

Extensive Myelonecrosis: A Clinicopathological Study from A Tertiary Care Center

Neela Nirmala Jyothi¹, Pramod Kumra Pamu^{1*}, T Roshni Paul¹, Shantveer G. Uppin¹, Megha S Uppin¹
Sadashivudu Gundeti² and K. Radhika³

¹Department of Pathology, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, Telangana State. INDIA

²Department of Medical Oncology, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, Telangana State. INDIA

³Department of Hematology, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, Telangana State. INDIA

ABSTRACT

Background: The pathophysiology of bone marrow necrosis (BMN) remains unclear; however, the occlusion of microcirculation, accompanied by hypoxemia, causes damage to the cells and plays an important role in development of BMN.

Methods: This is a descriptive study; a retrospective review of all trephine biopsies done over period of 22 months January 2017 to October 2018 in Department of pathology showing BMN were included. Only cases identified which showed extensive myelonecrosis > 20% of the diameter of trephine biopsy specimen was included in the study and BMN had to be diagnosed during life were included. Thirty cases met these criteria over this period.

Result: In the study period, BMN was diagnosed in 30 samples among 3000 trephine biopsies showed extensive necrosis accounting for 1.0%. Almost all patients on peripheral blood examination shows anemia (100%), around 50% patients present with pancytopenia, followed by anemia with thrombocytopenia. From bone marrow aspiration and trephine biopsy examination shows 30 cases MN, among them 16 patients were acute leukemia either newly diagnosed or post chemotherapy follow-up cases, 10 out of 12 patients had severe bone pain before intuition of chemotherapy, acute leukemia followed by necrotizing granulomatous inflammation metastatic carcinoma were other causes for MN and one case was sickle cell hemolytic anemia.

Conclusion: BMN is associated with many diseases, and yet presents with no clear patho physiology. In addition, clinical and laboratory characteristics are non-specific and, in many cases, symptoms are related to the causal condition that is most commonly a hematological disease.

Keywords: Myelonecrosis, Bone Marrow Necrosis, Leukemia, Trephine Biopsy, Bone Marrow Aspiration

Introduction

BMN was initially described in a patient with sickle cell disease by Wade and Stevenson in 1941 [1]. Myelonecrosis (MN) or Bone marrow necrosis (BMN) is rare clinical entity and may be associated with hematologic malignancies, metastasis, AIDS and other conditions [2]. Extensive myelonecrosis (MN) is defined as necrosis of the myeloid tissues and stroma evident in a substantial (> 20%) area of the bone marrow (BM) parenchyma, without cortical bone involvement [3]. An uncertain etiology only adds to the complexity of diagnosing BMN, which remains controversial, and is often only made post mortem [1, 4, and 5]. Histological analyses of BMN cases show eosinophilic amorphous material with destruction of the normal BM architecture, together with fat-cell depletion [6, 7]. Some authors advocate that the extensive myelonecrosis should only be diagnosed if the necrotic zone involves at least half of the specimen [1-8]. This study was designed to evaluate the causes of extensive bone marrow necrosis and correlate the morphology with the clinical features. To

identify the rate of prevalence, the symptoms and signs, the underlying disease associations, and the usefulness of diagnostic procedures.

Materials and Methods

This is a descriptive study; a retrospective review of all trephine biopsies done over period of 22 months January 2017 to October 2018 in Department of pathology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana State. The cases diagnosed ante mortem and the cases which showed extensive myelonecrosis > 20% of the diameter of trephine biopsy specimen were included in the study. Thirty cases met these criteria during study period. The bone marrow examination was done as a part of diagnostic work-up and written informed consent was taken from all the patients as per the institution protocols. Bone marrow aspiration and biopsy were done from the posterior superior iliac spine. Peripheral smear, bone marrow aspiration slides were stained with Giemsa stain. The trephine biopsies were stained with hematoxylin and eosin stain (H & E). Special stains like Periodic Acid

Schiff (PAS), Gomori-methenamine silver (GMS) for fungus, Ziehl-Neelsen Staining for Acid-fast bacilli, and immunohistochemistry (IHC) was done in the trephine biopsies wherever necessary. The clinical details and follow-up were obtained from the patient files. The results are expressed as percentage of total number of cases.

Results

In the study, MN was diagnosed in 30 samples among 3000 trephine biopsies showed extensive necrosis accounting for 1.0%. Median age was 44 years and male to female ratio is 1: 1 (Table 1). None of the patients had disseminated intra vascular coagulation. 10 out of 12 patients had severe bone pain before initiation of chemotherapy. All the patients had anemia with hemoglobin less than 10 grams /dL, 5 patients had leucopenia, and 9 patients had leucocytosis. Platelet count was normal within normal range in 8 cases;

thrombocytopenia was noted in 22 cases and 12 cases of thrombocytopenia patients had count below 1 lakh. Nucleated RBCs were noted in 6 cases with more than 5 nucleated RBCs per 100 WBCs. Blasts in peripheral blood were noted in 16 cases (45%) of the cases (Table 2). Bone marrow cellularity was good to necrotic; majority of the cases showed particulate marrow material (Table 3). The classification of bone marrow necrosis is based upon the extent of bone marrow involvement and ranges from grade I to III depending on the percentage of necrosis, grade I –less than 20 % necrosis, Grade II – 20 to 50 % necrosis and grade III – more than 50 % necrosis. Clinical summary, peripheral blood smear examination and bone marrow findings are tabulated in table 4. List of disorders associated with Bone Marrow Necrosis or Myelonecrosis in this study are tabulated in Table No: 5

Table 1: Age and Sex distribution of the cases.

AGE GROUP	MALE	FEMALE	TOTAL
01-10 years	01	01	02
11-20 years	04	02	06
21-30 years	03	02	05
31-40 years	00	01	01
41-50 years	03	03	06
51-60 years	02	04	06
61-70 years	01	02	03
71-80 years	01	00	01
Total	15	15	30

Table 2: Hematological parameters on Peripheral blood examination (N=30 cases).

PARAMETER	CRITERIA /RANGE	NUMBER OF CASES (N=30)	PERCENTAGE (%)
Hemoglobin	<10 gm/dl	30	100%
Total leukocyte count	>11000 cells/cu.mm	09	30%
	4000-11000cell/cu.mm	16	53 %
	< 4000 cells/cu. mm	05	17 %
Platelet Count	>1.5 lakh/cu.mm	08	27 %
	1-1.5lakh/cu.mm	10	33%
	<1.0 lakh/cu.mm	12	40%
Leuco-Erythroblastic picture	>5 N-RBC /100 WBC	06	20%
Blasts in peripheral blood.	> 20 blasts /100 WBC	12	40%
	<20 blasts /100 WBC	04	5%

Table 3: Bone marrow aspiration cellularity.

BONE MARROW CELLULARITY	NUMBER OF CASES
Particulate marrow	08
Scanty particulate	12
A particulate / dry tap.	09
Total Necrotic material	01
TOTAL	30

Table 4: Summary of Peripheral blood, Bone marrow aspirate, Trephine biopsy, Histopathological Findings and underlying disease of Patients with Bone Marrow Necrosis.

Patient no.	Age/sex	Peripheral blood	Bone marrow& Trephine Biopsy	Underlying diagnosis
01	30/M	No blasts	Particulate 45% blasts	AML - M2
02	23/M	Leucopenia No blasts	Scanty particulate, 5% blasts	Treated case of AML -M1
03	73/F	Pancytopenia	Dry tap,	Metastatic carcinoma with Myelofibrosis
04	55/F	Pancytopenia	A particulate	Metastatic carcinoma
05	02/F	58% blasts	A particulate	ALL-L2
06	45/M	WNL	Particulate	Granulomatous inflammation
07	35/M	30 n-RBC/100WBC	Particulate	Granulomatous inflammation
08	15/M	WNL	Particulate	Granulomatous inflammation
09	25M	n-RBC, blasts	Particulate	Acute leukemia -- AML-M5
10	23F	Lymphocytosis	Particulate	Granulomatous inflammation
11	54M	Left shift	A particulate	Metastatic carcinoma with Myelofibrosis
12	45F	Bi cytopenia	A particulate	Severe Hypo cellular marrow
13	4M	Pancytopenia	Scanty particulate	Complete remission of ALL
14	38M	Lymphocytosis	Particulate	Necrotizing granulomatous inflammation
15	59M	Left shift	A particulate	Relapse AML-M5
16	13M	70% Atypical cells	Particulate	Malignant round tumor
17	57M	Pancytopenia	Scanty particles	Extensive myelonecrosis
18	59F	Pancytopenia	Scanty particles	Metastatic carcinoma
19	17M	7 % blasts	A particulate	Partial remission ALL
20	27M	WNL	Pus like material	Granulomatous inflammation
21	23F	Sickle cells	Particulate	Extensive myelonecrosis
22	57M	60% blasts	Dry tap	Acute leukemia AML -M5
23	63F	Pancytopenia	Scanty particles	Metastatic carcinoma
24	54F	13% blasts	Particulate	Acute leukemia ALL
25	20F	60% blasts	A particulate	Persistence of disease AML-M5
26	20M	Pancytopenia 10% blasts	Dry tap	Acute leukemia ALL
27	49F	WNL, No blasts	Particulate	Complete remission AML-M4
28	44M	52% blasts	Particulate	Acute leukemia AML -M2
29	14 M	11% blasts	Scanty particulate	Partial remission ALL
30	57M	n-RBC 20/100 wbc	Dry tap	Myelofibrosis

*M=Male, F=Female, WNL =Within Normal Limits, AML=Acute Myeloid Leukemia, ALL=Acute Lymphoblastic Leukemia, n-RBC= Nucleated Red Blood Corpuscles / RBC.

Table 5: Disorders associated with BMN diagnosed in vivo.

UNDERLYING DISORDER	NUMBER OF PATIENTS
Acute leukemia (newly diagnosed)	12
Acute lymphoblastic leukemia	04
Acute myeloid leukemia	08
Acute leukemia (post chemotherapy):	04
Metastatic tumors	04
Myeloproliferative syndrome - Myelofibrosis	02
Round cell tumor involvement	01
Necrotizing granulomatous inflammation	08
Sickle cell anemia disease	01

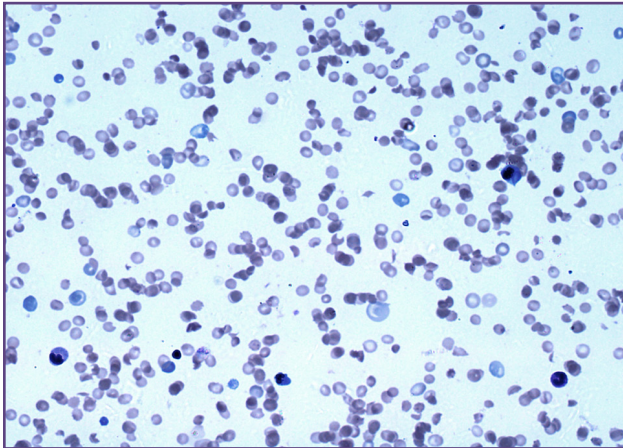


Fig. 1: Photomicrograph showing leukoerythroblastic picture with Nucleated RBCs. (Leishman's Stain; 40 X magnification).

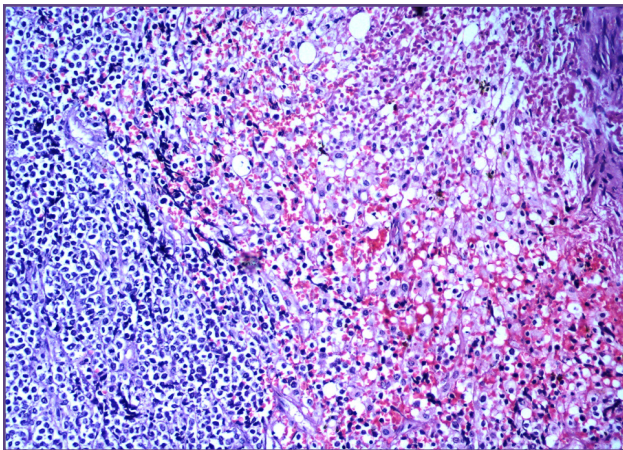


Fig. 2: Photomicrograph showing Myelonecrosis in a case of Acute Leukemia (Leishman's Stain; 40 X magnification).

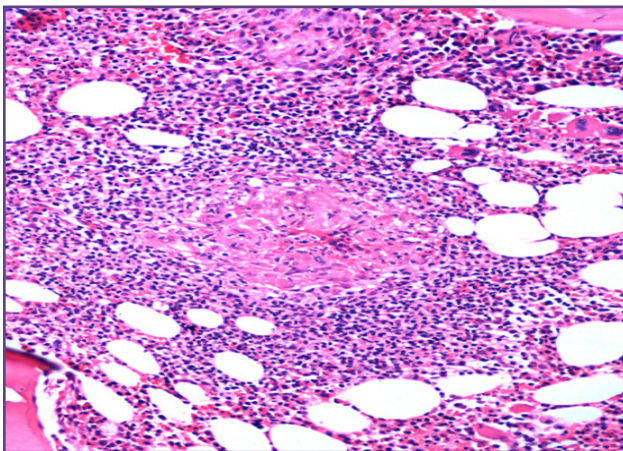


Fig. 3: Photomicrograph showing Bone Marrow Necrosis and Granulomatous Inflammation (H & E Stain; 40 X magnification).

Discussion

Extensive BMN is rarely diagnosed in living patients. The ante mortem diagnosis of myelonecrosis has been noted in association with wide variety of clinical conditions. Bone marrow necrosis is seen across a wide range of conditions, including sickle cell diseases, Acquired Immuno Deficiency Syndrome (AIDS), leukemia, lymphoma, metastatic carcinoma, anemia, sepsis and other systemic diseases. Excluding sickle cell disease, all cases of bone marrow necrosis diagnosed during life were associated with a neoplastic process involving the marrow BMN usually demonstrate only small foci of necrosis (Grade I). Moderate (Grade II) and severe (Grade III) bone marrow necrosis are often associated with life threatening illnesses, with most of these being hematologic malignancies or bone marrow metastases [9]. The prevalence of this entity changes according to the series from 0.3% to 37% [10]. The prevalence of BMN in our BM biopsy samples was found to be 3%, Hematological Malignancy is seen 70% of the cases, In one series, BMN was classified into grade I (mild necrosis) defined as focal necrosis occupying less than 20% of marrow, grade II (moderate necrosis) involving 20–50%, and grade III (severe necrosis) occupying more than 50% of bone marrow biopsy. However, more extensive bone marrow necrosis is more commonly associated with hematological malignancies [3, 9, 11, 12, and 13]. Over all, hematological malignancies account for half of cases of BMN, followed by granulomatous inflammation and solid malignancies account for one-third. Among the hematolymphoid malignancies, acute myeloid leukaemia (AML) is the most common. AML can present with BMN at presentation, after induction or at relapse. AML presents with BMN usually at presentation which is different from other studies Dunn et al, Jensen et.al and Sreerekha et al [5, 14]. In other studies acute lymphoblastic leukemia was most common malignancy. All our post chemotherapy cases with MN were myeloid type only.

In our series, among 16 patients were having hematological malignancy 12 out of 16 cases were newly diagnosed acute leukemia's either of lymphoid or myeloid type. Acute leukemia undergoing therapy has been showing BMN in 4 out of 16 patients during chemotherapy response evaluation. Its association has been noticed more frequently in AML than ALL. Among 12 cases of acute leukemia 8 cases were AML, 4 patients had lymphoid leukemic type, among AML 22% had the FAB-M5 histology, None of the patients in our series had the FAB-M 7 histology suggesting that, its association with marrow fibrosis, the M7 histology is not associated with BMN, Among the evaluable patients with ALL and with BMN, all had B cell lineage disease and none had T-cell lineage. Necrotizing

granulomatous inflammation was second most commonest etiological cause in our study, among 30 cases of BMN 8 (8/30) patients were having necrotizing granulomatous lesion noticed in trephine biopsy study and an one case on aspiration pus like material was yielded. Necrotizing granulomatous inflammation was higher incidence than other similar studies like Sreerekha et al, Basu et al and Jensen's et al studies. The association of MN with solid tumors is also known [6]. In our study, non-hematological solid tumor involvement in trephine biopsy showing extensive BMN; metastatic carcinoma in 4 out of 30 patients. Details of primary cancer in the cases diagnosed as metastatic carcinoma in trephine biopsy sections were not available in 3 out of 4 cases; one patient had signet ring cell carcinoma of colon earlier, before metastatic tumor involvement in the trephine biopsy section. However, in our study clinical outcome and survival details were lacking in many reports of myelonecrosis because loss of follow-up. BMN is less commonly associated with chronic myelo-proliferative neoplasms [7]. In this present study, two cases diagnosed as idiopathic myelofibrosis on trephine section were associated with BMN.

The most common presenting symptom is fever seen in our study in 80%. Fever as the common presenting feature was also described in other studies [8, 10]. Fever can be attributed to the pyrogenes released from the necrotic marrow. The most common symptom of myelonecrosis described in the literature is bone pain [7]. Bone pain that occurs in MN is described as an acute, intense debilitating pain that is usually located in the lower back [7]. All newly diagnosed acute leukemia patients were complain severe bone pains and tenderness over the sternal area, it was the primary clinical complaint for visiting the primary physician, bone pains followed by peripheral blood cytopenias were identified as direct complications of marrow necrosis.

The most common peripheral smear findings described in MN are anemia and thrombocytopenia as seen in our study, seen in 100% and 76% of cases. These may or may not be associated with a leucoerythroblastic blood picture. Leucoerythroblastic blood picture was noticed on peripheral smear 6 out of 30 cases, among these four cases were shows metastasis and two patients showing myelofibrosis on trephine biopsy. In our study, 10 out of 16 cases of leukemia and 4 out of 4 cases of metastatic malignancies presented with anemia and thrombocytopenia. Pancytopenia was seen 40% of our cases and is also a significant peripheral blood finding. Hematological abnormalities necessitate bone marrow examination and often give a clue to diagnosis [3, 6]. Our study is in correlation with other studies in the literature by Paydas et al and Sreerekha et al [6].

Myelonecrosis appears to result from ischemic infraction from bone; it is not caused by chemotherapy because myelonecrosis MN can even precede leukemia. Niebrugge and Benjamin describe two patients who initially presented with BMN and subsequently developed ALL emphasizing the need for close monitoring of patients with unexplained myelonecrosis [9]. In patients with leukemia and metastatic carcinoma, development of severe pancytopenia with or without chemotherapy and which does not respond to supportive measures, the possibility of myelonecrosis should be considered [3, 6].

Most common infectious cause of BMN in our study was tuberculosis (TB). Tuberculosis shows varied clinical as well as hematological manifestations. Anemia is the most common manifestation but other abnormalities like leucopenia, thrombocytopenia, monocytosis, basophilia, disseminated intravascular coagulopathy (DIC), leukemoid reaction, thrombocytosis, or a pancytopenia can also occur [11]. Pancytopenia is associated with a poor prognosis in TB [12]. The pathogenesis of myelonecrosis is controversial and subject to debate [3]. It could be due to infiltration by neoplastic cells and decreased oxygen tension due to increased proliferative activity of tumour cells, elaboration of tumour necrosis factor, vasoocclusion, and thrombosis, radiation injury or the effect of chemotherapy [3, 6, 8, and 15]. It can be seen prior to chemotherapy as seen in 12 of our cases of leukemia and may be due to occlusion of medullary nutrient vessels by blasts [2, 6, and 8]. In disseminated tuberculosis the toxic effects on the marrow by large amounts of tuberculin protein may lead to marrow necrosis [8].

Our study confirms that causes of BMN are varied and hematopoietic malignancy is the most common cause. The clinical features of BMN are nonspecific. Hematological abnormalities are commonly present and are clue to the diagnosis. Myelonecrosis may obscure the underlying disorder and hence a thorough search in the bone marrow biopsy itself may be the key to diagnosis. Apart from one series, to date there is no standardized grading system to evaluate the extent of necrosis, and the clinical impact of the extent of BMN remains unknown. Furthermore, the underlying pathophysiology of BMN remains poorly understood. Although hypoxemia resulting from the failure of the microcirculation may be a critical event, the role of various toxins, cytokines, and vasoactive substances released from the malignant cells as well as the supporting cells. As the underlying causes of MN are varied, the disease process may get obscured by extensive necrosis of the marrow. In our study 40% of cases showed a particulate or dry tap aspirate and the final diagnoses were made only on the trephine biopsy in all the cases, after having

to resort to deeper cuts, histochemistry, and application of IHC. Trephine biopsy provides the pathologist with material for taking deeper sections to identify a viable focus of cells, to do IHC to identify the possible primary malignancies and immunophenotyping in hematolymphoid malignancies. Some immunohistochemical markers like CD45, CD3, CD20, S100, and cytokeratin AE1/AE3 retain reactivity even in the necrosis ghost cells, thus helping the pathologist in identifying the underlying disease [15].

Conclusion

Based on this review, we conclude that BMN is associated with many diseases, and yet presents with no clear path physiology. In addition, clinical and laboratory characteristics are non-specific and, in many cases, symptoms are related to the causal condition that is most commonly a hematological disease. Finally, the most important conclusion is that in all cases of BMN a malignant disease must be ruled in or out, given that malignancies are the most common cause of this lesion.

Acknowledgements

I would like to thank my Post graduates, residents and technicians for helping me in providing the case details, slides and slide images.

References

1. Wade L, Stevenson L. Necrosis of bone marrow with fat embolism in sickle cell anemia. *Am J Pathol* 1941; 17:47-54.
2. Naeim F. Abnormal morphology: General considerations. In *Pathology of Bone Marrow*. Williams & Wilkins, 2nd ed. p99-100.
3. Bernard C, Sick H, Boilletot A, Oberling F. Bone marrow necrosis: acute microcirculation failure in myelomonocytic leukemia. *Arch Intern Med* 1978; 138:1567-9.
4. Jain D, Singh T, Kumar N. Hypo cellular acute myeloid leukemia with bone marrow necrosis in young patients: two case reports. *J Med Case Rep*. 2009; 3: 27-31.
5. Janssens A, Offner FC, van Hove WZ. Bone marrow necrosis. *Cancer*. 2000; 88: 1769-80.
6. Paydas S, Ergin M, Baslamisli F, et al. Bone marrow necrosis: clinicopathologic analysis of 20 cases and review of the literature. *Am J Hematol*. 2002; 70: 300-5.
7. Bashawri L, Satti MB. Bone marrow necrosis: report of five cases and review of the literature. *Ann Saudi Med*. 2000; 20: 78-82.
8. Campiotti L, Codari R, Appio L, et al. Bone marrow necrosis related to imatinib mesylate therapy for CML bilateral blast crisis. *Leuk Res*. 2007; 31: 1765-72.
9. Maisel D, Lim JY, Pollock WJ, Yatani R, Liu PI. Bone marrow necrosis: an entity often overlooked. *Ann Clin Lab Sci*. 1988;18(2):109-115.
10. Norgard MJ, Carpenter JT, Conrad ME. Bone marrow necrosis and degeneration. *Arch Intern Med* 1979;139:905-911.
11. Macfarlane SD, Tauro GP. Acute lymphocytic leukemia in children presenting with bone marrow necrosis. *Am J Hematol*. 1986;22(4):341-346.
12. Kiraly JF, 3rd, Wheby MS. Bone marrow necrosis. *Am J Med*. 1976; 60(3):361-368.
13. Forrest DL, Mack BJ, Nevill TJ, Couban SH, Zayed E, Foyle A. Bone marrow necrosis in adult acute leukemia and non-Hodgkin's lymphoma. *Leuk Lymphoma*. 2000;38(5-6):627-632.
14. Dunn P, Shin LY, Liaw S, Sun C. Bone marrow necrosis in 38 cancer patients. *J Formos Med Assoc*. 1985; 92: 1107-10.
15. Debdatta Basu, Parasappa J Yaranal Myelonecrosis – clinicopathological significance of a rare bone marrow lesion. *Case Rep Clin Pract Rev*, 2005; 6: 261-264.

*Corresponding author:

Dr. Pramod Kumar Pamu, Flat No: 204, Kothapet, Dilsukhnagar, Hyderabad, Ranga Reddy District, Telangana State -500035. INDIA

Phone: +91 87621 37568

Email: pramodkumarpamunims@gmail.com

Financial or other Competing Interests: None.