

Original Article

Bone Marrow Macrophages in Waldenström's Macroglobulinemia: A Report of Four Cases

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It is well known that some B-cell lymphomas are accompanied by a prominent epithelioid cell response, caused by activated macrophages, such as marginal zone B-cell lymphoma of a mucosa-associated lymphoid tissue. We investigated six bone marrow samples from four cases of Waldenström's macroglobulinemia and report a unique observation that large conjugates of tumor cells around a macrophage were prominent in all cases, particularly in one case, the bone marrow of which contained increased CD163-positive macrophages. Mast cells were increased in all the samples, some of which seemed to be in close contact with tumor cells. We consider that the conjugates represented close interactions of tumor cells, macrophages, and mast cells by cell-to-cell contact. Three of the present cases showed a favorable course. On the other hand, one case suffered from severe anemia and thrombocytopenia due to hemophagocytic syndrome at the second admission and showed a severe clinical course. Clinicians should be aware of the risk of lymphoma-associated hemophagocytic syndrome in this low-grade lymphoma, although many of the patients with hemophagocytic syndrome in Japan have aggressive lymphomas such as diffuse large B-cell lymphoma. [*J Clin Exp Hematop* 54(2): 103-110, 2014]

Keywords: Waldenström's macroglobulinemia, macrophage, mast cell, hemophagocytic syndrome, Oct-2

INTRODUCTION

Waldenström's macroglobulinemia (WM) is defined as bone marrow (BM) infiltration primarily by lymphoplasmacytic lymphoma (LPL) along with IgM monoclonal gammopathy. LPL is a B-cell neoplasm composed of small lymphocytes, plasmacytoid lymphocytes, and plasma cells, involving BM, lymph nodes, and spleen, which does not fulfill the criteria for any other B-cell neoplasm with plasmacytic differentiation, defined in the 2008 WHO classification.¹

WM is an incurable B-cell lymphoproliferative disorder with current therapy, with median survival of approximately 5 years.^{2,3} Because of elevated IgM levels, symptoms associated with immunodeposits or hyperviscosity are observed. Rouleaux formation is frequently seen; however, here, we report a unique observation that large cellular conjugates,

containing tumor cells around a macrophage, are observed in BM smears of patients with WM.

MATERIALS AND METHODS

Case presentation

We identified 4 patients admitted to our hospital with WM during the period between October 2008 and September 2012. One patient with stage I LPL without BM invasion or IgM-M protein was excluded.

Clinical characteristics of the 4 patients are summarized in Table 1. In 2 patients (cases 2 & 3), BM samples were evaluated repetitively at intervals of 9 months (at second admission) and 4 years (for follow-up), respectively.

Two patients showed multiple lymph node swelling, and 1 patient was suffering from severe splenomegaly. Case 4 showed only BM lesion, and case 1 was leukemic. None of them manifested neuropathy or hyperviscosity symptoms. All cases showed moderate-to-severe anemia. However, thrombocytopenia seemed not to be common, except in case 3, probably because of severe splenomegaly. On the other hand, case 2 was associated with severe anemia and thrombocytopenia at the second admission. Serum chemistry revealed almost normal levels, including of aspartate aminotransferase, alanine transaminase, lactic dehydrogenase, and calcium, except for elevated C-reactive protein and soluble IL-2 receptor

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Table 1. Clinical characteristics of the patients

Clinical data	Case 1	Case 2-1st	Case 2-2nd	Case 3-1st	Case 3-2nd	Case 4
Age/sex	75/F	67/F	67/F	61/M	65/M	88/M
WBC ($\times 10^9/L$)	5.25	4.13	3.24	4.82	4.47	5.54
ML cell %	13	0	0	0	0	0
Hb (g/dL)	7.2	6.9	4.8	7.4	9.8	8.7
PLT ($\times 10^9/L$)	266	243	35	79	86	219
LDH (IU/L)	115	124	129	110	103	131
CRP (mg/dL)	5.6	10.8	12.4	4.1	3.3	1.1
Alb (g/dL)	2.9	2.1	1.7	2.5	3.2	2.2
IgG (mg/dL)	1,354	375	< 100	695	628	1,390
IgA (mg/dL)	63	17	7	60	43	124
IgM (mg/dL)	2,573	3,688	3,740	6,643	3,960	2,235
ferritin (ng/mL)	162	364	788	158	131	43
sIL-2R (U/mL)	5,121	nd	12,200	4,842	6,457	4,540
M protein	IgM- κ	IgM- κ	IgM- κ	IgM- λ	IgM- λ	IgM- κ
β_2 -microglobulin (mg/L)	3.8	nd	nd	nd	nd	4.3
DAT	-	nd	-	-	nd	nd
PAIgG	nd	nd	19	nd	nd	nd
BM NCC	13.8	2.4	11.7	12.6	8.5	7.9
BM Meg	33	3	9	3	15	16
ML cells%	32.4	47.7	74.7	75.7	42.5	60.4
Karyotype	46XX	46XX	Abnormal ^a	46XY	46XY	46XY
LN swelling	-	+	+	+	+	-
Splenomegaly	-	-	-	++	++	-
Bone lesion	-	-	-	-	-	-
IPI	L-I	L-I	H-I	L-I	L-I	L-I
Outcome	alive	unknown		alive		alive

^a, 46, XX, del(7)(q ?) [2/20]/46, sl, t(3;9)(p21;q34) [9/20]/46, XX [6/20]

LN, lymph node; IPI, international prognostic index; L-I, low-intermediate; H-I, high-intermediate; ML, malignant lymphoma; LDH, lactic dehydrogenase; CRP, C-reactive protein; sIL-2R, soluble IL-2 receptor; DAT, direct anti-globulin test; PAIgG, platelet-associated IgG; BM, bone marrow; NCC, nuclear cell count; nd, not determined

(sIL-2R). Direct anti-globulin test (DAT) was negative in the examined cases. IgM- κ or - λ M protein was detected with elevated IgM.

RESULTS

Histological and cytological findings of BM

All BM samples showed normocellular to hypercellular marrow in biopsy or clot section. Small to medium-sized lymphoid cells proliferated in BM (Fig. 1a-1d). In the second BM sample of case 2, erythrophagocytosis was observed (Fig. 1e).

On BM smears, nuclear cell count of each sample ranged from 2.4 to $13.8 \times 10^4/mm^3$ with 3 to $33/mm^3$ megakaryocytes. Large conjugates of tumor cells were prominent in all cases (Fig. 3a-3d), particularly in case 1. The cells were small to medium-sized lymphoid cells with a high N/C ratio, which had round to oval nuclei with irregular-shaped cytoplasm, with a nuclear cell count ranging from 32.4 to 75.7%. Some of them had Dutcher bodies (Fig. 3e). In cases 1 and 4, although cells with wider cytoplasm were also observed, suggesting the differentiation to plasma cells, typical myeloma cells were not seen. Mast cells were increased in all the

samples; some of them seemed to be in close contact with tumor cells (Fig. 3c, 3f). Hemophagocytosis of normal blood cells by macrophages in addition to tumor cell conjugates was observed in the second BM sample of case 2 (Fig. 3g-3i).

Immunohistochemical study

An immunohistochemical study demonstrated (Table 2) that, in all samples examined, tumor cells were positive for CD20, CD79a, and BCL2, and negative for CD3, CD4, CD5, CD8, CD10, CD56, and cyclin D1. Although Ig heavy chains or light chains were hardly stained in all the samples, IgM and monoclonal light chain were stained in Dutcher bodies. In cases 1 and 3 and the first sample from case 2, CD27 (Fig. 2d), BOB.1 (Fig. 2e), and Oct-2 (Fig. 2f) were positive, and CD43 was positive, except for in case 3. However, in the second sample from case 2, none of CD27, CD43, BOB.1, and Oct-2 was positive.

Many CD68-positive large cells were observed in all cases, especially in case 1. CD163-positive macrophages increased in all cases, especially in cases 1 and 3 (Fig. 2a, 2b). In the second BM sample of case 2, no increase of CD163-positive macrophages was observed compared with that in the first sample of the case. Mast cells were prominent

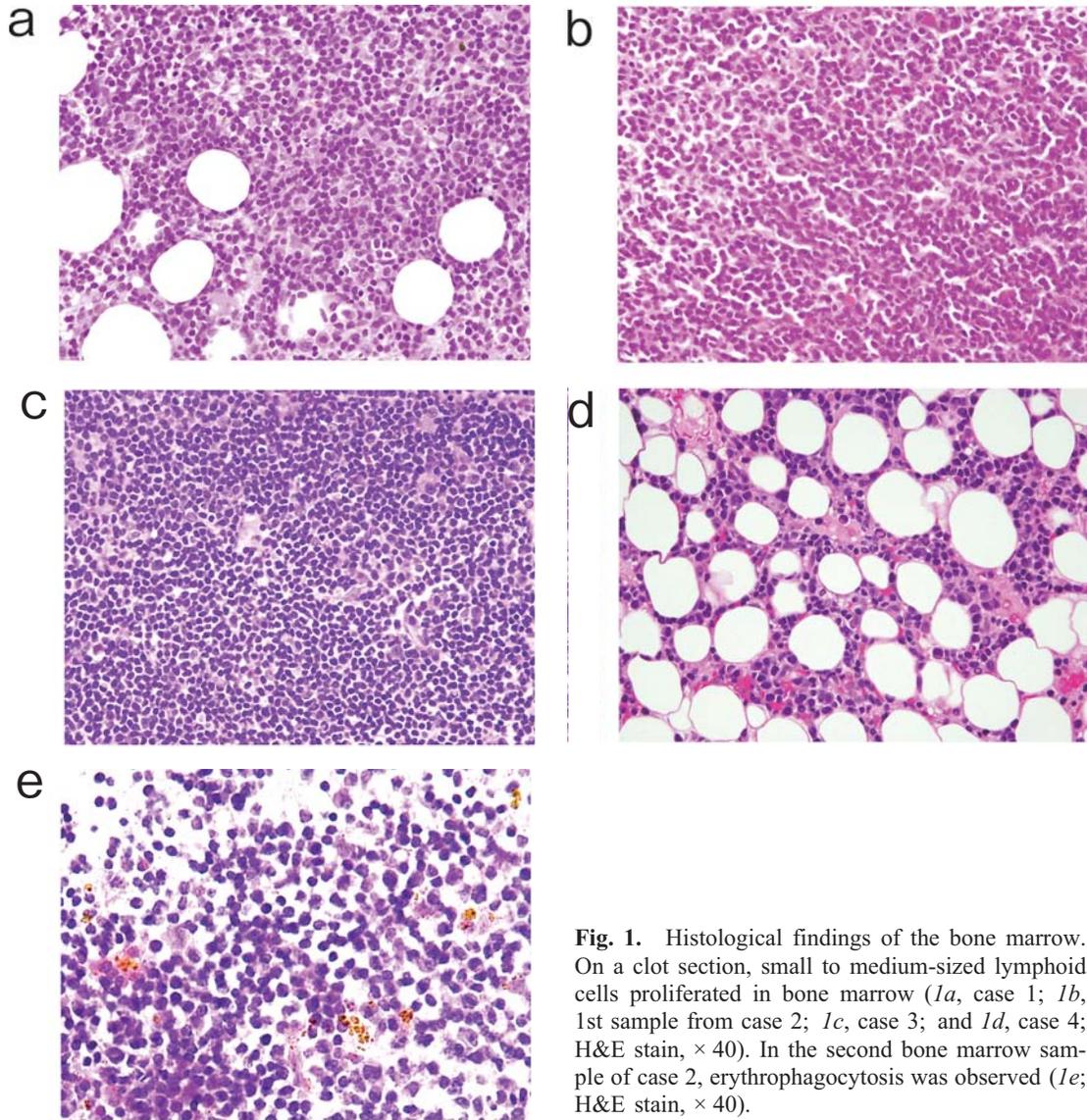


Fig. 1. Histological findings of the bone marrow. On a clot section, small to medium-sized lymphoid cells proliferated in bone marrow (*1a*, case 1; *1b*, 1st sample from case 2; *1c*, case 3; and *1d*, case 4; H&E stain, $\times 40$). In the second bone marrow sample of case 2, erythrophagocytosis was observed (*1e*; H&E stain, $\times 40$).

with positive reactivity for c-kit in all cases (Fig. 2c).

Flow cytometric analysis

On flow cytometric analysis (Table 2, Fig. 2g), tumor cells in all samples examined demonstrated CD3⁻, CD4⁻, CD5⁻, CD7⁻, CD8⁻, CD10⁻, CD11c⁻, CD19⁺, CD20⁺, CD25⁻, CD30⁻, CD34⁻, and CD56⁻. In the examined cases, CD27, CD43, and CD40 were positive. Both CD38 and CD138 were positive to various extents (Fig. 2g, 2h). Surface or cytoplasmic IgM and monoclonal light chain were also positive.

Chromosomal analysis

Chromosomal analysis demonstrated a normal karyotype in 3 patients. Case 2 demonstrated an abnormal karyotype [t(3;9)(p21;q34) in 9 cells, and del(7)(q?) in 11 of 20 cells] in the second BM sample.

DISCUSSION

WM is defined as BM infiltration primarily by LPL along with IgM monoclonal gammopathy.¹ WM/LPL cells have been reported to express monoclonal Ig light chains, CD19, and CD20. The expression of CD11c, CD22, CD25, CD38, CD52, PAX-5, and CD79a has also been reported to various extents. The frequencies of CD5, CD10, and CD23 positivity

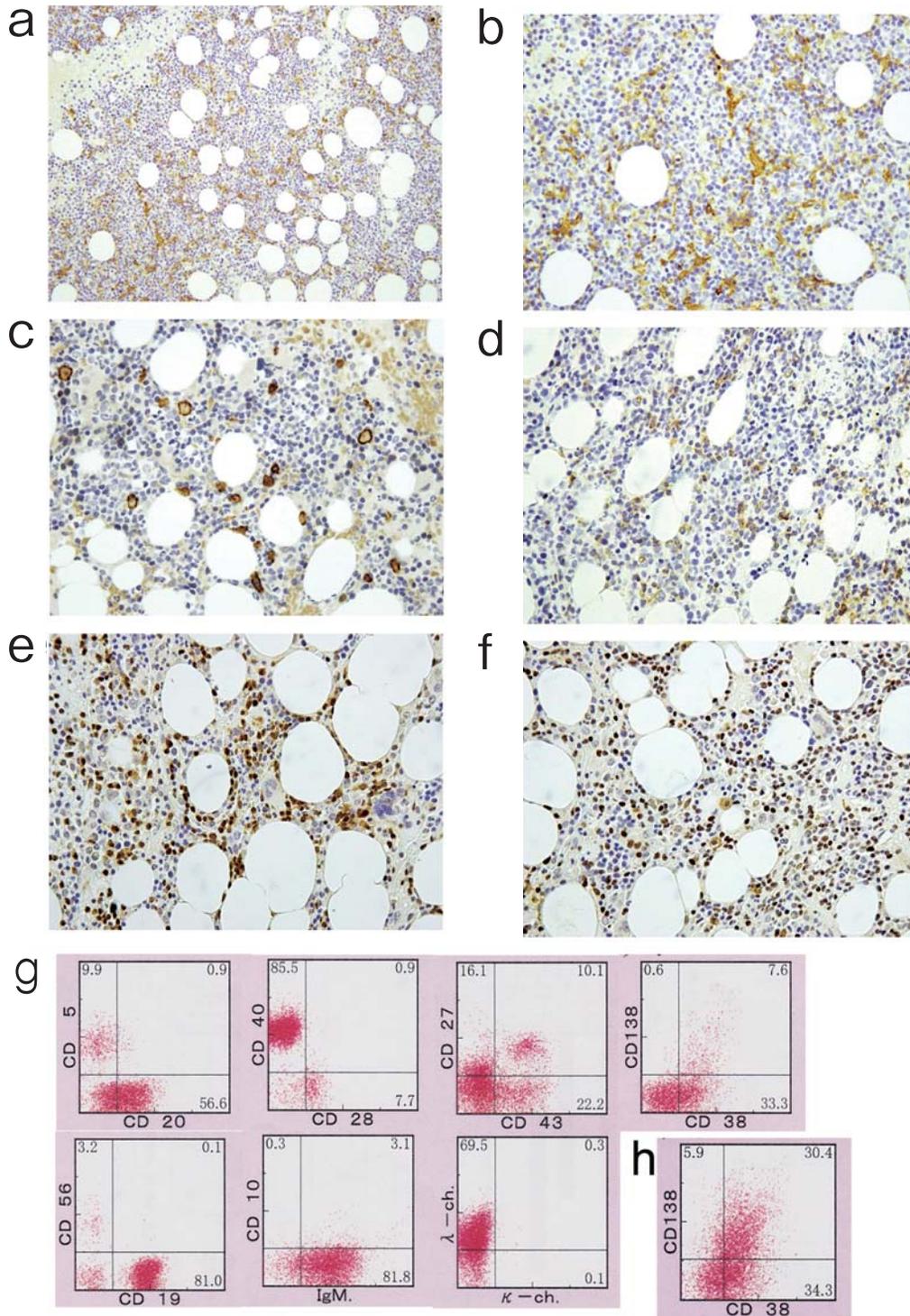


Fig. 2. Immunohistochemical findings and flow cytometric analysis of the bone marrow. CD163⁺ macrophages were increased, especially in case 1 (2a, $\times 20$; 2b, $\times 40$). Mast cells were manifested by c-kit stain (2c, case 1; $\times 40$). The 1st sample from case 2 was CD27⁺ (partially) (2d, $\times 40$), BOB.1⁺ (2e, $\times 40$), and Oct-2⁺ (2f, $\times 40$); however, none of CD27, BOB.1, and Oct-2 was positive in the 2nd sample (*not shown*). Flow cytometric analysis of bone marrow cells (case 3) showed that tumor cells were positive for CD19, CD20, CD40, IgM, and λ , partially positive for CD27, CD43, CD38, and CD138, and negative for CD5, CD10, CD28, CD56, and κ (2g). Tumor cells expressed both CD38 and CD138 more strongly in case 1 (2h).

Table 2. Immunohistological findings (IM) and flow cytometric analysis (FC) of 6 bone marrow samples of 4 patients

Antigen	Case 1		Case 2-1st		Case 2-2nd		Case 3-1st		Case 3-2nd		Case 4	
	FC	IM	FC	IM	FC	IM	FC	IM	FC	IM	FC	IM
CD3	-	-	-	nd	-	-	nd	-	-	-	-	-
CD4	-	nd	-	nd	-	-	nd	-	-	-	-	-
CD5	-	-	-	nd	-	-	-	-	-	-	-	nd
CD7	-	-	-	-	-	-	nd	-	nd	-	nd	-
CD8	-	nd	-	nd	-	-	nd	-	-	-	-	-
CD10	-	-	-	nd	-	nd	-	-	nd	-	-	-
CD19	+	-	+	-	+	-	+	-	+	-	+	-
CD20	+	+	+	nd	+	+	+	+	+	+	+	+
CD23	nd	nd	nd	nd	-	+	-	nd	nd	-	nd	-
CD25	-	-	nd	-	-	-	-	-	-	-	-	-
CD27	nd	+	nd	+/-	nd	-	nd	+	+	nd	+	nd
CD38	+	-	nd	-	nd	-	+	-	+	-	+	-
CD40	nd	+	nd	nd	nd	nd	nd	nd	+	nd	+	nd
CD43	nd	+	nd	+	nd	-	nd	-	+	nd	+	nd
CD56	-	-	-	nd	nd	nd	-	nd	-	nd	-	-
CD138	+	-	nd	-	nd	-	nd	-	+	-	+	-
IgM ^a	+	-	nd	nd	nd	-	nd	-	+	DB +	+	DB +
κ^a	+	+	nd	nd	+	-	-	-	-	-	+	DB +
λ^a	-	-	nd	nd	-	-	+	-	+	DB +	-	-
cyclin D1	-	-	-	nd	-	-	-	nd	-	-	-	-
BCL2	-	+	-	nd	-	nd	-	+	-	+	-	+
BOB.1	-	+	-	+	-	-	-	+/-	-	nd	-	nd
Oct-2	-	+/- ^b	-	+	-	-	-	+	-	nd	-	nd

nd, not determined; DB, Dutcher body; ^a, surface or cytoplasmic expression, ^b, +/- (partially or weakly positive)

vary widely, and CD138 expression is controversial.⁴⁻⁹

In the present cases, tumor cells showed positive reactivities for CD19, CD20, and BCL-2 and negative for CD5, which is frequently positive in chronic lymphocytic leukemia cases. They contained CD38⁺/CD138⁺ cells, suggesting plasma cell differentiation. CD27 expression, which correlates with commitment to the plasma cell lineage,¹⁰ was also observed in all cases. However, tumor cells were negative for CD56, which is positive in many cases of plasma cell myeloma and negative in WM/LPL cells.¹¹⁻¹³ CD27 is a TNF-family member expressed by several types of cell, including memory B cells from which WM cells originate. It has been reported that CD27-CD70 interaction is related to mast cell-WM cell signaling, which provides growth and survival ability to WM cells, and is important in the pathogenesis of WM.¹⁴ They were positive for CD43, except in case 3. Most T-cell malignancies and a group of small lymphocyte B-cell malignancies, chronic lymphocytic leukemia/small cell lymphoma, and mantle cell lymphoma are often positive for CD43; marginal zone lymphoma and LPL are weakly positive, whereas follicle center cell lymphoma is usually negative.^{15,16}

BOB.1 and Oct-2 are B-lymphocyte-specific transcription coactivators with essential roles in immunoglobulin production. In classical Hodgkin's lymphoma, Reed-Sternberg and Hodgkin's cells lack mRNA transcripts and proteins for B-

cell-specific antigens and immunoglobulin because of the downregulation of transcription factors. The inadequate expression of BOB.1 and/or Oct-2 is useful in the differential diagnosis of classical Hodgkin's lymphoma.¹⁷ In non-Hodgkin's lymphoma, some cases with chronic lymphocytic leukemia/small cell lymphoma demonstrate insufficient expressions of BOB.1/Oct-2, although their expressions are observed in the majority of B-cell lymphomas.^{18,19} The expression profiles of BOB.1/Oct-2 have not been reported in WM/LPL. In the present cases, BOB.1 and Oct-2 were positive in examined cases, although each case showed partial or weak reactivity. On the other hand, our patient with stage I LPL without M protein was positive for CD27 and CD43, whereas BOB.1 was weakly positive or negative, and Oct-2 was negative (data not shown), suggesting the important role of BOB.1/Oct-2 in producing immunoglobulin.

In the present study, cell conjugates around a macrophage were prominent in all cases. It is well known that some B-cell lymphomas are accompanied by a prominent epithelioid cell response, caused by activated macrophages, such as marginal zone B-cell lymphoma of a mucosa-associated lymphoid tissue, diffuse large B-cell lymphoma, and follicular lymphoma of germinal center cell origin.^{20,21} However, the observation that macrophages are surrounded by many lymphoma cells has not been reported in each type of B-cell lymphoma.

In our cases, the central macrophage was not phagocytos-

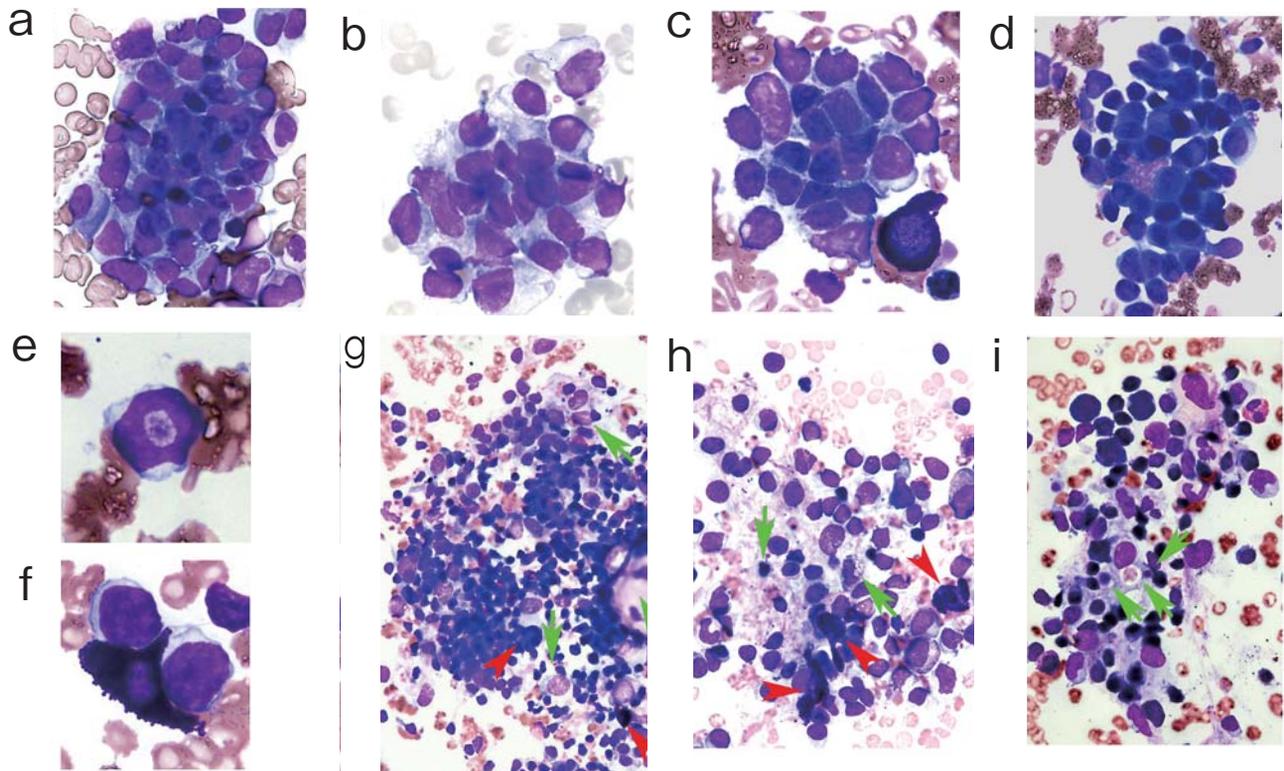


Fig. 3. Cytological findings of bone marrow (BM) smears. In BM smear samples, the cells were small to medium-sized lymphoid cells with high N/C ratio, which had round to oval nuclei with irregular-shaped cytoplasm. Cells with wider cytoplasm were also observed. Large conjugates of tumor cells were prominent in all cases (3a, case 1; 3b, 1st sample of case 2; 3c, case 3; and 3d, case 4; May-Giemsa, × 100). Dutcher bodies were observed in all samples (3e, case 4; × 100). Note the increased mast cells (3c, case 3; and 3f, case 4; × 100). In the second BM sample of case 2, macrophages phagocytosing normal blood cells in addition to tumor cell conjugates were observed (3g-3i). (3g) In the huge cell aggregation containing many macrophages and mast cells (red arrowheads), some phagocytosing macrophages (green arrows) were observed (May-Giemsa, × 20). (3h, 3i) Mast cells (red arrowheads) closely contacted macrophages phagocytosing normal blood cells (green arrow). Erythrophagocytosis was also observed (3i) (May-Giemsa, × 40).

ing normal blood cells because of an absence of fragments of other digested cells, except for in the second BM sample of case 2. In addition, hyperferritinemia, which is reflected by the activation of reticuloendothelial systems and a useful marker of hemophagocytic syndrome (HPS),^{22,23} was not observed. Macrophages in the marginal zone express a scavenger receptor.²⁴ The most prominent cell conjugates were observed in case 1. CD163-positive macrophages^{25,26} were increased, especially in BM of case 1, suggesting the possibility that macrophages were surrounded by tumor cells via CD163 scavenger receptors. Meanwhile, mast cells were increased in all the samples, with some of them seeming to be in close contact with tumor cells. Mast cells support LPL cell growth through CD154/CD40 signaling in WM.²⁷ Macrophages are also activated via CD40/CD154 interaction²⁸ or CD40 ligation on their surface.^{29,30} Close interactions of WM cells, macrophages, and mast cells are supposed in the involved BM.

In contrast, macrophages phagocytosing normal blood

cells in addition to tumor cell conjugates were observed in the second BM sample of case 2. No increase of CD163-positive macrophages was observed compared with the first sample of the case; however, erythrophagocytosis was observed in the BM clot sample. Although BM was occupied by increased tumor cells (74.7%), megakaryocytes were not reduced, suggesting that thrombocytopenia was not due to decreased production. Her severe bicytopenia was combined with continued fever, hyperferritinemia, coagulopathy (prothrombin time-international normalized ratio 1.52, activated partial thromboplastin time 38 seconds, and D-dimer 1.81 µg/mL), highly elevated sIL-2R (12,200 U/mL), and increased macrophages phagocytosing blood cells in BM, which was compatible with HPS.³¹⁻³³ DAT, platelet-associated IgG, and autoantibodies examined were negative, suggesting that autoimmune-associated HPS could be ruled out. Although chromosome del(7)(q?) was observed in 11 of 20 cells, dysplasia was not seen in three lineages in BM cells, suggesting that HPS associated with myelodysplastic syndrome was also

ruled out. Case 2 demonstrated highly elevated sIL-2R compared with ferritin when the second BM aspiration was examined, compatible with lymphoma-associated HPS (LAHS).³⁴ None of our patients demonstrated chromosomal abnormality such as del(6q).^{1,4} Case 2, however, showed an abnormal karyotype: t(3;9)(p21;q34) in 9 of 20 cells, when she was complicated by HPS, suggesting the possibility of aggressive transformation. In addition, disappearance of the expression of CD27, CD43, BOB.1, and Oct-2 was observed, suggesting the conversion to B-cell lymphoma of early maturation.³⁵

In Japan, many of the patients with LAHS were cases with aggressive lymphomas such as diffuse large B-cell lymphoma.^{34,36,37} LAHS is rarely observed in low-grade lymphoma. Three of the present cases (cases 1, 3, & 4) showed a favorable course. On the other hand, case 2 had poor outcome because of HPS. Clinicians should be aware of the risk of LAHS in this low-grade lymphoma.

In summary, we demonstrated a unique observation of cell conjugates containing a gathering of tumor cells around a macrophage in BM from patients with WM. Although the precise mechanism is unknown, we consider that the conjugates represent a close interaction of WM cells, macrophages, and mast cells by cell-to-cell contact.

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