Royal College of Physicians

Guy's and St Thomas' NHS
NHS Foundation Trust

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Session 2: How I treat ….. an update on current best management endocrinology cases

Advances in the understanding of Hypophysitis

Paul Carroll
paul.carroll@gstt.nhs.uk

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Definition of hypophysitis

- Hypophysitis is defined as an inflammatory condition of the pituitary gland that leads to pituitary dysfunction

- Pathogenesis incompletely defined
- Heterogeneity of the disease
- ‘New’ aetiologies

Takahashi. *Hand Clin Neurol*. 2014 ; 124: 417-22

Structure of presentation

- Case based- real cases presenting to medicine
- Current understanding of lymphocytic hypophysitis (AH)
  - Treatment
- ‘New’ conditions
  - IgG4 related disease
  - Immune checkpoint inhibitors/ ipilimumab
- Summary/ TTOs

Case 1; 31 yo woman

- 38 weeks gestation
- **Headache**, nausea, **hyponatraemia** (Na 125 mmol/L)
- Cortisol 25 nmol/L (AM sample)
  - ACTH <5 ng/L
- Free T4 10.3 pmol/L
  - TSH 3.1 mU/L
- No polyuria
- Normal vision

Management

- Presumed pituitary insufficiency
- Likely lymphocytic hypophysitis
- Imaging/ antibodies/ documentation of visual fields
- **Treatment** & birth plan

Management

Lymphocytic hypophysitis

[redacted]

- Presumed pituitary insufficiency
- Likely lymphocytic hypophysitis
- Imaging/ antibodies/ documentation of visual fields
- **Treatment** & birth plan

Progress

- Prednisolone 40 mg/d
  - Serial MRI
  - Tapered
- Headache improved
- Delivered SVD 38/40
  - Spontaneous menstruation
- Permanent ACTH/ GH D
- Subsequent pregnancy with recurrence of inflammation

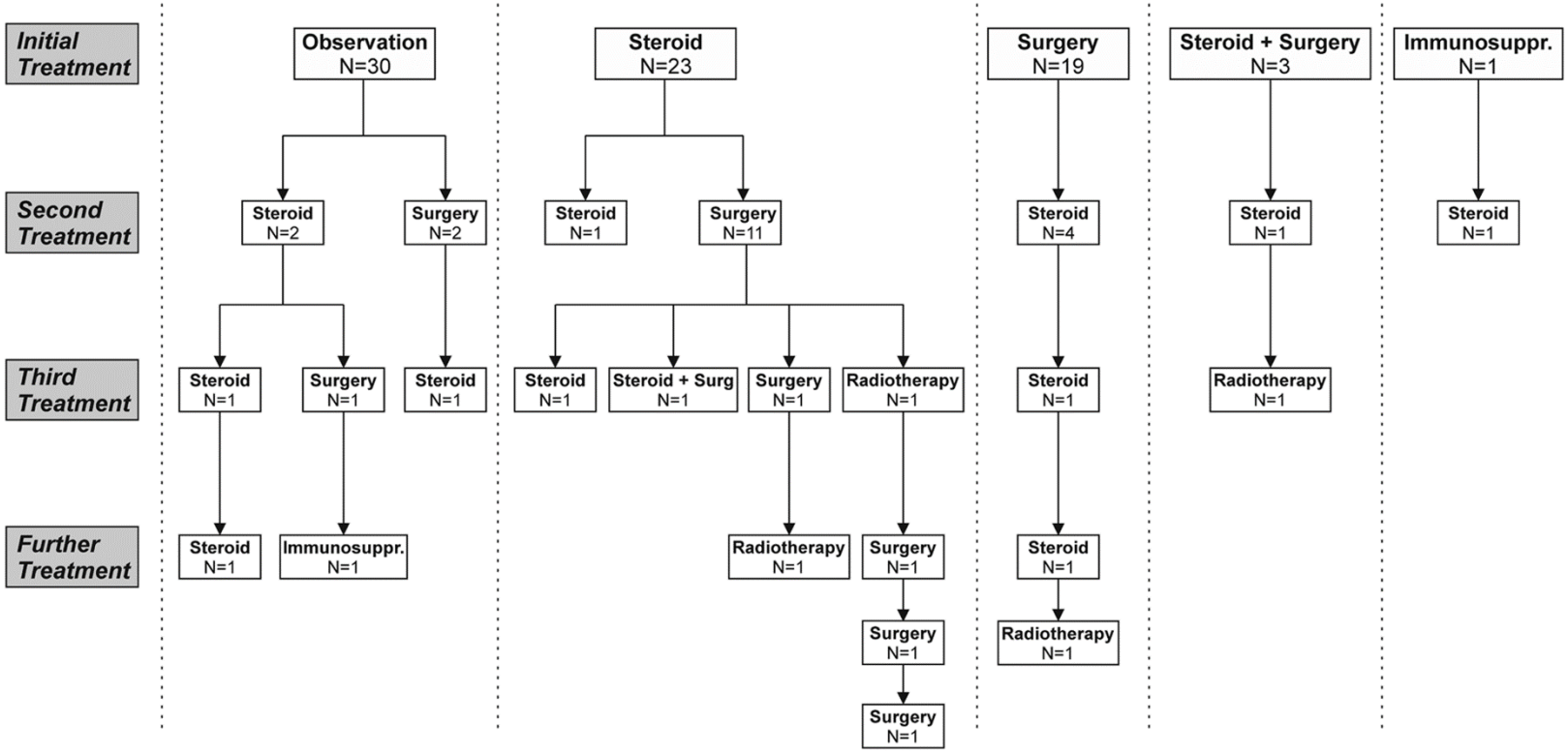
General characteristics of lymphocytic (autoimmune) hypophysitis

- Very rare & poorly understood
- Gender, F/M 8/1
- Mean age (years): 34.5 (F)–44.7 (M)
- Correlation with pregnancy (approx 40%)
- Familial or personal history of autoimmunity
- Characteristic pituitary hormone deficiency
- No treatment guidelines

Treatment of Primary Hypophysitis in Germany

- Pituitary Working Group of the GES
  - **Primary Hypophysitis**
- 9 centres, 76 patients
- Relapse was observed in as many as 38% of our cases
- Surgical failure with progression or recurrence was detected in 25%
- Regression on MRI in 46% and stable size in 27%
- We found a high rate of significant adverse effects under glucocorticoid pulse therapy, with 63% of our patients afflicted

JCEM. April 2015



From: Treatment of Primary Hypophysitis in Germany
J Clin Endocrinol Metab. 2015;100(9):3460-3469. doi:10.1210/jc.2015-2146

Recommendations from study

- In patients without severe symptoms ***we recommend observation with a close follow-up schedule***
- Observation is even justified in the presence of pituitary failure
- Recovery of endocrinological deficits was more frequent with observation than with glucocorticoid therapy
- ***Only intolerable headache should be treated either with glucocorticoids or with surgery***

https://doi.org/10.1210/jc.2015-2146

Classification of hypophysitis

- **Primary**
  - Lymphocytic hypophysitis
  - Granulomatous hypophysitis
  - Xanthomatous hypophysitis
- **Secondary**
  - Sellar diseases (eg Rathke's cleft cyst, craniopharyngioma)
  - Systemic disease (eg SLE)
  - Langerhan's cell histiocytosis
  - Sarcoidosis
  - Takayasu's disease
  - Infective (bacterial, viral, fungal)
  - Immune checkpoint inhibitors
  - IgG4 Related Disease

J Clin Endocrinol Metab. 2011 Jul; 96(7): 1971–1980

Case 2; 75 yo man

- **Headaches** for >12 m
- **Hypopituitarism**
- **‘Atypical’ mass** in the pituitary fossa
- No polyuria
- Normal vision
- Hypophysitis?

J Clin Endocrinol Metab. 2011 Jul; 96(7): 1971–1980

Case 2; 75 yo man

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- Pituitary replacement
- Surgery for therapeutic and diagnostic reasons
- Second procedure

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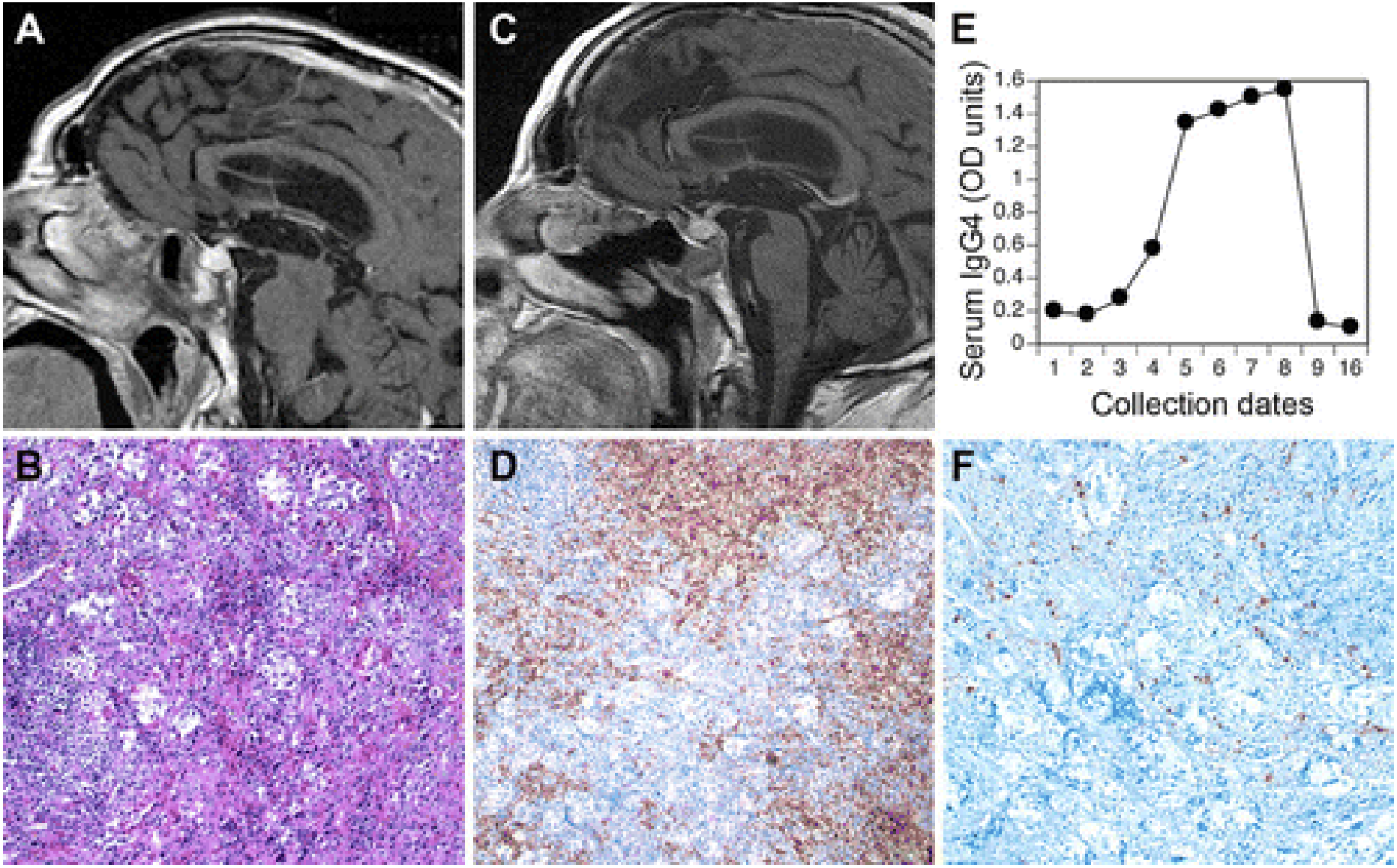


J Clin Endocrinol Metab. 2011 Jul; 96(7): 1971–1980

IgG-4 hypophysitis

- Features
  - 2004, pathophysiology?
  - Hypopituitarism
  - Mass, involving stalk
  - Perhaps response to GC treatment
  - More common in men
  - ? Accounts for cases previously considered LH
- Diagnostic criteria
  1. Histopathology
  2. MRI appearance
  3. Biopsy proven other sites
  4. Serology [IgG-4]
  5. Clinical and radiological response to GC

J Clin Endocrinol Metab. 2013 May;98(5):1808-11

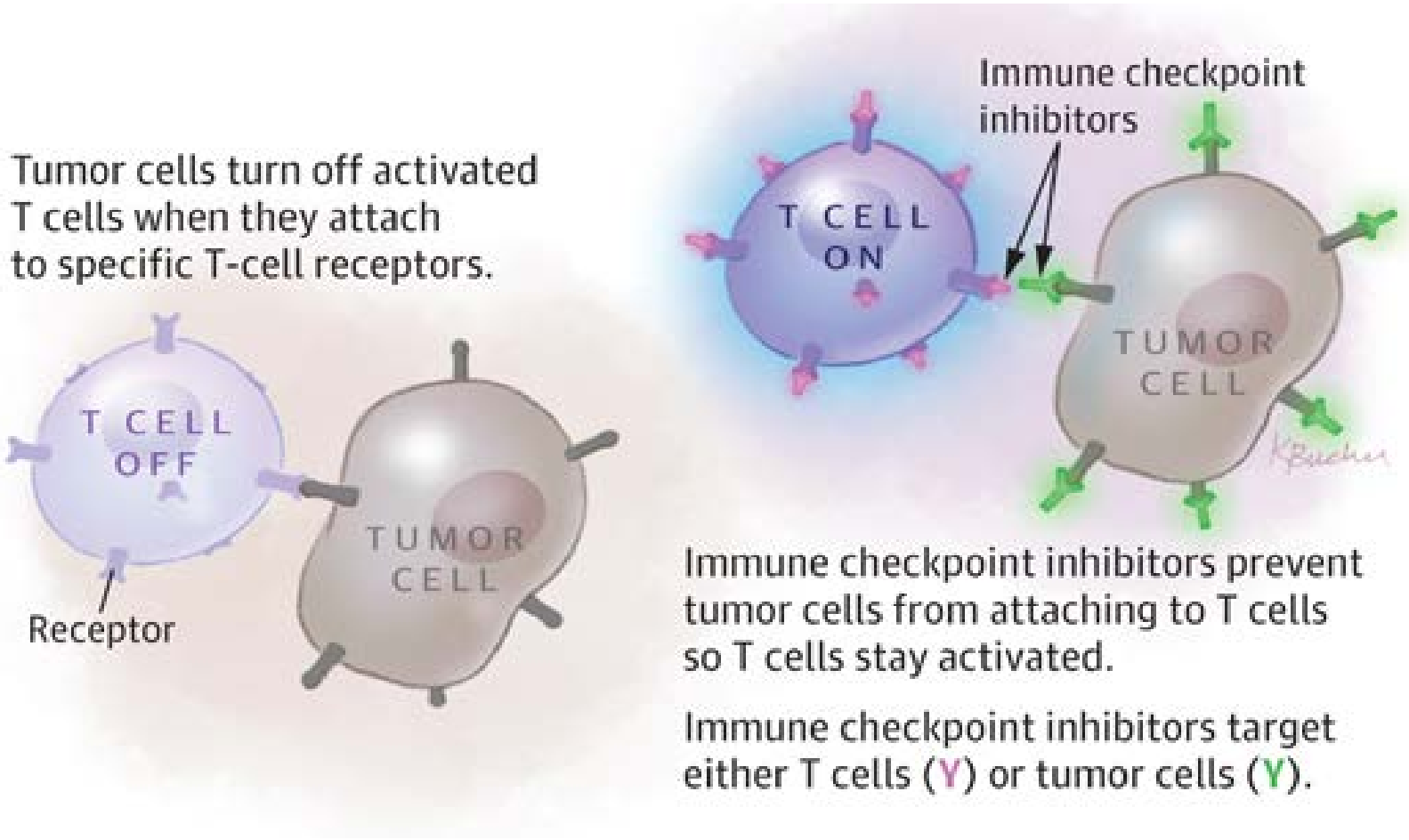
Case 3; 58 yo woman

- Background:
  - Mid-back malignant melanoma - stage 3A, diagnosed 2006
  - Wide local excision followed by chemotherapy
  - Resection of intra-clavicular metastasis 2013
  - Started on ***ipilimumab*** two months prior to presentation
  - Investigated for short history of **headaches** & fatigue

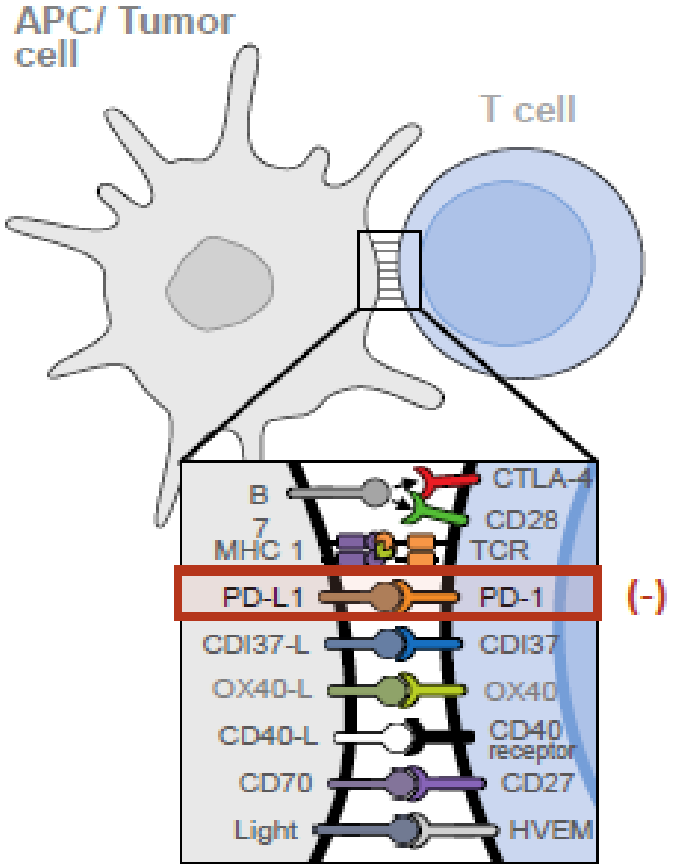
IPILIMUMAB

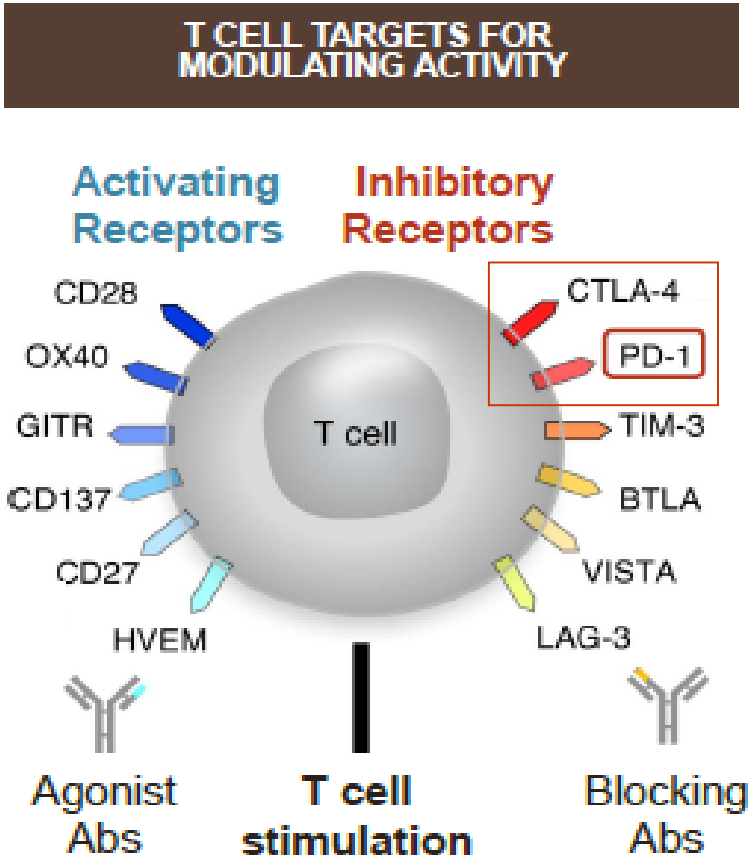
- Immunomodulatory therapy in oncology
- First “immune checkpoint inhibitor”
- Licensed for use in refractory metastatic malignant melanoma (2011)
- Increasingly used in management of variety of refractory cancers

Basic mechanism



JAMA Oncol. 2015;1(1):115. doi:10.1001/jamaoncol.2015.0137.





Mellman et al, Nature Vol 480, 22: 29 Dec 2011

Targets and related drugs

- **CTLA-4 Ab**
  - **Ipilimumab (Yervoy®)**
  - **Tremelimumab**
- **PD-1 Ab**
  - **Nivolimumab (Opdivo®)**
  - **Pembrolizumab (Keytruda®)**
- **PD-L-1 Ab**
  - **Pidlizumab**

Incidence of hypophysitis

- Ipilimumab : 0-17%
- Tremelimumab : 0.4-5%
- Nivolimumab : <1%
- Pembrolizumab : <1%
- Ipilimumab and Nivolimumab : 9.9-22% thyroid dysfunction

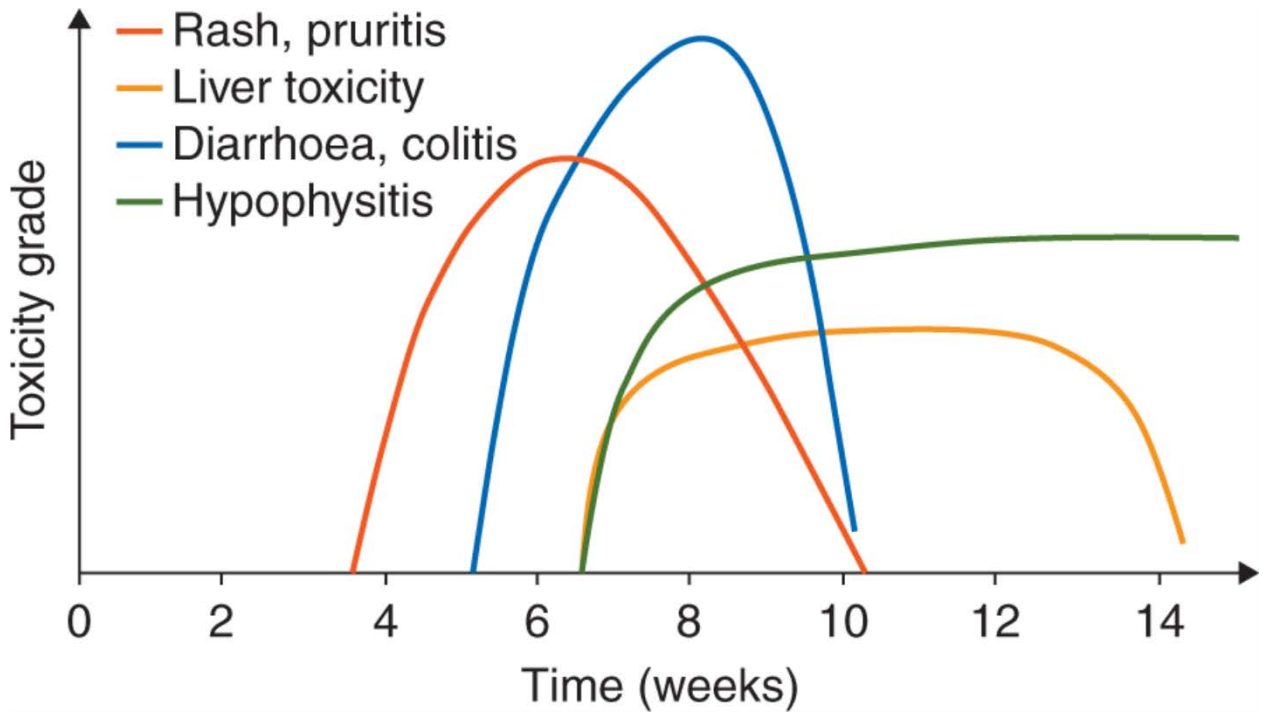
- **Presentation**
  - Mass effect & headache
  - Visual disturbance
  - Consequences of hypopituitarism
    - Median 6 weeks (5-36) after initiation

Clinical Cancer Research. 2015;21(4):749-55. *Journal of Clinical Endocrinology & Metabolism*. 2014;99(11):4078-85.

Management of immune checkpoint inhibitor hypophysitis

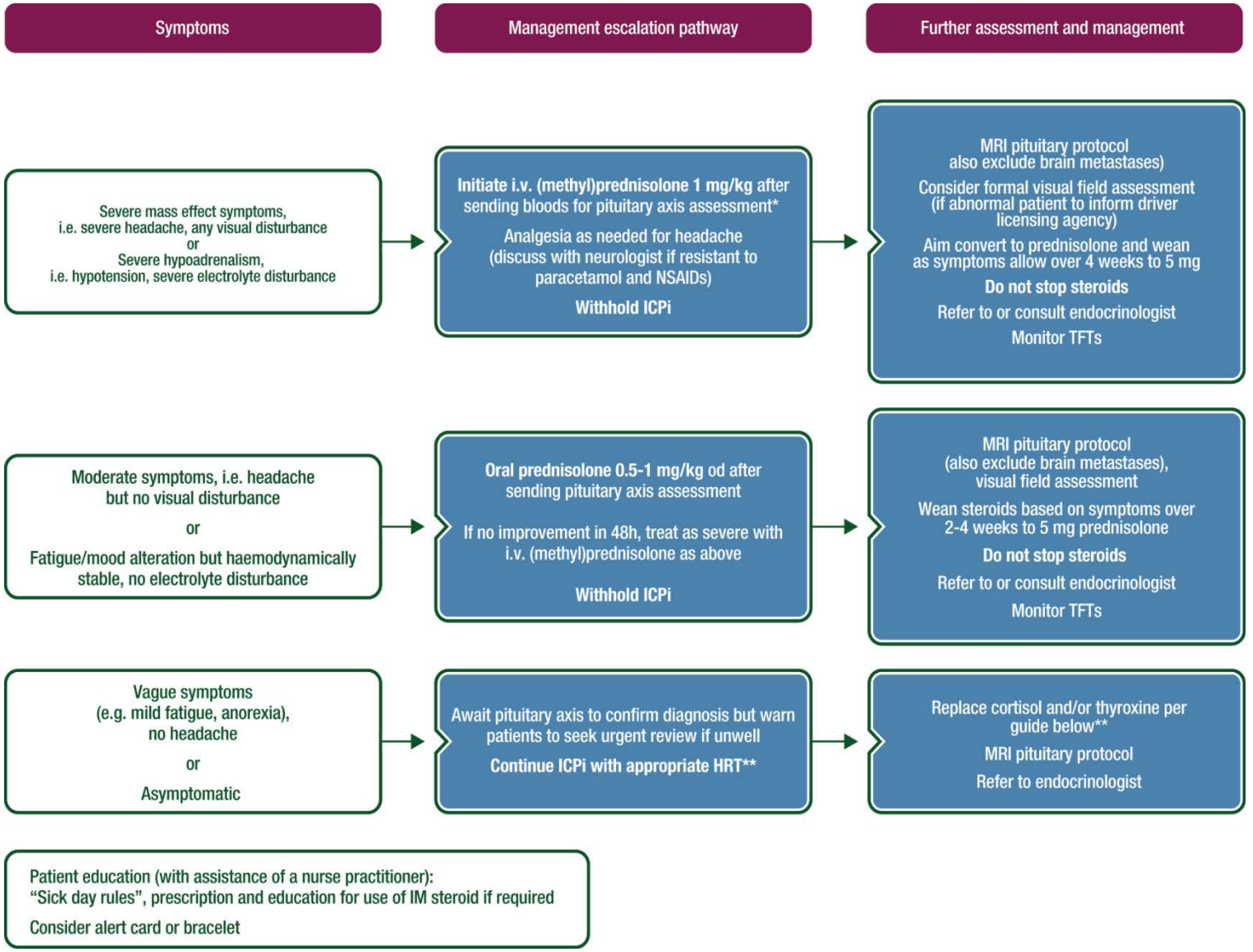
- **Diagnosis**
  - Awareness v screening
  - Headache
  - Imaging
  - Context
  - Resolution
- **Management**
  - Stop agent?
  - High dose GC?
  - Variable recovery
    - Not of HPA
  - Liaison and protocol

Society for Endocrinology



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

Ann Oncol. 2017;28(suppl_4):iv119-iv142. doi:10.1093/annonc/mdx225



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Summary/ TTOs

- **Consider hypophysitis**
  - Headache, pituitary insufficiency
    - Pregnancy
    - Systemic diseases
    - Immunotherapy
- **Classification** of hypophysitis
  - Careful evaluation of atypical pituitary presentations
- **Recognise**
  - IgG4 RD
  - Immune checkpoint inhibitors/ ipilimumab
- Conservative management of lymphocytic hypophysitis
- Refer to guidance for acute presentations

- Mamta Joshi
- Ben Whitelaw
- Patients & Pituitary team