Healthy Tadulako Journal (Jurnal Kesehatan Tadulako)
Vol. 11 No.2, April 2025
P-ISSN : 2407-8441/e-ISSN : 2502-0749

Case Report

A Rare Case of Aplastic Anemia in Toxic Typhoid Fever

Mutiara Putri Novita[1*], Irma Zaimatuddunia[2],

[1]*Departement of Internal Medicine, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang*
[2]*Departement of Internal Medicine, Loekmono Hadi Hospital, Kudus*

Email Corresponding:
mutiarapn04@gmail.com

Page : 257-264

Keywords:
pancytopenia
toxic typhoid fever

Article History:
Received: 2024-11-12
Revised: 2024-11-25
Accepted: 2025-04-30

Published by:
Tadulako University,
Managed by Faculty of Medicine.
Email: healthytadulako@gmail.com
Phone (WA): +6285242303103
Address:
Jalan Soekarno Hatta Km. 9. City of Palu, Central Sulawesi, Indonesia

ABSTRACT

Background: Typhoid fever is a prevalent febrile illness in tropical regions where public health infrastructure and sanitation are limited. Pancytopenia resulting from hemophagocytic lymphohistiocytosis (HLH) is a rare but severe complication of typhoid fever that can be fatal without proper management. **Objective:** This case report aims to describe the clinical presentation, management, and outcome of a typhoid fever patient who developed pancytopenia, altered consciousness, and speech impairment. **Methods:** A comprehensive evaluation was conducted, including the patient's medical history, physical examination, and various diagnostic tests. Laboratory workups revealed pancytopenia, positive TUBEX IgM for Salmonella, lymphadenopathy, and bone marrow aplasia. Differential diagnoses were considered and ruled out to confirm HLH as the underlying mechanism. **Results:** The patient responded positively to a regimen including ceftriaxone, steroids, and supportive care. The presence of pancytopenia in this typhoid fever case was linked to HLH. **Conclusion:** Early diagnosis and appropriate antibiotic therapy are critical for managing severe typhoid fever cases with complications such as HLH, helping prevent further complications and improving patient outcomes.

Introduction

Typhoid fever is a systemic disease caused by Salmonella enterica typhi. World Health Organization (WHO) reports an increase in confirmed cases, more than 25 million cases during one year. Children under 15 years old and young adults have a higher risk case of typhoid fever[1]. Typhoid fever poses a substantial global health burden, particularly in Southeast Asia where Indonesia contributes significantly. Annually, Indonesia experiences an increase of up to 500 typhoid cases per 100,000 individuals, resulting in a mortality rate between 0.6 and 5%. Southeast Asia contribute 14.1% of worldwide typhoid cases stem, highlighting the endemic nature and annual recurrence of this disease[2].

Typhoid fever is transmitted through food or drinks contaminated with the Salmonella typhi bacteria. This disease can be transmitted through direct contact with the feces, urine, or secretions of a typhoid fever patient. Poor hygiene and sanitation are the primary factors contributing to its spread[3]. Inadequate hygiene practices and poor water treatment can lead to fecal-oral contamination, increasing the risk of bacterial infections such as typhoid fever. Contaminated drinking water, which may contain the feces or urine of infected individuals, is a significant public health concern[4].

Symptoms of Typhoid fever such as constipation, body aches, diarrhea, and fever. Clinical deterioration may occur in untreated

typhoid fever after a few days[5]. Laboratory diagnosis of typhoid fever typically involves the microbiological culture of clinical specimens, including blood, stool, urine, and bone marrow. Molecular techniques, such as polymerase chain reaction (PCR), have emerged as sensitive and specific tools for detecting Salmonella Typhi DNA directly from clinical samples. Serological tests, including the Widal test, were historically used, their diagnostic accuracy and specificity are limited, rendering them less reliable in modern clinical practice[6].

Healthcare provider better diagnosed and treatment with an appropriate antibiotic to prevent complications and decreased mortality. We report an Indonesian female with severe typhoid fever complicated by unconsciousness with multiple organ dysfunction syndrome, and pancytopenia. The primary objective of this case report is to investigate a clinical case presenting with toxic typhoid fever complicated by pancytopenia. The authors aim to describe the clinical presentation, diagnostic workup, and therapeutic approach, contextualizing the management strategy within the framework of current medical literature and guidelines.

Materials and Methods

Research Design

This research is designed as a case report study with a descriptive approach, focusing on a single patient case. The study aims to evaluate a specific case, analyzing the appropriateness of the therapeutic regimen provided during treatment.

Sample

The sample in this study is one patient admitted to Dr. Loekmono Hadi Hospital with a primary diagnosis of typhoid fever, complicated by pancytopenia and loss of consciousness. This sample was chosen to analyze the therapeutic approach and its clinical outcomes.

Data Collection Techniques

Data were obtained through direct examination and the patient's medical records. Data collection involved monitoring the patient's condition from the beginning of hospitalization until recovery and discharge. Information gathered included medical history, examination results, and detailed records of the therapy administered during the treatment period.

Data Analysis Techniques

A descriptive analysis was performed to assess the appropriateness of the treatment regimen received by the patient. This assessment included evaluating the effectiveness of the treatment, the progression of the patient's clinical condition, and the presence or absence of adverse effects during the course of treatment.

Ethical Consideration

This study received ethical approval from the ethics committee of Dr. Loekmono Hadi Hospital, ensuring compliance with medical ethics principles. Informed consent was also obtained from the patient or the patient’s family prior to the use of patient data for research purposes.

Results

Examination the patient vital signs were were fever (38.7 C), GCS E4V3M5 (apathy), and weakness. Laboratory examination results on March 28 2023 showed Hemoglobin 9.8 g/dL, TEC 3.38 million/µL, TLC 2.7 thousand/µL (N75%, L20.9%, M3.7%, E0.0%, B0.4%), Platelets 29 thousand/ul, urea 16.4 mg/dL, HBsAG rapid negative, Anti HIV negative, Anti HCV negative, Calcium 1.92 mmol/L, Sodium 125 mmol/L, and Chloride 88 mmol/L. The peripheral blood smear showed normochromic normocytic anemia, the leukocyte count decreased without morphological abnormalities, the platelet count decreased without morphological

abnormalities, the impression on examination was aplastic anemia (pancytopenia). Pansitopenia led to a decision for external immunology examination ANA test on March 30, 2023. The TUBEX Anti-Salmonella IgM examination showed a positive result of 8 (a strong indication of active typhoid fever infection).

Based on physical examination patient have epigastric pain or abdominal pain. Abdominal ultrasonography examination on March 28 2023 showed lymphadenopathy in the ileocaeoal region measuring (± 0.78 x 0.65 cm) suspicious for an inflammatory process and sonography of other solid abdominal organs within normal limits. Patient vital sign shows apathy and unconsciousness we performed non-contrast Cranial or Brain CT-Scan examination on March 30 2023. Brain CT-Scan showed no intracranial bleeding and no signs of increased intracranial pressure. This examination shows no brain damage or brain infection in the patient for her apathy sign and unconsciousness symptomps. Based on the results of the patient's examination, the patient's diagnosis was typhoid fever followed by aplastic anemia.

Discussion

A 20-year-old woman came to the Emergency Room, Dr. Loekmono Hadi Hospital on March 28 2023 with complaints of fever from three weeks before. Fever appears suddenly and increases slowly. The patient's consciousness began to decline approximately one week before entering the hospital. The patient did not respond and answer questions from family members. Other complaints were bone pain and decreased appetite. The patient does not have drug allergies and does not have comorbid diagnose. The patient's diagnosis was typhoid fever followed by aplastic anemia.

The patient's family was given an explanation regarding the examination results, diagnosis, prognosis, and complications that can occur. After listening to the explanation, the parents were given informed consent to refer the patient but refused to be referred for further treatment and agreed to be hospitalized for typhoid fever in Dr. Loekmono Hadi Hospital. The patient was given antibiotic therapy of Ceftriaxone 1 gram/12 hours intravenously for five days, Paracetamol 1 gram/ 24 hours intravenous, and Ringer lactate intravenous 100 mL/24 hours. Treatment was carried out for 2 days, the patient condition got worse with language disfunction, agitation the confusion. Patient could have toxic reaction, we add corticosteroids (prednisone 5 mg/8 hours) start for three days.

The neurological symptomps improved after the first dose of prednison. Day 5 after treatment patient had no fever and the patient's consciousness had increased. Laboratory blood examination on 1 April 2023 shows Hemoglobin 8.5 g/dL, TEC 2.98 million/µL, TLC 3.1 thousand/µL, and Platelets 39 thousand/ul. Patient vital signs were within normal range and the blood laboratory have increased platelets but lowering hemoglobin counts so patient was given iron suplement for seven days.

Patient got discharged with minimal sign pf neurological and had no fever. Corticosteroid treatment was continued at the same dose with ceftriaxone until day 12. Patient returned to the Internal Medicine Polyclinic Dr. Loekmono Hadi Hospital Kudus after 2 weeks with ANA Immunological examination ANA Test ELISA method obtained a result of 0.3 (negative). Laboratory blood on 26 April 2023 this patient shows increase in platelet count to 269 thousand/ul, an increase in TLC 10.4 thousand/ul, and Hemoglobin 11.7 g/dL.

Typhoid fever is primarily treated with antibiotics targeting Salmonella typhi. the efficacy of antibiotic treatment for typhoid fever hinges on the susceptibility of the Salmonella Typhi strain involved[7]. Due to limited resources, countries often lack access to

advanced diagnostic tools and efficient reporting systems, making it difficult to accurately assess the prevalence of typhoid fever[8]. Fluoroquinolones, such as ciprofloxacin, are a common treatment option, especially in resource-limited settings[9]. Ciprofloxacin inhibits bacterial DNA replication by targeting DNA gyrase and topoisomerase II. A retrospective study showed that ceftriaxone is the preferred treatment for hospitalized typhoid fever patients, offering faster fever reduction, shorter treatment duration, fewer side effects, and lower treatment failure rates compared to chloramphenicol[10]. Patient should take antibiotic consistent to prevent resistance. Irregular medication adherence can contribute to the development of antibiotic resistance, increasing the chances of genetic mutations that confer resistance[11]. Paracetamol is used to reduce fever by inhibiting prostaglandin E2 synthesis, leading to decreased body temperature[12].

This patient was given antibiotic ceftriaxone injection 1 gram/ 12 hours for five days. Intravenous antibiotics are used for various infections, from mild to severe. A study found that ceftriaxone and cefixime significantly reduced febrile episodes within one week of treatment. Chloramphenicol, amoxicillin, and trimethoprim-sulfamethoxazole may still be considered in regions with low antibiotic resistance or where fluoroquinolones are unavailable[13]. Cephalosporins and fluoroquinolones are now the recommended antibiotics due to the high prevalence of multidrug resistance among first-line agents such as penicillins, chloramphenicol, and trimethoprim-sulfamethoxazole. Based on British Guidelines Enteral Fever which mostly originates from South Asia ceftriaxone is the recommended first-line agent for the treatment of typhoid fever. Ceftriaxone 2 gram IV/ day for adult dose and 80 mg/kg (maximal 2 gram) IV/ day. This antibiotic safe for women pregnancy and does not have side effect for pediatric patient like chloramphenicol[14].

Typhoid fever caused by Salmonella Typhii can cause complications of various severity in 10-15% of patients, the most common of which are typhoid encephalopathy (toxic typhoid), gastrointestinal bleeding, and intestinal perforation. Intermittent confusion, insomnia and dizziness are reported in 3-10% of cases[15]. These symptoms are associated with high mortality such as hemophagocytic syndrome with blood disorders similar to those of aplastic anemia[16]. Patient received Corticosteroid (prednisone 5 mg/8 hours) on day 2 inpatient treatment and shows great improvement for neurological symtomps from toxic typhoid. Case of severe typhoid with encephalitis and neurogical symptomp from patient that travelled from Philippines had been given corticosteroids (prednisone 1 mg/kg/day) shows symptomps improved and minimal sign of neurogical symptomps[17]. Severe typhoid fever can manifest with neurological complications, which attributed to the neurotoxic effects of bacterial endotoxins released during bacterial cell death. Severe typhoid fever needs high-dose corticosteroid therapy, such as dexamethasone. Corticosteroids used for considered to mitigate neurological symptoms and improve patient survival. The efficacy of dexamethasone in treating enteric fever encephalopathy shows that endotoxins released by Salmonella Typhi may stimulate macrophages to produce inflammatory mediators, such as cytokines and arachidonic acid metabolites, which contribute to neurological complications[18].

Dexamethasone have beneficial effects by reducing the production of these inflammatory mediators or by counteracting their physiological effects and being antioxidant properties, which could further contribute to reduced mortality[19]. Younger adults are more susceptible to neuropsychiatric complications

of typhoid fever compared to older adults[20]. Early initiation of corticosteroid therapy before clinical deterioration can significantly improve outcomes. Delayed administration of corticosteroids may increase the risk of mortality or disease relapse. Therefore, while dexamethasone is generally not required for most typhoid fever patients, it is strongly recommended for individuals presenting with severe neurological manifestations, such as delirium, obtundation, stupor, coma, or shock, as it may be life-saving in these critical cases[17]. Two distinct neurological manifestations have been recognized in association with typhoid fever. The initial presentation, occurring prior to antibiotic initiation, is believed to be a direct consequence of Salmonella Typhi invasion of the central nervous system[21]. This early neurological involvement may manifest as altered mental status, seizures, or focal neurological deficits. The second type of neurological complication typically arises following antibiotic therapy and is hypothesized to be mediated by a cytokine storm resulting from bacterial lysis. The rapid release of bacterial endotoxins triggers an exaggerated inflammatory response, leading to systemic inflammatory response syndrome (SIRS) and potential neurological sequelae[22].

Pancytopenia and typhoid fever have been described in several reports from Asia during the last two decades. Typhoid fever can affect the bone marrow, resulting in a decrease in the volume of packed cells and an increase in neutrophils[23]. A significant decrease in the number of erythrocytes and platelets in patients positive for typhoid fever compared to patients with negative fever for Salmonella typhi. These changes occur as a result of the body's metabolic response process in the form of hemophagocytosis to the release of toxins from Salmonella enterica typhi. This mechanism involves hematopoiesis organs such as lymph nodes, bone marrow, and spleen[5]. Salmonella Typhii stimulates macrophages to engulf blood cells, infected macrophages engulf more erythrocytes potentially transition to chronic infection[24].

The occurrence of pancytopenia in typhoid fever patients is linked to the mechanism HLH (Hemophagocytic lymphohistiocytosis). The incidence of HLH as a complication of typhus is rarely reported. Pathophysiology of HLH due to hypersecretion of cytokines by lymphocytes[25]. HLH is diagnosed using clinical and molecular criteria. This patient has four diagnoses from five clinical findings required fever, splenomegaly, hypofibrinogenemia/ hemophagocytosis, and cytopenia, the other was hypertriglyceridemia which is not diagnosed. Demonstration of hemophagocytosis in lymph nodes was also diagnosed in this patient, but decreased natural killer cell function and an elevated soluble CD25 or IL-2Rα chain ≥ 2,400 IU/mL were not diagnosed[26]. The TUBEX Anti-Salmonella IgM examination was the only basis for diagnosis in this patient. Though TUBEX test and Widal test has often been used controversially to diagnose typhoid fever in developing countries, we presumptively treated her as such[27].

Typhoid toxic should be included in the differential diagnosis of pancytopenia in fever unconsiuous kids. It must be managed with treatment of an appropriate antibiotic and adequate hydration to prevent complications. Intravenous fluid resuscitation and blood product transfusions may be required to compensate for fluid and blood losses. Adequate nutrition is crucial for optimal physical recovery and growth in adolescents following inpatient treatment[28].

Conclusion

In conclusion, this case highlights the complexity and potential severity of typhoid fever when accompanied by pancytopenia and neurological complications, likely due to hemophagocytic lymphohistiocytosis (HLH).

Early and accurate diagnosis, combined with prompt and appropriate antibiotic treatment, corticosteroids, and supportive care, proved essential for improving the patient's clinical outcome. The successful management of this case underscores the importance of recognizing typhoid toxicities and including HLH in the differential diagnosis of typhoid fever patients presenting with pancytopenia and altered mental status. Timely intervention and close monitoring are vital to prevent complications and enhance recovery, especially in resource-limited settings where advanced diagnostics may be unavailable. This case further emphasizes the critical role of adherence to antibiotics to prevent resistance and the potential benefit of corticosteroids in managing severe neurological symptoms in toxic typhoid cases.

Acknowledgment

The author would like to express sincere gratitude to all clinical colleagues in the Department of Internal Medicine, Faculty of Medicine, Sultan Agung Islamic University, and the Department of Internal Medicine at Loekmono Hadi Hospital Kudus, for their invaluable assistance on providing clinical data, reviewing the manuscript, and offering expert advice during the writing process.

References

1. WHO. Typhoid vaccine: WHO position paper - March 2018. *Wkly Epidemiol Rec*. 2018;13(93):153-172. https://www.who.int/publications/i/item/typhoid-vaccines-who-position-paper-march-2018
2. Sukmawati, I.G.A.N.D., Jaya, M.K.A, Swastini DA. Evaluasi Penggunaan Antibiotik pada Pasien Tifoid Rawat Inap di Salah Satu Rumah Sakit Pemerintah Provinsi Bali dengan Metode Gyssens dan ATC / DDD diikuti dengan mual , muntah , anoreksia , dan diare kesehatan global , diperkirakan 11-20 juta orang mengi. *J Farm Udayana*. 2020;9(1):37-44.
3. Levani Y, Prastya AD. Demam Tifoid: Manifestasi Klinis, Pilihan Terapi Dan Pandangan Dalam Islam. *Al-Iqra Med J J Berk Ilm Kedokt*. 2020;1(2):10-16. doi:10.26618/aimj.v3i1.4038
4. Nitami M, Deey S VE. Gambaran Personal Higiene Dan Higiene Sanitasi Pengolahan Depot Air Minum Isi Ulang (Damiu) X Di Desa Karang Satria Kecamatan Tambun Utara, Kabupaten Bekasi Tahun 2022. *Healthy Tadulako J (Jurnal Kesehatan Tadulako)*. 2024;10(1):63-69.
5. Ndako JA, Dojumo VT, Akinwumi JA, Fajobi VO, Owolabi AO, Olatinsu O. Changes in some haematological parameters in typhoid fever patients attending Landmark University Medical Center, Omuaran-Nigeria. *Heliyon*. 2020;6(5):e04002. doi:10.1016/j.heliyon.2020.e04002
6. Kim J, Erickson D. Detection of Malaria and Typhoid Fever. *HHS Public Access*. 2024;93(36):12175-12180. doi:10.1021/acs.analchem.1c03298.Two-Color
7. Amare A, Asnakew F, Asressie Y, et al. Prevalence of multidrug resistance Salmonella species isolated from clinical specimens at University of Gondar comprehensive specialized hospital Northwest Ethiopia: A retrospective study. *PLoS One*. 2024;19(5 May):1-18. doi:10.1371/journal.pone.0301697
8. Athifah F, Akune K, Setyawati T. Demam Tifoid dengan Komplikasi Sepsis. *J Med Prof*. 2021;3(1):115-120.
9. Parry CM, Qamar FN, Rijal S, McCann N, Baker S, Basnyat B. What Should We Be Recommending for the Treatment of Enteric Fever? *Open Forum Infect Dis*.

2023;10(Suppl1) :S26-S31. doi:10.1093/ofid/ofad179

10. Oktaviana F, Noviana P. Efektivitas Terapi Antibiotika Demam Tifoid Pada Pediatrik Di Rumah Sakit X Kota Kediri. *J Syifa Sci Clin Res*. 2021;3(2):63-70. doi:10.37311/jsscr.v3i2.11688
11. Auliandari RA, Sutiningsih D, Laksono B, Sakundarno M. Tinjauan Literatur: Faktor Klinis Yang Berhubungan Dengan Kejadian Resistensi Obat Pada Pasien Tuberkulosis. *Healthy Tadulako J (Jurnal Kesehatan Tadulako)*. 2023;9(3):331-339.
12. Patrekar P V, Kashid K, More S, Dongare SD. Indian Journal of Pharmaceutical and Biological Research (IJPBR) A overview : non-steroidal anti-inflammatory drugs and mechanisms. *Indian J Pharm Biol Res*. 2014;2(4):9267.
13. McCann N, Scott P, Parry CM, Brown M. Antimicrobial agents for the treatment of enteric fever chronic carriage: A systematic review. *PLoS One*. 2022;17(7 July):1-16. doi:10.1371/journal.pone.0272043
14. Nabarro LE, McCann N, Herdman MT, et al. British infection association guidelines for the diagnosis and management of enteric fever in England. *J Infect*. 2022;84(4):469-489. doi:10.1016/j.jinf.2022.01.014
15. Parry CM, Thompson C, Vinh H, et al. Risk factors for the development of severe typhoid fever in Vietnam. *BMC Infect Dis*. 2014;14(1):1-9. doi:10.1186/1471-2334-14-73
16. Perin ME, Kanna S, Sai V. Unusual Presentation of Typhoid Fever. *J Res Med Dent Sci*. 2022;10(7):134-136.
17. Mellon G, Eme AL, Rohaut B, Brossier F, Epelboin L, Caumes E. Encephalitis in a traveller with typhoid fever: Efficacy of corticosteroids. *J Travel Med*. 2017;24(6):1-4. doi:10.1093/jtm/tax063
18. Nain Z, Abqari S, Kulshrestha S. High Dose Dexamethasone in Complicated Typhoid Fever: What Is the Evidence? *Acad J Pediatr Neonatol*. 2024;13(3):1-6. doi:10.19080/ajpn.2024.13.555920
19. Marie W Munch, Sheila N Myatra, Bharath Kumar Tirupakuzhi Vijayaraghavan, Sanjith Saseedharan, Thomas Benfield, Rebecka R Wahlin, Janus Engstrøm, Vivekanand Jha BVAP. Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive without Life Support in Adults with COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial. *JAMA - J Am Med Assoc*. 2021;326(18):1807-1817. doi:10.1001/jama.2021.18295
20. Ukwaja KN. Typhoid fever presenting as a depressive disorder--a case report. *Rural Remote Health*. 2010;10(2):1276. doi:10.22605/rrh1276
21. Leung DT, Bogetz J, Itoh M, et al. Factors associated with encephalopathy in patients with Salmonella enterica serotype typhi bacteremia presenting to a diarrheal hospital in Dhaka, Bangladesh. *Am J Trop Med Hyg*. 2012;86(4):698-702. doi:10.4269/ajtmh.2012.11-0750
22. Xiong D, Song L, Chen Y, Jiao X, Pan Z. Salmonella Enteritidis activates inflammatory storm via SPI-1 and SPI-2 to promote intracellular proliferation and bacterial virulence. *Front Cell Infect Microbiol*. 2023;13(May):1-14. doi:10.3389/fcimb.2023.1158888
23. Kashif Raza S, Javaid H, Bajwa H, Saleem K, Hashim M. Evaluation of haematological variables in patients with typhoid in Pakistan. *Pakistan J Heal Sci*. Published online 2022:73-77. doi:10.54393/pjhs.v3i06.104

24. Pilonieta MC, Moreland SM, English CN, Detweiler CS. Salmonella Enterica infection stimulates macrophages to hemophagocytose. *MBio*. 2014;5(6):1-14. doi:10.1128/mBio.02211-14

25. Kim YR, Kim DY. Current status of the diagnosis and treatment of hemophagocytic lymphohistiocytosis in adults. *Blood Res*. 2021;56(April):17-25. doi:10.5045/br.2021.2020323

26. Dulal HP, Vance DJ, Neupane DP, et al. Neutralization of Typhoid Toxin by Alpaca-Derived, Single- Domain Antibodies Targeting the PltB and CdtB Subunits. *Infect Immun*. 2022;90(2):1-13. doi:10.1128/iai.00515-21

27. Rupendra Nath Saha, Jayachandran Selvaraj, Stalin Viswanathan VP. Typhoid with pancytopenia: Revisiting a forgotten foe: Two case reports. *World J Hematol*. 2023;6204(1). doi:10.5315/wjh.v10.i1.9

28. Millatashofi AS, Adi AC. Hubungan Tingkat Kecukupan Asupan Zat Gizi Dan Kebiasaan Jajan Dengan Status Gizi Pada Remaja Santriwati Di Pondok Pesantren Surabaya. *Healthy Tadulako J (Jurnal Kesehatan Tadulako)*. 2023;9(2):121-127. doi:10.22487/htj.v9i2.672