Hepatic Sinusoidal Obstruction Syndrome During Chemotherapy for Childhood Medulloblastoma: Report of a Case and Review of the Literature

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Summary: Hepatic sinusoidal obstruction syndrome (HSOS), also known as veno-occlusive disease, is a well-recognized toxic complication after autologous and allogeneic hematopoietic stem cell transplant, during treatment of Wilms tumor and rhabdomyosarcoma associated with actinomycin-D, and during acute lymphoblastic leukemia therapy due to oral 6-thioguanine. However, its occurrence in the context of chemotherapy regimens for other childhood malignancies is rare. We report a 5-year-old girl with high-risk anaplastic medulloblastoma, who developed severe HSOS during her second cycle of maintenance chemotherapy, consisting of vincristine, cisplatin, and cyclophosphamide. She was treated with defibrotide with complete resolution of the HSOS. These findings and a review of the literature, highlight the occurrence of HSOS in children outside the established settings of hematopoietic stem cell transplantation, Wilms tumor, rhabdomyosarcoma, and acute lymphoblastic leukemia.

Key Words: hepatic sinusoidal obstruction syndrome, medulloblastoma, childhood, veno-occlusive disease

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Medulloblastoma is the most common malignant brain tumor of childhood. Surgery and chemotherapy are integral parts of treatment, with craniopetal radiotherapy also utilized in patients over 3 years of age. Although an increase in the intensity of therapy over time has led to an improved overall survival, this has conversely led to a higher frequency of short-term and long-term complications of therapy.

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Hepatic sinusoidal obstruction syndrome (HSOS), also known as veno-occlusive disease, is a clinical syndrome characterized by tender hepatomegaly, hyperbilirubinemia, and weight gain due to fluid retention. The underlying pathogenesis is complex and thought to involve toxic injury to sinusoidal endothelial cells.1 Histologic confirmation with liver biopsy is the gold standard for diagnosis; however, due to the procedural risk and invasive nature of a biopsy the majority of cases are diagnosed clinically. Diagnosis is based on either the McDonald (modified Seattle) or Jones (Baltimore) criteria. The McDonald criteria require the presence of 2 features from hepatomegaly with right upper quadrant pain, total bilirubin of 34.2 μmol/L or more (normal range <20 μmol/L), and ascites or unexplained weight gain >2% baseline.2 The Jones criteria require a total bilirubin of 34.2 μmol/L or more and presence of at least 2 of the following: hepatomegaly, ascites, and weight gain >5% baseline.3 These criteria allow a diagnosis of HSOS with good specificity and negative predictive value,2 but they have a relatively low sensitivity.2 Additional characteristic features that may assist in diagnosis include thrombocytopenia refractory to platelet transfusions and an increase in fibrinolytic parameters, particularly plasminogen activator inhibitor-1 antigen in combination with elevated D-dimer and bilirubin.2 Doppler-ultrasonographic findings can help to support the diagnosis of HSOS and may include hepatomegaly, splenomegaly, ascites, gallbladder wall thickening, elevation of the hepatic artery resistive index, and reversal of flow in the portal vein.2

HSOS is most frequently reported as a complication of autologous and allogeneic hematopoietic stem cell transplantation (HSCT) and in patients receiving chemotherapy for Wilms tumor and rhabdomyosarcoma. However, HSOS is a rare occurrence in the context of conventional chemotherapy for other childhood malignancies. We report a 5-year-old girl who developed severe HSOS during therapy for high-risk anaplastic medulloblastoma and was treated using defibrotide with resolution of the HSOS. Consent for publication of the case report was obtained from the parents of the patient.

CASE REPORT

A 5-year-old Aboriginal girl presented with a 2-week history of ataxia and speech disturbance. Magnetic resonance imaging of the brain and spine showed a localized 46 mm × 37 mm mass present within the posterior fossa comprising of a solid and cystic component with no evidence of drop metastases or leptomeningeal spread. Gross total resection was performed with operative findings consisting of a right-sided cerebellar tumor extending through the foramen of Luschka into the cerebello-ponsine angle. Secondary
hydrocephalus was present due to compression of the fourth ventricle. Histologic examination revealed a diffusely anaplastic medulloblastoma, with no C-MYC or N-MYC amplification detected by fluorescence in situ hybridization.

She was treated according to the Children’s Oncology Group high-risk medulloblastoma protocol ACNS0332. She received 36 Gy craniospinal radiation therapy with a 19.8 Gy boost to the posterior fossa along with weekly vincristine (1.5 mg/m² per dose). After a 6-week rest period, maintenance chemotherapy was started comprising six 29-day cycles, each consisting of cisplatin (75 mg/m² on day 1, vincristine (1.5 mg/m²) on day 1 and 8, and cyclophosphamide (1000 mg/m²) on day 2 and 3. Pegylated human granulocyte colony stimulating factor was administered on day 4 of each cycle. The first cycle of chemotherapy was well tolerated. Three days into her second cycle she developed low-grade fever and was commenced on intravenous antibiotics as part of our institutional protocol. The following day she was noted to have developed thrombocytopenia (7x10⁹/L, normal range 150 to 400 x10⁹/L) and parainfluenza type 1 was isolated on nasopharyngeal aspirate. At this stage her liver function tests were normal. By day 6 of her second cycle she was noted to have a mildly enlarged and tender liver. There was no significant weight gain and no evidence of HSOS on abdominal ultrasound. However, by day 8 she had an 11% increase in weight, a tense, tender and distended abdomen, ascites, hepatomegaly, and persistent thrombocytopenia. HSOS was diagnosed and she was started on heparin.30 The second was a 14-year-old boy who initially developed fatal HSOS after 8 days of a vincristine, carboplatin, and cyclophosphamide regimen. He was treated with 1 week of oral ursodeoxycholic acid and heparin.30

Data from the Children’s Oncology Group trials, and reports from other studies, suggest that HSOS is a well-reported complication of oral 6-thioguanine during therapy for pediatric ALL23,24 and induction therapy for pediatric HSCT.20 In addition, HSOS is a well-reported complication of oral 6-thioguanine during acute lymphoblastic leukemia (ALL) therapy,21,22 where there have been anecdotal reports of HSOS during induction therapy for pediatric ALL23,24 and induction therapy for primary CNS lymphoma.25

Although the incidence of HSOS in children undergoing HSCT, treatment for Wilms tumor, rhabdomyosarcoma, and ALL, has been established within large cooperative group trials, there are no reports within such trials of HSOS in children undergoing therapy for medulloblastoma.26–29 Outside of the large cooperative group trials, there have only been 2 prior case reports of HSOS following standard-dose chemotherapy for medulloblastoma.30,31 One patient was a 19-month-old girl who developed fatal HSOS after 8 days of a vincristine, carboplatin, and lomustine based regimen, despite supportive measures and treatment with low-molecular weight heparin.30 The second was a 14-year-old boy who initially received 36 Gy craniospinal radiation with a 20 Gy boost to the posterior fossa with concurrent weekly vincristine and developed severe HSOS 4 days after completion of the first cycle of a vincristine, carboplatin, and cyclophosphamide based regimen. He was treated with 1 week of oral urso-deoxycholic acid and 3 days of parenteral N-acetylcysteine, with resolution of the HSOS. To prevent recurrence, the patient subsequently received a reduction in the frequency of cyclophosphamide, with administration every second cycle.11 Our case further highlights the occurrence of HSOS outside the traditional settings discussed above. HSOS may have been precipitated in our patient by a number of factors including cyclophosphamide, young age, and scatter to the liver from her prior craniospinal radiotherapy. Notably, the only feature common to all 3 cases was the administration of vincristine, which also forms part of therapy for Wilms tumor, rhabdomyosarcoma, and ALL. This suggests that vincristine may not be an innocent bystander, but could have a potentiating role in the development of HSOS.
severe disease, however, assessment of severity is difficult as it is generally retrospectively defined. Three grades of increasing severity have been classified: mild (resolution of symptoms, decrease of serum bilirubin < 34.2 μmol/L, with or without specific treatment), moderate (clinical signs and symptoms of progressive disease, including ascites and/or pleural effusion but no multiorgan failure), and severe (multiorgan failure needing oxygen or mechanical ventilation and/or renal failure and/or encephalopathy). In addition to supportive care measures, a number of therapeutic strategies have attempted to improve outcome including N-acetylcysteine, high-dose methylprednisolone, recombinant human tissue plasminogen activator alone and in combination with heparin, antithrombin III, and prostaglandin E1 in combination with heparin and thrombomodulin, although the data for their use is limited. There is increasing evidence, however, for the use of defibrotide, a polydisperse oligonucleotide with local antithrombotic, anti-ischemic, and anti-inflammatory activity. The therapeutic potential of defibrotide has largely been studied in patients who developed HSOS after HSCT. Our case reports successful treatment with defibrotide for HSOS after standard-dose chemotherapy for childhood medulloblastoma, with the dose of 25 mg/kg/d based on the recommendations from the outcome of a recent dose-finding trial.

In summary, our case highlights the occurrence of HSOS in a child receiving standard-dose chemotherapy for medulloblastoma after craniospinal radiotherapy. A diagnosis of HSOS should not be excluded based on the absence

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**GRAPH 1.** Liver transaminase profile during second cycle of maintenance chemotherapy. Days on which defibrotide was started and stopped are shown on x-axis.

**GRAPH 2.** Bilirubin profile during second cycle of maintenance chemotherapy. Days on which defibrotide was started and stopped are shown on x-axis.
of classic risk factors and disease settings, with early consideration given in the presence of premature, unexplained thrombocytopenia after chemotherapy. Defibrotide was an effective therapeutic strategy in our case.

REFERENCES

1. Cefalo MG, Maurizi P, Arlotta A, et al. Hepatic veno-occlusive disease: a chemotherapy-related toxicity in children with malignancies. *Paediatric drugs* 2010;12:277–284.
2. McDonald GB, Sharma P, Matthews DE, et al. Venoocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. *Hepatology* 1984;4:116–122.
3. Jones RJ, Lee KS, Beschoner WE, et al. Venoocclusive disease of the liver following bone marrow transplantation. *Transplantation* 1987;44:778–783.
4. Cesaro S, Spiller M, Sartori MT, et al. Veno-occlusive disease in pediatric patients affected by Wilms tumor. *Pediatr Blood Cancer* 2011;57:258–261.
5. Corbacioglu S, Cesaro S, Faraci M, et al. Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. *Lancet*. 2012;379:1301–1309.
6. Sartori MT, Cesaro S, Peruzzo M, et al. Contribution of fibrinolytic tests to the differential diagnosis of veno-occlusive disease complicating pediatric hematopoietic stem cell transplantation. *Pediatr Blood Cancer* 2012;58:791–797.
7. Lassau N, Leclere J, Auperin A, et al. Hepatic veno-occlusive disease after myeloablative treatment and bone marrow transplantation: value of gray-scale and Doppler US in 100 patients. *Radiology*. 1997;204:545–552.
8. Corbacioglu S, Kernan N, Lehmann L, et al. Defibrotide for the treatment of hepatic veno-occlusive disease in children after hematopoietic stem cell transplantation. *Expert Rev Hematol*. 2012;5:291–302.
9. D’Amiga L, Baker A, Pritchard J, et al. Veno-occlusive disease with multi-organ involvement following actinomycin-D. *Eur J Cancer*. 2001;37:1141–1148.
10. Bisogno G, de Kraker J, Weirich A, et al. Veno-occlusive disease of the liver in children treated for Wilms tumor. *Med Pediatr Oncol*. 1997;29:245–251.
11. Flentje M, Weirich A, Potter R, et al. Hepatotoxicity in irradiated nephroblastoma patients during postoperative treatment according to SIOP/GPOH. *Radiother Oncol*. 1994;31:222–229.
12. Jagt CT, Zuckermann M, Ten Kate F, et al. Veno-occlusive disease as a complication of preoperative chemotherapy for Wilms tumor: a clinico-pathological analysis. *Pediatr Blood Cancer*. 2009;53:1211–1215.
13. Adachi N, Matsuda I. Veno-occlusive disease of the liver after combined adjuvant chemotherapy for a 1-year-old boy with rhabdomyosarcoma: potential usefulness of the gabexate mesylate (FOY). *J Pediatr Gastroenterol Nutr*. 1992;14:314–318.
14. Arndt C, Hawkins D, Anderson JR, et al. Age is a risk factor for chemotherapy-induced hepatoatrophy with vincristine, actinomycin, and cyclophosphamide. *J Clin Oncol*. 2004;22:1894–1901.
15. Ceen E, Uysal KM, Orguven A, et al. Veno-occlusive disease in a child with rhabdomyosarcoma after conventional chemotherapy: report of a case and review of the literature. *Pediatr Hematol Oncol*. 2007;24:615–621.
16. Chen IL, Yang SN, Hsiao CC, et al. Treatment with high-dose methylprednisolone for hepatic veno-occlusive disease in a child with rhabdomyosarcoma. *Pediatr Neonatol*. 2008;49:141–144.
17. Kamarov VS, Albuquerque ML, Ribeiro RC, et al. Veno-occlusive disease of the liver after chemotherapy for rhabdo-myosarcoma: case report with a review of the literature. *Med Pediatr Oncol*. 1995;24:334–340.
18. Ortega JA, Donaldson SS, Ivy SP, et al. Venoocclusive disease of the liver after chemotherapy with vincristine, actinomycin D, and cyclophosphamide for the treatment of rhabdomyosarcoma. A report of the Intergroup Rhabdomyosarcoma Study Group. *Childrens Cancer Group*, the Pediatric Oncology Group, and the Pediatric Intergroup Statistical Center. *Cancer*. 1997;79:2435–2439.
19. Sulis ML, Bessmertny O, Granowetter L, et al. Veno-occlusive disease in pediatric patients receiving actinomycin D and vincristine only for the treatment of rhabdomyosarcoma. *J Pediatr Hematol/Oncol*. 2004;26:845–846.
20. Lee AG, Lau YL. Chemotherapy-induced veno-occlusive disease of the liver. *Med Pediatr Oncol*. 1995;25:485–486.
21. Vora A, Mitchell CD, Lennard L, et al. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukemia: a randomised trial. *Lancet*. 2006;368:1339–1348.
22. Stork LC, Matloub Y, Broxson E, et al. Oral 6-mercaptopurine versus oral 6-thioguanine and veno-occlusive disease in children with standard-risk acute lymphoblastic leukemia: report of the Children’s Oncology Group CCG-1982 clinical trial. *Blood*. 2010;115:2740–2748.
23. Mertens R, Brost H, Granzen B, et al. Antithrombin treatment of severe hepatic veno-occlusive disease in children with cancer. *Eur J Paediatr*. 1999;158(suppl 3):S154–S158.
24. Sahoo RK, Sharma A. Sinusoidal obstruction syndrome during induction therapy for acute lymphoblastic leukemia managed with N-acetyl Cysteine. *Pediatr Blood Cancer*. 2011;57:700.
25. Yamamoto S, Akiyama K, Oyama N, et al. Fatal hepatic sinusoidal obstruction syndrome in a child with primary CNS lymphoma during induction therapy. *Int J Hematol*. 2012;96:284–286.
26. Taylor RE, Bailey CC, Robinson KJ, et al. Outcome for patients with metastatic (M2–3) medulloblastoma treated with SIOP/UKCCSG PNET-3 chemotherapy. *Eur J Cancer*. 2005;41:727–734.
27. Taylor RE, Bailey CC, Robinson K, et al. Results of a randomized study of preradiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: the International Society of Paediatric Oncology/United Kingdom Children’s Cancer Study Group PNET-3 Study. *J Clin Oncol*. 2003;21:1581–1591.
28. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *J Clin Oncol*. 2006;24:4202–4208.
29. Lanning B, Rutkowski S, Doz F, et al. Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial. *Clin J Oncol*. 2012;30:3187–3193.
30. EllI M, Pinarli FG, Dagdemir A, et al. Veno-occlusive disease of the liver in a child after chemotherapy for brain tumor. *Pediatr Blood Cancer*. 2006;46:521–523.
31. Ishaqi MK, Jamal A, Khani M, et al. Hepatic sinusoidal obstruction syndrome in a child after chemotherapy for medulloblastoma. *J Neurooncol*. 2010;97:137–141.
32. Ringden O, Remberger M, Lehmann S, et al. N-acetylcysteine for hepatic veno-occlusive disease after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2000;25:993–996.
33. Myers KC, Lawrence J, Marsh RA, et al. High-dose methylprednisolone for veno-occlusive disease of the liver in pediatric hematopoietic stem cell transplantation recipients. *Biol Blood Marrow Transplant*. 2013;19:500–503.
34. Yu LC, Malkani I, Regueira O, et al. Recombinant tissue plasminogen activator (rt-PA) for veno-occlusive liver disease in pediatric autologous bone marrow transplant patients. *Am J Hematol*. 1994;46:194–197.
35. Feldman L, Gabai E, Khavlov V, et al. Recombinant tissue plasminogen activator (rtPA) for hepatic veno-occlusive disease after allogeneic BMT in a pediatric patient. *Bone Marrow Transplant*. 1995;16:727.
36. Leahey AM, Bunin NJ. Recombinant human tissue plasminogen activator for the treatment of severe hepatic veno-occlusive disease in pediatric bone marrow transplant patients. *Bone Marrow Transplant*. 1996;17:1101–1104.

37. Bajwa RP, Cant AJ, Abinun M, et al. Recombinant tissue plasminogen activator for treatment of hepatic veno-occlusive disease following bone marrow transplantation in children: effectiveness and a scoring system for initiating treatment. *Bone Marrow Transplant*. 2003;31:591–597.

38. Morris JD, Harris RE, Hashmi R, et al. Antithrombin-III for the treatment of chemotherapy-induced organ dysfunction following bone marrow transplantation. *Bone Marrow Transplant*. 1997;20:871–878.

39. Schlegel PG, Haber HP, Beck J, et al. Hepatic veno-occlusive disease in pediatric stem cell recipients: successful treatment with continuous infusion of prostaglandin E1 and low-dose heparin. *Ann Hematol*. 1998;76:37–41.

40. Yamamoto S, Yagawa A, Toyama D, et al. Successful treatment of hepatic sinusoidal obstructive syndrome after hematopoietic stem cell transplantation in a child using recombinant thrombomodulin. *Acta Haematol*. 2013;129:62–64.

41. Richardson PG, Soiffer RJ, Antin JH, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multi-organ failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. *Biol Blood Marrow Transplant*. 2010;16:1005–1017.