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Severe Motor Weakness Due to Disturbance in Peripheral Nerves Following Tisagenlecleucel Treatment

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Abstract. *Background: Neurotoxicity is one of the dangerous complications of chimeric antigen receptor (CAR) T-cell therapy, while its pathophysiology remains to be fully understood. Motor weakness not associated with central nervous system (CNS) toxicity has rarely been reported after CAR T-cell therapy. Case Report: A 42-year-old female with a refractory diffuse large B-cell lymphoma received tisagenlecleucel (tisa-cel) and developed cytokine release syndrome (CRS) on day 3. She was treated with tocilizumab and methylprednisolone, which resolved CRS promptly. On day 7, motor weakness in lower extremities appeared, and she gradually became unable to walk without showing any other symptoms attributed to CNS disturbances. Whereas dexamethasone and tocilizumab were ineffective, neuropathy improved after high dose chemotherapy followed by autologous stem cell transplantation. Nerve conduction study (NCS) in lower extremities showed a decline in compound muscle action potential amplitude along with worsening of motor weakness, which was restored after improvement of symptoms. Based on symptoms and NCS, her motor weakness was thought to be due to disturbance in peripheral nerves. Conclusion: This study reports a patient who developed severe motor weakness due to disturbance in peripheral nerves after tisa-cel therapy. Neurotoxicity of non-CNS origin should also be noted in CAR T-cell therapy.*

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Anti-CD19 chimeric antigen receptor (CAR) T-cells are a groundbreaking treatment option for relapsed or refractory B-cell malignancies(1-7). Tisagenlecleucel (tisa-cel) is an anti-CD19 CAR T-cell therapy that was approved in 2017 by the Food and Drug Administration followed by rapid worldwide spread (8). While tisa-cel has shown dramatic results, it can cause unique adverse effects, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) (9-11). ICANS is defined by the American Society for Transplantation and Cellular Therapy (ASTCT) toxicity consensus group, and the spectrum of neurological symptoms ranges from delirium and language dysfunction to seizures and coma (12). Cognitive impairment is the most common symptom, and it is usually resolved by appropriate therapy. On the other hand, there are few reports on motor weakness associated with CAR T-cell therapies, the details of which remain unclear (13-16).

Herein, we report a case of severe motor weakness possibly due to disturbance in peripheral nerves occurring after tisa-cel therapy in a patient with relapsed diffuse large B-cell lymphoma (DLBCL). Her neurological symptoms were thought to be limited to those attributable to peripheral nerves and were irresponsive to dexamethasone.

Case Report

A 42-year-old woman with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) was admitted to our hospital to receive CAR T-cell therapy. Four years before, she was diagnosed with CD5-positive DLBCL. She achieved complete response (CR) after eight cycles of dose adjusted EPOCH-R [etoposide (ETP), prednisolone, vincristine (VCR), cyclophosphamide (CPA), doxorubicin (DXR) and rituximab (R)], followed by two cycles of high-dose methotrexate (MTX) for CNS prophylaxis. Three years later, she had a relapse with the left inguinal lymph node. Salvage chemotherapy and autologous peripheral blood stem cell

(PBSC) harvest were performed; however, her disease progressed before autologous transplantation. The patient was admitted to our hospital and underwent leukapheresis for creating the tisa-cel.

She received tisa-cel after lymphodepletion chemotherapy with fludarabine and CPA. The clinical course is illustrated in Figure 1. Three days after tisa-cel infusion, she developed CRS with high fever, tachycardia, and headache and was treated with tocilizumab, followed by intravenous methylprednisolone (mPSL). CRS was immediately resolved after starting mPSL. Motor weakness in both lower limbs without any symptoms attributed to CNS disturbance such as aphasia and impaired consciousness, appeared from day 7 and gradually progressed. Physical exam showed a decrease in deep tendon reflex in all four limbs. Magnetic resonance imaging (MRI) of the brain and the whole spine showed no abnormal findings and cerebrospinal fluid examination showed no abnormalities in total protein, cell count, or cytology. A motor nerve conduction study (NCS) was performed in right tibial nerve. Compound muscle action potentials (CMAPs) were recorded from abductor hallucis muscle and electrical stimulation was delivered at the ankle and popliteal fossa. The distal CMAP amplitude (normal lower limit; 13.4 mV) and motor nerve conduction velocity (MCV) (normal lower limit; 43.7 m/s) were normal, 17.6 mV and 45.5 m/s, respectively (Table I). Although it is not typical, we considered her motor weakness as ICANS since it developed after CRS. Motor weakness of the lower limbs continued to progress, and she was unable to walk. She was treated with dexamethasone from day 29, but her symptoms did not improve. Simultaneously, lymphoma progressed to the para-aortic lymph node and local radiotherapy was started. Radiotherapy was discontinued due to severe cytopenia. A bone marrow smear was significantly hypocellular and showed no infiltration of lymphoma cells, and administration of filgrastim was ineffective. After starting filgrastim, a high fever was observed again. Since the clinical symptoms were similar to those of the first CRS, we considered the fever to be a CRS-like symptom and started tocilizumab. The high fever improved promptly, but the neurological symptoms were completely unaffected. The patient's lymphoma gradually worsened thereafter, but the severity of the cytopenia made it difficult to continue therapy. Therefore, we decided to perform an autologous PBSC transplant (aPBSCT) using the previously collected PBSCs. She returned to the previous hospital. The NCS showed a significant drop in the distal CMAP amplitude (5.4 mV) on day 71 when her motor weakness worsened (Table I), and the patient was unable to walk. After she received high-dose chemotherapy with R-MEAM(17) followed by aPBSCT on day 81, she achieved a CR with full neutrophil recovery. Her motor weakness which had persisted over two months from the onset, gradually improved after aPBSCT, and she regained the ability to walk with a caster walker for a short distance. The distal CMAP amplitude on NCS was restored to 13.5 mV on day 179 (Table I).

Discussion

Neurotoxicity caused by anti-CD19 CAR T-cell therapy has been reported in 20%-60% of patients (3-7). For tisa-cel, neurologic events were reported in 21% of patients (12% ≥ Grade 3) for relapsed/refractory DLBCL and 40% of patients (13% ≥ Grade 3) for relapsed/refractory B cell acute lymphoblastic leukemia (5, 6). Neurotoxicity after CAR T-cell therapy was previously termed CAR T-cell related encephalopathy (CRES), but is now referred to as ICANS due to the observation of similar neurotoxicity after other cell-based immunotherapies (12).

ICANS, like CRS, is a severe adverse effect of CAR T-cell therapy, and the mechanisms are poorly understood. Motor weakness is a symptom of ICANS; however, there have been a few reports on motor weakness after CAR T-cell therapy (13-16). In a report specific to neurotoxicity following CAR T-cell therapy, 11 cases of focal weakness were reported (15). In that report, many cases were complicated by encephalopathy-related symptoms such as aphasia, suggesting that the motor weakness originated from the CNS. The ASTCT defines ICANS as a disorder characterized by a pathologic process involving the CNS (12). In our case, there was no evidence of CNS lymphoma invasion and no other disease explaining motor weakness, suggesting that it was related to the CAR T-cell therapy. However, since the decreased CMAP amplitude was seen only when the motor weakness was the most severe in her clinical course, the neurotoxicity was thought to have emerged through a non-CNS mechanism. Previous studies have reported a few cases of neuropathy after CAR-T cells (14) and Guillain-Barré syndrome has been reported with cell-based immunotherapy other than CD19 CAR T-cells (18). This suggests that the neurotoxicity of non-CNS origin may also be observed in some patients.

Steroid treatment is recommended for treating severe neurotoxicity (9, 19); however, most reports are based on CNS-related neurotoxicity, and the efficacy of steroids for the disturbance in peripheral nerves is unknown. In our case, steroids, as well as tocilizumab, were completely ineffective, and the symptoms improved after high-dose chemotherapy followed by aPBSCT. Previous reports have shown that CPA, anti-thymocyte globulin, and intrathecal chemotherapy, which directly affect T lymphocytes, are effective in cases of steroid/tocilizumab refractory neurotoxicity (20-22). CAR and non-CAR T-cells have been reported to infiltrate the cerebrospinal fluid and brain parenchyma, consistent with encephalitis, in a non-human primate model (23). It is thought that some neurotoxicity may be caused and maintained by CAR and non-CAR T-cell infiltration, and removal of these cells may have allowed the patient to recover from the severe neurotoxicity.

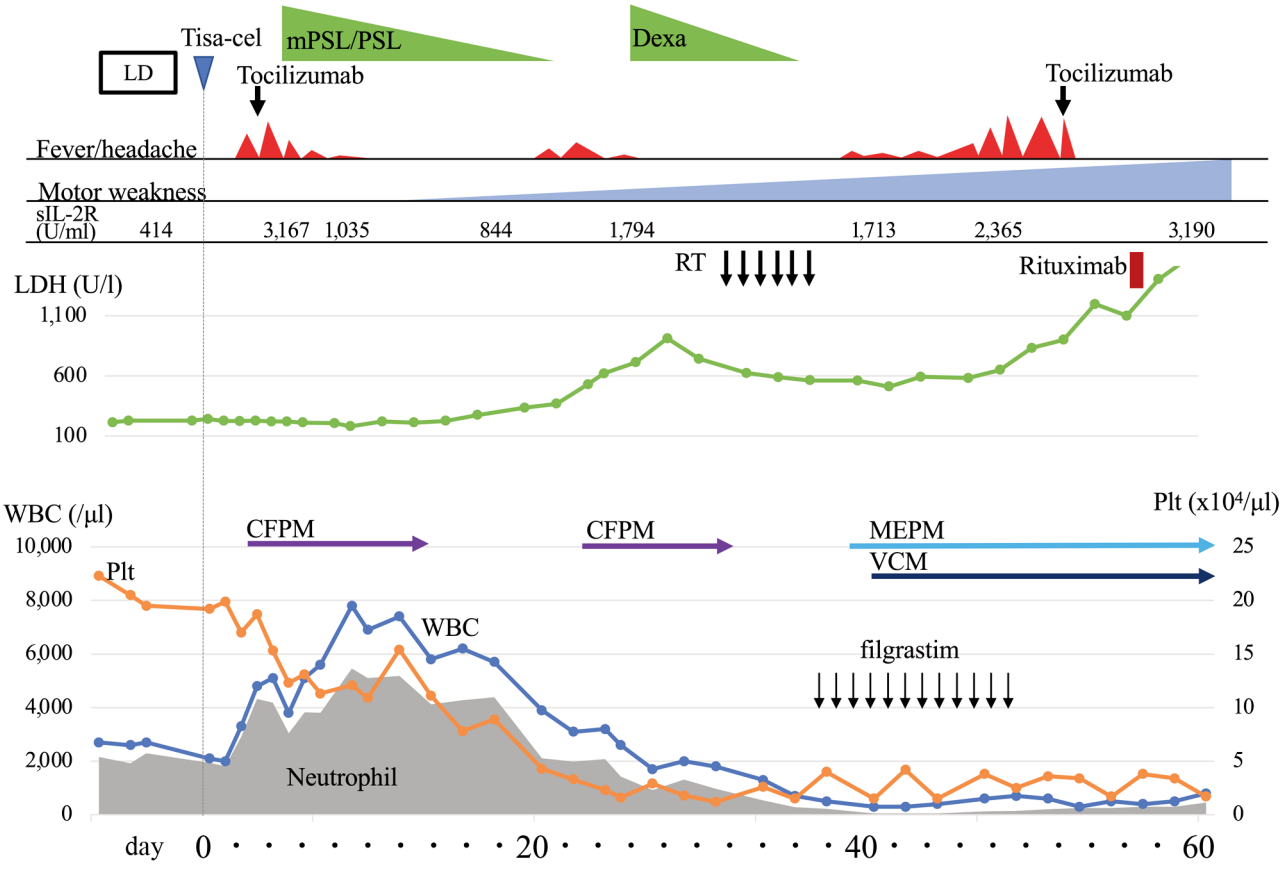

Figure 1. *Clinical course after tisa-cel infusion. CFPM, Cefepime; Dexa, dexamethasone; RT, radiation therapy; LD, lymphodepletion; LDH, lactate dehydrogenase; mPSL, methylprednisolone; MEPM, meropenem; Plt, platelet; PSL, prednisolone; sIL-2R, soluble interleukin-2 receptor; Tisa-cel, tisagenlecleucel; VCM, vancomycin; WBC, white blood cell.*

Table I. *Nerve conduction study of the right tibial nerve.*

	Day 24		Day 71		Day 179	
Stimulation site	Ankle	Knee	Ankle	Knee	Ankle	Knee
CMAP Amplitude, mV	17.6	13.6	5.4	4.2	13.5	9.6
MCV, m/s	45.5		43.2		49.3	

Day 24; initial phase of worsening motor weakness, day 71; advanced phase that the patient was not walking, day 179; restoring phase that the patient could walk for short distances. MCV, motor nerve conduction velocity; CMAP, compound muscle action potential.

Conclusion

In this report, we described a patient with motor weakness without CNS disorder following treatment with tisa-cel. Most cases of neurotoxicity are related to the CNS in patients treated with tisa-cel, but neurotoxicity not originating in the CNS should also be noted. Further research is required to reveal the mechanism of non-CNS related neurotoxicity, which will lead to optimal diagnosis and patient management.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

M.K., Y.U. and M.Y. provided concept and design; M.K., Y.U., O.M. and M.Y. wrote and reviewed the manuscript; M.K., Y.U., Y.M., K.O., A.N., T.N. and M.Y. acquired data and managed the patient.

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