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【 CASE REPORT 】

Recurrence of Acute Lymphoblastic Leukemia with Bone Marrow Necrosis: A Case Report and Review of the Literature on the MRI Features of Bone Marrow Necrosis

Naonori Harada[1], Mitsutaka Nishimoto[1], Aya Ikemoto[2], Hiroshi Okamura[1], Shiro Koh[1], Satoru Nanno[1], Yasuhiro Nakashima[1], Hideo Koh[1], Takahiko Nakane[1], Yuko Kuwae[3], Masahiko Ohsawa[3], Masayuki Hino[1] and Hirohisa Nakamae[1]

Abstract:
Bone marrow necrosis (BMN) is a rare but important complication of hematological malignancies. We report the case of a 52-year-old male patient with a recurrence of acute lymphoblastic leukemia (ALL) accompanied by BMN. After re-induction therapy, bone marrow aspiration (BMA) and biopsy from the iliac bone showed necrotic cells and eosinophilic debris, respectively. Magnetic resonance imaging (MRI) showed heterogeneous signals in the bilateral iliac bone, possibly reflecting various stages of BMN. BMA from the sternum eventually revealed the recurrence of ALL after a few weeks. Comprehensive assessments, including MRI and repeated bone marrow tests, are required when evaluating the underlying hematological malignancies of patients with BMN.

Key words: bone marrow necrosis, bone marrow aspiration from the sternum, acute lymphoblastic leukemia, magnetic resonance imaging

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Introduction

Bone marrow necrosis (BMN) is an extremely infrequent phenomenon, defined as necrosis of the myeloid tissue and medullary stroma. The prevalence of BMN was reported to be between 0.3% and 2% antemortem of patients eligible for bone marrow examination, and BMN is often detected on autopsy (1, 2). The causes of BMN have been identified, including hematological malignancies, solid tumors, infectious disease, chemical exposure, radiation, sickle cell disease, antiphospholipid syndrome, and disseminated intravascular coagulation (2-13). Moreover, acute lymphoblastic leukemia (ALL) accompanied by BMN has been reported to have a poor prognosis (14). The main clinical symptoms of BMN are fever and bone pain. Laboratory findings, such as severe pancytopenia and elevated levels of lactate dehydrogenase (LDH) are generally indicative of BMN (1, 2). However, these features can be absent in some cases (15). Magnetic resonance imaging (MRI) findings can be helpful but are nonspecific in the evaluation of bone marrow disorders (16). The morphological assessment of bone marrow aspirate and the pathological findings of bone marrow biopsy (BMB) specimens are most essential for the diagnosis of BMN. Many hematologists report difficulty in assessing the disease status of hematological malignancies by bone marrow aspiration (BMA) because they cannot obtain appropriate samples in cases of extensive BMN and 'dry tap', defined as failure to obtain bone marrow on attempted marrow aspiration (6). We herein report a case in which an appropriate disease evaluation was performed using bone marrow aspirate obtained from the sternum of a patient with recurrent ALL accompanied by BMN after re-induction therapy. The MRI features of BMN are also taken into consideration.

[1]Department of Hematology, Graduate School of Medicine, Osaka City University, Japan, [2]Department of Clinical Laboratory, Osaka City University Hospital, Japan and [3]Department of Diagnostic Pathology, Graduate School of Medicine, Osaka City University, Japan
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Correspondence to Dr. Naonori Harada, harada.naonori@med.osaka-cu.ac.jp

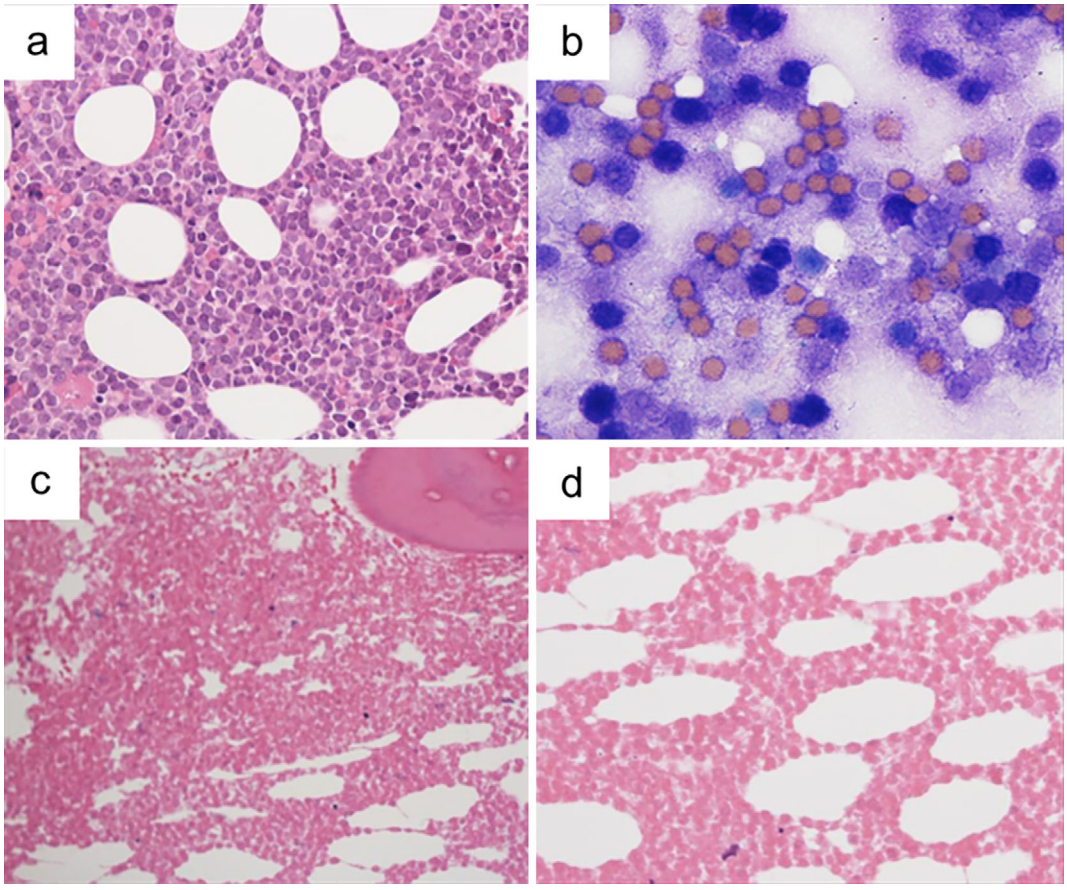

Figure 1. **Pathological findings of bone marrow biopsy (BMB) and bone marrow aspiration (BMA). (a) Pathological findings of BMB on admission. Hematoxylin and Eosin (H&E) staining (×400). (b) Pathological findings of BMA on day 28 of mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC) therapy. May-Giemsa staining (×400). (c) Pathological findings of BMB on day 35 of MEC therapy. H&E staining (×200). (d) Pathological findings of BMB on day 35 of MEC therapy. H&E staining (×400).**

Case Report

A 52-year-old male patient received cord blood transplantation for Philadelphia chromosome-positive ALL without T 315I mutation. One year later, he was diagnosed with recurrent ALL accompanied by severe bone pain. He was transferred to our institution for re-induction therapy. A BMA specimen could not be obtained due to 'dry tap'; however, BMB showed numerous blast cells before re-induction therapy, as shown in Fig. 1a. On hospital admission, he had high-grade fever, and a blood culture test was negative; however, a rapid diagnostic test for influenza virus using a nasopharyngeal swab specimen was positive for influenza A. Thus, the patient was treated with mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC) therapy and intravenous peramivir (300 mg, once daily). His high-grade fever temporarily improved after treatment; however, his severe fever symptom was exacerbated again on day 16 of MEC therapy. At the time, *Aspergillus fumigatus* invasion was detected and intravenous voriconazole (VRCZ) was initiated (Fig. 2). His high-grade fever did not improve, despite the antifungal treatment, even after almost recovering from pancytopenia during the nadir period (white blood cell count, 6.8×10^3/μL with 0% blast cells; hemoglobin, 8.7 g/dL; and platelet count, 14.8×10^3/μL).

To estimate the disease status, a BMA test was performed from the right iliac bone on day 28 of MEC therapy, but we only obtained a muddy and jelly-like specimen. When this sample was centrifuged, a cloudy pink precipitate was obtained (Fig. 3). A BMA smear from the specimen showed irregular and indistinct margins, and the cytoplasm appeared fused, as shown in Fig. 1b. In addition, a peripheral blood analysis revealed a high LDH level of 551 IU/L. Subsequently, both BMA and BMB tests were performed from the left iliac bone on day 35 of MEC therapy. We could not obtain sufficient BMA specimens because of 'dry tap' aspiration. The findings of the BMB tests showed that most of the bone marrow space was replaced by eosinophilic debris. Although a very small number of blast cells remained, an accurate evaluation was difficult, as shown in Fig. 1c, d. We switched the antifungal agent from VRCZ to liposomal amphotericin B (L-AMB; 3 mg/kg, daily) on day 35 of MEC therapy because his high-grade fever had not improved. On

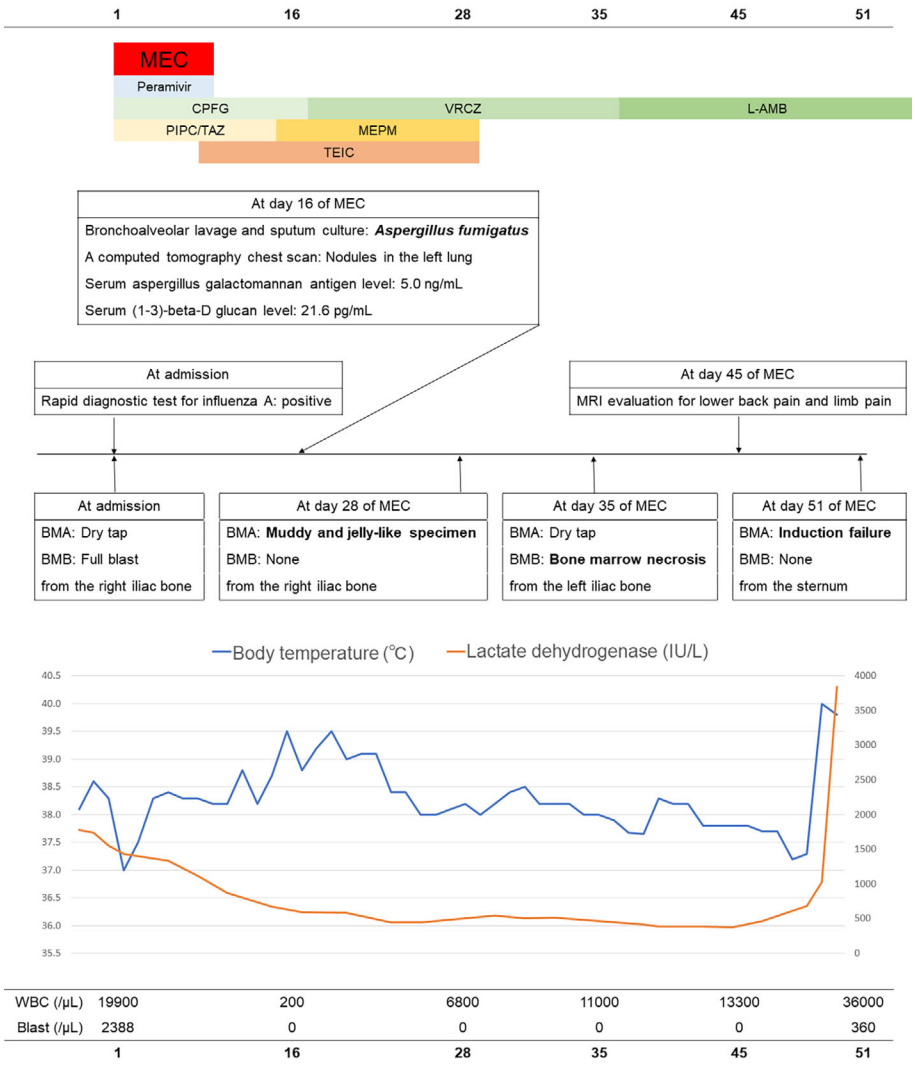

Figure 2. **The clinical course. BMA: bone marrow aspiration, BMB: bone marrow biopsy, CPFG: caspofungin, L-AMB: liposomal amphotericin B, MEC: mitoxantrone, etoposide, and intermediate-dose cytarabine, MEPM: meropenem, MRI: magnetic resonance imaging, PIPC/TAZ: piperacillin/tazobactam, TEIC: teicoplanin, VRCZ: voriconazole, WBC: white blood cell**

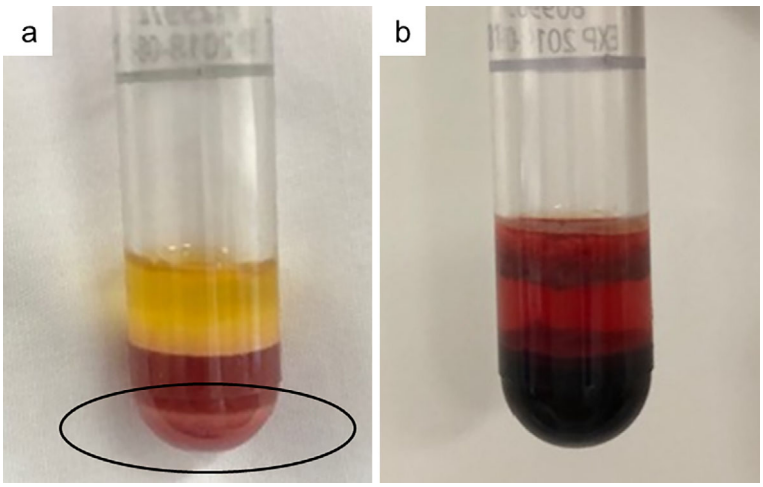

Figure 3. **Centrifuged bone marrow sample. (a) A centrifuged sample of the present patient with bone marrow necrosis (BMN). (b) A centrifuged sample of another patient with acute lymphoblastic leukemia, without BMN.**

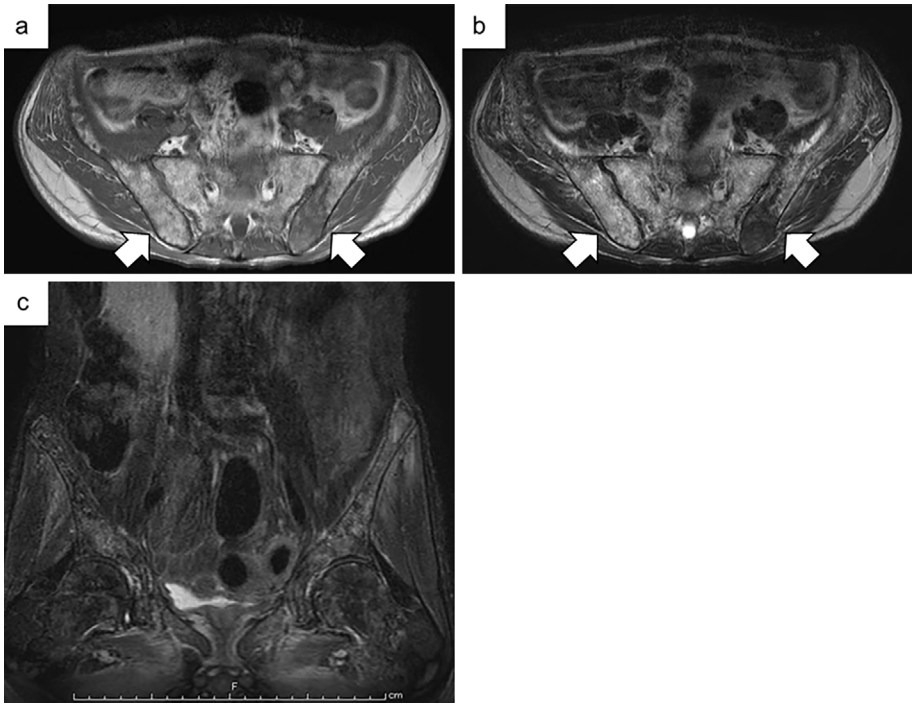

Figure 4. **Magnetic resonance images showing different abnormal signals in the bilateral iliac bone marrow (arrow). (a) Axial T1-weighted magnetic resonance image. (b) Axial T2-weighted magnetic resonance image. (c) Coronal high short T1 inversion recovery image.**

day 45 of MEC therapy, the patient's lower back and lower limb pain gradually worsened. MRI showed heterogeneous patchy areas of high signal intensity at the right iliac bone and sacrum on T1-weighted and T2-weighted imaging. In contrast, MRI showed heterogeneous patchy areas of signal intensity at the left iliac bone on T1-weighted and T2-weighted imaging. In addition, high short T1 inversion recovery imaging of both the bilateral iliac bone and sacrum showed partially high signal intensity, as shown in Fig. 4. These findings appeared to reflect a bone marrow abnormality, including BMN, however a further qualitative evaluation was difficult. On day 50 of MEC therapy, his bone pain drastically deteriorated. On day 51 of MEC therapy, BMA from the sternum revealed 59% blast cells, and ALL induction failure with T315I mutation was confirmed (Fig. 2). The patient was treated with inotuzumab ozogamicin, which was ineffective. Furthermore, invasive pulmonary aspergillosis was also refractory, although we added micafungin to L-AMB on day 50 of MEC therapy. The patient did not desire further treatment and was transferred to a nearby hospital to receive the best supportive care.

Discussion

We detected two important clinical issues. The first is that the MRI features of BMN can vary depending on the location and stage. The second is that severe BMN can hinder the assessment of underlying hematological malignancies.

First, MRI of BMN can differ based on the condition. In general, MRI allows clinicians to noninvasively evaluate abnormal bone marrow and is complementary to a bone marrow examination. On MRI, the signal intensity of the bone marrow mainly reflects the proportion of fatty and serous materials. Tang et al. reported that the MRI features of BMN showed slight variation, depending on the stage. They categorized the different stages of BMN into four classes (Table a) (16). In an earlier BMN stage (class A or B), fatty cells remained in the bone marrow. Thus, T1-weighted MRI showed hyperintensity. The signal on T1-weighted MRI became hypointense as the fatty material was gradually lost. The characteristic MRI features of BMN include extensive, diffuse, geographic patterns of signal abnormalities, and the MRI findings of these four different stages, as we mentioned above, can coexist in the same site. Moreover, the central regions of the BMN were sometimes surrounded by peripheral bands of low intensity, and the peripheral rims became enhanced when gadolinium was administered (16). Although these features are nonspecific, clinicians should take these MRI features into consideration when assessing patients with suspected BMN.

In our case, MRI was performed after obtaining the BMA and BMB findings, which matched BMN in the bilateral iliac bone. The MRI features of the right iliac bone, the surface side of the left iliac bone, and the central side of the left iliac bone corresponded to classes B, D, and B, respectively (Table b).

Of note, the pathological BMB finding of the left iliac bone showed necrotic tissue without fibrotic tissue, which was in contrast to the MRI findings. BMB from the left iliac bone was performed 10 days before MRI. During that time,

Table a. Classification Based on the Qualitative Assessment of Alterations in MRI Signal Intensity in BMN.

BMN stage	Class A	Class B	Class C	Class D	Hematological malignancies
T1 weighted	Hyperintensity	Hyperintensity	Hypointensity	Hypointensity	Hypointensity
T2 weighted	Isointensity-mild hyperintensity	Hyperintensity	Hyperintensity	Hypointensity	Nonspecific
STIR	Hypointensity	Unknown	Unknown	Unknown	Hyperintensity
What does this finding mainly reflect?	Fatty materials	Blood and proteinaceous materials	Denaturation of protein	Fibrosis tissue	

This table was made by the authors based on reference 16-18.

BMN: bone marrow necrosis, MRI: magnetic resonance imaging, STIR: short TI inversion recovery

Table b. Pathological Features and MRI Findings of Bone Marrow.

	Right iliac	Left iliac
BMA on day 28 of MEC	Muddy and jelly-like specimen (Figure 1b, 3)	None
BMA on day 35 of MEC	None	Dry tap
BMB on day 35 of MEC	None	Bone marrow space was mostly replaced by eosinophilic debris (Figure 1c, d)
MRI feature on day 45 of MEC	Class B	Class B (central) Class D (peripheral)

BMA: bone marrow aspiration, BMB: bone marrow biopsy, MEC: mitoxantrone, etoposide, and intermediate-dose cytarabine, MRI: magnetic resonance imaging

the bone marrow fibrosis was considered to have progressed. Thus, clinicians should note that MRI of BMN can differ depending on the location and timing. MRI performed just before a bone marrow examination is very useful, and clinicians could choose the best part for proper evaluation of BMN. Class A (earliest stage) and class D (end stage) mainly show fatty marrow and fibrosis, respectively (Table a, b), and BMA can result in 'dry tap' aspiration. Moreover, the disease status of BMN in each of the stages is likely to be less active. Thus, a bone marrow examination from the part containing class B or C findings on MRI may be helpful when assessing BMN.

Second, hematologists have sometimes experienced difficulty when assessing the therapeutic effects in patients with hematological malignancies and BMN because BMN and relapsing hematological malignancies have similar clinical symptoms, including fever and bone pain, as well as laboratory data, such as cytopenia and elevated LDH. Moreover, as mentioned above, MRI is a useful and noninvasive method for assessing the features of BMN, which can differ by stage. However, MRI cannot precisely distinguish BMN from hematological malignancies because the MRI features of hematological malignancies are partially similar to those of BMN. In patients with hematological malignancies, are hypointense signals are observed on T1 images, while the signal characteristics are nonspecific on T2 images (Table a) (17, 18). In addition, in some cases, BMA specimens cannot be obtained due to 'dry tap,' and even if the specimens are obtained, they may be jelly-like or muddy, which makes it difficult to accurately evaluate the therapeutic effect (2). This diagnostic dilemma caused by necrotic tissue without evaluable cells could be solved by repeated BMA and BMB from not only the bilateral iliac bone but also the sternum, as was performed in our case. However, clinicians are not always able to assess the underlying hematological malignancies by bone marrow examinations from either the bilateral iliac bone or sternum because of the extremely extensive BMN. Miyoshi et al. reported a case of BMN in which an evaluable specimen of underlying ALL could not be obtained, even with repeated bone marrow examinations from both the sternum and iliac bone (5). In view of the severity of the illness of this patient, combination chemotherapy for lymphoid malignancies was immediately started based on the clinical features, which included systemic lymphadenopathy, hepatosplenomegaly, pancytopenia, and high LDH. One month later, leukemia cells appeared in the peripheral blood, leading to a diagnosis of ALL. In addition, Moritake et al. showed that leukemic cell-eliciting Fas-ligand and macrophage-eliciting tumor necrosis factor-alpha could be associated with the molecular mechanism underlying BMN with ALL (19). Thus, because these cytokines from leukemic cells can cause BMN, reducing the tumor burden via chemotherapy, as was reported by Miyoshi et al., could be effective for relieving BMN and may be useful for making a reliable disease assessment.

In conclusion, MRI is helpful for an extensive assessment of the site and status of BMN. Although the disease status is sometimes difficult to assess in the case of hematological malignancies with BMN due 'dry tap' or a non-evaluable muddy and jelly-like specimen, a more appropriate examination site could be selected by performing MRI just before a bone marrow examination.

Written informed consent for publication was obtained from

the patient's wife.

The authors state that they have no Conflict of Interest (COI).

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References

1. Janssens AM, Offner FC, Van Hove WZ. Bone marrow necrosis. Cancer **88**: 1769-1780, 2000.
2. Deucher A, Wool GD. How I investigate bone marrow necrosis. Int J Lab Hematol **41**: 585-592, 2019.
3. Thuerl C, Altehoefer C, Spyridonidis A, Laubenberger J. Imaging findings in the rare catastrophic variant of the primary antiphospholipid syndrome. Eur Radiol **12**: 545-548, 2002.
4. Ishitsuka K, Shirahashi A, Iwao Y, et al. Bone marrow necrosis in a patient with acute promyelocytic leukemia during re-induction therapy with arsenic trioxide. Eur J Haematol **72**: 280-284, 2004.
5. Miyoshi I, Daibata M, Ohtsuki Y, Taguchi H. Bone marrow necrosis. Br J Haematol **130**: 467, 2005.
6. Ozkan A, Ozkalemkas F, Ali R, Ozkocaman V, Ozcelik T. Severe bone marrow necrosis without suggestive features. Am J Hematol **81**: 386-387, 2006.
7. Ifran A, Safali M, Kaptan K, Beyan C. Bone marrow necrosis in a patient receiving high dose chemotherapy for ALL. Turk J Haematol **24**: 36, 2007.
8. Otrock ZK, Taher AT, Makarem JA, Kattar MM, Nsouli G, Shamseddine AI. Thrombotic thrombocytopenic purpura and bone marrow necrosis associated with disseminated gastric cancer. Dig Dis Sci **52**: 1589-1591, 2007.
9. Rossi P, Curiel M, Demoux AL, et al. Bone marrow necrosis and sickle cell crisis associated with double heterozygosity for HbS and HbOARAB. Am J Hematol **86**: 309-310, 2011.
10. Osuorji I, Goldman L. G-CSF-associated bone marrow necrosis in AML after induction chemotherapy. Case Rep Hematol **2012**: 314278, 2012.
11. Willekens C, Boyer T. Bone marrow necrosis: a culture medium for bacteria. Blood **122**: 2775, 2013.
12. Daskalakis M, Caballero M. Bone marrow necrosis in de novo AML. Blood **123**: 2137, 2014.
13. Hilal T, Bansal P, Kelemen K, Slack J. Nivolumab-associated bone marrow necrosis. Ann Oncol **29**: 513-514, 2018.
14. Badar T, Shetty A, Bueso-Ramos C, et al. Bone marrow necrosis in acute leukemia: clinical characteristic and outcome. Am J Hematol **90**: 769-773, 2015.
15. Paydas S, Ergin M, Baslamisli F, et al. Bone marrow necrosis: clinicopathologic analysis of 20 cases and review of the literature. Am J Hematol **70**: 300-305, 2002.
16. Tang YM, Jeavons S, Stuckey S, Middleton H, Gill D. MRI features of bone marrow necrosis. AJR Am J Roentgenol **188**: 509-514, 2007.
17. Vogler JB 3rd, Murphy WA. Bone marrow imaging. Radiology **168**: 679-693, 1988.
18. Negendank W, Soulen RL. Magnetic resonance imaging in patients with bone marrow disorders. Leuk Lymphoma **10**: 287-298, 1993.
19. Moritake H, Obara M, Sameshima N, et al. Analysis of the molecular mechanism underlying bone marrow necrosis with acute lymphoblastic leukemia. Int J Hematol **102**: 349-356, 2015.