Haemophagocytic Lymphohistiocytosis following Epstein-Barr Infection in an adult, Presented as Pyrexia of Unknown Origin

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Abstract

Epstein-Barr viral infection in an adult is rare in India. Patient presented with pyrexia of unknown origin & was diagnosed to have Epstein-Barr virus infection. Haemophagocytic lymhohistiocytosis following various infection is known. A case of haemophagocytic lymphohistiocytosis following Epstein-Barr virus infection responded to immunosuppression is reported for its varied clinical presentation.

Introduction

It is a clinical condition associated with variety of underlying diseases leading to hyperinflammatory syndrome with hypercytokinaemia and excessive activation of lymphocytes and macrophages. When immune system is triggered in a healthy person, histiocytes, natural killer (NK) cells and cytotoxic T lymphocytes (CTL) are all activated which then naturally stimulate each other by receptor interaction as well as secretion of inflammatory cytokines and chemokines.

Case Report

A 52 year old female presented with complaints of fever (102 deg F) with vague abdominal discomfort since 10 days. Fever was continuous, high grade with chills & was not responding to antipyretics. She also had dry cough, nausea, anorexia, severe weakness since last few days. She is a known case of diabetes mellitus since years and hypertension since 3 years. She has been detected to have hypothyroidism since 2 years and she is taking these drugs Glimipiride- M (1 mg) 1- 0 - 1, Amlodipine (5 mg) 1-0-0 and Eltroxin (100 mcg) 1-0-0. No history of urinary tract infection, chest pain, breathlessness. Patient has no history of joint pain, morning stiffness and has not travelled outside Mumbai. Patient was taking treatment from private practitioner without any relief.

Physical Examination revealed

Pulse 86/minute

Blood Pressure: 130/80 mmHg in supine position

Temperature varying from 102 deg F to 104 deg F

Respiratory Rate 22/minute.

Further examination revealed mild hepatosplenomegaly, mild cervical lymphadenopathy with pallor. After 5 days of hospitalisation, the patient developed petechial rash over both lower limbs. Examination of the other systems was supportive.

Investigations on admission

Haemoglobin of 9.3 g/dl which after 6 days dropped to 6.7 g/dl.

Total leucocytes were 3300 and Platelets 104000 which dropped to 70000.

Malarial parasite and rapid malaria control test and peripheral smear were negative.

Dengue panel (NS 1, IgM, IgG): Negative.

Blood culture was sterile and Widal test was negative.

Urine and stool examinations were normal.

Amylase, lipase, creatinine, D-dimer, serum electrolytes and PT/INR were within normal limits.

Fasting blood sugar : 110 and Post prandial blood sugar 140

Procalcitonin : 0.825 ng/ml moderate risk of infection or shock. Normal range (0.01-0.05)

C Reactive Protein : 118.9 range (0-5) which after

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6 days had become 200.5.

Ultrasonography of the abdomen and pelvis showed hepatosplenomegaly with no other significant abnormality. Computed Tomography (CT Scan) of chest, abdomen and pelvis revealed gross hepatomegaly with generalised fatty infiltration with thin walled cyst in the left lobe. Mild to moderate splenomegaly without any focal lesion. There was no evidence of significant mediastinal lymphadenopathy or lung or pleural involvement.

Discussion

In view of high fever with hapatosplenomegaly with pancytopenia with very high C reactive protein and mild rise in Procalcitonin, inflammatory pathology like Haemophagocytic lymphohistiocytosis was considered and the following investigations were carried out.

Lactate dehydrogenase	854 u/l	range (313-618)
Serum triglycerides	388 mg/dl	range (50-150)
Serum ferritin	587 ng/ml	range (11-264)
Serum fibrinogen	120 mg/dl	range (250-950)
CD 25 counts	2468	
IgM/IgG Cytomegalovirus	Not significant	
IgM VCA for EpsteinBarr virus	33.90	range (N<8)
IgM/IgG Toxoplasmosis	Not significant	
DNA PCR EBV	Positive	

Since there was sufficient evidence of Haemophagocytic lymhohistiocytosis (HLH) and patient did not give consent for bone marrow aspiration, diagnosis of HLH following Epstein-Barr virus infection was made. Patient was given intravenous immunosuppressant drugs which she responded to and gradually tapered over a period of six weeks.

Haemophagocytic lymphohistiocytosis can be classified as:

1. Primary
2. Secondary or Acquired

Primary Haemophagocytic lymphohistiocytosis :

- Restricted to babies and young children (80% of them present when less than one year of age)
- Familial
- Immune deficiency syndromes
- Perforin (PFR) gene mutation

Secondary or Acquired Haemophagocytic lymphohistiocytosis :

1. Infection
   a) Epstein-Barr virus
   b) Cytomegalovirus
   c) Measles
   d) Human Immunodeficiency virus (HIV)
   e) Malaria
   f) Tuberculosis
   g) Salmonella
   h) Kala azar
2. Autoimmune disorders
3. Malignant diseases
4. Immune suppression / Organ transplantation
5. Rheumatologic (Macrophage Activation Syndrome)

Clinical Presentation Of Haemophagocytic lymphohistiocytosis (HLH) :-

Prolonged fever due to increase III Interlukin-l, TNF-alpha, interlukin-6 Hepatosplenomegaly due to organ infiltration by activated immune cells. Cytopenia due to suppression by TNF-alpha and TNF-gamma and consumption by haemophagocytosis Anaemia and thrombocytopenia are more common.

Neurological manifestation: organ infiltration by activated immune cells.

Less common: lymphadenopathy, rash and jaundice.

Laboratory values:

Elevated ferritin levels > 500 ng/ml, most likely due to secretion by activated macrophages

Elevated triglycerides > 265 mg/dl due to increased levels of TNF-alpha which suppress activity of lipoprotein lipase.

Elevated lactate dehydrogenase

Depressed fibrinogen levels < 150 mg/dl due to increased levels of plasminogen activator secreted by activated macrophages

Impaired activity of natural killer (NK) cells

Elevated soluble Interlukin-2 receptor (> 2400)

Perforin by flow cytometry

Gene sequencing to identify mutation

Granules release assay (GRA) test

Haemophagocytosis : although it has been considered the gold standard for Haemophagocytic lymphohistiocytosis, it is not required for diagnosis of Haemophagocytic lymphohistiocytosis.

Treatment

I) Immediate goal is to

A. Suppress the severe hyperinflammation:
   1) Steroids
   2) Cyclosporine A

B. To kill the overstimulated antigen presenting cells
   1) Etoposide
   2) Treat trigerring agent (infection, neoplsms)
   3) Anti Thymocyte Globulin
   4) Rituximab
   5) Intravenous Immunoglobulins
   6) Plasmapharesis

C. Stem cell transfusion

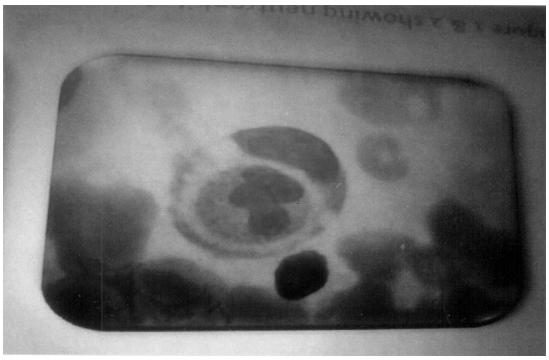

Fig. 1 : Neutrophil phagocytosis

Haemophagocytic lymphohistiocytosis is not uncommon. It is life threatening disease and we get these types of patients in tertiary care set up. Haemophagocytic lymphohistiocytosis should be suspected especially when patients present with fever, hepatosplenomegaly, evolving cytopenia, disturbances in liver function tests or coagulopathy. Immediate blood investigations like serum ferritin, serum triglycerides, lactate dehydrogenase, coagulation profile and serum electrolytes should be done. Bone marrow examination should be done to confirm haemophagocytosis.

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Acute Appendicitis - Appendectomy or the "Antibiotics First" Strategy

The use of advanced imaging and laparoscopy may have increased the number of patients with the diagnosis, a certain proportion of whom may have a resolution of symptoms without appendectomy or may never have progression to clinical appendicitis.

Growing evidence also suggests that perforation is not necessarily the inevitable result of appendiceal obstruction. Perforated appendicitis and nonperforated appendicitis appear to be different entities.

The diagnosis of appendicitis is supported by a history of abdominal pain that begins in the central abdomen and migrates to the right lower quadrant, tenderness to palpation on physical examination of that area, nausea or vomiting mild leucocytosis, and low-grade fever, but these features are inconsistently present, and fewer than 50% of patients may have all these features. In a study involving patients with abdominal pain in whom appendicitis was suspected (but ultrasonography was nondiagnostic), the strongest predictors of appendicitis were migration of pain to the right lower quadrant (odds ratio, 3.4; 95% condifence interval [CI], 1.5 to 7.8) and vomiting (odds ratio, 5.4; 95% CI, 2.4 to 12.4). The use of diagnostic imaging, most often CT or ultrasonography, can minimise the risk that a diagnosis will be missed and can reduce the rate of unnecessary appendectomy.

If high quality ultrasonography is not available or if ultrasonography fails to visualise the appendix, CT with lower-dose radiation protocols if often used.

In the United States, appendectomy is performed laparoscopically in 60 to 80% of cases, with hospitalisation lasting in average of 1 to 3%.

Although it has been routine practice to perform appendectomy promptly after diagnosis, the value of early appendectomy has been called into question.

A major uncertainty in the management of appendicitis is whether an appendectomy is needed or whether antibiotics alone, with an appendectomy performed only if the appendicitis does not resolve (an "antibiotics first" strategy), is a reasonable alternative. The treatment of appendicitis with an antibiotics-first strategy was historically reserved for patients who were many days into an inflammatory process, with **phlegmon** and perhaps an abscess.

Success with an antibiotics-alone approach in Navy personnel in whom appendicitis developed while they were at sea (and did not have access to an operating room) supports this strategy in patients with uncomplicated appendicitis as well. Subsequently, several randomised trials compared appendectomy with an antibiotics-first strategy (with appendectomy as needed) for uncomplicated appendicitis and showed that most patients in the antibiotics-first group were able to avoid appendectomy.

A typical protocol included 24 hours of intravenous antibiotics while the patient was in the hospital, followed by 7 days of oral antibiotics that are sensitive to the typical organisms found in intraabdominal infection (e.g., ciprofloxacin and metronidazole), and did not include repeat imaging to confirm resolution of appendicitis.

In the United States, the usual treatment recommendation for people with uncomplicated appendicitis is a prompt appendectomy.

I recommend that, pending more information regarding the effectiveness of an antibiotics-first approach and the longer-term outcomes of this strategy, patients interested in considering an antibiotics-first approach should be encouraged to participate in clinical trials.

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