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Original Article

A study of haematological and bone marrow changes in symptomatic patients with human immune deficiency virus infection with special mention of functional iron deficiency, anaemia of critically ill and haemophagocytic lymphohistiocytosis

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ARTICLE INFO

Article history:
Received 31 July 2012
Accepted 12 November 2012
Available online 23 February 2013

Keywords:
CD4 cell count
Bone marrow examination
HIV infection
Anaemia of critically ill
Haemophagocytic lymphohistiocytosis

ABSTRACT

Background: Haematological abnormalities are among the most common complications of HIV. These involve all lineages of blood cells. Bone marrow studies form integral part of complete workup of the HIV positive patients specially when they present as case of pyrexia of unknown origin (PUO), refractory anaemia and pancytopenia.

Method: 55 HIV infected symptomatic patient requiring bone marrow examination were included in the study. Relevant clinical history, baseline haematological investigations including full blood count, CD4 cell counts using flow cytometry were recorded.

Results: Median ANC values in males were found to be significantly lower than females ($p = 0.046$). CD4 cell count statistically significantly correlated with age, TLC, ANC & platelet count. Anaemia was present in 45 patients and out of which 66.66% patients had normocytic normochromic anaemia. Iron deficiency anaemia was present in (37.77%) patients and anaemia of chronic disease in (62.22%) patients. 2 patients had anaemia of the critically ill.

Two patients had non-Hodgkin's lymphoma (NHL) and showed lymphoma deposit in the bone marrow. Gelatinous degeneration was seen in 3 patients. Ill formed epithelioid cell granulomas were seen in 7 cases, and 2 cases were positive for acid fast bacilli (AFB). Haemophagocytosis was seen in 8 cases; two cases later diagnosed as a case of infection induced HLH. Leishmania donovani (LD) bodies seen in 2 cases.

Conclusions: Bone marrow study is an important investigation in HIV infected symptomatic patients with peripheral haematological abnormalities.

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http://dx.doi.org/10.1016/j.mjafi.2012.11.002

Introduction

Haematological abnormalities are among the most common complications of human immune deficiency virus (HIV) infection. These involve all the lineages of blood cells.[1] The mechanisms of these changes are multiple. It causes both quantitative and qualitative marrow defects. Immune cytopenias can occur directly due to HIV infection, whereas the effects of opportunistic infections, lymphomas, malignancy and anti-retroviral therapy (ART) also play an important role. Bone marrow abnormalities are common in HIV infection and increase in frequency with advancing disease.[1] The consequences of these haematologic problems are twofold. First, they are associated with morbidity in themselves that can adversely alter the patient's quality of life such as from anaemia (fatigue and dyspnoea), leucopenia (infections) and thrombocytopenia (bleeding). Second, they hinder treatment of the primary viral infection, secondary infections and neoplastic complications.

In our scenario, every microcytic hypochromic anaemia is considered as iron deficiency anaemia. But now we know that it can be anaemia of chronic disease or anaemia of critically ill. Their differentiation from iron deficiency anaemia is of utmost importance because of difference in treatment.[2]

Bone marrow studies form integral part of complete workup of the HIV positive patients especially when they present as a case of pyrexia of unknown origin (PUO), refractory anaemia and pancytopenia. A number of characteristic but nonspecific, morphologic abnormalities of the bone marrow of AIDS patients have been reported.[3]

Haemophagocytic lymphohistiocytosis (HLH) is a hyper inflammatory syndrome characterised by fever, hepatosplenomegaly, cytopenias and evidence of lymphophagocytosis by lymphocytes along with and other characteristic lab abnormalities.[4] HLH can be primary (familial) or secondary (acquired). Secondary (acquired) HLH has been associated with a variety of viral, bacterial, fungal, and parasitic infections, as well as collagen-vascular diseases.[5–8] Few case reports of HIV infected individuals also developing this dreadful and fatal condition has been published.[9] Extra lymphatic presentation of non-Hodgkin's lymphomas occurs in up to 90% of patients with HIV infection and lymphoma has been reported to involve the bone marrow in 50% of cases.[10]

The present study is aimed to assess the various haematological and bone marrow abnormalities seen in symptomatic HIV patients requiring bone marrow studies with special mention of functional iron deficiency, anaemia of critically ill and HLH.

Materials and methods

A cross sectional study was carried out in Dept of Pathology, at a tertiary health care centre between June 2009 and June 2012. All the HIV positive symptomatic patients requiring bone marrow examination were included. Bone marrow aspirate and biopsy was performed as a part of investigation of pyrexia of unknown origin (PUO), unresolving hepatosplenomegaly, anaemia, leucopenia, neutropenia, lymphopenia and thrombocytopenia. Patients who were on antiretroviral therapy were excluded. This was done to reduce the confounding effect of antiretroviral drug induced bone marrow suppression. Diagnosis of HIV was made in these patients by ELISA and Western Blot. A total of 55 patients were studied. Detailed clinical history was obtained. The following haematological investigations were carried out for all patients: haemoglobin, total leucocyte count (TLC), differential leucocyte count (DLC), erythrocyte sedimentation rate (ESR), platelet count, mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular haemoglobin (MCH), packed cell volume (PCV), reticulocyte count, peripheral smear for blood picture. Absolute lymphocyte count was calculated as absolute lymphocyte count (ALC) (cells/μL) = TLC × DLC (%). Serum iron studies were carried out in all the anaemic patients. CD4 count was carried using flow cytometry in all the patients.

We studied bone marrow for cellularity, dysplasia, plasma cell numbers, dysplastic changes, fibrosis, bone marrow iron status with special mention of diagnosis of anaemia of critically ill (functional iron deficiency), granulomas, evidence of haemophagocytosis, opportunistic infections and other pathognomonic features of systemic infections or malignancies. Bone marrow aspiration smears were stained using Leishman's stain, whereas trephine biopsy was stained with haematoxylin and eosin stain. Iron stores in bone marrow aspirates were assessed in 50 patients and grading of 0–6 was done as per Gale et al.[11] In remaining 5 cases where bone marrow aspirate were suboptimal, assessment of iron status was done on the bone marrow biopsy. Patients were categorised into Cat 1 = grade 0 & 1 (absence & diminished iron store), Cat 2: grade ≥2 (normal to increased iron stores). For assessment of bone marrow fibrosis, reticulin stain was done on 5 u thick sections and semi quantitative grading (0–3) was done as per Bauermeister's/WHO grading (2008).[12] Bone marrow plasma cells were assessed in the percentage on bone marrow aspirates and bone marrow biopsies. Ziehl–Neelsen (ZN) staining for Acid fast bacilli (AFB) was done in selected cases. Special stains for fungus and immunohistochemistry was done on case to case basis. All the bone marrow aspiration and biopsy specimens were examined and interpreted by the same pathologist, to avoid inter-observer variation.

Statistical analysis

Statistical analysis was done using SPSS version 17. Mean and median values were compared for various quantitative variables. Non-parametric tests were used wherever medians were compared. A p value <0.05 was taken as statistically significant.

Results

The mean age ± SD of 55 HIV infected individual was 41.15 ± 9.96. About two third of individuals, 69% ($n = 38$) were males and 31% ($n = 17$) were females. On initial presentation, patients presented with fever (54.5%; 30), generalised weakness (36.3%; 20), diarrhoea (9.1%; 5), loss of weight/appetite (9.1%; 5), and others (12.7%; 7) with non-specific symptoms. Out of 55 patients, 35 patients had more than one symptom.