Bone Marrow Necrosis: An Entity Often Overlooked

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ABSTRACT

Bone marrow necrosis is a poorly understood and frequently an unrecognized finding in routine bone marrow biopsies. Previous reports indicate the incidence of bone marrow necrosis ranges from 0.5 percent (rare) to approximately one-third of all bone marrow biopsies examined. Our studies indicate that the presence of bone marrow necrosis depends on the clinical condition of the patient. Overall, our incidence of bone marrow necrosis was 37 percent of the bone marrow biopsies examined. Of these, 26.4 percent was mild, 7.5 percent moderate, and 3.1 percent severe. The mechanism in most cases had an identifiable underlying etiology such as a malignancy, or vascular or cytotoxic damage, with a small percentage being unexplained.

Bone marrow necrosis is seen across a wide range of conditions, including sickle cell diseases, AIDS, leukemia, lymphoma, metastatic carcinoma, anemia, sepsis, and other systemic diseases. Patients at the extremes of age, less than 20 years and greater than 70 years, 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. The prognosis associated with bone marrow necrosis seems to be dependent on the underlying primary clinical condition regardless of the degree of necrosis observed.

Introduction

It is well known to both pathologists and hematologists that bone marrow...
necrosis may occur from diffuse fibrin obstruction of blood vessels, as seen in disseminated intravascular coagulation, from intravascular occlusion by deformed red blood cells, as seen in sickle cell diseases, and in association with either primary or metastatic bone marrow tumors. More recent studies, however, indicate that necrosis can also be seen in a variety of clinical settings, ranging from anemia, to starvation states and infections. The reported frequency of bone marrow necrosis ranges from 0.5 percent to as high as 33 percent of the bone marrows examined. Bone marrow necrosis has been described in the literature indicating that the finding may or may not be a poor prognostic sign in acute lymphocytic leukemia and in other malignancies.

It is our observation that bone marrow necrosis is often seen but is rarely a described finding in bone marrow biopsy reports. In order to understand the frequency of bone marrow necrosis and the related clinical entities, bone marrow necrosis was investigated. A simplified grading system for bone marrow necrosis was devised so that pathologists could evaluate the degree of the lesion in a standardized fashion.

**Materials and Methods**

Two hundred and seventy consecutive bone marrow biopsies received in our institution between July 1985 and August 1986, from both hospitalized and ambulatory patients, were examined by two independent observers for the presence of bone marrow necrosis.

Bone marrow necrosis was defined as a loss of normal architecture, including marrow hematopoietic elements and fat spaces, with a surrounding zone of normal hematopoietic elements, and the replacement of these spaces by faintly granular eosinophilic amorphous material and/or cellular debris. Possibly necrotic areas lying on the edge of the biopsy, and those associated with an obviously crushed region of the biopsy were considered artifact and counted as negative.

Hematoxylin and eosin (H&E), periodic acid Schiff stain counterstained with hematoxylin (PASH), and reticulin stained sections were studied. Each biopsy containing necrosis was graded jointly by the observers based upon the following grading system:

Grade I (mild) necrosis was defined as small foci of necrosis occupying one high power field or less and/or having a combined area of involvement occupying less than 20 percent of the entire bone marrow specimen (figure 1).

Grade II (moderate) necrosis was defined as foci of necrosis, each occupying greater than one high power field but less than one 10 × field and with the combined areas of necrosis occupying between 20 and 50 percent of the biopsy (figure 2).

Grade III (severe) necrosis was defined as large foci of necrosis occupying greater than 50 percent of the biopsy (figure 3).

**Results**

The incidence and degree of bone marrow necrosis among various age groups is illustrated in table I. Of the 270 bone marrow biopsies examined, approximately 37 percent demonstrated some degree of bone marrow necrosis as defined by our criteria, with 67 percent of these exhibiting grade I necrosis, 19 percent exhibiting grade II, and eight percent exhibiting grade III necrosis. Sixteen of the biopsies examined were insufficient for evaluation and therefore excluded from the statistics.

The PASH stain was useful in differentiating areas of necrosis from areas of hemorrhage. The reticulin stain was
Figure I. Grade I bone marrow necrosis, H&E; ×100.
Figure II. Grade II bone marrow necrosis, H&E; ×100.
Figure III. Grade III bone marrow necrosis, H&E; ×100.
TABLE I  
Incidence and Degrees of Bone Marrow Necrosis  
Among Various Age Groups

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Total Necrosis 1+</th>
<th>Degree 2+</th>
<th>Degree 3+</th>
<th>Subtotal</th>
<th>Percent Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>10-19</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>44.4</td>
</tr>
<tr>
<td>20-29</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>30-39</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>13</td>
<td>40.6</td>
</tr>
<tr>
<td>40-49</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>8</td>
<td>30.8</td>
</tr>
<tr>
<td>50-59</td>
<td>9</td>
<td>4</td>
<td>1</td>
<td>14</td>
<td>44.7</td>
</tr>
<tr>
<td>60-69</td>
<td>20</td>
<td>3</td>
<td>2</td>
<td>25</td>
<td>41.7</td>
</tr>
<tr>
<td>70+</td>
<td>17</td>
<td>3</td>
<td>0</td>
<td>20</td>
<td>40.0</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
<td>19</td>
<td>8</td>
<td>94</td>
<td>37.0</td>
</tr>
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</table>

used in an attempt to identify loss of the reticular network and normal architecture but was proven useless.

There was a significant increase in the number of bone marrow biopsies with increasing age, with only 24 of the biopsies coming from the population under 20 years of age. The percentage of the biopsies exhibiting necrosis increased significantly after the age of 30, reaching a frequency of 40.6 percent in the 30 to 39 year age group from a 20 percent frequency in the 20 to 29 year age group. There was no significant difference between the number of males and females examined; however, there was a very slight increase in the frequency of bone marrow necrosis seen in the male group. This difference was statistically insignificant.

The clinical settings encountered within each age group in association with necrosis are illustrated in table II. In all age groups studied, the most common finding was mild (grade I) necrosis, which was found in association with various clinical conditions ranging from metastatic disease, to systemic diseases such as diabetes, hypertension, cirrhosis, and anemia. It occurred most often, however, in association with more serious illnesses such as lymphoma, leukemia, metastatic tumors, AIDS, and sickling diseases, with AIDS and sickling diseases being the most notable. More extensive necrosis (grade II or III) was almost, without exception, always found in association with severe life threatening clinical conditions, including malignancies, AIDS, severe anemia, and hemoglobinopathies.

The incidence and degree of bone marrow necrosis found in various clinical conditions are shown in table III. Those clinical conditions associated with a high incidence (>50 percent) of bone marrow necrosis included AIDS, bone marrow metastases, and hemoglobinopathies. Other diseases such as diabetes mellitus, anemia, and alcoholism showed a 20 to 25 percent incidence of bone marrow necrosis.

Discussion

The reported incidence of bone marrow necrosis in the literature varies from 0.5 percent22 to 33 percent. Bone marrow necrosis was found in 37 percent of the 270 bone marrow biopsies reviewed at our institution. Severe (Grade III) bone marrow necrosis was identified in only three percent of the bone marrow biopsies, with moderate (Grade II) and mild (Grade I) necrosis identified in 7.5 percent and 26.4 percent, respectively. The incidence and degree of bone marrow necrosis was found to be related to the patient’s clinical condition. Bone marrow biopsies from patients with AIDS, metastatic disease to the bone marrow, leukemia, and sickle cell diseases, showed a 50 percent incidence of some degree of necrosis. Severe (Grade III) bone marrow necrosis was more frequently seen in carcinomas with metastasis to the bone marrow, leukemia, and sickle cell diseases.

The etiology of bone marrow necrosis is multifactorial, with some but not all factors defined. The defined etiologies include vascular occlusion secondary to tumor emboli or tumor compression, vascular occlusion by fibrin thrombin in
TABLE II
Clinical Settings Encountered Within Each Age Group, in Association with Bone Marrow Necrosis in Various Degrees

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>&lt;9</th>
<th>10-19</th>
<th>20-29</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>&gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Sickle Cell Disease</td>
<td>Lymphoma</td>
<td>Bone Marrow Transplant</td>
<td>Lymphoma</td>
<td>AIDS (2)</td>
<td>Neutropenia (2)</td>
<td>Leukemia</td>
<td>Lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Leukemia (2)</td>
<td>Anemia</td>
<td>Sickle Cell Disease</td>
<td>Anemia</td>
<td>Lymphoma</td>
<td>AIDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Sickle Cell Disease</td>
<td>Hodgkin's Disease</td>
<td>Lung Carcinoma</td>
<td>Leukemia (3)</td>
<td>Breast Carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

() Indicates multiple cases.

the case of disseminated intravascular coagulation, a rapidly growing tumor replacing normal bone marrow elements, cytotoxic injury to the bone marrow due to chemotherapy, or toxic effect owing to infection. The end result of defined or undefined factors is the initiation of an oxygen deficient state with a decrease in necessary nutrients, and/or accumulation of toxic products at the cellular level resulting in cell death and marrow necrosis.

TABLE III
Incidence and Degree of Bone Marrow Necrosis with Clinical Conditions

<table>
<thead>
<tr>
<th>% with Necrosis</th>
<th>100%</th>
<th>75%</th>
<th>50%</th>
<th>25%</th>
<th>10%</th>
<th>0%</th>
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</thead>
<tbody>
<tr>
<td>1+</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>12</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2+</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
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<tr>
<td>3+</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total # Positive</td>
<td>3</td>
<td>10</td>
<td>13</td>
<td>16</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total # Negative</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

( ) Indicates multiple cases.
Bone marrow necrosis has been reported to precede the development of poorly differentiated lymphocytic lymphoma, small cell carcinoma of the lung, and acute lymphocytic leukemia. Bone marrow necrosis has also been found in aplastic crisis associated with sickle cell thalassemia, in sickle cell trait, in disseminated carcinoma-tosis, in leukemia, and in small cell carcinoma of the lung. A case of mucor infection resulting in ischemic necrosis secondary to vessel wall invasion and subsequent thrombi formation in a diabetic patient has also been reported. Patients presenting with extensive bone marrow necrosis were characterized by bone pain, prolonged leukopenia, thrombocytopenia, anemia, and occasionally with fever.

The relationship between bone marrow necrosis and prognosis has been studied with conflicting conclusions. The prognosis of most patients with bone marrow necrosis secondary to malignancies was found to be extremely poor, with the exception of childhood cases, in which a poor prognosis was not necessarily indicated. Others observed that patients with bone marrow necrosis associated with acute leukemia had a poor response to therapy, while some suggest that bone marrow necrosis may not after all be a poor prognostic sign in acute leukemia. It is our observation, however, that the prognosis associated with bone marrow necrosis depends primarily on the underlying clinical condition, regardless of the degree of necrosis observed.

It has been suggested that malignancies should always be excluded in patients with bone marrow necrosis without an obvious cause, and that patients with severe bone marrow necrosis requiring frequent transfusions be assessed by technetium-99M sulfur colloid radioisotopic techniques to determine the extent of involvement.

Although the pathogenesis of bone marrow necrosis is not always well defined, its presence may indicate an associated treatable disease. It is our opinion, therefore, that bone marrow necrosis should be properly documented and commented upon in routine bone marrow reports.

Acknowledgments

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References