We report a case of a 53-year-old male presenting with a history of prolonged fever for one and a half years along with passage of frequent loose stools with occasional hematochezia, significant weight loss and pancytopenia, subsequently diagnosed to suffer from idiopathic hemophagocytic lymphohistiocytosis in the background of non specific colitis. No viral or bacterial pathogen, neoplasm, or autoimmune pathology for such causation could be delineated. To our knowledge this is the first reported case of such an association though very few sporadic case reports of such association with ulcerative colitis and Crohn’s disease have been found in literature.

**Key words:** Hemophagocytic lymphohistiocytosis, non-specific colitis, pancytopenia

**INTRODUCTION**

Hemophagocytic syndrome is an extremely uncommon condition, more so for adults. It is observed mostly in children below 2 years of age. The entity is differentiated into primary and secondary, based on whether an underlying genetic disorder or some other conditions e.g. viral infections are present. It has been associated with viral infections such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), parvovirus, herpes simplex virus (HSV), varicella-zoster virus, Hepatitis A virus, measles, human herpes-8, and HIV. Some cases have also been linked to bacterial and parasitic infections. In adults, most cases are associated with an underlying autoimmune disorder such as lupus, rheumatoid arthritis, sarcoidosis, Sjogren syndrome, polyarteritis nodosa, or a mixed connective tissue disease. It has also been known to be associated with leukemias and lymphomas. Bacterial infections that have been reported in association with hemophagocytic syndrome include Mycobacterium tuberculosis, Brucella sp, and nosocomial infections like Burkholderia cepacia and Acinetobacter baumanii. We report a case of hemophagocytic syndrome who presented with prolonged fever, pancytopenia and colonic ulcers due to non-specific colitis. To our knowledge, this is the first reported case of such an association.

**CASE REPORT**

A 53-year-old non-diabetic, non-hypertensive male, was admitted with history of recurrent episodes of intermittent high fever without chill or rigor for one and a half years duration. He also had frequent loose stools with episodic hematochezia and significant weight loss. He was evaluated earlier in different hospitals. Colonoscopy done outside showed an ulcer in the colon with inconclusive histopathology report. He was put on oral Mesalamine without any overall improvement over next 2 months. He had no history of chronic cough, expectoration, dyspnea, hemoptysis, dysuria, hematuria, jaundice, joint pain, morning stiffness, proximal muscle weakness, or rashes. He had no history of contact with tuberculosis or high risk sexual behavior.

Clinical examination revealed poor nutritional status, coarse dry skin, purpuric spots over anterior trunk, moderate pallor and hepatosplenomegaly. However, there was no icterus, lymphadenopathy, sternal tenderness or ascites.

Initial blood report revealed normocytic anemia (Hb: 7.7 gm/dl, MCV: 88.1 fl), leukopenia (TLC: 2, 100/mm³), neutrophil: 86%, lymphocyte: 9%, monocyte: 4%, eosinophil 1%, basophil: 0%, thrombocytopenia (platelet count: 45,000/mm³), ESR: 46 mm in the first hour, corrected reticulocyte count: 0.5%, fasting blood glucose: 102 mg/dl (normal range: 70-100 mg/dl), urea: 30 mg/dl (normal range: 10-45 mg/dl),
creatinine: 0.8 mg/dl (normal range: 0.8-1.2 mg/dl), bilirubin: 1.9 mg/dl (unconjugated: 1.2 mg/dl), ALT: 274 U/l (normal range: 0-30 U/l), AST: 271 U/l, (normal range: 0-30 U/l), elevated alkaline phosphatase: 640 U/l ((normal range: 30-120 U/l), serum Na+:137 meq/l (normal range: 135-145 meq/l), serum K+: 4.8 meq/l (normal range: 3.5-5 meq/l), serum LDH: 728 U/l (normal range: 140-280 U/l). Routine microscopic examination of stool and urine were normal and stool was positive for occult blood. Ultrasound whole abdomen showed enlarged liver with normal echotexture, no focal lesion or dilated intrahepatic biliary radicles, enlarged spleen, normal diameter portal vein with normal flow pattern, no intra-abdominal lymphadenopathy or ascites. The chest X-ray was unremarkable. Sputum microscopy and culture, Mantoux test, viral markers and HIV serology were negative. CT scan of thorax was non-contributory but CT scan of abdomen showed thickening of antero-lateral aspect of ascending colon and loss of haustrations in descending colon suggestive of chronic inflammatory activity. Repeat colonoscopy showed multiple discrete ulcers in right colon with normal appearing intervening mucosa. Histopathological examination of colonoscopic biopsy from the ulcer was consistent with non-specific colonic inflammation without evidences of cryptitis, crypt abscess or granuloma [Figure 1]. Anti-nuclear antibody, Rheumatoid factor, HLA B 27 and VDRL test were negative. Blood and urine culture showed no growth. Bone marrow aspirate showed hypocellular marrow, hemophagocytosis and increased stainable storage iron [Figure 2-3]. Bone marrow culture for tuberculosis was negative. Serum ferritin was extremely elevated (14191 ng/ml) (normal range: 18-270 ng/ml) and serum triglyceride was also elevated (334 mg/dl) (normal range: <151 mg/dl)

Based on the above findings, a diagnosis of idiopathic haemophagocytic lymphohistiocytosis (HLH) was made. The patient was started on intravenous dexamethasone 10 mg/m² daily for 2 weeks along with oral pantoprazole after consultation with a hematologist. He became afebrile and we started tapering the dose of dexamethasone after 2 weeks. There was no relapse of the fever and the patient was discharged in a stable condition. He is asymptomatic at present and under regular surveillance on out-patient basis.

DISCUSSION

The diagnosis of hemophagocytosis is based on five major and three minor criteria and usually requires all five major criteria. The five major criteria include fever, splenomegaly, cytopenia in a minimum of two cell lines, hypertriglyceridemia or hypofibrinogenemia, and tissue demonstration of hemophagocytosis. The additional minor criteria include low or absent NK cell activity, serum ferritin concentration of greater than 500 ng/L, and soluble CD25 (IL-2 receptor) greater than 2,400 U/mL. Elevated serum ferritin and soluble CD25 may substitute for a major criterion. Diagnosis is difficult, and often multiple bone marrow samples are required for the analysis.[13] Our patient fulfilled these criteria with fever, splenomegaly, pancytopenia, hypertriglyceridemia, bone marrow involvement, and also had markedly elevated serum ferritin. An underlying etiology could not be pinpointed despite extensive searching. However, investigations revealed one associated finding in our patient which included colonic ulcers, histopathologically reported as non specific colonic inflammation. Non specific colitis...
has not been earlier found in association with HLH. The viral markers were, however, negative in our patient.

The essential abnormality in hemophagocytic syndrome seems to be cytokine dysfunction resulting in accumulation of activated histiocytes in multiple organs such as bone marrow, liver and spleen. In these patients, the immunoglobulin levels are normal, but inflammatory markers such as tumor necrosis factor alpha and interleukin (IL)-6, -10, -12, and -16 may be elevated. Some studies have indicated that elevated IL-16 recruits macrophages, IL-18, if elevated, may also stimulate macrophages. Furthermore, a reduction in natural killer (NK) cells and cytotoxic T-cell activity has also been seen in these patients.

The hallmark pathologic finding in the bone marrow is histiocytic hyperplasia with prominent phagocytosis of mature and immature hematopoietic elements. The histiocytes show abundant cytoplasm containing the phagocytized cells; cytoplasmic vacuoles and granules are also frequently seen. The remainder of the marrow usually shows hypoplasia of granulocytic and erythroid lines with megakaryocytic hyperplasia.

The main differential diagnosis is a histiocytic sarcoma, which, in contrast to hemophagocytic syndrome, presents as large atypical histiocyte nuclei and usually a minimal degree of hemophagocytosis. There is also an entity known as macrophage activation syndrome (MAS), which occurs in patients with juvenile rheumatoid arthritis and lupus, has most of the clinical features of HLH, and has been considered by some authors as an acquired form of HLH.

Treatment of HLH is not well defined in the adult population. A consensus statement for children was published in 2004. Initial treatment with etoposide and dexamethasone followed by pulse therapy and cyclosporine demonstrates a 55% survival for a median follow up of 3.1 years in children. Hematopoietic stem cell transplantation can also be used following drug therapy and offers the best hope for a curative effect; however, mortality even in this subset can be as high as 46%. A protocol for chemotherapy in adults with HLH has not yet been established due to scarcity of adult patients with this diagnosis. Our patient responded excellently to steroid monotherapy.

In summary, clinicians must have a high suspicion of idiopathic hemophagocytic syndrome when evaluating patients presenting with long-standing fever, organomegaly and pancytopenia. Any delay in diagnosis and treatment can result in poorer outcome. The association of hemophagocytic syndrome with non-specific colitis should also be worked upon. Once more data on adults with hemophagocytic syndrome have been accumulated; a consensus should be established to develop a standardized optimal therapeutic approach for treating this patient population.

REFERENCES


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