Progressive Multifocal Leukoencephalopathy in Chimeric Antigen Receptor T-Cell Therapy Recipients: A Case Study

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy is a novel immunotherapy modality that has shown remarkable response rates in refractory hematologic malignancies, including multiple myeloma (MM). Cytokine release syndrome (CRS) and neurotoxicity are well-described side effects of this therapy. CAR T-cell therapy recipients are also at increased risk for infections due to immune dysfunction, history of multiple lines of therapy, history of lymphodepleting chemotherapy prior to cell infusion, and prolonged B-cell aplasia. Progressive multifocal leukoencephalopathy (PML) is an opportunistic disease of the central nervous system caused by the reactivation of JC virus (JCV) in the setting of immunosuppression, which leads to increased morbidity and mortality. Here, we present a patient treated with ciltacabtagene autoleucel for refractory MM who presented with PML around 2 months after receiving CAR T-cell therapy. This case emphasizes the risks for the development of PML in immunocompromised patients potentially related to persistent B-cell aplasia, hypogammaglobulinemia, and prolonged immunosuppression and discusses treatment approaches. Treatments for PML are mostly focused on reconstituting immunity. However, no adequate treatment strategy for PML has yet been established and further research is needed.

CASE STUDY

The following is a case of a patient treated with ciltacabtagene autoleucel (Carvykti) for relapsed/refractory multiple myeloma who presented with progressive multifocal leukoencephalopathy (PML) about 2 months after receiving CAR T-cell therapy. Consent was obtained from the patient's health-care proxy to review and utilize patient-related information for educational purposes. This case emphasizes the risks for development of PML in this immunocompromised population potentially related to persistent B-cell aplasia, hypogammaglobulinemia, and prolonged immunosuppression.

Diagnosis and Treatment History

A 59-year-old female with a history of relapsed/refractory multiple myeloma was first diagnosed in March 2014 with stage II disease using International Staging System (ISS) and extensive bone involvement. The patient received multiple lines of treatment, including systemic treatment with proteasome inhibitors (carfilzomib and bortezomib), immunomodulatory agents (lenalidomide and pomalidomide), immunotherapy (daratumumab), and dexamethasone and local radiation to lytic bone lesions.

CAR T-Cell Therapy Administration

After her last disease progression status, she was deemed eligible for chimeric antigen receptor (CAR) T-cell therapy. She underwent leukapheresis for the manufacturing of ciltacabtagene autoleucel. Upon cells being returned to the center, she received lymphodepleting chemotherapy with fludarabine and cyclophosphamide for three consecutive days (days −5, −4, −3) as a standard regimen, followed by cell infusion on day zero.

Posttreatment

Her hospital course after receiving cells was complicated by worsening cytomegalovirus (CMV) viremia that started prior to admission for CAR T-cell therapy, for which she received treatment with valganciclovir. She was also evaluated by the orthopedic service for an ovoid lucent lesion in the proximal left femur seen on hip X-ray, which required no immediate intervention. She did not develop any CRS or neurotoxicity and was discharged on day 10.

Three days after her discharge, she presented to the emergency room with acute renal failure, hyponatremia, and grade 1 CRS. A head CT was done and revealed new asymmetric subcortical hypodensity in the left posterior temporal lobe concerning for vasogenic edema and multiple calvarial and skull base lytic lesions consistent with MM. A brain MRI showed vasogenic edema in the left occipital lobe without associated contrast enhancing lesion, concerning for posterior reversible encephalopathy syndrome (PRES).

She received one dose of tocilizumab and one dose of intravenous (IV) dexamethasone 10 mg but had no significant neurological findings despite mild difficulty reading, transient right lower extremity increased tone, grade 1 micrographia, and radiographic changes. Thus, she was discharged home on levetiracetam (started on the day of cell infusion) and dexamethasone tapering with improved symptoms and baseline cognitive status. A lumbar puncture (LP) was intended as a crucial step in the evaluation process; however, it was necessary to defer the procedure due to the patient's severe thrombocytopenia.

The patient was temporarily on high-dose vitamin C and E for neuroprotection in the event she was experiencing CAR T-cell mediated injury to her basal ganglia (Van Oekelen et al., 2021). As per the institution's protocol, she was kept on daily acyclovir and pentamidine infusion every 21 days. Additionally, her myeloma protein studies, bone marrow biopsy, and imaging at that time showed complete remission. Her blood counts failed to fully recover after undergoing lymphodepleting chemotherapy followed by CAR T-cell therapy, leading to her dependence on transfusions and the need for frequent administration of growth factors to address severe neutropenia. Following a consultation with neurology, her neurofilament light chain (NfL) level was evaluated, revealing a concerning progressive increase that correlated with her clinical symptoms (Table 1).

Neurologic Deterioration

Approximately 2 months after ciltacabtagene autoleucel infusion, the patient presented with

Table 1. Blood Test Results on Day of CAR T-Cell Infusion and at Post-Infusion Days 30, 60, and 90

Blood test (reference range)	D0	D30	D60	D90
NFL (≤ 20.8 pg/mL)	No result	188	437	952
CD3+CD4+ absolute quantitative (263–1,426 cells/µL)	120	73	85	49
Immunoglobulin G level	462	510	706	No result
Platelets (140–440K/µL)	92	21	26	20
Hemoglobin (12.0–16.0 gm/dL)	8.1	11.9	8	9.8
WBC (4.0–11.0 K/µL)	0.9	2.2	2.3	2.4
ANC (1.00–4.80 K/µL)	0.79	1.58	1.01	1.32
CMV PCR (≤ 0.0 IU/mL)	111.0	62.6	462	< 34.5

Note. Patient was receiving ganciclovir to treat CMV infection and dependent of blood products transfusions and growth factors. WBC = white blood cell; NFL= neurofilament light chain; ANC = absolute neutrophil count; CMV= cytomegalovirus.

progressive neurologic deterioration, manifesting with difficulty finding words and writing simple sentences. She was admitted to a local hospital out of state with worsening symptoms of ataxia and altered mental status. A brain MRI was done and revealed brain enhancement lesion in the right cerebellum and left thalamus. An LP was performed locally and initially only showed increased protein. An electroencephalogram (EEG) was also done and revealed no epileptiform discharges or electrographic seizures.

She was started on IV dexamethasone 10 mg every 6 hours; however, she continued to have significant difficulty with language and higher visual functions, which was concerning for late onset of neurotoxicity related to CAR T-cell therapy (Belin et al., 2020; Jung et al., 2020). The dexamethasone dose was increased to 20 mg every 6 hours for 48 hours, and thiamine was added. In addition, because of the neurologic deterioration, oral acyclovir was switched to IV ganciclovir to extend viral coverage to include CMV due to the patient's prior history, and lacosamide was added to levetiracetam for seizure prophylaxis. Due to prolonged cytopenias and a concern for meningitis, she was also receiving IV ceftriaxone and ampicillin empirically while undergoing workup.

A repeat brain MRI revealed more extensive T2/fluid-attenuated inversion recovery (FLAIR) changes on the brain affecting the left occipital lobe, temporal occipital area, splenium of corpus callosum, left thalamus, and right cerebellum, concerning for PML. Moreover, a second LP revealed the presence of John Cunningham virus (JCV) in the cerebrospinal fluid (CSF), solidifying the diagnosis of PML caused by neuroinvasive JCV.

Two weeks later, she was transferred back to the institution for clinical management. She arrived awake but was unable to consistently communicate, was disoriented, perseverative, and not following one-step directions. She had symmetric strength, normal tone without cogwheeling, anomia, visual agnosia, and positive bilateral Babinski signs. Corticosteroids were being tapered, and she received an experimental product for the treatment of PML. Repeat brain MRI revealed a progressive increase in confluent T2/FLAIR hyperintensity, increased enhancing lesions in the right cerebellum and thalamus, which in the context of neuroinvasive JCV positivity reconfirmed the PML diagnosis. She underwent a repeat EEG, which showed left posterior dysfunction and mild diffuse slowing but no electrographic discharges or seizures. Other than being positive for JCV, her CSF was negative for toxoplasmosis, meningoencephalitis panel, CMV, cryptococcal, acid-fast bacillus, Epstein-Barr virus, and human herpesvirus 6 (HHV6). A flow cytometry for myeloma was also negative.

Imaging Findings

Imaging performed at day 13 showed a new patchy area with FLAIR signal hyperintensity in the occipital lobe that conformed to subcortical white matter, demonstrating T2 shine-

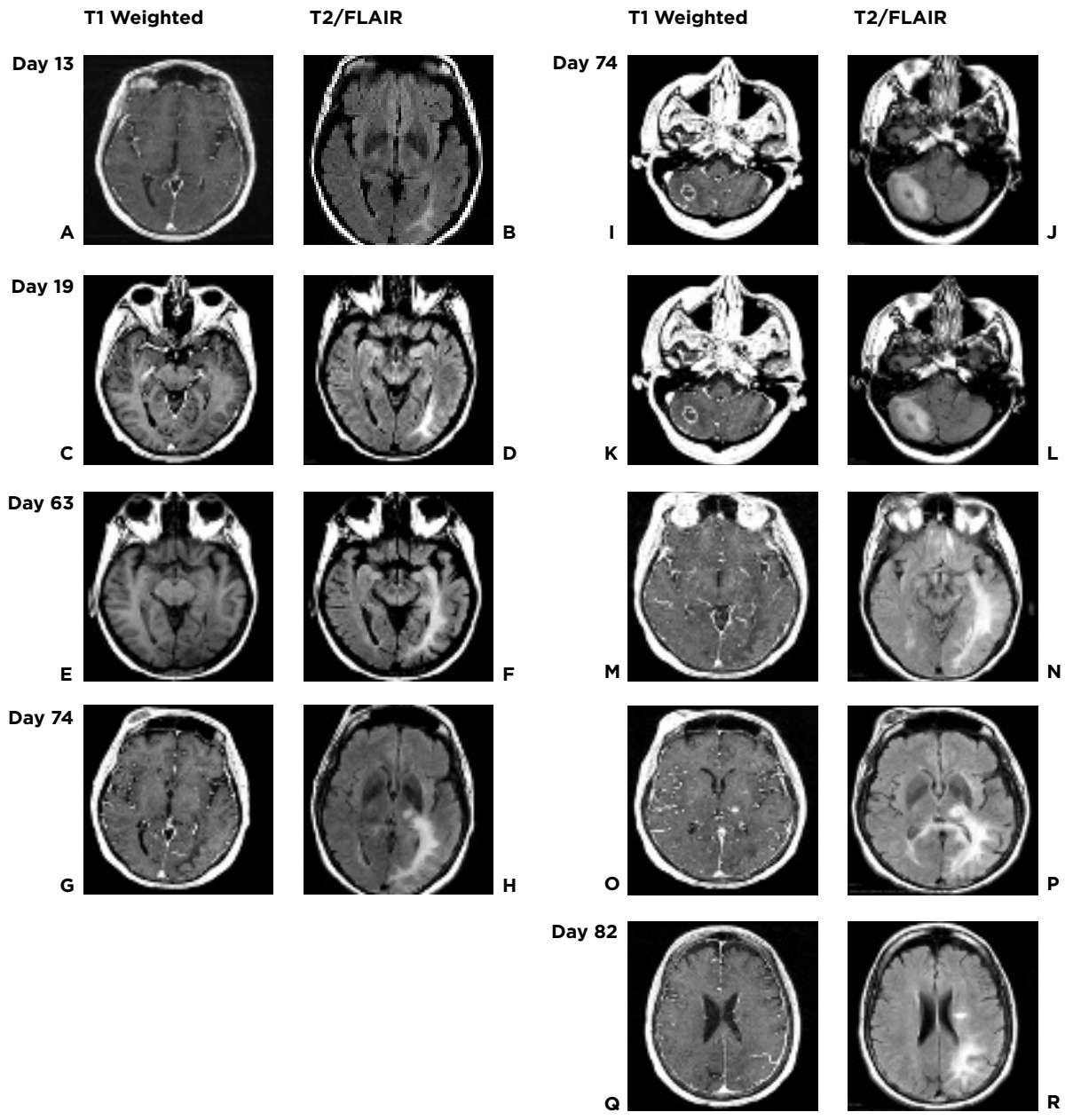

Figure 1. Progressive changes in the brain in a chimeric antigen receptor T-cell therapy recipient from day 13 to day 82.

through on diffusion-weighted images and consistent with vasogenic edema (B; Figure 1). In addition, a circumferential thin pachymeningeal enhancement and a developmental venous anomaly was seen in the left cerebellum (A). Also, diffuse myelomatous involvement of the calvarium and skull base were noted. The radiological differential diagnosis at that time included PRES (a condition that the patient had previously experienced) and reversible cerebral vasoconstriction syndrome (A, B). A repeat brain MRI on day 19 revealed that the FLAIR-hyperintense lesion in the left occipital lobe, although stable, continued to extend

to the subcortical U fibers of the white matter without gyral expansion (D). Additionally, there was new serpiginous intrinsic T1 hyperintense signal that likely represented developing gliosis (C). On day 63, a brain MRI without contrast showed a remote-appearing infarct within the right cerebellar hemisphere and left parietal-occipital junction (E). It also demonstrated asymmetric white matter abnormality within the left temporal lobe and splenium of the corpus callosum (F). A hypodense rounded focus (~9 mm in diameter) was also seen within the right cerebellum. Had gadolinium (Gd)-based contrast been administered, the T1-contrast enhancing lesions could have been monitored. The lesion in the left parietal lobe was evident on the T2/FLAIR-weighted scan that does not require Gd contrast (F). Eleven days later, on day 74, repeat brain MRI revealed confluent T2/FLAIR hyperintensity, centered predominantly within the left parietal-occipital white matter (G, H, N). There was also an interval increase in size and enhancing lesions within the cerebellum and thalamus, which was surrounded by vasogenic edema (I, J, K, L, M). The last brain MRI (done at day 82) revealed worsened ring-enhancing focus in the right cerebellum and left thalamus (O, P), progressive surrounding edema (O, P), and a small new ring-enhancing lesion seen in the left basal ganglia (K), which could represent neoplasm, abscess, or other conditions such as demyelination. There was no significant interval change in the previously seen extensive T2/FLAIR hyperintensity centered in the left parietal, occipital, and temporal lobes with extension across the splenium of the corpus callosum (N). There was an expansile T2 hyperintensity and mild associated increased diffusion-weighted imaging (DWI) signal in the right hippocampus, which was new compared to the prior scan (N, P, R). A heterogeneous soft tissue lesion in the right frontal scalp measuring 3.4 cm × 1.3 cm had also enlarged (M, O, P). These neuroradiological findings were highly suggestive of PML in the context of JCV neuroinvasion.

Retreatment

The patient received one dose of IV immunoglobulin (IVIg) and one single dose of the experimental infusion for PML. There was a plan to either repeat the investigation product infusion or give pembrolizumab 2 weeks afterwards; however, she had a seizure (left head version, gaze deviation, followed by secondary generalization to a tonic-clonic seizure) and became stuporous with right gaze preference. A brain MRI revealed progressive ring-enhancing lesions as well as right hippocampal DWI/FLAIR signal. A decision was made by the patient's significant other to stop PML treatment and transition to hospice. Despite all the efforts made by the multidisciplinary team, she passed away 2 weeks later.

Chimeric antigen receptor (CAR) T-cell therapy is a novel immunotherapy modality that has demonstrated remarkable response rates in refractory hematologic malignancies (Zhang et al., 2022), including in multiple myeloma (MM). Cytokine release syndrome (CRS) and neurotoxicity are major side effects of this therapy and are well described in the literature (Siegler & Kenderian, 2020). Cytokine release syndrome is a group of symptoms caused by an inflammatory response. It includes fever, hypotension, and hypoxia, usually occurring a few days after cells are infused (Gauthier & Turtle, 2020). Additionally, CRS can lead to serious complications, including the development of coagulopathies and multi-organ dysfunction. Neurotoxicity, on the other hand, usually has a later onset and can present without prior CRS (Chou & Turtle, 2020). Common manifestations of neurotoxicity include encephalopathy, aphasia, poor concentration, delirium, tremors, seizures, and possibly brain edema (Lee et al., 2019; Reveron-Thornton et al., 2022).

Patients who receive CAR T-cell therapy are also at increased risk for infections due to immune dysfunction, history of multiple lines of therapy, history of lymphodepleting chemotherapy prior to cell infusion, prolonged B-cell aplasia (Bupha-Intr et al., 2021), and delayed immune reconstitution (Sterner & Sterner, 2021). B-cell aplasia and

subsequent hypogammaglobulinemia (defined as immunoglobulin G level < 400 mg/dL) are well-recognized conditions that occur post CAR T-cell therapy due to the on-target off-tumor effect (Wat & Barmettler, 2022), which further increases the risk for opportunistic infections such as progressive multifocal leukoencephalopathy (PML). After disease progression, infections become a significant contributor to mortality among CAR T-cell therapy recipients (Stewart & Henden, 2021) which can be life-threatening not only in the immediate post-infusion phase but also for years afterward (Wat & Barmettler, 2022). Remarkably, low B-cell counts may persist for over 6 months and can continue for several years (Bhoj et al., 2016).

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Progressive multifocal leukoencephalopathy is an opportunistic disease of the central nervous system (CNS) caused by the reactivation of John Cunningham virus (JCV) in the setting of impaired cellular immunity (Cortese et al., 2024). Contaminated water or food and person-to-person contact are the main transmission mechanisms of JCV. In healthy individuals, it asymptomatically infects the kidneys and establishes latency (Bernard-Valnet et al., 2021). However, in the setting of immunosuppression, JCV is reactivated and PML can occur, leading to significant increased morbidity and mortality risks (Mian et al., 2021). The reactivated virus can cross the CNS barrier and cause significant demyelination and destructive cerebral lesions (Baldassari et al., 2022). The clinical presentation of PML includes altered mental status, deficit in motor function, and ataxia. It is often lethal (Muftuoglu et al., 2018). The mortality associated with PML varies according to the level of immunosuppression and primary cause (Cortese et al., 2019).

Risk Factors

Although past studies mostly focused on HIV/AIDS-related PML, health-care providers are now focusing their attention to the risks of developing PML in the setting of immunomodulatory therapies (Dunham et al., 2020). Progressive multifocal leukoencephalopathy occurs extraordinarily in immunocompromised individuals, and the lengthy weakening of cellular immunity becomes an increased risk factor for reactivation of JCV, especially in CAR T-cell therapy recipients who are known to have prolonged immunodeficiency (Cortese et al., 2020). Furthermore, while CAR T-cell therapy itself can be considered immunosuppressive due to the potential for significant immune cell depletion following treatment, the medications often used to manage its toxicities, like tocilizumab and steroids, further contribute to overall immunosuppression in the patient, potentially leaving them vulnerable to infections.

Pathophysiology and Clinical Presentation

Progressive multifocal leukoencephalopathy is characterized by the infection of oligodendrocytes and astrocytes causing demyelination in the brain. It presents with new onset of weakness and worsening progressive sensory, motor, coordination, and cognitive dysfunctions (Tan & Koralnik, 2010). It develops from the depletion of cytotoxic T cells that are responsible for killing and suppressing cells infected by the latent JCV (Bohra et al., 2017). Progressive multifocal leukoencephalopathy occurs in approximately 0.9 cases per 1,000 recipients of CD19-directed CAR T-cell therapy (Goldman et al., 2023). Due to its associated rapid and progressive neurological deterioration, along with the absence of established guidelines for treatment and prevention, PML is considered a highly concerning condition (Nelson et al., 2021). Therefore, it is essential to identify and diagnose PML as early as possible in its course to ensure better clinical outcomes.

Diagnosis

The diagnostic criteria for PML includes clinical findings, brain imaging (MRI of the brain being the first choice), JCV presence in the CSF or brain biopsy (Koutsavlis, 2020). The brain lesions are usually noticed in the white matter and imaging reveals areas of hyperintensity on T2-weighted and FLAIR images and hypointensity on T1-weighted images (Tan & Koralnik, 2010). Pathologically, despite noted areas of demyelination, immunohistochemical staining of JCV in the nuclei of astrocytic and odd large astrocytes altered by JCV infection are also noted (Dunham et al., 2020). Additionally, levels of neurofilament light chain (NfL) have the

potential to be a reliable blood biomarker associated with neuronal damage in neurological diseases (Barro et al., 2018). There is also evidence that NfL levels are elevated in the settings of inflammation and decreased in normalized brain volume, which supports the hypothesis that NfL levels can quantitatively monitor the rate of loss of neurons in the CNS (Barro et al., 2018).

Differential Diagnosis

There are overlapping clinical (e.g., encephalopathy, seizures, and visual changes) and radiographic (e.g., intrinsic T1 hypointensity and T2 hyperintensity on MRI) features of PRES and PML. Therefore, an important question is raised as to whether the brain MRI findings at days 13 and 19 may have represented early radiographic signs of PML (e.g., extension into the subcortical U fibers without gyral expansion; Weber, 2008). In the clinical context of prior PRES and MRI signal changes in the occipital lobe, PRES was the working diagnosis at that time.

A study based on the FDA Adverse Event Reporting System (FAERS) database of BCMA-directed T-cell therapies in multiple myeloma found that PML was reported in 3 of 584 cases (0.5%) treated with idecabtagene vicleucel, 0 of 477 cases treated with ciltacabtagene autoleucel (which the case study patient received), and 0 of 723 cases treated with teclistamab (Gong et al., 2024). Although it is unclear whether the history of PRES increased the patient's risk for PML, there is a case report of PRES masquerading as PML in rituximab-treated neuromyelitis optica (Berger et al., 2014). After the patient tested positive for JC virus, the radiographic interpretation of the later MRI scans favored PML due to the multifocal findings and increased pre-test probability of PML.

Treatment

Usually, neurologic damage in PML is irreversible and leads to death (Nelson et al., 2021). The backbone therapy of PML aims at reestablishing immunity (Bernard-Valnet et al., 2021), which can be extremely difficult in patients with malignant hematological diseases (Möhn et al., 2022). When restoration of immunity is not possible, the clinical outcome is extremely poor. In the setting of MM where genetic variations and T-cell dysfunction caused by previous therapies can occur, the transformation of JCV into a pathogenic archetype infection is more likely to support the development and continuous growth of the disease (Koutsavlis, 2020) consequently leading to poorer clinical outcomes.

Because JCV is only found in humans, research has been challenging using animal models (Tan & Koralnik, 2010). Therapeutic approaches have been studied but there is still a significant need for methods of immune restoration and treatments in individuals whose immunosuppression cannot be easily reversed. The benefits of mirtazapine have been studied but are restricted to natalizumab-related PML, and no positive impact on disease outcome was noted (Jamilloux et al., 2016). Pembrolizumab (Keytruda), a PD-1 blocker, has been used in PML treatment and shown some clinical improvement and stabilization of the disease. However, it has only been documented in small case studies (Bernard-Valnet et al., 2021) without concrete evidence of the benefits in PML superimposed on hematologic diseases as the underlying cause (Cortese et al., 2019). Although JCV-specific T cells have also been shown to be promising, this therapy is not widely available (Koutsavlis, 2020), and a limited number of institutions offer this novel therapy (Berzero et al., 2021).

Thus, no adequate treatment strategy for PML has yet been established (Möhn et al., 2022). Likewise, no guidelines or algorithms for clinical surveillance or stratification of PML risk have been determined due to the rarity of the disease and the emerging use of newer therapies in hematological malignancies (Yeung et al., 2019). Thiamine (vitamin B1) is also well known to have an important role in enhancing nerve functioning in the CNS (Calderón-Ospina & Nava-Mesa, 2020). Restoring cellular immunity using adoptive transfer of T cells has yielded positive results, but further research is needed (Nelson et al., 2021).

IMPLICATIONS FOR PRACTICE

Chimeric antigen receptor T-cell therapy targeting B cells can cause significant B-cell depletion, leading to hypogammaglobulinemia (low antibody levels), which severely compromises the body's ability to fight infections. After treatment is administered, the immune system takes a considerable time to

fully recover, leaving a window of increased vulnerability to infections during this period. Due to the profound immune suppression, infections in relapsed/refractory multiple myeloma patients receiving CAR T-cell therapy can be severe and life-threatening, requiring early diagnosis and aggressive treatment to decrease mortality.

IMPLICATIONS FOR APPS

Progressive multifocal leukoencephalopathy is a serious opportunistic infection affecting the CNS, typically arising from the reactivation of JCV in immunocompromised individuals. The management of PML can be challenging due to the lack of established guidelines. Advanced practice providers (APPs) are essential in early recognition of signs and symptoms of PML, ordering appropriate diagnostic testing in a timely manner, and providing supportive care to facilitate the restoration of immune function. Additionally, APPs should ensure well-timed referrals to neurology and infectious disease specialists and implement preventative measures such as prophylactic antibiotics to prevent opportunistic infections. Effective communication and prompt interventions are fundamental for improving patient outcomes. However, further research is necessary to identify patients at higher risk for developing PML and to establish standardized protocols for prompt restoration of immunity.

CONCLUSION

The use of CAR T-cell therapy to treat hematologic malignancies has been a breakthrough in the field of oncology and continues to evolve. However, because of the prolonged immunosuppression caused by this therapy, patients are prone to developing delayed opportunistic infections such as PML. Active JCV infection in the CNS is associated with a high morbidity and mortality; thus, any new neurological deficit in such patients should be addressed without delay by a multidisciplinary team including oncologists, neurologists, infectious disease specialists, and advanced practice providers.

Despite the persistent risk of PML among patients with immunosuppressive conditions and a growing risk of PML among patients treated with immunomodulatory agents, no therapeutics have been formally approved or indicated for the treatment of PML. This case highlights a fatal late outcome related to prolonged immunodeficiency in a patient receiving CAR T-cell therapy for the treatment of MM. Larger clinical trials are critically warranted to develop evidence-based guidelines to prevent and treat PML in immunocompromised patients as well as to develop effective strategies to reconstitute their immune functions. ●

Disclosure

The authors have no conflicts of interest to disclose.

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