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# Durable Response to Brentuximab Vedotin-Based Chemotherapy in Refractory Hodgkin Lymphoma with Central Nervous System (CNS) Involvement

## Authors' Contribution:

Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

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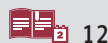
<b>Patient:</b>	<b>Female, 29-year-old</b>
<b>Final Diagnosis:</b>	<b>Refractory Hodgkin lymphoma with CNS involvement</b>
<b>Symptoms:</b>	<b>Blurred vision</b>
<b>Medication:</b>	—
<b>Clinical Procedure:</b>	—
<b>Specialty:</b>	<b>Hematology</b>
<b>Objective:</b>	<b>Rare disease</b>
<b>Background:</b>	CNS involvement in Hodgkin lymphoma is rare. Despite various treatment options, median overall survival is only 13 months after diagnosis of CNS involvement in relapsed/refractory HL.
<b>Case Report:</b>	A 29-year-old woman with classical HL (mixed cellularity) in clinical stage IIB was treated with multilineage chemotherapy and radiotherapy without achieving a sustained complete remission. Systemic and CNS progression of HL occurred at the age of 32 years and the patient received 2 cycles of brentuximab vedotin with bendamustine alternating with 2 cycles of high-dose methotrexate-based treatment and achieved partial remission. She then underwent autologous stem cell transplantation followed by brentuximab vedotin consolidation. The disease progressed and the patient died 6 months after the last dose of brentuximab vedotin.
<b>Conclusions:</b>	We demonstrated a durable response to brentuximab vedotin-based chemotherapy in a patient with refractory Hodgkin lymphoma with CNS involvement. Prognosis of these patients is poor and new treatment options are needed.
<b>MeSH Keywords:</b>	<b>Antineoplastic Agents • Central Nervous System • Hodgkin Disease</b>
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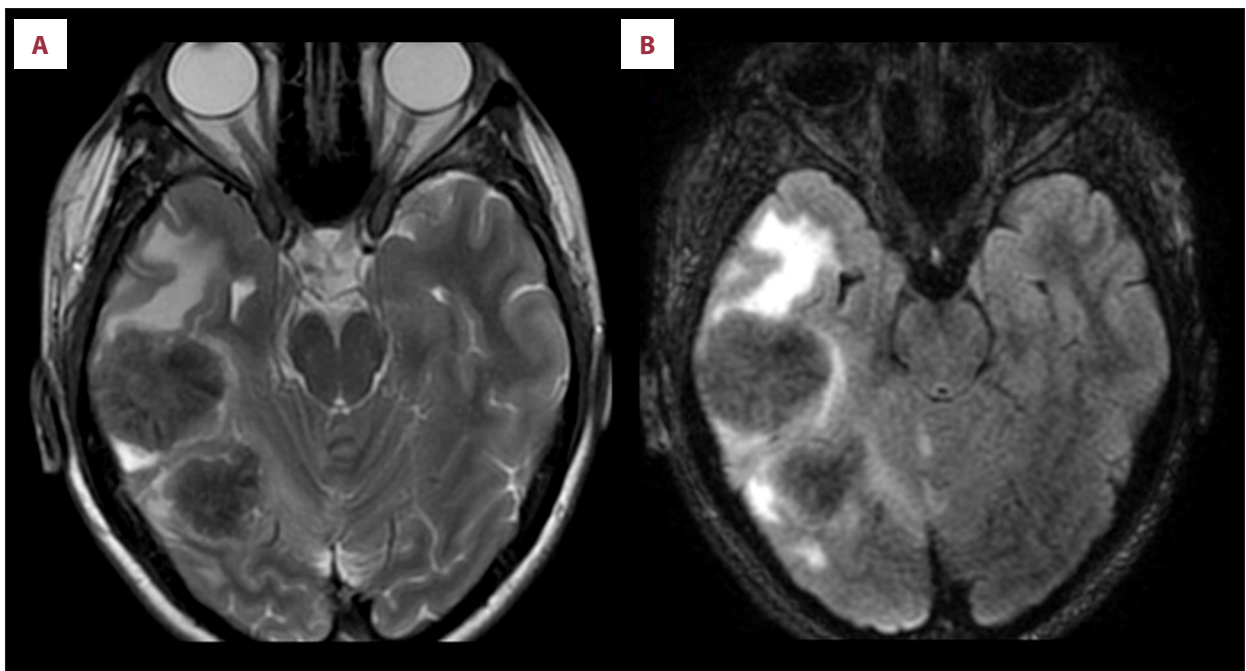
## Background

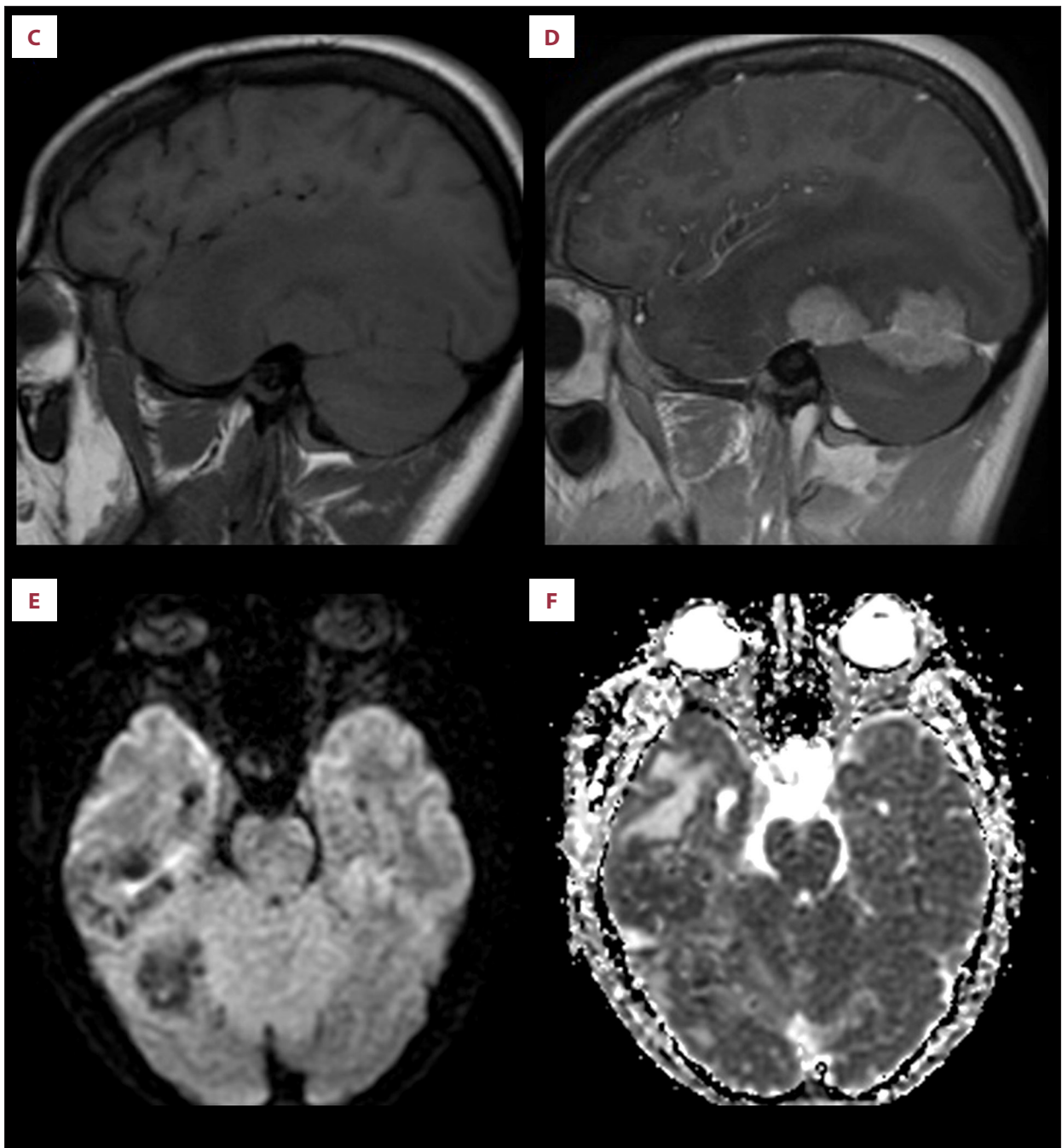
The incidence of CNS involvement in Hodgkin lymphoma (HL) is 0.07% [1]. It can occur at the time of diagnosis or in the case of relapsed/refractory disease. Cerebral parenchymal disease, as well as meningeal involvement without parenchymal lesions, can be detected [2]. Risk factors for the dissemination of HL into CNS are unknown due to the limited number of patients and heterogeneity of data. Various treatments were used in these patients, including surgical resection, corticosteroids, radiation, multiagent systemic chemotherapy, and autologous stem cell transplantation (ASCT) [1]. We report the case of a patient with refractory Hodgkin lymphoma with CNS involvement who achieved durable response with brentuximab vedotin-based chemotherapy.

## Case Report

A 29-year-old female patient with classical HL (mixed cellularity, EBV-negative) in clinical stage IIB was treated with multilincage chemotherapy (6x ABVD, 3x ICE, 4x ASHAP, involved field irradiation of 30 Gy on cervical lymph nodes, 2x gemcitabine and vinorelbine, steroid treatment) without achieving a sustained complete remission, and HL was considered refractory to conventional chemotherapy and radiotherapy. After the above-mentioned treatment at the age of 32 years, the patient suffered from headache and blurred vision. A new biopsy of the cervical lymph node confirmed the diagnosis of HL (type nodular sclerosis with aberrant expression of CD3 and CD4). A whole-body positron emission tomography/computed

tomography (PET/CT) scan confirmed clinical stage IVA: fluoro-deoxyglucose (FDG) avid lymph nodes on both sides of the diaphragm with diffuse skeletal, muscle, liver, and right lung involvement. Head/neck magnetic resonance imaging (MRI) revealed involvement of cervical lymph nodes, parotid glands, and prominent intracranial meningeal lesions, with perifocal edema (Figure 1). The MRI indicated per continuitatem propagation of lymphoma from extra-cranial lesions through the external auditory canal and mastoid cells to the CNS. A lumbar puncture was performed and cerebrospinal fluid tested negative for lymphoma involvement (cytology, biochemistry, flow-cytometry). A neurological examination revealed no abnormalities. Treatment consisted of 2 cycles of BVB: brentuximab vedotin 1.8 mg/kg i.v. on day 1 and bendamustine 90 mg/m<sup>2</sup> i.v. on days 1–2 (q 3 weeks) alternating with 2 cycles of high-dose methotrexate 3.5 g/m<sup>2</sup> i.v. and procarbazine 100 mg/m<sup>2</sup> orally on days 2–8 (q 2 weeks). Concurrent steroid treatment included daily dexamethasone 16 mg administered orally with a tapering dose of 4 mg weekly. CNS prophylaxis with methotrexate 12 mg, hydrocortisone 50 mg, and cytarabine 40 mg was delivered during the first cycle of BVB. Peripheral stem cell collection was performed after the second cycle of BVB, and filgrastim 10 ug/kg/d s.c. with plerixafor 0.24 mg/kg s.c. was used for stem cell harvesting. The patient underwent 2 sessions of apheresis and 4.03×10<sup>6</sup>/kg CD34+ cells were collected. The patient achieved a partial remission according to the whole-body and brain PET/CT after 4 cycles of salvage treatment before high-dose chemotherapy. The conditioning regimen included carmustine 400 mg/m<sup>2</sup> i.v. day –5, thiotepa 2×5 mg/kg i.v. days –4 and –3, etoposide 150 mg/m<sup>2</sup> i.v. days –5 to –3, followed by stem cell infusion on day 0. Neutrophil





**Figure 1.** Initial brain MRI. Two communicating intracranial extra-axial lesions, both hyposignal on T1 WI, T2 WI, and DWI, with significant postcontrast enhancement on SE T1 WI. Both lesions are surrounded by perifocal edema (A, TSE T2 WI axial scan; B, T2 FLAIR axial scan; C, D, native and postcontrast SE T1 WI, sagittal scans; E, F, DWI and ADC map, axial scans).

and platelet engraftments were reported day +10 after ASCT, without significant toxicity. Consolidation treatment with BV 1.8 mg/kg i.v. (16 cycles) was commenced on day +30 after ASCT. Both systemic and CNS progression of HL occurred 6 months after the last dose of BV and the patient died due to progression of HL.

## Discussion

Standard treatment of HL in CNS is not established, as the incidence is very low and few case reports have been published. Cheah et al. summarized international data from 21 patients with primary or secondary CNS involvement in HL [1]. With the exception of surgical intervention and RT (median dose of

30 Gy), various chemotherapy regimens were used (BEACOPP escalated, HD MTX+cytarabine+thiotepa, ESHAP, prednisone and intrathecal MTX, ABVD, dexamethasone alone, rituximab+ifosfamide+etoposide+cytarabine alternating with 2x HD MTX, ICE, BV+bendamustine, ifosfamide+mitoxantrone+dexamethasone followed by 4x BV, intrathecal liposomal cytarabine). Two patients with CNS refractory disease underwent second-line chemotherapy and consolidative autologous stem cell transplantation. The overall response rate was 65%. A median follow-up of 3.6 years (range 0.8–13.2) since diagnosis of CNS HL was observed, and the median progression-free survival (PFS) and overall survival (OS) were 7.6 and 29 months, respectively [1]. Relapsed/refractory HL in CNS had an inferior median PFS (4 vs. 14 months,  $P=0.002$ ) and OS (13 vs. 105 months,  $P=0.004$ ) as compared to initial CNS involvement. The BV chemotherapy regimen is highly effective in relapsed/refractory systemic HL [3], and the addition of filgrastim with plerixafor enables collection of a sufficient amount of stem cells. Despite the fact that there is no evidence that brentuximab vedotin can cross the blood-brain barrier (BBB), penetration is potentially possible if the BBB is disrupted by dissemination of systemic lymphoma into the CNS. BV alone is not sufficient to control CNS disease [4]; however, combined regimens like BV with high-dose methotrexate or hyperCBAD (modified HyperCVAD with BV instead of vincristine) were successfully used in 2 patients with refractory anaplastic large T cell lymphoma with CNS disease [5,6]. BV and topotecan were used in a patient with refractory CD30+ diffuse large B cell lymphoma with leptomeningeal involvement and resulted in a significant response [6]. Bendamustine alone has shown efficacy in refractory HL and a transient effect in refractory primary CNS lymphoma [7]. Treatment with high-dose methotrexate, procarbazine, and dexamethasone, as well as thiotepa-based

high-dose chemotherapy, were chosen in our patient as these drugs are commonly used in primary CNS lymphomas [8,9]. The above-mentioned chemotherapy combination achieved a partial remission. BV consolidation is indicated in patients with a high risk of progression after ASCT [10]. Radiotherapy of the brain was not indicated, as the patient was refractory to irradiation during the initial treatment. The checkpoint inhibitor nivolumab is active in relapsed systemic HL [11] and it was used in 4 patients with relapsed/refractory PCNSL and in 1 primary testicular lymphoma patient with CNS relapse. All 5 patients had clinical and radiological responses and 3 patients remained progression-free at 13+ to 17+ months [12]. Other new drugs like ibrutinib, temsirolimus, lenalidomide, and pomalidomide are being tested in primary CNS lymphomas in ongoing trials.

## Conclusions

We demonstrated partial response lasting 18 months after combined treatment with BV in a pretreated HL patient with systemic and CNS involvement. Prognosis of these patients is poor and new treatment options should be investigated.

## Department and Institution where work was done

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## Conflict of interest

None.

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