



Original Research

# Myositis and neuromuscular side-effects induced by immune checkpoint inhibitors



Alvaro Moreira <sup>a</sup>, Carmen Loquai <sup>b</sup>, Claudia Pföhler <sup>c</sup>,  
Katharina C. Kähler <sup>d</sup>, Samuel Knauss <sup>e</sup>, Markus V. Heppt <sup>f</sup>,  
Ralf Gutzmer <sup>g</sup>, Florentia Dimitriou <sup>h</sup>, Friedegund Meier <sup>i</sup>,  
Heidrun Mittel-Rink <sup>b</sup>, Gerold Schuler <sup>a</sup>, Patrick Terheyden <sup>j</sup>,  
Kai-Martin Thoms <sup>k</sup>, Matthias Türk <sup>l</sup>, Reinhard Dummer <sup>h</sup>,  
Lisa Zimmer <sup>m</sup>, Rolf Schröder <sup>l</sup>, Lucie Heinzerling <sup>a,\*</sup>

<sup>a</sup> Department of Dermatology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Germany

<sup>b</sup> Department of Dermatology, University Hospital of Mainz, Mainz, Germany

<sup>c</sup> Department of Dermatology, Saarland University Medical School, Homburg, Germany

<sup>d</sup> Department of Dermatology, Skin Cancer Center, University Hospital Schleswig-Holstein (UKSH), Campus Kiel, Kiel, Germany

<sup>e</sup> Department of Experimental Neurology, Charité Universitätsmedizin Berlin, Germany

<sup>f</sup> Department of Dermatology and Allergy, University Hospital, LMU Munich, Frauenlobstr. 9-11, 80337 Munich, Germany

<sup>g</sup> Skin Cancer Center Hannover, Department of Dermatology and Allergy, Hannover Medical School, Germany

<sup>h</sup> Department of Dermatology, University Hospital Zurich, Switzerland

<sup>i</sup> Department of Dermatology, University Hospital Dresden, Germany

<sup>j</sup> Department of Dermatology, University of Lübeck, Lübeck, Germany

<sup>k</sup> Department of Dermatology, University Hospital Göttingen, Germany

<sup>l</sup> Department of Neuropathology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Germany

<sup>m</sup> Department of Dermatology, University Duisburg-Essen, Germany

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## KEYWORDS

Myositis;  
Immune checkpoint

**Abstract** *Aim:* To characterise clinical presentation, laboratory and histopathologic characteristics and assess the treatment and outcome of neuromuscular side-effects of checkpoint therapy. *Methods:* The side-effect registry and the institutional database from ten skin cancer centres were queried for reports on myositis and neuromuscular side-effects induced by checkpoint inhibitors.

*Abbreviations:* CXP, checkpoint inhibitors; irAEs, immune-related adverse events; sAEs, serious adverse events; CK, creatine kinase.

\* *Corresponding author:* Department of Dermatology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), 91054 Erlangen, Germany. Fax: +49 9131 85 33096.

*E-mail address:* [Lucie.Heinzerling@uk-erlangen.de](mailto:Lucie.Heinzerling@uk-erlangen.de) (L. Heinzerling).

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inhibitors;  
Neuromuscular side effects;  
Tocilizumab

In total, 38 patients treated with ipilimumab, tremelimumab, nivolumab and pembrolizumab for metastatic skin cancer were evaluated and characterised.

**Results:** Myositis was the most frequent neuromuscular adverse event. In 32% of cases, myositis was complicated by concomitant myocarditis. Furthermore, cases of isolated myocarditis, myasthenia gravis, polymyalgia rheumatica, radiculoneuropathy and asymptomatic creatine kinase elevation were reported. The onset of side-effects ranged from the first week of treatment to 115 weeks after the start of therapy. Most of the cases were severe (49% grade III–IV Common Terminology Criteria for Adverse Events), and there were two fatalities (5%) due to myositis and myositis with concomitant myocarditis. Only half of the cases (50%) completely resolved, whereas the rest was either ongoing or had sequelae. Steroids were given in 80% of the resolved cases and in 40% of the unresolved cases.

**Conclusion:** Immune-mediated neuromuscular side-effects of checkpoint inhibitors greatly vary in presentation and differ from their idiopathic counterparts. These side-effects can be life threatening and may result in permanent sequelae. Occurrence of these side-effects must be taken into consideration for patient information, especially when considering adjuvant immunotherapy with anti-programmed cell-death protein 1 (PD-1) antibodies and monitoring, which should include regular surveillance of creatine kinase.

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### Key points

- Question: Are neuromuscular side-effects of immune checkpoint inhibitors a different entity than classic neurologic disorders?
- Findings: Neuromuscular side-effects of checkpoint inhibitors are still underdetected and underreported, which probably delays proper treatment. Clinical presentation, laboratory findings and pathology of immune-related myopathies differ greatly from those of idiopathic inflammatory myopathies.
- Meaning: Characterisation of the new entities of checkpoint-induced pathologies should lead to a harmonised approach for detection, diagnostic workup and treatment especially for rare events.

## 1. Introduction

Checkpoint inhibitors (CXP) induce substantial clinical benefit in multiple tumour entities, including melanoma, non-small-cell lung cancer and renal cell cancer. However, with their increasing use, a growing number of physicians will be confronted with immune-related adverse events (irAEs), some of which are serious and may have fatal outcomes [1–3].

While monotherapy with anti-programmed cell-death protein 1 (PD-1)/programmed cell-death protein-ligand 1 (PD-L1) antibodies induces grade III/IV side-effects in 10–20% of patients [4,5], monotherapy with the anti-CTLA-4 antibody ipilimumab is more likely to induce serious adverse events (sAEs) with 27% grade III/IV sAEs [6] and for combination immunotherapy, 55% grade III/IV side-effects were documented [7]. While thyroid

dysfunction and arthralgias are more frequent with nivolumab and pembrolizumab, colitis and hypophysitis are more commonly observed with ipilimumab [4,5,7]. However, the spectrum of side-effects is similar for the checkpoint inhibitors, and all organ systems can be involved. For combination therapy, more than one organ system is involved in about one-third of patients [8,9].

Some adverse events, such as autoimmune myocarditis, may be more common than previously thought [10–12]. A multicentre study of 35 cases showed that various presentations, such as cardiovascular death, cardiogenic shock, cardiac arrest and haemodynamically significant complete heart block, can be induced and that early diagnosis and treatment with corticosteroids is crucial [13]. Myocarditis was reported in clinical trials with anti-PD-1 antibodies and in postmarketing use [10,12,14–19]. Cardiac failure was induced by pembrolizumab in 0.4% of the patients (KEYNOTE-006 trial) and myocarditis in 0.5% and 0.2% in patients with Hodgkin lymphoma (KEYNOTE-087 trial) [20,21] and the adjuvant melanoma trial [22], respectively. The prescribing information of, e.g. nivolumab, states 5% cardiologic events as compared with 0% in the control group.

Neuromuscular side-effects include musculoskeletal pain, myositis, polymyalgia rheumatica and ocular myositis, among others. Myositis, a known autoimmune side-effect induced by checkpoint inhibitors (irMyositis), occurs in 1% of patients treated with anti-PD-1 antibodies (prescribing information of Opdivo®) with one fatality in the adjuvant pembrolizumab trial [22] and in less than 1% of ipilimumab-treated patients (prescribing information of Yervoy®). Outcomes and risk factors are not yet fully characterised. Cases of myositis induced by nivolumab [23–29] and ocular myositis [30–32] and myopathy induced by ipilimumab [8,33–35] have been reported.

Myalgia was reported in 4–5% of patients in two clinical studies investigating anti-PD-1 monotherapy with only one grade III/IV event in a total of 224 patients [36,37]. No other musculoskeletal disorders were reported in these studies. However, it is of note that many of these studies do not report side-effects below a certain threshold or if they are not ‘of special interest’. In the prescribing information of pembrolizumab, musculoskeletal pain is reported as a common adverse reaction (reported in  $\geq 20\%$  of patients).

An analysis of the adverse event register for CXP side-effects including 496 patients treated with anti-PD-1 therapy documented arthralgia in eight patients (1.6%), myositis/myalgia in seven patients (1.4%) and polymyalgia rheumatica and muscle spasms or muscle weakness in two patients (0.4%) each. Grade I–IV musculoskeletal irAEs were treated with systemic corticosteroids in 52% of cases (n = 21) with a prompt response in 45% (n = 5), while 55% (n = 6) did not fully resolve [3]. The 120 documented side-effects of patients treated with ipilimumab reported only one patient with myalgia and another one who developed myocardial fibrosis [38]. A study from the Mayo Clinic with 654 patients receiving PD-1 inhibitors (pembrolizumab = 389; nivolumab = 264; both = 1) identified five patients (0.7%); all of them receiving pembrolizumab with myopathies (two necrotising myopathies, one early dermatomyositis (DM) and two non-specific myopathies) [39].

Serious muscular complications of CXP such as myasthenia gravis (MG) [40–44] and myopathy leading to respiratory symptoms [45] have been reported after therapy with nivolumab or ipilimumab and with combination of CTLA-4 and PD-L1 inhibitors [46]. A Japanese study with 10,277 patients who received monotherapy with either nivolumab or ipilimumab reported 12 MG cases among patients treated with nivolumab but none among patients treated with ipilimumab [47]. In the present study, we retrospectively analysed the side-effect registry and the institutional database from ten centres for reports on myositis and neuromuscular side-effects with special focus on clinical presentation, laboratory and histopathologic characteristics and treatment and outcomes.

## 2. Methods

### 2.1. Patient and treatment characteristics

All cases of autoimmune neuromuscular disorders associated with checkpoint inhibitor therapy reported in our side-effect register were analysed. Additionally, skin cancer centres in Germany and Switzerland were queried for submission of cases of patients with immune-related neuromuscular adverse events induced by treatment with CXP from institutional databases. Supplemental data were collected retrospectively. A total of 38 patients from

ten cancer centres with neuromuscular side-effects in association with checkpoint inhibitor treatment were characterised. The observation period was 5 and a half years from February 2013 to July 2018. Patients included suffered from metastatic Merkel cell carcinoma or melanoma.

They were treated with anti-PD-1 antibodies (pembrolizumab, n = 22; nivolumab, n = 5), the anti-CTLA-4 antibody ipilimumab (n = 2) or combination immunotherapy (ipilimumab + nivolumab, n = 8; ipilimumab + pembrolizumab, n = 1). For patients' characteristics, see Table 1.

The institutional review board of the Friedrich-Alexander-University Erlangen-Nuremberg approved this study (Nr. 17\_16 Bc).

## 3. Results

Neuromuscular toxicity induced by checkpoint inhibitor therapy was reported in 38 patients with metastatic disease including one patient receiving adjuvant treatment. Patients received anti-PD-1 antibodies, the anti-CTLA-4 antibody ipilimumab or combination immunotherapy (Table 1). Patients had a mean age of 68 years (range 21–88); 71% were men, and the median onset of the symptoms was 19 weeks after the start of therapy (range 1–115 weeks). Myositis (19 cases) was the most frequent event and was complicated in 32% of cases (n = 6) by concomitant myocarditis. There were four cases of myocarditis without clinical signs of myositis. Myalgia (seven cases), polymyalgia rheumatica (three cases), asymptomatic elevated serum creatine kinase (CK; two cases), radiculoneuropathy (one case), DM (one case) and MG (one case) were also reported (Table 2). Side-

Table 1  
Description of the cohort of patients.

Characteristic	Patients (n = 38)
Neoplasm	
Merkel cell carcinoma	1
Cutaneous melanoma	28
Mucosal melanoma	1
Uveal melanoma	1
MUP	6
Not specified	1
Checkpoint inhibitor	
Pembrolizumab	22
Nivolumab	5
Ipilimumab	2
Ipilimumab + nivolumab	8
Ipilimumab + pembrolizumab	1
Stage (AJCC)	
IIIC	8
IV	30
Mutation status	
BRAF mutant	6
NRAS mutant	9
BRAF, NRAS, c-Kit wild type	7
BRAF wild type (further mutations not tested)	8
BRAF and NRAS wild type (c-Kit not tested)	2
Unknown or not applicable	6

Table 2  
Information on the treatment and adverse event.

Patient	Side-effect	Grade	CK levels	Type of CXP-therapy	Treatment of side-effect	Outcome of side-effect	Action regarding CXP	Antibodies
1	Asymptomatic CK elevation	2	CK was elevated until a maximum of 680 U/l	Nivolumab	None	Ongoing	Continued	Not measured
2	Asymptomatic CK elevation	2	CK was elevated until a maximum of 493 U/l	Pembrolizumab	None	Ongoing	Continued	Not measured
3	Dermatomyositis	3	CK normal during side-effect but troponin was elevated until a maximum of 23 ng/l	Ipilimumab	Steroids and immunoglobulin therapy	Resolved	Stopped	Negative
4	Myalgia	1	CK normal during side-effect	Pembrolizumab	None	Ongoing	Continued	Not measured
5	Myalgia	1	CK normal during side-effect	Nivolumab	None	Ongoing	Continued	Not measured
6	Myalgia	1	CK was elevated until a maximum of 195 U/l	Pembrolizumab	None	Ongoing	Continued	Not measured
7	Myalgia	1	N/A	Pembrolizumab	None	Ongoing	Continued	ANA borderline positive
8	Myalgia	2	CK was slightly elevated until a maximum of 222 U/l	Pembrolizumab	None	Resolved	Interrupted	Negative
9	Myalgia and arthralgia	3	CK normal during side-effect	Pembrolizumab	Steroids	Resolved	Continued	Negative
10	Myalgia and enthesopathy	3	CK normal during side-effect	Ipilimumab	Steroids	Resolved	Stopped	Not measured
11	Myasthenia gravis	3	CK was elevated until a maximum of 1959 U/l	Pembrolizumab	Steroids and pyridostigmine	Sequelae	Stopped	Negative
12	Myocarditis	2	CK normal during side-effect	Ipilimumab + nivolumab	Steroids	Ongoing	Stopped	Not measured
13	Myocarditis	4	Three months before diagnosis of side-effect CK 501 U/l, during side-effect normal levels	Ipilimumab + nivolumab	Steroids	Sequelae	Interrupted	Not measured
14	Myocarditis	4	One week before diagnosis of side-effect CK 288 U/l, during side-effect normal levels	Ipilimumab + pembrolizumab	Steroids	Resolved	Stopped	Not measured
15	Myocarditis	4	N/A	Nivolumab	Steroids	Resolved	Stopped	Not measured
16	Myositis	1	CK 2235 U/l at presentation; during side-effect, elevated until a maximum of 7697 U/l	Pembrolizumab	None	Sequelae	Interrupted	Negative
17	Myositis	1	CK at presentation 1716 U/l; troponin at presentation 164 ng/l	Ipilimumab + nivolumab	Steroids	Resolved	Stopped	Negative
18	Myositis	1	CK at presentation 1075 U/l; troponin at presentation 54 ng/l	Ipilimumab + nivolumab	Steroids	Resolved	Stopped	Not measured
19	Myositis	2	N/A	Pembrolizumab	Steroids	Sequelae	Stopped	Anti-TIF1-gamma positive
20	Myositis	2	CK was elevated until a maximum of 263 U/l	Pembrolizumab	None	Resolved	Interrupted	Anti-SRP positive
21	Myositis	2	CK was elevated until a maximum of 500 U/l	Pembrolizumab	None	Resolved	Continued	Negative

(continued on next page)

Table 2 (continued)

Patient	Side-effect	Grade	CK levels	Type of CXP-therapy	Treatment of side-effect	Outcome of side-effect	Action regarding CXP	Antibodies
22	Myositis	3	CK was elevated until a maximum of 1836 U/I and troponin to a maximum of 199.1 pg/ml	Pembrolizumab	Steroids	Sequelae	Stopped	Negative
23	Myositis	3	Normal	Nivolumab	Steroids	Resolved	Interrupted	ANA borderline positive
24	Myositis	4	CK normal during side-effect	Ipilimumab + nivolumab	Steroids	Sequelae	Stopped	Negative
25	Myositis	4	CK already elevated before side-effect as myositis has known medical condition, which worsened with CXP	Pembrolizumab	Steroids and immunoglobulin therapy	Resolved	Stopped	Negative
26	Myositis	4	CK elevated until 3051 U/I; CK-MB elevated until 66 U/I	Pembrolizumab	None	Resolved	Stopped	Not measured
27	Myositis and myasthenia gravis	5	CK was elevated until a maximum of 5800 U/I and troponin to a maximum of 743 pg/ml	Pembrolizumab	Steroids and pyridostigmine	Death	Stopped	Negative
28	Myositis and polyneuropathy	3	CK normal during side-effect	Ipilimumab + nivolumab	Steroids	Resolved	Interrupted	Negative
29	Myositis and myocarditis	1	CK at presentation 1626 U/I; troponin at presentation 332 ng/l	Pembrolizumab	Steroids	Resolved	Stopped	Negative
30	Myositis and myocarditis	2	CK was elevated until a maximum of 2505 U/I and troponin to a maximum of 170 pg/ml	Pembrolizumab	Steroids	Death (suicide)	Stopped	Negative
31	Myositis and myocarditis	3	CK normal during side-effect	Pembrolizumab	Steroids	Ongoing	Stopped	Negative
32	Myositis and myocarditis	3	CK was elevated until a maximum of 6000 U/I	Pembrolizumab	Steroids and immunoglobulin therapy	Ongoing	Stopped	Negative
33	Myositis and myocarditis	4	CK was elevated until a maximum of 6991 U/I and troponin to a maximum of 547 pg/ml	Ipilimumab + nivolumab	Steroids and immunoglobulin therapy	Resolved	Stopped	Ro52-B positive, EJ-B borderline positive
34	Myositis and myocarditis	5	CK was elevated until a maximum of 5618 U/I and troponin to a maximum of 10.000 pg/ml	Nivolumab	Steroids	Death	Stopped	PL-7-B borderline positive, PL-12B positive, SRP-B positive
35	Polymyalgia rheumatica	3	CK normal during side-effect but troponin was elevated until a maximum of 670 pg/ml	Pembrolizumab	Steroids	Resolved	Interrupted	PL-7-B borderline positive
36	Polymyalgia rheumatica	3	CK normal during side-effect	Pembrolizumab	Steroids and tocilizumab	Ongoing	Continued	SRP-B positive
37	Polymyalgia rheumatica	N/A	Normal	Pembrolizumab	Steroids	Resolved	Interrupted	Not measured
38	Radiculoneuropathy	3	CK normal during side-effect	Ipilimumab + nivolumab	Steroids	Resolved	Continued	Not measured

CK, creatine kinase; CXP, checkpoint inhibitors; ANA, antinuclear antibody; MB, muscle/brain.

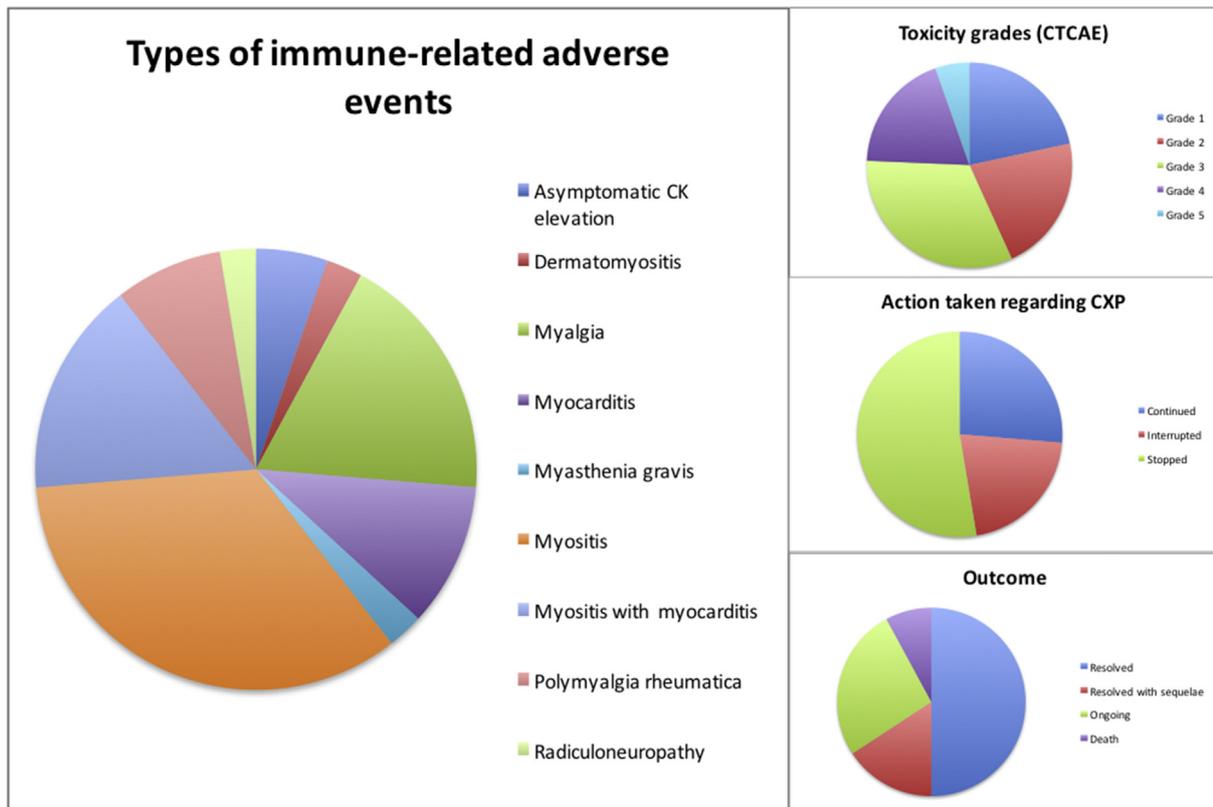


Fig. 1. Types of immune-related adverse events, toxicity grades, action taken regarding checkpoint inhibitors on side-effect and outcomes. CK, creatine kinase; CTCAE, Common Terminology Criteria for Adverse Events.

effects were severe in 49% of the cases (CTCAE grade III–IV) and fatal in two cases (5%; see Fig. 1). These two patients died of myositis (patient #27) and concomitant myositis and myocarditis (patient #34), respectively. A third patient died by suicide.

### 3.1. Signs and symptoms

Symptoms included ocular symptoms (two cases), dyspnoea (three cases), problems in speaking/swallowing (five cases), proximal muscle weakness of the limbs (12 cases) and myalgia (16 cases). While some of the patients were highly symptomatic (pain on VAS 5 of 10 or almost complete inability to walk) with no CK elevation, others were asymptomatic with only CK elevation as a sign of muscular involvement. CK was elevated in about 43% of patients. If CK was elevated, values increased to  $\geq$  grade III CTCAE in ten of 14 cases. Grade IV CK elevation ( $>10 \times$  ULN) was seen in seven of the 14 cases with a maximum of  $>6000$  U/l in three patients. Myositis-associated autoantibodies were assessed in 24 patients, being negative in 67% of cases with detection in only 8/24 patients (patient #19: anti-TIF1-gamma; patient #20: anti-SRP; patient #33: anti-Ro52; patient #34: anti-PL-7, anti-PL-12 and anti-SRP; patient #35: anti-PL-7; patient #36: anti-SRP; in two other patients, antinuclear antibodies test was borderline positive). Muscle biopsies were examined in four patients and showed infiltrates mainly

with CD4+ and CD20+ lymphocytes (Fig. 2). Furthermore, necrotising myopathic changes were seen in three of the four biopsies. Interestingly, in patient #25 without any antibodies, enhancement of muscles in the PET scan (see Fig. 3) and a complete response symptoms progressed still 24 months after discontinuation of CXP therapy.

### 3.2. Concomitant side-effects

In 20 of the 38 (54%) patients, other organ systems were also affected by immune-related side-effects, including autoimmune thyroiditis (13% of all patients), hepatitis (13%), nephritis (5%), vitiligo (5%), pneumonitis (5%), hypophysitis (5%) and colitis (5%). In most of the cases, the other immune-related side-effects occurred before the neuromuscular side-effect (65%, 13/20), whereas in six patients (30%), the other side-effects had the same time of onset as the neuromuscular ones.

There was only one patient (5%) who had another side-effect after the neuromuscular side-effect. In this case, 32 weeks after the onset of myositis and 35 weeks after the initiation of therapy, the patient developed lichen planus mucosae.

### 3.3. Steroids and immunosuppression

Steroids were administered in 63% of the cases ( $n = 24$ ). Notably, 55% of the patients not treated with steroids

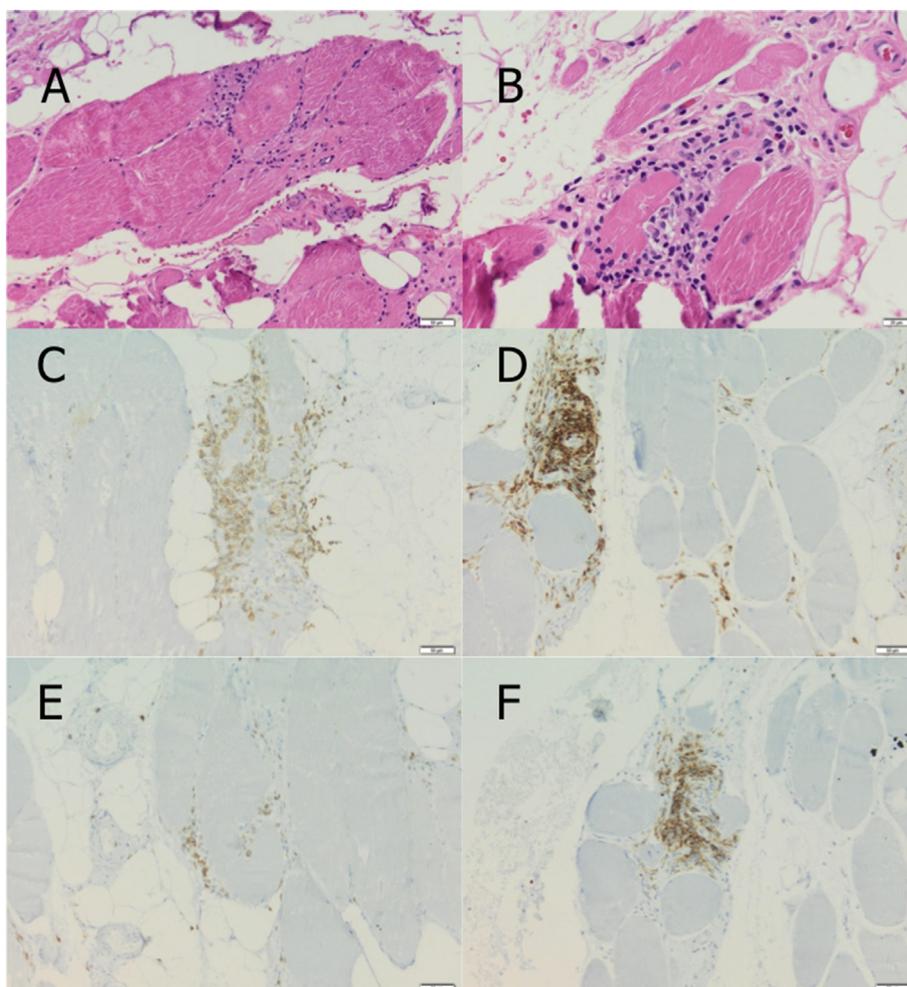


Fig. 2. Myositis induced by CXP: histopathological analysis of skeletal muscle from the left quadriceps femoris of patient # 25 as stained by hematoxylin and eosin (A, B) shows increased fatty tissue, highly variable fiber fibre size diameters and endomyrial lymphocytic infiltrates. Immunohistochemical staining reveals endomyrial lymphocytic inflammation with predominant expression of (C) CD3 and (D) CD4; (E) fewer CD8; and only (F) CD20-positive lymphocytes.

were reported as still having an ongoing event at the time of this analysis compared with 17% of those who were treated with steroids. From the cases treated with steroids, only two had an ongoing myositis. However, one patient with a grade IV myositis was not treated with steroids but the side-effect resolved on permanent discontinuation of CXP (patient #26).

Three cases were treated with intravenous immunoglobulin in addition to the application of systemic steroids. Those three cases were patients with myositis (two grade III CTCAE and one grade IV CTCAE case). One of the polymyalgia rheumatica patients was treated with a 162 mg weekly dose of tocilizumab, a humanised monoclonal antibody against the interleukin-6 receptor, along with systemic steroids. This case was anti-SRP positive (patient #36) and ongoing at the time of this analysis. One myositis/MG patient died, despite therapy with steroids and with the acetylcholinesterase inhibitor pyridostigmine (patient #27). The latter was also used in the treatment of the case with MG (patient #11), which resolved with sequelae.

### 3.4. Resolution

In total, half of the cases (50%) completely resolved, whereas the rest was either ongoing (26%) or had sequelae (16%). There were two fatalities (5%) attributed to the side-effect, one due to myositis and the other due to myositis with concomitant myocarditis, and a third patient (3%) died by suicide.

In the majority of the resolved cases that resolved completely ( $n = 19$ ), CXP was permanently stopped ( $n = 10$ ), while in six cases, it was only interrupted. In another three resolved cases, CXP was continued. Of the three patients who stayed on CXP treatment, two resolved with immunosuppressive treatment with steroids (patients #9 and #38) and one without treatment (patient #21).

### 3.5. Adverse events in adjuvant therapy

A patient with cutaneous melanoma (stage III) receiving adjuvant treatment with pembrolizumab developed a grade III myositis 6 weeks after the initiation of therapy.

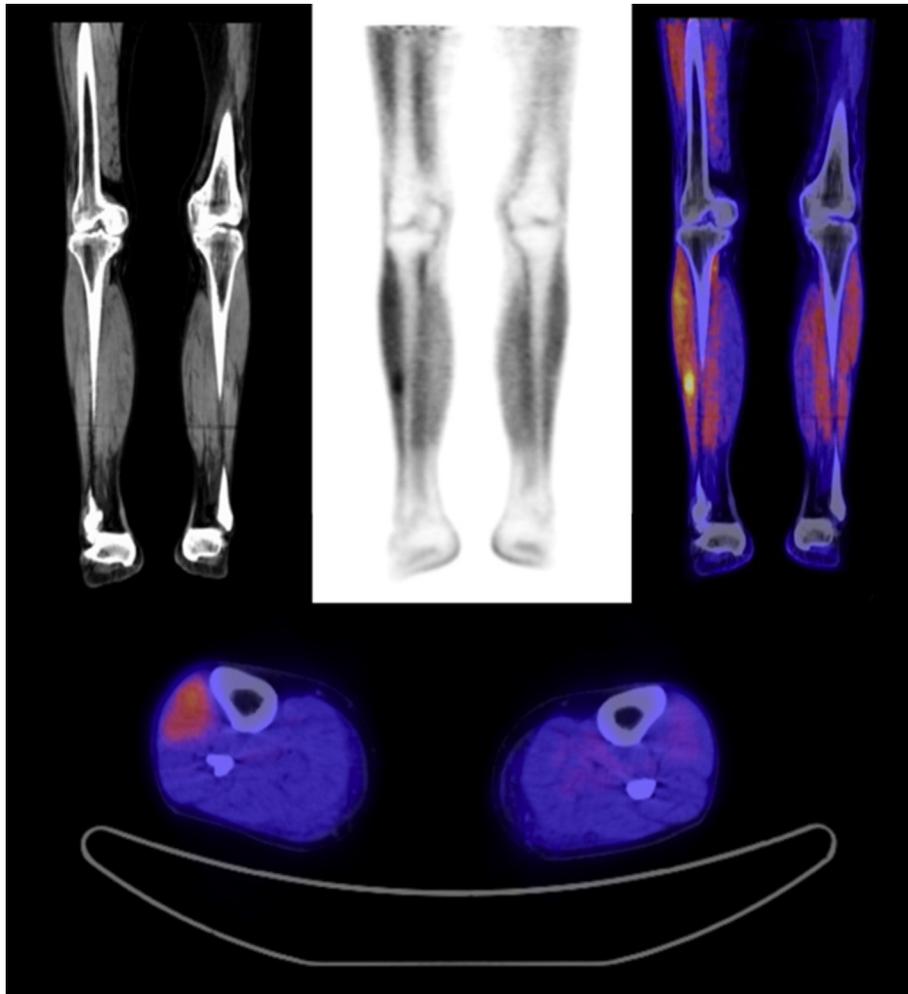


Fig. 3. PET-CT of patient #25 with symptomatic myositis that was responsive to therapy. PET, positron-emission tomography; CT, computed tomography.

At presentation, the patient reported impaired speech, difficulties in swallowing and muscle pain and was treated with prednisolone 1 mg/kg p.o., while pembrolizumab was permanently discontinued. At that same time, the patient developed pericarditis and thyroiditis. Unfortunately, the patient only recovered with sequelae but was still progression free at the time of this report.

In this cohort, a certain overlap of myositis with cardiomyositis and neuropathy/MG was detected (Fig. 4). However, the checkpoint-induced side-effects differ in their presentation from the idiopathic forms with respect to diagnostic findings and response to therapy.

#### 4. Discussion

This is, to our knowledge, the largest case series to date describing neuromuscular side-effects to CXP and the first report of an autoimmune myositis in a patient receiving adjuvant treatment with an anti-PD-1 antibody. It shows that although neuromuscular side-effects are rare, they are potentially life threatening and often do not fully resolve. In this study, neuromuscular

side-effects resulted in sequelae in at least one-third of the patients and were fatal in 5% of cases. Previously, reported fatalities induced by neuromuscular side-effects have been caused by myocarditis, MG and rhabdomyolysis [1]. Strikingly, this series reports on a fatal myositis without myocarditis. The most common side-effect was myositis, which was complicated in 32% of cases by concomitant myocarditis. This is in accordance with findings from a World Health Organization registry where myocarditis was associated with myositis in 25% of cases and with MG in 11% [12].

Myocarditis is increasingly recognised as an immune checkpoint-induced side-effect, and reporting has increased [12]. However, it seems likely that neuromuscular side-effects are still underdetected and underreported. This is especially lamentable because they seem to respond well to corticosteroids. Furthermore, they are often not described with the level of granularity desired.

Thus, exact case definitions should be introduced and used for CXP-associated myositis/MG/myocarditis as they are currently being developed after a *Food and Drug Administration* workshop (Neilan oncologist 2018). This

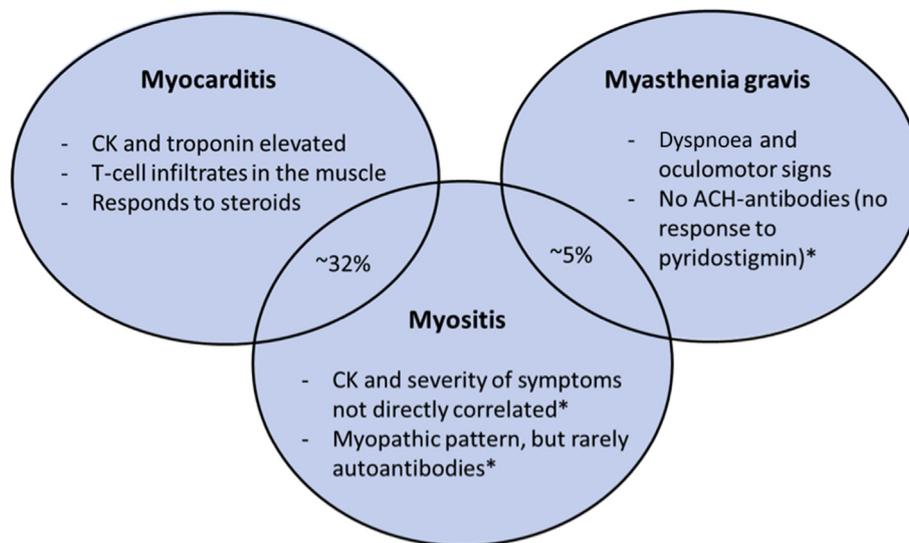


Fig. 4. Overlap of neuromuscular pathologies in CXP-induced side-effects; \* differences to idiopathic pathologies. ACh, acetylcholin; CK, creatine kinase.

would improve characterisation of the new entities of CXP-induced pathologies and lead to a harmonised approach for detection and treatment. In accordance with other reports, neuromuscular adverse events appear to be more common on therapy with anti-PD-1 antibodies than with ipilimumab [47]. And while we saw an increased incidence in men, this trend has not been confirmed when analysing numbers of the national authority (Paul Ehrlich Institute; personal communication).

When comparing CXP-induced myositis (irMyositis) with idiopathic inflammatory myopathies (IIM) such as DM and polymyositis (PM), CXP-induced myositis has a more sudden onset of symptoms with no reported fluctuation of symptoms or fatigability in our experience and that of others [48]. CXP-induced myositis symptomatically resembles MG with limb-girdle distribution and often oculomotor symptoms [30–32]. While CXP-induced irAEs are presumably mostly T-cell mediated [49], DM represents a complement-mediated microangiopathy [50]. Myositis autoantibodies are mostly negative (29% positive) in irMyositis, whereas in patients with IIM (PM/DM), autoantibodies are present in up to 80% of the cases [51,52]. Here, we show predominantly CD4-positive endomysial lymphocytic infiltrates with only few CD8+ lymphocytes. In contrast, other reports document a predominance of CD8+ cells in CXP-induced myositis [47] and in a patient with CXP-induced PM of autochthonous muscles [46]. In addition, there is a pathologic picture of multifocal necrosis with sparse T-cell infiltrates [53], which was found to be associated with an especially grave prognosis [54].

Although irAEs are typically associated with lymphocyte infiltration of the affected organ, in some irAEs such as hypophysitis, owing to ipilimumab, the expression of CTLA-4 could also play a role [55].

Interestingly, CXP-induced myositis and MG seem to have some overlap [56] with some ACh-negative cases resembling MG but showing elevated CK or concurrent manifestation [7]. Here, muscle biopsies can help to distinguish patients with necrotising myopathy from MG. Taken together, there seems to be an overlap or coexistence of pathological and clinical signs of myositis and MG.

In general, patients who experience one irAE should be carefully monitored for others. In our cohort, 50% of the patients exhibited side-effects in other organ systems besides the neuromuscular system. Importantly, in most of the cases, the other immune-related side-effects preceded the neuromuscular symptoms. Because neuromuscular side-effects usually start with a mild presentation, regular inquiry about muscle weakness, movement of the ocular muscles, difficulty in swallowing or breathing [46] in combination with careful monitoring of serum CK levels and troponin are crucial to detect cases early. However, laboratory values might only be slightly elevated. The only myositis autoantibodies detected in our patient cohort were anti-TIF1-gamma, anti-SRP, anti-Ro52, anti-PL-7 and anti-PL-12. While autoantibodies associated with irMyositis are usually negative, muscle biopsy, electromyoneurography, nerve conduction studies and imaging examinations should be considered. Positron-emission tomography shows muscles with enhancement; however, findings are not pathognomonic for myositis. Magnetic resonance imaging can support the diagnosis of myositis and guide therapy by determining whether muscle weakness is related to oedema (active inflammation) or muscle atrophy/fat replacement (chronic damage) [57].

When side-effects are diagnosed, prompt initiation of steroids improves the symptoms rapidly [58,59]. Immunoglobulins have also shown effect on our cohort.

Reinduction of PD-1 inhibitor therapy after moderate symptoms of the skeletal muscles can be discussed once the side-effect has resolved because in one-third of our patients, this was feasible. However, in case of severe side-effects, especially those involving the heart, reinduction can potentially be fatal [11]. Because cases were reported voluntarily in the side-effect registry or collected retrospectively from cancer centres, it is possible that there is still an underreporting particularly in patients with mild side-effects. In our cohort, 71% of the patients were men—contrary to idiopathic forms of inflammatory myopathies, such as DM and PM, which are more common in women than in men (2:1 ratio) [48]. Although pre-existing autoimmunity may increase the likelihood of myositis [8,33–35], predictive biomarkers, which could help identify patients at risk for neuromuscular immune-related toxicity, are lacking [60].

This is, to our knowledge, the largest case series to date describing neuromuscular side-effects induced by immune checkpoint inhibitors and the first report of an irMyositis in a patient receiving adjuvant treatment with an anti-PD-1 antibody. Although rare and/or potentially underreported, patients under treatment with immune checkpoint inhibitors should be carefully evaluated for neuromuscular side-effects.

## 5. Conclusions

Autoimmune neuromuscular side-effects induced by checkpoint inhibitors although rare can be severe and sometimes fatal. Early diagnosis and prompt treatment can decrease morbidity and possibly mortality because patients often respond well to corticosteroid therapy. Potential sequelae have to be considered before treatment with CXP, especially in patients contemplating adjuvant therapy. Further studies to characterise risk factors and management strategies are needed.

## Conflict of interest statement

Carmen Loquai is an advisory board member, received speaker's fee and travel reimbursement from BMS, MSD, Novartis, Roche, Amgen, Pierre Fabre, Sun Pharma and Idera outside the submitted work. Claudia Pföhler received honoraria from Novartis, BMS, GSK, MSD, Roche, Amgen and Merck Serono; is a consultant or advisor for Novartis, Amgen, Roche and Merck Serono and received travel reimbursement from Novartis, GSK, MSD, BMS, Amgen, Roche and Merck Serono outside the submitted work. Katharina C. Kähler received consultant fees from Roche, BMS and MSD and travel reimbursement and speaker fees from Roche, BMS, MSD and Amgen outside the submitted work. Markus V. Heppt received speaker's fee from Roche, Novartis, BMS and MSD and travel reimbursement from BMS outside the submitted work. Ralf Gutzmer received research

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