Severe Extensive Bone Marrow Necrosis From Miliary Tuberculosis Without Granulomas and Pulmonary Presentations

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Bone marrow necrosis (BMN) is a rare clinicopathologic entity caused by hypoxemia after failure of the microcirculation, which frequently manifests with bone pain, fever, and peripheral cytopenia. In most reported cases of BMN resulting from miliary tuberculosis (TB), the presence of marrow granulomas, pulmonary infiltrates and/or extrapulmonary involvement is common. We report a female patient with extensive BMN from miliary TB, whose initial presentation was only severe peripheral cytopenia with extensive marrow necrosis, with neither evident pulmonary manifestations nor granulomas in the marrow biopsy. Serial Ziehl–Neelsen stains and *Mycobacterium tuberculosis* cultures were negative. The diagnosis of suspected miliary TB was made by consecutive positive results from polymerase chain reaction analysis for TB of marrow samples at 2 separate examination time points and a good treatment response to anti-TB therapy. Magnetic resonance imaging showed a geographic pattern of multiple signal abnormalities, indicating bone infarcts over the bilateral iliac bones and T-L-spine vertebral bodies, compatible with extensive BMN. The unusual presentation of extensive BMN with severe peripheral cytopenia in the absence of granulomas or pulmonary presentations should alert clinical physicians in epidemic areas. We discuss the use of polymerase chain reaction analysis for TB and magnetic resonance imaging for diagnosis of these patients. [*J Chin Med Assoc* 2010;73(4):208–211]

Key Words: bone marrow necrosis, miliary tuberculosis, pancytopenia

Introduction

Bone marrow necrosis (BMN) is defined as "necrosis of myeloid tissue and medullary stroma in large areas of the hematopoietic bone marrow (BM)",[1] and frequently manifests with bone pain, fever, and peripheral cytopenia.[2,3] Magnetic resonance imaging (MRI) features of BMN typically show a characteristic diffuse, extensive, and geographic pattern of signal abnormalities over the spine and pelvis.[4] The underlying diseases of BMN are diverse, with the most common being hematological malignancies, followed by non-malignant causes such as sickle cell disease, infections, drugs, and others.[2,3] Among the infectious etiologies of BMN, miliary tuberculosis (TB) can be diagnostically troublesome because of its variable hematological manifestations.[5,6] In most reported cases of BMN resulting from miliary TB, the presence of marrow granulomas, pulmonary infiltrates and/or extrapulmonary involvement is common.[2,3,5,7] We report a very rare case of diffuse BMN without evident granulomas or pulmonary presentation, which we believe was caused by miliary TB. We discuss the use of polymerase chain reaction for TB (TB-PCR) and MRI for diagnosis of these patients. All of the procedures that the patient received were considered necessary and

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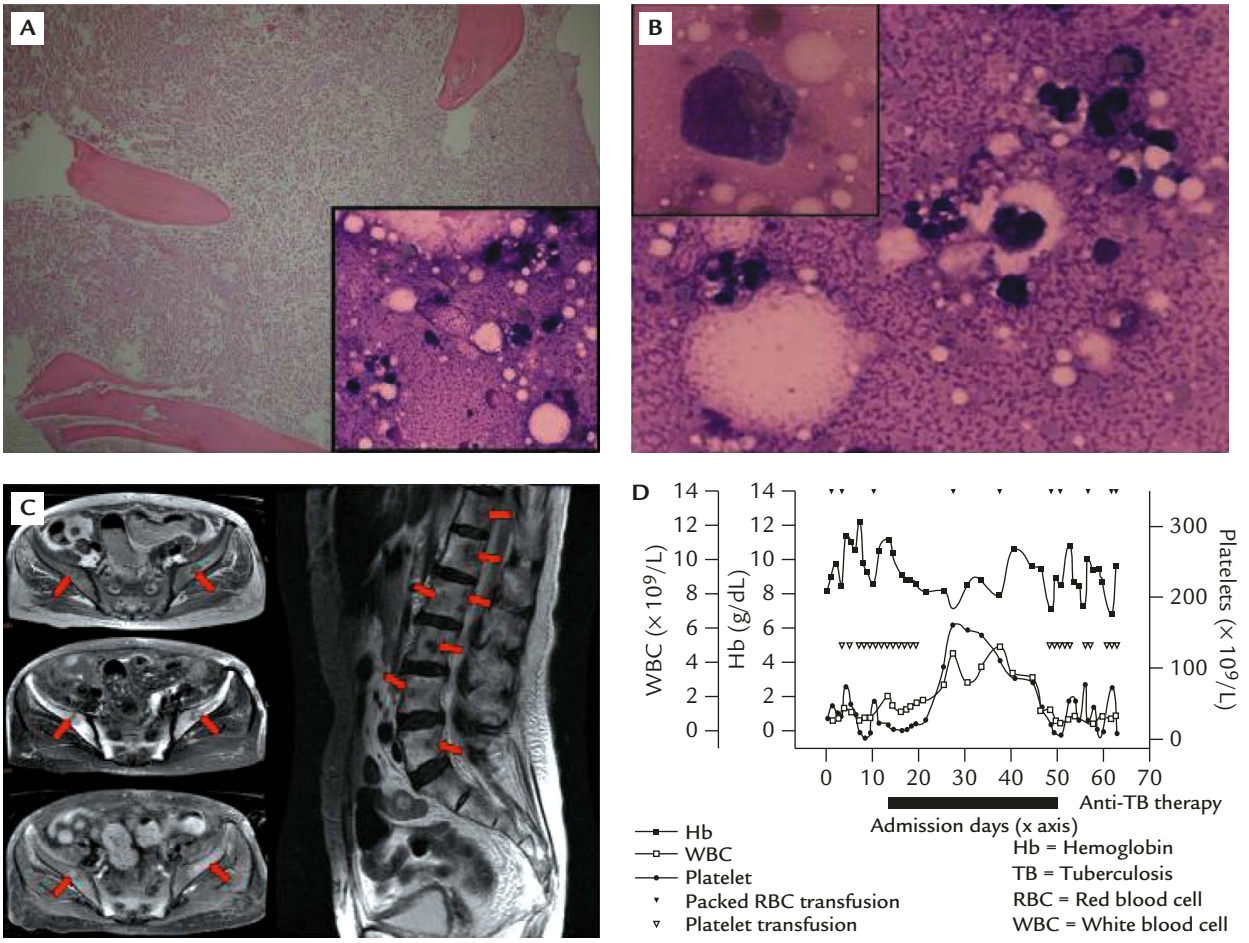

Figure 1. (A) Bone marrow aspiration (inset, Wright's stain, 100×) shows cells losing normal staining characteristics, with karyorrhexis and pyknosis. Biopsy pathology (hematoxylin & eosin, 40×) at diagnosis reveals diffuse bone marrow necrosis without identifiable hematopoietic cells. (B) Follow-up bone marrow smear (Wright's stain, 100×) shows similar necrosis, except for some viable hematopoietic cells (inset, Wright's stain, 100×). (C) Magnetic resonance images of the patient (left upper = axial T1-weighted, left middle = axial T2-weighted, left lower = axial T1-weighted with gadolinium enhancement, and right = sagittal T2-weighted). Both T1- and T2-weighted images show geographic patterns of central low signal abnormalities (arrows in the left upper and left middle insets), and a contrasted T1-weighted image shows gadolinium-enhancement (arrows in the left lower inset) over the bilateral iliac bones and vertebral bodies of the L-spines. (D) Schematic drawing demonstrating changes in peripheral cell counts in association with anti-tuberculosis treatment.

ethical, with informed consent obtained before each procedure.

Case Report

A 66-year-old woman presented with fever, diffuse bone pain and pancytopenia, with a white blood cell count of 0.8×10^9/L, a hemoglobin level of 8.1 g/dL, and a platelet count of 31×10^9/L. The peripheral blood smear was consistent with leukoerythroblastosis without parasites. The patient had no evidence of human immunodeficiency virus infection but acute cholecystitis was indicated by abdominal computed tomography. Other microbiological surveillance of sputum, urine and blood cultures were sterile. The patient had no other signs indicative of sepsis or septic shock except for elevated serum D-dimer levels and fibrin degradation products, with a normal prothrombin time and activated partial thromboplastin time. There was no bleeding diathesis suggesting coagulopathy. She was initially treated as having occult infection.

Due to the persistent severe pancytopenia despite adequate antimicrobial treatment, a BM examination was performed. Unexpectedly massive BMN was observed with the absence of viable hematopoietic cells or granulomas, except for nuclear karyorrhexis and pyknosis (Figure 1A). MRI showed multiple lesions with geographic patterns of signal abnormalities,

indicating bone infarcts over the bilateral iliac bones and T-L-spine vertebral bodies (Figure 1C), compatible with extensive BMN. There were no fungi identified in the BM biopsy specimens. Unfixed aliquots of BM aspirates and biopsy specimens were stained by the Ziehl–Neelsen method but showed no acid-fast bacilli. Consecutive examination by TB-PCR of marrow samples at 2 time points showed positive results.

The patient was diagnosed with a suspected case of miliary TB after thorough surveillance for alternative etiologies, and had clinical and hematological improvement after anti-TB treatment for more than 2 weeks (Figure 1D). In particular, platelet transfusion independence and recovery of white blood cell counts without support by granulocyte colony-stimulating factor were observed during the anti-TB therapy period. In addition, the patient's D-dimer levels and fibrin degradation products returned to within normal limits. The subsequent BM exam revealed similar necrosis pattern to previous biopsied bone marrow pathology, except that viable hematopoietic cells were identified, suggesting that the marrow was recovering (Figure 1B). Unfortunately, the patient succumbed to a second insult of severe bacterial sepsis and septic shock 8 weeks after the diagnosis of extensive BMN.

Discussion

The mechanism of BMN appears to involve a diversity of events, among which failure of the microcirculation is the most critical.[2] Other critical events contributing to BMN include the toxic effects of chemotherapy, irradiation, bacterial endotoxins, tumor cell involvement in marrow microvasculature,[8] and aberrant cytokine production, particularly tumor necrosis factor (TNF), a well-known vascular-disrupting agent.[9] Our case had 3 notable features. First, it was difficult to differentiate the etiology of BMN under the circumstances of severe and extensive marrow destruction. There were no other possible infectious etiologies and no hematological malignancies identified in our case. The immunological and toxicological surveys were all inconclusive. Although there was no solid evidence showing the definite diagnosis of miliary TB, the consecutive positive results of TB-PCR, the clinically and hematologically excellent response after anti-TB treatment, and the exclusion of alternative etiologies strongly suggested miliary TB as the most likely etiology of BMN. TB-PCR has been shown to be highly specific in a large study,[10] which demonstrated that in comparison with culture, the sensitivity, specificity, and positive predictive values of TB-PCR were 83.5%, 99.0%, and 94.2%, respectively.[10] The TB-PCR assay used in our institute (an in-house IS6110-based nested PCR assay) is reported to have a high specificity (95.5%) in diagnosing TB pleurisy.[11] Moreover, the possibility of false-positive TB-PCR results for the present case was excluded by our laboratory internal control. It is often difficult to identify the primary infection site of disseminated TB. Samples obtained from extrapulmonary sites are often paucibacillary in nature, and Ziehl–Neelsen staining for acid-fast bacilli has a low sensitivity, which requires a sample amount of 10^4 bacilli/mL for positivity.[12] TB culture, which is the reference method, is often negative in cases of extrapulmonary TB.[12] Moreover, the long incubation time of TB culture may delay diagnosis and treatment. In contrast, analysis of BM with TB-PCR may facilitate the early diagnosis of disseminated TB, particularly in paucibacillary clinical specimens from extrapulmonary TB patients.[11,13] In addition, responsiveness to empirical anti-TB therapy alone has also been widely used as a diagnostic tool in many case studies.[12] Taken together, these results suggest that miliary TB was the most likely etiology of BMN in our patient.

The second feature observed in our case was the unusual presentation of BMN from miliary TB in the absence of granulomas or pulmonary symptoms. There are 2 possibilities that could explain the absence of granulomas in BM. First, it may have been a result of aberrant cytokine (mainly TNF together with interferon-γ)[14] release elicited by miliary TB infection, which results in severe systemic inflammation and disruption of the microvasculature. Consequently, the BMN becomes severe and this may mask the formation of granulomas. In contrast, there is evidence showing that granuloma formation requires a balanced expression of several cytokines and chemokines, particularly TNF-α.[15,16] Mitsuyama et al[17] showed that a single deletion of the TNF-α gene could lead to multiple severe necrotic lesions without granuloma formation in cytokine-knockout mice. Therefore, it is also possible that our patient was TNF-deficient. However, since we did not measure cytokine levels in our patient, it is difficult to further elucidate the exact mechanism.

The third notable feature in our case was the characteristic MRI findings of diffuse BMN, which typically consist of a geographic pattern of a central area with variable signal intensity, surrounded by a distinct gadolinium-enhanced peripheral rim on T1- and T2-weighted images.[4] The variation of MRI signal intensity in the central area may reflect the different evolutionary stages of BMN.[4] In our patient, both T1- and T2-weighted images showed central areas of low signal intensities, with contrasted T1-weighted images showing

blurred gadolinium-enhanced rims (Figure 1C), all of which indicated a later stage of BMN.[4] However, it should be noted that osteonecrosis (avascular necrosis) and BMN share similar MRI features but are differentiated on imaging on the basis of the site, extent of distribution, and natural history of the lesions.[4] Compared with avascular necrosis and bone infarcts, BMN is anatomically more extensive, involving the marrow of the spine and pelvis, whereas avascular necrosis is usually focal and in a periarticular distribution or is located in the appendicular skeleton.[4]

In conclusion, we have described the unusual presentation and fatal outcome of our case with severe extensive BMN caused by probable miliary TB. Miliary TB should always be considered in patients with extensive BMN, even in the absence of granulomas or pulmonary/extrapulmonary presentations, particularly in areas of high prevalence for TB. MRI and TB-PCR are useful diagnostic tools in such patients.

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