ESA CLINICAL WEEKEND 2019 FULL CASE STUDIES

1

Genetics for the practicing endocrinologists in 2019: a mass of information or a mess?

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Most endocrinologists have cared for individuals with monogenic endocrine diseases since day 1 of their training – from congenital adrenal hyperplasia to multiple endocrine neoplasia to phaeochromocytoma to osteogenesis imperfecta to androgen insensitivity. Most endocrinologists have also cared for individuals with polygenic endocrine conditions since day 1 – from type 1 diabetes to type 2 diabetes to autoimmune thyroid disease to osteoporosis. What has changed since day 1 – and dramatically – is the way the genetics of these diseases are investigated, and how these results can be applied in the clinical care of an individual. Knowing what options are available locally and what might be best in an individual situation is not always straight-forwards: in Australia currently there are various state-by-state (and indeed hospital-by-hospital) idiosyncrasies to negotiate. Additionally, many of the individuals we care for are taking matters into their own hands, availing themselves of direct-to-consumer on-demand testing, and arriving to their appointment with results that they expect their specialist to discuss with them in-depth. This can be challenging! This talk aims to provide context and practical considerations for practising endocrinologists in 2019.

2

Hot Topics in Thyroid Disease

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In this session, Dr. Angela M. Leung, Editor-in-Chief of *Clinical Thyroidology*, a journal of the American Thyroid Association in which experts comment on the most impactful articles from the current clinical thyroid literature, will present a selection of the journal's top highlighted papers from 2019. Hot topics regarding both benign and malignant thyroid disease will be covered. Clinically relevant themes to be discussed include the longterm risks of undertreated hypothyroidism and hyperthyroidism, pediatric thyroid disease, novel thyroid eye disease therapies, sonographic and novel nuclear approaches to evaluating thyroid nodules, active surveillance of low-risk thyroid cancers, and measures of quality of life and worry among thyroid cancer patients.

3

Personalised Medicine in Diabetes: Dream or Reality?

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Although distinct entities, type 1 and type 2 diabetes share many underlying aetiological factors. Indeed, many patients with type 1 diabetes exhibit insulin resistance and, conversely, patient with type 2 diabetes are relatively insulin-deficient. The overlapping features of these related, but distinct, diseases dictates a rethinking of current diabetes classification and raises the possibility that classification based on a combination of aetiological, serological and phenotypic features will be more fruitful. Such an approach would allow the development of personalised approaches to management of glycaemia. There are currently limited available tools to allow the selection of a specific medication for an individual patient that will maximize efficacy and minimize the risk of adverse effects. Furthermore, many patients are non-responders to diabetes medications. A personalised medicine approach in diabetes requires: (i) detailed phenotypic and 'omic characterization of the person with diabetes (or prediabetes), including profiling of lipidomic, metabolomic, microbiomic and, possibly, genetic/genomic factors; and (ii) elucidation of the mechanism of action, and long-term safety and benefits, of diabetes medications. With that information, it may be possible to more accurately select the 'right' drug for the 'right' patient and to possibly expand the indications for existing medications. Metformin may be a useful adjunct to insulin to target insulin resistance in some patients with type 1 diabetes. Additionally, SGLT2-inhibitors are being trialled in type 1 diabetes with promising results. Future research to elucidate and examine personalised approaches to diabetes management is required to ensure that the 'dream' of personalised medicine becomes reality.

4

Emerging enteroendocrine therapies for obesity

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Obesity is a complex disorder arising from a combination of genetic predisposition, socioeconomic determinants of health, and the influence of an obesogenic environment. Population-wide interventions will likely be required to modify public behavior, at multiple ages. Given the considerable morbidities and excess mortality associated with obesity, individualized approaches to obesity are also needed. Several medical therapies are approved for the treatment of obesity, yet exhibit only modest efficacy. Bariatric surgery is the most effective intervention for obesity that is also associated with reduction of obesity-associated comorbidities. Circulating levels of a subset of distal gut hormones with anorectic and ancillary metabolic properties are elevated following RYGB and VSG metabolic surgery. Enthusiasm for gut-derived medical therapies stems from a precise understanding of the physiological and pharmacological roles of gut hormones in control of normal and disordered energy homeostasis. Interrogation of gut hormone action and potential therapeutic efficacy requires understanding of hormone synthesis and secretion, clearance and degradation, receptor signaling and PK-PD relationships, receptor desensitization, communication with the CNS, and evaluation of the utility of preclinical models. Improved understanding of enteroendocrine science has yielded a number of gut-derived therapies, principally GLP-1 based, for treatment of diabetes and obesity. The pleiotropic actions and striking efficacy of the GLP-1R agonists, coupled with the enigmatic yet unparalleled benefits of bariatric surgery, has validated the enteroendocrine system and peptide hormone-based therapies as viable targets and platforms for development of improved next generation therapies for treatment of energy homeostasis. Here I review preferred peptide and non-peptide partners for co-agonist and tri-agonist therapies, with a focus on current benchmarks, strategies for improving efficacy, yet ensuring safety of new peptide hormone combinations. The considerable preclinical development and early clinical testing of multiple new co-agonist candidates raises new optimism for the success of efforts directed at development of novel, improved, efficacious and safe gut-derived therapies.

5

Thyroid cancer – evolving disease and evolving therapy

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Case Report

Mrs L, a previously well 42-year-old-carer, noted a palpable cervical lymph node (LN) in 1995. A fine needle biopsy revealed metastatic papillary thyroid cancer (PTC), confirmed as classical PTC with no evidence of dedifferentiation at total thyroidectomy. Two doses of radioactive iodine in 1995 and 1997 were given, but due to recurrence in the neck without distant metastases, she had six further surgeries from 1997-2012. Subsequent recurrent neck disease was not considered surgically amenable and she had multiple ethanol injections to cervical nodes 2011-14. Thyroxine suppression was maintained with TSH<0.1mIU/L.

Stimulated I^{131} thyroid uptake and FDG-PET scans in 2014 showed non-iodine avid FDG avid lesions in the right level IIA, III, and paratracheal regions, histologically confirmed as metastatic PTC on neck exploration.

In 2015 Mrs L developed a symptomatic 6cm mediastinal mass and lung nodule, with resection via median sternotomy. Histology demonstrated poorly differentiated insular carcinoma arising from classical variant PTC (40% insular), BRAFV600E positive by mutation specific immunohistochemistry, with high mitotic count and involvement of surgical margins (Figure 1). Mrs L then received adjuvant external beam radiotherapy to the neck and mediastinum.

FDG-PET scan post-radiotherapy demonstrated a new lung metastasis, right pleural effusion and new FDG-avid cervical LN. With symptomatic progressive non-iodine avid disease not amenable to further surgery, Mrs L was commenced on compassionate access lenvatinib 24mg daily in January 2016, complicated by hypertension, myalgia, diarrhea and headaches. Despite dose reduction to 20mg and dose interruption, she was unwilling to restart treatment. She had progressive disease which became symptomatic again in April 2017 and she restarted lenvatinib 14mg in November 2017. This was better tolerated at the lower dose, with additional antihypertensives, increase in thyroxine and monitoring of resolving proteinuria. Her disease demonstrated significant reduction at 12 weeks, and Mrs L was maintained at 10-14mg with stable disease on 2-3 monthly imaging.

In December 2018, Mrs L developed haemoptysis. CT revealed invasive LN of the trachea and oesophagus, refractory to lenvatinib treatment. Surgical options were limited as these were within the field of previous radiotherapy. As her original tumour was BRAF mutated, compassionate access to dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) was sought.

Mrs L developed dysphagia in January 2019 due to the rapidly enlarging new mass of confluent adenopathy posterior to the carina compressing the oesophageal lumen (Figure 2a). There was also evidence of new intracranial and pulmonary metastases. An endoscopically guided oesophageal stent was inserted with improvement in dysphagia. She was then able to commence dabrafenib and trametinib therapy in mid-January 2019.

In February 2019 Mrs L presented to hospital with a productive cough and fevers. A CT chest demonstrated a new tracheo-oesophageal fistula adjacent to previous obstruction and aspiration pneumonia (Figure 2b). Elsewhere, Mrs L's mediastinal disease had significantly improved with treatment. Barium swallow demonstrated no apparent leak through the fistula. Mrs L's cough improved with antibiotics and her fistula was managed conservatively after consultation with cardiothoracic surgery, respiratory and gastroenterology.

She re-presented 2 weeks later with an obstructive food bolus and further aspiration pneumonia, and was no longer able to tolerate dabrafenib and trametinib. After the food bolus was relieved via urgent endoscopy, Mrs L was kept nil by mouth including all oral medications, and alternate feeding strategies were sought to improve her deconditioning. Nasogastric feeding was attempted but resulted in aspiration. PEG insertion was attempted but Mrs L developed respiratory failure during intubation for the procedure, with evidence of obstructive tumour within the bronchus. Despite successful extubation, respiratory failure recurred rapidly. Nasendoscopy and CT scan both demonstrated interval development of a large mass of tumour within the trachea with subtotal obstruction in a fortnight (Figure 2c). In discussion with family and Palliative Care involvement, a decision was made to cease active measures. Mrs L passed away shortly thereafter. Post-mortem histology of the obstructing tumour was consistent with anaplastic thyroid carcinoma, BRAFV600E positive (Figure 1).

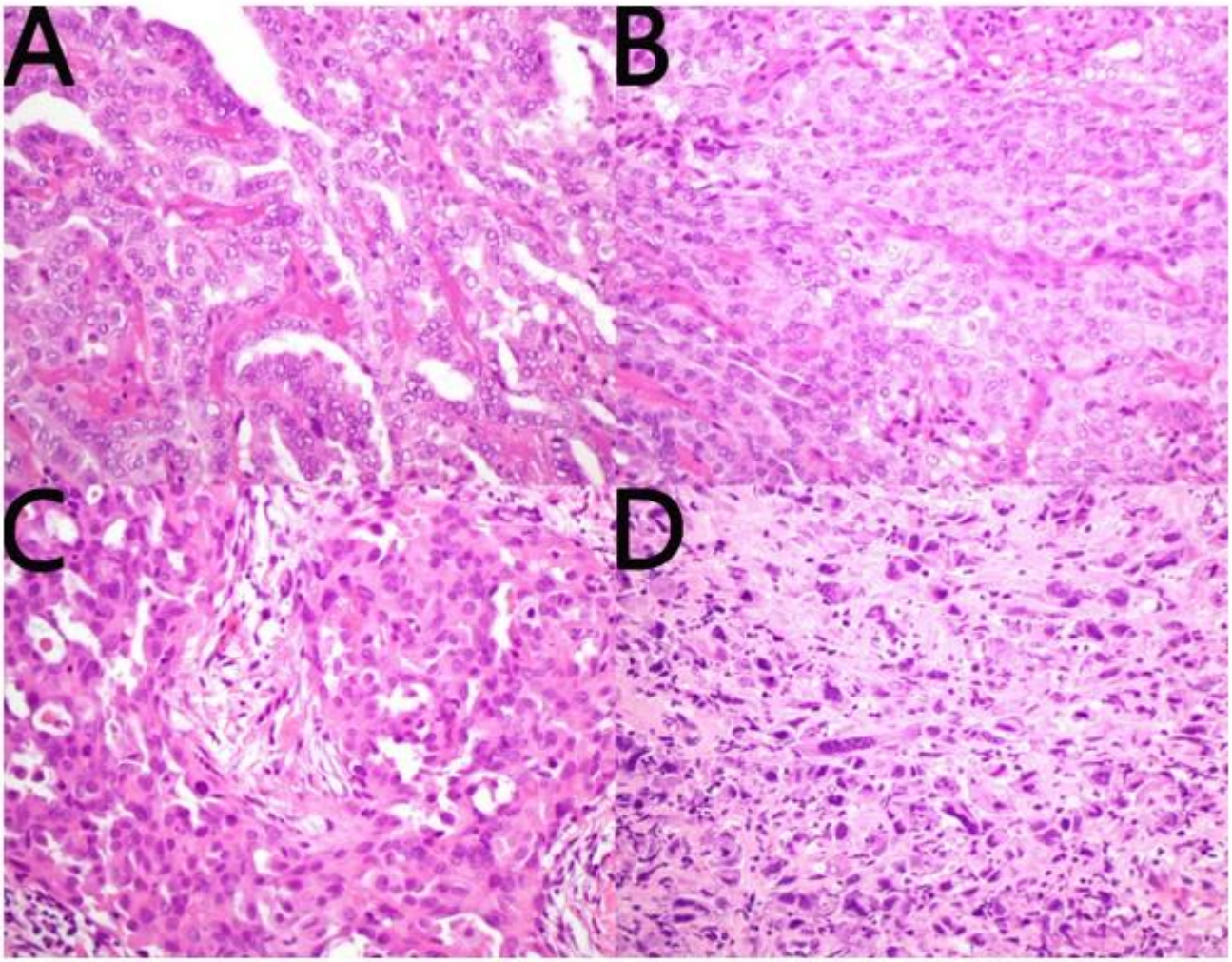

Figure 1. Histological evidence of progression of the tumour from classical papillary carcinoma to anaplastic carcinoma over years. A) Initially the tumour demonstrated classical nuclear features of papillary carcinoma (2015). B) Subsequently the tumour developed a more solid architecture, but maintained recognizable nuclear features of papillary carcinoma and therefore was considered higher grade but not poorly differentiated (insular) carcinoma (2015). C) Subsequently the tumour lost recognisable nuclear features of papillary carcinoma and therefore fulfilled the Turin criteria for poorly differentiated (insular) carcinoma (2015). D) Eventually the tumour showed frank sarcomatous dedifferentiation and therefore fulfilled WHO 2017 criteria for anaplastic thyroid carcinoma (2019). (H&Es, original magnifications 400x).

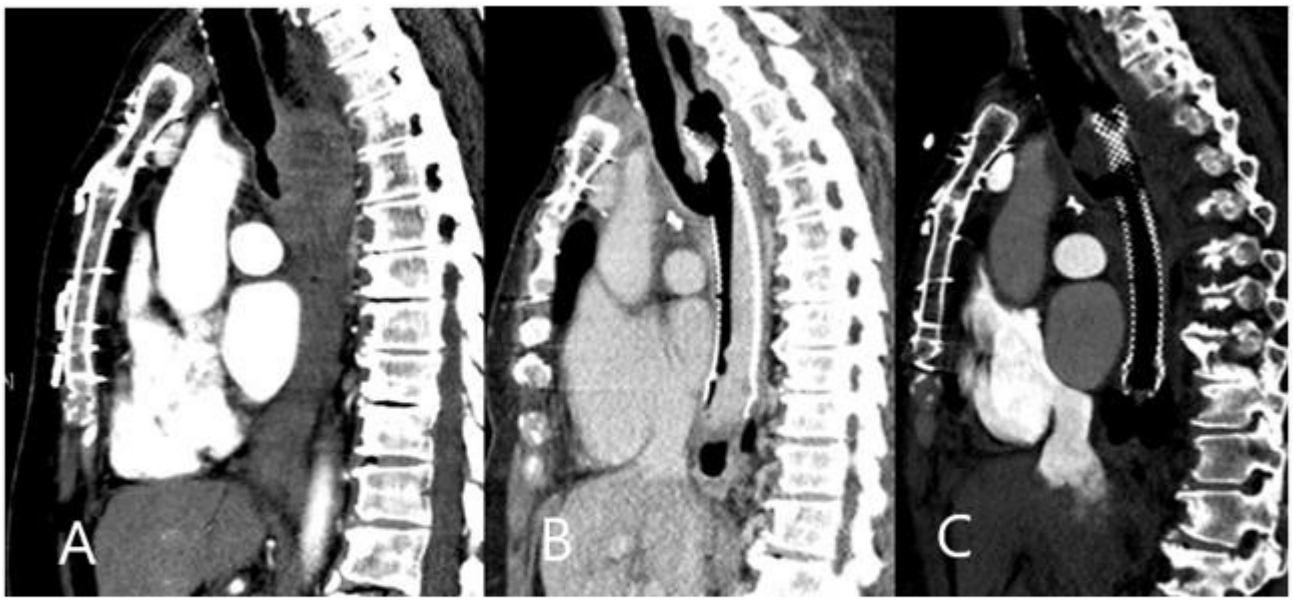

Figure 2. Sagittal CT imaging of fluctuating extent of mediastinal tumour burden. A) CT chest at presentation with oesophageal obstruction secondary to mediastinal disease, on lenvatinib therapy (January 2019) B) CT chest at presentation with tracheo-oesophageal fistula, with interval insertion of oesophageal stent, on dabrafenib and trametinib (February 2019). C) CT pulmonary angiogram at time of respiratory deterioration from tracheal obstruction, off all therapy (March 2019).

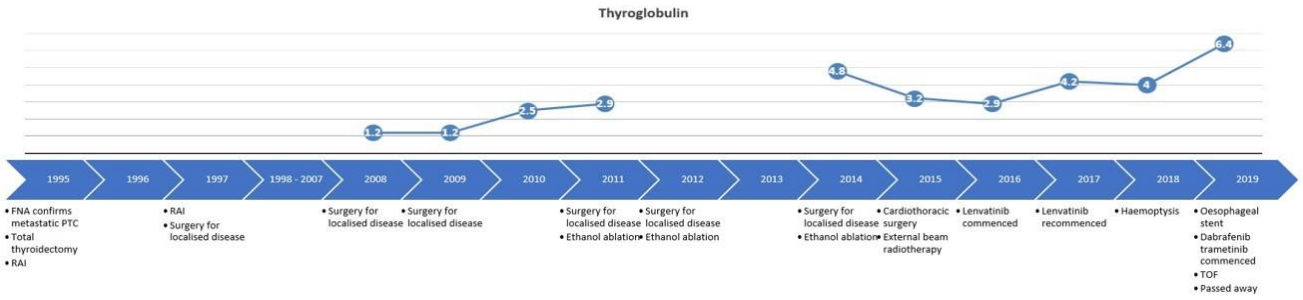

Figure 3. Serial thyroglobulin (ug/L) measurements and summary of treatment

Discussion

Evolution of thyroid cancer

Anaplastic thyroid cancer is amongst the most feared of cancers, portending a median survival of 3-5 months[1]. Although majority of anaplastic cancer arises de novo, 20-25% have a history of differentiated thyroid cancer[2]. Molecular studies support the concept of anaplastic transformation secondary to disease progression from differentiated thyroid cancer. Differentiated thyroid tumours with *BRAF* and *RAS* mutations are more likely to progress to poorly differentiated cancer, although do not appear sufficient alone. Hypothesised 'second hit' mutations include *TP53*, which is mutated in 80% of anaplastic thyroid cancer as well as *PI3K* which is constitutionally activated in 53%[3,4].

Treatment of RAI refractory thyroid cancer

Whilst surgery, RAI and thyroxine with TSH suppression remain the mainstays of treatment for differentiated thyroid cancer, 15% develop recurrent or metastatic disease[5]. Just as our understanding of the evolution of thyroid cancer tumorigenesis is evolving, the treatment landscape for RAI refractory (RAIR) thyroid cancer has changed. Surgery is preferred for treatment of local disease if feasible and given the lack of high quality data on efficacy of ethanol ablation this is generally limited to use in poor surgical candidates[6].

Traditional chemotherapy has little benefit in RAIR thyroid cancer and targeted therapies are increasingly used for systemic therapy. Amongst FDA approved medications for treatment of RAIR disease; only lenvatinib is available on PBS. Lenvatinib is a multi-targeted tyrosine kinase inhibitor with anti-angiogenic properties shown in Phase III trials to improve progression free survival in patients with RAIR cancer[7]. Dabrafenib is a BRAF selective kinase inhibitor shown to improve progression free survival in combination with MEK inhibitor trametinib[8] in treatment of BRAFV600E mutant thyroid cancer in a Phase I trial[10] and anaplastic thyroid cancer in a Phase II trial[9]. Further studies are required to ascertain the role and timing of the expanded suite of available molecular targeted therapy in thyroid cancer.

Balancing the potential efficacy of treatment in progressive thyroid cancer and the adverse effects (AE) of targeted therapy is a major consideration. AE from kinase inhibitors are usually mild to moderate, including hypertension, proteinuria, fatigue, palmar-plantar erythrodysesthesia and diarrhoea, occurring in first 3 months of treatment. In a case series of 3 patients with aerodigestive

fistulae after targeted therapy for RAIR thyroid cancer, all patients had previous radiotherapy or tumour invasion of the trachea[10]. As in this case, the hypothesis is that in a predisposed area of previous surgery and radiotherapy, anti-tumour effect via targeted therapy may lead to rapid tumour shrinkage, anatomical distortion and fistulae formation. Impairment in healing may also occur due to targeted therapy. There may be a window of opportunity during the progression of RAIR cancer wherein targeted therapy is safe, after which disease progression and local organ invasion may lead to devastating consequences once administered.

Take Home Messages

- Thyroid cancer can have variable prognosis, often with a long period of indolent disease. Some may de-differentiate, which portends a poorer prognosis.
- Therapeutic options for RAIR thyroid cancer are changing. RAIR cancer can be amenable to local and systemic approaches. The mainstays of therapy include surgery for localized resectable disease and targeted therapies such as lenvatinib for systemic therapy.
- Although severe adverse events in targeted therapies are rare, they can be devastating as shown in this case. There may be a therapeutic window beyond which the risks of therapy outweigh the benefits.

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6

Saved by the resident! Investigation in the nick of time averts transfer to nursing home care.

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Case presentation:

68 year-old woman was admitted to transitional care in February 2019 with a view to nursing home placement. She had sustained multiple vertebral fractures and an atraumatic pubic rami fracture over the preceding 6 months. Her assessment for osteoporosis revealed vitamin D deficiency with a mildly elevated PTH and normal calcium and phosphate. Her background included long-standing pulmonary nodules that had been stable on serial imaging since 2015. She also suffered from type 2 diabetes, hypertension, obesity and obstructive sleep apnoea. She had a left hemithyroidectomy for follicular adenoma in 1990 and a right hemithyroidectomy for multinodular goiter in 2015.

The admitting resident noted a recent deterioration in blood glucose control on Metformin, with insulin therapy commenced in September 2018. The patient gave a history of 20kg weight gain, progressive immobility and easy bruising over the preceding 12 months, leading the resident to wonder if she may be suffering from hypercortisolism. Full Cushing's syndrome work up was commenced starting with a through examination. Pertinent findings included evidence of noticeable lower limb bruising, female pattern baldness, central adiposity, buffalo hump and moon facies. She had no evidence of purple striae, facial plethora or proximal muscle wasting. Assessment of proximal weakness was difficult due to her severe back pain (Figure 1).

A morning cortisol was 566 nmol/l *[RR: 100 – 540nmol/L]*, prompting a salivary cortisol test (28 nmol/L, *[RR: <8nmol/L]*) and 1mg oral overnight dexamethasone suppression test (566nmol/L *[RR: 100 – 540nmol/L*]). A paired random (1120am) cortisol and ACTH were 698nmol/L *[RR: 100-540nmol/L]* and 136.3ng/L *[RR: 7.2-63.3ng/L]* respectively. The possibility of ACTH-dependent Cushing's syndrome was entertained and the patient was transferred to Endocrinology for further investigation.

Results of confirmatory testing for Cushing's syndrome are presented in table 1. High dose dexamethasone testing with 8mg intravenously at midnight failed to suppress cortisol levels (376nmol/L [reference range: 100-540nmol/L]). Repeat testing with dexamethasone 2mg intravenously 6 hourly for 48 hours noted unsuppressed cortisol (530nmol/L *[RR: 100-540nmol/L]*) and elevated ACTH (81.3ng/L *[RR: 7.2 – 63.3ng/L])*. Corticotrophin releasing hormone stimulation test failed to increment adequately, suggesting an ectopic source of ACTH. Given the history of previous thyroidectomies, a calcitonin level was performed for possible medullary thyroid carcinoma (MTC), this returned markedly elevated at 410pmol/L *[RR: <3pmol/L]*. Histopathology of previous thyroid tissue samples were reviewed and discussed with the anatomical pathologist. Calcitonin staining had been performed on the 2015 right thyroid tissue and the result was negative for MTC. Thyroid bed ultrasound revealed no remnant/abnormal thyroid tissue. MRI brain / pituitary results were normal (Figure 2) and 68Ga-tate PET scan revealed uptake in a conglomerate of enlarged right lower para-tracheal nodes (Figure 3).

The patient was referred for robotically assisted resection of the right mediastinal mass. The patient received perioperative hydrocortisone treatment and her post-operative course was complicated by pain and a further atraumatic vertebral (L2) fracture. On macroscopic examination, histopathology report revealed the specimen contained three discrete nodules (largest 24x27x16mm), normal tracheal adventia, benign hilar lymph nodes and adipose tissue. No thyroid or thymic tissue was evident. Pathologists were unable to differentiate if nodules represented primary or secondary disease, but noted lymphovascular invasion. Tumour foci were seen in lymph nodes. Immunohistochemical staining of nodules were positive for ACTH, calcitonin, TTF1, chromogranin, CD56 and Ki67 index was 4.3%. Initial report concluded a diagnosis of neuroendocrine tumour (NET), likely atypical carcinoid. However, TTF1 staining is more commonly associated with MTC. Given her high pre-operative calcitonin level, a CEA stain was performed as per algorithm for diagnosing neuroendocrine tumours (Figure 4). This returned strongly positive and the pathologists subsequently changed the diagnosis to be supportive of a MTC lesion. Table 2 illustrates patient's post-operative serum markers. Notably the patients' 8am serum cortisol and ACTH were 36nmol/L and ACTH 3.7 respectively, after withholding afternoon hydrocortisone dose the day prior to sampling. Calcitonin level demonstrated a near 40-fold reduction.

The patient was referred to medical oncology and clinical genetics for consideration of treatment options and multiple neoplasia (MEN) syndromes, respectively. Molecular tissue analysis revealed a positive RET Exon 16 variant (c.2753T>C p.(MET918Thr) or M918T variant. The somatic M918T variant is the most common cause of sporadic MTC [2]. Germline genetic testing is presently in progress. The patient was slow to convalesce post operatively, secondary to pain, mobility and glycaemia. Currently, the patient remains on hydrocortisone 20mg BD and is undertaking rehabilitation with a view to discharge to her home.

Discussion:

There are many causes of hypercalcitoninemia.[3] Elevated gastrin stimulates the secretion of calcitonin, thus conditions associated with hypergastrinemia (e.g. gastrinoma) may cause hypercalcitoninemia.[3] Hypercalcemia is a strong calcitonin secreatgogue.[3] Side effects of medications including omeprazole and glucocorticoids have also been associated with hypercalcitoninemia.[3] Neuroendocrine tumours may secrete calcitonin, despite staining negatively for calcitonin on immunohistochemistry.[3] Neuroendocrine tumors co-secreting ACTH and calcitonin are less common.

A systematic review of ectopic ACTH syndrome revealed elevated serum calcitonin level in 44% of patients (including MTC).[4] Calcitonin levels were not specified in this study.[4] A case series by Salgado found 8% of ectopic ACTH syndrome cases had an elevated calcitonin level in the absence of a MTC.[5] Similarly in this study the calcitonin levels were not provided. Isidori

reported 50% of patients with ectopic ACTH syndrome had elevated calcitonin levels varying between the 25-75th percentile (including patients with MTC). [6]
Based on a study of 5817 patients who had serum calcitonin levels sampled Constante et al concluded the risk of MTC was 100% when calcitonin levels exceeded 367pmol/L (table 2).[7] At lower levels the other causes of hypercalcitoninemia should be considered.

In these aforementioned studies of NET causing hypercalcitoninemia, calcitonin immunohistochemical staining strongly positive in cases of MTC only.[4-6] Weakly positive calcitonin was seen in metastatic lung carcionoid and malignant phaemochromocytoma. [4]

In well-differentiated NET staining with TTF-1 is strongly suggestive of MTC, but can also be seen in pulmonary NET. [1] CEA staining can differentiate between the two [1] Diffusely positive CEA is diagnostic of MTC when present with positive TTF-1 and calcitonin. [1]

MTC has been reported to account for 2.2-7.5% of ectopic Cushing's syndrome.[8] Of patients with MTC, 0.7% of them have ectopic ACTH.[8] Only 10% of individuals presenting with MTC have metastatic disease at diagnosis.[8] Recurrence of MTC and ectopic ACTH production with resultant Cushing's syndrome may develop decades after initial diagnosis of MTC and total thyroidectomy.[8] Whilst delayed recurrence from a known previous MTC and newly diagnosed metastatic MTC have been documented, to date there are no reported cases of an extra-thyroid MTC causing Cushing's syndrome in the absence of primary thyroid MTC.

One hypothesis for our patient's presentation includes an unrecognized medullary thyroid carcinoma +/- micrometastasis. However, careful reexamination of histology by pathologists did not reveal suggestion of MTC. An alternate explanation may be that the right paratracheal lesion originated from ectopic thyroid tissue. Aberrant thyroid embryogenesis has been documented to cause ectopic thyroid tissue in the mediastinum.[9]

Take home messages:

- Cushing's syndrome should be considered in patients presenting with multiple vertebral fractures
- In cases of ectopic ACTH consider testing calcitonin level.
- Marked elevation of calcitonin level should raise clinical suspicion of MTC and a level over 367pmol/L is almost diagnostic of MTC.
- CEA and TTF1 immunohistochemical staining are useful markers for differentiating neuroendocrine tumour and MTC

Figure 1: Physical appearance of patient

**Published with permission from patient*

Figure 2: Normal MRI brain and pituitary

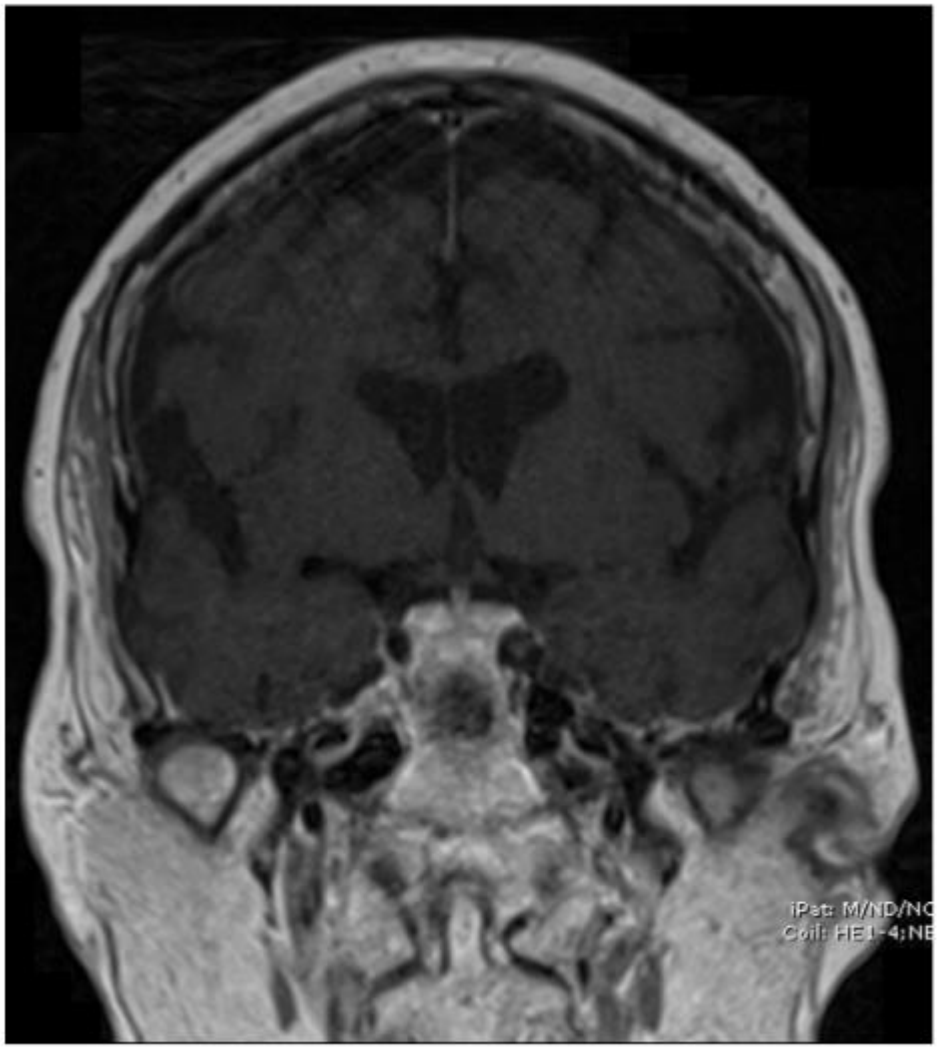


Figure 3: 68Ga-tate PET scan demonstrating right para-tracheal nodes

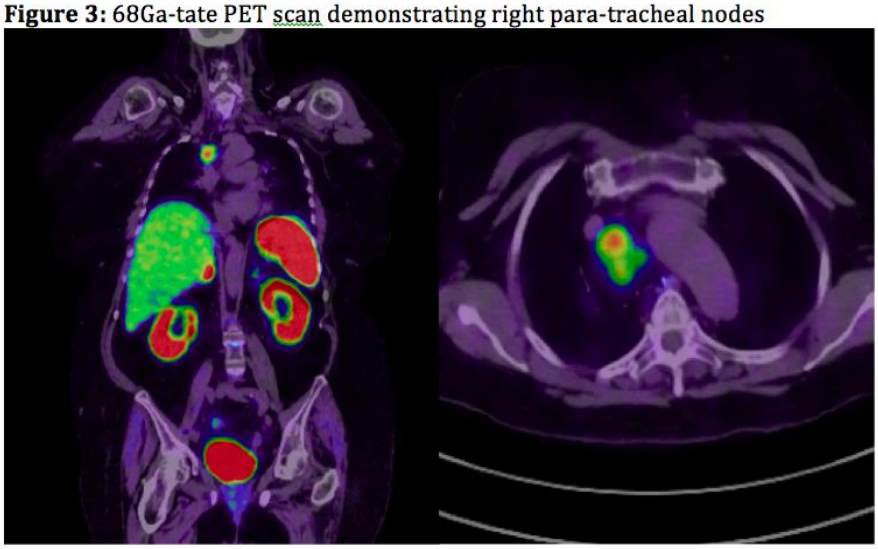
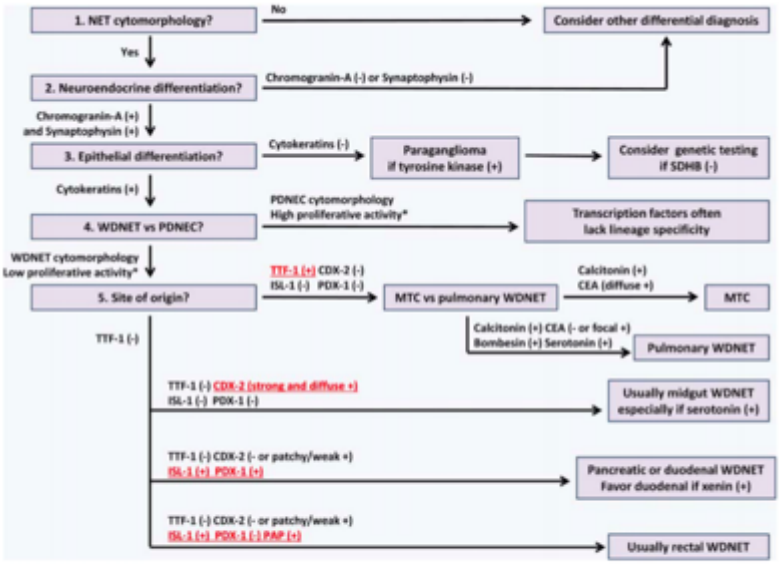


Figure 4: Algorithm for differentiating neuroendocrine tumors



WDNET- well differentiated neuroendocrine tumour
NET – neuroendocrine tumour
PDNEC – poorly differentiated neuroendocrine carcinoma
MTC – medullary thyroid carcinoma

Duan et al, 2016 [1]

Table 1: Cushing's Syndrome confirmatory investigations

	Serum cortisol [100-540 nmol/L]	Serum ACTH [7.2 – 63.3ng/L]
High dose dexamethasone suppression test		
8mg IV (midnight) stat	376 (not suppressed)	
2mg IV QID for 48 hours	530 (not suppressed)	
Corticotrophin releasing hormone (CRH) stimulation test		
Time:		
• - 5 minutes	530	84.3
• -1 minute	526	65.1
• +15 minutes	620	91.1
• +45 minutes	640	96.4
• + 60 minutes	644	94.1
• +90 minutes	607	49.9

Table 2: Post operative investigations

Time	Pre-op	Post operative day and time Day 0 1300	Day 1 0655	Day 2 0800	Day 3 0810	Day 4 0855	Day 7 1115	Day 21	Day 49
Cortisol [100 – 540 nmol/L]	575	476	2019		93	36*			428
ACTH [7.2 – 63.3 ng/L]	69.8	10.3	2.4	2.6	2.7	3.7*			
Calcitonin [<3pmol/L]	410						10.7	11.2	22.9
CEA [<5.0 ug/L]	15.6						7.6	5.1	2.9

** Hydrocortisone dose withheld night prior, blood test taken before morning hydrocortisone dose*

Table 3: Calcitonin values and risk of medullary thyroid carcinoma

Value pg/ml	Value pmol/L	Risk for MTC
<8.5 men, <5 female	< 31 men, < 18 female	Normal
>20 and < 50	> 73 and <183	Low (8.3%)
>50 and < 100	> 183 and <367	Moderate (25%)
>100	> 367	Extremely high (100%)

Modified from Costante et al, 2007 [7]

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7

Pain in the neck - Thinking outside the box

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Case 1–A 69 year-old retired restaurant owner was admitted for resection of a tongue squamous cell carcinoma (SCC) with level II and III cervical lymphadenopathy. Medical history included ischaemic heart disease and paroxysmal atrial fibrillation (AF) diagnosed 2 months previously, managed with amiodarone. He underwent a hemiglossectomy, bilateral neck dissection, tracheostomy, pharyngectomy and marginal mandibulectomy. Histology showed a poorly differentiated SCC, lymphovascular invasion and invasion into skeletal muscle and fat with clear margins (T4N3bM0).

He had a prolonged admission during which he had multiple episodes of AF, however his TSH was normal(0.73 and 2.46mU/L). Amiodarone was ceased after 6 weeks and changed to sotalol. He then developed neck pain and fevers day47 of admission. Repeat imaging revealed a 5cm complex neck mass with associated lymphadenopathy and a new lung nodule. Due to airway patency concerns, he underwent a trachestomy. Biopsy confirmed SCC with no evidence of infection. He was commenced on dexamethasone and Tazocin but continued to have fevers and paroxysmal AF. Thyroid function tests on day 57 showed a TSH of 0.06mU/L, T4 32.5pmol/L(9-19pmol/L), T3 5.1pmol/L(2.6-5.7pmol/L). He was treated for amiodarone-induced thyrotoxicosis with carbimazole and dexamethasone.

His fevers resolved until he was changed to oral antibiotics on day 64. He continued to have progressive neck erythema, pain and worsening neutrophilia (white cell count $40x10^9$/L[$4-12x10^9$/L])**.** Blood cultures and septic screen were negative. Repeat thyroid function showed: TSH<0.01mU/L, T463.6pmol/L, T37.3pmol/L. A CT was requested to investigate for a thyroid abscess(Figure 1) and this showed an increase size of the mass with involvement of right thyroid lobe, sternocleidomastoid and strap muscles and extensive spread to bilateral lymph nodes. The differential included suppurative thyroiditis and malignant pseudothyroiditis given the clinical course and imaging characteristics as well as the notion that painful thyroiditis is not a feature of amiodarone-induced thyrotoxicosis.

Given his prognosis, our patient declined further investigations or management. He died a week later.

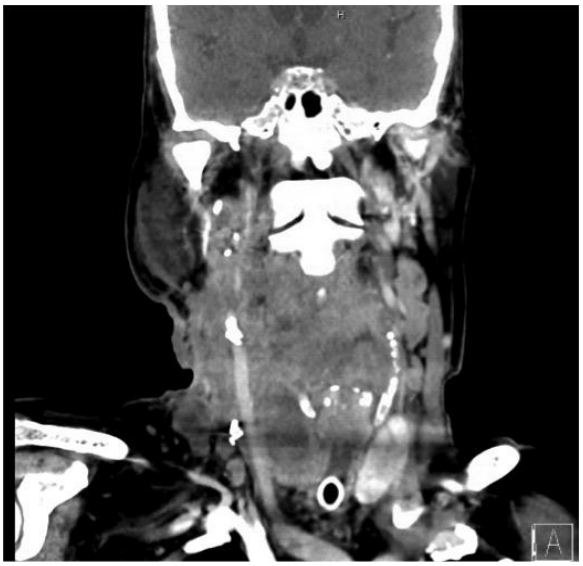

Figure 1

Case 2–A 38-year-old Malaysian builder with no previous medical history presented to the emergency department with a 2-week history of worsening right neck pain associated with odynophagia, fevers, weight loss of 6kg and palpitations. On initial assessment, he was alert and oriented, his temperature was 39.4ºC, with a sinus tachycardia at 120bpm. His right thyroid lobe was enlarged, firm and tender to palpation.

Investigations showed marked thyrotoxicosis with serum free T4 73.8pmol/L (12-22pmol/L), free T3 15.9pmol/L (3.1-6.8pmol/L) and suppressed serum TSH <0.01mIU/L (0.27-4.20mIU/L). White cell count was raised $21.2x10^9$/L ($4-10x10^9$/L) with 78.5% neutrophilia, and ESR was markedly elevated at 92mm/hr (1-10mm/hr). Thyroid ultrasound demonstrated a heterogenous appearance of the right thyroid lobe without increased vascularity, and the possibility of 'mobile material' in this area, reported to be consistent with a large nodule or coalescent nodules with features suggestive of recent haemorrhage without infection. The left thyroid lobe was reported to show small areas of nodule formation which were non-specific. A 99Tc-Thyroid scan showed generalised reduced uptake of 0.7% (normal 1-4%).

He was treated for suspected subacute thyroiditis with prednisolone 25mg daily. Propranolol 40mg three times a day was commenced for tachycardia, and he was admitted for monitoring. There was no clinical improvement. On day 3, a fine needle aspirate was performed of the right thyroid lobe, draining 7ml of frank pus. The diagnosis of suppurative thyroiditis was made and piperacillin/tazobactam commenced. Cultures grew Streptococcus anginosus and mixed anaerobes with normal histology. At no time was his airway compromised. Flexible nasoendoscopy showed no pyriform sinus which is usually associated with left-sided suppurative thyroiditis.

Despite initial improvement on antibiotics, the patient continued to be febrile with increasing enlargement of the right side of his neck and overlying skin erythema. MRI neck on day 5 demonstrated significant enlargement of the right thyroid lobe and additional involvement of the right sternomastoid muscle. (Figure 2).

Surgical exploration revealed a multiloculated abscess in the right thyroid lobe, and a separate abscess in the right sternomastoid, but no evidence of necrotizing fasciitis. He had a further washout and three drain tubes were inserted. Intravenous broad-spectrum antibiotics were continued for 19days, and the surgical drains were removed after 13 days. He became afebrile on day1 post final surgical washout (day4 of antibiotics treatment) and he was discharged on day20 of admission.

Four blood cultures sent prior to antimicrobial therapy demonstrated no growth. Further investigations did not reveal a definitive source for these two abscesses. Despite the patient's poor dentition, no active perioral infection was noted on CT scan and there was no evidence of tonsillitis. Gastrointestinal endoscopies showed no abnormality and liver ultrasound was normal apart from incidental haemangiomas. HIV serology was negative and he had normal glycaemic status.

Figure 2

Discussion

The most common cause of painful thyroiditis is subacute thyroiditis (SAT). SAT is a self-limiting condition that has an incidence of 3-4.9:100,000/year [1], presents in up to 50% with a transient thyrotoxic phase, and which can be treated with anti-inflammatory drugs or glucocorticoids[2]. Clinical response to glucocorticoid in SAT is often dramatic within the first 24-48hours[3].

However, one must consider rarer causes of painful thyroiditis, especially when patients do not improve clinically. Differentials include acute suppurative thyroidits (AST), malignant pseudothyroiditis and traumatic thyroiditis[4].

Acute suppurative thyroiditis (AST) is very rare, comprising 0.1-0.7% of all thyroid disease[5]. As in case2, presentation with neck pain, fever, elevated white cell count, elevated ESR and hyperthyroidism makes it difficult to clinically distinguish AST from SAT. Thyrotoxicosis that can accompany AST occurs in 12% of reported cases, is transient given there is release of preformed thyroid hormones due to follicle disruption[6]. Moreover, both conditions show reduced 99Tc-thyroid scan uptake.

Although ultrasound and CT thyroid may readily identify a thyroid abscess, findings in early stages of inflammation are indistinct. Helpful findings may include fluid around the affected thyroid lobe, heterogenous low-density areas within the thyroid gland and unifocal hypoechoic lesions[7]. Where there is clinical suspicion of AST, thyroid fine-needle aspiration is diagnostic [5]. Initial treatment comprises prompt commencement of broad-spectrum antibiotics and drainage of the abscess either by ultrasound-guided fine needle aspiration, occasionally required multiple times or by surgical washout[5].

Malignant pseudothyroiditis can also mimic SAT with a painful neck, elevated ESR and reduced 99Tc-thyroid scan uptake[8]. Malignant pseudothyroiditis is very rare, with only a few case reports and case series described in the literature. It can be caused by primary thyroid cancers (especially anaplastic thyroid cancer) or secondary from metastases including breast, lung and rectal cancer, among others[9][10][11]. The similarity in presentation to SAT can lead to delay in the diagnosis of malignancy[4]. Malignant pseudothyroiditis carries a poor prognosis.

Only one case has been described to our knowledge of an extra-thyroidal neck malignancy directly infiltrating and causing thyroiditis[9]. In case 1 an FNA would have confirmed the diagnosis of malignant pseudothyroiditis or AST however it was declined by the patient and would have not changed his outcome.

ESA CLINICAL WEEKEND 2019 FULL CASE STUDIES

Take home messages

- SAT is the most common cause of painful thyroiditis.
- AST and malignant pseudothyroiditis can both present similarly clinically, biochemically and radiographically to SAT which may delay diagnosis
- Poor initial response to prednisolone and suggestive findings on thyroid ultrasound should prompt consideration for early fine needle aspiration to exclude AST
- Patients with a history of previous malignancy and a rapidly enlarging painful thyroid, malignant pseudothyroiditis should be considered

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8

A bone to pick with denosumab – the dangers reaching new depths

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Skeletal metastases are common in advanced prostate cancer[1] and can result in skeletal-related events (SRE) such as pathologic fractures, spinal cord compression and pain. Treatment with denosumab has been shown to reduce SRE in men with castrate-resistant prostate cancer[2], with a lower SRE incidence (risk ratio 0.84) and delayed onset to first SRE (risk ratio 0.83) compared to zoledronic acid reported in a systematic review[2]. This oncologic benefit of denosumab is considered to be due to its more potent suppression of bone turnover compared to zoledronic acid, but may also be responsible for an associated increased risk of hypocalcaemia[3]. Previous studies have shown a higher incidence of hypocalcaemia[2-4] and shorter median time to hypocalcaemia[4,5] in patients treated with denosumab compared to zoledronic acid.

Case Presentation

A 59 year old male presented for management of severe hypocalcaemia 4 days following administration of his first dose of subcutaneous (SC) denosumab at the standard dose of 120mg as part of treatment for advanced metastatic prostate cancer.

His prostate cancer was diagnosed 2 months prior, when he presented with non-resolving right hip pain after playing sport. He had no significant past medical history. An MRI revealed a large prostatic malignancy and whole body CT and PET revealed extensive skeletal metastases throughout the spine and pelvis (Figure 4a) in association with an elevated PSA 18.4mmol/L (<3.50). Histology from an iliac bone biopsy confirmed poorly differentiated prostate adenocarcinoma. Carboplatin/Docetaxel-based chemotherapy was commenced, and he underwent transurethral resection of the prostate. Androgen deprivation therapy with Goserelin, a GnRH analogue, was started. Given extensive bone metastases, and a rise in alkaline phosphatase (ALP) from 800 to 1402mmol/L (30–110), there was concern regarding castrate resistant disease, and the patient was given 120mg of subcutaneous denosumab.

Four days later, he presented to the emergency department with widespread paraesthesia, tetany and carpopedal spasm. He also reported diarrhoea for several days preceding presentation. Trousseau's sign was positive after 30 seconds. An ECG showed a normal QTc interval. Albumin-adjusted serum calcium (aaCa) was 1.34mmol/L (2.10–2.60), ionised calcium 0.61mmol/L (1.12–1.30), hypophosphataemia 0.42mmol/L (0.75–1.50) and hypokalaemia 3.0mmol/L (3.50–5.20). In retrospect, he had mild hypocalcaemia preceding denosumab (aaCa 2.18mmol/L), and untreated vitamin D deficiency (23nmol/L). Estimated GFR was >90mL/min/1.73m^2. Serum alkaline phosphatase (ALP) and procollagen type 1 N-propeptide (P1NP) were 1402mmol/L (30–110) and >1200mcg/L (15–80) respectively, in keeping with a high bone turnover state from osteoblastic metastases. Urine calcium was low (1.8mmol/day), consistent with hungry bone syndrome.

He initially received a rapid infusion of 8.8mmol intravenous (IV) calcium gluconate (356mg of elemental calcium), followed by a continuous IV calcium infusion, with Phosphate and potassium replacement. Oral calcitriol, calcium carbonate, magnesium and colecalciferol were uptitrated to maximum daily requirements of 4mcg calcitriol, 9.6g calcium carbonate and 10,000 IU of colecalciferol. Ionised calcium levels stabilised after 72 hours from admission and remained above >1.0mmol/L.

The total duration of IV calcium gluconate treatment spanned 23 days with a net total of 659mmol (26.7g) of elemental calcium infused and 122g of elemental calcium taken orally. A total of 73mcg of calcitriol and 200,000IU of colecalciferol were prescribed.

He was discharged after 24 days with 3mcg calcitriol, 3.6g calcium carbonate and 10,000IU colecalciferol daily. Seven weeks after discharge, he maintained normocalcaemia with 1.2g of calcium carbonate and 2000IU colecalciferol daily.

Following 6 cycles of chemotherapy, ALP nadired to 140units/L. P1NP fell from >1200 to 23mcg/L while CTX nadired to 55ng/L. PTH peaked at 30.3pmol/L and decreased to 4.8pmol/L upon calcium normalisation. A repeat PET scan showed excellent metabolic response (Figure 4b). DEXA revealed elevated spine bone density T-score of 4.4 consistent with osteoblastic skeletal metastases.

Nineteen weeks after the first dose of denosumab, he a test dose of 30mg subcutaneously while on two tablets of calcium carbonate, calcitriol and 2000IU daily of colecalciferol with good tolerance and maintenance of normocalcaemia.

Discussion

Here we report an unusually severe case of denosumab-induced hypocalcaemia in a man with recently diagnosed bone-metastatic prostate cancer necessitating a prolonged hospital admission due to ongoing intravenous calcium requirement despite high dose oral treatment with 1,25-OH vitamin D, colecalciferol and oral calcium supplementation. Risk factors included hungry bone syndrome due to extensive osteoblastic metastases with pre-existing hypocalcaemia, compounded by unrecognized vitamin D deficiency and intercurrent diarrhoea. There was evidence of compensatory secondary hyperparathyroidism. Other recognized risk factors for denosumab-associated hypocalcaemia not present in this case include chronic kidney disease (CKD)[6], hypomagnesaemia[4], and use of glucocorticoids[4].

Comparison to previous cases

We identified a total of 13 published cases of severe denosumab-induced hypocalcaemia (necessitating IV calcium treatment) in men with prostate cancer, all of whom, had skeletal metastases[4, 7, 8]. Previously reported cases were mostly older, had a longer history of prostate cancer, and the majority had received prior bisphosphonate therapy. Nadir serum calcium ranged from 1.13 to 1.90nmol/L. Half of previous cases had renal impairment and five of the 13 patients vitamin D insufficiency (25 OH-vitamin D <50nmol/L). PTH levels were uniformly elevated (12.4 to 57pmol/L) and ALP levels were elevated in the majority (65 – 1387U/L). Unusual features in our case include the unique combination of risk factors including the very high ALP (initially >1400U/L), pre-existing borderline hypocalcaemia and low serum vitamin D (22nmol/L) which likely contributed to the early presentation (4 days after denosumab); in previous case reports, time to presentation ranged from 14 to 106 days. The prolonged requirement for intravenous calcium is one of the longest reported to date, and the total dose of intravenous calcium administered (26.6g) the highest reported to date, ranging from 0.47 to 7.44g in previous reports.

Pathophysiology

Extensive osteoblastic activity (evidenced by the high levels of ALP, the bone formation marker P1NP and consistent skeletal imaging) likely contributed to subclinical hungry bone syndrome, further compounded by underlying vitamin D deficiency. Increased PTH (i.e. secondary hyperparathyroidism), via osteoclast activation, maintained a low-normal serum calcium level. Denosumab, via inhibition of receptor activator of nuclear factor-kappa β ligand (RANKL)[9] potently inhibits this compensatory osteoclast activity, leading to an inhibition of calcium release from bone, and consequently, marked hypocalcaemia. CTX levels,

while not available prior to denosumab, were low on admission, consistent with rapid denosumab-associated suppression of bone resorption. Based on the much slower decline in ALP and P1NP, bone formation (a calcium-requiring process) remained high for several weeks, explaining the ongoing large calcium requirements. With disease control (Figure 1b), calcium requirements reduced, and a second, albeit lower dose of denosumab did not cause hypocalcaemia. The importance of bone resorption in maintaining serum calcium levels in men with osteoblastic metastases from prostate cancer was first recognized in the 1980s, when profound hypocalcaemia associated with oestrogen treatment was reported and postulated to be due to its anti-resorptive actions[10].

Conclusion/Take home messages

- Severe hypocalcaemia can occur in patients with metastatic castrate-resistant prostate cancer treated with denosumab given the necessary predisposing risk factors
- Risk factors for denosumab-associated hypocalcaemia include osteoblastic metastases causing hungry bone syndrome, vitamin D deficiency, hypomagnesaemia, renal impairment and others
- Screening for risk factors of hypocalcaemia is therefore important for its prevention
- Rechallenging denosumab can be done safely with prophylactic calcitriol and colecalciferol supplementation with close monitoring of serum calcium

Table 1: Biochemistry parameters pre and post-denosumab

Variables	Pre-denosumab	4 days post-denosumab
Haemoglobin (130-170 g/L)	132	129
iCa (1.12-1.3 mmol/L)	NA	0.61
Ca (2.10-2.60 mmol/L)	2.01	1.28
aaCa (2.10-2.60 mmol/L)	2.18	1.34
Mg (0.70-1.10 mmol/L)	0.90	0.90
PO4 (0.75-1.50 mmol/L)	1.20	0.42
Vit D (nmol/L)	23	22
PTH (1.6-6 pmol/L)	NA	12.7
Creatinine (60-110 μmol/L)	68	73
eGFR (mL/min/1.73m^2)	>90	>90
Albumin (35-50 g/L)	32	37
ALP (30-110 U/L)	>1400	1402
CTx (100-600 ng/L)	NA	137
P1NP (15-80 mcg/L)	NA	312
24-hour urine Ca excretion (2.5-7.5 mmol/day)	NA	1.8

Table 1: Biochemistry parameters pre and post-denosumab
iCa = ionised calcium, Ca = calcium, aaCa = albumin-adjusted calcium, Mg = magnesium, PO4 = phosphate, PTH = parathyroid hormone, ALP = alkaline phosphatase, CTx = C-terminal telopeptide of type 1 collagen, P1NP = procollagen type 1 N propeptide, eGFR = estimated glomerular filtration rate (Cockcroft-Gault calculation), NA = not available

Figure 1a: Trend of albumin-adjusted calcium (aaCa) and ionised calcium (iCa) over time from admission day

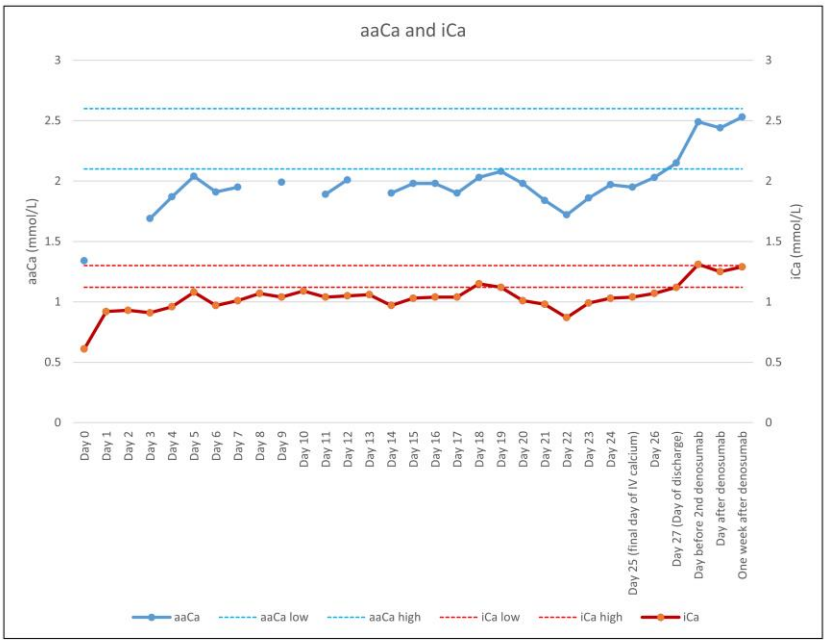
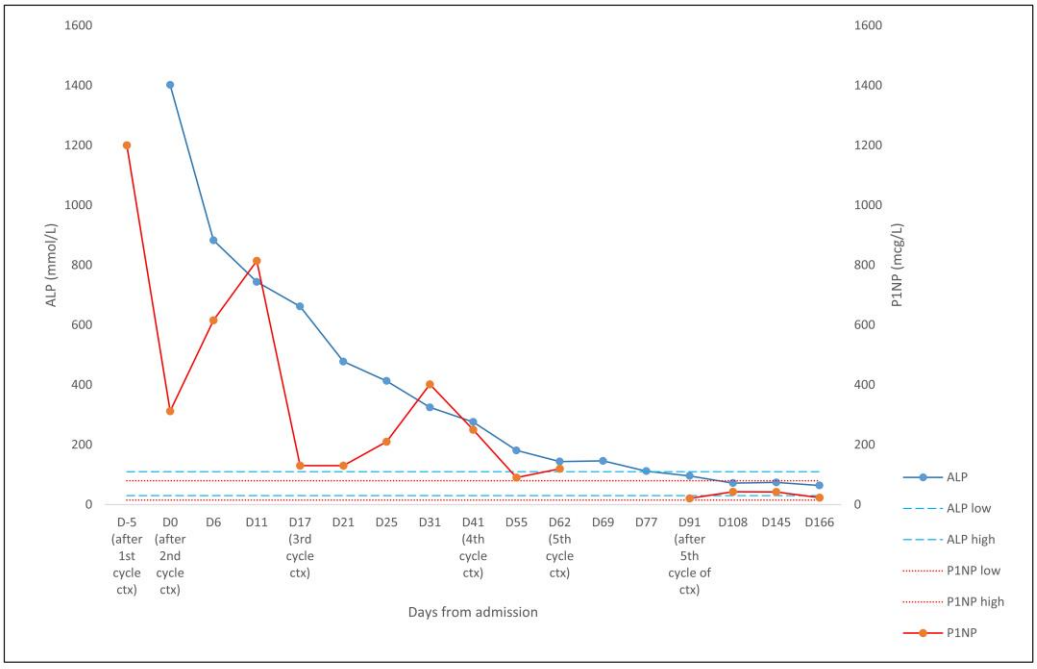


Figure 1b: Trend of ALP and P1NP over time and in relation to chemotherapy (ctx) cycles



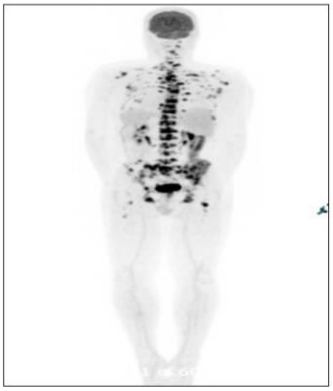


Figure 2a – PET scan before chemotherapy

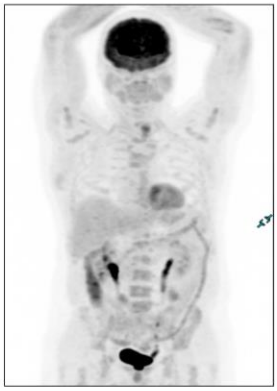


Figure 2b – PET scan after fifth cycle of chemotherapy

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9

Breast cancer in transgender patients- questions about testosterone

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JP is a 44-year-old premenopausal female to male transgender (FtM) individual referred to our endocrinology department for hormonal gender transition therapy, on the background of long standing gender dysphoria. JP's past medical history was unremarkable, and his family history unknown. Baseline blood tests and hormonal panel was normal.

He was commenced on 1000mg IM testosterone undecanoate 3-monthly. Two months after commencing on testosterone therapy, JP was referred to a plastic surgeon for consideration of chest reconstructive surgery. He was noted to have some thickening in the left breast and underwent diagnostic investigation with mammography, ultrasound and core biopsy. Core biopsy showed invasive ductal carcinoma. He proceeded to have a left mastectomy and axillary node clearance. Histology revealed 25mm BRE grade 2 invasive ductal carcinoma. ER+ >95%, PR+ >95%, Her2- >10% weak staining. Ki 67<10%. 3/10 lymph nodes had macrometastases. CT chest, abdomen and pelvis and bone scan showed no distant metastases. An echocardiogram and DEXA scan were normal.

Given treatment with exogenous testosterone, an androgen receptor (AR) assay was performed, which revealed strongly positive expression >95%. Serum total testosterone was within normal male range, and serum estradiol was in the low-normal range for females. At this time testosterone injections were ceased, as it was though that this might further drive tumour proliferation. After cessation of testosterone JP experienced deterioration in mental health with suicidal ideation, and expressed a strong desire to restart hormonal therapy. Although there was limited evidence to support or oppose the possibility of testosterone therapy causing breast tumour proliferation, after lengthy discussion with the patient regarding possible risks testosterone therapy was restarted. He was recommenced on topical testogel 25mg daily- aiming for a lower dose to attenuate higher doses being aromatized to estradiol.

Table 1:*hormonal assay results pre- and post-commencement of testosterone therapy*

	Pre-testosterone	**2 months post-commencement testosterone**	**2 weeks after recommencement of testosterone**	**Reference range (adult premenopausal female)**	**Reference range (adult male)**
Total testosterone(nmol/L)	1.3	12.5	25.4	0.3 –1.9	10.0 – 31.0
FSH (IU/L)	37			1 – 20	1 – 10
LH (IU/L)	82			1 – 100	1 – 10
Oestradiol(pmol/L)	820	>587	193	70 –1300	50 – 150

JP delayed adjuvant chemotherapy in favour of having a prophylactic right mastectomy. He then underwent adjuvant chemotherapy followed by radiotherapy. Given the ER positive nature of the cancer, hormonal therapy was recommended and tamoxifen versus total abdominal hyersterctomy and bilateral salpingo-oopherectomy (TAHBSO) then aromatase inhibitor (AI) therapy was discussed. JP's preference was for TAHBSO with AI therapy, which he is currently awaiting.

Discussion

One major issue raised during this case is whether testosterone therapy would accelerate breast cancer growth, or whether it is associated with a higher risk of breast cancer.

There have been fewer than 20 cases published in the literature of breast cancer occurring in female to male transgender individuals on testosterone therapy (1-8). A recent systematic review revealed 8 articles, with 17 documented cases of female to male breast cancer (9). The majority of cases were ER receptor positive. Very few cases tested for androgen receptor positivity. Two studies looked at a large number of transgender patients (both MtF and FtM), most who underwent hormonal therapy, and found the incidence of breast cancer to be within age standardized national norms for natal males (1,5). There were similar findings were in a recent Dutch cohort study, with overall incidences of breast cancer in the transgender cohort being lower then the general female population (13).

Breast cancer cases occurred at earlier ages in these patients than the general population- median 44.5 years compared to the natal female median age of 62 years, as well as after relatively short duration of hormonal therapy 5-10 years (1,3,4,9). However, this is in contrast to our patient who was only treated for a few months.

The association between higher estrogen levels and breast cancer development is well established, but it is not clear yet what the role of testosterone is in the pathophysiology of breast cancer. Some studies have proposed a link between higher circulating androgen levels and development of breast cancer. Two proposed mechanisms of excess androgen-related breast cancer development include aromatization of testosterone to estrogens in peripheral tissues and the activation of androgen receptors, which leads to cellular growth and proliferation, particularly in mammary tissues (8,14,15).

Circulating testosterone can be converted to dihydrotestosterone by 5 alpha-reductase or to estradiol by the aromatase enzyme (3). Administered testosterone is partially aromatized to estradiol, and serum estradiol levels do not decrease substantially as a result of testosterone treatment of FtM persons- they generally remain in normal to low normal range (13).

Another mechanism of testosterone's stimulatory effect is through the direct activation of the androgen receptors (ARs). ARs are widespread in normal mammary tissue and in the majority of breast cancer cell lines (3,7). AR is expressed in >70% of breast cancers, however the role of AR in breast cancer remains uncertainas a predictive or a prognostic factor and the clinical significance of its expression in breast cancer patients is unclear. However it does appear to have a somewhat more favourable prognosis (12).

Conversely, in mice breast cancer models and in vitro studies, androgen action is antiproliferative and proapoptotic, and is mediated via the androgen receptor, despite the potential for testosterone and dehydroepiandrosterone to be aromatized to estrogen (11).

Several studies have looked at the association between plasma androgen levels and risk of breast cancer with conflicting results. Key et al (10) showed that a pooled analysis of 9 prospective studies in postmenopausal women found a strong association of breast cancer risk with serum concentration of testosterone. Conversely, subgroup in Womens Health Initiaitve did not show increased breast cancer rate in those treated with estrogen and testosterone (15). However these studies were all in postmenopausal women, and there is very limited data on premonopausal women and transgender individuals.

Although adequate androgen replacement is necessary to preserve both patient's reassigned gender and masculinity, these benefits must be balanced against the theoretical risk that androgen therapy may promote recurrence of their breast cancers.

Another question is regarding optimal hormonal therapy after breast cancer in transgender FtM, while on testosterone therapy. Aromatase inhibitors (AIs) may mitigate the conversion of exogenous testosterone by inhibiting aromatization. Inhibition of peripheral aromatization of adrenal androstenedione to estradiol minimizes circulating estrogens in postmenopausal women but the efficacy of aromatase inhibitors in the presence of exogenous androgens has not been well studied (3,4).

Another consideration in our case is the ethical dilemma balancing uncertainty regarding ongoing cancer risk and treatment with testosterone versus the patient's wishes to continue testosterone therapy. This highlights the fact that patients have the right to informed decision-making, even in the face of clinical uncertainty. From JP's perspective, the psychological ramifications in relation to his gender dysphoria outweighed the potential risks for cancer proliferation or recurrence.

This case raises numerous points of consideration:

- Effect of testosterone therapy on breast cancer risk in FtM transgender- potentially increased risk
- Significance of androgen receptor positivity in breast cancer
- Continuing testosterone therapy post breast cancer and recurrence risk
- Hormonal therapy after breast cancer in the presence of testosterone therapy
- Complexity in biopsychosocial management of transgender individuals

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10

Throwing the Kitchen Sink at Thyroid Cancer

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Case

SS is a 59-year-old woman who presented with a rapidly-growing neck lump in 2016. Thyroid ultrasound demonstrated a large heterogeneous area in the right lobe with multiple hypoechoic areas. FNA was suspicious for poorly differentiated thyroid carcinoma (PDTC). She underwent total thyroidectomy with right central neck dissection at a secondary hospital in November 2016, revealing a 49mm PDTC with extracapsular invasion, extrathyroidal extension into anterior fibrofatty tissue and extensive lymphovascular invasion with 8/19 lymph node involvement (pT3pN1a).

Post-operative positron emission tomography (PET) revealed two hypermetabolic neck nodes and a large fluorodeoxyglucose (FDG)-avid mass involving the upper right lobe of the liver with two satellite foci. Given the potential for two separate malignancies, she was referred to the upper GI surgical team of our hospital, where she underwent right hemihepatectomy and wedge of segment 4 lesion in December 2016. Histopathology confirmed thyroid origin, demonstrating anaplastic thyroid carcinoma (ATC) with a small area of PDTC. Retrospective independent review of her thyroid histopathology corroborated diagnosis of PDTC but there was a small area displaying anaplastic features (BRAF negative). PET in January 2017 showed no evidence of FDG-avidity in the residual liver. However, there was increase in size and metabolism of neck nodes, right supraclavicular fossa node, left fifth rib and T3 vertebral body.

She was subsequently referred to the endocrinology team and underwent 200mCi I-131 therapy in March 2017. Post-therapy scan showed uptake in the thyroid remnant, thoracic spine, posterior right flank and posterior to the hepatic flexure, potentially reflecting the PDTC component of her disease. PET in April 2017 (Fig. 1) confirmed disease progression, with increase in size of existing lesions, new lymph nodes, new metastasis in the right middle lobe (RML) and new rib involvement.

SS was commenced on lenvatinib 24mg in April 2017. Two month progress PET (Fig. 2) showed partial response with neck nodes being smaller and less FDG-avid and rib and T3 lesions no longer FDG-avid. The RML lesion remained FDG-avid. Significant adverse effects including tiredness, diarrhoea, proteinuria (grade 3), hypertension (grade 3) and palmar-plantar erythrodysaesthesia syndrome (PPES) (grade 2) necessitated multiple temporary 2-4 day dose interruptions and gradual reductions down to 14mg between August 2017 and April 2018, but progress imaging during this period indicated continued response.

Unfortunately, PET in June 2018 (14 months post-commencement of lenvatinib, 9 months on 14 mg) was suspicious for reactivating disease, with increased metabolism of lung lesions, new subcarinal node involvement and return of FDG-avidity in neck nodes.

SS sought opinion from and underwent bilateral radical neck dissection under the care of an overseas surgeon in August 2018, with a 5-week perioperative suspension of lenvatinib. 8/51 nodes demonstrated ATC. Imaging in October 2018 (Fig. 3) was consistent with disease progression in context of lenvatinib suspension, with extensive metabolism throughout right-sided pleura and subcarinal lymph nodes and new rounded cavitating lesions in the left lung in January 2019. She developed right-sided pleural effusion and cytology was consistent with metastatic ATC.

Her unstimulated thyroglobulin levels (unstimTg) reflected disease activity, with a peak of 594µg/L pre-hepatectomy, likely reflecting PDTC component of her hepatic metastases, decreasing to 3.26µg/L post-operatively, climbing to 19.2µg/L at time of disease progression in July 2018 and increasing further to 130µg/L following the period of lenvatinib suspension.

Given disease progression and dose-limiting toxicities of lenvatinib, SS was commenced on self-funded pembrolizumab in combination with lenvatinib 14mg in February 2019. Most recent PET in April 2019 was suggestive of sarcoid-like changes with increased metabolism in hilar and mediastinal nodes. It is currently unclear if these reflect treatment-related changes or progressive disease. She remains alive and highly functional (ECOG 0) 54 months following diagnosis of stage IVC PDTC/ATC.

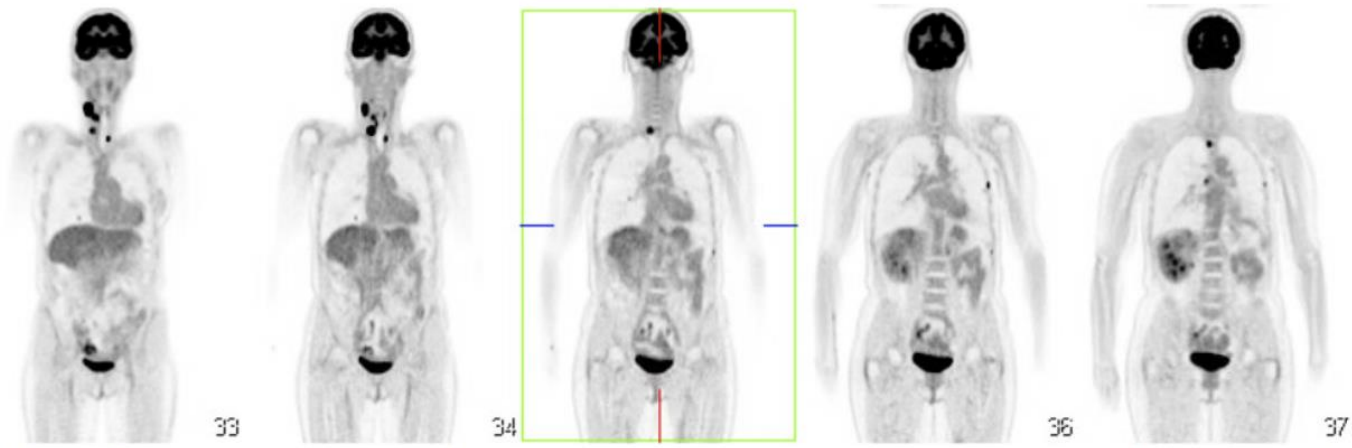

Figure 1: Disease progression in April 2017, involving 20mm right level III node, new node at level of hyoid bone, right level IV node, left superior mediastinal paratracheal node, subcarinal node, T3 vertebra, left fifth rib, left ninth rib and right middle lobe of lung.

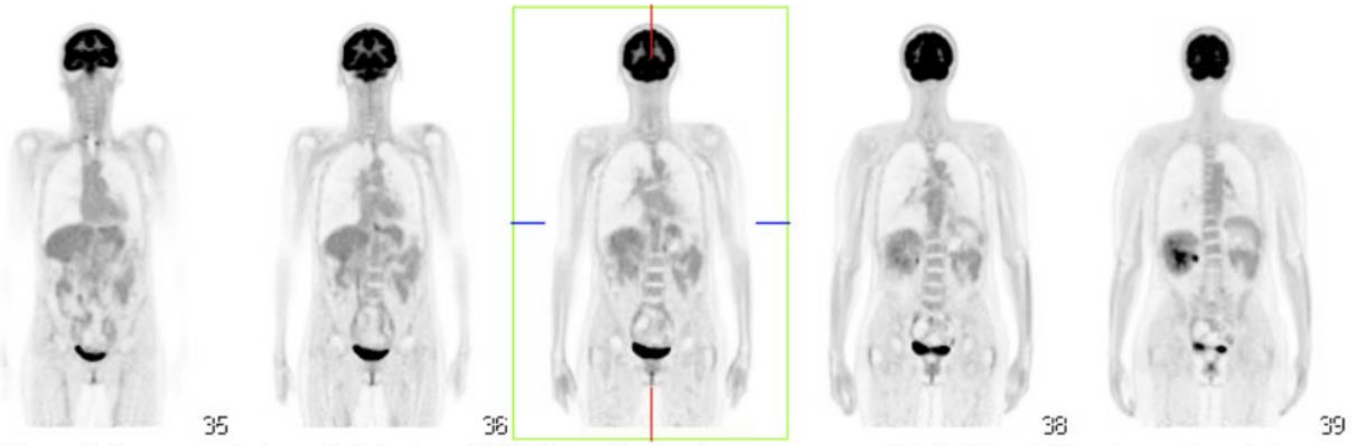

Figure 2: Response to lenvatinib in June 2017 (2 months post-commencement). Right level III node smaller at 5mm and less avid (SUV 6.8, previously 68.1), smaller neck nodes no longer evident, right paratracheal (SUV 10.4, previously 58.1) and left paratracheal nodes smaller and less avid (SUV 13.4, previously 62.3). T3 and rib lesions no longer glucose avid. Right middle lobe lesion still evident.

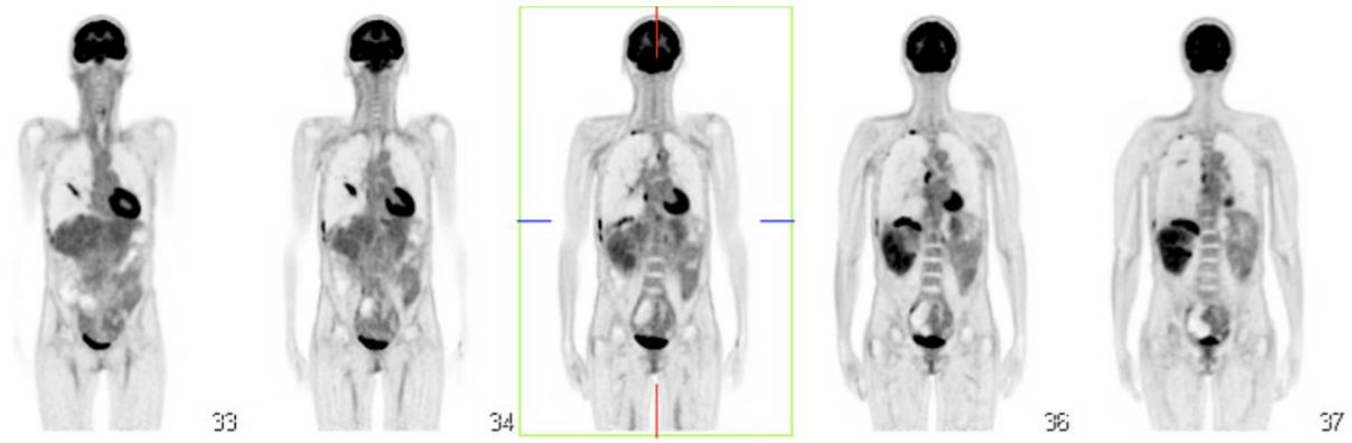

Figure 3: Disease progression in October 2018 in context of lenvatinib suspension. Extensive increased metabolism in right pleura with pleural effusion, increased subcarinal metabolism and new AP window node involvement

Discussion

This case highlights the extended survival of a patient with metastatic PDTC/ATC, with prolonged response to lenvatinib followed by use of combination pembrolizumab and lenvatinib.

Targeted therapy with tyrosine kinase inhibitors (TKI) has shown promising results. Lenvatinib, a multi-targeted TKI, is used for treatment of radioiodine refractory DTC based on the SELECT trial, which demonstrated significant prolongation of progression-free survival (PFS) (18.3 vs 3.6 months, hazard ratio 0.21, P<0.001) (1), with durability of responses to a median of 30 months confirmed on follow-up analysis (2).

The role of lenvatinib in ATC remains unclear. A phase 2 study assessing safety as the primary outcome reported an overall response rate (ORR) of 24%, disease control rate (DCR) of 94%, median PFS of 7.4 months (95% CI 1.7-12.9) and overall survival (OS) of 10.6 months (95% CI 3.8-19.8). However, the majority (70.6%) had discontinued lenvatinib prior to study completion due to disease progression (3). A retrospective study of 23 patients with ATC receiving lenvatinib was less promising, reporting ORR 17.4%, DCR 43.5% and OS 5.5 months (4). Phase 2 studies assessing efficacy as the primary outcome have been mixed, with one being terminated and the results of another (HOPE trial) pending (5). It is possible that certain subsets of ATC may be more likely to demonstrate response. In our case, the histopathology, I-131 uptake and fluctuation in unstimTg with disease activity suggest that the PDTC component may have contributed to prolonged response.

Almost all patients experience treatment-related adverse effects, with the most common in SELECT including hypertension, gastrointestinal toxicity, PPES and proteinuria. These can usually be managed with dose modifications but led to discontinuation in 14% (6). Given its anti-angiogenic effect, lenvatinib is usually withheld at least one week preoperatively but the minimum safe duration of suspension remains unclear, with recommencement needing individualisation and recognition of the potential for rapid disease progression off therapy.

There are no established therapeutic options when there is disease progression on TKI. PD-1/PD-L1 pathway-targeting immunotherapy has revolutionised treatment of many solid-organ cancers and PD-L1 has been shown to be highly expressed by ATC in contrast to DTC (7,8). A retrospective study in which 12 ATC patients received pembrolizumab upon progression on TKI reported 5 (42%) and 4 (33%) patients with partial response and stable disease respectively, with median PFS of 3.0 months and OS of 5.6 months after its addition. Notably, 3 patients showed complete response in distant metastases and were alive over 12 months since addition of immunotherapy (9). There are multiple active phase 2 trials evaluating the efficacy of pembrolizumab either as mono or combination therapy (5). Pseudoprogression is a recognised phenomenon, with new or enlarging lesions mimicking disease progression due to immunotherapy inciting inflammatory responses (10).

This case illustrates durable response of metastatic PDTC/ATC to lenvatinib, with continued response until 14 months. Rapid radiological progression was observed after this, but in context of 5-week perioperative suspension. Treatment was complicated by dose-limiting toxicities. Addition of pembrolizumab to lenvatinib has demonstrated promise but given the potential for treatment-related inflammation, true disease response to combination therapy remains to be seen.

Learning points

- Lenvatinib has shown promise in improving PFS in radioiodine refractory DTC but benefit in ATC is unclear
- Lenvatinib toxicities include hypertension, proteinuria, gastrointestinal and anti-angiogenic effects, often necessitating dose interruptions and reductions
- Optimal duration of perioperative suspension of lenvatinib is unknown but prolonged suspension is associated with rapid disease progression
- Potential role for PD-L1-targeting immunotherapy such as pembrolizumab in ATC is being investigated
- Imaging following commencement of immunotherapy can demonstrate pseudoprogression due to induction of an inflammatory response

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11

Cushings and conception – a novel approach

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We present a case of a 33-year-old lady with synchronously identified recurrence of Cushing's disease (CD) and early pregnancy. She was treated with cabergoline from 9 weeks gestation, which effectively stabilised her condition.

The patient presented initially in January 2015 with some features of Cushing syndrome (CS).

Unfortunately she was lost to specialist follow-up from May 2015. She was re-referred in December 2016 after suffering a L4 vertebral compression fracture and requiring surgical management of a non-healing, infected left foot wound.. She had central adiposity, violaceous abdominal striae and buffalo hump. Biochemical evaluation was suggestive of ACTH dependent Cushings syndrome (table 1). Her clinical course was fulminant, presenting to .the Emergency Department in January 2017 with florid psychosis, hypertension, bruising and breakdown of the foot wound, necessitating treatment be commenced prior to investigations into cause being completed. Treatment with metyrapone and ketoconazole achieved rapid normalisation of 24h urine free cortisol (24h UFC) and resolution of psychosis followed. 2T pituitary MRI, whole body CT and Ga Dotatate scan did not reveal the source of cortisol excess. Additional healing fractures were identified in multiple ribs, the T7 vertebral body and the left ilium. Zoledronate infusion was administered 2 months later after planned dental treatment.

	Jan-Feb 2015	Jan-Feb 2017	Oct-Nov 2018	Reference
Cortisol post 1mg ODST (nmol/L)	606	1000	610*	<50
Cortisol post 8mg ODST (nmol/L)	5.9	840		
Late night salivary cortisol (nmol/L)	13 12	110	17	<5.7
24h UFC (nmol/day)	540	1800	600 880	<330
ACTH (pmol/L)	3.6	30.9	13.4	2.0-10.0

Table 1; *Biochemical evaluation at initial evaluation in 2015, presentation with florid Cushing's syndrome in 2017, and at recurrence during 1st trimester pregnancy in 2018. Multiple values are included where a test was repeated in the relevant time period. *Note – serum total cortisol values during pregnancy may be raised due to effect of pregnancy related increase in CBG.*

Inferior petrosal sinus sampling demonstrated maximum central to peripheral ACTH gradient of 7.7, confirming a pituitary source of ACTH excess. A 3T Gadolinium contrast pituitary MRI demonstrated a 2mm well circumscribed pauci-enhancing focal lesion to the left of the pituitary stalk.

No adenoma was identified on endoscopic transsphenoidal surgery in May 2017. Central and four quadrant biopsy demonstrated normal pituitary tissue. On an admission for epistaxis two weeks following surgery, the patient was found to have symptomatic hypocortisolemia which persisted after cessation of adrenal enzyme blockade.

The patient remained in remission from CD with ongoing need for glucocorticoid replacement over the next 16 months (see table 2), although serial ACTH and morning cortisol suggested gradual HPA axis recovery.

	May 2017	July 2017	Sept 2017	Nov 2017	Feb 2018	May 2018	Sept 2018
Morning cortisol (nmol/L)	<20	21	41	99	140	190	400
Cortisol post synacthen (nmol/L)					290 at 30 mins 350 at 60mins		
ACTH (pmol/L)	3.0		4.1	5.3	6.1	7.1	

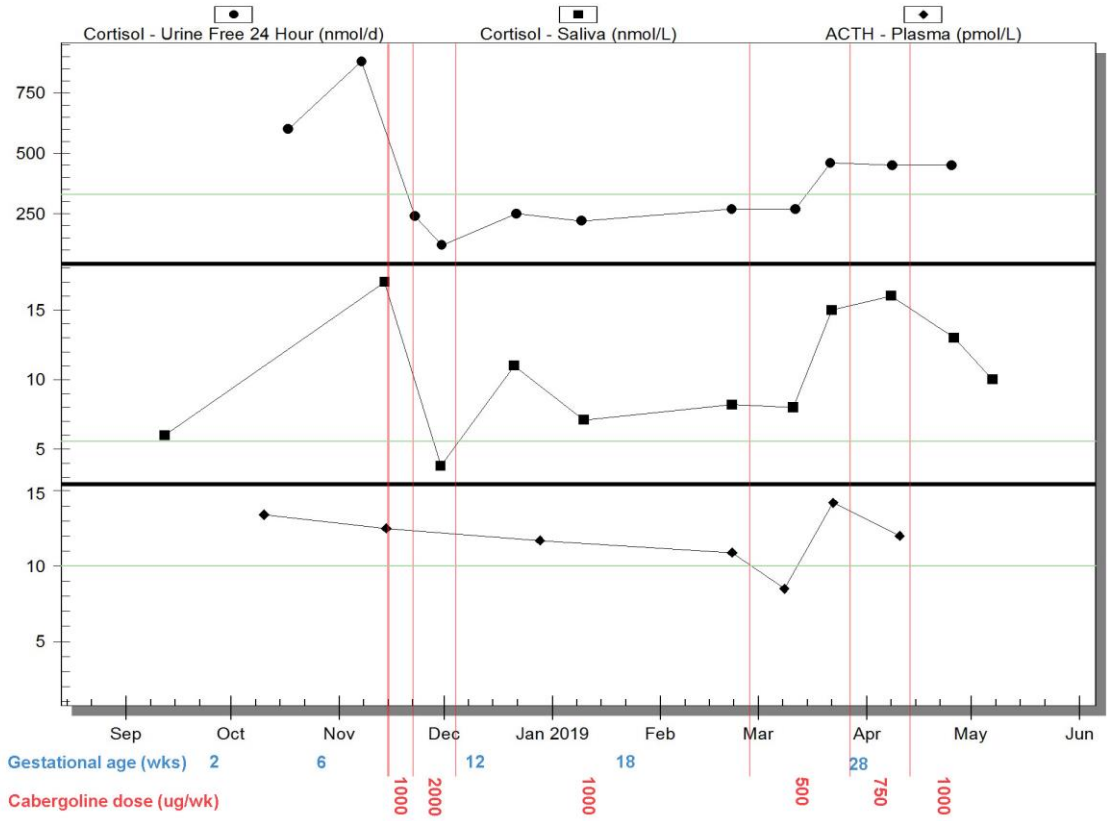
Table 2; *Biochemical evidence of central adrenal insufficiency with gradual recovery after trans-sphenoidal surgery in May 2017.*

In September 2018.the patient had experienced 4kg of weight gain, and had normalised early morning cortisol levels and elevated late night salivary cortisol (LNSC). Menses remained regular in the absence of hormonal contraception. The patient expressed a desire for more children and was advised to cease hydrocortisone and avoid pregnancy until her CD was further managed.

Further investigation demonstrated elevated 24h UFC and unsuppressed 1mg overnight dexamethasone suppression test (ODST) (see table 2) and a pituitary MRI remained normal. At follow-up, early pregnancy was suspected due to amenorrhoea, and confirmed on ultrasound with gestational age of 6.3 weeks. Her blood pressure was normal but oral glucose tolerance test in the first trimester confirmed GDM. Previous pregnancies in 2010 and 2012 were complicated by gestational diabetes (GDM) and gestational hypertension (GHT).

Given the early stage of her pregnancy and the morbidity of total hypophysectomy, a decision was made in conjunction with the patient to trial cabergoline before initiating metyrapone. In mid-November, at 9 weeks gestation, the patient commenced Cabergoline at 1 mg/week in divided doses for the first week to ensure tolerability, progressing 2 mg/week thereafter. 24h UFC normalised within 2 weeks of initiation. Dosage was titrated to a target 24h UFC in the high-normal reference range*(figure 1)*. Her GDM remains diet controlled. Estimated foetal weight by ultrasound at 30 weeks is at the 18thcentile.

Figure 1; 24 hour urine free cortisol, late night salivary cortisol and plasma ACTH throughout pregnancy



Discussion

Plasma cortisol is difficult to interpret during pregnancy due to physiological elevation of corticosteroid binding globulin (CBG). Urine and salivary cortisol are not affected by CBG and are therefore more reliable in pregnancy. In normal pregnancy HPA axis activation via placental CRH and ACTH increase 24h UFC in the 2ndand 3rdtrimesters to 1.4-1.6x the non-pregnant reference range(1). LNSC is reliable using either non-pregnant reference ranges(2), or slightly adjusted ranges after the first trimester(3).

Although extremely rare, active CS during pregnancy is associated with excess risk of maternal and foetal complications. Foetal loss is reported in 24% of cases, with significant foetal morbidity in 33%(4). Risk of pregnancy related complications are high; GDM in 37%, GHT in 41% and preeclampsia in 26%(4). Maternal mortality, osteoporotic fracture and psychiatric decompensation have been reported less frequently(5).

Active CS during pregnancy warrants close monitoring and treatment for complications including GDM and GHT. Additional medical or surgical options to treat cortisol excess should be considered. The optimal treatment strategy is unclear due to rarity and heterogeneity of CS in pregnancy.

Several authors have advocated for surgical cure where possible as first line treatment for active CS during pregnancy(5, 6). The optimal timing for surgery is during the second trimester; balancing risks to organogenesis against maternal risk from increased physiological demands in late pregnancy. Unilateral adrenalectomy for adrenal adenoma or pituitary adenectomy for CD account for the majority of reported surgical cure of CS in pregnancy(4). Bilateral adrenalectomy has been described during pregnancy for CS due to bilateral adrenal disease and could be considered for CD(6). Total hypophysectomy during pregnancy has not been reported for CD, but has historically been reported for other indications with successful pregnancy outcomes.

Metyrapone is the most frequently reported medical treatment for CS in pregnancy but carries a risk of iatrogenic maternal adrenal insufficiency. Accumulation of deoxycorticosterone leading to mineralocorticoid excess may potentially exacerbate GHT or pre-eclampsia. Finally, metyrapone crosses the placenta and may potentially affect foetal steroidogenesis. Ketoconazole, the other commonly used agent for adrenal enzyme blockade, is teratogenic – reported use in pregnancy is limited to where metyrapone was unavailable(1, 4, 6).

Cabergoline can achieve and maintain remission of persistent CD after surgery in 40% of patients followed over 2 years(7). Doses required are typically higher than for prolactinoma (median 3.5mg/week). In pregnancy, cabergoline has a favourable safety profile in the prolactinoma population. There are three reported cases of cabergoline use during pregnancy to treat recurrent CD after surgery. In one, the relevance of cabergoline was unclear as ongoing active CD was not established at transition from ketoconazole to cabergoline despite prior pituitary radiotherapy(8). In the remaining two, patients declined further surgery or radiotherapy and were commenced on cabergoline before conception. Ongoing control of CD was demonstrated throughout pregnancy with serial 24h UFC. The doses of cabergoline required to maintain remission were 9mg/week and 3.5mg/week before

pregnancy, and 10mg/week and 2mg/week respectively by the end of pregnancy. Pregnancy carried to term without complication in both cases(9, 10). Breastfeeding will likely not be feasible post partum with continuation of cabergoline.

Ours is the first reported case of cabergoline introduced during pregnancy for active CD. The required dose was lower than expected from previous studies.

Learning points

- CS in pregnancy is associated with excess maternal and foetal mortality.
- 24h UFC and LNSC can be used to diagnose cortisol excess during pregnancy, but may require adjustment in reference ranges after the first trimester.
- Surgical cure of active CS during pregnancy should be considered where feasible and optimally performed in the second trimester.
- Cabergoline is an effective alternative to metyrapone for controlling CD in pregnancy and offers an attractive safety profile.

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12

If you can't beat them, remove them – a rare complication of pregnancy.

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Introduction

Hormonal changes in pregnancy lead to a 2-to-3 fold increase in serum triglyceride levels(1). In women with normal baseline triglyceride levels and normal lipid metabolism, this increase is not clinically significant and no specific intervention is required. Rarely, women with genetic abnormalities that affect lipid metabolism develop gestational hypertriglyeridaemia which can be severe and associated acute complications including pancreatitis, pre-eclampsia or foetal demise.

We present a case of a female whose pregnancy has been complicated by severe hypertriglyceridaemia which we postulate is due to lipoprotein lipase(LPL) deficiency.

Case

A primiparous 19-year-old female presented to the birth unit at 25 weeks gestation with worsening abdominal pain and nausea. She reported dysuria and was commenced on intravenous ceftriaxone for a presumed urinary tract infection. Her background was significant for hypertriglyceridaemia diagnosed in infancy after an episode of pancreatitis. She was managed by an endocrinologist in her native country of Lebanon and was previously prescribed medium chain triglyceride supplementation. Prior to pregnancy, her baseline triglycerides fluctuated between 10 to 25mmol/L. Her preconception weight was 60kg(body mass index 22kg/m^2) and triglycerides shortly following conception was 25.6mmol/L.

There was an unconfirmed family history of hypertriglyceridaemia affecting her brother and a paternal cousin who developed pancreatitis at a young age in the context of consanguinity in the family. There was no family history of diabetes or early-onset coronary artery disease or cerebrovascular accidents. She did not have any tendon xanthomata, lipaemia retinalis or hepatosplenomegaly.

At 25 weeks gestation, she developed fevers and abdominal pain and bloods revealed leucocytosis with predominant neutrophilia, raised C-reactive protein as well as raised amylase and lipase levels. Her lipid profile showed triglycerides 41.4mmol/L(RR<2.0mmol/L) and elevated cholesterol of 9.3mmol/L(RR 3.0-5.5mmol/L)(Fig.1). Ultrasonography revealed a bulky pancreas with peripancreatic free fluid. The liver had a normal sonographic appearance and there was no cholelithiasis. There was no evidence of pyelonephritis.

A diagnosis of pancreatitis secondary to hypertriglyceridaemia was made. Insulin infusion was commenced at 2units/hr with concurrent 10% dextrose to prevent hypoglycaemia. Bowel rest was initiated, and she was kept in a fasting state . She was also commenced on subcutaneous heparin at 5000IU three times daily as well as fish oil 9g daily. Betamethasone was administered to promote lung maturation in the foetus.

Her triglycerides initially improved and reached a nadir at 10mmol/L with insulin, heparin, fasting and fish oil and her symptoms resolved over the proceeding 72 hours. Insulin was ceased and she commenced a fat-restricted diet < 10g dietary fat per day. She was commenced on gemfibrozil 200mg three times daily(pregnancy category B3).

A 75g oral glucose tolerance test performed at 26 weeks of gestation was not diagnostic for gestational diabetes. She was trialled on insulin detemir as a means to reduce triglyceride levels but this was ceased due to hypoglycaemia. Despite continuing a fat-restricted diet, fish oil, heparin and gemfibrozil, her triglyceride level rose again over the course of a week and reached 24mmol/L. On such a restrictive diet, there were concerns with weight loss of 2.2kg over two weeks.

Due to risk of recurrent pancreatitis with persistently elevated triglycerides despite these therapeutic strategies, a joint multidisciplinary decision was made to pursue therapeutic plasma exchange(TPE) following consultation between endocrinology, maternal-foetal medicine, lipidology and haematology.

She first underwent TPE at 28weeks gestation and 2500ml of plasma was exchanged with 4% albumin(Fig.2). This achieved a reduction in her plasma triglycerides from 25mmol/L to 13 mmol/L. She continued to undergo weekly TPE, which she tolerated well, though trough and peak triglycerides were rising as her pregnancy progressed. Therefore, the frequency and volume of her TPE was increased to twice weekly at 32 weeks gestation which was effective in reducing her triglycerides. She underwent 10 sessions to date without any significant maternal or foetal complications(Graph 1).

During this episode, foetal ultrasound and cardiotocography(CTG) were reassuring. The estimated foetal weight remained between 30-44th centile on ultrasonography between 25- and 32-weeks gestation. The amniotic fluid index(AFI) and umbilical systolic/diastolic ratio was appropriate for gestation age at each scan.

She is currently 35 weeks gestation and the outcome of her pregnancy will be presented. Plans for gene testing is underway.

Discussion

Triglycerides represent an important energy source in normal metabolism. Hypertriglyceridaemia may result from underlying genetic abnormalities involving pathways responsible for lipid metabolism and is also seen in patients with metabolic syndrome, excessive alcohol intake, chronic kidney disease or excessive dietary fat intake.

Hormonal changes in pregnancy, particularly those mediated by progesterone, oestrogen and human placental lactogen, lead to an overall increase in plasma lipids(2). The physiological basis of these hormone-induced lipid changes is to ensure adequate energy source in the mother to ensure nutrient delivery to the foetus. The most profound change is in the triglyceride levels which can increase 2-to-3 fold during the third trimester. These physiological changes in serum triglyceride levels can be problematic when a genetic abnormality in lipid metabolism exists(familial hypertriglyceridaemia), leading to gestational hypertriglyceridaemia.

Complications arising from gestational hypertriglyceridaemia include pancreatitis preterm labour, pre-eclampsia and foetal-death-in-utero.

Genetic studies have identified that patients with severe hypertriglyceridaemia typically present in childhood and adolescence and display classic autosomal recessive pattern of inheritance. These patients are homozygous or compound heterozygous for large-effect, loss-of-function mutations in genes that regulate catabolism of triglyceride-rich lipoproteins. These include genes coding LPL – which mediate catabolism of chylomicrons and very-low-density-lipoproteins(VLDL), apoprotein C-2 – which activate LPL, and genes responsible for maturation, transport and surface expression of LPL. (3). Traditional classification of

familial hypertriglyceridaemia relied on appearance on lipid electrophoresis(EPG). In our case, her lipid EPG revealed chylomicronaemia.

The available therapies for gestational hypertriglyceridaemia such as omega-3 fatty acids, gemfibrozil and insulin, predominantly rely on the augmentation of lipoprotein lipase activity to catabolise triglyceride-rich lipoproteins.(4) TPE is a safe and effective procedure in the management of hypertriglyceridaemic pancreatitis and its use has been described in multiple case reports as a treatment and for the prevention of hypertriglyceridaemia-induced pancreatitis in pregnancy(5, 6). TPE may also represent the only effective option in patients with severe LPL deficiency given their partial response to pharmacological treatment.

Overall, the hormonal changes in pregnancy, particularly the rise in progesterone, oestrogen and human placental lactogen, leads to an increase in serum triglyceride levels. These changes may be significant in patients whose lipid metabolism is impaired by genetic abnormalities such as LPL deficiency, Following delivery, prudent diet and exercise remain mainstays of treatment, particularly if she plans to breastfeed as the safety of statins and fibrates are unclear in lactation.

Key Points

- Hypertriglyceridaemia can result from genetic abnormalities in the genes coding lipoprotein lipase which can lead to severe hypertriglyceridaemia.
- Hormonal changes in pregnancy lead to a physiological rise in plasma lipids, with the most profound increases seen in triglyceride levels which increase 2-3 fold. This can significant exacerbate underlying hypertriglyceridaemia.
- Management options are limited in pregnancy, due to concerns for harm to the foetus, and rely on the augmentation of lipoprotein lipase activity to reduce triglyceride levels.
- TPE represents an effective mechanism to reduce serum triglycerides levels in pregnancy and in cases where the action of lipoprotein lipase cannot be augmented due to deficiency.

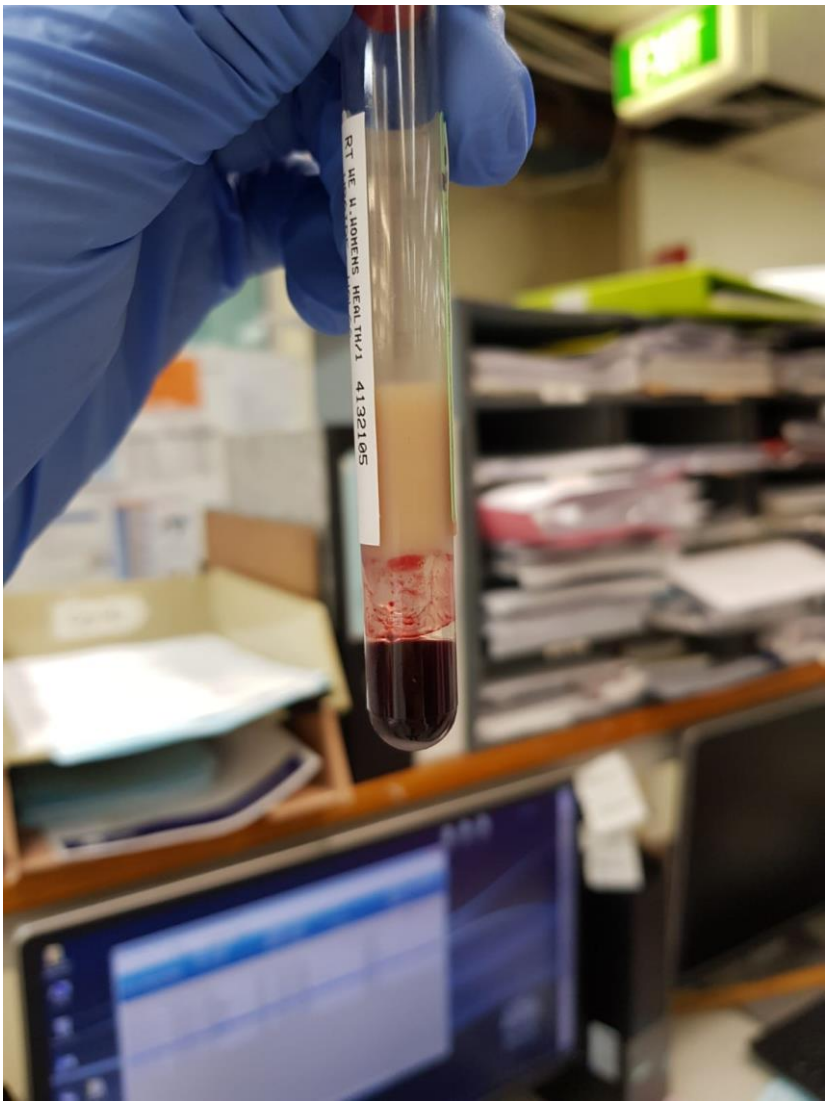
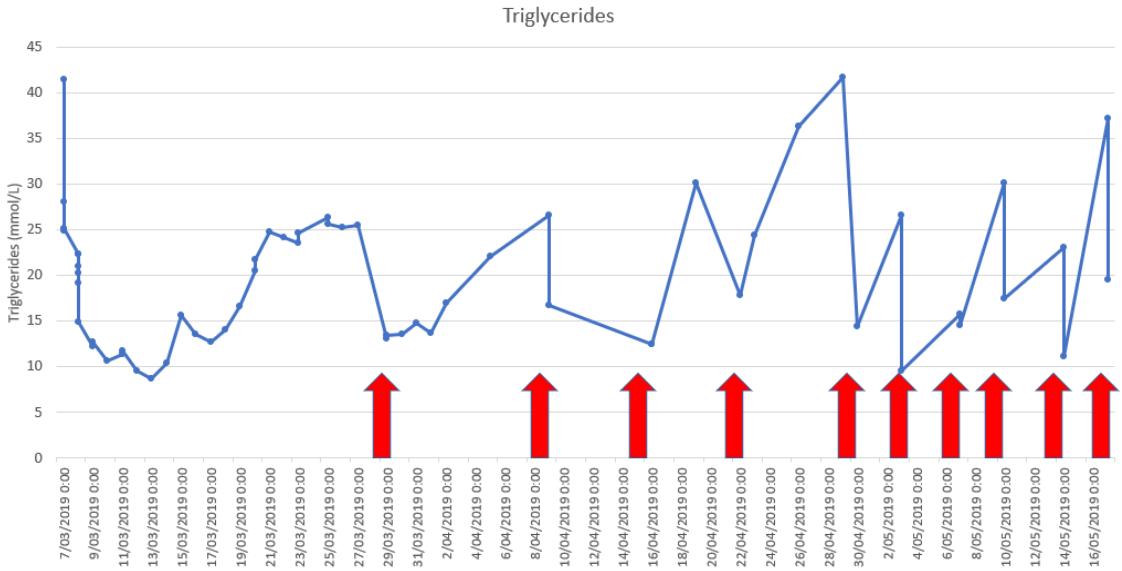


Figure 1. Blood following centrifugation. Layer of lipid-rich plasma (A)

Figure 2. Apheresed plasma following TPE.



Graph 1. TPE marked by red arrows.

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13

Baby Brain: A case of pituitary apoplexy in pregnancy

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Case Report

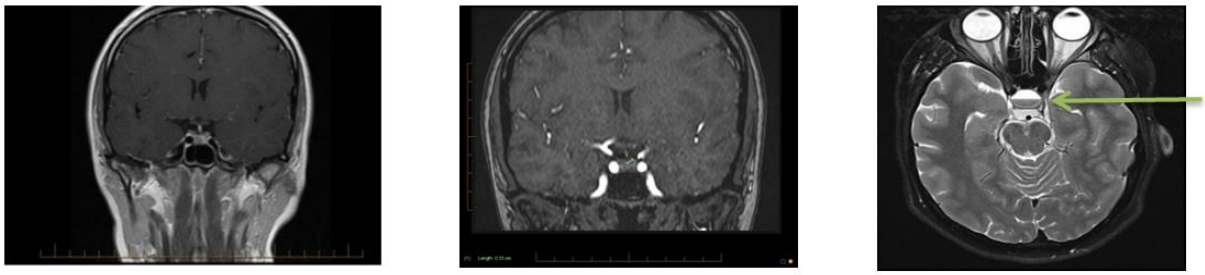
A thirty year old woman, G2P1 presented with worsening headaches at 29 weeks gestation. Her medical history was remarkable for a pituitary microprolactinoma diagnosed in 2012, in the context of oligomenorrhoea. Her MRI then showed a 5x 4mm pituitary microadenoma (Figure 1a) and an incidental right parietal arteriovenous malformation (AVM), which was resected in 2013. She conceived her first child while on cabergoline later that year which was ceased on confirmation of pregnancy. She breastfed for two years, but upon cessation of breastfeeding, she had ongoing galactorrhoea requiring recommencement of cabergoline. MRI one year post AVM resection showed a stable microadenoma of 4mm (Figure 1b,). She conceived again late 2018, and ceased cabergoline in early pregnancy.With current pregnancy she remarked having headaches in the first trimester which initially resolved but recurred at 26 weeks gestation. This was characterised by right sided, post ocular with radiation through to the jaw, and pulsatile in nature. Formal visual fields revealed bilateral temporal upper quadrantanopia, and relevant laboratory investigations are shown in Table 1.

Table 1 Laboratory results

	March 2019	October 2018	July 2018	August 2017	December 2016	January 2015	September 2013
Prolactin (mIU/L)	3693	2689	270	1281	295	810	935
Post maroPRL precipitation (mIU/L)				954		708	756
TSH (mIU/L)	1.15						
T4 (pmol/L)	12.7						
T3 (pmol/L)	3.9						
IGF-1 (nmol/L)	17.9						
Cortisol (nmol/L)	647						

Pituitary MRI (Figure 1c,) showed a new 18 x 13 x 19 mm lesion in the pituitary fossa which exhibited a fluid level and hyperintensity suggestive of haemorrhage +/- necrosis. There was suprasellar extension and evidence of mass effect on the optic chiasm. She was referred for urgent neurosurgical opinion.

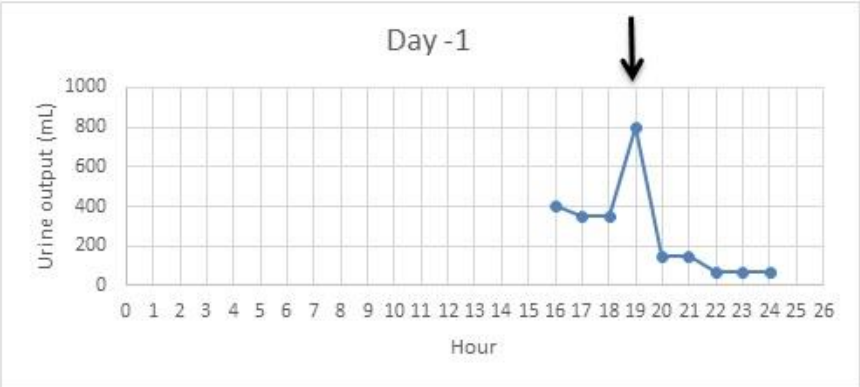
Figure 1: MRI pituitary showing lesion from 2012, 2014 and 2019



a b c

She underwent planned trans-sphenoidal resection at 33 weeks gestation. She developed polyuria days preceding surgery and was commenced on desmopressin nasal spray for management of evolving diabetes insipidus. Urine output pre and post administration of desmopressin before surgery as shown in (figure2, black arrow).

Figure 2: Hourly urine output on day prior to resection



She received parenteral stress dose hydrocortisone coverage in the peri-operative period which was tapered to oral hydrocortisone 30 mg in divided dose on discharge due to suboptimal post-operative morning cortisol levels (Table 2).

Management of diabetes insipidus was challenging. She had persistent high-volume urine output postoperatively, requiring moderately high doses of desmopressin, which were adjusted according to serum sodium and urine osmolality (Table 3). She was eventually discharged on oral desmopressin 300 micrograms three times daily.

Table 2: Post-operative morning cortisol levels and hydrocortisone replacement plan

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Morning cortisol level (nmol/L)	-	290	514	-	164	-	162
Hydrocortisone dose							
Morning	50mg IV	50mg IV	50mg IV	24 mg PO	24 mg PO	20mg PO	20mg PO
Midday	50mg IV	50mg IV	25mg IV	-	-	10mg PO	10mg PO
Night	50mg IV	50mg IV	-	-	-	-	

Table 3: Paired serum sodium and urine osmolality during polyuric episodes

	Day 0	Day 0	Day 1	Day 1	Day 2	Day 2	Day 2	Day 3	Day 3
Serum sodium (mmol/L)	139	149	139	132	131	129	135	137	141
Urine osmolality (momol/kg)	-	79	188	93	158	220	63	103	122
	Day 3	**Day 3**	**Day 4**	**Day 4**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**
Serum sodium (mmol/L)	140	134	142	144	-	137	132	-	136
Urine osmolality (momol/kg)	143	353	65	55	80	-	638	58	-

Visual field testing one week post resection showed resolution of visual field defect.

She underwent an elective Caesarean section at 38 weeks gestation; five weeks post pituitary surgery, delivering a healthy baby boy.

One week postpartum, she remained on low dose hydrocortisone, desmopressin and was commenced on Thyroxine (thyroid function as shown in Table 4). She has elected not to breastfeed. She will remain under close surveillance to determine if her pituitary function recovers.

Table 4: Pathology results pre and post birth

	28th April 2019 (Post birth)	14th April 2019 (Pre -birth)	March 2019
Prolactin (mIU/L)	202		3693*
TSH (mIU/L)	0.28*	0.48*	1.15
T4 (pmol/L)	12.7	14.2	12.7
T3 (pmol/L)	3.0*	3.8	3.9
IGF-1 (nmol/L)			17.9
Cortisol (nmol/L)			647

Discussion

Pituitary apoplexy in pregnancy is a rare, but potentially life threatening event[1]. Its exact incidence is unknown, with only 15 cases published in the literature[1]. It is defined as the abrupt destruction of the pituitary, secondary to infarction or haemorrhage, usually in the setting of a pre-existing pituitary tumour[1]. It may occur without a pre-existing lesion, occasionally when the pituitary enlarges, as in the case of physiological pregnancy induced changes [1], principally due to hyperplasia of the prolactin producing lactotroph cells[2]. Post infarction, the enlarged pituitary or tumour may become haemorrhagic and swollen, and pituitary hormonal deficiencies can develop [1]. If symptoms are confined to headache and/or hormonal deficiencies, the recommendation is for surveillance, replacement of deficient hormonal axis and dopamine agonists, if bleeding into a prolactinoma has occurred[1]. If there are progressive neuro-ophthalmological symptoms, then urgent trans-sphenoidal surgery is advised[1]. However, isolated ocular paresis is not an indication for surgery, as this will likely spontaneously improve in days to weeks [3]. The management of the conscious patient with mild, stable neuro-ophthalmological signs is far more contentious, with the argument that early surgery performed by an experienced pituitary neurosurgeon has low morbidity and mortality, and a significant improvement in visual symptoms [3].

There are difficulties in recognising adrenal insufficiency in pregnancy, as pregnancy is considered a state of 'physiological' hypercorticolism, with production, secretion and plasma concentrations of cortisol increase progressively beginning in the first trimester[4]. Adrenal insufficiency in pregnancy can be associated with significant morbidity and mortality, especially if there is a delay in diagnosis and treatment. Maternal total plasma cortisol, CBG, plasma free cortisol and 24 hour urine free cortisol have all been shown to be increased in normal pregnancy, peaking in the third trimester[5]. Mean total cortisol concentrations measured via liquid chromatography–mass spectrometry have been demonstrated to be higher in pregnancy with 1.6, 2.4 and 2.9 fold elevations during the first, second and third trimesters, respectively, compared to non-pregnant controls[5]. As such, an adrenal deficient pregnant woman may present with a cortisol result which is within the normal laboratory range for a non-pregnant adult. Additionally, the use of the standard 250 microgram ACTH stimulation test is limited, given the lack of available data to determined specific cut off values validated in pregnancy[6]. Given such constraints, there must be a high index of suspicion when considering adrenal insufficiency in pregnancy.

Diagnosing diabetes insipidus in pregnancy is challenging, given the alteration of water metabolism. The majority of diabetes insipidus worsens during pregnancy (58% of cases), while 20% improve and 15% remain stable[7]. During pregnancy there is a lowering of the serum osmolality set point by approximately 10 mOsm/kg and as a result serum sodium is decreased by 4–5 mmol/L by this reset osmostat[8]. Placental vasopressinase results in increased degradation of ADH, which may uncover sub clinical diabetes insipidus or worsen established diabetes insipidus in pregnancy[8]. It is imperative to recognise and treat it promptly as water restriction can lead to harmful maternal and foetal neurologic consequences. Given the concerns regarding the water deprivation tests causing significant dehydration in pregnant women, plasma and serum osmolality should be used to investigate diabetes insipidus in pregnancy. There should be a low threshold to investigated polyuric pregnant women, especially if they are polydipsic, have increased serum sodium above 140 mmol/L, and an inappropriately diluted urine (osmolality <300 mOsm/kg)[9]. Treatment should involve the use of desmopressin, which is not degraded by placental vasopressinase.

During pregnancy, the pituitary increases in all dimensions. In-vivo studies have established increasing pituitary volumes, with gland size increasing up to 136% compared to controls[2]. The Endocrine Society guidelines recommend against measuring prolactin during pregnancy, given its difficulty in distinguishing between the normal pregnancy associated rise in prolactin, from that associated with pituitary growth[10]. In those with a known pituitary adenoma, visual field testing should be considered if visual changes or worsening headaches develop, with those who develop a field defect being referred for MRI[10].

Pituitary apoplexy is considered a medical emergency, due to its impairment on pituitary function. There are unclear guidelines regarding the management of pituitary apoplexy in pregnancy, ultimately relying on the presence, severity and stability of neurological signs[3]. Often such complex cases necessitate the involvement of a multidisciplinary team involving obstetricians, endocrinologists and neurosurgeons in order to minimise maternal and foetal morbidity and mortality.

Take home messages

1. The physiology of pregnancy alters the course, diagnosis and management of many pituitary disorders
2. Investigations and references ranges during pregnancy need to be interpreted with caution
3. There needs to be a high index of suspicion with regards to timely diagnosis and prompt treatment because of high maternal and foetal morbidity and mortality if untreated

14

Crisis cardioverted

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Case

A 58-year-old female was referred to the Neuroendocrine Tumour Multidisciplinary Team (NET MDT) for consideration of peptide receptor radionuclide therapy (PRRT) for progressive metastatic NET. She presented in 2018 with abdominal pain; other symptoms included flushing, diarrhoea and palpitations. Imaging prompted by abnormal liver function tests identified multiple liver lesions and biopsy revealed Grade 2 (Ki-67 4.8%) NET. Ga-68 DOTATATE-PET (Figure 1a) identified a likely small bowel primary lesion with metastases to liver, lymph nodes and bones. Urinary 5-HIAA and chromogranin A were both markedly elevated (Table 1).

Octreotide long-acting release (LAR) was commenced at 30mg monthly. Baseline transthoracic echocardiogram (June 2018) showed non-specific mild changes, considered normal for her age (Figure 2).

PRRT was recommended following evidence of symptomatic and radiological progression over the next six months (Figure 1b). The patient was advised to take her last dose of Octreotide LAR four weeks prior to planned date of therapy. Therapy was delayed a week and in the interim, due to worsening symptoms, she was started on subcutaneous octreotide 100mcg tds, with final dose two days prior to PRRT.

On the day of PRRT (February 2019), the patient developed nausea and vomiting 15 minutes after commencement of reno-protective amino acid infusion (arginine and lysine) which resolved with intravenous metoclopramide and dexamethasone. She subsequently received 8.1GBq of ^{177}Lu-DOTATATE radionuclide therapy.

Following completion of PRRT she again developed nausea and vomiting with transient syncope. On regaining consciousness her blood pressure was 95/40mmHg with heart rate 78bpm. Five minutes later, she had a pulseless electrical activity (PEA) cardiorespiratory arrest. Return of spontaneous circulation (ROSC) occurred after two minutes of cardiopulmonary resuscitation (CPR). An hour later, she had a further PEA cardiorespiratory arrest with no ROSC despite 20 minutes of CPR. ROSC was only achieved following intravenous bolus of octreotide (100mcg). She was transferred to ICU with a continuous octreotide infusion (100mcg/hour). Octreotide LAR 30mg was given the following day. Her octreotide infusion was weaned over three days with subcutaneous octreotide at weaning doses given over the following four days. During the wean, she had one episode of flushing and diarrhoea which resolved with temporary dose increase.

Retrospectively she described progressive symptoms of heart failure for two months. Following resuscitation she had biventricular failure which did not improve significantly during her ICU stay. Transthoracic and transoesophageal echocardiogram confirmed right- and left-sided carcinoid heart disease with moderate to severe regurgitation of tricuspid, mitral and aortic valves (Figure 3). The patient subsequently underwent triple mechanical valve replacement and patent foramen ovale closure, in part to allow for future PRRT administration.

Figure 1a: Initial Ga-68 DOTATATE-PET scan showing multiple DOTATATE avid liver lesions, mesenteric lesions and a T7 lesion. **Figure 1b**: Progress Ga-68 DOTATATE-PET scan showing new DOTATATE avid lesion in left lobe of liver, increased size of right lobe lesions, increased intensity of T7 lesion consistent with progressive metastatic disease.

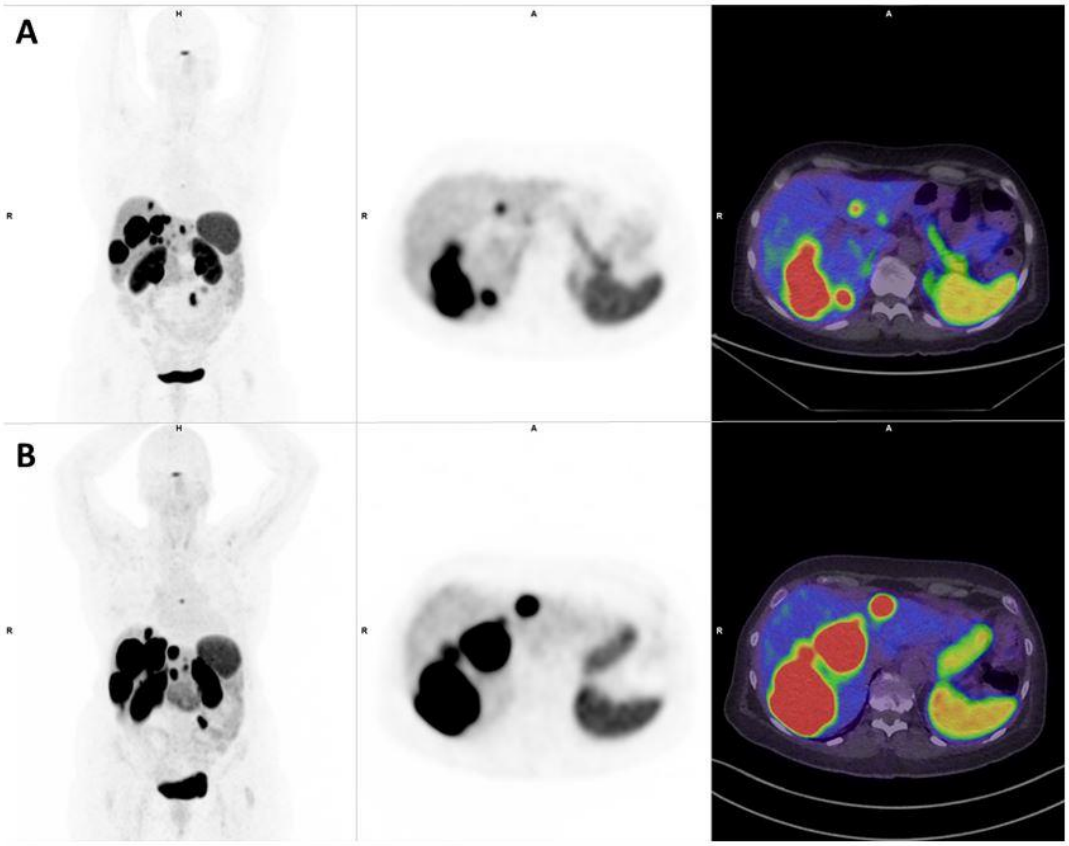

Table 1: Relevant laboratory investigations

	At diagnosis	Before PRRT	Following arrest	Following PRRT	
Chromogranin A	3022	6242	10070	3553	ug/L (20-102)
Urinary 5-HIAA			733	268	umol/24hr (<40)
Urinary 5-HIAA			120	53	mmol/mol cr (<4.0)

Abbreviation: 5-HIAA, 5-hydroxyindole acetic acid. Cr, creatinine.

Figure 2: Initial transthoracic echocardiogram

Normal left ventricular size and systolic function.
Normal right ventricular size and systolic function.
Left and right atrial size is normal. Atrial septum appears intact.
Mitral valve is normal in structure and function with trace mitral valve regurgitation.
The tricuspid valve is structurally normal in appearance. There is mild to moderate tricuspid regurgitation.
There is mild aortic valve regurgitation.
The pulmonary valve appears structurally normal.

Figure 3: Progress transoesophageal echocardiogram

Upper normal left ventricular size with low normal function (in the setting of mitral regurgitation).
Dilated right ventricle with preserved systolic function.
Dilated left and right atria. The interatrial septum is aneurysmal and bows towards the left atrium.
Agitated saline bubble study with abdominal pressure. No left to right cross over demonstrated with bubbles although some colour Doppler images are suggestive.
Mildly thickened mitral valve leaflets with immobile posterior leaflet. Moderate-to-severe mitral regurgitation.
Thickened and relatively immobile tricuspid valve leaflets with failure of coaptation. Severe tricuspid regurgitation (4/4).
Thickened aortic valve leaflets with relatively immobile right coronary cusp. Aortic regurgitation which is at least moderate.
The pulmonary valve appears structurally normal.

Discussion

This patient had rapid progression of carcinoid syndrome and carcinoid heart disease from metastatic small bowel NET, culminating in carcinoid crisis and a PEA cardiorespiratory arrest precipitated by PRRT.

NETs are a heterogeneous group of neoplasms arising from neuroendocrine cells. NETs can occur throughout the body, but most commonly develop within the gastrointestinal tract (GEP-NETs). They are often indolent; their slow growth with few symptoms mean they are often diagnosed only when they are large or have metastasised to the liver[1].

NETs synthesise and secrete hormones and vasoactive peptides, which include 5-hydroxytryptamine (serotonin), tachykinins (neuropeptide K, substance B, NKA), histamine, prostaglandins and bradykinins[2]. Principal features include diarrhoea, flushing, abdominal pain +/- bronchospasm which collectively comprise carcinoid syndrome. These symptoms usually only arise after liver metastases are present as first-pass metabolism of these compounds reduces systemic exposure.

Carcinoid heart disease is due to serotonin excess. Serotonin is normally released in the gastrointestinal tract in response to food, increasing gut motility, and is also involved in neurotransmission systemically. Serotonin excess stimulates fibroblast growth and fibrogenesis[3]. Carcinoid heart disease affects approximately half of patients with carcinoid syndrome[4]. It is characterised by endocardial plaque-like deposits of fibrous tissue that cause retraction and fixation leading to a combination of valvular regurgitation and stenosis. The right side of the heart is most often affected (90% of cases) as the left is relatively protected by pulmonary metabolism of vasoactive peptides. Aortic and/or mitral valve involvement suggest a right-to-left shunt (e.g. patent foramen ovale), bronchial carcinoid, or severe carcinoid syndrome overwhelming the degradative capacity of the lungs[3].

Patients with carcinoid heart disease often present with fatigue, dyspnoea and peripheral oedema. They generally have higher urinary 5-HIAA levels and elevated BNP, although there are no reliable markers to identify all patients at risk, thus regular echocardiograms are recommended although optimum frequency is unknown. Somatostatin analogues (SSAs) have not been shown to prevent carcinoid heart disease although may be useful in preventing the negative haemodynamic effects of fluctuating serotonin elevation[5,6]. Standard management for heart failure is usually implemented; however, valve surgery is the only definitive treatment option for severe carcinoid heart disease, improving both quality of life and survival[4].

A life-threatening complication of carcinoid syndrome is carcinoid crisis, from release of large quantities of serotonin and other vasoactive amines and peptides, manifested by severe flushing, abdominal pain, diarrhoea, blood pressure instability (hypo- and hypertension) and heart rate variability (tachy- and bradycardia). Although crisis can occur spontaneously, it is often precipitated by stress, anaesthesia, tumour manipulation, arterial embolisation, or chemotherapy[7,8].

Several case reports of carcinoid crisis following PRRT have been published, with putative mechanism of tumour cell lysis from radiation causing massive release of vasoactive peptides[9]. Current clinical practice is that PRRT is usually given just before the next dose of long-acting SSA is due or after short-acting octreotide is withheld for 24 hours [10] thus patients may be at particular risk of crisis as they are at the nadir of medical management. Notably, evidence that SSAs affect PRRT response (e.g. competitively binding and/or downregulation of surface somatostatin receptors on tumour cells) is not established.

Two mechanisms of cardiorespiratory arrest from carcinoid crisis are documented in case reports. Serotonin can cause both vasoconstriction and vasodilation. If endothelial dysfunction is present (e.g. coronary atherosclerosis) the main effect is vasoconstriction. This causes coronary vasospasm resulting in myocardial infarction, arrhythmias and cardiorespiratory arrest. Alternatively, hypotension from vasodilation reduces right ventricular preload and in the presence of severe tricuspid regurgitation can cause circulatory shock and PEA cardiorespiratory arrest.

There are no guidelines on the prevention and management of carcinoid crisis with PRRT. A proposed protocol for high-risk patients was presented as part of a recent case series[2]. The learning points below include some of the key issues discussed in this publication. Investigation of telotristat etiprate - an FDA-approved tyrosine hydroxylase inhibitor - may be useful to prophylactically reduce serotonin levels prior to PRRT and cardiac surgery in patients at high risk for carcinoid crisis.

Key learning points:

- Routinely and regularly assess all patients with carcinoid syndrome for carcinoid heart disease (clinical symptoms, examination, BNP, echocardiogram)
- Use a multidisciplinary team in management of carcinoid heart disease
- Identify patients and precipitating events that are at high risk of carcinoid crisis

- Develop protocols to decrease risk of carcinoid crisis following PRRT
    - Timing (+/- necessity) of SSA cessation
    - Pre-medication with hydrocortisone, antihistamines
    - PRRT dose
    - Timing of SSA reinstitution
- Minimise harm in the event of carcinoid crisis with specialised staff who can recognise and treat carcinoid crisis
    - Easy access to IV octreotide and resuscitation equipment
    - Appropriate periods of observation after PRRT.

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15

An exploration of a rare case of adrenocortical carcinoma, and the effects and side-effects of immunotherapy

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Mr F was a well 38 year-old carpenter and father-of-two, who presented to our hospital in January 2017 with abdominal pain and bloating. His only past medical history was depression and a prolactinoma for which he took low-dose cabergoline. A Computerised Tomography (CT) scan of his abdomen revealed a huge, 16.7*14.6*12.8-centimetre heterogenous left-sided adrenal mass, with infiltration into the inferior vena cava and also pulmonary emboli.

Preoperatively it was known the tumour was secreting excess cortisol, as lab results showed the following:

Date, Time	Test	Result	Normal Range	Units
15 / 01 / 2017, 0900	24hr Urine Cortisol	793 *	100 - 379	nmol/day
18 / 01 / 2017, 1800	Spot Serum Cortisol	450 *	74 – 291	nmol/L
18 / 01 / 2017, 1800	ACTH	5.0 *	7.2 – 63.3	ng/L
28 / 01 / 2017, 0743	1mg DST Cortisol	68 *		
01 / 02 / 2017, 0707	1mg DST Cortisol	91 *		
14 / 01 / 2017	Metanephrines	88	<500	pmol/L
14 / 01 / 2017	Normetanephrines	139	<900	pmol/L
14 / 01 / 2017	Creatinine	102	62 – 106	micromol/L
14 / 01 / 2017	eGFR	79 *	>90	ml/min
14 / 01 / 2017	Aldosterone:Renin Ratio	4	<70	

Despite the biochemistry, the patient himself was surprisingly free of any signs or symptoms of Cushing's disease (with stable weight, no bruising, weakness, striae or moon facies).

He underwent a left-sided adrenalectomy and nephrectomy, with a 2.1kg tumour removed. Histology confirmed an adrenocortical carcinoma with an extremely high mitotic rate (>50/50hpf). An early-morning cortisol level done post-operatively was low at 25nmol/L [172-497nmol/L], and he was commenced on Hydrocortisone replacement (40mg mane, 20mg midi).

Date, Time	Test	Result	Normal Range	Units
10 / 03 / 2017, 0917	Serum Cortisol	25 *	172 - 497	nmol/L
10 / 03 / 2017, 0917	ACTH	5.2	1.6 – 13.9	ng/L

Subsequent imaging revealing metastatic disease to the lungs and liver. One month post-operatively he was commenced on adjuvant chemotherapy of cisplatin and etoposide, as well as mitotane. His treatment course was marred by febrile neutropenia, rash, severe nausea and fatigue, and peripheral neuropathy. Mitotane was intermittently withheld and dose-reduced to minimise the nausea and rash, causing low serum mitotane levels.

Cortisol levels having withheld his morning cortisol showed slow rise over six months with ACTH notably *elevated*, consistent with ACTH-secreting tumour. Hydrocortisone was ceased.

Date, Time	Test	Result	Normal Range	Units
29 / 05 / 2017, 0833	Serum Cortisol	167 *	172 - 497	nmol/L
20 / 09 / 2017, 0845	Serum Cortisol	277	172 – 497	nmol/L
17 / 11 / 2017, 0923	Serum Cortisol	468	172 - 497	nmol/L
17 / 11 / 2017, 0923	ACTH	23.2 *	1.6 – 13.9	pmol/L

After eight months of mitotane, CT scans in October 2017 demonstrated a new metastasis in his right adrenal gland, and progression of his lung metastases With few treatment options in this young man, he proceeded to stereotactic radiotherapy of his remaining right adrenal gland; as this would leave him completely adrenally insufficient, he was commenced on glucocorticosteroids.

Mr F remained very fatigued at this stage, so testosterone levels were checked which were normal at 25.4nmol/L [12.0 – 30.0], with normal testicular volumes. Prolactin was stable at 444nmol/L [90-400].

Due to progressive disease, Mr F was commenced on a Rare Cancer trial of experimental Nivolumab (PD-1 inhibitor) and Ipilimumab (CTLA-4 inhibitor) in December 2017, ten months after his initial presentation. After cycle 2 of this therapy, he had an emergency admission into hospital in January 2018 with severe fatigue, hypotension and generalised pain. Biochemistry revealed hepatitis, and presumed adrenalitis and thyroiditis.

Date, Time	Test	Result	Normal Range	Units
30 / 01 / 2018	TSH	0.01 *	0.27 – 4.20	mU/L
30 / 01 / 2018	T3	14.2 *	3.1 – 6.8	pmol/L
30 / 01 / 2018	T4	46.0 *	12.0 – 22.0	pmol/L
17 / 01 / 2018	Sodium	132 *	135 – 145	mmol / L
17 / 01 / 2018	Potassium	5.4 *	3.5 – 5.2	mmol / L
16 / 01 / 2018	ALT	451 *	5 – 40	units/L
16 / 01 / 2018	ALP	211 *	30 – 110	units/L
16 / 01 / 2018	GGT	186 *	<60	unit/L
17 / 01 / 2018, 1620	Cortisol	112	74 – 291	nmol/L
01 / 02 / 2018	DHEAS	0.15 *	2.4 – 11.6	micromol/L
18 / 01 / 2018	Anti-TPO	9.9	<34	IU/L
18 / 01 / 2018	Anti-Tg	<10	<10	IU/L
18 / 01 / 2018	TSH-Receptor Antib.	0.33	<1.22	IU/L

High-dose prednisolone was commenced for immunotherapy-induced hepatitis, and presumed thyroiditis and adrenalitis. He had some symptomatic benefit from this. Fludrocortisone was also commenced for the presumed adrenalitis. Abdominal pain required escalating use of oxycodone and then methadone.

Immunotherapy was ceased, with high recurrence risk of the toxicities with restarting treatment. On prednisolone, his hepatitis improved, his adrenal insufficiency was managed on prednisolone and fludrocortisone, and he became biochemically euthyroid over four weeks.

Despite normal thyroid function and adequate adrenal hormone replacement, he remained severely fatigued (sleeping most of the day, poor energy), with low libido affecting his quality of life. Repeat testosterone, FSH and LH was now consistent with primary hypogonadism:

Date, Time	Test	Result	Normal Range	Units
19 / 07 / 2018	Total Testosterone	2.29 *	9.9 – 27.8	nmol/L
19 / 07 / 2018	Free Testosterone	177	170 – 670	pmol/L
19 / 07 / 2018	FSH	58.3 *	1.5 – 9.7	IU/L
19 / 07 / 2018	LH	70.1 *	1.8 – 9.2	IU/L
19 / 07 / 2018	SHBG	22	17 – 56	nmol/L

Mr F had not complained of overt testicular pain nor swelling, though his generalised unwellness and high-dose opioids may have masked his symptoms. Opiates were progressively weaned, and he remained hypogonadal (with elevated FSH and LH) presumed to be immunotherapy-related orchitis. Treatment with testogel and then Reandron therapy to therapeutic levels led to good improvements in his energy levels.

Further questioning of his family history revealed that his father had bowel and bladder cancer, and his paternal grandfather had died from an unknown cancer. Genetic studies in Mr F confirmed the MSH2 mutation, thus diagnosing Lynch Syndrome, a familial cancer syndrome. A screening colonoscopy resected two sigmoid polyps.

Most remarkably: Mr F has had no further chemo/radiotherapy nor immunotherapy since January 2018, but his subsequent CT and Positron Electron Tomography (PET) scans still show complete resolution of metastases. He remains cancer-free and continues on hydrocortisone 20mg/10mg daily, fludrocortisone 0.1mg daily and testosterone undecanoate 1000mg IM 6-weekly replacement. He is now looking for a job!

Discussion

Ectopic ACTH production from adrenocortical carcinoma

Adrenocortical Carcinoma is a rare malignancy, with rates of 1 per million per year[1], and whilst ACTH-independent Cushing's syndrome has been commonly reported, there are no reports in the English literature of ectopic ACTH syndrome arising from a malignant adrenocortical carcinoma[2]. The hallmark of Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is colorectal cancer and initial presentations with adrenocortical carcinoma are very atypical (13 prior cases reported in the literature) [3]. Screening for adrenocortical carcinoma is typically not performed for those with Lynch syndrome.

The role of Immunotherapy

The prognosis of adrenocortical cancer has historically been poor, as most patients present with advanced disease at the time of diagnosis. The five-year survival for metastatic adrenocarcinoma has been 13%. The mainstay of treatment is surgery, chemo/radiotherapy and the adrenolytic mitotane[1].

Checkpoint-inhibition has now heralded a new era of cancer therapies, with previously incurable malignancies showing substantial rates of remission. The effect of these therapies can be prolonged, with disease improvement seen even months after the cessation of treatment. Their use in adrenocarcinoma is still experimental. An In-vitro study has shown that PD-1 was expressed in 22 out of 28 histological adrenocarcinoma specimens[4]. The complete tumour response of Mr F's refractory metastatic disease over 12 months after only 2 cycles of nivolumab and ipilimumab has been unexpected and remarkably sustained.

Mr F's massive autoimmune endocrine response was also associated with disease response. Despite some data [5,6] that incidence of toxicities may reflect increased immunotherapy activity, thus leading to superior response rates, this is certainly not conclusive and further studies are required.

Immunotherapy-induced orchitis

Immunotherapies are known to cause potentially severe toxicities and diverse endocrinopathies including autoimmune thyroid disease, diabetes and hypophysitis can occur with such treatments. The occurrence of however, is exceedingly uncommon. Only two previous case reports have described the experience of orchitis in patients on checkpoint inhibitors [7,8] for melanoma. Unfortunately one did not appear to have a testosterone level checked; the other had low testosterone which normalised after steroid therapy. Both patients described scrotal swelling and tenderness [7,8]. Our patient had not noted scrotal symptoms whilst very unwell and on opioids. Nonetheless, the result of normal testosterone prior to therapy, time course of his immunological response during therapy, and severely deficient testosterone (with elevated gonadotrophins) is entirely consistent with acute-onset of primary hypogonadism due to autoimmune orchitis which has been sustained requiring ongoing testosterone replacement.

Conclusion

Adrenocortical carcinoma presenting as Lynch Syndrome is highly unusual and is the first case of ectopic-ACTH causing biochemical Cushing's syndrome arising from a malignant adrenal tumour. Despite a very poor prognosis in a young man with progressive metastases following first line treatment, he has had a remarkable sustained disease response to two cycles of immunotherapy and remains cancer-free. His massive autoimmune toxicity arising from immunotherapy involved multiple organs, including primary hypogonadism due to autoimmune orchitis which has only been reported in two other cases in the literature.

This case highlights the potential for checkpoint-inhibitors to cause toxicity in multiple endocrine organs which may reflect greater immunotherapy activity to potentially shift the treatment paradigm in advanced adrenocortical carcinoma.

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A Broken Heart Leaves the Adrenals Gasping for Air

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Case

A 48-year-old woman with partial situs inversus and Eisenmenger's syndrome secondary to congenital ventricular septal defect was admitted to hospital for combined heart and bilateral lung transplantation. Severe pulmonary hypertension with hypoxic respiratory failure had been present for >15 years pre-transplant, and during the 12 months directly preceding admission oxygen saturations routinely measured between 75 and 80% when assessed via oximetry. Surgery was complicated by major bleeding and prolonged intraoperative hypotension necessitating initiation of extracorporeal membranous oxygenation to achieve hemodynamic stability. The patient was admitted to the intensive care unit for post-surgical management and within hours of arrival developed paroxysms of pronounced hypertension during which the systolic blood pressure repeatedly exceeded 230 mmHg. On each occasion the hypertensive episode was self-limited and followed by a period of marked hypotension requiring maximal inotropic support to maintain pressures above 80 mmHg.

Investigations

Plasma catecholamine metabolite concentrations were elevated with metanephrines of 1.00 nmol/L (normal range [NR] <0.4) and normetanephrines of 8.00 nmol/L (NR <0.9). Computed tomography of the abdomen and pelvis demonstrated adrenal lesions measuring 18x22x21 mm on the right and 39x38x42 mm on the left. Both adrenal masses were gallium-68 DOTATATE PET-CT avid with maximum standardised uptake values (SUVmax) of 5.9 in the right adrenal and 17.3 in the left (Figure 1). No pathologic extra-adrenal DOTATATE avidity was present.

Management

An anti-hypertensive treatment plan tailored to a transplant recipient with a denervated heart and vulnerable lung reserve was devised under multi-disciplinary guidance. Due to this risk, the adrenal glands were excised at separate surgical procedures. The left adrenal tumour was histologically confirmed as a phaeochromocytoma/ paraganglioma (PPGL, Figure 2). The second surgery two months later revealed the right adrenal gland with an adjacent discrete paracaval mass- both of which were excised. Histology of the right adrenal gland was unremarkable, but pathologic examination of the extra-adrenal mass was consistent with PPGL. Immunohistochemistry staining in both tumours was positive for synaptophysin, chromogranin, CD56 and succinate dehydrogenase B (SDHB). Germline mutation screening was negative for pathologic variants in the known PPGL susceptibility genes and whole genome sequencing was unremarkable apart from a variant of uncertain significance in the LZTR1 gene (associated with susceptibility to schwannomatosis and Noonan's syndrome, but not PPGL). Tumour DNA was isolated from formalin-fixed paraffin embedded sections and sequencing of the EPAS1 variant hotspot within exon 12 (p.529-532) was performed. A pathogenic somatic EPAS1 c.1589C>T variant (altering the encoded HIF2α protein, p.Ala530Val) was detected in the left adrenal PPGL (Figure 3). Pathogenic variants within exon 12 of EPAS1 were not be detected in the right adrenal PPGL or the left adrenal cortex.
Hypertension improved following surgery. Three months following the second adrenalectomy, her plasma metabolite levels were within the normal reference interval (metanephrines 0.14 nmol/L [NR <0.4]; normetanephrines 0.56 nmol/L [NR <0.9]). A further three months later, antibody mediated graft rejection developed in the transplanted organs. Despite intensive medical intervention there was progressive multi-organ failure and the patient succumbed approximately 14 months after her combined heart-lung transplant.

Discussion

Phaeochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumours of the adrenal medulla or autonomic nervous system. Chronic exposure to hypoxaemia is proposed to be a risk factor for PPGL. People living at high altitude and those with cyanotic congenital heart disease appear to develop PPGL at increased rates relative to the general population (1-3). Driver mutations have not been determined in most cases, but they appear phenotypically similar to tumours arising from the known cluster 1 gene mutations which simulate chronic hypoxia via regulation of hypoxia inducible factor alpha (HIFα) (3). Normally, HIFα undergoes rapid oxygen-dependent enzymatic modification leading to proteasomal degradation (4). However, in the absence of oxygen or under conditions where oxygen cannot be utilised, HIFα avoids destruction and functions as a coactivator with HIFβ to increase transcription of downstream hypoxia responsive genes (4).
Hypoxia inducible factors regulate the physiologic response to hypoxia. Changes are adaptive in the setting of tissue hypoxia or injury, but constitutive activation is maladaptive and increased expression of HIFs has been associated with a range of human cancers including PPGL (5). In PPGL, HIF2α mutated tumour secretion is noradrenaline predominant, similar to SDHx, von Hippel-Lindau (VHL) and other cluster 1 genes that promote a pseudo-hypoxic state (6). At present, mutations in HIF2α account for approximately 5% of PPGL with an identifiable gene mutation. Multiple tumours occur commonly and there is an association with congenital polycythaemia or somatostatinoma in many of the reported cases, although isolated PPGL without erythrocytosis has been reported (6, 7). A recent case series of 5 adult patients with cyanotic congenital heart disease of multiple etiologies and PPGL reported pathogenic somatic HIF2α mutations in 80% (8).
Our case is unique as we identified a pathogenic mutation in EPAS1 (c.1589C>T) - which affects codon 530 of the HIF2α protein (p.Ala530Val) - in one of the two PPGLs identified. Mutations in this domain distort the conformational properties of HIF2α such that prolyl sites cannot be bound by prolyl hydroxylase domain-containing (PHD) proteins in the usual fashion. Non-hydroxylated HIF2α escapes ubiquitination by the VHL protein complex and translocates to the nucleus where it regulates target gene

expression through the hypoxia response element as a heterodimer with HIFβ and other coactivators (9). It is not possible to determine whether longstanding hypoxaemia in our patient resulted in genetic or epigenetic changes that promote PPGL development. The prevalence of PPGL is clearly increased in subjects with cyanotic heart conditions or in those living at high altitude where oxygen tension is lower (1, 8), which lends biological plausibility to a role for chronic hypoxia in the development of HIF2α-mutated PPGL. However, the absolute incidence of PPGL in these conditions is low suggesting that factors other than hypoxia are necessary to promote tumour development (2, 3). It remains unclear whether restoration of normal oxygenation, such as following a heart lung transplant, would lead to tumour regression or non-progression in the setting of HIF2α-mutated PPGL. Improvement would seem unlikely as mutations in codon 530 of HIF2α result in an oxygen sensing defect whereby oxygen-dependent hydroxylation of HIF2α by PHD proteins is disrupted. Despite a similar oxygen sensing defect in SDHx-related disease, SDHD-mutated PPGL occurring at lower altitudes have been associated with reduced penetrance and a less severe phenotype compared to those living at higher altitude suggesting hypoxia may be a phenotypic modifier (10).

Conclusion

Our case reports a pathogenic mutation of EPAS1 (the gene encoding HIF2α) in only one of two PPGLs in a patient with congenital heart disease, chronic hypoxaemia and bilateral phaeochromocytoma.

1. Hypoxaemia predisposes to driver mutations that lead to PPGL (ie. EPAS1, which encodes the HIF2α protein)
2. Mutations affecting the HIF2α pathway are highly prevalent in PPGL that develop in patients with cyanotic congenital heart disease.
3. Multiple driver mutations for PPGL may occur in the same patient but not all are identifiable as pathogenic due to the rarity of this phenotype.
4. Patients with congenital chronic hypoxaemia should be evaluated for a PPGL if developing clinical features such as hypertension.

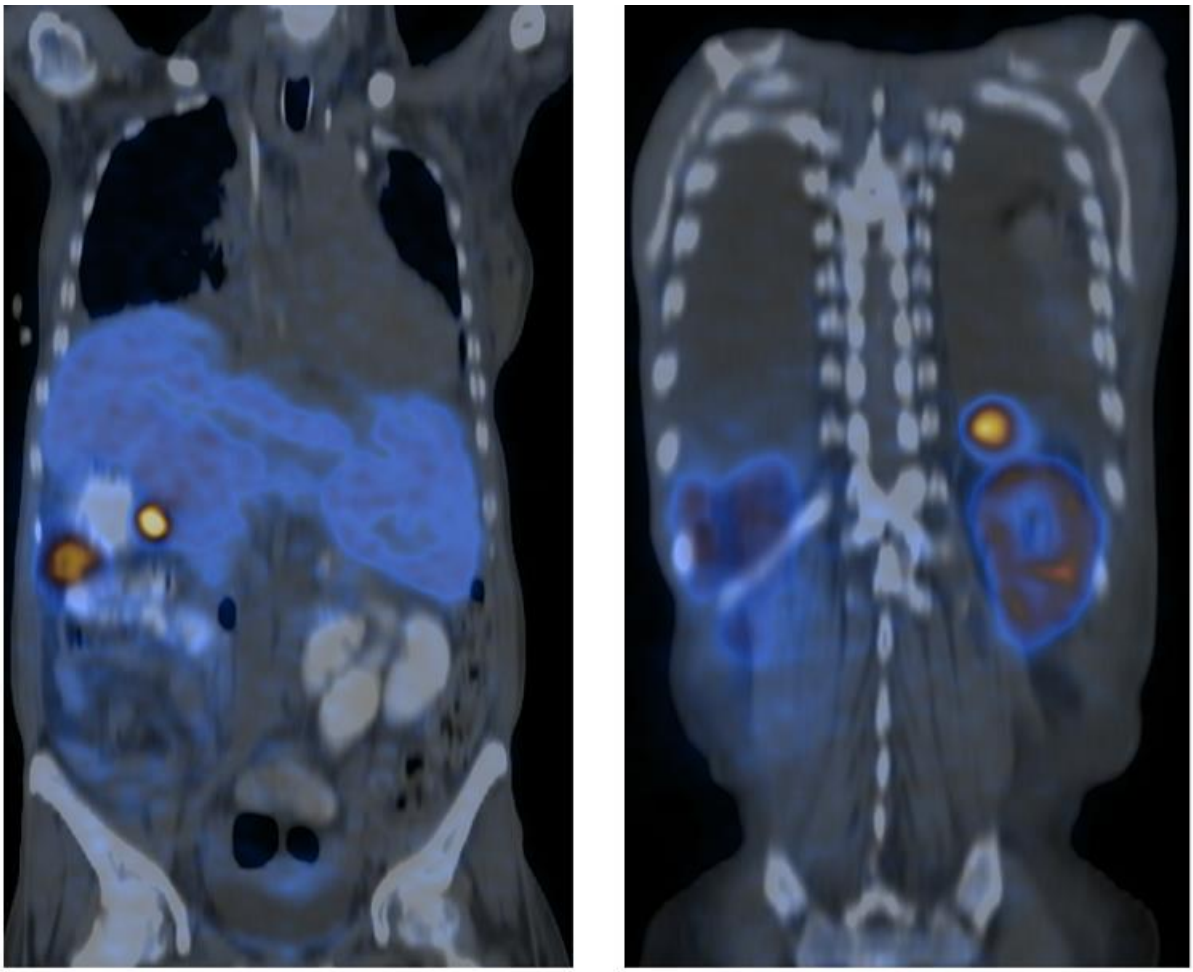

Figure 1: DOTATATE imaging confirming bilateral Paragangliomas

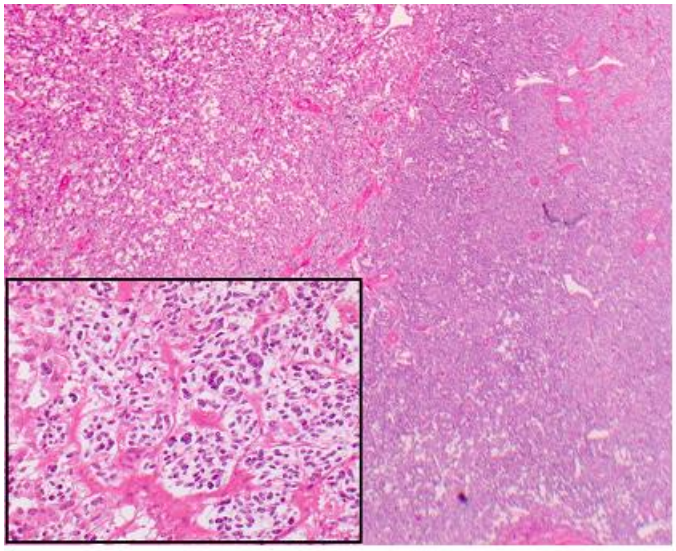

Figure 2: Histopathology of left adrenal confirming paraganglioma

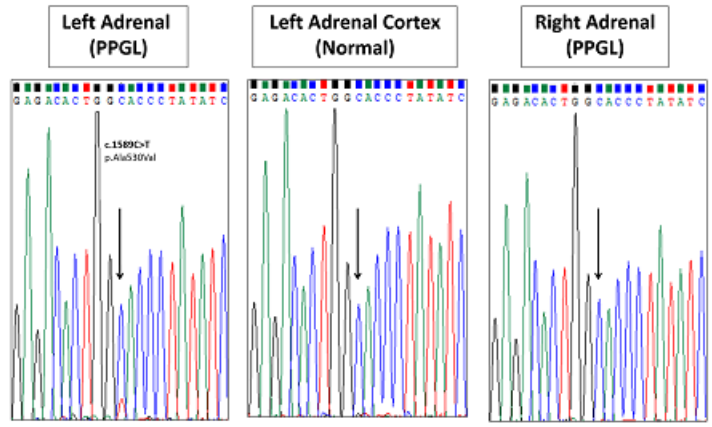

Figure 3: Confirmation of *EPAS1* **c.1589C>T (p.Ala530Val)** variant in left paraganglioma alone

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