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LETTER TO THE EDITORS

Stuttering as the first sign of CAR-T-cell-related encephalopathy syndrome (CRES)

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A 26-year-old right-handed woman with treatment-refractory mediastinal diffuse large B-cell lymphoma (DLBCL) was admitted for chimeric antigen receptor (CAR) T-cell therapy with axicabtagene ciloleucel. Within hours of the infusion, she became tachycardic and developed fevers up to 102.9°F. The patient had undergone lymphodepletion with cyclophosphamide and had leukopenia and neutropenia at the time of her infusion. She was already on prophylactic famciclovir, atovaquone, and fluconazole. Cefepime was started empirically after the onset of her fever. An infectious evaluation with a chest X-ray and blood cultures did not reveal an infectious cause for her fever. The next morning (day 1) she had hypotension (BP 85/51) responsive to IV fluids, consistent with grade 2 cytokine-release syndrome (Porter et al. 2015). Ferritin and C-reactive protein (CRP) were elevated (465 µg/L and 37.3 mg/L, respectively) and increasing (558 µg/L and 45.1 mg/L, respectively, the following day). Tocilizumab was administered for the treatment of cytokine-release syndrome and levetiracetam was initiated for neurotoxicity prophylaxis. However, fever, tachycardia, and hypotension persisted. Ferritin and CRP continued to rise (834 µg/L and 55.8 mg/L, respectively), on day 3. On day 4, the patient developed headache and difficulty speaking, characterized by stuttering and hypophonia. The patient did not have a history or neurologic disease. She remained febrile (102.2°F) and tachycardic (100–110 bpm), and was fatigued and in moderate distress. She was awake, alert, and oriented to self, place, and time, able to count from 100 to 0 by 10 s, and able to name three different objects and her country's prime minister. Writing was intact. Her CARTOX-10 [a recently proposed screening instrument for CAR-T-cell-related encephalopathy (CRES), where one point is assigned for orientation to year, month, city, hospital, and country's President/Prime Minister (total of 5 points); naming three objects (maximum of 3 points), writing a standard sentence and counting backwards from 100 in tens (1 point), where normal cognition is defined by an overall score of 10 (Neelapu et al. 2018)] was 10, not meeting diagnostic criteria for CRES. However, her speech was markedly dysfluent with profound stuttering. The remainder of her neurologic examination was normal. Ferritin and CRP levels were improving (723 µg/L and 18.6 mg/L, respectively).

Overnight, the patient became less arousable and aphasic. Her eyes were closed, but she would open them to voice, regarding the examiner but not following axial or appendicular commands. There was no speech output. Her gaze was midline and pupils were equal and reactive to light. Her muscle tone was mildly increased, and she was equally withdrawing to painful stimuli in all extremities. Her CARTOX-10 score was 0, meeting criteria for grade 4 CRES. Levetiracetam 1000 mg IV was given and the patient was started on dexamethasone 10 mg every 6 h. She was transferred to the Neurological ICU for further monitoring. Her head CT was normal. EEG revealed continuous diffuse irregular delta–theta slowing as well as intermittent periods of generalized rhythmic delta activity at 1–3 Hz at times associated with sharp waves (GRDA + S) and generalized periodic discharges (GPDs), consistent with CRES (Herlopian et al. 2018). Her exam began to improve after administration of dexamethasone, and on day 6, she began to follow commands and provide one-word answers. The next day her cognition markedly improved, and she was able to name and repeat; however, residual stuttering and dysgraphia were persistent (Fig. 1). Her CARTOX-10 score was 8. She was discharged home on day 12. At a follow-up appointment 2 weeks later, her neurologic exam was normal, including speech fluency and handwriting (Fig. 1). The patient provided consent for the publication of her case at this time.

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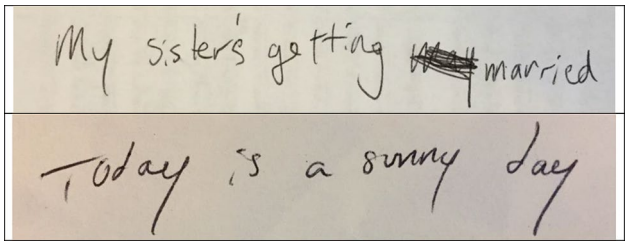

Fig. 1 Top: writing sample from patient while in the ICU (CARTOX-10 of 8). Bottom: writing sample from patient at follow-up appointment after discharge (CARTOX-10 of 10)

CAR-T-cell neurotoxicity is well known to affect language networks though patient presentation is highly variable. No validated consensus guidelines exist to guide patient management. While the CARTOX-10 scale is designed to screen for aphasia (Neelapu et al. 2018), acquired disfluency, resulting from impairment of both cortical language networks and the basal ganglia (Ludlow and Loucks 2003), is not captured by this screening instrument. To our knowledge, this is the first report of dysfluency (stuttering) as the presenting sign of CRES. Given the subsequent rapid neurologic deterioration seen in our patient, dysfluency warrants consideration as an early sign of neurotoxicity when evaluating patients for CRES. In light of the limitations of the current screening instruments for CRES (e.g., CARTOX-10), clinicians caring for patients at risk of CRES are best served by relying on their clinical judgment when evaluating these patients. If there has been a clear deviation from neurologic baseline, patients should be evaluated (EEG, brain imaging) and treatment should be instituted regardless of the score reported on the screening instrument.

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Compliance with ethical standards

Conflict of interest Dr. Gonzalez Castro declares that he has no conflict of interest. Dr. Dietrich declares that he has no conflict of interest. Dr. Forst declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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