

BONE MARROW NECROSIS: REPORT OF FIVE CASES AND REVIEW OF THE LITERATURE

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Bone marrow necrosis (BMN) is a rare antemortem diagnosis mostly diagnosed at postmortem examination, but which is also seen during the course of different diseases, mostly malignant.¹⁻¹⁰ It is characterized morphologically by destruction of hemopoietic tissue, including the stroma, with preservation of the bone.⁴

Conditions associated with BMN include infections,² acute and chronic leukemia,^{2,5,6} Hodgkin's and non-Hodgkin's lymphoma,^{1,2,7,8} primary thrombocytopenia,⁹ and metastatic carcinoma.¹⁰ It has also been reported in the presence of antiphospholipid antibodies,⁴ previous irradiation,³ antineoplastic chemotherapy,³ and during treatment with all-transretinoic acid,¹¹ fludarabine,¹² interferon alpha,¹³ and granulocyte-colony-stimulating factor (G-CSF).¹⁴ Other non-neoplastic conditions include disseminated intravascular coagulation (DIC), sickle cell disease, anorexia nervosa and idiopathic conditions.²⁻³ The finding of BMN on biopsy is significant in that it has been reported to be an indication of a poor prognosis.^{1,2} It has also been reported as obscuring the diagnosis of some diseases,⁵ and preceding others.^{3,15,16} The cases reported here agree with previous observations.

Patients and Methods

All bone marrow trephine biopsies received at the Pathology Department, King Fahd Hospital of the University, Al-Khobar, between January 1988 and December 1998 were retrospectively reviewed. The biopsies were obtained from the anterior or posterior iliac spine, with either Jamshidi or Islam bone marrow biopsy needle. The biopsies were stained with hematoxylin and eosin (H&E), reticulin and Perls's stain for iron. The corresponding bone marrow aspiration slides, stained with Wright's stain and cytochemical stains—PAS, Sudan black and acid phosphatase—were also reviewed for their findings and/or correlations. Only those with bone marrow necrosis, defined as necrosis of bone marrow elements and

stroma with the exclusion of bone, were selected for this study (Figure 1). The charts of these patients were reviewed for age, sex, clinical diagnosis, indication for bone marrow examination, final diagnosis, duration of follow-up and outcome. Their bone marrow paraffin sections were stained with Ziehl-Neelsen, PAS and immunohistochemically for antibodies to CD45 (LCA), B cell CD20, T cell CD3, cytokeratin, EMA and CEA, in an attempt to identify the phenotype of the cellular components in the necrotic areas for the underlying etiology.

Results

A total of 1065 bone marrow biopsies were retrospectively reviewed, the results of which are the subject of an ongoing study. Of all the biopsies, five were identified with a variable extent of bone marrow necrosis, accounting for a relative frequency of 0.47%. The bone marrow biopsy findings included necrosis of all hemopoietic elements and stroma (Figure 1), where it was difficult to venture a morphologic diagnosis except BMN.

Of the five patients, two were female and three were male. All were adults with an age range between 26 and 57 years. Follow-up bone marrow and other investigations revealed that two of the cases were related to malignancy, i.e., acute lymphoblastic leukemia and gastric carcinoma, respectively, whereas in the third case, it was related to chemotherapy for acute leukemia. In the remaining two cases, the causes were not identified. Three of the patients died, one recovered and the fifth was lost to follow-up. The clinical data, laboratory findings, management and outcome of these patients are presented.

Case 1

A 27-year-old Bangladeshi male presented with a history of generalized weakness and fever for one week. Examination showed an ill, pale man with generalized lymphadenopathy and hepatosplenomegaly. CBC showed WBC of $170 \times 10^9/L$ ($3.8-9.8 \times 10^9/L$), RBC $4.08 \times 10^{12}/L$, ($4.5-5.7 \times 10^{12}/L$), Hb 124 g/L (140-180 g/L), and platelets $44 \times 10^9/L$ ($140-440 \times 10^9/L$). Differential WBC included neutrophils 21%, lymphocytes 27%, eosinophils 10%, atypical lymphocytes 5%, myelocytes 1%, and lymphoblasts 36%. Bone marrow aspiration revealed sheets of lymphoblasts with marked reduction of normal

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hemopoietic tissue and megakaryocytes. Lymphoblasts (80%) were monomorphic with high nuclear/cytoplasmic (N/C) ratio. The minority of lymphoblasts (2%) were large with prominent nucleoli. Cytochemistry showed positivity for PAS, focal-positive acid phosphatase and negative staining for Sudan black. The diagnosis was acute lymphoblastic leukemia. The patient was started on induction chemotherapy according to standard protocol. Bone marrow examination repeated about a month later revealed bone marrow necrosis on biopsy. At this time, the patient's Hb was 102 g/L, WBC was $9 \times 10^9/L$ and platelets were $57 \times 10^9/L$. His LDH was 95 U/L (100-190) and alkaline phosphatase was 63 U/L (50-140). The patient went into clinical and hematological remission and opted to continue consolidation and maintenance therapy abroad. As a result, no repeat bone marrow examination was obtained.

Case 2

A 26-year-old Filipino male was referred from a private hospital as a case of fever, bone pain and pancytopenia for investigation. On examination, the patient was ill-looking, febrile, jaundiced and had hepatosplenomegaly and ascites. His CBC showed marked pancytopenia with a differential WBC of neutrophils 33%, lymphocytes 60%, eosinophils 3%, atypical lymphocytes 4% and reticulocytes of 0.2%. Ham's test was negative. His liver function tests and renal function tests were abnormal, with BUN of 95 mmol/L, (2.9-8.9 mmol/L), creatinine 309 $\mu\text{mol/L}$ (44-150 $\mu\text{mol/L}$) total bilirubin 599 $\mu\text{mol/L}$ (5.13-18.8 $\mu\text{mol/L}$), direct bilirubin 291 $\mu\text{mol/L}$ (0-3.4), albumin 12 g/L (36-50 g/L), and total protein 43 g/L (62-82). Alkaline phosphatase was 203, AST 306 (7-41 U/L), ALT 44 (20-65 U/L), LDH 3376 U/L, and GGTP 19 U/L (5-85 U/L). All septic work-up and limited virology studies were negative. Serum α -fetoprotein and CEA were within normal limits. Chest x-ray was normal, but CT scan of abdomen showed enlarged liver with faint focal calcification. Bone marrow biopsy showed bone marrow necrosis (Figure 1). The patient was started on broad spectrum antibiotics and amphotericin B following growth of aspergillus in sputum, however, his condition deteriorated with worsening renal failure, and he expired three weeks after admission, with BMN of undetermined etiology.

Case 3

A 57-year-old female presented in January 1996 with low back pain, melena, palpitations, dizziness and night sweats. The patient had had previous subtotal gastrectomy for carcinoma of the stomach in 1988. She was ill-looking and severely pale. Cardiovascular examination revealed an ejection systolic murmur. The liver was enlarged 4.0 cm below the costal margin, with a span of 14 cm, firm, smooth, and non-tender. Musculoskeletal examination revealed severe tenderness at the lumbosacral spine and iliac crest with no signs of arthritis. CBC showed Hb 66

g/L (120-150 g/L), WBC $8.0 \times 10^9/L$, platelets $32 \times 10^9/L$ and a leukoerythroblastic blood picture. Her liver function tests showed albumin 32 g/L, alkaline phosphatase 421 U/L, AST 13 U/L, ALT 72 U/L, LDH 1611 U/L and GGTP 139 U/L. Skeletal survey, chest x-ray, ECG and CT scan were normal. Upper GIT endoscopy showed bleeding stoma, but no ulcer or mass, and a biopsy taken was negative for malignancy. Bone marrow biopsy showed necrosis. The patient started to have fever with worsening back pain. She developed ascites, progressive increase in liver size, laboratory evidence of DIC, and died 19 days after admission. Immunohistochemistry done on review of bone marrow paraffin sections showed immunoreactivity in some of the cell clusters to cyokeratin (Figure 2) and EMA, while the reaction to CD45 was negative, confirming a diagnosis of metastatic carcinoma.

Case 4

A 26-year-old female presented with fever, joint pains and body rash of 10 days' duration that followed intake of cephalosporin for an upper respiratory tract infection. On examination, she was febrile (40°C), ill-looking, with generalized macular rash and tender posterior cervical and bilateral inguinal lymphadenopathy. She had a palpable liver of 3 cm, with a span of 14 cm and lower limb edema. The provisional diagnosis was a viral infection, but a drug reaction was also considered. Investigations revealed normal CBC, except for platelet count of $80 \times 10^9/L$ and atypical lymphocytes of 18%. Liver function tests revealed total protein of 65 g/L, albumin 28 g/L, alkaline phosphatase 150 U/L, AST 116 U/L, ALT 264 U/L, LDH 543 U/L, and GGTP 153 U/L. Prothrombin time was 19.5 seconds (control 11.5 sec.), PTT 47.1 sec (control 24.9), fibrinogen 170 mg/dL (control 255) and FDP >40 <80 $\mu\text{g/mL}$. Septic and virology work-up was negative. Serology for ANA was positive (1:80), but anti-DNA was negative. Cold agglutinins and mycoplasma antibodies were negative. The patient was started on broad spectrum antibiotics, but her condition deteriorated, and she became more febrile, hypotensive, and leukopenic, and the rash became more widespread. Methyl prednisolone was started, covering the possibility of vasculitis. A bone marrow aspirate and biopsy taken showed bone marrow necrosis, the etiology of which was undetermined. Fluconazole antifungal, acyclovir, and ciprofloxacin were started, with continuation of pulse therapy of steroids. She developed episodes of tonic-clonic convulsions and was started on diphenylhydantoin and insulin (due to steroid-induced hyperglycemia). Because of leukopenia and fever, granulocyte macrophage-colony-stimulating factor (Gm-CSF) was added for one week to the previous therapy. She showed clinical improvement, was afebrile with stable vital signs and no rash. After six weeks of illness, she improved with minimal weakness, and was discharged on valproic acid and prednisolone in good condition.



FIGURE 1. Bone marrow necrosis. Coagulation necrosis of all cellular elements with ghost cell outlines in the background (H&E, 275x, case 2).



FIGURE 2. Immunohistochemistry using ABC immunoperoxidase method for cytokeratin. Clusters of positive malignant cells are seen (275x, case 3)



FIGURE 3. Hypercellular marrow infiltrated by malignant leukemic cells of ALL (275x, case 5).



FIGURE 4. Immunohistochemistry using ABC immunoperoxidase method for CD3. Cells show membrane positivity, confirming T-cell lineage of ALL (275x, case 5).

Case 5

A 37-year-old man presented in August 1996 with a two-week history of low-grade fever, low back pain, epistaxis and bleeding gums. Clinical examination revealed pallor, temperature of 39°C, and an ecchymotic area involving the trunk and hepatomegaly. His CBC showed WBC $7.9 \times 10^9/L$, with a differential of: neutrophils 27%, bands 14%, lymphocytes 42%, monocytes 1%, atypical lymphocytes 12%, metamyelocytes 2%, myelocytes 2%, Hb 105 g/L, platelets $6 \times 10^9/L$. Biochemical profile revealed total protein 54 g/L, albumin 19 g/L, alkaline phosphatase 769, AST 128, ALT 65, LDH 2913, and GGTP 61 U/L. Bone marrow aspiration revealed a hypocellular bone marrow with necrotized particles, and the biopsy showed BMN. Septic work-up, virology studies and investigations for connective tissue disease were negative. The patient was covered empirically with antibiotics but continued to have low-grade fever. Repeat of CBC showed leukocytosis, with presence of blastocytes in the peripheral blood. WBC

was $66.3 \times 10^9/L$, neutrophils 6%, band forms 5%, lymphocytes 10%, atypical lymphocytes 22%, lymphoblasts 57%, Hb 98 g/L, and platelets $52 \times 10^9/L$. A repeat bone marrow aspiration done seven weeks after presentation identified numerous blastocytes with features of acute lymphoblastic leukemia (ALL). The bone marrow biopsy showed hypercellularity and infiltration by immature blastocytes consistent with ALL (Figure 3). Induction chemotherapy was started according to standard protocol for ALL. A repeat bone marrow a month later revealed an aplastic bone marrow. This was soon followed by relapse of the patient's ALL, further deterioration, candida sepsis, disseminated intravascular coagulation (DIC) and death five months after admission, with a diagnosis of ALL preceded by extensive bone marrow necrosis. Immunohistochemistry performed on review of both biopsies showed CD45 and CD3 immunoreactivity of the malignant cells (Figure 4), confirming ALL of T-cell lineage.

Discussion

Bone marrow necrosis has been described in several clinical conditions, but is generally more commonly diagnosed at autopsy.² The relative frequency of BMN varies among different reports, ranging between 0.37%-6.5%.^{3,7} Our five cases account for a relative frequency of 0.47%. BMN is commonly the end result of infiltration by a neoplastic process, chemotherapy or vaso-occlusion.²⁻¹⁰ It has also been related to the presence of antiphospholipid antibodies⁴ and chemotherapy for cancer with a variety of agents.¹¹⁻¹⁴ The pathophysiology of BMN has been a subject of controversy and debate,³ and has included toxic effects of chemotherapy, microvascular infarction, decreased oxygen tension due to increased proliferative capacity of infiltrating malignant cells,³ tumor necrosis factor (TNF),¹⁷ and thrombosis.^{3,4} In this study, the BMN had different underlying disease processes that were initially obscured in some patients because of the necrosis, just as in previous reports.⁵⁻¹⁶ Similar to the report of Niebrugge et al.,¹⁶ BMN preceded the diagnosis of ALL in our case 5, while in case 2, the diagnosis was not established, as the patient died early. For case 1, BMN was the result of chemotherapy, while in case 3, it was associated with metastatic carcinoma, as in a previous report,¹⁰ which in our case, was documented by immunohistochemistry (Figure 2). In case 4, the patient recovered after an initial diagnosis of BMN associated with multisystem failure, the exact etiology of which was not established. Associated clinical features reported include fever and/or bone pain,¹⁻³ which were present in most of our patients (Table 1). Likewise, laboratory findings seen in our patients and commonly associated with BMN include pancytopenia, microangiopathic features and a leukoerythroblastic blood picture.^{2,3,7} Elevated serum lactate dehydrogenase and alkaline phosphatase levels are known associated laboratory features,^{2,3,7} and were also seen in four of our patients (Table 1).

The prognosis of patients with BMN has been considered poor,^{1,2} however, there have been reports of recovery in some cases with adequate supportive management.^{8,18} MacFarlane and Tauro reported complete recovery of four children with ALL who presented with bone marrow necrosis.¹⁹ Pui et al.²⁰ reported their experience with a total of seven children, five with ALL and two with neuroblastoma, who had bone marrow

necrosis. Six of these children were in complete remission, reaffirming the fact that the prognosis in BMN is not always dismal. Likewise, an adult patient with hairy cell leukemia and BMN, treated with deoxycoformycin, showed an excellent response.²¹ In our case 4, the patient recovered, and a repeat bone marrow biopsy showed a normocellular marrow with no evidence of necrosis. The outcome of patients with BMN is, therefore, not always fatal and seems to relate to age, underlying disease and therapy administered. Correlation of bone marrow aspiration findings with that of the biopsies is variable. There have been reports of BMN leading to difficult aspiration and a dry tap.⁷ This occurred in one of our patients, whereas in the others, necrotized particles were observed. Furthermore, MRI scanning has previously been used to assess the extent of bone marrow involvement.²²

The clinical management of patients with BMN is difficult, and cases should be investigated to exclude a neoplastic process where multiple biopsies may be needed.^{5,7} It has been suggested that therapy for patients with BMN be aimed at promoting recovery of marrow stroma by the use of cytokines and chemotherapy not highly toxic to bone marrow stem cells and stroma.²

In conclusion, our findings confirm that the conditions associated with BMN are varied and malignancy remains common. BMN may precede or obscure the diagnosis, and repeat biopsies are indicated to secure a diagnosis. Pyrexia, bone pain, pancytopenia, elevated LDH and alkaline phosphatase levels are common associates of BMN. In the presence of malignancy, BMN is considered a poor prognostic indicator. This, however, may not always be the case, as the outcome seems to be age- and etiology-dependent.

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TABLE 1. Clinical and laboratory features and outcome of patients with BMN.

Age/ Sex	Bone Pain	Hb g/L	WBC x10 ⁹ /L	Platelet x10 ⁹ /L	LDH U/L	Alk-ph U/L	Diagnosis	
27/M	Y	N	102	9.0	57	95	63	ALL
26/M	Y	Y	51	1.0	10	376	203	Unknown
57/F	Y	Y	66	8.0	32	611	421	Carcinoma
26/F	Y	N	113	8.6	80	543	150	Unknown
37/M	Y	Y	105	7.9	6	2913	769	ALL

Normal range:LDH 100-190 U/L; alkaline phosphatase 50-140 U/L.

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