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Hemophagocytic lymphohistiocytosis probably triggered by critical lower leg ischemia

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Abstract

A case of hemophagocytic lymphohistiocytosis in a patient with acute critical lower leg ischemia is presented. The association of both conditions is commented on.

Keywords

Hemophagocytic lymphohistiocytosis; Syndrome; Kawasaki disease.

Introduction

Hemophagocytic Lymphohistiocytosis (HLH), also known as hemophagocytic syndrome, is a rare life-threatening systemic disease, characterized by a severe generalized inflammation. It occurs as a result of inappropriate and dysregulated activation of CD8+ cytotoxic T-lymphocytes and macrophages. Those cell secrete high amounts of cytokines, including interferon-γ, tumor necrosis factor-α, interleukin (IL)-1b, and IL-18 [1,2]. The condition is closely related to clinical presentations described as "Macrophage Activation Syndrome", "Cytokine Storm", "Cytokine Release Syndrome", "Hyperinflammatory Reaction", etc. and probably they should all be considered a same entity [3]. Kawasaki disease, toxic shock syndrome, septic shock, and other multisystem diseases also exhibit a very similar pathogenesis [4,5].

HLH is classified as either genetic, most commonly presenting in children, or acquired, most commonly presenting in adults. The second one is generally triggered by malignancy, autoimmune disease, drugs, or infections. Covid-19 has been consistently reported as a predisposing cause of the disease [6].

Herein we report a case of HLH in a patient with acute critical lower leg ischemia, and speculate about the possible relationship between both conditions.

Case presentation

A 54-year-old man presented with acute critical ischemia of his right lower leg, fever, lethargy, and loss of appetite. His past medical record included smoking, hypertension, hypercholesterolemia, myocardial infarction, acute ischemic stroke with complete recovery, and chronic right lower leg ischemia treated with a stent a year earlier. He was on treatment with aspirin, bisoprolol, and atorvastatin.

An emergency femoropopliteal bypass procedure was carried out, but amputation of the third and fourth right toes was needed. Piperacillin-tazobactam was empirically prescribed. Recovery from surgery was uneventful, but lethargy, fever and loss of appetite persisted over the next days. One day after surgery, Glasgow coma scale was 12 points, blood pressure was slightly increased, heart rate was 50 per minute (after stopping bisoprolol), and tympanic temperature was 38.8ºC; otherwise physical examination was unrevealing.

Blood analysis showed increased acute phase reactants, with ferritin 2,540 ng/mL (normal range 12-300), D-diners 35,200 ng/mL (normal range 3-500), fibrinogen 162 mg/dL (normal range 200-400), lactic-dehydrogenase 17,500 U/L (normal range 140-280), slightly increased liver enzymes, mild normocytic anemia and thrombocytopenia, moderately increased white blood cell count with left shift, and hypertriglyceridemia; all other results, including autoantibodies determination, procalcitonin, and troponin were normal. A peripheral blood smear disclosed a leukemoid reaction with the presence of myelocytes, metamyelocytes, and erythroblasts. A bone marrow exam disclosed hemophagocytosis. A lumbar puncture obtained a transparent cerebrospinal fluid; analysis results were: Glucose 53 mg/dL (in blood 143 mg/dL), proteins 108 mg/dL, and white blood cells 54 per µL (65% lymphocytes). A right foot skin sample culture grew Pseudomonas aeruginosa, susceptible to piperacillin-tazobactam. Blood cultures, serologies, and multiple bacteria PCR detection tests of the blood and cerebrospinal fluid were negative. An abdominal ultrasound revealed a 14 cm splenomegaly; while an electrocardiogram, chest radiographs, and a CT-scan of the head were normal.

Intravenous fluid replacement, dexamethasone 16 mg per day, intravenous immunoglobulins 0,5 g/kg per day, and meropenem 1 g every 8 hours were instituted. The patient's condition progressively improved over the next days, and finally he completely recovered.

Discussion

Our patient presented with the typical clinical picture of acquired HLH, but he did not suffer any of the predisposing conditions described in the majority of HLH reported cases so far [2]. A culture from his skin grew P aeruginosa, but the organism was not found in his blood, serum procalcitonin was normal, pyogenic bacteria rarely cause HLH, and he was receiving an antibiotic active against the bacteria. For all those reasons, we believe that the isolation was most probably a contaminant, unrelated to the HLH that he presented [1,7].

In a review of the literature in PubMed, using the terms "Hemophagocytic AND (ischemia OR ne-

crosis)", we have found no cases of HLH associated with acute ischemia. Nonetheless, tissue necrosis and ischemia are a well-known cause of cytotoxin liberation, and therefore it seems reasonable to consider it as a potential predisposing condition of HLH [8]. Moreover, a few cases of HLH related to arteriosclerosis have been described [9]. And interestingly enough, in relation with the recent coronavirus pandemic, an association of arteriosclerosis, covid-19 and cytokine storm syndrome has been hypothesized [10].

HLH is a rare but likely under-recognized syndrome. In acute systemic conditions without an obvious cause, the disease should be considered as a possibility. A timely diagnosis is of particular importance, because delay in treatment has been shown to significantly contribute to a poor outcome [1,2].

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