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【 CASE REPORT 】

Methotrexate-associated Hodgkin Lymphoma in a Patient with Rheumatoid Arthritis Successfully Treated with Brentuximab Vedotin in Combination with Doxorubicin, Vinblastine, and Dacarbazine (BV+AVD)

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Abstract:
A 53-year-old woman had been diagnosed with rheumatoid arthritis (RA) in X-6. She was started on methotrexate (MTX) in X-1. She developed a cough, and chest computed tomography showed abnormalities. In X, MTX was discontinued, but the cough persisted. A lung biopsy revealed a diagnosis of nodular sclerosis classic Hodgkin lymphoma (CHL-NS). She was considered to have "other iatrogenic immunodeficiency-associated lymphoproliferative disorders" (OIIA-LPD), MTX-associated Hodgkin lymphoma (MTX-HL). She received six courses of brentuximab vedotin (BV) in addition to AVD (BV+AVD). A complete metabolic response was obtained, and the RA went into remission. This is the fourth reported case of BV+AVD for MTX-HL.

Key words: Rheumatoid arthritis (RA), Methotrexate (MTX), Other iatrogenic immunodeficiency associated lymphoproliferative disorders (OIIA-LPDs), Hodgkin lymphoma (HL), BV+AVD (brentuximab vedotin, doxorubicin, vinblastine, dacarbazine)

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Introduction

Brentuximab vedotin (BV) is a novel antibody-drug conjugate (ADC) targeting the cell surface marker, CD30 (1). The efficacy and safety of brentuximab vedotin administered in combination with doxorubicin+vinblastine+dacarbazine (BV+AVD) for untreated Hodgkin lymphoma (HL) was demonstrated in an international collaborative phase III study (ECHELON-1) (2). In addition, the efficacy and safety of BV monotherapy for recurrent/refractory HL was also demonstrated in Japanese phase I/II studies (3) and non-Japanese phase II studies (1). However, thus far, BV has been administered to only seven patients with methotrexate (MTX)-associated HL (MTX-HL), including the present case (4-7), and its efficacy and safety profile remain unknown. In addition, BV monotherapy or BV+AVD was used in three previous cases each, and the present case is only the fourth reported case in which BV+AVD was used. The efficacy and safety of BV or BV+AVD in rheumatoid arthritis (RA) are unclear.

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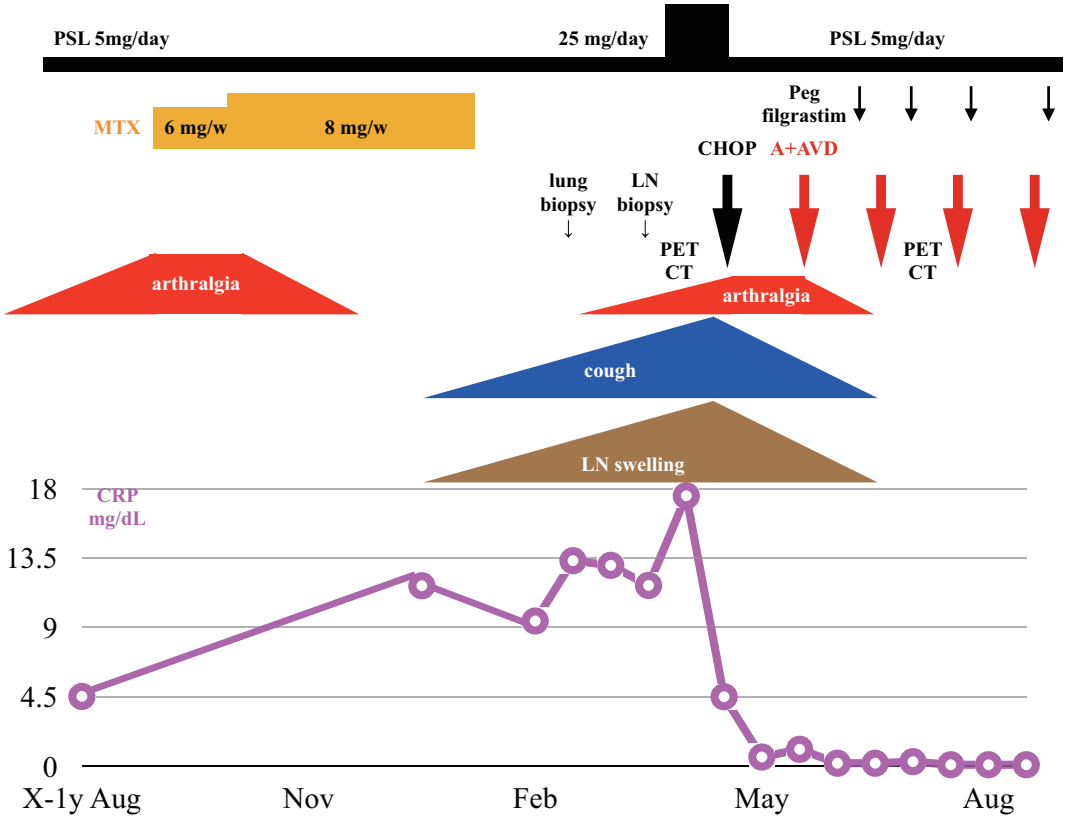

Figure 1. **Clinical course.**

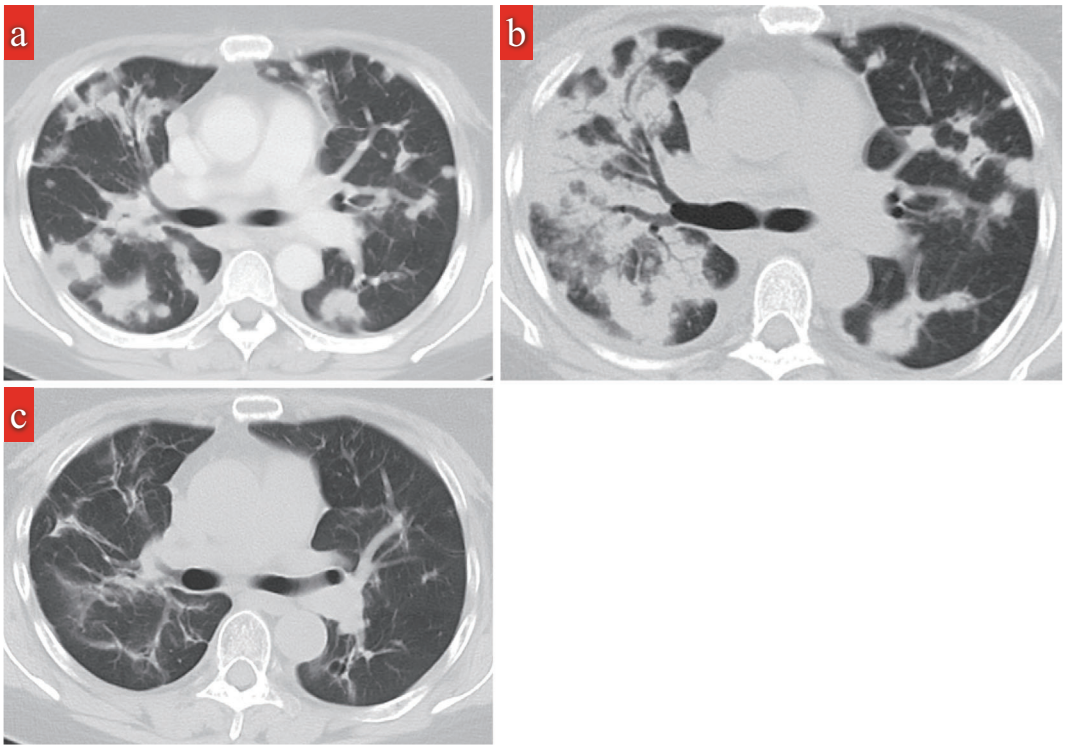

Figure 2. **a: Chest CT in December X-1; Multiple patchy infiltrative opacities are seen in both lungs. b: Chest CT in mid-April X; Multiple patchy infiltrative opacities in both lungs, that look worse than before. c: Chest CT in December X; Multiple patchy infiltrative opacities are not seen in both lungs.**

Table 1. Laboratory Findings at the Patient's First Visit to Our Hospital.

CBC		Biochemistry		Immuno-Serological findings	
WBC	15,600 /μL	T.P	6.9 g/dL	IgG	1,124 mg/dL
Neut	91.7 %	Alb	3.4 g/dL	IgA	268 mg/dL
Ly	3.4 %	AST	15 IU/L	IgM	41 mg/dL
Mono	2.5 %	ALT	21 IU/L	ANA	negative
Eo	1.6 %	LDH	184 IU/L	sIL-2R	6,260 U/mL
Ba	0.3 %	ALP	460 IU/L	HTLV-1 Ab	negative
RBC	445×10^4 /μL	AMY	48 IU/L	HIV Ab	negative
Hb	12.1 g/dL	γ-GTP	72 IU/L	RF	<5 IU/mL
Hct	37.2 %	T-Bil	0.6 mg/dL	ACE	8.9 U/L
MCV	83.5 fL	BUN	15 mg/dL	CCP Ab	<0.6 U/mL
MCH	27.2 pg	Cr	0.53 mg/dlL	IL-6	5.3 pg/mL
Plt	31.0×10^4 /μlL	CRP	9.4 mg/dL	β-D glucan	<5.0 pg/mL
Reti	1.7 %	Fer	908.6 ng/mL	PR3-ANCA	<1.0 U/mL
				MPO-ANCA	<1.0 U/mL
				KL-6	404 U/mL
Coagulation		Urine		SP-A	78.9 ng/mL
PT	85 %	Normal		SP-D	32.5 ng/mL
APTT	32.2 sec			EBV DNA titer in plasma	not detected copies/mL

WBC: white blood cells, Neut: neutro, Ly: lymphocyte, Mono: monocyte, Eo: eosinophil, Ba: basophil, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, Plt: platelet, Reti: reticulocyte, PT: prothrombin time, APTT: activation partial thromboplastin time, T.P: total protein, Alb: albumin, AST: aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, AMY: amylase:γ-GTP: γ-guanosine triphosphate, T-BIL: total-bilirubin, BUN: blood urea nitrogen, Cr: creatine, CRP: C-reactive protein, Fer: ferritin, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, ANA: antinuclear antibody, sIL-2R: soluble interleukin-2 receptor, HTLV-1 Ab: human T- cell leukemia virus antibody, HIV Ab: human immunodeficiency virus antibody, RF: rheumatoid factor, ACE: angiotensin converting enzyme, CCP Ab: cyclic citrullinated peptide antibody, IL-6: interleukin-6, PR3-ANCA: proteinase3-antineutrophil cytoplasmic antibody, MPO-ANCA: myeroperoxidase-antineutrophil cytoplasmic antibody, KL-6: krebs von den lungen-6, SP-A: pulmonary surfactant protein A, SP- D: pulmonary surfactant protein D

Case Report

A 53-year-old woman who had been diagnosed with RA in X-6 presented to us with a chief complaint of cough. In August X-1, when her arthralgia was aggravated [Disease Activity Score 28 with C-reactive protein (CRP) (DAS-28-CRP) score of 4.1], she was started on prednisolone (PSL) at 5 mg/day. As PSL was not sufficiently effective (see her clinical course in Fig. 1), she was started on MTX at 6 mg/week in September of the same year, and in October, the MTX dose was increased to 8 mg/week. While her arthralgia improved, she developed a cough in December.

Plain chest computed tomography (CT) showed abnormalities suggestive of atypical pneumonia (Fig. 2a), and she was started on antibiotic treatment. As no improvement was noted, MTX-associated pneumonia was suspected, and MTX was discontinued in January X. However, clinical evidence of pneumonia persisted, and the patient visited our hospital in February X. See Table 1 for the laboratory findings. The DAS-28-CRP score was 2.3. In February, a bronchoscopic lung biopsy (data not shown) and inguinal lymph node biopsy were performed, revealing scattered cells or aggregates of Hodgkinoid cells in the nodule. Numerous small- to medium-sized lymphocytes and eosinophils were detected around the lesion (Fig. 3a). Immunohistochemistry revealed positive staining for CD15, CD30, Paired box 5 (PAX5) and programmed death ligand 11 (PDL-1) (Fig. 3b, c, e, f) and negative staining for CD3, CD20 and *in situ* hybridization EBV-encoded small RNA (EBER-ISH) (Fig. 3d, g, h). These findings led to the diagnosis of nodular sclerosis-type classic Hodgkin lymphoma (CHL-NS), and due to her history of having received MTX, she was diagnosed with "other iatrogenic immunodeficiency-associated lymphoproliferative disorders" (OIIA-LPD) (8), MTX-HL.

The plasma EBV-DNA titer was negative (not detected copies/μL). F^{18}-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT revealed an accumulation in multiple areas, including in the lymph nodes, lungs, liver, spleen and bone marrow (Fig. 4a). Bone marrow and cerebrospinal fluid examinations revealed no abnormalities (data not shown). The clinical disease stage (Ann Arbor classification) was IVB. Her international prognostic score (IPS) was 5 (serum albumin 3.4 g/dL, age 53 years old, clinical stage IV,

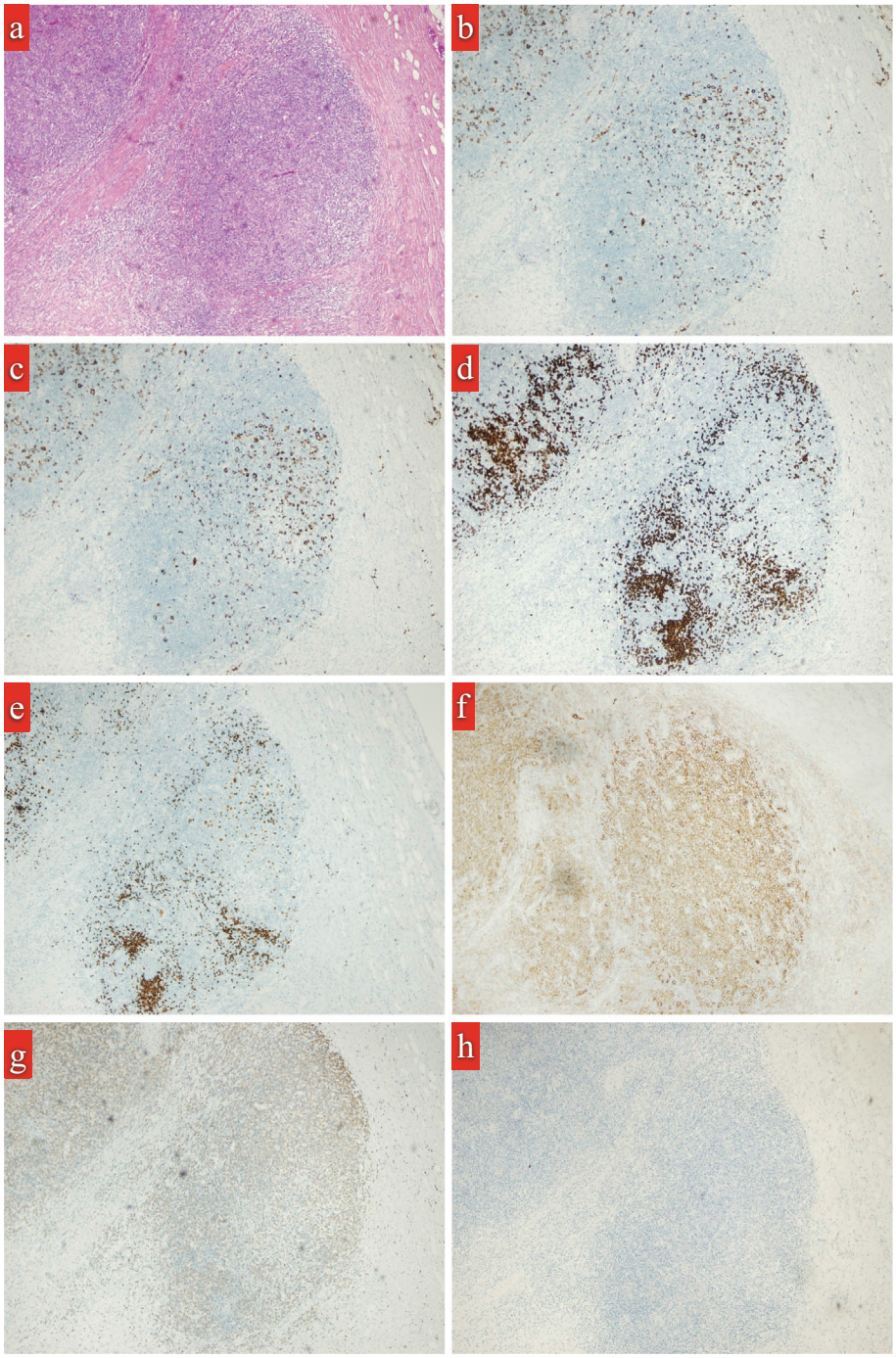

Figure 3. **Left inguinal lymph node biopsy findings. a: Hematoxylin and Eosin staining ×40; The nodular lesion is composed of collagen bundles. The lymph node capsule is thickened. Hodgkinoid cells are scattered or found in aggregates in the nodule. There are many small- to medium-sized lymphocytes and eosinophils around the lesion. b: CD30 ×40: positive. c: CD15 ×40: positive. d: CD20 ×40: negative. e: Paired box 5 (PAX5) ×40: positive. f: Programmed death ligand 1 (PDL-1) ×40: positive. g: CD3 ×40: negative. h: *In situ* hybridization EBV-encoded small RNA (EBER-ISH) ×40: negative.**

white blood cell count 15,600/μL, and differential lymphocyte count 530.4/μL).

In April, her cough and CT findings worsened (Fig. 2b), and the dose of PSL was increased from 5 to 25 mg/day. Even by 3 months after the discontinuation of MTX, her cough showed no improvement; therefore, she was started on CHOP (cyclophosphamide 750 mg/m^2, day 1; hydroxydaunorubicin 50 mg/m^2, day 1; vincristine 1.4 mg/m^2, day 1; PSL 100 mg/body, days 1-5), a regimen that was selected because, at that time, we had received only a preliminary report of a tentative pathological diagnosis of lymphoma. By May, the histopathological diagnosis was confirmed to be CHL-NS (see above), and the treatment was changed to BV +AVD [brentuximab vedotin 1.2 mg/kg by intravenous (iv)

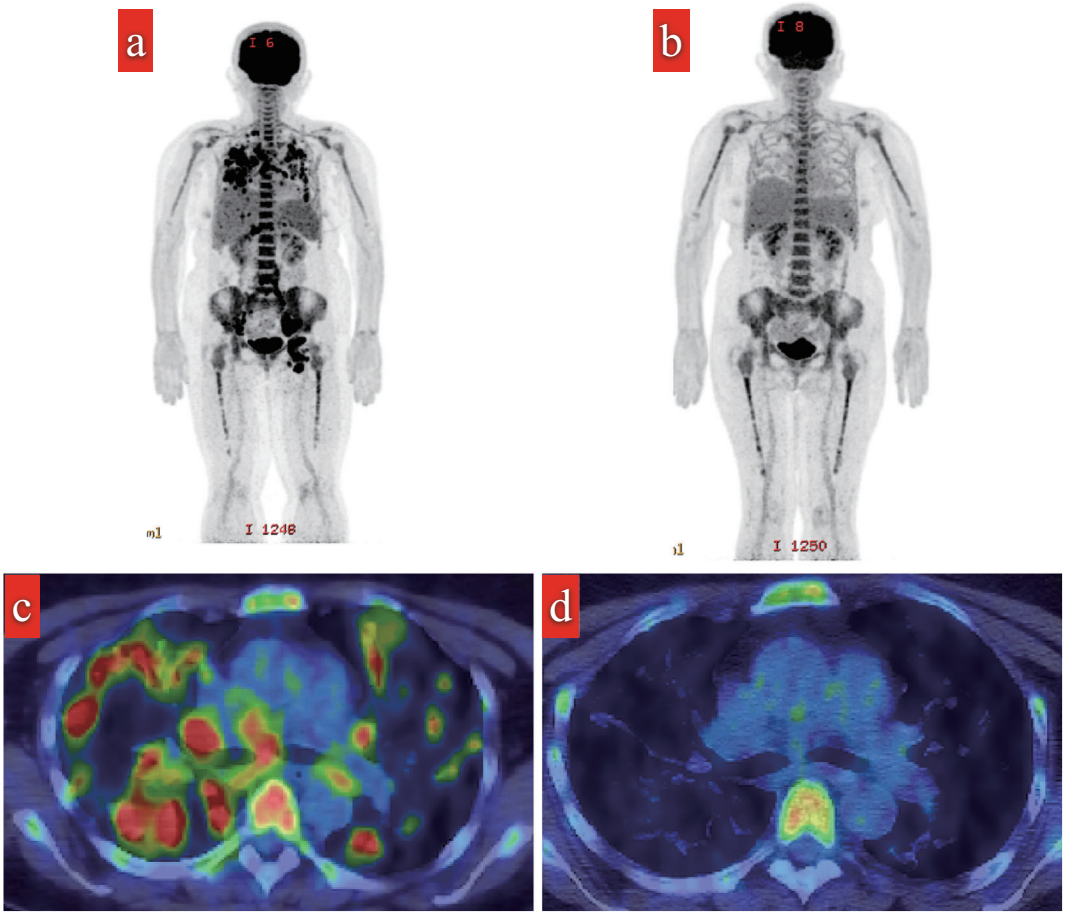

Figure 4. **PET/CT findings. a, c; The accumulation of FDG is seen in the bilateral supraclavicular, mediastinal, abdominal para-aortic, upper abdominal and iliac artery regions as well as in the left inguinal lymph nodes [maximum standard uptake value (SUVmax), 7.04-14.37]. Multiple areas of FDG accumulation are observed, including in the liver (SUVmax, 6.92), spleen (SUVmax, 6.07) and both lungs (SUVmax, 14.26). b, d; There is no significant FDG accumulation, suggesting CMR.**

drip infusion; adriamycin 25 mg/m^2 by iv injection, days 1, 15; vinblastine 6 mg/m^2 by iv injection, days 1, 15; dacarbazine 375 mg/m^2 by iv drip infusion, days 1, 15]. After completing 2 courses of BV+AVD, PET/CT confirmed a complete metabolic response (CMR) (Fig. 4b). She has completed six courses thus far, and the CMR of MTX-HL has been maintained. Multiple patchy infiltrative opacities are no longer present in either lung on CT (Fig. 2c). Grade 1 [Common Terminology Criteria for Adverse Events (CTCAE) v5.0] peripheral neuropathy was the only adverse event (AE) encountered, and there were no serious AEs. RA remission has also been maintained, with a DAS-28-CRP of 2.3.

Discussion

MTX-LPD is a type of OIIA-LPD that occurs in patients treated with MTX for autoimmune diseases (AIDs), such as RA (8). The number of patients receiving MTX for RA is increasing, and the incidence of MTX-LPD is also thought to be increasing (8, 9). MTX-HL is the second-most common MTX-LPD after diffuse large B-cell lymphoma (DLBCL) (8, 10-12).

Regarding treatment, the incidence of spontaneous remission after discontinuation of MTX is lower in MTX-HL than in MTX-DLBCL, and MTX-HL often requires additional chemotherapy (11, 13). The EBER-positive rate is also reported to be higher in MTX-HL than in MTX-DLBCL (8, 13).

There are no established standard chemotherapy regimens for MTX-HL, and a search of the literature showed that adriamycin, bleomycin (BLM), vinblastine and dacarbazine (ABVD), which are considered standard agents for the treatment of HL (*de novo* HL, also called non-MTX-HL), have been used (9, 13). However, BLM-induced lung toxicity has been reported to develop in 10-50% of CHL patients who receive ABVD treatment (7). MTX-CHL develops in patients with AIDs, such as RA frequently have pulmonary complications (7). In addition, MTX administration in patients with AIDs can also result in pulmonary adverse effects (7). Therefore, it would be ideal to avoid using BLM in the treatment of MTX-CHL (7), especially in patients with pulmonary complications.

The results of the ECHELON-1 study showed a signifi-

Table 2. Reports on the Treatment of MTX-HL with BV.

Case	age/sex	Primary immune disease	Immunom odulator	Biopsy site	Extra nodal site	Clinical stage	EBER
1	53/F	RA	PSL	Lung Inguinal LN	Lung	IV	-
2	55/F	RA	MTX	Axillary LN	-	III	n.a
3	83/M	RA	MTX	Supraclavicular LN	CBD Duodenum	IV	+
4	76/F	RA	Infliximab MTX PSL	n.a	n.a	IV	n.a
5	56/F	RA	MTX Golimuma b	Cervical LN	Bone Intestine	IV	-
6	45/F	RA	MTX	Cervical LN	-	III	+
7	40/F	SLE DM	MTX PSL CY	Axillary LN	-	III	+

Case	Immuno phenotype	Response after MTX discontinuation	Chemoprior BV	BV	Period from MTX-HL diag to initiation BV
1	CD15, 30, PAX5, PDL1	PD	PSL CHOP 1course	BV+AVD 6 courses	3M
2	CD15, 30	Failed to regression	ABVD 8 courses	BV 12 courses	ABVD 8 courses+12M
3	CD30, PAX5, IMP3, ki-67	Partially resolved→ PD	R-chemo 4 courses	BV 6 courses	2M+R-chemo 4 courses
4	CD15, 30, PAX5	n.a	-	BV 16 courses	n.a
5	n.a	Partially improved	-	BV+AVD 6 courses	soon
6	n.a	improved→ recurrence	-	BV+AVD 6 courses	immediately
7	n.a	regression	-	BV+AVD 6 courses	soon

Case	Response to BV	Final state MTX-HL	Final state immune disease	Final outcome	Follow up duration after MTX-HL diag	Ref
1	CR	CR	CR	Alive	12M	This Case
2	CR	CR	CR	Alive	ABVD 8 courses + 12M + A 12 courses	4
3	Markedly reduce	Progression	n.a	Dead after nivolmab 3 cycle	2M+R-chemo 4 courses + BV 6 courses + 1M + nivolmab 3 courses	5
4	CR	CR	CR	Alive	BV 16 courses	6
5	CR	CR	well control	Alive	BV+AVD 6 courses	7
6	CR	CR	well control	Alive	BV+AVD 6 courses	7
7	CR	CR	well control	Alive	BV+AVD 6 courses	7

EBER: EBV-encoded small RNA, MTX: methotrexate, BV: brentuximab vedotin, HL: Hodgkin lymphoma, diag: diagnosis, RA: rheumatoid arthritis, Ref: reference, F: female, M: man, PSL: prednisolone, LN: lymph node, n.a: not available, CBD: common bile duct, SLE: systemic lupus erythematous, DM: dermatomyositis, CY: cyclophosphamide, PAX5: paired box 5, PDL1: programmed cell death ligand 1, IMP3: insulin-like growth factor 2 mRNA-binding protein-3, PD: progression disease, CHOP: cyclophosphamide: doxorubicin: vincristine: prednisolone, ABVD: adriamycin, bleomycin, vinblastine, dacarbazine, R-chemo: rituximab-chemotherapy, BV+AVD: brentuximab vedotin, adriamycin, vinblastine, dacarbazine, CR: complete remission, M: months, ref: reference

cantly longer modified progression-free survival (mPFS) following BV+AVD than with ABVD in primary HL, suggesting that BV+AVD may become the standard treatment in the future (2). In addition, as the incidence of MTX-HL is also expected to increase in the future (8, 9), BV+AVD may see even more frequent use.

However, BV has thus far been administered only to seven cases with MTX-HL, including the present case, and this is only the fourth case of MTX-HL treated with BV+AVD (cases 1, 5-7 in Table 2). The underlying AID in six of the seven cases with MTX-HL treated with BV or BV+AVD was RA (cases 1-6 in Table 2) (4-7); the remaining patient had overlap syndrome of systemic lupus erythematous and dermatomyositis (case 7 in Table 2). The safety profile remains unknown.

In the present case, a complete response (CR) of HL was achieved after two courses of BV+AVD, and six courses have been completed so far. There have been no serious AEs, and the clinical course has been uneventful. A CR of RA has also been maintained.

A CR of HL was achieved in six of the seven cases, including the present case (cases 1, 2, 4-7 in Table 2) (4, 6, 7), with a marked reduction of the lesion size in the remaining one case (case 3 in Table 2) (5). However,

case 3 developed progressive disease (PD) after six courses of BV and received an additional three courses of nivolumab. Despite additional treatment, the patient died of PD. None of the seven cases developed any serious AEs.

Regarding RA, a CR or good control was maintained in six of the seven evaluable cases (cases 1, 2, 4-7 in Table 2) (4, 6, 7), and the status was unknown in the remaining case (case 3 in Table 2) (5). At present, there are no guidelines concerning the treatment of RA complicated by MTX-HL (4), and BV also appears to be a promising treatment for RA. The detailed mechanism of action of BV in patients with RA is unknown (4, 6). In RA patients, a high level of soluble CD30 (sCD30) has been reported in the blood and synovial fluid (4, 14). The complex CD30/CD30-ligand (CD30L) signaling pathway is involved in the pathogenesis of RA synovitis (4, 15). BV may alter the CD30/CD 30L interaction in RA (4).

In conclusion, BV+AVD is considered a safe and effective treatment for RA patients with MTX-HL, including those with pulmonary complications. The accumulation of more cases and the long-term follow-up of cases are needed in the future.

The authors state that they have no Conflict of Interest (COI).

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