Two and Half Years Later: Cytomegalovirus and Ebstein Barr Virus Infection Leading to Sinusoidal Obstruction Syndrome in Liver Transplant Recipient

Cyriac Abby Philips1*, Philip Augustine2, Pushpa Mahadevan3

ABSTRACT
Veno-occlusive disease or sinusoidal obstruction syndrome (SOS) occurring after LT is quite rare often taking a life-threatening course. The causes of SOS in a liver transplant recipient have been found to be associated with certain factors such as azathioprine use, acute rejection and tacrolimus, mostly presenting in the immediate post op period or within 3 months. However SOS occurring in a liver transplant recipient beyond 2 years has not been documented. We report a stable post-transplant recipient with dual viral (CMV and EBV) insults 2 and half years later leading to steroid and anti thymocyte globulin resistant late acute severe rejection with rapidly progressive SOS.

Key words: CMV, EBV, Veno-Occlusive disease, Acute cellular Rejection, Liver transplant, SOS, Immunosuppression.

INTRODUCTION
Sinusoidal obstruction syndrome is a rare, unique disorder with the unique etiology and pathogenesis of endothelitis of hepatic sinuses, leading to progressive fibrotic obliteration of centrilobular veins. Sinusoidal obstruction syndrome occurs mostly in post-hematopoietic stem cell transplantation (HSCT) patients related to preconditioning treatment. This disease is unusual in liver transplant recipients. Herein, we present a case of difficult to treat, fatal SOS occurring 2 and half years after LT, in a patient with severe CMV and EBV virus related enterocolitis.

CASE REPORT
A 37 year old male underwent ABO compatible deceased donor liver transplant (CMV D+R+) for decompensated alcoholic cirrhosis in April 2014. His immediate post-operative period was complicated by lung sepsis, followed by biopsy proven steroid resistant acute cellular rejection (TCMR, Banff 5/9) managed with anti thymocyte globulin (ATG) on 9th day. Mycophenolate mofetil was changed over to azathioprine 24 days post-transplant in view of resistant acute cellular rejection (TCMR, Banff 5/9). Corticosteroid pulse therapy proved futile. Clinical evaluation at our center revealed a hemodynamically stable, deeply icteric and drowsy patient with distended tender abdomen with sluggish bowel sounds. Contrast enhanced computed tomography of the abdomen revealed normal graft liver parenchyma and vasculature without biliary tract disease; extensive mesenterico-omentral inflammation and loss of fat tissue with severe enterocolitis (Figure 1A-C). Subsequently, CMV DNA in peripheral blood was 1.5 x 104 copies/mL and IgM viral capsid antigen to EBV was positive. The patient was started on gancyclovir, aggressive hydration, bowel rest and broad spectrum antibiotics. Tests for C.difficile, enteric pathogens, hepatitis C, hepatitis B, hepatitis A and E, and opportunistic fungal infections were negative. Endoscopy...

Cite this article: Philips CA, Augustine P, Mahadevan P. Two and Half Years Later: Cytomegalovirus and Ebstein Barr Virus Infection Leading to Sinusoidal Obstruction Syndrome in Liver Transplant Recipient. OGH Reports. 2018;7(1):35-7.
directed biopsies of the gastrointestinal tract was avoided in view of high risk of perforation in the background of steroid therapy and severe enterocolitis. Five days later, bowel symptoms subsided. However, progressive liver dysfunction ensued (TB 38.6 mg/dL, AST 564 IU/L, ALT 663 IU/L, international normalized ratio 1.88) which warranted ATG (3 mg/kg daily once for 3 days with CD3 count monitoring) therapy. Post ATG, the TB decreased to 24.6 mg/dL on the 4th day with improvement in transaminitis. However, liver function worsened over the next 6 days along with transfusion resistant severe thrombocytopenia. Repeat screens for sepsis and hepatic outflow obstruction were negative. Clinical evaluation suggested worsening icterus, diffusely tender abdomen, and weight gain of 13 kilogram with new onset shifting dullness. An expert review of initial biopsy in the light of current findings was asked for which suggestive of TCMR, Banff 7/9, negative for c4d staining (Figure 2A-C), with predominant central venulitis with hemorrhagic confluent necrosis, involving hepatic veins and sinusoids with excessive neutrophilic inflammatory exudates within the sinusoidal spaces producing zone 3 fibrosis (Figure 2D-F) leading to SOS. Tacrolimus was held and cyclosporine commenced to target trough levels (150 to 180 ng/dL) with intravenous corticosteroids. However, progressive liver failure ensued with development of hepatic encephalopathy and acute kidney injury. Plasmapheresis sessions were called for and super urgent listing for re-transplantation was initiated. However, in view of poor performance status and onset of multi-organ failure, the patient was delisted and family members counseled regarding poor prognosis. They chose non-aggressive management, palliation and comfort care.

**DISCUSSION**

Sinusoidal obstruction syndrome [first described by Bras and co-workers],[3] is a rare but devastating complication seen in patients of HSCT. In LT, SOS is unusual, and azathioprine therapy or severe acute rejection is considered common causes. Severe infections leading to acute rejection are rarely associated with SOS in a liver transplant recipient. These patients poorly respond to immunosuppression and antimicrobials, in the background of SOS. Patients have mortality ranging from 30 to 50% in mild to moderate SOS and > 90% in severe disease. Tacrolimus has been implicated in SOS in post LT patients due to its potential for endothelial cytotoxicity which was the reason why we shifted to cyclosporine regimen.[4] Diagnosis of SOS is based on clinical criteria described within the Revised Seattle and the Baltimore Criteria, based on presence of jaundice, weight gain, hepatomegaly and ascites within the first 3 weeks after HSCT.[5] The European Society for Blood and Marrow Transplantation recently revised diagnostic and severity criteria for SOS in adult patients.[6] Classically, the “20 by 20” rule: a bilirubin of 20 by day 20,
predicts a poor outcome. When a patient develops rapid rise in bilirubin level even after second line powerful immunosuppressant treatment, ascites causing weight gain, and right upper quadrant pain, the diagnosis of SOS should be high on the list of differential diagnoses. Histologically, fibrous obliteration of small hepatic veins by connective tissue and centri-lobular hemorrhagic necrosis define the distinctive pattern of SOS.\(^7\) Sebagh and colleagues have previously shown that SOS is strongly associated with a particular form of acute rejection i.e, prominent endothelial involvement.\(^8\) Treatment of mild and moderate SOS is supportive. Ursodeoxycholic acid and low dose heparins are prophylactic therapies for SOS. However, specific pharmacotherapy is warranted in patients with severe SOS. Defibrotide is probably the drug that has most promise in SOS. It is a poly-deoxy-ribonucleotide derived from mammalian lung or mucosa, with intrinsic anticoagulant and anti-inflammatory activity, increasing levels of tissue plasminogen activator, thereby increasing fibrinolysis. It has been shown to be relatively safe in the setting of thrombocytopenia. Therapy is started at 6.25 mg/kg intravenously every 6 hours and continued until the patient's bilirubin levels have normalized. In the United States, defibrotide can be obtained through a Gentium-sponsored “Expanded Access, Treatment IND Protocol and is marketed in the European Union as Defitelio.\(^9\) Availing defibrotide in developing countries is subject to import policy agreements with prolonged waiting times, incurring heavy expenses. Other drugs are used in treatment of SOS however, without expected outcomes including alteplase and heparin, steroids, anti-thrombin concentrate, alprostadil and extreme measures such as transjugular intrahepatic porto-systemic shunt (poor long-term survival) and finally, LT has also been reported but these patients are very sick at this stage and unlikely to survive such a procedure.\(^{10}\)

**REFERENCES**


**Cite this article:** Philips CA, Augustine P, Mahadevan P. Two and Half Years Later: Cytomegalovirus and Ebstein Barr Virus Infection Leading to Sinusoidal Obstruction Syndrome in Liver Transplant Recipient. OGH Reports. 2018;7(1):35-7.