ACU Sağlık Bil Derg 2019; 10(2):322-324
https://doi.org/10.31067/0.2019.157



# A Patient Admitted With Diabetic Ketoacidosis and Developing Secondary Hemophagocytic Syndrome

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**Received :** June 03, 2015
**Revised :** July 07, 2015
**Accepted :** July 21, 2015

**ABSTRACT**

**Hemophagocytic lymphohistiocytosis is characterized by high body temperature, splenomegaly, bicytopenia, hypertriglyceridemia, hyperferritinemia, hypofibrinogenemia, decreased natural killer cell activity, increased soluble CD25 activity and the presence of hemophagocytosis in organs such as the bone marrow, the lymph glands, spleen and liver. We described a patient who was admitted to the intensive care unit with a diagnosis of diabetic ketoacidosis and transferred to the ward when her general condition improved, but who was also diagnosed with hemophagocytic lymphohistiocytosis by bone marrow investigation performed due to a resistant fever, splenomegaly, bicytopenia and hyperferritinemia.**

**Keywords:** Hemophagocytic lymphohistiocytosis, Diabetes Mellitus

**DİABETİK KETOASİDOZ TANISIYLA YATIRILAN VE SEKONDER HEMOFAGOSİTİK SENDROM GELİŞEN BİR OLGU**

**ÖZET**

**Hemofagositik lenfohistiositoz, yüksek ateş, splenomegali, bisitopeni, hipertrigliseridemi, hiperferritinemi, hipofibrinojenemi, doğal öldürücü hücre aktivitesinde azalma, çözünür (solüble) CD25 aktivitesinde artma, kemikiliği, lenfbezi, dalak, karaciğer gibi organlarda hemofagositoz varlığı ile karakterizedir. Burada diabetik ketoasidoz tanısı ile yoğun bakım ünitesine yatırılan,genel durumunun düzelmesi üzerine serviste takibine devam edilen ancak dirençli ateş, splenomegali, bisitopeni, hiperferritinemi nedeniyle yapılan kemikiliği incelemesi ile hemofagositik lenfohistiositoz tanısı alan hasta sunulmuştur.**

**Anahtar sözcükler:** Hemofagositik lenfohistiositozis, Diabetes Mellitus

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive, life-threatening syndrome of excessive immune activation. Prompt initiation of treatment for HLH is essential for the survival of affected patients.

## Case report

An 11-year-old girl under monitoring with a diagnosis of Type 1 diabetes mellitus and using subcutaneous insulin for the previous 3 years presented to our emergency clinic due to nausea, lethargy and distraction (agitation). We learned that these symptoms had persisted for 2 days and that insulin therapy had not been performed/injected/taken during that time. Blood sugar was 550 mg/dl, urine sugar: positive, urine acetone: positive, arterial blood gas pH: 6.9 and $HCO_3$: 7meq/L. The patient

was diagnosed with diabetic ketoacidosis and admitted to the intensive care unit. Diabetic ketoacidosis protocol was applied, and the patient was placed on subcutaneous insulin therapy and transferred to the pediatric ward on the 3rd day of hospitalization. Lobar pneumonia was determined by PA chest radiography performed due to the rising temperature and decreased respiratory sounds in the right hemithorax. Blood, urine and throat culture were taken, and the patient was started on antibiotherapy. Insulin requirement increased from 1 unit/kg per day to 3.5 units/kg per day. However, the fever could not be brought under control. Hemophagocytic syndrome was suspected when splenomegaly developed and WBC was determined at 2700/mm$^3$, Hgb at 7.6 gr/dl and ferritin at 1574 gr/dl. Bone marrow aspiration was performed. Hemophagocytosis was determined by bone marrow investigation (Figure 1). Intravenous immunoglobulin (IVIG) 1 gr/kg per day was administered for 2 days. Fever decreased on the 2nd day of treatment, and blood sugar regulation was achieved. Clinical condition and laboratory findings improved and the patient was discharged and asked to attend subsequent check-ups.

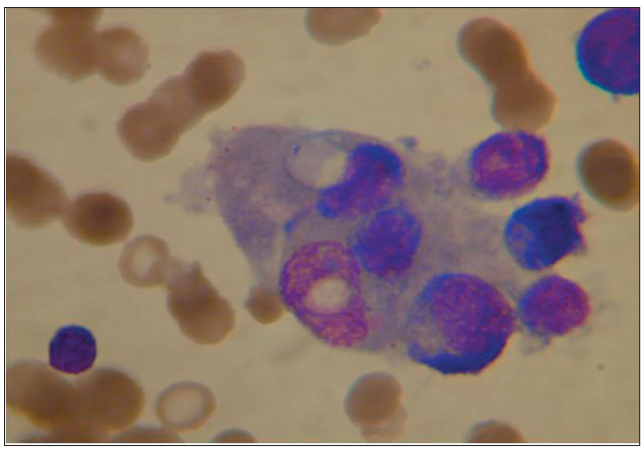

**Figure 1**. Hemophagocytosis in the bone marrow(Wright stain x100)

## Discussion

Hemophagocytic lymphohistiocytosis is an immune system disorder characterized by hemophagocytosis in the bone marrow, uncontrolled T cell and macrophage activation and overproduction of inflammatory cytokines. It is characterized by high body temperature, hepatosplenomegaly,cytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, decreased natural killer (NK) cell activity, increased soluble CD25 activity, and the presence of hemophagocytosis in organs such as the bone marrow, lymph glands, the spleen and liver and the central nervous system (1,2). It may also be accompanied by LDH elevation in blood biochemistry. Nonspecific eruption has been determined in 65% of patients with hemophagocytic lymphohistiocytosis. Neurological symptoms such as convulsion, ataxia, hemiplegia, mental state disorder and irritability have also been reported. Lethargy, lack of appetite and weight loss may be seen. Hemophagocytic lymphohistiocytosis was diagnosed in our case on the basis of high body temperature, splenomegaly, bicytopenia, hyperferritinemia and erythrocytes that have been phagocyted by macrophages in the bone marrow smear.

Secondary hemophagocytic lymphohistiocytosis can appear in all age groups. It may occur in viral (Epstein Barr virus, cytomegalovirus, Parvovirus, Herpes simplex, Varicella zoster, Rubella, HHV8 and HIV), bacterial (Brucella and tuberculosis), parasitic (Leishmania) and fungal infections, as well as with malignancy (leukemia and large cell anaplastic lymphoma), metabolic diseases (lysinuric protein intolerance and multiple sulfatase deficiency), immune deficiency and collagen tissue diseases, inflammatory bowel diseases, sarcoidosis and Kawasaki disease. It is seen sporadically in Chediak-Higashi syndrome 1, Griscelli syndrome 2 and X-linked lymphoproliferative syndrome (3,4).

Determination of infections in cases of hemophagocytic lymphohistiocytosis is not sufficient for the differentiation of primary from secondary disease. Both forms can begin with an infection. Secondary infections can develop easily in cases of familial hemophagocytic lymphohistiocytosis due to decreased NK cell activity and cytopenia. A familial disease or the presence of a known genetic defect, or at least 5 laboratory diagnostic criteria are required for the diagnosis (5). Our patient had no family history and no genetic defect was identified.

Our scan of the literature revealed two cases of diabetes mellitus accompanied by hemophagocytic syndrome (6,7). One involved a case undergoing chronic hemodialysis with hemophagocytic syndrome developing secondary to infection, while the other was a case of hemophagocytic syndrome developing secondary to mucormycosis and with multiple organ failure. We think that hemophagocytic syndrome also developed secondary to infection in our case.

The target of the treatment is the suppression of hyperinflammation and elimination of the stimulus triggering the event. When hemophagocytic lymphohistiocytosis secondary to infection is suspected, treatment of the underlying infection and monitoring with 8-week treatment of the HLH-2004 treatment protocol, and maintenance of treatment in the event of reactivation are recommended. However, corticosteroid and intravenous immunoglobulin

may be sufficient in some mild cases caused by infection (8,9). High-dose corticosteroid and/or cyclosporine A are recommended in patients with macrophage activation syndrome (10). Clinical and laboratory findings improved after IVIG therapy in our case, and no additional treatment was necessary.

This case is reported to emphasize that hemophagocytic lymphohistiocytosis should be considered in the differential diagnosis of patients with fever and diabetes mellitus with increased insulin requirements, and to remind physicians that good results can be achieved with early diagnosis.

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