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CASE BASED REVIEWS

Tocilizumab in immune checkpoint inhibitor-induced myositis, myocarditis and myasthenic syndrome: a rare case report and review of the literature

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ABSTRACT

Immune-related adverse events (irAEs) associated with immune checkpoint inhibitors (ICI) are becoming more frequent with the growing use of these agents in routine clinical oncology. This mechanism enhances the anti-tumor immune response, increasing the risk of activating autoreactive T cells, and leading to immune-mediated manifestations. The spectrum of these manifestations is widely variable. ICI-associated myositis is among the most severe irAEs, being a rare but serious complication with significant morbidity and mortality, particularly when accompanied by myocarditis and/or myasthenic crisis, which can all occur concurrently and worsen clinical outcomes. We report the case of a 78-years-old man with poorly controlled diabetes mellitus and metastatic colon adenocarcinoma who developed ICI-associated myositis with concomitant myocarditis and myasthenic syndrome. In the presented case, the use of tocilizumab, an anti-interleukin 6 (IL-6)-receptor monoclonal antibody, was effective in treating the myositis and myocarditis, but not the myasthenic component of this ICI-associated myositis.

Keywords: Immune checkpoint inhibitors; Immune-related adverse events; Immune-checkpoint inhibitors associated myositis; Myocarditis; Myasthenic crisis.

INTRODUCTION

Recent advances in Oncology improved overall survival, disease-free survival, and recurrence-free survival for cancer patients, while also enhancing quality of life. This progress is largely due to new drugs with innovative mechanisms of action that allow better disease control. One such class of drugs is immune checkpoint inhibitors (ICIs), available since 2011. These are mainly used for advanced cancers exhibiting programmed death-ligand 1 (PD-L1) overexpression and solid tumors with high microsatellite instability or mismatch-repair deficiency.

The most used ICIs in cancer immunotherapy include anti-CTLA-4 agents (e.g., ipilimumab) and anti-PD-1/PD-L1 agents (e.g., nivolumab, pembrolizumab, atezolizumab). These agents promote tumor growth control by the immune system, through co-stimulation of T cells. The hyperactivation of the immune system caused by ICIs can lead to immune-related adverse events (irAEs), which may manifest in various ways, including arthritis, colitis, hepatitis, hypophysitis, skin rash, myositis, and myocarditis. This case report highlights the importance of recognizing life-threatening immune-mediated manifestations as side effects of ICI therapy [1,2].

ICI-associated myositis is a rare irAE. As a matter of fact, in a large cohort study involving 9088 patients treated with ICI, only 36 patients (about 0.40%) developed ICI-associated myositis and, among them, and 19 showed overlapping syndromes: 5 patients with myocarditis; 5 patients with myasthenia gravis and 9 patients with both myocarditis and myasthenia gravis[3]. A recent 2025 nationwide French study reported 682 cases of myocarditis and 963 of myositis between over 170 000 patients treated with ICI, estimating a yearly incidence of 0,40% and 0,57% respectively[4]. Conversely, the overlap syndrome of myocarditis, myositis and myasthenia gravis remains rare, occurring in approximately 0.1-0.3% of patients[5]. According to the Common Terminology Criteria for Adverse Events (CTCAE) classification, the irAE hereby described would be considered a grade 3/4 myositis (severe muscle weakness limiting activities of daily living and with life-threatening cardiac involvement)[6]. Anquetil et al. showed that ICI-associated myositis causes significant morbidity and mortality, with a 21.2% mortality rate,

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which rises to 51.7% if myocarditis is concomitant (vs. 14.9%; p<0.0001), and a 49.4% rate of serious complications (prolonged hospitalization and life-threatening events)[7].

CASE REPORT

A 78-year-old man with colon adenocarcinoma with peritoneal metastases and high microsatellite instability, under palliative treatment with pembrolizumab, was admitted for generalized muscle weakness developing three days after taking a second dose of pembrolizumab. Prior medical history included type 2 diabetes mellitus, diagnosed more than 10 years ago treated with gliclazide, metformin, empagliflozin and sitagliptin with poor metabolic control and last glycated hemoglobin (HbA1c) of 8,5%.

Prior to this, he could walk with a cane, but following the second infusion of pembrolizumab, he became bedbound or dependent on a wheelchair for mobility. He also presented with dysphagia, binocular diplopia, blurred vision, dyspnea, and bilateral lower limb edema. Other potential causes of rhabdomyolysis like alcohol abuse, trauma or statin-use were excluded.

On physical examination, he was afebrile, normotensive (blood pressure 137/65 mmHg), with a regular heart rate (67 bpm), and no skin rash. Pulmonary auscultation revealed bibasilar crackles. Muscle strength (Medical Research Council scale) assessment showed weakness in thigh flexion (grade 2), arm abduction and flexion (grade 3), and forearm and leg flexion and extension (grade 4). There was pitting edema of the lower limbs up to the knees. Neurological examination was notable for limitation of eye abduction.

Laboratory tests (Table I) revealed raised liver enzymes — aspartate aminotransferase (AST) 451 U/L (normal 12–40), alanine aminotransferase (ALT) 183 U/L (normal 7–40); rhabdomyolysis markers—total Creatine kinase (CK) 4542 U/L (normal 46–171), myoglobin 5000 ng/mL (normal <110); cardiac injury marker—troponin I 3.042 ng/mL (normal <0.045); and inflammation marker—C-reactive protein (CRP) 14 mg/L (normal <5). Antinuclear antibodies and anti-acetylcholine receptor antibodies were negative. Anti-Signal recognition particle (Anti-SRP) and anti-synthetase antibodies were not tested.

A diagnosis of ICI-induced myositis was established after evaluation by Rheumatology and Oncology teams.

Electrocardiogram and echocardiogram were unremarkable. However, cardiac muscle involvement by myositis was considered probable after Cardiology assessment, adressing the new-onset heart failure and raised troponin levels, in the absence of acute coronary syndrome. Based on cardiology assessment, cardiac magnetic resonance imaging was considered unnecessary for diagnosis purposes.

Given the severity of the clinical picture: pembrolizumab-induced myositis with possible involvement of cardiac, swallowing and extraocular muscles; and the presence of poorly controlled diabetes - after discussion with the Oncology team, high-dose steroid therapy was initiated with 500 mg methylprednisolone pulses for 3 days, followed by prednisolone 0.5 mg/kg/day and Pembrolizumab was definitively discontinued. Due to the severity of the disease and the poorly controlled diabetes mellitus, and after negative infection screening (blood cultures, chest X-ray, urine cultures), intrave-

TABLE I. Laboratory Parameters at Admission, Discharge, and Readmission of the reported patient in this clinical case.

Parameter	(1) At admission	(2) At discharge	(3) At readmission	(4) Reference values
Hemoglobin (g/dL)	10.3	11.2	11.2	13-17
Erythrocyte Sedimentation Rate (mm/h)	22	–	–	< 30
AST (U/L)	451	113	55	12–40
ALT (U/L)	183	178	113	7–40
Total CK (U/L)	4542	707	39	46–171
Myoglobin (ng/mL)	5000	1618	104	<110
Troponin I (ng/mL)	3.042	1.154	0.052	<0.045
CRP (mg/L)	14	1.06	2.26	<5
ANA	Negative		NA	
AChR antibodies	Negative		NA	

AChR – Anti-acetylcholine receptor; ALT – Alanine aminotransferase; ANA – Antinuclear antibodies; AST – Aspartate aminotransferase; CK – Creatine kinase; NA – Not applicable.

nous tocilizumab 8 mg/kg was introduced as a biological disease modifying anti-rheumatic drug (bDMARD) and as a steroid-sparing agent.

One week after therapy initiation, clinical improvement was remarkable: proximal muscle strength increased to grade 4 in upper and lower limbs, and the patient was able to walk again with a cane, as before. Rhabdomyolysis markers improved as well (Table I): AST 113 U/L; ALT 178 U/L; CK 707 U/L; troponin I 1.154 ng/mL; myoglobin 1618 ng/mL. Despite that, limitation of extraocular movements persisted and did not parallel the improvement of limb muscle strength.

The patient was discharged 12 days after admission with prednisolone 30 mg/day, with scheduled evaluation in Rheumatology clinic after 2 weeks. He was however readmitted shortly after for nosocomial pneumonia and decompensated heart failure leading to respiratory insufficiency. The patient started on broad-spectrum antibiotics, specifically piperacillin-tazobactam. A decision was made to hold a new tocilizumab infusion at least until the infection was resolved. During hospitalization, peripheral muscle weakness did not worsen, and laboratory results (Table I) showed resolution of rhabdomyolysis and myocardial injury (CK 39 U/L; myoglobin 104 ng/mL; troponin I 0.052 ng/mL). Relevant laboratory values at admission, at discharge, and upon readmission are summarized in Table I.

Despite infection and rhabdomyolysis resolution, respiratory failure and dysphagia worsened. After Neurology assessment, it was also considered likely that the patient had a myasthenic crisis related with the ICI-associated myositis. Intravenous immunoglobulin (30 grams daily for 5 days) was administered without significant benefit. Electromyography was requested to confirm the diagnosis, but the patient did not undergo the test before dying.

At this point, after multidisciplinary discussion with Infectious Diseases and Medical Oncology, a second tocilizumab infusion was administered but did not show evident benefit on the myasthenic syndrome. During this second hospitalization, unfortunately, the patient died following a progressive degradation of the clinical status, progression of the neoplasm and a new infectious complication.

DISCUSSION

After multidisciplinary discussion, the diagnosis of an ICI-associated myositis with concurring myocarditis and myasthenic syndrome was established. It was challenging due to the incomplete confirmatory testing. The patient was observed by different clinical services (Oncology, Neurology, and Cardiology). Cardiology assessment considered heart involvement of ICI-associated myositis likely and therefore cardiac magnetic resonance imaging unnecessary, while Neurology assessment diagnosed a myasthenic crisis related to ICI-associated myositis based on clinical findings. Electromyography was still requested but the patient died before the exam could be performed. We acknowledge the absence of confirmatory electrophysiological and advanced cardiac imaging, such as cardiac magnetic resonance as a limitation of this case report.

Other differential diagnoses like idiopathic inflammatory myopathy, viral myositis, paraneoplastic myositis, traumatic or alcohol-related rhabdomyolysis were considered, as well as ischemic cardiomyopathy as an alternative cause for the acute heart failure. Nevertheless, the abrupt clinical picture, together with the markedly elevated muscle enzymes and troponin rise (along with an unremarkable electrocardiogram and echocardiogram) temporally related with pembrolizumab administration strongly supported the ICI-related myositis with probable myocarditis association. Myasthenic syndrome (ocular weakness, dysphagia and respiratory decline) was serologically negative for AchR antibodies, although muscle-specific kinase (MuSK) antibodies were not excluded and electromyography was not timely performed. Despite this, the association between ICI-myositis and myasthenic crisis relationship is well described in the literature, making this diagnosis very likely. Additionally, up to a third of immune-related myasthenia gravis patients lack detectable autoantibodies and 60% may have normal electrophysiological studies[4].

The described case fits into the spectrum of pembrolizumab-associated myositis with cardiac involvement and myasthenic syndrome.

Treatment of ICI-associated myositis involves high-dose steroids, usually methylprednisolone pulses, followed by prednisolone 1 mg/kg/day aiming for rapid tapering due to risk of tumor progression[8,9]. In this case, the patient's poorly controlled diabetes made it important to use lower steroid doses to avoid metabolic decompensation. The European Society for Medical Oncology (ESMO) recommends the use of immunoglobulins, plasmapheresis, or anti-IL6R therapy in refractory cases of ICI-associated myositis. In life-threatening cases, early escalation to bDMARD is advised, preferably anti-IL6R therapy over anti-Tumoral necrosis factor (TNF) agents[9]. Given the severity, with probable myocarditis at presentation, and in accordance with ESMO guidelines, we initiated anti-IL6R treatment with tocilizumab. Poor metabolic control and the need to limit steroid exposure reinforced our decision. In this patient, anti-TNF agents and immunoglobulins were discussed but not used due to acute heart failure, as

anti-TNFs are contraindicated and immunoglobulins would add excessive fluid load.

Evidence for the use of biologic DMARDs in treating rheumatological conditions and irAEs of ICIs in cancer patients is scarce. Usual practice recommends their use only after oncological remission. In this case the severity of the presentation and the need to spare steroids justified the approach. Interleukin-6 (IL-6) is known to promote neoplastic cell proliferation via signal transducer and activator of transcription 3 (STAT3) activation and redundant cell cycle progression[10,11]. Immunohistochemical studies have demonstrated increased IL-6 expression in tumor tissue and elevated serum IL-6 in patients with various cancers[11,12]. This suggests that IL-6 blockade, via monoclonal antibodies like tocilizumab, might have antitumor effects as well, as seen with IL-6 blockers in prostate adenocarcinoma, renal cell carcinoma, and multiple myeloma[10]. Moreover, IL-6 seems crucial in ICI-induced irAEs, since IL-6 dysregulation promotes T helper 17 cell differentiation, neutrophil recruitment, and tissue damage in patients treated with ICIs[10]. IL-6 blockade has shown benefit in controlling diverse irAEs in at least 31 patients[13] and randomized controlled trials are at this moment testing combination therapy of ICI and IL-6 receptor inhibition for both inducing tumor response and irAE prevention[12]. Despite this, specific evidence on tocilizumab for ICI-induced myositis is limited due to the rarity of this condition and the novelty of ICI use. However, tocilizumab has shown efficacy as a steroid-sparing agent for other ICI-related irAEs (notably ICI-induced polyarthritis and colitis), with 15 of 19 patients reaching primary endpoints (improved CTCAE grade) and clinical remission after steroid withdrawal at 24 weeks[14].

In most severe and life-threatening cases of immune-related myasthenia gravis, most recent guidelines, case reports and review of the literature series recommend the use of immunoglobulins or plasma exchange[3]. There is currently no published evidence, including case reports, of tocilizumab being used for the treatment of ICI-induced myasthenia gravis.

In this case, despite the rapid improvement in muscle strength and CK reduction after the first tocilizumab dose, the lack of therapeutic response in myasthenia gravis may suggest distinct underlying pathogenic mechanisms. This divergence implies that ICI-associated myositis and myocarditis are at least partially IL-6 mediated, whereas the myasthenic syndrome likely follows a classical antibody-mediated pathway. However, this partial efficacy of Tocilizumab (mainly in the muscle and heart involvements) must be interpreted with caution, as this was a single uncontrolled case and the patient ultimately died from infection, tumor progression, and myasthenic crisis. Given the very limited existing evidence, this case report therefore reinforces the importance of documenting such rare presentations and treatment responses to inform future management of similar cases of ICI-induced myositis with associated myocarditis and myasthenic syndrome, especially since specific antibodies are absent is up to one-third of cases[3].

In summary, this case highlights the need for close clinical monitoring of all patients starting ICI immunotherapy, since rare but potentially fatal adverse events such as myocarditis require early recognition and treatment. It illustrates a very positive clinical response to tocilizumab in ICI-induced myositis and myocarditis, although not in associated myasthenia. Finally, it highlights the value of a multidisciplinary approach in managing these manifestations.

Ethics Statement

This case complied with institutional ethical standards, and written informed consent for publication was obtained from the patient prior to his death.

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