

NEUROMUSCULAR COMPLICATIONS OF THERAPY WITH IMMUNE CHECKPOINT INHIBITORS

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DISCLOSURE OF INTEREST

PD Dr. Berit Jordan

- Alexion
- Temmler
- Hormosan
- Biomarin
- Novartis

Neurological complications of immune checkpoint inhibitors: what happens when you 'take the brakes off' the immune system



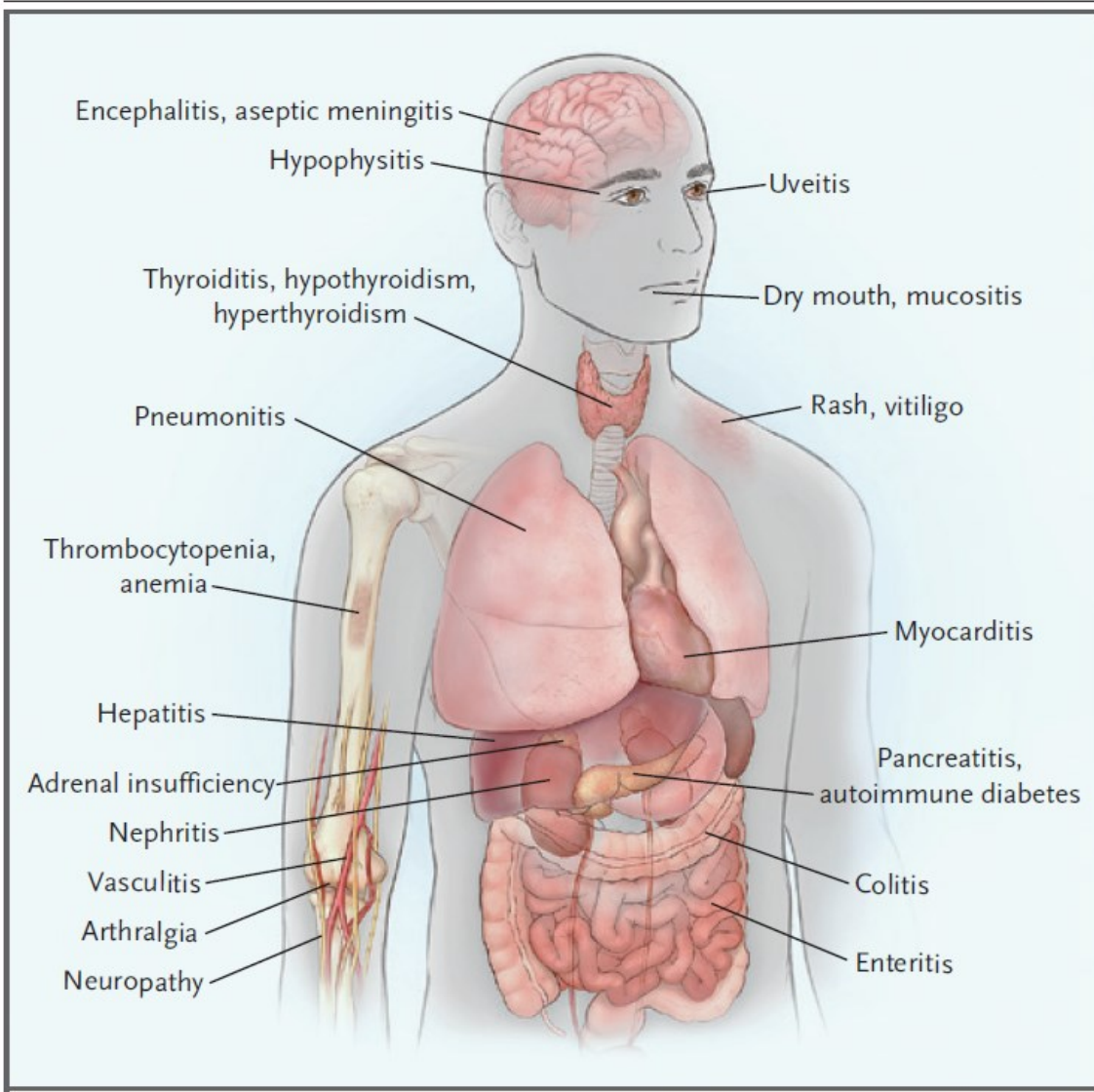
(Zimmer, Goldinger et al. 2016)

Organs affected by Immune Checkpoint Blockade

immunotherapy against co-stimulatory molecules activates previously normal T cells to kill tumor cells

but >

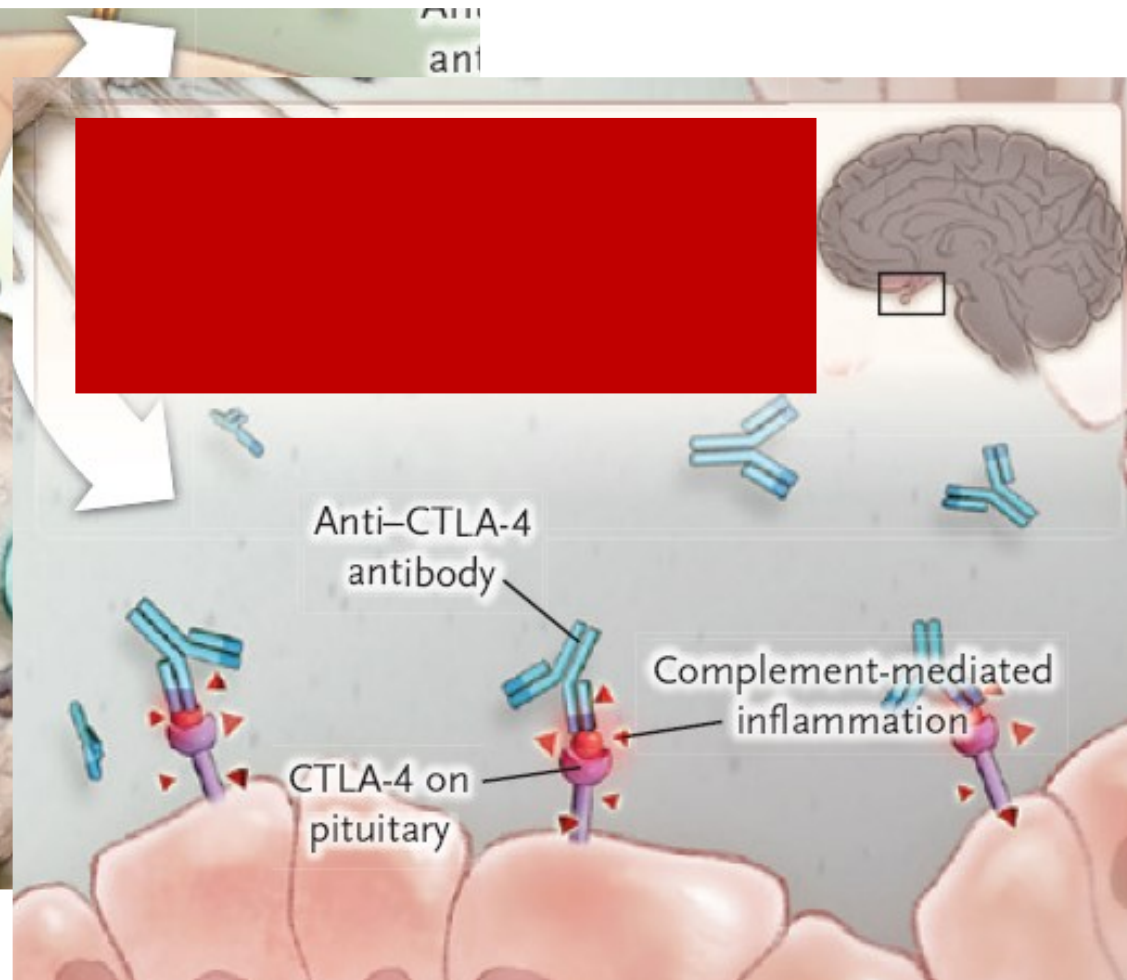
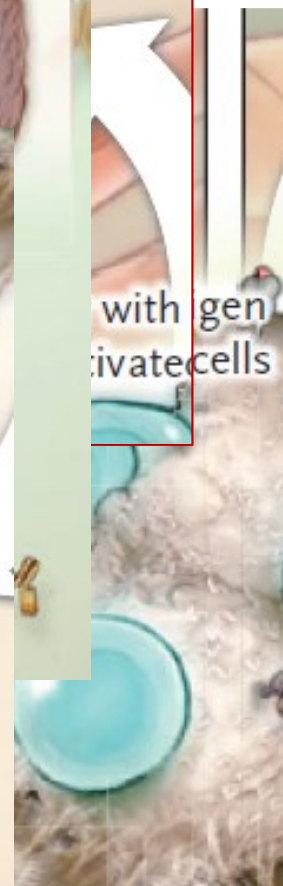
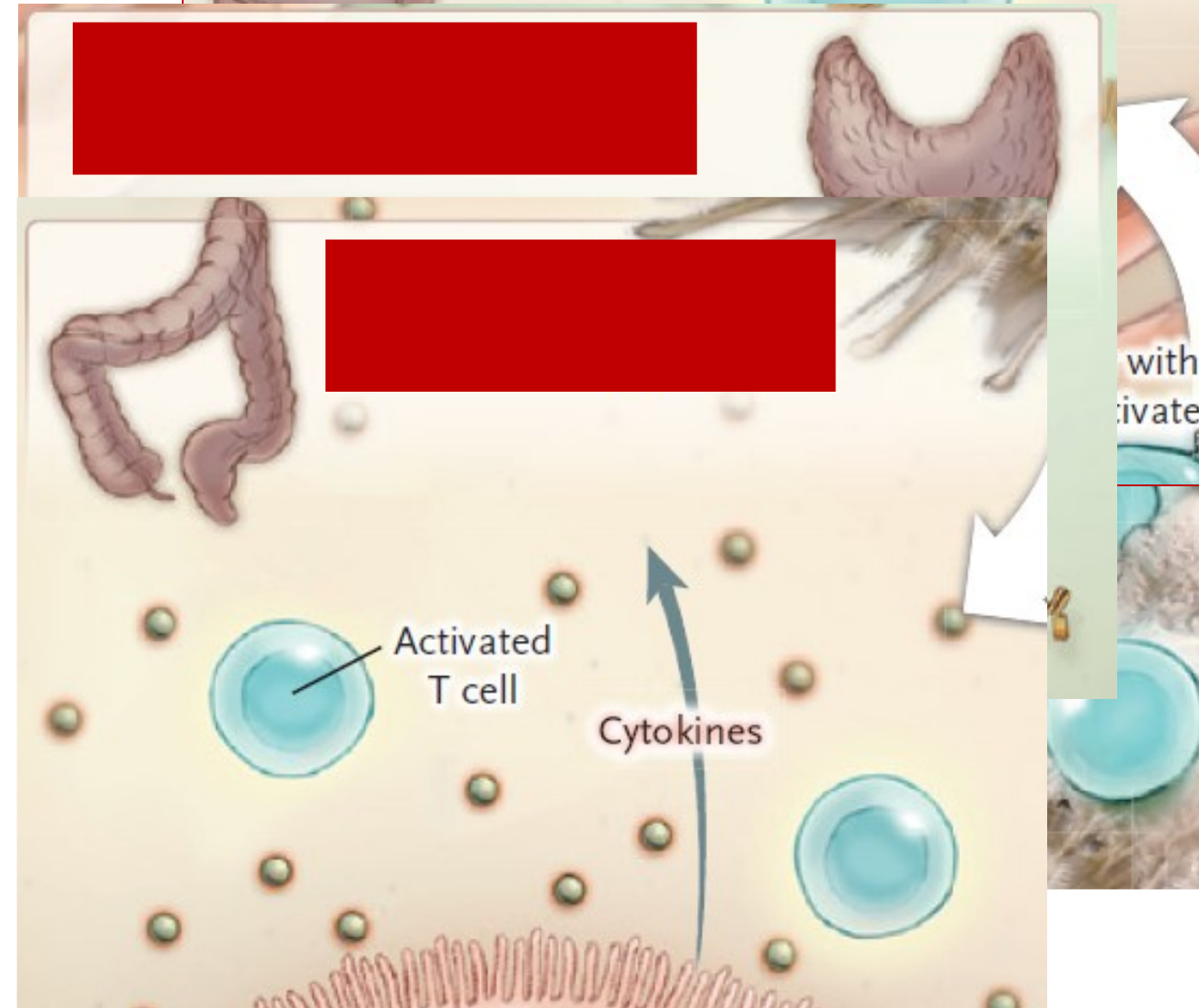
in so doing, the T cells become unrestrained, triggering other autoimmune diseases



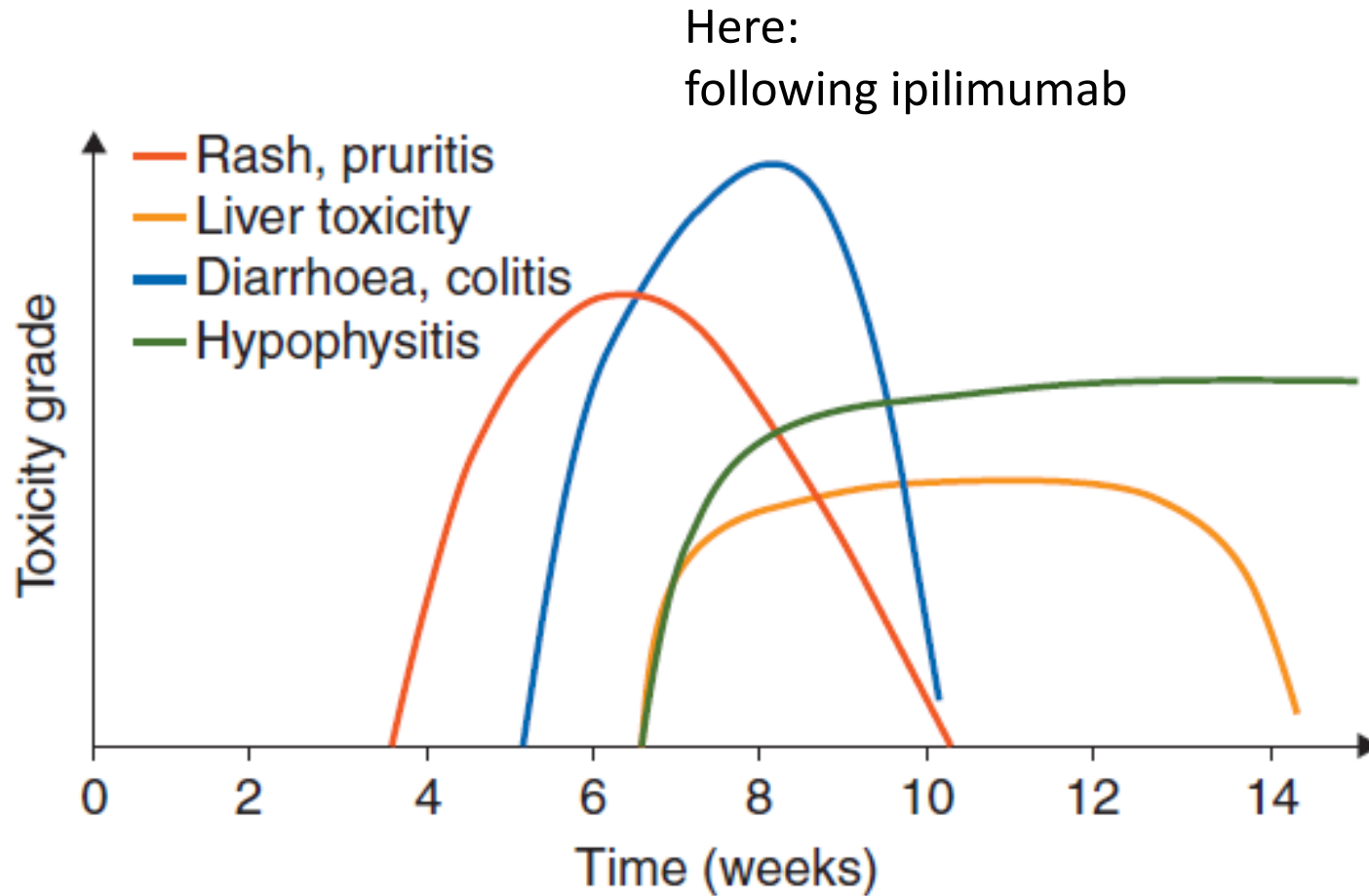
(Postow, Sidlow et al. 2018)

Mechanisms of AE in Immune Checkpoint Blockade

(Postow, Sidlow et al. 2018)



Timing of occurrence of AE in Immune Checkpoint Blockade



Neuromuscular events

- Vary in severity
- occur at any point
- but 60–80% occur early, *within the first 4 months of therapy initiation*

(Haanen, Carbonnel et al. 2017)

Neuromuscular ICI-rAE: Epidemiology

overall incidence of neurological complications on ICI: 2% to 4% > **60-75% are neuromuscular**

Mild events (grades 1–2): 6–12% of patients (nonspecific: headaches, dizziness, paresthesias or small-fiber sensory neuropathies) > do not overall impact ICPI continuation

More serious events (grades 3–4): fewer than 1%, frequency

- ranging from **0.2%- 0.4% with nivolumab and pembrolizumab**
- **0.3–0.8% with ipilimumab** and
- **2.4–14% with the combination of PD-1 and CTLA-4 inhibitors**

ICPIs can also ***precipitate preexisting autoimmune diseases with an estimated 27–42% risk*** for mild to moderate exacerbations

Types of neuromuscular ICI-rAE

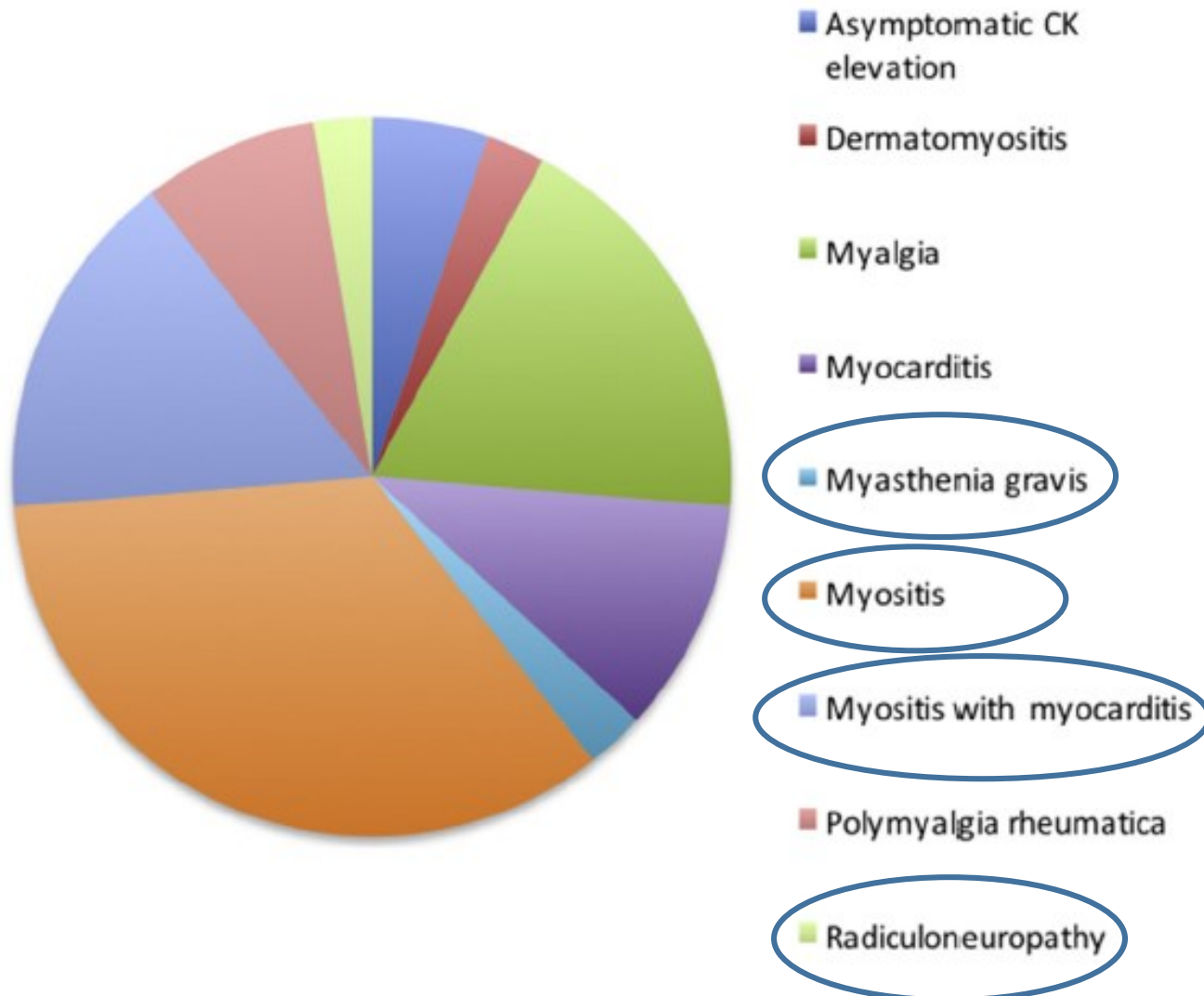
Typical neuromuscular ICI rAE:

- **Neuropathies** (acute/chronic demyelinating polyradiculoneuropathies, vasculitic, isolated cranial neuropathies) >
- **myasthenic syndromes**
- **inflammatory myopathies**

ICI-rAE usually occur within 2–12 weeks after ICI initiation

347 patients treated → 10 pts. developed neuromuscular complications (Kao 2016)

Neuromuscular ICI-rAE



Moreira, A. et al. (2018). "Myositis and neuromuscular side-effects induced by immune checkpoint inhibitors." *Eur J Cancer* **106**: 12-23.

ICI related **Myasthenia gravis (MG)**



Kopp, C. R. et al. (2018).



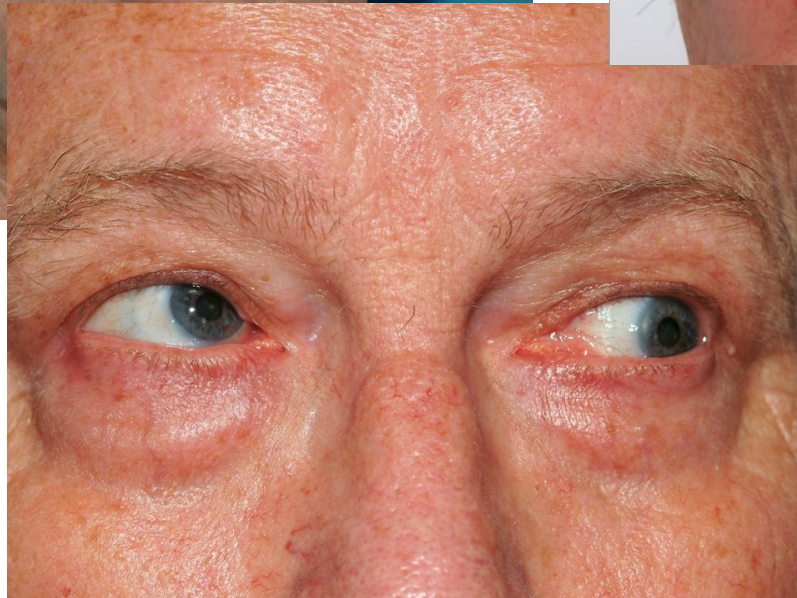
Incidence 0.12%
(12/9869) pts. on
nivolumab

(Suzuki, Ishikawa et al.
2017)

Incidence 0.15-0.2 % in
all PD1 therapies

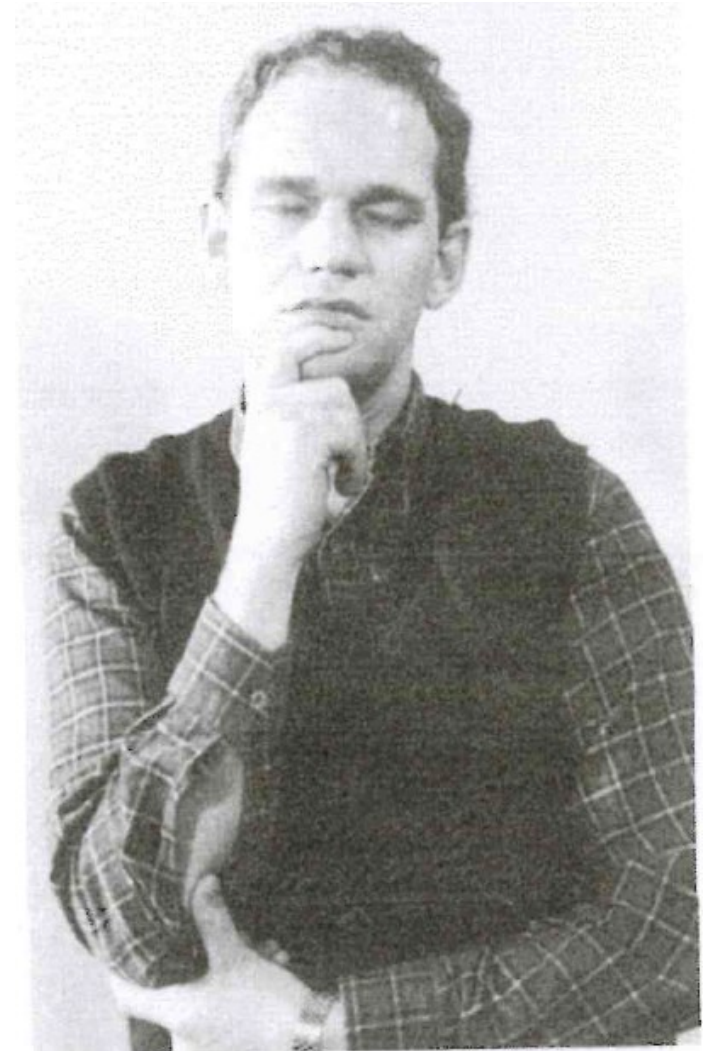
(Liewluck, Kao et
al. 2018)

MG clinical picture



Ptosis unilateral/bilateral
Double vision
Facial weakness

Bulbar: dysarthria, dysphagia,
dypnoea,
tetraparesis



Normal eyelid position



The upper lid covers 1 to 2 mm of the upper limbus. The lower lid covers the lower limbus minimally. The central light reflex can be seen within the pupil. The margin reflex distance is measured from this reflex to the

Courtesy of Michael S Lee, MD.

Patient with ptosis of the right upper lid secondary to levator dehiscence



Note the absence of the right upper lid crease. The patient is raising the right eyebrow to try and compensate for the ptosis. The left lid shows normal innervation.

Dermatochalasis



Redundant skin overflows past the upper eyelid margin. The clinician must lift the excess skin in order to find the eyelid margin.

Courtesy of Michael S Lee, MD.

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MG as ICIr AE: clinics

Phenotype: 6/33 (18%) pure ocular
dropped head ,
proximal tetraparesis
12/24 (50%) myasthenic crisis

(in indiv. reported cases by Kao 2018)

very often **Overlap** : myalgia, paraesthesia,
myositis, rhabdomyolysis (CK elevation in
20/23 (87%), mean 4800U/l)

Frequency of myocarditis in PD1 –MG: 25%



(Dalakas 2018)

12 MG cases in 9869 nivolumab pats.

12 MG cases (4 mild, 8 severe)
none on 408 pts. treated with ipil.

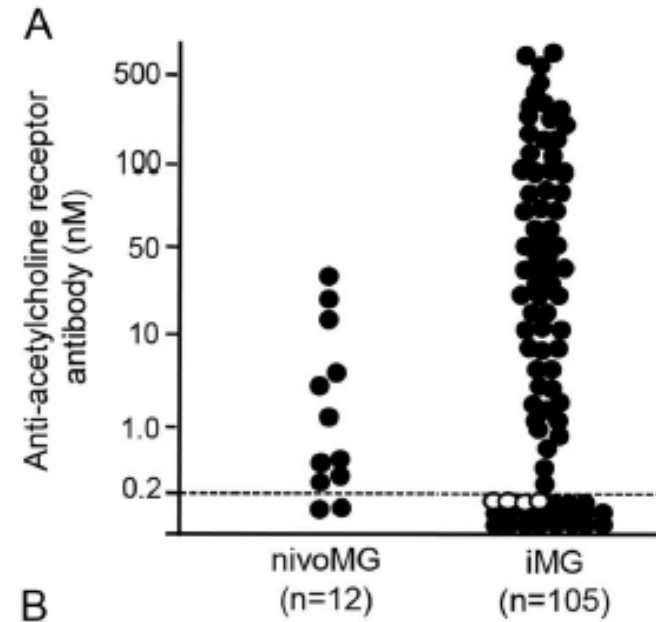
2/3 de novo presentations
2/3 AChR-ab +, no Musk ab

3 times more likely to develop **bulbar weakness > crisis**
(more often in de novo MG),
early and rapid deterioration

CK elevation may be asymptomatic,
but **4/12 with myositis, 3/12 myocarditis**

> CK elevation tends to respiratory failure

Figure 2 Distribution of anti-acetylcholine receptor antibodies and creatine kinase



Median AChR-ab
titre 6nmol
(8.5 times lower
than in idiop.
MG)

Suzuki, S. et al. (2017). "Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan." *Neurology* **89**(11): 1127-1134.

MG as ICI rAE: treatment and outcome

Generally responds well to corticosteroids, IVIG or plasmapheresis

Treatment	In 12 cases by Suzuki
Pyridostigmine	5 (42)
Prednisolone	10 (83)
Other immunosuppressive agents	1 (8)
IV methylprednisolone pulse therapy	5 (42)
IV immunoglobulin	6 (50)
Plasma exchange	4 (33)
Thymectomy	0 (0)
Respiratory support	5 (42)

Outcome:

- 2 pts. with mild MG were subsequently restarted on PD-1 inhibitor therapy without further relapse
- 4/12 PR or MM, 2/12 deaths (crisis, myocarditis), 5/12 still experience relevant ADL limitation after 3 month

(Kao, Brickshawana et al. 2018)
(Suzuki, Ishikawa et al. 2017)

ICI related Myositis

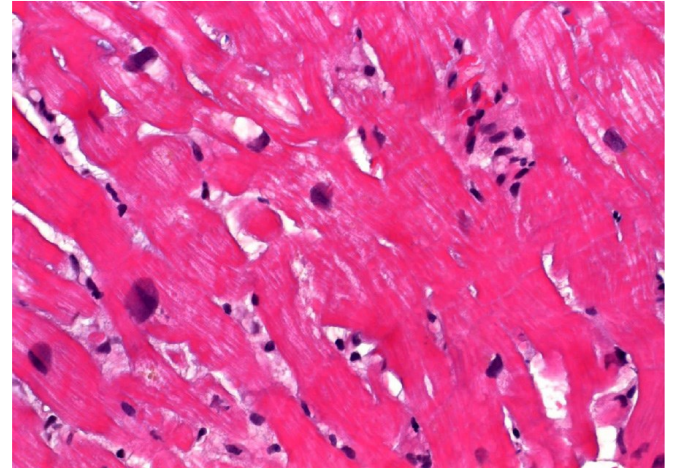


ICI related Myositis

proximal limb weakness (60%)
myalgia(45%)
dyspnea (35%)
dysphagia or dysarthria (25%)
head drop (15%)

CK 70-31000 U/I (median 2500, mean 6100),
myositis ab neg, despite anti-striational in MG

50% with concomitant ptosis/diplopia
were diagnosed with concomitant MG



Cave: myositis accompanied by life threatening myocarditis > mortality 20%

(Johnson, Chandra et al. 2018)
(Moreira, Loquai et al. 2018)
(Heinzerling, Ott et al. 2016)

ICI related Myositis

At least 32 patients (16 nivolumab, 12 pembrolizumab, and 4 combined nivolumab and ipilimumab) were reported with various AE affecting skeletal muscle, **incidence 0.58-0.76% among in PD1 therapy**

myositis de novo in all but one patient

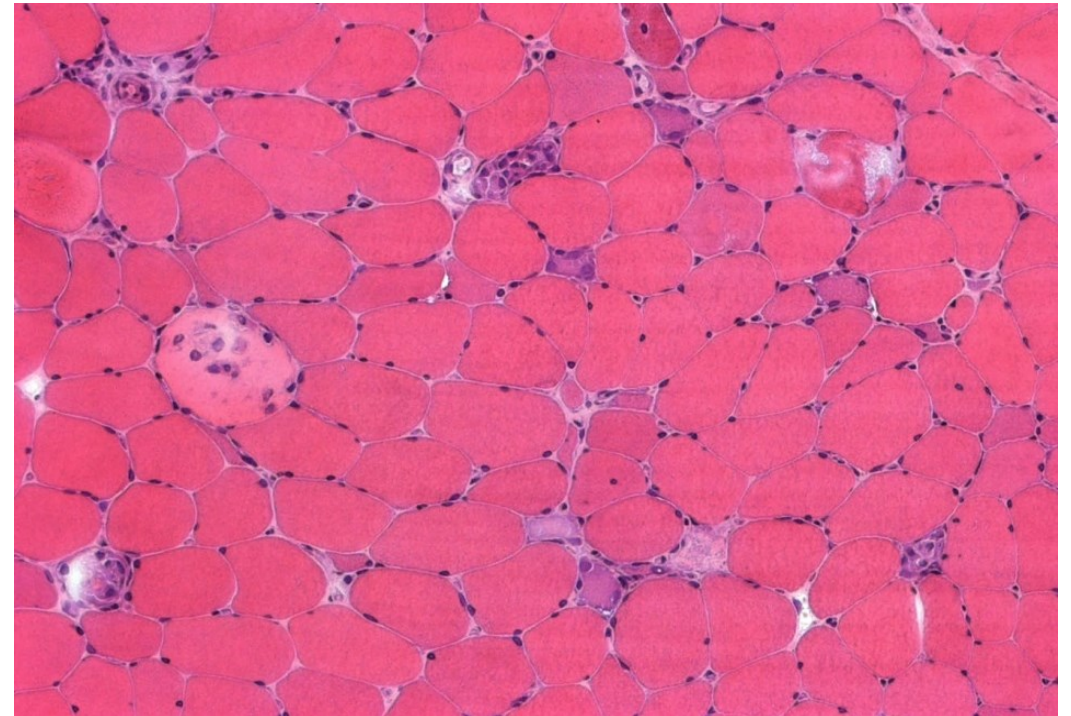
Necrotizing autoimmune myositis (NAM) 3 pt

(most common in ICI)

Dermatomyositis (DM) 2pt

Polymyositis (PM) 6pt

Others: granulomatous myositis,
eosinophilic fasciitis, orbital myositis



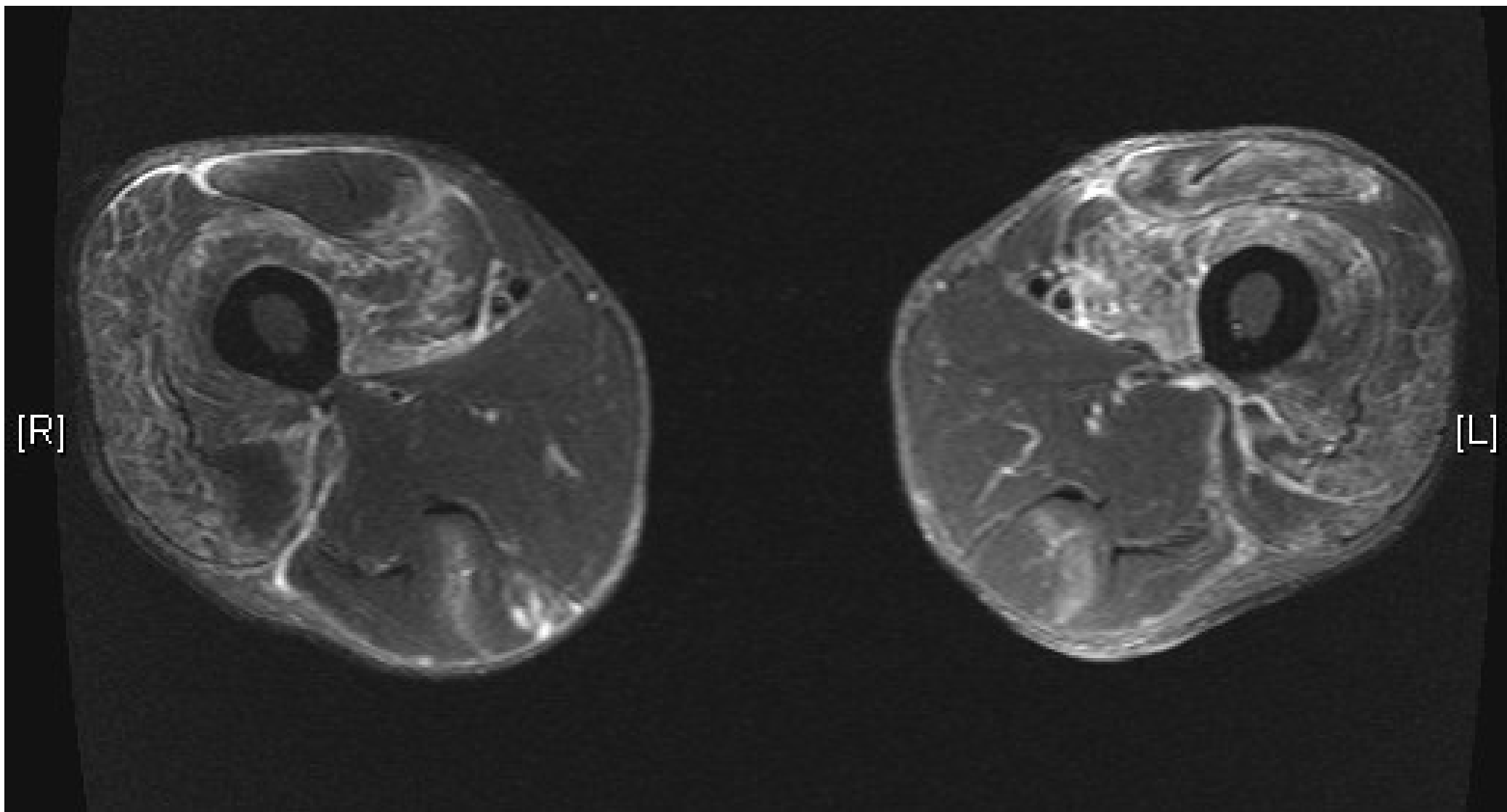
necrotizing myositis

(Kao, Brickshawana et al. 2018)

(Kao, Liao et al. 2017)

Dermatomyositis
- erythema
- oedema
- itching



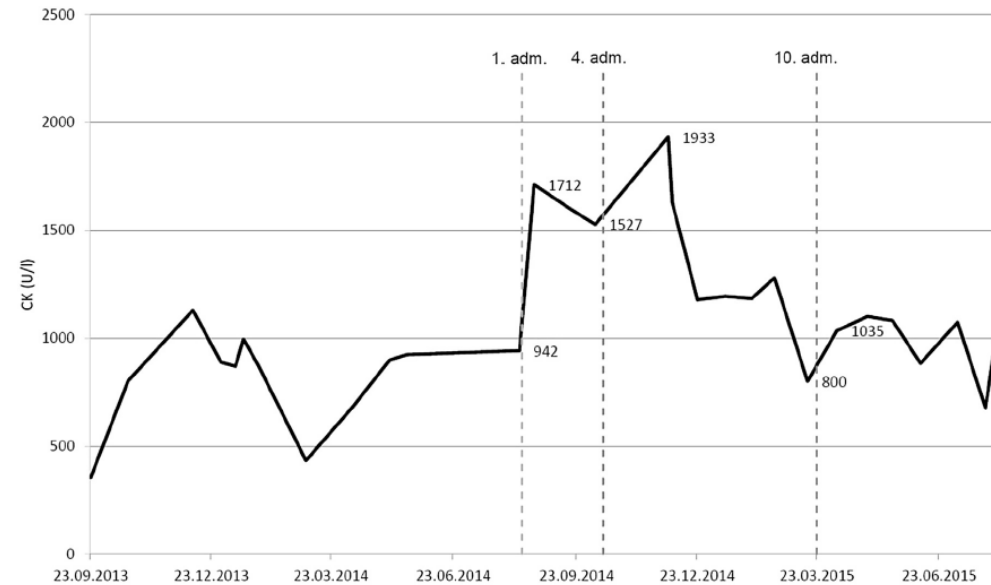


MRT T2 , TIRM
Dermatomyositis

ICI related Myositis: treatment

About 75% of pts. responded favorably to treatment

- **High-dose steroid** was given as an initial treatment in 16/31 patients followed by
 - a) either **immunomodulation** in some or
 - b) remaining high-dose steroid accompanied by **IVIg or plasma exchange**
- Cave: deterioration of weakness may appear, especially if bulbar or respiratory muscles affected, cardiac arrhythmia ... even after initial improvement



CK doubled 10 days after pembrolizumab

(Dalakas 2018)

ICI related neuropathies

occur in about 1.2-1.6.% pf pts. undergoing PD1 therapy and vary in severity from

- the small-fiber sensory type (as commonly seen with chemotherapies, not affecting the continuation of ICPIs)

to more typical immune-mediated

- Guillain–Barré syndrome (occurring in 0.1–0.2%) and
- chronic inflammatory demyelinating polyneuropathy (CIDP)

Neuropathy may be axonal (if prior exposure to chemotherapy) or demyelinating with conduction block (immune mediated)

ICI related Guillain Barre Syndrome (GBS)

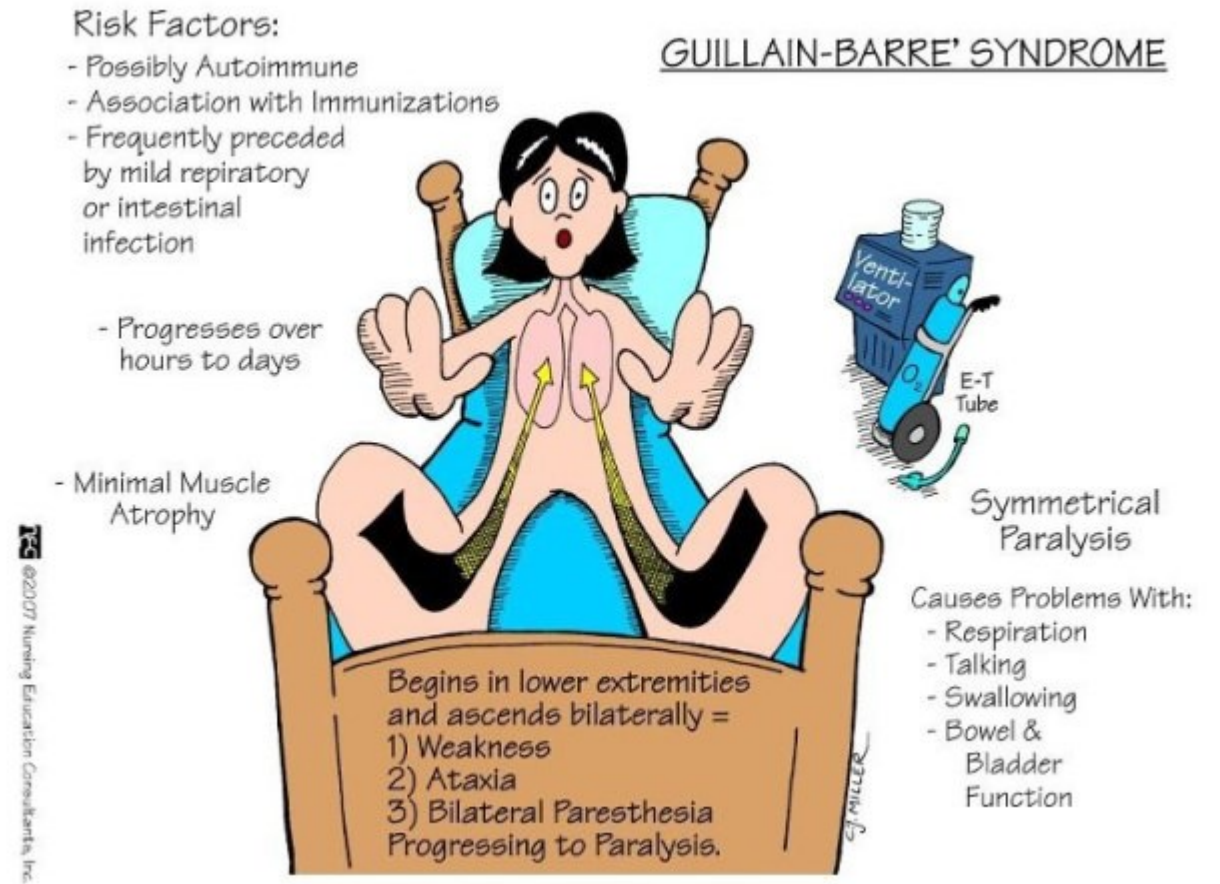
Incidence:

- 0.2-0.3% of PD1 treated pts.
- duration between onset and initiation of ICI ranged from 4-68 weeks (median 12 weeks)

Diagnosis based on:

- demyelination
- polyradiculoneuropathy
- albuminocytic dissociation
- MRI enhancement of nerves involved

Treatment with IVIG or even steroids, plasmapheresis



(Dalakas 2018)

Other ICI related neuropathies

Chronic inflammatory demyelinating Polyneuropathy (CIDP): less common, casually older woman with paraesthesia, proximal/distal weakness, areflexia >> treated with IVIG or steroids

Motor polyradiculoneuropathy : GBS like, only ventral roots > only weakness

Vasculitic neuropathy: casually , more painful >> treated with steroids !



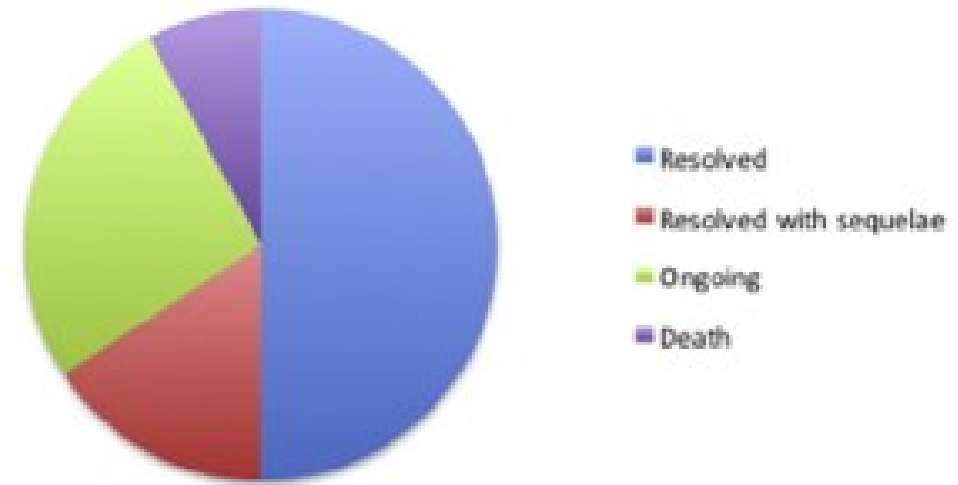
CIDP

Discontinuation of ICI and pt. outcome

Action taken regarding CXP



Outcome



The safety of retreatment with ICI remains unsettled.
Depending on: life expectancy, the severity of the ICIrAE.

Using a different ICI may be an option, because AE using another class may not necessarily reoccur.

Moreira, A et al. (2018). "Myositis and neuromuscular side-effects induced by immune checkpoint inhibitors." Eur J Cancer **106**: 12-23.

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

J. B. A. G. Haanen¹, F. Carbonnel², C. Robert³, K. M. Kerr⁴, S. Peters⁵, J. Larkin⁶ & K. Jordan⁷, on behalf of the ESMO Guidelines Committee*

Take home message: Neuromuscular ICirAE

Clinical features vary from mild to severe. They may develop rapidly and may be fatal.

Early recognition (weakness, ptosis, bulbar symptoms) may help reduce morbidity and mortality rates.

If promptly treated (steroids, IVIG, plasmapheresis) AE can be reversed.

Immunosuppression should be started because deterioration may also appear after completing ICI.

Think of myositis and myasthenia as overlapping features including myocarditis. Check CK !

Think of uncertainties regarding risk factors and the decision to administer ICI in a setting of an active or preexisting autoimmune neurological disease (Abdel –Wahab 2018)

Think on restarting or modifying ICI in mild cases.

bon voyage

счастливого пути....

have a nice trip

buen viaje

boa viagem ...

buon viaggio ...

კარგი მოგზაურობა ...

hea reis

