Hemophagocytic Lymphohistiocytosis Masking the Diagnosis of Lymphoma in an Adolescent Male

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Abstract Hemophagocytic lymphohistiocytosis (HLH) association with an underlying lymphoma is an uncommon entity in paediatrics. It may precede lymphoma diagnosis by several years or may occur at the time of remission or relapse of lymphoma. Simultaneous occurrence of HLH & lymphoma is rare. We here with report a case where HLH was the initial presentation which masked the diagnosis of lymphoma, however tissue biopsy revealed the underlying non-Hodgkin's lymphoma.

Keywords Hemophagocytic lymphohistiocytosis · Lymphoma · Tissue diagnosis

Introduction

Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome is a clinicopathologic syndrome characterized by proliferation of histiocytes and hemophagocytosis involving the bone marrow, liver, spleen and lymph nodes. Hemophagocytic lymphohistiocytosis can be primarily due to congenital deficiency of perforin or secondary to infection, inflammation or malignancy. HLH may be the initial presentation of a lymphoma or it may precede the recognition of underlying lymphoma or it can occur at remission, relapse or transformation [1]. The clinical, pathologic and pathogenetic features of HLH associated lymphomas remain ill-defined due to rarity of clinical cases and

difficult diagnosis [2, 3]. We report the case of an adolescent boy where the underlying lymphoma was masked initially by features of HLH and the method in which accurate diagnosis was finally made.

Case Report

A 12 year old male presented with complaints of fever for 1 week, facial puffiness, abdominal pain and erythematous rash for 3 days. On admission, child was febrile, sick looking with pallor and findings of third spacing suggestive of volume overload and moderate hepatomegaly. Investigations revealed neutrophilic leucocytosis, haemoglobin 9.8 g/dL, platelets 1.6 lakhs/mm³, peripheral smear showed toxic granules; serum sodium was 133 mEq/L with other electrolytes and liver enzymes within normal range. On the basis of the above findings, scrub typhus and enteric fever with third spacing were the provisional differential diagnosis. Child was started on antibiotics (Ceftriaxone and doxycycline) pending blood culture and scrub typhus IgM reports. At 48–72 hr of hospitalisation, his symptoms persisted with poor response to antibiotics. On the fourth day of admission he developed generalised significant lymphadenopathy involving bilateral jugulodigastric, cervical, axillary and inguinal nodes. Chest X-ray was negative for mediastinal nodes. Ultrasonogram of abdomen revealed mild hepatomegaly, moderate splenomegaly, few nodes at the porta hepatis and free fluid in the abdomen. Infectious mononucleosis was considered as a possibility and EBV VCA IgM was done. In view of persisting fever spikes, complete blood count was repeated on the seventh day of hospital stay. Investigations revealed persisting leucocytosis, falling haemoglobin (8.9 g/dL) and falling platelet count (50,000/mm³). Blood culture was sterile; WIDAL was

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negative, EBV VCA IgM negative, scrub typhus IgM negative. With evidence of poor response to treatment, antibiotics were escalated to piperacillin-tazobactam. Child continued to have fever spikes, hepatosplenomegaly and bicytopenia 2 weeks after initiation of treatment. Therefore, alternative diagnoses of hemophagocytic lymphohistiocytosis, disseminated tuberculosis, connective tissue disorder and lymphoreticular malignancy were suspected. Fibrinogen levels were low, ferritin and triglycerides were elevated but not characteristic of HLH. Bone marrow aspiration revealed reactive marrow. Meanwhile, the child's condition worsened with increasing third spacing, progressive pallor and thrombocytopenia. Azithromycin was added to increase antibiotic coverage. During the third week of illness, with no significant improvement in child's condition, HLH workup was repeated. A significant fall in fibrinogen levels (63 g/L) and moderately raised triglycerides (266 mg/dL) and ferritin levels (4,588 µg/L) were noted. Bone marrow showed the presence of histiocytes. ESR, LDH and uric acid were normal. Gastric juice was negative for Acid fast bacilli thrice. TB Quantiferon and Brucella IgM; ANA and ANCA were negative. Considering the patient's deteriorating clinical condition and inconclusive laboratory findings, cervical lymph node biopsy was done for want of clue to diagnosis. With laboratory parameters suggestive of HLH, treatment was started for the same with HLH 2004 protocol. Within 72–96 h of initiation of HLH protocol, child's condition started improving with increasing total counts, decreasing third spacing and regressing lymphadenopathy and hepatosplenomegaly. Cervical lymph node biopsy report was obtained which revealed Non-Hodgkin's lymphoma (NHL). Sub categorisation based on immunohistochemistry was suggestive of T cell lymphoma. At this stage, we were faced with the diagnostic dilemma of two diagnoses in the same patient—HLH and NHL. Chemotherapy for lymphoma was initiated and HLH protocol was abandoned. The boy has now completed all cycles of chemotherapy and radiotherapy. He is presently in remission and doing well.

Discussion

HLH is a clinicopathological syndrome consisting of abnormal proliferation of histiocytes and presence of hemophagocytes in reticuloendothelial cells and tissue. In majority of cases, treatment of HLH abates the underlying disorder such as infection. However, sometimes, HLH can be the initial presentation of an underlying malignancy particularly lymphoma. HLH secondary to malignancy can manifest as an aggressive disease, masking and delaying the diagnosis of underlying malignancy. HLH can present at relapse or remission of malignancy also. HLH has also been reported to precede the diagnosis of malignancy by

many years. Therefore, regular follow up is of utmost importance. In patients who present with HLH and malignancy, treatment is aimed at the malignancy rather than continuing HLH directed therapy. Case study analysis reveals that mortality in such children has always been high compared to those without HLH. There are published case reports, in adults and children, of HLH presenting as malignancy and/or progressing to malignancy years after diagnosis. Yves Allory et al. [4] studied bone marrow involvement in lymphomas with hemophagocytic syndrome at presentation. Out of 11 adults with lymphoma associated with HLH, 10 of them were diagnosed to have HLH at presentation and subsequently diagnosed to have lymphoma, while one patient had HLH 5 years prior to lymphoma diagnosis. Six of them had characteristic hemophagocytic histiocytes in their bone marrow. Majority of them succumbed to death either as a result of disease progression or overwhelming sepsis, with a mortality rate of 82 %. In another similar study by Falini et al. [5] where nine adults with peripheral T cell lymphoma and HLH were studied, hepatosplenomegaly and pancytopenia was present in all of them. However, lymphadenopathy was a rarity seen only in one out of nine patients. Diagnosis based on bone marrow was possible only in five of them. Case reports and studies in children with similar disease patterns have been found in literature. Bibishahin et al. [6] reported the case of a 12 year old girl who was diagnosed to have HLH and treated with immunosuppressive therapy. After a 2 year follow up, the patient developed secondary T cell acute lymphoblastic leukaemia (T-ALL) as confirmed by flow cytometric studies. Treatment was started as per T-ALL protocol; however patient died as a result of relapse and sepsis. This case highlights the issue of secondary malignancy following HLH and demonstrates the need for continued follow up in such patients. Sevilla et al. [7] described two children with anaplastic T cell lymphoma presenting as HLH. Both of them suffered from prolonged fever with non-specific constitutional symptoms. One of them had mediastinal lymphadenopathy as noted on CT chest and the other had lung infiltrates seen on X-ray chest. On extensive evaluation, investigations were suggestive of HLH. Bone marrow revealed features of hemophagocytosis. Tissue diagnosis (mediastinal node biopsy) revealed anaplastic T cell lymphoma. Both were started on anthracycline based chemotherapy. One of them succumbed to death due to severe aspergillus sepsis and the other survived with 3 years disease free interval at the time of publication. Celkan et al. [8] have published a study of 29 children with HLH and malignancy. 20 of them had acute leukaemia, the rest had rhabdomyosarcoma, neuroblastoma, Hodgkin's and NHL. One had LCH associated with HLH. Mortality in this case series was found to be 34 %, with 50 % of the causes for death being directly attributed to HLH. In this case series,

fever, anaemia and hypertriglyceridemia were found in all 29 children. Neutropenia and thrombocytopenia were found in 80 % of children, hepatomegaly and splenomegaly in 60 % and hypofibrinogenemia in 90 % of children. Clinical presentation in our patient is consistent with the above described reports, with prolonged fever, cervical lymphadenopathy and organomegaly. Our patient has leucocytosis with bicytopenia of the other two cell lines, which is in contrast to those described by Falini et al. where severe pancytopenia was found. Although initial investigations were inconclusive, subsequent investigations were consistent with HLH. Tissue biopsy however, provided the final diagnosis of NHL. In all of the above described cases including our patient, the underlying malignancy was masked by HLH and diagnosis of NHL was possible only through tissue (lymph node) biopsy. If the node would not have been biopsied, and the child would have been treated for HLH, then there is the possibility that he would have presented at a later date with NHL of a higher grade with poor prognosis. This case report therefore emphasizes the importance of tissue diagnosis.

Conflict of interest None.

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