Case report

Two cases of follicular lymphoma with MYC gene abnormalities that presented with bone marrow necrosis

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Bone marrow necrosis (BMN) occurs most frequently in hematological malignancies and sometimes in non-hematological disorders. Lymphoid diseases causing necrosis are regarded as high-grade disease. B-lymphoblastic leukemia/lymphoma is the most common malignant cause of BMN. Here, we present two patients with follicular lymphoma (FL) and MYC gene abnormalities who developed BMN. In one case of BMN, the necrosis disappeared in response to chemotherapy, and the patient survived with complete remission. In the other case, BMN remained even after chemotherapy, and effective chemotherapy could not be administered due to suppressed hematopoiesis, which led to the lymphoma worsening and the patient’s death. Indolent lymphomas, such as FL, as in these cases, have the potential to develop BMN. It is important to detect the development of BMN and administer chemotherapy early to improve patient prognosis, since severe BMN prevents patients from receiving effective treatment.

Keywords: bone marrow necrosis, follicular lymphoma, MYC abnormalities, hematopoiesis

INTRODUCTION

Bone marrow necrosis (BMN) is a unique clinicopathologic entity characterized by necrosis of the medullary stroma and myeloid tissues in large areas of the hematopoietic bone marrow (BM), exhibiting amorphous granular eosinophilic-staining debris, shadows of cells (ghost cells) with indistinct cellular margins, and preserved cortical bone. A previous retrospective review showed the antemortem prevalence of BMN as varying between 0.3 and 2%, depending on the population. Numerous causes of BMN have been identified, including BM carcinoma, radiation/chemotherapy, medication, infection, autoimmune disease, disseminated intravascular coagulation, antiphospholipid syndrome and other thrombotic disorders, granulocyte colony-stimulating factor exposure, and hemoglobinopathies. Most cases were secondary to metastatic tumor or hematolymphoid malignancy (together constituting 90% of necrosis cases). The overall incidence of BMN in hematological malignancies is in the range of 0.15–0.32%, as previously reported in unselected antemortem bone marrow biopsies. The pathophysiology of BMN is not well understood. It is generally considered that ischemia of the BM occurs due to intravascular occlusion caused by tumor cells, to deformed sickle-shaped red cells, or to impaired BM microcirculation caused by immune complexes. Moreover, it has been shown that necrosis is mediated by cytotoxic T cells or the release of either toxins or soluble mediators by malignant cells. Additionally, cytokines, such as tumor necrosis factor (TNF), may induce the expression of leukocyte adhesion receptors on endothelial cells. The resultant granulocyte activation with the generation and release of superoxide has a prothrombotic effect on endothelial cells.

Clinical findings associated with BMN include bone pain and fever, cytopenia, elevated LDH and ferritin levels, and leukoerythroblastosis. Rarely, as in fat embolization syndrome, BMN may be associated with thrombotic microangiopathy, neurologic dysfunction, and multiorgan failure. In hematopoietic malignancy, both lymphoid and myeloid neoplasms have been shown to cause BMN, although previous
studies have reported that cases of lymphoid malignancies predominated over cases of myeloid malignancies. Lymphoid disease is associated with BMN with osteonecrosis, potentially reflecting a global ischemic marrow state induced by highly proliferative malignant lymphoid cells. Alternately, it has been suggested that the expansive growth of tumor cells within the noncompliant space of the BM cavity impedes blood flow, causing ischemic necrosis. Therefore, lymphocytic diseases causing BMN are often myeloid malignancies, such as acute myeloid leukemia. Lymphoblastic leukemia, diffuse large B-cell lymphoma (DLBCL)/high-grade B-cell lymphoma, or Burkitt lymphoma (BL) and rarely indolent lymphoma may cause BMN, and that is important to administer chemotherapy before the BMN becomes severe.

**CASE REPORT**

Case 1. A 68-year-old man with no medical history presented with leukoerythroblastosis, fever, and disseminated intravascular coagulation (DIC). The patient was Eastern Cooperative Oncology Group performance status (ECOG-PS) 1 on admission. A complete peripheral blood analysis showed a white blood cell count of 3,300/µL (neutrophils 41.0%, metamyelocytes 13.0%, myelocytes 2.5%, myeloblasts 0.5%, eosinophils 2.5%, lymphocytes 38.0%), hemoglobin of 13.2 g/dL, platelet count of 3.8 × 10⁹/µL, lactate dehydrogenase (LDH) level of 6502 U/L, C-reactive protein (CRP) level of 8.7 mg/dL, and soluble interleukin-2 receptor (sIL-2R) level of 2540 U/L. The serum immunoglobulin levels were low (IgG 561 mg/dL, IgA 88 mg/dL, IgM 32 mg/dL) (Table 1). The supraclavicular, mediastinal, and para-aortic lymph nodes were enlarged on computed tomography (CT), and thus, BM examination and lymph node (LN) biopsy were performed. The BM smears (Figure 1a, b) and biopsy (Figure 1c, d) showed hypercellular marrow due to a large amount of abnormal, diffuse, large malignant lymphoid infil-

| Table 1. Laboratory data on admission |
|--------------------------------------|
| **CASE 1**                          |
| **CASE 2**                          |
| Hb 13.2 g/dL                        | Hb 10.6 g/dL                        |
| MCV 91.3 fl                         | MCV 84.8 fl                         |
| MCH 32.0 pg                         | MCH 29.3 pg                         |
| RBC 413 ×10⁹/µL                     | RBC 362 ×10⁹/µL                     |
| Reti 2.9 ×10⁹/µL                    | Reti 1.4 ×10⁹/µL                    |
| ALT 52 IU/L                         | ALT 41 IU/L                         |
| LDH 6502 IU/L                       | LDH 2739 IU/L                       |
| WBC 3300 /µL                        | WBC 700 /µL                         |
| seg 28.0 %                          | seg 70.0 %                          |
| stab 13.0 %                         | stab 1.0 %                          |
| meta 13.0 %                         | meta 3.0 %                          |
| myelo 2.5 %                         | myelo 1.0 %                         |
| mbl 0.5 %                           | Na 139 mEq/L                        |
| ly 38 %                             | K 4.7 mEq/L                         |
| eo 2.5 %                            | Cl 102 mEq/L                        |
| mono 2.5 %                          | Ca 8.9 mg/dL                        |
| Pt 3.8 ×10⁹/µL                      | Glu 118 mg/dL                       |
| Fbg 493 mg/dL                       | UA 5.7 mg/dL                        |
| PT 106 %                            | CRP 8.7 mg/dL                       |
| PT-INR 0.9                         | sIR2R 2540 U/mL                     |
| APTT 26.2 sec                       | FDP 1.0 ×10⁹/µL                     |
| FDP 49.1 µg/dL                      | D-dimer 13198.5 ng/mL               |
| D-dimer 43.4 µg/dL                  | Ferritin 7671.9 ng/mL               |

Abbreviations: Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RBC, red blood cells; Reti, reticulocyte; WBC, white blood cells; seg, segmented leukocyte; stab, stab form leukocyte; metamyelocyte; myelocyte; myelo, myelocytes; mbl, myeloblast; ly, lymphocytes; eo, eosinophils; mono, monocytes; Pt, platelets; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TP, total protein; Alb, albumin; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-guanosine triphosphate; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; Glu, glucose, UA, uric acid; CRP, C-reactive protein; sIL-2R, soluble interleukin 2 receptor; ANA, antinuclear antibody; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M.
tration with no hemophagocytosis but with areas of necrosis. Immunophenotyping of the BM by flow cytometry (FCM) revealed a discrete lymphoid population (bright CD45 and low side scatter) that expressed CD19 and CD20 (6.4%, 490/7649 cells) with an absence of surface immunoglobulin light chain expression (Figure 2a). Immunohistochemical staining of the BM showed that the atypical cells were positive for CD20, Bcl-2, and Bcl-6, and negative for CD3, CD5, CD10, MUM-1, and MYC (Figure 1f). The average Ki-67 score was 15%, but it reached ≥50% locally (Figure 1f). BM metaphase cytogenetic analysis revealed that the karyotype was 46, XY in 1/1 cell, and fluorescence in situ hybridization (FISH) performed with an MYC probe and a BCL2-IGH probe demonstrated MYC split signals and BCL2-IGH fusion signals (Figure 2b). On histopathological examination of the lymph nodes (LN), a diagnosis of follicular lymphoma (FL) grade 1-2 was made (Figure 1g-i). Immunohistochemical staining of the LN was the same as that of BM immunostaining, although the atypical LN cells were positive for MYC. The average Ki-67 score was ≥50% locally (Figure 1i). LN FCM analysis and chromosomal analysis could not be performed due to an insufficient sample volume. LN FISH analysis of a paraffin-embedded tissue section performed with an MYC probe showed MYC split signals (Figure 2c).

The patient underwent one cycle of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), five cycles of dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab), two cycles of high-dose methotrexate, and five courses of intrathecal chemotherapy consisting of methotrexate, cytarabine, and dexamethasone, resulting in complete remission (CR). BM aspiration after two courses of chemotherapy showed normal cellularity, and the disappearance of BMN (Figure 1e). His blood cell counts normalized after the above chemotherapy. However, the patient relapsed to FL grade 1-2 1.5 years after the end of the initial chemotherapy, for which he received six cycles of obinutuzumab, bendamustine with the achievement of a second CR.

Case 2. A 70-year-old woman with no significant medical history presented with leukoerythroblastosis, fever, DIC, and severe pancytopenia. The patient was ECOG-PS 3 on admission. A complete peripheral blood analysis showed a white blood cell count of 70/μL (neutrophils 71.0%, metamyelocytes 3.0%, myelocytes 1.0%, lymphocytes 21.0%), hemoglobin of 10.6 g/dL, platelet count of 1.0 x 10^10/μL, LDH level of 2739 U/L, CRP level of 11.8 mg/dL, and sIL-2R level of 2123 U/L. The serum immunoglobulin levels were low (IgG 491 mg/dL, IgA 48 mg/dL, IgM 12 mg/dL) (Table 1). CT revealed swelling of the LNs in the left neck, as well as of the bilateral axillary, mediastinal, para-aortic, pelvic, and inguinal LNs, and hepatosplenomegaly, bilateral pleural effusions, a mass around the thoracolumbar spine, and bilateral internal iliac vein thrombosis. BM smears (Figure 3a, b) and biopsy (Figure 3c, d) showed massive BMN with sheets of necrotic ghost cells and no hemophagocytosis. FCM of the BM detected no cells in the bright CD45 region (Figure 4a). On immunohistochemical staining of the BM the atypical cells were positive for CD20, CD10, Bcl-2, and Bcl-6, and negative for CD3, CD5, MUM-1, MYC, and cyclinD1 (Figure 3f). The average Ki-67 score was 30% (Figure 3f). BM metaphase cytogenetic analysis could not be performed due to an insufficient number of cells, while FISH performed with an MYC-IGH probe and a BCL2-IGH probe showed no MYC-IGH fusion signals, but a triplod of MYC and BCL2-IGH fusion signals (Figure 4b).

On histopathological examination of the LN, the diagnosis was DLBCL arising from FL, because FL Grade 3A (Figure 3g-i) and DLBCL (Figure 3j-l) were mixed in the same LN. Immunophenotyping of the LN by FCM revealed a discrete lymphoid population (bright CD45 and low side scatter) that expressed CD19 and CD20 and was negative for both light chains (Figure 4c). Immunohistochemical staining of the LN was the same as BM immunostaining, but atypical LN cells were positive for MYC. The average Ki-67 score was 59% in FL and 75% in DLBCL (Figure 3i, l). LN FCM analysis and chromosomal analysis could not be performed due to an insufficient sample volume. FISH performed with an MYC-IGH probe and a BCL2-IGH probe showed the same results as BM (Figure 4d).

The patient underwent six cycles of R-CHOP, along with granulocyte colony stimulating factor (G-CSF) and blood transfusions as supportive care, leading to a partial response and normalization of LDH after two cycles of R-CHOP. BM biopsy after three cycles of R-CHOP showed collagen fibrosis and necrosis (Figure 3e). The patient’s leukocyte count was < 200/μL for more than five days despite G-CSF administration as primary prophylaxis, and she also required weekly red blood cell transfusion and once or twice weekly platelet transfusion per cycle of R-CHOP. Additionally, the treatment interval was extended due to progressive cytopenia and infection. Consequently, terminating in death of the patient. The overall survival period was six months after the first diagnosis.

**DISCUSSION**

Both of the present patients exhibited FLs with MYC gene abnormalities and BMN at diagnosis, but with different outcomes. In case 1, the pathological diagnosis of the LNs was FL, but the cells infiltrating the BM were clinically considered transformed FL based on the presence of B symptoms, markedly high LDH, and infiltrating large lymphoma cells. However, due to the BMN, it was not possible to pathologically diagnose that the large malignant lymphocytes infiltrating the BM were transformed FL cells. Case 1 was considered to be double-hit follicular lymphoma because it was accompanied by MYC abnormality in both the LN at the time of the initial onset, which was histologically FL, and the LN at the time of recurrence, which was FL both histologically and clinically. The difference in terms of detection of the MYC split signal at the first onset and the IGH-MYC translocation in the LN at the time of recurrence was probably due to the different probes used. Since malignant lymphoma cells in the BM were detected by FCM, it is likely that non-necrotic malignant lymphoma cells remained. In
Fig. 1. Pathological examinations in case 1. (a) (b) Bone marrow aspiration smear showing necrosis. A small amount of hematopoietic cell debris with unclear boundaries and necrotic cell stains with unclear edges. May-Giemsa stain ×100 (a); ×400 (b). (c) (d) Bone marrow trephine biopsy showing bone marrow necrosis with mostly bare nuclei, along with infiltrated areas with a population of atypical cells with large nuclei. Hematoxylin-eosin stain. ×100 (c), ×400 (d). (e) Bone marrow trephine biopsy after two courses of chemotherapy showing recovery of hematopoietic cells in the bone marrow. Hematoxylin-eosin stain ×100. (f) Immunohistological findings of the lymphocytes infiltrating the bone marrow ×400. Immunohistochemical analysis demonstrated positivity for CD20, CD10, Bcl-2, Bcl-6, and Ki-67, and negativity for MUM-1 and MYC. (g-i) Lymph node biopsy showing morphological and immunohistological findings ×40 (g), ×400 (h, i). Immunohistochemical analysis demonstrated positivity for CD20, CD10, Bcl-2, Bcl-6, MYC, and Ki-67, and negativity for MUM-1.
BMN in FL with MYC abnormalities

Fig. 2. Flow cytometry and cytogenetic analysis in case 1. Flow cytometry (a) and cytogenetic analysis and fluorescence in situ hybridization (b) of BM. Fluorescence in situ hybridization for paraffin-embedded tissue of LN (c).

| Cytogenetics | Normal karyotype |
|--------------|------------------|
| MYC:1 / 5'MYC:1 / 3'MYC:1 | 52% |
| MYC:1 / 5'MYC:2 / 3'MYC:1 | 3% |
| IGH-BCL2 fusion signal:1/BCL2:2/IGH:1 | 52% |

Paraffin-FISH MYC MYC:1 / 5'MYC:1 / 3'MYC:1 98.5%
Fig. 3. Pathological examinations in case 2. (a) (b) Bone marrow aspiration smear showing necrosis. May–Giemsa stain ×100 (a); ×400 (b). (c) (d) Bone marrow trephine biopsy showing bone marrow necrosis with ghost cells and mostly bare nuclei, along with infiltrated areas with a population of atypical cells with medium nuclei. Hematoxylin–eosin stain ×100 (c); ×400 (d). (e) Bone marrow trephine biopsy after three courses of chemotherapy. There was no recovery of hematopoietic cells in the bone marrow. Hematoxylin–eosin stain ×100. (f) Immunohistological findings of the lymphocytes infiltrating the bone marrow ×400. Immunohistochemical analysis demonstrated positivity for CD20, CD10, Bcl-2, Bcl-6, and Ki-67, and negativity for MUM-1 and MYC. (g–l) Lymph node biopsy showing morphological and immunohistological findings. The frames in the small rectangles on the lower left sides of panels g and h show the follicular dendritic cell network with CD21 staining, and the yellow ellipse in the same frame shows the same location. Histological appearance of follicular lymphoma Grade 3A: g–i, and diffuse large B cell lymphoma: j–l; ×40 (g), ×400 (h, i, k, l). Immunohistochemical analysis demonstrated positivity for CD20, CD10, Bcl-2, Bcl-6, MYC, and Ki-67, and negativity for MUM-1.
Fig. 4. Flow cytometry and cytogenetic analysis in case 2
Flow cytometry (a) and cytogenetic analysis and fluorescence in situ hybridization (b) of BM. Flow cytometry (c) and cytogenetic analysis and fluorescence in situ hybridization (d) of LN.
addition, cells were detected in the region of CD45 with moderate and low to high side scatter by FCM, suggesting the existence of hematopoietic stem cells and granulocytic cells, and the white blood cell count of the peripheral blood was also maintained. In contrast, in case 2, which was diagnosed with transformed FL by LN biopsy, BM biopsy showed the diffuse spread of ghost cells with severe necrosis. However, since the case was not pathologically diagnosed as FL at any time point, the accurate pathological diagnosis of the LN was composite lymphoma of FL Grade 3A and DLBCL, although lymphoma cells in both the LN and BM had IGH-BCL translocation. Therefore, it was clinically considered to be transformed FL. FCM analysis of the BM sample did not show a cell population in the region of bright CD45 and low side scatter, indicating that most of the lymphoma cells infiltrating the BM were massively necrotic. In addition, the cells in the low to high side scatter region had few CD45 dim to moderate cells, indicating a decrease in granulocytic cells, and the peripheral blood leukocyte count was markedly lower. In case 1, tumor cells in the BM disappeared in response to chemotherapy and hematopoiesis recovered, but in case 2, although tumor cells in the BM decreased with chemotherapy, normal hematopoiesis did not recover. Since it has been reported that patients who develop BMN due to B lymphoblastic leukemia (B-ALL) with rapid tumor growth have a better prognosis than patients who develop BMN due to other background diseases,10 the differences in outcome between the two cases may have been due to the degree and extent of BMN at diagnosis, and not the FL grade. Previous studies recommend 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) / CT and magnetic resonance imaging (MRI) to determine the degree of BMN.11,12 Because of our lack of basic knowledge about the BMN and the rapid progression of the disease, there was no time for FDG-PET/CT and MRI examination in our patients. In both cases, the Ki67 index in BM was considered to be relatively low, and immunostaining for MYC was positive in the LNs, but not in many of the BM cells. This may be because the nuclear proteins Ki67 and MYC are thought to lose their stainability in necrotic lymphoma cells with highly degenerated nuclei.

If patients with BMN are young, allogeneic hematopoietic stem cell transplantation (allo-SCT) may be considered at an early stage in anticipation of hematopoietic recovery and antitumor effects. Although there is concern about graft failure following haemopoietic cell transplantation in the necrotic BM, several cases of BMN following allo-SCT have been reported.13-15 As mentioned above, BMN patients with B-ALL as the background disease reportedly have a better prognosis than those with other background diseases,10 although B-ALL patients with BMN tend to have a worse prognosis than B-ALL patients without BMN.3 However, there are several reports of cases of B-ALL with BMN at the time of diagnosis who survived for a long time following treatment with chemotherapy or allo-SCT.15,16 In malignant lymphoma, Xu et al. reported a patient with cell lymphoma, BMN, and hemophagocytosis who achieved a good prognosis with treatment with sequenced mini-CHOP and CHOP (CHOP plus etoposide) therapy.17 In addition, Cerny et al. reported a BL case in which BMN developed after recurrence, with subsequent remission with EPOCH-R followed by allo-SCT, resulting in long-term survival.15 The patients with long-term survival mentioned above were those in which hematopoiesis recovered along with reduction in the size of tumors in the BM by chemotherapy, or in whom continuous chemotherapy could be performed. Furthermore, BMN develops not only in lymphoid neoplasms, but also in myeloid neoplasms. Myeloid neoplasms associated with BMN are primarily acute myeloid leukemia (AML) cases, although necrosis is also rarely seen in association with chronic myeloid neoplasms. Necrosis is greater in AML with monocytic features.1 This is in contrast to the findings that AMLs with monocytic differentiation are a minority of AML cases overall. As in B-ALL, AML patients with BMN tend to have a poor prognosis compared to AML patients without BMN.3 BMN is also associated with the use of antineoplastic drugs such as fludarabine,18 imatinib,19 interferon alpha, nivolumab,20 rituximab,21 and blinatumomab.22

MRI is being used increasingly in the evaluation of diseases of the BM, and it is also used to assess BMN. BMN characteristically has an extensive, diffuse geographic pattern of signal abnormality, consisting of a central area of variable signal intensity surrounded by a distinct peripheral enhancing rim. The various appearances of the central area may reflect different stages of BMN, which are divided into four classes, from the initial stage (class A) to the most advanced stage (class D), with class D showing the signal characteristics of low-intensity fibrous tissue in all sequences. In previous reports, patients died shortly after a class D appearance was seen on MRI.12 Although the degree of BMN was not evaluated by MRI in the present two cases, Case 2 would probably have shown a class D-like appearance, which would have prevented hematopoietic recovery. Based on the above discussion, MRI may be useful for the early diagnosis of BMN and assessment of the degree of BMN, and may be a method for assessing the potential for the recovery of hematopoiesis.

In conclusion, we presented two cases of FL with MYC gene abnormalities with BMN. The lymphoma with severe BMN in case 2 grew more aggressively. This patient could not receive adequate chemotherapy due to severe cytopenia and had a poor prognosis, as previously reported in a patient with severe BMN.3 Our experience suggests that patients with severe BMN at diagnosis may have aggressive lymphoid malignancies, and that earlier lymph node biopsy and BM MRI examination are important for a rapid diagnosis. In addition, in cases of BMN in which hematopoietic recovery cannot be obtained, allo-SCT may be considered.

**CONFLICT OF INTEREST**

None of the authors have any financial competing interests to declare.
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