EEG findings in CAR T-cell therapy-related encephalopathy

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Chimeric antigen receptor (CAR) modified T cells emerged as promising immunotherapy in refractory lymphoid malignancies.[1] Despite efficacy, toxicities include cytokine release syndrome (CRS) and neurotoxicity.[1] We report EEG findings in patients with chemotherapy-refractory stage IV diffuse large B-cell lymphoma (DLBCL-4) who received CAR T cells and developed neurotoxicity.

Case 1

A 38-year-old woman developed aphasia and somnolence 14 days postinfusion. On day 15, she was minimally responsive. Continuous EEG (cEEG) showed generalized periodic discharges (GPDs) (figure). Lorazepam and levetiracetam caused transient improvement. Brain MRI and CSF were normal. On day 16, she deteriorated; fosphenytoin and lacosamide were added. Due to increasing inflammatory biomarkers, dexamethasone was administered. She became obtunded, requiring intubation and burst suppression on day 17. On day 19, after weaning midazolam, GPDs re-emerged. On day 21, after receiving the 10th dose of dexamethasone, cEEG showed diffuse slowing. On day 23, she was extubated; cEEG was normal. In 2 months, antiepileptic drugs (AEDs) were discontinued. Neurotoxicity completely resolved.

Case 2

A 74-year-old man developed confusion and myoclonus on day 10 postinfusion. On day 11, cEEG revealed GPDs despite levetiracetam (figure). On day 12, dexamethasone was initiated due to electroclinical worsening. On day 13, myoclonus resolved. On day 14, cEEG was normal; neurotoxicity completely resolved.

Four months later, rituximab-lenalidomide cycle was initiated for lymphoma recurrence. On day 11 of the third cycle, the patient developed confusion and myoclonus. On day 12, MRI brain revealed frontoparietal cortical fluid-attenuated inversion recovery hyperintensities. CSF was normal; cEEG showed GPDs. Dexamethasone was initiated; AED doses were escalated. After 4 doses of dexamethasone, he improved electroclinically. On day 16, fosphenytoin was discontinued; levetiracetam and lacosamide were continued. Neurotoxicity completely resolved.

Case 3

A 51-year-old man developed confusion on day 4 postinfusion. On day 7, levetiracetam was started. On day 8, his encephalopathy worsened; dexamethasone was administered. cEEG showed GPDs (figure). He became obtunded requiring intubation. On day 9, MRI brain was normal. After 5 doses of dexamethasone, he improved electroclinically. On day 13, levetiracetam was discontinued. He remained intubated on propofol due to respiratory and cardiovascular failure that required tocilizumab on day 14. On day 19, EEG was normal; clinical neurotoxicity resolved.

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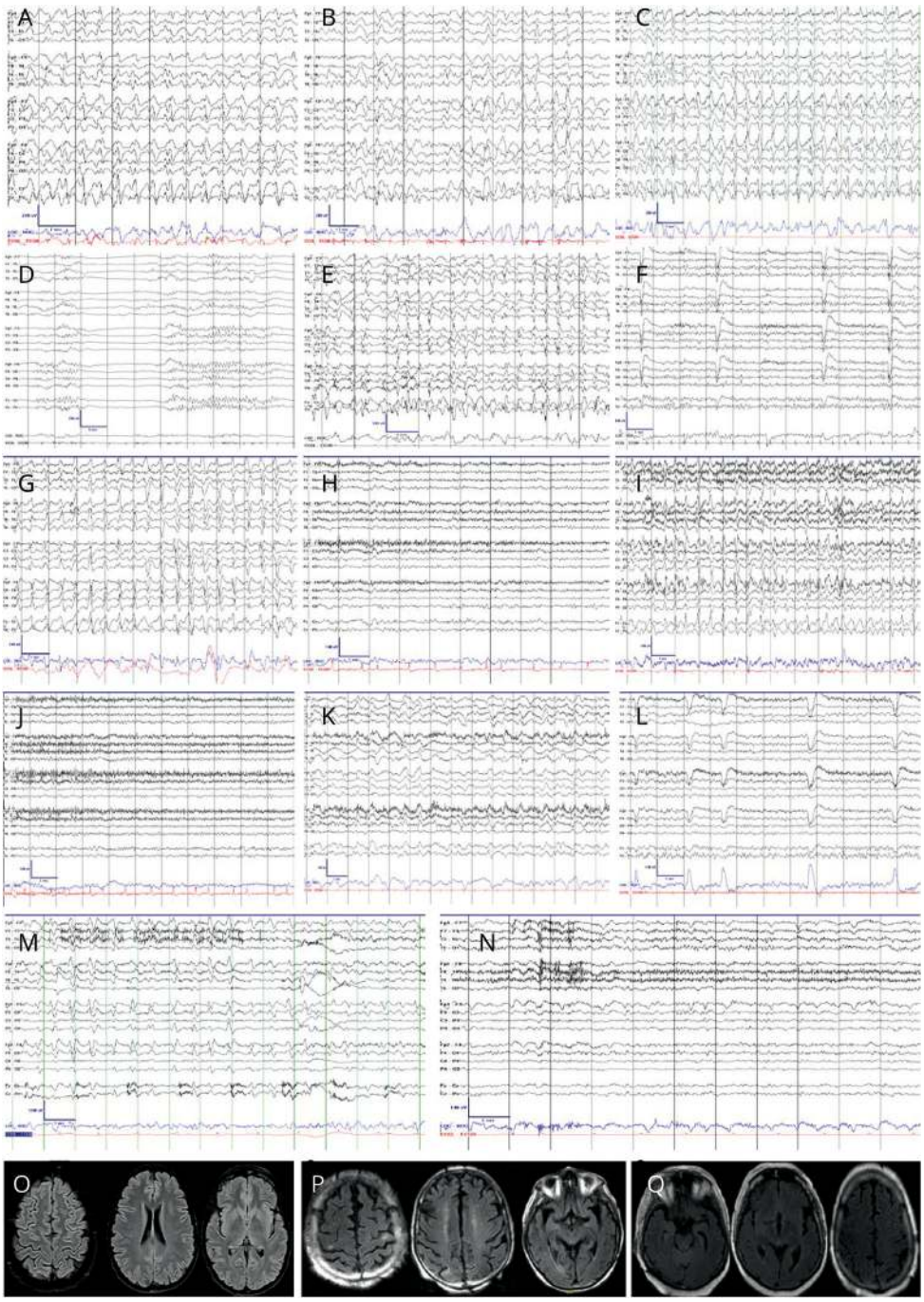
Figure Snapshots of the continuous EEG (cEEG) monitoring in patients 1–4



(A–N) Longitudinal bipolar montage (left-right-left-right-midline), sensitivity 7 μV/mm, timebase 30 mm/s, low frequency filter 1 Hz, high frequency filter 70 Hz, notch 60 Hz. Scale is provided with y-axis representing voltage amplitude (μV) and the x-axis representing the time (second). (O–Q) MRI brain with and without contrast T2 fluid-attenuated inversion recovery (FLAIR) axial sequences in patients 1, 3, and 4. (A) Patient 1 day 15, 2 Hz, 50 μV frontally predominant generalized periodic discharges (GPDs). (B) Transient electrographic improvement after 2 trials of 1 mg lorazepam and IV levetiracetam. (C) Day 16, 2–2.5 Hz, 80–100 μV frontally predominant GPDs congruent with clinical worsening. (D) Day 17, burst suppression pattern seen after intubation and IV midazolam and propofol with continuation of all antiseizure medications and dexamethasone. (E) Day 19, after discontinuing midazolam, emergence of 2.5–3 Hz centrally predominant near continuous GPDs. (F) Day 23, emergence of normal posterior dominant rhythm (PDR) while on 3 antiepileptic drugs (AEDs) and after 10th dose of dexamethasone. (G) Patient 2 day 11, 1.5–2.25 Hz, 60 μV frontally predominant GPDs after 2 doses of 500 mg IV levetiracetam. (H) Day 14 emergence of normal PDR after completion of 4 doses of dexamethasone while on AEDs. (I) Day 11, near continuous 2–2.5 Hz, 150 μV frontally predominant GPDs after rituximab-lenalidomide therapy while on levetiracetam. (J) Day 15 normal PDR after 4 doses of dexamethasone, while on 3 AEDs and after completing 4 doses of dexamethasone. (K) Patient 3 day 8, intermittent 0.5–1 Hz GPDs on a diffuse delta-theta range slowing of background prior to intubation and after administration of 10 mg IV dexamethasone and 3 doses of 500 mg IV levetiracetam. (L) Day 19, postextubation, emergence of almost normal PDR with rare diffuse theta slowing. (M) Patient 4 day 18, 1.25–1.5 Hz, GPDs while on levetiracetam and prior to dexamethasone. (N) Day 23, normal PDR after 5 doses of dexamethasone. (O–Q) MRI brain with and without contrast. (O) Patient 1 on day 15, normal MRI brain with and without contrast, T2 FLAIR axial sequences. (P) Patient 2 MRI brain done while the cEEG revealed simultaneously near continuous 2–3 Hz GPDs. Axial cuts of T2 FLAIR images reveal curvilinear and ovoid areas of T2-FLAIR hyperintense signal in the juxtacortical white matter of the right superior parietal lobule and both precentral gyri and asymmetric, confluent elevated T2-FLAIR signal in the right peritrigonal white matter. (Q) Patient 3: normal MRI brain (axial cuts of T2/FLAIR sequences) on D9 with 0.25–0.75 Hz GPDs on cEEG.

Case 4

An 82-year-old man developed confusion and somnolence on day 17 postinfusion. After levetiracetam administration, cEEG showed GPDs (figure). On day 18, transient electroclinical improvement occurred after levetiracetam increase. On day 20, dexamethasone was initiated. On day 22, the cognition significantly improved. On day 23, his cEEG was normal; levetiracetam was continued.

Discussion

Among all patients with chemotherapy-refractory DLBCL-4 receiving JCAR017 at Massachusetts General Hospital, 4 had neurotoxicity and GPDs. Encephalopathy developed 5–17 days after infusion, lasting 4–14 days, consistent with literature.[1] Only 2/4 patients had low-grade fever at neurotoxicity onset. Neurotoxicity resolved after fever abatement. Only patient 3 had severe persistent CRS despite resolved neurotoxicity. We diagnosed CRS based on clinical signs and symptoms.[1] CRS grading was based on management algorithm ranging from mild (grade 1) to life-threatening (grade 4).[1] All patients had increasing CRP and ferritin associated with electroclinical worsening. These trended down after dexamethasone initiation and preceded electroclinical improvement. Only patient 3 had CRS at time of neurotoxicity onset. CRS usually presents 6–20 days postinfusion, likely due to proinflammatory cytokines.[1] Neurotoxicity varies from mild encephalopathy to status epilepticus.[1] In the TRANSCEND trial, 0% had ≥3 grade CRS and 14% neurotoxicity.[2] In the Zuma-1 trial, 20% displayed ≥3 grade CRS and 29% neurotoxicity.[3] It is unknown whether the same mechanisms underlie both neurotoxicity and CRS.[2] The second patient developed recurrent neurotoxicity during the third rituximab-lenalidomide cycle, 3 months after JCAR017. One possible explanation could be that lenalidomide may have potentiated the JCAR017-related neurotoxic adverse effects as seen postinfusion. Two studies reported in vivo potentiation of CAR T cells in animal models after receiving lenalidomide.[4,5] However, this observation has so far not been described in humans. Another possibility would be an independent neurotoxic process as can be seen in posterior reversible encephalopathy syndrome secondary to lenalidomide/rituximab infusion.

Clinical worsening correlated with peak worsening of GPDs, 24–72 hours after encephalopathy onset. AED addition or escalation did not result in electroclinical response. All patients showed sustained improvement to dexamethasone. Levetiracetam was the first line, followed by fosphenytoin, then lacosamide.

Animal and human studies reveal cortical and subcortical involvement in generating GPDs.[6] Potential mechanisms of GPDs and encephalopathy include neuronal dysfunction by proinflammatory cytokines, or direct T-cell-mediated effects on the brain, resulting in thalamocortical network disruption generating synchronous GPDs.[7]

Our patients received 10 mg IV dexamethasone every 12 hours, similar to concurrent CAR T-cell-related grade 3 or 4 neurotoxicity recommendations. Our patients received dexamethasone until improvement to grade 1 neurotoxicity. It is possible that dexamethasone halted cytokine-mediated effects that caused neuronal and thalamocortical hyperexcitability evidenced by GPDs.

Author contributions

Aline Herlopian: acquisition of data, drafting, preparation, finalization of manuscript, picture preparation, data analysis, submission. Jorg Dietrich: acquisition of data, editing the manuscript, data analysis. Jeremy AbramsoEn: editing the manuscript, data analysis. Andrew Cole: editing the manuscript, data analysis. Brandon Westover: editing the manuscript, data analysis.

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