Case Report / *Olgu Sunumu*

DOI: 10.5578/ced.68699 • *J Pediatr Inf 2020;14(1):e35-e37*

Salmonella ser. Typhimurium Bacteremia Related Hemophagocytic Lymphohistiocytosis: A Case Report

Salmonella ser. Typhimurium Bakteremisi ile İlişkili Hemofagositik Lenfohistiyositoz: Bir Olgu Sunumu

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Cite this article as: Yaşar Durmuş S, Tanır G, Öz FN, Aydın Teke T, Kaman A. *Salmonella* ser. Typhimurium bacteremia related hemophagocytic lymphohistiocytosis: A case report. J Pediatr Inf 2020;14(1):e35-e37.

Abstract

Salmonella enterica Serovar Typhimurium (*Salmonella* ser. Typhimurium) may cause invasive non-typhoidal *Salmonella* infections. Being a facultative intracellular bacteria, they are found within diversity of cells like as macrophages and manipulate these cells for erythrophagocytosis. Here, we report a 9-year-old boy who had *Salmonella* ser. Typhimurium bacteremia related hemophagocytic lymphohistiocytosis.

Keywords: Bacteremia, hemophagocytic lymphohistiocytosis, *Salmonella* ser. Typhimurium

Öz

Salmonella enterica Serovar Typhimurium (*Salmonella* ser. Typhimurium) non-tifoidal invaziv *Salmonella* enfeksiyonlarına neden olabilir. Fakültatif hücre içi bakteri olduğundan makrofajlar gibi pek çok farklı hücrede bulunabilir ve bu hücreleri eritrofagositoza yönlendirir. Burada dokuz yaşında *Salmonella* ser. Typhimurium bakteremisi ile ilişkili hemofagositik lenfohistiyositozu olan bir erkek olgu sunulmuştur.

Anahtar Kelimeler: Bakteremi, hemofagositik lenfohistiyositoz, *Salmonella* ser. Typhimurium

Introduction

Non-typhoidal *Salmonella* (NTS) infections usually cause self-limiting acute gastroenteritis in healthy children. In the case of impaired innate and adaptive defence mechanisms, susceptibility to invasive NTS infections increase. Several factors such as young age (particularly < 1 year), HIV infection, congenital defects in humoral immunity and chronic granulomatous disease are risk factors for bacteremia and focal infection. One of the common pathogens of invasive NTS is *Salmonella* ser. Typhimurium (1,2). In this report, we presented a previously healthy 9-year-old boy with *Salmonella* ser. Typhimurium bacteremia complicated by hemophagocytic lymphohistiocytosis (HLH).

Case Report

A 9-year-old male presented to our hospital with fever, vomiting and diarrhea for five days. On physical examination, his body temperature was 39°C and he had Traube's space dullness without palpable spleen. His other vital signs and physical findings were normal. Laboratory results included hemoglobin 11.4 g/dL, white blood cell count of 3510/mm^3 with neutrophils 48%, lymphocytes 32%, monocytes 20%, platelet count 41.000/mm^3, erythrocyte sedimentation rate (ESR) 17 mm/hour, C-reactive protein (CRP) 142 mg/L (< 3 mg/L), potassium 2.5 mEq/L, aspartate transaminase 96 U/L (0-31 U/L), alanine transaminase 67 U/L (0-39 U/L), prothrombin time 13.8 sec, activated prothrombin time 27.7 sec, fibrinogen

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Received: 21.06.2019 **Accepted:** 03.09.2019 **Available Online Date:** 26.03.2020

136 mg/dL, trygliceride 364 mg/dL, ferritin 3510 ng/mL. Abdominal ultrasonography demonstrated hepatomegaly and splenomegaly. Blood culture was obtained and intravenous ceftriaxone (100 mg/kg/day) was commenced emprically for suspected sepsis. Furthermore, the presence of fever, leukopenia, thrombocytopenia, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia and splenomegaly suggested us the diagnosis of HLH. For this reason, bone marrow aspiration was performed on the second hospitalization day, but neither blast nor hemophagocytosis was detected on bone marrow smear. The day after, blood culture yielded ceftriaxone susceptible *Salmonella* ser. Typhimurium. The patient was diagnosed with secondary HLH relying on *S. Typhimurium* bacteremia. Intravenous immunoglobulin [IVIG, (1 g/kg/day, for 2 days)] was initiated. Clinical and laboratory improvement was noted 72 hours after initiating antibiotic and IVIG. Immunological investigations were as follows: negative anti-HIV antibody, normal absolute neutrophil and lymphocyte counts, normal quantitative serum immunoglobulin levels (IgG, M, A, E), normal lymphocyte subset analysis, normal total complement level and normal dihydrorhodamine test. However, the patient could not be examined for inherited disorders of IL-12-IFN-gamma axis. He was discharged after 10 days of IV antibiotic treatment. He is in good clinical condition after a one-year period of outpatient follow-up.

Discussion

The patient was diagnosed as having *Salmonella* ser. Typhimurium bacteremia related HLH. The main pathophysiologic feature of HLH is the proliferation of lymphocytes, which results in intense proinflammatory cytokines release, increased cytotoxic CD8+ T cells and activation of macrophages (3). Hemophagocytic lymphohistiocytosis is usually diagnosed on the basis of the HLH-2004 diagnostic criteria. These criteria include fever, splenomegaly, bi- or pancytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low/absent NK-cell activity, hyperferritinemia and high soluble interleukin-2-receptor levels. In the absence of a family history or molecular diagnosis consistent with HLH, five or more of the eight criteria must be fulfilled for diagnosing HLH. Although hemophagocytosis is a characteristic finding of HLH, it is not essential for diagnosis. Hemophagocytic lymphohistiocytosis is classified as primary and secondary HLH based on the presence of a genetic mutation in primary disease. Primary HLH is a hereditary immune disorder but secondary HLH is related to various settings like infections, malignancies and autoimmune diseases (4). Age of onset is less than one year of age in 70% of cases but there is no known upper age limit for the onset of primary HLH (5). For this reason, it is recommended that all patients with infection associated HLH should have genetic testing for familial HLH. It is impossible to distinguish primary from secondary HLH on clinical characteristics (6). Our patient had six of the eight criteria of diagnostic HLH criteria. Unfortunately, we could not perform a genetic analysis to our patient. The patient was diagnosed as *S. Typhimurium* bacteremia related HLH.

Viral infections (herpesviridae, human immunodeficiency virus, parvovirus, influenza, adenovirus and post vaccination) and other infections (mycoplasma, bacterial, protozoal, fungal, and mycobacterial) have been reported to be related with secondary HLH (7).

Salmonella are facultative intracellular bacteria found within a diversity of phagocytic and non-phagocytic cells in vivo (8). *Salmonella* are found within macrophages during both acute and chronic infection. Cell culture assays have shown that *Salmonella* preferentially survive in hemophagocytic macrophages because of appropriate iron concentration and less toxic environment than other macrophages (9,10). A recent study evaluating *Salmonella* ser. Typhimurium infected mices has demonstrated that infection of the macrophages with *Salmonella* ser. Typhimurium promotes hemophagocytosis by directly manipulating macrophages to erythtophagocytosis and provides the bacterium with a survival niche in vivo (10). Cases of HLH with typhoid fever, caused by *Salmonella enterica* serovars Typhi and Paratyphi, have also been reported (11). Hemophagocytic lymphohistiocytosis due to *Salmonella* ser. Typhimurium bacteremia has been reported once in a child suffering from chronic granulomatous disease (12). Our patient did not have primary or secondary immunodeficiency.

Recommended therapy for infection related HLH is IVIG at a dose of 1 g/kg/day and treatment of the underlying infection. In cases without appropriate immunomodulatory therapy, mortality rate of HLH has been reported as 40% (4,13). Although antibiotic resistance is an emerging problem in *Salmonella*, isolated *Salmonella* ser. Typhimurium was susceptible to ceftriaxone in this case, and the patient was successfully treated with ceftriaxone and IVIG.

We concluded that HLH should be kept in mind in patients with persistent fever, organomegaly, and cytopenias in the setting of bacteremia particularly due to *Salmonella* infection though being previously healthy. Management of HLH relies on early diagnosis and identification of the triggering pathogen and control of the lymphocyte/macrophage proliferation and activation. Specific antimicrobial therapy can be beneficial in selected cases like ours (14).

Informed Consent: Patient concent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - FNÖ, SYD; Design - SYD, AK; Supervision - FNÖ, GT, TAT; Data Collection and/or Processing - SYD,

AK; Analysis and/or Interpretation - SYD, FNÖ, TAT; Literature Review - SYD, AK, GT; Writing - SYD, FNÖ; Critical Review - TAT, GT.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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