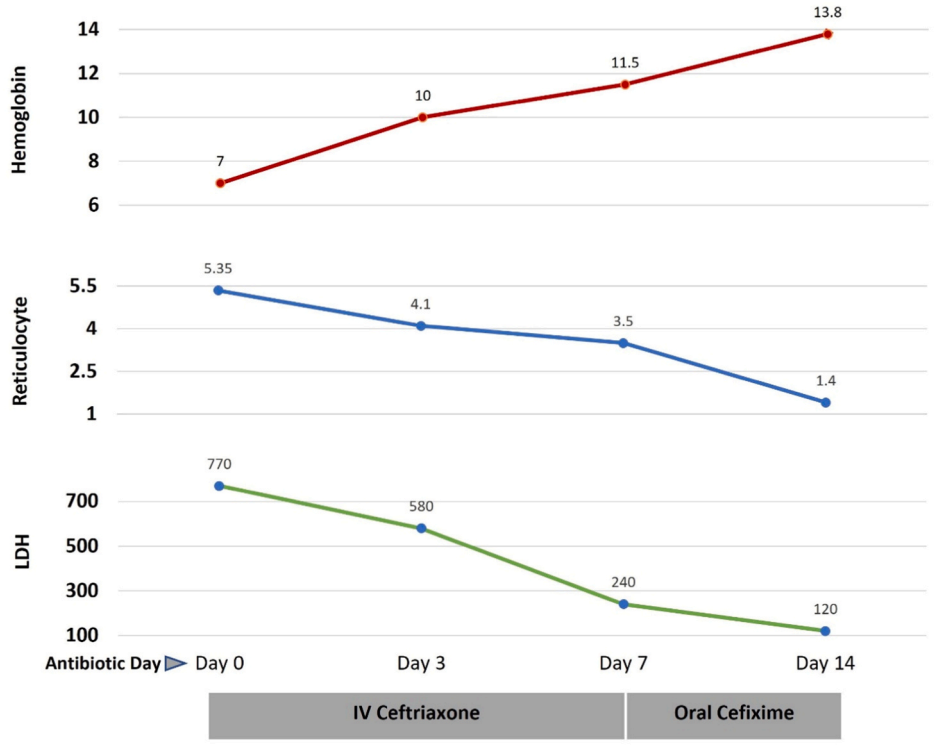

	Day 0	Day 3	Day 7	Day 14
Reticulocyte	5.35	4.1	3.5	1.4
Hb	7	10	11.5	13.8
LDH	770	580	240	120

Fig. 1. Hemoglobin, reticulocyte and LDH levels of the patient during antibiotic course. Note that there is an elevation in hemoglobin levels, accompanied by a reduction in both LDH and reticulocyte levels after initiation of intravenous ceftriaxone. This trend continues as we switch to oral cefixime.

Table 1
Comparison of relevant investigations conducted before and after the initiation of treatment.

Investigation	Before starting antibiotics	On Ceftriaxone		On Cefixime	Normal values
		Day 3	Day 7	Day14	
Hemoglobin	7 gm/dL	10 gm/dL	11.5 gm/dL	13.8 gm/dL	Male: 13.5–17.5 gm/dL
WBC	4000/mm^3	4800/mm^3	6000/mm^3	9500/mm^3	4500–11,000/mm^3
ESR	124 mm in the 1st hour	76 mm in the 1st hour	36 mm in the 1st hour	15 mm in the 1st hour	0–22 mm/h for men
C-reactive protein	17 mg/dL	12 mg/dL	4 mg/dL	0.6 mg/dL	0.3–1.0 mg/dL
LDH	770 U/L	580 U/L	240 U/L	120 U/L	45–200 U/L
Haptoglobin	14 mg/dL	22 mg/dL	70 mg/dL	112 mg/dL	41–165 mg/dL
Reticulocyte	5.35 %	4.1 %	3.5 %	1.4 %	0.5–1.5 %
Total bilirubin	2.9 mg/dL	2.5 mg/dL	1.2 mg/dL	0.5 mg/dL	0.1–1.0 mg/dL
Direct (conjugated) bilirubin	0.9 mg/dL	0.8 mg/dL	0.5 mg/dL	0.1 mg/dL	0–0.3 mg/dL
Indirect (unconjugated) bilirubin	2 mg/dL	1.7 mg/dL	0.7 mg/dL	0.4 mg/dL	0.2–0.8 mg/dL
ALT	98 U/L	70 U/L	50 U/L	38 U/L	10–40 U/L
AST	99 U/L	63 U/L	46 U/L	30 U/L	12–38 U/L

range: 0–0.3 mg/dL). Liver function tests were also elevated (alanine transaminase (ALT) 98 U/L; normal range: 10–40 U/L and aspartate aminotransferase (AST) 99 U/L; normal range: 12–38 U/L).

His fecal occult blood testing was negative. Urinalysis showed mild proteinuria and bilirubinuria. Random blood sugar, serum creatinine, and electrolytes were within normal limits. Ultrasonography of the whole abdomen showed a thickened GB wall and grade-I fatty changes in the liver. Dengue IgM antibody was negative, but Dengue IgG antibody was positive. HBsAg, anti-HCV, anti-HAV, anti-HEV, HIV test, Sickling, Peripheral smear for parasites including malaria, and Coomb's test were negative. Later, his blood culture and sensitivity test revealed the growth of nalidixic acid-resistant Salmonella enterica serotype Typhi.

Based on the overall clinical and laboratory investigations, a diagnosis of enteric fever with non-immune hemolytic anemia was made. He was given intravenous Ceftriaxone 2 gm twice daily and 2 units of whole blood transfusion along with other supportive treatments. The patient responded well to the treatment with visible improvement. With the subsidence of fever, he was discharged on the 7th day of admission with an additional 7 days of oral cefixime. His subsequent clinical course was favorable. Both hemoglobin and intravascular hemolysis markers returned to normal levels. (Fig. 1) Later, his G6PD activity was tested normal.

The relevant investigation results conducted before and on days 3, 7, and 14 after the initiation of ceftriaxone therapy are shown in Table 1.

3. Discussion

Normochromic normocytic anemia is the most common type of anemia found in enteric fever [10]. Anemia may occur due to gastrointestinal blood loss, bone marrow suppression, and hemolysis which could be due to inherited causes such as G6PD deficiency-related hemolysis and thalassemia, or acquired causes that also can be further classified into immune causes and non-immune causes such as hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), microangiopathic hemolytic anemia (MAHA) or toxin mediated [10,11,12,13,14,15]. *Salmonella* is usually non-hemolytic during culture, but adding bacteriophage to a freshly inoculated sheep-blood-agar plate may turn a non-hemolytic culture of *Salmonella* into a hemolytic [16]. Exposure of *Salmonella* to neuroendocrine stress hormones can also result in the release of hemolysin E in membrane vesicles, which can cause hemolysis [17]. Hemolysis usually begins within the first two weeks of disease onset and during the first week of illness, when bacteremia is known to be maximal [8,9]. In most studies regarding hemolytic anemia due to typhoid, underlying causes are found, but Reteif & Hofmayer described a case where they suspected toxin as the underlying cause [8].

As with the case of our patient, he presented to us after 1 week of onset of symptoms. Hemolysis was evident by pallor, jaundice, and fall of hemoglobin level with increased reticulocyte count and LDH level. As a dramatic rise of hemoglobin concentration and fall of reticulocyte count occurred after initiation of antibiotic therapy, it highly suggests that the hemolytic anemia in this patient was due to nalidixic acid-resistant Salmonella enterica serotype Typhi [18].

Regarding causes other than hemolysis, a negative fecal occult blood test ruled out gastrointestinal loss, and an increased reticulocyte count ruled out bone marrow suppression. Regarding the causes of hemolysis, normal G6PD enzyme assay, and thalassemia screening ruled out inherited causes. Among acquired causes, our patient's recovery without steroid therapy ruled out immune hemolytic anemia, and among non-immune causes, normal serum creatinine ruled out HUS, and lack of neurological features ruled out TTP [19]. So, it can be abstracted that the anemia that occurred in this patient was due to non-immune hemolytic anemia, most probably due to the toxic effects of the nalidixic acid-resistant Salmonella enterica serotype Typhi.

4. Conclusion

Nalidixic acid-resistant Salmonella enterica serotype Typhi can present with acute non-immune hemolytic anemia. In endemic areas, patients with high-grade fever and acute anemia should be evaluated for enteric fever. Blood culture and sensitivity tests could be done early if clinical suspicion is high. Early treatment with appropriate antibiotics will prevent morbidity and mortality resulting from the delay in diagnosis.

Ethical approval

Ethics approval is not required for de-identified single case reports based on institutional policies.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of interest

All the authors of this manuscript have no conflict of interest.

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CRediT authorship contribution statement

Sourav Saha: Conceptualization. **Md. Mohaiminul Islam:** Writing – review & editing. **Abdullah Al-Jubair:** Writing – original draft. **Ashif Istiak:** Writing – original draft. **Mohammad Rasel:** Conceptualization, Supervision, Writing – review & editing.

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