Hemophagocytic lymphohistiocytosis secondary to hemodialysis catheter-related blood stream infection

U. Anandh, S. Johari[1], B. Vaswani[2]

Departments of Nephrology, [1]Laboratory Medicine and [2]Clinical Hematology and Oncology, Yashoda Hospitals, Secunderabad, Telangana, India

ABSTRACT

A 57-year-old man on dialysis presented with fever due to *Pseudomonas* septicemia. Workup revealed very high triglycerides and serum ferritin levels. A bone marrow examination showed hemophagocytosis. A diagnosis of hemophagocytic lymphohistiocytosis (HLH) was made and steroids were started. He was put on automated peritoneal dialysis. Patients' condition continued to deteriorate and he succumbed to his illness. This case illustrates the development of HLH secondary to infections which are increasingly being recognized in the literature. Often this diagnosis is missed as it becomes difficult to differentiate between sepsis and HLH. The presence of high ferritin, hypertriglyceridemia, and hemophagocytosis in the bone marrow confirms the diagnosis.

Key words: Catheter infection, hemodialysis, hemophagocytic lymphohistiocytosis

Introduction

Hemodialysis catheter related infections are common in clinical practice. Often they are medically managed with intravenous antibiotics and catheter removal. In certain cases the infection becomes difficult to treat and the patient develops life threatening sepsis. HLH secondary to persistent dialysis catheter infection is a rare occurrence. We report a case of secondary HLH a hemodialysis patient secondary to persistent blood stream infection.

Case Report

A 57-year-old man with chronic kidney disease due to diabetes, was admitted with progressive swelling of legs, shortness of breath, lack of appetite, and vomiting to a hospital elsewhere 6 weeks back. He was evaluated and found to have severe renal failure (serum creatinine 11.3 mg/dl) hyperkalemia (serum potassium 6.0 meq/L), low hemoglobin (9.4 g/dl), normal leukocyte (10,400 cells/mm^3), and platelet (179,000/mm^3) counts. His erythrocyte sedimentation rate (ESR) was 126 mm.

Hemodialysis was started through a right internal jugular dialysis catheter. An arteriovenous fistula was constructed which did not work. He was then continued on dialysis with the right jugular catheter, and his uremic symptoms improved. Two weeks after starting dialysis, he started having fever. Hematological evaluation showed leukocytosis (total count 25,900/mm^3), normal hemoglobin, and normal platelet count. He was started on meropenem and tigecycline initially and subsequently changed over to meropenem when the blood culture grew carbapenem sensitive *Pseudomonas aeruginosa*.

Address for correspondence:
Dr. U. Anandh,
Yashoda Hospitals, Alexander Road, Secunderabad - 500 014, Telangana, India.
E-mail: uanandh@gmail.com

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He showed clinical improvement with meropenem and removal of his dialysis catheter. A repeat blood culture grew no organism, and a left internal jugular dialysis catheter was inserted. He had recurrence of fever within 48 h of the dialysis catheter placement. At this time, the family of the patient requested discharge and was evaluated in our hospital. Clinical examination revealed a sick looking gentleman who was febrile, pale, and icteric. His heart rate was 112/min and his blood pressure was 110/50 mmHg. Systemic examination revealed the presence of hepatosplenomegaly. The patient was drowsy with minimal response to oral commands. The initial laboratory investigations revealed anemia, thrombocytopenia, leukocytosis, and renal failure. His C-reactive protein levels were raised. His ESR was 22 mm. Liver functions revealed conjugated hyperbilirubinemia and raised aspartate aminotransferase levels. Blood glucose levels were reasonably controlled (HbA1c - 6.3). Further investigations showed high serum triglyceride and serum ferritin [Table 1]. Blood culture grew *P. aeruginosa* sensitive to colistin. He was started on appropriately modified dose of intravenous colistin. Tests for dengue and malarial infections were negative. There was no evidence of chest or urinary tract infection. The internal jugular dialysis catheter was removed and a Tenckhoff peritoneal dialysis catheter was placed. Peritoneal dialysis was started after 2 days. Based on the laboratory results, a diagnosis of hemophagocytic lymphohistiocytosis (HLH) secondary to the catheter-related bloodstream infection was considered and a bone marrow was done. The bone marrow aspirate revealed a hypercellular marrow with adequate erythro- and megakaryopoiesis with scattered hemophagocytic macrophages [Figure 1]. A hematology consult was taken and it was decided to start methylprednisolone for the hemophagocytic syndrome. Cyclosporine, etoposide, and other agents were not considered as the patient had ongoing blood stream infection. The patient, despite treatment, continued to remain febrile. His platelet count showed progressive decline (45,000/mm^3). On the 7th day of his hospital stay, he developed hypotension, mucosal bleeding, and respiratory distress. He was intubated and ventilated. Inotropic support was instituted. On the 9th day, he succumbed to his illness.

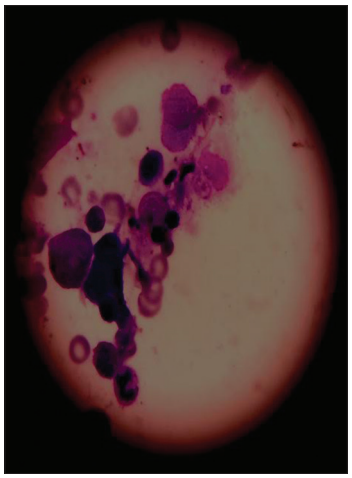

Figure 1: Bone marrow aspirate showing a hemophagocytic macrophage

Table 1: Relevant laboratory investigations of the patient

Laboratory parameter	Test result	Reference range
Hemoglobin (g%)	5.3	13-17
Total leukocyte count (cells/cu mm)	17,300	4000-11,000
Platelet count (lakhs/cumm)	0.9	1.5-4.1
ESR (mm)	22	0-15
PT (s)		
Test	16.8	11-16
Control	13.6	
INR	1.31	
APTT (s)		
Test	31.7	26-40
Control	28.4	
Blood urea (mg/dl)	59	19-43
Serum creatinine (mg/dl)	6.1	0.6-1.5
Serum potassium (mmol/L)	3.74	3.5-5.1
Serum sodium (mmol/L)	142.2	137-145
C-reactive protein (mg/dl)	23.4	>1.0
Bilirubin (mg/dl)		
Total	15.73	0.2-1.3
Conjugated	14.29	0.0-0.3
Alkaline phosphatase (IU/L)	197	38-126
AST (IU/L)	128	17-59
ALT (IU/L)	28	21-72
Total protein (g/dl)	6.3	6.3-8.5
Albumin	2.3	3.5-5.1
Globulin	4.0	2.3-3.5
Serum ammonia (mmol/L)	<9	9-30
Lipid profile*		
Total cholesterol (mg/dl)	128	200-239
HDL cholesterol (mg/dl)	34	30-60
LDL cholesterol (mg/dl)	<30	100-129
Triglyceride (mg/dl)	791	150-199
Serum ferritin (ng/ml)	3246	11.1-264

*All parameters directly assayed as triglycerides were high. ESR: Erythrocyte sedimentation rate, PT: Prothrombin time, APTT: Activated partial thromboplastin time, INR: International normalized ratio, AST: Aspartate aminotransferase, HDL: High density lipoprotein, LDL: Low density lipoprotein, ALT: Alanine aminotransferase

Discussion

HLH is a potentially fatal clinical syndrome which is characterized by activation of T-lymphocytes and macrophages. This hyperinflammation results in excessive release of cytokines.[1] HLH is classified as primary and secondary syndromes. Primary HLH is associated with rare autosomal recessive forms of disease and often manifests in early childhood. Secondary HLH is associated with autoimmune diseases (systemic onset juvenile idiopathic arthritis, systemic lupus erythematosus, etc.), malignancies (lymphoma, leukemia, etc.), and

infections.[2] The secondary HLH associated with autoimmune diseases is often referred to as macrophage activation syndrome.[3] Recently, infections such as dengue and Ebola have been implicated in acquired HLH.[4] Besides infections, drugs especially biologic agents are implicated in secondary HLH.[5]

The most common findings are fever, hepatosplenomegaly, and cytopenias. Other findings include hypertriglyceridemia, coagulopathy, liver dysfunction, elevated levels of ferritin, and serum transaminases. Neurological abnormalities may be associated with cerebrospinal fluid hyperproteinemia and pleocytosis.[6] Histopathological findings include increased maturation of lymphocytes and macrophages which exhibit hemophagocytosis. This atypical cells are demonstrated in spleen, liver, bone marrow, and enlarged lymph nodes.[7] Our patient had many of these typical findings.

The diagnosis of HLH is based on eight criteria, of which five need to be fulfilled for establishing the diagnosis.[8] These criteria are: fever, splenomegaly, cytopenias affecting at least two of three cell lineages, hypertriglyceridemia/hypofibrinogenemia, hemophagocytosis in the bone marrow, spleen, or lymph nodes, low or absent NK-cell activity, hyperferritinemia, and high levels of soluble interleukin -2 receptor (sIL-2r). Our patients had most of the clinical and laboratory findings. Levels of NK-cell activity and sIL-2r were not tested in our patient.

Infections are increasingly recognized as possible cause of HLH in our country.[9] Infections postrenal transplant has been complicated with HLH.[10] However, there is scant literature on bloodstream infections as a cause of HLH. This may be because of lack of clinical suspicion as sepsis can be a presenting feature of blood stream infections and there is a considerable clinical and laboratory overlap between sepsis and HLH. In our patient, the low ESR and high triglycerides made us suspect HLH and further investigations were done. Steroids, cyclosporine, etoposide, and other immunosuppressive agents are considered the mainstay of therapy. It is often difficult to use these agents when there is an ongoing infection and our hematologist advised only steroids as therapy. It is a potentially fatal disease and prognosis is considered to be very poor in patients with multiple organ involvement as was seen in our patient.[11]

Conclusion

HLH should be considered in patients with persistent infection. The diagnosis is often made with laboratory investigations and confirmed with the histopathological evidence of hemophagocytosis. Early diagnosis and institution of therapy in patients with infection is often difficult in many instances as illustrated in our case.

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Conflicts of interest
There are no conflicts of interest.

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