HP Groups

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Case Report

A Rare Side Effect of a Commonly Used Chemotherapy Agent

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Abstract

Burkitt's lymphoma is a type of non Hodgkin's lymphoma which is associated with translation of myc-oncogene located on immunoglobulin heavy chain IGH on chromosome 14. Vincristine is used in treatment of several types of cancers including Burkitt's lymphoma. We present the case of a 22 year old male with stage IV Burkitt's lymphoma who received Vincristine as part of this chemotherapy regimen and developed a rare side effect of autonomic dysfunction. He developed orthostatic hypotension and syncope and a full work-up ruled out other causes of syncope. His symptoms resolved with discontinuing Vincristine and starting mineralocorticoids. This effect has been described in literature in case studies in the 1980s. It is a diagnosis of exclusion when encountered and can have debilitating effects on the patients. We think it is important to know about it because early detection and appropriate management lead to dramatic resolution of symptoms.

Keywords: Burkitt's; Heavy chain; Hypotension; mineralocorticoids; Myc-oncogene; Orthostatic; Syncope; Vincristine

Abbreviations

CT

EBV: Ebstein Barr Virus

EEG

EKG

GI

Hyper CVAD

IGH

Myc

R-EPOCH

RICE

Introduction

Burkitt's lymphoma is an uncommon type of non Hodgkin's lymphoma and its yearly incidence is approximately 1200 in the United States [1]. It was first described in the 1950s by Dennis Burkitt in children with jaw tumors in Uganda [2]. The pathophysiology of Burkitt Lymphoma includes translocation of myc-associated oncogene that is located at chromosome locus 8q24.21 with the immunoglobulin heavy chain gene, IGH, located on chromosome 14 leading to over expression of myc [3]. This translocation when associated with other hematologic malignancies may present as aggressive and treatment refractory disease [4]. Ebstein Barr Virus (EBV) has been associated with 98% of endemic cases, as well as 20% of sporadic cases [5]. Vincristine, a well studied chemotherapeutic agent used in treatment of several types of cancers, is a derivative of purified alkaloid from Periwinkle plant Vinca Rosea of the family *Apocynaceae* [6].

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Case Presentation

A 22 year old white male with stage IVB Burkitt's Lymphoma primarily refractory to 2 cycles of Rituximab, Etoposide, Prednisolone, Vincristine, Cyclophosphamide, Hydroxydaunorubicin (R-EPOCH) and intrathecal methotrexate [7], had an initial response to 2nd line Rituximab, Ifosfamide, Carboplatin, Etoposide (RICE) after 2 cycles but progressed by his 4th cycle. He had multiple admissions for neutropenic fever during his therapy and complained of presyncopal episodes when standing. He was then started on Rituximab, Cytarabine and methotrexate (Hyper CVAD part B with Rituximab) [8]. After his first cycle, he was admitted for fever, neutropenia and upper GI bleed with thrombocytopenia. Due to this, his remaining doses of chemotherapy were reduced by 20%.

After cycle 2 of Hyper CVAD part B, he was again admitted for sepsis and aspergillus pneumonia with neutropenia. During Hyper-CVAD part A (cyclophosphamide, Vincristine, adriamycin,

dexamethasone), the patient had a syncopal episode while standing up in the shower during which he became unresponsive for 1-2 minutes, with bladder incontinence and dilated pupils bilaterally. Glucose at the time was 121. A stat EEG showed runs of diffuse theta waves, but otherwise no seizure activity. EKG showed sinus tachycardia, and CT head showed no acute abnormalities. He was placed on telemetry, which showed no arrhythmias. Nephrology believed that this hypotension was not secondary to volume depletion since the patient was not retaining sodium based on urine studies and had no response to fluid bolus. After volume depletion and cardiogenic causes were ruled out, it was believed that his symptoms were related to orthostatic hypotension leading to cerebral hypoxia as the patient was symptomatic with orthostatic vitals. His systolic blood pressure dropped 30 points and the diastolic dropped 19 on changing position from sitting to standing. The patient did report that he had had similar events during and after prior chemotherapy treatments but this had never been worked up. Per neurology recommendations, fludrocortisone was started for suspected neurogenic orthostatic hypotension. Since he continued to remain symptomatic with orthostatic vitals, midodrine was added a few days later. His symptoms of orthostatic hypotension and presyncopal episodes did resolve and he was able to walk down the halls with physical therapy and was considered safe for discharge. His orthostatic hypotension and presyncopal/syncopal episodes are consistent with a diagnosis of autonomic dysfunction from Vincristine therapy. The patient had received Vincristine-based Chemotherapy (R-EPOCH) in the past and had reported a prior history of such episodes that were not further worked up. Moreover, his symptoms resolved after discontinuation of the Vincristine and addition of fludrocortisone and midodrine.

Discussion

Peripheral sensory motor neuropathy from Vincristine-based chemotherapy, used in treatment of Burkitt's lymphoma, has been well studied. Presentation typically includes dysesthesia, areflexia and dysautonomia [9,10]. The earliest symptoms typically include paresthesias of fingers and toes. In addition, loss of Achilles tendon reflex has been documented in children receiving Vincristine-based therapy for treatment of acute lymphoblastic leukemia [11]. In the same study, vagal chronotropic control of the heart was presumably impaired by Vincristine and was measured in terms of heart rate variability. These effects were found to be similar to vagal blockade and diabetic cardioneuropathy and resolved after vincristine therapy was stopped Vincristine-induced vocal cord dysfunction and laryngeal nerve paralysis and return of function upon completion of therapy has been reported as well [11-13].

Vincristine-induced orthostatic hypotension does occur but the documented cases are rare worldwide. In a case study published by Carmichael et al., a 26 years old patient showed no signs of sympathetic dysfunction prior to receiving Vincristine and dexamethasone to treat a frontal lobe tumor, and received 1mg intravenously weekly, and then biweekly. He experienced tingling and occasional numbness in his extremities, and developed postural hypotension and tachycardia at rest, but had a mostly normal neurological exam with the exception of hypoactive deep tendon reflexes, decreased vibration sense in the feet and ankles and marked hyperesthesia. His low blood pressure and high heart rate increased when sitting and were exaggerated when standing. The Vincristine treatment was stopped, and the patient was switched to a high salt with fludrocortisone acetate diet. Two weeks post Vincristine, he showed improved postural symptoms. By six weeks post Vincristine, the patient had low normal norepinephrine levels in the urine, although he passed away during a round of radiation therapy and the severity of his illness prevented further evaluation of the postural hypotension [14].

A case review published in 1980 presented twenty six cases with only one case of orthostatic hypotension. This case presented very similarly to the one described by Carmichael et al., with a decrease in blood pressure and increase in pulse from the supine to standing position. It was indicated that the orthostatic symptoms were not dose related as the affected patient only received a cumulative 6 mg of Vincristine while other patients included in the study were given a median of 20 mg, with some patients receiving over 50 mg. The case review also included reports of seven of the twenty six cases having neurotoxic effects as a result of Vincristine therapy [15]. In each case, orthostatic symptoms were resolved after discontinuing the therapy. Vincristine is associated with causing motor neuron failure and is likely a culprit explaining the symptoms described in our case [16]. As chemotherapeutic drugs may be associated with debilitating side effects, this has prompted investigators to look into alternative therapies as shown by Bhattacharya (2016) resulting in bed to bench preliminary translational work [17].

Conclusion

Similar to the cases discussed, our patient's orthostasis resolved quickly after discontinuing Vincristine and initiating fludrocortisone and midodrine. The severity of these symptoms strongly supports monitoring and awareness of this side effect for all patients on Vincristine containing regimens to allow early discontinuation of the offending drug. Awareness is especially important due to quick resolution of orthostatic symptoms with mineralocorticoid treatment. Given the rarity of this side effect, publication of this rare side effect is extremely important.

References

1. Perkins AS, Friedberg JW (2008) Burkitt lymphoma in adults. Hematology Am Soc Hematol Educ Program 341-348.
2. Coakley D (2006) Denis Burkitt and his contribution to haematology/oncology. Br J Haematol 135: 17-25.
3. Cai Q, Mederios LJ, Xu X, Young KH (2015) MYC-driven Aggressive B-cell Lymphomas: biology, entity, differential diagnosis and clinical management. Oncotarget 6: 38591-38616.
4. Li Y, Hu S, Wang SA, Li S, Huh YO, et al. (2016) The clinical significance of 8q24/MYC rearrangement in chronic lymphocytic leukemia. Mod Pathol 29: 444-451.
5. Brady G, MacArthur GJ, Farrell PJ (2007) Epstein-Barr virus and Burkitt lymphoma. J Clin Pathol 60: 1397-1402.
6. Kassem LA, Gamal El-Din MM, Yassin NA (2011) Mechanisms of Vincristine-induced neurotoxicity: Possible reversal by erythropoietin. Drug Discov Ther 5: 136-143.
7. Dunleavy K, Pittaluga S, Shovlin M, Steinberg SM, Cole D, et al. (2013) Low-intensity therapy in adults with Burkitt's lymphoma. N Engl J Med 369: 1915-1925.
8. Thomas DA, Faderl S, O'Brien S, Bueso-Ramos C, Cortes J, et al. (2006) Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 106: 1569-1580.

9. Courtemanche H, Magot A, Ollivier Y, Rialland F, Leclair-Visonneau L, et al. (2015) Vincristine-induced neuropathy: Atypical electrophysiological patterns in children. Muscle Nerve 52: 981-985.

10. Holland JF, Scharlau C, Gailani S, Krant MJ, Olson KB, et al. (1973) Vincristine treatment of advanced cancer: a cooperative study of 392 cases. Cancer Res 33: 1258-1264.

11. Hirvonen HE, Salmi TT, Heinonen E, Antila KJ, Välimäki IA (1989) Vincristine treatment of acute lymphoblastic leukemia induces transient autonomic cardioneuropathy. Cancer 64: 801-805.

12. Samoon Z, Shabbir-Moosajee M (2014) Vincristine-induced vocal cord palsy and successful re-treatment in a patient with diffuse large B cell lymphoma: a case report. BMC Res Notes 7: 318.

13. Whittaker JA, Griffith IP (1977) Recurrent laryngeal nerve paralysis in patients receiving vincristine and vinblastine. Br Med J 1: 1251-1252.

14. Carmichael SM, Eagleton L, Ayers CR, Mohler D (1970) Orthostatic hypotension during vincristine therapy. Arch Intern Med 126: 290-293.

15. DiBella N (1980) Vincristine-induced Orthostatic Hypotension: A Prospective Clinical Study. Cancer Treat Rep 64: 359-356.

16. Brunton L, Chabner B, Knollman B (2011) Goodman and Gilman's The Pharmacological Basis of Therapeutics, Twelfth Edition. McGraw Hill Professional, New York, USA.

17. Bhattacharya D (2016) A Novel Anti-Metastasis and Chemotherapy's Side Effect Reducer. Translational Medicine 6: 168.