CASE REPORT

Familial Hemophagocytic Lymphohistiocytosis in Two Brothers

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Summary

Familial hemophagocytic lymphohistiocytosis is a disorder which presents with fever, pancytopenia, liver dysfunction and also an increase in non-malignant histiocytes with prominent hemophagocytosis in various organs. It is usually difficult to distinguish from other hemophagocytic syndrome in the absence of family history. It rarely manifests in adults. Chemotherapy is usually indicated. Here, we report the occurrence of this disorder in two brothers in their twenties.

Key Words: Familial hemophagocytic lymphohistiocytosis, Hemophagocytic syndrome

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is not a common disease and is characterised by generalised non-malignant histiocytic proliferation with prominent hemophagocytosis. There are two major types of HLH; primary or familial hemophagocytic lymphohistiocytosis (FHL) which is usually seen in pediatric age group and secondary HLH which can be associated with underlying infection for example Epstein Barr virus (EBV) and underlying malignancy[1].

FHL is an autosomal recessive disorder and most patients with FHL develop the disease within the first 2 years of life. The disease is characterised by fever, hepatosplenomegaly, pancytopenia (at least 2 cells lineages), marrow findings of non-malignant hemophagocytosis and generalised lymphadenopathy. Some may have neurological signs with elevated protein in the cerebrospinal fluid. This disease can be fatal if not treated[1].

Here, we would like to report an unusual presentation of FHL whereby the patients presented at their twenties.

Case Report

CSB, a 21-year-old man presented in September 2000 with pyrexia of unknown origin and significant weight loss for the past 9 months. He has had several hospital admissions for the above problems but no definite diagnosis was made. Physical examination revealed a cachexic looking young man. He was pale on admission with a purplish rash on the thighs. The liver was grossly enlarged extending about 9cm below the right costal margin. The spleen was also enlarged. There was no palpable lymph node.

Investigations done prior to this admission include repeated blood cultures which did not grow any organism. A transthoracic 2D Echocardiogram was normal. Screening tests for typhoid, malaria and leptospirosis were negative. CT scan of the abdomen 9 months ago showed a mild hepatosplenomegaly. Chest radiography was normal. Liver enzymes (ALT and AST) were elevated, at least 4 times the normal value. Total cholesterol was 2.5 mmol/l with a high triglyceride (2.7mmol/l). The hemoglobin was then 11.8g/dl, white cells count of 6.7 x 10^9/l and platelet of 163 x 10^9/l. Anti-

This article was accepted: 18 May 2003

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HIV, Hepatitis B surface Ag and VDRL were not detected. Connective tissue disease screens were negative.

This admission, a full blood picture showed a hemoglobin of 7.6g/dl, white cells count of 2.5 $x10^9$/L and platelet counts of 151 x 10^9/l. A bone marrow aspirate and trephine biopsy was done and this demonstrated about 10% malignant looking histiocytes with demonstrable hemophagocytosis (Fig.1). T cell receptor (TCR) gene rearrangement was not detected from the bone marrow. The liver enzymes were elevated about 2 times the normal value, triglyceride level was high at 3.1mmol/L. ESR was elevated at 50mm/hr. Lactate dehydrogenase was raised (862U/L). Ultrasound of the abdomen at this admission showed hepatosplenomegaly with no enlarged node.

CSH, brother of CSB presented in December 2000 (3 months later from CSB) with one month history of fever and weight loss. Initial investigation in the first admitting hospital was not conclusive. On presentation, he was febrile with herpes simplex infection on the lips. There were no hepatosplenomegaly but bilateral inguinal nodes were palpable. There were also multiple indurated plaque like lesion on both lower limbs and trunk.

A full blood counts showed a hemoglobin of 10.0g/dl, white blood cells of 7.8 $x10^9$/l and platelet counts of 111x 10^9/l. In view of the family history, a bone marrow aspirate and trephine was done and that showed similar findings as CSB i.e increase in histiocytes and hemophagocytosis with a slight increase in plasma cells seen. A biopsy of the skin lesion revealed septal panniculitis consistent with erythema nodosum. EBV serology and connective tissue screens were all negative. Liver function test however was not available.

Both patients were treated with intravenous cyclophosphamide, etoposide and prednisolone monthly for 6 months. There was marked improvement in their symptoms and blood counts. A repeat marrow after 6 months of chemotherapy showed marked improvement though there was still residual hemophagocytosis. Both of them were subsequently maintained on oral cyclosporin for a year. A repeat bone marrow after a year of cyclosporin showed a normal looking marrow for both brothers. There was no longer lymphadenopathy or organomegaly. The blood counts had also returned to normal.

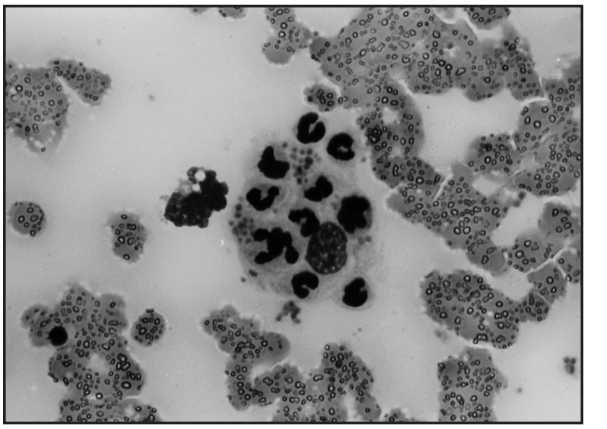

Fig 1: Bone marrow aspirate showing hemophagocytosis

Discussion

HLH is not a common disease in general and even less so in the adult population. It encompasses two different entities which is difficult to distinguish; familial hemophagocytic lymphohistiocytosis (FHL) or primary HLH and secondary HLH[1]. FHL or primary HLH is usually a childhood disease and manifests commonly in the first 2 years of life in about 70% of the cases. It is difficult to distinguish secondary HLH from FHL as both have similar clinical presentation and absence of family history does not exclude one from the other. FHL is an autosomal recessive disease and can also occur sporadically. Secondary HLH has been showned to be associated with various infections including viruses, bacteria and parasites. The known viruses involved are the EBV, CMV, HSV and parainfluenza II. Other associations are autoimmune diseases for example systemic lupus erythematosus (SLE) and malignancy especially lymphoma[2].

Patients commonly present with fever and hepatosplenomegaly. Other clinical features are jaundice, weight loss, lymphadenopathy and neurological signs in the children. Laboratory investigations will reveal elevated liver enzymes, raised LDH concentration, hypertriglyceridemia, hypofibrinogenemia and increased ferritin level. CSF may show elevated protein levels with pleocytosis. The main histology of the various organ involved especially bone marrow will demonstrate an increase in histiocytic activity with increased hemophagocytosis. The criteria for diagnosis according to Henter et al 1991 includes: 1) fever, 2) splenomegaly, 3) hypertriglyceridemia/

hypofibrinogenemia, 4) cytopenia (at least 2 lineages) and 5) bone marrow demonstrating increased hemophagocytosis without evidence of malignancy[3]. It is a highly fatal disease when left untreated with a high chance of relapse[1].

The etiology of this disease is not well documented and it is thought to be related to immune dysregulations causing a hypercytokinemia. There have been reports to suggest that this is due to a defect in the NK-T cell activities which normally regulate the normal apoptosis process in the reticuloendothelial system. It was showned that mutation of perforin gene located at.chromosome 10q22 is associated with FHL. Perforin is contained in the granules of cytotoxic T lymphocytes and its secretion contribute to T cell destruction of the target cells. Hence, with the NK/T cell dysfunction, it predisposes the patients to overwhelming infection[4].

Kaito et al has suggested that certain prognostic factors be taken into consideration before the commencement of treatment in the adults. The reported bad prognostic factors are age over 30 years, anemia and thrombocytopenia on admission, worsening of anemia and thrombocytopenia, absence of lymphadenopathy, elevation of alkaline phosphatase and total bilirubin, presence of DIC and elevation of ferritin[2]. If the patient has any of the bad prognostic factors, chemotherapy should be started as soon as possible. The mortality for this disease is high with documented fatality rate of more than 50% in non familial HLH and even higher in FHL without treatment[1].

Treatment strategies differ slightly between adults and children due to the different etiology of the disease. In adults, the etiology is usually secondary and hence treatment should be focus on treating the underlying disease. However, initial treatment similar to that of FHL may be necessary to halter unrestricted disease activity. The treatment usually involves chemotherapeutic agents and perhaps bone marrow transplantation. There is no definite treatment strategy because of the complicated state of this disease. The Hemophagocytic Lymphohistiocytosis Study Group of the Histiocyte Society recommends that the initial therapy to be a combination of chemotherapeutic regimen consisting of mainly epipodophyllotoxin group,e.g etoposide (VP16) and dexamethasone. Other drugs used are vinka alkaloids and intrathecal methotrexate. Steroids and methotrexate therapy are important in patients with central nervous system involvement. Combination of cyclosporin is then given to maintain remission while minimizing the risk of secondary leukemia or myelodysplastic syndrome due to VP16[1]. The duration of the maintenance therapy is not definite and should be individualised. In FHL, subsequent allogeneic bone marrow transplantation should be recommended or at least contemplated since chemotherapy is usually not curative and the chance of relapse is very high[1,5]. The use of matched sibling may be limited since HLH may develop in the donor sibling and this may lead to recurrence of the disease in the recipient following transplantation. Some centres have relative good experience in related and unrelated matched bone marrow transplantation with an overall survival rate of 45% in 3 years[5]. At present, allogeneic bone marrow transplantation offers the only curative options for such patients in a disease which is almost always fatal.

In our patients, both of them showed the typical bone marrow findings with consistent peripheral blood findings. Both of them responded well with the chemotherapy given. Allogeneic bone marrow transplantation is not currently offered due to financial constrain. However, this will be not be delayed if either of them shows any signs of relapse.

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