It's in the Eye of the Beholder: Ocular Ultrasound Enhanced Monitoring of Neurotoxicity after CAR T-cell therapy

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Case Report

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Abstract

Usually used in emergency settings, bedside sonographic measurement of optic nerve sheath diameter can aid in diagnosing elevated intracranial pressure. We report a case of a 26-year-old male hospitalized for CAR T-cell therapy with Axicabtagene Ciloleucel for treatment of relapsed diffuse large B-cell lymphoma, who developed progressive symptoms of immune effector cell-associated neurotoxicity syndrome. Fundoscopic examination suggested the presence of blurred optic disc margins. Bedside ocular ultrasound revealed wide optic nerve sheath diameters and bulging optic discs bilaterally. The patient had a ventriculostomy placed for monitoring and received treatment with steroids and mannitol, as well as tocilizumab. After 7 days in the ICU, the patient recovered with no evidence of long-term neurological deficits.

Introduction

Immunotherapy with chimeric antigen receptor (CAR) modified T-cells is a promising treatment for patients with refractory B-cell leukemia and lymphoma¹⁻⁴. Toxicities include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)⁵. These unique toxicities can be fatal, especially in cases of raised intracranial pressure (ICP) and cerebral edema^{6,7}. Penissi *et al.* analyzed 102 patients that received CAR T-cell therapy, 53 with B-cell acute lymphoblastic leukemia (B-ALL), and 49 with diffuse large B-cell lymphoma (DLBCL). They found that ICANS was present in 50% of patients (55% in the B-ALL group and 45% in the DLBCL group)⁸. Other analyses have identified ICANS in up to 67% of patients with B-ALL and 62% of patients with DLBCL⁹.

Various systems have been used for grading neurotoxicity. The most recent consensus criteria by the American Society for Transplantation and Cellular Therapy (ASTCT) include the 10-point Immune Effector Cell-Associated encephalopathy (ICE) score (a modified version of the CARTOX-10)⁸, which evaluates orientation, naming, following commands, writing, calculation, level of consciousness, seizures, motor deficits and signs of increased intracranial pressure, using a 10 point-based system. Grades 1 and 2 are defined by the degree of encephalopathy (ICE 9 – 6 points). Grade 3 is defined by a more severe encephalopathy, seizures, or local edema on imaging. Grade 4 ICANS is defined as stupor or coma, ICE score of 0, prolonged or repetitive seizures, motor deficits, or signs of elevated ICP. Grade 5 describes death due to ICANS⁵.

Due to the high frequency of neurotoxicity, close monitoring with a neurologic exam and noninvasive tools is imperative for prompt therapeutic interventions to avoid dire outcomes. Invasive or noninvasive methods can detect elevated intracranial pressures. The sonographic measurement of the optic nerve sheath diameter (ONSD) has been described as a sensitive and specific noninvasive method to detect increased ICP¹⁰. The optic nerve sheath contains the extension of the subarachnoid space.

The subarachnoid space surrounds the optic nerve and is circumscribed by the optic nerve sheath that is an anatomical extension of the dura mater around the nerve. In cases of increased ICP, the optic nerve

sheath gets dilated due to the elevated cerebrospinal fluid (CSF) pressure¹¹. ONSD measurement is performed using a linear probe placed on the closed upper eyelid, with the patient in the supine position. ONSD is measured 3 mm behind the globe in the two-dimensional mode¹². Sonographic ONSD higher than 5.0 mm has been proposed as a cutoff for identifying increased ICP in adults¹³.

We report a case of ICANS, monitored with ONSD ultrasonography, with a favorable outcome after aggressive treatment of intracranial hypertension.

Case Report

A 26-year-old male with refractory diffuse large B-cell lymphoma involving the mediastinum was treated with axi-cel CAR T-cell therapy. His neurological exam and brain MRI were normal before therapy. He was placed on seizure prophylaxis with levetiracetam per institutional guidelines. The first-day post-infusion, he developed fever and tachycardia consistent with grade 1 CRS. On day 4, he developed rapidly progressive ICANS that started with handwriting impairment and 7 hours later became encephalopathic with an ICE score of 3. Examination revealed expressive aphasia, nystagmus, and mild tremor. Due to agitation, the fundoscopic examination could not be reliably performed to assess for papilledema. Head CT was unremarkable. He received intravenous tocilizumab and dexamethasone 10 mg. Continuous EEG showed a moderate generalized slowing of the background activity. Over the next 6 hours, he became lethargic. ONSD measured with ultrasound were 6.5 and 6 mm (Fig. 1). He was intubated for airway protection. Lumbar puncture was performed with an opening pressure of 44 cmH₂O. After removing 80 mL of cerebrospinal fluid, closing pressure was 15 cmH₂O, and ONSD was 3.2 and 3.1 mm. He was treated with high-dose methylprednisolone, hyperosmolar therapy, and sedation for grade 4 ICANS. An external ventricular drain (EVD) was placed for monitoring (first measure after placement was 3 cm H₂O). MRI brain showed increased T2-hyperintensity in the thalami and dorsal pons (Fig. 2). He received 3 doses of tocilizumab and 3 doses of methylprednisolone (1,000 mg per dose). Serial ONSD measurements continued to remain low and were consistent with low ICP as measured by EVD. He was extubated 48 hours after onset of neurotoxicity, and EVD was removed 2 days later. Neurotoxicity symptoms resolved one week after onset. Repeated MRI 3 weeks later showed resolution of the abnormalities. Lymphoma restaging one month after treatment revealed a complete response to therapy. A timeline depicting changes in temperature, CARTOX-10 and handwriting can be seen in **Figs. 3, 4 and 5**.

Discussion

Neurological toxicities have been observed in up to 77% of patients treated with CAR-T-cells¹⁴, with grade 3–5 in 25–57% of patients⁶. The underlying pathophysiology of ICANS remains unclear, with possible mechanisms including an inflammatory process triggered by CAR-T-cells, with subsequent secretion of monocyte-derived cytokines like IL-1, IL-6, and GM-CSF, as well as a widespread endothelial activation with increased permeability of the blood-brain barrier (BBB). Studies of CSF from patients who developed severe forms of ICANS showed a 17-fold increase in CD14 + myeloid cells' levels compared to patients

with low-grade ICANS. Therefore, ICANS might be the result of systemic inflammation triggered by CAR T-cell infusion and activation, which leads to endothelial activation, BBB disruption, and inflammatory infiltration of central nervous tissues¹⁵. The most common neurological symptoms include encephalopathy, tremor, aphasia, and focal weakness¹⁴. Expressive aphasia is the most specific first sign of severe neurotoxicity⁵. We report a case of raised intracranial pressure with cerebral edema in which noninvasive monitoring of intracranial pressure with ONSD serial measurements allowed for rapid identification and initiation of aggressive treatment and monitoring of response with good correlation with invasive EVD-ICP measurements.

A meta-analysis by Cai *et al.* assessed the incidence and characteristics of fatal toxicity associated with CAR T-cell therapy. After analyzing 19 clinical trials with a total of 890 cases and 33 treatment-related deaths, they found that the most common causes of CAR T-cell therapy-related mortality were CRS (30.3%), nervous system disorders (18.2%) and infections (12%). Other causes included blood, cardiac, respiratory, gastrointestinal and hepatobiliary disorders¹⁶. Regarding nervous system involvement, cases of raised intracranial pressure with and without cerebral edema after CAR T-cell therapy have been reported³ and represent the most devastating sequelae of ICANS and the leading cause of neurologic CAR T-cell therapy-associated mortality¹⁷.

Prompt recognition of intracranial hypertension after CAR T-cell therapy is necessary to mitigate adverse outcomes. However, assessment of papilledema in patients with encephalopathy using fundoscopy is challenging and, most of the time, inaccurate¹⁸. Additionally, obtaining imaging studies such as CT or MRI may be delayed due to logistical reasons and the hemodynamical/neurological stability of the patient, which can create critical delays in the initiation of lifesaving therapeutic interventions.

Moreover, the gold standard assessment of ICP using invasive (lumbar puncture opening pressure) may be contraindicated due to coagulopathy, thrombocytopenia, or clinical instability, and poses a risk of complications such as herniation and bleeding¹⁹.

Our case demonstrates sonographic measurement of ONSD as a bedside, noninvasive test is a reliable method to monitor intracranial pressure and ICANS in patients undergoing CAR-T-cell therapy. This tool can be used for effective monitoring of critically ill patients that require early and aggressive management. Bedside ocular ultrasound can be used serially for early detection of increased intracranial pressure after cellular therapy enabling early and aggressive management of cerebral edema which can be a devastating neurologic complication of CAR T-cell therapy.

Declarations

Conflicts of Interest and Source of Funding

The authors report no disclosures relevant to this manuscript.

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The data included in this case report was approved for publication by our ethics committee at Mayo Clinic Arizona. The need for consent was waived by this internal institution, as no harm of any kind is provided to the patient, as well as no personal identifying information is shared.

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Figures

Figure 1

A) Optic nerve sheath diameter measurements pre lumbar puncture were 6.5 and 6 mm. B) Optic nerve sheath diameter measurements post lumbar puncture were 3.2 and 3.1mm

Figure 2

Brain magnetic resonance imaging, axial fluid attenuation recovery sequence, showing abnormally increased T2 hyperintensity most prominent in bilateral thalami, but also present at the external capsules and dorsal pons.

Neurological assessment after ICANS onset

Figure 3

CARTOX-10 score since development of ICANS until discharge.

Body temperature after CAR-T cells infusion

Figure 4

A timeline depicting changes in temperature, CARTOX-10 and handwriting

Figure 5

A timeline depicting changes in temperature, CARTOX-10 and handwriting