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# Revealing a hidden severe adverse event: Rapid-onset acute edema following CAR T-cell therapy.

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**Abstract**

**Chimeric Antigen Receptor (CAR) T-cell therapy is the modern tool in the armamentarium of hematologists to treat patients with several hematological malignancies. Although very effective for advanced disease, it comes with its own limitations and adverse events. We present a unique case of hyperacute acute cerebral edema following (CAR) T-cell therapy in a young male who was treated for B-cell acute lymphoblastic leukemia. Shortly after therapy initiation, the patient developed seizures and rapid deterioration in consciousness. After initiation of treatment of seizures, and medical stabilization, imaging revealed diffuse cerebral edema on brain Magnetic Resonance Imaging (MRI). Subsequent brain CT 10-hours later confirmed progressive brain damage. The patient was given maximal medical treatment for acute cerebral edema, however, he succumbed to this acute adverse event of (CAR) T- cell therapy. This case highlights the importance of recognizing the hyperacute presentation of severe adverse events associated with (CAR) T-cell therapy. It also highlights the high risks associated with this unique treatment. Enhancing patient safety and treatment outcomes is highly recommended through the review of infusion protocols and the implementation of preventive measures.**

**Keywords**: (CAR) T-cell therapy, Neurotoxicity syndrome, Anti-IL-6 therapy, CD-20

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## Introduction

Chimeric Antigen Receptor (CAR) T-cell therapy represents an innovative and potential treatment approach for various hematological malignancies, including B-cell Acute Lymphoblastic Leukemia (B-ALL) [1,2]. While this therapy has shown remarkable efficacy in achieving remission, it is important to acknowledge and address potential adverse events, including neurological side effects, associated with its administration. Two specific toxicities have been linked with this therapy are Cytokine-release Syndrome (CRS) and Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) [3]. CRS was considered the most common adverse event observed after CAR T-cell therapy, manifesting as an escalated immune response and, in rare cases, progressing to fulminant Hemophagocytic Lympho-Histiocytosis (HLH). CRS is characterized by disturbed vital signs like fever, hypotension, and oxygen desaturation, which can lead to multiorgan toxicity. These side effects typically occur within the first 14 days after CAR-T cell re-infusion.

ICANS is the second most common adverse event, coexisting with or occurring after CRS in up to 60% of patients, with 30% experiencing severe (≥ grade 3) symptoms [3]. ICANS presents as a toxic encephalopathic state, with early manifestations such as tremor, dysgraphia, and expressive dysphasia [3]. Unfortunately, it can rapidly progress to severe toxicity, including seizures and cerebral edema. Severe ICANS involves neurological symptoms and signs like seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure, papilledema, and cerebral edema.

ICANS can manifest in a biphasic manner, with an initial phase concurrent with high fever and other CRS symptoms within the first 5 days after cellular immunotherapy. A second phase may occur after the fever, as other CRS symptoms subside, often beyond 5 days after cell infusion. Delayed neurotoxicity, with seizures or episodes of confusion, has

been reported in 10% of patients during the third or fourth week after CAR-T cell therapy [3,4]. The underlying mechanism behind ICANS is not fully understood, but it likely involves the release of inflammatory cytokines by macrophages and monocytes, leading to increased vascular permeability, endothelial activation, and blood-brain barrier breakdown. CAR-T cells themselves are not thought to directly mediate ICANS. Anti-IL-6 therapy can reverse ICANS during the first phase, but is ineffective in the second phase, where corticosteroids are the preferred treatment [4,5].

In our case, the patient developed an exceptionally rapid and unusual hyperacute ICANS manifestation, including rapid cerebral edema and herniation within a timeframe of less than 10 hours from the initiation of therapy.

## Case Presentation

A 32-year-old man with no significant medical history, was diagnosed with refractory large B-cell lymphoma based on PET scan and lymph node biopsy. The patient initially had no neurological symptoms and maintained a normal level of consciousness. Initially, was started on CHOP regimen which is a combination of (cyclophosphamide, doxorubicin hydrochloride, hydroxydaunorubicin, vincristine sulfate (Oncovin), and prednisone) then upgraded to DA-EPOCH approach (infusion dose-adjusted) due to the aggressive nature of CD-20 negative and because of the recurrence it was given (CAR) T-cell therapy.

After several hours of initiating (CAR) T-cell therapy, he experienced a rapid deterioration in his level of consciousness and subsequently developed generalized tonic-clonic seizures. He was tachycardic with low grade fever. His neurological assessment showed preserved but weak brainstem reflexes, no motor response, and hyperreflexia in all limbs. According to the protocol for CAR-T cell therapy, he received lorazepam and a loading dose of levetiracetam, but there was no improvement in his level of consciousness. As a result, he was intubated, sedated with midazolam, and an immediate EEG was performed, which showed no active subclinical seizures. A brain MRI was obtained (Figures 1 and 2).

Revealing diffuse brain edema along with high signal changes in the sulci and CSF space with abnormal leptomeningeal hyperintensity. Given the high-grade fever, he was started on anti-meningeal coverage and septic work up obtained. He was also started on high-dose steroids (1000 mg intravenous daily) and tocilizumab (558.4 mg, adjusted to weight) as per the protocol for ICANS. Six hours later, the patient's pupils were dilated at 7 mm and non-reactive, while rest of the brainstem reflexes were absent. A brain CT scan was performed, which showed herniated brain with diffuse brain edema (Figure 3). The patient continued to receive high-dose steroids and tocilizumab for the next five days, but there was no improvement observed. During the following next three days, routine EEG studies were done that showed electro cerebral inactivity. Brain death protocol was done one week later, and death was announced.

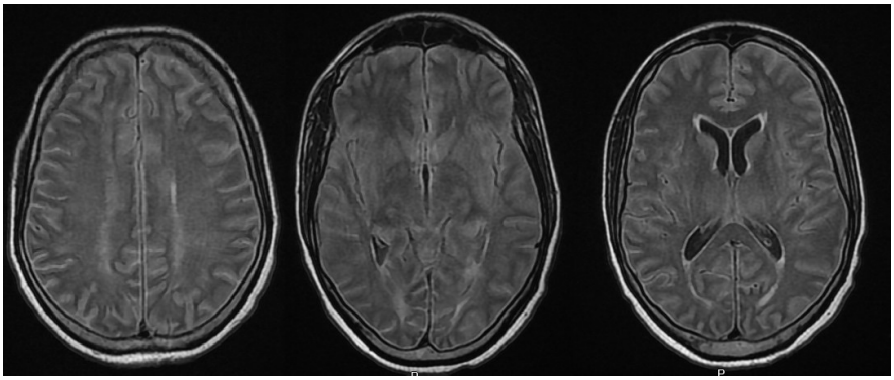

***Figure 1.*** *FLAIR sequence, brain MRI showing diffuse brain edema along with high signal changes on the sulci and CSF space with abnormal leptomeningeal signal.*

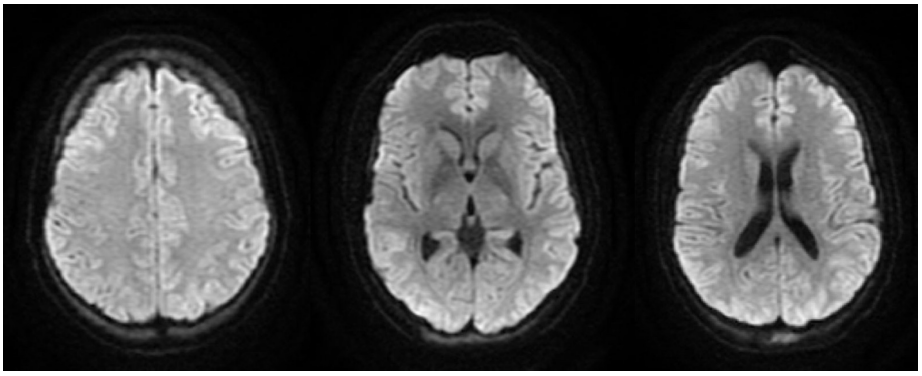

***Figure 2.*** *DWI sequence, brain MRI showing diffuse cortical diffusion restrictions.*

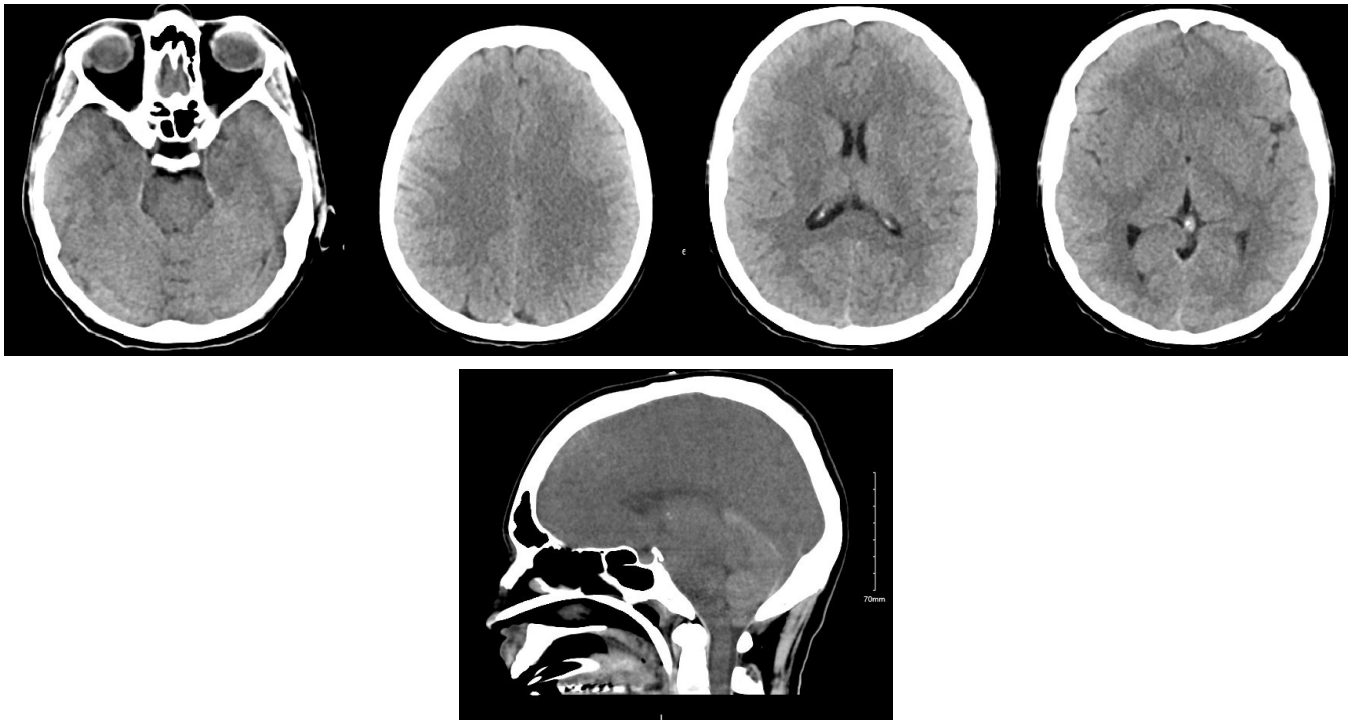

***Figure 3.*** *Non-contrast brain CT showing progressive worsening in cerebral edema with disappearance of cistern and brain herniation in the sagittal section.*

## Results and Discussion

Despite advancements in the management of hematological malignancies, there is still a need for more sophisticated treatments for patients who do not respond to first-line therapies. One such treatment is CAR-T cell therapy, which has been introduced for refractory hematological malignancies [1]. This therapy involves genetically engineering the T cells with Chimeric Antigen Receptors (CARs) in the laboratory. These modified T cells are then cultured and expanded in the lab. The goal is to enable these CAR T-cells to recognize and target a specific protein on the surface of cancer cells, ultimately leading to an attack on the cancer cells [2,3]. The emergence of Chimeric Antigen Receptor (CAR) T-cell therapy has revolutionized the treatment landscape for patients who do not respond to conventional therapies. This innovative approach has delivered overwhelming benefits, offering renewed hope for those facing dire circumstances. However, this cutting-edge therapy is not without its risks, particularly in the field of neurological adverse events.

One of the unique toxicities associated with CAR T-cell therapy is Cytokine Release Syndrome (CRS), characterized by an aggressive immune response that can, in rare instances, lead to the life-threatening condition of burst Hemophagocytic Lympho-Histiocytosis (HLH). CRS typically manifests within the first 2-weeks after CAR T-cell infusion, with altered vital signs, and multiorgan toxicity [3]. Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) is another significant adverse event, often occurring concurrently with or after the resolution of CRS. ICANS presents as a toxic encephalopathy, which can rapidly progress to severe toxicity, manifested as multiple neurological symptoms including seizures and cerebral edema. Patients may exhibit a wide range of neurological symptoms, such as seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure causing cerebral edema which might end by life threatening condition. The condition has multiple phases, with an initial phase occurring alongside high fever and other CRS symptoms, followed by a second phase after the resolution of fever and CRS symptoms, often beyond 5 days after cell infusion [3,4].

Notably, delayed neurotoxicity, such as seizures or episodes of confusion, can even occur during the third or fourth week after CAR T-cell therapy. The management of these neurological complications requires a nuanced approach, with anti-IL-6 therapy proven effective in reversing the initial phase of ICANS, while corticosteroids are typically preferred for the second phase.

Upon conducting a literature review, no cases with early side effects were found. The case presented here is particularly noteworthy due to its exceptionally unusual manifestation of hyper acute ICANS, with rapid onset of cerebral edema and herniation in under 10 hours. This highlights the urgency of recognizing and addressing such severe adverse events promptly. As the field of cellular immunotherapy continues to evolve, it is important for healthcare providers to maintain a deep understanding of the potential neurological side effects associated with this transformative treatment. By diligently monitoring patients and implementing appropriate interventions, clinicians can navigate these challenges and optimize the benefits of this ground breaking therapy for those in dire need.

## Conclusion

Our case highlights an unfortunate consequence of (CAR) T-cell therapy with severe adverse event of acute cerebral edema following the therapy in a patient with B-ALL. The rapid onset and progression of cerebral edema necessitated immediate intervention but could not prevent irreversible brain damage. This case underscores the critical need for healthcare providers to be aware of the potential for such severe side effects associated with (CAR) T-cell therapy and to communicate this information effectively to patients and their families prior to initiation of the therapy. Future research should focus on identifying risk factors, refining treatment protocols, and developing strategies for early detection and management of acute cerebral edema associated with (CAR) T-cell therapy.

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## Declaration

The authors declare no conflicts of interest regarding the publication of this case report.

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