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Bone marrow necrosis: literature review

Necrose de medula óssea: revisão da literatura

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ABSTRACT

Introduction: Bone marrow necrosis (BMN) is a rare pathologic entity that is commonly undiagnosed, and often associated with hematologic diseases. **Methodology:** We conducted a literature review at PubMed using "bone marrow necrosis" as key words. Our search retrieved 25 articles written in English, and a further 65 case reports. **Results and discussion:** BMN pathophysiology is not well understood, but appears to be associated with vascular injuries that lead to oxygen and nutrient deprivation. Destructive tumor necrosis factor alpha (TNF-α) activity is also likely involved in the development of endothelial and bone marrow sinusoidal lesions. Diagnoses of BMN are commonly indicated by anemia, thrombocytopenia, high levels of lactic dehydrogenase and alkaline phosphatase, and the identification of leukoerythroblastic reactions. Bone marrow (BM) aspirate and biopsy, and magnetic nuclear resonance imaging are the main diagnostic options. The only available treatments are those directed against the primary cause, with associated supportive care for what is ordinarily a rapidly lethal state. **Conclusion:** The search for an underlying associated malignancy is important for the management of BMN.

Key words: bone marrow necrosis; tumor necrosis factor alpha; leucoerythroblastic; bone marrow aspirate; bone marrow biopsy.

INTRODUCTION

Bone marrow necrosis (BMN) is a rare clinical entity commonly defined as necrosis of the myeloid tissues and stroma evident in a substantial (> 50%) area of the bone marrow (BM) parenchyma, without cortical bone involvement. Since its initial description by Wade and Stevenson in 1941, in a patient suffering from sickle-cell disease, BMN has been associated with a variety of medical conditions. An uncertain etiology only adds to the complexity of diagnosing BMN, which remains controversial, and is often only made *post mortem*[1-8].

Histological analyses of BMN cases show eosinophilic amorphous material with destruction of the normal BM architecture, together with fat-cell depletion[6, 8]. Some authors advocate that the BMN should only be diagnosed if the necrotic zone involves at least half of the specimen[3-17]. As peripheral blood draws usually indicate anemia, thrombocytopenia, and leukoerythroblastic pictures, the relevant differential diagnoses naturally encompass the causes of cytopenia such as aplastic anemia (AA), myelofibrosis, and avascular bone necrosis. Preservation of the BM architecture, with replacement of hematopoietic tissue with adipocytes, rules out a BMN diagnosis in cases of AA. In addition, unlike BMN histopathology, avascular bone necrosis is evident by damage to cortical tissue alone[4, 8, 9].

Given the recent recognition of this lesion as a distinct clinical entity, and its complex diagnosis, we undertook a literature review of this topic to highlight the key clinical, etiologic, and pathophysiologic data.

METHODOLOGY

We conducted a literature review using PubMed and the search term "bone marrow necrosis". Our criteria for article inclusion were: 1) an English language publication; 2) a publication date prior to June 2014; 3) open access text; 4) a definition of BMN that agrees with that already described in this article, i.e. necrosis of the myeloid tissues and stroma in more than 50% of the specimen, with no cortical involvement. With these filters in place, we recovered 25 articles and 65 case reports. Epidemiological descriptors of these data are provided in **Table 1**.

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TABLE 1 – Epidemiologic description of BMN articles compiled in the literature

Variables	Paydas *et al.*[6]	Katayama *et al.*[14]	Godeau *et al.*[17]	Chim *et al.*[9]	Campiotti *et al.*[3]	Rossi *et al.*[12]	Lee *et al.*[11]	Kumakura *et al.*[13]	Azuma *et al.*[4]	Markovic *et al.*[10]	Al-Gwaiz *et al.*[15]	Bashawri *et al.*[7]	Ianotto *et al.*[18]	Lee *et al.*[5]	Invernizzi *et al.*[16]	Jain *et al.*[2]	Khoshnaw *et al.*[19]	Aras *et al.*[20]	Khalil *et al.*[21]	Aydogdu *et al.*[22]	Ozkan *et al.*[23]	Vermeersch *et al.*[24]	Rossi *et al.*[25]	Adamskii *et al.*[26]	Noguchi *et al.*[27]	Total
n	20	1	1	1	1	1	1	1	1	1	16	5	1	1	1	1	1	1	1	1	1	1	1	3	1	65
Age (years)	15-65	38	24	39	67	67	66	41	80	70	5-80	26-57	53	67	67	32	10	67	40	26	19	66	39	25-53	66	5-80
M:F	13:7	1:0	0:1	0:1	1:0	1:0	0:1	1:0	1:0	1:0	10:6	3:2	1:0	1:0	1:0	0:1	1:0	0:1	0:1	1:0	1:0	1:0	1:0	1:0	1:0	44:21
Etiology																										
AML	3	1		1						1	2		1			1						1				11
ALL	1										7	2			1		1									12
NHL	4					1					1															6
HL	4										3									1						8
CML	2				1			1																	1	5
MDS/MPS	1																									1
Solid malignancy	3								1		2	1		1				1								9
AFS	1																		1							2
DIC				1									1													2
TTP														1												1
HbS			1																				1	3		5
TB	2						1																			2
Drugs	1	1			1			1				1	1					1		1						8
Unknown												2														2
Degree																										28
I	3															1										4
II	5																									5
III	12			1		1	1							1						1				2	1	19
Symptoms																										
Fever	+		+		+	+	+	+	+	+	+	+		+	+	+	+	-		+	+		+	+	+	
Bone pain	+	+	+	+	+	+	+	+		+	+	+			+		+	-	+	+			+	+	+	
Jaundice	+											+		+				-					+			
Laboratory																										
Anemia	+		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leucopenia	+	+		+	+	+	+			+	+	+	+		+			-	-	+	+	-	-	+	+	
Thrombocytopenia	+			+	+	+	+			+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	
Leucoerythroblastic reaction					+	+	+					+		+	+			-						+		
LDH	+				+	+			+		+	+		+	+			-		+	-		+	+	+	
AF					+	+			+		+	+		+	+			-		+	-		+	+	+	
Prognosis	10d-22m (105,8d)	70d	¥	†	¥	¥	¥	¥	¥	¥	-	20d - ¥	¥	¥	120d	-	6,5m	¥	¥	¥	21d	¥	¥	¥	2m	

BMN: bone marrow necrosis; n: population of the study; M: male; F: female; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma; CML: chronic myeloid leukemia; MDS: myelodisplastic syndrome; MPS: myeloproliferative syndrome; AFS: antiphospholipid syndrome; DIC: disseminated intravascular coagulation; TTP: thrombotic thrombocytopenic purpura; HbS: sickle-cell disease; TB: tuberculosis; LDH: lactic dehydrogenase; AF: alkaline phosphatase; +: present; -: absent; †: premature death, without known time; ¥: survival not achieved.

EPIDEMIOLOGY

The incidence of bone marrow necrosis is extremely variable in the literature and ranges from 0.3% to 37% according to whether analyses were conducted *in vivo* or *post mortem*, the expertise of the pathologist, and the used diagnostic criteria[4, 6, 10, 12, 19, 23, 27]. Including the caveat that necrosis should be found in more than half of the specimen reduces incidence to 0.3%-12%[4]. Using the same criteria, Dunn *et al*. (1995)[28] and Pennaforte *et al*. (1986)[29] determined remarkably similar incidences of 0.3% and 0.4%, for BMN detected *in vivo*.

ETIOLOGY

BMN has been associated with many diseases, and multiple contributory factors are not infrequent. Possible causes include hematological diseases such as sickle-cell disease, hemolytic uremic syndrome, graft-versus-host disease, megaloblastic anemia, malignancies, and disseminated intravascular coagulation. In addition, infectious diseases, anorexia nervosa, and drugs/biologics such as alpha-interferon (IFN-α), fludarabine, granulocyte-colony stimulating factor (G-CSF), tretinoin, diclofenac, and paracetamol, are occasionally linked to diagnoses of BMN. Idiopathic cases have also been described[5, 6, 8-10, 12, 14, 15, 17, 24, 25, 29, 30]. **Table 2** indicates the causal features of 240 cases of BMN published in 2000 by Janssens *et al*. (2000)[8].

Neoplasia underlies 90% of diagnosed cases of BMN; of these, hematological malignancies constitute 60% of cases, with BMN identified at primary diagnosis of the neoplasia, or at relapse[6, 8]. Acute lymphoblastic leukemia is the most common cause in adults and children (18%)[8], with acute myeloid leukemia being second to it, although no subtype (using the French-American-British criteria) predominates. Non-Hodgkin lymphomas (NHL) are also commonly involved (10%-15%), with chronic myeloproliferative neoplasms and myelodysplastic syndromes being less common. In chronic myeloid leukemia, BMN is associated with blast crises[21]. Ordinarily, a diagnosis of BMN can accompany the primary diagnosis of a neoplasia or the detection of its recurrence. However, BMN might also be diagnosed prior to, or following a diagnosis of neoplasia, or during subsequent treatments with chemotherapy or radiotherapy. Clearly, any suspicion of BMN should be accompanied by a rigorous assessment of any underlying malignant disease[4, 6, 8, 12, 16].

The association of BMN with solid malignancy is less consistent. Gastric tumors are most frequently implicated, with other lesions involving prostate, colon, and lungs[4, 6, 8]. Janssens *et al*. (2000)[8]

TABLE 2 – Disorders associated with BMN diagnosed *in vivo*

Disorder	Nº of patients
Malignant disorders	218
Hematologic malignancies	145
Acute leukemia	98
Acute lymphoblastic leukemia	43
Acute myeloid leukemia	31
Acute leukemia (not specified)	24
Myeloproliferative syndrome	13
Chronic myeloid leukemia	11
Essential thrombocythemia	1
Myelofibrosis	1
Lymphomas	35
Non-Hodgkin lymphoma	26
Chronic lymphocytic leukemia	2
Hairy cell leukemia	1
Multiple myeloma	1
Hodgkin disease	5
Solid tumors	72
Unspecified	34
Primary tumor of unknown origin	12
Stomach	14
Lung	3
Breast	1
Ovary	3
Prostate	1
Carcinoid	1
Kaposi	1
Esophagus	1
Neuroblastoma	2
Medulloblastoma	1
Non-malignant disorders	22
Infections	17
Sepsis	12
Pneumonia	1
Mucormycosis	1
Q fever	1
Tuberculosis	2
Parvovirus	4
HIV	1
Drugs	8
Sulfasalazine	1
Interferon-alpha	3
All-transretinoic acid	4
Fludarabine	1
Granulocyte-colony stimulating factor	1
Sickle-cell disease	6
Others	12
Hyperparathyroidism	1
Anorexia nervosa	1
Hemolytic uremic syndrome	1
Antiphospholipid syndrome	3
Disseminated intravascular coagulation	4
Idiopathic	2

BMN: bone marrow necrosis; HIV: human immunodeficiency virus.

showed infection as an important non-neoplastic cause of BMN, especially if associated with other comorbidities such as sickle-cell disease. The most common infectious agents include *Escherichia coli*, *Streptococcus* sp., *Staphylococcus* sp., *Citrobacter freundii*, *Salmonella* sp., and *Pseudomonas aeruginosa*. However, other more unusual agents have also been described. These include the Mucoromycotina fungi that cause mucormycosis, the bacterium *Coxiella burnetii* (Q fever), B19 erythrovirus, and tuberculosis[6, 8, 11, 12, 20]. Drug use is rarely associated with BMN and, when implicated, usually occurs because of chemotherapeutic applications[8]. It is important to be aware that BMN may arise prior to clinical disease, making its diagnosis far from straightforward[6, 7].

PATHOPHYSIOLOGY

While the pathophysiology of BMN remains unclear and involves multiple mechanisms, the vascular damage that causes cell hypoxia appears to be a commonly accepted causal injury. BM infiltration by non-hematologic cells may also disrupt its microenvironment and provoke an unbalance in the delivery of oxygen and nutrients. The mechanical obstruction of BM sinusoids by sickle cells, or neoplastic cells, together with the vascular obstruction provoked by inflammatory products, or as a byproduct of certain drugs, irradiation, and endotoxins, also constitutes potential causal mechanisms[3, 4, 6-8, 10-13]. The role of tumor necrosis factor alpha (TNF-α) derived from macrophages and monocytes, which subsequently causes lesions in endothelial and bone marrow sinusoids, leading to BM infarct and necrosis, is also well known (**Figure 1**)[4, 11, 13]. The release of superoxide free radicals by activated granulocytes may also activate pro-thrombotic mechanisms that lead to BM endothelial cell commitment[19].

Following ischemic injury, necrotic cells are cleared by phagocytosis, with repair mechanisms resulting in vascular and fibroblast proliferation. As a result, normal bone marrow tissue should replenish the injured marrow microenvironment. However, marrow reconstruction with abnormal or atypical cells may occur. Likewise, prolonged injury and suboptimal tissue recovery can also result in fibrotic tissue deposition, which impairs tissue architecture and function[6, 8, 11].

DIAGNOSIS

The main clinical features associated with BMN are non-specific, with the most common being bone pain that occurs in 80% of patients. This pain is severe, of acute onset, and generalized; when localized, the affected area is commonly the lumbar region. Pain management is difficult and frequently necessitates hospitalization[3, 6, 8, 20, 22]. Fever, anemia, and jaundice are seen in 55% to 70% of cases and are related to the cytokine release provoked by tissue necrosis or infection[3, 5, 6, 18, 26].

BMN is a rare cause of BM failure (0.5%-1%), with cytopenias being the main laboratory abnormality detected following the onset of bone pain[6,8]. Anemia and thrombocytopenia are seen in 90% and 80% of cases, respectively. The white blood count is not stereotypically altered and may be normal or reduced. However, if the patient presents with leukocytosis, abnormal cells are commonly identified. A leukoerythroblastic finding in the peripheral blood is present in 50% of cases (**Figure 2**)[5, 6, 8, 22, 26, 27]. In addition, the patient can present with elevated transaminases and uric acid; high levels of

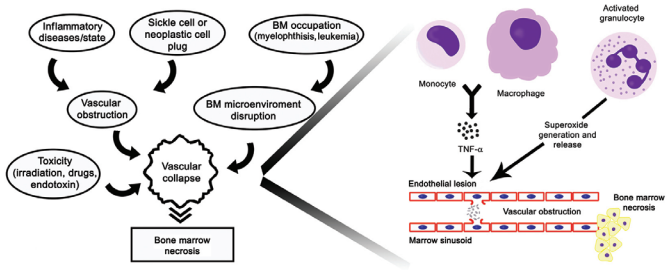

FIGURE 1 – *BMN pathophysiology: inflammation and plugs of sickle cells or neoplastic cells cause vascular obstruction and disrupt oxygen/nutrient delivery to hematopoietic tissue. BM infiltration (for example, by leukemic cells) can provoke microenvironment imbalance, as does cytotoxicity induced by irradiation, or drugs – either can cause vascular collapse –. TNF-α produced by monocytes and macrophages, and superoxide released by granulocytes, induce endothelial lesions with platelet aggregation, and vascular obstruction. All of these events can lead to BMN*

BMN: bone marrow necrosis; TNF-α: tumor necrosis factor alpha; BM: bone marrow.

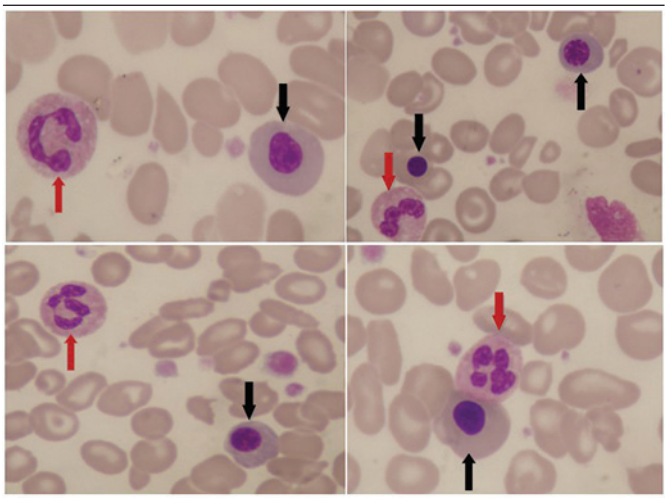

FIGURE 2 – *A peripheral blood smear (100×): Leishman's stain indicating leukoerythroblastic picture in a case of BMN. Black arrows show nucleated erythrocyte precursors, with red arrows indicating granulocytes*

BMN: bone marrow necrosis.

lactic dehydrogenase and alkaline phosphatase are found in 41% and 51% of cases, respectively. There are no laboratory abnormalities associated specifically with BMN and, if suspected, its diagnosis should be supported by confirmatory data collated from a number of different approaches[6, 8, 22].

The main procedures needed to reach a diagnosis of BMN are BM aspiration, BM biopsy, and magnetic nuclear resonance (MNR) imaging. However, BM biopsy is the most illustrative and requires evaluation by an expert pathologist[16, 19]. Although BM aspirates are not commonly dry, their morphology may indicate a gelatinous degeneration, including cellular debris. The main findings observed from BM histology are amorphous and eosinophilic material dispersed in the extracellular spaces that should be quantified to permit lesion classification (see below). Rare cells with poorly delimited cytoplasmic membranes, irregular nuclei, and shrunken or vacuolated cytoplasm may be also found[6, 8, 15, 18]. In some instances, coagulative necrosis may be observed with "ghost" cells that may reveal neoplastic features and even a diagnostic immune phenotype (**Figure 3**). Bone destruction with a lack of osteoblasts, osteoclasts, and osteocytes, together with empty osteocytic lacunae, may also occur in more advanced lesions[8].

The classification of BMN is based upon the extension of BM involvement and ranges from grade I to III (**Table 3**). Bone scintigraphy using ^{99}technetium may also prove to be useful in reaching a diagnosis of BMN. Like MNR, it is a noninvasive technique and can also be used as a guide for the optimal sampling of a BM aspirate and/or biopsy. Areas with ^{99}technetium uptake higher than 2 cm are suggestive of BMN[8]. By MNR, a diffuse and extensive increase of liquid content, usually in the vertebral body and pelvic bones, may be seen (**Figures 4** and **5**)[3, 8, 11]. The BMN lesion is more extensive and diffuse compared to avascular bone injury, which involves more focal and periarticular necrosis.

TABLE 3 – Classification of BMN according to the extent of BM involvement in a biopsy

BMN grade	Classification	Extent
I	Slight	< 20%
II	Moderate	20%-50%
III	Severe	> 50%

BMN: bone marrow necrosis; BM: bone marrow.

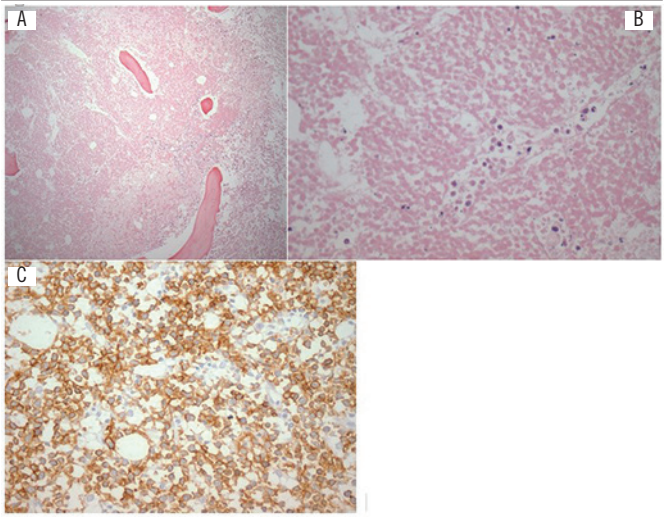

FIGURE 3 – *BM biopsy in BMN: A) BM biopsy of a patient with Burkitt lymphoma showing severe necrosis (HE, 100×); B) BM coagulative necrosis with "ghost" neoplastic cells (HE, 200×); C) CD20 staining, 400×*

BM: bone marrow; BMN: bone marrow necrosis; HE: hematoxilin and eosin.

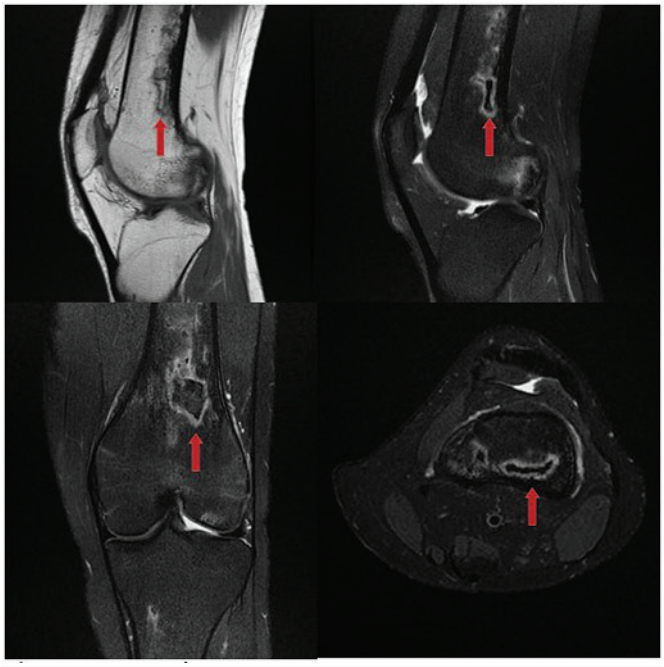

FIGURE 4 – *MNR in BMN 1: upper left to lower right – MNR sagittal T1, sagittal, coronal, and axial T2 with fat saturation. A patient with dermatomyositis diagnosed with BMN. Red arrows indicate areas of increased liquid content*

MNR: magnetic nuclear resonance; BMN: bone marrow necrosis.

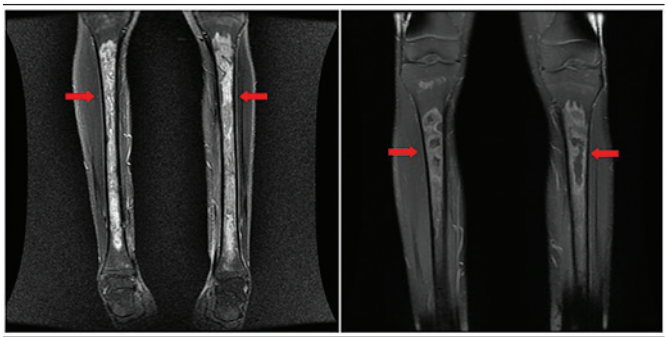

FIGURE 5 – *MNR in BMN 2: left to right – MNR coronal STIR, axial T2 with fat saturation, T1 after contrast with fat saturation. Red arrows indicate areas of increased BM liquid*

MNR: magnetic nuclear resonance; BMN: bone marrow necrosis; STIR: short-TI inversion recovery; BM: bone marrow.

TREATMENT

The approach to BMN involves treatment of the primary cause together with supportive care with antibiotics and blood transfusion. Most studies consider that a diagnosis of BMN implies a poor prognosis that, ordinarily, will rapidly lead to death. However, new studies indicate that survival may be prolonged if BMN is not associated with neoplasia[7, 8, 15]. In cases associated with neoplasia, overall survival remains poor, although a lack of data precludes more succinct outcome descriptions. Moreover, a rare but possible complication of BMN is the embolism of necrotic bone marrow tissue that then blocks vessels in multiple organs, to provoke infarct.

CONCLUSION

Based on this review, we conclude that BMN is associated with many diseases, and yet presents with no clear pathophysiology. 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.

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CONFLICT OF INTEREST

None of the authors have any conflict of interest regarding financial, ethical, or any other personal issues concerning this article.

CONTRIBUTORS

All authors have materially contributed to this article in terms of their research, written contributions, revision, or selection of appropriate supporting material including figures.

All authors have approved the final version of this article.

RESUMO

Introdução: *Necrose de medula óssea (NMO) é uma entidade rara, frequentemente não diagnosticada e mais comumente associada a doenças hematológicas.* ***Metodologia:*** *Realizou-se revisão da literatura na base de dados do PubMed, utilizando o termo "necrose de medula óssea". Foram encontrados 25 artigos em inglês e 65 relatos de caso.* ***Resultados e discussão:*** *A fisiopatologia da NMO não é bem elucidada e parece estar associada a lesão vascular com consequente hipóxia celular por desbalanço na oferta de oxigênio e nutrientes. O fator de necrose tumoral alfa (TNF-α) provavelmente também está implicado na lesão endotelial e nos sinusoides da medula óssea. Sugere-se o diagnóstico pela presença de anemia, trombocitopenia, reação leucoeritroblástica, níveis elevados de desidrogenase lática e fosfatase alcalina. Aspirado e biópsia de medula óssea e ressonância nuclear magnética são os principais exames diagnósticos. As únicas possibilidades terapêuticas são tratamento da causa de base e medidas suportivas.* ***Conclusão:*** *O ponto mais importante no manejo da NMO é a busca por condições neoplásicas associadas.*

Unitermos: *necrose de medula óssea; fator de necrose tumoral alfa; leucoeritroblástica; aspirado de medula óssea; biópsia de medula óssea.*

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