

Child was managed conservatively and was given pulse dose methyl prednisolone (30 mg/kg/day) for 3 days followed by tapering doses, in view of high inflammatory markers and no evidence of bacterial infection. Antibiotics and acyclovir were stopped after the confirmed diagnosis of SARS-CoV-2 induced meningoencephalitis on day 4 of illness. Injection remdesivir was not given as a unit protocol as growing evidence did not find it beneficial to prevent mortality in SARS-CoV-2 positive patients and there is not much data of its use in children. Child's sensorium gradually improved in next few days along with downward trend in inflammatory markers. His repeat RNA-PCR for SARS-CoV-2 on nasopharyngeal swab was again positive on day 7 of illness and second CSF examination for the same was refused by the parents. In view of clinical improvement, he was subsequently discharged on request on day 10 of illness as per the government's discharge policy with strict home isolation advice. Subsequent RNA-PCR for SARS-CoV-2 on nasopharyngeal swab became negative on day 15 of illness. Child is in close follow up and is doing well so far.

Most coronaviruses (CoVs) share a similar viral structure and infection pathway, therefore the neurotropic mechanisms previously found for other CoVs may also be applicable for SARS-CoV-2 [1-3]. It is associated with a wide spectrum of neurological manifestations, including encephalopathy, Guillain-Barré syndrome (GBS), and perfusion abnormalities in the brain [put Indian GBS, and encephalitis ref]. However, attempts to detect the virus in the CSF of patients with neurological manifestations have not been widely reported. Only two cases in adults around the world has been reported so far out of which one showed the virus using gene sequencing of the CSF and the other one showed RT-PCR positive in CSF (similar to our case), suggesting that the virus has the potential to cross the blood brain barrier [3,4]. The SARS-CoV-2 receptor for cell entry i.e., membrane-bound angiotensin converting enzyme 2 (ACE2) which is also expressed in neurons, as well as endothelial and arterial smooth muscle cells in the brain potentially allowing

SARS-CoV-2 to cross the blood-brain barrier and cause viral meningitis [5]. Panciani, et al. [6] hypothesized a three-step model to explain the neuroinvasive potential of SARS-CoV-2, suggesting that the viral load in CSF progressively increases and it triggers an inflammatory response, but the viral clearance precede the occurrence of indirect SARS-CoV-2 effects on the CNS [6].

This case highlights the neurotropism of SARS-CoV-2 virus, and that meningoencephalitis may be the initial presentation of SARS-CoV-2 even without respiratory symptoms. We feel early use of immunosuppressants like methylprednisolone, especially in the setting of hyperinflammatory syndrome, is crucial for better outcome.

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## Hepatic Visceral Larva Migrans Causing Hepatic Artery Pseudo-Aneurysm

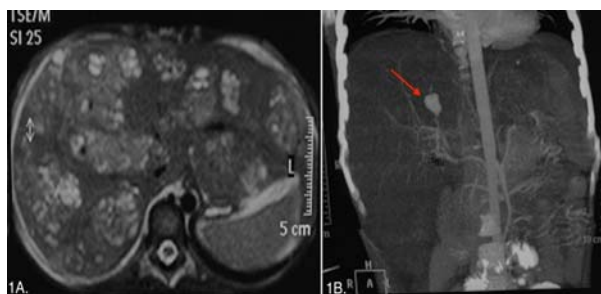
Visceral Larva Migrans refers to migration of second stage nematode larvae through human viscera most commonly the liver and lungs. This entity usually presents with fever, abdominal pain, hepatomegaly and respiratory symptoms. Here we describe hepatic visceral larva migrans causing hepatic artery pseudoaneurysm and presenting with upper gastrointestinal bleeding and its management.

Parasitic infections of liver are commonly encountered in clinical practice and can have myriad presentations posing a clinical diagnostic challenge. Hepatic visceral larva migrans (VLM) is one such entity presenting with prolonged fever and

liver involvement especially in areas endemic for the parasite. Hepatic artery pseudoaneurysm is a complication described mostly with traumatic liver injury and post-surgery [1]. We describe this complication secondary to hepatic VLM and its successful management.

A 12-year-old girl presented with high grade fever, jaundice and right upper abdominal pain with progressive abdominal distension associated with weight loss for four months and a history of recurrent black tarry stools requiring blood transfusions. She was resident of a rural area and her family of seven lived in an overcrowded house, belonged to lower socioeconomic status with poor hygiene practices, consumed vegetarian diet and had exposure to pet animals in neighborhood. On examination she was underweight (BMI 12.5 kg/m<sup>2</sup>), febrile and tachypneic, had severe pallor with pedal edema and no skin lesions. Systemic examination revealed firm tender

hepatomegaly (liver span:17 cm) without ascites or splenomegaly and crepitations on right side of chest. Ophthalmoscopic examination was unremarkable. Investigations revealed anemia (hemoglobin 5.7g/dL), and leukocytosis ( $16 \times 10^3/L$ ) with eosinophilia ( $1.4 \times 10^3/L$ ). Liver function tests were alanine aminotransferase 23 U/L, aspartate aminotransferase 19 U/L, alkaline phosphatase 590 U/L, total bilirubin 1.5 mg/dL with direct fraction 1.2 mg/dL, serum albumin 1.9 g/dL with albumin:globulin ratio of 0.4. As the child was sick at arrival, she was started on broad spectrum antimicrobials and supportive treatment (blood transfusion and albumin). Ultrasonography showed hepatomegaly with diffuse hypoechoic cystic lesions in both lobes of the liver. MRI abdomen showed lesions in the liver appearing hypointense on T1-weighted and hyperintense on T2-weighted images (**Fig.1a**) with mildly dilated common bile duct and normal intrahepatic biliary radicles. Dual phase CT scan of abdomen revealed multiple discrete and confluent hypodense lesions in both lobes of liver along with a 1.5 cm pseudoaneurysm (arrow) arising from the posterior branch of the right hepatic artery (**Fig.1b**). Based on clinical and radiological findings, a differential diagnosis of visceral larva migrans, cat scratch disease, Fascioliasis, disseminated tuberculosis and invasive candidiasis with underlying immunodeficiency along with pseudoaneurysm with suspected hemobilia was kept. The patient underwent digital subtraction angiography (DSA) and successful embolization of the pseudoaneurysm with n-butyl cyanoacrylate glue. Subsequent investigations revealed normal stool examination and negative Toxocara IgG serology, Echinococcus IgG serology, procalcitonin, Mantoux test, gastric aspirate genexpert for Tuberculosis, and HIV serology. Bacterial and fungal blood culture was sterile and upper GI endoscopy was normal. Percutaneous liver biopsy demonstrated ill-defined eosinophilic granulomas suggesting parasitic infiltration. Special stains and tissue culture were negative for acid fast bacilli (AFB), Bartonella and fungal elements. Based on clinical, radiological and histopathological findings, diagnosis of visceral larva migrans was made and child was started on albendazole (10mg/kg/day), diethylcarbamazine (4mg/kg/day) and oral steroids (1mg/kg/day) in 3 cycles of 3 weeks each with gradual tapering of steroids over next one month. Follow up imaging at six months showed resolution of hepatic lesions.



**Fig. 1** (a) Axial T2 weighted MR image shows multiple conglomerate heterogeneous lesions in both lobes of liver, (b) Coronal CT angiography image shows a pseudoaneurysm (arrow) arising from the posterior branch of right hepatic artery.

Visceral larva migrans (VLM) refers to migration of second stage nematode larvae through human viscera most commonly liver and lungs. The etiological agents include *Toxocaracanis*, *Toxocaracati*, *Baylisascarisprocyonis*, *Cappilaria hepatica*, and *Ascarissuum* [2]. Humans are accidental hosts and acquire infection by ingestion of food contaminated with infective eggs. The clinical manifestations are fever, hepatomegaly, weight loss and respiratory symptoms mimicking asthma. An IgG ELISA based on 30 kDa recombinant Toxocara excretory–secretory antigen has 92% sensitivity and 89% specificity [3]. Features suggestive of VLM on CT are presence of multiple confluent peripheral and periportal ill-defined hypodense, oval or elongated nodular lesions scattered throughout liver parenchyma with peripheral rim enhancement and MRI shows T2 hyperintense/T1 hypointense lesions with restriction on diffusion weighted sequences [4]. Confirmation is by histopathological examination which shows presence of eosinophilic granuloma, palisading histiocytes and very rarely larva may be visualized. The slow migration of larva through the tissue incites a host inflammatory response along with eosinophilic infiltration and destruction of liver parenchyma. The cytotoxic eosinophil derived proteins may damage the endothelium causing vascular complications [5]. Hepatic artery pseudoaneurysm, a rare complication has not been previously described with VLM. Pseudoaneurysm develops due to the erosion of the eosinophilic abscesses into the hepatic artery. Rupture of the aneurysm results in hemobilia and the patients may present with hematemesis or melena or both. In cases of rupture of the aneurysm, early intervention by angio-embolisation of feeding artery should be considered. The embolizing agents used include coils, n-butyl cyanoacrylate glue and thrombin [1]. Medical therapy includes diethyl-carbamazine, mebendazole or albendazole for 2-3 weeks. Steroids are indicated in cases of ocular and neurological toxo-cariasis and in acute inflammatory manifestations of VLM [6].

We conclude that hepatic VLM can be a rare cause of hepatic artery pseudoaneurysm resulting in upper gastrointestinal bleeding. Early recognition and comprehensive management is of utmost importance.

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## Tocilizumab Use in Children with Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a constellation of symptoms arising as a result of sudden and rapid release of cytokines into the blood from immune cells. CRS is characterized by high fever, hypotension, hypoxia, and/or multiorgan toxicity. Elevated liver enzymes and renal impairment are also noted and severe CRS can lead to life-threatening cardiorespiratory compromise [1]. CRS is increasingly seen as a medical emergency in children with blood disorders, and this could either be a presenting feature of their underlying disorder or a therapy-related event. Early recognition and therapy are essential, especially in severe cases. Scant data is available on the use of interleukin 6 (IL-6) inhibitor tocilizumab in very young children. We present a series of clinical situations in which we had used the CRS grading criteria to make a diagnosis and plan risk-based use of tocilizumab.

A 15-month-old girl presented with failure to thrive, generalized hypotonia, oral thrush and recurrent respiratory infections. She was diagnosed to have severe combined immune deficiency with *ORAI1* mutation. She underwent haploidentical stem cell transplantation with post-transplant cyclophosphamide and conditioning including fludarabine/treosulphan. After infusion of stem cells, she developed progressive symptoms suggestive of CRS including fever, tachycardia, and hypertension with one episode of posterior reversible encephalopathy syndrome, elevated liver enzymes and respiratory distress (requiring oxygen supplementation with high flow nasal cannula). Hypertension was noted, which was most likely secondary to the underlying calcium channelopathy associated with the mutation. CRS progressed to grade IV 11 days post-infusion. Serum ferritin, when elevated, suggests a cytokine surge in response to inflammation. The serum ferritin measured was 73000 mg/L. She was treated with 4 mg/kg of tocilizumab and made a dramatic recovery with a serial drop in serum ferritin within 48 hours.

An 8-year-old boy presented with fever, tachycardia, hypotension, cervical and axillary lymphadenopathy, hepatosplenomegaly, elevated liver enzymes and pancytopenia. Ferritin was elevated with levels up to 98000 mg/L. He has respiratory distress and required inotropes and oxygen supplementation. In view of features suggestive of grade 4 CRS, he was treated with one dose of tocilizumab in the intensive care unit. His symptoms recovered dramatically and serum ferritin dropped to 2700 mg/L in 72 hours. Bone marrow aspiration

cytology was unremarkable. Axillary lymph node biopsy and immunohistochemistry confirmed the diagnosis of classical Hodgkin lymphoma. We could commence chemo-therapy for Hodgkin lymphoma five days later, which was complicated by *E.coli* sepsis. He remains in remission over a year from diagnosis.

A 12-year-old boy presented with fever, tachycardia, tender hepatomegaly, and elevated liver enzymes (serum glutamic pyruvic transaminase, of 2500 IU/L and serum glutamic oxaloacetic transaminase, 2500 IU/L). He subsequently developed features of grade 3 CRS with respiratory distress and hypotension. Investigations revealed a serum ferritin of 69,000 mg/L, and Hepatitis A infection. He received one dose of tocilizumab at 4 mg/kg. The neutropenic phase following the drug was complicated by candida sepsis. He showed a complete recovery with normal blood counts, and remains on tapering steroids and cyclosporin.

There are several grading systems for CRS, where it is graded as grade I, II, III, IV, with grade I including fever without constitutional symptoms, grade II including hypotension responding to fluids and/or hypoxia responsive to <40% FiO<sub>2</sub>, grade III including hypotension requiring pressor and/or hypoxia requiring oxygen >40% FiO<sub>2</sub> and grade IV consisting of life-threatening complications [2]. Several mouse-models have demonstrated the elaboration of cytokines namely IL2, IL3, IL6, interferon-gamma and GM-CSF in CRS with macrophages and monocytes being direct mediators of CRS [3]. Serum ferritin is an easily accessible diagnostic tool in these children and serial values help guide therapeutic interventions. CRS needs to be carefully distinguished from sepsis, and the clinical background and active surveillance for infections is crucial to prevent immediate mortality from sepsis.

Cytokine release syndrome has been reported by several groups in recent years post T cell replete peripheral blood haploidentical stem cell transplantation with post-transplant cyclophosphamide, with IL-6 being the most prominent biomarker. CRS also has an impact on increased risk of graft versus host disease [4]. Tocilizumab has been shown to be safe and effective in curbing the adverse effects associated with severe CRS [3,5] in especially post-transplant and rheumatological conditions. There is an ongoing clinical trial (NCT03533101) where tocilizumab will be administered pre-emptively prior to transplantation in the above group of patients.

We report that tocilizumab can be used safely even in the very young children at a dose of 4 mg/kg intravenously to provide immediate relief in life-threatening situations. The use of high dose steroids in these critically ill children with profound