

CASE REPORT

Successful treatment with bortezomib for refractory fever associated with myelodysplastic syndrome with underlying lymphoplasmacytic lymphoma

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Funding information

Not applicable

Abstract

We report a case of fever of unknown origin in a patient with MDS associated with IgM-MGUS. The patient was positive for MYD88 mutation, and chemotherapy for LPL/WM improved the fever. Analysis of MYD88 and the effect of chemotherapy on LPL/WM finally revealed the latent LPL/WM in this case.

KEYWORDS

Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia, myelodysplastic syndrome, myeloid differentiation primary response 88

1 | INTRODUCTION

Patients with myelodysplastic syndrome (MDS) experience fever caused by infection associated with febrile neutropenia and tumor fever due to progression to acute leukemia. Approximately 10%–30% of MDS cases have immune system disorders leading to fever.¹

Lymphoplasmacytic lymphoma (LPL) is a lymphoid malignancy with immunoglobulin M (IgM) monoclonal gammopathy comprising minute monoclonal B cells, including mature B cells, differentiating into plasma cells. LPL with bone marrow invasion is defined as Waldenström's macroglobulinemia (WM).² In the 2008 World Health Organization classification, characteristic cytogenetic and chromosomal abnormalities for LPL/WM were unclear; in a 2003 study, however, ~90% of

LPL/WM cases had L265P mutation in MYD88 (myeloid differentiation primary response gene 88). The rate of malignant cells in the bone marrow of patients with WM has not been clearly defined.² The pathological diagnosis for WM is occasionally difficult if the tumor burden is low in the bone marrow without extramedullary disease.

We have encountered an MDS case with recurring fever of unknown origin. No evidence of infection, tumor fever, or immunological diseases was found via various examinations. Bone marrow aspiration was consistent with low-risk MDS as observed at diagnosis. Monoclonal IgM was positive but at low levels, consistent with monoclonal gammopathy of undetermined significance (MGUS).

The positive MYD88L265P mutation and good response to LPL/WM-targeted therapy were useful for diagnosing underlying LPL/WM, a rare complication of MDS.

2 | CASE REPORT

A 55-year-old man was diagnosed with classical Hodgkin's lymphoma and achieved complete remission by chemotherapy. At the age of 60, he was diagnosed with left renal cell carcinoma and achieved remission by left kidney resection. In November of 2016, at the age of 73, the patient was hospitalized for pneumonia and determined to have anemia. During the same hospital stay, he was also diagnosed with treatment-related MDS (also known as MDS with multilineage dysplasia; International Prognostic Scoring System: low risk) by bone marrow aspiration, and with IgM-MGUS by serum

protein electrophoresis and immunoelectrophoresis (Figure 1). His marrow cells contained clonal B cells (Figure 2B and Table 1).

In August of 2017, the patient experienced a transient fever of over 38°C. Because his white blood cell and neutrophil counts were 1,430 and 286/μL, respectively, the fever was considered febrile neutropenia. Renal dysfunction progressed because the patient had only one kidney (Table 1). No infections were detected by physical examination, various cultures, or fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomography (CT) or other imaging. Serum examinations for bacterial, fungal, and viral infections were nondiagnostic.

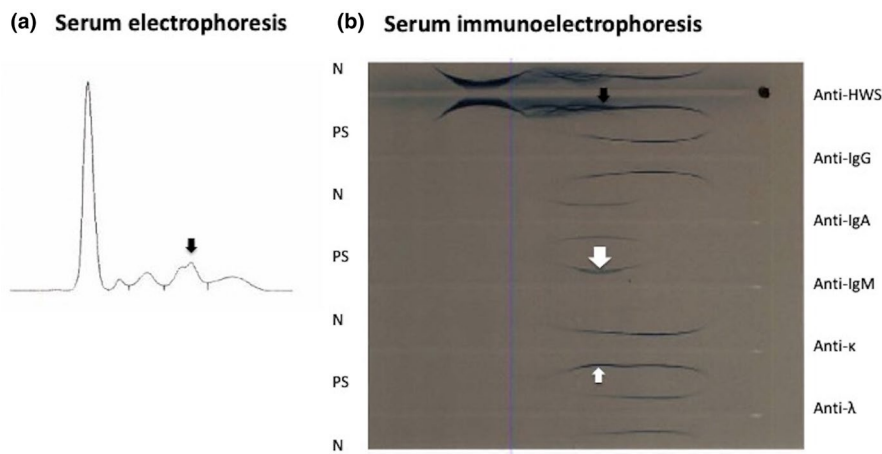


FIGURE 1 Serum protein electrophoresis and serum immunoelectrophoresis at diagnosis of MDS and IgM-MGUS. a, Serum electrophoresis at diagnosis of MDS and IgM-MGUS. A small M-peak was seen (black arrow). b, Serum immunoelectrophoresis at diagnosis of MDS and IgM-MGUS. An M-bow was observed in response to anti-IgM antibody (white arrow), and anti-κ antibody (white smaller arrow), indicating the presence of monoclonal IgM-κM protein. An M-bow was also observed in response to anti-HWS serum (black arrow). N: normal serum; PS: patient's serum; HWS: human whole serum

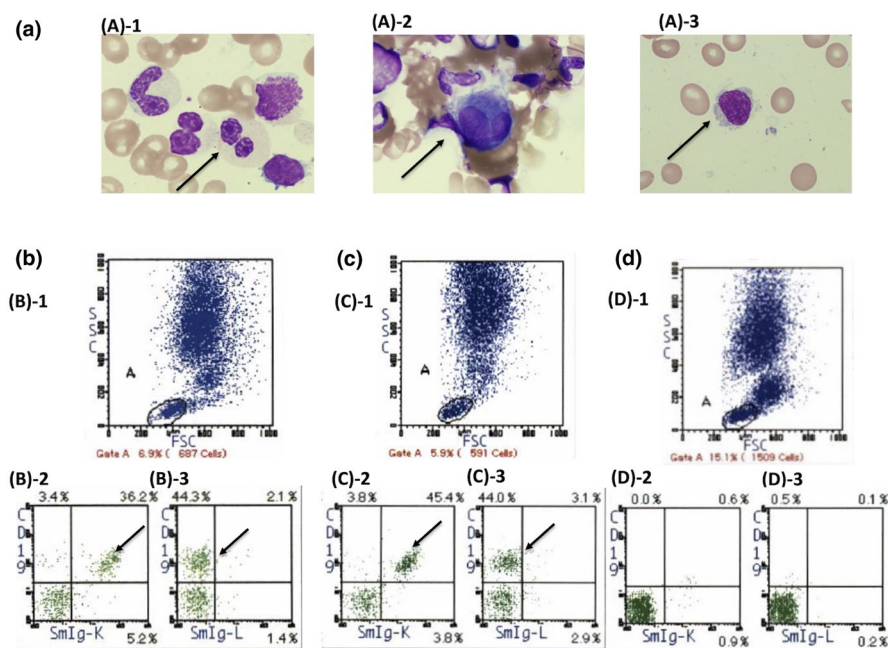


FIGURE 2 Bone marrow examination at repetitive fever onset (Aug 2, 2018). a, Bone marrow smear (Wright-Giemsa staining, ×1,000). MDS-specific dysplasia including pseudo-Pelger-Huët anomaly (A-1, arrow) and micro-megakaryocytes (A-2, arrow) and abnormal lymphocytes (A-3, arrow) were present. b, c, d, Flow cytometry at diagnosis of MDS (b, Dec. 15, 2016), before BDR therapy (c, Aug. 2, 2018) and after BDR therapy (d, Jan. 31, 2019). Flow cytometry revealed that 2.5% (B-2 and B-3, arrow) and 2.7% (C-2 and C-3, arrow) of nucleated cells were monoclonal B cells. FSC: forward scatter, SSC: side scatter

TABLE 1 Laboratory data at diagnosis of MDS, on admission and after BDR therapy

	[Complete blood count]			[Serology Immunology]			[Bone marrow]		
	Dec.15, 2016	Aug.2, 2018	Jan.31, 2019	Dec.15, 2016	Aug.2, 2018	Jan.31, 2019	Dec.15, 2016	Aug.2, 2018	Jan.31, 2019
WBC	3230	2720	2400	CRP	6.04	1.22			
	/μl				mg/dl		Ncc	18.6	14.5
Neut	22.4	16.6	10.6	IgG	786	339		6	25
	%				mg/dl		MegK		
Lym	44.7	12.7	60.7	IgA	147	50		3.6	2.2
	%				mg/dl		M-bl		%
Mon	32	69.3	27.3	IgM	1113	532		2.1	1.1
	%				mg/dl		Promyel		%
Eos	0.7	0	0.7	sIL-2R	1484	1460		22	18.4
	%				IU/ml		Myel		%
Bas	2	0	0.7	B-2 MG	16.7	11.3		21	22.9
	%				mg/L		Metamyel		%
Atyp. Lym	0.4	1.3	0	WT1 mRNA	<50	120		18.8	19.2
	%				Copy/μg RNA		Stab		%
Hb	8.4	6.5	8.9	[Chemistry]			Seg	15.5	10.2
	g/dl						Eos	0.1	0.4
MCV	118	108	122	T-Bil	0.3	0.4		0.3	0.4
	Mm ³				mg/dl		Bas	0.2	0.2
Ret	2.7	1	1.3	AST	19	17		0	0.2
	%				IU/L		Lym	9.9	12.6
Plt	14.9	22.2	12.1	ALT	23	20		12.8	12.6
	×10 ⁴ /μl				IU/L		Mon	1.9	1.8
				γ-GTP	67	135		2.1	1.8
				LDH	148	223		1.2	0.2
				Alb	3.7	3.7		1.2	0.2
				UA	6	4.7		1.6	8.0
				BUN	19.7	21.8		45.75	9.33
				Cre	1.17	2.89		3.2	1
					mg/dl		Atyp. lym	0.2	%
					mg/dl		Abnormal. Lym	2.4	1.3
					mg/dl				%

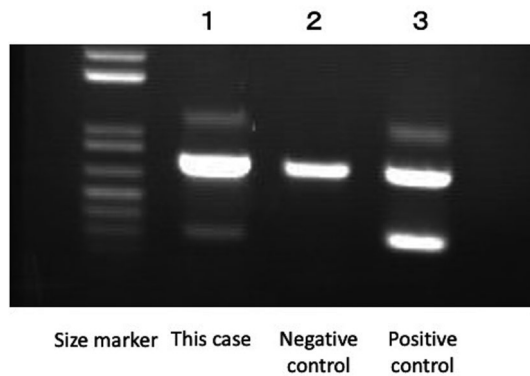


FIGURE 3 Analyses of MYD88L265P mutation using allele-specific polymerase chain reaction (PCR). Genomic DNA from bone marrow mononuclear cells from the patient (lane 1) and those from patients negative and positive for MYD88L265P mutations (lanes 2–3) were analyzed at Tokyo Medical and Dental University using the allele-specific polymerase chain reaction (PCR) method. The positions of the PCR products representing wild-type MYD88 and MYD88L265P are illustrated

Autoimmune antibodies, including antinuclear antibody, were negative. Beginning in February 2018, his fever began to repeat periodically. Antibiotics or low-dose steroids were ineffective.

Bone marrow aspiration/biopsy revealed hypercellular bone marrow with dysplasia, including pseudo-Pelger-Huët anomaly and micro-megakaryocytes, compatible with MDS (Figure 2A). Bone marrow aspiration also revealed that 2.4% of lymphocytes were abnormal (Table 1), and flow cytometry showed that 2.7% of nucleated cells were clonal B cells ($k >> L$) (Figure 2B).

Allele-specific polymerase chain reaction (PCR) for MYD88L265P using marrow cells was positive (Figure 3),^{2,3} and no lymphadenopathy was observed on CT.

Based on the history of IgM-MGUS, monoclonal B cells in the bone marrow, and positive MYD88L265P mutation, we considered that the tumor fever was due to LPL/WM developed from MGUS as a differential diagnosis.

Disease	Frequency	Reference
LPL/WM	91% (52/57)	Treon SP et al.(2012) ⁴
LPL/WM	93% (97/104)	Xu L et al. (2013) ⁵
LPL/WM	100% (58/58)	Varettoni M et al. (2013) ⁶
IgM-MGUS	10% (2/21)	Treon SP et al. (2012) ⁴
IgM-MGUS	54% (13/24)	Xu L et al. (2013) ⁵
IgM-MGUS	47% (36/77)	Varettoni M et al. (2013) ⁶
PCNSL	72% (26/36)	Nayyar N et al. (2019) ⁷
Primary testicular lymphoma	68% (25/37)	Kraan W et al. (2013) ⁸
DLBCL (ABC type)	29% (13/45)	Ngo VN et al. (2011) ⁹

TABLE 2 Lymphoma or IgM-MGUS with high frequency of MYD88L265P mutation

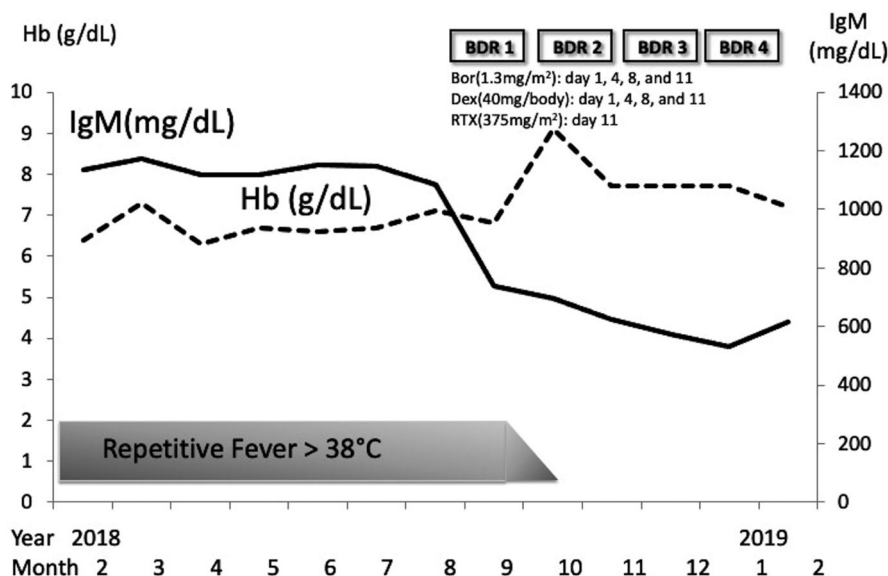


FIGURE 4 Clinical course of the patient. Bor, bortezomib; Dex, dexamethasone; RTX, rituximab

Although MYD88 mutation has a high sensitivity for LPL/WM, its specificity is low. A search of the literature (Table 2)⁴⁻⁹ revealed high MYD88-positive rates in primary central nervous system lymphoma and testicular lymphoma. Therefore, other low-grade B-cell lymphomas could have the mutation. However, this case was clinically unlikely to be a primary central nervous system lymphoma, primary testicular lymphoma, or diffuse large B-cell lymphoma based on PET/CT and repeat CT imaging studies.

The MYD88-positive rate is also high in IgM-MGUS. We thus could not rule out IgM-MGUS from LPL/WM. Therefore, in August of 2018, we administered bortezomib, dexamethasone, and rituximab (BDR) (bortezomib [1.3 mg]/m² on days 1, 4, 8, and 11; dexamethasone [40 mg] /body on days 1, 4, 8, and 11; and rituximab 375 mg/m² on day 11¹⁰) targeted for possible symptomatic LPL/WM. After four cycles of BDR, IgM M-proteins decreased from 1113 mg/dl to 532 mg/dl (partial remission). The recurring fever over 38°C dramatically improved to a normal level. Flow cytometry showed that the clonal B cells that had been previously detected had almost completely disappeared (Figure 2B-D). Also, the bone marrow aspiration showed that the number of abnormal lymphocytes was reduced to 1.3% (Table 1). BDR therapy was considered to have been successful (Figure 4).

3 | DISCUSSION

In patients with MDS, infections, malignancies, or autoimmune diseases cause fever. In the patient in this case report, bone marrow examination with flow cytometry and chromosomal analysis did not reveal the diagnosis of LPL/WM.

In our patient, it was important to determine the cause of the increase in serum monoclonal IgM, because it could have been derived from various B-cell malignancies other than LPL/WM.

For these reasons, MYD88 mutation analysis is useful for diagnosing LPL/WM. In our patient, the good response of the fever of unknown origin to BDR therapy confirmed the diagnosis.

MYD88L265P mutation may be an early oncogenic event in LPL/WM,⁴ and MYD88L265P-positive IgM-MGUS cases are more likely to progress to LPL/WM than MYD88L265P-negative ones.⁵ Therefore, we should exercise caution regarding the malignant transformation of MYD88L265P-positive IgM-MGUS.

In a study involving 40 patients with MDS, stem cells were shown to overexpress the MYD88 protein. However, MYD88L265P was not found in all cases was not found in any cases.¹¹ Therefore, MYD88L265P might be derived from LPL/WM but not MDS.

The International Workshop on Waldenström's Macroglobulinemia provides the criteria for starting treatment for LPL/WM.¹² In this case, the recurring fever and anemia met the criteria for LPL/WM treatment despite low IgM levels. Although the anemia might have been derived from MDS, it improved after four cycles of BDR therapy, suggesting that LPL/WM caused both fever and anemia.

Many rituximab-containing regimens are effective for WM/LPL based on phase II trials. In this case, BDR was selectively administered because of the renal impairment (creatinine clearance rate: 18 ml/min/1.73 m²).

The prevalence of MGUS in patients with MDS ranges between 2% and 10%. Moreover, in a study on 1,198 patients with MDS, 6 patients had complications of LPL.¹³ This finding would suggest that MDS with associated IgM-MGUS or LPL/WM is not especially rare.

Clinicians should watch for symptomatic LPL/WM in their patients with MDS, as in the present patient, whose IgM level and rate of tumor cells were low. In this patient, MYD88 mutation analysis and BDR therapy played a significant role in diagnosing LPL/WM and informing the treatment strategy.

ACKNOWLEDGMENT

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Yotaro Motomura drafted the article and provided and cared for study patients. Yoshihiro Umezawa and Osamu Miura served as scientific advisors. Tomoyuki Arimatsu and Keigo Okada provided and cared for study patients. Takashi Kumagai critically revised the article for important intellectual content.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Motomura Y, Umezawa Y, Arimatsu T, Okada K, Miura O, Kumagai T. Successful treatment with bortezomib for refractory fever associated with myelodysplastic syndrome with underlying lymphoplasmacytic lymphoma. *Clin Case Rep*. 2022;10:e05372. doi:[10.1002/ccr3.5372](https://doi.org/10.1002/ccr3.5372)