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Vinblastine-Induced Posterior Reversible Encephalopathy Syndrome in Pediatric Hodgkin Lymphoma

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a critical care scenario seen with several etiologies. We report a pediatric case of Hodgkin lymphoma presenting with paraneoplastic features of nephrotic syndrome (NS). Diagnosis was confirmed with positron emission tomography-computed tomography scan and immunohistochemistry of the tissue biopsy. Remission for NS was achieved within a week of starting chemotherapy (ABVD–adriamycin, bleomycin, vinblastine, and dacarbazine). After the second cycle, he developed headache, seizures, and hypertension, requiring intensive care management. Magnetic resonance imaging brain was suggestive of PRES. The condition was managed with antihypertensives, antiepileptics, and supportive care. Considering all the risk factors for PRES including the drug, vinblastine, further chemotherapy was administered with only ABD regimen. The child attained complete remission after six cycles of chemotherapy and did not have any further episodes of hypertension or seizures. This case highlights the rare complication of vinblastine in a complicated lymphoid malignancy.

Keywords
- adverse drug event
- pediatric lymphoma
- paraneoplastic syndrome
- nephrotic syndrome
- vinca alkaloids

Introduction

In children, lymphoma accounts for the third most common malignancy, following leukemia and tumors of the central nervous system.[1] Hodgkin lymphoma is the most frequently observed neoplasm. Paraneoplastic syndrome (PNS) is a rarer event in pediatric malignancy with little published literature. Nephrotic syndrome (NS) as PNS is uncommon in HL, with very few and distinctly available pediatric case reports.[2] Posterior reversible encephalopathy syndrome (PRES), a critical event, has been associated with several pediatric disorders. Children with hematological malignancies are at a higher risk of developing PRES during the course of treatment.[3] This syndrome is a spectrum of clinical and radiological features including elevated arterial blood pressure and neurological manifestations such as headache, vomiting, seizures, vision abnormalities, motor deficits, and altered sensorium. The distinct neuroimaging findings in PRES include symmetric distribution in parieto-occipital regions seen as hyperintensities in fluid-attenuated inversion recovery (FLAIR) and T2-weighted magnetic resonance imaging (MRI) images reflecting vasogenic edema. The incidence of PRES in the general pediatric population is only 0.04%, whereas it affects 0.7% of children with cancer.[4]

The majority of published literature on PRES in pediatric hematological malignancies has shown a temporal association with cancer treatment.[5] The drugs known to cause PRES

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are vincristine, cisplatin, methotrexate, L-asparaginase, carboplatin, and cytarabine. Vinca alkaloids, in particular, have been shown to be associated with neurological complications. Vinblastine has been reported in literature to cause PRES in a patient undergoing chemotherapy for HL.[6] The other triggering factors for PRES include underlying kidney diseases, blood transfusions, and invasive procedures.

We are presenting a pediatric case of HL for its rare occurrence, as this case presented with PNS of NS and also developed vinblastine-induced PRES after the second cycle of chemotherapy.

Case Presentation

An 8-year-old child presented with intermittent high-grade fever and chills for 2 months and pedal edema and abdominal distension of 2 days of duration. On examination, he had pallor and bilateral pitting type of pedal edema. Growth parameters were normal, body surface area 0.98 m^2. His vital signs were stable (heart rate 80 beats per minute, blood pressure [BP] 100/70 mm hg, respiratory rate 22 cpm, saturation 99% on room air, temperature 98.3F), and there was no palpable external lymph node. The abdomen was nonuniformly distended, more in the lower quadrant with positive shifting dullness. No distinct mass was palpable due to the presence of ascites. Preliminary blood and urine investigations were suggestive of NS. Urine analysis showed nephrotic range proteinuria; dipstick urine of 4+ protein, spot protein-creatinine ratio was 5.4, and 24-hour urine protein was 57 mg/m^2/hr. Hemogram revealed hemoglobin 7.6 g/dL, total leukocyte count of 9,900 cells/cu mm, platelets 641,000/cu mm, and erythrocyte sedimentation rate of 60 mm/hr. Peripheral smear was suggestive of microcytic hypochromic anemia with neutrophilia (75%) and no atypical cells were seen. In view of the atypical features of NS and suspicious mass per abdomen, abdominal imaging with contrast-enhanced computed tomography (CT) was done. CT scan showed multiple enlarged retroperitoneal lymph nodes (largest measuring 6×4 cm along the right external iliac artery) and paraaortic nodes (largest measuring 12×15 mm, encasing the aorta and iliac vessels). The diagnosis of lymphoma presenting with the PNS of NS was considered. Further, a positron emission tomography-CT (PET-CT) scan confirmed the lymphomatous involvement of left cervical, retroperitoneal, right iliac, and inguinal nodes, with bilateral pleural effusion, mild ascites, hepatomegaly, and splenomegaly with increased fluorodeoxyglucose uptake (►**Fig. 1A**). The superficial palpable mass per abdomen was identified and a trucut biopsy from the mass was sent for histopathological examination. Large atypical cells with enlarged vesicular nuclei and prominent nucleoli with an admixed polymorphic population of cells composed of small lymphocytes, plasma cells, neutrophils, and few eosinophils were identified suggestive of classical HL (►**Fig. 1B**). Immunohistochemistry was positive for CD 15 (►**Fig. 1C**), CD 30 (►**Fig. 1C**), PAX 5, and MUM 1 and negative for CD 45, CD 20, and ALK-1 confirming classical HL–mixed cellularity type. Bone marrow biopsy showed focal hematopoietic cells of trilineage hematopoiesis with no evidence of lymphomatous cells. As per the Lugano classification, the disease was classified as stage IV B.

Chemotherapy with ABVD regimen (adriamycin 20 mg, bleomycin 8 units, vinblastine 6 mg, and dacarbazine 300 mg) was started. He tolerated the first cycle without any side effects and also achieved remission for NS. However, during the follow-up after the second cycle of chemotherapy, he presented with complaints of abdominal pain, multiple episodes of vomiting, headache, and blurring of vision with three episodes of generalized tonic-clonic seizures lasting for 5 minutes. He was hospitalized in our pediatric critical care unit and vital parameters were monitored. Continuous blood pressure recordings obtained were showing fluctuating readings. The readings varied between the normal centile to above the 95th centile as per the American Academy of Pediatrics charts for blood pressure levels for boys by age and height percentile.[7] The highest BP recorded was 140/100 mm Hg with a mean arterial pressure (MAP) of 113. After the initial stabilization of the airway and breathing, hypertensive emergency management (intravenous labetalol [1 mg/kg] injection) was initiated. A target fall of MAP to 30% over the next 4 hours was planned and the drug was titrated accordingly. Antiepileptics such as intravenous injection lorazepam (0.05 mg/kg) followed by an injection levetiracetam (20 mg/kg) were administered to abort the seizures. Neuroprotective strategies (intravenous infusion of 3% [hypertonic] saline [0.5 mL/kg/hr] and head-end elevation) were followed and controlled fall in BP readings strictly monitored for the next 48 hours. MRI brain showed T2/FLAIR hyperintensities along the cortices of the left parieto-temporo-occipital lobe, left dorsomedial thalamus, and right frontal and occipital lobes, showing diffusion restriction suggestive of PRES (►**Fig. 2A** and **B**). Electroencephalogram showed abnormal epileptiform discharges, necessitating continuation of oral levetiracetam during maintenance phase. Cerebrospinal fluid analysis could not be performed, as the child was in hemodynamical instability. After the initial management and graded reduction in BP readings over 24 hours, oral antihypertensives (amlodipine 5 mg once a day) were added. In the setting of a child undergoing chemotherapy for lymphoma with the occurrence of PRES, the drug and their adverse effects need to be scrutinized. Considering the possible side effects of the drugs and thorough literature search, vinblastine was identified as the probable cause for PRES. As the interim PET-CT showed remission, further course of chemotherapy was continued without the drug vinblastine as an ABD regimen. The repeat PET-CT imaging after six cycles of chemotherapy showed a status of remission. During the follow-up, his blood pressure readings were stable. Repeat MRI brain was not done, as the child did not have any further episodes of seizures. Levetiracetam and amlodipine tapered gradually and stopped. He is currently under follow-up for postchemotherapy and continues to be in clinical and PET remission.

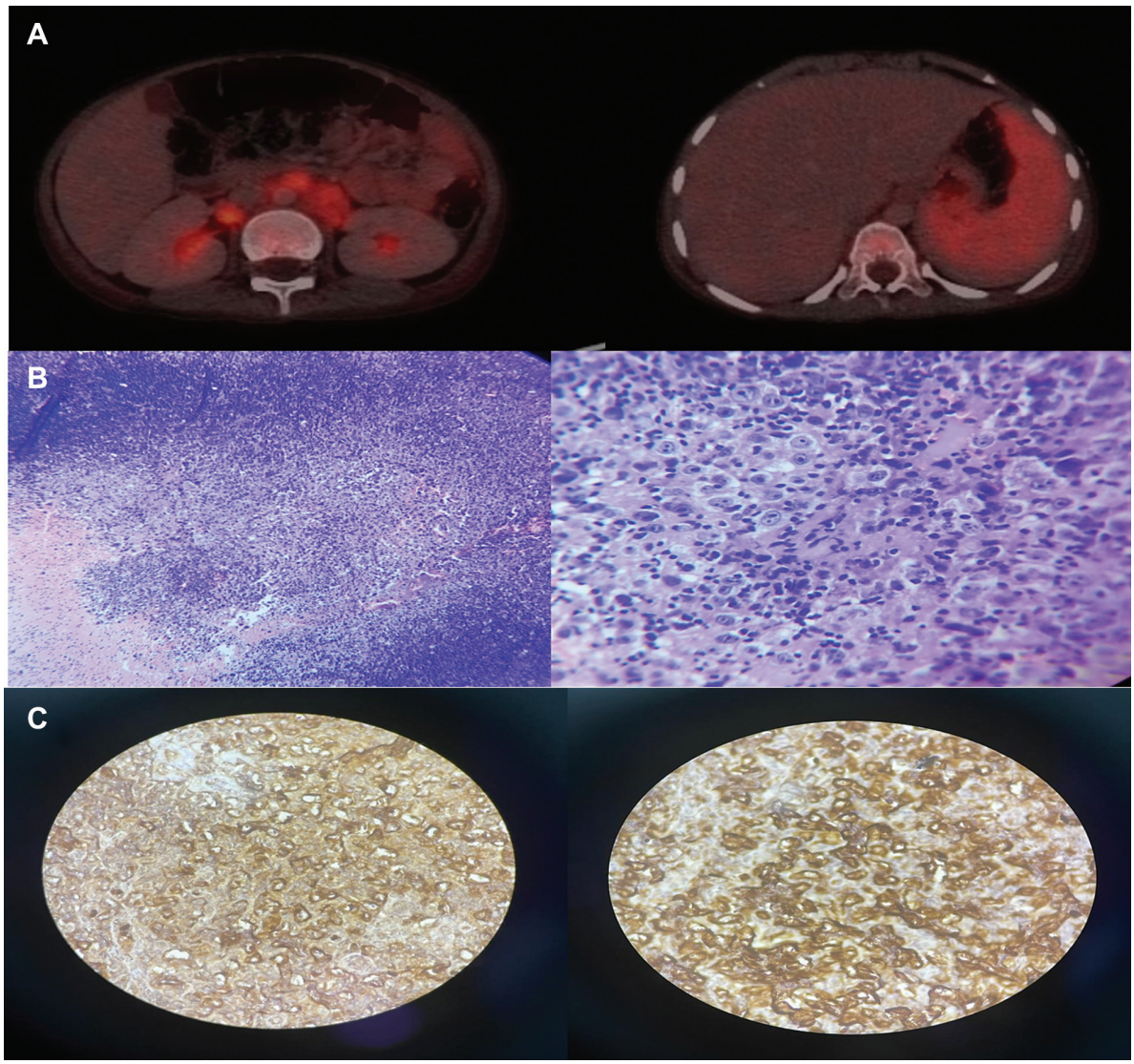

Fig. 1 (A–C) Hodgkin's lymphoma was confirmed with positron emission tomography-computed tomography (PET-CT) scan, histopathology, and immunohistochemistry.

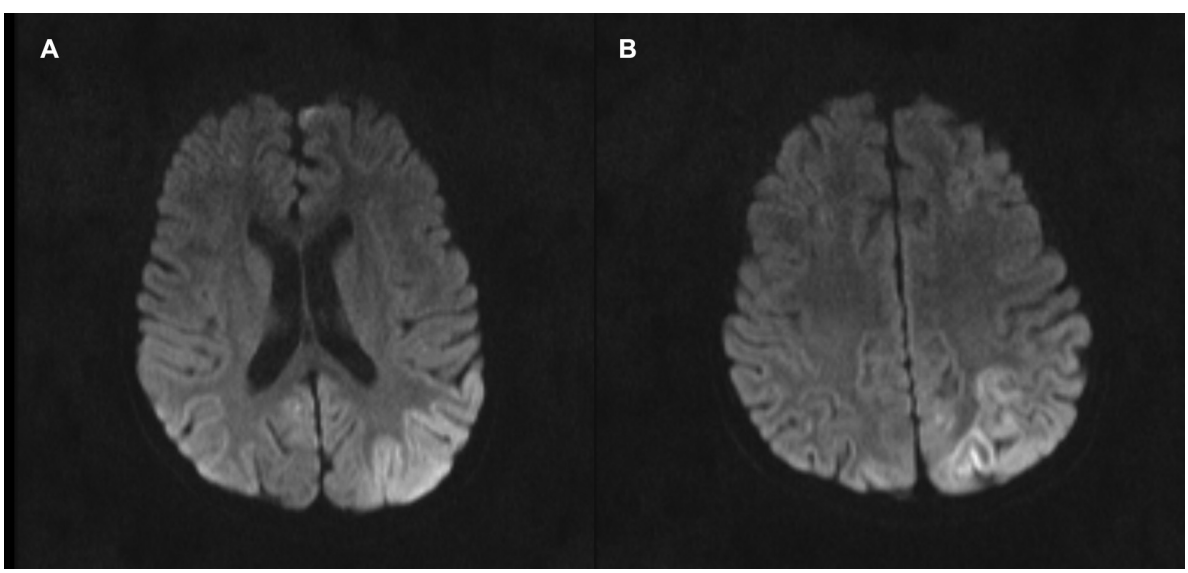

Fig. 2 (A and B) Two sections of magnetic resonance imaging (MRI) brain – hyperintensities along the cortices of the left parieto-temporo-occipital lobe, left dorsomedial thalamus, and right frontal and occipital lobes, showing diffusion restriction.

Outcome and Follow-Up

Complete clinical and metabolic remission has been attained after six cycles of chemotherapy of ABD regime. In the last 12 months of completing his chemotherapy sessions, he does not have any sort of B symptoms or adverse effects of the drugs, thus maintaining the remission status.

Discussion

In children, lymphomas account for 8.8 to 17.7% of overall cancers.[8] HL affects patients in the age group between 15 and 30 years and followed by another peak at 55 years or older. It is one of the most curable pediatric cancers with long-term survival rates exceeding more than 90%.[9] Though the disease is less common in children younger than 15 years, it may be associated with complications.[10] As lymphomas arise from germinal center B cells, they are associated with an inflammatory response. This mechanism would result in dysregulation of the immune system, resulting in autoimmune phenomena. PNS in patients with HL can involve any system. In pediatric HL, cerebellar degeneration, NS, and vanishing bile duct syndrome are a few of the rare PNS described.[11–13] Though NS is commonly described the incidence remains less than 1%.[14]

In a series of 21 adult patients of HL recruited from different centers in France, NS preceded the diagnosis of HL in 38%.[12] Remission was achieved once the appropriate management of HL was begun. Pediatric patients presenting with NS as an initial manifestation are reported by only a few authors. Sfrijan et al, Devi Padmanaban et al, and Pourtsidis et al have published either one or two pediatric cases of NS with HL across different centers.[2,14,15] All these patients achieved complete remission of NS while on treatment for lymphoma. Similarly, in our case, within a week of starting chemotherapy, complete remission was achieved with nil protein in the urine dipstick.

PRES is more commonly associated with renal disease, autoimmune conditions, and malignancies. In a retrospective study of 19 pediatric cancer patients diagnosed with PRES, HL was the primary malignancy in only two cases, the majority of them being non-HL ($n = 9$).[16] The authors quote that among all the lymphomas ($n = 542$), the complication of PRES occurred in only 2% of children. Similar to our patient, the study describes that the most common presenting complaints of PRES included seizures, hypertension, and altered mental status in more than 90% of patients, requiring antiepileptics. Neuroimaging findings were similar to the index case, showing bilateral symmetrical subcortical white matter involvement of the occipital and parietal lobes without diffusion restriction or hemorrhage. The etiology of encephalopathy in these children was majorly contributed by chemotherapy agents. Reported incidents of PRES secondary to vinca alkaloids are very few. Helissey et al published the first case of PRES secondary to the administration of vinflunine in a 67-year-old female diagnosed with urothelial carcinoma of the bladder.[17] In a 34-year-old lady suffering from invasive ductal cancer of the breast, intravenous infusion of vinorelbine resulted in PRES.[18]

From the country Jordan, Ayesh et al reported a case of HL presenting with PRES after receiving two courses of adriamycin, bleomycin, vinblastine, and dacarbazine chemotherapy.[6] This condition was reported in a 35-year-old female. There is no reported case of vinblastine-induced PRES in a pediatric patient. The index case presented here was managed in the pediatric intensive care unit with complaints of confusion, visual disturbance, aura, seizures, and hypertension. Similar to the above study, the symptoms in the index case occurred after two cycles of chemotherapy. The occurrence of PRES could have been due to multiple triggers in this child as mentioned earlier. Vinblastine was withheld from further cycles of chemotherapy after serial consultations with the oncologist due to its neurotoxicity as well as referring to the previously reported cases.[5] The decision was taken to continue chemotherapy without vinblastine as ABD regimen for the next four cycles. The patient went into remission through this regime of chemotherapy.

This case is being reported to highlight the serious adverse event of posterior reversible encephalopathy following chemotherapy including vinblastine regimen in a child with HL complicated by NS.

Conclusion

- PRES can occur in pediatric malignancies as chemotherapy-related adverse events.
- PRES has a favorable outcome if identified early and treated.
- Multiple factors play a role in single or as combination, in causing PRES which include blood transfusions, invasive procedures, and most commonly cancer treatment.
- In spite of an advanced grade of malignancy and complications, the disease was cured completely in the index case.

Competing Interest

Signed consent form has been obtained from the parents for the case discussion in scientific forum.

Disclosure

This case report is original and authors have not presented or published it elsewhere before submission to this journal.

Authors' Contributions

K.M.T.S. was actively involved in the case management under the supervision of S.P.S. and V.S. S.P.S. and K.M.T.S. have collected the literature and written the draft. S.P.S. and V.S. have critically reviewed the article for its intellectual content.

Declaration of the Patient Consent Form

Consent has been obtained from the parents for the publication.

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Conflict of Interest
None declared.

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