Diffuse Idiopathic Pulmonary Neuroendocrine cell hyperplasia (DIPNECH): two unusual cases of cyclical ectopic Adrenocorticotrophic hormone secretion

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CASE 1: Mrs SH 62 yr old Caucasian lady

March 2013: Presented with easy bruising, generalised weakness & osmotic symptoms. No past medical history, on no regular medications.
At local Endocrine services, initial investigations: ◦ hypokalaemia (2.6 mmol/l) ◦ diabetes mellitus (HbA1c 62mmol/mol) ◦ raised cortisol 1710nmol/l with an inappropriately raised ACTH 610ng/l (10-50). Initial LDDST: failure to suppress cortisol levels. Initial radiology: ◦ normal MRI pituitary scan ◦ CT adrenal scans showed bilateral adrenal hyperplasia, confirming diagnosis of ACTH-dependent Cushing's syndrome.
Mrs SH was commenced on Sando K, Metyrapone and insulin.
May 2013: Presented with left leg cellulitis requiring hospitalisation. Inpatient stay complicated with severe hospital-acquired bilateral pneumonia requiring ITU admission and NIV. Transferred to Endocrine team at Hammersmith Hospital. On admission, on Metyrapone 500mg tds, examination findings confirmed a Cushingoid appearance, abdominal striae, proximal myopathy, normotension (BP 120/80) and lumbar spine tenderness. Investigations on Metyrapone 500 mg tds included ◦ Cortisol day curve: adequate cortisol levels (200 -400 nmol/L) ◦ Lumbar spine X-Ray: T12-L1 collapse with osteopenia ◦ CT chest: Rt LL nodule.
In order to investigate the source of ACTH secretion, an Inferior Petrosal Sinus Sampling (IPSS) was planned, Metryapone was withdrawn and cortisol levels were monitored. 2 wks post-Metyrapone cessation, cortisol levels normalised: 125 – 250 nmol/l, midnight cortisol 41 nmol/L (NR <50) and normalised ACTH 43ng/l. In addition, there was resolution of Diabetes. This was **consistent with spontaneous resolution of Cushing's Syndrome** and the IPSS postponed. Baseline cortisol now very low and therefore, an Insulin Tolerance Test performed, now confirming cortisol deficiency: Baseline cortisol 40 nmol/L , peak cortisol 409nmol/L (NR > 450), baseline ACTH 22.1.(NR 10-40). She therefore required Hydrocortisone replacement (10mg/ 5mg/ 5mg).
August 2013 4 weeks later in clinic: complete resolution of muscle weakness and easy bruising. Pre-Hydrocortisone Cortisol level low (40 nmol/l) with ACTH 22ng/ml, **consistent with continued remission of the Cushing's syndrome.**
Oct 2013 in clinic: Increasing muscle weakness and tanned. Recent admission to local hospital with hypokalaemia (2.2 nmol/L). Hydrocortisone stopped. O/E: Cushingoid, plethoric, hyperpigmented and had proximal myopathy. Once again, cortisol levels significantly raised with an inappropriately raised ACTH level (random cortisol >2000 nmol/L , ACTH 431 ng/ml). Repeat LDDST: **recurrence of ACTH-dependent Cushing's syndrome**: midnight cortisol 1400 nmol/L (NR<50), T=48hrs cortisol >1600nmol/L.
Oct 2013: IPSS confirmed **ectopic source of ACTH**. Restarted on Metyrapone 250mg tds. Repeat CT thorax: 1.3 cm Rt LL nodule (Fig. 1). 68-Gallium DOTATATE PET CT scan: increased uptake of Rt LL nodule, consistent with a lung neuro-endocrine tumour (Fig. 2). Lung MDT decision: Rt LL resection.
Nov 2013: on Metyrapone, prompt reduction of ACTH to 46 mg/ml and Cortisol to 79nmol/L. **Once again cycled out of Cushing's syndrome.** Commenced on 'Block & Replace regimen' of Metyrapone and Hydrocortisone and she underwent an uncomplicated Rt lower lobectomy. Discharged home well with Hydrocortisone replacement.
Histology: confirmed a well-differentiated neuroendocrine tumour, with features of typical carcinoid pT1a, rare mitoses, Ki-67 index < 3% and no lymphovascular invasion. In addition, there was evidence of **diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH).**
Dec 2013: she remained cortisol deficient (& pre-Hydrocortisone cortisol level = 63 nmol/l) with a low ACTH (16.6). Confirmatory Glucagon Stimulation Test: peak cortisol 353nmol/L. She required ongoing hydrocortisone replacement. **Consistent with Pituitary corticotroph suppression from previous high ectopic ACTH secretion.**
Sept 2015 in clinic: Well. Continues on Hydrocortisone, with adequate cortisol levels on HCDC. Resolution of Diabetes.. Normal BMD on DEXA scan.

FIG. 1: CASE 1 CT CHEST

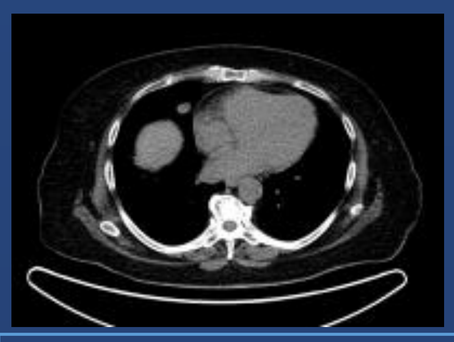


FIG. 2: CASE 1 68-Ga DOTATATE PET/CT

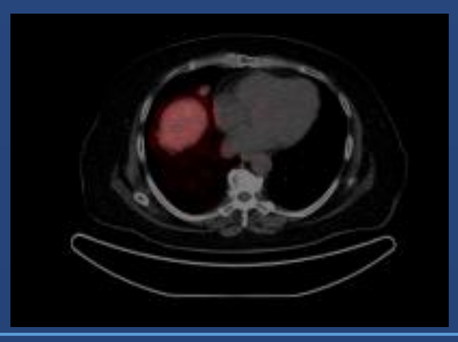


FIG. 3: CASE 2 CT CHEST

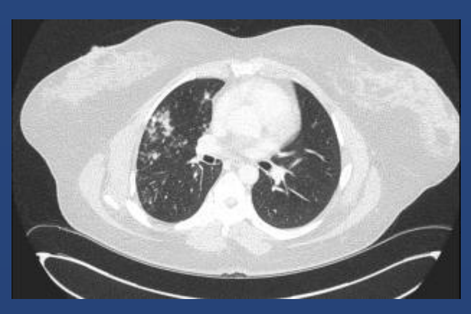


FIG. 4: CASE 2 CT CHEST

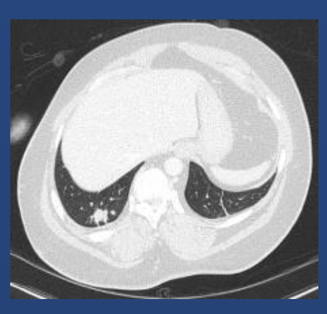


FIG. 5: CASE 2 H&E STAIN (x4)

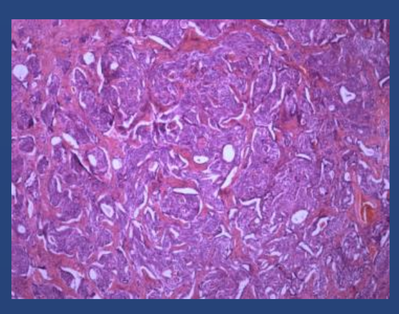
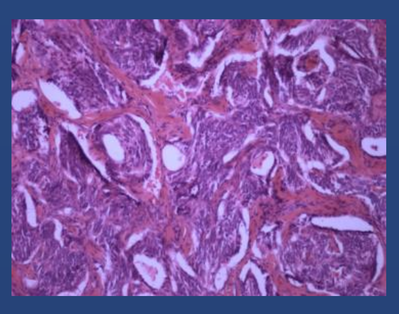


FIG. 6: CASE 2 H&E STAIN (x10)



Case 2: Miss MB 33yr old Ghanian lady

June 2015: Presented with short history of weight gain, abdominal striae, proximal myopathy & secondary amenorrhoea. There was a past medical history of asthma. Clinical features of Cushing's syndrome were present despite stopping all inhalers & medications several months prior to presentation.
Initial investigations: ◦ raised random cortisol 4000nmol/L, inappropriately raised ACTH 98ng/L. ◦ LDDST: failure to suppress cortisol levels, T=48hr Cortisol 409nmol/L with ACTH 35.2ng/L. Initial MRI pituitary scan showed a possible 5.5mm non-enhancing left-sided pituitary adenoma.
July 2015: Referred to Hammersmith Hospital. History reviewed in Endocrine clinic. Of note, **previous episode** of weight gain, abdominal striae, proximal myopathy and secondary amenorrhoea **ONE YEAR EARLIER, which spontaneously resolved** after a few weeks. On examination: hirsuitism, moon face, acanthosis nigricans, abdominal striae, proximal myopathy, BP 165/80mmHg. Repeat Investigations: ◦ Random cortisol 1,170nmol/L, inappropriately raised ACTH 98.3ng/L. ◦ Repeat LDDST: failure to suppress cortisol levels. ◦ IPSS: No central to peripheral ACTH gradient. **Unlikely to represent pituitary-driven Cushing's disease** and ectopic source of ACTH was sought. ◦ CT T/A/P: multiple small pulmonary nodules & dominant right lower lobe nodule persistent since a CT KUB in 2006; some progression locally, adrenal glands normal (Fig 3 & 4). ◦ 68-Gallium DOTATATE PET CT scan: no abnormal uptake.
31st August 2015: CT scans reviewed in the Lung MDT. Lung nodules larger, more spiculated compared with 2006; unlikely to represent infection/ TB. She was commnced on oral Metyrapone 250mg tds.
7th September 2015 - one week later: Metyrapone stopped due to low cortisol levels.
14th September 2015 - one week later: Off Metyrapone and on no treatment, cortisol levels remained low (116 to 209nmol/L) with concomitant reduction in ACTH levels (12-20ng/L), indicating **spontaneous remission of Cushing's syndrome**.
October 2015: Following MDT discussion, she underwent an excision biopsy of right lung nodule. Histology confirmed tumourlets with a typical carcinoid appearance on a background of DIPNECH (Fig. 5 & 6). There was focal positive staining for ACTH. Post-operatively, she was commenced on Hydrocortisone while awaiting an Insulin Tolerance Test, which showed a normal peak cortisol level of 552nmol/L.
March 2016 in clinic: she is clinically remission, recent ONDST: 82nmol/L confirming that she is post-operatively in remission and is not requiring HC replacement.

CONCLUSION: Whilst Cyclical Cushing's syndrome is rare but well recognised in ACTH secreting pituitary adenomas, it is very rarely reported with ectopic ACTH secretion. Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) is an unusual lung disorder, consisting of nodular proliferation of airway neuroendocrine cells affecting the small bronchi and bronchioles. DIPNECH has rarely been associated with ectopic ACTH production, with only one case reported in the literature. The mechanism for intermittent secretion of ACTH from these pulmonary tumourlets in DIPNECH is unclear. It is evident from our cases that DIPNECH not only produces cyclical ACTH secretion but significant and severe cortisol excess, with a clinical presentation that resembles ectopic ACTH syndromes associated with small cell primary lung tumours. The cyclical nature of ACTH secretion and evidence of multiple pulmonary nodules makes management challenging and will require long-term clinical, biochemical and radiological follow-up.

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