



LITERATURE REVIEW

Bone Marrow Necrosis: An Unusual Misdiagnosed Serious Complication

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Abstract

Bone Marrow Necrosis (BMN) is an uncommon syndrome characterized by destruction of hematopoietic tissue with preservation of the bone. It presents as localized or diffuse generalized process. Many underlying diseases can lead to marrow necrosis: most commonly malignancies and rarely sickle cell disease. Although there are no clinical nor laboratory pathognomonic signs, clinicians must keep a high index of suspicion whenever there is fever, severe bone pain, elevated lactate dehydrogenase, and anemia. Bone marrow biopsy remains the mainstay of the diagnosis. BMN associated with sickle cell disease is usually of better prognosis compared to BMN secondary to malignancies.

Keywords

Bone marrow necrosis, Sickle cell, Bone marrow biopsy

Methodology

Review of the literature at PubMed using “bone marrow necrosis” as key words. The search retrieved 30 articles written in English, and a further 70 case reports.

Introduction

Bone Marrow Necrosis (BMN) is a rare life threatening condition defined as necrosis of myeloid tissue and medullary stroma in large areas of the hematopoietic bone marrow. It is characterized by destruction of Bone Marrow (BM) architecture, together with fat cell depletion, without cortical bone involvement [1]. Wade and Stevenson were the first to describe it in an autopsy of a Sickle Cell Disease (SCD) patient in 1941 [2]. Although many cases were described in different medical conditions, BMN remained a post mortem diagnosis in most of the reports. Most common causes were BM infarction during or following sickle cell vaso-occlusive crisis

and BM infiltration with malignant cells, often of hematopoietic origin [3]. Here I am writing a review article based on literature reviews concerning BMN and related case reports. I will try to focus on clinical presentation, differential diagnosis, different etiologies, and its correlation with SCD, prognosis, and treatment. The aim of this review is to keep clinicians aware of this distinct, rare and fatal clinico-pathological entity, resulting in early suspicion, diagnosis, and thus better prognosis.

Discussion

Bone marrow necrosis is an infrequent entity where BM is replaced by necrotic material with cells having indistinct cellular outlines and smudged nuclei, surrounded by amorphous eosinophilic material [4].

It ranges from localized to widespread generalized processes and is graded semi-quantitatively according to the extent of necrosis evident in the bone marrow biopsy. Grading was described by Maisel, et al. as follows: grade I (mild), less than 20% of the biopsy; grade II (moderate to intermediate), 20% to 50% of the biopsy; and grade III (severe to extensive), more than 50% of the biopsy specimen [5].

Most of the available data about bone marrow necrosis are from the post mortem studies because there was the lack of awareness and lack of documentation of the very few cases which were diagnosed during the lifetime of the patient. The incidence of BMN varies from 0.3 to 37% among different reports, with 90% of the cases being related to malignancy [3]. Of these, hematologic malignancies account for 60% of the cases with BMN identified at primary diagnosis or at relapse.

Acute lymphoblastic leukemia is the most common cause in adults and children (18%), followed by acute myeloid leukemia, then non Hodgkin lymphomas [3,6]. The association of BMN with solid malignancy is less consistent. Gastric tumors are most frequently implicated [6]. However, SCD was found to be the primary cause in only 2% of the cases [5]. Other reported causes include direct damage to bone (radiation, trauma), infection, auto-immune diseases (anti-phospholipid syndrome, lupus erythematosus), drugs, and anorexia nervosa (gelatinous degeneration of the marrow with serous fat atrophy) [3,6].

The pathophysiology of BMN remains unclear. The most important cause is the vascular damage leading to cell hypoxia. Any unbalance in the delivery of oxygen and nutrients, as seen in BM infiltration by neoplastic processes, may provoke necrosis. Sick cell disease is associated with abnormal cell adhesiveness to capillary endothelium, leading to a mechanical obstruction of BM sinusoids. Furthermore, the inflammatory products will worsen the vascular obstruction. An important common factor seen in inflammatory processes and malignancies is the Tumor Necrosis Factor alpha (TNF- α), which its subsequent lesions in endothelial and bone marrow sinusoids, leading to BM infarct and necrosis [3,6-8].

Clinical features of BMN are heterogeneous and non-specific, with the most common symptom being bone pain (80%): it is of acute onset, severe and generalized. Fever is seen in 55% of cases. BMN will lead to BM failure, with anemia and thrombocytopenia being the main cytopenias, associated with leukoerythroblastic findings in the peripheral blood. Other laboratory abnormalities are increased Lactate Dehydrogenase (LDH) in 41%, increased alkaline phosphatase in 51%, and disturbed liver enzymes [3,5,6].

The mainstay of diagnosis is the bone marrow biopsy with necrotic features of BM trephine showing disruption of normal architecture with loss of fat spaces, but generally with preservation of the specular architecture [3]. The other differential diagnosis of cytopenias and leukoerythroblastic changes may include aplastic anemia, myelofibrosis, and avascular bone necrosis. In aplastic anemia, there is preservation of the BM architecture, with adipocytes replacing hematopoietic tissue. Avascular bone necrosis, unlike BMN, leads to damage to cortical tissue alone [6].

Sickle cell disease can cause many types of injuries to the skeletal system: bone marrow necrosis, infarction, osteomyelitis, and avascular necrosis have been the most frequent complications [9]. Although BMN was first reported in SCD, their association was reported in only 2% of the cases. The paucity of their correlation may be explained by the fact that BM biopsies are not usually performed during a painful crisis [10].

Tsitsikas, et al. underwent one of the largest reviews on BMN in SCD, identifying 58 cases of BMN with Fat

Embolization Syndrome (FES) and 16 cases of BMN without FES. In both groups there were a number of patients who were not known to have SCD prior to the presentation of BMN: 19 (33%) and 4 (25%), respectively. They also conclude that patients with genotype SS were at low risk for BMN/FES and, paradoxically, those with mild phenotypes were at higher risk of this catastrophic complication [11]. This can be explained by the fact that SD genotype is associated with increased blood viscosity on top of the known abnormal cell adhesiveness that it shares with SS genotype [8].

BMN treatment consists in treating the underlying primary etiology with adequate supportive care: transfusion as per requirement, pain management in case of sickle cell crisis and antibiotics if needed.

Old reviews noted a poor prognosis of BMN rapidly leading to death. However, newer studies revealed a better prognosis when it is not associated with malignancy [6,7].

Conclusion

BMN is an uncommon entity that every clinician should consider whenever a patient presents with the triad of severe bone pain, fever, and severe anemia. However, it is a major feature of sickle cell disease. To establish this diagnosis during life (before the postmortem examination), one must have a degree of clinical suspicion sufficiently high to warrant the conduct of a bone marrow biopsy, which is the mainstay of BMN diagnosis. SCD patients will gradually recover with supportive treatment. Thus, their prognosis is usually better than patients developing BMN secondary to malignancy. It is important to rule out neoplastic process or sickle cell disease every time there is bone marrow necrosis.

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