Case Report

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Hemoophagocitic Lymphohistiocytosis: A Case Report

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Abstract

Hemophagocytic Lymphohistiocytosis (HLH), a rare but life-threatening condition characterized by uncontrolled inflammation, is increasingly recognized in adults. The management of adult onset HLH is challenging, in part due to gaps in current state of knowledge on etiology, clinical presentation, diagnosis, and management. HLH secondary to triggers such as infections, autoimmune disorders, and malignancy are more commonly seen in adults although cases of familial form have also been reported. Underlying conditions such as sepsis, or malignancy could pose as major confounders while applying universal diagnostic criteria, and therefore could lead to delay in diagnosis. Despite advent of newer therapeutic agents, outcomes of adults continue to remain poor. Future efforts need to be orchestrated to develop evidence-based tailored therapies to improve outcomes of this under recognized heterogeneous entity.

Keywords: Hemoophagocitic; Lymphohistiocytosis

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Case Report

Patient Z.D, M, 68 years old from Tirana had approximately one month with: physical weakness, severe abdominal pain, intermittent temperature (above 39'C) and one week before hospitalization at QSUT (dated 12/01/2013) had been hospitalized in Greece (was there - in Kalamata first and then in Athens), where he underwent a series of examinations. Appears urgently as a febrile condition with ascitic fluid and is admitted to gastrohepatology as: Ascitic fluid for determination. S. Decompensated Cirrosis, febrile condition, pleural version.

Life history: Alcohol consumer 200-300 g / day for 10-15 years

Family history: Nothing important

Objective examination

C-V system: FC=88/min; TA 110/70 mmHg, no pathological noise, normal ECG

Vital signs: Temp. 39.8 C, Sat O2 98% (RA)

Respiratory System: Weakened respiration at the base

On palpation: Treatable soft abdomen, liver 3 cm below the costal arch, spleen 1-2 cm below the costal arch; Normosthenic constitution

Subcutaneous skin and mucous membranes

Genitourinary tract normal

Normal reflexes present without pathological reflexes

Inpatient examinations (dated 12/01 /2013)

Blood count: Rbc: 3.700.000/mm3 Hgb: 8.8 g / dl Hct: 28.5% PLt: 57,000 / mm3 Wbc: 6.300/mm3 lymphocite=34% monocite=44% granulocite=22%

Biochemical values: Glucose: 122 mg/dl, Urea: 45.5mg/dl, Creat: 0.67mg/dl, AST: 193U/L, ALT: 99 U/L, Bil.tot: 2.1 mg/dl, Prot tot: 5.7 g/dl

Abdominal ultrasound: Liver is hyperechogenic, d.max: 168mm, gallstone with no stones, free bile ducts, the pancreas is hyperechogenic,normal kidneys,spleen with d.max-135mm,urinary tract and normal prostate. Liquid is found around liver, spleen and in Douglas area.

ECG: Sinus rhythm, Prothrombin level: 52% LDH 2324

Imaging and endoscopy

Abdominal echo: liver maximal diammeter 16 cm homogeneous, without focal lesions, marginal and flat. V.Porta 1.3 cm, gallblader with no calculi, pancreas without lesions. A mass with max diammeter 1.3 cm is observed near the head of the pancreas, spleen 13 cm homogeneous. Urinary bladder with urine. Both kidneys without stones, without stasis. Ascitic liquid in medium quantities.

FGS- Diffuse erosive gastritis

Cardiac echo-VM with normal FS size. Lightly claimed anterior leaf. Minimum mitral regurgitation, normal left atrium, easily calcified, non-dilated right cavities. Pericardium without liquid.

Thorakoabdominal CT Scan-Moderate bilateral pleural effusion normal lungs, free mediastinum, free axils, hepatomegaly, without structural changes, splenomegaly, superior polar splenic infarction, no lymphadenopathy, urinary tract is normal. No digestive lesions. No bone lesions.

Protein electrophoresis: Albumin=55.7% (L) Alpha 1=9.9%, (H) Alpha 2=8.0%, (L) Beta 1=4.2%, Beta 2=4.4% (L) Gamma=17.8% (N) ... Rap A/G=1.26 (normal)

Complete urine; albumin neg; leukocytes 8-10/field; some oxalates

Whole blood; (dt: 15/01/2013) (pancitopenia) Rbc: 3,510,000/mm3; Hgb=8.8g/dl, Hct=26.6%; Wbc: 2500/mm3 differential: seg=25%, sh=8%, limf=28%, mono=34%, mieloc=5% .Plt (microscopic)=32000/mm3. Nb.oxi. 15/100.

HIV Ab-neg; HBsAg neg, HBcAb-neg; HBcAb-neg; HCVAb neg; Wright test-neg; LDH=1912; Ferriti =5677; haptoglobin=1; PCR-966mg/l

Serological tests for: Brucellosa, Leishmania, CMV, HSV, EBV were negative

Mantoux neg, Hemoculture- sterile, Uroculture-sterile

Peripheral blood: leukoerythroblastosis, monocytosis and immature monocytes

Myelogram: Immature monocyte components added in number. Phagocytes with red series cells are observed in their cytoplasm.

Immunophenotype of marrow: 2% myeloid blasts, 22% monocytes (CD 64+ 22%, CD14 + 10%, CD14-=12%), sCD25=3800

Therapy

Ceftriaxone, Elektrolite (NaCl10%; MgSO4 25%), Spironolactone, PFN, Human albumin, Red cell mass transfusions, Vit B1,Vit B6,Vit C, Vit E, Paracetamol (in febrile episodes) , Pantoprazol

Progress and changes in therapy

Based on the examinations, the patient was diagnosed as HLH (Hemophagocytic lymphohistiocytosis) as 5 out of 8 diagnostic criteria were met (biopsy-phagocytes with red series cells and platelets inside were noticed - HLH0. HD Dexa (HLH protocol 2004).

During the stay in gastrohepatology the patient continued with high fever despite antibiotics administered Whole blood (date: 15/01/2013): Rbc: 3,310,000/mm3;

Hgb=8.0g/dl, Hct=29.6%; Wbc: 1370/mm3 differentials: Seg 48%, bands 17%, limf 7%, mono 23%, mielocite 5%. Plt (microscope) 14000/mm3. Nb.oxifile. 20/100. while LDH continues to rise to 3921 and Ferritinemia 8760.

Declining total protein 4.5 and rising triglycerides 593.7

On the 20th the patient's condition is aggravated by abdominal pain with hydroaeric levels, GI hemorrhage and pronounced decrease of the hematological framework: Rbc 2060000/mm3 Hgb.=6.6g/dl Wbc 23000/mm3; Plt=85,000, tital bilirubine 6.5, AST 426, ALT 129.

Direct abdominal radiography: Hydroaeric levels are observed

Surgeon consultation: Impossible to benefit from surgery due to severe compromise of hemostasis.

Hemotransfused with ME, PFN and MT. In resuscitation he is sent with nasogastric tube and dopamine where they continue to be resuscitated with hypertonic drugs but the patient collapses cardiocirculatory and on 21 exitus lethalis

HLH (limfohistiocitoza hemofagocitare)

Hemophagocytic Lymphohistiocytosis (HLH) is a progressive syndrome of unexplained activation of present antigen cells (macrophages and histiocytes) and T- cells. $CD8^{+}$ .Most known genetic causes affect T and NK cell function by impairing normal immune mechanisms. HLH is fatal if left untreated, due to the MOF it causes. It was described as nosology on its own in 1952 by two Scottish pediatricians. A protocol for the treatment of HLH was first developed in 1994 (HLH-94).The biggest barrier to successful treatment is the delay in diagnosis. Many factors influence this delay: the variety of clinical presentation, the low frequency of the disease, and the lack of specific tests or screenings for it.

Clinic: Temperature, Hepato/splenomegaly, polysoliths, weakness

headache, dyspnoea, jaundice, adenopathy +/-,vomiting/diarrhea

Etiology

A-Primary

Family / Genetics

Related Deficiencies-Chediak-Higashi Syndrome, Griscelli syndrome, x-linked proliferative syndrome

Onset of the disease: infections <1 year

B-Secondary

Viral: Herpes virus (50%), especially EBV, CMV (resp 30-50%)

Bacteria (mycobacteriet) fungal

Protozoal (leishmania)

Malignancies

Lymphoma (lymphomaT, HL)

Rheumatological diseases (juvenile arthritis, LES, Macrophage activation syndrome)

Diagnostic criteria

Clinical and testing criteria

Hemophagocytic lymphohistiocytosis can be diagnosed if there is a mutation in a known causative gene or if at least 5 of 8 diagnostic criteria are met:

Fever (peak temperature of >38.5° C for >7 days)

Splenomegaly (spleen palpable >3 cm below costal margin)

Cytopenia involving >2 cell lines (hemoglobin <9 g/dL [90 g/L], absolute neutrophil count < 100/mcL [0.10 × 10^9/L], platelets <100,000/mcL [100 × 10^9/L])

Hypertriglyceridemia (fasting triglycerides >177 mg/dL [2.0 mmol/L] or >3 standard deviations [SD] more than normal value for age) or hypofibrinogenemia (fibrinogen <150 mg/dL [1.5 g/L] or >3 SD less than normal value for age)

Hemophagocytosis (in biopsy samples of bone marrow, spleen, or lymph nodes)

Low or absent natural killer cell activity

Serum ferritin >500 ng/mL (>1123.5 pmol/Lng/mL)

Elevated soluble interleukin-2 (CD25) levels (>2400 U/mL or very high for age)

Genetic mutations associated with HLH include

PRF1

UNC13D

STX11

STXBP2

RAB27

XLP

Because some of these tests may not be widely available and HLH is uncommon, patients are usually referred to specialized centers for evaluation (Figure 1).

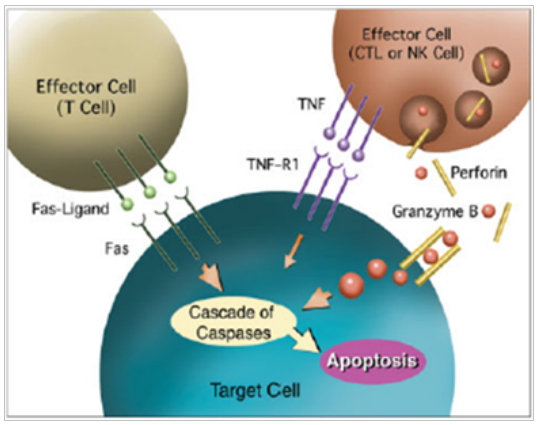

Figure 1: Schematic illustration of major pathways involved in apoptosis triggering. Effector cells such as the cytotoxic T lymphocyte (CTIL) and NL cells may initiate apoptosis of target cells through the release of granzyme B and perforin. Perforin perforates the cell membrane allowing entrance of the toxic granzyme into the target cell. Other mechanisms to induce apoptosis include the tumor necrosis factor (TNF) pathway and Fas/Fas ligand interaction. Fas is deficient in ALPS type I, whereas ALPS type II affects caspase 10 in the cascde of acspases. In FHL, mutations in the gene encoding perforin have been revealed recently.

Citokins

Temperature-IL-1, IL-6

Cytopenia

Hemophagocytosis

Hematopoiesis is suppressed by: IFN-g, TNF-a, IL-B

Increased ferritin - High level of IL-1B, secreted by macrophages

HyperTG-TNF-inhibitor of lipoprotein lipases

Coagulopathy

IL-1B plasminogen activation

KID from increased IFN-g, TNF-a

Dysfunction I Heparit

IFN-g cholestasis, Fas/Fas-ligand apoptosis

Renal insufficiency-increase in IL-6

Increased CD25-secreted by activated T lymphocytes

Prognosis

Mortality rate 22-59%.

Prognostic Factors for Death

30 years

Underlying disease process

Hb <9.0 g/dL

Platelet <100,000/µL

Ferritin> 500 ug / l

Increased bilirubin or ALP

Diferential diagnosis

PTT (fragmentocyte)

LA

Macrophage Activation Syndrome (Still's Disease)

Tuberculosis

George Syndrome (del 22q11.2 conjunctival heart defects)

Kawasaki disease (pediatric age)

Therapy

1. Steroids (Steroids + Etoposide + Cyclosporine A)
2. Other therapeutic options (AntiThymociteGlobluline ,ImunoGlobuline)
3. Bone marrow transplant
4. Immunomodulators TNF- a blockade; infliximab, Target new therapies: anti IL1; antiCD 20 (mabthera) anti cd25 (Daclizumab), Interferon a, etc.
5. In case of complication from EBV: antiviral therapy for EBV has no effect

Discussion

Hemophagocytic Lymphohistiocytosis (HLH) has become more widely recognized in adults, with all ages affected. Patients often suffer from recurrent fever, cytopenia, liver dysfunction, and a sepsis-like syndrome that may rapidly progress to terminal multiple organ failure. Subspecialists in hematology/oncology, infectious diseases, rheumatology/clinical immunology, gastroenterology/hepatology, neurology, emergency medicine, intensive care, and general medicine are challenged by this rare multifaceted syndrome. Physicians should be aware of HLH, because early recognition may prevent irreversible organ damage and subsequent death.

Although familial (primary) HLH (FHL), a major HLH subtype in children, can also occur in adolescents and young adults, secondary (acquired) HLH (sHLH) is by far the most common in these age groups. The treatment protocols HLH-94 and HLH-2004 have been established as scientific cornerstones for diagnosis, classification, and treatment of HLH in patients younger than 18 years.

Our current views on HLH are driven by lessons learned in pediatrics, and pediatricians still often consult on adults with HLH. However, HLH triggers, organ reserve, fitness, and clinical presentation

differ between the pediatric and adult age groups. Transferring pediatric precepts regarding pathogenesis, diagnostics, and treatment of HLH to adult patients may confer risks. Therefore, the HLH Steering Committee of the Histiocyte Society developed these recommendations for diagnosis and treatment of HLH in adults, as a complement to previously published recommendations on etoposide-based therapy in HLH.

In recent years, interest in adult HLH has increased markedly; as a result, HLH is more frequently diagnosed in adults. The dramatic therapeutic success in pediatric HLH has also positively affected the survival of adults with HLH. However, there are profound differences between adult and pediatric HLH; genetic HLH is rare in adults, pediatric diagnostic criteria are suboptimal, frequent (often occult) underlying malignancies or other conditions require a different diagnostic workup, and pediatric treatment regimens may have to be adapted on a case-by-case basis.

In adults, HLH-associated mortality remains high, especially in patients with underlying malignancies. Although the drugs used in pediatric HLH are effective in adult HLH, there is a need for novel agents. Interesting trials testing alternative therapeutic approaches have been initiated, including those incorporating ruxolitinib (JAK1/2 inhibitor; ClinicalTrials.gov identifiers NCT02400463, NCT03795909, NCT03533790), anakinra (IL-1 blockade; NCT02780583), alemtuzumab (NCT02472054), and emapalumab (anti–IFN-γ monoclonal antibody; NCT01818492). It is anticipated that the increased awareness of HLH, together with a more rapid diagnostic workup and new therapeutic approaches, will improve the prognosis of HLH in adults, as has been the case in children [1-5].

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