



## Letter to the Editor

## Concomitant myasthenia gravis, myositis, myocarditis and polyneuropathy, induced by immune-checkpoint inhibitors: A life-threatening continuum of neuromuscular and cardiac toxicity



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## Dear Editor,

Immune-checkpoint inhibitors (ICIs) represent a novel therapeutic approach for numerous tumors. However, checkpoint blockade may be complicated by a unique spectrum of immune-related adverse events (irAEs), even severe (grade 3–4) in 5–24% of patients treated with ipilimumab and nivolumab [1]. Various neurological irAEs that involve the central and peripheral nervous systems have been reported, including polyneuropathy (3%), myasthenia gravis (0.2%) and necrotizing myositis, predominantly after nivolumab [2]. Also myocarditis is an increasingly reported irAE of ICIs [3]. Herein we report two cases: a 72-year-old female and a 71-year-old male with renal cancer, where a complex neuromuscular disorder, encompassing also myocarditis, was induced by immune checkpoint inhibitors. The outcomes were opposed one to the other, i.e. complete recovery in the former and death in the latter. Both patients had a similar clinical presentation after the first cycle of nivolumab i.e. dropped head, limb weakness progressing to inability to walk. Also the first neurophysiological investigation revealed quite a similar pattern, i.e. sensori-motor symmetrical polyneuropathy, with axonal and demyelinating features. Furthermore, a decremental response was detected at the repetitive 3 Hz stimulation, without post-exercise increase. The concentric needle electrode revealed a myopathic pattern at interference; spontaneous activity appeared two weeks later.

Intravenous immunoglobulins (0.4 g/kg for 5 days) and steroids (1 g/Kg) were administered. Although the female patient had a rapid treatment response, in only two days the male developed lipotimic episodes, cardiovascular instability and an atrioventricular block; myocarditis was diagnosed and a pace-maker implanted. Nevertheless, the patient worsened further and was admitted to the Intensive Care Unit for cardio-respiratory failure. Despite a second immunoglobulin cycle and intravenous steroid bolus, the patient died. No previous autoimmune disease nor antecedent infection was found at anamnesis in

either patient. Both patients had been treated with pazopanib, before nivolumab. The male had a more severe hyperCKemia early on at laboratory tests, in line with his more severe necrotizing myopathy.

A continuum of neuromuscular dysfunction, involving the peripheral nerve, the neuromuscular junction and the skeletal muscle, as well as the cardiac muscle in the male, was induced by ICIs, maybe due to an autoimmune mechanism. A small percentage of myasthenic patients also have myocarditis and myositis [4], suggesting that heart and skeletal muscles may become concomitant autoimmune targets.

The reported cases extend and confirm previous evidence of a broad clinical spectrum of autoimmune-mediated, life-threatening, neuromuscular and cardiac toxicity of ICIs. Therefore, a question arises as to the safety of ICIs in patients with history of autoimmune disease [2]. Leading to the challenge to identify individual risk profiles for neuromuscular and cardiac toxicity in ICI-treated patients and the putative predisposing role of previous treatment, like with the tyrosine-kinase inhibitor pazopanib, which is known to physiologically modulate angiogenesis also in skeletal muscles and the mitochondrial metabolism [5].

Furthermore, special attention is to be paid to neuromuscular and cardiac symptoms in these patients, since a prompt clinical and electrophysiological diagnosis and treatment are mandatory as an attempt to halt progression to severe complications or even death.

## Disclosure

The authors have declared no conflicts of interest.

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Eugenia Rota<sup>a,\*</sup>, Paola Varese<sup>b</sup>, Sergio Agosti<sup>c</sup>, Lorenzo Celli<sup>a</sup>,  
Elisabetta Ghiglione<sup>a</sup>, Irene Pappalardo<sup>a</sup>, Gabriele Zaccone<sup>c</sup>,  
Alba Paglia<sup>d</sup>, Nicola Morelli<sup>e</sup>

<sup>a</sup> Neurology Department, ASL Alessandria, Italy

<sup>b</sup> Internal Medicine Unit, Ovada Hospital, Ovada, AL, Italy

<sup>c</sup> Cardiology Unit, San Giacomo Hospital, Novi Ligure, AL, Italy

<sup>d</sup> Intensive Care Unit, San Giacomo Hospital, Novi Ligure, AL, Italy

<sup>e</sup> Neurology and Radiology Unit, Guglielmo da Saliceto Hospital, Piacenza,  
Italy

E-mail address: [eugenia.rota.md@gmail.com](mailto:eugenia.rota.md@gmail.com) (E. Rota).

\* Corresponding author at: Department of Neurology, ASLAL, San Giacomo Hospital, Via E. Raggio 12, 15067 Novi Ligure, Alessandria, Italy.