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Nivolumab: An “immune storm” in a patient with history of myasthenia gravis[☆]



Nivolumab: «Tormenta inmune» en paciente con miastenia gravis previa

Dear Editor:

In recent years, new treatments have been developed for metastatic cancer. The most relevant of these aim to stimulate the patient's immune response against tumour cells. The discovery of the molecules CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), PD-1 (programmed cell death protein 1), and PD-L1 (programmed cell death ligand 1) by Krummel and Allison¹ and Ishida et al.² in the 1990s enabled the development of a novel line of cancer treatments known as immune checkpoint inhibitor (ICI) therapy.

Antibodies targeting CTLA-4 (ipilimumab), PD-1 (nivolumab, pembrolizumab), and PD-L1 (atezolizumab, avelumab, durvalumab) increase antitumour immunity by blocking the T-cell inhibitory receptors expressed by tumour cells.³

However, proteins PD-1 and CTLA-4 play a major role in human self-tolerance. Therefore, adverse reactions to ICIs are associated with increased autoimmune response in the host (immune-related adverse events),⁴ with the digestive system, liver, lungs, and skin being the organs and systems most frequently involved.⁵

Although neurological adverse reactions are rare (0.3%–0.8% in patients receiving anti-CTLA-4 treatment and 0.2%–0.4% in those receiving anti-PD-L1 treatment), they can be very severe. These reactions include several types of encephalopathy (eg, demyelinating and vasculitic encephalopathies, posterior reversible

encephalopathy syndrome),^{6,7} myelopathy, meningitis, Guillain-Barré syndrome, peripheral neuropathy, and myasthenic syndromes.^{6,8} Myasthenic syndromes may follow an aggressive course and show poor response to treatment, particularly when they appear in association with inflammatory processes in other areas (eg, myositis, myocarditis). ICIs may also exacerbate pre-existing autoimmune diseases; the risk of mild-to-moderate exacerbation is estimated at 27%–42%.⁶

We describe the case of a patient with generalised myasthenia gravis in remission who presented a severe myasthenic crisis associated with myocarditis and myositis after treatment with nivolumab.

Our patient was a 72-year-old man with arterial hypertension and myasthenia gravis (stage IIB) with anti-acetylcholine receptor antibodies (AARA), diagnosed in 2010; he was clinically stable with pyridostigmine 60 mg/8 h and prednisone 10 mg/24 h. In 2016, the patient was diagnosed with epidermoid carcinoma of the left parotid gland (stage pT4pN2b), and underwent surgical excision of the tumour, jugulodigastric lymphadenectomy, and radiation therapy.

A PET/CT scan performed in November 2017 revealed metastatic progression, and the patient started treatment with platinum and cetuximab. As he developed treatment-related axonal polyneuropathy and local tumour progression and metastasis, we started compassionate use treatment with nivolumab (3 mg/kg). Given the stability of myasthenia gravis, risk of reactivation was considered to be low. Treatment was started in July 2018.

Two weeks before administration of the third dose of nivolumab, the patient was admitted to our hospital's emergency department due to a one-week history of progressive dyspnoea, orthopnoea, diplopia, dysphagia, and generalised muscle weakness. A physical examination revealed tachypnoea, intercostal retractions, and generalised hypophonesis, as well as dysarthria, right ptosis, fatigable diplopia in all gaze positions, facial weakness, and generalised, fatigable weakness of limb muscles, with muscle strength of 3/5 proximally and 4+/5 distally. A peak flow study revealed a forced vital capacity of 0.7 L.

An arterial blood gas test performed at the emergency department revealed compensated metabolic acidosis (pH

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7.46; PCO₂ 24 mm Hg; PO₂ 84 mm Hg; HCO₃⁻ 17 mEq/L; Lac 3 mmol/L). A blood analysis revealed multiple alterations compatible with liver, heart, and muscle damage (LDH 1571 U/L [normal range, 240–480], CK 2361 U/L [1–190], CK-MB 117 ng/mL [0.1–5], troponin I 28.8 ng/mL [<0.05], proBNP 9828 pg/mL [1–125], ALT 145 U/L [5–40], AST 222 U/L [5–40], GGT 721 U/L, alkaline phosphatase 202 U/L). An electrocardiography study showed right bundle branch block and second-degree atrioventricular block (Wenckebach block). The initial study revealed left ventricular dysfunction with a left ventricular ejection fraction (LVEF) of 40% (biplane method). AARA determination showed strong positivity (>20 nmol/L).

Based on our patient's symptoms and complementary test results, we established a diagnosis of myasthenic crisis, myositis, and myocarditis associated with severe nerve conduction disorder probably secondary to nivolumab toxicity. The patient was admitted to the intensive care unit, where he started treatment with intravenous methylprednisolone 1 g plus intravenous immunoglobulins dosed at 0.4 g/kg for 5 consecutive days.

Despite treatment, the patient presented a progressive clinical deterioration. Systolic dysfunction worsened (LVEF 10%–15% at 48 h) and the patient presented cardiogenic shock with systemic hypoperfusion, hyperlactacidaemic metabolic acidosis, coagulopathy, and multiple organ failure, with lack of response to volume therapy and treatment with inotropic agents. Plasmapheresis was ruled out due to the severity of heart disease. The patient died 72 h after admission.

Our case underscores the potential severity of some adverse reactions to ICIs. Among the neurological complications described, exacerbation or de novo onset of myasthenia gravis are the most frequent immune-related adverse events, representing up to 0.1% of all severe adverse reactions to ICIs.^{6,8,9}

Myasthenia gravis associated with ICIs seems to be more severe and to progress more rapidly than idiopathic myasthenia gravis.⁹ These clinical characteristics and their frequent association with other immune disorders (eg, myositis and myocarditis) underscore the importance of early detection of this complication. Although diagnosis of myasthenia gravis is mainly clinical, it may be supported by AARA positivity (identified in over 60% of patients with myasthenia gravis associated with ICIs).¹⁰ Elevated serum levels of CK and markers of myocardial damage are also frequent in these patients.^{9,10}

The safety of ICIs in patients with known autoimmune disease is not clearly established; use of these medications requires close monitoring. According to published studies of patients with known myasthenia gravis, the percentage of myasthenic crises after onset of treatment with ICIs seems to be higher among those with active forms than in those showing clinical stability (60% vs 30%) and in those receiving immunosuppressants of any type as compared to those receiving no treatment (50% vs 31%).^{11,12} However, the severity of pre-existing myasthenia gravis may not be decisive: the literature includes the case of a patient with ocular myasthenia gravis in remission who presented a myasthenic crisis with severe respiratory involvement and died as a result of treatment with nivolumab.¹³

Management of immune-related adverse reactions to ICIs is complex and requires a multidisciplinary approach. Initial management involves immediate discontinuation of the drug and initiation of high-dose corticosteroid therapy.¹¹ Patients with severe symptoms should also receive intravenous immunoglobulins or plasmapheresis from the beginning of treatment.^{8,10} Response to treatment for myasthenia gravis associated with ICIs is variable, with some patients requiring ventilatory support.⁹ At present, no recommendations have been established on the most appropriate dose at treatment onset, the duration of maintenance treatment, or the benefits of intravenous immunoglobulins as compared to plasmapheresis in these patients.

Other immunomodulatory treatments may play a role in the treatment of myasthenia gravis associated with other systemic inflammatory disorders; this was the case with a patient who showed complete response to abatacept (CTLA-4 agonist) after presenting severe, corticosteroid-refractory myocarditis secondary to nivolumab.¹⁴

In conclusion, the use of ICIs in patients with history of myasthenia gravis is controversial. Further research is needed to establish a treatment plan for patients presenting exacerbation of myasthenia gravis after treatment with ICIs. Administration of ICIs to patients with myasthenia gravis should be based on a thorough multidisciplinary assessment and close monitoring of clinical and laboratory parameters, given the potentially severe complications of this treatment.

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A Spanish family with a compound heterozygous mutation in *SPG7*: From uncertainty to clinical reality

Familia española portadora de una mutación en heterocigosis compuesta en el gen *SPG7*: de la incertidumbre a la realidad clínica

Spastic paraplegia type 7 (SPG7; OMIM #607259) is an autosomal recessive disorder caused by mutations in the *SPG7* gene, which encodes the mitochondrial metalloprotease paraplegin.¹ It accounts for approximately 5%–12% of all autosomal recessive forms and up to 7% of sporadic cases in adults. It has also been associated with symptoms of cerebellar ataxia,² which may constitute the most relevant clinical manifestation. However, phenotypic variations are more complex; the literature includes cases of chronic progressive external ophthalmoplegia,³ primary lateral sclerosis,⁴ and parkinsonism.⁵

Over 131 pathogenic variants have been described (Human Gene Mutation Database, accessed 14 July 2019). We report the cases of 3 sisters from a Spanish family, who presented ataxia and spasticity and were carriers of 2 single nucleotide variants of uncertain significance in the *SPG7* gene.

We studied a family of 7 siblings born to non-consanguineous parents and with no family history of neurological disease. Three of them (3 women) reported

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progressive difficulty walking, with instability and dysarthria appearing in the third decade of life. A clinical examination performed after 20 years of disease progression revealed multidirectional nystagmus, dysarthria, global hyperreflexia with bilateral extensor plantar reflex, and marked spasticity of the lower limbs, with the patients requiring bilateral support to walk. The eldest of the 3 sisters also presented cognitive impairment, ophthalmoparesis, upper limb dysmetria, and wide-based gait. All 3 showed cerebellar atrophy on MR images (Fig. 1). The remaining siblings were not affected (Fig. 2A).

After ruling out secondary causes and the mutations most frequently associated with ataxia and spastic paraparesis in the proband, we conducted a genetic study of the *SPG7* gene. We detected 2 missense mutations, and decided to perform the genetic study in the remaining siblings.

Peripheral blood samples were collected and we performed DNA amplification by PCR and traditional DNA sequencing with the ABI 3730[®] analyser (Applied Biosys-

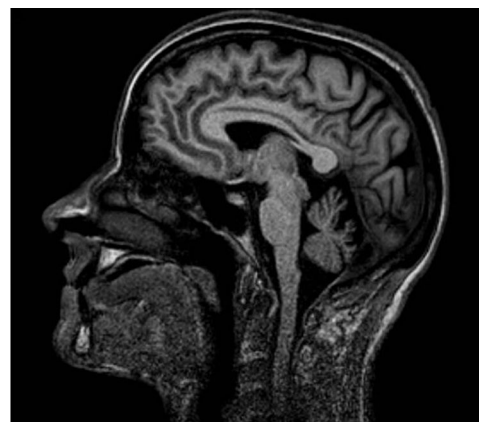


Fig 1 T1-weighted sagittal brain MRI scan showing cerebellar atrophy.

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