Section Editor: Laura Zitella

Orthopnea From Phrenic Nerve Palsy After Ciltacabtagene Autoleucel CAR T-Cell Therapy in a Patient With Multiple Myeloma

ELIZABETH C. FITZGERALD, MMS, PA-C, CAQ-PMHC, DEVON ALTSHULER, PA-C, ALLISON M. TANNER, MMS, PA-C, SUPRIYA GUPTA, MBBS, and YI LIN, MD, PhD

From Mayo Clinic Rochester, Rochester, Minnesota

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

Correspondence to: Elizabeth C. Fitzgerald, 201 W. Center Street, Rochester, MN 55905

E-mail: fitzgerald.elizabeth@mayo.edu

https://doi.org/10.6004/jadpro.2026.17.7.27

Abstract

Chimeric antigen receptor (CAR) T-cell therapy has transformed the management of relapsed/refractory multiple myeloma (MM), particularly with the advent of ciltacabtagene autoleucel (cilta-cel). As its clinical use expands, novel and delayed toxicities are increasingly recognized. We report the first documented case of bilateral phrenic nerve palsy following cilta-cel infusion, presenting with acute dyspnea and profound orthopnea. Diagnostic evaluation was challenged by the patient's inability to tolerate the supine position, delaying definitive imaging. Ultimately, diaphragmatic ultrasound and phrenic nerve conduction studies confirmed isolated bilateral phrenic neuropathy without evidence of myopathy or cervical radiculopathy. The patient was treated with intravenous immunoglobulin (IVIG), high-dose corticosteroids, and prolonged bilevel positive airway pressure (BiPAP) support. Despite this neurologic complication, he achieved minimal residual disease (MRD)–negative complete remission. This case highlights an emerging neurotoxicity of cilta-cel, underscores the importance of early recognition of diaphragmatic dysfunction, and outlines diagnostic and management considerations for advanced practice providers (APPs).

CASE STUDY

A 70-year-old man with high-risk IgG κ multiple myeloma underwent treatment with ciltacabtagene autoleucel (cilta-cel) after progressing through multiple lines of therapy. On day +8 post-infusion, he developed sudden dyspnea, tachypnea, and severe orthopnea. Evaluation was

limited due to intolerance of supine positioning. Diaphragmatic ultrasound on day +11 suggested bilateral hemidiaphragm dysfunction, and subsequent phrenic nerve conduction studies confirmed isolated bilateral phrenic nerve palsy. He required nocturnal and positional bilevel positive airway pressure (BiPAP), intravenous immunoglobulin (IVIG), and high-dose corticosteroids. On day +30, he was in MRD-negative complete remission, but diaphragmatic weakness persisted. This is the first reported case of bilateral phrenic nerve palsy following cilta-cel.

Patient Presentation

The patient's past medical history included benign prostatic hyperplasia, hypothyroidism, vitamin B deficiency, obstructive sleep apnea, and a history of colon polyps. Notably, during his chimeric antigen receptor (CAR) T-cell evaluation, he was also diagnosed with cholangiocarcinoma in March 2024, which added medical complexity and influenced treatment planning.

His multiple myeloma was Revised International Staging System (R-ISS) stage III and cytogenetically high-risk, with del(13q), t(11;14), and del(17p). At initial presentation, his IgG level was 10,300 mg/dL, κ light chains were 110.6 mg/dL, and bone marrow biopsy revealed 80% plasma cell involvement. PET-CT imaging demonstrated multiple lytic lesions.

He received multiple prior lines of therapy, including five cycles of bortezomib, lenalidomide, and dexamethasone (VRd), followed by autologous stem cell transplantation, after which he experienced an early relapse. He subsequently received additional VRd; carfilzomib, pomalidomide, and dexamethasone (KPd); venetoclax, bortezomib, and dexamethasone; and bridging therapy with selinexor, bortezomib, and dexamethasone (SVd). He then underwent standard lymphodepletion with fludarabine and cyclophosphamide, followed by infusion of cilta-cel.

Early complications included grade 1 cytokine release syndrome (CRS) on days +3 and +5

Table 1. Case Study Treatments for Cytokine Release Syndrome

Day post infusion	CRS grade	Dexamethasone dose (IV)	Tocilizumab dose (IV)	Additional medications	Additional workup
Day 3	Grade 1	10 mg IV	680 mg (8 mg/kg)	Acetaminophen 1,000 mg Cefepime 2 g every 12 hours	Blood cultures, respiratory pathogen panel, urine culture, urinalysis, chest X-ray
Day 5	Grade 1	10 mg IV every 6 hours	680 mg (8 mg/kg) × 2 doses	Acetaminophen 1,000 mg × 2 doses Cefepime transitioned to piperacillin-tazobactam to avoid cefepime-induced encephalopathy	Cytokine panel
Day 6	Grade 1	10 mg IV every 6 hours		Acetaminophen 1,000 mg Anakinra 100 mg every 12 hours	Cytokine panel
Day 7	Grade 1	10 mg IV every 6 hours		Acetaminophen 1,000 mg Anakinra 200 mg every 12 hours Siltuximab 11 mg/kg IV × 1 dose	
Day 8	Grade 0	10 mg IV every 12 hours		Anakinra 200 mg every 12 hours	
Day 9	Grade 0			Anakinra 200 mg daily through day 12 post infusion	

requiring tocilizumab and dexamethasone, with initiation of anakinra for recurrent symptoms. His CRS course and treatments implemented are outlined in Table 1.

Workup, Diagnosis, Treatment, and Clinical Course

On day +8, the patient developed abrupt-onset dyspnea characterized by tachypnea and profound orthopnea. He was unable to recline beyond 45 degrees and reported near-syncope when attempting to lie supine. Despite significant respiratory distress, his oxygen saturation remained greater than 96% on 2 liters of supplemental oxygen via nasal cannula.

The initial diagnostic evaluation was challenging due to his inability to tolerate the supine position. A CT angiogram of the chest was limited for this reason. Transthoracic echocardiography demonstrated a lack of inferior vena cava collapse, raising concern for possible fluid overload, although chest radiography remained clear. A trial of intravenous furosemide did not result in clinical improvement. Arterial blood gas analysis revealed a primary respiratory alkalosis with appropriate metabolic compensation. Given his worsening symptoms, a rapid response was activated, and he was transferred to the intensive care unit for further management.

Alternative etiologies for his presentation were evaluated and excluded. Lower extremity Doppler ultrasonography was negative for deep vein thrombosis. Flexible nasolaryngoscopy demonstrated normal vocal cord mobility. Neurology consultation determined that the clinical picture was not consistent with steroid-induced myopathy or brachial plexopathy. MRI was deferred due to the patient's inability to lie flat.

Definitive diagnostic evaluation was subsequently achieved. On day +11, diaphragmatic ultrasonography demonstrated a reduced thickening ratio of both hemidiaphragms, consistent with bilateral diaphragmatic dysfunction. CT of the thorax and cervical spine, performed with BiPAP support, revealed stable lytic lesions without evidence of compression or a structural etiology. On day +18, phrenic nerve conduction studies confirmed isolated bilateral phrenic neuropathy, without evidence of myopathy or cervical radiculopathy.

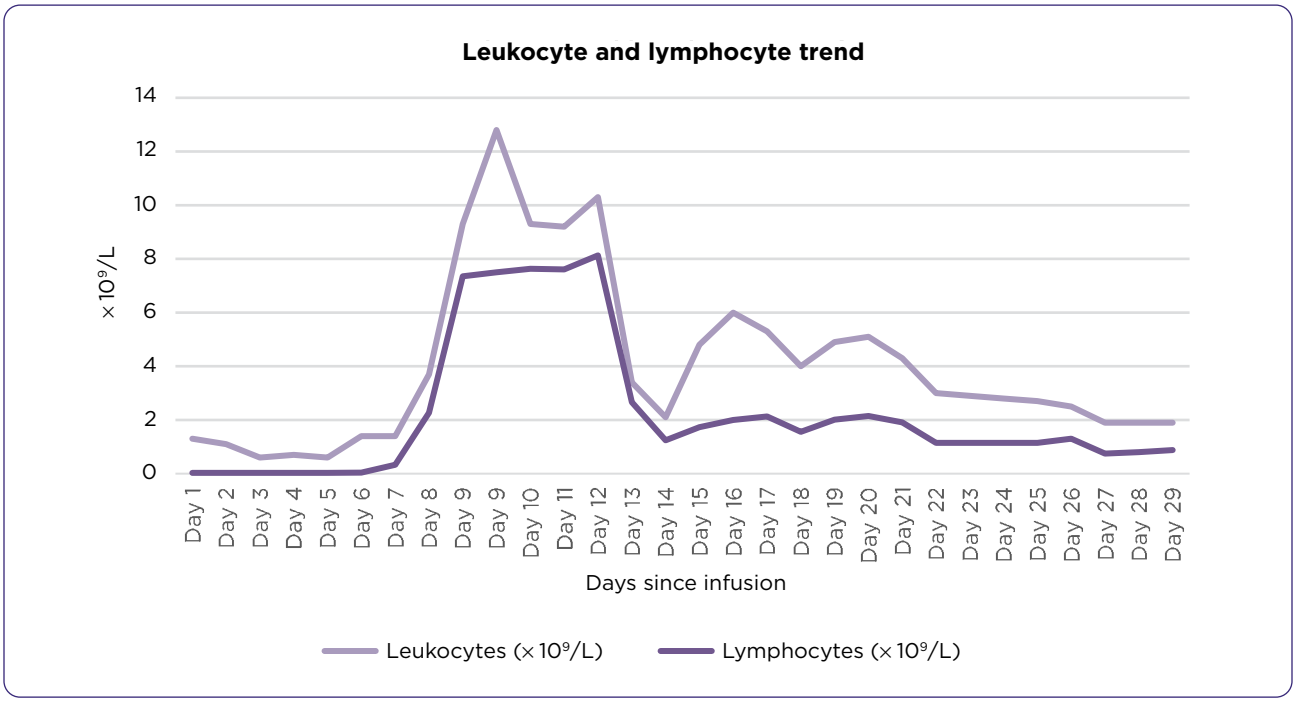

Figure 1. Case study leukocyte and lymphocyte trend.

Therapeutic interventions included administration of intravenous immunoglobulin at a dose of 1 g/kg for two doses, as well as high-dose methylprednisolone followed by a prolonged prednisone taper. A third dose of IVIG was administered on day +64 due to persistent symptoms. The patient required BiPAP therapy during sleep and whenever supine, and future consideration was given to placement of a phrenic nerve stimulator.

At follow-up on day +30, bone marrow examination was morphologically normal and minimal residual disease testing was negative. PET-CT demonstrated a complete metabolic response, with the exception of a stable cholangiocarcinoma lesion. The patient continued to rely on BiPAP when lying flat. He later developed additional cranial neuropathies, consistent with delayed neurotoxicity associated with cilta-cel.

Multiple myeloma remains incurable despite significant therapeutic advances. Ciltacabtagene autoleucel (Carvykti; cilta-cel) is a second-generation, BCMA-directed chimeric antigen receptor (CAR) T-cell construct featuring two single-domain antibodies, which contributes to deep and durable responses even in heavily pretreated patients. In the CARTITUDE-1 trial, cilta-cel demonstrated overall response rates exceeding 95% with high minimal residual disease (MRD) negativity rates (San-Miguel et al., 2023). However, novel toxicities—including delayed neurotoxicity and cranial neuropathies—have been increasingly recognized (San-Miguel et al., 2023).

RISK FACTORS FOR BILATERAL PHRENIC NERVE PALSY

Emerging data from cilta-cel clinical trials provide insight into cranial nerve neurotoxicity following treatment. Among patients in the CARTITUDE-1 and CARTITUDE-4 studies, cranial nerve palsies occurred in 7% (19/285) of patients, with grade ≥ 3 events in 1% (1/285). Median time to onset was 21 days (range: 17–101 days), and 89% of events resolved, with a median duration of 70 days (range: 1–262 days). Specific cranial nerves affected included the 7th (most common), as well as III, V, and VI. Incidence varied by study: 9% in CARTITUDE-4 (1% grade 3–4) and 3% in CARTITUDE-1 (1% grade 3–4; San-Miguel et al., 2023; Lim et al., 2025a).

Phrenic nerve palsy is rare and is most commonly associated with infections such as herpes zoster, Lyme disease, and COVID-19; surgical trauma, particularly following cardiac or thoracic surgery; cervical spine pathology; autoimmune neuropathies including chronic inflammatory demyelinating polyneuropathy and Guillain–Barré syndrome variants; neuralgic amyotrophy; toxic neuropathies, including those related to chemotherapeutic agents; and critical illness polyneuropathy as well as metabolic disturbances (Natrajan et al., 2024).

Immune-mediated neuropathies have also been described as delayed toxicities of CAR T-cell therapy, particularly with cilta-cel (Lim et al., 2025a). High absolute lymphocyte counts (ALC) emerging 1 to 2 weeks post-infusion have been associated with delayed neurotoxic syndromes (Lim et al., 2025b). In this case, the patient had an ALC that began to rise on day 8 after infusion, with a peak of 8.13×10^9/L on day 12 after infusion. This coincided with the onset of symptoms (Figure 1).

Emerging data from cilta-cel studies highlight predictors of cranial nerve and delayed neurotoxicities. Notable risk factors for these toxicities include high baseline tumor burden, prior history of immune effector cell–associated neurotoxicity syndrome (ICANS), and elevated CAR T-cell expansion, measured as absolute lymphocyte count (ALC) > 3.0×10^9/L (Lim et al., 2025a). Patients with these factors demonstrate a substantially increased risk, with 33% developing cranial neuropathies compared to 5% in those without these characteristics (Lim et al., 2025b).

Notably, no clear pretreatment patient characteristics, such as age, sex, or baseline comorbidities, have been definitively linked to increased risk, highlighting the importance of careful post-infusion monitoring for all patients. These findings are consistent with guidance from the National Comprehensive Cancer Network and American Society of Clinical Oncology (Lim et al., 2025b).

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION OF BILATERAL PHRENIC NERVE PALSY

Pathophysiology

The phrenic nerve arises from the C3 to C5 nerve roots and provides the primary motor innervation to the diaphragm. Bilateral involvement results in near-complete loss of diaphragmatic excursion, leading to significant respiratory compromise (McCool & Tzelepis, 2012). In the setting of CAR T-cell therapy, immune-mediated injury has been proposed as a potential mechanism for neuropathy. This may occur through T-cell–driven inflammation, cytokine-induced neurotoxicity, or direct neuroinflammatory processes.

Clinical Presentation

Patients typically present with acute or subacute dyspnea accompanied by tachypnea. Orthopnea is a prominent feature, often with an inability to tolerate the supine position. Paradoxical abdominal motion may be observed on examination. Oxygenation is frequently preserved at rest until the disease becomes severe. Arterial blood gas analysis commonly demonstrates a respiratory alkalosis (Law et al., 2022; McCool & Tzelepis, 2012; McEnery et al., 2017; Yekzaman et al., 2022).

Diagnosis and Differential Diagnosis

In post–CAR T-cell therapy patients presenting with dyspnea and orthopnea, a broad differential diagnosis must be considered. This includes pulmonary embolism, cardiac dysfunction or pericardial effusion, fluid overload, steroid-induced myopathy, myasthenia gravis, cervical radiculopathy, brachial plexopathy, vocal cord dysfunction, chemotherapy-induced neuropathy, and immune-mediated neuropathies, including phrenic nerve involvement.

Diagnostic Workup

The diagnostic evaluation relies on a combination of bedside and advanced studies. Diaphragmatic ultrasound may demonstrate a reduced thickening fraction, while fluoroscopy with a sniff test can reveal paradoxical diaphragmatic motion, although this may not be feasible in all patients (Law et al., 2022; McEnery et al., 2017). Phrenic nerve conduction studies typically show reduced amplitude and delayed latency (McEnery et al., 2017). MRI of the cervical spine is useful for excluding compressive pathology (Yekzaman et al., 2022). Arterial blood gas analysis often reveals respiratory alkalosis with a normal alveolar–arterial gradient (McCool & Tzelepis, 2012). In this case, the patient's inability to lie flat significantly delayed imaging, underscoring the importance of bedside diaphragmatic ultrasound as an early diagnostic tool.

TREATMENT

Immunomodulatory Therapy

Management includes immunomodulatory therapy, with intravenous immunoglobulin serving as a standard treatment for immune-mediated neuropathies. High-dose corticosteroids are also commonly used to reduce inflammation and immune-mediated nerve injury.

Ventilatory Support

Ventilatory support is an important component of care and may include the use of bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP) to augment ventilation, particularly when the patient is in the supine position. Air travel should be avoided during the acute phase due to the risk of respiratory decompensation.

Rehabilitative and Long-Term Options

Rehabilitative strategies include inspiratory muscle training to improve respiratory muscle strength. In refractory cases, phrenic nerve pacing may be considered as a long-term therapeutic option.

Clinical Trial Considerations

Enrollment in clinical trials evaluating biomarkers and management strategies for CAR T-cell–associated neurotoxicity should be considered when available. The patient received guideline-concordant therapy for immune-mediated neuropathy and showed partial symptomatic improvement.

IMPLICATIONS FOR ADVANCED PRACTICE PROVIDERS

Advanced practice providers increasingly lead the front-line management of patients receiving CAR T-cell therapy. This case highlights the importance of early recognition of atypical respiratory symptoms, prompt use of bedside ultrasound to

rapidly assess diaphragmatic function when formal imaging is not feasible, and close coordination across multiple specialties, including pulmonology, neurology, sleep medicine, and the intensive care unit. It also underscores the need for awareness of emerging CAR T-cell–associated toxicities beyond cytokine release syndrome and ICANS, as well as the long-term management of chronic respiratory deficits, including ongoing ventilatory support and monitoring for delayed neurotoxicity. Advanced practice providers play a critical role in surveillance, diagnosis, patient education, and coordination of complex post–cellular therapy care.

CONCLUSION

This is the first reported case of bilateral phrenic nerve palsy following cilta-cel, representing a novel and potentially severe neurologic toxicity. The patient's presentation was defined by abrupt dyspnea, tachypnea, and profound orthopnea, with diagnostic evaluation complicated by the inability to lie supine. Bedside diaphragmatic ultrasound and phrenic nerve conduction studies were essential in establishing the diagnosis. Although the patient required prolonged BiPAP support and immunomodulatory treatment, he achieved MRD-negative remission.

KEY TAKEAWAYS

Sudden onset of orthopnea following CAR T-cell therapy should raise clinical suspicion for diaphragmatic dysfunction. Early use of bedside ultrasound can expedite diagnosis when standard imaging is not feasible. In this setting, bilateral phrenic nerve palsy is most likely immune-mediated. Advanced practice providers must be prepared to recognize and manage emerging complications associated with CAR T-cell therapy. As CAR T-cell use expands, awareness of rare, immune-mediated neuropathies, including phrenic nerve palsy, will be critical for timely intervention and improved outcomes.

Disclosure

The authors have no conflicts of interest to disclose.

References

McCool, F. D., & Tzelepis, G. E. (2012). Dysfunction of the diaphragm. *The New England Journal of Medicine, 366*(10), 932–942. https://doi.org/10.1056/NEJMra1007236

McEnery, T., Walsh, R., Burke, C., McGowan, A., Faul, J., & Cormican, L. (2017). Phrenic nerve palsy secondary to Parsonage–Turner syndrome: A diagnosis commonly overlooked. *Lung, 195*(2), 173–177. https://doi.org/10.1007/s00408-016-9972-2

Law, S. M., Scott, K., Alkarn, A., Mahjoub, A., Mallik, A. K., Roditi, G., & Choo-Kang, B. (2022). COVID-19 associated phrenic nerve mononeuritis: A case series. *Thorax, 77*(8), 834–838. https://doi.org/10.1136/thoraxjnl-2021-218257

Lim, K. J. C., Chhabra, S., Corraes, A. D. M. S., Parrondo, R. D., Gertz, M., Hwa, L., Stephens, H., Bansal, R., Jankowski, M., Kapoor, P., Hayman, S. R., Kourelis, T., Warsame, R., Cook, J., Binder, M., Dingli, D., Bergsagel, P. L., Kumar, S., Ailawadhi, S.,...Lin, Y. (2025a). Risk factors for delayed neurotoxicity in patients with relapsed myeloma who received ciltacabtagene autoleucel (cilta-cel). *Transplantation and Cellular Therapy, 31*(2), S202. https://doi.org/10.1016/j.jtct.2025.01.313

Lim, K. J. C., Parrondo, R. D., Chhabra, S., Dooley, K., Corraes, A. D. M. S., Gertz, M. A., Hwa, L., Stephens, H., Kapoor, P., Tan, M., Kourelis, T., Warsame, R. M., Cook, J., Binder, M., Bergsagel, P. L., Geyer, S. M., Kumar, S., Ailawadhi, S., Fonseca, R., & Lin, Y. (2025b). Investigating the association between peak post-infusion absolute lymphocyte count (ALC) and delayed toxicity in myeloma (MM) patients (pts) receiving cilta-cel. *Journal of Clinical Oncology, 43*(16_suppl), 7522. https://doi.org/10.1200/JCO.2025.43.16_suppl.7522

Natrajan, K., Kaushal, M., George, B., Kanapuru, B., & Theoret, M. R. (2024). FDA Approval Summary: Ciltacabtagene Autoleucel for Relapsed or Refractory Multiple Myeloma. *Clinical Cancer Research, 30*(14), 2865–2871. https://doi.org/10.1158/1078-0432.CCR-24-0378

San-Miguel, J., Dhakal, B., Yong, K., Spencer, A., Anguille, S., Mateos, M.-V., Fernández de Larrea, C., Martínez-López, J., Moreau, P., Touzeau, C., Leleu, X., Avivi, I., Cavo, M., Ishida, T., Kim, S. J., Roeloffzen, W., van de Donk, N. W. C. J., Dytfeld, D., Sidana, S.,...Einsele, H. (2023). Ciltacel or standard care in lenalidomide-refractory multiple myeloma. *The New England Journal of Medicine, 389*(4), 335–347. https://doi.org/10.1056/NEJMoa2303379

Yekzaman, B. R., Minchew, H. M., Alvarado, A., & Ohiorhenuan, I. (2022). Phrenic nerve dysfunction secondary to cervical neuroforaminal stenosis: A literature review. *World Neurosurgery, 167*, 74–77. https://doi.org/10.1016/j.wneu.2022.09.009