

CASE REPORT

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Cite as:

Chirito Carbajal M, Viñas Mendieta A, García Cárdenas M, Valencia Mesías G, Ruiz Mendoza R, Rioja Viera P, *et al.* Immune-Mediated Overlap Syndrome After Adjuvant Pembrolizumab in Melanoma: A Case Report of Severe Multisystem Immune-Related Adverse Events. *Onkoresearch*. 2025;3(4). doi: 10.69482/onkoresearch.v3i4.99

Received:

05/11/2025

Approved:

15/12/2025

Author's contributions:

MCH: conceptualization and writing - original draft. AV, ER, MG: clinical evaluation and cardiologic interpretation, writing - review & editing. HF, GV, RR, PR, MH, OP, ZM, BM, MC, CC: patient clinical management and manuscript review. SN: writing - review & editing. TV: supervision, conceptualization, and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

Financing:

None.

Conflicts of interest:

The authors declare that they have no conflicts of interest related to this work.

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Immune-Mediated Overlap Syndrome After Adjuvant Pembrolizumab in Melanoma: A Case Report of Severe Multisystem Immune-Related Adverse Events

Síndrome de superposición inmunomediado posterior a pembrolizumab adyuvante en melanoma: reporte de caso de eventos adversos inmunorrelacionados graves multisistémicos

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ABSTRACT

Immunotherapy with immune checkpoint inhibitors (ICIs) has significantly improved survival in advanced and high-risk resected melanoma; however, it can induce multisystem immune-related adverse events (irAEs). ICI-induced myocarditis is rare, occurring in approximately 1% of cases, but it is potentially fatal, especially when it coexists with myositis and myasthenia gravis within the immune-mediated overlap syndrome. We report the case of a 50-year-old woman with stage IIIC dorsal epithelioid melanoma who underwent surgery and received adjuvant pembrolizumab, presenting with eyelid ptosis, acute dyspnea, and tachyarrhythmia after the second cycle. Clinical, biochemical, and imaging evaluation confirmed an immune-mediated overlap syndrome with myocarditis, myositis, pneumonitis, and thyroiditis. The patient developed severe complications that required invasive mechanical ventilation and prolonged hospitalization in the intensive care unit (ICU) for five months, with progression to proximal and distal quadriplegia secondary to myositis. Treatment with high-dose methylprednisolone, followed by mycophenolate and plasmapheresis, achieved clinical stabilization with normalization of cardiac biomarkers. This case highlights the importance of multidisciplinary management, early recognition, and immunosuppressive treatment to improve the prognosis in severe irAEs associated with ICIs.

Keywords

Melanoma; Immune Checkpoint Inhibitors; Myocarditis; Myositis; Immune-Related Adverse Events (source: MeSH-NLM).

RESUMEN

La inmunoterapia con inhibidores de puntos de control inmunitario (ICIs) ha mejorado significativamente la supervivencia en melanoma avanzado y reseccionado de alto riesgo; sin embargo, puede inducir eventos adversos inmunomediados (irAEs) multisistémicos. La miocarditis inducida por ICIs es poco frecuente, aproximadamente 1%, pero potencialmente mortal, especialmente cuando coexiste con miositis y miastenia gravis dentro del síndrome de superposición inmunomediado. Reportamos el caso de una mujer de 50 años con melanoma epitelioide dorsal estadio IIIC operada que recibió pembrolizumab adyuvante presentando después del segundo

ciclo ptosis palpebral, disnea aguda y taquiarritmia. La evaluación clínica, bioquímica y por imágenes confirmó un síndrome de superposición inmunomediado con miocarditis, miositis, neumonitis y tiroiditis. La paciente presentó complicaciones graves que requirieron ventilación mecánica invasiva y hospitalización prolongada en la unidad de cuidados intensivos (UCI) durante cinco meses, con progresión a cuádruplejía proximal y distal secundaria a miositis. El tratamiento con metilprednisolona a altas dosis, seguido de micofenolato y plasmaféresis logró estabilización clínica con normalización de biomarcadores cardíacos. Este caso resalta la importancia del manejo multidisciplinario, reconocimiento temprano y tratamiento inmunosupresor para mejorar el pronóstico en irAEs graves asociados a ICIs.

Palabras clave

Melanoma; Inhibidores de puntos de control inmunitario; Miocarditis; Miositis; Eventos adversos inmunorrelacionados (fuente: DeCS-BIREME).

INTRODUCTION

The use of immune checkpoint inhibitors (ICIs) has transformed the treatment of various neoplasms, particularly early-stage and advanced cutaneous melanoma, by restoring cytotoxic activation of T lymphocytes through blockade of PD-1, PD-L1, and CTLA-4 pathways. Agents such as pembrolizumab have demonstrated significant and sustained benefits in recurrence- and metastasis-free survival, establishing them as a standard of care in both early and advanced disease⁽¹⁻⁵⁾. However, immune-related adverse events (irAEs) may affect various organs, including ICI-associated myocarditis, with an incidence of approximately 1% and high mortality in severe cases⁽⁶⁾. It typically occurs early during treatment and often coexists with autoimmune manifestations such as myositis, myasthenia gravis, pneumonitis, or thyroid disorders, a condition known as immune-mediated overlap syndrome. Clinical series have described the coexistence of myocarditis with neuromuscular toxicities, particularly the myocarditis-myositis-myasthenia gravis (MMM) overlap syndrome, reported in up to 30-40% of cases⁽⁷⁾.

Diagnosis requires a high index of suspicion supported by cardiac biomarkers, electrocardiographic findings, and multimodal imaging⁽⁸⁾. Although cardiac magnetic resonance imaging is the main noninvasive diagnostic tool, its sensitivity may be limited; therefore, endomyocardial biopsy remains the gold standard when feasible. Management relies on early initiation of high-dose corticosteroids with prompt escalation to additional immunosuppressive therapies in refractory or severe cases⁽⁹⁾.

The pathophysiology is thought to involve shared autoreactive T-cell clones targeting both skeletal muscle and myocardial tissue, which may explain the frequent coexistence of these conditions and their association with worse outcomes^(6,10-12).

CLINICAL CASE

A 50-year-old woman with morbid obesity (BMI 40.3 kg/m²) and no known cardiovascular history was diagnosed with stage IIIC (pT3b pN1a) surgically resected invasive dorsal epithelioid melanoma. She received adjuvant treatment with pembrolizumab 200 mg intravenously every 3 weeks, having received two cycles at the time of the event. One day after the second cycle, she presented with left eyelid ptosis and went to the emergency room. During hospitalization, she developed progressive dyspnea, tachycardia, and acute oxygen desaturation; computed tomography pulmonary angiography ruled out pulmonary thromboembolism, see Figure 1. Due to respiratory deterioration, she was transferred to the intensive care unit (ICU), requiring endotracheal intubation and invasive mechanical ventilation for severe immune-mediated pneumonitis associated with rapid neurological deterioration that progressed to proximal quadriplegia.



Figure 1. Chest computed tomography angiography showing laminar pleural effusion in the left hemithorax with associated passive atelectasis and posterior basal consolidations. Findings were interpreted in the clinical context as compatible with immune-mediated pneumonitis.



Figure 2. Electrocardiogram demonstrated sinus rhythm (100 bpm) with a new right bundle branch block and ST-segment elevation in the inferior leads (II, III, aVF) with reciprocal ST depression in leads I and aVL, mimicking an acute inferior myocardial infarction.

The electrocardiogram demonstrated sinus rhythm (100 bpm) with a new right bundle branch block and ST-segment elevation in the inferior leads (II, III, and aVF), accompanied by reciprocal ST-segment depression in leads I and aVL, mimicking an acute inferior myocardial infarction, see Figure 2. The patient subsequently developed sustained ventricular tachycardia, requiring electrical cardioversion and continuous amiodarone infusion. Echocardiography was performed during

hospitalization; however, formal imaging records were not available for review, and no major structural abnormalities were reported. Cardiac computed tomography coronary angiography, see Figure 3 revealed no obstructive coronary artery disease; however, delayed transmural iodine enhancement in the inferolateral basal and mid-ventricular segments supported the diagnosis of acute immune-mediated myocarditis.

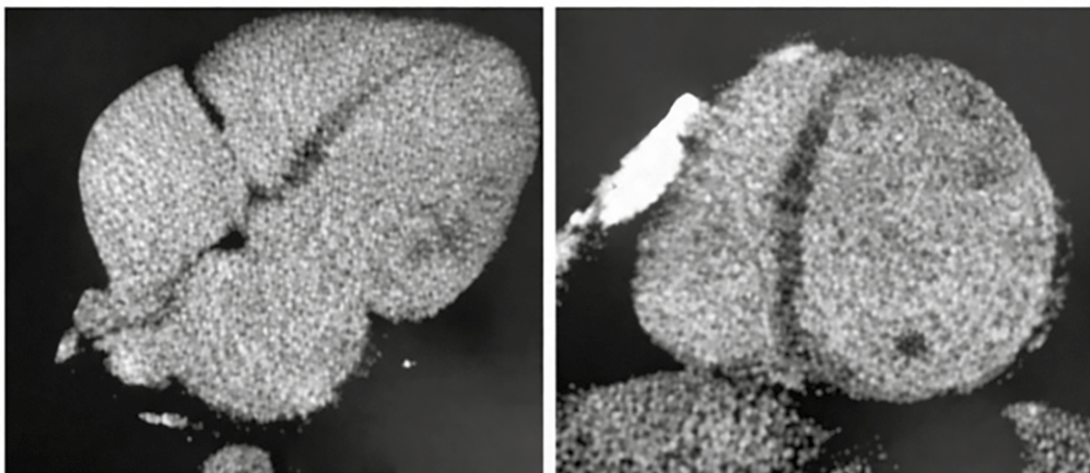
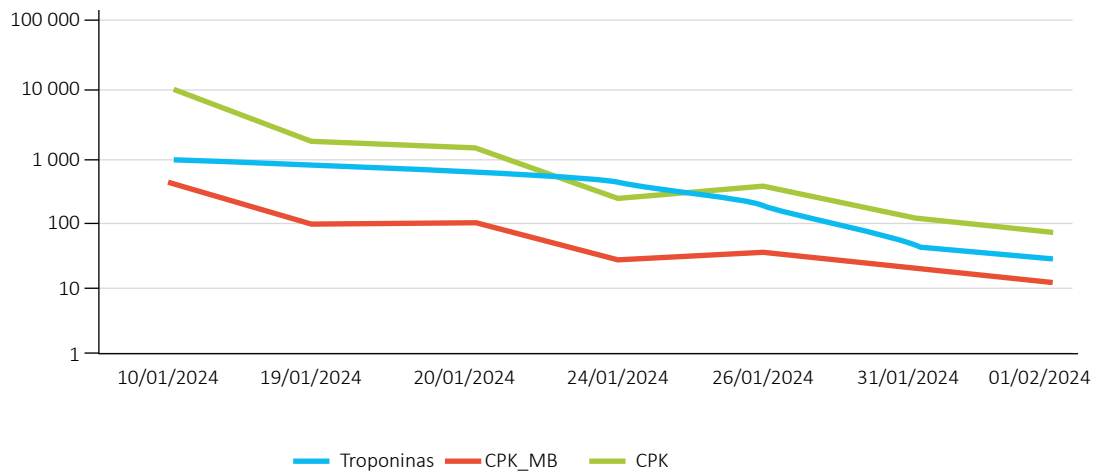


Figure 3. Cardiac computed tomography angiography showing delayed transmural iodine enhancement in the inferolateral basal and mid-ventricular segments, supporting the diagnosis of acute immune-mediated myocarditis after exclusion of obstructive coronary artery disease.



| | 10/01/2024 | 19/01/2024 | 20/01/2024 | 24/01/2024 | 26/01/2024 | 31/01/2024 | 01/02/2024 |
|------------|------------|------------|------------|------------|------------|------------|------------|
| Troponinas | 1010 | 893 | 763 | 465 | 222 | 53 | 44 |
| CPK_MB | 453 | 107.6 | 122.1 | 26.3 | 32.7 | 24.8 | 17.6 |
| CPK | 10700 | 1591 | 1420 | 269 | 366 | 143 | 98 |

Figure 4. Evolution of cardiac biomarkers (troponin T, CPK-MB, and total CPK) showing progressive decline after initiation of immunosuppressive therapy. Values are displayed on a logarithmic scale.

Initial biomarkers showed significant elevation: troponin T peaked at 1010 ng/L (normal value <34), CPK-MB 453 U/L (normal value 0-6), and total CPK 10,700 U/L (normal value 30-135), see Figure 4. The thyroid profile revealed probable immune-mediated hypothyroidism (TSH 28.77 μ IU/mL, free T4 0.52 ng/dL, T3 0.28 ng/mL), and levothyroxine was initiated. Pembrolizumab was discontinued upon suspicion of immune-related toxicity. High-dose methylprednisolone (1 g/day for three days) was administered, followed by mycophenolate 1 g/day. Management followed a stepwise immunosuppressive approach, with corticosteroids as first-line therapy and subsequent escalation due to disease severity. Plasmapheresis was later added given the significant neuromuscular involvement and suspected overlap syndrome. After five days of immunosuppressive therapy, troponin T decreased from 893 to 465 ng/L, with subsequent normalization, accompanied by resolution of electrocardiographic abnormalities and absence of new arrhythmias. Due to proximal muscle strength 0/5 and distal strength 1/5 in all four limbs, electromyography was consistent with inflammatory myopathy and myositis, establishing an immune-mediated overlap syndrome; pyridostigmine and plasmapheresis were added, achieving progressive improvement in strength and gradual normalization of muscle biomarkers.

After an approximately five-month stay in the ICU, she was discharged. At 12-month follow-up, PET-CT showed no recurrence of melanoma. She currently continues levothyroxine for controlled hypothyroidism, with no cardiac or pulmonary sequelae and ongoing recovery from critical illness-associated neuropathy.

Ethical considerations

This case report was prepared in accordance with the ethical principles established in the Declaration of Helsinki and its updates. Written informed consent was obtained from the patient for the publication of the clinical case and corresponding images, guaranteeing the confidentiality and anonymization of clinical information. During the preparation of the manuscript, the principles of autonomy, beneficence, non-maleficence, and justice were respected.

Limitations

This report presents the limitations inherent in a descriptive single-case study, which restricts the possibility of generalizing the findings. No endomyocardial biopsy was performed for histological confirmation of myocarditis, nor was cardiac magnetic resonance imaging available during the acute phase, which could have provided

further tissue characterization. However, the diagnosis was based on clinical criteria, biomarkers, electrocardiographic findings, and exclusion of obstructive coronary artery disease, in accordance with current recommendations in cardio-oncology. Additionally, formal echocardiographic imaging data were not available for review.

DISCUSSION

Immune checkpoint inhibitors (ICIs), particularly anti-PD-1 agents such as Pembrolizumab, have significantly improved outcomes in high-risk resected melanoma; however, they may induce severe multisystem immune-related adverse events (irAEs)¹⁰⁻¹¹. This case illustrates an early and fulminant presentation of immune-mediated overlap syndrome, with simultaneous cardiac, neuromuscular, pulmonary, and endocrine involvement requiring prolonged intensive care support. In comparison to international series of ICI-associated myocarditis, which report an incidence of approximately 1% but high mortality, the degree of multiorgan involvement and prolonged ICU stay in this patient suggest a particularly aggressive immune-mediated phenotype⁶.

Globally, up to 30–40% of patients with ICI-associated myocarditis present with concomitant myositis and/or myasthenia gravis; however, the additional coexistence of severe pneumonitis and endocrine dysfunction, as observed in this case, is less frequently reported and has been associated with worse outcomes^{6,10-12}. In Latin American reports, evidence remains limited and is largely based on small series or isolated case reports, making it difficult to define the true incidence and clinical spectrum in this population. Nevertheless, available data suggest similarly severe presentations, often compounded by diagnostic delays or limited access to advanced modalities such as cardiac magnetic resonance imaging or endomyocardial biopsy^{11,18}.

In this context, the current case offers pertinent evidence that a comprehensive clinical diagnosis and efficient management can be attained even in resource-limited environments. The diagnosis of immune-mediated myocarditis was corroborated by significant biomarker elevation, electrocardiographic abnormalities, and the exclusion of obstructive coronary artery disease. The significant increase in troponin (>1000 ng/L) observed in this patient has been associated with severe presentations and worse prognosis¹⁶, consistent with the initially critical clinical course. Furthermore, according to the 2022 ESC cardio-oncology guidelines, this case fulfills criteria for probable ICI-associated myocarditis¹⁴, despite the absence of histological confirmation.

An important clinical feature was the initial presentation with ptosis, which preceded systemic deterioration. This finding, often underrecognized, has been described in international series as an early indicator of neuromuscular involvement and possible overlap syndrome, suggesting that neuromuscular symptoms may precede life-threatening cardiac manifestations¹³. The rapid progression to respiratory failure, malignant arrhythmias, and quadriplegia in this case underscores the fulminant nature of this condition and highlights the need for close monitoring during the early cycles of immunotherapy.

From a therapeutic perspective, current international guidelines recommend immediate discontinuation of ICIs and early initiation of high-dose corticosteroids, with rapid escalation in refractory cases^{14,15}. However, in real-world practice, particularly in Latin America the availability of rescue therapies such as abatacept or targeted immunomodulators may be limited¹⁷. In this patient, a stepwise immunosuppressive strategy including corticosteroids, mycophenolate, and plasmapheresis resulted in clinical stabilization and recovery, underscoring that accessible treatment strategies can still be effective when implemented promptly.

Finally, this case further contributes to the accumulating evidence on ICI-related cardiotoxicity and multisystem irAEs described in recent global analyses¹⁹. It underscores a persistent gap between guideline-based recommendations and real-world practice in regions such as Latin America. Despite diagnostic limitations, the favorable outcome observed highlights the importance of early recognition, clinical judgment, and coordinated multidisciplinary care in improving outcomes in these complex and potentially life-threatening toxicities.

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