Side-effects of checkpoints inhibitors

Endocrinologic and nephrologic syndromes

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No conflicts of interest

Organs affected by immune checkpoint blockade

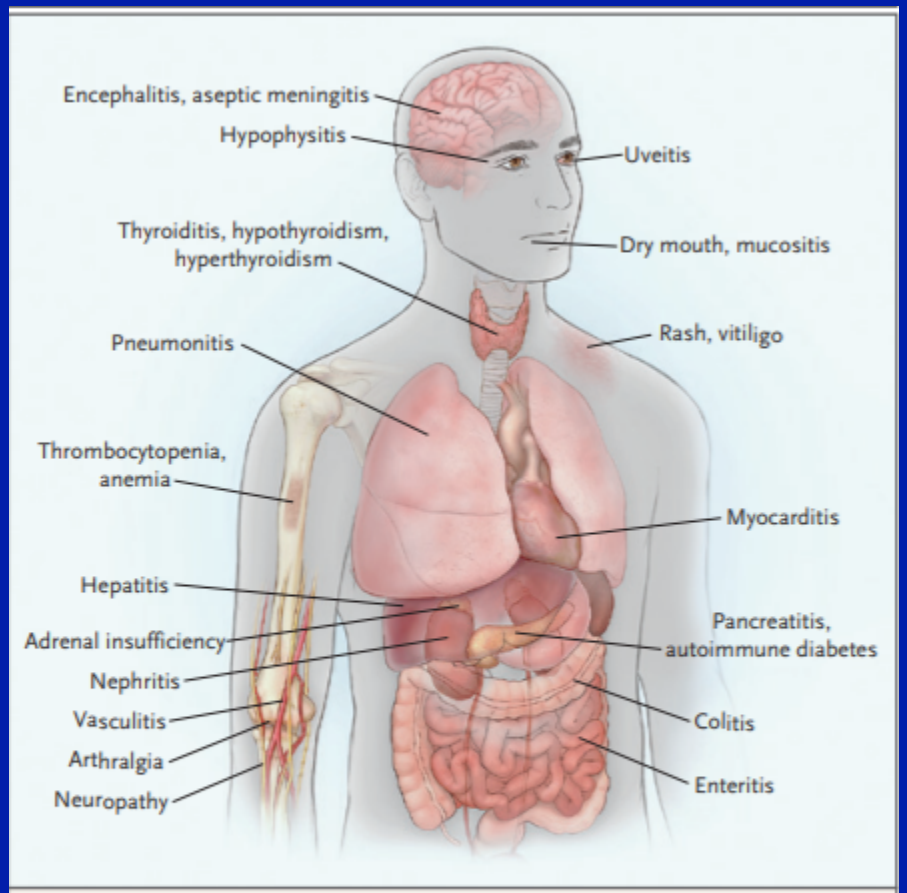
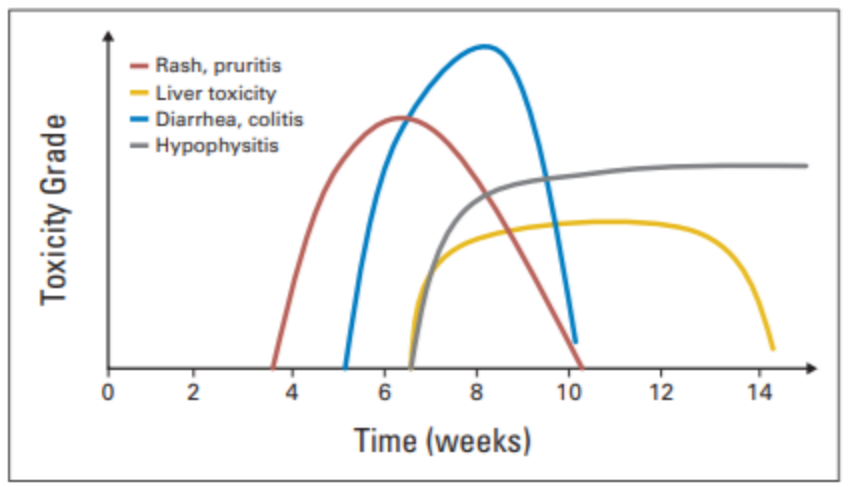


Figure 1. Organs Affected by Immune Checkpoint Blockade.

Immune checkpoint blockade can result in inflammation of any organ. Shown are the most common immune-related adverse events that clinicians encounter in patients treated with immune checkpoint blockade.

Postow MA et al. N Engl J Med 2018

Kinetics of appearance of immune-related adverse event



Weber JS et al. JCO 2012

NCI-NIH Grading system of selected endocrine toxicities as reported in the Common Terminology Criteria for Adverse Events

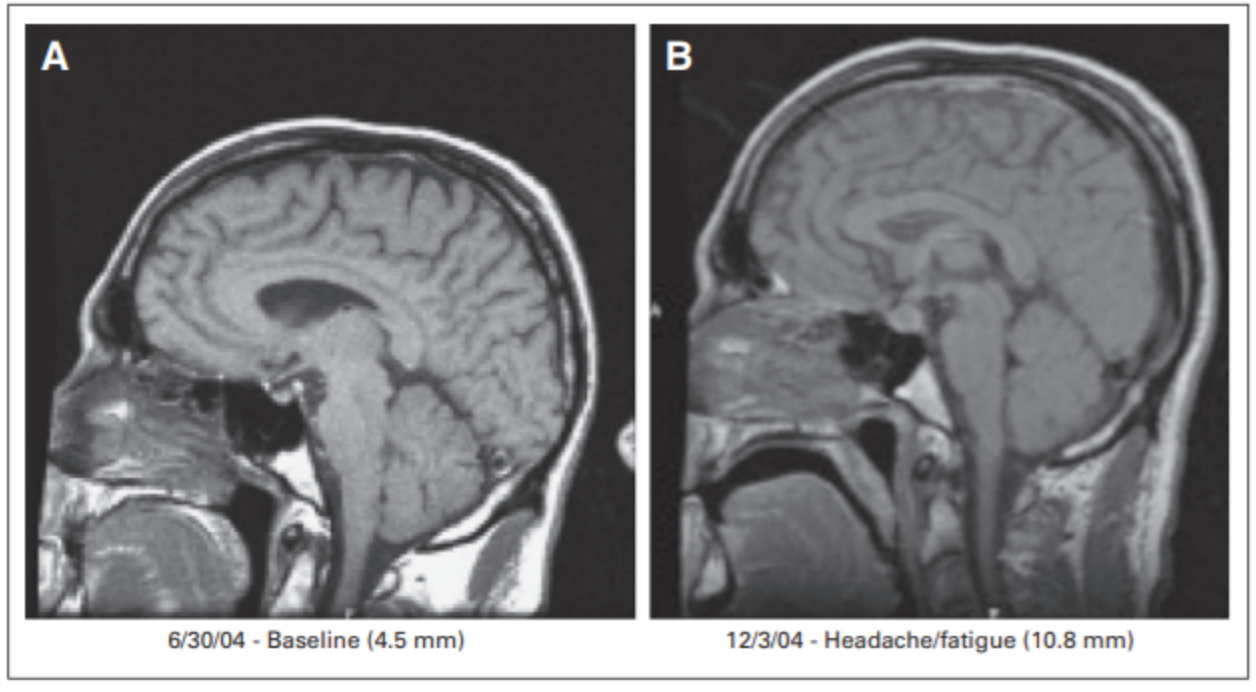
Grade	1	2	3	4	5
Toxicity grading applicable to hypophisitis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequence; urgent intervention indicated	Death

Torino et al., Curr Opin Oncol 2016

Characteristics of hypophysitis in ipilimumab-treated melanoma patients

Cohort size (n° patients):	154
Male / female:	99/55
Hypophysitis (n° patients)	17 (11%)
Grade 3/4	8 (5%)
Time to onset after therapy	8.4 weeks
Pituitary enlargement	34 (22%)
Presenting symptoms	
headache	31 (20%)
fatigue	17 (11%)
Hormonal disturbances	
thyroid	34 (22%)
adrenal	21 (13%)
gonadal	30 (29%)
growth hormone	7 (4%)
prolactine low	12 (8%)
prolactine high	26 (16%)
diabetes insipidus	17 (11%)
Discontinuation due to hypophysitis	34 (22%)

Faje et al., J Clin Endocrinol Metab. **2014**



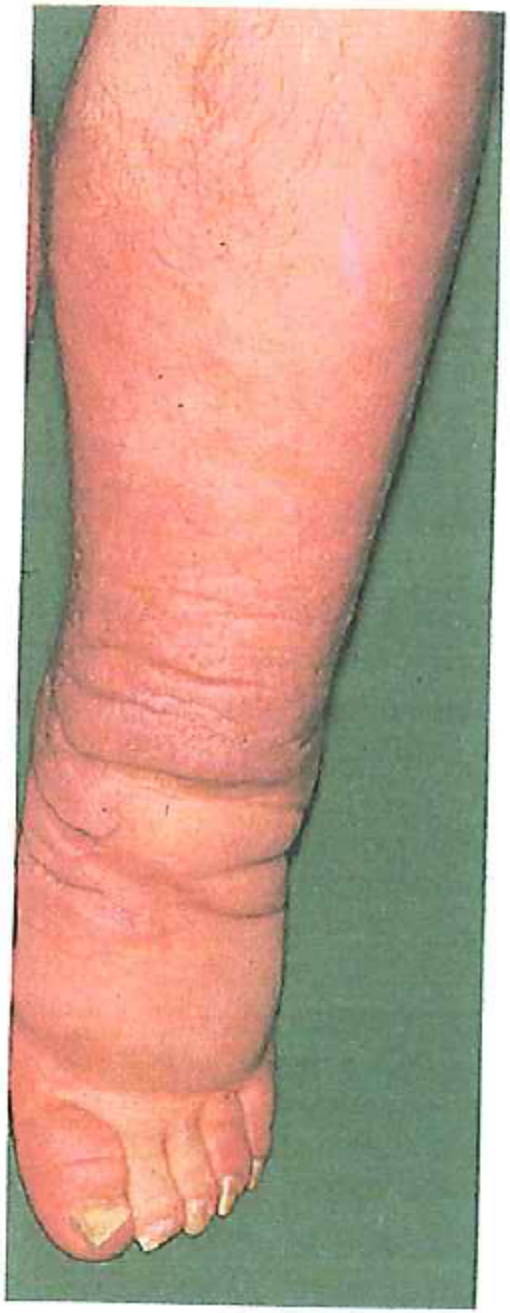
Weber JS et al. JCO 2012;2691-2697

Endocrinologic side-effects of antagonists of CTLA-4 and PD-1

(All grades / grades 3 and 4)

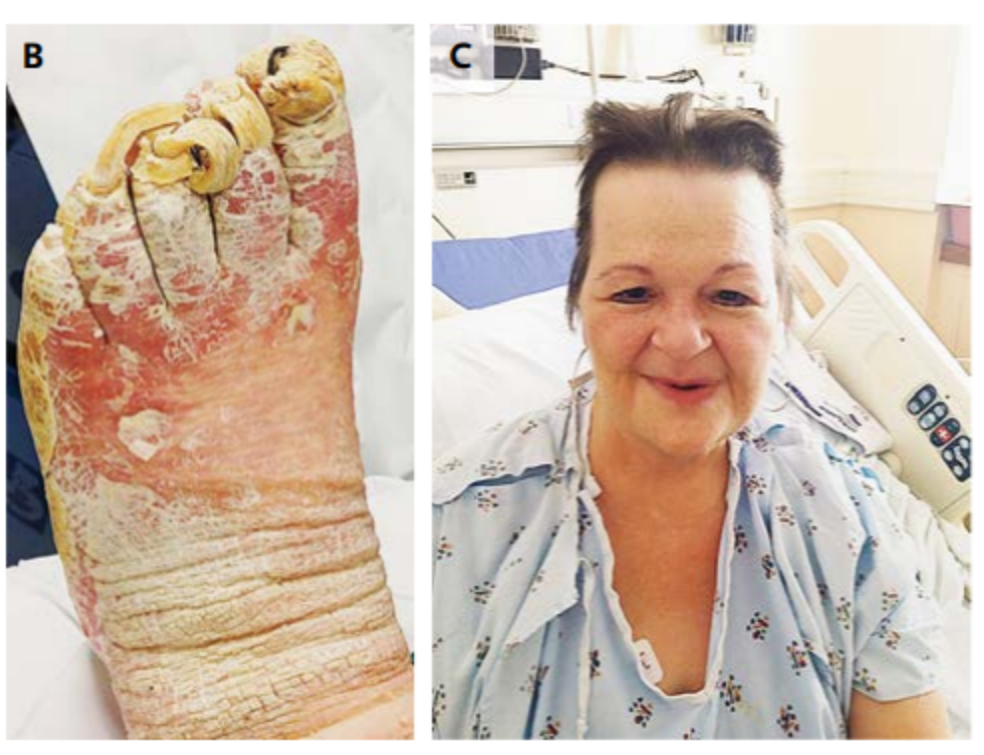
Medication N° (N° studies)	Hypo-thyroidism	Hyper-thyroidism	Hypophysitis	Adrenal insufficiency
Ipilimumab 919 (3)	11 (1.2%) /1	3 (0.3%) /1	24 (2.5%) /22	5 (5.5%) /2
Tremelimumab 576 (2)	25 (4.3%) /?		1 (1.8%) /1	4 (6.9%) /?
Nivolumab 1234 (4)	52 (4.2%) /0	17 (1.3%) /1	2 (0.6%) /1	1 (0.3%) /1
Lambrolizumab 135 (1)	11 (7.9%) /1	1 (0.8%) /1	0	1 (0.8%) /0
Pembrolizumab 2446 (5)	175 (7%) /2	67 (2.8%) /1	7 (0.3%) /4	5 (0.2%) /1
Ipilimumab + Nivolumab 494 (3)	67 (1.4%) /1	35 (7.1%) /3	37 (7.2%) /8	8 (1.9%) /1

Torino et al., Curr Opin Oncol 2016



7.56 Graves' disease. This usually affects women between the ages of 20 and 40 years. This patient presented classically with a diffuse goitre over which a vascular bruit could be heard, and with eye signs.

Myxedema



Baden LR et al. NEJM 2015

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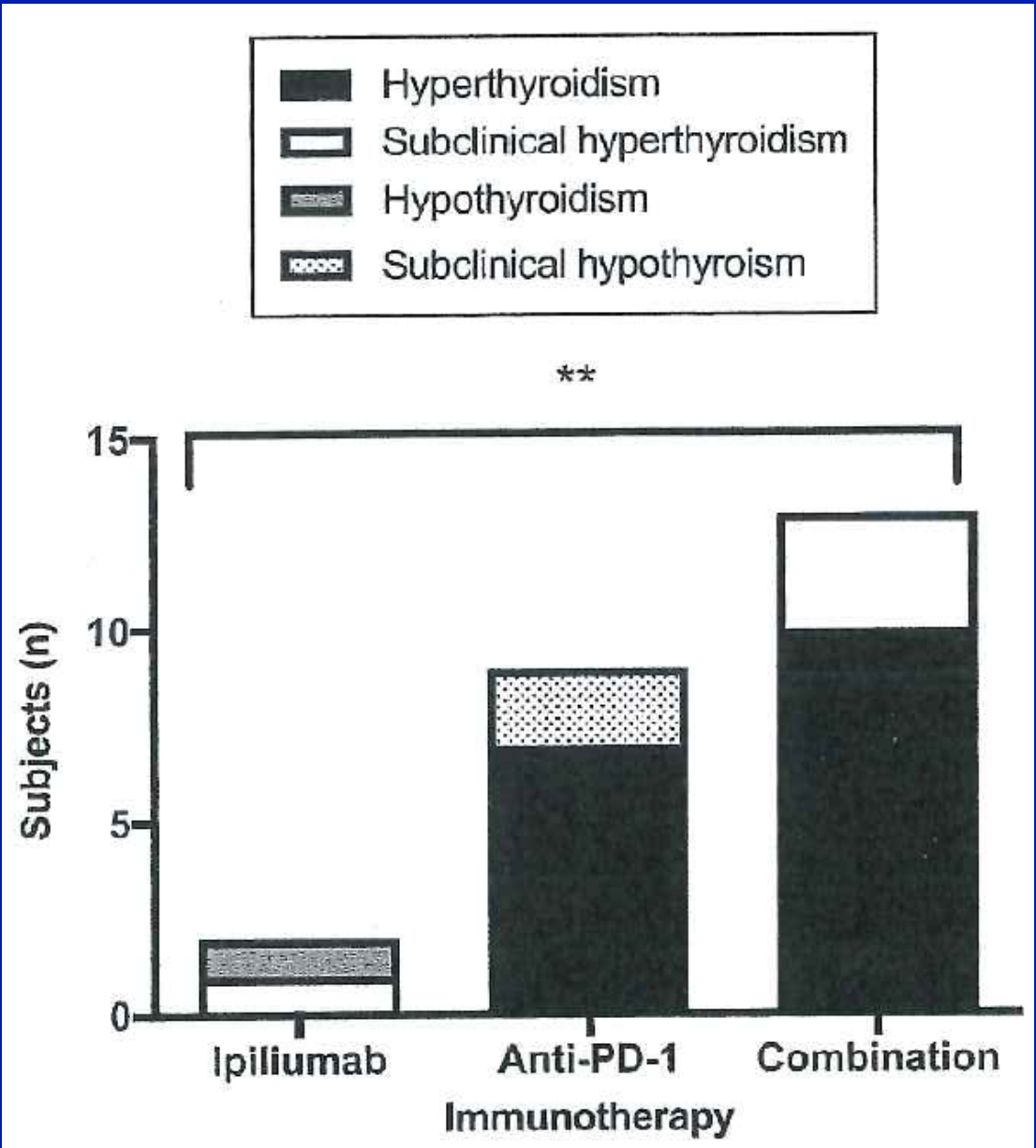

Scott ES et al., Eur J Endocrinol 2018

Rakotoarivelo *R et al., NEJM 2014; 371: 1446*

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Torino et al., Curr Opin Oncol 2016

Type 1 diabetes mellitus and/or diabetic ketoacidosis can occur with each ICI at the rate of less than 1%, independently of the drug, the dose and clinical indication. Interestingly, the incidence of type 1 diabetes mellitus and/or diabetic ketoacidosis doubled (1,5%) with the use of ipilimumab + nivolumab combination.

Insulin therapy is recommended, and steroids are not indicated

Torino et al., Curr Opin Oncol 2016

Diagnosis and management of immune checkpoint inhibitors – associated endocrine toxicities

- **Diagnosis:** high level of suspicion and liberal use of regular biological tests

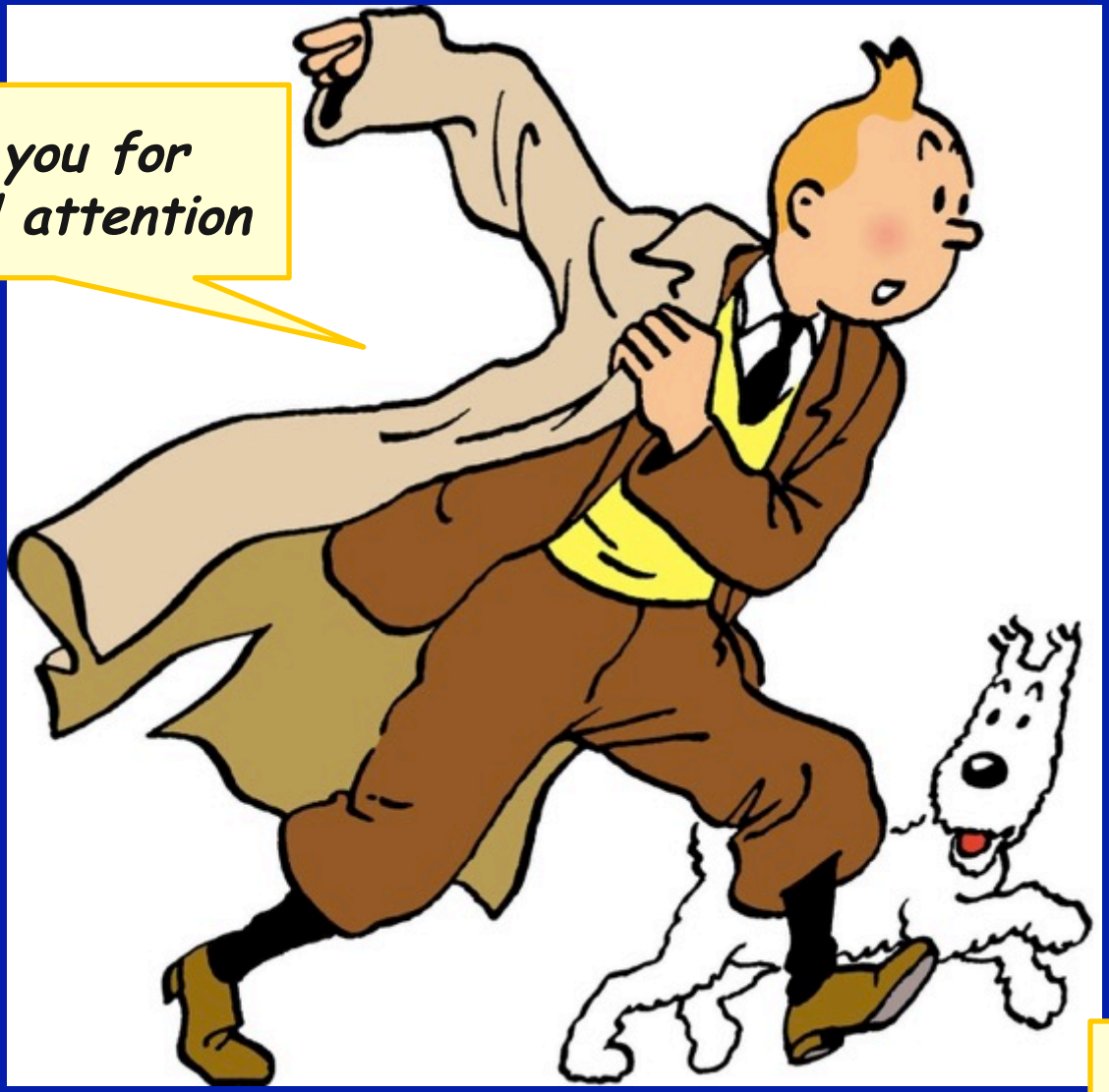
- **Management:**

1. Withdrawal or discontinuation of ICI depending on grade and response to therapy
2. Substitution or specific treatment for specific endocrine syndromes
3. High dose corticosteroids if severe signs or symptoms in spite of specific substitution therapy

Renal complications of immune checkpoint blockade

- Acute kidney injury is rare (1,5%; G ¾: 0,5%)
- Ipilimumab = Nivolumab
- Clinical presentation: acute interstitial nephritis (90%)
- Monitoring: creatinine level (G 3 > 3mg%; G 4 > 6mg%)
- Therapy : high dose corticoids + withold/ discontinue ICI

Thank you for your kind attention



See you later !