LETTER TO THE EDITORS

Fulminant cerebral edema following CAR T-cell therapy: case report and pathophysiological insights from literature review

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Dear Sirs,

Chimeric antigen receptor (CAR) T-cell therapy is a novel immunotherapy that has demonstrated remarkable remission responses in refractory hematological cancers [1]. However, its high efficacy is hampered, in a subset of patients, by an exaggerated systemic hyper-inflammatory response, namely cytokine release syndrome (CRS), and neurological adverse events, namely immune effector cell-associated neurotoxicity syndrome (ICANS) [2]. Clinical manifestations of ICANS are heterogeneous, ranging from language disturbances and frontal-predominant encephalopathy to akinetic mutism and, anecdotally, fulminant diffuse cerebral edema [1–3]. The latter is characterized by rapid neurological deterioration which may lead to death within 24 h, therefore representing the most fearsome complication of CAR T-cell therapy [1, 4, 5]. Nonetheless, its underpinning biologics, incidence, risk factors, and best management strategies remain currently unclear, thus representing an urgent

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unmet need. Hereby, we describe a case of fatal fulminant diffuse cerebral edema related to CAR T-cell therapy and critically review the literature on this peculiar neurological presentation to shed light on its pathophysiological mechanisms. This was the only case that developed this complication among 46 patients affected by refractory large B cell lymphoma who received CAR T-cell therapy at our hospital.

A 35-year-old woman, affected by chemo-refractory primary mediastinal large B cell lymphoma, received CAR T-cell therapy at the IRCCS AOU Bologna. A comprehensive neurological screening evaluation (neurological examination, EEG, nerve conduction study, brain MRI and neuropsychological tests) was unremarkable. The patient received five cycles of pembrolizumab (the first before leukapheresis and the other four as bridging therapy) and lymphodepleting chemotherapy according to the standard conditioning with fludarabine (30 mg/m^2 once daily for three days) and cyclophosphamide (500 mg/m^2 once daily for three days), prior administration of axicabtagene ciloleucel (*Axi*-cel; 2×10^6 anti-CD19 CAR T-cells/kg). Twelve hours after CAR T-cells infusion, she developed a grade 1 CRS, which resulted refractory to tocilizumab given for three doses on days + 2 and + 3 post CAR T-cells infusion, according with EBMT and ASTCT guidelines [2, 6]. Tocilizumab was started concomitantly with a slight increase of both IL-6 (34.9 pg/ml, normal value < 5.9 pg/mL) and C-reactive protein (5.05 mg/dL, normal value < 0.5 mg/dL) plasma level. A chest computed tomography (CT) scan and several blood cultures, performed according to the internal protocol, excluded an infectious etiology. CRS did not progress to a higher grade and neurological evaluations were repeatedly unremarkable. Nonetheless, during the night between day + 3 and + 4, she developed vomiting in addition to fever and, on the following morning, she presented with non-fluent expressive aphasia and myoclonic postural tremors (ICANS grade 2), becoming

rapidly lethargic. Intravenous dexamethasone (10 mg/q6h) was promptly started and she was transferred to the intensive care unit, where she was sedated and intubated. Few hours later, following sedation weaning, the patient was comatose (GCS = 7; E3, V1, M3) and her right pupil was fixed and dilated, yet the other brainstem reflexes were preserved (ICANS grade 4). Diffuse slowing was observed at EEG, while laboratory blood tests showed a dramatic increase of IL-6 (2144 pg/mL) and D-dimer levels (12.14 mg/dL), yet other inflammatory markers were only slightly increased, such as C-reactive protein (9.50 mg/dL) and ferritin levels (134 ng/mL) (Supplementary Table 1). Brain CT scan revealed diffuse cerebral edema (Fig. 1). The patient was promptly managed with both pharmacologic and non-pharmacologic interventions, including intravenous methylprednisolone (1000 mg), hyperventilation, head and trunk elevation up to 30 degrees, hypertonic saline and mannitol. Ultimately, a ventriculostomy with intraventricular intracranial pressure (ICP) monitoring was placed, showing an ICP of 90 mmHg. This remarkably
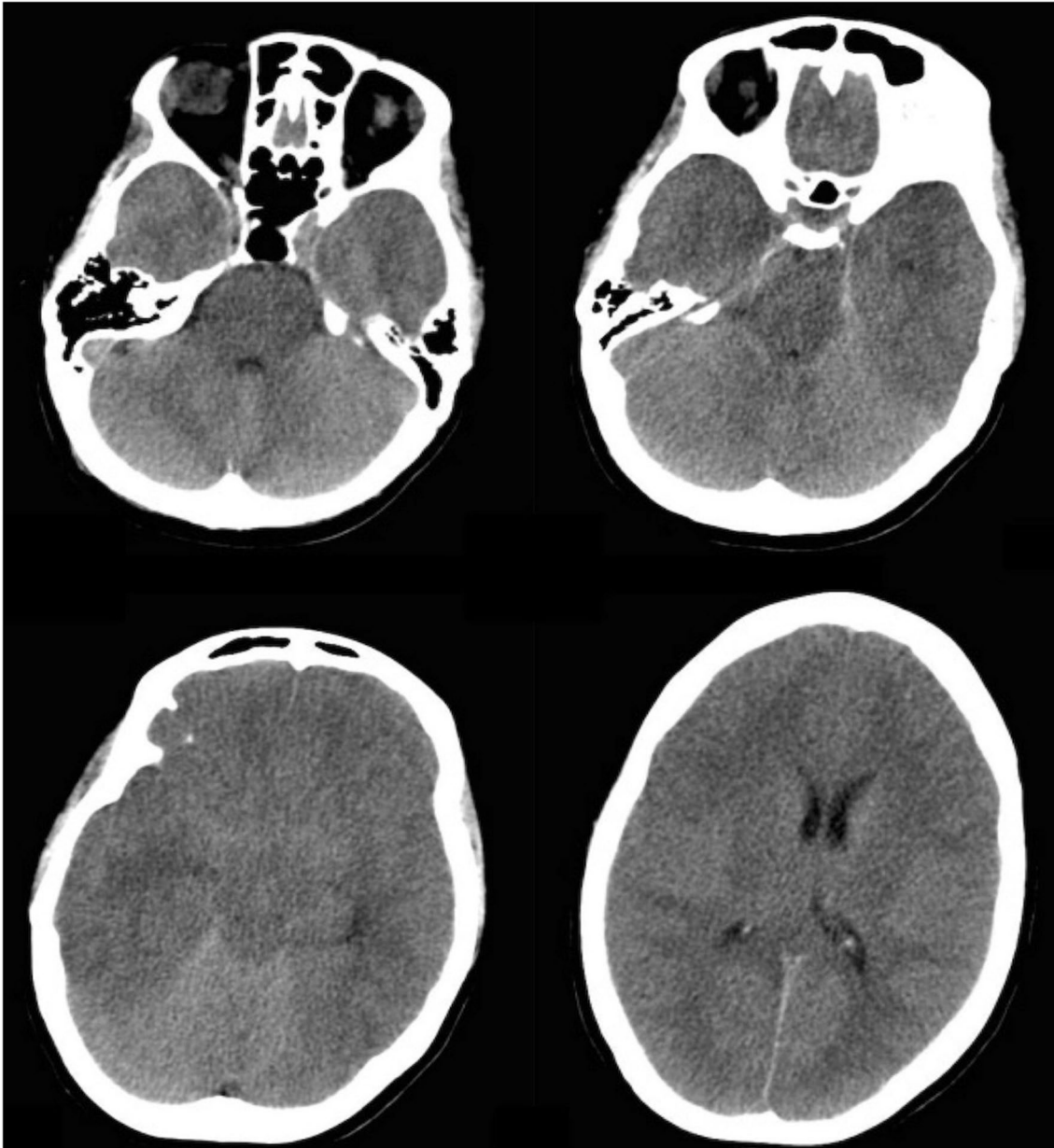

Fig. 1 Head CT signs of diffuse cerebral edema. Axial non-contrast-enhanced head computer tomography (CT) shows diffuse brain swelling predominantly involving infra-tentorial brain structures, associated with effacement of sulci and ventricles and decreased gray–white matter differentiation. The brainstem appears hypo-attenuated compared to other infra-tentorial brain structures

elevated value raised suspicion of brain death, thus postponing decompressive craniectomy until CT angiography (CTA) that confirmed the absence of cerebral blood flow. Notably, during the venous phase of CTA, cerebral veins were not detectable, yet a mild homogeneous contrast opacification was observed in the dural venous conduits. Brain death occurred in less than 12 h since the onset of neurological deterioration. Her family declined autopsy.

Our case illustrates the potentially fatal evolution of neurotoxicity related to CAR T-cells therapy resulting from fulminant cerebral edema. It has been estimated that 1–2% of anti-CD19 CAR T-cells recipients develop rapidly progressive neurotoxicity, even though very few cases have been described in detail so far [1, 4]. While no reliable risk factor has yet been determined, early and severe CRS arguably plays a major contributing role [4]. Additionally, we cannot exclude that in our patient tocilizumab might have played a role in aggravating neurotoxicity, related to peripheral IL-6 receptors blockade, resulting in an increase in passive diffusion of IL-6 into the central nervous system (CNS). The rapid evolution of neurotoxicity precluded us to perform a comprehensive investigation to exclude possible infectious etiologies in CNS, yet blood cultures were negative for bacteria and fungi and weekly monitoring of cytomegalovirus and Epstein–Barr virus DNAemia was negative.

Cerebral venous thrombosis (CVT) was also considered, yet typical neuroradiological and clinical features were absent, and serum D-dimer levels elevation is frequently observed following CAR T-cells infusion, irrespective of the presence of thrombotic events, as a reflection of endothelial activation and cytokine storm [7]. Additionally, acknowledging all limitations of evaluating the intracranial venous system in the context of very low cerebral perfusion, a mild homogeneous contrast opacification was observed in the dural venous conduits, further excluding CVT.

Underpinning pathophysiology of fulminant cerebral edema following CAR T-cell therapy remains not fully elucidated, yet histological and neuroimaging evidence supports cerebral vasogenic edema triggered by cytokine-mediated blood–brain barrier (BBB) dysfunction as the underlying mechanism [1–4].

In our patient, in spite of extremely elevated serum IL-6 levels, other inflammatory markers (C-reactive protein, ferritin) were only slightly increased (Supplementary Table 1). Furthermore, the clinical condition was stable until fulminant cerebral edema occurred. Nonetheless, a delayed elevation of peripheral inflammatory markers might have not been detected due to the rapid evolution of the neurological condition. Another possibility is that a disproportionate neuro-inflammation, far more exaggerated compared to the peripheral hyperimmune state, might have developed due to individual immune system and BBB characteristics, and, likely, other contributing factors not yet identified.

In the RocKet trial, a study evaluating anti-CD19 CAR T-cells in adult patients with B cell acute lymphoblastic leukemia, five patients developed fatal cerebral edema, leading to early termination of the study [8]. A root-cause analysis conducted on these patients, concluded that multiple factors were at play on, suggesting that cerebral edema could result from a combination of factors that includes both patient characteristics (i.e., younger than 30 years of age) and product attributes [9]. Furthermore, autopsies data suggested that the breakdown of the BBB and subsequent cerebral edema were probably owing to the inflammatory cytokine surge rather than to CAR T-cells infiltration into the CNS [10].

Strongly supporting cytokine-driven neuro-inflammation as the main putative mechanism, there is a remarkable clinical-radiologic overlap between several neuro-inflammatory conditions associated with elevated cytokine levels, such as ICANS, including acute fulminant cerebral edema (AFCE), COVID-19-related encephalopathy, cerebral malaria, macrophage activation syndrome and Kawasaki-related encephalopathies [11–14]. Similarly to ICANS, elevated CSF and serum cytokine levels leading to systemic and intracranial cytokine storm have been consistently reported in the above-mentioned disorders, thus supporting a similar pathophysiology underlying the development of acute cerebral edema [12, 15]. Interestingly, these conditions have been reported mostly in pediatric and young adult patients, potentially reflecting an age-related predisposition of the immune system or a decreased ability to compensate cerebral edema through intracranial compliance mechanisms. Therefore, the underlying pathophysiology of fulminant cerebral edema may be more peculiar from that of the more common manifestations of encephalopathy seen with ICANS. This clinical–radiological syndrome arguably represents a final common pathway triggered by peripheral hyper-inflammation in predisposed individuals, suggesting that distinctive neurological disorders may represent a pathophysiological coherent continuum, sharing cytokine-mediated neuro-inflammation as the underlying mechanism [16]. Notably, this condition frequently has a fatal prognosis despite aggressive medical and surgical therapy, such as prompt administration of intravenous corticosteroids and craniotomy [1, 4], as in our case. Thus, new strategies to allocate pre-emptive therapies, even by means of novel effective anti-inflammatory treatments, are urgently warranted.

Declarations

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