Journal of clinical and experimental hematopathology
Vol. 60 No.2, 51-54, 2020

Case report

Hepatitis B virus reactivation in a myeloma patient with resolved infection who received daratumumab-containing salvage chemotherapy

Takaki Kikuchi,[1)] Shigeru Kusumoto,[1)] Yasuhito Tanaka,[2)] Yoshiko Oshima,[1)] Haruna Fujinami,[1)] Tomotaka Suzuki,[1)] Haruhito Totani,[1)] Shiori Kinoshita,[1)] Yu Asao,[1)] Tomoko Narita,[1)] Asahi Ito,[1)] Masaki Ri,[1)] Hirokazu Komatsu,[1)] Shinsuke Iida[1)]

A 72-year-old female complaining of back pain was diagnosed with IgG-κ multiple myeloma. After osteosynthesis for fracture of the left femoral shaft due to myeloma, she received bortezomib, melphalan, and prednisolone as an initial regimen for multiple myeloma, but discontinued it after three courses due to progressive disease. The patient subsequently received lenalidomide and dexamethasone as a second-line regimen for 2.5 years, and pomalidomide and dexamethasone as a third-line regimen for only 2 months. An anti-CD38 monoclonal antibody, daratumumab (DARA), and bortezomib and dexamethasone (DVd) as a fourth-line regimen were administered for refractory myeloma. However, hepatitis B virus (HBV) reactivation occurred on day 15 of the third course of DVd. The HBV DNA level in peripheral blood suddenly increased to 2.2 log IU/mL. An anti-HBV nucleotide analog, entecavir, was subsequently administered when the HBV DNA level increased to 2.6 log IU/mL. No HBV-related hepatitis was observed during follow-up. DARA can improve the prognosis of patients with multiple myeloma, but also potentially increase the risk of HBV reactivation. Host and viral risk factors need to be identified in such patients in order to implement a more cost-effective strategy against HBV reactivation.

Keywords: HBV reactivation, daratumumab, HBV DNA monitoring, resolved infection, myeloma

INTRODUCTION

Daratumumab (DARA), an anti-CD38 monoclonal antibody, has been demonstrated to improve response rates and progression-free survival in patients with relapsed/refractory multiple myeloma in combination with bortezomib and dexamethasone (DVd)[1] or lenalidomide and dexamethasone.[2] However, DARA treatment may be associated with an increased risk of viral infection; specifically, cytomegalovirus (CMV) reactivation occurs in patients with multiple myeloma after DARA administration.[3-6] Hepatitis B virus (HBV) reactivation is also a potentially fatal complication of DARA treatment.[7,8] Rituximab, an anti-CD20 monoclonal antibody, plus steroid combination chemotherapy is a risk factor in patients with resolved HBV infection, defined as being seronegative for hepatitis B surface antigen (HBsAg), but seropositive for antibodies against hepatitis B core antigen (anti-HBc) and/or antibodies against HBsAg (anti-HBs).[9] However, data regarding HBV reactivation after DARA administration are markedly limited.[10] We report HBV reactivation in a myeloma patient with resolved HBV infection who received a salvage DVd regimen.

CASE REPORT

A 72-year-old female complained of back pain in September 20XX. She underwent osteosynthesis for fracture of the left femoral shaft. After surgery, she was diagnosed with IgG-κ multiple myeloma as follows: serum monoclonal protein was detected; bone marrow aspiration revealed an increase in the plasma cell ratio to 18.2%. Computed tomography demonstrated multiple osteolytic lesions and compression fractures

Received: September 14, 2019. Revised: February 16, 2020. Accepted: February 28, 2020. J-STAGE Advance Published: May 13, 2020
DOI:10.3960/jslrt.19034

[1)]Department of Hematology and Oncology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, [2)]Department of Virology and Liver unit, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

*Drs. Kikuchi and Kusumoto contributed equally to this case report

Corresponding author: Shigeru Kusumoto, M.D., Ph.D., Department of Hematology and Oncology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-chou, Mizuho-ku, Nagoya, Aichi, 467-8601, Japan. E-mail:skusumot@med.nagoya-cu.ac.jp

of the thoracolumbar spine. Blood tests at the time of admission to our hospital revealed the following: white blood cells 3500/μL, hemoglobin 9.4 g/dL, platelets 18.4 × 10^4/μL, total protein 8.7 g/dL, albumin 3.7 g/dL, lactate dehydrogenase 128 U/L, creatinine 0.86 mg/dL, blood urea nitrogen 18.2 mg/dL, corrected calcium 11.0 mg/dL, IgG 4564 mg/dL, IgA 139 mg/dL, and IgM 26 mg/dL. In addition, screening the blood sample for HBV demonstrated it to be seronegative for HBsAg, but seropositive for anti-HBc (114.8 cutoff index), and seronegative for anti-HBs. Serum HBV DNA was not detectable, suggesting that the HBV infection had resolved. To prevent HBV reactivation-related hepatitis, the patient underwent regular HBV DNA monitoring during and at least one year after myeloma treatment.

The patient received a bortezomib, melphalan, and prednisolone (VMP) combination regimen as the initial treatment for multiple myeloma. However, this was discontinued after three courses of VMP (total doses of bortezomib, melphalan, and prednisolone: 10.4 mg, 87 mg, and 754 mg per body surface area, respectively) due to progressive disease (PD). The patient subsequently received a lenalidomide and dexamethasone (Ld) combination regimen (lenalidomide at 15 mg/day as an initial dose, up to 25 mg/day) as second-line treatment, and continued Ld therapy (total doses of lenalidomide and dexamethasone: 11,641 mg and 2,493 mg per body surface area, respectively) for 2.5 years. A pomalidomide and dexamethasone (Pd) combination regimen (pomalidomide 3 mg/day) was next started as the third-line treatment for relapsed myeloma; however, this was discontinued after only two courses of Pd (total doses of pomalidomide and dexamethasone: 76 mg and 116 mg per body surface area, respectively) due to PD, including bone pain, anemia, and hypercalcemia.

The patient received a DVd regimen as the fourth-line treatment for refractory myeloma, and symptoms gradually improved after one course. However, HBV reactivation occurred on day 15 of the third course of the DVd regimen (total doses of daratumumab, bortezomib and dexamethasone; 144 mg per kg, 10.4 mg and 319 mg per body surface area, respectively; November 20, 20XX + 3 years) because the HBV DNA level in her peripheral blood suddenly increased to 2.2 log IU/mL. Her laboratory data at the HBV reactivation are summarized in Table 1. A course of an anti-HBV nucleotide analog, entecavir, was started when the HBV DNA level increased to 2.6 log IU/mL (Figure 1). Her HBV DNA level decreased thereafter, and remained under the limit of detection during entecavir treatment (January 22, 20XX + 4 years). No HBV reactivation-related hepatitis was observed during follow-up, and DVd therapy was thus continued until PD.

On retrospective analysis using serum samples, HBsAg (11.6 mIU/mL) was detected by a highly sensitive Lumipulse HBsAg-HQ assay (detection limit, 5 mIU/mL; Fujirebio, Tokyo, Japan) when HBV DNA appeared in the peripheral blood (HBV DNA 2.2 log IU/mL), as shown in Table 1 and Figure 1. Furthermore, the analysis demonstrated that the virus had no mutations in the precore region or basal core promoter, which may be associated with the rapid increase in HBV DNA level and fulminant hepatitis B; no HBsAg escape mutation was found. This retrospective analysis was approved by the institutional review board of Nagoya City University.

Table 1. Laboratory data at hepatitis B virus reactivation

WBC	3.8	×10^3/μL	TP	5.4	g/dL
Neutrophils	57	%	Alb	3.4	g/dL
Eosinophils	0	%	T-Bil	0.5	mg/dL
Basophils	0	%	CRP	0.08	mg/dL
Monocytes	7	%	CK	39	U/L
Lymphocytes	36	%	AST	13	U/L
Atyp. Lym.	0	%	ALT	9	U/L
RBC	2.98	×10^6/μL	LDH	204	U/L
Hb	10.3	g/dL	ALP	493	U/L
Plt	127	×10^3/μL	γ-GTP	34	U/L
			ChE	269	U/L
PT	11	sec	Cre	0.55	mg/dL
PT-INR	1		Glu	82	mg/dL
APTT	26.5	sec	Na	142	mmol/L
Fibrinogen	295	mg/dL	K	3.9	mmol/L
FDP	4.5	μg/mL	Cl	108	mmol/L
			Ca	8.3	mg/dL
HBV DNA	2.2	Log IU/mL (+)			
HBsAg-HQ	11.6	mIU/mL (+)			

HBsAg-HQ, highly sensitive Lumipulse HBsAg-HQ assay (detection limit, 5 mIU/mL; Fujirebio, Tokyo, Japan).

DISCUSSION

To our knowledge, this is the first case report regarding HBV reactivation in a myeloma patient with resolved HBV infection after DARA-containing chemotherapy. Regular HBV DNA monitoring diagnosed HBV reactivation at an early stage when HBV-related hepatitis was not observed.

In this case, several chemotherapy regimens for multiple myeloma were administered over a long period of time, making it difficult to identify the drug related to HBV reactivation. However, the clinical course suggested that DARA-containing chemotherapy is associated with HBV reactivation. HBV reactivation was previously reported in a myeloma patient with resolved HBV infection who received bortezomib and dexamethasone,[11] but in this case, three courses of VMP were administered during the initial treatment and no HBV reactivation was observed. In addition, although Ld was continued for approximately 2.5 years, HBV reactivation was not observed. Of note, a Japanese multicenter retrospective study suggested that lenalidomide can reduce the risk of HBV reactivation during the treatment of multiple myeloma.[12]

DARA can potentially increase the risk of viral infection,[5] but the pathogenesis is unclear. DARA is an IgG1 kappa monoclonal antibody targeting CD38 that that is expressed not only in myeloma cells, but also in non-malignant T cells, natural killer (NK) cells, B cells, and plasma cells.[13,14] Recently, DARA-containing chemotherapy was reported to

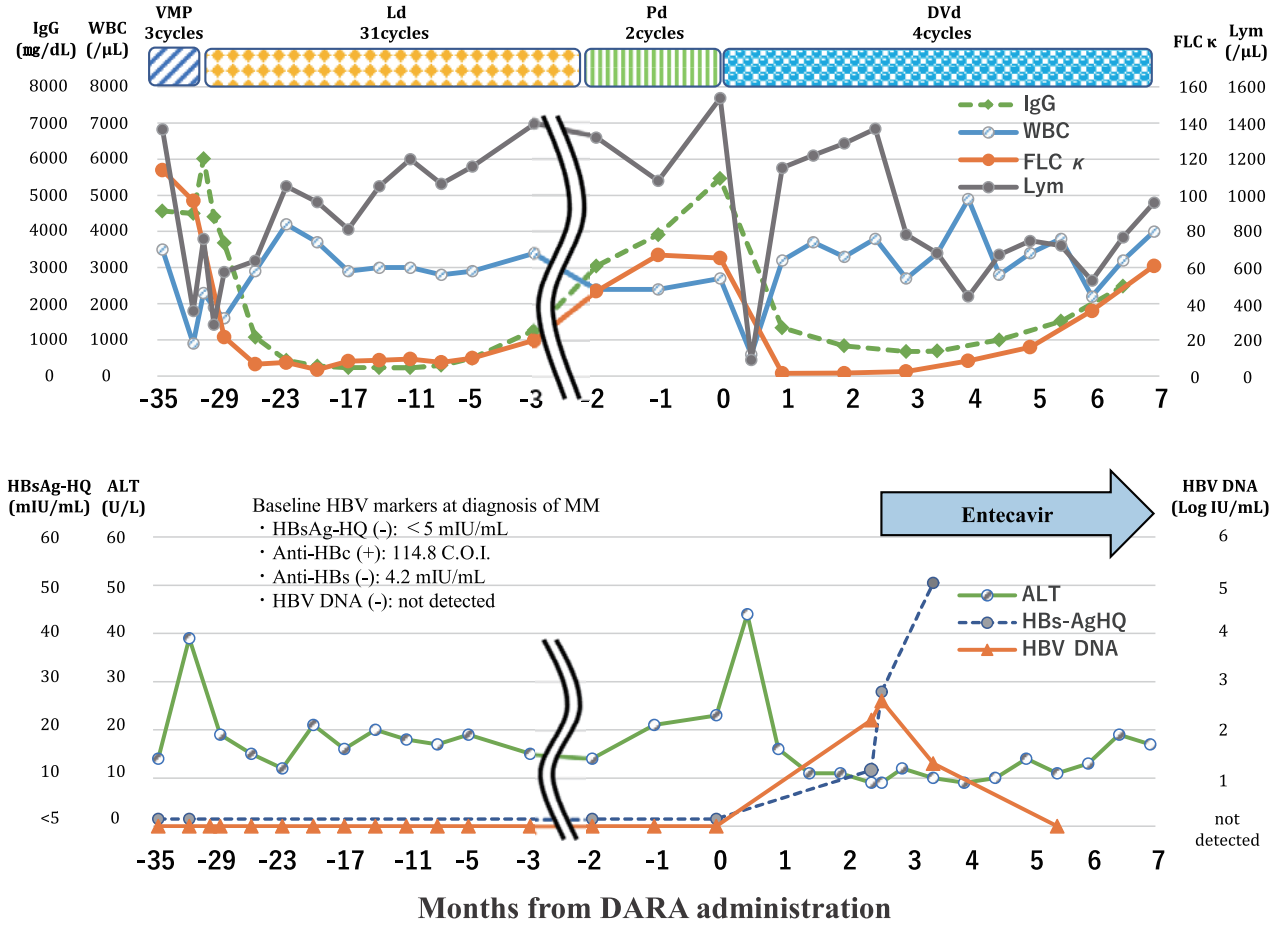

Fig. 1. Clinical course of hepatitis B virus reactivation during myeloma treatment with regular HBV DNA monitoring
VMP, bortezomib, melphalan, and prednisolone; Ld, lenalidomide and dexamethasone; Pd, pomalidomide and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; DARA, daratumumab; WBC, white blood cell; FLC, free light chain; Lym, lymphocyte; HBV, hepatitis B virus; MM, multiple myeloma; Anti-HBc, antibodies against hepatitis B core antigen; Anti-HBs, antibodies against hepatitis B surface antigen; ALT, alanine transaminase; HBsAg-HQ, highly sensitive Lumipulse HBsAg-HQ assay.

be associated with CMV infection,[3,4,6] suggesting that cellular immunity was suppressed in some patients who received DARA-containing chemotherapy. More recently, a retrospective study assessing circulating lymphocytes revealed that DARA can selectively deplete NK cells, which may lead to viral reactivation.[5] Furthermore, the CD38 antigen is considered to be expressed in blood cells, with the highest expression in plasma cells.[15] Therefore, a decrease in the number of non-malignant plasma cells may lead to the suppression of humoral immunity after DARA administration, which may have increased the risk of HBV reactivation.

Anti-HBs antibody titers at baseline (before lymphoma treatment) have been identified as an important host risk factor for HBV reactivation in lymphoma patients with resolved HBV infection who received anti-CD20 antibody,[16,17] which suggested that an antibody against HBV is essential to maintain HBV under immune surveillance and B-cell based humoral immunity may act as a key element for HBV control.[18] Moreover, our patient was seronegative for anti-HBs at baseline, suggesting that HBV reactivation was more likely.

Of note, our retrospective analysis using stored samples revealed that a highly sensitive HBsAg-HQ assay can diagnose HBV reactivation at an early stage. This suggests that monitoring of the HBsAg level is an alternative cost-effective method to prevent HBV-related hepatitis, although limited evidence exists regarding the usefulness of such surveillance.[19]

In conclusion, HBV reactivation occurred in a myeloma patient with resolved HBV infection who received DARA-containing salvage chemotherapy, in whom HBV DNA monitoring-guided preemptive antiviral therapy prevented HBV-related hepatitis. Well-designed clinical studies are warranted to identify host and viral risk factors in such patients to implement a more cost-effective strategy against HBV reactivation.

ACKNOWLEDGMENTS

We would like to thank the patient for consenting to the publication of her clinical details.

We also thank Ms. Chiori Fukuyama and Dr. Shintaro Ogawa (Nagoya City University Graduate School of Medical Sciences, Nagoya) for keeping and evaluating stored samples.

This work was supported in part by Grants-in-Aid from

the Research Program on Hepatitis from Japan Agency for Medical Research and Development (AMED: 16fk0310512h0005, 17fk0310101h0001, and 18fk0310101h0002) and a grant-in-aid from the Ministry of Education, Culture, Sports, Science, and Technology (Scientific Research (C) no. 16K09876).

CONFLICT OF INTEREST

Shigeru Kusumoto: Research funding from Janssen, Celgene, Daiichi Sankyo, Takeda, Ono, Bristol-Myers Squibb, Novartis, Chugai, Kyowa Kirin, Sanofi, Abbvie, MSD, Gilead, Astellas, and Teijin Pharma, and honoraria from Janssen, Takeda, Bristol-Myers Squibb, Chugai, and Kyowa Kirin.

Yasuhito Tanaka: Research funding from FUJIFILM Corporation, Board of Trustees of the Leland Stanford Junior University, and honoraria from FUJIREBIO Inc. and Gilead Sciences Inc.

Masaki Ri: Research funding from Janssen, Celgene, Daiichi Sankyo, Takeda, Ono, Bristol-Myers Squibb, Novartis, Chugai, Kyowa Kirin, Sanofi, Abbvie, MSD, Gilead, Astellas, and Teijin Pharma, and honoraria from Janssen, Celgene, Ono, Takeda, Sanofi, Bristol-Myers Squibb, Chugai, and Kyowa Kirin.

Shinsuke Iida: Research funding from Janssen, Celgene, Daiichi Sankyo, Takeda, Ono, Bristol-Myers Squibb, Novartis, Chugai, Kyowa Kirin, Sanofi, Abbvie, MSD, Gilead, Astellas, and Teijin Pharma, and honoraria from Janssen, Celgene, Daiichi Sankyo, Ono, Takeda, Sanofi, Bristol-Myers Squibb, and Novartis.

REFERENCES

1 Palumbo A, Chanan-Khan A, Weisel K, *et al.*; CASTOR Investigators. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med. 2016; 375 : 754-766.
2 Dimopoulos MA, Oriol A, Nahi H, *et al.*; POLLUX Investigators. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016; 375 : 1319-1331.
3 Lavi N, Okasha D, Sabo E, *et al*. Severe cytomegalovirus enterocolitis developing following daratumumab exposure in three patients with multiple myeloma. Eur J Haematol. 2018; 101 : 699-702.
4 Frerichs KA, Bosman PWC, Nijhof IS, Zweegman S, van de Donk NWCJ. Cytomegalovirus reactivation in a patient with extensively pretreated multiple myeloma during daratumumab treatment. Clin Lymphoma Myeloma Leuk. 2019; 19 : e9-e11.
5 Nahi H, Chrobok M, Gran C, *et al*. Infectious complications and NK cell depletion following daratumumab treatment of Multiple Myeloma. PLoS One. 2019; 14 : e0211927.
6 Nakagawa R, Onishi Y, Kawajiri A, *et al*. Preemptive therapy for cytomegalovirus reactivation after daratumumab-containing treatment in patients with relapsed and refractory multiple myeloma. Ann Hematol. 2019; 98 : 1999-2001.
7 Umemura T, Tanaka E, Kiyosawa K, Kumada H; Japan de novo Hepatitis B Research Group. Mortality secondary to fulminant hepatic failure in patients with prior resolution of hepatitis B virus infection in Japan. Clin Infect Dis. 2008; 47 : e52-e56.
8 Kusumoto S, Tanaka Y, Mizokami M, Ueda R. Reactivation of hepatitis B virus following systemic chemotherapy for malignant lymphoma. Int J Hematol. 2009; 90 : 13-23.
9 Hui CK, Cheung WWW, Zhang HY, *et al*. Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. Gastroenterology. 2006; 131 : 59-68.
10 Janssen Pharmaceutical Companies, Darzalex (daratumumab) and risk of reactivation of hepatitis B virus. Internet Document: 26 Jun 2019. Available from: URL: https://assetspublishingservicegovuk/media/5d2dbdbbe5274a14e7135640/Darzalex_DHPC-June_2019pdf. 2019.
11 Tanaka H, Sakuma I, Hashimoto S, *et al*. Hepatitis B reactivation in a multiple myeloma patient with resolved hepatitis B infection during bortezomib therapy : case report. J Clin Exp Hematop. 2012; 52 : 67-69.
12 Tsukune Y, Sasaki M, Odajima T, *et al*. Incidence and risk factors of hepatitis B virus reactivation in patients with multiple myeloma in an era with novel agents: a nationwide retrospective study in Japan. Blood Cancer J. 2017; 7 : 631.
13 Krejcik J, Casneuf T, Nijhof IS, *et al*. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood. 2016; 128 : 384-394.
14 van de Donk NWCJ, Richardson PG, Malavasi F. CD38 antibodies in multiple myeloma: back to the future. Blood. 2018; 131 : 13-29.
15 Deaglio S, Mehta K, Malavasi F. Human CD38: a (r)evolutionary story of enzymes and receptors. Leuk Res. 2001; 25 : 1-12.
16 Kusumoto S, Tanaka Y, Suzuki R, *et al*. Monitoring of hepatitis B virus (HBV) DNA and risk of HBV reactivation in B-cell lymphoma: A prospective observational study. Clin Infect Dis. 2015; 61 : 719-729.
17 Kusumoto S, Arcaini L, Hong X, *et al*. Risk of HBV reactivation in patients with B-cell lymphomas receiving obinutuzumab or rituximab immunochemotherapy. Blood. 2019; 133 : 137-146.
18 Zhang S, Zhao J, Zhang Z. Humoral immunity, the underestimated player in hepatitis B. Cell Mol Immunol. 2018; 15 : 645-648.
19 Shinkai N, Kusumoto S, Murakami S, *et al*. Novel monitoring of hepatitis B reactivation based on ultra-high sensitive hepatitis B surface antigen assay. Liver Int. 2017; 37 : 1138-1147.