Infection Associated with Hemophagocytic Lymphohisticytosis triggered by nosocomial Infection

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) can occur as primary idiopathic syndrome or secondary to neoplastic, infection or autoimmune processes. It is characterized by the proliferation of histiocytes with phagocytosis of formed elements of blood. Clinical manifestations include signs and symptoms of immune activation and pancytopenia. This report presents a child with infection associated with HLH trigged by *Acinetobacter baumannii* sepsis. Multidrug-resistant *Acinetobacter*, an emergent nosocomial pathogen but so far in the literature, it has not been reported to cause HLH.

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Introduction

Hemophagocytic syndrome (HLH) is a nonmalignant disease characterized by an expansion of the monocyte - macrophage population and intensehemophagocytosis.[1] It may occur de novo but often associated with an infection most commonly with *Epstein-Barr* (EBV) Virus. EBV associated HLH may mimic T-cell lymphoma and is treated with cytotoxic drugs, while HLH associated with non-viral pathogens often responds to treatment of the underlying infection.[2] This report presents a three year old boy with in fection associated HLH due to *Acinetobacter baumannii* septicemia following urinary tract infection.

Case History

A three-year -old boy born out of non-consanguineous marriage, with normal growth and development presented with high-grade irregular fever for one month, jaundice and pallor for two weeks. There was no similar type of history in the family. Past history revealed that he was quite healthy since birth and only once hospitalized for diarrhea with severe dehydration and oliguria one and half month back in a local hospital. He was treated with intravenous fluid, antibiotics, and urinary catheterizationon admission, which remained until discharge on the 4th day.

Clinical examination revealed an irritable, febrile (102^{0}F), icteric, moderately pale child with hepatosplenomegaly. The lower border of the liver was 5 cm palpable below the right costal margin with a span of 9 cm which was soft in consistency and the spleen was 3.5 cm below left costal margin. Othersystemic examinations were unremarkable.

Case Report

Laboratory investigations revealed pancytopenia (hemoglobin-7.5gm/dl), total leukocyte count was 1000/cumm (neurophil 5%, lymphocyte 95%, platelet 80,000/cumm) with increased erythrocyte sedimentation rate (52 mm/ 1st hour) and grossly depressed reticulocyte count (0.50%) along with significant elevation of C- reactive protein (16 mg/dL). Malarial parasite was absent in peripheral smear. Cerebrospinal fluid analysis showed; cell count of 10/ cumm, all of which were lymphocytes, protein was formed to be 40 mg/dl and sugar 65mg/dl without any abnormal cell. Liver function test detected serum bilirubin 7.5mg/dl, conjugated 5.5 mg/dl, unconjugated 2 mg/dl, alanine aminotrasferase 4026 U/L (normal 0 -40), aspertate aminotrasferase 3890 U/L (normal 0-40) and alkaline phosphatase was 463U/L.

Total protein was 7.2gm/dl (albumin 3.9gm/dl, globulin 3.3gm/dl). Prothrombin Time was 16.1 second (Control 12.8 sec with International Normalization Ratio of 1.25). Urine for routine and culture detected pus cell 15-20 /High Power Field, red blood cell 10-12/HPF, albumin was one plus and in urine culture grew multi - drug resistant (aminoglycosides, cephalosporins, fluoroquinolones, ampicilline, vancomycin) *Acinetobacter baumannii* 23,0000 colony forming unit/ml of urine. Blood culture was also detected *A. baumannii* with similar pattern of drug resistance.

Serum triglyceride was 275mg/dL (normal 35-114mg/dL) and serum ferritin was 300 microgram/L (15 -140 microgram/L). Blood urea and creatinine were within normal limit. Widal test, HBsAg, malarial antigen (vivax, falciparum), direct hemagglutination test (DAT) for leishmaniasis, Ebstein- Barr virus DNA PCR were all negative. Bone marrow aspiration was performed to rule out any malignancy, but it revealed erythroid hyperplasia with megakaryocytosis and few macrophages with hemophagocytosis. The patient was treated with meropenem and sulbactam, along

with multiple doses of granulocyte colony stimulating factor (G-CSF), packed red blood cell and platelet transfusion without any cytotoxic or immunotherapy. He had improved and was discharged after complete recovery and follow up visit revealed no abnormality.

Discussion

Acinetobacter baumannii is a Gram-negative, non- fermenting coccobacillus, which is present almost every where in nature. *Acinetobacter baumannii* has non- fastidious growth requirements and can grow at various temperature and pH.[3] It can survive in moist or dry conditions in the hospital environment and has intrinsic resistance to many antimicrobial agents. These factors have contributed to the emergence of *A. baumannii* as a leading pathogens in nosocomial infections.

Infections caused by *Acenitobactor* are increasingly being reported as the cause of outbreaks and nosocomial infections such as blood-stream infections ventilators-associated pneumonia and urinary tract infections or wound infections. *Acinetobacter* isolates demonstrate increasing resistance to commonly prescribed antimicrobials.[4] The Multidrug- resistant *Acinetobacter (MDRAB)* was first reported in Taiwan in 1998, after that it has been reported worldwide and is now recognized as one of the most difficult health care-associated infections to control and treat.[5,6] MDRAB is resistant to almost all commercially available antibiotics, including carbapenems, cephalosporins, aztreonam, aminoglycosides and fluoroquinolones. A combination therapy of carbapenem (meropenem) with sulbactam was used to treat the patient and the clinical response was fairly satisfactory. In all probability our patient acquired resistant *A. baumannii* from the hospital one and half month back at the time of urinary bladder catheterization and undue delay of its removal, which is a mal- practice of primary health care centers of developing countries including India.

Hemophagocytic syndrome is an uncommon non-neoplastic disorder of the mononuclear phagocytic system. The pathogenesis of this syndrome is related to uncontrolled activation of the cellular immune system. Evidence suggests that patients have an inability to down regulate immune activation set off by a trigger, usually an infection.[1] The syndrome, which has also been referred to as histiocytic medullary reticulosis, was first described by Scott and Robb-Smith in 1939. HLH was initially thought to be a sporadic disease caused by neoplastic proliferation of histiocytes. Subsequently, a familial form of the disease which is now referred to as familial hemophagocytic lymphohistiocytosis (FHLH) was described. However, the nearly simultaneous development of fatal HLH by a father and son in 1965 indicated that infection might play a role.

Since then, infections associated HLH are considered to be the commonest cause of secondary HLH which include viral infectious such as *Epstein-Barr virus, Cytomegalovirus, Parvovirus, Herpes simplex, Varicella-zoster, measles,* human *Herpes virus-8* and HIV infection. HLH may occur shortly after the initiation of antiretroviral therapy in treatment of HIV-AIDS. HLH may be caused by various other infections like *brucella*, gram negative bacteria, *rickettsia*, *leptospira*, tuberculosis, malaria, leishmania and fungal infections.[7] Other than infection, secondary HLH may be associated with collagen-vascular diseases and malignancies, particularly T-cell lymphomas.

Biopsy specimens of involved organs and bone marrow reveal a generalized histiocytic expansion with marked hemophagocytosis by these histiocytes. The diagnostic criteria are given by Henter et al.[8] It includes (a) Clinical criteria of fever and splenomegaly. (b) Laboratory criteria: cytopenias (≥ 2 cell lines), haemoglobin (<9.0 g/dl), platelets (< 100 × 10 9 / l) neutrophils (<1.0 × 10 9 /L) hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides 2 .0 mmol / l or 3 SD of the normal value for age, fibrinogen 1.5 g/ l or 3 SD of the normal value for age, Ferritin ≥ 5 0 0 μ g/ L, C D2 5 ≥ 2400 U/mL, decreased or absent NK –cell activity. (c) Histopathological criteria: hemophagocytosis in bone marrow, spleen or lymph nodes with no evidence of malignancy.

Certain other associated abnormalities are hyperbilirubinemia, coagulation derangements, elevated serum transaminases and cerebral symptoms with moderate pleocytosis and/or elevated protein, LDH > 1000 U/L. HLH triggered by viral infection may be difficult to distinguish from familial HLH, Although familial HLH (FHLH) should be considered in an infant even in the absence of any positive family history.[9] Patients with FHLH may have hemophagocytic syndrome after a documented viral infection. The treatment of choice for FHLH is allogenic bone marrow transplantation.[10] The EBV associated HLH mimics T-cell lymphoma with higher mortality. In which case cytotoxic chemotherapy and or immunotherapy should be initiated as early as possible. On the contrary, non-EBV associated HLH may be cured by treatment of the underlying infection.[1]

Conclusion

Multidrug- resistant *Acinetobacter* has gradually increased in importance as a nosocomial pathogen with considerable health care expenditure and mortality. Proper sterilization at the time of invasive procedure should be maintained by all hospitals. On the other hand prompt identification and treatment of the underlying triggering factor in the case of infection associated HLH may save the patient's life.

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