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Car T-Cell Treatment-Associated Parkinsonism and Bilateral ^{18}f Fdg-Pet Increased Uptake of Basal Ganglia

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Abstract

Objectives: To underscore the clinical characteristics of an atypical presentation of immune effector cell-associated neurotoxicity syndrome (ICANS) secondary to the infusion of axicabtagene ciloleucel in a patient affected by high-grade diffuse large B-cell lymphoma (DLBCL).

Methods: Neurological examination, neuroradiological imaging and neurophysiological tests were performed at our Hospital before and after CAR T-cell administration. Regular follow-up evaluations were conducted to monitor the clinical complications.

Results: We report a case of Parkinsonian syndrome with symmetric bilateral ^{18}F FDG-PET increased uptake of thalami and basal ganglia, secondary to CAR T-cell therapy. The magnetic resonance imaging (MRI) alterations suggested the hypothesis of direct damage to the central nervous system due to CAR T-cell infusion. The syndrome was managed with low-dose steroids with complete clinical and radiological remission.

Discussion: Although CAR T-cell therapy represents an innovative treatment for hematological malignancies, it is unclear

how to manage the atypical manifestations of ICANS. The remission of the symptoms with mild immunosuppressive therapy supports the inflammatory pathogenesis of this peculiar neurological side effect.

Keywords: Neuroimmunology; CAR-T Cell Treatment; ICANS; Neurological Toxicities; Parkinsonism

Introduction

We reported a reversible case of Parkinsonism with cognitive symptoms secondary to CAR-T cell therapy. While similar neurological disturbances have been previously described, our case is the first to demonstrate simultaneous functional hyperactivity of basal ganglia and thalamic structures on 18F-FDG-PET, contrasting with the hypometabolism or normal uptake typically observed in earlier reports. [1, 2]

Materials and Methods

Baseline neurological examination, and extensive laboratory, neuroimaging and neurophysiological tests were performed at our Hospital before CAR T-cell administration. Regular follow-up evaluations, including neurological assessment, and the ICE-score, were conducted to monitor the clinical complications, and the therapeutic algorithm for the diagnosis and management of ICANS. PET scans were acquired using a digital PET/CT scanner (GE Discovery MI). Patients were in a fasting state prior to the intravenous injection of 18F-FDG, and image acquisition started 30-40 minutes after tracer administration. PET images were reconstructed using an iterative algorithm (VPFX and QClear).

Case Description

A 72-year-old Caucasian man, otherwise healthy, was diagnosed with an Ann Arbor stage IIIB germinal center (GCB) high--grade diffuse large B-cell lymphoma (DLBCL) in June 2022, characterized by rearrangement of c-myc and BCL-2. The patient underwent a first-line chemotherapy treatment based on six cycles of R-COMP chemotherapy, associated with 4 central nervous system (CNS) prophylactic methotrexate intrathecal injections and consequent salvage chemotherapy based on R-GEMOX. After demonstrating treatment failure, the patient was referred to our Hospital for chimeric antigen receptor T-cell therapy (CAR-T). The leukapheresis was successfully performed on 18th September 2023. A bridging radiotherapy was administered (36cGy). The patient underwent lymphodepleting conditioning (Cyclophosphamide 500mg/sqm/die i.v from -5 to-3; Fludarabine 30 mg/sqm/die i.v. from -5 to -3). On 20th November 2023, the patient was infused with 180 million CAR-T cells (Yescarta™).

The baseline neurological examination showed a mild cognitive decline, and the performing of electroencephalography (EEG) demonstrated occasional intermittent left frontotemporal abnormal slowing. Brain computed tomography (CT) revealed mild cerebral microvascular disease and modest cortical atrophy. Given the patient's high-risk profile for both severe cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) due to refractoriness of chemotherapy treatments, bulky disease, elevated LDH (U/L), fibrinogen levels (mg/dl) and C-reactive protein levels (g/L), prophylactic measures were implemented. Levetiracetam 500 mg every 8 hours was started two days before initiating lymphodepleting therapy, and dexamethasone 10 mg daily from -1 to +1 after Axicabtgene autolecleucel infusion.

Twenty hours after infusion, he developed a fever > 38°C (CRS grade 1); between day +2 and +3, fever was accompanied by confusion, writing difficulties (ICANS grade 1, ICE score 7), and, on day +4, mild right arm hyposthenia, motor aphasia with anomyas, hesitation, poor language and progression to lethargy (ICANS grade 2, ICE score 5). [3] The initial non-contrast computed tomography (NCCT), conducted after the onset of mental confusion, showed no acute abnormalities. The EEG was not re-

markable. Intravenous dexamethasone (10 mg/6h) was started, and the patient was transferred to the intensive care unit, where he received high-dose anakinra due to worsening of ICANS (grade 4, ICE score 2).

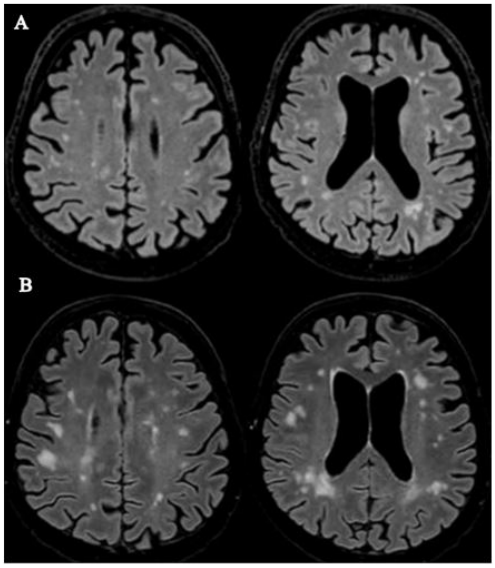

Figure 1. Imaging alterations on MRI two weeks (A), and six weeks (B), after the development of severe ICANS.

The patient slowly improved in the following days. Two weeks after the development of severe ICANS, a brain magnetic resonance imaging (MRI) demonstrated the presence of coarse and widespread bilateral hemispheric white matter lesions, consistent with cerebral microangiopathy, as indicated by previous CT exams (Figure 1.A); no acute findings were seen on imaging. On day +28, the patient manifested spatial and temporal disorientation, confabulation, limb rigidity, slowness, and behavioral anomalies. At the neurological evaluation, he presented bradykinesia, reduced speed and amplitude of repetitive actions, and axial rigidity. Deambulation was possible but was slow and magnetic, with some difficulties in direction changes. Apathy, hypomimia, and hypophonic speech were present. No rest tremor was documented, but a modest bilateral postural tremor of the upper limbs and mild action tremor were observed. Upward gaze deficit and smooth pursuit saccadic movements were reported as ocular anomalies. ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) detected symmetric bilateral ^{18}FDG increased uptake of thalami and basal ganglia, in particular of striata nuclei referred to as "functional". Cortical uptake showed an asymmetrical uptake with a fronto-occipital gradient (Figure 2).

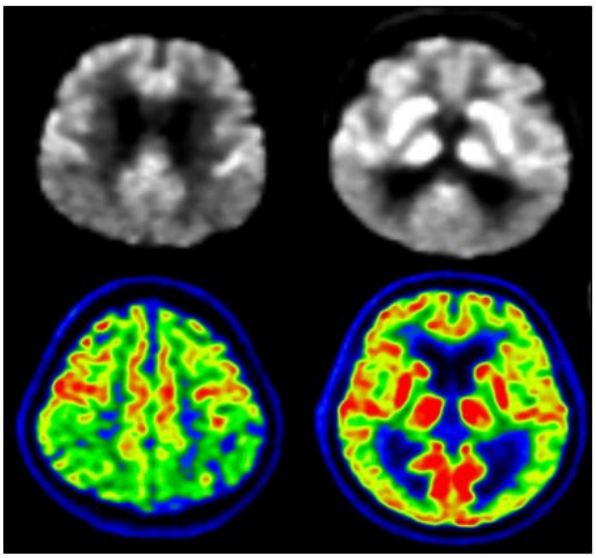

Figure 2. ^{18}F FDG-PET showing increased uptake of bilateral basal ganglia and thalami.

A week later, on day +43 from infusion, the motor slowing and psychomotor agitation worsened, and dexamethasone for three days (30 mg in total) was administered. Another brain MRI showed new widespread foci of T2 hyperintensity in the white matter of both cerebral hemispheres, affecting primarily the centrum semiovale, corona radiata, and periventricular zones, mostly U-fiber sparing (Figure 1.B). On day +45, clinical and neurological improvement was observed, and the patient was dismissed the following week. One month later, the last MRI did not detect new signal abnormalities, while functional anomalies on ^{18}FDG-PET disappeared four months later. Figure 3 illustrates the timing of all clinical events. Two months later, the patient was evaluated in a routine neurological follow-up visit, which showed complete remission of the hypokinetic and behavioral complications.

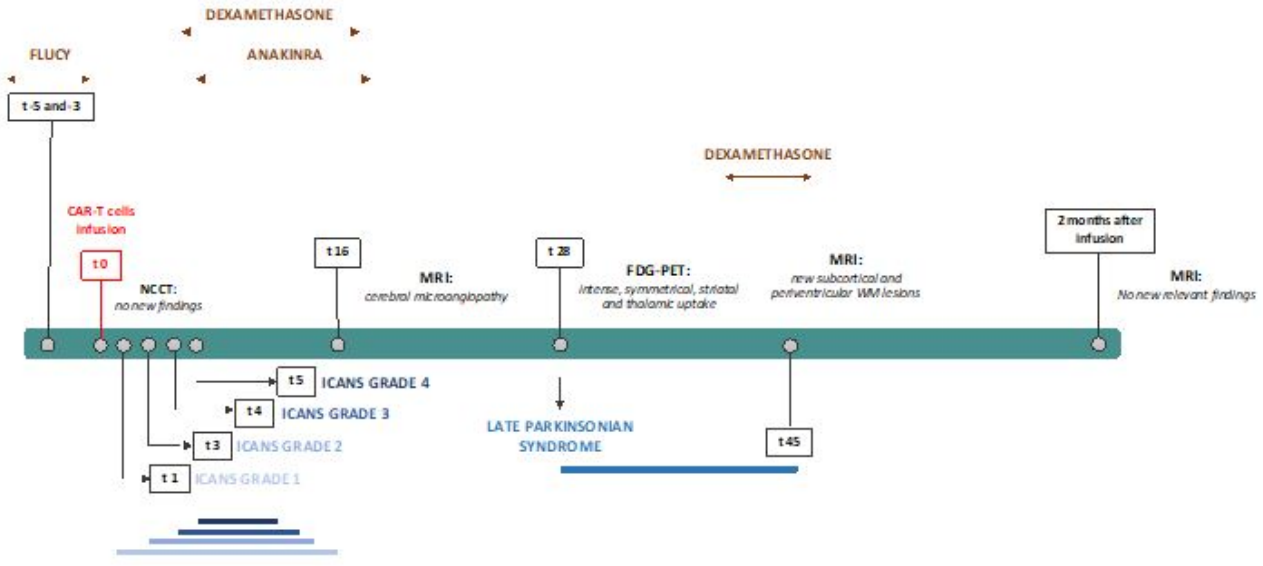

Figure 3. Timeline of onset of CRS, ICANS, and resolution of symptoms.

Discussion

This case highlights a rare and reversible form of parkinsonism secondary to ICANS after CAR T-cell therapy, characterized by functional hyperactivity of subcortical nuclei. The observation suggests a dynamic and potentially reversible disruption of basal ganglia–thalamo-cortical circuits.

CAR T-cell therapy has emerged as a promising therapy for relapsed or refractory hematological malignancies. [4-6] However, despite its remarkable efficacy in clinical responses, some major toxicities, constituting the ICANS, limit its use in a subset of patients. Clinical manifestations of ICANS range from mild frontal encephalopathy to epileptic seizures. [3] Movement disorders have been reported in a few cases, multiple weeks to months after CAR T-cell infusion. [7, 8] This subacute hypokinetic disorder was first described in five patients of the CARTITUDE-1 study for ciltacabtagene autoleucel; after some years, Karschnia et Al. reported another movement disorder for idecabtagene vicleucel. [7, 9] Our patient is a unicum in literature since he presented a hypercaptation of striata nuclei, which appears to conflict with other data that showed decreased or normal sub-cortical structures uptake; moreover, the diffuse cortical hypometabolism with frontal lobes relative sparing is in conflict with previous reports. [10, 11, 2]

The pathogenesis of Parkinsonism in ICANS has not been fully understood, and diverse mechanisms have been suggested, varying from increase of permeability of the blood-brain barrier (BBB) to direct infiltration of CAR-T cells into the CNS, with *in-loco* inflammation and induced release of cytokines. [7, 9, 2, 10] Imaging of ICANS (brain MRI or NCCT scans) often looks normal or shows no changes compared to images taken before the CAR T-cell therapy infusion. [11] The incidence of imaging ab-

normalities grows as ICANS grade increases, despite representing a rare event. [12] The most common alterations involved white matter, corpus callosum, pons, thalamus, leptomeninges, and temporal lobes, possibly reversible. [12, 13] The mechanisms leading to imaging alterations can be attributed to compromised BBB, demyelination, cerebrovascular effect, excitotoxic effects, and a combination of those caused by CAR-T therapy. [13] According to the literature, in the second MRI, our patient displayed new widespread subcortical white matter spots of T2 prolongations and without postcontrast T1 weighted enhancing neither restriction of protons diffusivity (ruling out cytotoxic edema). Given that the scans before therapy with axicabtagene ciloleucel were negative, findings can be defined as "new" and suggested damage to the CNS due to CAR-T therapy. Indeed, it can be assumed that neurological complications in ICANS are not only a consequence of a frontal predominant encephalopathy but also subcortical structures may play a determinant role in the pathogenesis of this side effect.

Conclusion

This case underscores the importance of recognizing atypical ICANS presentations with parkinsonian features and reversible neuroimaging findings. The complete resolution of symptoms following immunosuppressive therapy supports an inflammatory and functional pathogenesis.

From a clinical standpoint, the presence of parkinsonian features during or after ICANS should prompt early functional imaging assessment and timely anti-inflammatory treatment, as these manifestations may be reversible when recognized early. Larger multicenter case series and longitudinal imaging studies are warranted to clarify whether basal ganglia hypermetabolism may serve as an early biomarker of ICANS-related movement disorders, guiding both prognosis and therapeutic decisions in patients undergoing CAR T-cell therapy.

Author Contributions

SS, IC, and FA conceived the article. SS, IC, CN, CC, LF, BP, AP, EF and FA collected the data. SS, IC, GUM, and FA wrote the paper. All authors discussed the case and contributed to the final manuscript.

Potential Conflicts of Interest

All authors declare no conflict of interest.

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