

Massive bone marrow necrosis associated with Waldenström's macroglobulinemia

Abstract

Here, we report a rare case of massive bone marrow necrosis, which – from the clinical findings and images – mimics disseminated bone metastasis. The patient was suffering from severe bone pain with elevated levels of serum alkaline phosphatase (ALP) and lactate dehydrogenase (LDH); moreover, strong incorporation of ¹⁸F-fluorodeoxyglucose in multiple bones was observed by positron emission tomography/computed tomography.

The underlying disease was Waldenström's macroglobulinemia, which was thought to transform to cluster of differentiation 5 (CD5)-positive diffuse large B-cell lymphoma (DLBCL). The case showed a highly aggressive course, although the original Waldenström's macroglobulinemia was in the stable state.

Clinicians should be aware of the co-occurrence of non-immunoglobulin-producing immature lymphoma, even with good course of Waldenström's macroglobulinemia, and should pay attention to accompanying massive bone marrow necrosis, which mimics multiple cancer metastases to the bone. To the best of our knowledge, the present case is the first report of CD5-positive DLBCL transformed from CD5-negative Waldenström's macroglobulinemia.

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Introduction

Bone marrow (BM) necrosis is a rare clinicopathological entity. The most common underlying diseases are leukemia and lymphoma, particularly high-grade lymphoma [1, 2].

Waldenström's macroglobulinemia (WM) is defined as BM infiltration primarily by lymphoplasmacytic lymphoma (LPL) along with immunoglobulin M (IgM) monoclonal gammopathy. LPL is a B-cell neoplasm composed of small lymphocytes, plasmacytoid lymphocytes, and plasma cells, involving the BM, lymph nodes (LNs), and the spleen, which does not fulfill the criteria for any other B-cell neoplasm with plasmacytic differentiation, defined by the World Health Organization (WHO) in 2008.

WM is an indolent mature B-cell neoplasm, and the survival outcomes of the patients have improved. However, it may occasionally transform to histologically more aggressive lymphoma, such as diffuse large B-cell lymphoma (DLBCL). Transformation to DLBCL is associated with poor prognosis [3–6].

Here, we report a rare case of WM accompanied by massive BM necrosis. The original WM seemed to be in a stable state without increase of serum IgM levels, change in splenomegaly status, or LN swellings.

Case presentation

A mid-60s patient was admitted to the hospital due to lumbago and severe pain of the extremities. The patient had been diagnosed with WM 9 years ago, when the laboratory findings had revealed relatively normal levels of markers, including alkaline phosphatase (ALP), lactate

dehydrogenase (LDH), and C-reactive protein (CRP), except for reduced hemoglobin level (4.6 g/dL) and platelet count ($53 \times 10^9/L$), as well as elevated levels of soluble interleukin (IL)-2 receptor (sIL-2R) (5720 U/mL). IgM- λ M protein was detected, with elevated IgM (6130 mg/dL) and relatively normal IgG and IgA levels (803 mg/dL and 136 mg/dL, respectively). BM examination revealed hypercellular marrow (nuclear cell count was $24.0 \times 10^4/mm^3$) with $0/mm^3$ megakaryocytes. Lymphoid cells were increased (80.8%) and were diffusely infiltrated into residual normal BM cells. The cells were small-to-medium-sized ones, with a high nucleus-to-cytoplasm (N/C) ratio and round-to-oval-shaped nuclei. An immunohistochemical study and flow cytometric (FCM) analysis demonstrated that the tumor cells were positive for cluster of differentiation (CD)19, CD20, CD79a, CD38, CD138, IgM, and λ , as well as being negative for CD3, CD4, CD5, CD8, CD10, CD23, cyclinD1, and k. Some cells had Dutcher bodies, and mast cells were increased. Chromosomal analysis demonstrated a normal karyotype.

Upon administration of steroids and three lines of chemotherapy with two to six courses of fludarabine, WM remained in a stable state for a long period of time (Fig. 1). Administration of prednisolone (PSL) (45 mg/day orally, then tapered) ameliorated the patient's symptoms and anemia for an extended duration. However, 32 months and 72 months later, anemia and elevation of IgM-M protein were exacerbated. The patient received two (FLU-1 in Figure 1) and six (FLU-2 in Figure 1) courses of chemotherapy with fludarabine (40 mg/day orally for 5 days), resulting in amelioration of hemoglobin (7.2 g/dL to 9.7 g/dL, 7.2 g/dL to 10.4 g/dL, respectively), platelet count ($79 \times 10^9/L$ to $99 \times 10^9/L$, $61 \times 10^9/L$ to $76 \times 10^9/L$, respectively), sIL-2R (4896 U/mL to 4408 U/mL, 6129 U/mL to 5158 U/mL, respectively), and IgM (6960 mg/dL to 5200 mg/dL, 9230 mg/dL to 4055 mg/dL,

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respectively). Moreover, 99 months later (22 months after the patient's second period of treatment with fludarabine [FLU-2 in Figure 1]), anemia and elevation of IgM-M protein had gradually worsened. The patient received readministration of five courses of fludarabine (FLU-3 in Figure 1), which reduced the serum IgM levels (5120 mg/dL to 2298 mg/dL); however, anemia remained progressive (8.0 g/dL to 6.1 g/dL).

At the present admission, laboratory findings revealed a normal white blood cell (WBC) count of $4.66 \times 10^9/L$ without abnormal cells, reduced hemoglobin (6.0 g/dL), and platelet count of $20 \times 10^9/L$. Serum chemistry revealed elevated levels of ALP (713 U/L), LDH (1698 U/L), and CRP (14.9 mg/dL). Although IgM level was stable (2178 mg/dL), sIL-2R was elevated (25800 U/mL).

^{18}F -Fluorodeoxyglucose positron emission tomography (PET)/computed tomography (CT) findings revealed very strong accumulation in multiple bones, without prominent swelling of LNs. Spleen was enlarged; however, only a fine incorporation of ^{18}F -fluorodeoxyglucose was observed, and the size was not increased throughout the course (Fig. 2 A and B). As the patient was suffering from severe bone pain with elevated levels of serum ALP and LDH and because strong incorporation of ^{18}F -fluorodeoxyglucose in multiple bones was observed on PET/CT, multiple cancer metastases to the bones was suggested.

BM biopsy demonstrated extensive necrosis (Fig. 3 A and B). In addition to the necrotic tissue, small-to-medium-sized WM cells and large lymphoid cells with high N/C ratio were also observed (Figure 3 C and D). Normal BM cells were rarely observed. Immunohistochemical study demonstrated that both the small-to-medium-sized cells

and the larger cells were CD20+ (Fig. 3 E). Some larger cells were also CD5+ (Fig. 3 F). In situ hybridization test for Epstein-Barr virus-encoded RNA was negative.

FCM analysis showed that the smaller cells were positive for CD19, CD20, IgD, and λ ; partially positive for CD27, CD38, CD43, CD138, and IgM; and negative for CD2, CD3, CD4, CD5, CD8, CD10, CD11c, CD16, CD23, CD25, CD30, CD34, CD56, and κ (Fig. 3 G). On the other hand, the large cells were positive for CD5, CD19, CD20, and λ and were negative for CD43, CD138, IgD, and IgM (Fig. 3 H). Southern blot analysis for the Ig heavy chain (*IgH*) gene revealed rearranged bands, suggesting clonal proliferation. Chromosomal analysis revealed complex abnormality: 47,XY, add(1)(q32), add(2)(p11.2), add(3)(q21), der(3)add(3)(p13)add(3)(q27), del(7)(q22), der(8)add(8)(p11.2)add(8)(q24), add(12)(q13), add(14)(q32), -15, +del(16)(q?), +mar1 in 19/20 cells.

The patient was diagnosed as having CD5-positive DLBCL, which was transformed from CD5-negative WM, and received chemotherapy (48 mg of pirarubicin, 1.6 mg of vincristine sulfate, 800 mg of cyclophosphamide, and 45 mg of PSL for 5 days), which was followed by only transient resolution of the patient's symptoms. The patient died due to the progression of DLBCL 7 weeks after the present admission, 110 months after the first visit to the hospital.

Discussion

WM is usually an indolent and slowly progressive disease, and the overall survival of patients has improved over the past decade [4]. WM may transform to DLBCL rarely [3–6]. The interval

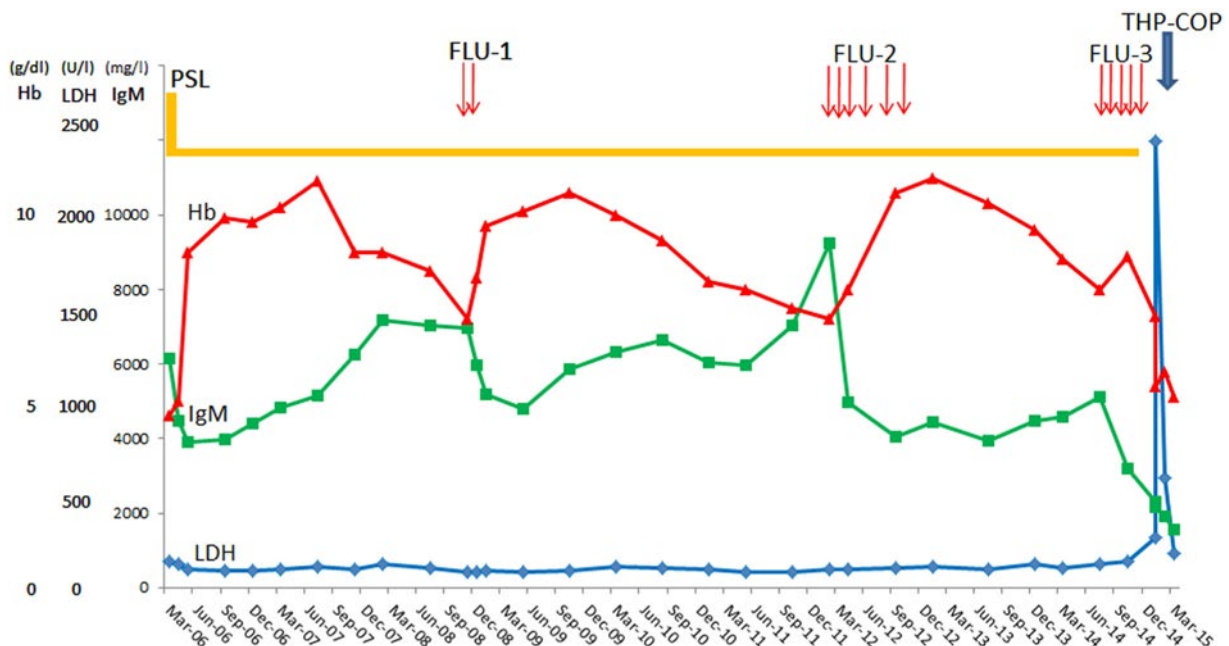


Fig. 1. Clinical course of the patient

Administration of PSL (45 mg/day, then tapered) ameliorated the patient's symptoms and anemia, and the patient remained in a stable state for a long period of time. However, 32 months and 72 months later, anemia and elevation of IgM-M protein were exacerbated. The patient underwent two (FLU-1) and six (FLU-2) courses of chemotherapy with fludarabine (40 mg/day for 5 days), respectively, resulting in amelioration of the symptoms and stabilization. The patient underwent readministration of five courses of fludarabine (FLU-3), which reduced the serum IgM levels; however, anemia remained progressive.

Abbreviations: Hb: hemoglobin, IgM: immunoglobulin M, LDH: lactate dehydrogenase, PSL: prednisolone, FLU: fludarabine, THP-COP: pirarubicin, vincristine sulfate, cyclophosphamide, and PSL

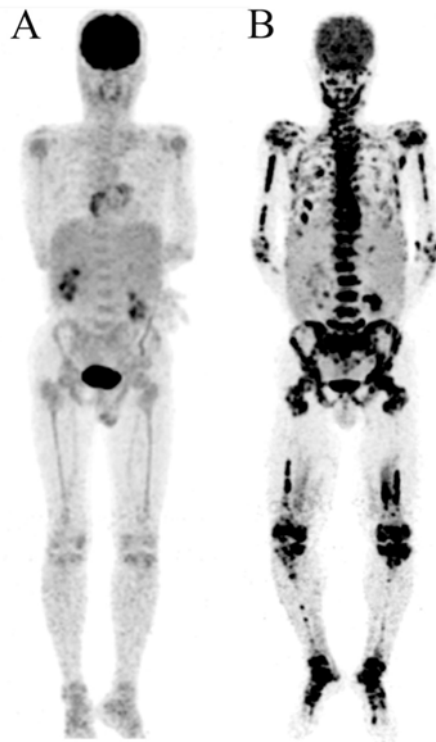


Fig. 2. Images of the patient

(A) FDG PET/CT findings at the patient's first visit to the hospital 9 years ago demonstrated marked splenomegaly without prominent swelling of LNs. No masses or necrosis was observed in the spleen. Only fine FDG accumulation was observed in the enlarged spleen.

(B) FDG-PET/CT findings at the present admission revealed very strong accumulation of FDG in multiple bones. Only fine FDG accumulation was observed in enlarged spleen.

Abbreviations: CT: computed tomography, FDG: 18F-fluorodeoxyglucose, LN: lymph node, PET: positron emission tomography

from the diagnosis of WM to transformation to DLBCL is reported to be 10-128 months [3, 4, 6]. Most patients have generalized lymphadenopathy and hepatosplenomegaly with B symptoms at the onset of DLBCL. The interval between the occurrence of WM and DLBCL in the present case was approximately 107 months. The patient's symptoms, images, and laboratory findings at the onset of DLBCL, such as severe bone pain, elevated levels of serum ALP and LDH, and strong incorporation of ^{18}F -fluorodeoxyglucose in multiple bones, resembled bone metastasis. Increase in size of the spleen or prominently enlarged LNs were not observed.

There are two types of DLBCL transformed from WM: one is clonally identical to the original WM, and the other is different from the co-occurring WM [5]. In the BM of the present patient, clusters of DLBCL were observed within the nodular proliferation of WM cells, and these were not independently proliferating, suggesting that the DLBCL had been transformed from WM. Whether the DLBCL and WM were clonally identical could not be established, due to the inability to analyze the third complementarity determining region (CDR3) sequence in the *IgH* gene. However, FCM analysis showed that both the smaller and the larger cells were positive for λ , and Southern blot analysis for the *IgH* gene revealed rearranged bands, suggesting clonal proliferation.

WM cases express IgM and pan-B markers, such as CD19 and CD20, and are usually negative for CD5, CD10, and CD23 [7]. In the present case, WM cells had been negative for CD5; however, DLBCL cells later demonstrated CD5 positivity. It is well known that CD5-positive

DLBCL cases show poorer prognosis than CD5-negative DLBCL cases [8]. Transformation of CD5-negative low-grade lymphoma to CD5-positive DLBCL is very rare. Particularly, to the best of our knowledge, this is the first report of CD5-positive DLBCL transformed from CD5-negative WM. The transformed DLBCL cells were negative for CD43, CD138, IgD, and IgM, with the original WM cells being positive for the same, and showed complex chromosomal abnormality, suggesting an immature aggressive type.

In the present case, first and second chemotherapy with fludarabine ameliorated both the patient's anemia and M-proteinemia. On the other hand, although the third administration of fludarabine was able to reduce the serum IgM levels, anemia was progressive, suggesting that the BM was gradually being occupied by non-Ig-producing immature lymphoma cells during the third administration of fludarabine. Several months later, highly progressive development of DLBCL was readily apparent, accompanied by BM necrosis.

In our patient, transformation to DLBCL occurred shortly after the third administration of fludarabine. Immune suppression by purine analogues may lead to aggressive transformation because of defects in tumor surveillance [9]. The potential relationship between transformation to high-grade lymphoma and treatment with purine analogues has been controversial [10, 11]. Moreover, histological transformation could occur not only in patients who received chemotherapy with alkylating agents and/or purine analogues but also in treatment-naïve patients [4].

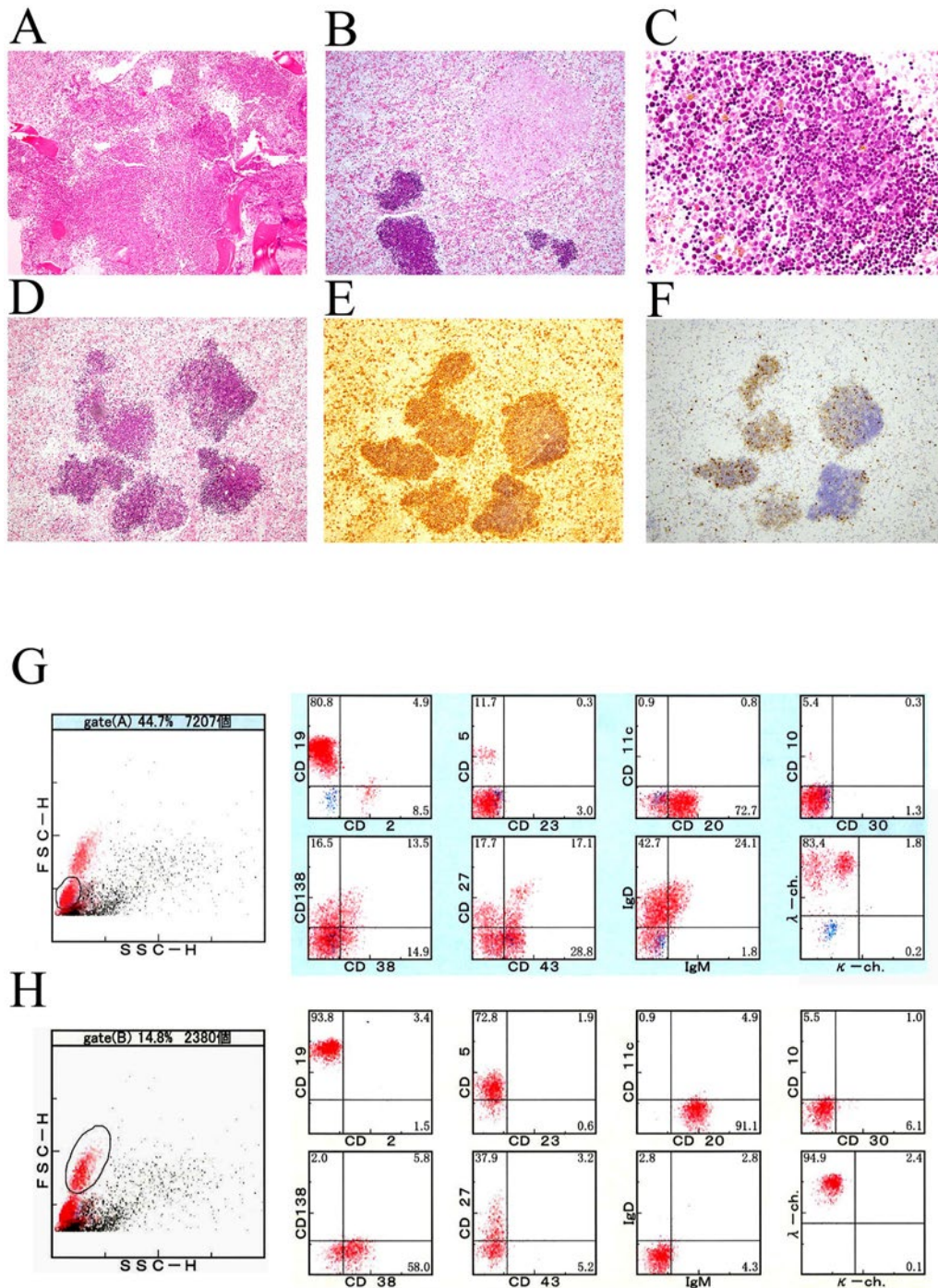


Fig. 3. Histological, immunohistochemical, and flow cytometric analysis of the BM. (A-F) Histological and immunohistochemical findings of the BM

(A, B, D) In a low-power field of BM biopsy (A) and clot section (B, D), massive amorphous granular material with degenerated cells was observed. BM was hypercellular and occupied by small-to-large-sized lymphoid cells. Normal BM components were rarely observed (HE: $\times 10$).

(C) In a high-power field, in addition to the small-to-medium-sized cells, many larger cells with high N/C ratio also demonstrated proliferation. Some small-to-medium-sized cells had Dutcher bodies. Hemophagocytosis was also observed (HE: $\times 40$).

(E) Both small-to-medium-sized cells and larger cells were CD20+ ($\times 10$). (F) Some larger cells were also CD5+ ($\times 10$).

(G, H) Flow cytometric analysis of BM cells.

(G) The smaller cells were CD19+, CD20+, IgD+, and λ positive. Cells were partially positive for IgM, CD43, CD38, and CD138 but negative for CD5 and CD10.

(H) The larger cells were positive for CD19, CD20, CD5, and λ and were partially positive for CD38. These cells were negative for IgD, IgM, CD10, CD43, and CD138.

Abbreviations: BM: bone marrow, CD: cluster of differentiation, HE: hematoxylin-eosin, Ig: immunoglobulin, N/C ratio: nucleus-to-cytoplasm ratio

On the other hand, some antineoplastic drugs such as fludarabine may cause BM necrosis [12]. However, in the present case, extremely elevated sIL-2R level was observed when the patient suffered from BM necrosis, suggested that the rapidly progressive DLBCL was the underlying cause of BM necrosis.

WM is incurable with currently available chemotherapy, and there is no standard therapy. Alkylating agents and purine analogues are the most commonly used agents. Our case was an indolent outpatient and preferred oral administration of fludarabine [11, 13]. Recently, however, combination chemotherapy regimens containing rituximab are recommended for first-line therapy [14]. Moreover, the most common therapy used to treat DLBCL transformed from WM is the combination consisting of rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine (Oncovin), and prednisone (R-CHOP) [4]. Unfortunately, in our patient, rituximab could not be administered due to the need to avoid tumor lysis syndrome because of the patient's extremely high tumor burden. The patient died due to the progression of DLBCL, which is the most common cause of death in WM patients with histological transformation [4]. In summary, we demonstrated a rare CD5-positive DLBCL transformed from CD5-negative WM. The

DLBCL was highly aggressive and accompanied by BM necrosis. Clinicians should be aware of the co-occurrence of non-Ig-producing aggressive lymphoma, when inexplicable anemia is observed even with good response of low-grade lymphoma to chemotherapy, in addition to paying attention to accompanying massive BM necrosis, which mimics multiple cancer metastases to the bone.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

RT treated the patient; CT gave clinical suggestions; RY contributed to histological discussion; CT and RT contributed to the drafting of the manuscript.

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