ORIGINAL RESEARCH PAPER

General Medicine

UNUSUAL PRESENTATION AND SPONTANEOUS RECOVERY OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) DUE TO URINARY TRACT INFECTION: UNCOMMON ASSOCIATION OF A COMMON DISEASE.

KEY WORDS: HLH, Urinary tract infection, Fever, Hepatosplenomegaly, macrophage

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ABSTRACT

Hemophagocytic Lymphohistiocytosis (HLH) is an under diagnosed condition which has fatal outcome if not recognized during initial period and effective medical therapy is not prioritized to control the cytokine storm at the outset. It masquerades as multiple diseases and has a variable yet unpredictable clinical course and corollary. We report the uncommon manifestation and outcome of HLH in a patient who presented to our centre with urinary tract infection.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a non-malignant condition associated with profound hemophagocytosis and proliferation of monocyte macrophage cell lines. This syndrome is noted throughout all age groups and it has no definite sex preference. Viral infection like Epstein Bar virus (EBV) has been observed as the commonest trigger.[1] Hemophagocytic lymphohistiocytosis is an often fatal and an under diagnosed disorder which can mimic multiple clinical entity. Early initiation of treatment is vital to control hypercytokinemia associated with HLH; which is the final common pathway resulting in organ failure and death.[2] Spontaneous regression of the condition has also been reported. Seasonal variation with more cases during summer has been reported.[3] The index patient was that of a previously healthy thirty one years old male who was admitted with features suggestive of urinary tract infection that triggered development of HLH.

CASE SUMMARY:

We report the case of a thirty one years old adult man who was hospitalized due to fever, chills and rigor for one week accompanied by fatigue and night sweats. He also had anorexia, poly-arthralgia, burning micturation and hypo gastric pain. He was a fruit vendor by profession and with no history of recent travel. He had taken acetaminophen and cefuroxime tablet for fever but was ineffective.

On admission, patient was febrile with temperature 104° F, pulse rate-100/minute, blood pressure- 100/60 mm Hg. Patient had facial flushing, minimal terminal neck rigidity and without other significant clinical examination findings. No skin rash, lymph node enlargement or hepatosplenomegaly was noted. Radiographs of chest, hands and wrists were normal. Abdominal ultrasound revealed splenomegaly (14 cm).

Blood investigation (on admission) reports revealed leukocytosis, anaemia with hemoglobin of 8.8 g/dL and moderate thrombocytopenia (platelet count: 45 x 10^3 / microlitre. Peripheral smear examination did not reveal any abnormal cells and no hemoparasites could be identified. IgM anti-HAV, HBsAg, Anti HCV, HIV1 and 2, Leptospira serology, Dengue serology as well as anti-nuclear antibody and anti-cardiolipin antibody assays were negative. Urine culture noted infection with multi drug resistant (MDR) *Klebsiella*, resistant to cephalosporins, ampicillin, and gentamicin and sensitive to meropenem as well as imipenem. Blood culture also revealed presence of MDR *Klebsiella* with similar antibiotic sensitivity. Liver function test revealed low albumin (2.7 g/dL) with reversal of albumin and globulin ratio (Globulin: 2.9 g/dL) and elevated transaminase levels (AST: 250 U/L, ALT: 190 U/L). Serum ferritin was >5000.0 ng/mL (30-400 ng/mL) and serum triglyceride was 581 mg/dL (40-160 mg/dL) while thyroid profile was normal. Bone marrow study revealed presence of Hemophagocytic macrophages. Cerebrospinal fluid analysis was normal.

Patient was started on injection ceftriaxone, injection vancomycin and injection dexamethasone empirically on day one due to meningeal signs. Antibiotics were hiked up to injection meropenem on day 4 once culture reports were obtained. The fever decreased on day 7 and completely resolved on day 10. Total leukocyte count decreased to 10000 from 18000 and platelet count spontaneously improved without transfusion on day 7. Platelet count returned to normal level on day 10 with resolution of ancillary symptoms. The diagnosis of Hemophagocytic lymphohistiocytosis due to urinary tract infection was made as per the 2004 HLH diagnostic criteria which resolved spontaneously with resolution of predisposing urinary tract infection. The patient was discharged on day 11 in ambulatory state.

DISCUSSION:

Risdall and his associates initially identified HLH in organ transplantation patients who were suffering from viral infection, later on this syndrome was also reported to occur in immunocompetent subjects as well.[4] Acquired HLH was not reported in the literature with any genetic condition or immunodeficiency state. The actual incidence rate of HLH is still not known. Many studies suggest that HLH is significantly under recognized in adult populations. Many conditions commonly infection and malignancy has been associated with occurrence of HLH, although medical therapy and metabolic causes have been shown to be complicated by HLH as well.[5,6]

Numerous infectious agents was reported as triggering factor of HLH out of which viruses like Epstein Barr virus, Herpes Simplex virus, various viruses causing hepatitis, measles, Mumps, Rubella, Dengue virus, Hanta virus, Parvovirus B19 and enterovirus have been documented most commonly.[7-9] Occurrence of HLH due to Influenza virus has become a major cause of concern of late.[10] HLH have also been documented as one of the initial presentation of HIV infection in case reports.[11] Malaria parasite (Plasmodium vivax and P. falciparum),

toxoplasmosis and babesiosis have also been described as triggers for HLH.[11] Among bacterial agents that have been identified as causative factor of HLH includes *Staphylococcus species* as well as many gram negative bacteria including *E. coli, Klebsiella pneumoniae*, mycobacteria and tuberculosis.[12] The mechanism through which an array of infective agents trigger the auto activation of macrophage and monocyte in HLH remains ill defined.[12]

CONCLUSION:

The mortality due to HLH is very high. A timely diagnosis is essential. Early diagnosis and appropriate management of the precipitating condition is the key management requirement of HLH. Infectious agents have been postulated as an identical triggering event not only in acquired but also in genetic form of Hemophagocytic Lymphohistiocytosis. Most studies in HLH have been conducted in pediatric population; hence it is unknown whether the adults who present with HLH behave in a similar manner. Further studies are required to ascertain the precise pathogenesis of the aberrant immune response in HLH in response to different exogenous triggering factors. This case report aims to show that a very common condition like urinary tract infection can herald the onset of HLH, which has a grave outcome if it is not recognized in a timely manner.

Hemophagocytic syndrome is an uncommon disorder which requires an eagle's eye of the clinician for detection although the manifestations can be associated with variety of etiologies ranging from common infections to rare malignancies. An early detection can lead to improvement in morbidity and mortality in our patients.

AUTHORS CONTRIBUTION:

Dibya Jyoti Sharma: Concept, design, manuscript writing and final approval of manuscript; **Dr. Parvathy Rajmohan:** Manuscript writing; **Phulen Sarma:** Manuscript modification.

CONFLICTS OF INTEREST:

None declared.

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REFERENCES:

1. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med. 2012; 63:233-46. doi: 10.1146 / annurev-med-041610-134208. PMID: 22248322.
2. Rosado FG, Kim AS. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. Am J Clin Pathol. 2013 Jun; 139(6):713-27. doi: 10.1309 / AJCP4ZDKJ4ICOUAT. PMID: 23690113.
3. Chen RL, Su IJ, Lin KH et al. Fulminant childhood hemophagocytic syndrome mimicking histiocytic medullary reticulosis. An atypical form of Epstein-Barr virus infection. Am J Clin Pathol. 1991 Aug; 96(2):171-6. doi: 10.1093 /ajcp/96.2.171. PMID: 1650532.
4. Risdall RJ, McKenna RW, Nesbit ME, Krivit W, Balfour HH Jr, Simmons RL, Brunning RD. Virus-associated hemophagocytic syndrome: a benign histiocytic proliferation distinct from malignant histiocytosis. Cancer. 1979 Sep; 44(3):993-1002. doi: 10.1002/1097-0142(197909)44:3 <993::aid-cncr2820440329>3.0.co;2-5. PMID: 225008.
5. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Eur J Pediatr. 2007 Feb; 166(2):95-109. doi: 10.1007/s00431-006-0258-1. PMID: 17151879.
6. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007 Feb;48(2):124-31. doi: 10.1002/pbc.21039. PMID: 16937360.
7. Suzuki N, Morimoto A, Ohga S, Kudo K, Ishida Y, Ishii E; HLH/LCH Committee of the Japanese Society of Pediatric Hematology. Characteristics of hemophagocytic lymphohistiocytosis in neonates: a nationwide survey in Japan. J Pediatr. 2009 Aug; 1 55(2):235-8.e1. doi: 10.1016 /j. jpeds. 2009. 02.050. PMID: 19446847.
8. Rouphael NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. Lancet Infect Dis. 2007 Dec; 7(12):814-22. doi: 10.1016/S1473-3099(07)70290-6. PMID: 18045564; PMCID: PMC7185531.
9. Katsibardi K, Moschovi MA, Theodoridou M, Spanakis N, Kalabalikis P, Tsakris A, Tzortzatou-Stathopoulou F. Enterovirus-associated hemophagocytic syndrome in children with malignancy: report of three cases and review of the literature. Eur J Pediatr. 2008 Jan; 167(1):97-102. doi: 10.1007/s00431-007-0436-9. Epub 2007 Feb 22. PMID: 17318619.
10. Lai S, Merritt BY, Chen L, Zhou X, Green LK. Hemophagocytic lymphohistiocytosis associated with influenza A (H1N1) infection in a patient with chronic lymphocytic leukemia: an autopsy case report and review of the literature. Ann Diagn Pathol. 2012 Dec; 16(6):477-84. doi: 10.1016/j. anndiagpath.2011.03.009. Epub 2011 Jul 2. PMID: 21724431.
11. Sun HY, Chen MY, Fang CT, Hsieh SM, Hung CC, Chang SC. Hemophagocytic lymphohistiocytosis: an unusual initial presentation of acute HIV infection. J Acquir Immune Defic Syndr. 2004 Dec 1; 37(4):1539-40. doi: 10.1097/01.qai.0000136725.92886.b8. PMID: 15602134.
12. Brastianos PK, Swanson JW, Torbenson M, Sperati J, Karakousis PC. Tuberculosis-associated haemophagocytic syndrome. Lancet Infect Dis. 2006 Jul; 6(7):447-54. doi: 10.1016/S1473-3099(06)70524-2. PMID: 16790385.