증례보고
Lab Med Online
Vol. 8, No. 4: 171-176, October 2018
https://doi.org/10.3343/lmo.2018.8.4.171

진단혈액학 LMO

골수괴사로 발현된 필라델피아 염색체 양성 B급성림프모구백혈병 환자의 사례

A Case of Bone Marrow Necrosis in B-Acute Lymphoblastic Leukemia with Philadelphia Chromosome at Presentation

정인화[1] · 안규대[1] · 임현호[1] · 우광숙[1] · 김경희[1] · 김정만[1] · 이지현[2] · 한진영[1]
In Hwa Jeong, M.D.[1], Gyu Dae An, M.D.[1], Hyeon Ho Lim, M.D.[1], Kwang Sook Woo, M.D.[1], Kyeong Hee Kim, M.D.[1], Jeong Man Kim, M.D.[1], Ji Hyun Lee, M.D.[2], Jin Yeong Han, M.D.[1]

동아대학교 의과대학 진단검사의학교실[1], 내과학교실[2]
Department of Laboratory Medicine[1], Division of Hematology-Oncology, Department of Internal Medicine[2], Dong-A University College of Medicine, Busan, Korea.

Bone marrow necrosis (BMN) is a pathologic state which is derived from various disease entities. Most commonly, it is accompanied by hematologic malignancies such as acute leukemia. The patients with marrow necrosis are generally known to have dismal prognoses but variations exist according to early diagnosis. Here we report a case of BMN in an acute lymphoblastic leukemia patient with Philadelphia chromosome at presentation.

Key Words: Bone marrow necrosis, B-ALL, Philadelphia chromosome

INTRODUCTION

Bone marrow necrosis (BMN), which is usually associated with hematologic malignancies and solid tumors, is an infrequent pathologic status. In a ten-year retrospective study, about 90% of BMN were resulted from metastatic tumor or hematolymphoid malignancies [1]. Upon bone marrow aspiration and biopsy observations, destruction of normal bone marrow structure and necrosis of medullary stroma and tissue with preservation of cortical bone are found. Herein we report a case of BMN in acute lymphoblastic leukemia (ALL) with Philadelphia (Ph) chromosome, especially at initial presentation, which is believed to be the first case in Korea, to the best of our knowledge.

Corresponding author: Jin Yeong Han
Department of Laboratory Medicine, Dong-A University College of Medicine, 26 Daesingongwon-ro, Seo-gu, Busan 49201, Korea
Tel: +82-51-240-5323, Fax: +82-51-255-9366, E-mail: jyhan@dau.ac.kr

Received: December 8, 2017
Revision received: March 27, 2018
Accepted: April 4, 2018

This article is available from http://www.labmedonline.org

CASE

A 58-year-old man was admitted to our hospital with fever (37.7˚C), lower back pain, noted thrombocytopenia (43,000/μL), and increased percentage of atypical lymphocytes (40%) on peripheral blood smears examined at a local hospital. He had a history of pituitary tumor undergone removal, diabetes mellitus, and hypertension. His initial complete blood count revealed pancytopenia (hemoglobin 11.6 g/dL, white blood cell 3,220/uL, platelet 43,000/uL) and relative lymphocytosis (34% neutrophils, 55% lymphocytes, 3% monocytes, 3% eosinophils) and slight shift to the left of maturation pattern (2% metamyelocytes, 3% myelocytes). Other laboratory findings were: blood urea nitrogen (BUN) 29 mg/dL, creatinine 1.31 mg/dL, alkaline phosphatase 235 U/L, lactate dehydrogenase 2,288 U/L, and CRP 17.64 mg/dL.

After admission, he suffered from pleuritic pain and consequent chest computed tomography showed pleural effusion, atelectasis, and multiple lymph node enlargements on left supraclavicular

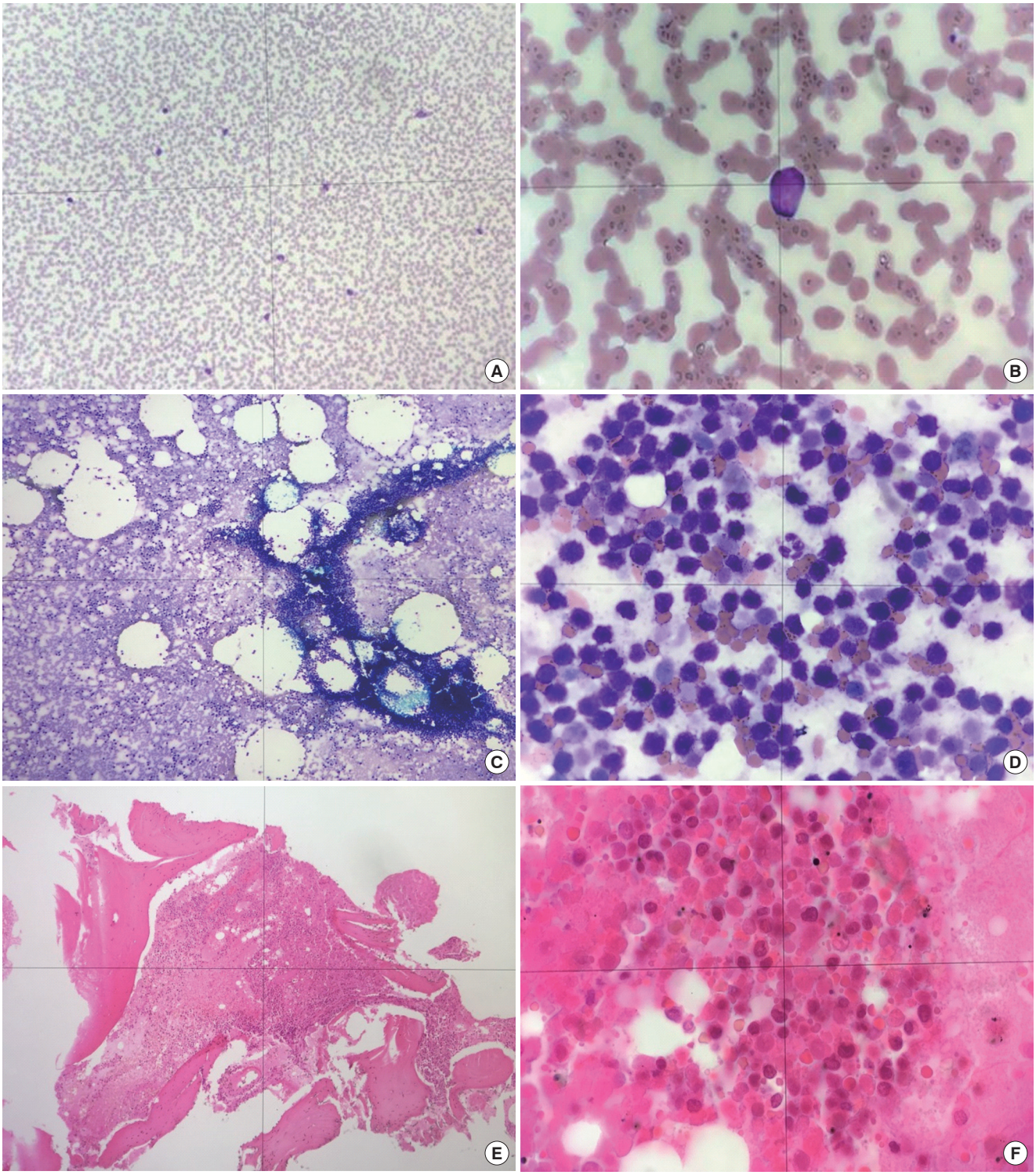

Fig. 1. Peripheral blood smear showing atypical lymphocytes and a few blast cells (Wright-Giemsa stain, ×200, ×1,000) (A, B). Bone marrow aspirate smear showing hypercellular marrow and coagulative necrosis (Wright-Giemsa stain, ×200) and magnified view of mostly ghost cells and one hematopoietic granulocyte (Wright-Giemsa stain, ×1,000) (C, D). Bone marrow biopsy showing almost no normal hematopoietic elements and only a few fat cells (Hematoxin and eosin stain, ×200) and magnified view of mostly amorphous, eosinophilic substance on bone marrow biopsy (Hematoxylin and eosin stain, ×1,000) (E, F).

https://doi.org/10.3343/lmo.2018.8.4.171

and both paratracheal areas. First clinical impression was costochondritis due to viral infection. However, virology workups including Rickettsia typhus, Orienta Tsutsugamushi antibody, Leptospira antibody, cytomegalovirus, Ebstein-Barr virus, and mycoplasma did not show any meaningful results. Further evaluation of autoimmune markers such as C3, C4, CH50, anti-RNP, anti-SSA (Ro), anti-SSB (La), anti-Sm, and anti-ds DNA IgG neither showed specific findings.

Serial peripheral blood smears conducted on the fifth day of his admission showed a few blast cells (7%) and atypical lymphocytes (Fig. 1A, B). Following bone marrow aspiration done on posterior superior iliac spine showed mostly necrotic blast-like cells against serous and amorphous background, accounting for almost all of the cellular components (Fig. 1C, D). The biopsy contained few parts of normal bone marrow fat spaces and some lymphoblast cells, but most of the components were unidentifiable and mostly

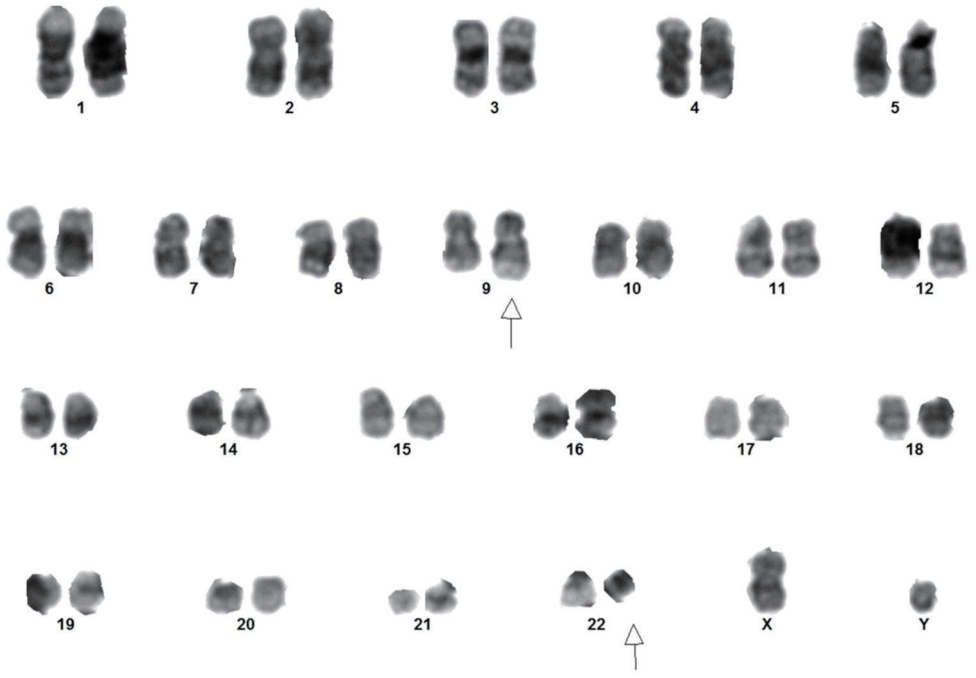

Fig. 2. Conventional karyotyping shows a 46,XY,t(9;22)(q34.1;q11.2)[13]/46,XY[7] (Giemsa-Leishman-Trypsin banding).

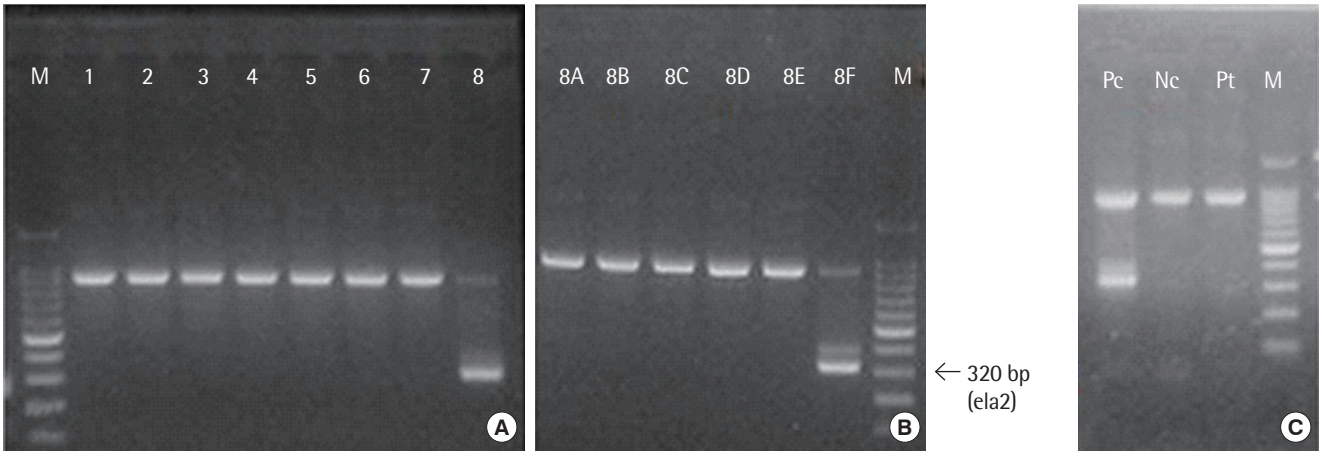

Fig. 3. (A) Reverse transcription polymerase chain reaction (RT-PCR) results showing band on eighth lane. (B) Split-out image showing bright band on 8F lane, corresponding to *BCL-ABL1* e1a2 fusion transcript (320 base pairs). (C) Follow-up RT-PCR showing no band on third lane.
Abbreviations: M, nucleic acid marker ladder; Pc, positive control; Nc, negative control; Pt, patient.

eosinophilic (Fig. 1E, F). Abdominal ultrasound showed splenomegaly.

Blast counts on serial peripheral blood smears increased to 29% and as he was suspected of having acute leukemia, additional laboratory tests were conducted. Flow cytometric analysis on peripheral blood showed that the cells were positive for CD10 (90.72%), CD19 (91.91%), CD20 (83.19%), cytoplasmic CD79a (70.31%), terminal deoxynucleotidyl transferase (62.61%), HLA-DR (93.87%), CD34 (91.40%), CD71 (48.05%) and negative for T-cell markers. The chromosome analysis showed 46,XY,t(9;22)(q34.1;q11.2)[13]/46,XY[7] (Fig. 2). Reverse transcription polymerase chain reaction (RT-PCR) analysis on peripheral blood showed *BCR-ABL1* (e1a2) fusion transcripts (Fig. 3). Fluorescence in situ hybridization (FISH) showed *BCR-ABL1* rearrangements, too (66.9%) (Fig. 4).

He was diagnosed as B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2), therefore Hyper-CVAD regimen (cyclophosphamide, vincrinstine, adriamycin, dexamethasone) and prophylactic intrathecal chemotherapy (methotrexate, Ara-C) were done for 14 days. He was also treated with tyrosine kinase inhibitors (Gleevec and Sprycel) and antibiotics (vancomycin).

After one month of treatment, bone marrow study, RT-PCR, FISH, and chromosome study were repeated for follow-up. RT-PCR, FISH, and chromosome study showed normal results but bone marrow aspiration and biopsy still showed diffuse coagulative necrosis with near total absence of viable hematopoietic cells but preserved bony trabeculae. During continued chemotherapy treatment, he expired on the 38th day of admission due to uncontrolled infection.

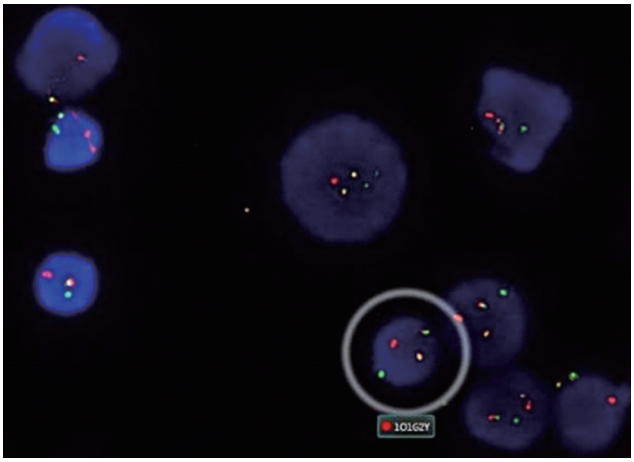

Fig. 4. Fluorescent in situ Hybridization study showing dual-color and dual-fusion translocation probes for *ABL1* (red) and *BCR* (green). The circled cell shows one red signal, one green signal, and two yellow signals, respectively.

DISCUSSION

There have been numerous reports of BMN subsequent to various etiologies. However, there are only a few cases of BMN associated B-ALL bearing Philadelphia chromosome, particularly at diagnosis. Especially in Korea, we believe this is the first case. B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2) is a neoplasm of lymphoblasts committed to the B-cell lineage in which the blasts harbor a translocation between *BCR* gene on chromosome 22 and the *ABL1* oncogene on chromosome 9 [2].

Six cases of B-ALL with *BCR-ABL1* presenting as BMN have been reported worldwide as shown in Table 1. In a 10-year-retrospective research conducted in the United States, there were 2 patients who had a Philadelphia chromosome [3]. In Hong Kong, there was a 73-year-old man with chronic obstructive lung disease who presented with BMN which later was diagnosed with ALL harboring *BCR-ABL1* mutation [4]. A 23-year-old woman in France was diagnosed with ALL showing t(9;22) with this specific mutation [5] and also there has been a published case report in China [6]. Lastly, there was a similar report in Japan as in our case whose BMN persisted after chemotherapy and use of tyrosine kinase inhibitors [7].

Bone marrow necrosis was first described by Wade and Steven-

Table 1. Literature of Philadelphia chromosome positive acute lymphoblastic leukemia presented with bone marrow necrosis

Case No.	Year	N	Sex/Age	Karyotype	References
1	1994	1	M/73	47,XY,+X,der(9)del(9)(p21)t(9;22)(q34;q11),der(22)t(9;22)(q34;q11)[6]/47,idem,del(13)(q22)[2]/46,XY[2]	[4]
2	2005	1	M/73	46,XY, t(9;22)(q34;q11)	[7]
3	2006	1	F/42	46,XX[20]	[6]
4	2009	1	F/23	46,XX,t(9;22)(q34;q11)	[5]
5	2015	2		Unspecified	[3]
6	2017	1	M/58	46,XY,t(9;22)(q34.1;q11.2)[13]/46,XY[7]	Current case

https://doi.org/10.3343/lmo.2018.8.4.171

son in 1941 in a sickle cell disease patient [8]. Since then, etiologies of BMN were investigated and prognoses have been analyzed. According to Argon et al. [9], malignancies account for 91% of BMN wherein 60% are hematological and 31% solid tumors. Among hematologic malignancies, B-lymphoblastic leukemia/lymphoma accounts for the most common etiology [10]. Others include acute myeloid leukemia, Hodgkin's lymphoma, thrombotic thrombocytopenic purpura, and mantle cell lymphoma. The non-malignant causes include mainly severe infections, sickle cell diseases, drugs, antiphospholipid syndrome and bone marrow transplant [1].

BMN itself is believed to have a dismal prognosis to patient survival. BMN in acute myeloid leukemia is associated with poorer outcome with significantly inferior overall survival and event-free-survival. Similarly, ALL patients with marrow necrosis had significantly inferior complete remission rate compared to those without BMN [3]. The patient from our case survived for only about a month even though the diagnosis was made no later than a week and chemotherapy was initiated 10 days after admission. According to Maisel et al. [11], BMN is classified into minor (grade I) involving <20% of bone marrow, intermediate (grade II) involving 20–50% of the bone marrow and severe (grade III) >50% of the bone marrow. Our patient had marrow necrosis of grade III both on the initial and follow-up studies.

Although the pathogenesis of bone marrow necrosis is not clear, the common hypothesis involves elevated tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) which lead to bone marrow endothelial cell injury with subsequent microvascular occlusion. Other than microvascular infarction, several other factors such as granulocyte activation, excessive oxygen consumption by rapidly proliferating tumor cells, and thrombosis have been also suggested for pathogenesis of BMN [12]. In the present case, BMN was still observed even after peripheral blast cells were decreased and chemotherapy with tyrosine kinase inhibitors were used. This might suggest that BMN was not caused by the proliferative effect of leukemic cells but rather by mechanical obstruction.

We report here a patient presenting with fever, bone pain, anemia, thrombocytopenia, and lymphocytosis, in which the symptoms are relatively similar to other cases of acute leukemia with BMN. However, laboratory workups found that he had *BCR-ABL1* gene rearrangement, which is a rare finding in B-ALL patient with BMN.

요 약

골수괴사는 여러 질환으로부터 수반될 수 있는 병적인 상태를 말하며 급성 백혈병과 같은 혈액학적 질환에서 가장 흔하게 동반될 수 있다. 골수괴사가 발생한 환자들의 예후는 대체로 나쁜 것으로 알려져 있지만 진단 시기에 따라 생존기간이 달라질 수 있다. 골수괴사로 발현된 필라델피아 염색체 양성 급성림프모구백혈병 환자 1예를 보고하고자 한다.

REFERENCES

1. Wool GD and Deucher A. Bone marrow necrosis: ten-year retrospective review of bone marrow biopsy specimens. Am J Clin Pathol 2015;143:201-13.
2. Swerdlow SH, Campo E, et al. eds. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: IARC Press, 2017:203-4.
3. Badar T, Shetty A, Bueso-Ramos C, Cortes J, Konopleva M, Borthakur G, et al. Bone marrow necrosis in acute leukemia: clinical characteristic and outcome. Am J Hematol 2015;90:769-73.
4. Kwong YL, Pollock A, Wei D, Lie AK. Philadelphia chromosome positive acute lymphoblastic leukemia masquerading as persistent asymptomatic bone marrow necrosis. Pathology 1994;26:183–5.
5. Petrella T, Bailly F, Mugneret F, Caillot D, Chavanet P, Guy H, et al. Bone marrow necrosis and human parvovirus associated infection preceding an Phl+ acute lymphoblastic leukemia. Leuk Lymphoma 1992;8:415-9.
6. Lin RF, Li JY, Lu H, Wu YJ, Qiu HR, Xiao B, et. al. Bone marrow necrosis as an initial manifestation of Philadelphia chromosome and myeloid antigens positive B acute lymphoblastic leukemia--a case report. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2006;14:832-4.
7. Matsue K, Takeuchi M, Koseki M, Uryu H. Bone marrow necrosis associated with the use of imatinib mesylate in a patient with Philadelphia chromosome-positive acute lymphoblastic leukemia. Ann Hematol 2006;85:542-4.
8. Wade LJ and Stevenson LD. Necrosis of bone marrow with fat embolism in sickle cell anemia. Am J Path 1941;17:47-54.
9. Argon D, Çetiner M, Adıgüzel C, Kaygusuz, I, Tuğlular TF, Tecimer, T, et al. Bone marrow necrosis in a patient with non-Hodgkin lymphoma. Turk J Haematol 2004;21:97-100
10. Foucar K, Reichard K, Czuchlewski D. Bone marrow pathology. 3rd ed. Chicago: American Society for Clinical Pathology, 2010:657-9.

11. Maisel D, Lim JY, Pollock WJ, Yatani R, Liu PI. Bone marrow necrosis: an entity often overlooked. Ann Clin Lab Sci 1988;18:109-15.
12. Elgamal BM, Rashed RA, Raslan HN. Prevalence of bone marrow necrosis in Egyptian cancer patients referring to the National Cancer Institute. J Egypt Natl Canc Inst 2011;23:95-9.

https://doi.org/10.3343/lmo.2018.8.4.171