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Research Article

# Chemotherapy Induced Sinusoidal Obstruction Syndrome in Children

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## Abstract

Sinusoidal obstruction syndrome (SOS) is a life-threatening complication that usually develops as a result of conditioning regimens for hematopoietic stem cell transplantation (HSCT). It is also less diagnosed after the use of chemotherapeutic agents, removal of alkaloid toxins, high-dose radiation therapy, or liver transplantation. It presents with hepatomegaly, right upper quadrant pain, jaundice and ascites [1-3]. Outside of the HSCT setting, only a few cases of SOS with Wilms tumor, rhabdomyosarcoma, acute lymphoblastic leukemia, and medulloblastoma have been reported. Here, we wanted to present our experience in 5 pediatric cases with SOS due to conventional treatment.

**Keywords:** Veno-Occlusive Disease; Hematopoetic Stem Cell Transplantation; Child

Sinusoidal obstruction syndrome (SOS) is an unpredictable, potentially life-threatening complication of conditioning regimens for hematopoietic stem cell transplantation (HSCT). It is also less diagnosed after use of chemotherapeutic agents, ingestion of alkaloid toxins, high-dose radiation therapy, or liver transplant. It presents with hepatomegaly, right upper quadrant pain, jaundice, and ascites [1-3]. As the name implies, SOS begins with complex activation of cytokine and complement due to toxic metabolites of chemotherapeutic agents that cause hepatic vascular endothelial damage [3,4]. Sinusoidal epithelium and and hepatic venules are more sensitive to toxicities than hepatocytes. The severity of the syndrome is related to the degree of liver damage, fibrosis and obstruction of hepatic venules can cause hepatic and multiorgan failure. It is estimated that the mortality risk is over 80% in untreated patients with multiple organ failure causing pulmonary and/or renal dysfunction [5,6]. Few cases of SOS with Wilms tumor, rhabdomyosarcoma, acute lymphoblastic leukemia, and medulloblastoma have been reported in outside the HSCT setting. Here, we wanted to present our experience in pediatric cases with SOS due to conventional treatment.

## Case 1

A six-year-old girl admitted with a complaint of right inguinal swelling and she was diagnosed as a spindle cell sarcoma. After 6th cure of VAC (Vincristine, Actinomycin-D and Cyclophosphamide) chemotherapy, right upper quadrant pain of the abdomen, marked abdominal distention, 10% weight gain, jaundice and significant hepatomegaly, developed. Laboratory workup indicated Hemoglobine (Hb): 5.6 g/dl, white blood cell (WBC) count 4.7 x $10^9$/L, absolute neutrophil count (ANC) 0.69 x $10^9$/L, platelets 55 x $10^9$/L, BUN: 22 mg/dl, creatinine 0.48 mg/dl, AST: 1521 IU/dl, ALT:808 IU/dl, LDH: 1217 UI/L, total bilirubin:4,48 mg/dl, direct bilirubin: 4.09 mg/dl, activated partial thromboplastin time (aPTT):33.6 sec (normal: < 35sec), prothrombin time (PT): 25.8 sec (normal: 10-14.5 sec), fibrinogen 367 mg/dl (170-400), and D-dimer 3526 mg/ml. Abdominal ultrasonography (USG) showed hepatomegaly with ascites and edematous appearance in periportal area and gall bladder region and Doppler USG revealed slight narrowing in hepatic venules. Defibrotide treatment was started on the third day of the first symptoms. Complete clinical and laboratory remission was achieved after defibrotide treatment on the third and eighth days of treatment.

## Case 2

A five-year-old girl was diagnosed with Wilms tumor of the left kidney. Nephrectomy and lymph no sampling were performed after preoperative treatment. Histopathologic examination showed mixed type Wilms tumor with focal anaplasia and lymph node involvement. After nephrectomy three weeks of radiotherapy was performed with weekly vincristine according to SIOP 2001 protocol and then chemotherapy was started according to SIOP 2001 stage III-intermediate group. Both vincristine and actinomycin treatment at 11$^{th}$ week and vincristine treatment at 12$^{th}$ week was administered. Abdominal distension and painful hepatomegaly occurred after 5$^{th}$ day of treatment. A 6% increase in body weight was also detected. Laboratory examination showed Hb: 8.2 g/dl, WBC: 2.8 x $10^9$/L, ANC: 0.98 x $10^9$/L, platelet 14 x $10^9$/L, BUN: 20 mg/dl, creatinine 0.52 mg/dl, AST: 2156 IU/dl, ALT: 924 IU/dl, LDH: 1980 UI/L, total bilirubin:7,48 mg/dl, direct bilirubin: 7.01 mg/dl, aPTT:42.1 sec (normal: < 35sec), PT: 24.9 sec (normal: 10 - 14.5 sec), fibrinogen 367 mg/dl (170 - 400), and D-dimer 4408 mg/ml. Abdominal USG revealed gall bladder thickening, hepatomegaly, and ascites. Doppler USG was normal. Bilateral pleural effusion was detected on posteroanterior chest X-ray. Defibrotide and supportive treatment were started together. Clinical and laboratory remission was achieved on the third and seventh days of treatment, respectively.

## Case 3

A 17-year-old girl was referred to the department of orthopaedics due to a painful mass 10 cm in diameter on the left forearm and a palpable mass in the axilla about the last three months. Alveolar rhabdomyosarcoma was diagnosed with histopathological examination of incisional biopsy. According to the Intergroup Rhabdomyosarcoma Study Group protocol (VAC: vincristine, actinomycin-D, and cyclophosphamide) was planned. On the 7$^{th}$ day of the 5$^{th}$ VAC chemotherapy, she admitted to emergency department with a neutropenic fever. No pathological findings were found except for mucosal ulceration on physical examination. Laboratory examination showed Hb: 7.5 g/dl, WBC: 0.78 x $10^9$/L, ANC: 0.15 x $10^9$/L, platelet: 35 x $10^9$/L, other biochemical parameters were normal. Cefoperazone/sulbactam and granulocyte colony stimulating factor was started. The fever resolved on the 2nd day of hospitalization but on the third day abdominal pain, distention, and jaundice were developed. The physical examination revealed weight gain of 11%, hepatomegaly, and ascites. Laboratory analysis showed Hb: 8.2 g/dl, WBC: 1.82 x $10^9$/L, platelet: 3 x $10^9$/L, AST: 980 IU/dl, ALT: 630 IU/dl, LDH: 975 UI/L, total bilirubin: 5,21 mg/dl, direct bilirubin: 4.8 mg/dl, aPTT:38.3 sec (normal: < 35sec), PT: 31.2 sec (normal: 10 - 14.5 sec), fibrinogen 296 mg/dl (170 - 400), and D-dimer 2521 mg/ml. Abdominal USG demonstrated an enlarged liver with a large amount of ascites. Doppler USG showed slight narrowing in hepatic venules. Defibrotide was started immediately. Clinical and laboratory remission were achieved on the third and seventh days of treatment, respectively.

## Case 4

A eight-year boy admitted with a complaint of orbital swelling and he was diagnosed as orbital rhabdomyosarcoma. According to the Intergroup Rhabdomyosarcoma Study Group protocol (VAC: vincristine, actinomycin-D, and cyclophosphamide) was planned. After 6th cure of VAC (Vincristine, Actinomycin-D and Cyclophosphamide) chemotherapy, she admitted to emergency department with a neutropenic fever. Laboratory examination showed Hb: 7.7 g/dl, WBC: 0.68 x $10^9$/L, ANC: 0.15 x $10^9$/L, platelet: 35 x $10^9$/L, other biochemical parameters were normal. Cefoperazone/sulbactam and granulocyte colony stimulating factor was started. 6th day of hospitalization jaundice, right upper quadrant pain of the abdomen and marked abdominal distention were developed. Laboratory workup indicated Hemoglobine (Hb): 7.6 g/dl, white blood cell (WBC) count 0.5 x $10^9$/L, absolute neutrophil count (ANC) 0.19 x $10^9$/L, platelets 45 x $10^9$/L, BUN: 22 mg/dl, creatinine 0.48 mg/dl, AST: 2521 IU/dl, ALT:1008 IU/dl, LDH: 2215 UI/L, total bilirubin:5,98 mg/dl, direct bilirubin: 5.09 mg/dl, activated partial thromboplastin time (aPTT):33.6 sec (normal: < 35sec), prothrombin time (PT): 28.8 sec (normal: 10 - 14.5 sec), fibrinogen 207 mg/dl (170 - 400), and D-dimer 5776 mg/ml. Abdominal ultrasonography (USG) showed hepatomegaly with ascites and edematous appearance in periportal area and gall bladder region and Doppler USG revealed slight narrowing in hepatic venules. Defibrotide treatment was initiated at the third day of the initial symptoms. Although liver enzymes decreased rapidly with treatment, a progressive increase in bilirubin values occurred. The patient developed hepatic and renal failure. During this period, the patient underwent plasmapheresis. Bilateral pleural effusion was detected on posteroanterior chest X-ray. The patient who developed ARDS rapidly deteriorated and died.

## Case 5

A 12-year-old patient has been treated for bone Ewing Sarcoma of the frontotemporal bone. He had neoadjuvant chemotherapy based on six cycles of Vincristine, Ifosfamide, Doxorubicin, and Etoposide (VIDE), eight cycles of Vincristine, Adriamycin, and Cyclophosphamide (VAC) and low-dose involved field radiotherapy according to Euro Ewing 2012 protocol. Two years later, he consulted our institution for metastasis of lung. Treatment according to the ICE regimen was started, which is consisting of ifosfamide 2 g/$m^2$ intravenously for 6 consecutive days (total dose 12 g/$m^2$), carboplatin 200 mg/$m^2$ intravenously for 6 consecutive days (total dose 1.2 g/$m^2$), and etoposide 2 × 100 mg/$m^2$ intravenously for 6 consecutive days (total dose 1.2 g/$m^2$). After first cure of ICE (ifosfamide,carboplatin,etoposide) chemotherapy jaundice, right upper quadrant pain of the abdomen and marked abdominal distention were developed. Laboratory analysis showed Hb: 8.2 g/dl, WBC: 1.42 x $10^9$/L, platelet: 35 x $10^9$/L, AST: 1230 IU/dl, ALT: 810 IU/dl, LDH: 975 UI/L, total bilirubin: 12 mg/dl, direct bilirubin: 7.8 mg/dl, aPTT:48.3 sec (normal: < 35sec), PT: 29.2 sec (normal: 10 - 14.5 sec), fibrinogen 376 mg/dl (170 - 400), and D-dimer 4001 mg/ml. Abdominal USG demonstrated an enlarged liver with a large amount of ascites. Doppler USG showed slight narrowing in hepatic venules. Defibrotide was started immediately. Clinical and laboratory remission was achieved on the seventh day of treatment.

## Material and Methods

Between 2008 and 2020, files of 252 patients treated at Mersin University Hospital for childhood cancers were reviewed retrospectively. Five of these patients (0.42%) were diagnosed with SOS due to conventional chemotherapy. The median age range was 6.0 years (0.2 - 15.0). The diagnosis of SOS was made according to the modified Seattle criteria [7]. Doppler ultrasonography (US) was performed in all patients. All patients treated with defibrotide, spironolactone, and hydrochlorothiazide). Defibrotide was started immediately after diagnosis, at a dose of 25 mg/kg/day, divided into 4 doses per day, for 14 days. Clinical response was defined as normalization of bilirubin and liver enzymes after initiation of defibrotide with resolution of SOS-related multiorgan failure. Clinical improvement in patients; the resolution of renal, pulmonary and central nervous system dysfunction was reflected in the clinic as decreased creatinine levels, resolution of oxygen demand and resolution of encephalopathy, respectively.

## Results

SOS is a complication of HSCT and chemotherapy in childhood cancers [1-3]. The results of this study show that SOS is not a rare complication of chemotherapy in children. In addition, resistant thrombocytopenia may be another determinant for SOS. It should be considered in patients receiving chemotherapy, in all patients with sudden weight gain, deterioration in liver function tests, jaundice, and painful hepatomegaly [3-5]. Transjugular liver biopsy and hepatic venous pressure gradient (HVPG) measurement are valuable for diagnosis and treatment in patients who cannot be diagnosed with clinical findings, scoring systems and Doppler ultrasonography. While the prognosis is good in mild and moderate cases, defibrotide treatment should be started in severe cases [3-6]. In necessary cases, early and rapid liver transplantation should be planned before the clinical worsening. However, the disadvantage of our study was that it included a small number of patients. Therefore, more multicenter studies with larger patient groups are needed to determine the incidence of SOS and risk factors.

## Discussion

SOS generally occurs after known hepatic veno-occlusive disease (VOD), high-dose chemotherapy or hematopoietic stem cell transplantation (HSCT) [8]. Studies have shown that the incidence of SOS is higher in children than in adults [9,10]. Our study emphasizes that susceptibility to chemotherapy-induced HSOS should be considered. Detecting SOS risk factors early, is critical for prophylaxis and preventing other morbidities from occurring. We think that the high incidence of HSOS after chemotherapy alone in our center may be due to many underlying patient related factors such as infection, prior abdominal radiation (as in case 2 and case 5), genetic predisposition, antiviral and antibiotic using (as in case 3 and case 4) radiotherapy treatment (as in case 5) [11-13].

The diagnosis of SOS is based on the use of the Baltimore [14] or modified Seattle criteria [15]. Unlike adults, in pediatric patients [11], there is no onset time and no time limit. At least two of the criteria must be met for diagnosis: refractory thrombocytopenia, unexplained weight gain despite diuretic use or 5% excess weight gain from baseline for 3 days, hepatomegaly, ascites, above baseline and repeatedly from baseline increased within 3 days or bilirubin ≥ 2 mg/dL within 72 hours. Although there are no specific imaging methods for SOS, diagnosis; established by clinical criteria [2,16]. In USG, which is the primary imaging method; Specific findings su-

ggestive of SOS, such as reversal of portal vein flow, abnormal portal vein waveform, ascites, gallbladder wall thickening, and hepatomegaly, morphological changes are detected. Currently, treatment options for SOS include; Defibrotide appears to be the only agent approved for the treatment of SOS. Agents such as Ursodeoxycholic acid (UDCA), defibrotide, and antithrombin, which have different mechanisms of action, are used for the treatment and/or prophylaxis of SOS. Transjugular intrahepatic porto-systemic shunt use, which is another treatment option, has been found to reduce acid formation in some patients with SOS [17-19]. Liver transplantation, which is another treatment option, is usually the last treatment option in cancer patients due to the risk of rejection [17].

## Conclusion

In conclusion, patients with high risk of SOS should be diagnosed and treated promptly.To prevent the development of SOS, the risk group should be well defined. In case of clinical suspicion hepatomegaly, weight gain, acidity or abdominal pain, in the presence of diagnostic criteria such as increased bilirubin, the diagnosis of SOS should be considered. Evaluation of such patients with imaging methods such as ultrasound in the early period can facilitate diagnosis and can be life-saving in the early period.

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