Turkish Journal of Neurology

Turk J Neurol 2025;31(4):463-467
Doi: 10.55697/tnd.2025.497

CASE REPORT

Immune checkpoint inhibitor-related myositis with ocular manifestations and fatal outcome

Nuri Tuğra Uslucan, Merve Yavuz, Esra Aşıkdoğan, Emre Kumral

Department of Neurology, Ege University Faculty of Medicine, İzmir, Türkiye

ABSTRACT

Immune checkpoint inhibitors are increasingly used in oncology and, while effective, may cause rare but severe immune-related adverse events, including myositis. Herein, we presented the case of an 82-year-old male with urothelial bladder cancer who developed myositis following pembrolizumab therapy. The clinical presentation included ptosis, ophthalmoplegia, dysphagia, dropped head, and respiratory involvement. Laboratory evaluation revealed markedly elevated creatine kinase and troponin levels, while electromyography demonstrated myopathic changes. Antibodies associated with myositis and myasthenia gravis were negative. Despite high-dose intravenous methylprednisolone and plasmapheresis, the patient died due to refractory hypotension and subsequent cardiac arrest during his stay in the intensive care unit. This case highlighted the potentially fulminant course of immune checkpoint inhibitor-associated myositis and underscored the importance of early recognition and aggressive management, particularly in cases with bulbar and respiratory involvement.

Keywords: Immune checkpoint inhibitors, immune-related neurological adverse events, myositis, pembrolizumab.

Immune checkpoint inhibitors (ICPIs) have transformed cancer treatment by enhancing the antitumor immune response.[1,2] By enabling the immune system to recognize and eliminate tumor cells, ICPIs have revolutionized oncology practice.[1,2] One such agent, pembrolizumab, is a humanized monoclonal antibody that binds to the programmed cell death protein 1 (PD-1) receptor and is used to treat various cancers, ranging from metastatic melanoma to bladder cancer.[3,4] However, these therapies may result in immune-related adverse events (irAEs), which can affect multiple organ systems and, in some cases, become life-threatening.[5-8] Under normal conditions, immune checkpoints such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), PD-1, and its ligand PD-L1 act as regulatory pathways that prevent excessive immune activation and maintain self-tolerance. Tumor cells exploit these checkpoints to evade immune surveillance. Immune checkpoint inhibitors, including agents such as ipilimumab (anti-CTLA-4), nivolumab and pembrolizumab (anti-PD-1), and atezolizumab (anti-PD-L1), block these inhibitory signals, restoring cytotoxic T-cell activity and promoting tumor cell destruction.

Pembrolizumab is a humanized monoclonal antibody against PD-1 and was first approved by the USA Food and Drug Administration (FDA) in 2014 for metastatic melanoma.[3] In 2017, it received FDA approval for the treatment of platinum-refractory metastatic urothelial carcinoma, marking a significant advancement in bladder cancer management.[4] Since then, pembrolizumab has been widely used in a variety of malignancies, including non-small cell lung cancer, gastric cancer, and renal cell carcinoma.[3]

Despite its therapeutic efficacy, pembrolizumab is associated with a wide range of irAEs resulting from the overactivation of the immune system. These irAEs may affect multiple organ systems, and although neurological complications are less

Correspondence: Nuri Tuğra Uslucan, MD. Ege Üniversitesi Tıp Fakültesi Nöroloji Anabilim Dalı, 35100 Bornova, İzmir, Türkiye.
E-mail: tugra.uslucan@gmail.com
Received: June 17, 2025 **Accepted:** August 27, 2025 **Published online:** December 08, 2025
Cite this article as: Uslucan NT, Yavuz M, Aşıkdoğan E, Kumral E. Immune checkpoint inhibitor-related myositis with ocular manifestations and fatal outcome. Turk J Neurol 2025;31(4):463-467. doi: 10.55697/tnd.2025.497.

common, they can be severe and potentially life-threatening. Reported neurological irAEs include encephalitis, aseptic meningitis, demyelinating polyneuropathy, myasthenia gravis, and myositis.[5,6]

Among these, myositis is a rare but increasingly recognized complication, typically presenting with proximal muscle weakness, elevated creatine kinase (CK) levels, and, in some cases, bulbar and respiratory involvement. The clinical course may be rapidly progressive and fatal if not promptly diagnosed and treated.[6,7]

In this case report, we described a patient who developed pembrolizumab-associated myositis with bulbar and respiratory involvement, which was refractory to aggressive immunosuppressive therapy and ultimately resulted in a fatal outcome.

CASE REPORT

An 82-year-old male with a history of hypertension and Stage IV urothelial bladder carcinoma diagnosed five months earlier was admitted to the neurology clinic. He previously underwent cystectomy with urinary diversion and was subsequently followed by the oncology department, where he received his first dose of pembrolizumab. Three weeks after treatment, the patient developed progressive periorbital pain, bilateral ptosis, and ophthalmoplegia. Shortly thereafter, he developed dropped head, dysphagia, and dyspnea. No fluctuation of symptoms was observed. Written informed consent was obtained from the patient.

Neurological examination revealed orbicularis oculi weakness, bilateral proptosis, complete ophthalmoplegia, hypophonic speech, moderate bulbar muscle weakness, and mild bilateral proximal weakness of both upper and lower limbs. The ice pack test showed no reversibility of ptosis.

Vital signs on admission were normal. Initial laboratory studies revealed a markedly elevated CK level of 7432 U/L (reference: 41-171 U/L) and troponin T level of 571 ng/L (reference: <14 ng/L). Aspartate aminotransferase and alanine aminotransferase levels were both approximately 200 U/L (reference: <45 U/L). Blood urea nitrogen level was 94 mg/dL (reference: 10-50 mg/dL), and creatinine level was 2.0 mg/dL (reference: 0.7-1.3 mg/dL; estimated glomerular filtration rate: 30.2 mL/min/1.73 m^2).

Preliminary diagnoses included bulbar-onset myasthenia gravis and myositis. Oral pyridostigmine was administered due to suspicion of myasthenia gravis; however, there was no clinical response. Antibody testing for acetylcholine receptor antibodies and myositis-specific autoantibodies was negative. Nerve conduction studies (median, ulnar, and sural sensory nerves; median, ulnar, tibial, and fibular motor nerves) and F-wave responses (median and posterior tibial nerves) were within normal limits.

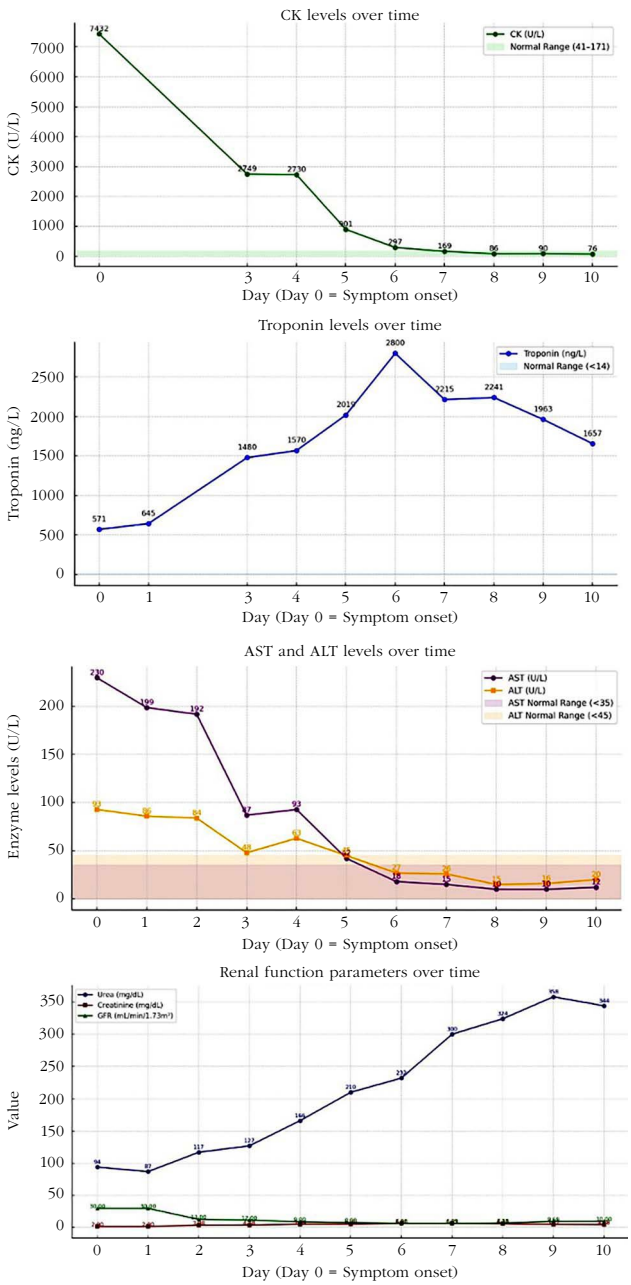

Figure 1. Laboratory findings over the 10-Day treatment period.

CK: Creatine kinase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

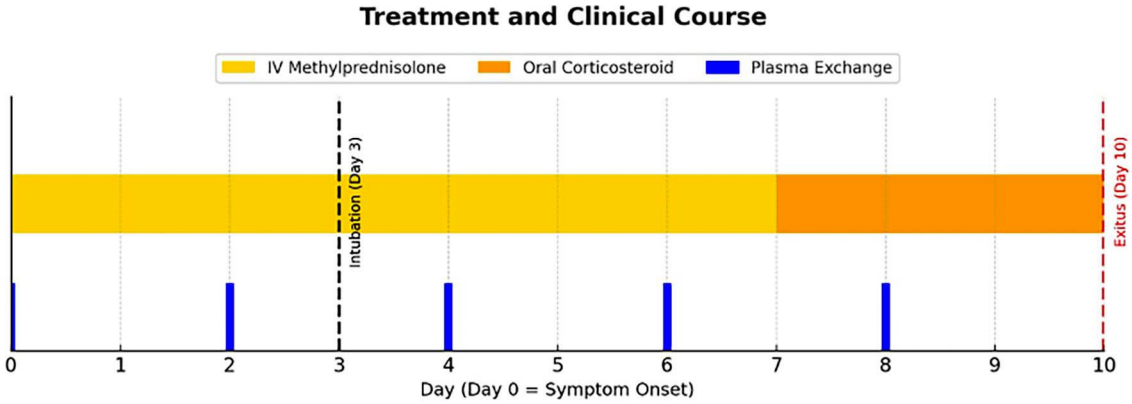

Figure 2. The treatment timeline and clinical course of the disease.

No decremental response was observed with low-frequency stimulation (2-3 and 5 Hz) during repetitive nerve stimulation, and postexercise facilitation was absent. Needle EMG demonstrated short-duration, polyphasic myopathic motor unit potentials in proximal muscles of the upper and lower limbs (deltoid, biceps, and iliopsoas), as well as in the trapezius and masseter muscles.

Due to the severity of symptoms, immediate treatment was required, and a muscle biopsy could not be performed. Based on clinical and laboratory findings, the patient was diagnosed with pembrolizumab-associated myositis. As his condition deteriorated, the patient was admitted to the neurology intensive care unit for further management.

Evaluation for myocarditis was also conducted. The patient denied chest pain. Serial electrocardiograms revealed no ischemic changes, and transthoracic echocardiography was within normal limits. Troponin T levels, however, continued to rise, peaking above 2000 ng/L; no associated arrhythmias, ischemic ECG changes, or echocardiographic abnormalities were observed.

Treatment consisted of intravenous methylprednisolone (1 g/day) and plasmapheresis administered every other day. Following therapy, significant biochemical improvement was observed: CK levels rapidly normalized, and aspartate aminotransferase and alanine aminotransferase levels returned to normal. Renal function partially recovered, with serum creatinine level decreasing to 2.0 mg/dL and the estimated glomerular filtration rate rising above 30 mL/min/1.73 m^2. However, troponin levels did not significantly decline. The laboratory results over 10 days are shown in Figure 1, while the treatment and clinical course are summarized in Figure 2.

Despite biochemical improvement, no meaningful neurological recovery was achieved. On the third day of treatment, the patient developed hypercapnic respiratory failure and required intubation for mechanical ventilation. He died on the 10th day following the development of refractory hypotension and subsequent cardiac arrest.

DISCUSSION

Immune checkpoint inhibitor-associated myositis is a rare but significant irAE, occurring in fewer than 1% of cases; however, it is associated with a mortality rate of up to 22%.[7,9] Clinically, it differs from classical idiopathic inflammatory myopathies. Notably, edema may be observed in the levator palpebrae superioris, extraocular muscles, posterior cervical muscles, and proximal muscle groups. This unique pattern of involvement can mimic a “myastheniform” syndrome, particularly in the early stages of the disease.[9,10] Ptosis, diplopia, and dropped head are frequently observed symptoms. However, unlike myasthenia gravis, the symptoms are typically nonfluctuating, and both acetylcholine receptor and muscle-specific tyrosine kinase antibodies are generally negative.[7,9,10]

Approximately 40% of ICPI-associated myositis cases present with myasthenia gravis-like or overlapping features.[11] The standard diagnostic workup includes elevated CK levels, magnetic resonance imaging demonstrating muscle edema, and muscle biopsy findings showing necrosis, regeneration, and CD8+ predominant lymphocytic

infiltration. Myositis-related antibodies (anti-signal recognition particle, anti-Ro, and anti-synthetase antibodies) may be positive in some cases; however, most patients are seronegative.[9]

Our patient initially presented with ptosis and extraocular muscle weakness, which progressed to dysphagia, dropped head, and symmetric proximal muscle weakness, mimicking myasthenia gravis, but ultimately ruled out by clinical tests. Elevated CK levels, myopathic EMG findings, and negative antibody results supported the diagnosis of ICPI-associated myositis. Notably, the involvement of extraocular muscles can resemble cranial nerve palsies, particularly abducens nerve palsy, as previously described in idiopathic orbital myositis.[12] This underscores the importance of careful differential diagnosis and neuroimaging to distinguish between inflammatory and neurogenic causes of ophthalmoplegia.

Cardiac involvement is a critical concern in ICPI-associated myositis, particularly with PD-1 inhibitors, where myocarditis may occur. This can present silently with elevated troponin levels or progress to fulminant cardiogenic shock and sudden death. The reported incidence of myocarditis ranges from 0.04 to 1.14%, with a mortality rate between 25% and 50%.[13] In our patient, the initial cardiac evaluation was unremarkable; however, the subsequent development of refractory hypotension and cardiac arrest in the intensive care unit suggested a missed silent myocarditis.

High-dose intravenous methylprednisolone and plasmapheresis are considered first-line treatments. In refractory cases, agents such as intravenous immunoglobulin (IVIG), rituximab, mycophenolate mofetil, and eculizumab have been used.[8,14] In our case, despite biochemical improvement following immunosuppressive therapy, the patient died from refractory hypotension and cardiac arrest. This outcome highlights that laboratory improvement alone may be insufficient, and more aggressive, individualized treatment strategies are warranted, particularly in cases with respiratory and cardiac involvement.

In conclusion, in patients who develop myositis following immune checkpoint inhibitor therapy, clinicians should keep in mind that these individuals are often end-stage cancer patients with multiple comorbidities. Even if laboratory parameters improve and no clinical deterioration is observed, complications might occur any time. Therefore, prompt recognition, rapid initiation of appropriate immunosuppressive treatment, and close clinical monitoring are essential for optimal management.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Followed the patient, collected the clinical data, wrote the manuscript draft, corresponded with the journal, and made the revisions: N.T.U., E.K.; Performed the EMG study and contributed to drafting the electrophysiology section: E.A.; Collected clinical data and prepared tables and figures: M.Y.; Contributed to the study conception, suggested references, and critically revised the final version of the manuscript: E.K. All authors read and approved the final manuscript.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64. doi: 10.1038/nrc3239.
2. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018;359:1350-5. doi: 10.1126/science.aar4060.
3. Kwok G, Yau TC, Chiu JW, Tse E, Kwong YL. Pembrolizumab (Keytruda). Hum Vaccin Immunother 2016;12:2777-89. doi: 10.1080/21645515.2016.1199310.
4. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015-26. doi: 10.1056/NEJMoa1613683.
5. Cuzzubbo S, Javeri F, Tissier M, Roumi A, Barlog C, Doridam J, et al. Neurological adverse events associated with immune checkpoint inhibitors: Review of the literature. Eur J Cancer 2017;73:1-8. doi: 10.1016/j.ejca.2016.12.001.
6. Roth P, Winklhofer S, Müller AMS, Dummer R, Mair MJ, Gramatzki D, et al. Neurological complications of cancer immunotherapy. Cancer Treat Rev 2021;97:102189. doi: 10.1016/j.ctrv.2021.102189.
7. Moreira A, Loquai C, Pföhler C, Kähler KC, Knauss S, Heppt MV, et al. Myositis and neuromuscular side-effects induced by immune checkpoint inhibitors. Eur J Cancer 2019;106:12-23. doi: 10.1016/j.ejca.2018.09.033.
8. Darnell EP, Mooradian MJ, Baruch EN, Yilmaz M, Reynolds KL. Immune-related Adverse Events (irAEs): Diagnosis, management, and clinical pearls. Curr Oncol Rep 2020;22:39. doi: 10.1007/s11912-020-0897-9.

9. Hamada N, Maeda A, Takase-Minegishi K, Kirino Y, Sugiyama Y, Namkoong H, et al. Incidence and distinct features of immune checkpoint inhibitor-related myositis from idiopathic inflammatory myositis: A single-center experience with systematic literature review and meta-analysis. Front Immunol 2021;12:803410. doi: 10.3389/fimmu.2021.803410.
10. Suzuki S, Ishikawa N, Konoeda F, Seki N, Fukushima S, Takahashi K, et al. Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan. Neurology 2017;89:1127-34. doi: 10.1212/WNL.0000000000004359.
11. Rajeev TP. Editorial comment to case of atypical femoral fractures that mimicked the typical imaging findings of prostate cancer-induced bone metastasis. IJU Case Rep 2019;2:306-7. doi: 10.1002/iju5.12116.
12. Balçık HH, Uzunkulaoğlu A, Dalkılıç T, Karadaş Ö. Idiopathic orbital myositis with pseudosixth nerve palsy: the importance of neuroimaging. Turk J Neurol 2023;29:38-40. doi: 10.4274/tnd.2022.40227.
13. Palaskas N, Lopez-Mattei J, Durand JB, Iliescu C, Deswal A. Immune checkpoint inhibitor myocarditis: Pathophysiological characteristics, diagnosis, and treatment. J Am Heart Assoc 2020;9:e013757. doi: 10.1161/JAHA.119.013757.
14. Rigamonti A, Mantero V, Milani R, Salmaggi A. Eculizumab as rescue therapy for relapse of myasthenia gravis after immune-checkpoint inhibitors: A case report. Neurol Sci 2025;46:2893-6. doi: 10.1007/s10072-024-07972-0.