Concomitant development of neurologic and cardiac immune-related adverse effects in patients treated with immune checkpoint inhibitors for melanoma

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Immune checkpoint inhibitors (ICI) have altered the prognosis of patients with melanoma over the past few years, with immune-related adverse effects (irAEs) being the only factor limiting their use. Neurologic and cardiac irAEs are rare, but usually severe. We reviewed the files of patients with melanoma treated with ICIs in one center to retrieve data from patients with neurologic irAEs. Patients with a combination of neurologic and cardiac manifestations were further analyzed. We also reviewed the literature for similar syndromes. Five out of 482 (1.01%) patients developed a neurologic syndrome and we present three patients with a constellation of neurologic and cardiac irAEs. A 66-year-old woman and a 68-year-old man presented with a constellation of findings after being treated with ipilimumab and nivolumab, respectively, for melanoma in the adjuvant setting and were eventually diagnosed with myasthenia gravis with cardiac involvement. An 80-year-old woman developed diffuse asymmetric muscle weakness, bilateral ptosis and asymptomatic high serum troponin levels after adjuvant treatment with nivolumab and ipilimumab for a stage IIIB melanoma. After excluding ischemic heart disease, she was diagnosed with axonal polyradiculoneuropathy and myocarditis. Neurologic or cardiac irAEs in patients treated with ICIs are uncommon (<1%), but usually severe, with high rates of morbidity and fatality. The co-development of neurologic and cardiac irAEs is even more rare and can arise soon after exposure to ICIs and escalate rapidly. Since more and more patients are now treated with ICIs in the adjuvant setting, prompt identification and management are essential to avoid serious complications or death. *Melanoma Res* 30: 484–491 Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Introduction

The introduction of immune checkpoint inhibitors (ICI), namely the cytotoxic T lymphocyte antigen-4 (CTLA4) and the programmed cell death protein 1 (PD1) inhibitors, has revolutionized the management of patients with advanced or metastatic melanoma. Nevertheless, the strong antitumor efficacy has been coupled with a unique but wide range of immune-related adverse effects (irAEs). The increasing use of ICIs has brought to light rare irAEs, highlighting the importance of aggressive surveillance for early detection and prompt management that can prevent life-threatening complications. This has become very important especially since, during the last few years, ICIs are being used in the adjuvant setting and thus irAEs may affect a much larger population of patients, a fraction of whom might have remained disease-free, irrespective of the use of adjuvant immunotherapy.

Neurologic and cardiac complications of immunotherapy are considered rare irAEs and are described scarcely as case reports or small patient series. The aim of the present study is to describe patients with combined cardiac and neurologic irAEs, analyze their clinical and laboratory characteristics and review the literature for similar syndromes, focusing on their pathogenesis and prognosis.

Patients and methods

We retrospectively analyzed the files of patients with melanoma treated with ICIs in a single Oncology Unit of a Tertiary University Hospital in Athens, Greece. We searched for patients without a previous medical history of neurologic conditions presenting with neurologic symptoms after treatment initiation with ICIs; CTLA4 inhibitors (ipilimumab), PD1 inhibitors (nivolumab and pembrolizumab) or PDL1 inhibitors (atezolizumab). After retrieving the files of patients with neurologic manifestations, we further analyzed only cases presenting with a combination of neurologic and cardiac manifestations. Furthermore, we reviewed the literature for similar cases

with complex neurologic and cardiac AEs attributable to the use of ICIs.

Results

Data analysis retrieved 482 patients with melanoma treated with ICIs in our center during the past 6.5 years (from January 2013 to June 2019). Data analysis showed that 124 patients were treated with ipilimumab, 216 with a PD1 inhibitor (nivolumab or pembrolizumab), 12 with atezolizumab, 39 with a combination of nivolumab and ipilimumab and 91 with ipilimumab and a PD1 inhibitor sequentially. Out of 482 patients, 374 (77.6%) were treated for inoperable or metastatic disease and 108 (22.4%) were treated in the adjuvant setting. Only five patients (1.01%) were found to have neurologic irAEs. One of them had a complex syndrome consisting of an inflammatory myopathy and axonal neuropathy emerging 15 days after treatment initiation with pembrolizumab for a stage IIIc melanoma [1] and another one presented with a Bell's palsy 10 days after the first dose of ipilimumab administered for metastatic melanoma. We chose to present in detail three patients treated with ICIs in the adjuvant setting that presented soon after treatment initiation with a combination of neurologic and cardiac manifestations attributed to the use of ICIs. The basic clinical and laboratory characteristics of the patients as well as the diagnostic and treatment approach are summarized in Table 1.

Case 1

A 66-year-old Caucasian woman was diagnosed with a nodal metastasis of malignant melanoma to her left axilla. At diagnosis, no primary lesion was found (T0, N2b, M0) and she was treated with ipilimumab in the adjuvant setting (10 mg/kg every 3 weeks). Her past medical history was significant for type 2 diabetes mellitus, arterial hypertension, hyperlipidemia and post-thyroidectomy hypothyroidism (history of autoimmune disorder), which were well-controlled with pharmacological treatment.

Fifteen days after treatment initiation, she was admitted due to dyspnea on exertion and orthopnea. High levels of creatine kinase–muscle/brain [CK-MB, 752 IU/L; upper limit of normal (ULN), 25 IU/L], lactate dehydrogenase (LDH, 950 IU/L; ULN, 240 IU/L) and high-sensitivity cardiac troponin T (hs-cTnT, 3210 mg/ml; ULN, 14 mg/ml) were found upon admission. An ECG showed a sinus rhythm and a transthoracic echocardiogram revealed a normal left ventricular (LV) ejection fraction (61%) with normal LV wall motion, a mild left atrial enlargement (43 mm, 35 ml/m^2), no pericardial effusion and a slight reduction in the global longitudinal strain (GLS, –15.7%). A coronary angiography was negative for coronary artery disease (Fig. 1a, b). Concomitantly with the cardiac manifestations, the patient complained of double vision. During her hospitalization, left unilateral ptosis, diplopia on right gaze, hoarseness and dysphagia for liquids also developed. The neurologic examination revealed a left ptosis with a positive fatiguability test, horizontal diplopia at the right outward gaze (paretic right lateral rectus muscle), hypernasal speech and dysphagia. The rest of the neurologic examination was unremarkable. An ophthalmologic and ear-nose-throat examination did not add any

Table 1 The table summarizes the basic clinical and laboratory characteristics of the patients presented in the study, as well as their management and outcome

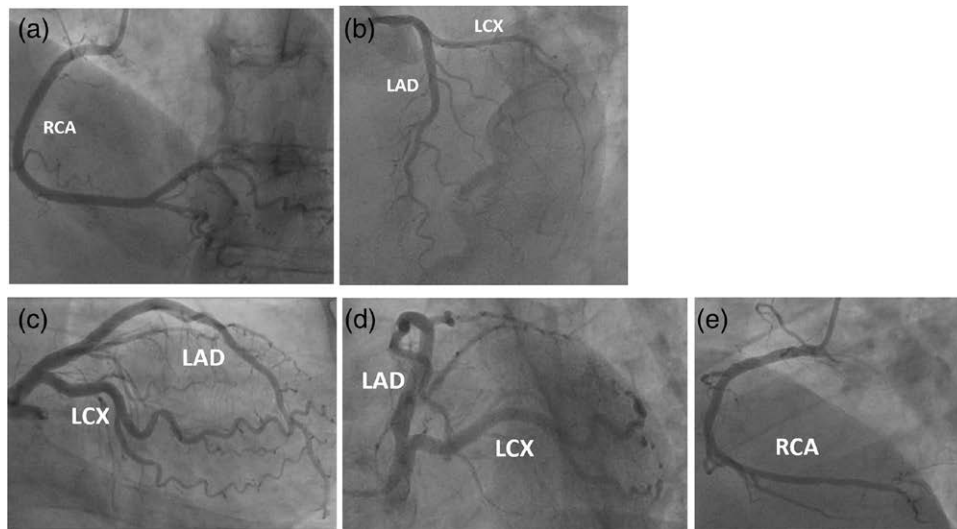| Age (years)/sex	Stage	Treatment (dosing schedule)	Time to onset of symptoms (days)	Presenting symptoms	CK-MB (IU/L)/ hs-cTNT (mg/ml)	LV-EF	Anti-AChR abs	EMG findings	Final diagnosis	Treatment	Outcome
66/F	T0, N2b, M0	Ipilimumab (10 mg/kg/3w)	15	Dyspnea, diplopia, ptosis, hoarseness, dysphagia	752/3210	61%	+	Negative	Myasthenia gravis with cardiac involvement	Pyridostigmine, prednisolone	Complete resolution after 3 weeks, no disease progression[a]
68/M	IV, M1b resected	Nivolumab (240 mg/2w)	21	Diplopia, hypophonia, dysphagia, ptosis	524/2130	58%	+	Not performed	Myasthenia gravis with cardiac involvement	Pyridostigmine, prednisolone, IVIG	Complete resolution after 2 weeks
80/F	T2a, N2b, M0	Ipilimumab (1 mg/kg/6w), nivolumab (240 mg/kg/2w)	21	Ptosis, proximal muscle weakness	729/3424	58%	−	Denervation and high frequency discharges[b]	Axonal polyradiculoneuropathy with myocarditis	Methylprednisolone, IVIG	Complete resolution after 13 weeks, no disease progression[a]

The rapid onset of symptoms after treatment with ICIs, the strikingly high levels of hs-cTNT with a preserved ejection fraction, and the complete recovery of all patients are the main conclusions derived by this table.
CK-MB, creatine kinase–muscle/brain; EMG, electromyogram; F, female; hs-cTNT, high-sensitivity cardiac troponin T; ICI, immune checkpoint inhibitors; IVIG, intravenous immunoglobulin; LV-EF, left ventricular ejection fraction; M, male; w, week.
[a]Referring to melanoma.
[b]Myositis confirmed with muscle biopsy.

Fig. 1

The coronary arteriography of patients 1 and 2 revealed normal epicardial arteries. Patient 1: (a) view RCA, LAO 29° CAU 1° and (b) view LAD and LCX, LAO 28° CRA 15°. Patient 2: (c) view, RAO 5° CAU 26°; (d) spider view, LAO 56° CAU 25°; (e) view, LAO 41° CRA 5°. CAU, caudal; CRA, cranial; LAD, left anterior descending; LAO, left anterior oblique; LCX, left circumflex; RAO, right anterior oblique; RCA, right coronary artery.

findings. A chest and brain computed tomography (CT) and a brain MRI revealed no clinically relevant findings. Serology tests for Herpesviridae (human herpes virus 1 and 2, varicella-zoster virus, Epstein–Barr virus and cytomegalovirus) were negative. The thyroid stimulating hormone (TSH) and B12 vitamin levels were within normal limits. The patient tested positive for antibodies against acetylcholine receptor (anti-AChR, 0.7 nmol/L, positive being >0.6). Anti-MuSK and anti-LPR-4 antibodies, as well as antibodies against heart and striated muscle were negative. The patient was started on pyridostigmine at 60 mg three times per day and prednisolone at 1 mg/kg/day and had a good clinical response. Neurophysiology testing including repetitive nerve stimulation (RNS) was negative for decrement while an electromyogram (EMG) did not show a myopathic pattern. It should be noted though that the patient had received a pyridostigmine dose 3 h before the test.

One week after treatment initiation, the neurologic and cardiac symptoms gradually started to resolve and the patient was completely asymptomatic 3 weeks after corticosteroid administration while the hs-cTnT levels remained high (well above 1500 mg/ml), but gradually returned to normal after corticosteroid initiation and remained so after a gradual tapering of the steroid dose over the following 2 months. Two months later, the GLS was normalized (−21.8%) and a gadolinium-enhanced cardiac MRI did not show any findings. No further antimelanoma treatment was administered and the patient remains free of disease 13 months after ipilimumab discontinuation.

Case 2

A 68-year-old Caucasian man was diagnosed with a lentigo maligna melanoma on the parietal region of his scalp (T2b, N0, M0). Five years following the initial diagnosis, a PET-CT revealed a hypermetabolic nodular lesion in the left upper lobe of the lung, which was proven to be metastatic and was resected (stage IV, M1b resected). The patient was treated with nivolumab at 240 mg every 2 weeks in the adjuvant setting, but after two treatment cycles he presented with diplopia that was investigated by an ophthalmologist with a brain and optic chiasm MRI that did not reveal any findings. During the following days, the patient developed a tingling sensation on his face, mild hypophonia, difficulty in swallowing, bilateral ptosis and horizontal diplopia that were compatible with bilateral peripheral facial nerve palsy, right lateral rectus palsy and fluctuating left medial rectus palsy. His neurologic symptoms showed a fluctuating intensity during the day, worsening in the evening. The rest of the clinical examination was unremarkable except for a grade 1 bilateral pedal edema. The initial laboratory evaluation was remarkable for high CK-MB (524 IU/L) and hs-cTnT (2130 mg/ml) levels. The levels of B12 vitamin and TSH were within normal limits. A lumbar puncture showed 10 lymphocytes per mm^2, and normal levels of protein and glucose. The CSF culture was negative as was a CSF PCR for HSV1, HSV2 and enterovirus, while no oligoclonal bands were found in the patients CSF or serum. The patient tested negative for the presence of voltage-gated calcium channel antibodies (type N and type P) by a radioimmunoassay. The anti-AChR antibodies were found positive (20 nmol/L, positive being >0.6). Moreover, a

neurophysiology testing including RNS was indicative of myasthenia gravis (MG) and the patient was started on pyridostigmine at 60 mg two times per day and prednisolone at 1 mg/kg/day. Due to high creatine phosphokinase (CPK) and hs-cTnT levels, a cardiac ultrasound was carried out showing a normal LV ejection fraction (58%) with normal LV wall motion but a myocardial perfusion imaging with 99mTc tetrofosmin following a pharmacological cardiac stress test with regadenosone was indicative of possible inferior wall myocardial ischemia. Nevertheless, a coronary angiography was negative for coronary artery disease (Fig. 1c–e). Due to bradycardia attributed to pyridostigmine, the drug was discontinued and the patient was started on intravenous immunoglobulin IVIG at 0.4 mg/kg/day for 5 days. A gradual and remarkable improvement of his symptoms and of the levels of CPK and troponin were noted during the following few days.

Case 3

An 80-year-old Caucasian woman was diagnosed with a stage IIIB cutaneous melanoma (T2a, N2b, M0). Her past medical history was significant for type 2 diabetes mellitus and arterial hypertension that were well-managed with pharmacological treatment. The patient was treated with a combination of ipilimumab (1 mg/kg every 6 weeks) and nivolumab (240 mg every 2 weeks) in the adjuvant setting, in the context of a clinical trial (Checkmate 915) [1]. After one dose of ipilimumab and two doses of nivolumab, she complained of rapidly worsening fatigue affecting the upper extremities at the beginning, but spreading to the lower extremities in a descending pattern during the following few days. On physical examination, bilateral ptosis and right abducens nerve paresis were noted, along with diffuse asymmetric (right>left) muscle weakness affecting primarily the proximal muscles of the upper limbs (grade 3–4/5). Loss of proprioception and vibration were noted at lower limbs distally. Left biceps, right triceps and knee reflexes were absent.

The initial laboratory evaluation revealed high hs-cTnT (3424 mg/ml) and CK-MB (729 IU/L) levels. An ECG showed a preexisting right bundle branch block while an echocardiogram revealed a preserved LV ejection fraction (58%), normal wall motion of LV segments, mild LV hypertrophy and left atrial enlargement, but the GLS was decreased (–15.7%). A dipyridamole-thallium scan was performed and was negative for myocardial ischemia.

A brain CT scan did not reveal any findings. The cerebrospinal fluid was negative for cells or increased protein levels. Moreover, no oligoclonal bands were detected and the IgG index was 0.72 (normal range 0.23–0.64). Serology for cardiotropic viruses (coxsackie, adenovirus, Epstein–Barr virus, cytomegalovirus, HIV and parvovirus), *Legionella* spp, *Borrelia* spp and *Rickettsia* spp was

negative. The TSH and B12 vitamin levels were within normal limits.

An electroneurogram was compatible with an axonal sensorimotor polyradiculoneuropathy (Fig. 2) and an EMG showed active denervation and high frequency discharges in all tested muscles but the rectus abdominis. The patient had a biopsy of the femoral muscle that confirmed a myositis (Fig. 3). Moreover, she tested negative for all tested autoantibodies for autoimmune inflammatory myopathies (Mi-2 alpha, Mi-2 beta, TIF1g, MDA4, NXP2, SAE1, K, PM-Scl100, PM-Scl75, Jo-1, SRP, PL7, PL-12, EJ, OK, Ro-52) as well as for anti-AChR and heart and striated muscle antibodies. Antibodies against gangliosides were also tested and anti-GM1 antibodies were reported marginally positive. The patient's symptoms worsened during the following two weeks with the addition of dysphagia and weakness of neck flexors (3/5).
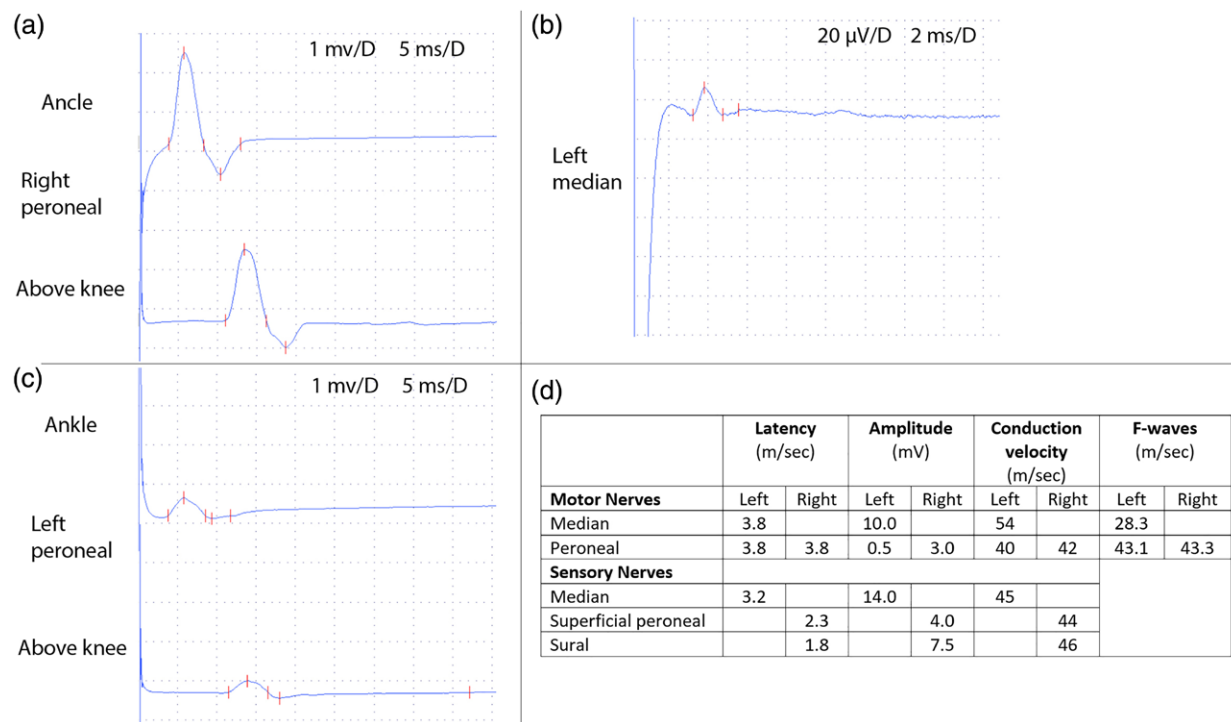
Treatment with methylprednisolone was started at 1 mg/kg/day along with IVIG (0.4 mg/kg/day for 5 days) in four-week cycles. Her hospitalization was complicated by several hospital-acquired infections (bacteremia from Enterobacter and urinary tract infection from *Proteus mirabilis*) that were effectively treated with broad-spectrum antibiotics. A gradual improvement was noted and she was eventually discharged after a 25-day hospitalization. A total of four cycles of IVIG were administered (the last three in an outpatient setting) along with physiotherapy and the patient had almost fully recovered by her last follow-up visit, 4 months after her admission, with normalization of the cardiac enzymes and GLS (–20.1%). No further antineoplastic treatment was administered.

Discussion

After reviewing the files of 482 patients treated with ICIs for melanoma in our center, we found five patients with neurologic irAEs. We present three patients with a combination of neurologic and cardiologic complications soon after treatment initiation with ICIs for melanoma in the adjuvant setting. The first two patients were diagnosed with MG with cardiac involvement and the third with axonal polyradiculoneuropathy and myocarditis. In all patients, symptoms developed only a few days after treatment initiation, and after only one and two cycles of treatment. This rapid immunological reaction has been readily characterized in the literature and dictates an active surveillance for the development of irAEs in patients treated with ICIs from the initiation of treatment and on.
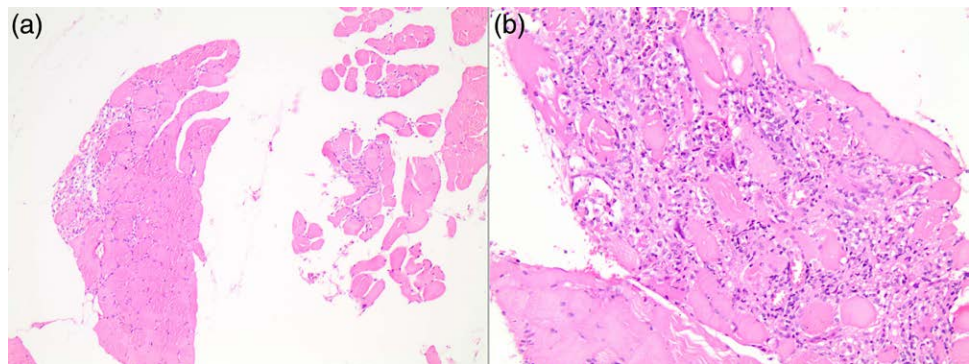
Neurologic irAEs are relatively uncommon while serious (grade 3/4) neurologic irAEs account for less than 1% of irAEs in patients treated with ICIs. They may affect the central or peripheral nervous system while a detailed clinical and laboratory characterization of these AEs is rarely available [2]. They typically develop when antitumor

Fig. 2

Patient 3: nerve conduction studies of peroneal nerves bilaterally (a and b) and the median nerve (c). Conduction velocities showing findings of mild sensorimotor axonal polyneuropathy (d).

	Latency (m/sec)		Amplitude (mV)		Conduction velocity (m/sec)		F-waves (m/sec)	
	Left	Right	Left	Right	Left	Right	Left	Right
Motor Nerves								
Median	3.8		10.0		54		28.3	
Peroneal	3.8	3.8	0.5	3.0	40	42	43.1	43.3
Sensory Nerves								
Median	3.2		14.0		45			
Superficial peroneal		2.3		4.0		44		
Sural		1.8		7.5		46		

Fig. 3

Patient 3: hematoxylin and eosin-stained sections of skeletal muscle (femoral muscle, a, 1 × 100; b, 1 × 200) showing variability of the diameter of the muscle fibers with disperse atrophic and hypertrophic fibers and intense inflammatory infiltration from mature lymphocytes.

immune response cross-react with antigens expressed by healthy neurons (on-target/off-tumor activity).

On the contrary, cardiac complications in patients treated with ICIs are rare with a few cases of myocarditis, cardiomyopathy, heart failure and cardiac fibrosis described in the literature so far. In a case series, preexisting cardiac pathology was present in five out of eight patients with ICI-related cardiotoxicity [3]. Although the pathophysiology of cardiotoxicity of ICIs is largely unknown, PD1 is known to protect against tissue inflammation and myocyte damage, and PD1 deficiency has been described to predispose to spontaneous myocarditis [4,5] and dilated cardiomyopathy caused by antibodies against cTn in animal models [6,7]. However, it has been shown that CTLA4-deficient mice rapidly develop severe myocarditis [8]. Thus, it has been proposed that the cardiotoxic effects of ICIs can be explained through

lowering of the threshold for activation of T cells specific to cardiac self-antigens [5]. About 30% of the cases develop after only one or two doses of ICIs, as was the case with our patients [5,9]. The rapid onset of myocarditis after initiation of ICIs suggests that preexisting autoimmunity may be boosted from PD1 blockade [8,10]. Thus, active surveillance is needed especially in patients with preexisting cardiac pathology or risk factors for cardiac diseases, such as diabetes mellitus and hypertension. It is established thought that combination immunotherapy is the predominant risk factor for the development of myocarditis. The combination of nivolumab and ipilimumab has been found to confer a 4.74-fold risk of developing myocarditis compared with nivolumab monotherapy, while myocarditis due to combination of ICIs is more likely to be severe and is correlated with increased fatality [11,12]. Moreover, it has been associated with increased rates of co-occurring MG [13].

According to the fourth definition of myocardial infarction [14], myocardiac injury is defined as the detection of an elevated cTn value above the 99th percentile upper reference limit value, which can be associated with cardiac or noncardiac conditions, such as the use of antineoplastic agents. In the presence of clinically evident myocardial ischemia and/or ECG findings along with elevated cTn levels, manifested by a rising and/or falling pattern, a diagnosis of acute myocardial infarction can be established. In the absence of clinical and ECG findings attributable to myocardial ischemia, the myocardial injury can be attributed to other offending factors. In all patients presented in this article, the myocardial injury was considered an immune-related effect of the administered ICIs on the myocardial cells, since high hs-cTnT levels were not coupled with any clinical, electrocardiographic or other evidence-indicating myocardial ischemia after a thorough investigation.

The use of cTn levels as a marker of cardiotoxicity is very useful and although increased levels usually do not indicate immune-related cardiotoxicity [15], a careful interpretation of high troponin levels even in asymptomatic patients, especially at the beginning of treatment with ICIs, enables the identification of subclinical myocarditis. In patients with very high levels, as those encountered in all our patients, every effort to exclude ischemic cardiopathy should be made since treatment with high corticosteroid doses is the mainstay of treatment of ICI-related myocarditis [16], although there are no randomized trials supporting this practice. Moreover, ignoring a high serum cTn level in an asymptomatic patient may lead to continuation of treatment with ICIs and possible fatal cardiac toxicity. Thus, several cases of asymptomatic myocardial injury correlated with the use of ICIs may escape prompt diagnosis and treatment. Cases of smoldering myocarditis have been reported [17], highlighting the fact that early detection with serial measurements of

serum troponin levels, especially in patients under combined immune checkpoint blockade, may prevent fulminant myocarditis. In a multicenter registry of 35 patients with ICI-related myocarditis, it was found that there was a four-fold increased risk of major adverse cardiac events when the levels of troponin were ≥1.5 ng/ml (hazard ratio: 4.0; 95% confidence interval: 1.5–10.9; *P* = 0.003) [18].

MG is a well-known complication of ICIs. Through a large safety database of 10 277 cancer patients treated with ICIs in Japan, drug-induced adverse events of the central and peripheral nervous systems were identified in 176 patients (1.7%) [19]. Among them, 12 cases of MG were identified, comprising 0.12% of 9.869 patients treated with nivolumab, but 0 out of 408 patients treated with ipilimumab. MG symptoms developed within 45 days from treatment initiation in 11/12 cases and usually after just one or two treatment cycles. Ten patients were positive for anti-AChR antibodies while one of the two seronegative patients had positive anti-striated muscle antibodies. A marked elevation of CPK levels was found in 10/12 patients with three of them being diagnosed with myocarditis. Two of them had a subclinical course with TnT elevation. Moreover, anti-AChR antibodies were relatively low in patients with nivolumab-associated MG in comparison to patients with idiopathic MG.

It is known that the heart muscle is a target for autoimmune inflammation in MG. Risk factors for cardiac involvement in MG are advanced age, the presence of thymoma and anti-Kv1 antibodies [20]. Anti-AChR antibodies specific to skeletal muscles do not bind to heart muscle [21], but 48% of all MG cases and 97% of all thymoma-associated cases have antibodies toward heart muscle [22,23]. The so-called striational antibodies are commonly reported in MG cases with cardiac involvement [24]. Although there is no data to strongly support a pathogenic role of these antibodies, it has been proven that striational antibodies activate the complement and cause T-cell proliferative responses [18,25] which may influence cardiac function. Three cases of ICI-related MG with cardiac involvement have been described [26–28]. Anti-striational antibodies were measured in only one of them and found negative. Anti-striational antibodies were also found negative in one of our patients (Case 1), who developed MG after treatment with ipilimumab monotherapy. Cases of ipilimumab-related MG are even more uncommon [29,30].

Two distinct types of cardiomyopathy have been associated with MG: giant cell myocarditis (GCM) [31] and Takotsubo cardiomyopathy [32]. Although a myocardial biopsy was not performed in any of our cases, GCM is usually fulminant and fatal; thus, it is not likely to be the cause of the myocardial injury of our patient (Case 3). On the contrary, Takotsubo cardiomyopathy is a transient reversible form of LV dysfunction, with pathognomonic wall motion abnormalities that were absent in our patient. The exact nature of cardiomyopathy in ICI-related MG

has not been studied mainly due to the rarity of the phenomenon, but it is likely different from that of idiopathic MG.

However, the co-development of an axonal neuropathy [with positive anti-GM1 (ganglioside isotype M1) antibodies] and myocarditis has never been described. Anti-GM1 antibodies have been implicated in the pathogenesis of Guillain–Barré syndrome (GBS, especially a motor axonal variant of GBS), multifocal motor neuropathy (MMN) and motor neuron disease as well as in several autoimmune diseases [33]. Reports of neurologic irAEs including cases of GBS and mono- or poly-neuropathies have never described a positivity for anti-GM1 antibodies so far. Nevertheless, since the sensitivity of anti-GM1 antibodies is relatively low (about 40–50%) in well-established cases of MMN [2], it is possible that the same applies for immune-related neuropathies. The coexistence of an axonal neuropathy with myocarditis should not be considered a random event, but rather a case of cross-reactivity of antitumor immune response with antigens expressed by healthy neurons and an unknown myocardial antigen. In a large pharmacovigilance study that identified and characterized significant cardiovascular irAEs through the WHO's global Individual-Case-Safety-Report database, it was identified that supraventricular arrhythmias attributed to the use of ICIs were associated, among others, with neurologic disorders including strokes and encephalitis in 12.6% of the identified cases, while myocarditis was reported to be frequently associated with myasthenia-like symptoms [34].

In conclusion, neurologic and cardiologic irAEs are rare, but usually severe, with high rates of morbidity and fatality. Indeed, in a large meta-analysis of fatal toxic effects associated with ICIs, the neurologic and cardiac toxic effects comprised nearly half (43%) of deaths [35]. The fact that ICIs are now being used in the adjuvant setting for melanoma, that is in patients a significant percentage of whom could have remained disease-free irrespective of the use of adjuvant treatment, makes the emergence of irAEs even more significant; hence, active surveillance for the timely detection and management of rare irAEs, such as neurologic and cardiologic ones, is of cardinal importance.

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Conflicts of interest

Panagiotis Diamantopoulos reports personal fees for presentations and advisory roles from Novartis, Sandoz, Genesis Pharma and Roche. Helen Gogas reports investigational grants and personal fees from BMS, Roche, MSD and Novartis, and personal fees from Amgen and Pierre Fabre. There are no conflicts of interest for the remaining authors.

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