Endocrine toxicity

Inma Peiró M.D.
Nutrition Functional Unit / Catalan Institute of Oncology

Immune checkpoint inhibitors (ICI) including anti-cytotoxic T lymphocyte antigen-4 (CTLA-4), anti-programmed cell death-1 (PD-1) and anti-programmed cell death ligand-1 (PD-L1) agents have shown antitumor activity by enhancing adaptive immune response against cancer cells, resulting in significant long-lasting responses. Although the toxicity profile of the immune checkpoint inhibitors is more favorable than conventional chemotherapy, immune-related adverse events (irAEs) can occur as a result of enhancing immune response in normal tissues. IrAEs induced by ICI can potentially affect every organ in the body, but gastrointestinal tract, skin, liver, and endocrine system are the most commonly involved sites.

The endocrine system is a common target for irAEs. Patients treated with ICI are at risk of developing hypophysitis, thyroiditis and less common, primary adrenal insufficiency and autoimmune diabetes. It is mandatory monitoring hormonal function with an "endocrinological blood assessment" containing TSH; Free T4, baseline serum cortisol, sodium, potassium and baseline glucose, before and during treatment with immunotherapy.

Along the treatment, the patient and the oncology team should be educated on recognizing clinical signs and symptoms suggestive endocrinopathies in order to detect and treat them promptly:

- Fatigue / hypotension / sudden headache / abdominal pain /nausea / vomiting -> suspected diagnosis of: hypophysitis / adrenal insufficiency. Contact with endocrinologist and assess baseline pituitary hormones and baseline cortisol.
- Tachycardia/ tremor/ weight loss/ sweating -> suspected diagnosis of: hyperthyroidism. Assess TSH, free T4. If abnormal, contact with endocrinologist.
- Fatigue/edema / constipation / cold / drowsiness -> suspected diagnosis of: hypothyroidism. Assess TSH, free T4. If abnormal, contact with endocrinologist.
- Polyuria / polydipsia / hyperglycemia -> suspected diagnosis of diabetes/ hypophysitis. Contact with endocrinologist. Assess baseline pituitary hormones, baseline cortisol and monitoring glucose.

Immune induced hypophysitis

Hypophysitis induced by ICI appears most often in men over the age of 60 years and in patients treated with anti CTLA4 (ipilimumab) alone or in combination with nivolumab. The prevalence varies between 4-20%, increasing in combined therapy. The pathophysiological mechanisms are not completely understood. In mice models of

hypophysitis treated with anti CTLA-4, lymphocyte infiltration of pituitary gland and the expression of CTL4-antigen on pituitary cells have been reported.

Clinical manifestations are often non-specific. The most frequent signs are headache and fatigue. Hyponatremia is present in almost 50% of the patients. Polyuric-polydipsic syndrome (diabetes insipidus) is very rare. Hormonal deficiencies are often multiples at the time of diagnosis: central hypothyroidism and central hypogonadism almost in 100% of the patients, hypoprolactinemia in 96%, ACTH insufficiency with adrenal insufficiency in 50% and GH insufficiency in 17% of cases. Recovery from hormonal deficiencies is variable and new deficiencies can appear along the follow up. ACTH insufficiency with chronic adrenal insufficiency persists in 86-100% of the cases, and patients require chronic therapy with hydrocortisone.

Pituitary RMI is the most sensitive imaging for diagnosis. In 30-100% of cases shows a moderate increase in pituitary volume and enlargement of the pituitary salk suggestive of hypophysitis. These findings are transitory and after 4-12 weeks pituitary RMI return to normality.

High-dose corticosteroids are not systematically recommended to treat hypophysitis. (It may be suggested in patients presenting with major headaches, visual aberrations or other severe symptoms).

Treatment of hormonal deficiencies:

- Acute adrenal insufficiency -> In case of signs of acute adrenal insufficiency (dehidratation, hypotension, tachycardia, hyponatremia…) emergency therapy with endovenous hydrocortisone + fluid therapy should be started.
- Chronic adrenal insufficiency -> (Low cortisol value with minor signs of no signs of adrenal insufficiency), therapy with oral hydrocortisone 15-30mg/day should be started.
- Hypothyroidism -> New assessment of thyroid function after 1-2 months, then treatment with levothyroxine should be considered on a case-to-case basis.
- Hypogonadism -> Assess gonadal function after 2-3months and then consider replacement therapy in the absence of oncological contraindication.

Thyroid dysfunction induced by immunotherapy

The thyroid gland is a common site for irAEs. The risk of thyroid dysfunction (TD) is higher in patients treated with antiPD1 alone or in combination with antiCTLA4, with an overall incidence of TD ranging from 4 to 21%. The TD includes hypothyroidism and thyrotoxicosis, which are generally mild to moderate. The cause of TD induced by targeting PD-1, as well as the timing, pattern of the TD and prognosis of patients who develop TD remain unclear. The most common TD consists of silent inflammatory thyroiditis with a transient thyrotoxicosis followed by hypothyroidism. Most of the cases are mild and do not require replacement therapy. Treatment of TD depends on the clinical severity and etiological diagnosis and it must be decided on agreement between the

endocrinologist and the oncologist. Assessment of thyroid function (TSH; free T4) at baseline and before each cycle during the first 6 months and then every 3-6 months is recommended.

large number of immunotherapy drugs approved as single agents in many different tumor types, but it is expected that there will be more new approvals of combinatory regimes in a forthcoming future. Indeed, combinations of immunotherapies with other agents have already been approved in melanoma, renal cell carcinoma or non-small cell lung cancer. Therefore, it is crucial that any healthcare professional involved in the care of cancer patients treated with immunotherapy is aware of these side effects and have enough knowledge to treat them or to refer the patient where appropriate.

The usual first treatment of severe immune-related adverse events is the administration of steroids, initially orally or intravenously in case that the toxicity is not improved or resolved after 48-72 hours of oral treatment. If toxicity persists in spite of several days of intravenous treatment, more potent immunosuppression drugs such as infliximab, mycophenolate or tocilizumab should be considered. Given the complexity of the management of some of these side effects and the potential life-threatening consequences of some of them, the involvement of a wide array of different medical specialities other than medical oncologists is essential in order to provide an optimal care to our cancer patients treated with immunotherapy.

Endocrine toxicity

Inma Peiró
Endocrinology-UFN ICO l'H

Endocrine toxicity in oncology

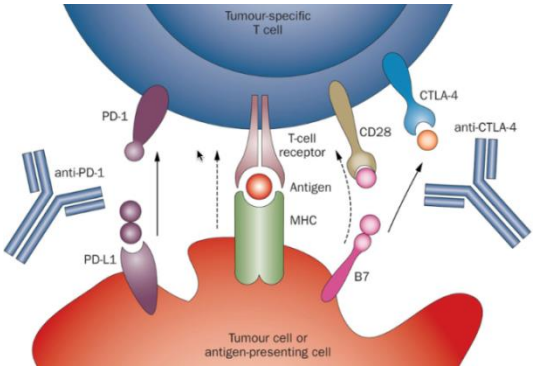
CLASSICS

- Steroid diabetes
- Fluid and electrolyte imbalance
- Glandular destruction

+

CURRENT

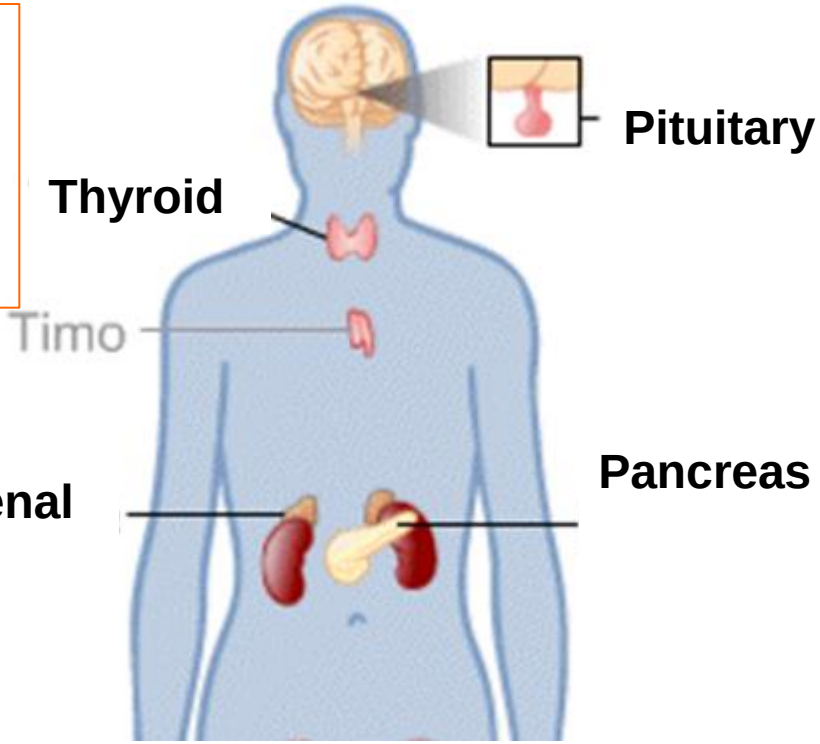
- Panhypopituitarism
- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
- Diabetes Mellitus
- Hypoparathyroidism



Endocrine system: target

Hypothyroidism
Hyperthyroidim

- AntiPD1>Anti-CTLA4



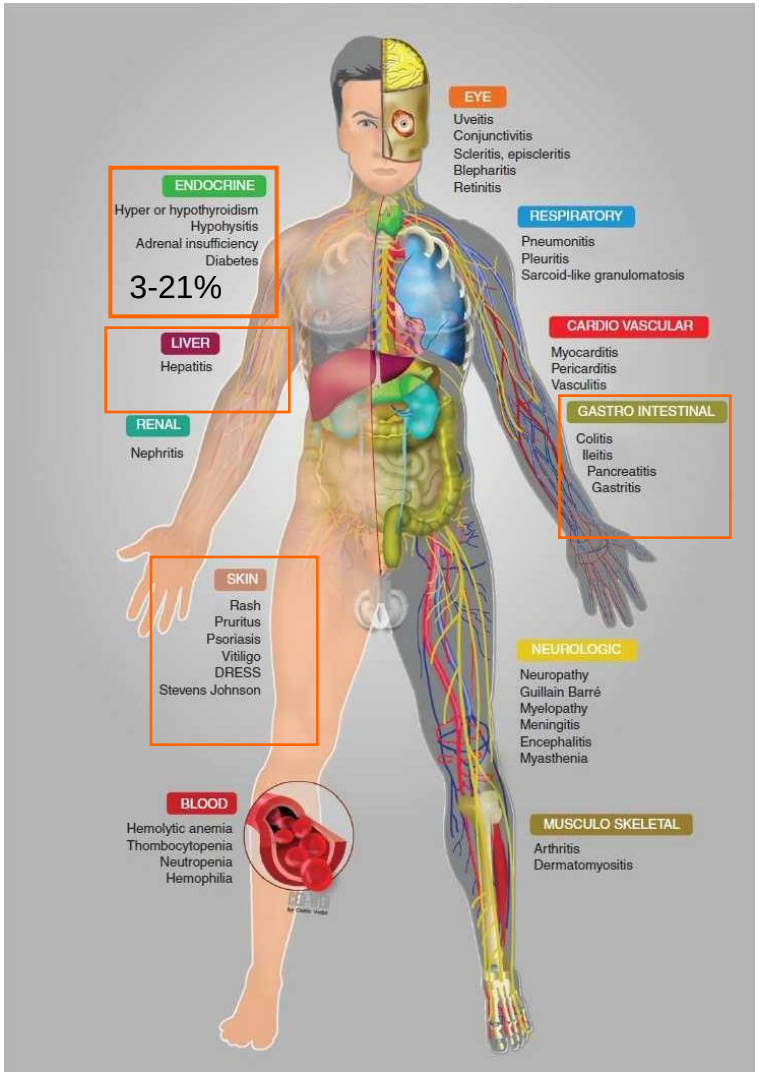
Hypophysitis

- AntiCTLA4>AntiPD1
  - Secondary hypothyr.
  - Secondary adrenal insufficiency
  - Hypogonadism
  - GH deficit

Adrenalitis

- Primary adrenal insufficiency

Diabetes



Endocrine toxicity: incidence 11%

Hypothyr>hyperthyr>Hypophysitis >adrenalitis>DM

Hypothyroidism: 6.6%

Hyperthyroidism: 2.9%

Hypophysitis: 1.2%

- AntiPD1—>1.1%
- AntiCTLA4→3.8%
- Combination→8%

Adrenalitis: 0.7%

Immune induced DM: 0.2%

Champiat S et al. Annals of Oncology 27: 559–574, 2016
R. Barroso-Sousa et al. Jama Oncol 2018; 1;4(2): 173-182

Case 1

- 64y. Choroidal melanoma →operated in 2010
- 2012 M1 liver → CT **Ipilimumab** 10mg/kg
  - C1 →22/1/13
  - C2 → 11/2/13
  - C3 → 4/3/13
  - C4 → 25/3/13

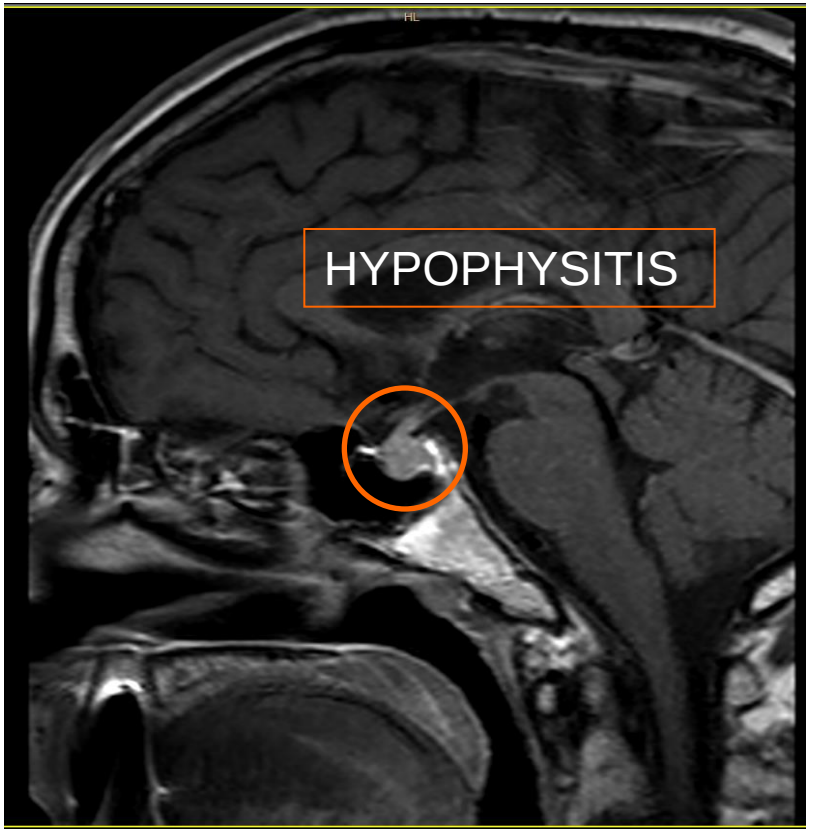
- Visit UACO on 5/4/13 (15d post-C4)→ fatigue, serious headache, G1 nausea and vomiting
  - AB normal. Glu 9.3 rest NORMAL (Na 135 K 4.73 creat. 86µmol/L)

- END: Clinical suspicion→ hypophysitis induced by Ipilimumab
  - Baseline pituitary hormones+ pituitary MRI

Prednisone
70mg/d

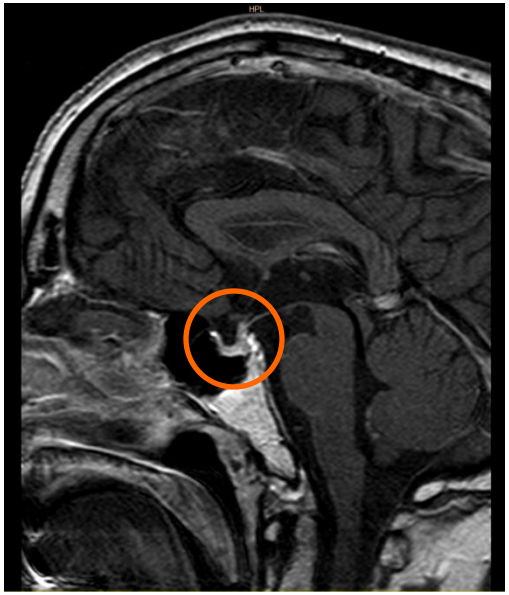
DATE	5/4/13 (Diagnosis)
TSH (0.48-4.3mUI/L) T4L (9.7-30.9pmol/L)	0.06 10.5
CORTISOL (155-678nmol/L) ACTH (2-12pmol/L)	137 5.3
LH (1.5-6.8UI/L) Testosterone (vn 7.6.23nmol/l)	3/0.7 <0.7
Prolactin (113-200UI/L)	71
GH (<3.5 mcg/L) IGF-1(7.8-26nmol/L)	0.79 23,1

Pituitary MRI 14/4/13



	Prednisone 70mg/d	Predn 10mg/d	Predn 10mg/d	Predn 10mg/d
DATE	**5/4/13 (Diagn)**	**5/12/13 (6m)**	**22/5/14 (1y)**	**7/11/14 (1,5y)**
TSH (0.48-4.3mUI/L) T4L (9.7-30.9pmol/L)	0.06 10.5	0.64 17	0.73 9.6	1.09 23.3
CORTISOL (155-678nmol/L) ACTH (2-12pmol/L)	137 5.3	98 5.2	<27.6 1.6	174 2.5
LH (1.5-6.8UI/L) Testosterone (vn 7.6.23nmol/l)	3/0.7 <0.7	3,5 3.1	3,7 12.2	6 7.6
Prolactin (113-200UI/L)	71	149	175	209
GH (<3.5 mcg/L) IGF-1(7.8-26nmol/L)	0.79 23,1	-- 20.1	-- 5.8	--- 4.7

Pituitary RMI
18/1/14 NORMAL



Case 2

60y. women

Seasonal lichen planus→ steroid treatment (spring) (last dose: 2015)

4/2016→ **Lung ADC** EGFR mut, **M1 (lung,skeletal and cerebral)**

- 3 previous line of treatment: TKI (erlo→afatinib), ChT (CDDP-Prem), BRAIN-RT
- 4L treatment EC Fase 1: **PDR001**+Ab anti IL1ß (C1: 5/2/18, C6:11/6/18)

INCIDENCE: Outbreak of lichen planus→PDN ± 10mg from 3/6/18 to 3/7/18.

Last RR 7/18: PR (TC and cerebral MRI)

- 8/8/18 →Emergency:
  - Nauseas, vomiting, fatigue
  - FE: 97/72 mmHg,105 bpm T 37.6º
  - BQ: EqAB OK. Glc 2,9. Na+ 142mmol/L creat 128 (improvement with hydration)
  - Plan → Discharge hospital (symptomatic treatment) and visit ONC in 72h

- 12/8/18 from ONC to UACO:
  - Serious fatigue, PS3, abdominal pain, G3 nausea and vomiting, dehidration, polyarthralgia.
  - FE: 105/62 mmHg, 84 bpm
  - BQ: Creat 147 Urea 15 EAB OK. Glu 3.5 Na 140 u-Na 175 K 4
  - Urine sediment: microhematuria and leukocyturia.

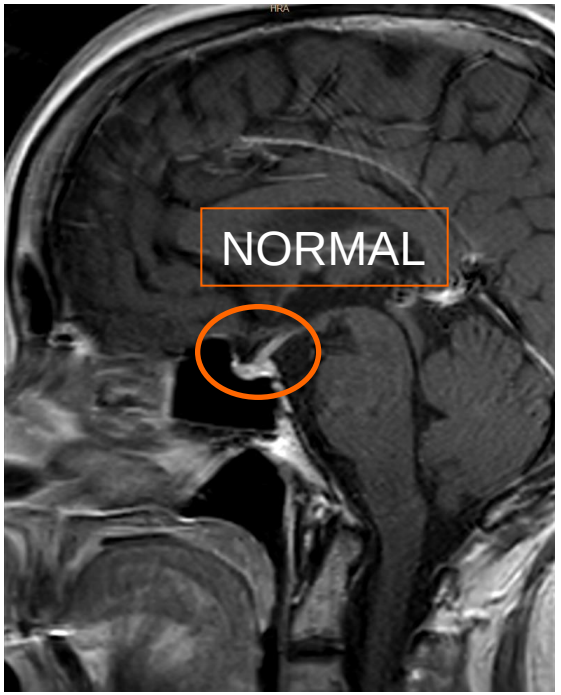
- From UACO to ONC hospital (renal vs END immuno induced toxicity)
  - END assessment → Clinical suspicion: Acude adrenal insufficiency

  → Baseline serum cortisol/ACTH

Metilpred 50mg/d

DATE	13/8/18 (Diagnosis)
TSH (0.48-4.3mUI/L) T4L (9.7-30.9pmol/L)	3.19 16.4
ACTH (2-12pmol/L) Serum CORTISOL (155-678nmol/L)	**<1.1** **7**
LH (6.7-50UI/L)/FSH (19.3-106)	16.2/25.1
Prolactin (113-200UI/L)	182
IGF-1(7.8-26nmol/L)	13,6

Pituitary MRI 14/8/18



DIAGNOSIS SUSPICION: ISOLATED ACTH DEFICIENCY

Normal renal function, improvement of gastrointestinal symptoms, PS1
Discharge hospital 18/8/18

Evolution

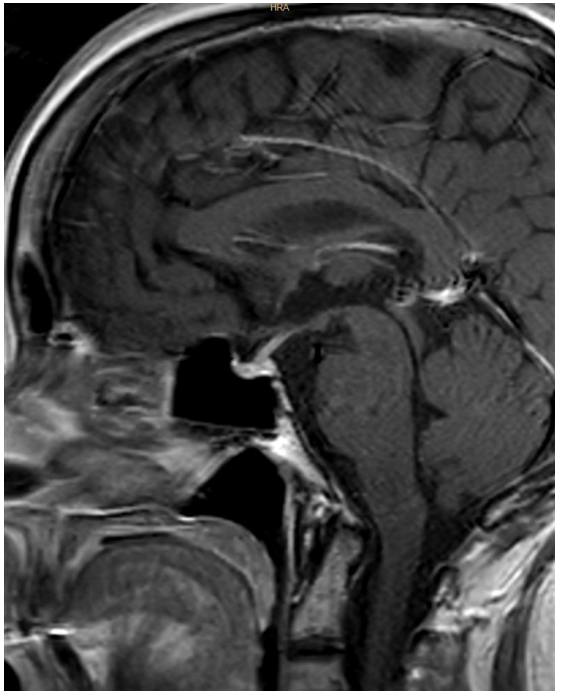
DIAGNOSIS: ISOLATED ACTH DEFICIENCY

Metilpred 50mg/d

Predn. 7.5mg/d

DATE	13/8/18 (Diagnosis)	22/12/18 (4m)
TSH (0.48-4.3mUI/L) T4L (9.7-30.9pmol/L)	3.19 16.4	3.75 20.5
ACTH (2-12pmol/L) Serum CORTISOL (155-678nmol/L)	**<1.1** **7**	**1.8** **<3**
LH(6.7-50UI/L)/FSH(19.3-106)	16.2/25.1	25.2/38.2
Prolactin (113-200UI/L)	182	174
IGF-1(7.8-26nmol/L)	13,6	22,4

Pituitary MRI 20/12
NORMAL



ONC ASS. DIC 2018 → PR (TC + Brain MRI)

Immune-induced hypophysitis

- Inflammation of the pituitary gland
- More frequent →Ab Anti CTLA-4 (Ipilimumab ≈17%)

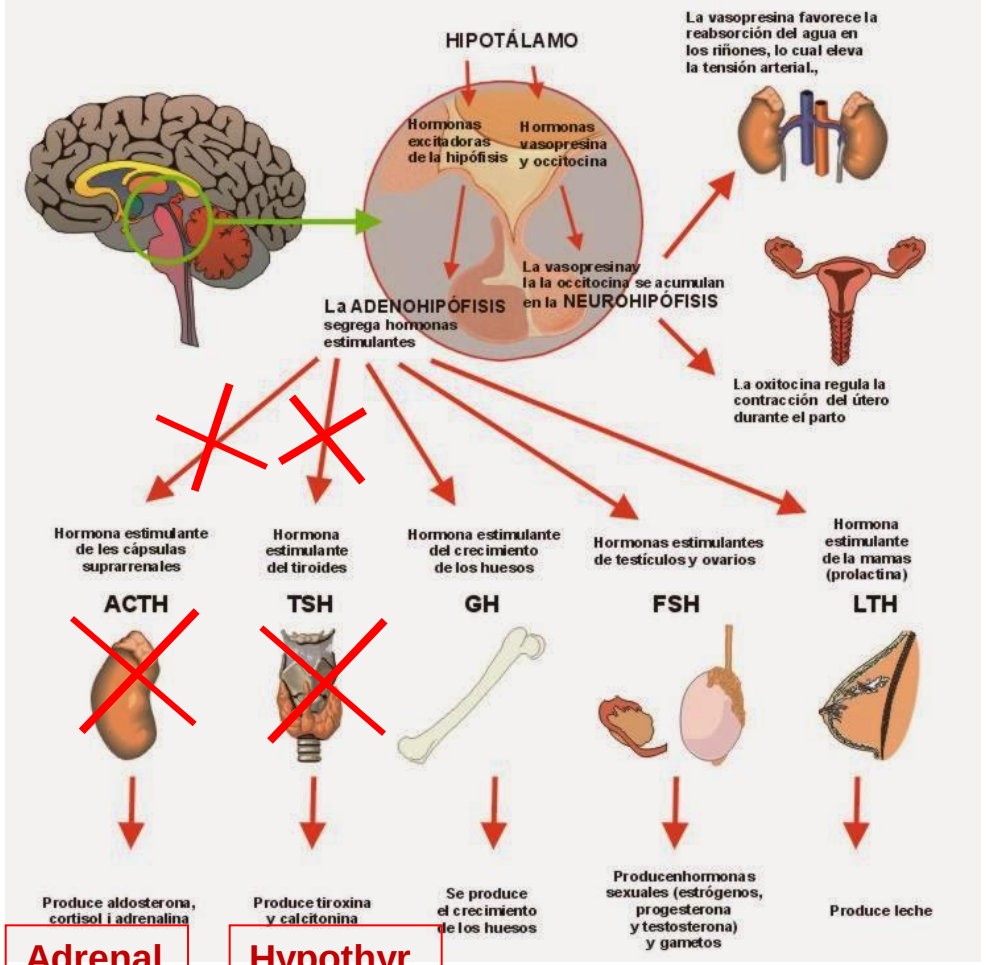
  →Men, mean age: 64y.
- Unknown etiopathogenesis (Pituitary CTLA-4¿?)
- Suspected diagnosis…
  - Headache(93%) → Compression syndrome
  - Fatigue (58.8%)
  - Anorexia (23.5%)
  - Cold intolerance
  - Confusional syndrome

  } Hormonal deficiencies

Faje et al. JCEM 2014; 99 (11): 4078-85

Immune-induced hypophysitis: hormonal deficits

- Hormonal deficit
- Central hypothyroidism → 100%
- Central hypogonadism → 100%
- Hypoprolactinemia → 92%
- ACTH insufficiency (adrenal insuff.)→ 50%
- Isolated ACTH insufficiency*
- GH insufficiency → 17%
- Laboratory
- Hyponatremia (113-134)→ 47%



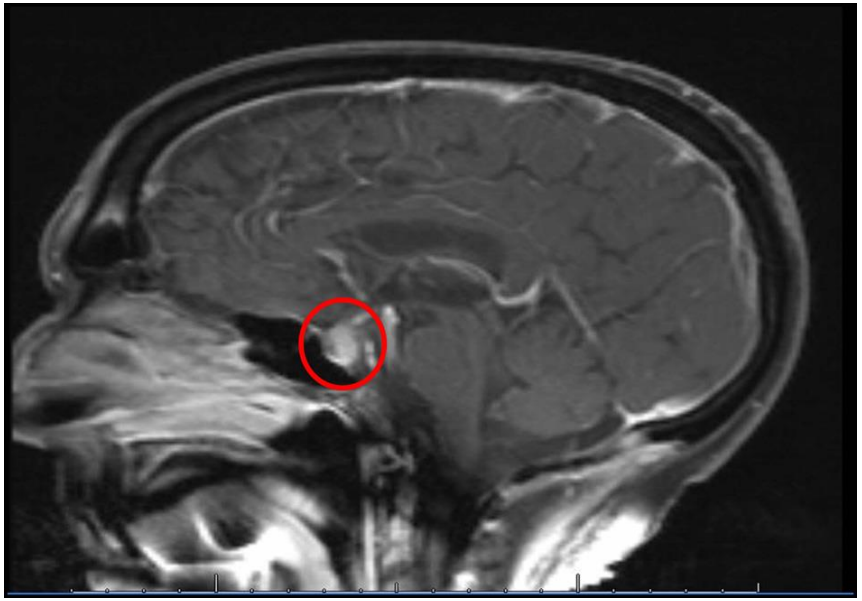
Adrenal Insuffic. (50%)

Hypothyr. (100%)

Faje et al. JCEM 2014
Ohara et al. Int Med 2018

Immune-induced hypophysitis: imaging and evolution

- **Imaging** → Pituitary MRI



Evolution

- Normal pituitary MRI
- Improvement/resolution compressive symptoms
- Chronic ACTH insufficiency→ 87%
- Long term improvement of the rest of pituitary hormones

Albarel et al. EJE 2015

Immune-induced hypophysitis: treatment

- Treatment
  - High-dose corticosteroids is not systematically recommended. (It can be suggested in patients presenting with major headaches, visual aberrations or other severe symptoms)
  - Treatment of hormonal defficiencies:
    - Acute adrenal insufficiency→ Ev hydrocortisone + fluid therapy.
    - Chronic adrenal insufficiency→Oral hydrocortisone 15-30mg/day.
    - Hypothyroidism →New assessment of thyroid function 1-2 months later, then treatment with levothyroxine should be considered on a case-by-case basis.
    - Hypogonadism → Assess gonadal function 2-3months later and then consider replacement therapy in the absence of oncological contraindication.

Castinetti et al. Endocrine related cancer 2019

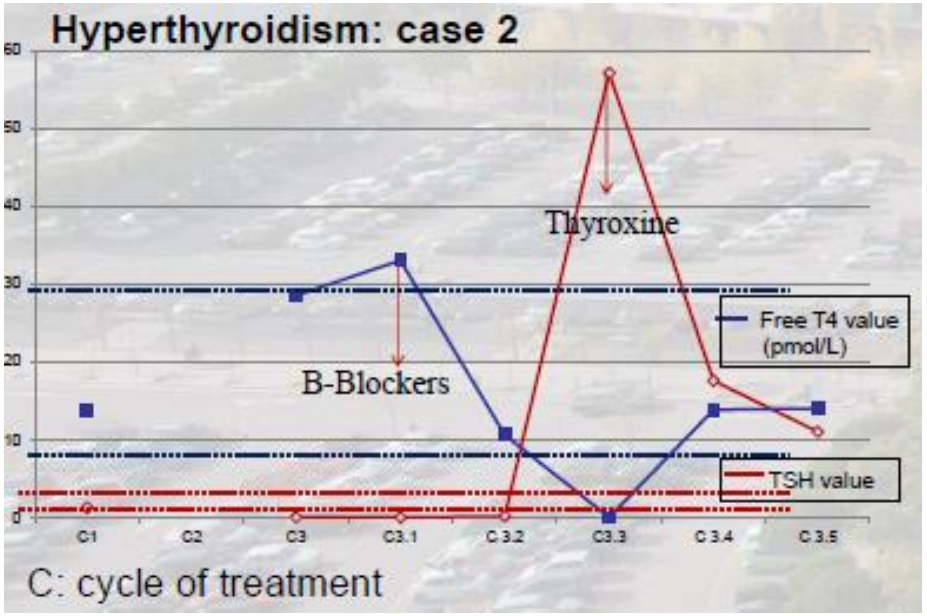
Case 3

- 35y woman. Hodgkin Lymphoma → **Nivolumab** (clinical trial):
- C1 Nivo+AVD (7/2/16)
- Pre C3 → tachycardia, tremor, weight loss (4 kg in 15 days), sweating.

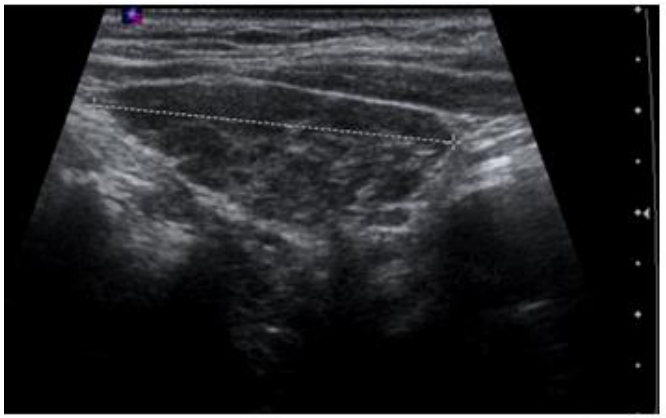
  TSH:→<0.01mUI/L (VN 0.48-4.36)

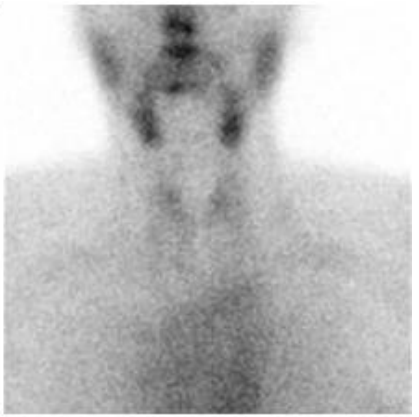
  Free T4: 34 pmol/L (VN 9.6-30.9 T3: 5pmol/L (VN 1-3 pmol/L)

  Ab Anti-TPO: positive



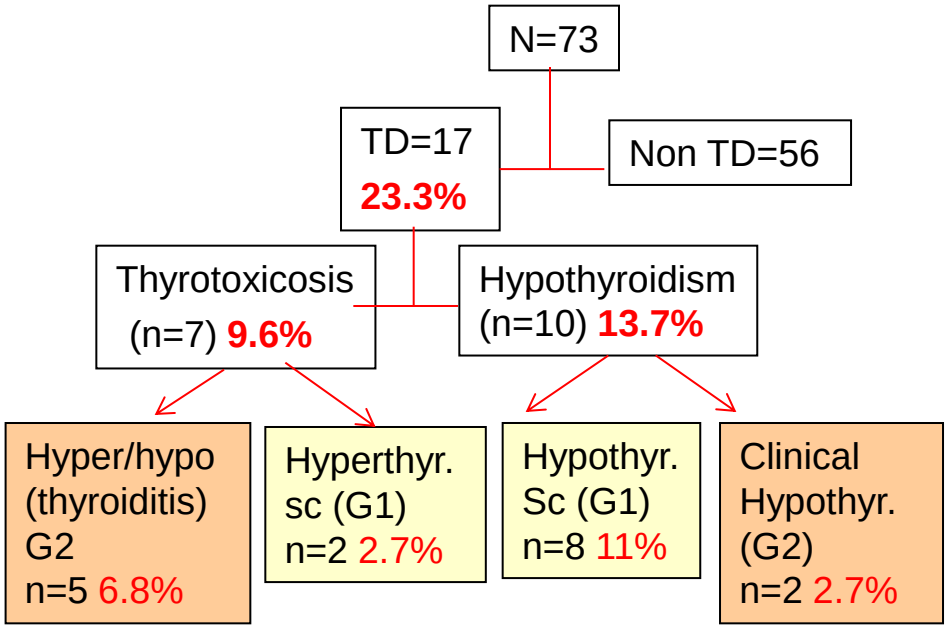
Thyroid US + scintigraphy→ **thyroiditis**





Thyroid dysfunction

- Pathophysiology not completely understood
  - thyroiditis ¿destructive, autoimmune?
  - Antitiroid antibodies?
  - Role of PDL1/PD1 in normal thyroid gland
- More frequent→antiPD1/AntiPDL1
- Variable clinical course
  - Clinical/subclinical hypothyroidism
  - Clinical/subclinical thyrotoxicosis
- Mostly G 1-2



Morganstein et al. Clin endocrinol 2017
Osorio et al. Ann Oncol 2017
Kobayashi et al. J Endocr Soc. 2018
Peiró et al. Submitted to Endocrine 2019

Thyroid dysfunction: treatment

- Hypothyroidism

  - Levothyroxine

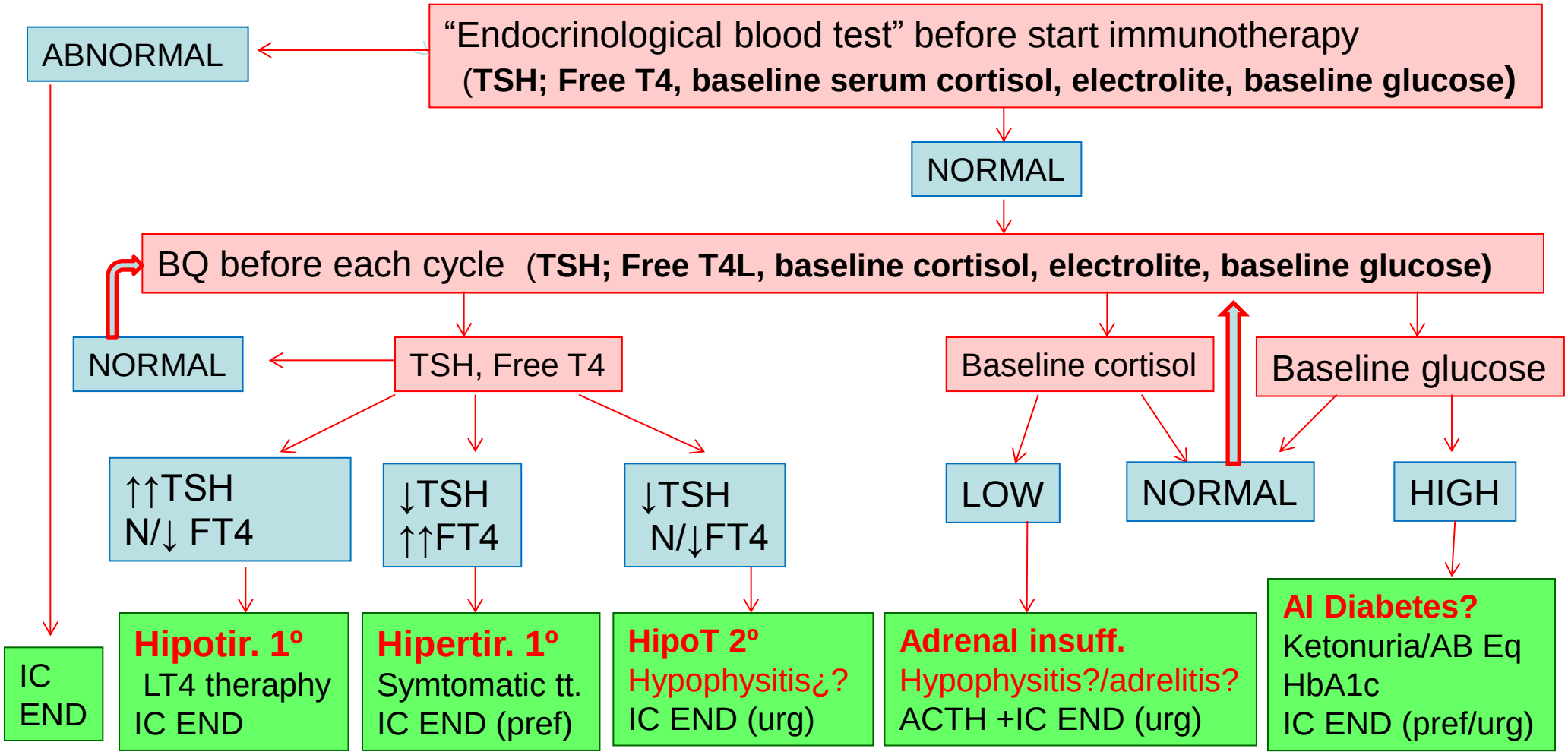
- Hipertiroidismo

  - Symptomatic treatment (Beta-Blockers)

  Metimazole/ steroids*

*only in clinically severe cases

Management of endocrine toxicity induced by immunotherapy



Adapted of F. Illouz et al.cancer medicine 2017; 6(8): 1923-29

Take home messages

- Pituitary and thyroid → Most common endocrine target toxicity of IT.
- Adrenal and pancreas less common.
- It's important to know and transmit to the patient the possible signs and symptoms of endocrinopathies :
  - Fatigue / hypotension / sudden headache / abdominal pain /nausea / vomiting →hypophysitis / adrenal insufficiency
  - Tachycardia/ tremor/ weight loss/ sweating → **hyperthyroidism**
  - Fatigue/edema / constipation / cold / drowsiness →**hypothyroidism**
  - Polyuria / polydipsia / hyperglycemia →**diabetes/hypophysitis**

Take home messages

- Most of the endocrine toxicities are grade 1-2
- Even severe endocrine toxicities, once treated, do not usually contraindicate immunotherapy.
- Endocrine toxicities can appear throughout the treatment, and many of them do not recover.
- It is important to monitor the patient with clinical/biochemical and hormonal control, in each cycle (first 6 cycles) and later every 3-6 months.
- It is mandatory a multidisciplinary approach in these patients.