

# **Renal Tubulopathy associated with Cytokine Release Syndrome after CD-19 CAR T Cell therapy in a patient with refractory DLBCL**

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## **INTRODUCTION**

Chimeric antigen receptor T-cell (CAR T-cell) therapy has been instrumental in the management of refractory adult Acute lymphoblastic leukemia and refractory Non Hodgkin's Lymphoma. CAR T-cell therapy involves harvesting autologous T cells which are genetically modified to recognize specific antigens (eg, CD 19, CD 22, Carbonic anhydrase IX) on the surface of tumor cells. The mechanism of action involves massive T cell response against the tumor. This, however can lead to a life threatening complication known as Cytokine Release Syndrome. It can lead to an array of systemic complications in the form of Cardiopulmonary decline, Neurotoxicity, Hematologic toxicity and Renal injury. Cardiopulmonary adverse events occur in over 10% patients receiving CAR T cell therapy and have a fatality rate of 17.4% <sup>1</sup>. Secondary Hemophagocytic Lymphohistiocytosis (carHLH) is seen in upto 60% patients with severe CRS (Grade 3-4) <sup>2</sup>. Acute kidney injury has been seen in upto 30% of patients receiving CAR T cell therapy upto 100 days after treatment <sup>3</sup>. Cytokines like IL-6, IL-1, and IFN- $\gamma$  have been implicated in pathogenesis of nephropathy by causing endothelial injury <sup>4</sup>.

## **CASE REPORT**

A 50-year old male with past medical history of refractory Diffuse Large B cell lymphoma, bowel perforation and paroxysmal atrial fibrillation, was admitted to the Critical Care Unit after developing fever, hypotension, tachycardia, shortness of breath after receiving CD-19 CAR T Cell therapy. About 4 weeks prior to the presentation, the patient's initial treatment plan for receiving CAR T therapy post LD chemotherapy was deferred due to acute gastric ulcer perforation. Imaging revealed an ulcerated mass along the lesser curvature. He underwent distal gastrectomy with Billroth II repair. Thus CAR T therapy post LD Chemo was delayed 3 weeks to allow the lesion to heal. A day after receiving CAR T cell therapy, the patient was re-admitted to the ICU in shock with respiratory failure. He required inotropic support with 3 vasopressors: Norepinephrine, Vasopressin and Angiotensin to maintain MAP > 60mmHg. The patient was in acute hypoxemic respiratory failure. He required mechanical ventilation with 90% FiO<sub>2</sub> and PEEP at 5 cm to maintain SpO<sub>2</sub>  $\geq$ 94%. CRS grade 4 was diagnosed based on the Lee's Criteria. Basic metabolic panel was remarkable for Hypokalemia (3.2), Hypophosphotemia (1.2), Hypocalcemia (7.9), metabolic acidosis (serum bicarbonate: 18). Urinary pH was high (7.5). The serum anion gap was 10. BUN was 16 and Serum Creatinine was 0.72. Complete blood count revealed severe leukopenia (<100/mm<sup>3</sup>), severe thrombocytopenia (17,000/ul), and anemia (Hb-6.4mg/dl). Serum Ferritin was 21,100. Lipid panel revealed hypertriglyceridemia (422mg/dl). Coagulation profile was remarkable for elevated D-dimer (1617ng/ml) and low fibrinogen (173mg/dl). The serum procalcitonin level was elevated (1.29ng/ml). Chest imaging revealed worsening pulmonary parenchymal involvement compared to imaging done prior to CAR T cell therapy. The patient was given 3 doses of Tocilizumab (8mg/kg) over the course of 48 hours on Day 3 and 4 of illness. He was also started on empiric antibiotics for severe Neutropenia. He was started on Lacosamide prophylactically for CAR-associated neurotoxicity. On day 4, he required vasopressors and his FiO<sub>2</sub> requirement was 90%. On day 4, the patient was started on methylprednisolone 250 mg. It was uptitrated to 1000mg/day for the following 5 days. The patient's cardiorespiratory status improved significantly over the next 24 hours after starting

Corticosteroids: His Ventilator requirements decreased from 90% to 50% FiO<sub>2</sub> and he became hemodynamically stable without the need for vasopressors . He was successfully extubated on day 8. His status continued to improve over the following two days and we started tapering methylprednisolone.

## **DISCUSSION**

Cytokine Release Syndrome (CRS) is a feared complication of CAR T-cell therapy which can present with multi-organ failure. His dyselectrolytemia was suggestive of renal tubulopathy resulting in wasting of potassium, phosphorus and calcium. In the setting of normal serum creatinine, non-anion gap metabolic acidosis, and elevated Urinary pH; this clinical picture is suggestive of Type II Renal Tubular Acidosis. Type II RTA occurs as a result of disruption in Bicarbonate absorption in the proximal tubule of the nephron. Cytokines are proteins that are filtered by the glomerulus and then reabsorbed to be metabolized by the proximal tubular cell. Elevated cytokines also contribute to vasodilation and third spacing; reduced perfusion to kidneys can further contribute to the AKI<sup>5</sup>. IL-6 which is markedly elevated in CRS, has been implicated in both acute and renal injury.<sup>6</sup> Furthermore resolution of the acidosis and dyselectrolytemia after Immunomodulatory therapy indicates that the cytokine storm was contributing to the nephropathy. Our case highlights that Cytokine Release Syndrome post CAR T-Cell therapy may be associated with a wider array of renal complications than documented: including isolated Renal tubulopathy.