

CASE REPORT

Effective treatment of advanced Hodgkin lymphoma with a modified BEACOPP regimen for a patient with demyelinating hereditary motor and sensory neuropathy type 1 (HMSN1)

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Abstract

Treatment for Hodgkin lymphoma (HL) in adults comprises substantial risk of chemotherapy-induced peripheral neurotoxicity. Here, we describe the case of patient with Charcot–Marie–Tooth disease or HSMN1 and advanced Hodgkin lymphoma undergoing treatment with modified BEACOPP achieving complete remission without major aggravation of neurological symptoms.

KEYWORDS

hematology, Hodgkin, lymphoma, neurology, neuropathy

1 | INTRODUCTION

The therapeutic strategy for Hodgkin lymphoma is designed according to the Ann-Arbor staging classification, additional risk factors and the age of the patient.¹ Depending on the country, two main regimens for Hodgkin lymphoma (HL) build the standard (individually or in combination), ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone). Advantages of the

ABVD regimen are the lower toxicities and overall costs. The BEACOPP regimen—originally developed by the German Hodgkin Study Group—provides higher and longer remission rates, but with more side effects and higher toxicities, such as neuropathies, lung damage and secondary acute myeloid leukemia/myelodysplastic syndrome (AML/MDS).¹ In many parts of the world, BEACOPP is the standard regimen to treat advanced HL followed by optional radiotherapy.^{2,3} Chemotherapy-induced toxicity to the lung caused by bleomycin is an important issue in the ongoing development of new treatment strategies.⁴

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However, chemotherapy-induced neurotoxicity mainly caused by etoposide, cyclophosphamide and especially vincristine remain a frequently observed side effect of actual treatment strategies.⁵

The hereditary motor and sensory neuropathy (HMSN), also known as Charcot–Marie–Tooth disease, is characterized by a dysfunction of the myelin sheath causing an innate neuropathic disorder.⁶ HMSN is caused by mutations in the genes that produce the proteins involved in the structure and function of either the peripheral nerve axon or the myelin sheath. Depending on the localization of the mutation (in chromosome 17 or 1), many forms of HMSN disease may occur, including a demyelinating type HMSN1,⁷ an axonal type HMSN2⁸ or an intermediate Type.⁶ HMSN1A is an autosomal dominant disease that results from a duplication of the gene on chromosome 17 that carries the instructions for producing the peripheral myelin protein-22 (PMP-22). The PMP-22 is a membrane protein that is a critical component of the myelin sheath.⁹ Overexpression of the respective gene disrupts the structure and function of the myelin sheath protein. The most frequent and relevant mutations for HMSN1 are duplications and point mutations in the PMP-22 gene. Further mutations in the MPZ, LITAF, SH3TC2, MTMR2, and GDAP1 genes may also cause HMSN1 but less frequently.¹⁰ The consequences of the mutations are shortened myelin sheath¹¹ and a neuropathic disorder characterized by progressive muscle weakness starting

on feet and hands, decrease of muscles mass, pes cavus, equine gait, loss of reflexes, painful dysesthesias, and distal sensory loss particularly of the lower limbs.¹² The clinical course of the HMSN1 subtype is characterized by a fast progression and a high risk for a non-ambulatory follow-up before the age of 20.¹³ However, despite the symptoms being frequently manifest during the first or second decade of life, some patients remain free of symptoms and present a cryptic form with mild or even without apparent clinical symptoms.

We report the first case of an effective treatment of a HMSN1 patient with HL and potentially neurotoxic chemotherapeutic regimen with achievement of complete remission and no clinically relevant treatment-related aggravation of neurologic symptoms.

2 | CLINICAL CASE

In April 2014, a 30-year-old male patient presented in our outpatient care unit with persistent lymphadenopathy of the right neck for several weeks. In addition, the patient presented B symptoms such as night sweats and weight loss (>10% body weight within 3 months). The patient had, as pre-existing disease, a demyelinating hereditary motor and sensory neuropathy (HMSN1), characterized by an heterozygous point mutation, c.256C>T, p.Gln86X(p.Q86X) in the PMP22-gene. A computed

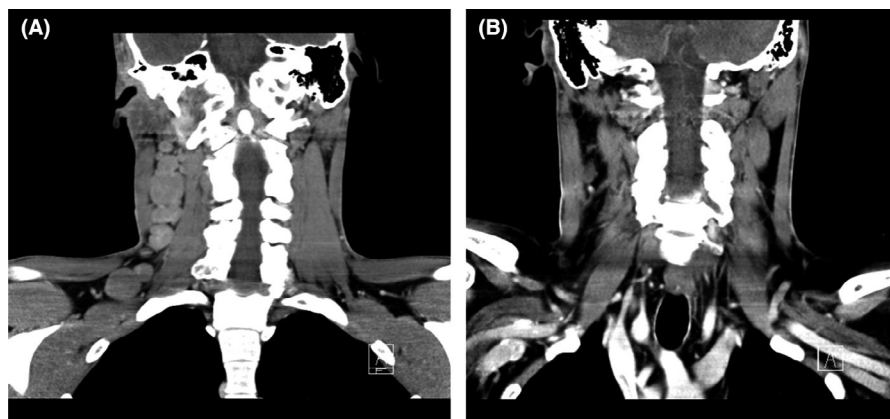


FIGURE 1 (A) CT scan before and (B) after 6 cycles modified BEACOPP

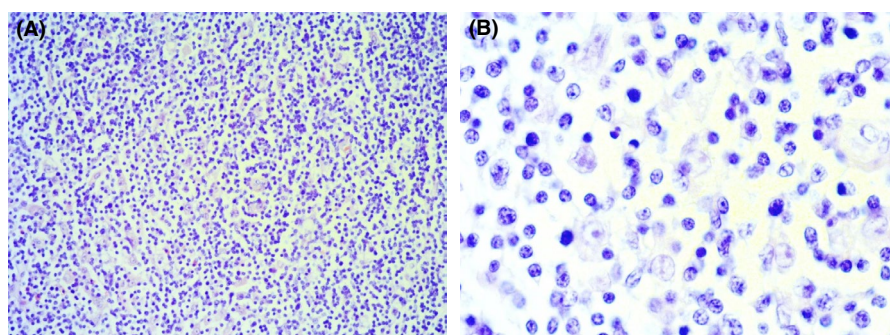


FIGURE 2 H&E staining of the right cervical lymph node. (A) 100× magnification, (B) 200× magnification

tomography (CT) scan showed suspicious lymph nodes in the right cervical and supraclavicular region (Figure 1) and in the left jaw angle, consistent with HL. Thorax and abdomen CT imaging did not show evidence of manifestations except for relevant splenomegaly. Cervical lymph node biopsy was carried out and histological analysis revealed an EBV positive mixed cellularity classic Hodgkin lymphoma (Figures 2 and 3). The patient was staged IIIB according to the Ann-Arbor classification. Considering the advanced staging and the increased patient's risk for substantial neurotoxic side effects due to HMSN1, a modified BEACOPP regimen (without vincristine) was used for treatment. The regimen was chosen and modified taken into account the previous published literature, the known neurotoxic effects of the respective substances and the need for treatment of the newly diagnosed Hodgkin lymphoma. The ABVD regimen was not chosen as first-line treatment due to reduced effectiveness of ABVD in the absence of vinblastine in advanced stages of HL and the expected substantially increased toxicity of salvage regimens as, for example, Brentuximab, DHAP followed by high-dose BEAM in HMSN1 patients in case of a relapse. The modified BEACOPP regimen was given with the standard dosages of bleomycin at 10 mg/m² (Day 8) etoposide at 200 mg/m² (Day 1–3), doxorubicin at 35 mg/m² (Day 1), cyclophosphamide at 1250 mg/m² (Day 1), procarbazine 100 mg/m² (Day 1–7) and prednisone 40 mg/m² (Day 1–14). The first cycle of modified BEACOPP was administered in the hematological hospital ward for best control of possible side effects. Since the first cycle was tolerated without any side effects, all subsequent cycles were administered in an outpatient setting. CT scan assessment after two and four cycles revealed a good partial response to the modified BEACOPP regimen. Light neuropathic symptoms described as tingling sensation in the fingers developed after the third therapy cycle. Based on the potential for neurotoxicity of cyclophosphamide and the good response to treatment, the drug was eliminated from the patient's regimen for the three remaining cycles. The tingling symptoms persisted but were manageable with administration of low-dose gabapentin. The modified BEACOPP regimen was completed as scheduled and without additional toxicities or adverse events. The final CT evaluation after 6 cycles of modified BEACOPP detected

a residual lymph node (with a diameter of 1.1 cm). An additional PET-CT scan showed no metabolic activity in the lymph node. No additional treatment was initiated and the patient remained in complete remission (CR) during regular clinical follow-up for over 6 years after end of treatment. In addition, the known HMSN1 did not show signs of progression or new symptoms (Table 1).

3 | DISCUSSION

Treatment of patients with HMSN and cancer is challenging, and few data are available regarding the oncologic^{14–21} and neurologic outcome of these patients.^{14–41} An established therapeutic strategy for patients with hereditary neuropathy with concomitant malignant diseases is not clearly defined. Regarding the literature, only a limited number of cases are described.^{14–44} Most of the case reports address the role of vincristine and the aggravation of neuropathic features in presence of cryptic or mild HMSN forms. Here, the diagnosis of HMSN was established based on the unsuspected chemotherapy-induced neurological aggravation. The most frequently reported symptoms of neurological deterioration were tetra-paresis, bulbar dysfunction as severe neurotoxic effects and hypesthesia and areflexia leading to substantially impaired quality of life.^{16,22,25,27,28,31,39,40}

Regarding the oncologic outcome, very few data are available.^{14–21} Some cases report good oncological responses in the majority of cases of acute leukemic leukemia (ALL) but also after renal tumors and non-Hodgkin lymphoma (NHL).^{14–21} However, clinically relevant and hardly controllable neurological side effects were again frequently observed, induced by the respective chemotherapies containing vincristine.^{14–21,44}

In our case, facing an already established diagnosis of HMSN1 and previously published literature on chemotherapy-induced neurotoxicity in HMSN1, we decided to adapt a BEACOPP regimen to treat a HL patient. The ABVD protocol without vinblastin was considered to be not sufficient to induce long-term remission in advanced Hodgkin disease. Brentuximab was also excluded due to the high rate of neurotoxicity. We modified the standard protocol by eliminating vincristine from the regimen, in order to avoid possible known vincristine-induced

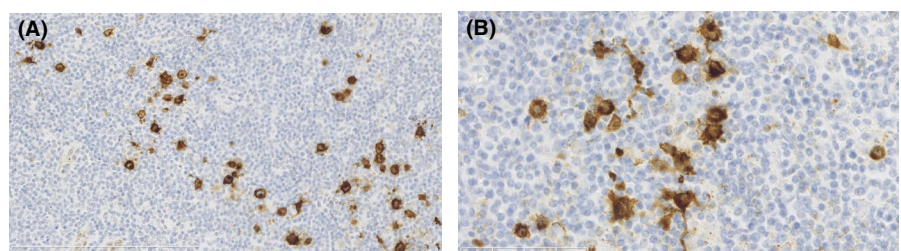


FIGURE 3 EBV positivity of the right cervical lymph node. (A) 20× magnification, (B) 40× magnification. Immunohistochemistry with antibodies against EBV-latent membrane protein (LMP)

	Nerve conduction velocity (before therapy [N. Medianus])	Nerve conduction velocity (3 years after therapy [N. Ulnaris])
Latency	12.8 ms	11.6 ms
Amplitude	1.5 mV	2.5 mV
NCV	14 m/s	13 m/s

TABLE 1 Nerve conduction velocity before and 3 years after modified BEACOPP

neurotoxic side effects. With additional modifications during therapy consisting in the elimination of cyclophosphamide caused by the suspicion of additional neurotoxicity plus the initiation of gabapentin for management of tingling symptoms, we were able to effectively treat the patient's HL using a modified BEACOPP regimen achieving long-lasting CR.

In summary, modified BEACOPP regimen can be a feasible and effective treatment for patients with advanced HL with underlying HMSN1. Intensive clinical monitoring of the neuropathic symptoms is needed, and adjustments to the therapy are required. The patient achieved and remained in CR for a follow-up period of now 6 years in the absence of severe (neurological) side effects.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

PPH wrote the manuscript and prepared the figures. MK, KZH, and MT were involved in the patient's diagnosis and treatment and revised the manuscript. MSVF, FH, and BR critically revised the manuscript and were involved in preparing the figures. FB was involved in the patient's diagnosis and treatment, were involved in preparing the figures and critically revised the manuscript. THB was the senior attending physician on the clinical case and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

ETHICAL APPROVAL

None.

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


Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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REFERENCES

1. FitzGerald TJ, Bishop-Jodoin M. Hodgkin lymphoma: differences in treatment between Europe and the United States/North America: evolving trends in protocol therapy. *Clin Med Insights Oncol*. 2018;12:1179554918754885.
2. Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin study group. *Lancet*. 2018;390(10114):2790-2802.
3. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet*. 2012;379(9828):1791-1799.
4. Della Latta V, Cecchetti A, Del Ry S, Morales MA. Bleomycin in the setting of lung fibrosis induction: from biological mechanisms to counteractions. *Pharmacol Res*. 2015;97:122-130.
5. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: a current review. *Ann Neurol*. 2017;81(6):772-781.
6. Bird TD. Charcot-Marie-Tooth Hereditary Neuropathy Overview. In: Adam MP, Ardinger HH, Pagon RA, et al. *GeneReviews*((R)). University of Washington, Seattle; 1993.
7. Bird TD. Charcot-Marie-Tooth Neuropathy Type 1. In: Adam MP, Ardinger HH, Pagon RA, et al. *GeneReviews*((R)). University of Washington, Seattle; 1993.
8. Bird TD. Charcot-Marie-Tooth Neuropathy Type 2. In: Adam MP, Ardinger HH, Pagon RA, et al. *GeneReviews*((R)). University of Washington, Seattle; 1993.
9. Li J, Parker B, Martyn C, Natarajan C, Guo J. The PMP22 gene and its related diseases. *Mol Neurobiol*. 2013;47(2):673-698.
10. Murphy SM, Laura M, Fawcett K, et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. *J Neurol Neurosurg Psychiatry*. 2012;83(7):706-710.
11. Lee S, Amici S, Tavori H, et al. PMP22 is critical for actin-mediated cellular functions and for establishing lipid rafts. *J Neurosci*. 2014;34(48):16140-16152.
12. Harding AE, Thomas PK. The clinical features of hereditary motor and sensory neuropathy types I and II. *Brain*. 1980;103(2):259-280.

13. Hoyle JC, Isfort MC, Roggenbuck J, Arnold WD. The genetics of Charcot-Marie-Tooth disease: current trends and future implications for diagnosis and management. *Appl Clin Genet*. 2015;8:235-243.
14. Cil T, Altintas A, Tamam Y, Battaloglu E, Isikdogan A. Low dose vincristine-induced severe polyneuropathy in a Hodgkin lymphoma patient: a case report (vincristine-induced severe polyneuropathy). *J Pediatr Hematol Oncol*. 2009;31(10):787-789.
15. Hildebrandt G, Holler E, Woenkhaus M, et al. Acute deterioration of Charcot-Marie-Tooth disease IA (CMT IA) following 2 mg of vincristine chemotherapy. *Ann Oncol*. 2000;11(6):743-747.
16. Mercuri E, Poulton J, Buck J, et al. Vincristine treatment revealing asymptomatic hereditary motor sensory neuropathy type 1A. *Arch Dis Child*. 1999;81(5):442-443.
17. Neumann Y, Toren A, Rechavi G, et al. Vincristine treatment triggering the expression of asymptomatic Charcot-Marie-Tooth disease. *Med Pediatr Oncol*. 1996;26(4):280-283.
18. Nishikawa T, Kawakami K, Kumamoto T, et al. Severe neurotoxicities in a case of Charcot-Marie-Tooth disease type 2 caused by vincristine for acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 2008;30(7):519-521.
19. Porter CC, Carver AE, Albano EA. Vincristine induced peripheral neuropathy potentiated by voriconazole in a patient with previously undiagnosed CMT1X. *Pediatr Blood Cancer*. 2009;52(2):298-300.
20. Schiavetti A, Frascarelli M, Uccini S, Novelli A. Vincristine neuropathy: neurophysiological and genetic studies in a case of Wilms tumor. *Pediatr Blood Cancer*. 2004;43(5):606-609.
21. Trobaugh-Lotrario AD, Smith AA, Odom LF. Vincristine neurotoxicity in the presence of hereditary neuropathy. *Med Pediatr Oncol*. 2003;40(1):39-43.
22. Aghajan Y, Yoon JM, Crawford JR. Severe vincristine-induced polyneuropathy in a teenager with anaplastic medulloblastoma and undiagnosed Charcot-Marie-Tooth disease. *BMJ Case Rep*. 2017;2017:bcr-2016-218981.
23. Ajitsaria R, Reilly M, Anderson J. Uneventful administration of vincristine in Charcot-Marie-Tooth disease type 1X. *Pediatr Blood Cancer*. 2008;50(4):874-876.
24. Chauncey TR, Showel JL, Fox JH. Vincristine neurotoxicity. *JAMA*. 1985;254(4):507.
25. Chauvenet AR, Shashi V, Selsky C, et al. Vincristine-induced neuropathy as the initial presentation of charcot-marie-tooth disease in acute lymphoblastic leukemia: a pediatric oncology group study. *J Pediatr Hematol Oncol*. 2003;25(4):316-320.
26. Cowie F, Barrett A. Uneventful administration of cisplatin to a man with X-linked Charcot-Marie-Tooth disease (CMT). *Ann Oncol*. 2001;12(3):422.
27. Dickerhoff R, Lindner W, Scheiber W. Severe vincristine neurotoxicity in a patient with Charcot-Marie-Tooth disease. *Pediatr Hematol Oncol*. 1988;5(1):61-64.
28. Geny C, Gao JM, Mallaret M, et al. Charcot-Marie-Tooth disease disclosed by a treatment with vincristine in familial Hodgkin's disease. *Ann Med Interne (Paris)*. 1990;141(8):709-710.
29. Graf WD, Chance PF, Lensch MW, Eng LJ, Lipe HP, Bird TD. Severe vincristine neuropathy in Charcot-Marie-Tooth disease type 1A. *Cancer*. 1996;77(7):1356-1362.
30. Griffiths JD, Stark RJ, Ding JC, Cooper IA. Vincristine neurotoxicity in Charcot-Marie-Tooth syndrome. *Med J Aust*. 1985;143(7):305-306.
31. Hogan-Dann CM, Fellmeth WG, McGuire SA, Kiley VA. Polyneuropathy following vincristine therapy in two patients with Charcot-Marie-Tooth syndrome. *JAMA*. 1984;252(20):2862-2863.
32. Ichikawa M, Suzuki D, Inamoto J, et al. Successful alternative treatment containing vindesine for acute lymphoblastic leukemia with Charcot-Marie-Tooth disease. *J Pediatr Hematol Oncol*. 2012;34(3):239-241.
33. Igarashi M, Thompson EI, Rivera GK. Vincristine neuropathy in type I and type II Charcot-Marie-Tooth disease (hereditary motor sensory neuropathy). *Med Pediatr Oncol*. 1995;25(2):113-116.
34. Martino MA, Miller E, Grendys EC Jr. The administration of chemotherapy in a patient with Charcot-Marie-Tooth and ovarian cancer. *Gynecol Oncol*. 2005;97(2):710-712.
35. McGuire SA, Gospe SM Jr, Dahl G. Acute vincristine neurotoxicity in the presence of hereditary motor and sensory neuropathy type I. *Med Pediatr Oncol*. 1989;17(6):520-523.
36. Nakamura T, Hashiguchi A, Suzuki S, Uozumi K, Tokunaga S, Takashima H. Vincristine exacerbates asymptomatic Charcot-Marie-tooth disease with a novel EGR2 mutation. *Neurogenetics*. 2012;13(1):77-82.
37. Olek MJ, Bordeaux B, Leshner RT. Charcot-Marie-Tooth disease type I diagnosed in a 5-year-old boy after vincristine neurotoxicity, resulting in maternal diagnosis. *J Am Osteopath Assoc*. 1999;99(3):165-167.
38. Orejana-Garcia AM, Pascual-Huerta J, Perez-Melero A. Charcot-Marie-Tooth disease and vincristine. *J Am Podiatr Med Assoc*. 2003;93(3):229-233.
39. Uno S, Katayama K, Dobashi N, et al. Acute vincristine neurotoxicity in a non-Hodgkin's lymphoma patient with Charcot-Marie-Tooth disease. *Rinsho Ketsueki*. 1999;40(5):414-419.
40. Weiden PL, Wright SE. Vincristine neurotoxicity. *N Engl J Med*. 1972;286(25):1369-1370.
41. Yerushalmi R, Levi I, Wygoda M, Ifergane G, Wirguin I. Are platinum-based chemotherapeutic drugs safe for patients with Charcot-Marie-Tooth disease? *J Peripher Nerv Syst*. 2007;12(2):139-141.
42. Chaudhry V, Chaudhry M, Crawford TO, Simmons-O'Brien E, Griffin JW. Toxic neuropathy in patients with pre-existing neuropathy. *Neurology*. 2003;60(2):337-340.
43. Naumann R, Mohm J, Reuner U, Kroschinsky F, Rautenstrauss B, Ehninger G. Early recognition of hereditary motor and sensory neuropathy type 1 can avoid life-threatening vincristine neurotoxicity. *Br J Haematol*. 2001;115(2):323-325.
44. Ibanez-Julia MJ, Berzero G, Reyes-Botero G, et al. Antineoplastic agents exacerbating Charcot Marie Tooth disease: red flags to avoid permanent disability. *Acta Oncol*. 2018;57(3):403-411.

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