Changing patterns of AIDS: impact on the indications and diagnostic yield of bone marrow biopsies

ABSTRACT

After the advent of HAART, the clinical course of HIV infection has dramatically improved. Therefore, it seems appropriate to reevaluate the performance of bone marrow biopsy (BMB) as a diagnostic tool. The aim of the present study was to compare the reasons for performing a BMB and its diagnostic yield in HIV-patients before and after HAART. A total of 165 BMB specimens obtained from HIV-infected patients receiving care at the Hospital of *Universidade Federal do Rio de Janeiro* in two different periods (1986-1994 and 1999-2004) were analysed. The main reason for BMB examination in the first period was fever (88%), which decreased in the second period (57%, $p < 0.0001$), when cytopenia (51%) was the leading reason for BMB, whereas in the first period it accounted for only 30% ($p = 0.008$). A definitive diagnosis (infection, granulomas or lymphomas) was obtained in 28% of patients in the first period and in 19% during the second period ($p = 0.20$). The diagnosis turned out as infections decreased from 16% in period 1 to 2% in period 2 ($p = 0.003$). Despite the the limitations in the evaluation of fever, the use of BMB must be considered on an individual basis, whenever less invasive alternatives have been exhausted, and should be complemented by a bone marrow aspiration for microbiological studies.

Keywords: bone marrow biopsy, HIV, HAART.

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INTRODUCTION

The role of bone marrow biopsy (BMB) as a diagnostic tool in human immunodeficiency virus (HIV) infection remains controversial. In the early days of the epidemic, many published studies evaluated the role of BMB, especially to elucidate persistent fever, secondary infections, cytopenias, and to stage malignancy.[1-7] After the advent of highly active antiretroviral therapy (HAART), the clinical course of HIV infection has dramatically improved.[8] As the clinical spectrum of this disease has changed, it is appropriate to reevaluate the performance of BMB as a diagnostic tool in the HAART scenario.[9-11] The aim of the present study was to compare the diagnostic yield of BMB in HIV infected patients before and after HAART introduction.

MATERIAL AND METHODS

All consecutive BMB specimens obtained from HIV-infected patients at the Hospital of Universidade Federal do Rio de Janeiro in two different periods were retrospectively analysed. Patients in group 1 had their BMB done from November 1986 to April 1994, before the introduction of HAART in Brazil. Patients in group 2 had undergone a BMB from January 1999 to May 2004, and were on HAART for at least three months. HIV infection was confirmed in all patients according to national guidelines. The institutional review board approved the study.

BMB samples were formalin fixed, decalcified and embedded in paraffin. Sections were cut at 5 μm and the following stains were routinely applied: Hematoxylin-eosin (HE), Ziehl-Neelsen (ZN) for the presence of acid-fast bacilli, and periodic acid-Schiff (PAS) and Grocott's methenamine silver (GMS) for the diagnosis of fungal infection. Each specimen was evaluated for overall cellularity, relative proportion of plasma cells, eosinophils, and for the presence of iron, dysplastic changes, abnormal localization of immature precursors (ALIP), serous degeneration, lymphoid nodules, granulomas and neoplasia. Bone marrow cellularity was defined as normocellular (40-60%), hypocellular (< 40%) and hypercellular (> 60%). Plasmacytosis and eosinophilia were defined as the presence of 5% or more of plasma cells or eosinophils, respectively.

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Baseline demographic and clinical characteristics retrieved from the patient record were age at the time of BMB, sex, stage according to the WHO staging system,[12] blood cell counts, clinical reason for BMB examination, and CD4 counts. CD4 counts were not available before 1994.

Categorical variables were compared with the chi-square test or Fischer's exact test, as appropriate. A p-value of < 0.05 was considered statistically significant. The SPSS software, (Chicago, IL, US) was used to analyze the data.

RESULTS

A total of 165 BMB samples were available for analysis: 102 from group 1 and 63 from group 2. The median age was 36 (11-67) years, and was not statistically different among the two groups (35 and 38 years, respectively). The proportion of females increased in group 2 (15% versus 32%, p = 0.01). The majority of the patients in both groups presented with stage 4 disease (77% in group 1 and 87% in group 2). BMB examination was mainly indicated in group 1 was the evaluation of fever (90/102, 88%), and this indication significantly decreased in group 2 (35/63, 57%, $p < 0.0001$). Conversely, the main reason for BMB in group 2 was the presence of cytopenias (32/63, 51%), significantly more often than had been observed in group 1 (30/102, 30%, p = 0.008). The third most common reason for BMB was the staging and/or investigation of lymphomas. In the first period, it accounted for 18% (18/102) of all indications, and 27% (17/63) in the second period (p = 0.17).

No differences in bone marrow histopathological features were observed between the two groups, except for the more frequent finding of a hypercellular bone marrow in group 2 (18% versus 38%, p = 0.015). Overall, the main histopathological findings were the presence of serous degeneration (90%), ALIPs (21%), lymphoid nodules (12%), plasmacytosis (22%), eosinophilia (30%), megakaryocytic dysplasia (85%), and iron deposits (58%).

The final diagnosis of the bone marrow examination was classified into four categories: infections, granulomas, lymphomas, and others (including myelodysplasia). A definitive diagnosis either of infection, granulomas, or lymphomas was obtained in 29 (28%) patients in group 1 and in 12 (19%) patients in group 2 (p = 0.20). However, BMB disclosing an infectious diagnosis decreased from 16% (16/102) in group 1 to 2% (1/63) in group 2 (p = 0.003) (Table 1). Patients who had undergone a BMB for the evaluation of fever, a diagnosis of infection was obtained in 25/102 (25.5%) in group 1, but in only 5/63 (7.9%) patients in group 2 (p = 0.007).

CD4 cell counts were available for 55/63 patients (87%) in group 2. Lower CD4 counts (< 200 cells/μL) were observed in 39 patients (71%). No differences were found between patients with lower and higher CD4 counts, in group 2, regarding the diagnostic yield of the BMB (20% versus 12%, p = 0.7).

Table 1. Final diagnosis of bone marrow involvement according to the use of highly active antiretroviral therapy (HAART)

	n = 165	**Group 1 Pre-HAART n = 102**	**Group 2 HAART n = 63**	**p-value**
Main indications*				
Fever	125	90 (88%)	35 (57%)	0.0001
Cytopenia	62	30 (30%)	32 (51%)	0.008
Lymphoma	35	18 (18%)	17 (27%)	0.17
Infections	17 (11%)	16 (16%)	1 (2%)	0.003
Tuberculosis	7 (4%)	6 (6%)	1 (2%)	-
Atypical mycobacteriosis	3 (2%)	3 (3%)	-	-
Hystoplasmosis	6 (4%)	6 (6%)	-	-
Cryptococcosis	1 (0.5%)	1 (1%)	-	-
Granuloma	16 (9%)	10 (10%)	6 (9%)	1.0
Lymphomas	8 (7%)	3 (3%)	5 (8%)	-
Hodgkin	4 (3%)	1 (1%)	3 (5%)	0.28
Non-Hodgkin	4 (4%)	2 (2%)	2 (3%)	-
Others	124 (75%)	73 (71%)	51 (81%)	-
Dysplasia	101 (61%)	59 (58%)	42 (67%)	0.32
Hipoplasia	6 (4%)	6 (6%)	-	-
Normal	17 (10%)	8 (8%)	9 (15%)	0.18

*More than one indication could be present.

DISCUSSION

Bone marrow biopsy has been largely used as a diagnostic tool in AIDS patients from the onset of the epidemic. Since the introduction of HAART, there have been substantial changes in epidemiological and clinical aspects of the epidemic. It is therefore appropriate to evaluate the impact of these changes on the indications and diagnostic yield of BMB in AIDS patients.

A comparison of the indications and results of BMB in patients treated before and after the introduction of HAART was performed. Some interesting findings emerged from this analysis: (1) The indication of BMB for evaluation of fever has decreased from 88% to 57%; and (2) a sharp decrease in the diagnosis of infections through BMB was observed, especially when BMB was performed for fever evaluation.

These findings most likely reflect the reduction in the incidence of opportunistic infections brought about by HAART, and also by the introduction of effective prophylactic measures. Moreover, the availability of less invasive medical procedures, such as imaging studies and specific laboratory tests, probably contributed to the lesser use of BMB in patients with fever.

On the other hand, no difference was observed regarding the overall diagnostic yield of BMB in the two periods, a finding in line with previous observations.[9] Also, no differences regarding the histological features in samples of BMB between the two periods were found.

Currently, the overall diagnostic yield of BMB in AIDS patients was 19%. Despite the somewhat limited yield in the evaluation of fever, the use of BMB must be considered on an individual basis whenever less invasive alternatives have been exhausted, and should be complemented by a bone marrow aspiration for microbiological studies.

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