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Case Report

Pattern of brexucabtagene autoleucel-related neurotoxicity on magnetic resonance imaging of the brain in a patient with relapsed/refractory B-cell acute lymphoblastic leukemia and prior leptomeningeal disease ☆

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ABSTRACT

Immune effector cell-associated neurotoxicity syndrome (ICANS) secondary to chimeric antigen receptor T-cell therapy is common in adult patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (ALL), but imaging findings during neurologic toxicity and their meaning have yet to be systematically described in this patient population. Brexucabtagene autoleucel (brexu-cel) is a CD19-directed autologous T-cell immunotherapy for the treatment of adult patients with R/R B-cell ALL that can enter the central nervous system. We present a case of an adult patient with R/R B-cell ALL and prior leptomeningeal disease who developed neurologic toxicity and new findings on magnetic resonance imaging of the brain while receiving brexu-cel. We interpret the patient's neuroimaging studies within clinical context to differentiate ICANS from active treatment of residual leukemia.

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Introduction

Approval of cellular immunotherapy products for adults with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (ALL) above the age of 25 years has been delayed mainly due to intolerable side effects, including immune effector cell-associated neurotoxicity syndrome (ICANS) [1]. Brexucabtagene autoleucel (brexu-cel) is the first commercial autologous anti CD19 chimeric antigen receptor (CAR) T-cell therapy product in this patient population [1]. In the ZUMA-3 clinical trial leading to its approval, 60% of patients experienced ICANS with 25% having grade 3 events [2]. However, little is known about the brain imaging patterns associated with this product's ICANS. This is particularly important because brexu-cel is known to penetrate the blood brain barrier [1], which means brain imaging findings could also be due to treatment of active leukemia as a proportion of patients with B-cell ALL have history of central nervous system (CNS) involvement. Here, we present a case of an adult patient with R/R B-cell ALL and history of CNS disease who developed grade 3 neurotoxicity while undergoing brexu-cel.

Case Presentation

A 43-year-old African American woman with R/R Philadelphia chromosome positive (Ph+) B-cell ALL diagnosed in September 2018, and neurologic history significant for peripheral neuropathy secondary to cancer therapy and migraines, received commercial brexu-cel as fourth-line therapy at our center. The patient had previously undergone induction with HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone), dasatinib, and prophylactic intrathecal chemotherapy achieving complete molecular remission, followed by consolidation with a mismatched unrelated donor hematopoietic stem cell transplant. After relapse of disease in the bone marrow 9 months later, the patient received second line therapy with blinatumumab and was switched to nilotinib due to dasatinib resistance, again achieving complete molecular remission.

Two years later, after presenting with headaches, patient was found to have relapse of disease in the CNS with 1.67% lymphoblasts in the cerebrospinal fluid (CSF) and leptomeningeal disease (Fig. 1A), as well as in the peripheral blood with 0.002% lymphoblasts and detectable BCR/ABL1. She did not have leukemia in the bone marrow. For control of disease, she was started on third-line therapy with systemic inotuzumab and intrathecal methotrexate, cytarabine, and hydrocortisone. Nilotinib was continued. Autologous CAR T-cell therapy was planned. Prior to leukapheresis, there was no evidence of disease on bone marrow biopsy, CSF flow cytometry, or radiologic imaging with magnetic resonance imaging of the brain (MRI Brain) (Fig. 1B) or ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan (Fig. 1C). The peripheral blood BCR/ABL1 was undetectable.

A month later, before CAR T-cell therapy, baseline MRI Brain did not show leptomeningeal disease (Fig. 1D), but BCR/ABL1 via peripheral blood polymerase chain reaction had become detectable again. Nilotinib was held and a kinase domain mutation screen sent for analysis.

After lymphodepletion with fludarabine 25 mg/m^2 on day -4 through -2 and cyclophosphamide 900 mg/m^2 on day -2, the patient was infused with 1×10^6 CAR-positive viable T-cells/kg of brexu-cel on day 0. Late on day 3, she started experiencing numbness and cramping of the hands with loss of strength in her dominant hand, affecting function. CT head without contrast and CT cervical spine did not reveal any acute abnormalities. Her upper extremity symptoms nearly resolved, but a headache that started on day 5 had become severe with 9/10 pain by day 6. On day 6, she also developed a neutropenic fever (Figs. 2A and B). Given infectious work up with blood cultures, urine studies, and chest radiograph was unrevealing, fever was attributed to grade 1 cytokine release syndrome (CRS). This toxicity was managed with acetaminophen initially, then one dose of tocilizumab 8 mg/kg on day 8 due to continued grade 1 CRS. CRS resolved promptly. During this time, the patient was placed on empiric cefepime. Later in the day on day 6, she also developed ICANS grade 3 with immune effector cell-associated encephalopathy (ICE) score 1/10 and was transferred to the medical intensive care unit for further care. Neurology was consulted and dexamethasone 10 mg every 6 hours was initiated. MRI Brain interestingly revealed a leptomeningeal process in a distribution similar to that at the time of CNS relapse (Fig. 1E). CSF analysis, however, was without evidence of leukemia or infection. Patient underwent electroencephalogram (EEG), which showed nonconvulsive seizure-like episodes. Since there was concern for cefepime toxicity, the antibiotic was discontinued, although a trough later resulted low (<2 mcg/mL). She continued on levetiracetam 750 mg twice daily. On day 9, due to lack of improvement, dexamethasone was escalated to methylprednisolone 1000 mg IV daily for 2 days. Later that day, ICANS improved to grade 1 with ICE score 9/10 and on day 10 resolved. All measured inflammatory markers remained within normal range (Fig. 2C), including interleukin 6, 5 (reference range, <6) pg/mL on day 7. Patient was transferred out of the medical intensive care unit and steroids tapered. She was discharged from the hospital on day 16.

After discharge, she finished her steroid taper on day 18 and was without delayed neurotoxicity. MRI Brain on day 80 showed almost near resolution of the previous leptomeningeal enhancement (Fig. 1F). CSF on days 48 and 124 was without leukemia. Peripheral blood BCR/ABL1 on day 55 was undetectable. Bone marrow biopsy on day 124 showed no evidence of leukemia, including by flow cytometry (limit of detection 0.0113%). Restaging studies demonstrated B-cell ALL was in complete remission. Patient was restarted on nilotinib as no mutations were identified via the kinase domain mutation screen.

Discussion

The anatomic location of ICANS secondary to CAR T-cell therapy can be challenging to pinpoint as it may occur with or without objective findings on imaging or focal deficits on

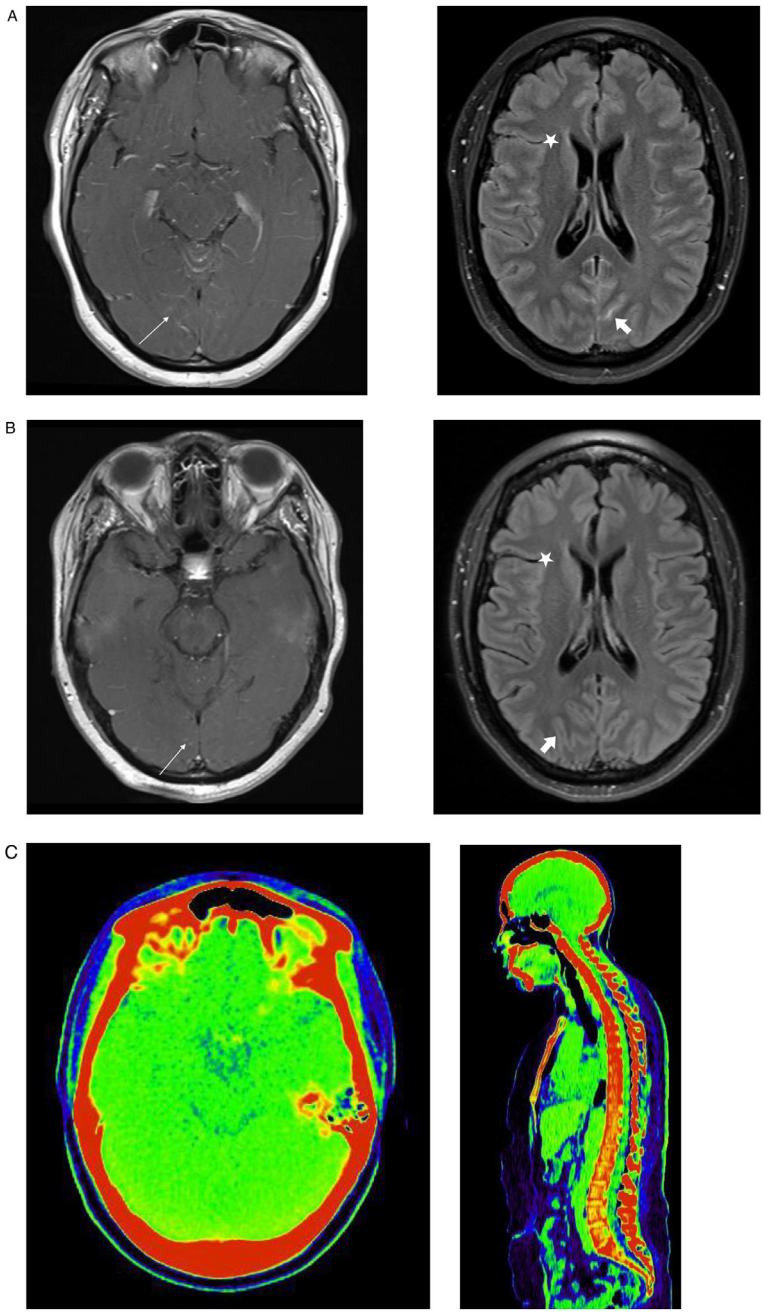

Fig. 1 – Imaging studies at time of disease relapse and pre-, during, and post-CAR T-cell therapy. (A) MRI Brain at the time of relapse of B-cell ALL in the CNS: T1 postcontrast shows bilateral leptomeningeal enhancement in the occipital regions (thin arrow), T2 FLAIR demonstrates incomplete CSF suppression consistent with meningeal pathology (thick arrow), compared with complete CSF suppression in the anterior Sylvian Fissure (star). (B) MRI Brain upon completion of salvage therapy: T1 postcontrast shows near complete resolution of bilateral leptomeningeal enhancement (thin arrow), T2 FLAIR demonstrates improved CSF suppression (thick arrow) compared with normal CSF suppression (star). (C) PET/CT upon completion of salvage therapy: axial head in similar plane to MRI Brain in (B) without abnormal uptake in the brain. Sagittal spine showing increased uptake in the axial skeleton consistent with hematopoietic stress, but without abnormality within the spinal canal. (D) MRI Brain postleukapheresis: T1 postcontrast shows complete resolution of bilateral leptomeningeal enhancement, T2 FLAIR demonstrates complete CSF suppression. (E) MRI Brain day 7 post-CAR T-cell therapy: T1 postcontrast shows bilateral leptomeningeal enhancement in the occipital regions (thin arrow), T2 FLAIR demonstrates incomplete CSF suppression consistent with meningeal pathology (thick arrows). (F) MRI Brain day 80 post-CAR T-cell therapy: near complete resolution of imaging findings following steroid treatment. T1 postcontrast shows marked decrease in bilateral leptomeningeal enhancement (thin arrows), T2 FLAIR demonstrates partial CSF suppression (thick arrows).

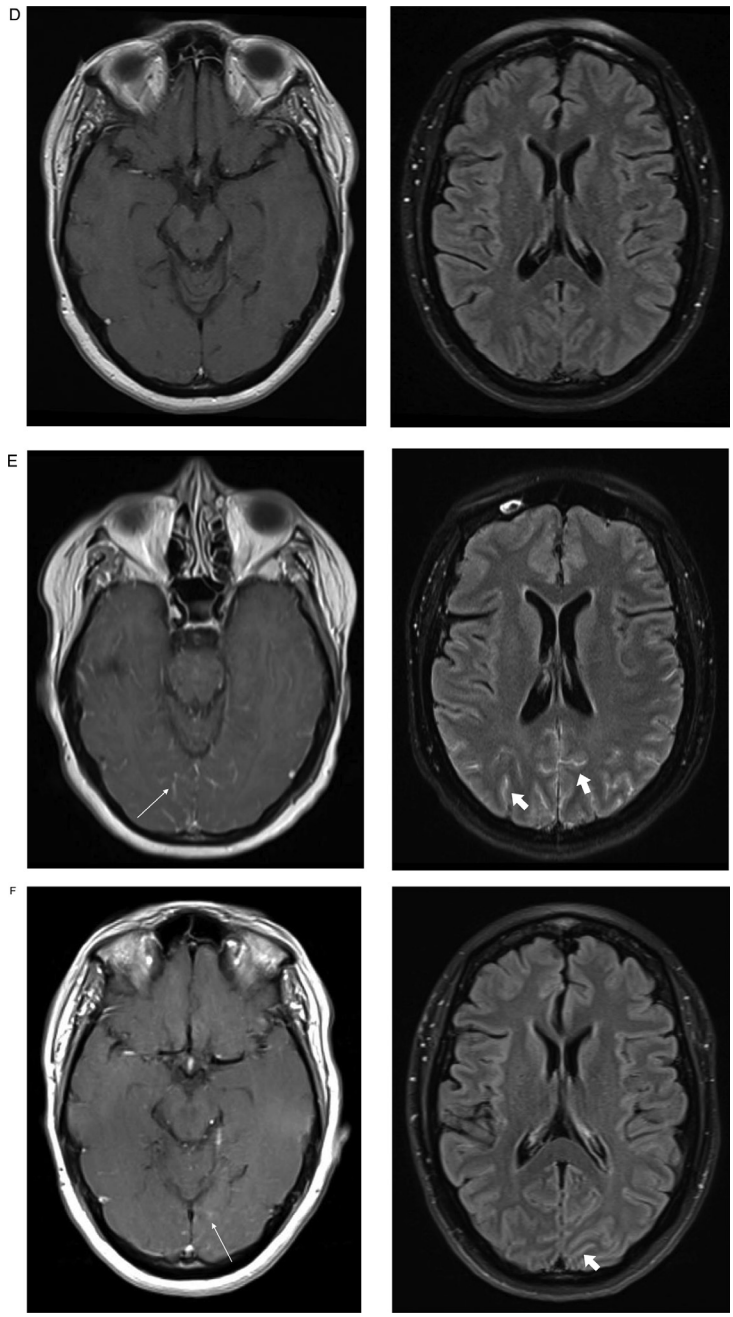

Fig. 1 – Continued

physical exam. Structural imaging studies in patients experiencing neurotoxicity are typically unremarkable [3], with presence of radiologic findings being linked to poor outcomes [4]. Vasogenic edema [5], leptomeningeal enhancement [4], multifocal microhemorrhages [6], and cytotoxic edema [6] have been observed on MRI Brain. Rare serious cases of acute leukoencephalomyelopathy leading to quadriparesis [7] and multifocal leukoencephalopathy [8–10] with corresponding MRI abnormalities have also been reported. Focal neurological deficits due to ICANS have been better detected on functional imaging, appearing as restricted EEG changes, hypometabolism on FDG-PET scan, and increased flow velocities on transcranial Doppler ultrasound [11].

Neurologic imaging findings in patients with R/R B-cell ALL and history of CNS involvement receiving brexu-cel may be due to ICANS or active treatment of leukemia. Our patient's MRI Brain during neurotoxicity demonstrated the presence of a leptomeningeal process, predominantly involving the bilateral posterior supra and infratentorial structures. The pattern and distribution of the process were similar to those seen on imaging at the time of CNS relapse of the leukemia. It appeared to be consistent with lymphomatous involvement of the leptomeninges, although there was no evidence of disease on CSF analysis at the time and the patient remained in remission on follow up. Absence of diffusion restriction on the MRI Brain suggested lower likelihood of an infectious

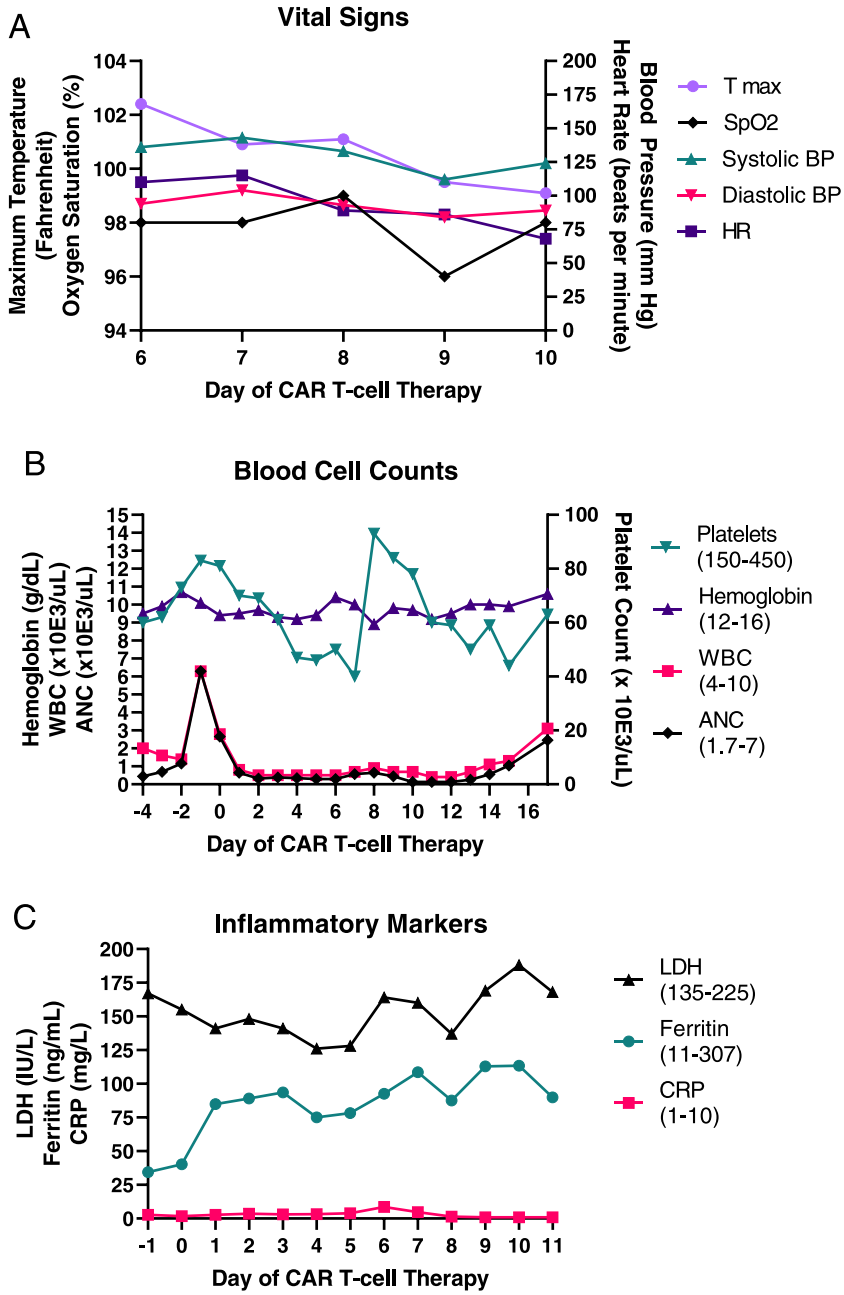

Fig. 2 – Inpatient clinical and lab data with brexu-cel administration. (A) During CRS grade 1, patient experienced fever and tachycardia, but did not develop hypotension or hypoxia. (B) She had neutropenia induced by lymphodepleting chemotherapy, while pre-existing moderate anemia and thrombocytopenia persisted and remained overall stable. (C) In the setting of no baseline overt tumor burden, inflammatory markers remained within normal ranges. Normal ranges of values are listed in parenthesis under each type of value. WBC, white blood cell count; ANC, absolute neutrophil count; LDH, lactate dehydrogenase; CRP, C-reactive protein.

etiology, as confirmed by CSF studies. EEG showed moderate diffuse encephalopathy consistent with nonlocalizing signs and symptoms.

Our patient's neurotoxicity was expected. At baseline, she had CNS-1 (no CSF blasts) and M1 (<5% lymphoblasts in the bone marrow) leukemia. However, her disease relapsed in the CNS within 12 months of CAR T-cell therapy infusion, which in pediatric studies, along with M3 (>25%) bone marrow tumor burden, has been associated with development of any grade neurotoxicity and non-significant increase in grades 3 and 4 neurotoxicity [12]. Higher blood brain barrier permeability and disruption of endothelial function preceding lymphodepletion, possibly due to neurologic comorbidities, have also been shown to contribute to neurotoxicity [13]. The patient's grade 3 neurologic toxicity occurred on day 6 and lasted 4 days, which was overall consistent with what was observed on ZUMA-3 with median time to onset 9 (interquartile range 7-11) days and median duration of 7 (interquartile range 4-19) days [2].

Management of her toxicity occurred per the existing brexu-cel adverse reaction management guide available through the Risk Evaluation and Mitigation Strategies program [14]. Given the lack of improvement in a 48-hour period, treatment was escalated to that of grade 4 neurotoxicity with quick resolution of symptoms within the next 24 hours. While neurotoxicity management of patients undergoing axicabtagene ciloleucel has become more aggressive based on the results of ZUMA-1 cohorts 4 [15] and 6 [16], there is not yet a corresponding study to support the early use and higher dose of corticosteroids with brexu-cel. If results from these safety-management studies are extrapolated to brexu-cel, this may help prevent development of high-grade ICANS and reduce the need for escalation of medical care. Given over a quarter of patients may experience high-grade ICANS with brexu-cel, early use and higher potency steroids than currently recommended may be considered to prevent clinical deterioration of patients until safety-management studies are conducted with brexu-cel to provide more data on the subject.

Conclusion

Neuroimaging patterns of ICANS due to CAR T-cell therapy can be complicated by prior history of structural CNS involvement in adults with R/R B-cell ALL. Neurotoxicity due to brexu-cel may appear in the same distribution of the leptomeninges on neuroimaging as prior leptomeningeal disease. CSF flow cytometry can aid in the interpretation of radiological findings and differentiate ICANS from treatment of residual leukemia. Given the high incidence of neurotoxicity in this patient population, awareness should be raised about the possibility of ICANS mimicking leptomeningeal disease radiologically in order to assist providers with clinical management.

Patient consent

Informed consent was obtained from the patient for publication of this case report, including images.

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