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Case report

Administration of brentuximab vedotin to a Hodgkin lymphoma patient with liver dysfunction due to vanishing bile duct syndrome resulting in a partial response without any severe adverse events

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Vanishing bile duct syndrome (VBDS) is a rare hepatic disorder which leads to liver failure as a result of progressive destruction of the intrahepatic bile ducts. There are no treatment modalities for VBDS itself and severe hepatic dysfunction restricts the treatment of underlying diseases. We safely treated a case of classic Hodgkin lymphoma (HL) with VBDS using brentuximab vedotin (BV). The patient was treated with 5 cycles of reduced BV and a partial metabolic response was obtained. Moreover, a standard dose of BV for another 5 cycles was accomplished with minimal adverse events. Our experience indicates that BV could be a treatment option for classic HL with VBDS.

Keywords: vanishing bile duct syndrome, Hodgkin lymphoma, brentuximab vedotin, liver failure

INTRODUCTION

Vanishing bile duct syndrome (VBDS) is a very rare hepatic disorder which leads to cholestasis, biliary cirrhosis, and severe hepatic failure as a result of progressive destruction of the intrahepatic bile ducts.[1] Although its cause is unknown, VBDS occurs secondarily as a complication of a variety of disorders such as infections, autoimmune diseases, adverse drug reactions, allograft rejection, and neoplasms, including Hodgkin lymphoma (HL).[2] There are no treatment modalities for this syndrome; however, it has been documented that VBDS can be ameliorated during improvement of the underlying disease.[3] The current standard chemotherapy for untreated classic HL is ABVD (doxorubicin 25 mg/m^2 days 1 and 15, bleomycin 10 IU/m^2 days 1 and 15, vinblastine 6 mg/m^2 days 1 and 15, dacarbazine 375 mg/m^2 days 1 and 15), but it is usually difficult for those with VBDS to receive ABVD at the standard dose due to hepatic dysfunction. Brentuximab vedotin (BV) is an alternative therapy for classic HL; however, a dose reduction of BV should also be considered in patients with hepatic dysfunction.[4,5] There have been few reports describing experiences of the treatment of HL patients with VBDS using BV.[6,7] Here, we present a Japanese patient with HL and VBDS who received BV, and obtained a short-term response in HL without any severe adverse events.

CASE REPORT

A 35-year-old male with no significant medical history was admitted to a local hospital due to fever and progressive paresis of the lower limbs. Computed tomography (CT) showed a paravertebral tumor and compression fracture at Th11, multiple swollen lymph nodes, and extranodal lesions on the lungs, spleen, ribs, sacrum, and small intestine. Biopsy of a right inguinal lymph node was performed.

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Large lymphocytes with multiple nuclei were seen with fibrosis and loss of the normal lymph node structure. Abnormal lymphocytes showed cohesive growth with eosinophil infiltration. The tumor cells were CD30-positive, CD3- and CD5-negative, CD15-negative, CD20-negative, and focally positive for CD45 and Granzyme-B. ALK was negative. Diagnosis of ALK-negative anaplastic large cell lymphoma (ALCL) at Ann Arbor stage IVB was given.

Shortly after hospitalization, the serum bilirubin level increased to over 5 mg/dL. Abdominal ultrasonography and CT were performed again but hepatic lesion of the lymphoma was not detected. Drugs which had a possibility of inducing drug-induced hepatic injury had not been administrated. Serological analysis did not detect hepatitis virus A, B, C, and E, or human immunodeficiency virus. In the evaluation of Epstein-Barr virus, VCA-IgM was negative, and VCA-IgG and EBNA were positive. Cytomegalovirus antigenemia was negative. Anti-nuclear antibody, anti-mitochondria M2 antibody, and anti-smooth muscle antibody were negative. From these results, hepatic infiltration of the lymphoma was suspected, and the patient was treated with high dose methylprednisolone (500 mg/day, 3 days) and ursodeoxycholic acid, but his jaundice continued to worsen. Subsequently, cyclophosphamide (375 mg/m^2, 1 day) and cisplatin (25 mg/m^2, 3 days) were administered, but these showed no therapeutic effect. Liver biopsy was performed after the administration of cisplatin, and no obvious findings of infiltration of the lymphoma cells were observed in the liver specimen.

One month after admission, the patient was transferred to our institution. The laboratory findings for liver function at this time are shown in Table 1. We performed liver biopsy again, and the liver specimen obtained at the previous hospital was also reviewed. A lack of bile ducts in more than 50% of the portal tracts and cholestasis were revealed in both samples, with no evidence of infiltration of lymphoma or fibrosis (Figure 1A–C). These findings were consistent with a diagnosis of VBDS. Although the association between VBDS and ALCL was unclear, we administered three salvage therapies with dose reduction. These were CHOP (cyclophosphamide 560 mg/m^2 day 1, doxorubicin 12.5 mg/m^2 day 1, PSL 100 mg/day days 1-5; vincristine was omitted), DeVIC (ifosfamide 1,500 mg/m^2 days 1–3, carboplatin 300 mg/m^2 day 1, dexamethasone 39.6 mg/day days 1–3; etoposide was omitted), and modified ESHAP (carboplatin AUC=1.25 days 1–4, etoposide 40 mg/m^2 days 1–4, cytarabine 2,000 mg/m^2 day 5, methylprednisolone 500 mg/day days 1–5); however, none of them were effective (Table 1). The patient and his family consulted another medical institution asking for a second opinion. The specimens of the lymph node sampled at the previous hospital were reviewed there with additional immunostaining using unstained specimens, and a diagnosis of nodular sclerosis classic HL was proposed. The lymph node specimens were also reviewed at our hospital (Figure 2). The large lymphocytes were mononuclear or had a bilobated nucleus with prominent nucleoli, being morphologically compatible with Hodgkin cells and Reed-Sternberg cells. Fibrosis and spindle-shaped cells were seen in the background. The tumor cells were CD30- and CD15-positive, CD3-, CD5- and CD7-negative, CD20-negative, ALK-negative, and PAX5-positive. EBV-encoded small RNAs -*in situ* hybridization (EBER-ISH) was negative. Because some cases of VBDS associated with HL had been reported,[8] whereas there had been few reports describing VBDS with ALCL, a diagnosis of HL was more consistent with his clinical course than ALCL. As a result of these evaluations and discussion, especially due to the PAX5-positivity, he was finally re-diagnosed with nodular sclerosis classic HL.

Because the tumors were refractory to the preceded multiple chemotherapies and his hepatic function was not recovered at all, we chose BV, not ABVD, as the next salvage therapy. The standard dose of BV is 1.8 mg/kg once every three weeks, but we reduced the dose to 1.2 mg/kg because of his hepatic dysfunction with a Child-Pugh score of 10 points and class C just before the start of BV. A reduction in the size of the lung tumors was revealed by chest radiography after the first administration of BV, and the serum bilirubin level decreased from over 12 mg/dL to around 9 mg/dL. After 5 cycles of BV, PET-CT showed a partial metabolic response in HL (Table 1). However, improvement of jaundice was temporal, and the serum bilirubin level increased and returned to

Table 1. Clinical course of the presented case

Time from diagnosis		Chemotherapy regimen	Number of courses	Pre-treatment			Post-treatment			Response in HL	
				LDH (U/L)	T. Bil (mg/dL)	ALP (U/L)	LDH (U/L)	T. Bil (mg/dL)	ALP (U/L)		
3	weeks	CY+CDDP	1	(transferred to our hospital after CY + CDDP)			341	15.6	3,023	Progressive disease	[PD]
2	months	CHOP	1	320	19.9	2,861	334	14.5	3,916	Progressive disease	[PD]
2.5	months	DeVIC	2	342	16.4	3,589	193	15.5	2,762	Progressive disease	[PD]
4	months	modified ESHAP	1	267	15.8	2,513	217	12.2	2,507	Progressive disease	[PD]
5	months	BV (1.2 mg/kg)	5	226	12.5	3,403	133	11.1	1,483	Partial response	[PR]
8.5	months	BV (1.8 mg/kg)	5	129	10.9	1,820	187	12.3	2,361	Stable Disease	[SD]
13	months	Gemcitabine	1	196	8.5	2,305	184	12.1	2,553	Progressive disease	[PD]

HL, Hodgkin lymphoma; CY, cyclophosphamide; CDDP, cisplatin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; DeVIC, ifosfamide, carboplatin, dexamethasone (etoposide was omitted); modified ESHAP, carboplatin, etoposide, cytarabine, methylprednisolone; BV, brentuximab vedotin; LDH, lactate dehydrogenase; T. Bil, total bilirubin; ALP, alkaline phosphatase.

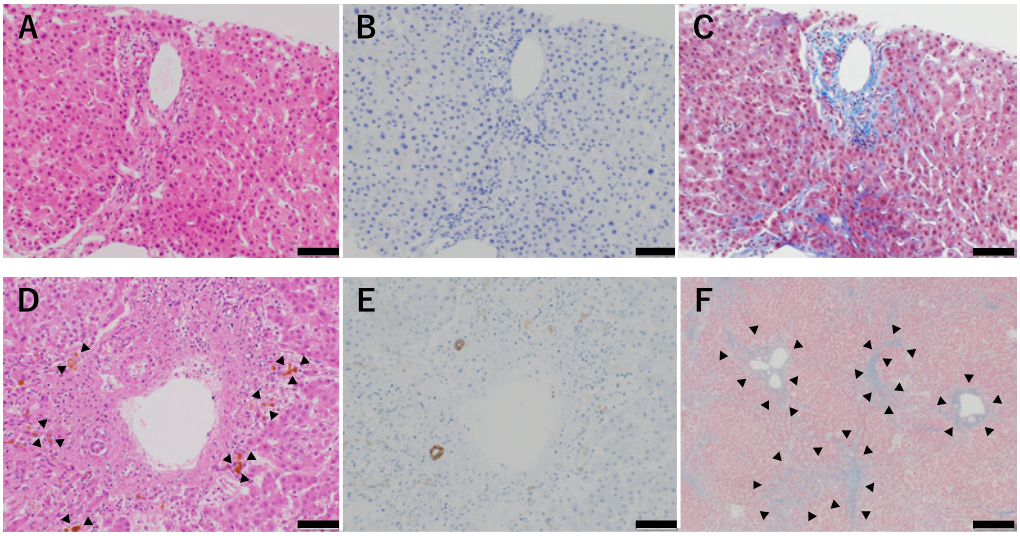

Fig. 1. Vanishment of bile ducts in the liver specimens
Microscopic findings of the liver biopsy at onset (***A***–***C***) and the autopsy (***D***, ***E***). Bile ducts were absent in the portal tracts [***A***, Hematoxylin and Eosin (HE) staining, ×200]. Cytokeratin 19 (CK-19) staining, a marker of epithelial cells of the bile ducts, was negative (***B***, ×200). Fibrosis was not detected at the disease onset [***C***, Masson's Trichrome (MT) staining, ×200]. In the autopsy samples, severe progression of cholestasis (arrowheads) was demonstrated (***D***, HE staining, ×200). The loss of bile ducts was still seen (***E***, CK-19 staining, ×200), and diffuse liver fibrosis (arrowheads) emerged (***F***, MT staining, ×100). Scale bars correspond to 100 μm (***A***–***E***), or to 500 μm (***F***).

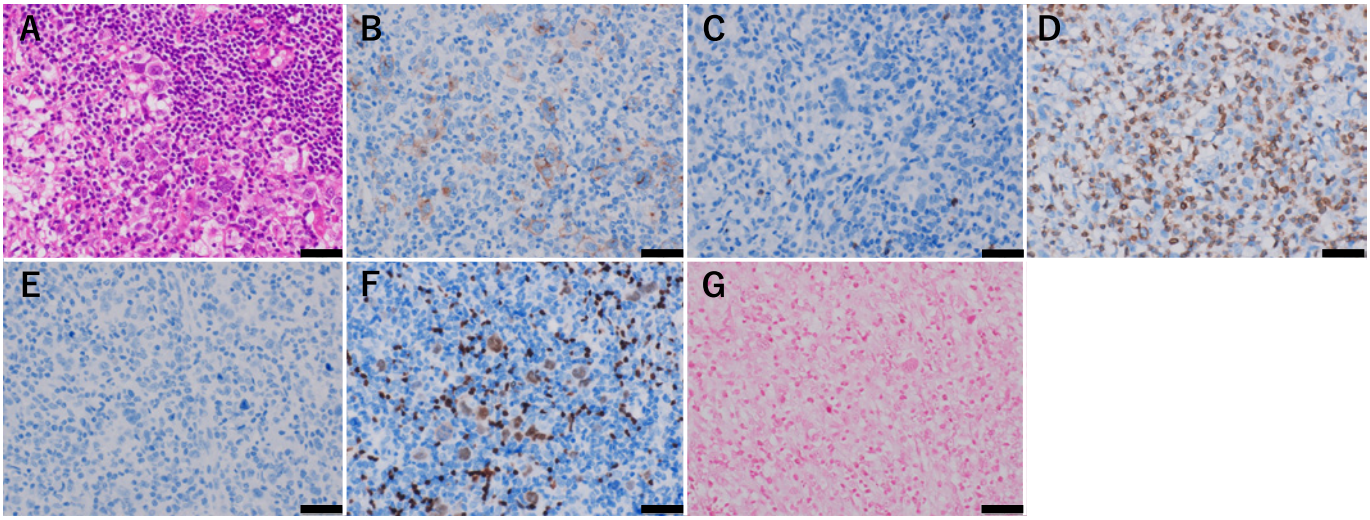

Fig. 2. Lymph node biopsy specimen
Hodgkin cells and Reed-Sternberg cells were observed (***A***, Hematoxylin and Eosin staining, ×200). The tumor cells were CD30-positive (***B***, ×200), CD20-negative (***C***, ×200), CD3-negative (***D***, ×200), ALK-negative (***E***, ×200), Pax5-positive (***F***, ×200) and EBER-ISH-negative (***G***, ×200). Scale bars correspond to 50 μm.

the level before BV administration. No adverse events occurred during 1.2 mg/kg of BV, thus, we increased the dosage of BV to 1.8 mg/kg. Although grade 2 stomatitis and grade 2 diarrhea in the Common Terminology Criteria for Adverse Events (ver. 4.0) occurred, almost all fluorodeoxyglucose-avid lesions diminished in PET-CT after 4 cycles of BV at 1.8 mg/kg. However, one viable lesion remained in the axis (C2), and the serum bilirubin level did not improve during the BV administration at 1.8 mg/kg. One month later, a new lesion developed in the spinous process of the atlas (C1), followed by emergence of peripheral neuropathy. After a total of 5 cycles at 1.8 mg/kg, BV was discontinued due to disease progression and neuropathy. Finally, systemic relapse of HL occurred, including growth of the tumor in C2, and his sensory disorder severely deteriorated even after cessation of BV. Gemcitabine was administered without any effects. The patient died due to progression of HL at 1 year and 9 months after the onset. In the autopsy, in comparison to the liver biopsy at the onset, the degree of bile duct loss showed no change or a slight improvement, but deteriorated cholestasis and severe fibrosis were seen (Figure 1D–F). Systemic involvement of HL was found but hepatic infiltra-

tion was still not detected. Any other pathological findings including sinusoidal obstruction syndrome (SOS) were not detected.

DISCUSSION

The detailed mechanism of how VBDS occurs along with HL is yet to be elucidated, but a previous report discussed it from clinical aspects.[1] One explanation is that infiltrated lymphoma cells in the portal vein may eradicate adjacent intrahepatic bile ducts directly. In our case, hepatic infiltration of the lymphoma cells was not observed, but it was difficult to exclude this possibility because the liver biopsies were performed only after initiation of the treatment for lymphoma. Another explanation is that destruction of the hepatic bile ducts may be caused by toxic cytokines released from lymphoma cells and recruited immune effector cells. Demonstration of this immunological mechanism is a challenge for the future.

In our case, severe liver fibrosis was found on the autopsy, but not at the onset of VBDS. A previous report described that periportal fibrosis appeared in a patient with HL and VBDS more than 1 year after the onset.[1] In this case, like ours, chronic liver failure had continued for a long time. Therefore, we presumed that sustained liver injury due to VBDS caused the gradual destruction of hepatic tissue leading to the diffuse fibrosis.

Standard treatments of VBDS have not been established. The only potential method for resolving VBDS is to treat and improve the underlying diseases. According to an analysis of 37 previously published cases of HL-related VBDS or idiopathic cholestasis, the 1 year overall and non-liver failure survival was 43% and 41%, respectively.[3] In this analysis, stage I/II HL, a complete response of HL, and delivery of radiotherapy were significantly associated with improved liver failure-free survival. However, the authors discussed that the better prognosis in the patients treated with radiotherapy could be confounded by more advanced diseases in the patients who received only chemotherapy. In fact, our case had advanced disease with no indication of radiotherapy.

Although BV is a good treatment option for relapsed/refractory classic HL,[4] we could find only two reports which described the experience of using BV in patients with HL and VBDS.[6,7] In one report, a case of HL with VBDS was treated with 4 courses of cyclophosphamide-based chemotherapy, and from cycle 5, after a partial metabolic response was obtained, BV was concomitantly administered with the chemotherapy.[6] In this case, the dose of BV was reduced to 1.2 mg/kg due to persisting liver dysfunction after obtaining partial remission. In another report, BV monotherapy was administered to 5 cases of HL with hepatic disorder, including 2 cases with VBDS.[7] The initial dose of BV was 1.2 mg/kg, and the dose was increased to 1.8 mg/kg if the serum bilirubin decreased to <5 mg/dL. The liver function became normal in all cases after 41 to 154 days from the start of BV. Subsequently, 6 courses of ABVD were performed. Complete remission was obtained in 2 cases with VBDS. Severe adverse events were not seen. In our case, BV was also started at 1.2 mg/kg, and the patient achieved a partial metabolic response without any adverse events, but the decrease in the serum bilirubin level was limited. We thought that amelioration of VBDS could not be obtained without remission of HL, and thus increased the dose of BV to 1.8 mg/kg. Although this resulted in a temporal but significant response of HL, improvement in the serum bilirubin level was not achieved. The patient showed numbness and paralysis of the lower limbs. These symptoms were probably due to neuropathy caused by spinal lesions of HL, not due to BV, because the symptoms continued to worsen despite cessation of BV.

The present case, together with the previously reported ones, indicates that a reduced dose of BV at 1.2 mg/kg could be an effective and relatively safe treatment option for patients with HL and VBDS. For the establishment of an optimal treatment strategy for HL with VBDS, further experiences are needed.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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