

Original Article

Bone Marrow Necrosis: Frequency and Clinicopathological Findings in Marrow Biopsies

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ABSTRACTS

Background and Objectives: Bone marrow necrosis (BMN) is a rare and ominous complication of wide variety of diseases including hematologic malignancy. This study was performed to identify frequency and the underlying associated diseases of marrow necrosis.

Materials and Methods: In this descriptive study, totally 850 bone marrow trephine biopsies related to living patients at the Pathology Department of Urmia Imam Hospital from March 1998 to January 2008, were retrospectively reviewed. The reviews included clinical and laboratory findings from files of the patients.

Results: Eight cases of bone marrow necrosis were found. Frequency was 0.94 percent. Ages of the patients were between 18 and 85 years, and four of them were female. Prominent symptoms of the patients were bone pain, fever, fatigue, and jaundice. The most common laboratory findings were anemia, cytopenia, elevated lactate dehydrogenase (LDH), and alkaline phosphatase (ALP). Underlying diseases of bone marrow necrosis in our patients includes systemic lupus erythematosus, multiple myeloma, metastatic gastric cancer, acute myeloid leukemia (M4), hairy cell leukemia, lymphoma, chronic myeloid leukemia and sepsis.

Conclusion: Our findings suggest that the conditions associated with BMN are varied and malignancy remains common. In cases presented with pyrexia, bone pain, pancytopenia, elevated LDH and ALK, marrow necrosis must be thought. Although prognosis is very bad, supplementary therapy, in addition to the underlying disease must be performed.

Key words: Bone marrow necrosis, Anemia, Cytopenia, Systemic lupus erythematosus

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Introduction

Bone marrow necrosis (BMN) is regarded as an uncommon entity that is associated with a poor prognosis. BMN described in 1941 (1) and is defined pathologically as necrosis of myeloid tissue and medullary stroma in large areas of the bone marrow with preservation of bone. It is estimated that about 250 to 300 cases of BMN have been reported (2-4). Clinically, it is characterized by bone pain and fever. Anemia and thrombocytopenia accompanied by a leukoerythroblastic feature in peripheral blood smear are the most frequent hematologic abnormalities (3, 5).

BMN has been associated with wide variety of disease, disorders and medications include: acute leukemia, lymphoma, chronic myeloproliferative disorders, some of solid tumors, metastatic carcinoma, sickle cell disease, sepsis, tuberculosis, parvovirus, human immunodeficiency virus, disseminated intravascular coagulation, antiphospholipid syndrome, after treatment with sulfasalazine, interferon, imatinib, paracetamol and idiopathic (3, 6-9).

In our practice we encountered a 21 year old pregnant woman that was presented with severe preeclampsia and was diagnosed later as systemic lupus erythematosus. Pancytopenia and severe progressive anemia in the patients was not improved after administration of corticosteroid. Massive BMN was observed in marrow biopsy.

With respect the first experience about BMN in our center we designed a retrospective study to determine BMN in bone marrow biopsy and clinical course of related patients.

Materials and Methods

All bone marrow trephine biopsies received at the Pathology Dept., Urmia Imam Hospital of from March 1998 to January 2008 were retrospectively reviewed. In the period of study, 850 specimens were evaluated. These were related to living cases. The clinical and laboratory findings were reviewed from the files of the patients. The specimens were stained with Hematoxylin and Eosin (H&E), reticulin and Perls's stain for iron. The related bone marrow aspiration slides 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

bone sparing, were selected for the study.

BMN was graded semiquantitatively according to the extent of necrosis in the BM biopsy described by Maisel *et al.* (10):

Grade I (mild): <20% of the biopsy;

Grade II (moderate-intermediate): 20–50% of the biopsy;

Grade III (severe-extensive): >50% of the biopsy.

Results

Eight cases of bone marrow necrosis were found among 850 marrow biopsies in a 10 year period. Frequency was 0.94 percent. The ages of the patients were between 18 and 85 years, and four of them were female. The most prominent symptoms of the patients were bone pain, fever, fatigue, and jaundice. Clinical findings were variable according to the underlying diseases. In the laboratory, the most common finding was anemia, which was found in all patients. Leukopenia was found in 5 cases and thrombocytopenia in 4 cases. LDH was found to be high in all of the cases.

Massive necrosis encountered in 2 cases, moderate necrosis in 4 and mild necrosis in other 2 cases. Clinical, laboratory and histopathologic findings of 3 cases with bone marrow necrosis was described, however other cases were illustrated in Table 1.

Case 1: A 21 year old pregnant woman was presented with severe preeclampsia and was admitted to Gynecology Department of our center. Gestational age was 34 week and she experienced first pregnancy. Past medical history was negative and any medical problem was not encountered during pregnancy. Regarding severe preeclampsia, pregnancy was terminated with cesarian section. In postoperative period mild decrease in platelet count was noted as compared to admitted laboratory data (Table 2). We did not detect significant fragmented erythrocytes in peripheral blood smear. Severe anemia and thrombocytopenia, mild leukopenia and gradual decrease in renal function progressed in next two weeks. Serum lactate dehydrogenase was 4373 U/L and alkaline phosphatase was 1565 U/L. Patient was evaluated for systemic lupus erythematosus. ANA and Anti dsDNA was positive with ANA of 3 u/md and anti dsDNA >60 u/md. Corticosteroid pulse (Methylprednisolone 500 mg, intravenous infusion for 3 days followed by 60 mg/

day oral prednisolone) was administered. Repeated packed cell transfusions were required. Significant improvement of clinical and laboratory finding was not occurred. We performed bone marrow aspiration and biopsy. Marrow aspiration was not successful (dry tap) but marrow biopsy revealed massive bone marrow necrosis (Fig. 1). Cyclophosphamide was added to prednisolone however patient's condition deteriorated and she died 50 days after cesarian section.

Case 2: A 42 year old mountaineer man was admitted to nephrology department of our center with bone pain, sever hypercalcemia, anemia and renal failure 2 weeks following last camp in the mountain. Pallor was the prominent physical finding and hepatomegaly, splenomegaly, and lymphadenopathy were not detected. He denied any important problem in his past medical history. Serum protein electrophoresis showed monoclonal (M) protein. Bone marrow aspiration and biopsy was performed. Bone marrow aspirate smears from the patient illustrated a prep-

ponderance of mostly immature-appearing plasma cells with eccentrically placed nuclei (Fig. 2). Bone marrow biopsy showed moderate (Grade II) necrosis (Fig.3). The patient underwent hemodialysis and treatment for multiple myeloma. Two months later he was admitted again in emergency department because of altered mental status and was evaluated for sepsis. Anemia and organ failure were developed and he was expired.

Case 3: A 24 year old female was evaluated for bone pain, pancytopenia and abdominal wall mass in right lower quadrant. The radionuclide bone scan was revealed multifocal involvement that was suspected metastatic disease. Histological examination of abdominal wall mass, confirmed metastatic adenocarcinoma. Massive bone marrow necrosis was observed in slides of bone marrow biopsy. Investigations to determine source of metastatic cancer was followed by upper gastrointestinal endoscopy which revealed advanced gastric adenocarcinoma. She died within 2 weeks.

Table 1: Clinical, laboratory, and histopathologic findings of patients

Age (yrs)	Sex	Presenting picture	Laboratory data					Grade of necrosis	diagnosis	Prognosis
			Hb (g/dl)	WBC ($\times 10^9/L$)	Platelet ($\times 10^9/L$)	LDH	Alk			
18	F	Menorrhagea	9.2	18.5	28			II	AML-M4	6 months
85	M	Pancytopenia	7.8	1.8	41			II	HCL	3 Weeks
74	F	Confusion	10.1	11.7	155		N	I	Sepsis	4 days
34	M	Fever	9.5	2.4	39		N	I	Lymphoma	Cure (4 years follow up)
60	M	Splenomegaly	8.5	33	178			II	CML	11 months

Abbreviations: AML, acute myeloblastic leukemia; CML, chronic myelocytic leukemia; N, normal; HCL, hairy cell leukemia

Table 2: Peripheral blood change of case 1

Date	WBC ($\times 10^9/L$)	RBC ($\times 10^{12}/L$)	Hb (g/dl)	Platelet ($\times 10^9/L$)	Differential WBC				
					PMN %	Lym %	Eos %	Mono %	Baso %
Day of admission	9.85	4.12	10.7	198	70	23	4	2	1
1 day after cesarian	10.5	3.91	9.8	145	67	29	3	1	0
7 days after cesarian	4.41	2.32	6.6	71	77	17	0.4	7.9	1.7
12 days after cesarian	6.86	2.16	6.1	41	46.2	41.9	0.5	4.1	1.2

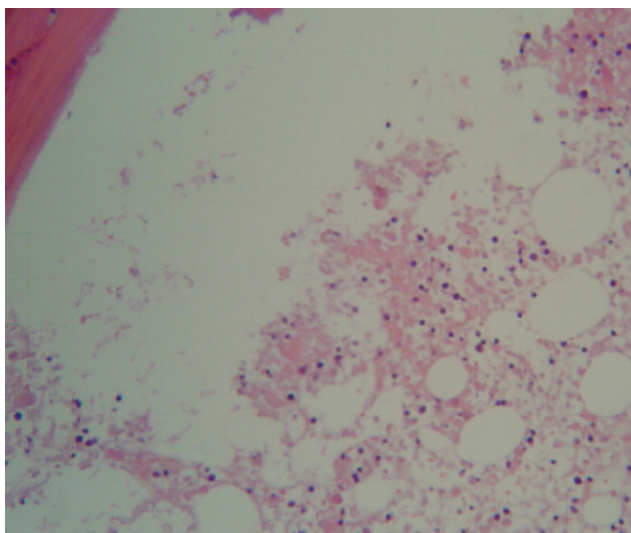


Fig. 1: Massive bone marrow necrosis in patient with SLE. (Bone marrow biopsy H&E, $\times 40$)

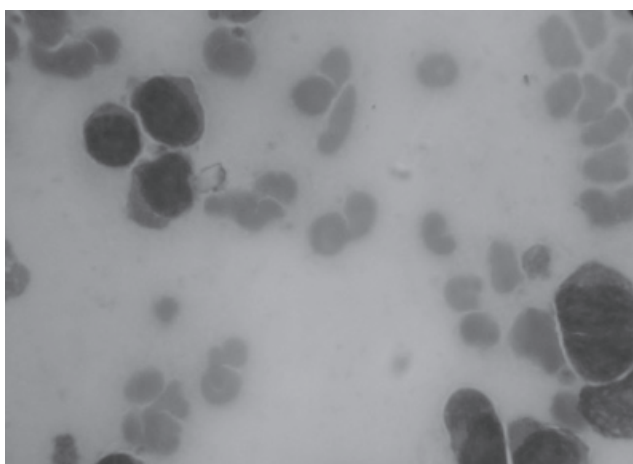


Fig. 2: Bone marrow smear show preponderance of mostly immature-appearing plasma cells with eccentrically placed nuclei. ($\times 100$)

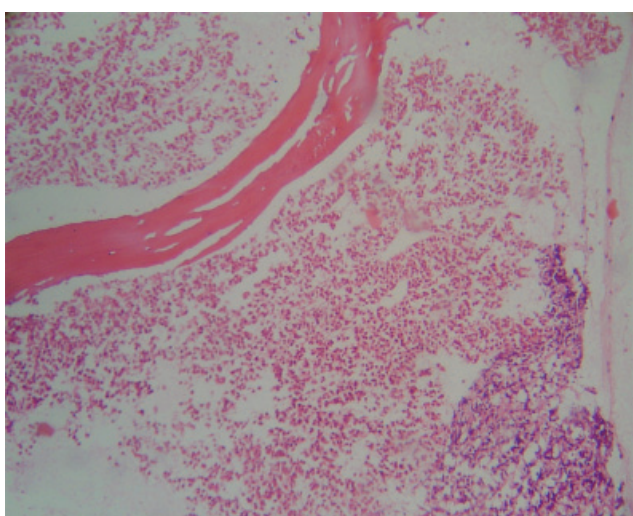


Fig. 3: Moderate bone marrow necrosis with infiltration in patient with MM. (Bone marrow biopsy H&E, $\times 40$)

Discussion

Bone marrow necrosis (BMN) is a unique clinicopathologic entity distinct from avascular necrosis (AVN) of bone and marrow aplasia. The histologic features of BMN are disruption of the normal marrow architecture and necrosis of myeloid tissue and medullary stroma with loss of fat spaces. Unlike in AVN, in BMN the spicular architecture is preserved, and unlike in aplastic anemia, in BMN the reticular structure is destroyed (3, 11, 12).

Frequency of BMN in 10 years period of our experience at the study was 0.94 percent. The relative frequency of the entity varies among different reports, ranging between 0.37%-6.5% (13, 14). These differences may be related to inclusion of living samples only in some series alike of our study, however bone marrow biopsy is not a routine practice in our department for all hematologic malignancy and is performed rarely for non hematologic malignancy. For these reasons our BMN prevalence is relatively lower than some other series.

Underlying diseases of bone marrow necrosis in our patients were neoplastic diseases in six and non malignant condition in two cases. Systemic lupus erythematosus, multiple myeloma, metastatic gastric cancer, acute myeloid leukemia (M4), hairy cell leukemia, lymphoma, chronic myeloid leukemia and sepsis were consisted causes of BMN in our practice. Hematopoietic neoplasias is the most frequent causes of BMN (5 of 8 cases) which is similar to previous reported series (10, 15-18). Although tuberculosis is common in our geographic region, we did not detect BMN in any case with tuberculosis.

We found marrow necrosis in a pregnant woman with severe preeclampsia and was diagnosed later as SLE. This entity is rare during pregnancy. Knoblauch *et al* reported marrow necrosis in a 23-year-old pregnant woman with severe anemia and thrombocytopenia due to bilateral ovarian carcinoma(19). Another case of marrow necrosis was reported in a pregnant woman with refractory HELLP syndrome in the setting of catastrophic antiphospholipid antibody syndrome (20). Therefore, bone marrow necrosis should be considered as an unusual adverse event in pregnant woman with severe catastrophic condition that was complicated pregnancy. To date seven cases of bone marrow associated with antiphospholipid syndrome have been reported but no case of marrow necrosis secondary to SLE have been reported (5, 10, 20-23).

The prognosis of patients with BMN is poor(24, 25)

however, there have been reports of recovery in some cases with adequate supportive management (26, 27). In the case of lymphoma and mild marrow necrosis, the patient recovered, and a bone marrow biopsy performed two years later showed a normocellular marrow with no evidence of necrosis. Outcome of other cases in our experience was very poor as reported in other studies and seems to be related with age, underlying diseases and therapy administered.

Conclusion

In conclusion, our findings confirm that the conditions associated with BMN are varied and malignancy remains common. In cases presented with pyrexia, bone pain, pancytopenia, elevated LDH and alkaline phosphatase, BMN must be considered as a possible cause and biopsy must be performed. Although prognosis is very bad, supplementary therapy, in addition to the underlying disease must be administered.

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