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BONE MARROW NECROSIS IN SICKLE CELL DISEASE, A CLINICAL & PATHOLOGICAL STUDY

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Abstract

Bone marrow necrosis (BMN) is a rare clinical-pathological entity. It is mostly associated with post-mortem changes. Ante-mortem existence of BMN is quite rare and usually indicates a poor prognosis. However, its association with non-hematological malignancies seems not to be as poor prognostic feature as in post-mortem changes. One of the most commonly disorders associated with BMN is sickle cell disease (SCD), which is common among people in Basrah province. The current study probably can put light on the incidence of such pathology among those with SCD, its most clinical presenting features and its relation with specific sickle disease genotypes. The incidence of BMN in this study was 4.9 %. The mostly encountered features with wide spread necrosis were bone pains, fever, and pallor. Peripheral blood showed a florid leuco-erythroblastic picture with reticulocytosis and leucopenia in another case with focal necrosis. On comparison with those patients without BMN, patients with BMN showed a significantly lower Hb concentration, higher Hb S concentration, lower Hb F concentration, smaller splenic size, higher number of irreversibly-sickled cells and more frequent painful crises during their life. Those results were compatible with some observations and contradict with other. However, there is no previous study conducted in Iraq to compare with.

Introduction

Bone marrow necrosis (BMN) is considered to be present when the marrow aspirate and or biopsy show areas of poorly defined (smudge) cells with basophilic indistinct nuclei surrounded by amorphous to granular acidophilic material[1,2].

It was described for the first time more than 50 years ago[3]. It is characterized morphologically by destruction of normal haemopoietic tissue including the stroma with the preservation of the bone[4]. It is a rare entity, most frequently associated with post-mortem changes[5] appearing in up to 19.8 % of all autopsies[4]. Severe necrosis of the marrow is infrequently diagnosed during life and its presence often indicates a poor prognosis[5]. BMN ranges from a localized to wide spread generalized process[6]. It is usually accompanied by hypercalcemia and elevation of lactate dehydrogenase (LDH) enzyme[7]. Peripheral blood usually shows anemia, leuco-erythroblastosis, and schisto-cytosis[8]. Marrow aspirate shows amorphous material with isolated cells in different stages of necrobiosis and variable degrees of pancytopenia[9]. Clinically it usually presents as severe bone pains, fever, and weight loss8. It is seen in association with haematological malignancies, like acute & chronic leukemia, malignant lymphomas, and multiple myeloma[5], in metastatic neoplasia, and bacterial infections especially when hypovolemia and septic shock are present. It can also be encountered with disseminated intravascular coagulation, and following irradiation, and anti-neoplasic therapy. Rare cases had been reported in association with antiphospholipid syndrome[10,11], and parvovirus B1 infections preceding the development of

hematological malignancies. BMN can also be associated with sickle cell disease[6,12]. Its prognosis is not so poor when associated with sickle cell disease and other non-malignant states[6].

Materials & methods

During a period of one year, 41 adult cases with various forms of sickle cell disease, from 4 Central Hospitals in Basrah, were studied. Sickle cell trait cases were excluded.

The study included a full history taking, including gender, age, residency, presence or absence of painful crises and their frequency, history of blood transfusion and its frequency and any other complaint related to their illness during their life. All cases were subjected to thorough physical examination, concentrating on height, body weight, the presence or absence of pallor, jaundice, bone tenderness, fever, hepatomegaly & splenomegaly (the sizes of the latter two were estimated clinically as fingers below the costal margin). Patients who did receive blood one month & less before & those who were on hyroxyurea therapy were excluded from the study.

All cases were subjected to peripheral blood examination, including a full blood count using the MS9 machine, blood film examination for cell morphology, sickling phenomenon, reticulocyte counting with correction, enumeration of irreversibly sickled cells, and performing Hb variant study, using the Bio-Rad Hb variant system/B-thal short Program (by the HPLC principle) after application of the standardized techniques[13] and taking into consideration manufacturers instructions. Cases were genotyped according to references13-15(Tables I & II).

All cases were subjected to bone marrow examination after a full explanation of the procedure had been done to each patient followed by obtaining a written legal agreement of each patient. Bone marrow aspiration had been performed by the standardized Salah BM needle from the right and or left posterior iliac spines using the standardized procedure after full aseptic precautions and ample local anesthesia. Smears were stained by the Leishmann's stain & one smear was stained by Prussian blue stain to study iron status of the marrow[13].

Bone marrow trephine biopsy was performed to each patient at the same session of marrow aspiratin, using the standardized Jamshidi needle from the right or left posterior iliac crest[13]. A core of bone & marrow material 1.5 cms long x 2 mm diameter was taken & touch smears were done & stained after drying with Laishmann's stain while biopsy materials were processed in paraffin sections using the standard paraffin embedding & sectioning technique[13]. Eosin & hematoxylin-stained sections were prepared & examined.

Statistical analysis was performed using the SPSS 12 version, by obtaining the descriptive values & the 2 x 2 Chi square test & the student t test.

Results

Two cases (4.9 %) had been shown to have bone marrow necrosis at the time of examination, while 39(95.1%) had not. (Table III).

first case was a female with extensive marrow necrosis with almost total loss of normal cellular elements, and replacement by homogeneous amorphous material seen in aspirate (Figure 1) while the H & E BM trephine biopsy showed a homogeneous acidophilic material with loss of cellular details (Figure 2). She was 35 years old, with blood group A Rh (D) positive. She presented with severe bone pains, running fever, and pallor. On examination she was frankly pale, there was no splenomegaly, nor hepato-megaly. Her Hb concentration was 68 g/L, Hb variant study showed Hb S

(82.7%), Hb F 7.7 % (Figure 3). She had a rapid sedimentation rate (145 mm/ 1st hr). The WBC count was 13.7 x 109/L with leuco-erythroblastic blood picture. She had a low MCV with reticulocytosis (16 %). ISCs were 0.2 %. Her skeletal X-ray screen showed osteonecrosis of hip bones. Her genotype was sickle-B+ thalassaemia (Hb S/B+ thal).

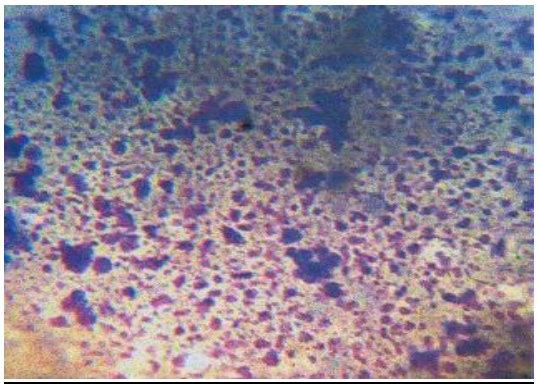

Figure 1: BM aspirate smear stained by Leishman,s stain shows total distortion of normal cellular details with replacement by amorphous basophilic material.

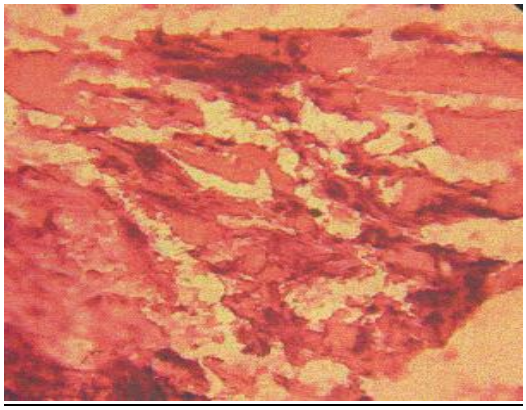

Figure 2: Bone marrow trephine biopsy section, stained with H & E from the first case shows complete destruction of normal cellular marrow elements with replacement by homogeneous acidophilic material.

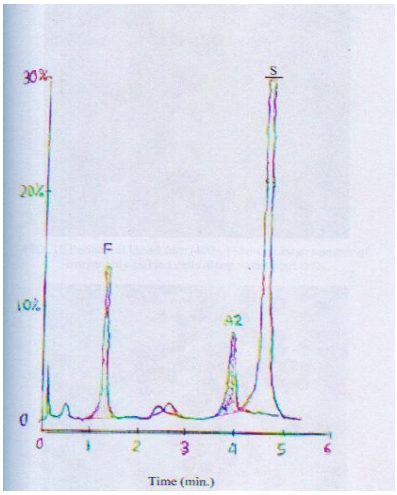

Figure 3: HPLC paper of the first case of BMN.

The second case was an 18 years old male who showed focal areas of necrosis in both right & left posterior iliac crest bones (Figure 4). His blood group was O Rh (D) positive, he presented with severe bone pains, running fever, & pallor. He has splenomegaly but no hepatomegaly. Hb S was 81.3 %, Hb F 16.1 %,. He had leucopenia, Hb 48 g/L, reticulocytes count 4 %& ISCs 1.5 %. He had a moderately elevated ESR but no leuco-erythroblastic blood picture. His genotype was sickle/Bo thalassaemia (Hb S/Bo thal)(Table IV).

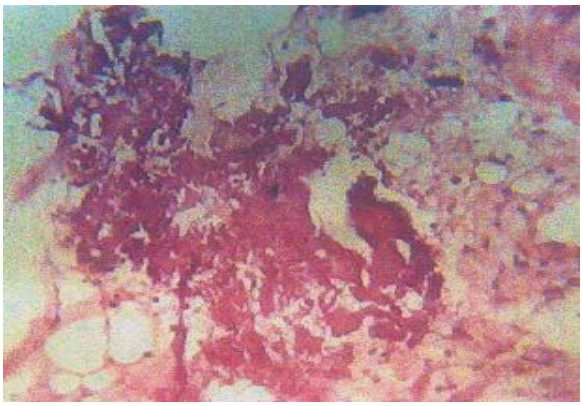

Figure 4: H & E section of the bone marrow of second case shows destruction of normal cellular elements with replacement by amorphous, homogeneous acidophilic material. Few normal cellular elements are seen as well.

Comparative study between cases with bmn & those without:

Cases with BMN had lower hemoglobin concentration (mean 58), than those without, higher Hb S concentration (mean 82 % vs 74.8 %), lower Hb F concentration (mean 12.9 % vs 14.6 %) & smaller splenic size (mean 1.5 CBCM vs 4.2) (Tables IV,V).

Bone marrow necrosis was found to have a significant relationship with the following parameters : Hb concentration, the number of painful crises the patient had suffered during life, body weight, MCH, & monocyte count ($P< 0.05$), while it showed no significant relation with other parameters using the t-Test (Table VI). Besides, BMN showed a significant correlation with fever, bone pains ($P <0.05$) & highly significance ($P<0.01$) with osteonecrosis using the Chi square test (Table VII).

Discussion

In our study, 2 cases (4.9%) showed the histological features compatible with bone marrow necrosis while the rest (39, 95.1 %) didn't show such features. Only one case, a female 35 years old, showed the florid clinical and hematological features of bone marrow necrosis (severe bone pains, fever, pallor, rapid sedmintation rate, leuco-erythroblastosis and features of necrosis). She was of sickle-B+ thalassaemia type. However, the second case didn't show the classical clinical and haematological features stated for BMN[6], yet bone marrow trephine biopsies taken from both right and left posterior iliac crests showed focal areas of necrosis. On reviewing the literature, very little had been found to compare with.

It seems that the first description of BMN in 1941 in a Greek woman with splenomegaly and sickled red blood cells in peripheral blood who died of cerebral fat embolism16.However, Charache-S and Page[17] reported 3 cases with sickle cell disease with BMN. Hemoglobin electrophoresis showed Hb SC, SD & SS

with an incidence of 6.8 %. It seemed that BMN was more common among those with Hb SC (50%) seen at autopsy rather than those with Hb SS disease (17%) and this had been attributed to the potentially high viscosity of blood in Hb SC due to the relatively high haematocrit in such disorder[17]. However, Al-Gwaiz, 1997, in her retrospective study showed that no case of sickle cell disease with BMN had been found[18]. To our knowledge, no prospective study had been previously conducted in Iraq to compare with. The paucity of descriptions probably doesn't reflect a low incidence but rather a little chance to examine the marrow by such an invasive marrow biopsy procedure during the painful crises of sickle cell-diseased patients as well as the unwilling of the patients and treating physicians to perform such an unnecessary investigation[17,18]. Our clinical findings in the first female case with widespread necrosis were compatible with those described by Janssen et al, 2000, who worked on ante-partum diagnosed cases with extensive BMN and found that bone pains, fever, were the most important symptoms followed by anemia, thrombocytopenia and leuco-erythroblastic picture[3]. Our incidence of BMN (4 %) seems much less than that reported by Maisel etal, 1988[19], who classified the BMN into 3 grades: grade 1 (only small foci of necrosis), grade II(moderate necrosis) & grade III (severe wide spread necrosis) and found an incidence of (26.4 %, 7.5 %, and 3.1 % for each of above grades respectively). This is attributed to the inclusion of wide range of other causes of BMN (rather than SCD) in their study[19]. However, the lack of facilities to diagnose the association of parvovirus B19 infection with sickle cell disease (using the polymerase chain reaction) in the pathogenesis of wide spread BMN seems to lead to an under-estimation of such process in SCD patients in our Country[20,21].

Table I: Genotyping of patients with sickle cell disease[13].

Genotype	MCV	S%	A%	A2%	F%
SS	N	88-93	0	<3.5	5-10
S/B^{o}thal	L	88-93	0	>3.5	5-10
S/B^{+}thal	L	50-93	3-30	>3.5	1-10
S/HPFH	N	65-80	0	<3.5	20-35

Table II:Genotyping of patients with sickle cell disease[14,15*]

Genotype	Cell. Acetate Hb electrophoresis	Hb F	Hb A2 (%)	Hb A (%)	Hb S (%)	Hb (g/L)	MCV (fl)	Cor. Retics (%)
Hb SS	S(+F)	1-20 (4.6*)	2-4	0	75-95	78	85.9	10.2
Hb S/B^{o}Thal	S+F	5-30 (5.2*)	4-8 (5*)	0	70-90	89	69.3	7.2
Hb S/B^{+}Thal	S+F+A	2-10	4-8	10-30	60-85	89-116	64-73	1.3-9.7
Hb S/HPFH	S+F	15-35 (25.8*)	1.5-3 (2*)	0	60-90	146	81.7	2.4

Table III: shows the frequency of BMN in cases under the study

BMN	No	%
Present	2	4.9
Absent	39	95.1

Table IV: A comparison between the two cases of BMN

Variables	Case 1	Case 2
Age (Years)	35	18
Duration of illness	15	10
Blood group	A Rh(D) +	O Rh(D) +
Crises/Life	10	10
Blood transfusion/Life	40	1
Liver size(cbcm)	0	0
Splenic size(cbcm)	0	3
Hb (g/L)	68	48
ESR(mm/1^{st} hr)	145	62
Hb S %	82.7	81.2
Hb F %	7.7	16.1
ISCs %	0.2	1.5
tWBC	13.7	1.8
Cor. Retics %	16	4
MCV(fl)	67.4	62
Blood film	Leuco-erythroblastic	Leucopenia
Osteonecrosis	Positive	Negative
Genotype	S/B^{+} thal	S/B^{o} thal
Iron stores in Marrow	Normal	Normal
Extent of BMN	Extensive	Focal

Table V:Comparative study between those without & others with BMN.

	Patients without BMN		Patients with BMN	
Variable	Mean	(SD)	Mean	(SD)
Age(Years)	19.6	(4.3)	26.5	(12)
Duration of illness(Years)	4.3	(3.5)	12.5	(3.5)
Painful crise/Life	22.4	(12.9)	10	(0)
Blood transfusion/Life	9.8	(8.3)	20.5	(27.5)
Splenic size(cbcm)	4.2	(4.2)	1.5	(2.1)
Hb(g/L)	95	(21)	58	(14)
WBCs	21.5	(17.5)	7.7	(8.4)
Corr. Retics(%)	4.5	(4.5)	10	(0.8)
ESR(mm/1^{st} hr)	18.3	(21.5)	103	(58)
MCV(fl)	77.4	(10.9)	64.7	(3.8)
MCH(pg)	25.4	(5)	16.9	(0.8)
MCHC(g/dl)	31.5	(3)	26.1	(0.2)
Neutrophils($x10^{9}$/L)	4.9	(12.2)	4.3	(11.3)
Lymphocytes($x10^{9}$/L)	4.4	(10.7)	5.2	(1.4)
Monocytes($x10^{9}$/L)	6.0	(7.1)	4.6	(2.2)
Hb A(%)	5.6	(7.4)	3.4	(4.8)
Hb A2(%)	4.2	(1.9)	5.3	(3.8)
Hb F(%)	14.6	(8.3)	12.2	(7.3)
Hb S(%)	74.8	(7.9)	82	(0.9)*
ISCs(%)	1.9	(2.1)	0.8	(0.9)

Table VI: BMN correlation (quantitative parameters)

Variable	t	df	Sig.(2-tailed)	Mean difference	St error difference
Age(Yrs)	2.017	39	>0.05	6.83	3.38
Duration of illness	3.21	39	<0.01	8.19	2.54
No. of crises/Life	-2.06	39	<0.05	-0.69	0.33
Splenic size(cbcm)	-.907	39	>0.05	-2.75	3.04
Liver size(cbcm)	-1.281	39	>0.05	-2.4	1.94
Weight(kg)	-2.214	39	<0.05	-22.4	10.12
Height(cm)	1.04	39	>0.05	9.35	8.94
ESR(mm/1st hr)	5.05	39	<0.01	85.1	16.8
Hb(g/L)	-2.402	39	<0.05	-3.77	-0.59
MCH(pg)	-2.376	39	<0.05	-8.56	3.60
MCHC(g/L)	-2.467	39	<0.05	-5.43	2.20
MCV(fl)	-1.632	39	>0.05	-12.76	7.82
Hb A(%)	-0.414	39	>0.05	-2.2	5.32
Hb A2(%)	0.749	39	>0.05	1.10	1.47
Hb F(%)	-.294	39	>0.05	-1.78	6.07
HbS(%)	1.256	39	>0.05	7.105	5.65
ISCs(%)	-0.708	39	>0.05	-1.11	1.57
WBCs(x10^9/L)	-0.378	39	>0.05	-4.77	12.62
Lymphocytes(x10^9/L)	0.097	39	>0.05	7.505	7.80
Monocytes(x10^9/L)	-.285	39	>0.05	-1.5	5.27
Neutrophils(x10^9/L)	-0.726	39	>0.05	-6.4	8.94
Cor.Retics(%)	1.608	39	>0.05	5.48	12.38

Table VII: BMN correlations (qualitative parameters)

Variable	Chi-Square	df	Sig.(2-sided)
Blood group	1.726	3	>0.05
Bone pains	0.510	1	<0.05
Erythroid hyperplasia	4.529	1	>0.05
Fever	5.734	1	<0.05
Gall stones	0.292	1	>0.05
Hypercellular BM	4.529	1	>0.05
RBC normochromia	0.632	1	>0.05
Osteonecrosis	9.226	1	<0.01
Sex	2.806	1	>0.05

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