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Low interleukin-10 level indicates good prognosis in salmonella enterica serovar typhimurium induced pediatric hemophagocytic lymphohistiocytosis: A case report

Yuan-Yuan Chen *et al.* IL-10 Level indicates prognosis in sHLH

Abstract

BACKGROUND

Secondary hemophagocytic lymphohistiocytosis (sHLH) triggered by *Salmonella enterica* serovar Typhimurium (*S. Typhimurium*) is rare in pediatric patients. There is no consensus on how to treat *S. typhimurium*-triggered sHLH.

CASE SUMMARY

A 9-year-old boy with intermittent fever for 3 d presented to our hospital with positive results for *S. typhimurium*, human rhinovirus, and *Mycoplasma pneumoniae* infections. At the time of admission to our institution, the patient's T helper 1/T helper 2 cytokine levels were 326 pg/mL for interleukin-6 (IL-6), 9.1 pg/mL for interleukin-10 (IL-10), and 246.7 pg/mL for interferon- γ (IFN- γ), for which the ratio of IL-10 to IFN- γ was 0.04. In this study, the patient received meropenem, linezolid, and cefoperazone/sulbactam in combination with high-dose methylprednisolone therapy (10 mg/kg/d for 3 d) and anti-shock supportive treatment twice. After careful evaluation, this patient did not receive Hemophagocytic lymphohistiocytosis chemotherapy and recovered well.

CONCLUSION

S. typhimurium infection triggered sHLH patients who had a ratio of IL-10 to IFN- γ \leq 1.33, an IL-10 concentration \leq 10.0 pg/mL, and/or an IFN- γ concentration \leq 225 pg/mL

at admission. Early antimicrobial and supportive treatment was sufficient, and the Hemophagocytic lymphohistiocytosis-94/2004 protocol was not necessary under these conditions.

Key Words: Hemophagocytic lymphohistiocytosis; Cytokine pattern; Interferon- γ ; Interleukin-10; *Salmonella enterica* serovar Typhimurium; Case report

Chen YY, Xu XZ, Xu XJ. Low interleukin-10 level indicates good prognosis in *salmonella enterica* serovar typhimurium induced pediatric hemophagocytic lymphohistiocytosis: A case report. *World J Clin Cases* 2024; In press

Core Tip: *Salmonella enterica* serovar Typhimurium (*S.Typhimurium*) is one kind of pathogens which can trigger secondary hemophagocytic lymphohistiocytosis (sHLH). There is no consensus on how to treat *S.Typhimurium* triggered sHLH. Compared to controls, *S.Typhimurium* triggered sHLH patient who showed a ratio of interleukin-10 (IL-10) to interferon- γ (IFN- γ) ≤ 1.33 , and IL-10 ≤ 10.0 pg/mL, and/or IFN- $\gamma \leq 225$ pg/mL on admission, Hemophagocytic lymphohistiocytosis -94/2004 protocol was not necessary, and early antimicrobial and supportive treatment would be enough.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome composed of clinical findings, such as fever, hepatosplenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis in the bone marrow or spleen or lymph nodes, low or absent NK-cell activity, and elevated levels of serum ferritin and soluble cluster of differentiation 25 (CD25)^[1]. HLH comprises two conditions: Primary HLH (pHLH) and secondary HLH (sHLH). pHLH occurs in the presence of an underlying predisposing genetic defect in the cytolytic pathway, while sHLH is acquired in the setting of an infectious, malignant, or autoimmune cause without genetic defects^[2].

sHLH can be triggered by the Epstein-Barr virus (EBV)^[3], cytomegalovirus^[4], *Salmonella enterica* serovar Typhimurium (*S. typhimurium*)^[5,6], etc. *S. typhimurium* is a gram-negative bacterium that depends on an essential inflammatory response to colonize the intestinal tract, causing self-limiting gastroenteritis in humans^[7,8]. *S. typhimurium* alone, in some animal models, could be an independent trigger of sHLH^[9]. In pediatric patients infected with *S. typhimurium*, some progress to sHLH^[10]. Cytokine storm syndrome is a life-threatening systemic inflammatory state characterized by elevated levels of circulating cytokines and immune cell hyperactivation^[11]. In our previous study, we reported a specific cytokine pattern for HLH: Interleukin-10 (IL-10) >60 pg/mL, interferon- γ (IFN- γ) >75 pg/mL, and interleukin-6 (IL-6) >51.1 pg/mL^[12]. Patients with a ratio of IL-10 to IFN- γ >1.33 combined with IFN- γ \leq 225 pg/mL were considered to have pHLH, while sHLH patients usually had a ratio of IL-10 to IFN- γ \leq 1.33^[13]. Moreover, an IL-10 concentration \geq 456 pg/mL was an independent prognostic factor for early death^[14]. In this study, a patient who developed HLH due to *S. typhimurium* infection is described; his IL-10 concentration was 9.1 pg/mL, and the ratio of IL-10 to IFN- γ was 0.04 at admission. Seven patients infected with *S. typhimurium* and three EBV-HLH patients were included as controls. The HLH patient did not receive chemotherapy, and after anti-infection therapy and supportive treatments, he recovered very well.

CASE PRESENTATION

Chief complaints

A 9-year-old Chinese boy was admitted to the hospital due to an intermittent fever for 3 d.

History of present illness

Approximately 3 d before admission, the patient presented with a fever of 39.3 °C without any inductive or provocative factors, and his complete blood count (CBC) showed pancytopenia: His white blood cell count was $2.33 \times 10^9/\text{L}$, his hemoglobin level

was 96 g/L, and his platelet was $25 \times 10^9/L$. He did not have any symptoms of cough, vomiting and diarrhea.

6 *History of past illness*

The patient had no relevant medical history.

Personal and family history

There were no special features in the patient's background or family history, and there was no consanguinity.

Physical examination

At the time of admission, this boy had an intermittent fever for 3 d. His abdomen was distended, and there was no enlargement of the spleen or liver below his costal margins. No palpable lymphadenopathy was observed. Physiological reflexes were normal. The Bacillus Calmette-Guerin vaccination scar was normal, and no rashes were observed on his skin. The vital signs of the patient during hospitalization are shown in Table 1.

Laboratory examinations

1 His soluble CD25 concentration was 2646.9 pg/mL. Bone marrow biopsy revealed some hemophagocytic histiocytes and a decreased number of megakaryocytes. T helper 1/T helper 2 (Th1/Th2) cytokine levels, including those of interleukin-2 (IL-2), interleukin-4 **1** (IL-4), IL-6, IL-10, tumour necrosis factor- α (TNF- α), and IFN- γ , were quantitatively determined by a Human Th1/Th2 Cytokine Kit II (BD Biosciences, San Jose, CA, USA) during the course of the disease (Figures 1 and 3). The results of the CBC comparison (Figure 2), C-reactive protein, procalcitonin, fibrinogen, triglyceride, and serum ferritin (SF) levels are shown in Table 1. The other laboratory findings are shown in Table 2.

Imaging examinations

B-ultrasound of the abdomen and chest computed tomography showed no abnormalities.

FINAL DIAGNOSIS

The final diagnosis was sHLH due to *S. typhimurium* infection. The diagnosis of HLH was established on the basis of fever, cytopenia, hypofibrinogenemia, hemophagocytosis in the bone marrow, elevated levels of SF, and increased soluble CD25, which fulfilled more than five criteria. The diagnosis of *S. typhimurium* infection was confirmed by blood culture.

TREATMENT

From September 25 to September 26, this patient received meropenem and linezolid anti-infection therapy. From September 26 to September 28, this patient received meropenem and high-dose methylprednisolone therapy (180 mg/d, with a body weight of 18.8 kg). From September 28 to October 11, this patient received cefoperazone/sulbactam as anti-infection therapy, and *S. typhimurium* was sensitive to the treatment. During the inpatient period, this boy experienced two episodes of shock, one on September 25 and one on October 3, during which his blood pressure decreased to 78/40 mmHg and 72/44 mmHg, respectively. Both episodes of shock occurred after the patient developed a fever, and his body temperature eventually returned to normal. After anti-shock therapy, his vital signs returned to stable. From October 11 to October 17, this patient received meropenem therapy again.

OUTCOME AND FOLLOW-UP

After careful evaluation, this patient did not receive HLH chemotherapy during the whole disease course and was discharged on October 17. During the nonhospitalized period, he was followed up by telephone for more than one year, and he recovered very well.

DISCUSSION

Currently, dexamethasone, etoposide, cyclosporine A, and ruxolitinib are the main choices for HLH treatment^[15]. Reliable laboratory markers that can differentiate subtypes of HLH at an early stage would provide tremendous help for treatment. Several researchers have shown that elevated IL-10 Levels are associated with poor prognosis in HLH^[16,17]. In this study, we examined eight children infected with *S. typhimurium*, and only one of them fulfilled the diagnostic criteria for HLH. The IL-10 Levels in these *S. typhimurium*-HLH patients and the seven controls with *S. typhimurium* infection were lower than 10.0 pg/mL, while the levels of IL-10 in the three EBV-HLH patients were all greater than 10.0 pg/mL. In our clinical practice, different cytokine patterns for differentiating various HLH subtypes could be obtained within 5 h, and eighty-eight patients with IFN- γ levels ≤ 225 pg/mL and a ratio of IL-10 to IFN- $\gamma \leq 1.33$ had the best outcome, showing that this subtype had the best outcome of all HLH subtypes^[13], which was verified by this study.

There is no consensus on how to treat *S. typhimurium*-triggered sHLH, and early intervention is needed to improve outcomes in patients with HLH^[18]. Most of the current research is empirical, and the decision-making process is relevant to the time point at which a positive culture results were obtained and based on the clinician's experience. Several researchers have shown that antimicrobial and supportive treatment alone are effective^[5,19-23]. However, many researchers have used both antimicrobial treatment and the HLH protocol to treat sHLH triggered by *Salmonella* infections^[6,10,24]. In this study, after careful evaluation, our patient did not receive HLH chemotherapy during the whole disease course. After receiving meropenem, linezolid, and cefoperazone/sulbactam for anti-infection therapy combined with high-dose methylprednisolone therapy, the patient recovered very well.

This study has several limitations. First, it was impossible to precisely distinguish pHLH from sHLH, as this patient did not undergo pHLH-related gene examinations during the study period. Second, the seven controls infected with *S. typhimurium* recovered well, and only some agreed to undergo a second recheck of their cytokines

and CBC, which led to missing data. Finally, only one patient infected with *S. typhimurium* progressed to sHLH, and we could not perform a cohort analysis of specific cytokine patterns.

CONCLUSION

In summary, if a *Salmonella*-triggered sHLH patient has a ratio of IL-10 to IFN- γ ≤ 1.33 , an IL-10 concentration ≤ 10.0 pg/mL, and/or an IFN- γ concentration ≤ 225 pg/mL at admission, early antimicrobial and supportive treatment may be sufficient. Eight weeks of dexamethasone treatment and the HLH-94/2004 protocol were not necessary under these conditions.

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