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The Curious Case of Pyrexia of Unknown Origin

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Case Report

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Abstract

Pyrexia of unknown origin (PUO) is a diagnostic challenge for many clinicians. The causes of PUO are diverse. Infections and malignancies are the most common causes of PUO. There are many rare causes of PUO like aorto-arteritis, Stills disease, sarcoidosis, and temporal arteritis. However, extensive diagnostic tests are required for diagnosis in some cases. We had a 47-year-old lady who presented to us as a rare case of PUO. After extensive investigations she was diagnosed as a case of Idiopathic Hemophagocytic Lymphohistiocytosis (HLH). HLH is a rare disease with high mortality. Most frequently the diagnosis of HLH is missed.

Keywords: PUO; Hemophagocytic Lymphohistiocytosis; HLH

Abbreviations: PUO: Pyrexia of Unknown Origin; HLH: Hemophagocytic Lymphohistiocytosis; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; PET-CT: Positron Emission Tomography-CT; FEL: Familial Erythrophagocytic Lymphohistiocytosis; HCT: Hematopoietic Cell Transplantation.

Introduction

Pyrexia of unknown origin (PUO) is a common condition, which has challenged many doctors to achieve a diagnosis in affected patients. By definition, PUO is a temperature of 38.3 degree Celsius on several occasions, accompanied by more than three weeks of illness and failure to reach a diagnosis even after one week of investigation. Additional categories are included such as nosocomial PUO, neutropenic PUO and HIV-associated PUO. There are many causes of PUO and as a result; investigation of any case of PUO requires knowledge of many diseases across a range of clinical specialties, as well as knowledge of less commonly used investigative tools [1]. The most common cause of PUO in tropical countries like India is infections. Other broad categories of causes of PUO include neoplasms, connective tissue disorders. Diagnosis of PUO is challenging in many cases. Here, we present a case of a 47-year-old woman who was initially diagnosed with PUO but ultimately after vigorous investigations, she was diagnosed with a rare disease.

Case Summary

A 47-year-old lady presented to our hospital with complaints of high-grade fever for 20 days. She also complained of fatigue and diffuse headache. There was no history of cough, cold, urinary symptoms, diarrhea or joint pains. There was no significant past medical history and no co-morbidities such as diabetes/hypertension or hypothyroidism. Her general physical examination and

systemic examination was normal. Vital signs were normal as well.

Prior to her admission, she had history of maculo-papular rash all over her body for which she was treated symptomatically. She was evaluated extensively for her fever. A routine blood workup revealed raised total leucocyte count (15600/dL with neutrophilia 80%); platelets were within normal limits and haemoglobin was 10gm/dL. Peripheral smear showed neutrophilic leukocytosis. On repeat complete blood count, erythrocyte sedimentation rate values had been consistently raised, with values of 88 and 95mmhr (normal 1-20). Repeated blood cultures were negative.

Infectious causes of fever like dengue, leptospira, brucella, Weil Felix and tuberculosis were negative. Widal test for Salmonella Typhi was negative. Peripheral smear for malaria was negative. Serology for HIV 1&2, HbsAg were negative. Mantoux test was also negative.

2D ECHO and X-ray were normal. Ultrasound abdomen and pelvis revealed no abnormality. Anti nuclear antibodies profile was found to be negative. Procalcitonin was borderline positive. Coagulation profile was within normal limits. Blood and urine culture were sterile.

CSF examination was done which showed:
-Cell count-87/dL (80% lymphocytes)
-Protein-50mg/dL
-Sugars-56 mg/dL

After a Syndrome Evaluation System of the cerebrospinal fluid, results were negative for all the organisms tested. Cerebrospinal fluid culture showed no growth (acid fast bacillus/India ink/grams stain showed no organisms).

Imaging modalities used for diagnosis such as computed tomography (CT) brain, revealed mild cerebral edema. Magnetic resonance imaging (MRI) brain was normal. In view of the above investigations, she was started on Ceftriaxone 2 grams BD and Acyclovir. She was also started on Artesunate and Doxycycline, as India is an endemic area for malaria and some rickettsial infections. Despite the extensive treatment, she continued to have fever. Positron emission tomography-CT (PET-CT) scan exhibited an uptake in the axillary and inguinal lymph nodes suggestive of an inflammatory or infective etiology; however these lymph nodes were not enlarged clinically.

Her serum ferritin levels were more than 2000. Serum Triglyceride levels was 520mg/dL. Bone marrow aspiration and biopsy were also done. Bone marrow aspiration showed mild dyserythropoesis, adequate number and morphology of megakaryocytes. Few macrophages engulfing neutrophils and lymphocytes were seen, suggestive of haemophagoctytosis. Bone marrow culture was negative.

In view of the bone marrow findings, elevated serum ferritin, serum triglycerides and presence of fever, a diagnosis of Hemophagocytic lymphohistiocytosis was made. She was then started on Dexamethasone 10 mg/m^2. Her fever came down and gradually she improved. Since the patient improved with Dexamethasone, she was not started on Etoposide. She is presently coming to us for follow up and is now symptom free.

Discussion

HLH may be genetic in origin or arise due to secondary causes like infectious, rheumatologic, malignant or metabolic disorders. HLH is a condition with major diagnostic and therapeutic challenges. The clinical features of HLH are due to unrestrained immune activation which may mimic sepsis with MODS, tropical infections (visceral leishmaniasis, disseminated tuberculosis, leptospirosis, scrub typhus and severe malaria), hematological malignancy and autoimmune disease in adults. Hemophagocytic lymphohistocystosis (HLH) is a rare but potentially fatal disease, which can be recessively inherited or more frequently acquired, usually precipitated by a viral (Epstein Barr or herpes viruses), bacterial or fungal infection [2].

The most accepted theory of HLH pathophysiology is inappropriate immune reaction due to macrophage activation, along with proliferation and activation of T cells associated with inadequate apoptosis of immunogenic cells [3]. It is seen in all age groups, but commonly during infancy. There is no gender predilection [4].

Primary hemophagocytic lymphohistiocytosis (i.e., familial erythrophagocytic lymphohistiocytosis [FEL]) is related to parental consanguinity. A strong immunologic activation, as seen in immunodeficiency, underlying malignancy or with systemic infection is probable cause in Secondary hemophagocytic lymphohistiocytosis. There is a characteristic activation of macrophages and normal T lymphocytes, in both forms of HLH which usually leads to clinical and hematologic alterations and death in the absence of treatment. The pathological hallmark of this disease is the vicious proliferation of activated macrophages and histiocytes, which phagocytose red blood cells, white blood cells, and platelets, leading to the

clinical symptoms. The uncontrolled growth is nonmalignant and does not appear clonal. The preferential sites of involvement include the spleen, bone marrow, lymph nodes, skin, liver and membranes that surround the brain and spinal cord [4].

There are 8 diagnostic criteria, which must be met to establish a diagnosis of HLH; of which our patient had 4.

1. Fever
2. Hypertriglyceridemia
3. Bone marrow biopsy revealed a normocellular marrow showing trilineage haemopoiesis with evidence of hemophagocytosis
4. Raised serum ferritin indicating macrophage activation

Supportive evidence includes elevated liver enzymes-AST, ALT, GGT and lactic dehydrogenase.

The criteria's not met by our patient are:

1. Splenomegaly
2. Cytopenia in two or more cell lines
3. Decreased or absent Natural Killer cell activity
4. Soluble CD25 >2400U/ml

The incidence is reported to be 1.2 cases per million persons per year. 2-6 months after diagnosis is the median survival time, as reported by various studies. The International Hemophagocytic Lymphohistiocytosis registry reports less than 10% probability that the patient survives for 3 years. Despite treatment only 21-26% is expected to survive for 5 years. Remission is always short-lived, as the disease unavoidably reoccurs. The only hope for cure is bone marrow transplant [4].

The exact prevalence of HLH in India is not known. In tropical countries like India, the common cause of PUO is tuberculosis. HLH can be considered and patients can be investigated in all cases of PUO where preliminary tests are negative [5]. According to a study, conducted in North India, malignancy associated HLH was seen in 76% of cases. HLH is likely to be under-diagnosed, which contributes to its high morbidity and mortality [6]. Early recognition is pivotal for survival. The aim of any curative therapy for patients with HLH is to suppress life-threatening inflammation by destroying immune cells [7]. The therapy includes a period of induction, followed by maintenance therapy.

The induction therapy based on the HLH-94 protocol comprises of weekly treatments with Dexamethasone and Etoposide (VP-16). In addition, for those suffering from central nervous system disorders, intrathecal Methotrexate and Hydrocortisone can be given. If the patient is recovering, they are weaned off the treatment; otherwise the therapy is continued before performing allogeneic hematopoietic cell transplantation (HCT).

Conclusion

HLH is an extremely rare cause of PUO. However the possibility of HLH has to be thought of if infectious and malignancies are ruled out. Elevated serum ferritin and triglycerides can raise the possibility of HLH, but bone marrow studies can confirm the diagnosis of HLH.

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