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Bone marrow findings inpatients with pulmonary tuberculosis

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Summary
The cytology and culture of bone marrow aspirate in sixty-two newly diagnosed patients with pulmonary tuberculosis were studied. The findings were depressed erythroid activity in 69% of the patients, micronormoblastic changes in 18% and megaloblastic changes in 16.6%. Myeloid activity was increased in 65% of the patients. Normal looking plasma cells above 5% was found in 17.7% of the bone marrow aspirates while 12.9% had eosinophilic precursors above 5% in the marrow. None of the marrow smears showed granuloma formation or caseation necrosis. The bone marrow cultures yielded no growth of *Mycobaterium tuberculosis* while stainable iron in the marrow was found to be low or negative in 88.8% of the patients.

Key words: *Pulmonary tuberculosis, bone marrow cytology, bone marrow culture*

Résumé
La cytologie et culture des moelles osseuses aspirés chez soixante nouveaux cas diagnostiqués ayant la tuberculose pulmonaire étaient étudiées. Les données étaient depressés de l'activité erythropéoitique chez 69% des patients; les changements micronormoblastiques chez 18% et les changements mégaloblastiques chez 16.6% des patients. L'activité myélinique était augmenté chez 65% des patients. Plus de 5 % des cellules normales du plasma était observé chez 17.7% des moélles osseuses aspirés alorsque 12.9% avait les precusseurs d'esinophiles. Aucun des prelevements de la moelle n'avaient une granulome or cessation nécrosique. Les cultures des moelles osseuses ne produisaient pas de development de mycobacterium tuberculeux alorsque le fer tainté dans les moélles était faible or négative chez 88.8% des patients.

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Introduction
In the past haematological parameters and bone marrow studies have been carried out in patients with disseminated tuberculosis [1,2,3,4,5,6,7], while microscopic examination of bone marrow smear for acid-fast-bacilli [AFB] in disseminated tuberculosis has also been studied. Bone marrow cytology has been recommended as a diagnostic procedure in this disease [4]. In pulmonary tuberculosis, examination of bone marrow aspiration can be an adjunct in making a diagnosis since in a few reported cases bone marrow aspirate smears stained for AFB were found to be positive[8]. Assessment of the marrow may reveal abnormal cellular response especially plasmacytosis, eosinophilia, dysplastic and megaloblastic features. And will also give an indication of iron reserve.

Oluboyede and Onadeko studied 9 pulmonary tuberculosis patients [5]. The findings in the study included myeloid hyperplasia in 56% of the patients and plasmacytosis in 11%. However 33% had normal morphology. Iron reserve in the marrow was normal in only 11% whereas iron was absent in 44.6% and found in excess in 44.4%. The study affirmed that myeloid hyperplasia, plasmacytosis and excess or absence of iron in the marrow are possible findings in pulmonary tuberculosis.

This present study critically investigated the possibility of morphological changes like dysplastic changes, megaloblastic changes, myeloid or erythroid hyperplasia, changes in eosinophils and plasma cells. It is expected that with appropriate treatment such haematological changes can be reversed and the recovery of patients on treatment for pulmonary tuberculosis can be monitored while this could serve as an adjunct in predicting the prognosis of the disease.

Materials and method
Sixty-two AFB-sputum-smear positive newly diagnosed pulmonary tuberculosis patients were recruited into the study. They were obtained from the Chest Unit of the Medical Outpatient department of University College Hospital, Ibadan. The study was carried out between January 1997 and February 1998.

Bone marrow aspiration was carried out from the posterior superior iliac spine on all the sixty-two patients after obtaining an informed consent. Local xylocaine infiltration was used as the anaesthetic agent. The procedure was well tolerated in all patients.

Four milliliters of marrow were aspirated and rapidly dispensed equally into two separate bottles containing Ethylene Diamine Tetra Acetic Acid {EDTA} and the bottles were gently rotated to prevent clot formation.

Ziehl Neelsen stain for AFB was performed and Lowenstein-Jensen inoculation (culture) was carried out on the bone marrow aspirates. Cytological examinations with differential counts were carried out on well-prepared Leishman stained-films aspirate. Ten slides were prepared on each sample from the patients. Three of each set of slides were stained with Leishman stain immediately and the other slides were fixed in 98% methanol and reserved for subsequent Prussian blue staining. While reviewing the films, particular attention was paid to probable presence of granulomatous inflammation, caseation necrosis and dysplastic cells.

All patients were screened for Human Immunodeficiency Virus (HIV) infection by the ELISA technique. The Joint Ethical Committee of the University College Hospital/University of Ibadan approved the study.

Results

Bone marrow histological examination confirmed normocelluar marrow in 35 [47.4%] patients while seven [11.2%] were hypocellular and 20 [32%] were found to be hypercellular.The Myeloid: Erythroid [M:E] ratio ranged from 1.3:1 to 7.5:1. Fourteen [22.6%] patients had M:E ratio above 5:1.

Erythroid series show increased erythroid activity in fourteen [22.6%] patients while 39 (65.2%) patients had normoblastic erythropoiesis and 11[16.6%] had megaloblastic erythropoiesis. The myeloid cells in the marrow films in all the patients showed sequential maturation. Bone Marrow films of nineteen patients showed increased eosinophilic precursors while eight (12.9%) patients had eosinophil counts above 5%. Twenty-one patients (33.9%) had no remarkable plasma cells in their marrow films. Forty-one patients (66.1%) had plasma cells ranging from 0.5%-13%. Eleven (17.7%) of the patients had marrow plasma cell count above 5%. The plasma cells however appear benign morphologically.

All the marrow smears reviewed had megakaryocytes that show budding. Twenty (32%) of the patients had 3-5 megakaryocytes per low power field.

Granuloma and caseation necrosis were not detected on the marrow aspirate films of any of the 62 patients reviewed while marrow smears stained for acid fast bacilli were negative. Bone marrow culture did not yield growth of *Mycobaterium tuberculosis* in any of the 62 patients and subsequent examination of smears stained for AFB of each of the culture samples was negative.

Examination of films stained for residual iron using Prussian blue revealed that 25[40.32%] were negative, 18[29.03%] had sub-normal (trace), and 19[30.64%] had normal iron stores. The frequency distribution of haematocrit level in these patients are as shown in table 1. Those with negative iron stain had haematocrit level that fall within the range of 0.22-0.32 whereas those with trace and normal iron had their haematocrit level within 0.32-0.38.

Discussion

Hematological abnormalities in the peripheral film and bone marrow have been found to correlate closely with severity of clinical disease in pulmonary tuberculosis [7,9]. In disseminated tuberculosis where the bone marrow is usually involved, bone marrow studies have proven to be of immense value [10]. Bone marrow cultures in the 62 pre-treatment pulmonary tuberculosis patients yielded no growth of *Mycobaterium tuberculosis*. Mash et al. [11] recorded similar finding. One hundred and twenty eight (128) bone marrow aspirate were subjected to culture, only 4 yielded growth of *Mycobaterium tuberculosis* and the four patients had Acquired Immunodeficiency Syndrome [AIDS]. Riley et al. [10] equally recorded a low culture yield. It was therefore suggested that culture should be reserved for immunocompromised patients with suspected tuberculosis. However, Lombard et al. recorded a yield of 25% by culture but a higher yield of 42% by polymerase chain reaction (PCR) [12]. The low marrow culture yield in our study is probably corroborated by the fact that only 3.5% of patients studied were ELISA reactive for HIV antibodies.

The morphology of the marrow revealed depressed erythroid activity in 69% of the patients studied.

Table 1: Correlation of haematocrit level with iron staining of the bone marrow

Haematocrit level	Negative iron	Trace	Normal iron	Total	%
0.22-0.27	11	4	-	15	24.2
0.28-0.32	8	5	3	16	25.7
0.33-0.38	6	9	12	27	43.7
0.39-0.44	-	-	4	4	6.4
	25	18	19	62	100

Micronormoblastic erythropoiesis, which was indicative of iron depletion was observed in 18% of the patients. Also 16% of the patients had megaloblastic erythropoiesis. Poor nutrition both during the pre-morbid and in the morbid period may be attributable to the iron, folate and probably vitamin B12 deficiency features present. Myelodysplastic changes were not observed. This differs from a report, which described a strong association between tuberculosis and myelodysplastic changes [13]. The depressed erythroid activity in the phase of this combined deficiency anaemia is rather paradoxical and it is thought that an inhibitory cytokine might be responsible.

On the contrary, myeloid activity was increased in 65% of the patients. Eosinophils precursors above 5% was found in 12.9% of patients and mature looking plasma cells above 5% was found in 17.7% of the patients. This cannot be said to be significantly abnormal in view of the prevailing parasitic and bacterial infection in this environment and coupled with absence of published figures of normal marrow differential in this environment. Oluboyede et al. equally recorded myeloid hyperplasia, increased eosinophilic precursors and increased plasma cells in the marrow of 9 pulmonary tuberculosis patients studied [5]. Granulomatous lesion was not seen in the marrow films of the 62 patients in this study. Studies have shown that these are better demonstrated in serial sections of paraffin embedded marrow aspirate [2].

The role of marrow iron status in erythropoiesis is clearly reflected by the level of haematocrit observed in those patients with negative, trace and normal iron status respectively. There was adequate iron reserve in the marrow in 30.64% of the patients while 40.32% had negative iron stain and 29.03% had traces.

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