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Fatal Case of Immune-Related Myocarditis and Myositis Due to Treatment with Immune Checkpoint and Tyrosine Kinase Inhibitors

Caso Fatal de Miocardite e Miosite Imunomediadas Associadas ao Tratamento com Inibidores de Checkpoint Imunitário e de Tirosina-Quinase

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ABSTRACT

Immune checkpoint inhibitor and tyrosine kinase inhibitor combinations have become the new standard of care in the first-line treatment of metastatic clear cell renal cell carcinoma. However, there is a growing concern regarding severe immune-related adverse events. A 78-year-old man with metastatic clear cell renal cell carcinoma, treated with pembrolizumab and axitinib, was admitted to the emergency department 30 days after initiating treatment due to rapidly progressive myositis. Myocarditis with severe ventricular dysfunction was identified. Muscular biopsy findings were compatible with inflammatory myopathy associated with immune checkpoint inhibitors. Initial treatment with high-dose corticosteroids showed an insufficient response. Therapeutic escalation on the third day with methylprednisolone, immunoglobulin, and abatacept resulted in clinical improvement. On the eleventh day, a sudden malignant arrhythmia occurred, followed by cardiac arrest. This represents one of the first case reports describing myocarditis and myositis during treatment with pembrolizumab-axitinib. While immune checkpoint inhibitor may play a major role, it is also possible that the tyrosine kinase inhibitor, while attempting to promote immune modulation, also increases severe toxicities.

Keywords: Carcinoma, Renal Cell/drug therapy; Immune Checkpoint Inhibitors/adverse effects; Myocarditis/chemically induced; Myositis/chemically induced; Tyrosine Kinase Inhibitors/adverse effects

RESUMO

Os inibidores de *checkpoint* imunitário e os inibidores de tirosina-quinase constituem o novo *standard of care* no tratamento de primeira linha do carcinoma renal de células claras metastático. Existe uma preocupação crescente com os eventos adversos imunomediados graves. Um homem de 78 anos com carcinoma renal de células claras metastático tratado com pembrolizumab e axitinib foi admitido no serviço de urgência, 30 dias após o início do tratamento, com miosite rapidamente progressiva. Foi identificada miocardite com disfunção ventricular grave. A biópsia muscular foi compatível com miopatia inflamatória associada aos inibidores de *checkpoint* imunitário. A abordagem inicial com corticosteroides em alta dose obteve resposta insuficiente. A escalada terapêutica ao terceiro dia com metilprednisolona, imunoglobulina e abatacept associou-se a melhoria clínica. No décimo primeiro dia documentou-se arritmia maligna seguida de paragem cardiorrespiratória. Este é um dos primeiros casos a descrever miocardite e miosite durante o tratamento com pembrolizumab-axitinib. O inibidor de *checkpoint* imunitário parece ter o papel mais preponderante, mas é possível que o inibidor de tirosina-quinase, ao tentar promover a modulação imunitária, também possa potenciar as toxicidades graves.

Palavras-chave: Carcinoma de Células Renais/tratamento farmacológico; Inibidores de Checkpoint Imunológico/efeitos adversos; Inibidores de Tirosina-Quinase/efeitos adversos; Miocardite/induzida quimicamente; Miosite/induzida quimicamente

INTRODUCTION

Immune checkpoint inhibitor (ICI) and second-generation tyrosine kinase inhibitor (TKI) combinations have proven to be effective with an acceptable safety profile as first-line treatment of metastatic clear cell renal cell carcinoma (mccRCC), thereby changing the standard of care.[1-4] However, there's a significant concern regarding the neuromuscular triad of immune-related adverse events (irAE) that includes myocarditis, myositis, and myasthenic syndrome, due to a significantly increased risk of death (up to 50% mortality rate).[5] Tyrosine kinase inhibitor cardiovascular toxicity, such as hypertension, thrombotic events, QT interval prolongation, cardiac dysfunction with reduced ejection fraction, and congestive heart failure, has rarely been reported.[6]

Real-world data showed a toxicity profile equivalent to clinical trials and lower rate of grade 3 - 5 adverse events (AE) (52% *vs* 71% - 82.4% reported in the phase III trials of first-line treatment with ICI/TKI).[7] Nevertheless, the potential synergistic toxicity of the ICI/TKI combination remains a concern among physicians.[8] Some data suggest a higher incidence of interstitial pneumonitis, hepatotoxicity, and colitis with the concurrent or sequential treatment with ICI and different TKI classes.[9-11] A retrospective cohort study of 252 patients with lung cancer found that patients pre-treated or receiving combined ICI and vascular endothelial growth factor inhibitors had an increased risk of major cardiovascular events (MACE) (HR: 2.15; 95% CI: 1.05 to 4.37; $p = 0.04$).[12]

Here, we present an uncommon, challenging, and fatal case of acute myocarditis and myositis during treatment with ICI and TKI.

CASE DESCRIPTION

A 78-year-old man, with an ECOG performance status

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of 0, had a pacemaker implanted previously due to sick sinus syndrome. He underwent regular follow-up in the cardiology outpatient clinic, with no previous observation of cardiac dysfunction in echocardiograms.

The patient was diagnosed with stage IV clear cell renal cell carcinoma, with metastasis to the pulmonary, cervical, mediastinal, retrocrural, and lumbar aortic lymph nodes. The primary lesion measured 120 mm on the long axis, causing compression of the inferior vena cava. Following discussion within a multidisciplinary team, the patient underwent cytoreductive nephrectomy without complications. Subsequently, he received systemic treatment with pembrolizumab (IV 400 mg every six weeks regimen, according to patient preference) and axitinib (PO 5 mg twice daily).

The patient was admitted to the emergency department 30 days after starting treatment with rapidly progressive generalized myopathy, cervical and limb weakness (grade 3/5 tetraparesis). Ten days before admission, symptoms of ptosis (without fatigability), ataxia, dysarthria, dysphonia, and mixed dysphagia were noted. Blood analysis revealed severe rhabdomyolysis (creatine kinase: 4226 U/L, normal range 24 - 204 U/L; myoglobin: 4226 U/L, normal range 28 - 72 ng/mL) and myocarditis (high-sensitivity troponin T: 2.71 ng/mL, normal < 0.014 ng/mL). The echocardiogram showed global and severe left ventricular dysfunction (non-measurable). Electromyography showed muscle fibrillation and positive waves as spontaneous activity, reduced amplitude, and early recruitment during voluntary activity, compatible with inflammatory myopathy (no decrement in repetitive nerve stimulation). Further studies excluded other toxic exposures or metabolic disorders, cerebrovascular disease or brain metastasis, paraneoplastic syndrome, or acute coronary syndrome. Muscle biopsy revealed necrotizing inflammatory myopathy, compatible with the clinical diagnosis of inflammatory myopathy associated with ICI (Fig. 1).

A multidisciplinary approach involving medical oncology, clinical immunology, neurology, and cardiology resulted in the decision to initiate upfront treatment with high-dose corticosteroids (IV 1 mg/kg/d of prednisolone equivalent).

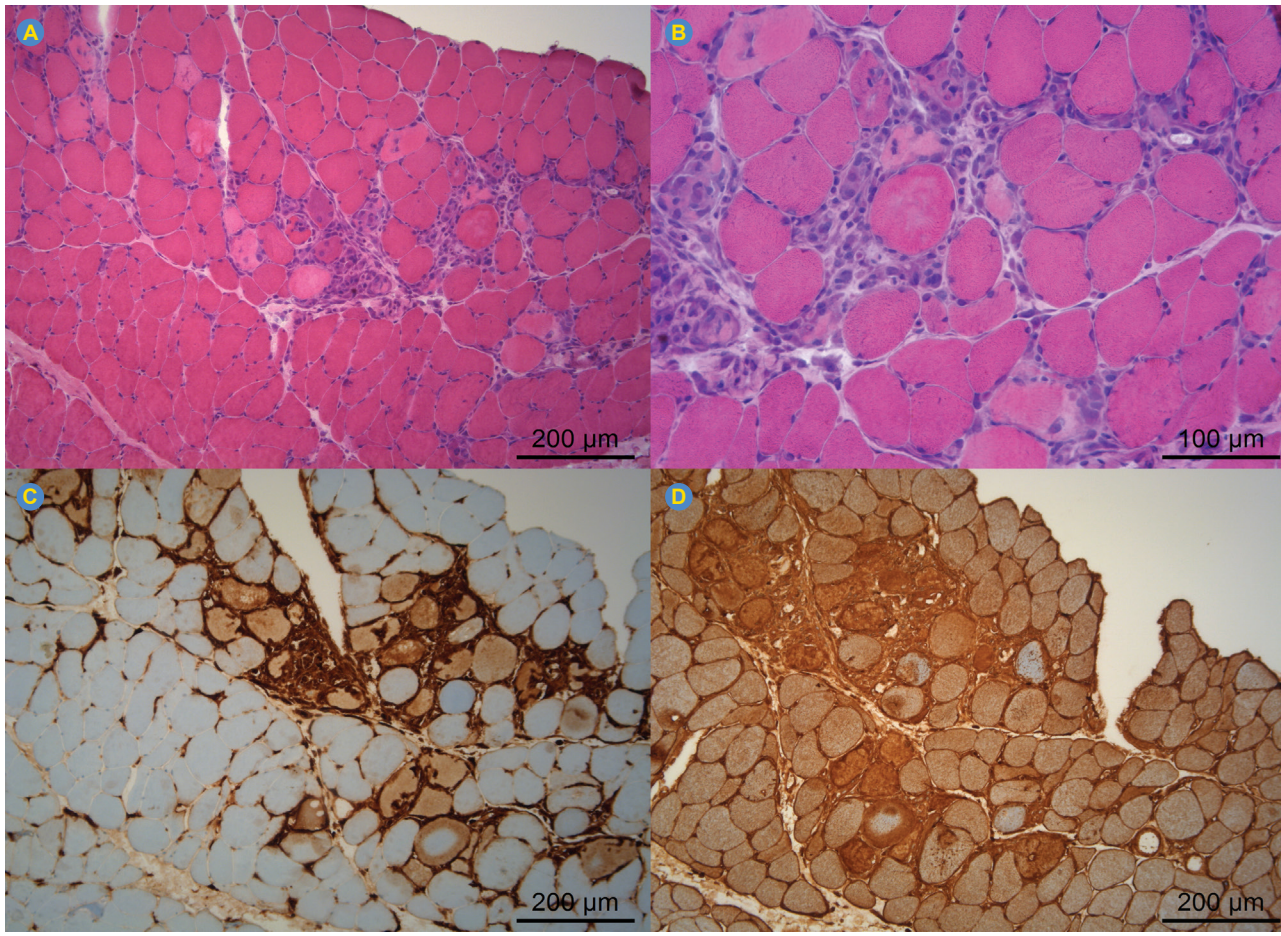

Figure 1 – Muscle biopsy showing areas of necrotic muscle fibers associated with mild inflammatory infiltrates composed almost exclusively of macrophages. There was a diffuse upregulation of MCH-1. (A) and (B) H&E; (C) CD69; (D) MHC-1.

Despite an immediate decrease in CK levels, no other clinical improvement was observed by the third day of follow-up. Therapeutic escalation included a methylprednisolone pulse (IV 1 g/d for three days followed by 1 mg/kg/d of prednisolone equivalent), intravenous immunoglobulin (IV 0.8 mg/kg/d for five days), and off-label use of abatacept (IV 10 mg/kg as a single dose). Figure 2 shows chronological changes in main laboratory markers and treatment.

Subsequent follow-up revealed resolution of myalgia, gradual improvement in cervical and limb motor strength, and a decrease in serum myocardial markers, which was more evident on day three following therapeutic escalation. However, on the eleventh day of hospitalization, the patient experienced a sudden malignant arrhythmia followed by cardiac arrest, which proved unresponsive to advanced cardiovascular resuscitation maneuvers.

DISCUSSION

The presented case highlights a rare and fatal occurrence of immune-related myocarditis and myositis associated with ICI and TKI treatment. The differential diagnosis concerning the toxicity of both pharmacological classes can be particularly challenging. The investigation found systemic inflammation with significant cardiac and skeletal involvement, indicating a substantial role of ICI. Nonetheless, it is plausible that the TKI, while enhancing immune modulation and efficacy, may also exacerbate severe systemic toxicities.

Tyrosine kinase inhibitors can cause off-target cardiotoxicity due to the highly conserved nature of the ATP-binding pocket of kinases across various organs. In contrast, immune-mediated myocarditis is postulated to be an exaggerated adaptive immune response against shared epitopes in the myocardium and tumor, characterized by extensive CD4+ T cell, CD8+ T cell, and macrophage infiltration.[13,14]

Early recognition is vital, as most of these events occur early during therapy, with a median onset ranging from 30 to 65 days.[12,15] Performing a differential diagnosis while acknowledging the distinct toxicity profiles of each class is crucial, as it provides a clear window of opportunity to address certain toxicities, particularly those driven by the immune system. Treatment of life-threatening situations may

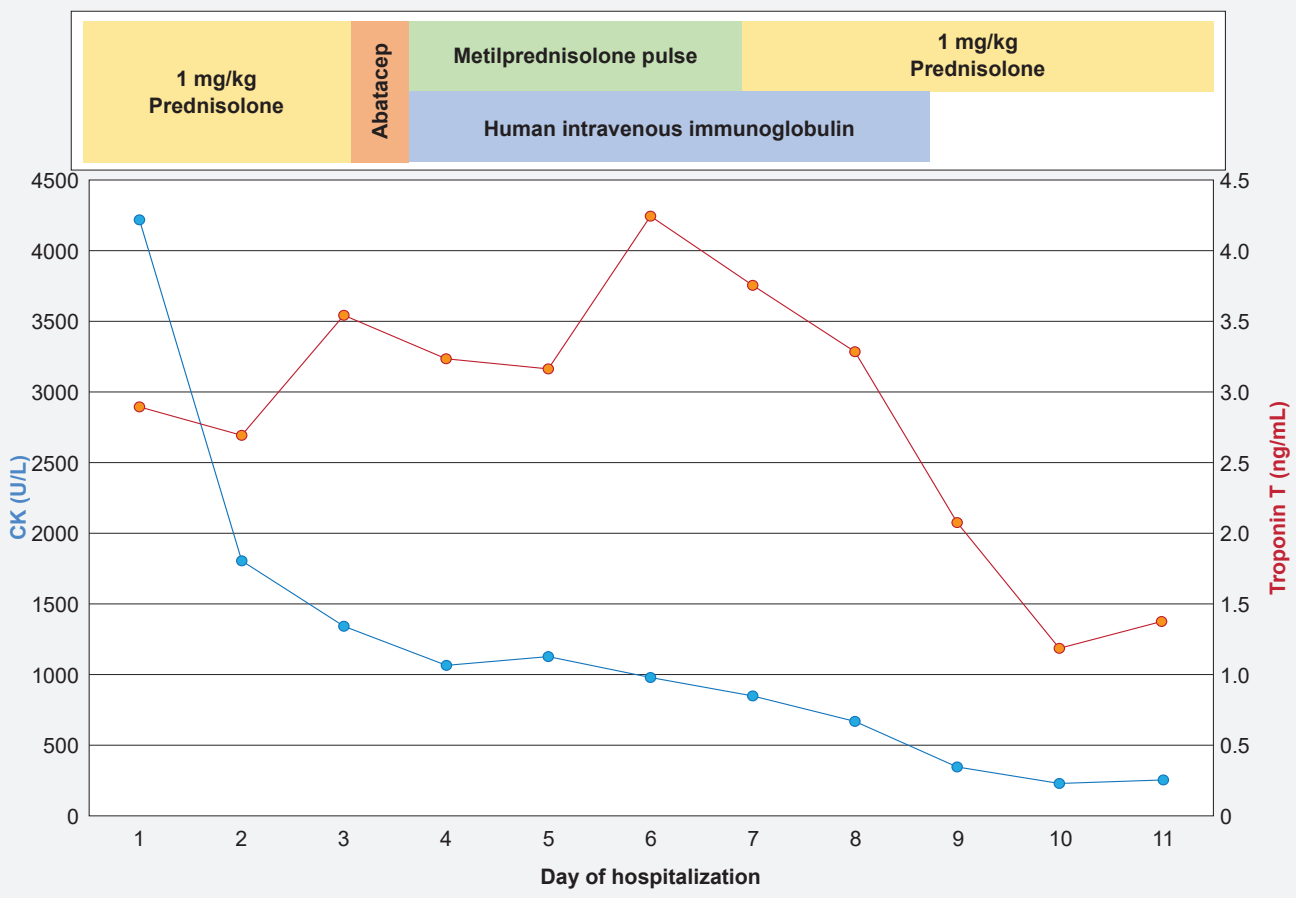

Figure 2 – Illustration of the main laboratory markers and treatment of the patient

not be fully supported by existing guidelines due to their rarity. Abatacept, a cytotoxic T-lymphocyte-associated antigen 4 agonist, is a recombinant fusion protein that can cause rapid and global T cell anergy, interfering with the PD-1/PD-L1 pathway. It has been described as an effective treatment in steroid-refractory ICI immune-related myocarditis in case reports, but it should be considered earlier if there are markers of poor prognosis due to the high associated mortality rate.[15]

Developing specialized multidisciplinary teams to address these issues is critical, not only for early identification of irAE but also for managing severe toxicities and initiating targeted therapies, often in an off-label regimen. The near future will clarify whether ICI and TKI can interact to potentiate toxicity and if this interaction could be class-specific. To the best of our knowledge, this is one of the first case reports regarding myocarditis or myositis during treatment with pembrolizumab-axitinib.

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AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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