Acta Biomed 2021; Vol. 92, N. Supplement 1: e2021060 DOI: 10.23750/abm.v92iS1.8836

Case report

Secondary hemophagocytic lymphohistiocytosis: a case report

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Summary. Hemophagocytic lymphohistiocytosis (HLH) is a rare hematologic syndrome presenting either as an inherited life-threatening inflammatory disorder in children or as a secondary disease in adults. Inherited HLH involves inborn defects in lymphocytes and includes autosomal recessive and X-linked disorders characterized by uncontrolled activation of T cells and macrophages and overproduction of inflammatory cytokines. Secondary or acquired HLH occurs in the settings of infections, systemic connective tissue disease and lymphoid malignancies, possibly due to underlying genetic predisposition to develop HLH. The mechanisms leading to secondary HLH have yet to be fully determined and the disease remains frequently undiagnosed and thereby untreated. Herewith we report the case of an 83-year old Caucasian male who referred to our Division of Internal Medicine and Nephrology due to marked asthenia associated with fever, mental confusion, drowsiness and hyporexia, who was ultimately diagnosed with HLH secondary to anaplastic B cell lymphoma. This case report illustrates the difficulties in the diagnostic workup of HLH, mainly related to early identification of the underlying disease and rapid instauration of appropriate therapy. (www.actabiomedica.it)

Key words: hemophagocytic syndrome; lymphoma; fever; hyperferritinemia

Background

Primary hemophagocytic syndrome or hemophagocytic lymphohistiocytosis (HLH) is a rare but severe inflammatory condition that mainly affects infants prior to the first year of life due to a variety of autosomal recessive and X-linked disorders (1). Non-inherited, i.e. secondary forms of HLH have also been increasingly reported in adults over the past 2 decades (2). HLH consists of an overwhelming, yet inappropriate, cytotoxic activation of natural killer cells and/or T lymphocytes, leading to increased serum cytokine levels, with accumulation of activated T cells and macrophages in target organs: spleen, liver, lymph nodes and bone marrow. Usually, HLH can be mainly attributed to a defect in perforin-mediated cytotoxic CD8+ cell and NK cell activities, thereby resulting in a persistent antigenic stimulus and consequent acute immune-mediated tissue damage (3).

While primary HLH is due to genes involved in the cytolytic secretory pathway, secondary HLH is mainly related to immunologic activation following infections, malignancies, autoimmune diseases and/or immune deficiency status (3-5). The therapy of HLH is based on the underlying condition and must start promptly in order to prevent irreversible tissue damage. Unfortunately, an early diagnosis is often lacking and most of HLH cases is either confused with sepsis, metabolic disorders and/or immune deficiency syndromes or remains totally undiagnosed.

Case report

The patient was an 83-years old Caucasian man with a personal history of aortic valve stenosis treated about 20 years ago with mechanical valve prosthesis and evidence of heart failure with reduced ejection

fraction (40%) since the last 5 years. Left atrium was markedly dilated (4.5 cm) and patient manifested with permanent atrial fibrillation under warfarin therapy. The patient also suffered from a previous stroke and presented chronic vascular encephalopathy with mild cognitive impairment. He was admitted to our Division of Internal Medicine and Nephrology due to marked asthenia associated with fever, mental confusion, drowsiness and hyporexia. At the admission, patient also presented hypotension (90/60 mmHg), tachycardia (115 bpm) and dehydration. Body temperature was constantly about 38°C.

Blood tests showed increased blood urea nitrogen (159 mg/dl) and serum creatinine levels (1.99 mg/dl) with hyperkalemia (5.9 mEq/L), increased LDH (2494 IU/L) and CRP concentrations (5.96 mg/dl), normochromic macrocytic anemia (Hb = 11.2 g/dl, MCV = 99 fl, MCHC = 34 g/dl), severe thrombocytopenia (platelet count of 30,000 per microliter) and mild hypertransaminasemia (AST = 141 UI/l, ALT= 40 UI/L). A brain CT scan without contrast confirmed previous stroke without any other relevant abnormalities while an electroencephalogram presented not relevant electrical alterations. Chest X-ray showed diffuse hypodiafania of both lungs and left pleural effusion. The whole abdomen ultrasound imaging revealed splenomegaly (bipolar diameter = 15.5 cm) and no other significant abnormalities.

During the hospitalization period the peripheral blood smear was not suggestive of noteworthy alterations and showed rare myeloid precursors and 3% metamielocytes. Blood tests showed: hyperferritinemia (2656 ng /ml), vitamin B12 (127 pg/ml) and folic acid deficiencies (3.3 ng/ml), mild hypothyroidism (TSH = 5.07 mU/ml, fT3 = 1.00 pg/ml, fT4 = 0.7 ng/dl), slight positivity of anti-platelet antibodies, hypertriglyceridemia (343 mg/dl), normal haptoglobin levels (100 mg/dl), and positive urine culture for Escherichia Coli. Procalcitonin, blood cultures and viral antibodies were all negative. Thus, an urine culture-guided antibiotic therapy with meropenem was started, together with the administration of cyanocobalamin, folates, levothyroxine and corticosteroids (methylprednisolone 1 mg/kg/day, given the presence of anti-platelet autoantibodies and laboratory findings possibily consistent with an autoinflammatory disorder). Absence of leukocytosis, negativity of procalcitonin and blood cultures as well of lacked response to meropenem made our initial tentative diagnosis of sepsis increasingly unlikely.

Therefore, bearing well in mind patients' clinical data and a progressive increment in serum ferritin concentration (from 2656 ng/ml on day 1 to 4500 on day 7), we focused our attention to the so-called hyperferritinemic syndromes such as Still's disease, catastrophic syndromes due to antiphospholipid antibodies, septic shock, and macrophage activation syndrome. Based on the available clinical data and laboratory elements the first three hypotheses were excluded, and a secondary form of HLH was considered. However, bone marrow examination showed no significant alterations. Despite of corticosteroids, platelet count tended to decrease and infusions of platelet pools were performed. Histological examination of the bone marrow clot sections showed a non-Hodgkin lymphoma of large B cells, derived from the activated B cell. Atypical lymphoid cells were CD20 +, MUM +, bcl-2 +, bcl-6 +, CD10-, with very-high proliferative index (Ki67 + in 100% of neoplastic cells) and coexistent aspects of hemophagocytosis (Figure 1). Thus, HLH diagnosis was made but, despite of immediate target therapy instauration, the patient died immediately after diagnosis due to acute pulmonary edema and cardiogenic shock.

Comment

The clinical features of HLH are extremely variable but the disease generally presents with fever associated with multiple organ involvement/failure. Although a definite consensus does not exist, diagnosis of HLH in adults is usually based on the HLH-2004 diagnostic criteria, which are validated for children and commonly applied, but not validated for adults. HLH can be diagnosed if there is a mutation in a known causative gene or if at least 5 of 8 diagnostic criteria are met (2) (Table 1).

A scoring system, the "H score", has been also developed to estimate the probability of HLH in adult patients. The score incorporates graded clinical and laboratory parameters, such as immunosuppression, fever, organomegaly, levels of triglycerides, ferritin,

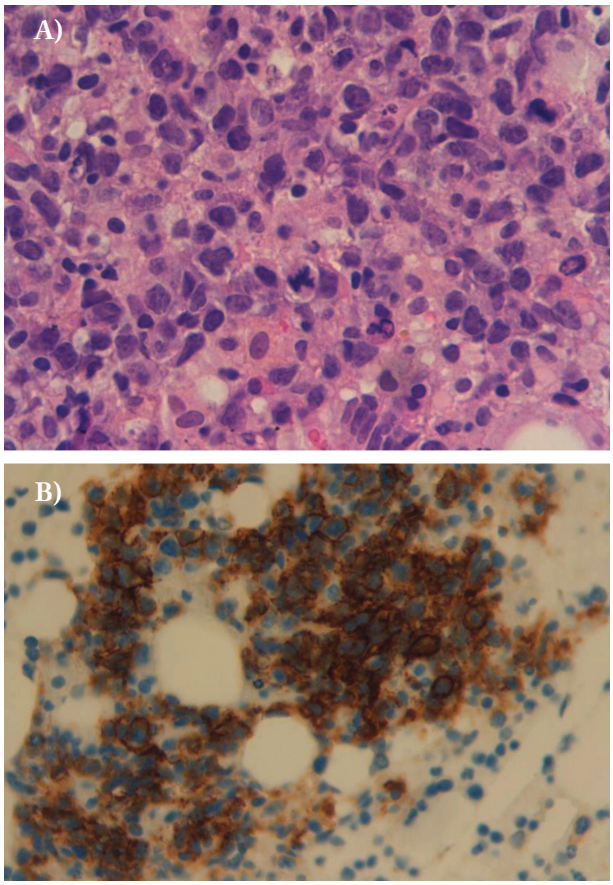

Figure 1. Bone marrow pathology. (A) Hematoxylin & eosin stain showing lymphoma infiltration of the bone marrow and hemophagocytosis. (B) Positive expression of CD20

alanine aminotransferase, fibrinogen, degree of cytopenias and the presence of hemophagocytosis on the bone marrow aspirate. An H score ≥250 confers a 99 percent probability of HLH, whereas a score ≤90 confers a <1 percent probability of HLH (6).

Our patient fullfilled 6 of 8 criteria, i.e. fever, splenomegaly, peripheral cytopenia, hypertriglyceridemia, hyperferritinemia and hemophagocytosis in bone marrow and the H Score revealed a 93-96% probability of HLH.

Prompt treatment of HLH is critical, but the greatest challenge to a successful outcome is the delay in diagnosis due to its rarity, variable clinical presentation, and lack of specificity of the clinical and laboratory findings. HLH as clinical presentation of a non-Hodgkin's large B-cell lymphoma is extremely unusual in clinical practice but seven patients with periferal B-cell lymphoma associated with HLH have been already reported (7). In all of the seven cases, the histologic subtype was diffuse large B-cell lymphoma and the phenotype was C19+, CD20+, S-Ig+, CD10-, with co-expression of CD5 in some cases. The pathogenesis of HLH was due to hypercytokinemia induced by a proliferation of reactive CD8+ cells and secretion of several proinflammatory cytokines and chemokines from neoplastic cells (7). In our case, the initial clinical picture suggested sepsis as a first diagnostic hypothesis. Fur-

Table 1. Diagnostic criteria for hemophagocytic lymphohistiocytosis

1. Molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below)
Fever
Splenomegaly
Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood)
Hemoglobin <90 g/L
Platelets <100 × 109/L
Neutrophils <1.0 × 109/L
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL)
Fibrinogen ≤1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes.
Low or no NK cell activity
Ferritin ≥500 μg/L
sCD25 (ie, soluble IL-2 receptor) ≥2400 U/mL

thermore, the vitamin B12 deficiency, the absence of leukopenia and the positivity of anti-platelet antibodies have strongly misled the correct diagnose. Only the response to corticosteroid therapy and hyperferritinemia shifted the focus to a form of dysregulation of the immune system and led to the subsequent execution of bone marrow aspiration, whose response, however, came too late and did not allow any targeted therapy.

In conclusion, HLH is a rare disease that must be always considered whenever there is a doubtful clinical picture combined with signs and symptoms such as fever and inflammation, particularly in the elderly and/or frail population (8), putting together both the laboratory elements and the instrumental data.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Received: 9 September 2019
Accepted: 3 November 2019
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