CASE REPORT OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AFTER INFLUENZA A INFECTION (H1N1) TREATED AT THE NATIONAL HOSPITAL FOR TROPICAL DISEASES

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Summary

Background: Influenza A (H1N1) usually causes mild clinical symptoms and can be self-limiting, in some cases, it may develop abnormally and cause hemophagocytic lymphohistiocytoic (HLH) is a serious, life-threatening medical condition.

Subjects and methods: Description of clinical, subclinical symptoms and results of treatment in a 13-year-old boy with hemophagocytic lymphohistiocytoic after influenza A(H1N1) infection, treated at the National Hospital for Tropical Diseases.

Results: BA 13-year-old boy had onset of symptoms with cough, fever, yellow skin and eyes, anemia, hepatosplenomegaly, no difficulty breathing, no rales in the lungs. PCR test for influenza A(H1N1) was positive, red blood cells decreased (2.8 2T/L), white blood cells decreased (2.6 T/L), platelets decreased (37 G/L), ferritin increased (950 ng/mL), myelogram showed blood phagocytosis. The patient was diagnosed with HLH - influenza A(H1N1) infection according to HLH - 2004 criteria, chemotherapy treatment according to HLH - 2004 regimen, anti-influenza virus and transfusion of red blood cells and fresh plasma. Treatment results, children responded well to treatment, gradually stabilized in clinical and subclinical conditions, and the children were discharged from the hospital.

Conclusion: Attention should be paid to secondary HLH in patients with an unusual course of infection.

Keywords: *Hemophagocytic lymphohistiocytoic, secondary, Influenza A(H1N1).*

OVERVIEW

Hemophagocytic lymphohistiocytoic (HLH) are rare, life-threatening medical conditions characterized by overstimulation of the immune system resulting in an excessive systemic inflammatory response leading to loss of immune balance control. Manifestations of the disease include: prolonged fever, hepatosplenomegaly, decreased blood cell lines, increased triglycerides, increased ferritin, and found phagocytosis of blood cells in liver, spleen, lymph nodes, bone marrow[1]. Currently, hemophagocytic lymphohistiocytoicis divided into primary phagocytic leukemia syndrome, which is caused by a gene mutation that reduces the cytotoxic function of natural killer (NK) cells, causing cytotoxicity and cytotoxicity. Usually occurs in infancy and childhood. Secondary phagocytosis caused by an immunoregulatory disorder such as malignancy (especially lymphoma), immunodeficiency or autoimmune disease and or "trigger" of infection most commonly Epstein infection - Barr virus (EBV), Cytomegalo virus (CMV), in addition to a number of other agents such as Dengue virus, SARS-CoV-2 … usually affect adolescents and adults and are not associated with defects known genetic defects. If HLH is not detected early and treated promptly, the disease will worsen and cause rapid death[2]. Currently, in the world and in Vietnam, the histological association's

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2004 guidelines for diagnosis and treatment of HLH (HLH-2004) are used to supplement the HLH-1994 protocol in diagnosis and treatment[3]. Thanks to this regimen, the survival rate of patients is higher and mortality is significantly reduced [4].

When the COVID-19 pandemic is temporarily brought under control, influenza A - a virus with the ability to change genetics through antigenic changes derived from the rearrangement of gene segments between viruses and can create development of a new antigenic virus with an increasing tendency to cause a worldwide pandemic. In a study by Ka-Fai To et al in 2001 in Hong Kong, the authors found that most of the deaths from H5N1 influenza were related to hematopoietic syndrome[5]. On the occasion of a case of hemophagocytic lymphohistiocytoic after influenza A(H1N1) infection treated at the National Hospital for Tropical Diseases, we would like to describe the clinical and subclinical progress and monitor the treatment results of the patient young.

CASE REPORT

13-year-old boy, healthy history, currently 8th grade student, living in Son La, H-Mong ethnic group. 4 days before admission, the child had a high fever, dry cough, poor appetite, no difficulty breathing, and went to Thao Nguyen general Hospital, Moc Chau district, Son La province with a diagnosis of A(H1N1) Influenza, after 02 days treatment of children with fever, jaundice, pale skin and mucous membranes, hepatosplenomegaly, blood count test with decreased red blood cells and platelets, moderate increase in AST, ALT test, increase in total and direct bilirubin, rate Prothrombin blood decreased severe prognosis should be transferred to the National Hospital for Tropical Diseases. Clinical symptoms: the child is awake, has a continuous fever of 38 - 39^{o}C, cough, no difficulty in breathing, clear yellow skin and eyes, anemia, regular heartbeat, no pathological murmur, clear alveolar murmur 2 lateral, no rales, soft abdomen, no distention, liver sloping costal margin, splenomegaly grade 1, yellow urine, normal defecation. Laboratory tests are described in Table 1.

Table 1. Results of subclinical tests of children

Test indicators	Result	Test indicators	Result
Red blood cell (T/L)	2.82	Triglycerid (mmol/L)	0.69
Hemoglobin (g/L)	80	Ferritin (ng/mL)	950
White blood cell (G/L)	2.6	Blood prothrombin rate: PT (%)	31
Neutrophils (G/L)	1.6	INR	2.3
Platele Count (G/L)	37	HIVAb	Negative
CRP (mg/L)	3.0	PCR CMV (UI/mL)	930
AST (U/L-370C)	76	PCR EBV (UI/mL)	Below threahold
ALT (U/L-370C)	78	PCR Influenza A(H1N1)	Positive
Total Bilirubin (µmol/L)	67.9	Antinuclear antibody	Negative
Direct Bilirubin (µmol/L)	32.8	Anti-DsDNA antibody	Negative

In addition, the results of blood culture, urine culture, and total urinalysis of 10 parameters were all normal. Chest X-ray normal. Abdominal ultrasound: enlarged liver, enlarged spleen, no abdominal fluid, no gallstones.

With the above test results, we suspect that the patient has hemophagocytic lymphohistiocytoic, but bacteremia has not been ruled out, so the child was treated with broad-spectrum antibiotics and had a blood marrow test done. After 5 days of antibiotic therapy and red blood cell transfusion, fresh plasma, clinical condition and total peripheral blood cell count did not improve, subsequent myelogram results: Red blood cell count and hemoglobin factor decreased, white blood cell count decreased, myeloid cell count was normal, met some activated macrophages, some were phagocytosis. No metastatic cancer cells were found.

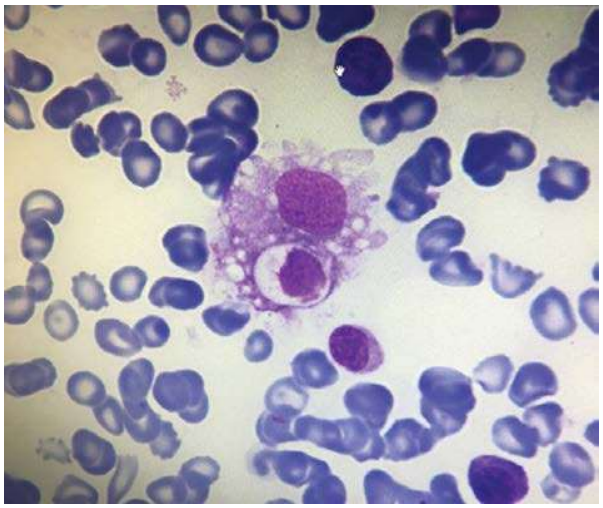

Figure 1. Macrophages phagocytosis of blood cells in the bone marrow of a child

With the results of myelogram blood test, compared with the diagnostic criteria for HLH-2004, we diagnosed the child with HLH after influenza A(H1N1) infection, consulted with a hematologist and treated according to the protocol. HLH - 2004, the results of clinical symptoms and subclinical tests of the children gradually stabilized, the children were discharged from the hospital. We continue to follow up this case after that.

DISCUSSIONS

Pandemics have always been a constant obsession of mankind, especially pandemics caused by influenza viruses. When we trace back the history of influenza pandemics, a repeating pattern can be observed, namely a limited episode the first year, followed by global spread the following year. In the 20th century alone, there have been three raging pandemics, in 1918 with an estimated 100 million deaths, 1957 and 1968, caused by H1N1 (Spanish flu), H2N2 (Asiaflu) and H3N2 (Hong Kong flu). In 1957 and 1968, excess mortality was recorded in infants, the elderly, and those with chronic illnesses, similar to what happened during pandemics. In 1918, there was a marked peak in mortality among 20 to 40 year olds; Leukopenia and hemorrhage are prominent features. Acute pulmonary edema and hemorrhagic pneumonia contribute to rapid mortality in young people. Autopsy showed multiple organ involvement, including pericarditis, myocarditis, hepatitis, and splenomegaly[6]. These findings are in part consistent with the clinical manifestations of human infection with avian influenza A(H5N1) virus, in which hemophagocytosis secondary to a characteristic pathological finding includes thrombocytopenia, abnormal liver function and multiple organ failure5. Today, humanity has made great strides in all fields, but still cannot prevent the great outbreak, typically the COVID-19 pandemic from 2019 to the present. So we can completely observe an influenza pandemic in the near future. In addition, after the flu pandemic has passed, most of the causes of the pandemic will remain and become seasonal flu. The host immune response plays an important role in diseases caused by emerging influenza viruses, such as the pandemic influenza strain of 1918 and the recent strain of avian influenza (H5N1). The continued activation of lymphocytes and macrophages after infection leads to a large cytokine response, which in turn leads to severe systemic inflammation. Further studies on how the virus interacts with the host immune system will be helpful in guiding future treatment strategies to face pandemic influenza. In our study in children In this case, the clinical presentation of influenza is abnormal with signs of hematologic disorders (reduced by 3 lines), gastrointestinal (hepatosplenomegaly, AST, ALT, increased bilirubin, decreased prothrombin ratio) not respiratory symptoms (cough, auscultation, dyspnoea), although leukopenia, elevated AST, and ALT may still occur in influenza patients. In addition, the child's symptoms are not commensurate with the rapid multi-organ failure in severe influenza infection. Although we have searched extensively about infectious diseases, cancers, immune disorders... however, influenza A(H1N1) was found on the results of nose and throat test by PCR method as positive result. Uniqueness explains the initial symptoms of the disease and HLH secondary to influenza infection is proposed. In this child, 5/8 criteria were met for diagnosis of HLH according to the diagnostic criteria of the HLH -2004 histological association although we have not tested 2 criteria for NK cells and soluble CD25. In addition, the patient responded very well to HLH-2004 chemotherapy immunotherapy and treatment of cause[3].

Hemophagocytic lymphohistiocytoic after influenza A(H1N1) - 2009 infection has been reported worldwide, in a study in Germany during the A(H1N1) influenza pandemic (2009), among 25 critically ill patients treated in the intensive care unit. 9 (36%) developed secondary HLH and 8 (89%) of these 9 patients died, whereas out of 16 survivors only 1 patient developed HLH ($p = 0.004$)[7]. Authors Ka-Fai To et al also reported a mortality association in A(H5N1) influenza patients with HLH5 or HLH secondary to influenza A(H3N2) infection by Masaru Ando et al in Japan[8].

CONCLUSION

Post-infectious phagocytosis syndrome is quite rare with diverse clinical and laboratory symptoms, the prognosis is often severe. Although rare, clinicians should be aware of this possibility for early recognition and treatment, especially in cases where the patient presents unusually from the diagnosis.

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