Hemophagocytic Lymphohistiocytosis Secondary to Salmonella paratyphi A Infection Presenting with Severe Pancytopenia and Multiorgan Dysfunction: The First Case Report

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome is a life threatening hyper-inflammatory condition caused by immune dysregulation and resulting in hemophagocytosis and organ damage by activated macrophages and histiocytes. The characteristic clinical features include fever, splenomegaly, cytopenias, liver dysfunction, and hyperferritinemia. HLH can be either primary (genetic), or secondary (acquired HLH) associated with infectious agents, autoimmune diseases, and malignancies. Majority of adult HLH cases are likely to be secondary to an underlying disease. The mortality rates in adults are high, and delayed diagnosis and multiorgan involvement are associated with poor prognosis. A high index of suspicion helps in early diagnosis, and prompt initiation of treatment is absolutely critical.

A few cases of secondary HLH associated with Salmonella Typhi infection have been reported in children and young adults. However a thorough literature search by the authors did not show any previous description of secondary HLH associated with Salmonella Paratyphi A infection.

In the present article, the authors report the case of an 18 year-old male patient who presented with severe pancytopenia and multiorgan dysfunction and was diagnosed to have secondary HLH, the etiology of HLH being Salmonella Paratyphi A infection. The patient responded to dexamethasone and appropriate antibiotics, with complete reversal of pancytopenia and organ dysfunction. To the knowledge of the authors, this is the first case report of secondary hemophagocytic lymphohistiocytosis caused by Salmonella Paratyphi A.

Keywords: Hemophagocytic lymphohistiocytosis; Multiorgan dysfunction; Pancytopenia; Salmonella paratyphi A

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is uncommon in adults and is usually fatal without treatment. A very high index of suspicion is critical for early diagnosis of HLH, and a thorough diagnostic evaluation should be undertaken to identify the underlying etiology. Early initiation of immunosuppressive treatment for HLH is warranted, and delayed diagnosis and treatment are associated with high mortality rates, with multi-system organ failure being the most common cause of death. Although cases of HLH secondary to Salmonella Typhi have been described, there is no report of secondary HLH caused by Salmonella Paratyphi infection. Herein, we report a case where an adult patient presented with severe pancytopenia and multiorgan dysfunction and was diagnosed to have secondary HLH, the etiology of HLH being Salmonella Paratyphi A infection. The patient responded to treatment, and survived without any relapse of HLH.

The Case

An 18 year-old male was brought to the emergency department with fever, cutaneous ecchymoses, melena, oliguria and altered sensorium. His parents informed that he had high grade fever during the previous four days, with headache, vomiting and vague abdominal pain. There was no history of head trauma or seizures. There was no past history of malaria, enteric fever, tuberculosis, leishmaniasis, jaundice, bleeding manifestations, blood transfusion, or known contact with tuberculosis. There was no history of any addiction or high risk sexual behaviour. There was no history of recent vaccination or travel, and his immunization was up to date. The family history was unremarkable. On examination he was febrile (oral temperature 40.5°C), drowsy and irritable, with a score of GCS 10 (E2 M3 V5) on Glasgow Coma Scale. There was tachycardia, tachypnea, hypotension (blood pressure 80/46 mm Hg), jaundice, multiple cutaneous ecchymoses, bilateral cervical lymphadenopathy (maximum dimension 1.5 cm x 1 cm), mild hepatosplenomegaly (liver and spleen palpable 2 cm and 1 cm below costal margin, respectively), and diffuse abdominal tenderness. There was no neck rigidity, or any focal neurodeficit.

The patient was resuscitated with intravenous fluids and inotrope support (noradrenaline), and blood samples were immediately sent for hemogram, malarial parasite and malarial antigens, bacterial cultures, coagulation profile, biochemistry and viral serology. Urine samples were also sent for routine tests and culture. Empiric antibiotic therapy was started with ceftriaxone and vancomycin in view of the altered sensorium associated with fever. He underwent an emergency CT scan of the head after initial resuscitation, which showed no evidence of intracranial hemorrhage. Blood counts revealed severe pancytopenia (hemoglobin 6.1 g/dl, total leukocyte count 0.8 x 10^9/L, and platelet count 5 x 10^9/L.

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The differential leukocyte count reported by automated cell counter showed 53% neutrophils, 35% lymphocytes and 12% monocytes; the absolute neutrophil count (ANC) was 0.42 x 10^9/L. The peripheral blood film did not show blast cells or any abnormal leukocyte, and the red blood cell morphology was normocytic normochromic with no obvious schistocyte, fragmented red cell, normoblast, or malarial parasite. Reticulocyte count was 1.5%, and direct antiglobulin test was negative. Erythrocyte sedimentation rate (ESR) was 10 mm/hour, but C-reactive protein (CRP) level was markedly elevated (172 mg/L). Screening tests for Coxsackie virus, adenovirus, Leptospira, Brucella, HIV and the hepatitis viruses (Hepatitis A, B, C, and E). Chest X-ray was normal. Abdominal ultrasound revealed a 2 cm x 1 cm), and free fluid in abdomen.

Mild hepatomegaly with normal liver echotexture, mild splenomegaly, and hyperferritinemia (serum ferritin 27,000 mg/L). The blood samples were non-reactive for malarial antigens (both Plasmodium falciparum and P. vivax). Dengue NS1 antigen and Dengue IgM antibody, serology for Leptospira, Brucella, HIV, and the hepatitis viruses (Hepatitis A, B, C, and E). Chest X-ray was normal. Abdominal ultrasound revealed mild hepatomegaly with normal liver echotexture, mild splenomegaly, multiple enlarged retroperitoneal lymph nodes (maximum dimension 2 cm x 1 cm), and free fluid in abdomen.

The results of laboratory tests at presentation are shown in table 1.

Bone marrow aspiration and trephine biopsy was performed for investigation of the pancytopenia, and bone marrow aspirates were also sent for bacterial, mycobacterial and fungal cultures. The bone marrow aspiration cytology showed normocellular marrow (Figure 1) with normoblastic erythropoiesis, adequate number of megakaryocytes, and marked hemophagocytosis of marrow erythroid precursors, granulocytes and platelets by many activated macrophages and histiocytes (Figures 2A and 2B). There was no significant myelodysplasia and blast percentage was normal; no hemoparasite was seen on bone marrow cytology. Intravenous dexamethasone 10 mg/m²/day was initiated for HLH on the basis of clinical features and laboratory results, and antibiotics and supportive treatment were continued. The patient received transfusion support with packed red cells, random donor platelets, fresh frozen plasma (FFP), and cryoprecipitate units.

The blood culture samples showed growth of gram negative bacilli after 48 hours and the organism was subsequently identified as Salmonella Paratyphi A. Vancomycin was stopped and patient received ceftriaxone plus ofloxacin according to the sensitivity pattern. Salmonella Paratyphi A was also isolated from the bone marrow culture.

Table 1: The laboratory test results at presentation.

| Investigation/Parameter | Results | Laboratory reference range |
|-------------------------|---------|---------------------------|
| Hemoglobin | 6.1 g/dL | 13-16 g/dL (adult males) |
| Total leukocyte count | 5.0 x 10^9/L | 4.0-10 x 10^9/L |
| Differential leukocyte count | 0.8% | 0.8-4.0% |
| Platelet count | 5 x 10^12/L | 150-450 x 10^12/L |
| Reticulocytes | 1.5% | 0.5-2.0% |
| Direct antiglobulin test | Negative | |
| Erythrocyte sedimentation rate (ESR) | 10 mm/hour | <20 mm/hour |
| C-reactive protein (CRP) | 10 mmol/L | <10 mmol/L |
| Activated partial thromboplastin time | 45 seconds | 11-14 seconds |
| Prothrombin time | 22 seconds | 22.1-27.8 seconds |
| Fibrinogen level | 0.9 g/L | <2.5 g/L |
| D-dimer level | <200 mg/L | <200 mg/L |
| Serum creatinine | 2.2 mg/dl | 0.5-1.2 mg/dl |
| Blood urea nitrogen (BUN) | 38 mg/dL | 7-20 mg/dL |
| Total bilirubin | 2.5 mg/dL | 0.3-1.3 mg/dL |
| Direct bilirubin | 1.2 mg/dl | 0.1-0.4 mg/dL |
| Alanine aminotransferase (ALT) | 458 U/L | 5-40 U/L |
| Aspartate aminotransferase (AST) | 380 U/L | 5-40 U/L |
| Serum Alkaline phosphatase | 772 U/L | 35-110 U/L |
| Gamma glutamyltransferase (GGT) | 152 U/L | 5-40 U/L |
| Plasma total protein | 6.2 g/dL | 6.8-7.5 g/dL |
| Plasma albumin | 3.1 g/dL | 3.5-5.5 g/dL |
| Serum Sodium | 131 mmol/L | 135-145 mmol/L |
| Serum Potassium | 2.6 mmol/L | 3.5-5.0 mmol/L |
| Serum LDH | 889 U/L | 115-220 U/L |
| Fasting plasma triglycerides | 332 mg/dL | 30-200 mg/dL |
| Serum ferritin | 27,000 mg/L | 29-248 ng/mL |

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a hyper-

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inflammatory condition caused by immune dysregulation and low or absent natural killer cell activity, resulting in activation and proliferation of CD8+ T lymphocytes, macrophages and histiocytes, organ infiltration and uncontrolled hemophagocytosis by these cells, and overproduction of cytokines [1,2]. The syndrome is characterized by fever, splenomegaly, cytopenias, liver dysfunction, and hyperferritinemia. HLH can be either primary (genetic), or secondary (acquired HLH) associated with infections (bacteria, viruses, protozoa and fungi), autoimmune diseases, and malignancies especially lymphoma. Majority of adult HLH cases are likely to be secondary to an underlying disease [2]. Whether primary or secondary, treatment for HLH needs to be started urgently to prevent irreversible tissue damage. Delayed diagnosis and multiorgan involvement are associated with poor prognosis [2,3]. The condition is frequently fatal despite treatment. Shabbir et al. in their series reported HLH mortality rate of 72%, with multi-system organ failure being the most common cause of death [3]. Tseng et al. reported 47% mortality in infection associated secondary HLH [4].

Pancytopenia in typhoid fever may result from either bone marrow suppression or infection-associated hemophagocytic syndrome (IAHS) [5,6]. Typhoid fever is rarely associated with HLH [7]. Brown et al. studied Salmonella Typhimurium infection in mice as a natural infectious disease model of secondary HLH for elucidating disease pathogenesis [8]. Secondary HLH associated with Salmonella typhi has been reported in children and young adults [7,9-12]. However a thorough literature search by the authors did not show any previous description of secondary HLH caused by Salmonella paratyphi A.

All patients with secondary HLH may not need to be started on the full HLH treatment protocol; corticosteroid monotherapy alone may be adequate in some cases of infection-associated secondary HLH [2]. Favorable outcomes are seen if prompt therapy is directed against the underlying infection [10]. However, the physician must be prepared to escalate to full HLH therapy if the patient does not respond rapidly (within 24-48 hours) or deteriorates [2]. In the present case, the patient responded to corticosteroid monotherapy and appropriate antibiotics, with complete reversal of pancytopenia and organ dysfunction.

Conclusion

This case report describes for the first time the association between Salmonella Paratyphi A and secondary HLH. It also emphasizes the fact that a high index of clinical suspicion is critical for early diagnosis of secondary HLH, and prompt initiation of HLH-specific immunosuppressive therapy combined with treatment directed against the causative infection can be life-saving in infection-associated hemophagocytic lymphohistiocytosis.

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