Original research article

Bone Marrow Necrosis: Report of five Cases from a Tertiary Centre During a Period of four years.

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Abstract

Background: Bone marrow is the major hematopoietic organ and is one of the largest organ in human body.[1]The causes of bone marrow necrosis (BMN) is varied & diverse. Among these cases, hematopoietic malignancy is the commonest. As it is a potential target organ of various disorders, the examination of blood and bone marrow becomes one of the important component for the evaluation of certain disorders.[1] It is a rare finding accounting for about 0.3 to 2.2%[2,3]. Bone marrow necrosis is defined as necrosis of the medullary stroma and myeloid tissues in large areas of the hematopoietic bone marrow (BM), leaving an amorphous eosinophilic background, poorly defined necrotic cells and preserved cortical bone.[4]

Objectives: The objective was to highlight these rare phenomenon of bone marrow necrosis and to analyse the underlying disease producing bone marrow necrosis.

Methods: All cases of bone marrow examination performed in the Pathology Department, JNIMS, Imphal Manipur where analysed during the four years period starting from 1st November 2017 to 30 November 2021. The clinical details and other parameters of all the cases were traced retrospectively from hospital record section. Archived bone marrow aspirate smears and biopsy sections were reviewed whenever required.

Result: A total of 346 bone marrow aspirations were performed in the department of Pathology during the study period. Five cases of bone marrow necrosis were detected producing a prevalence of 1.4%.

Conclusion: In our series of five cases, 2 cases (40%) of acute myeloid leukemia, 1 case (20%) of MDS-EB II, 1 case (20%) of disseminated tuberculosis and 1 case (20%) of hepatits B viral infection were included. To conclude, in cases of bone marrow necrosis, further investigations including ancillary techniques are strongly suggested to come to conclusive diagnosis as the causes of bone marrow necrosis vary from patient to patient.

Keywords: Trephine biopsy, bone marrow necrosis

Introduction

Wade and Stevenson described bone marrow necrosis (BMN) in 1942 for the first time in a patient of sickle cell anemia who died of cerebral infarction. Bone marrow necrosis is an unusual histological finding which may be associated with leukemia and sickle cell disease.[1] Bone marrow necrosis is classified into three types based on the area involved with necrosis. If the involvement of necrosis is focal, then it is referred to as mild, if intermediate involvement then it is termed as moderate and in extensive involvement then it is termed as severe type. Accordingly it is graded as Grade I- <20%, Grade II- 20-50%, Grade III- >50%[1]. The prevalence of bone marrow necrosis is found to range from 0.3% to 2.2%.[2,3] It is characterized by necrosis of the medullary stroma and myeloid tissues in large areas of the hematopoietic bone marrow (BM), leaving an amorphous eosinophilic background, poorly defined necrotic cells and preserved cortical bone[4]. Biopsy shows a disruption of normal marrow architecture with loss of fat spaces.[4] Hematopoietic malignancy is the most common cause of marrow necrosis followed by sepsis, infection like tuberculosis, disseminated intra-vascular coagulation, sickle cell disease, hemolytic uremic syndrome, drug ingestion etc.[4] Acute myeloid leukemia in adults and acute lymphoblastic leukemia in children are common cause of bone marrow necrosis.[5] Some of the clinical presentation of BMN include intense bone pain, often present on lower back that brings the patient to hospital.[5] Some cytokines and antineoplastic drugs such as interferon alpha, G-CSF, fludarabine are commonly used drugs in hematology that cause BMN.[3]A proper review of patient's clinical record that includes medical history, clinical presentation, laboratory findings, morphological review of bone marrow by using proper ancillary stains are required to find out the underlying cause of bone marrow necrosis.[6] MRI is also a very useful tool for the evaluation of marrow diseases and during the evaluation it frequently encounters marrow necrosis. So, MRI plays a very important role in early detection of bone marrow necrosis and thus helps to initiate an appropriate search for its cause.[7] In MRI, marrow necrosis is characterized by increased in water content and replacement of fat by serous fluid.[8]

Objectives: The Objective of the study is to highlight the rare phenomenon of bone marrow necrosis and to analyze the underlying disease producing bone marrow necrosis.

Patients and Methods: All cases of bone marrow examination performed in the Pathology Department, JNIMS, Imphal Manipur where analysed during the four years from 1st November 2017 to 30 November 2021. The clinical details and other parameters of all the cases were traced retrospectively from hospital record section. Archived bone marrow aspirate smears and biopsy sections were reviewed whenever required.

Results: A total of 346 bone marrow aspirations were performed in the department of Pathology during the study period. Five cases of bone marrow necrosis were detected producing a prevalence of 1.4%. The details of each case are described.

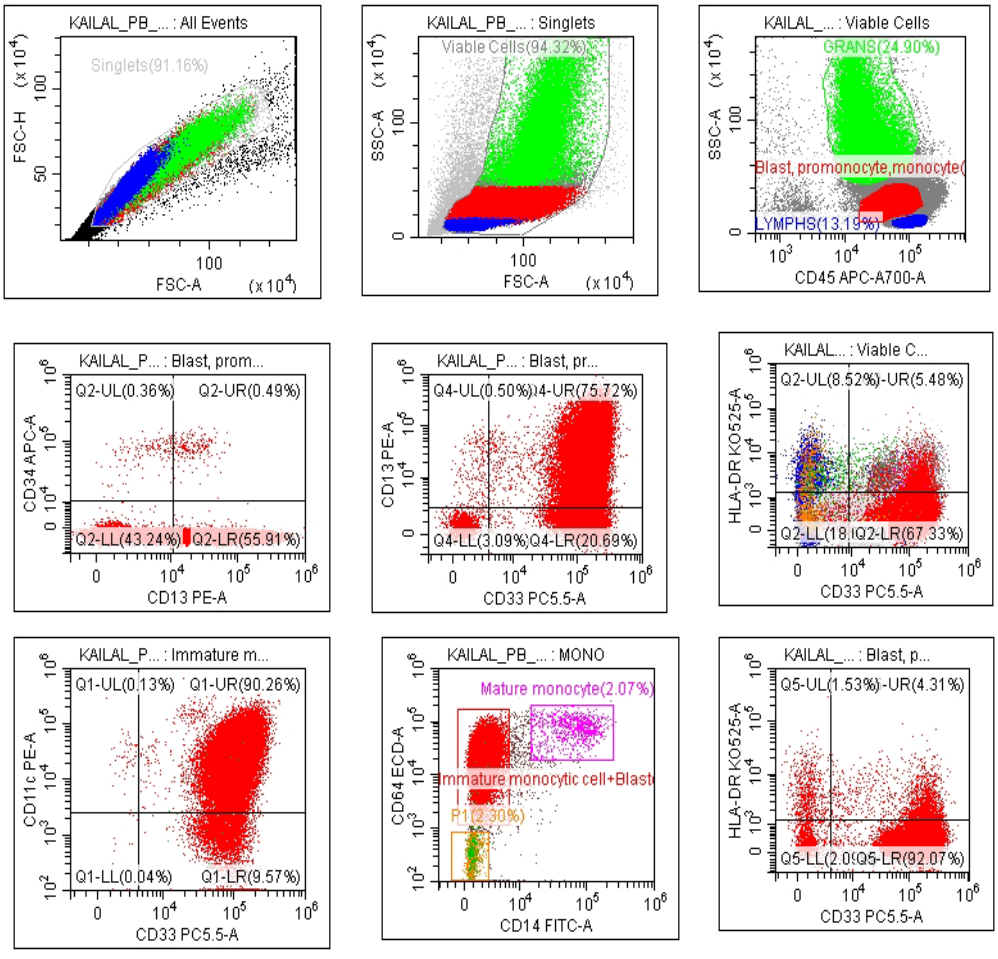
Case 1: A 24 years old male was admitted in medicine ward with history of fever and cough for 2 weeks. He was a case of bicytopenia under evaluation. He developed pharyngitis and mouth ulcer. His CBC shows Hb - 9.8gm/dl, PCV – 27%, corrected reticulocyte count- 0.6%, TLC- 4,600/cumm, platelets – 1.0 lac/cumm, Atypical lymphoid cell- 04%, myelocyte - 01%, metamyelocyte - 06%, neutrophil - 46%, lymphocyte - 41% and monocyte - 02%. These atypical cells have round to oval nuclei, inconspicuous nucleolus, clump chromatin and abundant basophilic cytoplasm. Test for Epstein Bar virus (EBV IgM) was done and it was found positive. Other investigations for fever including malarial parasite, blood culture, viral markers etc were negative. He received treatment for EBV infection. There was a transient

symptomatic as well as hematologic improvement however after a fortnight he became febrile. He had pharyngitis for the second time so he went to a higher centre for further management. Bone marrow was done followed by flowcytometric analysis of the bone marrow aspirate. In the flowcytometric analysis, there were 6% blasts with monocytic differentiation (positive for CD117, CD64, CD34 heterogenous, CD 14, CD33, CD11c and HLA DR. Negative for other T and B cell markers) were noted. He was diagnosed as Myelodysplastic syndrome with excess blast (MDS EB-II) and treatment was started. Some improvement was seen after the treatment. He came back. Four months later, he developed oral thrush and admitted to Medicine ward, JNIMS hospital. Bone marrow aspiration and biopsy was done. He complained of severe bony pain at the site of aspiration while performing the procedure. Aspiration yielded only serosanguinous material. His complete blood count from the sample collected at the time of bone marrow procedure showed Hb - 8.7g/dl, white blood cell count- 5,300/cumm, platelets count – 1 lac/cumm. Peripheral blood smear showed normocytic normochromic red cells with few macrocytes, macro-ovalocytes and elliptocytes. Neutrophils showed toxic granules and hypersegmentation. Platelets showed anisocytosis with many large and giant forms. Downey like atypical cells were present in peripheral smear. Bone marrow aspirate was aparticulate with necrotic material with few viable cells. All three haematopoietic elements were reduced. Unilateral bone marrow trephine biopsy measuring 0.8 cm showed 4 cores of tissue. 3 of these cores showed extensive necrosis with sparse polymorphs and lymphoid cells. Stain of Acid Fast Bacilli was negative. The other core showed mostly cortical bone. A diagnosis of bone marrow necrosis was rendered with a suggestion for further investigations. He went back to higher centre again for further management but unfortunately, he got expired at that centre.

Case 2: A 26 years old female was admitted in medicine ward with history of fever, cough and joint pain. Her Mantoux test was found positive (24mms). Ultrasonographic examination of the abdomen showed splenomegaly. Her urine and blood culture and sensitivity were found negative. ASO titre was less than 54.1IU/ml. Sputum culture and sensitivity was negative. Procalcitonin level was found to be more than 3.6 ng/ml. SGOT level was 75 U/L. Alkaline phosphatase level was 624 U/L. Antinuclear antibobody test was found negative. Routine haematological investigation was done and the reports were as follows- Hemoglobin- 9.6 g/dl, total leucocyte count- 6,400/cumm, platelets count- 1.3lacs/cumm. Bone marrow aspiration was done. Patient experienced a very painful bone marrow procedure. Aspiration smears showed necrotic material with occasional beaded bacilli on ZN stain, a few scattered surviving lymphocytes seen in the background and no other cellular elements seen. CT and MRI of the spine shows features of pott's spine. A diagnosis of tuberculosis was rendered.

Case 3: A 49 years old man was admitted to the medical ward with history of gastro-intestinal bleeding. Routine hematological investigation was done and the reports were as follows- Haemoglobin- 7.8 g/dl, total count- 2,940/cumm, platelets- 22,000/cumm, DLC- Blast- 20, Promyelocyte-3, Myelocyte-10, Metamyelocyte-4, Neutrophil-12, Lymphocyte-30, Monocyte- 16, Eosinophil- 5. Bone marrow aspiration and biopsy was done. Aspiration smears showed aparticulate, mostly necrotic material which is sparsely cellular. Flowcytometric immunophenotyping from the peripheral blood showed - blasts expressing Dim CD45, CD33, CD64, MPO; heterogenous expression of CD11c, CD13; doesn't express B cell marker such as CD19, CD10, CD20 and CD22 & T cell markers such as CD3, CD4, CD8, CD7 and CyCD3. Others markers such as CD38, CD34, CyCD79a, HLADR, CD14, CD15, CD117 were not expressed on the blast.

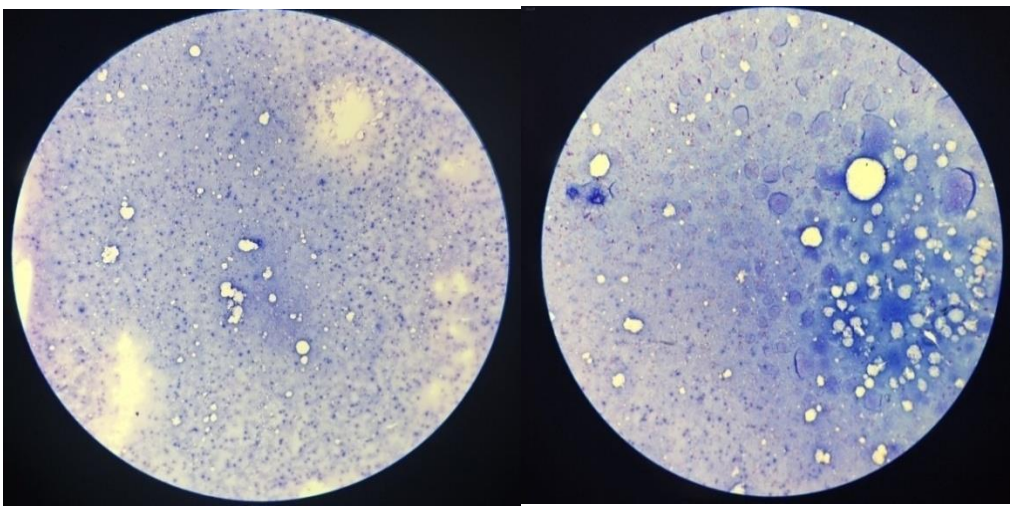
FLOW CYTOMETRY TRACING



So, the final diagnosis was made AML-M2 morphologically.

Case 4: A 70 years old man was admitted in medical ward with history of fever for the last one month and low back ache and diffuse bony pain for three months. He was tested for HBsAg and found positive. Subsequently his viral load was tested and confirmed infection. Liver function test was done and reports were as follows – Bilirubin- 3mg/dl, Alanine transferase - 200 U/L, Aspartate transferase – 250 U/L, Alkaline phosphatase – 170 U/L. Routine haematological investigation showed- Hemoglobin- 8.3 g/dl, total counts- 3600/cumm, platelets- 1.6 lacs/cumm, erythrocyte sedimentation rate- 34mm/hr. On Computed tomography scan, there was bilateral pleural effusion with mildly bulky bilateral thyroid lobes with multiple small colloid nodules. Antinuclear antibody was found positive. Bone marrow aspiration and biopsy was performed for bicytopenia. Patient experienced a very painful bone marrow procedure. Aspiration smears showed increase cellularity, mostly degenerated cells, fragments of degenerated cells and necrotic material. No malignant cells, granuloma and hemoparasite were seen on aspirate smears. Impression: overall morphological features were of bone marrow necrosis.

Case 5: A 43 years old man was admitted to medical ward with complain of weakness and bleeding gum for one week. The patient had no fever. There was no sign of hepatosplenomegaly and lymphadenopathy. There was history of repeated blood transfusion. Complete hematogram examination showed Hb- 7gm%, TLC- 3,000/cumm, platelets – 4,000/cumm. On differential count blasts constituted 21%, blasts were two to four times the size of a normal mature lymphocyte, have high N:C ratio, round to oval nuclei, prominent two to three nucleoli and scanty basophilic cytoplasm and a few Auer rods were noted. Stain for myeloperoxidase was positive. Bone marrow aspiration was done and smears studied show necrotic material and decreased cellular material. Flowcytometric immunophenotyping was suggested from the peripheral blood as the bone marrow was necrotic however patient expired on the next day.



(1) (2)

Figure1&2. Bone marrow aspirate showing an amorphous necrotic material.

Summary of the cases:

No. of cases	Clinical features	Important CBC findings	Ancillary technique	Diagnosis
	Fever, cough, pharyngitis and mouth ulcer	Hb-9.8gm/dl, TLC- 4600/cumm platelets- 1.2 lacs/cumm C- atypical lymphoid cell 04%, myelocyte 01%, metamyelocyte 06%, neutrophil 76%, lymphocyte 11%, monocyte 02%	EBV-positive, Flowcytometry- MDS-EB II	Myeolodysplastic syndrome with excess blasts II
	Fever, cough and joint pain	Hb- 9.6gm/dl, TLC- 6,400/cumm, platelets- 1.3 lacs/cumm	ASO< 54.1, Procalcitonin- >3.6ng/ml, SGOT- 75U/L, Alkaline phosphatase-624 U/L, ZN stain- positive	Disseminated tuberculosis
	Gastro intestinal bleeding	Hb- 7.8gm/dl, TLC- 2940/cumm, platelets- 22,000/cumm, DC- Blast 20%, promyelocyte 3%, myelocyte 10%, metamyelocyte 04%, neutrophils 12%, lymphocyte 30%, monocyte 16%, eosinophil 05%	Flowcytometry- acute myeloid leukemia	Acute myeloid leukemia(AML-M2)
	Fever, low back ache	Hb-8.3gm/dl, TLC- 3,600/cumm, platelets- 1.6 lacs/cumm, ESR- 34mm/hr	HBV- positive, ALT- 200 U/L, AST- 250 U/L, alkaline phosphatase- 170 U/L	Hepatitis-B
	Weakness and bleeding gum	Hb-7gm/dl, TLC-3,000/cumm, platelets-4,000/cumm, DC- blasts 21%	Myeloperoxidase stain-positive	Acute myeloid leukemia

Discussion:

Incidence: Bone marrow necrosis is a rare finding and accounting for about 0.3 to 2.2%.[2,3] The prevalence of bone marrow necrosis in our bone marrow aspiration and biopsy samples was found to be 1.4%.

The common symptom of bone marrow necrosis is bone pain that was seen in 80% of the cases, that might be generalized or localized in the lower back.[3] Bony pain is the most common symptom in bone marrow necrosis which is seen in 60% of our cases and it is mostly localized in lower back.

Malignancy was the main cause bone marrow necrosis and it was seen in 80% of the cases.[3] Two of our bone marrow necrotic cases (40%) were diagnosed as acute myeloid leukemia and during his bone marrow examination necrotic material was found with sparse cellular elements. We had only one case of MDS-EB II (20%) and one hepatitis B viral infection (20%) who had necrotic bone marrow.

Disseminated tuberculosis can also cause bone marrow necrosis, even though it happened rarely.[3,9] One of our bone marrow necrotic case was found suffering from tuberculosis (20%). During her bone marrow examination necrotic material was found positive ZN stain.

Anemia and thrombocytopenia is observed in 90% and 80% respectively.[1] Total leukocyte count may be normal, low or increased.[1] Lactate dehydrogenase, alkaline phosphatase, alkaline transaminase and uric aicd values may be increased.[1] In our study, all the cases had fever and 80 % of the cases had thrombocytopenia. 60% of our bone marrow necrotic cases had leucopenia.

Conclusion:
In our series of five cases 40% of Acute Myeloid Leukemia, 20% of MDS-EB II, 20% of disseminated tuberculosis, 20% of hepatits B viral infection were included. To conclude, in cases of bone marrow necrosis, further investigations including ancillary techniques are strongly suggested to come to conclusive diagnosis as the causes of bone marrow necrosis vary from patient to patient.
Conflicts of Interest: The authors declare that they have no conflicts of interest

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