Prevalence of bone marrow necrosis in Egyptian cancer patients referring to the National Cancer Institute

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Abstract Background: Bone marrow necrosis is a relatively rare entity which has been associated with a poor prognosis. It is most commonly found in patients with neoplastic disorders and severe infections.

Methods: The study comprised examination of 5043 bone marrow biopsy specimens performed at the National Cancer Institute, Cairo University, over 7 years period (March 2004–March 2011). It included 5 years retrospective (2867 archived samples) and 2 years prospective (2176 samples).

Results: Bone marrow necrosis was diagnosed in fifteen out of 5043 examined specimens with a percentage of 0.3% and ranged from mild to massive according to semiquantitative estimation. Prognosis of all patients was poor with survival not exceeding 6 months from the date of marrow necrosis diagnosis.

Conclusion: In Egyptian patients, bone marrow necrosis in association with malignancy is a rare disorder which is accompanied by a poor outcome.

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Introduction

Bone marrow necrosis (BMN) is a rare but serious finding in various malignant and non malignant disorders. It is usually a postmortem diagnosis. Bone marrow necrosis is regarded as an uncommon entity that is associated with poor prognosis. It was first described in 1941 [1], and is defined as necrosis of myeloid tissue and medullary stroma in large areas of the marrow with preservation of the bone. The first antemortem diagnosis was made in 1965 [2] in a patient with acute leukemia.

The pathophysiology of BMN has been a subject of controversy and debate [3] and included toxic effect of chemotherapy, microvascular infarction, and decreased oxygen tension due to increased proliferative capacity of infiltrating malignant cells, tumor necrosis factor and thrombosis [4].
The extent of BMN is graded semiquantitatively [5]. In BM examination, cells lose their normal staining pattern and have irregular shape and margin on cytology [6]. It is usually required to aspirate the marrow from multiple sites to obtain enough material [7]. The combination of gelatinous transformation and necrosis is the hallmark of BM biopsy.

Patients and methods

Patients

Retrograde examination of bone marrow biopsy slides from patients that were diagnosed and their slides were archived in the Hematology Unit, Clinical Pathology Department, National Cancer Institute, Cairo University, starting from April 2009 back to March 2004, searching for bone marrow necrosis, in addition to the examination of newly received bone marrow biopsy specimens until March 2011 for the same reason.

Bone marrow biopsy specimens were subjected to technical methods applicable to trephine biopsy specimens, including fixation, decalcification and processing. After that, slides were stained with hematoxylin and eosin [8]. We collected data of the patients who showed BMN from their files. We recorded their age, sex, symptoms, complaint at first presentation, clinical findings, diagnosis, and laboratory findings especially the levels of alkaline phosphatase and lactate dehydrogenase enzymes.

We were able to examine 3043 slides of bone marrow biopsy. BMN was graded semiquantitatively [5] according to the extent of necrosis in the bone marrow biopsy:

Grade I (mild): ≤20% of the biopsy,
Grade II (moderate – intermediate): 20–50% of the biopsy.
Grade III (severe – extensive): ≥50% of the biopsy.

The Olympus CH2 microscope was used for examination. Photos were captured using a digital camera (Olympus C 30 40 ADU) connected to a microscope (Olympus CX 50) and to a personal computer.

Results

The cases were as follows:

- A female patient, 32 years old. Examination of BM biopsy revealed an intertrabecular area with complete infiltration with primitive looking cells (blasts), among which rare mature neutrophilic series were seen and the remaining two areas showed a combination of primitive and necrotic cells. Examination of bone marrow aspirate showed complete infiltration (91%) of the marrow by blast cells, which were myeloperoxidase (MPO) negative by cytochemical stains, but which showed CD45, CD13 and CD36 positivity by immunophenotyping. Also, immunohistochemistry done on biopsy revealed CD36 positivity. A diagnosis of massive bone marrow necrosis on top of myeloid/NK cell precursor acute leukemia was made. The patient survived for 2 months after the biopsy was made.

- Massive marrow infiltration by non hematopoietic malignant sheets, together with massive bone marrow necrosis, in a female patient aging 34 years and having medullary carcinoma of the breast. The patient died 2 weeks after the biopsy was taken.

- Primary bone marrow high grade non Hodgkin’s lymphoma, with no evidence of other areas of lymphoreticular system involvement in a 58-years old male. Marrow revealed massive necrosis (Fig. 1) and immunohistochemistry revealed B-cell markers. The patient survived for 5 months after the biopsy was taken.

- A case of Hodgkin’s disease in an 18-years old male patient. He complained clinically of generalized lymphadenopathy, splenomegaly, with no fever or night sweats. Marrow examination revealed mononuclear HD cells, which were CD30 positive by immunohistochemistry and a focus of bone marrow necrosis of less than 15% of the biopsy area (1/6 intertrabecular areas). The patient survived for 1 month after the biopsy was taken.

- A 42-years old male with acute myeloid leukemia, hypocellular on bone marrow aspirate examination, MPO positive by cytochemistry, and myeloid phenotype by flowcytometry. Karyotyping revealed normal karyotype (intermediate grade). Diagnosed as AML-M1 FAB subtype. Moderate BMN was detected (3/7 intertrabecular areas) and MPO was positive by immunohistochemistry. The patient survived for 3 weeks after the biopsy was taken.

- A 56-years old male, diagnosed to have B-ALL by morphology (L2) and immunophenotyping (CD19, CD10 positive). A focus of BMN as well as multiple small foci of gelatinous marrow transformation were detected among a bone marrow biopsy specimen totally infiltrated by blasts. Immunohistochemistry revealed CD19 positivity. Cytogenetics showed hypodiploid karyotype. The patient survived for 3 months after the biopsy was taken.

- A 47-years old male with acute myeloid leukemia, hypocellular on bone marrow aspirate examination, MPO positive by cytochemistry, and myeloid phenotype by flowcytometry revealed normal karyotype (intermediate grade). Diagnosed as AML-M1 FAB subtype. Moderate BMN was detected (3/7 intertrabecular areas) and MPO was positive by immunohistochemistry. The patient survived for 3 weeks after the biopsy was taken.

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Figure 1 Bone marrow biopsy (H/E) in a case of high grade NHL showing massive necrosis with small areas of hemorrhage (×40).
A 12-years old male patient diagnosed to have B-ALL (L2) phenotype, with 89% blasts in the bone marrow and B-cell markers by flowcytometry. Karyotyping showed t(1;19). Mild BMN was detected, in the form of a small focus of necrotic cells in 1/6 of intertrabecular areas. Immunohistochemistry showed CD19 positivity and Lambda positivity. The patient died 1 month after the biopsy was taken.

A 52-years old male with advanced gastric cancer (poorly differentiated adenocarcinoma) complaining of fever and pancytopenia, bone marrow showed extensive bone marrow necrosis and the patient died 16 days after admission.

A 65-years old male with chronic myeloid leukemia was in chronic phase for 6 years developed B cell lymphoblastic crisis on top of CML, his marrow showed extensive necrosis and symptomatic hypercalcemia. The patient died 2 days after the biopsy was taken.

A 35-years old female whose bone marrow biopsy showed infiltration with reactive inflammatory back ground together with Hodgkin cells and Reed Sternberg cells and moderate BM necrosis. The patient took treatment for 3 weeks and she recovered the necrosis. One month later, she presented clinically with fever, night sweating, coughing, fatigue, shortness of breath and cervical lymphadenopathy and her CBC showed pancytopenia. Lymph nodes finding showed infiltration with Hodgkin disease and the patient died 1 month later.

A 10-months old male diagnosed to have spindle cell sarcoma. His B.M. was hypocellular for age with a small focus of marrow necrosis (10% of total marrow area) and a small area of grade II fibrosis. At the time of biopsy, the patient was on chemotherapy for 3 months. The patient died 3 months after the biopsy was taken.

A 4-years old female diagnosed to have neuroblastoma, disseminating to the marrow (stage IV). Her BM was hypocellular for age with two small areas of marrow necrosis (about 20% of total marrow area). At the time of biopsy, the patient was on chemotherapy for 5 months. The patient died 4 days after the biopsy was taken.

A 2.5-years old female diagnosed to have de novo neuroblastoma disseminating to the marrow (Stage IV), with massive BM necrosis. The patient died 3 days after the biopsy was taken.

As regards the most common complaints at presentation, 7 of the 15 patients had severe bone pains mostly in the lower back and 9 complained of fever. Laboratory workup of the patients revealed pancytopenia in 9, leukoerythroblastic picture in one and bicytopenia with leukocytosis in the other 5 patients. Serum lactate dehydrogenase and serum alkaline phosphatase levels were elevated in all patients. Table 1 demonstrates the prevalence of marrow necrosis within the different disease entities.

Discussion

In the present study, we examined bone marrow biopsy slides from 5043 patients presenting to the Hematology Unit in the Clinical Pathology Department, National Cancer Institute, Cairo University through a period of 7 years and detected 15 cases of bone marrow necrosis among them (0.3%). Bone marrow necrosis was ranging from mild to massive, according to semiquantitative estimation [5]. Five patients suffered from solid tumors (33.3%), while the other ten had hematologic malignancies (66.6%). 13/15 (86.7%) patients were newly diagnosed, while 2/15 were on chemotherapy (13.3%). All patients had poor survival, not exceeding 6 months after the time the diagnosis of bone marrow necrosis was made.

The relative frequency of bone marrow necrosis varies among different reports between 0.37% and 6.5% [3]. Given the high rate of malignancy as an underlying disease association, an extensive search for neoplastic disease is justified whenever BMN is diagnosed [9].

Argon et al., reported that malignancy constitutes 91% of the etiology of marrow necrosis, with hematologic malignancy constituting 60% and solid tumors constituting 31%.
of other conditions constitutes only 9% of the etiology of BMN, most importantly, severe infections, drugs, sickle cell disease and antiphospholipid syndrome [10]. In our study we agree with Argon et al., in that 66.6% of our patients suffered from hematologic malignancy, while only 33.3% suffered from solid tumors as an underlying cause of BMN.

We also agree in our results with Dunn et al. [9], who studied 10,856 consecutive bone marrow aspirate and biopsy cases through 13 years and reported 40 cases of BMN (0.37%), all but two of whom had underlying malignancies. The most common underlying malignant disease was acute leukemia (8/38, 21%), followed by nasopharyngeal carcinoma and cancer of unknown origin.

In our study, 2 of the 15 BMN cases were ALL (13.3%), 2 were AML (13.3%), 3 were H.D. (20%), 2 were NHL (13.3%), 1 was CML (6.7%) and 5 were solid tumors (33.3%). We agree in the relative frequency of the different disease entities comprising the BMN with Paydas et al. and the review article of Janssens et al. [5,6] as shown in Table 2. We disagree with Zhai et al. [11], who reports different relative frequencies concerning solid tumors (66.6%) and hematologic malignancies (33.4%).

We also agree with some other authors who reported sporadic cases of BMN, concerning the prevalence of the disease and the relative frequency of hematologic and solid tumors, such as Pui and Stass [12], who received records of 1419 children with acute leukemia and other malignant diseases involving the marrow and found 7 cases (0.49%), 5 of which were ALL (71.4%) and 2 (28.6%) were neuroblastoma.

Several other authors reported BMN to be a rare entity, such as Macfarlane and Tauro [13], who described 4 cases of childhood ALL that developed BMN. Bevilaqua et al. [14], and Niebrugge and Benjamin [15] described BMN which was diagnosed first, and eventually malignancy developed. The former described 7 cases of BMN; 6 proceeded to acute leukemia and 1 to lymphoblastic lymphoma, and the latter described 2 BMN cases that developed later ALL.

In Bone marrow necrosis, pancytopenia and embolic processes are major complications, which are life threatening, and that should be managed with supportive measures until effective treatment of the underlying disease has been administered [16].

When an underlying pathology was detected, vigorous supportive care together with special treatment must be started including transfusion of blood components, adequate antibiotic treatment, hydration, oxygenation and alkalinization to permit a time for spontaneous recovery of the normal hematopoiesis. Given the complex pathophysiology of BMN [3,4], some novel therapies such as anti tumor necrosis factor (TNF)-α antibodies and various cytokines may be promising modalities [10]. It has been suggested that therapy for patient with BMN aims at promoting recovery of marrow stroma by the use of cytokines and chemotherapy not highly toxic to bone marrow stem cells and stroma [17]. Also, allogenic or autologous bone marrow transplantation could be life saving treatment strategies [18,19].

The ultimate prognosis in patients with BMN on top of a malignant disorder is poor. In solid tumors, it implies widespread metastasis and in hematologic malignancies, it aggravates the condition and acute leukemia patients who suffer from BMN, even though they might acquire complete remission, they ultimately relapse [20].

**Conclusion**

We conclude that in Egyptian patients, BMN in association with malignancy is a rare disorder which is accompanied by a poor outcome.

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<tr>
<th>Table 1</th>
<th>Prevalence of bone marrow necrosis in different disease entities.</th>
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<tbody>
<tr>
<td>Diagnosis</td>
<td>Biopsies with necrosis (no/cases)</td>
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<tr>
<td>Acute lymphocytic leukemia</td>
<td>2/228</td>
</tr>
<tr>
<td>Acute myelocytic leukemia</td>
<td>2/216</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>3/1227</td>
</tr>
<tr>
<td>Non Hodgkin lymphoma</td>
<td>2/1473</td>
</tr>
<tr>
<td>Metastatic cancer (of which two were on chemotherapy)</td>
<td>5/1683</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>1'/198</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>0/18</td>
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<tr>
<td>Total</td>
<td>15/5043</td>
</tr>
</tbody>
</table>

* A case of blastic crisis.

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<th>Table 2</th>
<th>Different disease entities in BMN with their relative frequency.</th>
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<tbody>
<tr>
<td>Reference</td>
<td>Disease entities and their relative frequency</td>
</tr>
<tr>
<td>Number of cases</td>
<td>ALL</td>
</tr>
<tr>
<td>Present study</td>
<td>15</td>
</tr>
<tr>
<td>Janssens et al. [6]</td>
<td>218</td>
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<tr>
<td>Paydas et al. [5]</td>
<td>16</td>
</tr>
<tr>
<td>Zhai et al. [11]</td>
<td>12</td>
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</tbody>
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ET, essential thrombocythemia; MF: myelofibrosis; MDS/MPN: Myeloproliferative/myelodysplastic.
References