

Hammersmith Abstracts

8th December 2017

12th Hammersmith Multidisciplinary
Endocrine Symposium 2017



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Hammersmith Hospital 12th Multidisciplinary Endocrine Symposium

Friday 8th December 2017

Wolfson Education Centre, Hammersmith Hospital

8.30am Registration and Coffee

8.50am Welcome and Introduction: Mr Fausto Palazzo, Prof Karim Meeran and Prof Waljit Dhillon

Session 1: The Thyroid Clinic. Chair: Keith Steer, Northwick Park.

9.00am Thyroid storm in Graves' disease – Acute management & further treatment.
Prof Karim Meeran (Imperial College)

9.30am A multi-disciplinary approach to Graves' ophthalmopathy.
Miss Vickie Lee (Imperial College)

10.00am OC1: The challenge of second line immunotherapy in Graves' ophthalmopathy (X022)

10.15am OC2: Emergency Orbital Decompression is not a definitive treatment for Dysthyroid Optic Neuropathy (DON) (X032)

10.30am Coffee Break

Session 2: Multiple Endocrine Neoplasia. Chair: Jeannie Todd, Imperial College

11.00am Pheochromocytoma in MEN 2.
Mr Radu Mihai

11.30am Thyroidectomy for MEN 2 - when, who, how?
Prof David Scott-Coombes (Cardiff)

11.55am The follow up of Medullary thyroid cancer.
Dr Florian Wernig (Imperial College)

12.15pm Lunch & Poster session

12.15pm Lunch & Poster session

Session 3 New technologies in thyroid disease. Chair: Prof Neil Tolley

1.15pm Autofluorescence in thyroid and parathyroid surgery.
Miss Aimee DiMarco/Mr Fausto Palazzo.

1.35pm **Hammersmith International Guest Lecturer 2017:
Prof Paolo Miccoli (Pisa)**
Molecular testing in the diagnosis & treatment of papillary
thyroid cancer

2.20pm OC3: Advanced medullary thyroid cancer – when to start treatment?
(X017)

2.40pm Coffee break

**Session 4: Medical & surgical treatment in thyroid & parathyroid disease.
Chair: James Ahlquist, Southend.**

3.00pm Treatment options in tertiary hyperparathyroidism
Dr Neil Duncan

3.30pm The non surgical management of the benign goitre (RFA/HIFU/I131)
Dr Amir Sam (Imperial College)

3.55pm OC4 Resistant hypercalcaemia in pregnancy – medicine to surgery
(X023)

4.10pm OC5 The anomalous goitre: an unusual presentation of multi-nodular
goitre (X012)

4.35pm Feedback and Close

X001	Hypercalcaemia and Primary hyperparathyroidism in pregnancy
X002	An unusual case of asymptomatic primary adrenal insufficiency due to bilateral adrenal haemorrhagic infarcts
X003	The forgotten neoplasia of MEN-1 syndrome: thymic neuroendocrine tumours
X004	Familial hypocalciuric hypercalcaemia – a case report and review of the literature
X005	Amiodarone-induced thyrotoxicosis type 2 (AIT2).
X006	Alcoholic pseudo-Cushing's syndrome: mimics both the biochemistry and clinical features of Cushing's syndrome
X007	Heparin-induced hyperkalaemia due to hyporeninaemic hypoaldosteronism
X008	The challenges of investigating adrenal insufficiency in patients with immunotherapy related adverse reactions requiring glucocorticoid treatment
X009	Diagnostic and therapeutic role of GnRH analogue in postmenopausal hyperandrogenism
X010	A Tale of Two Brothers with Neuroendocrine Tumours
X011	Challenges in the management of a rapidly growing dedifferentiated parathyroid carcinoma
(OC5) X012	The anomalous goitre: an unusual presentation of multi-nodular goitre
X013	An Unusual Presentation of Partial Empty Sella Syndrome and Arnold Chiari Type 1 Malformation
X014	An unusual cause of leg weakness
X015	Single presentation, two lifesaving diagnosis'- Simultaneous new presentation of diabetic ketoacidosis and primary adrenal insufficiency

X016	Parathyroid nuclear medicine localisation - an unusual ectopic gland?
(OC3) X017	Advanced medullary thyroid cancer – when to start treatment?
X018	Hurthle Cell Tumour - A case of delayed metastatic disease causing abnormal thyroid function, acromegaly and hypercalcaemia.
X019	Persistently elevated plasma metanephrine levels in a patient with MEN2 – when to diagnose a pheochromocytoma?
X020	Unmasking of concurrent autoimmune disease or the emergence of Graves' precipitated by Adalimumab (Humira)?
X021	Paraneoplastic thyrotoxicosis secondary to advanced non-seminomatous germ cell tumour
(OC1) X022	The challenge of second line immunotherapy in Graves' ophthalmopathy
(OC4) X023	Resistant hypercalcaemia in pregnancy – medicine to surgery
X024	Incidental pheochromocytoma in an unsuspecting urological setting
X025	Thyrotoxic cardiomyopathy – a serious consequence of uncontrolled Graves thyrotoxicosis
X026	Two cases of hypophysitis presenting as pseudomacroadenoma and hyponatraemia
X027	The success of multimodality treatment in metastatic medullary thyroid cancer
X028	Bilateral adrenal histoplasmosis in an immunocompetent man
X029	Autoimmune primary adrenal insufficiency masked by chronic steroid inhaler use
X030	A rare presentation of TSH-secreting Pituitary macroadenoma (TSHoma) alongside an Autoimmune Primary Hypothyroidism -The management challenge

X031	Diffusion-weighted Magnetic Resonance Imaging (DWI MRI) provides a quantitative measure of disease activity and can be used as an adjunct to clinical assessment in Graves' Orbitopathy (GO)
(OC2) X032	Emergency Orbital Decompression is not a definitive treatment for Dysthyroid Optic Neuropathy (DON)
X033	Two cases of Primary thyroid lymphoma in hypothyroid patients presenting as goitres
X034	A challenging case of radioiodine-refractory Graves' disease
X035	Percutaneous microwave ablation of adrenal remnant tissue. A novel treatment modality for persistent Cushing's disease
X036	Erectile Dysfunction – An Under-Recognised Presentation of Acromegaly
X037	Pheochromocytoma
X038	How relevant is aldosterone and cortisol co-secretion?
X039	Iatrogenic nephrogenic diabetes insipidus secondary to demeclocycline misuse
X040	Optimising Follicular Growth for Oocyte Retrieval during IVF Treatment
X041	Fragile X premutation: A known under-diagnosed aetiology for premature ovarian insufficiency
X042	Fluconazole in the treatment of Cushing's disease

X001

Hypercalcaemia and Primary hyperparathyroidism in pregnancy

Fareeha Rizvi, Royal London Hospital, Barts Health NHS Trust

We present the case of a 39 year-old lady with primary hyperparathyroidism referred from Lister for further workup at Barts hospital. The corrected calcium at the time of referral was 2.82 and she was largely asymptomatic. She had a background of Coeliac disease, for which she had undergone a recent DEXA scan for this, (which was normal). Was on no regular medications, there was no significant family history and Clinical examination unremarkable.

An Ultrasound of the parathyroids was requested, which showed parathyroid gland enlargement just inferior to the lower pole of the LEFT thyroid lobe measuring up to 15 mm in craniocaudal dimension and approximately 9 x 6 mm in the short axis. She then underwent a CT neck, which confirmed the presence of a slightly exophytic thyroid nodule in the right lower pole which corresponds to the changes described on the ultrasound. The hypoechoic structure, adjacent to the lower pole of the left lobe of the thyroid was seen on CT and thought to be an anatomically a good location for a parathyroid gland, with no other candidate for parathyroid enlargement seen. She was referred to the Endocrine Surgical team, to aim for a left lower parathyroidectomy with removal the ipsilateral gland in order to confirm the absence of hyperplasia. However, at the surgical clinic appointment, she reported being 6weeks pregnant, and so a plan to defer her surgery, until later in pregnancy was made.

Our patient then moved to a different town, where she booked her pregnancy and regular follow up with Barts Hospital was unfortunately lost. She was eventually re-referred by her local physicians and was urgently contacted to attend the Barts Endocrine clinic, at which point she was 28 weeks pregnant and was admitted from clinic.

Whilst an in-patient her case was discussed with the local endocrine surgeons, obstetricians and maternal medicine specialists to formulate a plan for the management of her hyperparathyroidism in pregnancy. Her corrected serum calcium remained around 2.9 mmol/L, again, with minimal symptoms related to hypercalcaemia per se.

The obstetric team had multiple concerns, namely the

- Risk of developing pre-eclampsia and arrhythmias from the hypercalcaemia, which will require close monitoring. If discharged, it was advised that she have twice weekly BP monitoring and urine dipsticks. We will aim for a BP of less than 150/100 mmHg.
- The fetus is at risk of Intra uterine growth restriction and stillbirth – so will require urgent growth scans with dopplers, and the patient should monitor fetal movements.
- Delivery should be under consultant led care at the RLH, with input from neonatology (due to risk of neonatal hypocalcaemia).

- If an iatrogenic preterm delivery is planned she will require administration of steroids for fetal lung maturation.

All of the above was discussed with the patient and she wished to proceed to 30-32 weeks of pregnancy, maintaining an oral fluid intake until then, of 4L/day. The aim was to keep the serum Calcium level at <2.8 mmol/L (it was 2.77 on discharge).

The patient managed to maintain an impressive oral fluid intake of around 4-6 Litres/day, but was eventually admitted to the RLH during her 32nd week of pregnancy, under the obstetric and endocrine team, for an elective parathyroidectomy. Her corrected Calcium went from 2.94 (pre operatively) to 2.33 post operatively. She was well post operatively, with only transient symptoms of paraesthesia, related to the fall in the serum calcium.

The histology confirmed a simple parathyroid adenoma, and subsequent serum calcium readings were within the normal range (2.28mmol/L) on discharge.

This was a complex endocrine case, which highlighted how crucial good communication is across various specialities, across two hospital sites. (endocrinology, endocrine surgery, obstetrics and maternal medicine). The patient was continually involved in all decision making, and thus had a favourable and satisfactory outcome.

X002

An unusual case of asymptomatic primary adrenal insufficiency due to bilateral adrenal haemorrhagic infarcts

E Mills¹, S Wijetilleka¹, K Gulati², R Charif², E De Barra³ & F Wernig¹, Hammersmith Hospital (Imperial College Healthcare NHS Trust), ¹Imperial Centre for Endocrinology, ²Nephrology, ³Infectious Diseases

Background: The commonest cause for primary adrenal insufficiency in the developed world is autoimmune adrenalitis. Beyond this, rarer aetiologies exist, including thrombosis and haemorrhagic infarction. We report an unusual case of acute adrenal insufficiency due to bilateral adrenal haemorrhagic infarcts.

Case presentation: A previously well 57-year man from Ghana was transferred to our centre from a neighbouring hospital due to acute renal impairment requiring renal replacement therapy. He had recently returned from Ghana and had developed a proximal left leg deep vein thrombosis (DVT). Despite oral anticoagulation, this progressed requiring thrombolysis and insertion of an inferior vena cava filter. Following this, he developed heparin-induced thrombocytopenia (HIT). However, he also reported weight loss and night sweats, prompting a CT chest, abdomen and pelvis. This identified bilateral indeterminate adrenal masses and bilateral axillary lymphadenopathy. An MRI to characterise the adrenals in greater detail, raised the possibility of old haemorrhage, tuberculosis (TB) or lymphoma. Short synACTH test confirmed severe adrenal insufficiency: ACTH 838ng/L, and 0-, 30-, 60-minutes cortisol of 38nmol/L, 38nmol/L and 39nmol/L, respectively. Adrenal cortex antibodies were negative. Renal biopsy confirmed minimal change glomerulonephritis of unclear aetiology; with renal function improving following high-dose glucocorticoids. However, owing to the positions of his adrenals, adrenal biopsy was not feasible. CT FDG-PET confirmed no activity within the adrenal masses, suggestive of adrenal infarctions, thereby excluding TB and lymphoma. He was discharged from hospital with glucocorticoid and mineralocorticoid replacement with Prednisolone and Fludrocortisone respectively, along with anticoagulation for his DVT.

Conclusion: Acute adrenal insufficiency due to bilateral adrenal haemorrhagic infarction is rare. When it occurs, it is most commonly described in the setting of anti-phospholipid syndrome, but also rarely in conditions such as HIT, as was the case in our patient. It usually presents with flank pain or adrenal insufficiency. In our patient, the diagnosis was made following abnormal imaging. He will remain on continued Endocrine follow-up.

X003

The forgotten neoplasia of MEN-1 syndrome: thymic neuroendocrine tumours

E Mills, S Wijetilleka, R Agha-Jaffar, J Anderson, JF Todd, Hammersmith Hospital, Imperial College Healthcare NHS Trust

Introduction: Multiple endocrine neoplasia type 1 (MEN-1) is an autosomal dominant condition with tumours which mainly affect the parathyroid glands, pancreatic islets and pituitary gland. Patients are regularly evaluated to detect associated tumours with the aim of improving survival and quality of life.

Case presentation: We report a 39-year man with a history of MEN-1, which was diagnosed in 2008, when aged 30-years he presented with primary hyperparathyroidism requiring a two-gland parathyroidectomy. A 7-mm microprolactinoma was detected in 2012 and he remains on Cabergoline 0.5mcg three times weekly. In 2009, he presented with hypoglycaemia from an insulinoma, along with elevated gastrin levels from a gastrinoma, requiring surgical enucleation of two pancreatic tail lesions (February 2009), followed by a spleen preserving distal pancreatectomy (April 2009) for persistent and symptomatic hypoglycaemia. However, post-operatively gut hormones remained elevated and two further gallium avid lesions became apparent on Gallium-68 DOTATATE PET CT. The Neuroendocrine Tumours MDT offered a total pancreatectomy, which he declined. He has been referred for consideration of radio-frequency ablation to these tumours.

However, in June 2017, surveillance Gallium-68 DOTATATE PET CT for the pancreatic tumours, also demonstrated a new gallium avid lesion within the anterior mediastinum. Corresponding, CT thorax proved this activity to originate within the thymus. He therefore underwent a thymectomy via a video-assisted thoracoscopic approach. Histology confirmed a grade 2 thymic neuroendocrine tumour with Ki-67 proliferation index of 15%, tumour cells expressing CD56 and synaptophysin, and widespread lymphovascular invasion. Given that the tumour was present at the surgical margin and the other high-grade features, he is high-risk for recurrence and a 4-month post-operative Gallium-68 DOTATATE PET CT is planned. In addition, he has started somatostatin analogue therapy.

Discussion: Thymic neuroendocrine tumours, an uncommon manifestation of MEN-1, are rare neuroendocrine tumours with an estimated prevalence of 2-5%. They are commonly asymptomatic with a mean age at diagnosis of 42.7 years and occur almost exclusively in men. Current guidelines recommend CT or MRI chest imaging every 1-2 years with imaging universally positive at diagnosis. Although uncommon, they remain an important component of MEN-1 due to being a major determinant of life expectancy. Due to aggressive behaviour, they have an estimated 10-year survival rate of 25-45%. Surveillance therefore remains essential.

X004

Familial hypocalciuric hypercalcaemia – a case report and review of the literature

S Samarasinghe, M Martineau, West Middlesex University Hospital

Familial hypocalciuric hypercalcaemia (FHH) is characterised by mild to moderate hypercalcaemia in the setting of relative hypocalciuria and an inappropriately normal or marginally elevated parathyroid hormone (PTH) level. It is a relatively benign condition with no long-term sequelae in the majority of patients and is inherited in an autosomal dominant pattern. In most cases, FHH results from heterozygous inactivating mutations of the calcium-sensing receptor (CaSR) gene. It can be difficult to distinguish FHH from primary hyperparathyroidism (PHPT) in the clinical context but this is important to prevent unnecessary surgical interventions. Currently, FHH is differentiated from PHPT by clinical features (decreased bone density, symptomatic hypercalcaemia, nephrolithiasis) and biochemical factors (calcium creatinine clearance ratio (CCCR) < 0.01 is suggestive of FHH and level 0.02 or higher suggests PHPT). The presence of symptoms is therefore more suggestive of PHPT. Approximately 80% of PHPT patients in western countries are now identified by routine screening of serum calcium levels in asymptomatic patients.

We present the case of a 64-year-old woman referred to the endocrinology team with asymptomatic hypercalcaemia. She has a past medical history of type 2 diabetes mellitus, diabetic retinopathy, stroke and dyslipidemia. The patient was initially reviewed in 2005 for poorly controlled diabetes and routine bloods at the time showed hypercalcaemia (adjusted calcium 2.82 mmol/L) with a parathyroid hormone (PTH) 0.846 pmol/L and normal parathyroid ultrasound scan. On each admission to hospital, incidental hypercalcaemia was noted and she was referred for specialist advice. She has remained asymptomatic with no evidence of skeletal or renal involvement. A repeat PTH on her most recent admission was normal with a CCCR 0.0038. The patient has a suspended diagnosis of FHH.

Current guidelines have set the CCCR cut off value of < 0.01 for diagnosis of FHH and > 0.02 for PHPT with a sensitivity of 85% and a specificity of 88%. This is important as FHH is a benign condition which rarely requires intervention. A Danish study reported the cut-off value of < 0.0115 as optimal for diagnosis of FHH with a specificity of 0.88 and a sensitivity of 0.80. If there is strong suspicion for FHH, the presence of the CaSR gene mutation can be detected using polymerase chain reaction techniques. This genetic test provides diagnostic security when the CCCR is indicative of FHH. There are currently no international guidelines on when genetic testing should be undertaken in patients with suspected FHH. One group proposed using a 2-step screening process with CCCR as the initial screen and genetic testing for the CaSR gene reserved for patients with a CCCR < 0.02 . The most effective screening strategy is yet to be clearly defined but would ideally take into consideration the relative prevalence of FHH and PHPT, the costs of genetic testing vs misdiagnosis resulting in unnecessary/non-curative surgery.

X005

Amiodarone-induced thyrotoxicosis type 2 (AIT2)

S Samarasinghe, SA Qureshi, L Thurston, D Nelson, P Oddie, R Kaushal,

West Middlesex University Hospital

Amiodarone (AM) is the most commonly used antiarrhythmic drug which is effective in the treatment of both supraventricular and ventricular tachyarrhythmias. It contains iodine and has a structural resemblance to thyroid hormones. Two main types of amiodarone-induced thyroiditis (AIT) are reported in the literature: type 1 (iodine-induced hyperthyroidism) and type 2 (destructive thyroiditis). The British Thyroid Association (BTA) guidelines recommend thyroid function testing (TFT) prior to commencing treatment and then routine monitoring every 6 months thereafter. It is advised that follow up can be up to 12 months after cessation of therapy. There are currently no guidelines on duration of long-term follow up for patients with successfully treated AIT2.

We present the case of a 48 year-old man referred to the endocrinology clinic with thyrotoxicosis 3 years after initiation of AM (200 mg daily) treatment. His past medical history was significant for non-ischemic dilated cardiomyopathy, non-sustained ventricular tachycardia treated with insertion of an implantable cardioverter defibrillator (ICD). As per BTA guidelines, TFTs prior to commencing treatment with AM were normal (thyroid stimulating hormones (TSH) 1.67 mIU/L, free thyroxine (T4) 14.7 pmol/L). At the time of presentation, the patient had a free T4 35 pmol/L, TSH <0.01 mIU/L and thyroid peroxidase antibody (TPO) positive. His AM was discontinued and Carbimazole 5 mg daily was initiated. On examination, there was a palpable goitre but the patient appeared clinically euthyroid.

Repeat TFTs 6 weeks following treatment showed a free T4 13.0 pmol/l, TSH 0.01 mIU/L, with negative TPO and TSH receptor antibody. His TFTs at 6 months were normal and he continues to have routine 6 weekly follow up.

Learning Points:

1. Onset of thyrotoxicosis during AM therapy is considered to be unpredictable. It can occur at any time during therapy as well as after drug withdrawal.
2. Being a destructive thyroiditis secondary to a direct cytotoxic effect, it is very likely that high intrathyroid drug concentrations are needed before damage to thyroid follicular cells becomes clinically evident.

X006

Alcoholic pseudo-Cushing's syndrome: mimics both the biochemistry and clinical features of Cushing's syndrome

Fatima Alkaabi, Amir H Sam, Karim Meeran, Endocrine Unit, Charing Cross Hospital.

Diagnosis of Cushing's syndrome can be challenging. Many of the features of Cushing's syndrome such as weight gain, diabetes mellitus and hypertension are common in the general population. Therefore, biochemical investigations for suspected Cushing's syndrome should only be carried out when there is a high pre-test probability with presence of discriminatory features such as myopathy, diabetes or hypertension in young patients.

We report the case of a 37-year-old woman who presented with lower limb weakness and inability to stand from a seated position. She also complained of paraesthesia in her hands and feet. She reported weight gain and amenorrhoea over the last six months. She had a history of excess alcohol intake. Her BP was 181/102 mmHg and weight 115 kg. She had round facies, plethoric complexion and interscapular fat pad. There was no evidence of abdominal striae or bruising. Neurological examination revealed proximal muscle weakness in both upper and lower limbs, normal pin prick and vibration sensation and an ataxic gait.

Her initial investigations showed elevated fasting blood sugar (9.4 mmol/L) and HbA1c (63 mmol/mol), low serum potassium (2.8 mmol/L), normal vitamin B12 (418 ng/L) and folate (3.2 ng/ml) levels. She had raised GGT (1068 IU/L), low vitamin D levels (< 10 nmol/L). She was treated with potassium, vitamin D and thiamine replacement. She was also started on metformin, doxazosin, indapamide and pregabalin. Her serum cortisol level post overnight dexamethasone suppression test was 75 nmol/L. Her late night salivary cortisol was 6.2 nmol/L (reference range <2.6). Her 24 urine free cortisol was normal. She was asked to stop drinking alcohol. Her repeat investigations after one month of abstinence showed normal serum potassium, low dose dexamethasone suppression test (<20 nmol/L) and late night salivary cortisol (0.9nmol/L). Her aldosterone renin ratio measured off interfering medications was 342. Nerve conduction studies showed a sensorimotor polyneuropathy. Excess alcohol intake can present with the 'discriminatory features' of Cushing's syndrome. Investigations for Cushing's syndrome must be repeated after a period of abstinence to rule out false positive results.

X007

Heparin-induced hyperkalaemia due to hyporeninaemic hypoaldosteronism

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Heparin induces hyperkalaemia via a number of mechanisms including by inducing reversible aldosterone suppression without affecting the metabolism of corticosteroids. These effects are compounded by the presence of renal insufficiency, diabetes mellitus, in the elderly and the use of certain medications. It usually occurs after 4 – 6 days of therapy in about 7% of patients and resolve on discontinuing the drug.

Here we present a case of heparin-induced mineralocorticoid suppression in a 68-year-old female with left renal infarct caused by abdominal aortic thrombus in the immediate post-operative period following an emergency laparotomy for perforated duodenal ulcer that required the commencement of unfractionated heparin at therapeutic doses due to impaired renal function. Her thrombophilia, viral and autoimmune screen were negative.

During her prolonged hospital stay (173 days), she was found to have recurrent hyponatraemia (123 – 129 mmol/L), hyperkalaemia (5-6.4 mmol/L) with persistent renal impairment (Cr 249 μ mol/L, urea 20.2 mmol/L). Her serum bicarbonate ranged between 21 – 33 mmol/L. Her TSH was 5.41mIU/L (raised) and FT4 15.4pmol/L (normal). She did not have diabetes. She also had short synacthen test performed thrice during her admission which all demonstrated adequate adrenal cortisol response (60 min cortisol > 889 nmol/L). Her serum renin and aldosterone were suppressed at 0.1nmol/L/hr (reference range 0.3 -2.2 nmol/L/hr) and <50pmol/L (reference range: up to 630 pmol/L) respectively suggestive of hyporeninaemic hypoaldosteronism. Her sodium and potassium normalised with fludrocortisone 50 micrograms/day.

She also developed hypercalcaemia secondary to prolonged immobilisation (corrected calcium 3.12 mmol/L, intact PTH <0.7 pmol/L, alkaline phosphatase 92 IU/L– normal, vitamin D 50 nmol/L, Mg 1.15 mmol/L, PO₄ 1.78 mmol/L) which was managed with rehydration with infusion of 0.9% saline, intravenous frusemide and pamidronate infusion..

Our case demonstrates that the use of fludrocortisone is an effective therapeutic option that can bring about the significant and rapid resolution of hyperkalaemia where the continuation of heparin is necessary.

X008

The challenges of investigating adrenal insufficiency in patients with immunotherapy related adverse reactions requiring glucocorticoid treatment

Dr Ella Daniels¹, Dr Helen Bounds¹, Dr Daniel Morganstein^{1,2}, Professor Martin Gore¹, ¹ Medical Oncology, The Royal Marsden, ² Department of Endocrinology, Chelsea and Westminster Hospital NHS Foundation Trust

Background: Immunotherapy has revolutionised the management of malignancies such as melanoma, renal and lung cancer. With increased use of immune checkpoint inhibitors (ICPis), a diverse spectrum of immune-related adverse effects (irAEs) has emerged, most commonly effecting the gastrointestinal tract, lungs, skin, liver and endocrine organs. More severe toxicity is prevalent in patients with metastatic melanoma receiving combination immunotherapy, and multiple irAEs can occur in the same patient. irAEs frequently require treatment with high dose glucocorticoids, which could potentially mask autoimmune primary or secondary adrenal insufficiency and pose a diagnostic challenge.

Case presentation: A 77 year old gentleman with metastatic melanoma experienced headaches, fatigue and insomnia after three cycles of Ipilimumab and Nivolumab. A CT head was suggestive of an enlarged pituitary gland; MRI was contraindicated due to presence of a pacemaker. Biochemistry demonstrated mild hypothyroidism however cortisol was normal at this stage.

He subsequently developed sepsis and colitis requiring intensive care support, high dose steroids and a prolonged hospital admission. Following this, his thyroid function normalised but a short synacthen test was suggestive of adrenal insufficiency. ACTH was less than 5 and the remainder of his endocrine investigations were normal, confirming secondary adrenal insufficiency.

Due to prolonged use of steroids, it was difficult to determine if this was suppression secondary to exogenous steroids or ACTH deficiency from an irAE hypophysitis. Six months after weaning prednisolone to hydrocortisone, a cortisol measured prior to taking hydrocortisone in the morning was undetectable. This likely represents an ongoing adrenal insufficiency related to immunotherapy requiring permanent hydrocortisone replacement, rather than exogenous suppression from steroids.

Discussion: The management of irAEs involves glucocorticoids, often as high doses of intravenous methylprednisolone (up to 2g daily) in more severe cases. The differential diagnosis of adrenal insufficiency in these patients includes both autoimmune hypophysitis (with panhypopituitarism or isolated ACTH insufficiency) and exogenous adrenal suppression related to steroids. Primary adrenal insufficiency is also described but is recognised by elevated ACTH and renin levels. Differentiating between adrenal suppression related to steroids and autoimmune adrenal insufficiency is important to determine long term management in terms of steroid weaning or ongoing replacement. It is also important to monitor pituitary function in case of evolving hypophysitis and the possible need for replacement of other pituitary axis.

X009

Diagnostic and therapeutic role of GnRH analogue in postmenopausal hyperandrogenism

Seong Keat Cheah, Anitha Mathews, Singhan Murali Krishnan, Hinchingsbrooke Hospital, North West Anglia NHS Foundation Trust

A 48 years old lady with marked obesity had a CT abdomen due to non-specific abdominal discomfort. This revealed a 9mm lesion in right adrenal and a 18mm lesion in left adrenal, with fat content and appearance consistent with adenoma. Subsequent review at Endocrinology clinic unfolded a history of gradually worsening hirsutism which required daily chin shaving, while virilisation was absent. Her period stopped 4 years ago when she was 45 years old with no post-menopausal symptoms such as flushing. There was no recent change in her weight (115kg).

Her hyperandrogenism was confirmed biochemically with testosterone elevated at 6.5nmol/L (0.0-1.8) and remained high on repeated samples. The marked elevation led to a pursuit of adrenal and ovarian source. However, her adrenal androgens were normal: Androstenedione 3.3 nmol/L (0.9-4.8), DHEAS 0.9 μ mol/L (0.7-7.8), and 17-OH progesterone 3.4 nmol/L (0.0–5.0). Her FSH and LH were consistent with post-menopausal state. Thyroid function test, ACTH, 9am Cortisol, prolactin and CA125 were normal.

MRI adrenal showed right 19mm nodule with hyperplastic left adrenal. Signal drop on both adrenals again agrees with adenomatous nature. Technical limitation of ultrasound of pelvis due to body habitus had led to MRI pelvis showing ovaries of normal appearance with small follicles, not typical of hyperthecosis. A delineation between adrenal and ovarian aetiology was not clear at this stage while patient preference and body habitus limited the option for specific venous sampling.

An overnight dexamethasone suppression test had led to cortisol suppression to 38nmol/L excluding Cushing's syndrome, while testosterone remained non-suppressed at 5.8nmol/L, suggesting an ovarian androgen source (1,2). A trial of GnRH analogue (subcutaneous Leuprorelin 3.75mg monthly) was initiated. Suppression and normalisation of testosterone (0.6nmol/L) was observed after 2 months, a typical finding described in ovarian hyperandrogenism in multiple case reports (3–5). Long term treatment options were explored between the patient, Endocrinology and Gynaecology team. Laparoscopic bilateral oophorectomy was preferred by the patient because of intolerance to GnRH analogue (flushing).

References:

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2. Ambroziak U, Kepczynska-Nyk A, Nowak K, Morawska E, Kunicki M, Bednarczyk T. Overnight 1 mg dexamethasone androgen suppression test is useful diagnostic tool in hyperandrogenism. *Endocr Abstr. BioScientifica*; 2013 Apr 1

X010

A Tale of Two Brothers with Neuroendocrine Tumours

S Wijetilleka, E Mills, R Agha-Jaffer, D Spalding, JF Todd, Hammersmith Hospital, Imperial Centre for Endocrinology, Imperial College Hospitals NHS Trust

We report the case of a 59-year-old Arabic businessman with a 6-month history of type 2 diabetes, hypertension, hypercholesterolaemia and gastro-oesophageal reflux disease. Of note, his brother's medical history was significant for a large bowel neuroendocrine tumour, which had recently been resected and was under the care of another Endocrine Unit. Our patient was originally referred to the Respiratory Clinic with exertional dyspnoea, which was felt to be infective in aetiology and antibiotics were prescribed. However, 6kg weight loss over 6-months was noted. Owing to a plain chest radiograph which demonstrated an elevated right hemidiaphragm, further CT imaging was arranged. This confirmed a raised right hemidiaphragm, but also an incidental 2cm pancreatic mass lesion. This prompted referral to Hepatobiliary and Pancreatic Surgery.

Cytology via endoscopic guided ultrasound was consistent for a neuroendocrine tumour. Further MRI pancreas revealed a 2cm exophytic lesion without further metastatic spread. Gallium-68 DOTATE PET CT revealed avid disease within the pancreatic lesion, but no evidence of metastatic nodal or distant disease. Pre-operative gut hormones were normal and 24-hour urine 5-hydroxyindoleacetic acid (5-HIAA) levels were raised at 72.2 μ mol/L (NR 10-40 μ mol/L). The advice of the Neuroendocrine Tumours MDT was surgical excision.

He underwent a laparoscopic resection with the histology confirming a completely excised, 30mm well-differentiated and glucagon-staining neuroendocrine tumour with Ki67 index <5%. However, his post-operative CT imaging has since revealed a lesion within the surgical bed. Repeat Gallium-68 DOTATE PET CT confirms that this lesion enhances. Post-operative gut hormones remain normal. The consensus from the Neuroendocrine Tumours MDT is that this lesion likely represents residual disease and repeat surgery is being considered.

Discussion: Non-functioning pancreatic neuroendocrine tumours are defined by their absence of hormone hypersecretion. They can present as an incidental finding, such as the case with our patient. Surgical resection of lesions \geq 2cm or where there is growth on interval imaging may offer curative treatment in the absence of liver metastases. Crucially, patients with neuroendocrine tumours are best managed within a Neuroendocrine Tumours MDT setting.

X011

Challenges in the management of a rapidly growing dedifferentiated parathyroid carcinoma

Anastasia D Dede¹, Kate Newbold², Khin Thway³, Daniel Morganstein^{1, 2}

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Introduction: Parathyroid carcinoma is a rare cause of primary hyperparathyroidism, with a reported incidence of 2 cases per 10,000,000 person-years [1]. Treatment strategies include surgical resection and management of hypercalcemia. Chemotherapeutic agents have largely proved inefficient and there is lack of trials as the tumour is rare.

Case presentation: A 50-year old lady was referred for further management of a previously resected parathyroid carcinoma. She had been admitted to her local hospital in August 2015 with symptoms of hypercalcaemia. Adjusted serum calcium on admission was 3.28 mmol/l and PTH 31.3 pmol/l. Past medical history was unremarkable and her only medication was omeprazole. She had no family history of hyperparathyroidism. Localisation studies were negative. She underwent neck exploration 4 months later and had parathyroidectomy and right thyroid lobectomy. A right 38 mm parathyroid lesion was resected and the pathology report showed features of a parathyroid “atypical adenoma”. Calcium and PTH levels normalised post-operatively. 3-4 months after her operation she noticed a lump on the right side of her neck. She underwent extensive neck surgery in June 2016 to remove a recurrent tumour. Calcium pre-operatively was normal. The pathology showed a poorly differentiated malignant tumour.

At presentation, post her second surgery, calcium was normal. Imaging did not show any evidence of local recurrence or distant metastases. Pathology from both surgeries was reviewed and it was concluded that the first tumour had areas of poor differentiation and the second tumour was dedifferentiated parathyroid carcinoma. Genetic testing for CDC73 was negative. She was referred for post-operative radiotherapy to the right neck in November 2016. In August 2017 she noticed a lump on the left of her neck. Neck ultrasound showed a 1.2X0.7X1.6 cm tumour mass within strap muscles. Calcium and PTH remained normal. CT imaging did not identify any other local recurrence or distal metastases. FNA was compatible with recurrent parathyroid disease. She underwent surgical resection in September 2017 and pathology demonstrated extension to the resection margins. She developed hypoparathyroidism postoperatively and she is now due to have local radiotherapy on the left.

Conclusion: Parathyroid carcinomas are rare endocrine tumours and therefore management in specialised centres in an MDT setting is of paramount importance. Although non-functioning parathyroid cancer is described, de-differentiation of a functioning tumour to non-functioning has not been reported previously.

X012
OC5

The anomalous goitre: an unusual presentation of multi-nodular goitre

F Beatty, R Baburaj, The Hillingdon Hospital, F Palazzo, Imperial Healthcare NHS Trust.

A 39-year-old was seen at routine antenatal appointment when she was 6 weeks pregnant with her first child in 2013. She had noticed swelling in the neck consistent with an enlarged thyroid gland. Despite a family history of Graves' disease, her TFTs were considered normal for pregnancy and thyroid peroxidase antibodies were negative.

An ultrasound showed multi-cystic changes consistent with a multi-nodular goitre. There was one nodule of 6 x 2.3 cm in the right lobe but there was no evidence of posterior extension or tracheal narrowing. A FNA of the large nodule was Thy 2, i.e. benign. She remained asymptomatic and the remainder of her pregnancy was unremarkable.

Three years after her initial diagnosis with multi-nodular goitre, she started to experience intense burning pain in the left shoulder, radiating down the left arm, accompanied by mild swelling and dilatation of the superficial veins in the left arm.

Her pain settled for a brief period but returned in the left shoulder and again radiated down the left arm, this time in the exact distribution of the C7 nerve. In 5-6 weeks the pain had become constant. She returned to Endocrinology clinic and was clinically noted to have a large goitre.

An urgent CT neck with contrast showed no thrombosis, but a significantly enlarged thyroid gland causing extensive venous and tracheal compression. The goitre had compressed the trachea; at its narrowest point the coronal width of the trachea measured 3mm. She underwent an urgent total thyroidectomy with no post-operative complications.

Discussion

The majority of patients with cervico-mediastinal goitres are symptomatic, however the predominant symptoms are more commonly respiratory distress and superior vena cava obstruction (SVCO). This patient presented with symptoms and signs consistent with compression of the veins of the upper limb and the brachial plexus which is unusual.

It is not uncommon for the normal, physiological changes of pregnancy to reveal pre-existing thyroid pathology. What is unusual in this case is that the patient remained asymptomatic throughout pregnancy; her compressive symptoms began three years post-partum.

This presentation of multi-nodular goitre was therefore anomalous not only in its presentation but also in its timing, at 3 years post-partum.

X013

An Unusual Presentation of Partial Empty Sella Syndrome and Arnold Chiari Type 1 Malformation

Zeeshan Yasin, Emily Banks, Sagen Zac-Varghese, Samer Alsabbagh, Babak Langroudi, Lister Hospital Stevenage, East and North Hertfordshire NHS Trust

A 25 year old Caucasian female presented with a one month history of headache following head trauma. She described frontal headaches that radiated to her occiput, which worsened on standing and in the early morning. There was associated nausea and vomiting, but no photophobia, fever or neck pain. There was no reported vertigo, limb weakness or numbness. She reported no past history of lumbar puncture or epidural.

On examination: BP 115/89, heart rate; 80. No postural hypotension. BMI 37. Cranial nerves normal, no cerebellar signs. Normal power and sensations in legs. No signs of meningism. Rest of systemic examination unremarkable.

Bloods revealed normal full blood count, inflammatory marker and renal functions. CT Brain revealed a partial empty sella and slit shaped ventricles with evidence of intracranial hypertension. Further, MRI Brain showed a partial empty sella and cerebellar herniation of less than 5 mm. MRV Brain showed no venous sinus thrombosis seen.

We checked her pituitary profile and found a very severe cortisol deficiency with 9AM cortisol level of 30. The rest of pituitary profile was normal. The patient was commenced on oral Hydrocortisone replacement.

This is a challenging case as we were unable to do lumbar puncture to confirm intracranial hypertension due to the presence of cerebellar ectopia.

This is likely intracranial hypertension which may have resulted in partial empty sella syndrome.

X014

An unusual cause of leg weakness

Ambreen Qayum, Darshi Sivakumaran, Kingston Hospital, Surrey

A 30 years old Asian male presented to AE with an acute onset of progressive muscle weakness and was subsequently unable to mobilise with complete paraplegia.

Initial investigations showed a raised Creatine kinase of 3600 u/L, lactate of 3 mmol/L and potassium of 3.4 mmol/L

His symptoms quickly resolved after an IV infusion of Hartmann's solution. Although his presentation seemed to be suggestive of hypokalemic periodic paralysis, subsequent history, examination and thyroid function test confirmed primary hyperthyroidism in keeping with thyrotoxic periodic paralysis

He was commenced on carbimazole and beta-blockers at his first presentation and remains well since this episode.

Learning points: Thyrotoxic periodic paralysis is an uncommon disorder characterised by simultaneous thyrotoxicosis, hypokalemia and paralysis. The presentation is similar to hypokalemic/familial periodic paralysis and can be easily overlooked unless it is considered and thyroid function tests are checked. Failure to identify thyrotoxic periodic paralysis can result in presentations and puts patients at risk of rebound hyperkalemia due to excessive potassium replacement. We present the characteristic features of the condition, causes and treatment.

X015

'Single presentation, two lifesaving diagnosis'- Simultaneous new presentation of diabetic ketoacidosis and primary adrenal insufficiency

R Maniusyte, S Zaman, D Huntley, T Vakilgilani, St Marys Hospital, Imperial College Healthcare NHS Trust

56-year-old lady visiting from Russia, presented to A&E with a 5-day history of severe vomiting. She was otherwise fit and well and not on any medications. She was not a smoker and drank alcohol only occasionally. Her family history included maternal type 2 diabetes. She had a two-week history of polyuria and polydipsia, but denied any weight loss.

On arrival, she was found to be hypotensive with a BP of 85/60 mmHg and tachycardic, HR:110/min. Her GCS was 15/15 and systemic examination was unremarkable. Investigations showed sodium 101 mmol/L, potassium 5.0 mmol/L, pH 7.26, HCO₃ 17mmol/L, glucose 23.7 mmol/L, blood ketones 6 mmol/L, serum osmolality 234 mmol/L, urine osmolality 575 mOsm/L, urine sodium 85 mEq/L, random cortisol 129 nmol/L and normal renal, liver and thyroid function tests. The diagnosis of new onset diabetes presenting with diabetic ketoacidosis (DKA) was made. Additionally, the inappropriately low serum cortisol and persistent hypotension raised the possibility of adrenal insufficiency.

She was admitted to medical HDU and treated with IV hydrocortisone 100 mcg four times daily, insulin infusion and careful rehydration with IV fluids in view of severe hyponatraemia. Hypertonic saline was avoided due to the absence of neurological features. Her glucose and sodium were closely monitored and fluids were managed accordingly. DKA resolved and serum sodium increased appropriately to 128 mmol/L within the next 72 hours.

Further investigations were undertaken, including a short Synacthen test, which revealed cortisol 0 min – 208 nmol/L, 30 min – 213 nmol/L and 60 min – 184 nmol/L with significantly elevated ACTH of 1100 pmol/L. Adrenal antibodies were positive and CT pancreas and adrenals was normal. Renin and aldosterone were 22.9 pmol/ml/hr and <60 pmol/L respectively.

With regards to diabetes, C-peptide was 323 nmol/L with paired blood glucose of 15.3 mmol/L, HbA1C was 110 mmol/mol and islet cell and GAD antibodies were positive. Once she was able to eat and drink, her parenteral steroid was switched to oral prednisolone and she was commenced on oral fludrocortisone and subcutaneous insulin injections.

Her results were consistent with primary adrenal insufficiency and type 1 diabetes. She was educated about diabetes, insulin administration, steroid use and sick day rules. DKA and acute adrenal insufficiency have overlapping precipitating factors (eg. infection), clinical presentation (vomiting, general weakness, dehydration, confusion) and biochemical abnormalities (hyponatraemia, metabolic acidosis), therefore, a new diagnosis of acute adrenal insufficiency can be easily masked and missed.

X016

Parathyroid nuclear medicine localisation - an unusual ectopic gland?

Raya Almazrouei, Aimee Di Marco, Fatima Alkaabi, Amir H Sam, Karim Meeran, Fausto Palazzo. Hammersmith Hospital, Imperial Health Care NHS Trust

^{99m}Tc-MIBI SPECT/CT is a commonly used localizing study in patients with primary hyperparathyroidism. It localises up to 70% of adenomas and is particularly good at identifying single ectopic parathyroids. Negative scans may be due to small parathyroid size, adenoma composition, multi-gland disease, body habitus and coexistent thyroid disease. Here we report another potential reason for non-localization in the neck. A 57-year-old woman with a history of renal colic was found to have an elevated adjusted serum calcium (2.86 mmol/L), low normal serum phosphate (0.97 mmol/L), elevated PTH (13.9 pmol/L) and a urine calcium creatinine clearance ratio of 0.021 consistent with primary hyperparathyroidism. Localization studies performed in preparation for surgery included neck ultrasound and ^{99m}Tc-MIBI SPECT/CT, which were non-localizing. However, ^{99m}Tc-MIBI SPECT/CT scan revealed increased tracer uptake in the right frontal lobe in close proximity to the meninges, consistent with a meningioma on MRI head. The patient underwent neck exploration and a right inferior parathyroid adenoma was excised. ^{99m}Tc-MIBI uptake is related to hypermetabolic tissue and mitochondrial content, which could explain the high uptake by the meningioma and potentially the false negative localization study in the neck.

X017
OC3

Advanced medullary thyroid cancer – when to start treatment?

Camilla Lyttle¹, Kate Newbold², Daniel Morganstein¹, ¹Chelsea and Westminster Hospital, ²Royal Marsden Hospital

Introduction: Patients with MTC can have prolonged survival even in the presence of metastatic disease, but progressive disease can be life limiting. Treatment with TKIs prolongs progression free survival, but improvements in overall survival have yet to be demonstrated, and can have significant side effects. Therefore decisions about starting therapy in slowly progressive advanced disease can be challenging.

History: 30 year old male who presented in 2010 with fatigue and breathlessness. He was diagnosed with sporadic medullary carcinoma of the thyroid with metastasis to the mediastinum, liver, and bone. In January 2012 he underwent debulking thyroid surgery and followed by post-operative radiotherapy. He has been followed up in a specialist MTC clinic.

Calcitonin levels have remained high but broadly stable mostly between 108,000 – 146,000 (low of 65800, high of 185000) ng/L. A CT scan in Dec 2013 showed widespread metastatic liver disease, multiple bony metastases, a 12mm right hilum node, multiple lung cysts. Right-sided residual thyroid disease. He was monitored with serial imaging and a CT scan in Aug 2017 was largely unchanged from previous CT scans with no change in the deposit in the right thyroidectomy bed, the extensive pulmonary disease, or intrathoracic nodal disease, but marginal growth of the liver metastases.

He currently has no specific symptoms. Weight has increased from 41 – 44kg over 5 years. Able to tolerate a full diet, not complaining of fatigue or malaise, working full time. He therefore continues to have radiologically and symptomatically stable disease, despite extensive spread, raising the question as to if or when he should start systemic anticancer therapy with a tyrosine kinase inhibitor?

Discussion: This is a case of medullary carcinoma of the thyroid which has remained stable for 5 years, despite the fact no systemic therapy has been trialled. Although calcitonin levels have increased there has been little radiological progression, or symptomatic progression, of disease. This poses the question as to whether or not there is any benefit to starting systemic treatment in the absence of symptoms or rapid progression. It also highlights the need for more reliable biomarkers to accurately monitor the progression of medullary thyroid cancer and guide therapeutic decisions.

X018

Hurthle Cell Tumour - A case of delayed metastatic disease causing abnormal thyroid function, acromegaly and hypercalcaemia

Shoib Ur Rehman, Tom Roques, Jeremy Turner, Ketan Dhatariya, Norfolk and Norwich University Hospital

A 69-year old man presented with a low FT4 (<5pmol/L), normal TSH (1.22mU/L) and FT3 (5.9pmol/L) confirmed on multiple assay platforms. Pituitary testing was consistent with mild biochemical acromegaly [IGF1 29nmol/L, GH suppression nadir 0.92ug/L]. MRI pituitary was normal. He had undergone a right hemi-thyroidectomy in 2001 for a benign thyroid adenoma.

During his current investigations he was found to have a 9.4cm incidental liver mass by the gastroenterologists. Initial biopsy results were consistent with a primary hepatocellular carcinoma. However on review of the histology given his thyroid history the liver lesion was confirmed as metastatic follicular Hurthle cell carcinoma. Immunohistochemistry for TTF1 was positive and thyroglobulin levels were >30000ng/ml (NR<1). Review of his 2001 thyroid histology also confirmed a Hurthle cell tumour. His liver mass continued to grow and was deemed too large for surgical removal or ablation. After extensive national discussions it was felt he may benefit from radioiodine therapy after total thyroidectomy. The completion thyroidectomy specimen showed no signs of neoplasia. An I¹³¹ uptake scan of the liver mass showed no uptake, compatible with a de-differentiated tumour. The patient then developed severe refractory hypercalcaemia resistant to all conventional therapies (fluids, bisphosphonates, denosumab & cinacalcet). He developed cardiac and renal failure and he died 10 months after initial presentation. The family declined necropsy.

This case is unusual because of the abnormal TFT's – suggesting that the tumour may have been locally de-iodinating fT4, and it may have also produced protein fragments e.g. undetectable PTHrP like molecules causing malignant hypercalcaemia, and biochemical acromegaly.

Hurthle cell tumours constitute up to 5 % of all thyroid neoplasms. They metastasize more frequently than papillary and follicular cancers with an incidence of up to 33%. Fine needle aspiration alone may not be sufficient to differentiate between benign and malignant cells. A critical pathological review of Hurthle cell cancers resulted in diagnostic revision in 28% of cases. These tumours can behave very aggressively, with 5 year mortality rates approaching 80%.

X019

Persistently elevated plasma metanephrine levels in a patient with MEN2 – when to diagnose a pheochromocytoma?

Hannah Cheney Lowe¹, Kate Newbold², Daniel Morganstein¹, ¹Chelsea and Westminster Hospital, ²Royal Marsden Hospital

Background: MEN2 is a hereditary syndrome caused by mutations in the RET proto-oncogenes; characterised by medullary thyroid cancer in almost all individuals and pheochromocytomas in 50%. Hyperparathyroidism can also occur. Pheochromocytomas, catecholamine producing tumours of the adrenal medulla, can be diagnosed by elevated levels of catecholamines or metanephrines in urine or plasma. Surgery is the treatment of choice but requires lateralisation pre-operatively.

Case History: A 51 year old lady with background of medullary thyroid cancer (total thyroidectomy September 2007) and MEN2 (RET mutation L790F) has been under follow up in a specialist MTC clinic. She describes intermittent headaches, ear pain and episodes of 'electric shock-like' symptoms, as well as anxiety. Urinary metanephrine collection levels were persistently elevated - September 2015: 1.84, February 2016: 1.81 and August 2016: 1.73 (reference range 0-1.2 micromol/24 hrs). Plasma metanephrine levels were also raised at 1173 (reference range 80-510pmol/L). She was on no medication likely to cause a raised metanephrine level. She proceeded to imaging but CT and MIBG scans have not localised a pheochromocytoma. CEA and calcitonin remained stable.

Discussion: Urine and plasma metanephrines both have high sensitivity and specificity for the presence of a pheochromocytoma. Despite this both tests can have false positives, but in the presence of MEN2 the pre-test probability is high¹. Cross sectional and nuclear imaging have not identified a pheochromocytoma in this patient, but the possibility of a small lesion remains. This therefore leaves the options of bilateral adrenalectomy (with consequent hypoadrenalism in a young patient) vs watchful waiting with alpha blockade (with ongoing small risk of pheochromocytoma crisis).

References:

1. van Berkel et al. Diagnosis of Endocrine Disease: Biochemical diagnosis of pheochromocytoma and paraganglioma. European Journal of Endocrinology. R109–R119. 2014

X020

Unmasking of concurrent autoimmune disease or the emergence of Graves' precipitated by Adalimumab (Humira)?

Parizad Avari, Mushtaqur Rahman, Northwick Park Hospital, London North West Healthcare NHS Trust

Adalimumab (Humira) is a TNF α inhibitor commonly used in inflammatory bowel disease and inflammatory arthritides. Adalimumab also has a potential role in the treatment of active thyroid eye disease as a steroid sparing agent. Here we present a case of Graves' disease unmasked following the use of biologic agent, Adalimumab.

A 33-year-old lady with known Crohn's disease and previous proctectomy, was commenced on Adalimumab following initial treatment with infliximab and azathioprine. Only other significant past medical history includes depression, for which she was on citalopram.

Five months after adalimumab was commenced, she presented with symptoms of weight loss, tremor, heat intolerance, hair loss and palpitations. She also noted her neck was gradually enlarging. On examination, there was a firm goitre with enlarged palpable nodules at the upper poles. There was no associated lymphadenopathy and no signs of thyroid eye disease.

Biochemistry revealed a suppressed TSH <0.03 mIU/L with elevated Free T3 12.2 pmol/L and free T4 40.5 pmol/L. TPO antibodies negative with weakly positive thyroid receptor antibodies (TRAB 2.7 IU/L, ULN 1.8). ESR was elevated at 60 mm/hr. Ultrasound imaging of the thyroid suggested subacute thyroiditis. She was commenced on block-and-replace regimen of carbimazole 40mg od and levothyroxine 100mcg od. Thyroid uptake on technetium-99m scintigraphy showed only minimal uptake, but she was already on carbimazole.

In view of positive TRAB, the likeliest cause of her thyroid dysfunction is Graves' disease. Whilst an infrequent association of Graves' and ulcerative colitis has been reported, the preceding use of adalimumab is likely to have precipitated her Graves' disease. We recommend careful thyroid-function monitoring during immunosuppressive or anti-TNF- α therapy. Further studies are required to elucidate the pathogenesis of Graves' disease in patients receiving anti-TNF α therapy.

Questions to the Panel:

- 1) Is this concurrent autoimmune disease associated with ulcerative colitis, or Graves' triggered by Adalimumab?
- 2) Should duration of therapy be continued beyond cessation of treatment with Adalimumab and/or guided by presence of TRAB?
- 3) With thyroid dysfunction associated to immunosuppressive therapy, how may this affect its use in active Thyroid Eye Disease?

X021

Paraneoplastic thyrotoxicosis secondary to advanced non-seminomatous germ cell tumour

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Paraneoplastic thyrotoxicosis is a rare but recognized phenomenon associated with testicular germ cell tumours, although the exact prevalence is unknown. Most cases remain biochemically as subclinical hyperthyroidism. We report a case of symptomatic thyrotoxicosis with supraventricular tachycardias (SVT) associated with overt hyperthyroidism, likely to have been caused by metastatic germ cell tumour.

A 26 year old gentleman was diagnosed with advanced non-seminomatous germ cell tumour and liver metastases, and started on etoposide and cisplatin (EP) chemotherapy. Initial β -HCG levels were over 495,000 IU/L (normal range: 0 -5 IU/L), and he was subsequently switched to POMB-ACE chemotherapy a month later. Whilst undergoing his second cycle of POMB chemotherapy, he was admitted to the Emergency Department with chest pain and palpitations. ECG confirmed SVT, likely precipitated by hyperthyroidism (fT4 35 pmol/L; fT3 10.0 pmol/L; TSH <0.01 mU/L). There was no family history of autoimmune conditions, and no evidence of thyroid eye disease. He was started on carbimazole 30mg daily and beta blockade.

On subsequent follow-up, carbimazole dose was rapidly down-titrated as thyroid function improved in parallel with his normalising β -HCG levels on chemotherapy. Anti-thyroid medication was discontinued once negative TSH-receptor antibody status was known and to date thyroid biochemistry remains normal off medication (current β -HCG titre 42 IU/L). It is therefore likely the massive elevation in β -HCG and molecular mimicry between HCG and TSH caused cross reactivity with TSH receptors, precipitating thyrotoxicosis, well recognised in gestational thyrotoxicosis and gestational trophoblastic disease.

In conclusion, this case illustrates the rare occurrence of β -HCG driven thyrotoxicosis arising as a paraneoplastic syndrome associated with metastatic testicular tumour.

Questions for the Panel:

Should thyroid assessment be included as part of routine screening in Oncology Clinic chemotherapy protocols for HCG-associated tumours?

X022
OC1

The challenge of second line immunotherapy in Graves' ophthalmopathy

Alice Irwin¹, Aditi Sharma¹, Vassiliki Bravis¹, Vickie Lee², Tessa Fayers², Ahmad Aziz², Rashmi Akshikar², Stephen Robinson¹, ¹St Mary's Hospital, ²Western Eye Hospital, Imperial College Healthcare NHS Trust

The management of Graves' orbitopathy (GO) aims to tackle visual impairment, inflammation and ultimately long-term fibrosis. For patients with GO in the moderate-to-severe active phase, current evidence advocates intravenous (iv) glucocorticoids +/- orbital radiotherapy and the position of EUGOGO is clear on that. Second line or steroid-sparing immunotherapies have more sparse evidence, with cyclosporine, methotrexate and mycophenolate mofetil (MMF) being used by different units.

Cases: A 40-year old female non-smoker was diagnosed with bilateral GO in 2012, despite rendered euthyroid. She received 12 weeks of IV methylprednisolone and concomitant orbital radiotherapy. Her disease remained stable until 2016, when she developed sight-threatening orbitopathy. This improved with orbital decompression surgery and she reached stable visual acuity and colour vision. However, persistent pain and diplopia dictated escalation to MMF therapy. Multiple infections (chest, urine) and rectal bleeding were adverse effects that led to its discontinuation. Thyroid surgery is being considered.

A 79-year old male ex-smoker presented with sight threatening bilateral GO (right eye 6/36 best corrected (6/30 pinhole), left eye 6/18 best corrected (6/12 pinhole)) and restriction of gaze. He received inpatient IV pulsed methylprednisolone (3 days of 1g/day), followed by urgent orbital decompression surgery. He then completed weekly IV methylprednisolone with concomitant radiotherapy. At that point, his visual acuity remained compromised (right eye NPL best corrected, left eye 6/9 best corrected). MMF therapy was commenced but he discontinued that himself due to gastrointestinal symptoms. He currently has persistent diplopia but a CAS of 0 with stable optic nerve function bilaterally. With overall vision improvement compared to pre-treatment (right eye 6/36 unaided, left eye 6/12 unaided), he is not keen on further therapies.

A 72-year old female non-smoker presented with diplopia and restriction of upward gaze, in the context of a new diagnosis of Graves' disease in 2017. She was commenced on block and replace therapy and was rendered euthyroid. Weekly IV methylprednisolone was administered (12 weeks) but her CAS remained at 3. She was given oral prednisolone and MMF. She suffered intolerable leg cramps and discontinued the drug. She is now having a further course of IV methylprednisolone and concomitant orbital radiotherapy.

Discussion: Steroid sparing immunotherapy does not have a clear evidence base in GO. MMF is a generally well-tolerated immunosuppressive agent that is now also used in the treatment of GO. For such patients, there can be challenges with such second line, steroid-sparing immunosuppression often with difficult to tolerate side effects. An on-going MDT approach that supports informed patient choice is imperative, despite dilemmas for therapy.

X023
OC4

Resistant hypercalcaemia in pregnancy – medicine to surgery

Manish Modi, Catherine Mitchell, Binu Krishnan, Rajee Baburaj, The Hillingdon Hospitals NHS Foundation Trust

Primary hyperparathyroidism (PHPT) during pregnancy poses significant risks to the mother and foetus. Prompt identification and management are essential in reducing the risk of complications such as hyperemesis, miscarriage, pre-eclampsia, intrauterine growth restriction, preterm delivery and post-partum neonatal hypocalcaemia.

Case: A 29 year old lady, known to be 8 weeks pregnant, presented to Hillingdon Hospital with persistent vomiting. She was found to be profoundly hypercalcaemic (3.30 mmol/L), with elevated parathyroid hormone levels (17.3 pmol/L), consistent with PHPT. She was initially managed with aggressive fluid rehydration. Due to resistant hypercalcaemia, she was then commenced on subcutaneous calcitonin. She was discharged once her calcium levels improved, with frequent monitoring planned in the joint endocrine and obstetric antenatal clinic. However, she required re-admission the following day due to refractory vomiting and exacerbated hypercalcaemia (3.19 mmol/L). The decision was made to stop calcitonin due to lack of significant effect. Following this, aggressive fluid resuscitation was instituted, with approximately 5 litres of intravenous fluid being administered daily for a month. An ultrasound scan of the neck identified a hypoechoic lesion in the thyroid gland, consistent with a parathyroid adenoma. In light of refractory hypercalcaemia >3mmol/L and the localisation of a parathyroid adenoma, the patient was transferred to the Endocrine surgery team at Hammersmith Hospital for further management. Following discussion with the medical obstetric team at Queen Charlotte's Hospital, a parathyroidectomy was planned as she was now in her second trimester. She successfully underwent resection of two parathyroid glands. Her calcium levels returned to normal post operatively and she remains normocalcaemic with a normal parathyroid hormone level after 4 months.

Discussion: This case highlights that management of PHPT in pregnancy remains a significant challenge. As surgery remains the only definitive management most suited to the second trimester, the paucity of evidence on conservative treatment becomes more apparent. Appropriate management of this patient required valuable input from the multidisciplinary team, including the medical and surgical Endocrine teams, obstetrics and radiology.

X024

Incidental pheochromocytoma in an unsuspecting urological setting

M S Siddiqui, K Muralidhara, Central Middlesex Hospital, London Northwest Healthcare NHS Trust

A sixty five year old gentleman was admitted under urology with generalised abdominal pain, haematuria on urine dipstick and mild acute kidney injury. USS abdomen revealed a left sided hydronephrosis which was confirmed on CT urogram. The scan also showed an incidental right sided 3.5 cm adrenal lesion which was denser than 10 Hounsfield units and did not wash out well on contrast imaging. He was known to be hypertensive for nine years, well controlled on amlodipine monotherapy.

The patient underwent outpatient urological interventions in the subsequent months including dilatation of a urethral stricture, left ureteric biopsy and insertion of a left ureteric JJ stent. Two 24 hour urine samples collected six months after his initial presentation showed very high metanephrine levels at more than four times the upper limit of normal range. Plasma metanephrines were elevated at 55747 pmol/L (NR 0 – 510pmol/L). Of note, he had no symptoms of hormonal excess and was normotensive during all clinical assessments.

MIBG Iodine 123 SPECT CT scan showed increased uptake in right adrenal lesion consistent with a pheochromocytoma. Subsequent CT chest and NM Ga68 DOTATATE PET scan didn't demonstrate any paragangliomas or distant metastases.

He was adequately alpha blocked with phenoxybenzamine and underwent laparoscopic right adrenalectomy. Histology confirmed pheochromocytoma with PASS score of 5. The genetic testing for associated familial syndromes is awaited. The cause for the left sided hydronephrosis remains unknown and he awaits a left nephrectomy for minimally functioning left kidney.

Pheochromocytomas are rare endocrine tumours and can easily be missed in a non-specialist setting. The case demonstrates the importance of investigating all adrenal incidentalomas for hormonal excess and assessment by endocrinologists, as recommended in the guidelines. Normotensive pheochromocytomas have roughly similar per-operative hemodynamic instability comparing hypertensive pheochromocytomas and therefore require adequate alpha and beta blockade. Luckily, our patient underwent major urological interventions without developing a potentially serious hypertensive crisis.

X025

Thyrotoxic cardiomyopathy – a serious consequence of uncontrolled Graves thyrotoxicosis

M S Siddiqui, K Muralidhara, Central Middlesex Hospital, London Northwest Healthcare NHS Trust

A forty seven year old lady with known diagnosis of Graves' disease was admitted under cardiology with acute cardiac sounding chest pain, shortness of breath, and diaphoresis. ECG revealed atrial fibrillation with fast ventricular rate and troponins were elevated. She was clinically thyrotoxic with a prominent multinodular goitre and audible thyroid bruit. She also had profound proximal weakness, and pretibial myxoedema.

The diagnosis of Graves' disease was made 18 months prior to this presentation with elevated TSH receptor antibody (TRAb) titres at 49.1 u/ml (NR 0 – 0.4 u/ml) and a very high free T3 (>46 pmol/L). The thyrotoxicosis remained poorly controlled on variable doses of carbimazole. There was no concern about compliance with antithyroid medications.

A coronary angiogram to exclude coronary artery disease was normal. An echocardiogram demonstrated a reduced ejection fraction of 50% with hypokinesia of apical, mid and basal inferior septum. She was diagnosed with nonischemic thyrotoxic cardiomyopathy with atrial fibrillation which was managed with beta blockers, digoxin and anticoagulation.

The thyrotoxicosis was controlled with high doses of propylthiouracil and a brief period of steroids. A repeat TRAb titre during her admission was more than 100 IU/L (NR 0 – 1.8 IU/L). Over the course of next four months, she became clinically and biochemically euthyroid through careful outpatient monitoring and dose adjustment. She did not have thyroid eye disease which was further confirmed on assessment in thyroid eye clinic. The improvement in her thyroid function was associated with recovery in her cardiac function and follow-up echocardiogram demonstrated normal ventricular function with no regional wall motion abnormalities. However, she remains in atrial fibrillation and continues on beta-blockers and anticoagulation.

Following discussion in thyroid MDT, in view of large goitre with very high TRAb titres, she underwent total thyroidectomy. To our knowledge, she remains in remission with no new systemic manifestations of Graves' disease.

As reminded by this case, cardiomyopathy, although rare, is a well-recognised potentially serious complication of Graves' thyrotoxicosis. Conventional treatment for hyperthyroidism usually reverses the cardiac complications.

X026

Two cases of hypophysitis presenting as pseudomacroadenoma and hyponatraemia

Byron Lu Morrell¹, Nina Tanna², Lewis Saunders², Samantha Anandappa¹, Jesse Kumar¹, Siva Sivappriyan¹, ¹Maidstone & Tunbridge Wells NHS Trust, ²King's College London GKT School of Medical Education

Case 1: A 34-year-old female was admitted to our Hospital unwell, with headache, photophobia and. She also was seen in two other hospitals for similar symptoms. A CT head scan showed mucosal thickening within the paranasal sinuses with 'bulky pituitary gland'. Bearing this in mind, pituitary apoplexy was considered the most likely cause, and IV hydrocortisone was initiated.

Blood tests revealed a largely normal FBC, WBC but low MCV. She was hyponatraemic. CRP was 23mg/L. The free T4 was 14.4 pmol/L, with a TSH of 0.09 mIU/L, Prolactin was 1344mIU/l, IGF-1 34.7nmol/L. A pituitary MRI showed a pituitary macroadenoma and patient was referred to local a tertiary centre to undergo transphenoidal surgery. Histology showed a mononuclear inflammatory process consistent with lymphocytic hypophysitis. Further immunostaining with IgG4 revealed a high proportion of IgG4-positive plasma cells within the infiltrate, in keeping with a diagnosis of IgG4 hypophysitis.

Post operatively patient developed hypopituitarism with diabetes insipidus, and treated with levothyroxine 50 mcg daily and desmopressin 100mcg BD and prednisolone. This is currently being weaned off slowly.

Case 2: A 67-year-old gentleman was admitted to Maidstone Hospital with headache for 3 months associated with lethargy, muscle aches and a reduced appetite. Retrospectively, he also had a loss of libido for 4 months with erectile dysfunction. He was on escitalopram for depression.

On admission he was hyponatraemic (Na 122mmol/L) consistent with SIADH picture and thought to be secondary to escitalopram. During his stay, he became bradycardic and hypotensive. His cortisol was low and his cortisol response to synacthen test was inadequate. The rest of the bloods were consistent with panhypopituitarism. His pituitary MRI was reported as Rathke's cleft or adenoma, with abutting on chiasm with stalk deviation. His visual fields were normal.

The patient was treated with steroid, thyroxine and testosterone and referred to a tertiary centre. While he was waiting for surgery repeat MRI showed spontaneous resolution of the lesion with subtle but more noticeable nodular thickening of the infundibulum which consistent with hypophysitis. Again his replacement is currently being weaned off.

Both these cases presented as hyponatramia but turned out to be pituitary macroadenoma and hyponatraemia. Hypophysitis though rare is an important differential in an acute presentation resembling apoplexy, with raised inflammatory markers.

X027

The success of multimodality treatment in metastatic medullary thyroid cancer

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Introduction: Although medullary thyroid cancer can have a good prognosis even in the presence of metastatic disease, there are some patients who develop progressive metastatic disease that is life limiting. We describe a patient with advanced disease who has undergone multimodality treatment.

Case: A 43 year old gentleman presented with a neck mass in 2005. He was diagnosed with medullary thyroid cancer and managed with a total thyroidectomy. Genetic testing confirmed that it was sporadic. Subsequent recurrence of the medullary thyroid cancer meant that a radical neck dissection and removal of a paratracheal mass was performed in 2012. 65Gy in 30 fractions of radiotherapy was applied to the left side of the neck and thyroid mass with another 54 Gy in 30 fractions applied to the right side.

In February 2013, a Computer Tomography (CT) scan performed showed improved thyroid disease but progression of metastases with new lesions in the lungs, left parietal lobe and cerebellum and therefore whole brain radiotherapy was given. In April 2013, the patient was commenced on treatment with vandetanib which was well tolerated apart from some diarrhoea that was successfully managed with loperamide. Whilst another CT scan in February 2014 showed stable disease, vandetanib was stopped for a two week period due to reduced appetite and low mood in June 2014.

The patient represented in January 2016 with neurological symptoms and a CT head demonstrated a basal ganglia infarction, likely to represent a transient ischaemic attack. One year later a repeat staging CT found further disease progression, vandetanib was therefore stopped and instead the patient was entered into a clinical trial of nintedanib. Progression of liver and further brain metastases resulted in the patient being unblinded. As the patient was already found to already be in the treatment arm, he underwent re-irradiation of the brain from March to May 2017. Following this, cabozantinib was commenced on a compassionate funding basis giving a further six months of disease control. The patient's disease has now progressed in multiple sites and there are no further disease modifying options.

Discussion: This case illustrates that multiple lines of tyrosine kinase inhibitors in combination with locally ablative treatment can prolong progression-free survival and provide symptom control in metastatic medullary thyroid cancer.

X028

Bilateral adrenal histoplasmosis in an immunocompetent man

Mark Sutton-Smith, Shamaila Zaman, Fatima Saleh, Niels Larsen, Hardeep Singh, Georgina Russell, Onn Min Kon, Laura Martin, Stephen Robinson

A 75 year old man, a UK resident born in West Bengal presents with a seven month history of lethargy, dizziness, nausea and weight loss. He also has T2DM and prostatism. Initially investigated by ENT for a hoarse voice and a right vocal cord lesion later shown to be chronic granulation tissue with Actinomycosis; treated with Co-Amoxiclav. Cross sectional imaging (CT-CAP) demonstrated incidental indeterminate adrenal and mediastinal lesions. PET imaging showed intense metabolically active adrenals with low volume, but moderately active mediastinal and hilar lymphadenopathy. HIV, Hepatitis B and C screen were negative. Hb 116 g/L, WCC $5.6 \times 10^9/L$, Na $132 \times 10^9/L$, K $4.6 \times 10^9/L$. CRP 23.5 mg/L, ESR 27 mm/hr. In a Short Synacthen Test cortisol response was attenuated (381, 377 and 369 nmol/L) with an elevated ACTH 376 ng/L, Renin 5.3 pmol/mL/hr and low Aldosterone (< 60 pmol/L). Necrotising granulomatous disease was identified on adrenal biopsies. Empirical Tuberculosis (TB) treatment was started for an assumed TB adrenalitis and initial histoplasma serology was negative but with an elevated serum beta-D-glucan test. PAS stains were positive for fungal elements and subsequent panfungal PCR revealed *Histoplasma capsulatum* with negative TB culture and PCR. The overall diagnosis was therefore primary adrenal insufficiency with extensive bilateral adrenal histoplasmosis in an immunocompetent man. Treatment included managing his adrenal insufficiency with hydrocortisone (with education) and fludrocortisone. Broad spectrum anti-fungal treatment was instigated with Ambisome whilst awaiting fungal ID, then Itraconazole treatment trialled but complicated by suspected heart failure, now changed to Voriconazole.

Histoplasmosis is an endemic fungal disease that thrives in the soils of temperate environments worldwide; prevalent Areas include Central and Eastern America, particularly Ohio and Mississippi, South America, Africa, Asia and Australia. West Bengal has a very high rate of Histoplasmosis (9.4%) infection in the general population. Histoplasmosis infection occurs in one of two forms; these can be either manifest as pulmonary disease or disseminated disease commonly involving the adrenals in the immunosuppressed. Bilateral adrenal histoplasmosis in immunocompetent individuals is extremely rare with less than 100 reports of unilateral or bilateral disease worldwide. At a time before HIV became prevalent (1931-1981) necropsy material from 131,466 post-mortem examinations from São Paulo demonstrated 254 (0.2%) adrenalitis cases with only 3 cases (1.2%) caused by histoplasmosis. This case emphasizes that histoplasmosis disease should be considered as a differential diagnosis in adrenal insufficiency with bilateral adrenal masses even in the immunocompetent. Diagnosis can be made via histology, PCR tests, serology from blood or urine samples and the limitations of various tests should be taken into account.

X029

Autoimmune primary adrenal insufficiency masked by chronic steroid inhaler use

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A 17-year-old Irish girl presented with severe hyponatraemia following a 5-day history of unexplained vomiting and abdominal pain associated with dizziness and weakness. She was complaining of chronic fatigue and recurrent dizzy spells for the past few years. She was known asthmatic on regular steroid inhaler since the age of 6. She did not take her steroid for few days prior to her admission. There was no family history of note. Her BMI was 17kg/m² despite a good appetite and her examination was unremarkable apart from hyperpigmentation on her lower limbs.

Her initial investigations showed Na⁺ 119 mmol/L, K⁺ 4.9mmol/L urea 8.5 mmol/L and eosinophils 0.4*10⁹ /L. She had a compensated metabolic acidosis despite vomiting. She was noted to be constantly hypotensive despite adequate fluid replacement. Her sodium normalised to 135 mmol/L within 24 hours with fluid resuscitation alone. Paired plasma osmolality was 260 mOsm/kg with urine osmolality of 630mOsm/kg suggestive of borderline hypotonic hyponatraemia.

The possibility of adrenal insufficiency raised on the ground of clinical and biochemical picture. Subsequent short synacthen test showed cortisol at 0, 30 and 60 minutes as follows: 88, 100 and 99nmol/L respectively. She also had a raised ACTH level of 964ng/L and positive adrenal antibodies which confirmed primary adrenal failure. Remaining autoimmune screen, TFTs, immunoglobulins, coeliac screen, gastric parietal antibodies, TB monospot test and serum ACE were all normal. High urinary Na⁺ of 191 mmol/L with low urinary K⁺ combined with a very low aldosterone level and a markedly raised plasma renin were suggestive of mineralocorticoid deficiency. Her adrenal MRI showed bilateral small adrenal glands.

She was started on hydrocortisone replacement at a dose of 10mg, 5mg, and 5mg and fludrocortisone 100mcg once daily which resulted in rapid improvement in her symptoms.

This illustrates an interesting clinical case of underlying autoimmune primary adrenal insufficiency masked by exogenous steroid inhaler use for concurrent treatment of asthma. She was mildly symptomatic for adrenal insufficiency for years prior to admission. **Should patients on low dose exogenous steroid with similar symptoms and signs have a work up to rule out underlying adrenal insufficiency?**

X030

A rare presentation of TSH-secreting Pituitary macroadenoma (TSHoma) alongside an Autoimmune Primary Hypothyroidism -The management challenge

A Khan, AD Rajgor, University Hospitals of North Midlands

Thyrotropin-secreting pituitary adenomas (TSHomas) and Primary Hypothyroidism rarely present simultaneously.

We present a 46-year-old woman with both an autoimmune primary hypothyroidism (TPO +ve) and a newly detected TSHoma. This lady having primary hypothyroidism, on Levothyroxin for 3 years, presented with secondary amenorrhoea. The pituitary profile indicated raised prolactin level of 2750 µg/L. Rest of the pituitary profile was normal. MRI scan demonstrated pituitary macroadenoma with no evidence of mass effect or optic chiasm compression. She was already started on Cabergoline 250 microgram twice/week. Subsequently she was discussed at our multi-disciplinary meeting. This led to a diagnosis of a non-functioning pituitary macroadenoma with hyperprolactinaemia. The hyperprolactinaemia was thought to be a consequence of pituitary lactotroph disinhibition and pituitary insufficiency rather than a prolactinoma. Despite Cabergoline treatment reducing the prolactin levels (<10 µg/L) the mass persisted in size. Additionally, despite persistent treatment with levothyroxine at increasing doses (200 micrograms OD) the TSH (TSH 7.12 mU/L, T4 24.87 pmol/L) was not suppressed appropriately. Subsequently, she became clinically thyrotoxic with weight loss and thus levothyroxine was stopped. Her thyroid profile (TSH 67.03 mU/L, T4 7 pmol/L) after stopping levothyroxine provided a high suspicion of a TSHoma.

She was subsequently re-discussed at the MDT, where it was decided a transsphenoidal hypophysectomy would be in her best interest. Following a detailed explanation of the treatment options to the patient, she decided to opt for surgery and Transsphenoidal hypophysectomy was performed. Histopathological examination confirmed a TSHoma. Post operatively she became clinically hypothyroid and has thus restarted levothyroxine (100micrograms OD) with a stable thyroid profile (TSH 0.43 mU/L, T4 21pmol/L). This patient is currently recovering well and “feeling great.”

Conclusions/Learning Points: This case demonstrates a very rare phenomenon where a patient has both autoimmune hypothyroidism and a TSHoma. This makes biochemical and clinical analysis very problematic. Biochemically this patient had an elevated TSH and low/normal T4 and despite levothyroxine treatment the TSH would not be suppressed. The presence of a potentially autoimmune primary hypothyroidism masked the appearance of a TSHoma. The autoimmune hypothyroidism (raised TSH, low T4, TPO antibodies +ve) required levothyroxine but the TSHoma was already stimulating the thyroid gland resulting in secondary thyrotoxicosis. It is possible that she had a degree of primary hypothyroidism with Hashimoto's thyroiditis and now she has secondary hyperthyroidism making the clinical and biochemical picture very complicated.

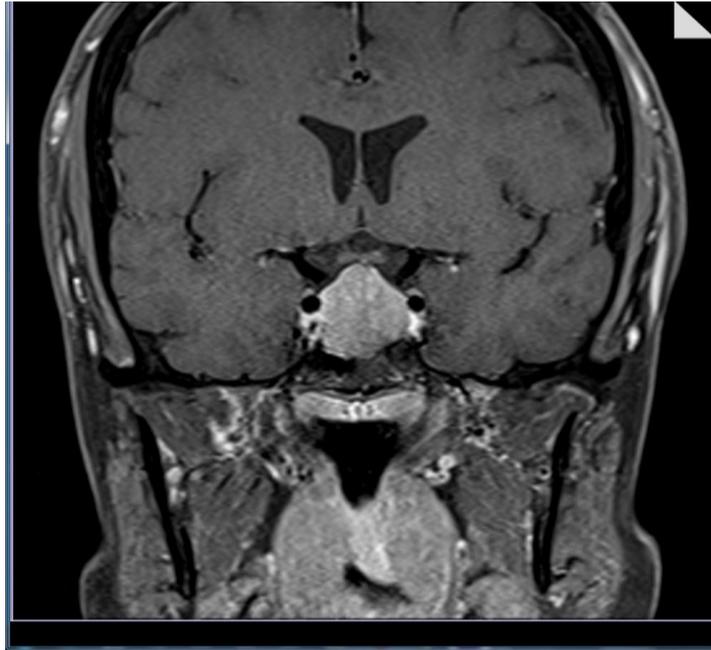


Figure 1: Large Pituitary Macroadenoma (MRI scan)

X031

Diffusion-weighted Magnetic Resonance Imaging (DWI MRI) provides a quantitative measure of disease activity and can be used as an adjunct to clinical assessment in Graves' Orbitopathy (GO)

Claire Feeney, Farzana Rahman, Ravi Lingam, Vickie Lee, Central Middlesex Hospital, London Northwest Healthcare NHS Trust

Early diagnosis and treatment of Graves' orbitopathy (GO) are essential to prevent physical and psychological burdens of advanced disease. MRI diffusion weighted imaging (DWI MRI) is an emerging modality to assist with timely diagnosis. We investigated the value of DWI MRI in early diagnosis and monitoring and its relationship with the clinical activity score (CAS) in a multidisciplinary thyroid eye clinic at Central Middlesex Hospital.

Methods: Ninety-one patients were referred to the clinic between 2011 and 2016. Forty-seven had clinical indices of orbital involvement and underwent MRI DWI imaging. Of these, 20 patients had at least one further scan during the course of the disease. The apparent diffusion coefficient (ADC) was calculated for the most affected muscle on each DWI scan and correlated with CAS.

Results: Thirteen patients received intravenous methylpredisolone, 5/20 completed orbital radiotherapy and 3/20 had an orbital decompression during monitoring. The most active muscle at presentation was the right inferior rectus (n=7, 35%). Mean CAS at presentation was 2.3/7, followed by CAS 1.2, 0.8 and 0.0 at scan 2, 3 & 4 respectively. Mean ADC value fell over the disease course during treatment from 1120.5 to 766.5. A positive correlation was found between initial CAS and ADC ($r=0.45$, $p=0.04$). All patients who did not subsequently develop significant disease had ADC values <1000 (mean 674.7) at baseline.

Conclusions: We present a positive correlation between orbital DWI MRI and CAS in GO. DWI MRI may offer predictive benefit in GO. High ADC values identified prior to other clinical disease parameters may help target patients at high risk of developing severe GO. DWI may also serve as a valuable adjunct in early diagnosis and monitoring with potential to identify low risk groups whereby low CAS at baseline combined with DWI <1000 may predict a relatively quiet disease course.

X032
OC2

Emergency Orbital Decompression is not a definitive treatment for Dysthyroid Optic Neuropathy (DON)

Claire Feeney, Farzana Rahman, Ravi Lingam, Vickie Lee, Central Middlesex Hospital, London Northwest Healthcare NHS Trust

Case 1: A 82 year old woman presented with thyrotoxic Graves' disease January 2015. She was started on carbimazole 20 mg and achieved biochemical control within 2 months of treatment. Several weeks later she started to complain of periorbital swelling and she was referred to the multidisciplinary thyroid eye clinic at Central Middlesex Hospital. On assessment she had bilateral proptosis with severe restriction of upgaze. Clinical activity score was 4/7. Diffusion-weighted Magnetic Resonance Imaging (DWI MRI) showed increased signal and enlargement of the inferior recti muscles bilaterally. She was diagnosed with moderate-severe Graves' Orbitopathy (GO) and a 12 week course of intravenous methylpredisolone (IVMP) treatment was recommended (total dose 4.5g). However her vision quickly deteriorated due to DON and she was admitted to hospital for pulsed methylpredisolone treatment for sight-threatening GO that failed to control her DON and she underwent successful emergency bilateral optic nerve decompression (endoscopic approach) with immediate improvement. Six months later she complained of persistent blurred vision in the left eye with mild relative afferent pupillary defect (RAPD) and DWI MRI confirmed persistent active GO. She went on to receive orbital radiotherapy to treat residual left DON. By August 2017 MRI DWI and clinical disease appeared quiescent and she was finally discharged.

Case 2: A 54 year old woman had sequential GO inflammation in the left then right orbit. She was first seen in the MDT GO clinic with mild left proptosis. Clinical activity score was 2/7 and there was no motility disturbance. She was initially managed conservatively but three months later left orbital inflammation increased substantially and weekly IVMP treatment was commenced for moderate-severe GO in her left orbit. The patient declined orbital radiotherapy and did not attend follow-up. Ten months later she returned to clinic complaining of right orbital pain and diplopia was treated with further IVMP with a reasonable initial response. However 6 months later her right colour vision deteriorated and a RAPD was noted in clinic with a diagnosis of DON. Initial medical treatment improved vision but later relapsed necessitating an urgent right medial wall orbital decompression. Her right vision initially improved then declined again post operatively. She continued to decline orbital radiotherapy and opted instead to take a prolonged course of oral prednisolone which finally brought the disease into remission several months later.

These 2 cases demonstrate the protean manifestations and persistent nature of GO and the need to continue to be vigilant and actively treat the orbital inflammatory disease with immunosuppression and orbital radiotherapy despite successful orbital decompression for DON.

X033

Two cases of Primary thyroid lymphoma in hypothyroid patients presenting as goitres

Razak Kehinde, Ana Pokrajac, Chantal Kong, West Hertfordshire NHS Trust

The first case is of a 79-year-old woman who presented with a rapidly enlarging goitre and shoulder discomfort in March 2017. PMH hypothyroidism. Examination revealed a hard, large mass on in the anterior aspect of the neck expanding to the Right shoulder. It was not mobile on swallowing. USS revealed a complex fleshy solid right sided mass with retrosternal extension (U4). FNA cytology showed a high-grade lymphoma with lymphoid cells positive for CD20, BCL6 and PAX5. Few CD3 and CD5 positive T cells were noted. Calcitonin, MNF116, Thyroglobulin, TTF1 and cyclinD1 were negative. PET CT demonstrated an intensely avid uptake in the right thyroid. Core biopsy confirmed a diffuse large B cell lymphoma, Stage 1Ae localised disease. Excellent response to the 1st cycle of chemotherapy with almost complete resolution of goitre when reviewed in clinic. The chemotherapy and adjuvant radiotherapy were completed in September 2017 and an end of treatment PET CT is booked for mid-November 2017.

Second case is of a 52year old man with PMH hypothyroidism, with a recent 3 week history of an enlarging left neck swelling in late September 2017. Neck USS revealed a 39x36x23mm vascular mass occupying most of the left thyroid lobe with no evidence of microcalcification(U4). USS-guided FNA revealed lymphoid blasts with body macrophages and lymphoglandular bodies, indicative of a high grade B-cell non-Hodgkins lymphoma. Immunocytochemistry stains strongly positive for CD20, CD3. He was urgently seen in the haematology clinic and has been booked to have chemo-immunotherapy using a combination of Rituximab plus CHOP followed by radiotherapy.

Thyroid lumps are rarely caused by lymphoma (1% of cases) but the index of suspicion increases with hard, fixed masses that are rapidly growing. These cases also demonstrate the additional risk of lymphoma that could be present in hypothyroid patients, due to Chronic Lymphocytic thyroiditis (Relative risk 67)¹.

References:

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X034

A challenging case of radioiodine-refractory Graves' disease

R Ramli, R Troke, F Wernig, A DiMarco, F Palazzo, S Kahn, Z Win, N Hill, G Williams, K Meeran, E Hatfield, Imperial Healthcare NHS Trust

Our patient initially presented 8 years ago with supraventricular tachycardia (SVT) at the age of 14, for which she underwent cardiac ablation. Her arrhythmia recurred and blood tests revealed thyrotoxicosis with positive TSH receptor antibodies (11.1 U/mL [0 - 0.3]). Her aunt had a thyroid goitre removed, but there is no family history of autoimmune thyroid disease. She had no evidence of Graves' ophthalmopathy.

She was started on thionamide treatment in addition to Ivabradine and Propranolol. Her adherence to therapy was suboptimal and she remained thyrotoxic with frequent attendances to casualty due to SVT. She therefore received radioiodine treatment (745 MBq, November 2015), but unfortunately returned a month later with SVT and persistent thyrotoxicosis. She was restarted on anti-thyroid treatment and received a second radioiodine dose (755 MBq, April 2016). This was again unsuccessful, and, as she declined total thyroidectomy, a third dose of radioiodine was administered (810 MBq, July 2016). A post-treatment 5-minute thyroid uptake Technetium scan showed good uptake within both lobes of the thyroid gland. She improved biochemically 10 weeks later (T4 8.4 pmol/L, TSH 0.01 mU/L), but unfortunately became thyrotoxic again soon after (T4 34.4 pmol/L, T3 >46.1 pmol/L, TSH <0.01 mU/L). A Technetium uptake scan showed diffuse increased homogenous distribution of tracer throughout both lobes of the thyroid gland with suppression of the normal background activity (uptake function 15.7%). Two further radioiodine treatments were given in February 2017 (780 MBq) and March 2017 (597 MBq) with Lithium administration 3 days prior to radioiodine. A day 1, 3 and 7 post-therapy whole body uptake technetium scan confirmed retention of radioiodine within the thyroid gland with no sites of extrathyroidal uptake. She unfortunately remained clinically and biochemically thyrotoxic and following further discussion, the patient finally agreed to have surgery. She received 10 days of high-dose potassium iodide which rendered her euthyroid and successfully underwent a total thyroidectomy in October 2017. She was commenced on Levothyroxine postoperatively, remains well and under close surveillance.

Radioiodine treatment is highly effective in the treatment of Graves' disease with cure rates approaching 100%. Rapid thyroidal iodine turnover and/or large, isoechoic goitres have been associated with poor response to radioiodine treatment. Pre-treatment with lithium may prolong radioiodine retention and may increase the efficacy of radioiodine therapy and was therefore used in our patient, but remained unsuccessful. This is an extremely unusual case of radioiodine-resistant Graves' disease whose disease remained active following a total of 5 doses of radioiodine.

X035

Percutaneous microwave ablation of adrenal remnant tissue. A novel treatment modality for persistent Cushing's disease

R Ramli, S Hameed, F Wernig, A Sam, E Leen, F Palazzo, N Mendoza, E Hatfield, N Martin, K Meeran, Imperial Healthcare NHS Trust

A 29-year-old lady presented with features of Cushing's syndrome in October 2014. Investigations confirmed ACTH-dependent Cushing's syndrome. An MRI scan showed a 4.5 mm right-sided pituitary lesion and subsequent inferior petrosal sinus sampling confirmed a central source of ACTH hypersecretion. She underwent trans-sphenoidal pituitary surgery in January 2015. Histology confirmed a corticotroph adenoma with a Ki-67 proliferation index of 1%. However, a mean cortisol of 298 nmol/L on a cortisol day curve was highly suggestive of persistent hypercortisolaemia. MRI scanning confirmed small-volume residual tumour in the right anterior sella. She remained symptomatic and underwent a second trans-sphenoidal pituitary surgery in April 2015. Histology from this surgery showed normal adenohypophysis only. The second surgery was complicated with a post-operative CSF leak and meningitis. A cortisol day curve 6 weeks later showed a mean cortisol level of 474 nmol/L and further biochemistry investigations confirmed persistent hypercortisolaemia. Following MDT discussions, the patient underwent bilateral adrenalectomy in March 2016, with some difficulty encountered during removal of the left adrenal gland. As expected, histology of both adrenals showed evidence of adrenal hyperplasia. She was commenced on Prednisolone and Fludrocortisone postoperatively.

She continued to have difficulty losing weight 5 months post-adrenalectomy. An overnight dexamethasone suppression test confirmed persistent Cushing's disease (9 am cortisol 383 nmol/L). Prednisolone was discontinued and she was commenced on Metyrapone. MRI Pituitary showed a right-sided pituitary adenoma extending between the intra- and supracavernous internal carotid artery segments. A Ga68 DOTATATE whole body PET CT showed appearance consistent with residual hyperplastic adrenal tissue in the left suprarenal region. She was discussed in the ICHNT Pituitary and Adrenal MDT meetings where percutaneous ablative approach of the residual adrenal tissue was considered the best management option due to the risks associated with further pituitary surgery or pituitary radiotherapy, or repeat abdominal surgery. Microwave ablation therapy was chosen as recent studies suggested similar or even superior efficacy when compared to radiofrequency ablation¹. She underwent CT-guided microwave ablation of the left adrenal remnant (120W) in July 2017, following which she was re-started on Prednisolone. Following the procedure, she improved significantly both clinically and biochemically. This case illustrates that percutaneous ablative approach of adrenal remnant tissue and possibly entire adrenal glands should be considered in the treatment of challenging Cushing's disease.

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Venkatesan AM, Locklin J, Dupuy DE, Wood BJ. Percutaneous Ablation of Adrenal Tumors. *Tech Vasc Interv Radiol*. 2010 Jun; 13(2): 89-99.

X036

Erectile Dysfunction – An Under-Recognised Presentation of Acromegaly

M Lepore, S Zaman, B Patel, R Kaushal

We present a 40 year old male who was referred by his GP with erectile dysfunction (ED). He and his wife had been trying to conceive for 5 years. He had a past medical history of obstructive sleep apnoea and was under the respiratory and ENT teams. He did not tolerate home CPAP and had a tonsillectomy in 2013. There was no history of diabetes or hypertension. During the initial consultation, he reported that his features had changed significantly over the past 10 years, specifically mentioning increasing shoe size. He denied headaches and sweating.

On examination he weighed 94kg and was normotensive. He had prominent nasolabial folds, macroglossia, prognathism and doughy hands. Cardiac auscultation was unremarkable. Visual fields were full to confrontation. There was no thyroid nodularity.

His investigations revealed IGF-1 133.9 (13-50 nmol/L), FSH 6.6 (1.3-19.3 IU/L) and LH 6.0 L (1.2 – 8.6 IU/L). Testosterone 4.1 (6.1 – 27.1 nmol/L). Prolactin 152 (56-278 mIU/L). Free T4 9.2 (8.4 – 19.1 pmol/L). Cortisol 390 (185 – 624 nmol/L).

MRI showed a 1.5 cm mass in the left side of the pituitary consistent with a macroadenoma. The mass extended inferiorly into the adjacent sphenoid sinus with no compression of the optic chiasm.

He was then referred to a tertiary centre for surgery.

It is not widely appreciated that ED is a recognised feature of acromegaly; up to 42% of patients with acromegaly report ED.¹ It is extremely important that patients presenting with ED are thoroughly assessed to exclude organic and potentially reversible causes of their symptoms.

References:

1 - <http://dx.doi.org/10.1111/jsm.12859>

X037

Pheochromocytoma

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The clinical presentations of the patient with pheochromocytoma -- a rare endocrine neoplasm -- include adrenal incidentaloma, hypertensive paroxysms, sustained apparent polygenic hypertension, hypertension in pregnancy, and hypertensive crisis induced by anaesthesia. Although when undiagnosed a pheochromocytoma can be lethal, it can usually be cured with surgery. Biochemical documentation with measurements of fractionated metanephrines and catecholamines should precede imaging studies. Abdomen and pelvis computed imaging is usually the first imaging test. Careful preoperative pharmacologic preparation is important for a successful surgical outcome. Adrenal pheochromocytomas can usually be removed laparoscopically, whereas, catecholamine-secreting paragangliomas typically require an open approach. All first degree relatives of pheochromocytoma patients should have biochemical testing. In addition, molecular genetic testing for germline mutations should be considered in most patients with adrenal pheochromocytoma and in all patients with paraganglioma.

I present a case of a 73 year old male with a background of HT, IHD, RA, IBD, Type 2 DM who while being investigated for iron deficiency anaemia, CT abdomen showed an incidental finding of 5cm adrenal mass, no symptoms of phaeochromocytoma

Investigations showed an elevated 24 hour metanephrines 1603 and normetanephrine 4423, 24 hour urine cortisol was normal.

Overnight dexamethasone and low dose dexamethasone suppression test did not suppress the cortisol suspecting that it is due to high CBG levels rather than co-existing Cushing's disease.

Hypertension was treated with doxazosin initially with 1 mg and gradually titrated to 16mg and bisoprolol 10mg.

Laparoscopic surgery was performed and histology confirmed pheochromocytoma, there were some mitotic figures but no other malignant features. He had an excellent recovery, doxazosin was stopped and echocardiogram showed good LV function and dilated left atrium. Referred to genetist to discuss susceptibility genes and also to factor in what his histology means in terms of angiomyolipoma in his daughter. Point of testing here would be to ensure that we are not dealing with VHL

X038

How relevant is aldosterone and cortisol co-secretion?

Padmanabh S Bhatt¹, Amir H Sam^{1,2}, Victoria Salem¹ and Karim Meeran^{1,2}, ¹Imperial College London School of Medicine, ²Hammersmith Hospital, Imperial College London NHS Trust

Background: Studies suggest that glucocorticoid hypersecretion alongside primary hyperaldosteronism (PA) is common and may contribute to the adverse metabolic phenotype. Adrenal crisis post-surgery for PA is rare.

Aim: To determine the prevalence of cortisol co-secretion in PA in patients at Imperial College London NHS Trust, Hammersmith Hospital (a tertiary referral centre for adrenal tumours).

Methods: Amongst patients who had undergone adrenal vein sampling for therapeutic stratification of PA over the past 5 years, 27 also had formal (overnight dexamethasone suppression) testing for hypercortisolism with overnight or low dose dexamethasone suppression test.

Results: Six patients were diagnosed as co-secretors (post dex cortisol range 75 – 435 nM) suggesting a prevalence of 22%. We describe their clinical history. Four co-secretors underwent unilateral adrenalectomy. Post-operatively, two failed a synacthen test (peak cortisol range 320-421) and one had a morning cortisol of 20 nmol/L. They were given glucocorticoid cover post-operatively but it is not known whether this was of benefit. Previously, no patients were given glucocorticoid cover, and there was no incidence of severe adrenal crisis post unilateral adrenalectomy for PA. No improvement in metabolic profile was seen in follow-up, except for the anticipated improvements in BP control.

Discussion: It is not clear whether co-secretion in PA is clinically relevant. The patients described here may not be entirely representative, since we have only recently prospectively assessed all PA patients for co-secretion. However we did not find differences in the metabolic profile at presentation between co-secretors and non-co-secretors. Perhaps co-secreting patients present earlier, and the burden of cortisol excess has not yet caused a dysmetabolic profile. In conclusion cortisol co-secretion in PA is more common than previously thought. Further studies are required to understand exactly what postoperative monitoring is required in this condition.

X039

Iatrogenic nephrogenic diabetes insipidus secondary to demeclocycline misuse

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We present the case of an 84 year old male who was admitted to the acute medical ward following a fall and increasingly agitated behaviour. During a previous admission he was persistently hyponatraemic (ranging 119-130mmol/L) and diagnosed with SIADH of unknown aetiology. Fluid restriction failed to normalise his sodium so he was discharged on 300mg demeclocycline. Upon re-attendance he was found to be profoundly hypernatraemic (162mmol/L) with a GCS score of 7/15. Clinically he was profoundly hypovolaemic, but despite this he was passing 2-3 litres of dilute urine per day. He was hypernatraemic at 162mmol/L with a serum osmolality of 397mosm/kg (275-295mosm/kg), a urine osmolality of 408mosm/kg (50-1200mosm/kg) and urinary sodium of 36mmol and a significant acute kidney injury.

A diagnosis of diabetes insipidus was made secondary to inappropriate use of demeclocycline. He was managed with 5% dextrose replacement as well as intravenous antibiotics for sepsis. His sodium rose to 177mmol/L but given his poor baseline and co-morbidities it was decided he was not for escalation to intensive care or the high dependency unit. Unfortunately he remained persistently drowsy and he continued to pass 2-3 litres of dilute urine. His renal function did not improve, his sepsis failed to respond to antibiotics, so the decision was made to withdraw care and the patient passed away the following day.

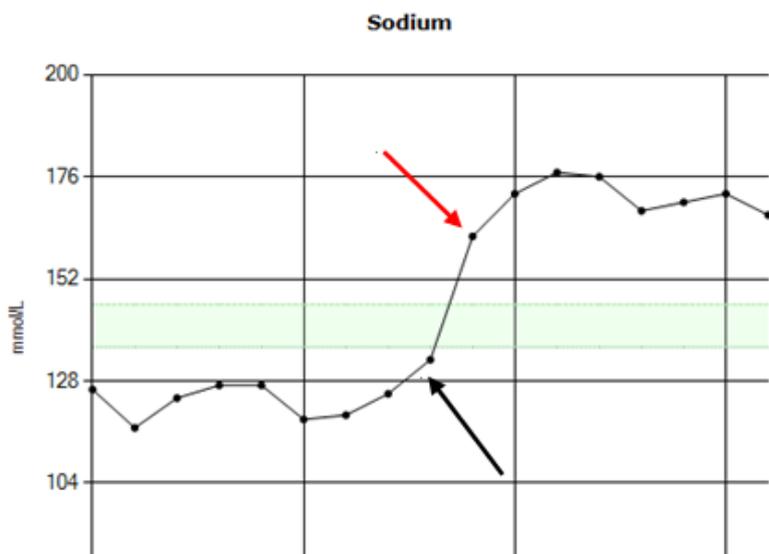


Figure 1: Serum sodium. **Black arrow** demonstrates when discharged with demeclocycline. **Red arrow** shows when readmitted two weeks later.

Learning Points:

1. This case highlights how inappropriate prescription and monitoring of demeclocycline can have serious adverse effects, in this case with severe, symptomatic hypernatraemic, volume depletion and acute kidney injury.
2. Our case highlights how great care should be taken when commencing a patient on demeclocycline as it typically takes days to weeks to take effect. It should be reserved for persistent severe hyponatraemia, should be undertaken under specialist endocrine supervision and should be monitored regularly on an endocrine ward.

X040

Optimising Follicular Growth for Oocyte Retrieval during IVF Treatment

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Background: *In vitro* fertilisation (IVF) is a valuable treatment for infertility, however insufficient egg (oocyte) retrieval frequently results in cycle cancellation. A trigger injection is administered once three ovarian follicles are ≥ 18 mm in diameter, to provide luteinising hormone (LH)-like exposure to mature oocytes in readiness for retrieval. However, this leading follicle size threshold is not evidence-based and the optimal follicular size for triggering oocyte maturation is not currently known. This study aims to identify the category of follicle diameters that should yield an oocyte if effective triggering is administered.

Methods: A retrospective analysis of datasets generated from three clinical trials using three triggers of oocyte maturation was conducted. Data from 358 patients was analysed: gonadotrophin releasing hormone agonist (GnRHa; n=165), human chorionic gonadotrophin (hCG; n=20) and kisspeptin-54 (KP; n=173). GnRHa and hCG data were collected at My Duc Hospital, Vietnam and KP data at Hammersmith Hospital IVF unit, London. Patients with the highest hormonal response to triggering were selected to ensure effective triggering had been administered. Linear regression analysis was used to identify the category of follicle size that best predicted the number of oocytes retrieved.

Results: The optimal category of follicle size was: 10-17mm for GnRHa ($r^2=0.46$, $P<0.001$), 13-17mm for KP ($r^2=0.73$, $P=0.004$) and 13-18mm for hCG ($r^2=0.42$, $P=0.022$). 'Oocyte yield' is defined as the proportion of mature oocytes collected from follicle sizes sufficient to yield an oocyte, and represents a measure of trigger efficacy. KP achieved 100% oocyte yield at effective doses of 12.8nmol/kg or more to generate a serum LH level of ≥ 10 iU/L at 12hrs following administration. hCG and GnRHa achieved optimal oocyte yields at the doses tested.

Conclusion: Identifying the target category of follicular size will guide IVF clinicians in appropriate timing of the trigger injection and accurate evaluation of trigger efficacy.

X041

Fragile X premutation: A known under-diagnosed aetiology for premature ovarian insufficiency

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Background: Premature ovarian insufficiency (POI) is defined by loss of ovarian activity before the age of 40. Chromosomal analysis, Fragile-X premutation testing and screening for 21OH-Ab are the basic recommended investigations for patients with non-iatrogenic POI. Two cases of POI with Fragile- X premutation are presented.

Case 1: 34 years old woman with past medical history of secondary amenorrhea and infertility from age 26. Prior to that, she had normal menarche at age 12 and regular periods with 1 child born while she was 23 years of age. Work up by her physician in obstetrics and gynecology division revealed POI. Further investigations revealed female karyotyping (46, XX) and absence of 21 hydroxylase antibodies (21OH-Abs). For sake of completion of POI investigation, Fragile X premutation testing was performed. It showed that she is a carrier of a premutated allele with presence of 78 CGG repeats in one of the allele (the second allele was normal with 30 CGG).

Case 2: 33 years old woman was seen for subacute thyroiditis. Further history revealed primary infertility for 10 years with oligomenorrhea and several failed IVF attempts. Previous work up showed POI with female karyotyping (46, XX). 21OH-Ab screening was negative. Fragile X premutation testing confirmed the carrier state for premutated allele with 85 CGG repeats (the second allele was normal with 30 CGG). Further history revealed that the two patients are second-degree relatives.

Discussion: Fragile-X syndrome is an X-linked inherited condition caused by a mutation of the fragile-X mental-retardation 1 (FMR1) gene. The full mutation (> 200 CGG repeats) can result in mental retardation but primarily in men who carry the mutation. Women who carry the premutation (55-200 repeats) do not have an increased risk of intellectual disability, but have an increased risk of 13-26% to develop POI. Studies on the Fragile-X premutation in women with POI have found a prevalence of 0.8 to 7.5% in women with sporadic POI (i.e. women without other family members with POI) and up to 13% in women with a positive family history of POI. Many women with non-iatrogenic POI are not screened for Fragile X premutation due to lack of awareness. In fact with the high rate of consanguinity marriage in our region, Fragile-X premutation in women with POI may have a higher prevalence than reported in other parts of the world.

Conclusion: The earlier diagnosis of premutation has several implications on patient and their families. Consequences such as risk for other associated features (ataxia), infertility options (early ovum preservation) and offering genetic counseling and testing to relatives of women with fragile-X premutation need to be discussed in advance.

X042

Fluconazole in the treatment of Cushing's disease

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We present a 73-year-old woman with a 15-year history of cyclical Cushing's on a background of hypertension, COPD, dyslipidaemia, thyroidectomy for multinodular goitre and osteoporosis.

She had remissions of Cushing's every 2 years to begin with, which settled spontaneously. These episodes were associated with candidiasis, facial swelling, hypokalaemia and hair loss, and were biochemically confirmed on Overnight (ODST) and Low Dose Dexamethasone Suppression tests (LDDST). An MRI Pituitary in 2014 showed slight asymmetry but no evidence of an intrinsic adenoma and MRI Adrenals in 2012 were normal. In 2016, she reported Herpes Zoster infection and recurrent respiratory and gastrointestinal viral illnesses. On clinical examination, her BP was normal (126/86 mmHg) and there were no evidence of bruises, striae or proximal myopathy. Biochemistry showed an afternoon cortisol of 461 nmol/L and ACTH of 45.2 ng/L. She failed to suppress on ODST (9 am cortisol 739 nmol/L) and LDDST (0h Cortisol 516 nmol/L; 48h Cortisol 1402 nmol/L and ACTH 103 ng/L). An interval MRI Pituitary did not show any interval changes. An inferior petrosal sinus sampling (IPSS) was initially planned, but as she continued to be asymptomatic and her ACTH fell to 37 ng/L, the procedure was postponed as she seems to have cycled out.

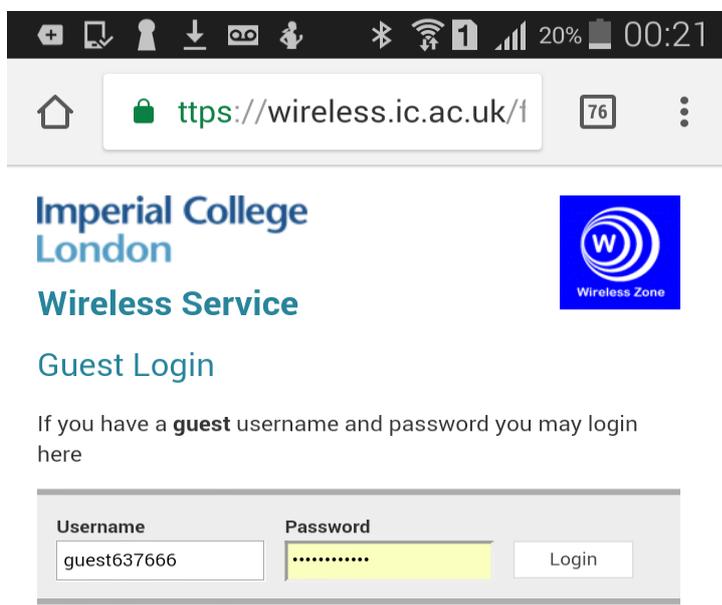
A year later, she presented to hospital with a fall. She reported worsening myopathy and easy bruising. Biochemical investigations showed hypokalaemia (K 2.8 mmol/L), raised 24-hour urinary cortisol (2052, NR 50-270) and she failed to suppress on ODST (9 am 1321 nmol/L). Results from an IPSS unfortunately were inconclusive. An MRI Pituitary showed no interval changes, and a Ga68 DOTATATE whole body PET CT did not show any evidence of DOTATATE avid lesions. She was commenced on Metyrapone but as she was unable to tolerate higher doses of Metyrapone and continued to have raised cortisol levels (365- 610 nmol/L), Fluconazole was added. She continued to feel unwell, and was readmitted to hospital where Metyrapone was stopped and the dose of Fluconazole was increased to 600 mg tds. Her cortisol levels improved (130-140 nmol/L).

Ketoconazole is more commonly used in management of Cushing's disease. Fluconazole inhibit cortisol production via inhibition of 17-hydroxylase and 11-beta hydroxylase, and potentially with less risk for hepatotoxicity compared to Ketoconazole. This case illustrates the efficacy of Fluconazole as a medical management in Cushing's disease.

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