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Review

Emerging PD-1 and PD-1L inhibitors-associated myopathy with a characteristic histopathological pattern

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ABSTRACT

Background and objective: Drug-induced myopathy is among the most common causes of muscle disease. An association has recently been described between programmed death-1 (PD-1)/PD-1 ligand (PD-L1) inhibitors and immune-related adverse events (irAE) affecting the muscle. Here, we report the clinical and pathological findings of nine unrelated patients with PD-1 and PD-L1 inhibitors-associated myopathy.
Methods: We retrospectively analyzed 317 muscle biopsies performed for diagnostic purposes from January 2017 to June 2019. Patients were attended in two tertiary centers and muscle biopsies were performed and analyzed by two myology experts. Muscle biopsies were frozen in cooled isopenthane, cryostat sectioned and stained. Immunohistochemistry studies were also performed as a routine procedure in our lab.
Results: We identified 9 patients receiving anti-PD-1 or PD-L1 inhibitors consulting for either muscle weakness, asthenia, myasthenic-like syndrome or other muscle related-symptoms, along with biopsy-proven inflammatory myopathy. One had concomitant myocarditis. In most of the cases muscle biopsy showed a marked phenomenon of necrosis, macrophagy and muscle regeneration with perivascular inflammatory infiltrates with a large component of macrophagic cells. A tendency to perifascicular atrophy was also noticed. The expression of MHC class I antigens predominated in the perifascicular zones. Raised muscle enzymes were detected in 7 patients.
Conclusion: A characteristic clinic-pathological pattern, including a myasthenia gravis-like syndrome plus myositis was found in patients receiving PD-1 and PD-1 L inhibitors. A large component of macrophages resembling granulomas seems to be the pathological hallmark of the syndrome. Further information is required to understand the wide spectrum of immune-related adverse events involving the muscle during or after treatment with anti-PD-1 inhibitors, but the pathological picture seems to be characteristic.

1. Introduction

The development of cancer is facilitated by a variety of immune mechanisms which include the expression of immune checkpoint molecules, such as programmed cell death 1 (PD1), PD1 ligand (PD-L1) and cytotoxic T-lymphocyte associated protein-4 (CTLA-4), which suppress effector T-cell responses. These inhibitory molecules are not only expressed on the membrane of antigen-stimulated T cells but are

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also observed on macrophages, antigen-presenting cells and other healthy hematopoietic and non-hematopoietic tissue [1].

With the expanding use of these agents the prognosis of patients with certain tumor types has dramatically improved, but their use can be hampered by the onset of specific immune-related adverse effects (irAE) involving any tissue or organ, especially the skin, colon, endocrine organs, lungs, and liver [2].

Despite the increasing reports of irAE as a consequence of the use of immune-checkpoint inhibitors (ICI) in cancer, this is not the case of the skeletal and cardiac muscle complications, with only a few patients reported in medical literature [3–5].

Previous data suggest that PD-1 and PD-L1 inhibitors-associated myopathy may present with a wide range of clinical manifestations and degrees of severity including myasthenia gravis (MG) [6–8], necrotizing myopathy [9–11] or even lethal cardiomyopathy [4,5,12,13]. However, to date, the full spectrum of muscular complications relating to anti-PD-1 therapy and the clinical phenotype are not well known, and neither are other main features concerning histopathology, treatment or outcome [12]. Moreover, the immunopathogenesis of muscle destruction remains unclear.

Here, we report the clinical and pathological findings of nine unrelated patients with PD-1 and PD-L1 inhibitors-associated myopathy.

2. Methods

2.1. Study population

The study was performed at the Muscle Research Unit of the Hospital Clinic of Barcelona (HCB), a referral center for muscle diseases. A retrospective search in our database of all muscle biopsies performed at our institution from January 2017 to September 2019 was made. A total of 317 muscle biopsies were performed for diagnosis purposes, independently of this study. We identified 9 unrelated cases that received treatment with at least one ICI before the onset of myositis. The diagnosis of myositis was supported by the presence of ≥ 3 out of 4 of the following elements: objective muscle weakness, raised serum creatine kinase (CK) levels, electrodiagnostic studies consistent with myopathic process without decrementing response during repetitive nerve stimulation (RNS), or muscle biopsy showing myositis.

2.2. Standard protocol approvals and patient consents

This study was approved by the Hospital Clínic de Barcelona Institutional Review Board, and written informed consent was obtained from each participant, given the non-invasive nature of the study and a minimal potential for harm to study participants. Every muscle biopsy was done exclusively for diagnostic purposes.

2.3. Clinical and demographic features

Patients were treated in their reference center (Hospital Clínic de Barcelona and Vall d'Hebron Hospital) by a multidisciplinary team of internists, neurologists and oncologists. Two myology experts (JMG and JCM) performed and analyzed the muscle biopsies. Clinical data were obtained by taking standardized history and conducting physical examination from the treating physicians at the referral institution and completed when necessary by patient medical records or phone contact. In occasional cases of uncertainty, the patients were invited to come for a personal interview and examination. Data regarding diagnosis at the time of the biopsy procedure and follow-up were registered. Clinical and laboratory findings were systematically collected, including demographic data, clinical patterns of muscle involvement, initial and final diagnoses, previous medical conditions, drug exposure, viral diseases, neoplasia, pulmonary involvement, and any evidence (clinical or biological) of alterations in autoimmunity.

2.4. Procedures

All participants underwent an extensive clinical examination by at least one specialist. Muscle strength was assessed by manual muscle testing. Electrodiagnostic studies were defined as consistent with a myopathic process if patients had abnormal spontaneous activity or myopathic units. Serum samples were tested for antibodies on HEp-2 cells (NOVA Lite®, INOVA Diagnostics, Werfen) and for the presence of myositis-specific and associated autoantibodies with the commercial immunoblot kit EUROLINE Autoimmune Inflammatory Myopathies 16 Ag(DL 1530–1601-4G, Euroimmun, Lübeck, Germany) which include anti-Mi-2 alpha, Mi-2 beta, TIF1g, MDA5, NXP2, SAE1, Ku, PM-Scl100,PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52. Anti hydroxymethylglutaryl-CoA, anti-acetylcholine receptor (AChR)-binding, and anti-muscle specific tyrosine kinase (MuSK) antibodies were tested with radioimmunoassay (RIA) or enzyme-linked immunosorbent assays (ELISA).

2.4.1. Muscle biopsy and staining techniques

Open muscle biopsies were made mainly from the vastus lateralis, deltoid or biceps. The muscle tissue was routinely frozen in isopentane cooled with liquid nitrogen and stored at $-80\,^{\circ}C$. Routine staining techniques included hematoxylin and eosin (H&E), modified Gomori trichrome, periodic acid-Schiff technique, oil red O, Congo red, reduced nicotinamide adenine dinucleotide-tetrazolium reductase, combined cytochrome C oxidase and succinate dehydrogenase, adenosine triphosphatase 9.4, acid phosphatase, alkaline phosphatase, non-specific esterase and myoadenylate deaminase. In addition, antigens of classes I and II (MHC-I and MHC-II), membrane attack complex (MAC) were determined, and anti CD4, CD20, CD68, and CD56 immunostaining was performed on 8-μm acetone fixed cryostat sections. All biopsies were reported by two experienced myopathologists (JMG and JCM). Muscle cell necrosis, muscle cell regeneration as well as inflammatory infiltrate were categorized as mild, moderate or severe in a qualitative fashion after agreement between the two myologists.

3. Results

3.1. Participants

The characteristics of the patients are reported in Table 1. We identified 9 patients with muscle weakness during anti-PD-1 or anti-PD-L1 treatment, 8 of whom were men. The median age at symptom onset was 71.6 years (range 60–84 years). Lung squamous cell carcinoma and melanoma (two each) were the most common cancer (n = 4), followed by pancreatic tumor (n = 2, 1 adenocarcinoma +1 neuroendocrine), thymic carcinoma type AB (n = 1), cholangiocarcinoma (n = 1), and oropharyngeal carcinoma (n = 1). All patients had stage IV metastatic disease and had previously received at least one oncologic treatment (including surgery, radiotherapy or chemotherapy) before immunotherapy, with the exception of one patient who had stage III disease (case 7).

Four patients presented complications during pembrolizumab therapy, two patients during atezolizumab therapy, two more during durvalumab treatment (one was concomitantly treated with tremelimumab), and one patient during nivolumab treatment. Muscle complications occurred after a median of 2.11 (range, 1–4) infusions of anti-PD-1 therapy. The patients receiving atezolizumab and one patient receiving pembrolizumab developed myositis after their first infusion.

3.2. Clinical features of patients with PD-1 and PD-1 L inhibitors-associated myopathy

The onset of clinical manifestations was acute or subacute in all the patients. The usual clinical presentation included asthenia (n = 9), both proximal and distal muscle weakness (n = 7) and also axial muscular

Table 1
Patients' characteristics.

Patient	Sex/Age	Cancer	Anti-PD-1 monoclonal antibodies	Treatment duration (cycles)	Dysphagia	Myasthenic syndrome	Proximal muscle weakness	Distal muscle weakness	Axial muscle weakness	Cardiac involment	CK (UI/L)	AutoAb	Myastheni a gravis Ab
1	Male/70	Pancreathic adenocarcinoma	Atezolizumab	1	Yes	Yes (Diplopia)	Yes	No	No	Yes (AV block)	4470	Ro-60 +	No
2	Male/69	Neuroendocrine pancreatic	Durvalumab	1	Yes	Yes (Diplopia) Drooling	No	No	Dropped-head syndrome	No	2430	Ro-52	AChR[a]
3	Male/84	Metastatic melanoma	Pembrolizumab	1	No	No	Yes	Yes	No	Yes (miocarditis)	359	No	No
4	Male/73	Lung squamous cell carcinoma	Durvalumab	2	No	No	Yes	No	Yes	No	261	No	No
5	Male/65	Thymic carcinoma type AB	Atezolizumab	4	No	No	Yes	No	Dropped-head syndrome	No	1.150	DNA[a]	No
6	Male/82	Lung squamous cell carcinoma	Nivolumab	3	No	Yes (Diplopia)	Yes	Yes	Yes	No	380	No	No
7	Female/60	Oropharingeal scamous cell carcinoma	Pembrolizumab	3	No	No	No	No	No	No	1900	No	No
8	Male/74	Metastatic melanoma	Pembrolizumab	2	Yes	No	Yes	Yes	Dropped-head syndrome	(Raised hs-cTnT[b])	4275	NXP2/Mi2	No
9	Male/68	Metastatic Cholangiocarcinoma	Pembrolizumab	2	Yes	Yes (Diplopia Ptosis palpebral)	Yes	No	No	(Raised hs-cTnT[b])	11,450	No	No

[a] Acetylcholine Receptor Antibody.
[b] hs-cTnT: High-sensitive cardiac troponin T.

weakness (n = 5). Axial weakness was most often at the cervical level (n = 3, dropped-head syndrome), whereas trunk weakness was rarely noticed. In most of the cases, myalgia preceded the muscle weakness. Other symptoms included dysphagia (n = 4), dyspnea (n = 2), and ocular symptoms such as diplopia (n = 4) or palpebral ptosis (n = 1) (Fig. 1).

The time to maximum symptom severity varied from days to months, but in most of the cases it increased to its maximal peak in the first two weeks from the onset. Cardiac impairment was found in three cases, with evidence of associated myocarditis in one case (Fig. 2). Two patients required invasive ventilation due to respiratory muscle involvement. Moreover, four patients presented with myasthenic-like syndrome three without anti-AchR or anti-MuSK antibodies.

Four patients died: two from cancer progression (lung and pancreatic tumor), one from fatal myocarditis and one because of myositis complications (respiratory failure due to respiratory muscle involvement).

3.3. Laboratory findings

Raised serum CK levels were detected in 7 out of 9 patients (median level 2.964 U/L). Troponin I levels were not routinely performed, but they were markedly increased when myocarditis was associated (case 3) and mild elevated in two other patients. Anti-AchR antibodies were positive in one patient, and anti-MuSK autoantibodies were negative in all of the patients. Importantly, myositis-specific antibodies were only detected in one patient (NXP2/Mi2), but this was likely a false positive result. One patient had high-titer antinuclear antibodies (1/640, fine speckled pattern) with positive anti SSA/Ro52 and Ro-60 autoantibodies with high grade atrioventricular heart block, and another patient developed anti-DNA and smooth-muscle antibodies without specific autoimmune-related features other than autoimmune hepatitis.

3.4. Electrophysiologic and imaging studies

Electromyoneurography (EMG) was performed in all the patients, showing a myopathic pattern, characterized by the presence of abnormal spontaneous activity and high frequency discharges, which were observed mainly in the proximal limbs, trapezius, and deltoid muscles. The motor action potential obtained was of low amplitude without changes after muscle contraction or repetitive nerve stimulation (RNS). Furthermore, single fiber stimulation consistently showed no significant increase in the jitter phenomenon in all the cases, including the two patients who presented with myasthenic-like syndrome.

3.5. Histopathology findings in skeletal and cardiac muscle

The results of the histopathologic analysis are shown in Fig. 2 and Table 2. In most of the cases a marked phenomenon of necrosis (n = 9, moderate to severe), macrophagy and muscle regeneration was observed. Moreover, histological studies revealed endomysial inflammatory infiltrates in all the samples and severe perimisial and perivascular inflammatory infiltrates with a large component of macrophagic cells, which were focally clustered (n = 9, severe). A tendency to perifascicular atrophy was also noticed.

The MHC-I expression predominated in the perifascicular zones of the affected areas, and MHC-II was positive in only three cases (patchy pattern). Sarcoplasmic deposits of C5b-9 were observed in both necrotic fibers and in some capillaries. The inflammatory infiltrate cells in all muscle biopsies were predominantly CD-68 + . A necropsy was carried out in one of the seven patients, showing acute multifocal myocarditis probably within the context of the systemic inflammatory myopathy, which was also attributed to anti-PD1 therapy. In the pathological examination of the myocardial tissue, multifocal confluent areas of myofiber necrosis with macrophages, and inflammatory infiltrates

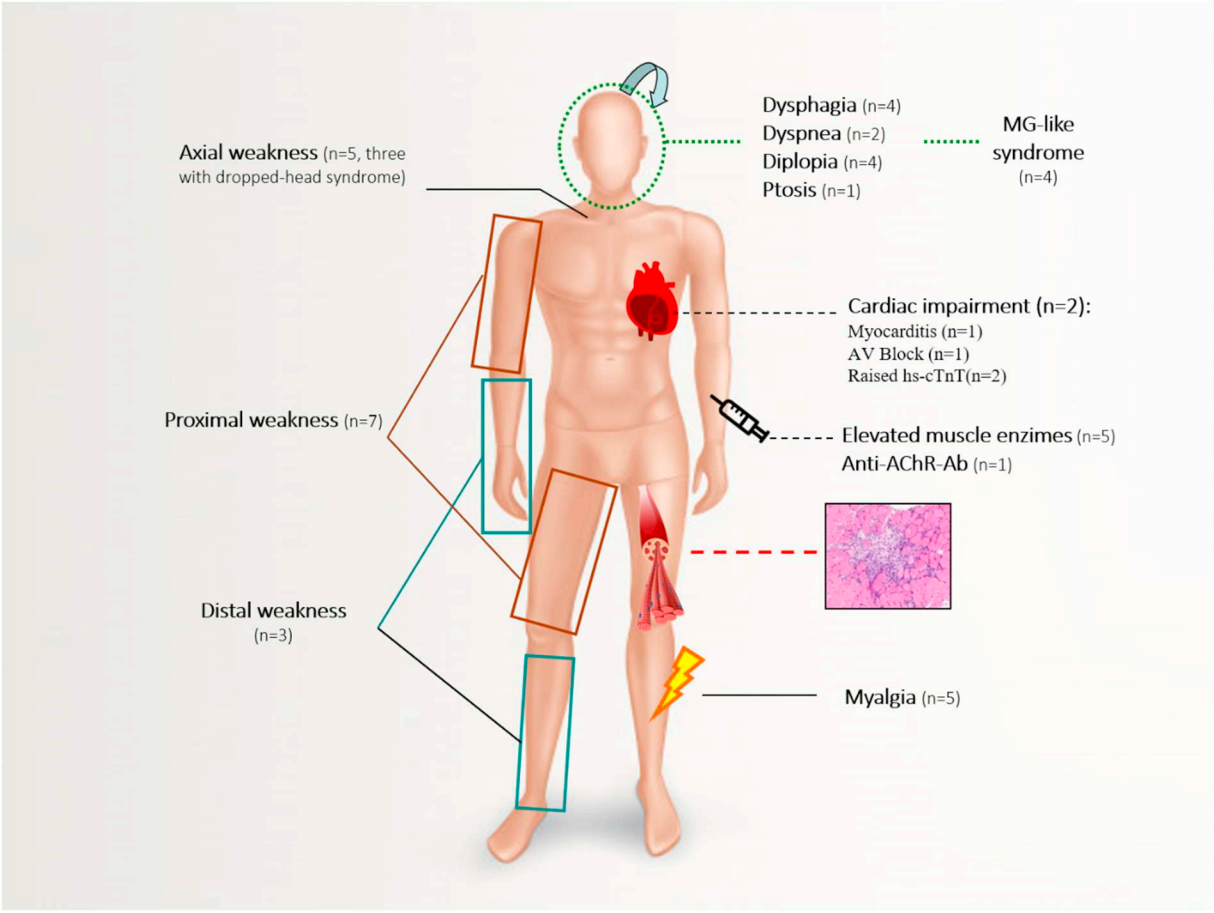

Fig. 1. Clinical and histopathological features of patients with PD-1 and PD-1L inhibitors-associated myopathy. MG: Myasthenia Gravis. hs-cTnT: High-sensitive cardiac troponin T.

consisting of CD3-positive and CD68-positive cells, as well as rare CD-20-positive cells, were observed (Fig. 3).

3.6. Treatment of myositis and outcome

Regarding therapeutic management, immunotherapy with ICI had been discontinued in all patients by the time of myositis diagnosis, with the exception of one patient who presented a mild variant of the disease in which it was initially possible to maintain immunotherapy (case 7). Nonetheless, all patients received immune-modulating therapy. The mean duration of symptoms until the initiation of immune treatment significantly differed among patients, being of 20.6 days (range, 1–65). Seven patients received high-dose IV corticosteroids (1000–2000 mg methylprednisolone daily) for three days and after they continued prednisone (0.5 mg/Kg/day); two patients received oral corticosteroids (1 mg/kg prednisone daily) at the beginning. Additionally, five patients received courses of intravenous immunoglobulin (2 g/kg, total dose) in association with methylprednisolone, of whom two also received plasma exchanges during the peak phase. Two of these patients required invasive ventilation due to respiratory muscle involvement and nutritional support. Both died after withdrawal of ventilatory support from acute respiratory failure due to respiratory muscle involvement and acute myocarditis, respectively.

All five patients who survived required subsequent maintenance oral prednisone in addition to monthly IV immunoglobulin (2 g/kg) or other immunosuppressant drug. The cause of death was attributed to immunotherapy in only 2 patients (cases 3 and 6).

Two patients are still on an oral prednisone regimen and mofetil mycophenolate due to recent diagnosis. Tumor response to treatment with ICI was difficult to assess taking into account the high rate of fatal outcome in our cohort. However, of the two survivors, one patient presented partial response and the other transient disease stabilization before starting a new oncospecific treatment. No patient received subsequent treatment with any ICI.

4. Discussion

In the present study, we describe a series of patients who developed adverse muscular events after immunotherapy treatment. A unique phenotype with a spectrum of clinical features and a characteristic muscle biopsy pattern is reported. Besides most common immune manifestations related to immunotherapy such as autoimmune endocrinopathies, hepatitis or arthritis, muscle involvement is rare.

Identification of new neuromuscular symptoms in patients receiving anti-PD-1 antibodies may be a challenge, as these patients may be at greater risk of developing muscular complications either related to their underlying disease or as a result of an irAE. For this reason, a careful differential diagnosis and search for other potential causes must be performed.

Muscle weakness must be distinguished from fatigue or asthenia, which are separate conditions that can coexist with weakness, and are frequently seen in metastatic cancer patients. Recent studies have found fatigue to be the most common irAE among patients treated with ICI, with an incidence of 16%–37% with anti-PD-1 agents and 12%–24% with anti-PD-L1 agents [14].

The pattern and the severity of weakness, as well as the existence of associated symptoms and the time of onset, can help clinicians determine whether the etiology of muscle weakness is related to their

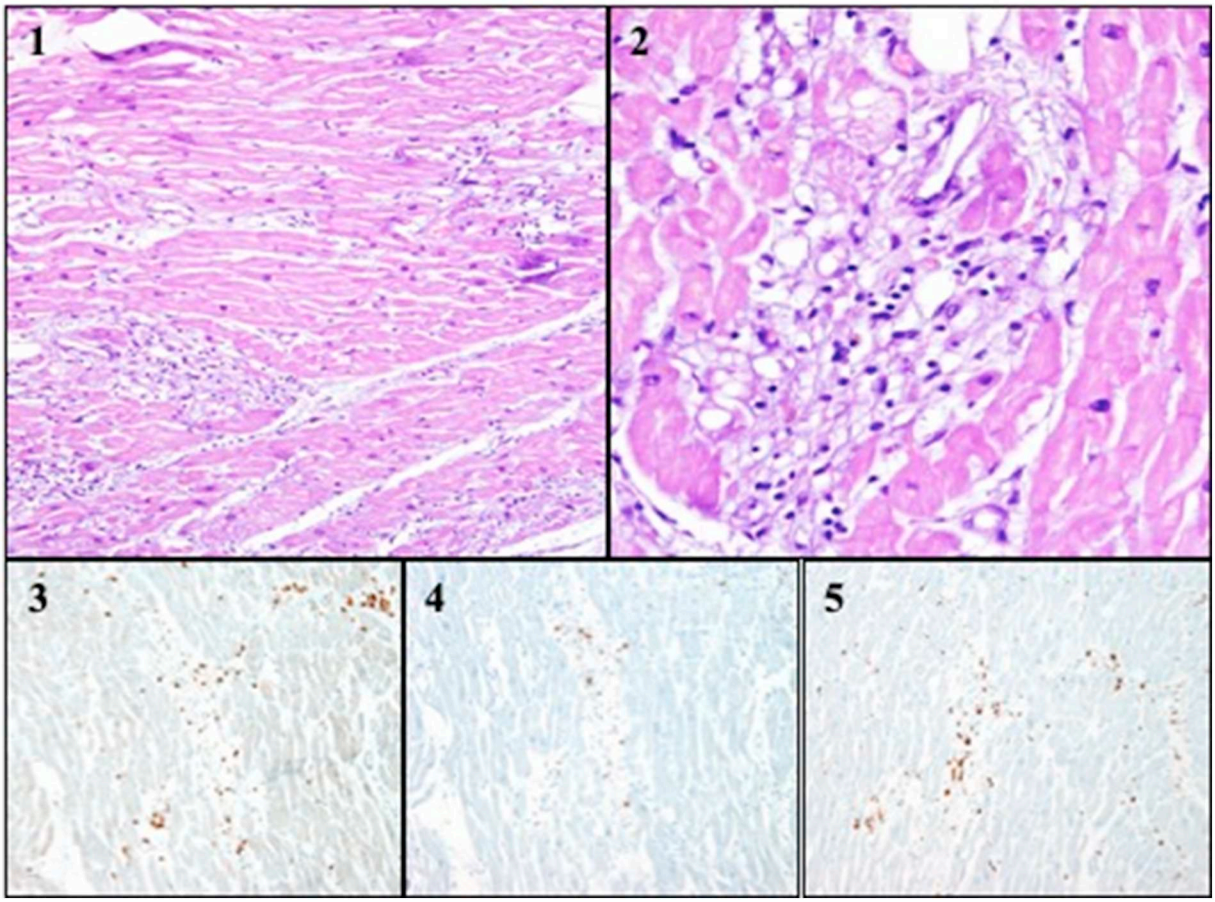

Fig. 2. 1–2) Hematoxylin-eosin stain of myocardium harboring multifocal confluent areas of myofiber necrosis replaced by macrophages. 3) Anti CD3 immunostaining. 4) anti CD20 immunostaining. 5) anti CD68 immunostaining.

underlying disease, drug-induced or related to other medical conditions. Fatigue or asthenia due to immunotherapeutic agents is usually mild and is not associated with other systemic symptoms. By contrast, muscle irAE seems to occur earlier and may appear in association with other symptoms such as myalgia, limb-girdle weakness, ptosis or oculomotor weakness, as described above. Another important feature is the fact that muscle weakness is often preceded by myalgia, and appears within a short period of time after treatment initiation.

Therefore, it is important to establish some defining criteria that allow the clinician to discern when a myopathy is due to ICI therapy, or instead, is related to the underlying disease. The ICI-related myopathy was characterized by an early onset of neuromuscular symptoms, occurring in most of the cases after a median of two infusions of anti-PD-1 therapy. Thus, in the first 30 days of ICI treatment the majority of patients were already symptomatic. The usual clinical presentation included asthenia, both proximal and distal limb muscle weakness, and also, axial muscular weakness, associating myalgia and oculomotor weakness in a non-negligible part of the cases. Additionally, a marked increase in CK levels with a myopathic pattern on EMG, as well as negative anti-myositis-associated autoantibodies were the rule.

Recent studies have shown a correlation between pre-existing muscle AChR Ab and the development of immune-related myositis in patients with recurrent thymoma or recurrent thymic carcinoma who were treated with avelumab. Although it is still unclear, the existence of AChR Ab seems to identify patients at risk for developing myositis with ICI. [15].

With respect to the histopathological features, myopathy due to ICI was characterized by necrosis with a large component of macrophage cells in clusters mimicking a pseudogranulomatous pattern [9]. Moreover, histopathological studies provided additional information

Table 2
Pathological findings.

Patient	Muscle necrosis	Muscle regeneration CD56	Endomysial inflammatory infiltrate	Perimysial and perivascular inflammatory infiltrate	Non-necrotic invasion cell by T lymphocytes	Positive for MHC-I immuno-staining	Positive for MAC immuno-staining
1	+ +	+ +	+	+ + +	+	Yes	Yes
2	+ +	+ + +	+	+ + +	+	Yes	Yes
3	+ + +	+ +	+	+ + +	+	Yes	Yes
4	+ +	+ + +	+	+ +	+	Yes	Yes
5	+ +	+ +	+	+ + +	+ +	Yes	Yes
6	+ +	+	+ +	+ + +	+	Yes	Yes
7	+ +	+	+	+ +	+	Yes	Yes
8	+ + +	+ +	+	+ + +	+	Yes	Yes
9	+ +	+ +	+ +	+ + +	+	Yes	Yes

+ (Mild), + + (Moderate), + + + (Severe).

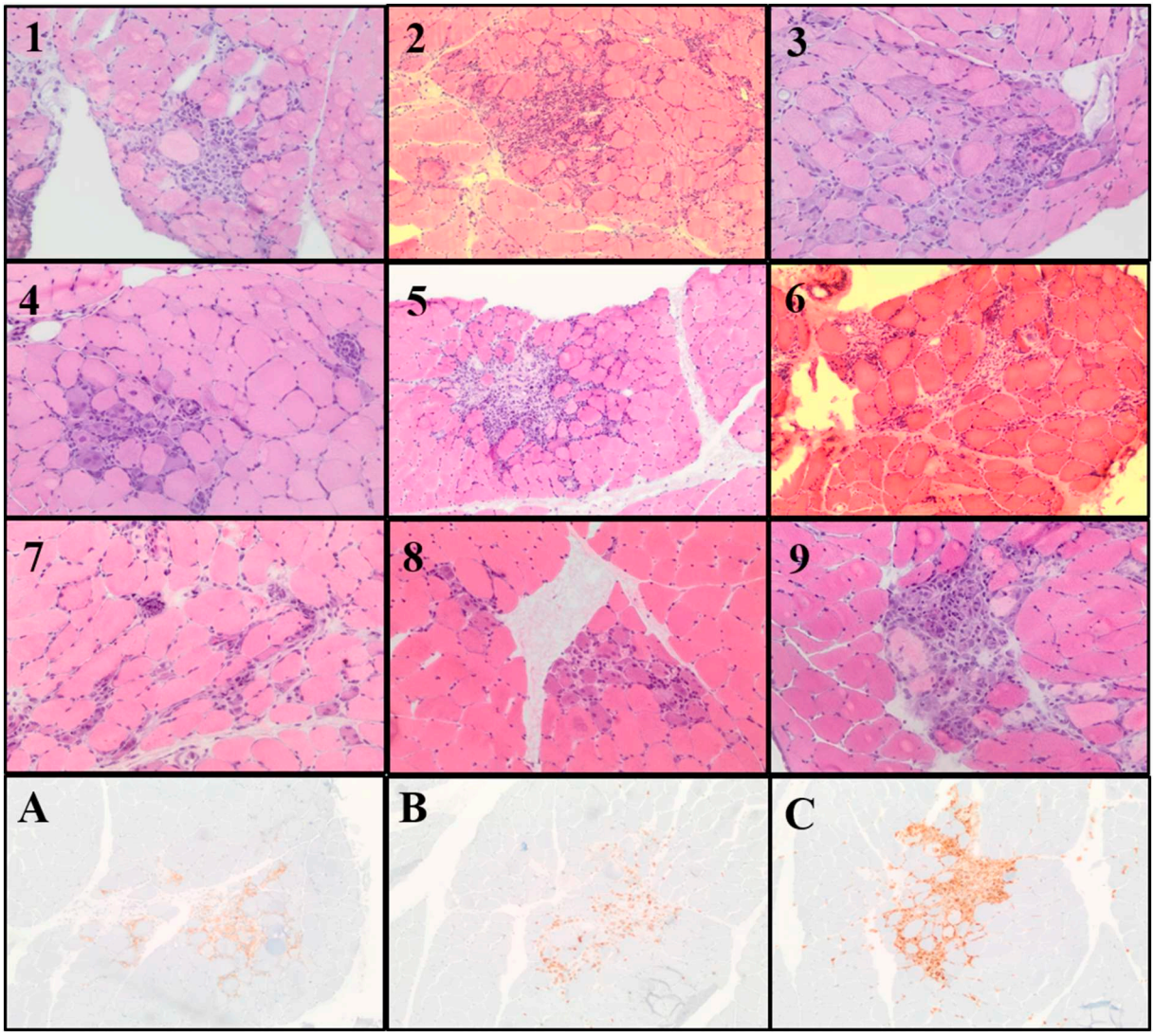

Fig. 3. 1–9 (patients one to nine). Cross-sectional H&E stained muscle-biopsy samples with perivascular inflammatory infiltrates. A) Anti CD 4 immunostaining. B) anti CD 20 immunostaining. C anti CD68) immunostaining.

regarding the suspected pathogenesis of irAE targeting the musculoskeletal system. Myopathy due to ICI appears in the muscle biopsy as a unique and characteristic pattern of inflammatory changes, far from any known inflammatory myopathy.

It is characteristic to observe extensive zones of necrosis with focal clusters of macrophages and T-cell infiltrates resembling a pseudogranulomatous pattern, as other authors have described [9]. Curiously, however, in our cohort we described for the first time that the histological pattern of the myocardial biopsy was consistent with the pattern found in the skeletal muscle biopsy.

While there has been a previous report of myocardial involvement in patients receiving ICI based on clinical or analytic data, our series demonstrates the first case to date of proven myocarditis with a histopathological pattern similar to the muscle biopsy. Touat et al. [16] described one case of myocardial involvement with focal areas of myofiber necrosis, foci of eosinophilic cardiomyocytes with large nuclei in the absence of the clusters of macrophage.

The differential diagnosis should essentially include a paraneoplastic inflammatory myopathy, the asthenia-cachexia syndrome due to disease progress or an irAE as a consequence of ICI therapy.

Many similarities to other publications were observed when performing this study. The baseline characteristics of the patients in other series appear to be consistent with our findings, with a similar median age at symptom onset, underlying cancer and median delay between ICI initiation and myositis onset, as well as the frequency of occurrence of other irAE [14,16]. Nonetheless, clinical features of patients with PD-1 or PD-L1-associated myopathy are similarly described with a higher incidence of myocarditis or MG in some other series in comparison to our own [4,5]. When considering laboratory findings, serum CK levels were found to be markedly increased in almost all the patients, and a negative antibody profile was the rule. As mentioned above, muscle biopsy revealed a characteristic pattern resembling a pseudogranulomatous pattern that has also been described in recent articles as “a severe necrotizing myositis with focal clusters of myofiber necrosis and significant macrophages and T-cell infiltrate” [9,16].

When suspected, PD-1 treatment discontinuation was recommended and corticosteroid treatment was the first line agent in a high-dose regimen in addition to intravenous immunoglobulin or plasma exchange in severe forms when required [16–18]. Although it is difficult to compare therapeutic strategies, our little experience indicates that rapid initiation of corticosteroids and ICI withdrawal are mandatory. Only three patients in our series remain alive, with both being close to discontinuing corticosteroid treatment because of improvement of their muscle symptoms.

In summary we want to emphasize that future identification of additional cases of ICI-related muscular disorder is quite probable

taking into account the approval of new monoclonal antibodies targeting immune-checkpoint proteins and their use as standard of care of different tumor types. Clinicians should be aware of this rare, albeit life threatening, iRAE and be able to achieve a good diagnosis. A characteristic clinicopathological phenotype that includes a different degree of combined limb-girdle, axial, and oculomotor weakness joined with a unique pattern of pseudogranulomatous necrotic infiltrate of macrophages and T-cells, will prompt the attention helping to reach the correct diagnosis and the appropriate early immunosuppressive treatment.

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