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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 craniospinal 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,[4] but they have a relatively low sensitivity.[5] 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.[6] 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.[7]

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-pontine 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/m^2 per dose). After a 6-week rest period, maintenance chemotherapy was started comprising six 29-day cycles, each consisting of cisplatin (75 mg/m^2) on day 1, vincristine (1.5 mg/m^2) on day 1 and 8, and cyclophosphamide (1000 mg/m^2) 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 (7×10^9/L, normal range 150 to 400×10^9/L) and parainfluenza virus 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 refractory to platelet transfusions. Laboratory investigations revealed hyperbilirubinemia (40 μmol/L, normal range < 20 μmol/L), low hemoglobin (77 g/L, normal range 115 to 155 g/dL), elevated liver enzymes alanine transaminase (ALT) (152 U/L, normal range < 30 U/L), aspartate transaminase (AST) (422 U/L, normal range < 50 U/L), and hypoalbuminemia (25 g/L, normal range 32 to 48 g/L). A large right-sided pleural effusion was present on chest x-ray. A repeat abdominal ultrasound scan and Doppler study demonstrated reversal in portal vein flow and increased peak velocity in the hepatic arteries (450 cm/s). HSOS was diagnosed and she was started on defibrotide (25 mg/kg/d) and ursodeoxycholic acid (20 mg/kg/d). Vincristine was withheld and she was transferred to the pediatric intensive care unit for supportive care, which included strict regulation of fluid balance and maintenance of urine output with frusemide and dopamine infusions, preservation of oncotic pressure with human albumin infusions, correction of coagulopathy using fresh-frozen plasma, supplementary oxygen, and broad spectrum intravenous antimicrobials for fever. Peak laboratory values included an AST of 3290 U/L, ALT of 1370 U/L, and a total bilirubin of 310 μmol/L, occurring 7, 8, and 12 days after the first manifestation of HSOS (thrombocytopenia), respectively. Her symptoms resolved over 19 days following supportive care and 2 weeks of defibrotide, with normalization of her liver function tests. Graphs 1 and 2 show the liver transaminase and bilirubin profiles during the second cycle of maintenance chemotherapy.

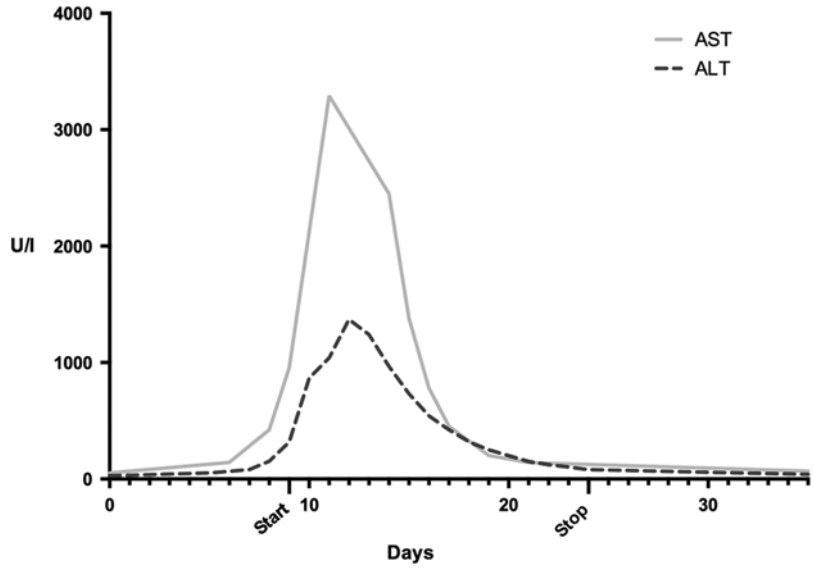
The patient was subsequently able to complete her remaining 4 cycles of chemotherapy. Audiometric evaluation revealed grade 2 ototoxicity, resulting in a 50% reduction in the cisplatin dose for her third cycle. In addition, there was a 25% dose reduction of cyclophosphamide due to delayed hematopoietic recovery and vincristine was omitted due to persistent hyperbilirubinemia (40 μmol/L). Grade 3 ototoxicity resulted in a 75% dose reduction of cisplatin for the fourth cycle with full-dose administration of cyclophosphamide and vincristine. Prophylactic defibrotide (25 mg/kg/d) was administered during the third and fourth maintenance cycles and ursodeoxycholic acid was continued throughout the duration of therapy. During cycles 5 and 6, cisplatin was completely omitted due to grade 4 ototoxicity and cyclophosphamide and vincristine were administered at full dose. There was no further recurrence of HSOS. The patient remained in clinical and radiologic remission for 8 months following the completion of therapy. Subsequent surveillance magnetic resonance imaging revealed disease recurrence in the right ventricular frontal horn.

DISCUSSION

The incidence of HSOS after HSCT in children has been reported by a number of groups and ranges between 11% and 60%, with a mean incidence of 25%.[8] Risk factors in HSCT recipients include younger age (< 6.7 y), previous liver irradiation, previous Gemtuzumab ozogamicin, prior hepatic disease, busulfan-containing conditioning regimens, and total body irradiation, with a higher risk for the latter 2 when administered in conjunction with cyclophosphamide. An increased risk is seen after HSCT for neuroblastoma, familial hemophagocytic lymphohistiocytosis, and osteopetrosis.[8] The incidence of HSOS after therapy for Wilms tumor ranges from 1.2% to 8%[9] with actinomycin-D identified as the primary etiological agent. Additional risk factors in this group include young age, previous abdominal radiotherapy, right-sided tumors, and lower body weight.[10–12] HSOS has also been reported during treatment for childhood rhabdomyosarcoma[9,13–19] with an incidence of 1.2% to 5.3%.[14,18] Identified risk factors in this population include VAC (vincristine, actinomycin-D, and cyclophosphamide) chemotherapy and age < 36 months. There is a single report of HSOS occurring in a 2-year-old boy with recurrent yolk sac tumor receiving VAC chemotherapy[20] and a report of HSOS after 2 doses of actinomycin-D in a 14-year-old girl with a paraspinal primitive neuroectodermal tumor who had received prior combination chemotherapy with etoposide, ifosfamide, cyclophosphamide, doxorubicin, vincristine, and external beam radiation partly involving the liver.[20] In addition, HSOS is a well-reported complication of oral 6-thioguanine during acute lymphoblastic leukemia (ALL) therapy,[21,22] while there have been anecdotal reports of HSOS during induction therapy for pediatric ALL[23,24] 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 co-operative group trials, there are no reports within such trials of HSOS in children undergoing therapy for medulloblastoma.[26–29] Outside of the large co-operative 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 ursodeoxycholic 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.[31] 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.

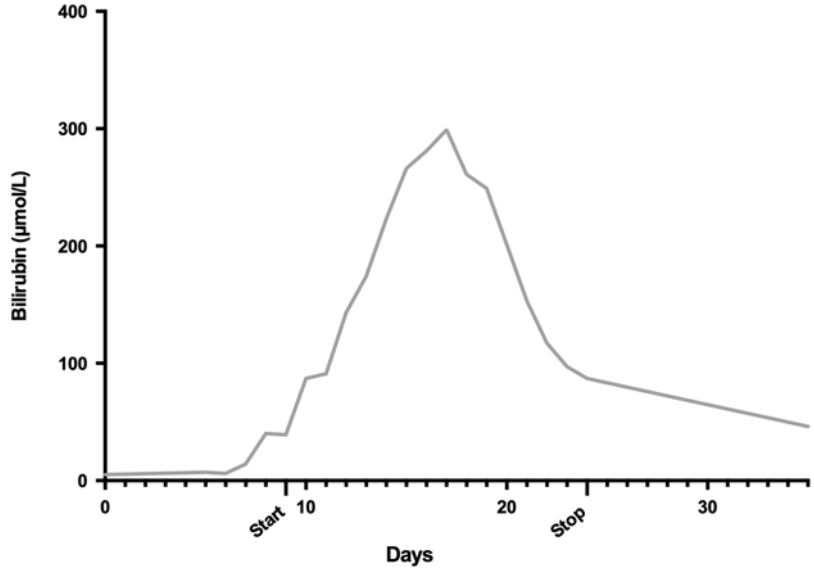
Severity of HSOS is one of the key factors influencing the outcome of patients, with mortality in excess of 85% in



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

severe disease,[5] 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 $< 34.2\,\mu mol/L$, 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).[1] In addition to supportive care measures, a number of therapeutic strategies have attempted to improve outcome including *N*-acetylcysteine,[24,31,32] high-dose methylprednisolone,[16,33] recombinant human tissue plasminogen activator alone[34,35] and in combination with heparin,[9,36,37] antithrombin III,[23,38] and prostaglandin E_1 in combination with heparin[39] and thrombomodulin,[40] 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.[41]

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



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.

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