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CORRESPONDENCE

CAR T-cell–associated acute myelopathy: a rare but critical neurologic toxicity to recognize

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Abstract
Chimeric Antigen Receptor T-cell (CAR-T) therapy has significantly improved outcomes in hematologic malignancies but may lead to rare and severe neurological complications beyond immune effector cell-associated neurotoxicity syndrome (ICANS), such as acute myelopathy. We report the case of a 59-year-old woman treated with CD19-targeted CAR-T cells for relapsed lymphoma, who developed grade IV ICANS followed by a clinical presentation of myelitis attributed to CAR T-cell therapy after exclusion of alternative diagnoses. Aggressive immunosuppressive treatment and supportive care failed to achieve neurological recovery. The patient remained ventilator-dependent due to cervical spinal cord lesions and ultimately died following transition to palliative care. This case underscores the diagnostic challenges posed by this medical emergency in critically ill patients since numerous confounding factors may obscure early signs of spinal cord involvement in the ICU setting. Early neurologic evaluation and multidisciplinary management are critical. This case aims to raise awareness on this rare yet dramatic complication, in which prompt initiation of treatment may prevent long term sequelae.

Introduction

Chimeric Antigen Receptor T-cell (CAR-T) therapy has revolutionized the treatment hematologic malignancies but is associated with toxicities, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) [1]. Apart from these entities, attention has recently shifted towards other non-ICANS neurological complications that also pose significant clinical concerns, including acute myelopathy, with, to our knowledge, only 24 cases reported to date in the literature [2].

Similarly to myelopathies of other etiologies, CAR T-cell–associated myelopathy can present with acute motor and sensory deficits [3]. In the initial phase, patients may exhibit features resembling spinal shock, including flaccid weakness and hypoesthesia with a defined sensory level; this is typically followed by the development of spasticity and hyperreflexia as the lesion evolves. Bladder dysfunction and quadriparesis may also occur.

However, recognizing these rare entities in the intensive care unit (ICU) can be particularly challenging, especially when overlapping with other neurological manifestations such as encephalopathy or seizures. Nevertheless, prompt diagnosis is critical because in these conditions, earlier management is recommended to minimize the risk of long term sequelae [3].

We herein present the case of a patient with grade IV ICANS presenting with sudden quadriplegia and bilateral phrenic nerve paralysis, ultimately attributed to treatment-refractory CAR T-cells associated myelopathy.

Clinical case

A 59-year-old female patient with a history of relapsing diffuse large B-cell lymphoma (DLBCL) was admitted to our ICU for altered mental status on day 5 following the infusion of a second-line therapy with CD19-targeting CAR-T cells (axicabtagene-ciloleucel). Prior to CAR-T cell infusion, she received lymphodepletion with cyclophosphamide and fludarabine.

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On day 1 after CAR-T cells, she developed grade 1 CRS, presenting with an isolated fever (38.6 °C). Empirical antibiotic therapy with cefepime was initiated for febrile neutropenia. CRS was treated with tocilizumab.

On day 5, the patient was admitted to ICU due to grade 2 CRS (fever, mild hypoxemia) and neurologic worsening (obtundation) with scores indicating grade 2 ICANS. Antibiotics were shifted to piperacillin-tazobactam and ICANS was treated with dexamethasone (10 mg every 6 h). Her neurological state rapidly declined after ICU admission to a Glasgow Coma Scale of 4/15 with clonic eye movements, raising suspicion for epilepsy, requiring intubation and mechanical ventilation. Neurologic decline was attributed to new onset status epilepticus confirmed on electroencephalogram (EEG), treated overall with levetiracetam, valproic acid, propofol, high-dose dexamethasone (40 mg every 6 h), and intravenous anakinra (100 mg daily). Brain MRI showed no acute structural abnormalities, and lumbar puncture was initially deferred due to severe thrombocytopenia.

Table 1 Comprehensive biological workup performed to rule out alternative etiologies of post-CAR T-cell therapy myelitis

Category	Tests performed	Results
Nutritional/metabolic	Serum zinc, copper, vitamin B1, vitamin B12, vitamin C, vitamin E, folate	Zinc 70 g/dL (ref. 70–120), Copper 58 g/dL (ref. 80–170), vit. B1 172 nmol/L (ref. 78–114), vit. B12 996 ng/L (ref. 239–931), vit. C 2.5 mg/L (ref. 4–15), vit. E 9.87 mg/L (ref. 5–20), folate: not assessed
Infectious (CSF)	Multiplex PCR panel (*E. coli* K1, *H. influenzae*, *L. monocytogenes*, *N. meningitidis*, *S. agalactiae*, *S. pneumoniae*, *M. pneumoniae*, *S. pyogenes*, *C. neoformans*/gattii, enterovirus, parechovirus, HSV-1/2, VZV, HHV6), CMV PCR, HHV6 PCR	Negative
Other infectious causes	HTLV-1/2 serology, syphilis serology (VDRL/TPHA), EBV serology, HIV serology	HTLV-1/2: negative; syphilis: negative; EBV: past immunization; HIV: negative
Autoimmune differential	Anti-AQP4 antibodies, anti-MOG antibodies	Not performed

Continuous EEG from day 7 to day 11 since CAR T-cells showed frequent paroxysmal activities. Serum peak lymphocytosis at day 7 after infusion (1970 lymphocytes/mm^3) signed expansion of CAR T-cells. Cerebrospinal fluid (CSF) analysis was performed on day 9 and showed moderately elevated proteinorrachia and normoglycorrachia with no evidence of infection. Flow cytometry of the CSF revealed that 69.8% of the analyzed lymphocytes were CAR T-cells (27 CAR T-cells/mm^3). After seizure control, sedation was reduced, and consciousness gradually improved by day 12. It then became apparent that the patient was suffering from flaccid quadriplegia, absent deep tendon reflexes and complete sensory loss. On day 15, spinal cord MRI was consistent with acute myelopathy. The EMG findings, including absent voluntary motor activity, unrecordable H-reflexes, and markedly reduced or absent motor responses, were consistent with a central motor deficit, supporting the diagnosis of acute myelopathy. Since all other causes could have been excluded, symptoms were attributed to *CAR T-cells associated myelopathy*. The patient was started on intravenous immunoglobulins (IVIG) and high dose thiamine, dexamethasone was continued and anakinra was increased to 100 mg every 6 h.

Detailed results of performed laboratory tests are summarized in Table 1.

The clinical course was marked by the development of tumor lysis syndrome, disseminated intravascular coagulation, and multiple septic episodes. Corresponding treatments and complications are presented in a timeline format in Fig. 1.

On day 28 after CAR-T infusion, no clinical improvement was noted despite maximal treatment. Weaning from mechanical ventilation was deemed impossible due to bilateral phrenic nerve paralysis secondary to cervical spinal cord lesions. Follow-up MRI revealed persistent diffuse spinal edema with worsening ischemic lesions at the C6 level. In contrast, a PET-scan showed a complete metabolic response of the lymphoma (Deauville score of 1).

The lack of neurological recovery and dependence on mechanical ventilation along with uncontrolled infection prompted an ethical discussion with the patient and her family. Spinal cord ischemia and poor neurologic prognosis led to a consensus decision to discontinue active treatments and shift towards palliative care, followed by the patient death on day 34.

Discussion

CAR T-cell therapy is associated with early-onset specific and sometimes life-threatening neurotoxicities. Besides ICANS, CAR T-cell therapy can cause rare but potentially

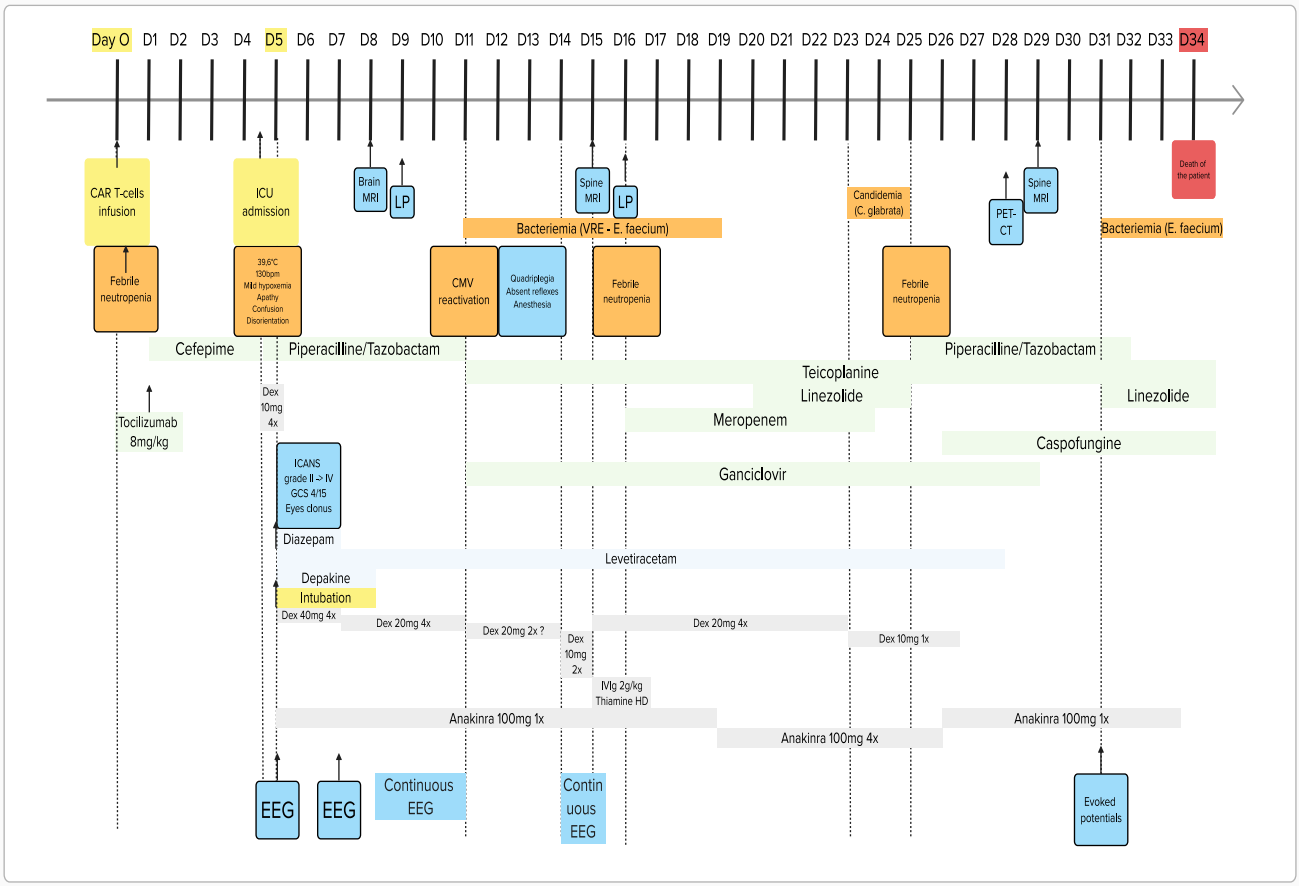

Fig. 1 Timeline summarizing the main complications, complementary investigations, and treatments administered to the patient

severe neurological complications such as acute myelopathy. All reported cases of myelopathy, including ours, have been temporally associated with CRS and typically occur concurrently with or shortly after severe ICANS (i.e. grade = >3), between 5 and 27 days following CAR T-cell infusion [3]. In our case, severe ICANS developed on day 5, consistent with the timing reported in the literature. Reported cases of adult CAR T-cell-associated myelopathies have typically occurred following CD19-targeted CAR T-cell therapy [2], as observed in our case.

Although the exact pathophysiology remains uncertain, several mechanisms have been proposed and were summarized in a recent literature review by Dechênes-Simard and colleagues [2]. It includes inflammatory mediator toxicity, blood-brain barrier disruption, impaired spinal cord perfusion due to increased intraspinal pressure, tumor inflammation–associated neurotoxicity (TIAN), viral reactivation (e.g., CMV, HHV-6), and off-target effects of CAR T-cells [2]. Spinal cord ischemia observed in some patients—including ours—raises the possibility of cytokine-mediated vasculopathy or perfusion-related injury. The detection of CAR T cells in the CSF may raise concerns about their direct involvement in the pathophysiology of myelopathy. However, we know that CAR T-cells are found in the CSF of most patients with successful CAR T-cell expansion, regardless of whether they develop ICANS [4], and the same could be true for myelopathy.

CAR T-cells associated myelopathy remains a diagnosis of exclusion due to the lack of specific clinical features. A comprehensive medication review is crucial, along with addressing potential contributors to neurotoxicity such as micronutrient deficiencies (e.g. thiamine) and hyponatremia. When infectious myelitis is suspected, targeted antimicrobial therapy should be promptly initiated. Once other differential diagnoses have been excluded, high dose corticosteroids are the recommended first-line treatment, in accordance with the recent EBMT Practice Harmonisation and Guidelines Committee recommendations [3]. Tocilizumab, an IL-6 receptor antagonist used for CRS treatment, is considered ineffective for neurotoxicity alone and is therefore not recommended, especially as it could increase the risk of neurologic events [5]. Direct inhibition of IL-6 with siltuximab has been described and failed to improve neurologic outcome in case reports [6, 7]. The IL-1 antagonist anakinra used in corticosteroid-refractory CRS and ICANS [8] is recommended by experts for refractory cases of CAR T-cells

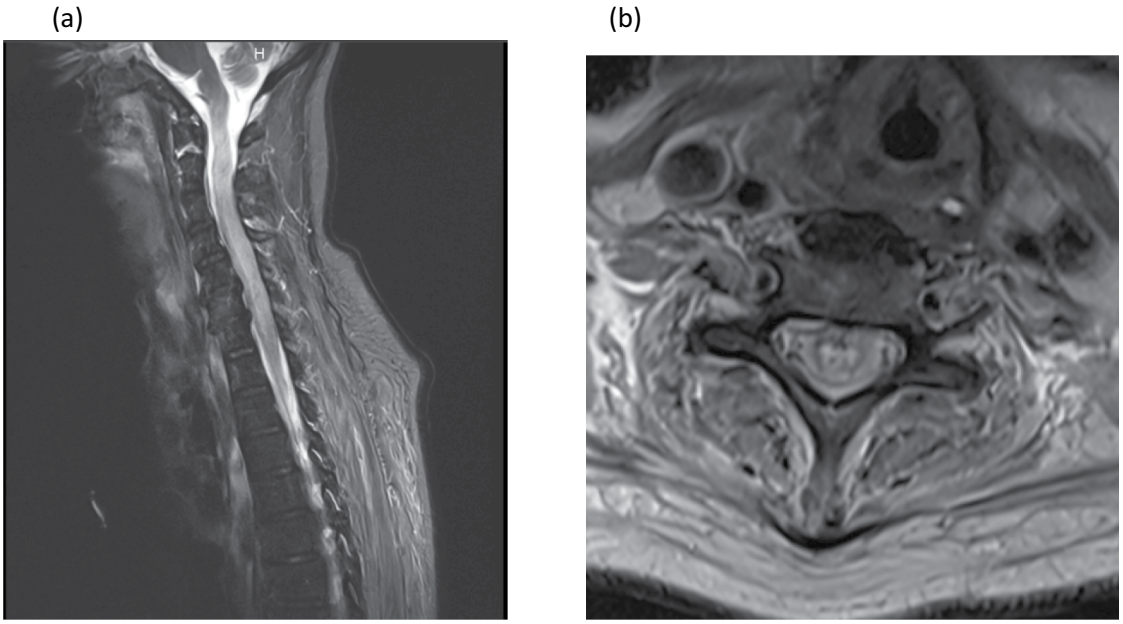

Fig. 2 (**a**) Sagittal MRI of the cervical spinal cord revealing pronounced, diffuse enlargement of the spinal cord encompassing the entire cervical segment, accompanied by a diffuse hyperintense signal within the spinal cord parenchyma on T2-weighted sequences, highly indicative of extensive myelitis. (**b**) Axial T2-weighted MRI at the C6 spinal level demonstrating the classic "owl's eye" sign, characterized by bilateral, symmetric hyperintense foci within the anterior horns of the spinal cord gray matter, indicative of spinal cord ischemia

related myelopathy given the favorable safety profile [2]. Additionally, IVIG or plasmapheresis could benefit patients with prior exposure to immune checkpoint inhibitor [2].

In our patient, extensive infectious and autoimmune evaluations failed to identify an alternative diagnosis. The rapid symptom progression and absence of brain MRI lesions argued against fludarabine-associated neurotoxicity. The onset of status epilepticus was likely related to ICANS, especially since cefepime—the main potential confounder—was discontinued upon admission, yet epileptic activity persisted on EEG for six days thereafter. Despite aggressive multimodal immunosuppressive therapy, including high-dose corticosteroids, anakinra, and IVIG, neurological recovery was not achieved. Importantly, oncologic efficacy was maintained, consistent with previous reports [2], indicating that early and sustained immunosuppression does not compromise CAR T-cell antitumor activity. These data support the early initiation of high-dose corticosteroids and adjunctive therapies in cases of severe acute neurotoxicity. This approach follows a 'time is brain' principle analogous to that used in acute ischemic stroke, and aims to optimally prevent long-term neurological sequelae.

Given the difficulty in identifying this clinical entity, heightened vigilance is warranted in the presence of risk factors, including the use of anti-CD19 CAR T therapy and the presence of severe ICANS [2]. The association between the magnitude of CAR T-cell expansion and neurologic toxicity is now well recognized [9]; however, it remains unclear whether this relationship also applies to acute myelopathy.

Importantly, this case underscores the diagnostic challenges posed by this medical emergency in critically ill patients since confounding factors – such as sedation, intubation and mechanical ventilation, encephalopathy, critical illness polyneuropathy, or status epilepticus - may obscure early signs of spinal cord involvement. Such clinical complexity can delay recognition of myelopathy, significantly narrowing the window of opportunity for timely intervention. We aim to raise awareness of this rare but serious complication and emphasize the importance of a comprehensive neurological examination by a neurologist, as subtle features of myelopathy might be missed by non-specialists. We would advocate performing a full spinal cord MRI in any patient presenting with clinical features suggestive of myelopathy when brain MRI findings are normal or non-contributory. A multidisciplinary approach involving hematologists, intensivists, and neurologists is essential to improve diagnosis and patient outcomes (Fig. 2).

Conclusion

This case aims to raise awareness on CAR T-cell-associated acute myelopathy as a rare yet severe complication of CAR T-cell therapy, frequently occurring alongside severe ICANS in an intensive care setting, which poses challenges

to early recognition and may consequently delay treatment initiation. Multidisciplinary approach is essential to improve neurologic outcomes as they may be poor, particularly in cases of spinal cord ischemia. Further studies and case reporting are needed to refine diagnostic and therapeutic strategies.

Author contributions A.G. and C.E. wrote the main manuscript text. All authors reviewed the manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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