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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 *ORAI 1* 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% FiO2, grade III including hypotension requiring pressor and/or hypoxia requiring oxygen >40% FiO2 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 GMCSF 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

neutropenia increases the risk of infection. Tocilizumab, in our experience, is a safer option even in infants and it provides immediate relief to the dramatic symptoms.

DR REVATHI RAJ, DR RAMYA UPPULURI* AND DR VENKATESWARAN VS

From Department of Pediatric Hematology, Oncology, Blood and Marrow Transplantation, Apollo Hospitals, Anna Salai, Teynampet, Chennai, Tamil Nadu, India

**ramya.december@gmail.com*

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Eosinophilic Meningitis in a Toddler

Eosinophilic meningitis (EM) is a chronic aseptic meningitis often caused by helminthic infestation. EM is defined as eosinophils>10 per mm^3 in CSF or >10% of total CSF leukocyte [1,2]. The most common infectious cause of EM worldwide are *Angiostrongylus cantonenis, Gnathostoma spinigerum and Basyliascaris procyonis* [1,2]. Non-infectious causes include malignancy like non Hodgkin lymphoma, multiple sclerosis, hypereosinophilic syndromes, malfunctioning ventriculoperitoneal shunt and adverse drug reactions [2]. Even though EM has been reported in adults and children from India, parasitic etiology has not been confirmed in those cases [4]. We report a one year old child, resident of South Kerala, India, who reported with prolonged fever due to confirmed helminthic infestation.

A 1-year-old female child presented with 3 weeks history of irregular fever, irritability and poor oral intake. Child was started on oral cefixime from suspecting UTI. On admission, she had continuous fever for 5 days with irritability and episodes of inconsolable cry for 3 days. No history of vomiting or seizure, ear infection, head trauma, recent vaccination or contact with Tuberculosis, or exposure to any drugs or allergens. On examination, vitals were stable with no features of raised intracranial pressure or signs of meningeal irritation and with a normal CNS examination. On investigation, white blood cell count was 14.8×10^9/L (36% neutrophils, 42% lymphocytes, 22% eosinophils) with peripheral smear showing eosinophilia and no parasites or abnormal cells. C-reactive protein was negative. Stool and urine examination did not reveal ova or cysts. In view of non remission of prolonged fever and history of irritability and headache, CSF study was done on second day of admission which revealed increased CSF pressure of clear fluid with 1150 whole blood cells, (30% neutrophils, 70% lymphocytes) with a protein 115 mg/dL and sugar 30 mg/dL (blood sugar- 89 mg/dL) suggestive of meningitis. Cultures of blood, CSF and urine were sterile. Tuberculosis PCR, CSF biofilm for bacterial and viral panel were negative. India Ink and CSF biofilm were negative for Cryptococcus, KOH wet mount did not reveal any fungal elements. Mantoux test and HIV ELISA were negative and Chest Roentgenogram was normal. MRI contrast study of brain showed multiple cortical infarcts with sub cortical and cortical hyper intensities in T2W/FLAIR, leptomeningeal enhancement suggestive of meningitis. In view of meningitis, she was initially treated with ceftriaxone, then upgraded to vancomycin, meropenem and acyclovir. Since fever and irritability persisted even after 7 days of antibiotics, repeat sepsis screen was done, which was negative, and had similar findings on repeat MRI. Therefore, correlating the peripheral eosinophilia with this history, EM was suspected. On revisiting the history, mother gave history of a pet dog at home with rat and snail infestation in the locality. Absolute eosinophil count was 3080/mm^3 on day 1, 5500/mm^3 on day 7, 2880/mm^3 on day12, 3102/mm^3 on day 17. Repeat CSF study revealed 295 white blood cell/mm^3 (5% neutrophils, 85% lymphocytes, 25% eosinophils) with protein 104 mg/dL, sugar 34 mg/dL (blood sugar-103mg/dL). Real Time PCR was

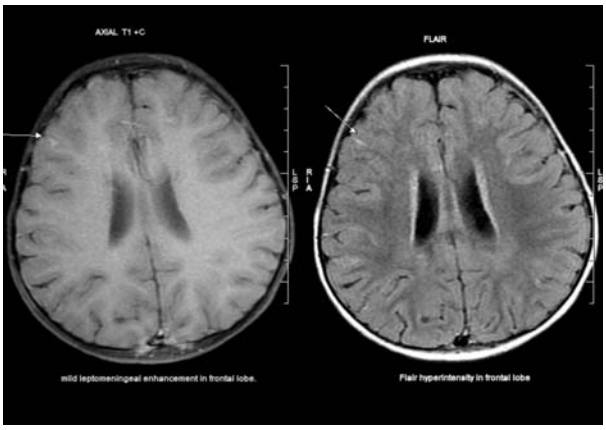

Fig.1 T1W/FLAIR images showing leptomeningeal enchancement/hyperintensity in frontal lobe.