

Hemophagocytic lymphohistiocytosis after trauma

Hemophagocytic lymphohistiocytosis

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Abstract

A 6-year-old female patient who had an out-of-car traffic accident, head trauma, increased fever during follow-up, splenomegaly and widespread maculopapular rashes in the whole body was evaluated as secondary hemophagocytic lymphohistiocytosis (HLH) according to laboratory findings of anemia, neutropenia, hyperferritinemia, hypertriglyceridemia and hypofibrinogenemia. Clinical improvement was achieved with intravenous immunoglobulin (IVIg) and steroid treatments. Interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor (TNF) and high concentration of cytokines originating from central nervous system after traumatic brain injury suggest that cytokines play an important role in this post-traumatic pathological process.

This case is presented because it is the first pediatric patient who developed HLH after trauma.

Keywords

Hemophagocytic lymphohistiocytosis; Head trauma

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is characterized by high fever, hepatosplenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, decrease in natural killer cells (NK) activity, increase in soluble (soluble) CD25 activity, the presence of hemophagocytosis in such organs as bone marrow, lymph node, spleen and liver [1].

Secondary HLH can occur in all age groups. Its development can be related to viral (EBV, CMV, Parvovirus, Herpes simplex, Varicella zoster, Rubella, HHV8, HIV), bacterial (Brucella, tbc), parasitic (Leishmania) and fungal infections, as well as malignancy (leukemia and large cell anaplastic lymphoma), metabolic diseases (lysinuric protein intolerance and multiple sulfatase deficiency), immunodeficiency and collagen tissue diseases, inflammatory bowel diseases, sarcoidosis and Kawasaki disease [2].

Case Report

A 6-year-old female patient was transferred to our hospital from the healthcare institution where she was admitted after an out-of-car traffic accident 7 days earlier. Her medical history revealed that she was unconscious when she was taken to the emergency room, was intubated and given respiratory support with mechanical ventilator for 10 days because of superficial respiration. The right leg was splinted due to tibial fracture.

It was learned that mannitol and dexamethasone treatment for brain edema was stopped and meropenem and vancomycin treatments was given for 7 days. Her general condition was poor and her consciousness was confused. Her temperature was 36.8 °C, blood pressure: 85/55 mmHg, peak heart rate: 20 / min respiration rate: 25 / min. Her breathing was superficial, breathing sounds were normal. Liver crossed 1 cm of rib bow

in the middle line.

The patient was re-intubated due to displacement of the endotracheal tube during the transportation and continued respiratory support with mechanical ventilator. Because of low blood pressure, intravenous fluid support was given and dopamine infusion was initiated upon the continuation of hypotension.

Sedation with ketamine and analgesia with fentanyl were achieved and paralysis was achieved with vecuronium. White blood cell count (WBC) was 16.7 / mm³, hemoglobin (Hgb): 9.3g / dL, hematocrit (Hct): 27.5%, platelet count (Plt): 601.000 / mm³, C-reactive protein (CRP): 24 mg / L, albumin: 2.9 g / dL, total protein: 5.6 g / dL, aspartate amino transferase (AST): 50 U / L, alanine amino transferase (ALT): 116 U / L, phosphorus: 0.7 mg / dL, fibrinogen: 491 mg / dL. Other serum electrolytes and biochemistry values were normal.

Antibiotic treatment was continued and phosphorus replacement was performed. Dopamine infusion was discontinued when the blood pressure returned to normal during follow-up.

Brain CT showed a hypodense appearance consistent with contusion in the left cerebellar hemisphere and occipital lobe and a view consistent with subdural effusion reaching a thickness of 6 mm in the right frontoparietal region. The patient was evaluated by the neurosurgery clinic and surgical intervention was not considered. Clinical follow-up was recommended. The patient was fed enterally through a nasogastric catheter. On follow-up, the patient had focal convulsion localized to the left arm and brain tomography was repeated. No difference was detected with the previous imaging.

Electroencephalography (EEG) was performed and interpreted as sleep and wakefulness without epileptiform activity. Ketamine infusion was discontinued and midazolam infusion



Figure 1. Pink colored, puffy, itchy, undefined papular rash occurred on arms.

was started and then phenobarbital was added to the treatment. We tried to reduce the ventilator support gradually, but the patient could not be extubated and tracheostomy was performed. During the follow-up, she had a fever of 39.5 C and simultaneously a pink colored, puffy, itchy, undefined papular rash occurred on her arms and legs (Figure 1). Consultation with dermatologist was performed, skin biopsy was taken and it was reported to be compatible with superficial perivascular dermatitis indicating collagen proliferation. The spleen was palpated 1 cm under the rib. Viral markers were studied and revealed to be negative. There was no growth in blood, urine and throat cultures. Laboratory results were as follows: WBC: 1700 mm³, PLT: 136,000 / mm³, Hgb: 8.9 g / dL, ferritin: 14.931 ng / mL, fibrinogen: 276 mg / dL, cholesterol: 209 mg / dL, triglyceride: 265 mg / dL, AST: 62 U / L, ALT: 106 U / L, Sodium: 130 mmol / L.

The patient was consulted with a pediatric hematology clinic and diagnosed with secondary HLH, then IVIG and steroid treatment started. The patient's fever was reduced, skin lesions faded and disappeared, and laboratory findings returned to normal limits. The patient was gradually separated from the ventilator, followed using a T tube for a while, and then tracheostomy was closed. The patient with good peroral nutrition, stable vital signs and no need for intensive care, was transferred to the pediatric ward to continue follow-up by orthopedics, neurosurgery, physical therapy and rehabilitation clinics.

Discussion

Production and secretion of proinflammatory cytokines after traumatic brain injury have been demonstrated in both human and experimental animal models.

Interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor (TNF) and high concentration of cytokines originating from central nervous system after traumatic brain injury suggest that they play an important role in the pathological process following trauma. Proinflammatory cytokines such as TNF, IL-1 β , IL-6 are synthesized within hours after injury. TNF α is a mediator involved in the pathogenesis of various immune processes, which can induce programmed cell death in neurons. It has been shown that mRNA expression of TNF α is maximal in the damaged cortex and hippocampus after closed head trauma at 1 hour, begins to decrease at 4 hours and is observed at low levels for 24 hours [3].

Systemic findings of HLH. T cells arise from the release of proinflammatory cytokines due to the continuous activation of histiocytes and macrophages.

An increase in serum levels of cytokines such as interferon, TNF- α , IL-6, IL-8, IL-10, IL-12, IL-18, macrophage inflammatory protein-1 α is observed during the active phase of the disease. Cytokines also cause tissue necrosis and organ failure [4].

Our case was diagnosed as HLH due to fever, splenomegaly, bicytopenia, hypertriglyceridemia, hyperferritinemia, hypofibrinogenemia and from supporting findings due to skin rashes and hyponatremia. NK cell activity and soluble interleukin 2 receptor levels could not be determined. In the literature, an adult case who developed hemophagocytic lymphohistiocytosis after closed head trauma has been reported. During the follow-up of a 26-year-old patient who had a traffic accident, due to

fever, pancytopenia and developed multiorgan failure HLH was suspected and ferritin and triglyceride levels were found to be high, and hemophagocytosis was detected in bone marrow examination [5].

Infections play an important role in the onset of the disease. No infectious agent was detected in our patient.

The goal of HLH treatment is to suppress the hyperinflammatory process and eliminate the stimulus that triggers the event. If clinical findings are progressing due to HLH, intravenous immunoglobulin, steroids or drugs such as cyclosporin A and etoposide may be used [6].

Since steroids are cytotoxic for lymphocytes, they inhibit the expression of cytokines, interacts with CD95L production, and provides differentiation of dendritic cells. Cyclosporin A suppresses the activation of T-lymphocytes; It is very effective when used with steroids in macrophage activation syndrome.

After steroid and IVIG treatments, clinical findings of the patient regressed, bicytopenia improved and ferritin level decreased. Tiffany et al. in their study pointed out that the level of ferritin can be used as a prognostic indicator. During the treatment, in the patients with HLH, the reduction of less than 50% in the level of ferritin according to initial values showed that their mortality increased by 17 times compared to observed patients with reduced 96% [7]. In patients who do not respond to treatment, disease activity can be suppressed via cytokine removal by plasma filtration [8].

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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