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FULL CASE STUDIES

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Plenary 1: A Patient-Centric, Evidence-based Approach to Shared Treatment Decision in Older Men with Testosterone Deficiency

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Testosterone levels decline gradually with advancing age; the trajectory of age-related decline in testosterone levels is influenced by adiposity, co-morbid conditions, and genetic factors. Low testosterone levels in men are associated with low sexual desire and erectile dysfunction; reduced muscle mass and strength, and impaired physical function; decreased bone mineral density (BMD) and increased risk of osteoporotic fractures. Low testosterone as well as SHBG levels are each independently associated with increased risk of type 2 diabetes mellitus (T2DM) and all-cause mortality. it is possible that low testosterone level is a marker of poor health.

Testosterone treatment of older men with low libido and low testosterone levels improves sexual activity, sexual desire, and erectile function. Testosterone treatment increases muscle mass, muscle strength and leg power, and modestly improves stair climbing power, aerobic capacity, and self-reported mobility. Testosterone modestly improves depressive symptoms and corrects unexplained anemia of aging. Testosterone treatment of older hypogonadal men increases areal and volumetric BMD and estimated bone strength in the hip and spine. Testosterone administration reduces whole body and visceral fat mass. In the T4DM Trial, testosterone treatment administered in conjunction with a lifestyle program for 2 years was more efficacious than placebo in reducing the proportion of men with diabetes.

The adverse effects of testosterone treatment include erythrocytosis, growth of metastatic prostate cancer, reduced sperm production, and increased risk of detection of subclinical prostate cancer. Testosterone treatment does not worsen lower urinary tract symptoms. However, no adequately-powered trial of sufficiently long duration has been conducted to determine the effects of testosterone on the risk of prostate cancer or major adverse cardiovascular events (MACE). An ongoing randomized trial (TRAVERSE Trial) in hypogonadal men, 45-80 years, at increased cardiovascular risk, will provide definitive information on the effects of long-term testosterone treatment on MACE and other efficacy and safety outcomes.

Because of the lack of evidence of long-term safety and limited evidence of long-term efficacy, testosterone treatment of all older men with low testosterone levels is not justified. Instead, an expert panel of the US Endocrine Society suggested that testosterone therapy should be offered on an individualized basis...in men >65 years who have symptoms or conditions suggestive of testosterone deficiency (e.g., low libido or unexplained anemia) and consistently low testosterone". The decision to offer testosterone treatment to older men with testosterone deficiency should be guided by an individualized assessment of potential benefits and risks, the burden of symptoms, and patient preferences. A shared decision to initiate testosterone treatment should be accompanied by a standardized monitoring plan.

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Plenary 2: Metabologenomics and biochemical diagnosis of phaechromocytoma and paraganglioma

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Considerable advances over the past two decades in biochemical testing and clinical genetics of phaeochromocytoma and paraganglioma underly emerging needs to integrate the two disciplines in order to improve diagnosis and management of affected patients. Laboratory testing most usually follows clinical suspicion based on signs and symptoms of presumed catecholamine excess or a finding of an incidentaloma, though is increasingly carried out in patients due to hereditary risk associated with mutations of upwards of 15 genes. These and various somatic pathogenic gene variants result in distinct catecholamine-related biochemical presentations that should be considered when interpreting laboratory results or selecting an appropriate test. For this, advances in understanding catecholamine metabolism have clarified why measurements of the O-methylated catecholamine metabolites rather than the catecholamines themselves or other metabolites are important for effective diagnosis. The critical metabolites, normetanephrine and metanephrine, produced respectively from noradrenaline and adrenaline, can be measured in plasma or urine. For patients with signs and symptoms of catecholamine excess, either test will invariably establish the diagnosis, whereas the plasma test provides higher sensitivity for patients screened due to an incidentaloma or a hereditary predisposition. Additional measurements of plasma methoxytyramine can be important for some tumours, such as paragangliomas and for surveillance of patients with certain gene mutations or who are at risk of metastatic disease. Avoidance of false-positive test results is best achieved by plasma measurements with appropriate reference intervals and attention to preanalytics, including sampling blood in the fully supine position. Follow-up of positive results, including optimisation of preanalytics for repeat tests or whether to proceed directly to anatomic imaging or confirmatory clonidine tests, depends on the nature of test results, which can also suggest likely size, adrenal versus extra-adrenal location, metastatic involvement or even underlying mutations of tumour susceptibility genes. For the latter application, information from catecholamine and energy pathway metabolomes can be used not only to point to the most likely mutated genes but also to establish pathogenic functionality of new variants. Modern biochemical testing now makes diagnosis of PPGL relatively simple and is also meeting needs for integration with genetic testing for improved diagnosis and management of patients with the tumours.

The descent of the testis: the ascent of man

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Case report

Mr CJ was referred to the Keogh Institute for fertility treatment. He had bilateral cryptorchidism at birth. This and been treated in infancy with a 2-month course of pulsed GnRH delivered subcutaneously via a programmed pump, developed in a research protocol. At 2 years of age he had a right sided orchidopexy. At the age of 14 years he required induction of puberty with intramuscular testosterone esters (Sustanon). The presence of subnormal testosterone, undetectable LH and FSH, anosmia and of mirror movements (described by his mother as "lack of dominance") led to the diagnosis of Kallmann syndrome, which was confirmed by identifying a mutation in the *ANOS1* gene. There was no other childhood illness.

At age 33 years he was 193 cm tall and weighed 100.4 kg. He was clinically euthyroid. He was well androgenised, without gynaecomastia. The penis and scrotum were normal. A small left testis was palpable at the external inguinal ring. The right testis was located in the scrotum and 6 ml in volume. Anosmia was confirmed and synkinesis demonstrated. Semen volume was 1.1 ml with azoospermia. Testosterone (on treatment) was 12 nmol/L (10-35) and LH and FSH were undetectable.

Testosterone was ceased and he was treated with regimen of hCG (Pregnyl, Organon Pharma Pty Ltd) 1500 units 3 times weekly and recombinant FSH (Gonal-F, Merck Healthcare Pty Ltd) 150 units 3 times weekly, delivered subcutaneously by self-injection. The patient was counselled at the outset that induction of spermatogenesis was a "long project" and that the time course for the appearance of one sperm in the ejaculate was prolonged (around 15 months from the literature and our own experience) and fertility might require IVF. However, his total sperm count at 12 months after starting gonadotrophin therapy was 25.5 million, a startling response which significantly surpassed the response of other patients with CHH undergoing fertility treatment. His wife conceived naturally without recourse to IVF and has delivered a healthy boy.

Discussion

In gestation, GnRH neurons migrate from the olfactory placode to the preoptic-hypothalamic continuum, from whence they send projections to the median eminence to secrete GnRH and stimulate gonadotropin release by the pituitary[2]. Failure of this process during embryological development results in congenital hypogonadotrophic hypogonadism (CHH), including Kallmann syndrome. Boys with CHH may present at birth with features of impaired androgen effect – cryptorchidism or micro-penis – and/or later in life with failure to progress into puberty.

GnRH secretion is also responsible for minipuberty, the brief activation of secretion of both LH and FSH that occurs in boys in the first few months after birth. Minipuberty is therefore expected to be absent in infants with CHH. The surge of gonadotrophins at minipuberty leads to LH-driven testosterone secretion and FSH-driven increase in the number of Sertoli cells[6]. Sertoli cells are critical for future sperm-producing capacity since each Sertoli cell can only support the development of a finite number of germ cells.

In men with CHH, fertility may be achieved by induction of spermatogenesis with gonadotrophins, but the time course for success is long and the response variable[4]. From 44 studies of induction of spermatogenesis in CHH, Young et al[5] showed that the mean delay for any sperm to appear in the ejaculate is 15 months. Factors associated with a longer time course for successful therapy are a congenital aetiology or prepubertal onset of hypogonadotropic hypogonadism, cryptorchidism, and being the initial course of induction of spermatogenesis. Factors associated with a more rapid response are postpubertal onset of hypogonadotropic hypogonadism and being a subsequent course of induction of spermatogenesis[4]. Therefore, CJ's response to his first course of induction of spermatogenesis is clearly unexpected. Given his clinical history, the contrast between CJ's response and that of comparative patients raises the possibility the treatment that he received as an infant, although given for cryptorchidism, in fact induced minipuberty.

CJ's response also raises questions about the significance of cryptorchidism in infants and about how it should be approached. In clinical practice, the increased prevalence of cryptorchidism in boys with CHH highlights the crucial role of androgens in the second, inguino-scrotal phase, of testicular descent[7]. Despite the recognised role of androgens in testicular descent, most guidelines recommend surgical orchidopexy as the first choice of treatment rather than hormonal therapy[8]. Identification of the possibility of underlying CHH in boys with bilateral cryptorchidism has important therapeutic implications. Pulsatile GnRH therapy induces LH and FSH secretion, which more closely reflects normal physiology. GnRH therapy stimulates androgen production to induce testicular descent, as well as proliferation of the immature Sertoli cells through FSH[6], thereby more closely replicating the events of minipuberty.

The use of LH, FSH and GnRH therapies for infants with cryptorchidism, with or without CHH, has been examined in multiple studies. While such treatments, if they contain FSH, could be expected to have favourable outcomes for Sertoli cell numbers, so far there has been no report of the long-term success of subsequent fertility treatments as adults, and more data are needed on the long-term outcomes of neonatal gonadotrophin administration[9].

What does this mean for the treatment of cryptorchidism? Whilst a number of aetiologies lead to cryptorchidism, including mechanical, obstructive, genetic and hormonal, the possibility of CHH should not be missed, since it has major implications for future fertility[3]. Testosterone, LH and FSH can be rapidly and accurately measured in infancy to screen for patients suspected to have CHH[10]. Definitive molecular genetics will take longer. For infants identified with CHH, replicating minipuberty by delivery of both LH and FSH, or of pulsed GnRH to stimulate LH and FSH secretion, may lead to a profound improvement in the induction of spermatogenesis in adulthood.

Take home messages

- Slow response to induction of spermatogenesis in men with CHH is likely due to low Sertoli cell numbers as a result of the absence of minipuberty and of FSH-driven Sertoli cell proliferation as an infant.
- Presentation with cryptorchidism at birth, with or without micropenis, should prompt screening for CHH and minipuberty by measurement of gonadotropins and testosterone in the window where minipuberty is expected.
- Appropriate hormonal management in infants with CHH, using GnRH therapy to stimulate minipuberty and increase Sertoli cell numbers, may have long term benefits for fertility management as adults.

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Gynaecomastia in a young gym enthusiast

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Gynaecomastia is a common condition of breast tissue growth in males. It is most commonly a physiological process, associated with neonatal period, puberty and in older men. The differential diagnosis for non-physiological gynaecomastia is broad.

A 19-year-old male was referred from the breast service with an approximate 9-month history of gynaecomastia. Investigations demonstrated an elevated total testosterone level (up to 43.2nmol/L [RR9-30], and oestradiol (374pmol/L [RI<200]), suppressed gonadotrophin and elevated hCG levels (670IU/L [RI <3]). SHBG was 20nmol/L (RI 13-71). AFP was normal. No testicular masses were found on clinical examination or ultrasound (testicular volume 10.3 & 12cc). Over a similar time-period, he reported use of supplements obtained from his gym and had noted a 12kg weight gain, predominantly in lean body mass. He denied use of exogenous hormones.

Examination findings included BMI 23kg/m2, muscular build and bilateral tender gynaecomastia. There were no other abnormal findings. CT abdomen demonstrated borderline retroperitoneal nodes of uncertain significance. FDG-PET revealed bulky markedly hypermetabolic palatine tonsils and nasopharyngeal mucosal space with small volume bilateral cervical adenopathy. ENT assessment demonstrated enlarged tonsils and an urgent diagnostic tonsillectomy performed. The histology demonstrated lymphoid hyperplasia only.

Following resection of the tonsils, biochemical changes persisted. Another review of the FDG-PET raised the suspicion of an avid area adjacent to the duodenum, that appeared to be greater than expected for physiological uptake. Interval imaging demonstrated growth of this node and biochemistry showed hCG continued to rise (5550IU/L). The testes remained normal. The diagnosis was consistent with non-seminomatous germ cell tumour. He was started on BEP chemotherapy with normalisation of tumour markers and regression of enlarged retroperitoneal nodes. Later resection of a persisting enlarged node demonstrated a necrotic tumour with diffuse hCG staining.

Testicular germ cell tumours are an uncommon cause of gynaecomastia, accounting for less than 5% of patients presenting with gynaecomastia (*Daniels et al 2003*). Gynaecomastia is the presenting symptoms for approximately 10% of males with testicular germ cell tumours (*Tseng et al, Hernes et al*), but is more common with hCG secreting tumours (*Polat et al 2019*).

Spontaneous tumour regression of the primary tumour is an uncommon phenomenon that has been reported in several cancer types, including testicular cancer (*Astigueta et al*). It was thought that these lesions may represent extragonadal germ cell tumours. However, it has been demonstrated that in patients with retroperitoneal nodal disease, with no evidence of testicular tumour on examination or ultrasound, do have evidence of a regressed tumour in the testis on histology (*Scholtz et al*).

This case demonstrates a rare cause of gynaecomastia due to metastatic non-seminomatous germ cell tumour of the testis, with spontaneous tumour regression of the primary testicular lesion. Careful investigation and follow-up identified a metastatic lesion that led to appropriate treatment. This case illustrates the importance of a high degree of suspicion, despite a history of gym and recent supplement use and the vital role of radiology review.

Take home messages

While many causes of gynaecomastia are benign, there are serious causes that require careful evaluation not to be missed.

Review of investigations including radiology is vital, when there is a clear pathogenic process without an explanation.

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Puberty strikes a discord: a rare case of Klinefelter syndrome

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Introduction

Klinefelter Syndrome (KS) most common sex chromosome aneuploidy, affecting 1 in 500-1000 males(1,2) with classical karyotype 47,XXY in >80%(1). Phenotype varies and influences age at diagnosis. The majority are diagnosed after puberty onset(1) and ~30% in adulthood with symptomatic androgen deficiency or infertility(2). Minor KS karyotypes include: 48,XXXY, 48,XXYY, 49,XXXXY and the extremely rare 46,XX/47,XXY mosaic with 20 cases reported(3,4).

"Disorders/difference of sexual development (DSD)" is an umbrella term for congenital conditions of atypical chromosomal, gonadal or anatomical sex development(5,6). Ovotesticular-DSD are a rare subgroup(<5%), incidence <1/20,000, in which ovarian and testicular tissue are present in the same individual. The most common karyotypes in Ovotesticular-DSD are: 46,XX, 46,XX/46,XY and 46,XY(3)

We describe a case of Ovotesticular-DSD occurring with 46,XX/47,XXY mosaic Klinefelter Syndrome with gender-discordant puberty.

Case Details

J is the second of four children to non-consanguineous parents, born via caesarian-section at 29+5 weeks' gestation (weight 1.2kg, 48th centile) for premature labour. He spent 7 weeks in NICU with complications including: transient tachypnoea of newborn, hypoglycaemia, suspected sepsis and periventricular leukomalacia.

At birth, ambiguous genitalia were noted: bilateral undescended testes, micropenis and severe hypospadias. Ultrasound confirmed gonads resembling testes in inguinal canals and a bladder-adjacent thick-walled cystic lesion. Genitogram and MRI suggested this was a Mullerian remnant. Ovaries were not visualised. Lymphocyte chromosomal analysis scored 54% of cells 47,XXY and remaining 46% 46,XX, diagnostic of mosaic KS, confirmed by fluorescence in-situ hybridisation.

Gonadotrophin and testosterone levels were consistent with normal neonatal pubertal surge: LH 3.5IU/L (0.5–1.9IU/L), FSH 1.6IU/L (0.2–1.8IU/L), testosterone 6.5nmol/L (0.03–6.14nmol/L). Oestradiol was not performed (inadequate sample). AMH measured 632pmol/L (22.8–489.1pmol/L male, 3.57-17.85pmol/L female).

Cystoscopy and laparoscopy confirmed urogenital sinus leading to a normal bladder, communicating with a hollow structure without obvious cervical or uterine tissue. Vas deferens and testicular vessels were normal on the right but appeared atrophic on the left. Left inguinal exploration and gonadopexy was performed, with normal-appearing, small testis(<1ml), normal epididymis.

Follow-up to 3 years was inconsistent. Weight, height and head circumference tracked along 25-50th centiles. Mild developmental delay was noted without signs of cerebral palsy. External genitalia matured with penile length 2.5cm at age 13 months. At 2years 3 months, penile length measured 3cm. Family confirmed preferential behaviour consistent with male phenotype and J was becoming distressed by his anatomy. Surgery was performed from age 3: right orchidopexy, laparoscopic excision of Mullerian remnant/utricle then hypospadias repair. Gonadal biopsy was consistent with prepubertal testis bilaterally.

12 months post surgery, J was progressing well developmentally, with little evidence of genital ambiguity and good urinary function. At 4yrs 7 months, stretched penile length was 3.2 cm, right scrotal testis ~2mL palpated normally and left scrotal testis ~1mL.

J was next seen at age 10 years 7 months with behavioural concerns. He measured 146.8cm (75th centile), 37kg (60th centile) with recent growth spurt and new body odour. He had Tanner 2 pubic hair, stretched penile length 4.5cm and testicular size 2mL right, 2-3mL left with no breast development.

At 12 years 2 months, with puberty progression, J had Tanner 3-4 pubic hair and stage 3 genitalia. Right testis was 6-7mL, left remained 2-3mL. Bilateral gynecomastia was present: 6-7cm discs breast tissue and secondary areola elevation. Ultrasound scrotum demonstrated right testis with epididymal cyst. An ovoid structure 14x14x7.6mm with heterogeneous echotexture was seen in the left hemi-scrotum, with no evidence of testis(Figure 1).

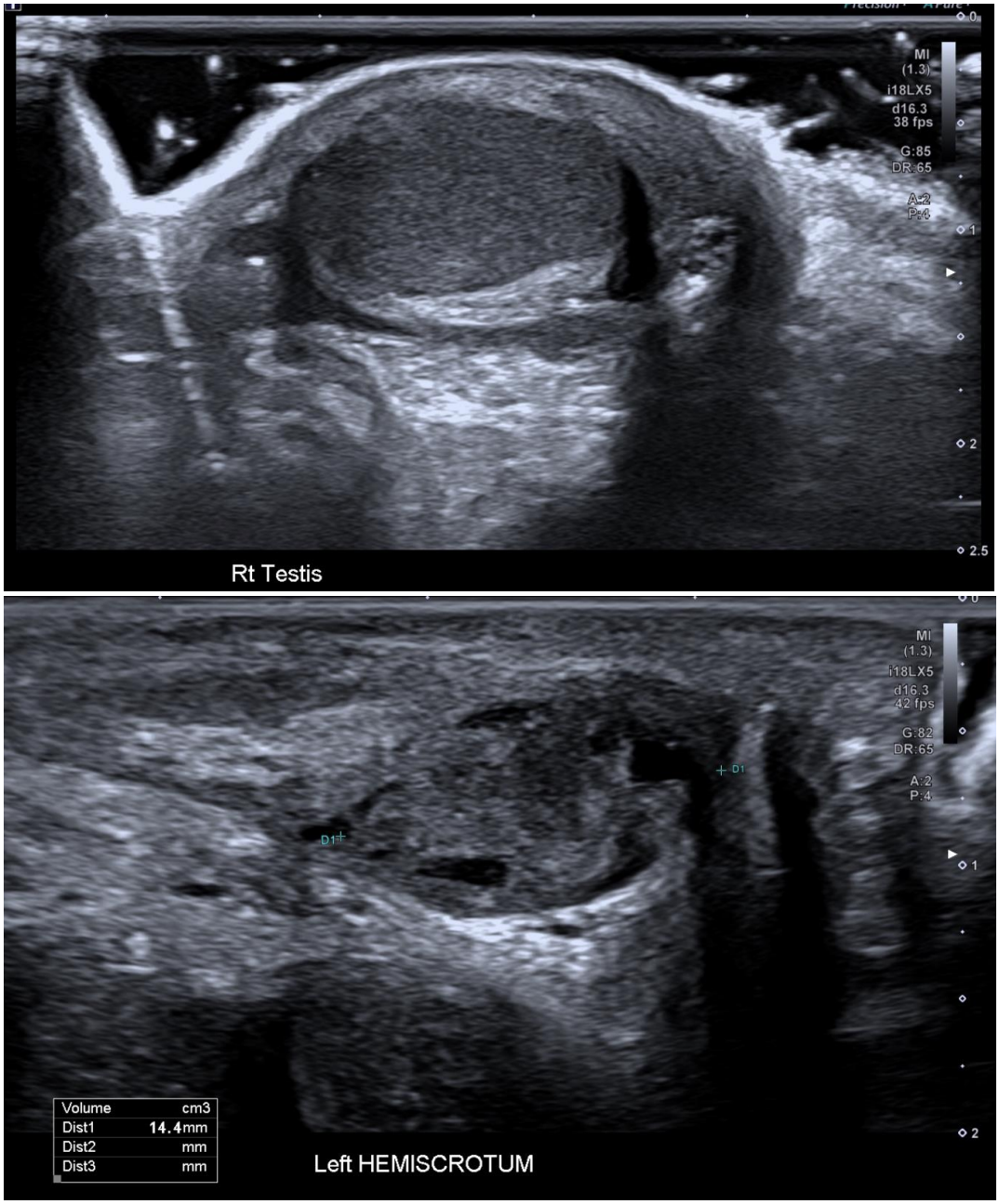

Figure 1: ultrasound scrotum demonstrating right testis with normal echo pattern and 14 mm heterogeneous focus in the left hemiscrotum with internal vascularity.

Biochemical analysis confirmed elevated oestradiol 214pmol/L (<160pmol/L) with low testosterone 0.8nmol/L (2.0-27nmol/L Tanner 3-4 male), LH 2.4IU/L (1.0-12IU/L) and FSH7.3IU/L (0.6-12IU/L). AMH was 5.3pmol/L (29-800pmol/L). Tumour markers were negative.

Family and J confirmed strong identification as male and a single injection depot leuprorelin acetate was given to facilitate further investigation. Provisional diagnosis was of gender incongruent puberty driven by oestrogen possibly from ovarian tissue in the left hemiscrotum.

Left gonadectomy was performed after DSD multidisciplinary review. Gross appearance of craggy, firm posterior pole mass, resected en-bloc with spermatic cord and epididymis. Microscopy confirmed ovotestis with almost completely atrophic testis and functioning ovarian tissue with no evidence of malignancy(Figure 2). Breast buds were noted post-operatively to be softened and decreased post GnRH analogue treatment.

Figure 2: [histology images to follow - result only just finalised and formal photography unfortunately not available at submission]

Discussion

This case is consistent with the 20 other reported cases of 46,XX/47,XXY KS mosaicism(3,4). Ambiguous genitalia occur in ~40%. Half have normal male external genitalia and present in adolescence with gynaecomastia and/or cyclical haematuria/scrotal pain. Most cases are raised male, although Mullerian structures occur in ~80%. A range of gonadal phenotypes is seen and left-right lateralisation is predictable, with right gonad likely to be pure testis and left most likely to be ovary or ovotestis. 46,XX predominates: in 88% peripheral blood cells and 83% of gonadal cells. This does not predict external

genitalia, nor gonadal histology. Testosterone and LH/FSH are low in prepubertal ages, and low testosterone with elevated LH/FSH in adolescence/adulthood, similar to classical KS. Our case also followed the typical approach to treatment: those with ambiguous genitalia were raised as male and underwent surgical removal of Mullerian structures and unilateral gonadectomy.

Concerns for ongoing care are consistent with typical KS patients: behaviour, metabolic comorbidities, reproductive functionality and malignancy risk(1,2). Germ cell tumour has been diagnosed in 2 46,XX/47,XXY cases. Rates in 47,XXY KS and general population are 1 in 4000 and 1 in 83,333 respectively. No data are available, but breast cancer risk is expected to mirror classical KS population (~3%)(2,3). There is no report of reproductive success in 46,XX/47,XXY and spermatogenesis has been generally absent in examined cases(3). Rare cases of spontaneous fertility occur in classical KS, and successful pregnancy is reported in 9 individuals with Ovotesticular-DSD(3).

The potential for Ovotesticular-DSD was understood from birth and efforts made to identify atypical gonadal tissue. Early intraoperative gross examination and subsequent biopsy of the left gonad were strongly suggestive of a testis, with minor size difference between gonads a non-specific clue. Loss to follow-up may have contributed to slight diagnosis delay.

Presentation at puberty resulted from functioning ovarian tissue producing oestradiol in response to pubertal gonadotrophins, supported by clinical response to depot GnRH analogue treatment. In classical karyotype KS, boys enter puberty regularly and testosterone rises, allowing development of secondary sexual characteristics, before evolution into hypergonadotrophic hypogonadism in young adults and sometimes later onset gynaecomastia(1).

Early sex assignment seemed relatively straightforward given strong male predilection from early age. This may be challenging in Ovotesticular-DSD and gender outcome is unpredictable in many cases(7-9). A pertinent consideration given recent local proposal of legislation criminalising deferrable sex assignment intervention in intersex children(10).

Learning points:

- Klinefelter syndrome and Ovotesticular-DSD can be variable phenotypically and genetically
- Presence of KS 47,XXY within a mosaic karyotype confers potential risk of the same long-term complications as typical KS
- Specialised tertiary DSD MDT care is required in all cases of DSD and regular follow-up is essential
- 46,XX/47,XXY KS should be treated as an Ovotesticular-DSD with MDT care
- Although rare, complexity combined with social challenges in this case contributes valuable lessons to legislation considerations

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Malignant transformation of a pituitary adenoma: an ongoing management difficulty.

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Case

A 65 year old woman, presented in 1977 at the age of 24 with amenorrhoea and visual loss, was diagnosed with a functioning lactotroph adenoma and underwent surgical resection with good recovery of vision post-operatively. She had an uncomplicated post-operative period and maintained a normal serum prolactin level without any need for dopamine agonist therapy.

24 years later, in 2001, she was diagnosed with Acromegaly and underwent surgical resection and adjuvant radiotherapy of her pituitary adenoma (Figure 1). Documented history suggests she achieved adequate resection with no residual tumour, but routine imaging 11 years later in 2012 discovered radiological recurrence followed by clinical and biochemical recurrence 2 years later in 2014. Treatment with Octreotide and Cabergoline were trialled unsuccessfully with ongoing tumour growth and compression of the optic chiasm. She underwent another surgical resection and radiotherapy in 2016 complicated by a prolapse of her optic chiasm, eventually requiring trans-sphenoidal chiasmopexy in 2018 due to visual deterioration. Her post-operative imaging demonstrated evidence of a 17 x 12 x 11mm hypoenhancing lesion in the left posterolateral aspect of the sella (Figure 2).

In January 2019 she had an increasing IGF-1 level 46nmol/L (reference range 7 – 26nmol/L) and residual adenoma growth now measuring 18 x 14 x 16mm in size. As such she was started on Pasireotide, but after 2 months on treatment presented to hospital with an acute T7 spinal cord compression requiring surgical decompression (Figure 3). Histopathology of the compressive lesion confirmed positive staining for growth hormone, Pit-1 transcription factor and Ki67 of 30%; overall appearances consistent with a pituitary carcinoma.

She underwent radiotherapy to her affected vertebrae, adjuvant Temozolomide and continued Pasireotide. Despite treatment, repeat imaging 2 months later showed enlargement of the T7 spinal metastasis and primary pituitary tumour now measuring 23 x 19 x 21mm in size. Her Temozolomide therapy was also complicated by prolonged pancytopaenia and an episode of sudden-onset visual deterioration in her left eye due to tumour haemorrhage requiring urgent surgical debulking and decompression. Post-operative imaging showed residual tissue abutting the left optic nerve and clinically she had ongoing obscured left eye visual acuity; registering hand movements only. Histopathology was in keeping with previous findings with a Ki67 of 30% and evidence of lymphovascular invasion.

In March 2020, MRI demonstrated evidence of tumour progression now measuring 13 x 18 x 12mm with an elevated IGF-1 of 39.3nmol/L (reference range 9.0 – 28.0nmol/L) and new adrenal insufficiency (early morning Cortisol 117nmol/L) requiring Hydrocortisone replacement therapy.

She underwent molecular profiling which demonstrated a low tumour mutational burden, CDK4 amplification, CCDN2 amplification, FGF23 amplification and FGF6 amplification. Due to her CDK4 amplification she was commenced on a phase 1 trial of a CDK inhibitor and underwent 2 cycles of treatment before developing complete loss of vision in her left eye, further tumour progression in Meckel's cave measuring 25 x 25mm and an increasing IGF-1 level now measuring 91.0nmol/L (reference range 9.0 – 28.0nmol/L).

She subsequently entered a different phase I trial with a humanised anti-CD47 IgG4 monoclonal antibody, but had further progression with an IGF-1 of 127nmol/L and a decision was made to attempt further neurosurgical bulking in March 2021. Post-operative imaging showed significant residual measuring 46 x 42 x 40mm encasing the Circle of Willis and supraclinoid ICA bilaterally (Figure 4, Figure 5). Based on ESE clinical practice guidelines and case reports, she underwent treatment with Bevacizumab (Avastin) but presented to hospital 2 months later with significant constipation and urinary retention. Her MRI demonstrated progressive spinal and leptomeningeal metastases in the lumbar and lower thoracic region, for which she received radiotherapy, but had worsening symptoms of faecal and urinary incontinence, abnormal gait and falls.

Follow-up MRI in late 2021 showed stable pituitary disease measuring 35 x 35 x 47mm, but now with extensive spinal disease with leptomeningeal features and a decision was made for palliative management. She passed away peacefully at home after withdrawal of active treatment.

Discussion

Pituitary carcinomas are rare, with a prevalence of 0.1-0.5% of all pituitary tumours (1), the most common of which are Prolactin and ACTH-secreting carcinomas. There are multiple case reports of malignant transformation of pituitary adenomas of varying lineages (1,2); including a recent review of 38 patients with malignant transformation of non-functioning pituitary adenomas (1). Average latency between first presentation of a pituitary adenoma and malignant transformation varies between 4.7 - 9.5 years depending on the function of the carcinoma (3). Monitoring and early diagnosis are important in cases of pituitary carcinoma due to their high mortality rate of 66% at 1 year and almost 80% within 8 years of diagnosis (3).

Treatment of pituitary carcinomas are still limited, usually consisting of surgery, radiation therapy and adjuvant medical therapy with varying levels of success; the majority of which are resistant to conventional treatment (4). The metastatic nature of the disease involving dual, spinal and leptomeningeal metastases further complicates management, but there is a reported a case of sellar pituitary carcinoma with dural and leptomeningeal disease that responded well to surgical resection and salvage radiation with no evidence of disease progression for 13 years (5). Biochemical monitoring can also be difficult with a reported a case of treatment-resistant metastatic GH-secreting pituitary carcinoma showing decreased GH levels, much like our patient, suspected to be due to dedifferentiation of the tumour (6).

Temozolomide, an alkylating agent usually used in the treatment of glioblastoma, has been effective in only 50-71% of case reports when used in pituitary carcinoma (3,4); highlighting the need for more effective therapies. The concept of molecular profiling and genetics of endocrine tumours has been reported since 1998 (7) and remains an ongoing field of research; with multiple genes and cell-cycle regulators identified that play a role in pituitary adenoma progression, malignant transformation and metastases (3,8,9,10). Future improvements in molecular profiling may identify biomarkers and molecular targets for treatment in patients with pituitary carcinomas; a step closer to personalised medicine.

Take home messages:

- Though rare, pituitary adenomas have the potential for malignant transformation; the mechanism of which is still not fully understood.
- In patients with known pituitary carcinomas presenting with extra-cranial localised symptoms, always consider imaging to rule out potential metastases.
- Survival of patients with pituitary carcinomas remains generally poor with minimal available treatment options.
- Tumour molecular profiling and biomarkers may assist in future targeted treatment options for patients.

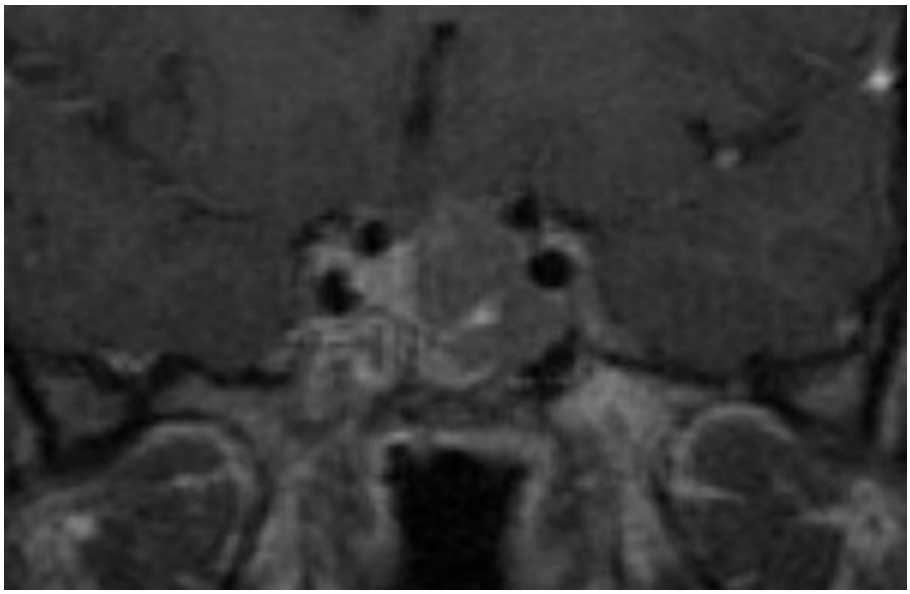


Figure 1.

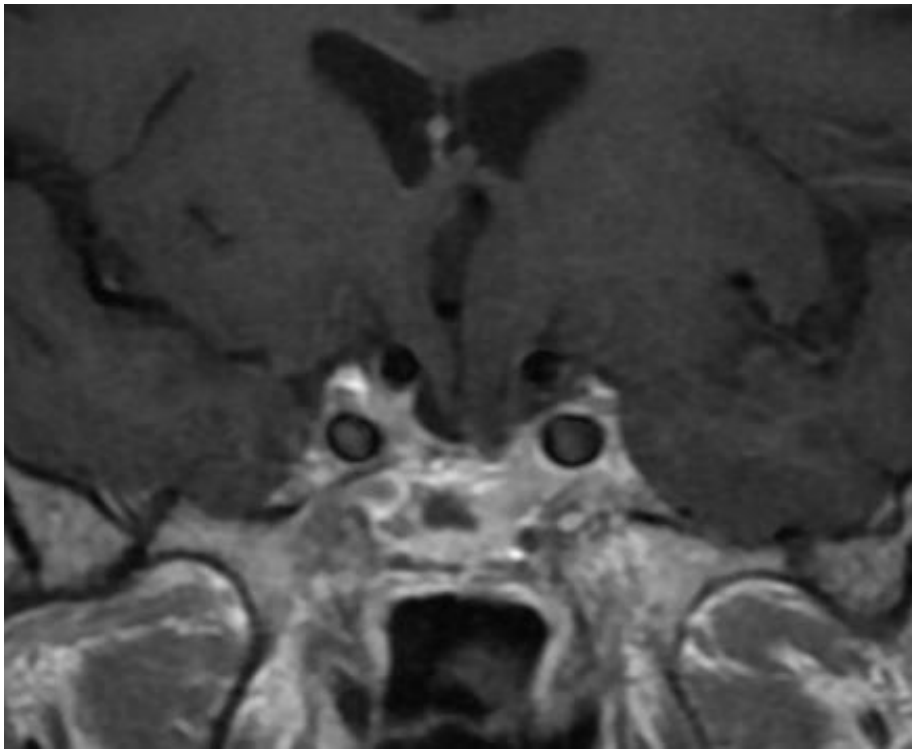
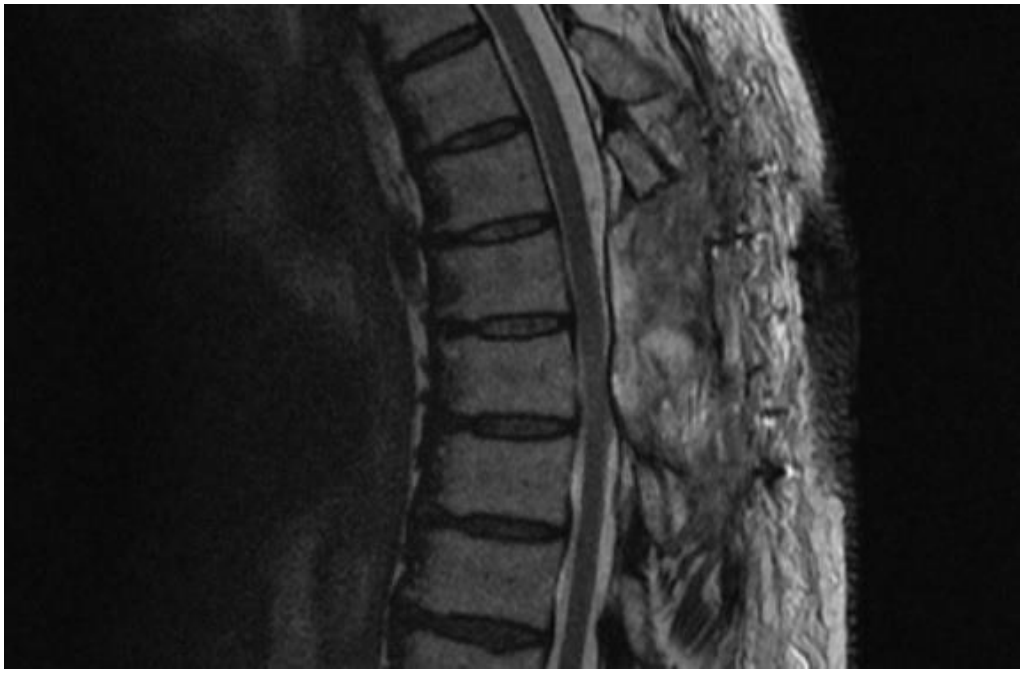


Figure 2



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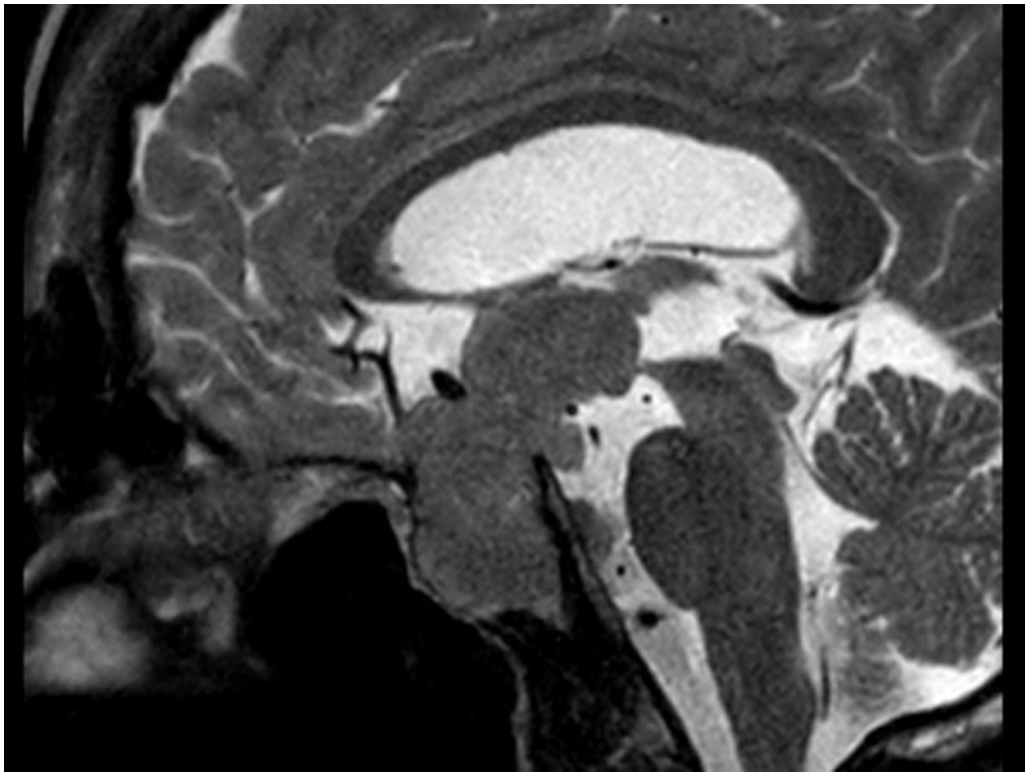

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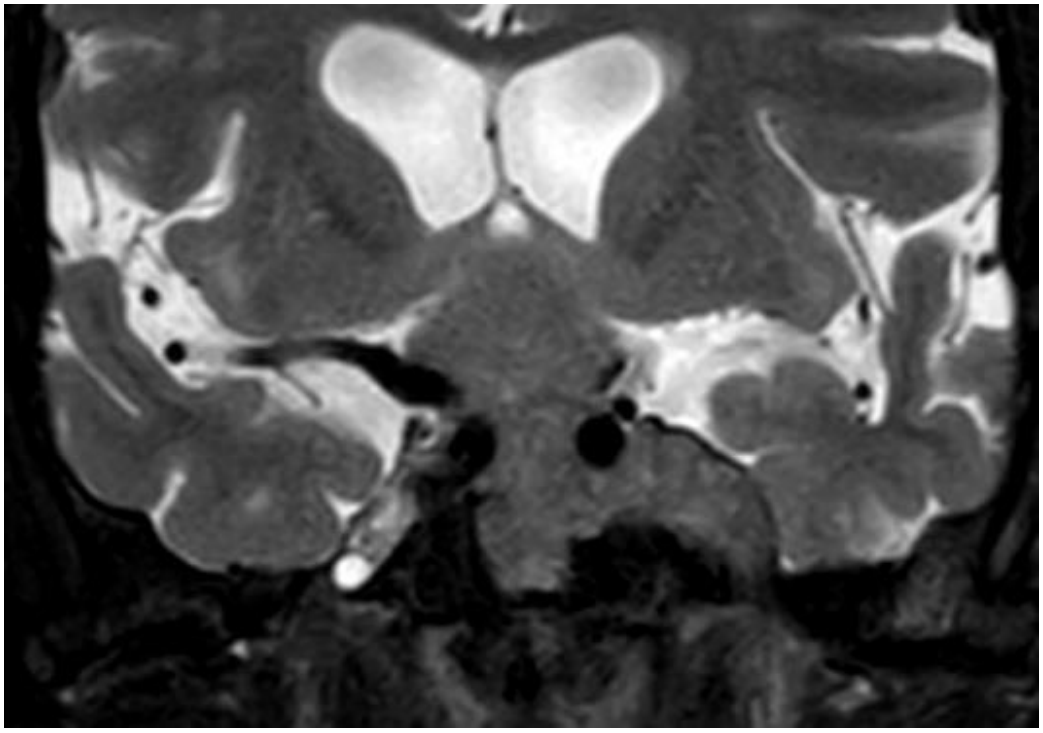

Figure 5.

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An interesting case of acromegaly

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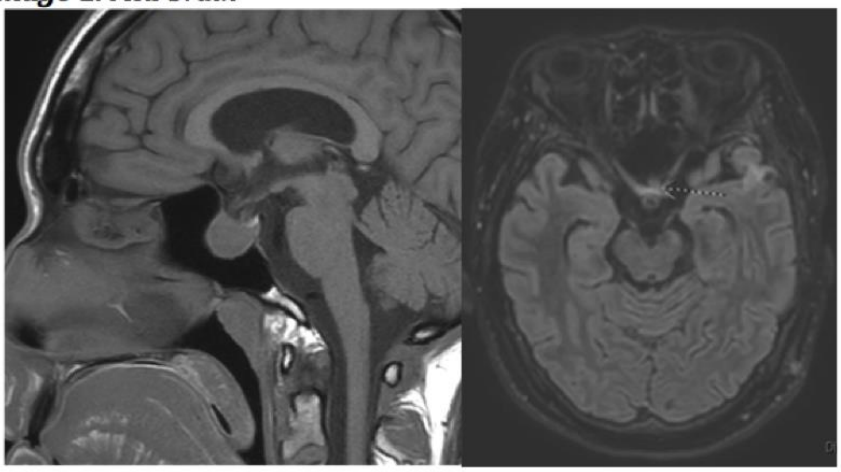
A 21-year-old female presented with a one-month history of worsening chest pain and shortness of breath. She was found to have a recurrence of a left atrial myxoma that was previously excised 5 year ago in the Philippines. She underwent an excision of a 27 x 25mm myxoma that was adhered to the foramen ovale. On weaning sedation she was noted to have a right-sided motor deficit and gaze palsy. A CT brain revealed a large MCA stroke with a large core and large penumbra. She underwent endovascular clot retrieval but had a malignant middle cerebral artery syndrome requiring a compressive hemicraniectomy and external ventricular drain placement. A repeat CT brain showed an incidental, marked enlargement of the pituitary gland with extension into the sella turcica. An MRI brain confirmed the presence of a 19 x 27 x 20mm 19 x 27 x 20mm T1 isointense, T2 isointense mass arising from the sella and extending superiorly into the suprasellar space. (Image 1)

***Image 1.** MRI brain*



19 x 27 x 20mm T1 isointense, T2 isointense mass arising from the sella and extending superiorly into the suprasellar space. Associated posterior, superior and rightward displacement of the normal pituitary gland, posterior pituitary focus and pituitary stalk. The lesion extends superiorly just anterior to the optic chiasm. The chiasm is mildly indented by the superior aspect of the mass just to the left of midline and there is minor oedema viaible within the chiasm on the flair axial sequence Partial erosion of the right posterior clinoid as well as the floor of the sella. There is tumour extension into the right cavernous sinus with tumour extending both inferior and superior to the horizontal cavernous segment of the right ICA .

The patient was reviewed by the endocrine team and was noted to have features of acromegaly including large hands, frontal bossing and prognathism (*Image 2*). Visual fields were intact. There was no evidence of pigmented skin lesions or cutaneous myxomas. There was no family history of endocrinopathy or cardiac tumours. A pituitary panel was sent, the results of which are summarized in table 1.

Image 2. Clinical features of acromegaly

Table 1. Endocrine panel

	5th May 2022	18th May	24th May	Reference range
GH	23.3		30.9	0.0-10.0 mU/L
IGF-1	66.9		82.9	15.5-50nmol/L
TSH	0.15	0.28		0.4-4.8mIU/L
T4	8.4	6.6		8.0- 16.0pmol/L
T3	9.0	8.8		4.0-6.0pmol/L
Prolactin	296			50-500mIU/L
FSH	4.3			
LH	3.7			
Cortisol	245			
ACTH	1.8			1.6-13.9pmol/L
TRAb		2.5		<1.8
TPO		447		0-10

A short synacthen test was performed in the context of a relatively low early morning cortisol. Baseline cortisol was 390nmol/L, ACTH 4.1pmol/L with a robust response to synacthen (600nmol/L and 665nmol/L at 30 and 60 minutes respectively).

A raised IGF-1 and clinical features of acromegaly along with an atrial myxoma raised the suspicion of Carney Complex. A thyroid ultrasound was performed and revealed multiple TI-RADS 1 nodules. A CT abdomen revealed nodular contour of the bilateral adrenal glands, more prominent on the left and mild on the right with a focal nodule of the left adrenal body, measuring 6mm axial with the following attenuation values: non-contrast 32 HU, portal venous 86 HU, delayed 44 HU, corresponding to an absolute washout of 78% and a relative washout 49%, compatible with an adrenal adenoma.

A biochemical evaluation of the adrenal adenoma was performed. A 1mg dexamethasone suppression test showed failure to suppress with a morning cortisol of 274nmol/L. A 24-hour urinary free cortisol failed to confirm hypercortisolism with a urine volume of 1.5L, cortisol concentration of 38nmol/L and cortisol excretion of 59nmol/d. 3-Methoxytyramine, plasma metanephrine and normetanephrine levels were within normal range at <25 (<100pmol/L), < 50 (<447pmol/L) and 425 (<560pmol/L) respectively. DHEAS was 1.1umol/L, oestradiol 81pmol/L, FSH 4.3IU/L, LH 3.7IU/L. Aldosterone/Renin was 0.8.

She was commenced on Lanreotide 90mg monthly for management of a growth hormone secreting pituitary adenoma and thyroxine 50mcg daily for the management of central hypothyroidism. Her genetic profile is pending however she was diagnosed with Carney Complex based on clinical features. She referred to the neurosurgical team for consideration of resection of the pituitary adenoma and was discharged home with a plan to follow up as an outpatient for further investigation and management.

Literature review

Carney Complex (CNC) is a rare, multiple endocrine neoplasia syndrome. It is characterized by pigmented lesions of the skin along with cardiac and cutaneous myxomas and multiple endocrine tumours (1). The mean age of presentation is 20 years and its prevalence remains unknown, though there have been over 750 cases reported in the literature (2, 3). It is most frequently inherited in an autosomal dominant fashion with mutations in the protein kinase A regulatory subunit gene (PRKAR1A), however approximately 25% of cases occur as a result of a de novo mutation (4).

Cutaneous manifestations are prevalent in more than 80% of patients and vary in presentation from lentigines, blue nevi and cutaneous myxomas (3). Lentigenes typically present early in life, become more prominent at puberty and fade during adulthood (3). Cutaneous myxomas are seen in less than one half of patients with CNC, but when histologically confirmed, strongly suggest diagnosis (3).

The most common non-endocrine tumors in CNC are cardiac myxomas, which affect 20-40% of patients (3). Most sporadic cardiac myxomas are definitively treated with surgical resection, however cardiac myxomas in Carney complex tend to occur at a younger age, and may be multiple and recurrent (5).

Endocrine abnormalities are associated with tumours of the adrenal and pituitary glands, and gonads (3). Primary Pigmented Nodular Adrenal Dysplasia (PPNAD) is the most common endocrine tumour in patients with Carney Complex. Individuals may develop Cushing's syndrome from ACTH independent hypercortisolism but atypical and cyclical Cushing's syndrome has also been reported (6).

Growth hormone secreting pituitary adenomas with clinical acromegaly occurs in approximately 10-12% of patients with CNC. This is usually the result of a solitary, underlying adenoma (3). However, up to 75% of patients have an asymptomatic elevation in growth hormone and IGF-1, even without the presence of a pituitary adenoma, suggesting the somatomammotroph hyperplasia is common among patients with CNC and is potentially a precursor of growth hormone secreting adenomas (7).

The diagnosis of CNC can be made on genetic testing or clinical features (table 2) (8). The diagnosis can be confirmed by the presence of two or more two or more major criteria or identification of a pathological variant of PRKAR1A or the presence of one major criteria and an inactivating mutation of PRKAR1A in a first-degree relative (8).

Guidelines for surveillance of patients with CNC are lacking, however, yearly follow up has been shown to improve prognosis (9, 10). Recommendations for ongoing surveillance include; yearly echocardiogram or biannual cardiac imaging if the patient has been diagnosed with a cardiac myxoma; regular skin checks; hormonal evaluation including GH, IGF-1, prolactin and investigations for Cushing's syndrome as appropriate; thyroid examination and ultrasound; imaging of the adrenals and pituitary; testicular examination and ultrasound for detection and follow up of LCCSCT; transabdominal ultrasound of the ovaries in females; close monitoring of linear growth rate and pubertal staging in children (9, 10).

Take home messages

- Carney complex is a rare syndrome caused by inactivating mutations in the PRKAR1A gene. It is usually inherited in an autosomal dominant manner, however 25% of cases occur as a de novo mutation.
- It is characterised by multiple, benign tumours affecting the skin, pituitary, thyroid, heart, adrenals and gonads.
- Diagnosis can be made in individuals with two or more major diagnostic criteria or those with confirmed mutation in the PRKAR1A gene.
- Individuals diagnosed with Carney Complex should undergo lifelong screening for manifestations and complications of the condition

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A diagnostic enigma – the issue without the right tissue.

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A 52-year-old woman presented to hospital with two years history of intermittent headache, polydipsia, polyuria, amenorrhea, weight gain and a pruritic nodular rash. MRI brain organised by the GP revealed a large ill-defined nodular lesion of the left hypothalamus, extending along the left lateral wall of the third ventricle and into the caudate nucleus. The pituitary gland and infundibulum otherwise were reported to be normal. Past medical history included sub-optimally controlled type 2 diabetes mellitus with admission HbA1c of 9.2%. Insulin was added to her regimen of metformin, gliclazide and dulaglutide. Primary sclerosing cholangitis (PSC) had been diagnosed one year earlier on magnetic resonance cholangiopancreatography and liver biopsy after presenting with liver function test derangement. She was managed with ursodeoxycholic acid and anti-histamines for troubling pruritus.

The patient was reviewed by Neurosurgery and deemed not suitable for brain biopsy due to high risk of developing hemiplegia. She was subsequently investigated by Endocrinology for her symptoms of polyuria and polydipsia. At water deprivation test confirmed central diabetes insipidus and she was commenced on desmopressin with good effect. Baseline pituitary panel noted an elevated prolactin level: 1270mIU/L [RR: 110-560mIU/L] and hypogonadotropic hypogonadism (LH 0.1 IU/L and FSH 2.2 IU/L). She was also found to have PTH independent hypercalcaemia (cCa 2.85mmol/L, PTH 2.8mmol/L) raising suspicion of an underlying malignant process. Extensive work up was then conducted.

Immunological screening, HIV serology, serum electrophoresis and IgG subsets were normal. Lumbar puncture noting mixed inflammation with a glucose of 5.7g/L, total protein of 0.96g/L; oligoclonal bands were not detected, culture and flow cytometry were negative. Serum flow cytometry detected minor population (2%) of CD4 / CD8 co-expressing T cells, although non-specific as per haematology review. The 1,25-Vitamin D level was elevated at 159pmol/L [RR: 35-120pmol/L] but serum ACE level was normal. Whole-body CT scan failed to identify any granulomatous or malignant foci. Multiple skin biopsy were performed of the nodular skin lesions, in conjunction with Dermatology and Haematology, but returned negative for lymphoma, histiocytosis and sarcoidosis. An FDG-PET scan was performed, with increased uptake detected in the left hypothalamus, right sacrum and posterior L2 spinous process. The pituitary gland, however, did not have increased avidity. The patient was then discharged home for ongoing outpatient investigation and active surveillance.

After discussion with Radiology team, outpatient MRI pelvis was performed to better characterise the PET avid lesion. The signal seen on FDG-PET was unrevealing on MRI, however a left great trochanteric intramedullary lesion was evident. Both lesions were further characterised on a technetium bone scan as showing no abnormal bone tracer uptake and therefore biopsy was not pursued. Repeat MRI demonstrated no significant interval change. The patient then developed central hypothyroidism and thyroxine was commenced.

She underwent bone marrow aspirate and trephine biopsy which was normal and was subsequently discharged from Haematology. Dermatology performed repeat outpatient biopsies of the persistent rash, which returned nonspecific and was managed on a presumptive diagnosis of pruritic, prurigo nodularis secondary to her progressive PSC.

Meanwhile, her PCS was monitored closely by Gastroenterology; on routine surveillance gastroscopy – an incidental inflammatory polyp revealed features suspicious for Whipple's Disease. In rare case reports, Whipple's disease has neurological involvement, and so repeat biopsies from the terminal ileum and transverse colon were pursued. These were inconsistent with Whipple's disease, but systemic causes including systemic Langerhans histiocytosis was re-considered, and indeed the tissue stained positively for CD1a and S100, confirming the diagnosis. Given these results, her previous liver biopsies were reexamined and identified CD1a sparsely in some cells. A diagnosis of multisystem Langerhans diagnosis was made, unifying all patient's presentation: liver, bone, DI, hypothalamic lesion and likely skin. Given cutaneous LCH can often be non-diagnostic on biopsy, Dermatology felt there was likely involvement despite no histological, or immunostaining evidence for Langerhans cell infiltration. The patient was subsequently re-referred to haematology for treatment.

The patient was commenced on cytarabine chemotherapy; she completed four cycles with improvement in her neurological symptoms, resolution of her central hypothyroidism and improvement to her skin. Follow up PET scan demonstrated complete metabolic response and MRI brain demonstrated dramatic improvement (Figure 2). Unfortunately, the PSC from occult LHC has caused persistent jaundice(bilirubin 308umol/L, RR <20umol/L). Without considering her liver disease, haematologists consider her response to treatment excellent, with 5 year survival over 80%. The patient is currently on the waitlist for Liver transplantation.

Discussion:

Langerhans cells histiocytosis (LCH) is a rare disorder characterised by neoplastic infiltration of histiocytes and may affect single- or multiple systems including pituitary, hypothalamus, pulmonary and bony involvement. Gastrointestinal involvement, as seen in our patient is less common with less favourable clinical outcomes. There is also case reports of LCH involving the thyroid gland [1, 2]]

LCH typically affects children aged 1 – 4 years old; adult onset LCH occurs in 1-2 million per year [3]. The diagnosis is made on histopathology, with affected tissue staining positive for CD1a, CD207 and S100 on immunochemistry study [4,5]. However, as seen in our case, this process can be challenging at times, CD1a staining can be scares leading to alternative diagnosis. In particular, liver biopsies could resemble those of PSC or even cirrhosis at later stage[6]. More recent genetic studies have revealed universal association with BRAF and /or MAP2K1 mutations in LCH, and this may provide future targeted therapeutic treatment options for these patients [5,7].

Diabetes insipidus (DI) is the most common endocrine manifestation of LCH, affecting approximately 25 percent of individuals. Unlike our case, individuals presenting with DI whom have evidence of pituitary disease, diagnostic biopsy is generally considered safe, with minimal surgical complications. Anterior pituitary hormone deficiency can be seen in LCH, including hypogonadotropic hypogonadism and less commonly ACTH deficiency and central hypothyroidism [4]. Prolactin elevation is thought to be due to stalk effect (LCH cell infiltrating the pituitary stalk, leading to reduced transmission of dopamine from the hypothalamus). Up to 50% of children with DI have growth hormone deficiency and may present with developmental delay [4,8]. Replacement of growth

hormone deficiency in the adult population has not been widely explored. These endocrinopathies, particular DI, maybe permanent despite effective treatment of LCH. [4,8].

LCH involving the hypothalamus is less frequently seen [4,8]. Hypothalamic involvement may cause issues with thermoregulation, obesity (secondary to increased appetite), neuropsychiatric, autonomic and metabolic abnormalities [4]. LCH may cause impaired glucose tolerance or worsening of diabetes mellitus – obesity and glycaemic issues were evident in our case study [4,8]. Interestingly, there has been another case report of non-PTH dependent hypercalcemia described in a LCH patient with elevated 125 vitamin D. The hypercalcaemia completed resolved with treatment LCH as seen in our patient. [9].

Compared to single organ LCH, multisystem LCH has less favourable prognosis; particularly with involvement of the haematopoietic system, liver or spleen [6,8,10]. For single organ LCH, treatment is guided by site and extent of disease. Options includes excision of solidary involvement, phototherapy for cutaneous disease and radiotherapy for bony LCH [10]. Systemic treatment is recommended in multisystem LCH. Mild cases may be managed with methotrexate, azathioprine or thalidomide, whilst severe disease have been successfully managed with cytarabine or etoposide [10]. Reactivation of LCH occurs in a quarter of adult patients, typically those with multisystem disease [10]

Take home messages:

- Langerhans cell histiocytosis is a rare condition that is difficult to diagnose; diagnosis is made based on histological assessment and can sometimes mimic other conditions such as PSC. Patient with high clinical suspicious should be considered for repeated sampling and careful reassessment of the tissues.
- Diabetes insipidus is the most common endocrine clinical presentation of Langerhans cell histiocytosis; other endocrinopathies involving anterior pituitary gland may occur and hypopituitarism maybe permanent. Worsening glycaemia and metabolic syndrome can be seen, especially when there is hypothalamic involvement. Rarely, non-PTH dependent hypercalcemia may occur.
- High prevalent detection of BRAFF/ MAP2K1 mutation in LCH patients may provide new therapeutic treatment options in future

FIGURE 1: A) MRI imaging demonstrating T2 lesion in the left thalamus, b) sagittal view

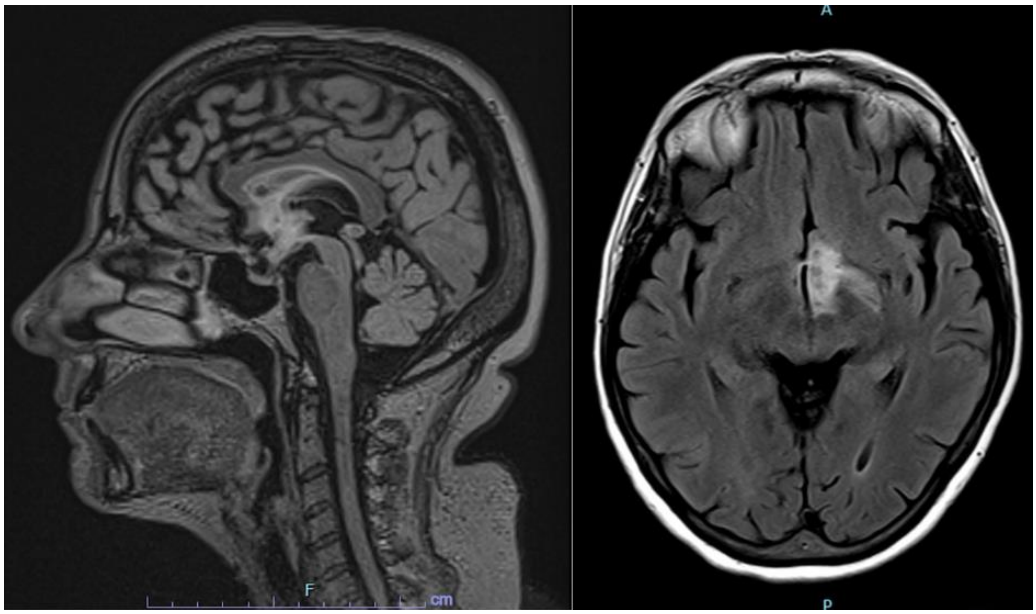


Table 1: Baseline pituitary panel at index admission

Pituitary panel	Result	Reference range
Cortisol	534	(100-540nmol/L)
ACTH	28.4	(7.2-63.3ng/L)
TSH	3.05	(0.35-4.94mU/L)
T4	10.7	(9-19pmol/L)
T3	3.4	(2.4-6.0pmol/L)
GH	0.43	(<8.00ug/L)
IGF1	3.58	(6.76-30.29nmol/L)
LH	**0.1**	IU/L
FSH	**2.2**	IU/L
Oestradiol	126	
Progesterone	**<0.6**	
Prolactin	**1270**	(110-560mIU/L)

Table 2: Water deprivation test: consistent with central diabetes insipidus

Time	Serum Sodium (mmol/L)	Serum Osmolarity (mOsm/kg)	Urine Sodium (mmol/L)	Urine Osmolarity (mOsm/kg)
0600	144	304	23	97
1200	147	317	35	185
1455	150	320	43	203
1700 (1 hour post 2 microgram Desmopressin)	147	311	54	311

FIGURE 2: FDG PET A) right sacral avid lesion B) left hypothalamic avidity

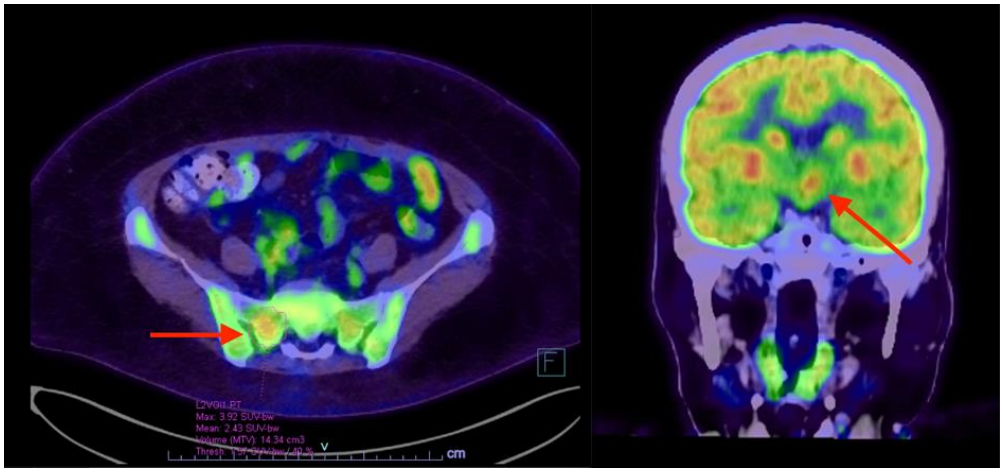
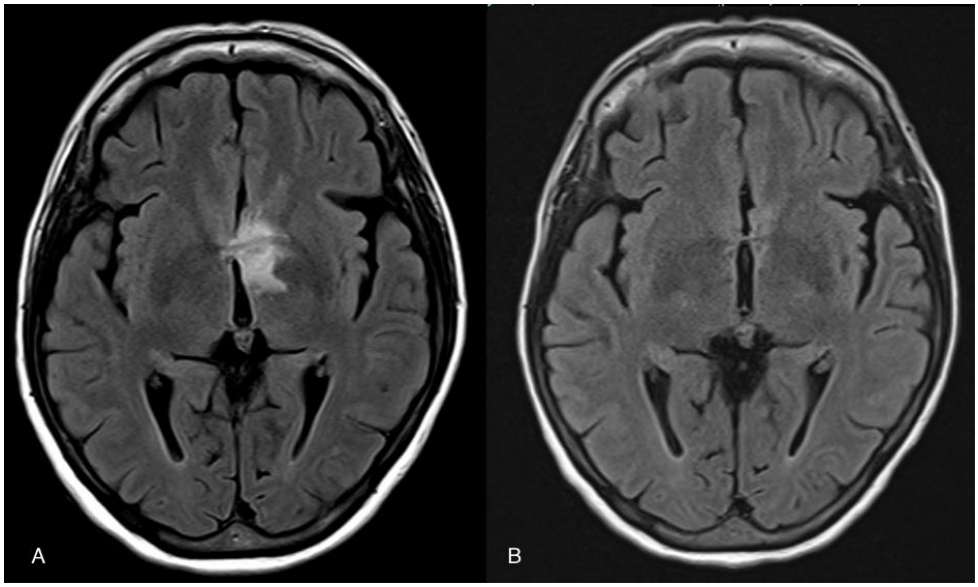


FIGURE 3: A) MRI Prior to treatment B) MRI post systemic chemotherapy showing resolution of the hypothalamic lesion



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An unusual cause of Cushing's syndrome and the role of bilateral adrenalectomy

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A 72 year-old man was admitted to hospital in May 2021 with bilateral pitting leg oedema, worsening hypertension (BP 202/89mmHg, compared to 138/86mmHg on enalapril and felodipine in 2020) and severe hypokalaemia (potassium 2.3mmol/L, sodium 145mmol/L).

He described a one-month history of increasing leg swelling and estimated 5kg weight gain. He did not have proximal myopathy, Cushingoid facies, bruising, thinned skin or striae. He had seen his GP three weeks prior, at which time serum potassium was normal (5.1mmol/L) and he had been commenced on bendroflumethiazide 5mg daily without improvement in oedema.

Initial management included oral and intravenous potassium replacement, and spironolactone 100mg daily. Serum potassium normalised after seven days and blood pressure improved to 160/78mmHg.

In addition to hypertension, past medical history was significant for metastatic prostate cancer, first diagnosed in August 2020 after presenting with abdominal pain. CT abdomen at that time showed prostatic enlargement, extensive para-aortic lymphadenopathy and multiple vertebral metastases. PSA was significantly elevated (53µg/L, normal <3.9µg/L). Core prostate biopsy confirmed adenocarcinoma (Gleason 5+5=10). Androgen deprivation therapy was commenced, with goserelin and bicalutamide. Docetaxel chemotherapy was given soon after diagnosis on account of the extent of disease, with 6 cycles completed February 2021.

Re-staging CT in May 2021 (at hospital admission) showed increased size of the prostate primary, multiple new pulmonary nodules, bilateral pleural effusions and a left segmental pulmonary embolus (PE). Serum testosterone was undetectable, indicating disease had become castrate-resistant. In contrast to the radiological progression, PSA was within the normal range at 2.1µg/L.

The CT findings were not thought to account for the presentation with bilateral leg swelling and further investigation was initiated for the hypertension and hypokalaemia. The very low potassium level was thought unlikely to be solely attributable to recent use of bendroflumethiazide.

Further results included undetectable plasma aldosterone (<103pmol/L) and low plasma renin concentration (5.5mIU/L, normal 4.2-59.7), suggesting non-aldosterone mediated hypervolaemia. Plasma cortisol was elevated with loss of diurnal variation (1673nmol/L at 0853hrs, 1534nmol/L at 1525hrs), with elevated ACTH (55.1pmol/L, normal 1.0-12.0). ACTH-dependent Cushing's syndrome (CS) was confirmed on 24-hour urine collection (total cortisol 13,584nmol, normal <380).

The rapid onset of ACTH-dependent CS in the setting of progressive malignancy was presumed to represent ectopic ACTH secretion. Immunostaining was retrospectively performed on the initial prostate biopsy of August 2020 and was negative for ACTH, however the development of radiological disease progression despite normal PSA and undetectable testosterone were suggestive of tumour transformation subsequent to that biopsy.

Ketoconazole and metyrapone were commenced. With up-titration to 1200mg ketoconazole and 2.45gm metyrapone daily there was improvement in 24-hour urine cortisol to 3,215nmol over the following two months. Due to the severity of CS and inability to control the disease with medical therapy, and after clear discussion of the risks with the patient, a referral was made for urgent bilateral adrenalectomy. This occurred in July 2021 with histology showing bilateral diffuse hyperplasia, consistent with ACTH excess. There were no post-operative complications. Hydrocortisone and fludrocortisone were commenced peri-operatively.

Following surgical cure of CS, further Oncology treatment included radiation treatment (8Gy/1# to lumbar spine August 2021, 60Gy/20# to prostate May 2022). Second-line carboplatin-etoposide chemotherapy was commenced May 2022 after staging CT showed further disease progression. ACTH was 42.0pmol/L prior to second-line chemotherapy and normalised to 6.0pmol/L in July 2022. Ongoing treatment also included abiraterone, a CYP17A1 inhibitor which decreases androgen synthesis. This is usually co-prescribed with prednisone or dexamethasone to suppress ACTH-mediated accumulation of steroids upstream of CYP17A1 with mineralocorticoid properties (1), however this was clearly not required here.

Adrenal insufficiency remains controlled on hydrocortisone and fludrocortisone replacement with no occurrence of adrenal crisis. As of July 2022, the patient describes good quality of life, enjoying walks in the local hills most days and good control of cancer-related pain.

Discussion

Ectopic CS is a rarely described complication of prostate cancer, with a small number of case reports describing transformation of adenocarcinoma into neuroendocrine small cell carcinoma, with positive staining for ACTH (2-4). We have seen two cases at our institution in the last two years.

A series of 58 patients with ectopic CS reported hypertension in 78% and hypokalaemia in 57%. The prevalence of hypokalaemia was significantly higher than in patients with other causes of CS and was significantly associated with 24-hour urine cortisol excretion (5). This is consistent with the presentation of our patient, in whom the absence of typical phenotypic features of CS presumably reflected the rapidity of onset.

The major management decision in this case was the referral for bilateral adrenalectomy. Although expected to provide a definitive cure of CS, bilateral adrenalectomy carries peri-operative risk (particularly in the setting of uncontrolled cortisol excess and previous PE) and requires lifelong glucocorticoid and mineralocorticoid replacement. These factors were weighed against the expected efficacy of alternative treatments, namely medical therapy for hypercortisolism and treatment of the underlying malignancy (which may control ACTH excess). It was also necessary to balance the expected prognosis of uncontrolled CS against that of the underlying malignancy, to determine if bilateral adrenalectomy would be expected to be of meaningful benefit.

Ectopic CS has a poor prognosis, attributable to both hypercortisolism and underlying malignancy, however specific data regarding the relative contribution of these factors are limited. A series of 418 patients with CS (6) included 33 patients with ectopic CS, in whom mortality was significantly increased (standardised mortality ratio=68.5, $p<0.001$ compared to general population). Of the 10 patients who died during follow-up, specific causes of death included sepsis in 3/10 (presumably attributable to hypercortisolism) and metastatic carcinomatosis in 4/10. In contrast, a meta-analysis of patients with Cushing's disease (CD) in remission after trans-sphenoidal surgery found mortality similar to the general population, indicating the possibility of a good outcome when hypercortisolism is treated and the underlying tumour is benign (7).

A 2013 systematic review of outcomes following bilateral adrenalectomy included 1320 patients. In the 13% of patients with ectopic CS, 30-day surgical mortality was 4% and long-term mortality was 39% over median follow-up of 35 months. In contrast, in patients with CD, surgical mortality was <1% and long-term mortality 9%. Overall cohort outcomes included clinical remission of CS in >95% and adrenal crises at a rate of 9.3 per 100 patient-years. Nelson's syndrome, although a described complication of bilateral adrenalectomy for CD, is not relevant in the setting of ectopic CS. (8)

A more recent study of 53 patients treated with bilateral adrenalectomy described similar outcomes (9). The authors proposed a definition of "catastrophic CS", in which massive cortisol excess (usually from ectopic ACTH) is life-threatening, and emergency bilateral adrenalectomy therefore indicated as first-line therapy. Our patient would meet proposed diagnostic criteria (table 1), which include serum potassium <3.0mmol/L and/or 0800hrs serum cortisol >1100nmol/L (the latter deriving from data showing this to predict severe infections (10)).

Clinical criteria: a patient with Cushing's syndrome and recent onset of one or more of the following: - Sepsis, opportunistic infection - Intractable hypokalaemia, uncontrolled hypertension - Heart failure - Gastrointestinal haemorrhage - Glucocorticoid-induced acute psychosis - Progressive debilitating myopathy - Thromboembolism - Uncontrolled hyperglycaemia and ketoacidosis
Biochemical criteria: a patient with Cushing's syndrome and at least one of the following: - Serum cortisol >1100nmol/L - Severe hypokalaemia (<3.0mmol/L)
Treatment: - Consider transfer to ICU - Control hypercortisolism with 2.5-3.0mg/hr etomidate IV (safe cortisol levels: in physiologically stressed patients 500-800nmol/L; in non-stressed patients 150-300nmol/L) - Treat complications - Plan bilateral adrenalectomy at the next available possibility

Table 1: Diagnostic criteria and specific treatment of catastrophic Cushing's syndrome. From Reincke et al. (9).

Take-home messages:

- Ectopic CS may develop following transformation of tumours without previous neuroendocrine activity.
- Ectopic CS should be considered in the differential diagnosis of hypertension and hypokalaemia, even in the absence of Cushingoid features.
- The overall prognosis of ectopic CS is poor, however may be improved by aggressive treatment of hypercortisolism.
- Emergency bilateral adrenalectomy should be considered as first-line treatment in patients with ACTH-dependent CS who have life-threatening complications of hypercortisolism at presentation.

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A Constipating Conundrum

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Case Report

A 46-year-old female presented to Emergency with a six-week history of progressive neck pain and hand paraesthesia. CT neck revealed a C3 lytic lesion with complete loss of vertebral height and retro-pulsed component with additional lytic lesions in C2, C6 and C7.

Hypertension was diagnosed at age 40 and had been progressively worsening over the past 12 months. Antihypertensives included amlodipine 10mg daily, valsartan 320mg daily and hydrochlorothiazide 25mg daily. Other significant history included severe constipation with anorexia, nausea and vomiting with 20kg weight loss in the preceding 6 months. Palpitations and anxiety precipitated an Emergency presentation in 2017.

MRI spine showed a C3 soft tissue mass resulting in vertebra plana and associated compression of the cervical cord (Figure 1). There were innumerable bony lesions throughout the spine in addition to destructive left fourth rib lesion extending into chest wall and extra-pleural space, para-aortic lymphadenopathy and pulmonary nodules.

Non-oliguric kidney injury was noted at admission with creatinine 259umol/L and eGFR 19ml/min/1.73m^2. Renal imaging revealed moderate left hydronephrosis with effacement of proximal ureter due to large para-aortic nodal mass.

Operative management for the C3 spinal lesion and ureteric obstruction were undertaken. The procedure was complicated by severe hypertension with systolic blood pressure reaching 240mmHg. High doses of antihypertensives were required including GTN infusion, esmolol, hydralazine and clonidine and post-operative intensive care admission was required for persistent hypertensive urgency.

Plasma metanephrines were markedly elevated (Table 1). FDG PET (Figure 2) revealed very intensely avid extensive skeletal metastasis in addition to widespread nodal disease above and below the diaphragm.

Endocrinology was consulted and antihypertensive therapy was changed to alpha blockade with phenoxybenzamine and subsequent addition of beta blockade (metoprolol). Histology was consistent with malignant phaeochromocytoma/paraganglioma with SDHA and SDHB positivity retained. Secretory paraganglioma genetic panel was requested and subsequently confirmed SDHB mutation.

^{68}Ga-DOTATATE PET imaging was performed to assess utility of peptide receptor radionuclide therapy (PRRT) and confirmed intense avidity in all sites of widespread disease (Figure 3). Predominant concerns for safety of PRRT therapy was risk of myelotoxicity associated with underlying renal impairment and precipitation of hypertensive crisis. Nuclear medicine renal GFR was calculated at 31 ml/min/1.73m^2. Reduced dose PRRT was planned following 20Gy palliative radiotherapy to spine disease.

Clinical course was complicated by recurrent intestinal pseudo-obstruction secondary to normetadrenaline elevation (Ogilvie syndrome) with associated intractable nausea and vomiting. Anti-emetic choice was limited by hypertensive crisis risk with metoclopramide and constipating effect of ondansetron. Palliative care managed this with regular levomepromazine, prucalopride, macrogol, bisacodyl, docusate-senna, cyclizine and picosulfate.

PRRT ^{177}Lu-DOTATATE (LuTate) therapy was commenced with dose reduction to 3.0 GBq given renal impairment and risk of hypertensive crisis. Renoprotective infusion of arginine and lysine was administered. Multi-time point dosimetry was utilised to guide subsequent LuTate doses with SPECT/CT imaging of abdomen and pelvis twenty hours after radionuclide administration showing intense tracer retention.

A further three cycles of LuTate therapy were administered with increasing LuTate dose to a peak of 6.1GBq based on personalised dosimetry. Phenoxybenzamine dosing was titrated to maintain normotension. Clinical improvement was seen following second cycle of LuTate therapy with resolution of pseudo-obstruction episodes, weight gain and improved performance status. Post treatment plasma metanephrines have markedly reduced (Table 1) and restaging Gallium DOTATATE scan has shown disease stability (Figure 4).

Questions for Discussion

1. What is the evidence for use of PRRT in PC/PGL?
2. What dose reduction is required for renal failure and how can this be ascertained?
3. What are the risks of PRRT therapy?
4. What are the molecular imaging characteristics of SDHB-associated paraganglioma?
5. Why does catecholamine excess cause intestinal pseudo-obstruction and what are the treatment options?
6. What is the recommended surveillance in family members to avoid this outcome in other mutation carriers?

Discussion

Paragangliomas (PGLs) are neuroendocrine tumours (NETs) that arise from chromaffin cells of the extra-adrenal paraganglia. They are divided into sympathetic paraganglioma which derive from sympathetic paravertebral ganglia in the thorax or abdomen and secrete catecholamines and non-functioning parasympathetic paraganglioma located at the glossopharyngeal and vagal nerves. Sympathetic paragangliomas are closely related to phaeochromocytomas (PCs) and present with the typical symptoms associated with catecholamine release including paroxysmal headache, palpitations and hypertension. A less common but debilitating complication of catecholamine release is inhibition of intestinal peristaltic activity leading to intestinal pseudo-obstruction.

Excess catecholamine levels lead to reduced intestinal motility and pseudo-obstruction by multiple mechanisms including reduction in intestinal secretion related to $alpha_2$-receptor activation (1), contraction of pyloric and ileocecal sphincter caused by activation of $alpha_1$-receptors (1, 3) and activation of $alpha_1$, $alpha_2$ and $beta_2$-receptors leading to reduced splanchnic vascular smooth muscle contraction (1, 3). The net effect of catecholamine action is to reduce intestinal motility and retain firm faecal material causing chronic constipation, acute or chronic pseudo-obstruction and in severe cases intestinal perforation.

Recent advances in genetics have enhanced understanding of the pathogenesis and physiology of PPGL, which in turn demonstrates specific molecular imaging characteristics. The resultant genotype-phenotype correlation informs the appropriate choice of radiotracer depending upon the underlying genetic mutation in addition to the clinical indication for the scan (4). Exceptionally intense FDG avidity is a feature of the pseudohypoxic phenotype of Cluster 1a-related PGL with periadrenal brown adipose tissue activity consistent with markedly elevated normetadrenaline levels (5). DOTATATE PET/CT is the most accurate molecular imaging modality for SDHB-related PGL and guides treatment with PRRT.

At the time of diagnosis 34% of paragangliomas are metastatic and reported five-year overall survival ranges from 40-77% (6). Traditional treatment options for non-operable metastatic disease include external beam radiation therapy, conventional chemotherapy and radiolabelled meta-iodo-benzyl-guanidine (MIBG). Recently peptide receptor radionuclide therapy (PRRT) has been used based on somatostatin receptor expression (SSTR) on PGLs. PRRT efficacy has been reported for advanced PC and PGLs in a systematic review with disease control rate (DCR) of 84%, mean overall survival (OS) of 54.4 months and median progression free survival (PFS) of 37.1 months (8).

Renal impairment is a concern with PRRT therapy due to prolonged tracer retention increasing risk of myelotoxicity. Short term myelotoxicity is reported in 10% of patients while long term toxicity (myelodysplastic syndrome) is reported in 1.4% of patients (9). Personalised dosimetry techniques are used to tailor the administered activity of LuTate in the context of end-stage renal impairment reducing complication risk (10).

LuTate has been highly effective in this patient to reduce plasma metanephrines thus controlling blood pressure and relieving the symptoms of Ogilvie syndrome. Early post treatment repeat ^{68}Ga-DOTATATE has shown partial disease response. Alpha blockade, aperients and anti-emetics have been weaned since PRRT with dramatic improvement in quality of life.

Take Home Messages

1. Ogilvie syndrome is a debilitating complication of very high catecholamine levels in patients with metastatic PC/PGL. Attention to bowel health is paramount.
2. LuTate therapy is efficacious and safe for treatment of patients with PC/PGL
3. Personalised dosimetry should be undertaken in patients with renal impairment to optimise lesional radiation dose and minimise risk of myelotoxicity.
4. Surveillance as per EviQ guidelines of known mutation carriers minimises the risk of developing untreatable metastatic disease

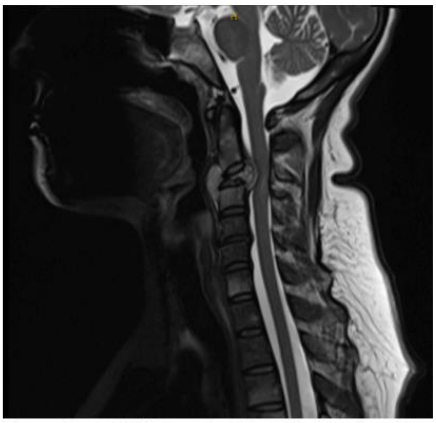

Figure One: MRI T2 sagittal images showing C3 soft tissue mass with bony destruction and resultant vertebra plana. Vertebrae extends into vertebral canal resulting in severe canal narrowing.

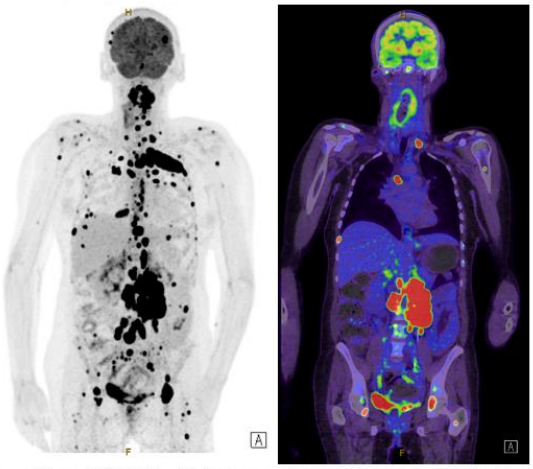

Figure Two: FDG PET which demonstrated intensely FDG avid nodal disease above and below diaphragm including left para-aortic nodal mass causing left ureteric compression and partially atrophic left kidney. Widespread FDG avid osseous metastasis. FDG avid pulmonary lesions in right upper lobe.

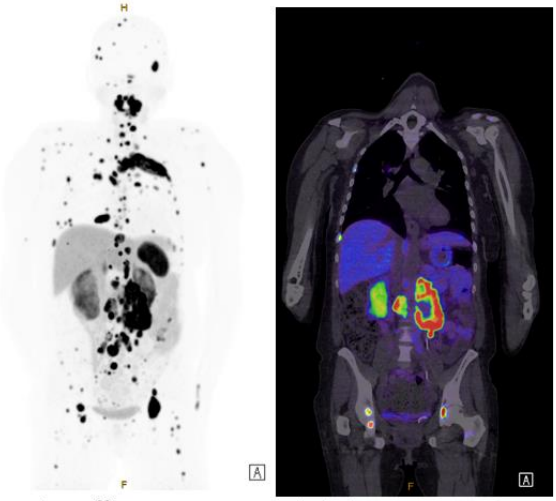

Figure Three: ^{68}Ga-DOTATATE PET which demonstrates widespread DOTATATE avid disease in similar distribution to FDG PET. Widespread bone metastasis including lesions not visible on FDG PET. Lymph node involvement above and below diaphragm identical distribution to FDG PET. Liver and lung metastasis.

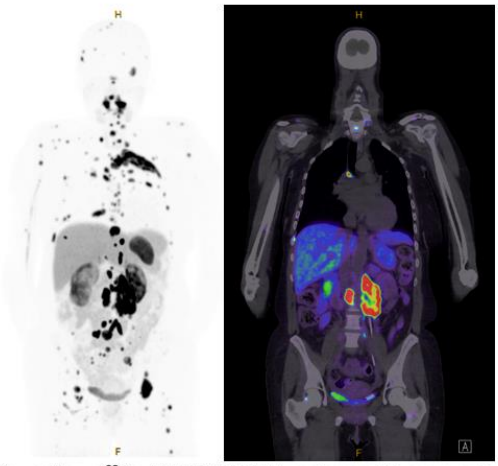

Figure Four: ^{68}Ga-DOTATATE PET performed three months following PRRT therapy. Imaging demonstrates favourable response to therapy with reducing size at most sites of disease. Increasing DOTATATE activity represents favourable response due to reduction of less differentiated lesion component. Single site of disease progression at left sacral alar metastasis. No new sites of disease.

Table One: Biochemical monitoring

Test	Initial Admission	Pre Cycle 1 LuTate	Post Cycle 1 LuTate	Cycle 2 LuTate	Post Cycle 4 LuTate	Reference Range
Normetadrenaline (pmol/L)	108 206	157 799	135 757	130 252	32 000	120 – 1300
Metadrenaline (pmol/L)	251	238	178	302	209	30 – 540
3 Methoxy tyramine (pmol/L)	1178	3265	1741	2609	673	<120
Chromogranin A (ug/L)	-	5444	-	-	2129	20-102
Creatinine (umol/L)	259	163	189	160	196	45 - 90
eGFR (ml/min/1.73m^2)	19	33	27	33	26	>90
Hb (g/L)	131	97	94	110	109	115 - 160
WCC (x10^9/L)	11.7	10.1	9.2	10.6	5.1	140 - 400
Platelets (x10^9/L)	445	261	306	293	214	4.0 – 11.0

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First description of ectopic ACTH-dependent Cushing's Syndrome following peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE in a case of metastatic pancreatic neuroendocrine tumour.

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Case

A 56-year-old female with history of gastroesophageal reflux disease, presented with eight weeks history of epigastric pain in November 2020. Initial laboratory studies revealed mild elevated lipase 94 U/L and liver dysfunction with normal liver screen. CT abdomen detected a 9mm low-density lesion in hepatic segment 3. Subsequent MRI liver showed multiple T2 hyperintensity liver lesions scattered throughout both left and right hemi-liver with no pancreatic lesion identified. She proceeded to have laparoscopic left hepatic lobe metastasectomy to evaluate the segment 3 liver lesion which confirmed to be well-differentiated, grade 3 metastatic pancreatic neuroendocrine tumour (pNET). Immunohistochemistry of tumour cells show diffuse labelling with chromogranin and synaptophysin, Ki-67 proliferation index 40-50%. Chromogranin A and gastrin were elevated at 2460 ug/L (27-94) and 198 pmol/L (6-55) respectively. She went on to have PET imaging for staging purposes and to identify the primary site. PET imaging was positive for DOTATATE- and FDG-avid pancreatic tail primary and liver metastatic disease. Given relatively asymptomatic and low-volume metastatic disease, she was commenced on Lanreotide and chemotherapy. Unfortunately, she had disease progression on somatostatin analogue and two cycles of cytotoxic chemotherapy (Carboplatin/Etoposide) (Figure 1). After discussion with multidisciplinary teams, the decision was made to proceed with peptide receptor radionuclide therapy (PRRT).

She had her first cycle PRRT ^{177}Lu 7.9 GBq with concomitant radiosensitising chemotherapy on 1st June 2021. Five days following her first cycle of PRRT, she presented to hospital with rapid weight gain 6kgs, facial rounding, upper body edema and easing bruising (Figure 2a and 2b). No symptomatology suggestive of carcinoid crisis with a normal 24-hr urinary 5-HIAA. Biochemistry revealed elevated early morning cortisol 1042 nmol/L (185-264nmol/L) with elevated ACTH 411 ng/L (7.2-63ng/L) and 24hour urinary free cortisol 9834 nmol/day (60-305nmol/day). She was hypokalemic 2.9mmol/L at presentation and her cortisol did not suppress on a low or high dose dexamethasone suppression test (cortisol 1209 nmol/L, ACTH 436 ng/L on 1mg dexamethasone suppression test ; cortisol 1444 nmol/L, ACTH 462 ng/L on 8mg dexamethasone suppression test). She was diagnosed with ectopic ACTH-dependent Cushing's syndrome and the timing in relation to PRRT making it suspicious for ACTH release following PRRT. Retrospective immunohistochemistry of liver metastasis tissue collected previously revealed ACTH staining in only 10% of tumour cells. Given disease control was unlikely to be achievable with chemotherapy alone, treatment with metyrapone alongside with recommencement of Lanreotide were initiated. Good response to treatment was shown as her cortisol and ACTH levels rapidly declined with therapy (Figure 3).

One month after commencement of steroidogenic enzyme inhibitor, she became hypocortisolism with cortisol 171 nmol/L and ACTH 123 ng/L. A "block and replace" method with hydrocortisone was applied given risk of both adrenal insufficiency and ACTH flare following next cycle of PRRT. She underwent second cycle PRRT without concomitant radiosensitising chemotherapy on 28th July 2021. Metyrapone was discontinued in September 2021 in the context of prolonged cytopenia (Platelet <80, neutrophil <1) with the likely attributable cause of bone marrow suppression from PRRT and previous chemotherapy. Despite cessation of metyrapone, she remained cortisone dependent as her pre-dose cortisol levels were low (60-78 nmol/L) with downtrending normal ACTH (16-25 ng/L) (Figure 4). In November 2021, she was started on clinical trial immunotherapy AK-117 which consisted of anti-CD47 monoclonal Ab + CTLA4 and PD1 bispecific Ab. The AK-117 trial concluded in May 2022 after total 10x cycles of therapy and only achieved partial response (51%). Interestingly, ACTH level has been slowly rising since April 2022 with subnormal cortisol response whilst on hydrocortisone 10/10mg (Figure 4). Her 24hr urinary free cortisol was normal at 100 nmol/day (<110). There is evidence of disease progression in hepatic metastases with new bone metastases in left 5th ribs on latest PET scan in June 2022. Most recently, she was started on another new THOR clinical trial (tyrosine kinase inhibitor). Progress and outcome of this trial will be followed.

Discussion

This is the first case report in the literature outlining ectopic ACTH-secreting Cushing's Syndrome as a hormonal crisis post PRRT in a case of pNET.

ectopic ACTH-producing pNET

Of pNET, 50-60% are functional with ACTH producing tumours being very rare, making up 7% of pNETs[1].Ectopic ACTH Cushing's syndrome caused by pNET are particularly aggressive with early metastases even before the development of Cushing's syndrome and carries a poor prognosis[2]. This may be due to the fact that the metastatic lesions are predominantly responsible for ACTH secretion, rather than the primary pancreatic lesion, resulting in diagnosis from a clinical presentation to occur late in the disease process. Metastasis has been reported to occur even after resection of the primary pancreatic tumor. Due to the aggressive nature of this tumour, the two-year survival rate is approximately 60% and five-year survival rate is only 16%[3].

Prognostic factors in ectopic Cushing's due to NET

Poor prognostic factors in ectopic Cushing's due to NET include age >60 years at diagnosis, pNET compared with bronchial carcinoids, presence of distant metastases, severity of hypercortisolism (higher serum cortisol, ACTH and 24hr UFC), higher grade NETs, and presence of hypokalemia and diabetes mellitus[4].

PRRT-related hormonal crises

PRRT exploits the fact that well differentiated NETs express somatostatin receptors on its surface to which radionuclide-bound somatostatin analogues will bind to. Hormonal crises after PRRT occur infrequently. In particular, carcinoid and catecholamine crises have been reported. Exact mechanism remains not fully elucidated, with putative mechanism of release of prestored

hormones or tumor lysis mechanism from beta-irradiation from ^{177}Lu. Other postulations include discontinuation of somatostatin analogue prior to PRRT and administration of amino acids (2.5% arginine and. 2.5% lysine) which may serve as a substrate for increased hormone synthesis by the tumor cells. Case series illustrates that patients who had hormonal crises from ^{177}Lu all had pre-existing clinically overt hormonal-release-related symptomatology and extensive metastatic disease in particular liver metastases[5]. Patients who did not have a crisis after the first administration of 177Lu also did not develop a hormonal crisis after subsequent cycles[5].

Take home messages

- Pancreatic NETs are the most frequent source of ectopic Cushing's among gastroenteropancreatic neuroendocrine tumors.
- ACTH-producing pNETs is uncommon. They usually present as advanced disease with early metastases even before the development of Cushing's syndrome.
- PRRT therapy can result in hormonal crises with catecholamine and carcinoid crises described previously.
- This case outlines the first description of ectopic-ACTH induced Cushing's syndrome as a hormonal crisis following PRRT.
- Severity of cortisol excess impacts on overall survival. Hence, the importance of prompt control of hypercortisolism by medical treatment or surgery.

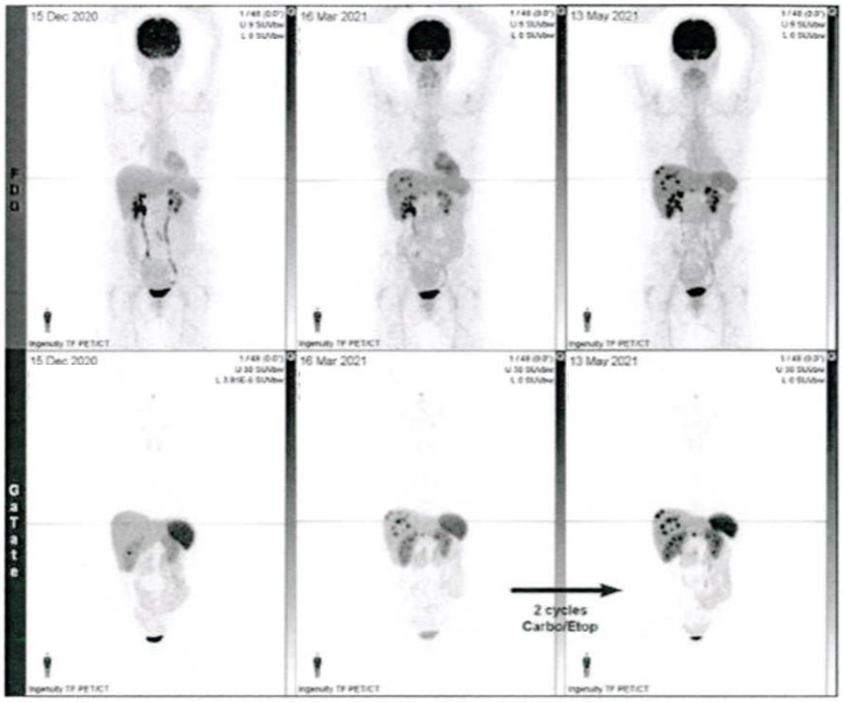

Figure 1. Progression of FDG avid and GaTate avid hepatic disease on Lanreotide and chemotherapy

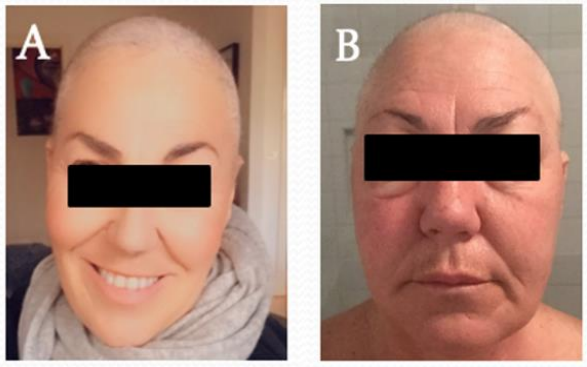

Figure 2. Images of patient before PRRT (A) and after PRRT (B)

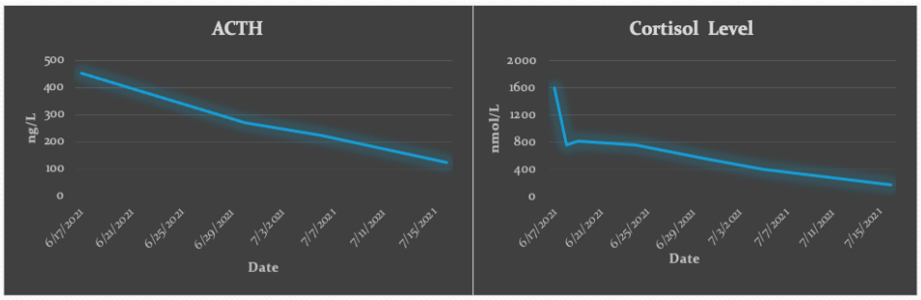

Figure 3. Plasma ACTH and cortisol levels following commencement of Lanreotide and Metyrapone

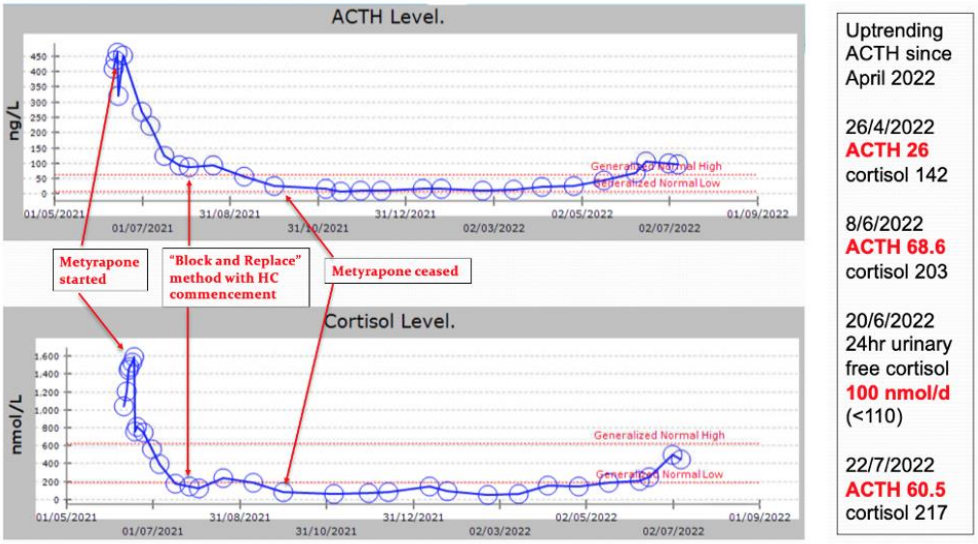

Figure 4. Trend of ACTH and cortisol level over time and in relation to metyrapone commencement and cessation

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How wide do we cast a net? Neuroendocrine tumours in lymph nodes without a primary

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Introduction

Neuroendocrine tumours (NETs) are rare malignancies, most often arising in the small bowel, lung and pancreas (1). Functional NETs cause classic presentations such as carcinoid, Zollinger-Ellison and Verner-Morrison syndromes that lead to their diagnosis; however, biochemical markers are often difficult to interpret, as chromogranin A (CGA) is affected by proton-pump inhibitors (PPIs) and somatostatin analogues (SSAs), whilst gastrin is also affected by histamine-2 receptor antagonists (H2RAs) (2,3). Surgical management is preferred for resectable disease, due to the malignant potential of most NETs, unless the multiple endocrine neoplasia 1 (MEN1) syndrome is present (1); primary lymph node disease appears to be a clear subset of sporadic NETs. We present a case of a 45-year-old man with a severe episodic vomiting and diarrhoea, who had two Ga68-DOTATATE-PET (DOTATATE) avid peri-pancreatic lymph nodes with no apparent primary in the pancreas, stomach or bowel.

Case

In June 2022, a 45-year-old Sudanese man was referred for inpatient endocrinology consultation to investigate a possible NET in the setting of recurrent abdominal pain, profuse vomiting and diarrhoea of 10-20 episodes daily with two DOTATATE-avid peri-pancreatic lymph nodes. This was his fifth admission in three months, during which he had repeated intensive care admissions with acute kidney injury and metabolic alkalosis requiring renal replacement therapy due to the severity of his losses. During this, his creatinine had peaked at 550 umol/L and serum bicarbonate rose to 56 mmol/L, with potassium requirements exceeding 160mmol/day. During the last two admissions, he also required total parenteral nutrition for ileus in the absence of surgery, and had very high nasogastric tube output totalling 4 – 8 L/day, which only responded to empirical octreotide. His medical history included type 2 diabetes with a HbA1c of 7.0%, alcohol excess, treated hypertension, thalassaemia minor and iron deficiency anaemia of one year. He had no family history of note, and his medications included telmisartan, amlodipine, nizatidine, magnesium, thiamine, vitamin D and a multivitamin.

A detailed review of his records showed 22 admissions from 2017 onwards, with similar but self-limiting presentations of 1-3 days. He had 6 CT scans and a MR enterography, which demonstrated eccentric gastric thickening and air fluid levels in the small bowels, as well as mildly prominent peripancreatic nodes up to 10mm. Two gastroscopies had shown duodenitis, mild chronic gastritis and oesophagitis.

During his admissions in 2022, he had 5 abdominal CT scans which showed circumferential gastric thickening, a distended stomach and jejunum, and a possible malrotation of the jejunum which spontaneously resolved; two 18mm peripancreatic nodes were noted. He underwent diagnostic laparoscopy, two gastroscopies and colonoscopy which only demonstrated duodenitis. The DOTATATE scan was prompted by a rapid response to short-term octreotide therapy and showed avidity in the peripancreatic lymph nodes (Figure 1); however, endoscopic ultrasound and fine needle aspiration (EUS-FNA) was non-diagnostic due to the absence of lymphoid cells, although there were small numbers of synaptophysin and chromogranin positive cells. At this point, a NET was suspected. A repeat gastroscopy for recurrent symptoms showed non-bleeding superficial duodenal ulcers despite maximal doses of nizatidine and pantoprazole; capsule endoscopy was non-contributory. Finally, a second EUS-FNA demonstrated CD56 and synaptophysin positive neuroendocrine tissue (Figure 2). An 18-fluorodeoxyglucose-PET (FDG-PET) scan showed mild avidity, and magnetic resonance (MR) enterography showed prominent gastric folds but no other lesions.

Biochemical markers were difficult to interpret in the setting of the PPI pantoprazole, H2RA nizatidine and later octreotide use (see Table 1). However, multiple 24-hour urine 5-hydroxy-indoleacetic acid (5HIAA) levels had been normal since 2017 and a VIP level was normal at 16.5 pmol/L [0-30]. Eventually, CGA remained elevated despite two weeks off pantoprazole and the presence of octreotide; gastrin likewise was elevated, but with the competing effect of nizatidine. A diagnosis of gastrinoma was made, octreotide was changed to lanreotide with ongoing symptom control, and evaluation for the MEN1 syndrome was unremarkable.

In July 2022, the patient underwent a pancreaticoduodenectomy which revealed a well-differentiated NET of 15mm diameter, present in two peripancreatic lymph nodes with no other lesions in the stomach, duodenum or pancreas. The tumor was WHO grade 1 with Ki67 <1% and mitotic rate < 1/hpf. His nizatidine was continued and lanreotide ceased; he is awaiting follow-up with chromogranin A levels and the results of his MEN1 genetic testing.

Discussion

Gastrinomas are rare neuroendocrine tumors (NETs) with an incidence of 0.5-2 per million person-years (4). The Zollinger-Ellison syndrome presents with recurrent peptic ulcer disease, as well as diarrhoea due to high acid output leading to enzymatic inactivation and epithelial damage. This diarrhoea contrasts with that of the Werner-Morrison syndrome from a vasoactive intestinal peptide-secreting NET (VIPoma), which is tea-coloured with minimal abdominal pain, but is difficult to distinguish from that of carcinoid syndrome, which is associated with abdominal cramping that is unrelated to flushing episodes (4). Traditionally, gastrinomas are diagnosed when gastrin levels are above 10 times the upper limit of the reference range in the presence of a gastric pH less than 2.0 or by high gastric basal acid output measured through nasogastric contents; however, this is rarely possible as gastric pH monitoring is rarely available, and acid output measurements even less so (5). As a result, the diagnosis is often based on the clinical presentation, with imaging or histological evidence of a NET; this is particularly true for sporadic gastrinomas, as diagnosis is often delayed by a median of 6 years when PPI withdrawal may no longer safe (5). Interestingly, prominent gastric folds are present in 90% of cases, as it was in this man (Figure 3).

Biochemical markers of gastrinoma are difficult to interpret. The chromogranin A (CGA) is elevated with no diagnostic threshold in the presence of PPIs, and possibly slightly decreased by SSAs (6,7). Gastrin is increased by H2RAs as well as PPIs whilst being decreased by SSAs, which were necessary in this case for symptom control (5). As a result, traditional diagnostic criteria

could not be applied. However, the clear progression of eccentric to circumferential gastric thickening with prominent gastric folds, duodenal ulceration despite nizatidine and pantoprazole, the rapid response to octreotide and finally the persistent elevation of CGA with a histologically-proven NET led to the correct diagnosis.

Surgical management is preferred for resectable gastrinomas (1). Pre-operative evaluation includes cross-sectional and functional imaging with CT, MR and DOTATATE, as well as biochemical and genetic studies for MEN1 syndrome which is present in 30% of cases; cure is rarely achieved in MEN1 syndrome due to multifocal disease (8). Over 80% of primary tumors lie within the gastrinoma triangle (8), and resection can be traditional or pancreas-sparing with careful intra-operative localisation. Primary lymph node gastrinoma comprises 11-28% of cases and can be cured with pancreas-sparing surgery in 80% (9,10). Symptoms are controlled with high-dose PPIs and occasionally H2RAs and SSAs. Post-operatively, PPIs often need to be continued for up to 8 years due to parietal cell hyperplasia (5).

Take home messages

Gastrinomas are difficult to diagnose using traditional criteria of gastrin with gastric pH or basal acid output.

Biochemical markers are difficult to interpret in gastrinoma; the effects of PPIs, H2RAs and SSAs should be considered when interpreting both chromogranin A and gastrin.

Primary lymph node disease is a well-recognised subset of gastrinomas, and can be treated with pancreas-sparing surgery.

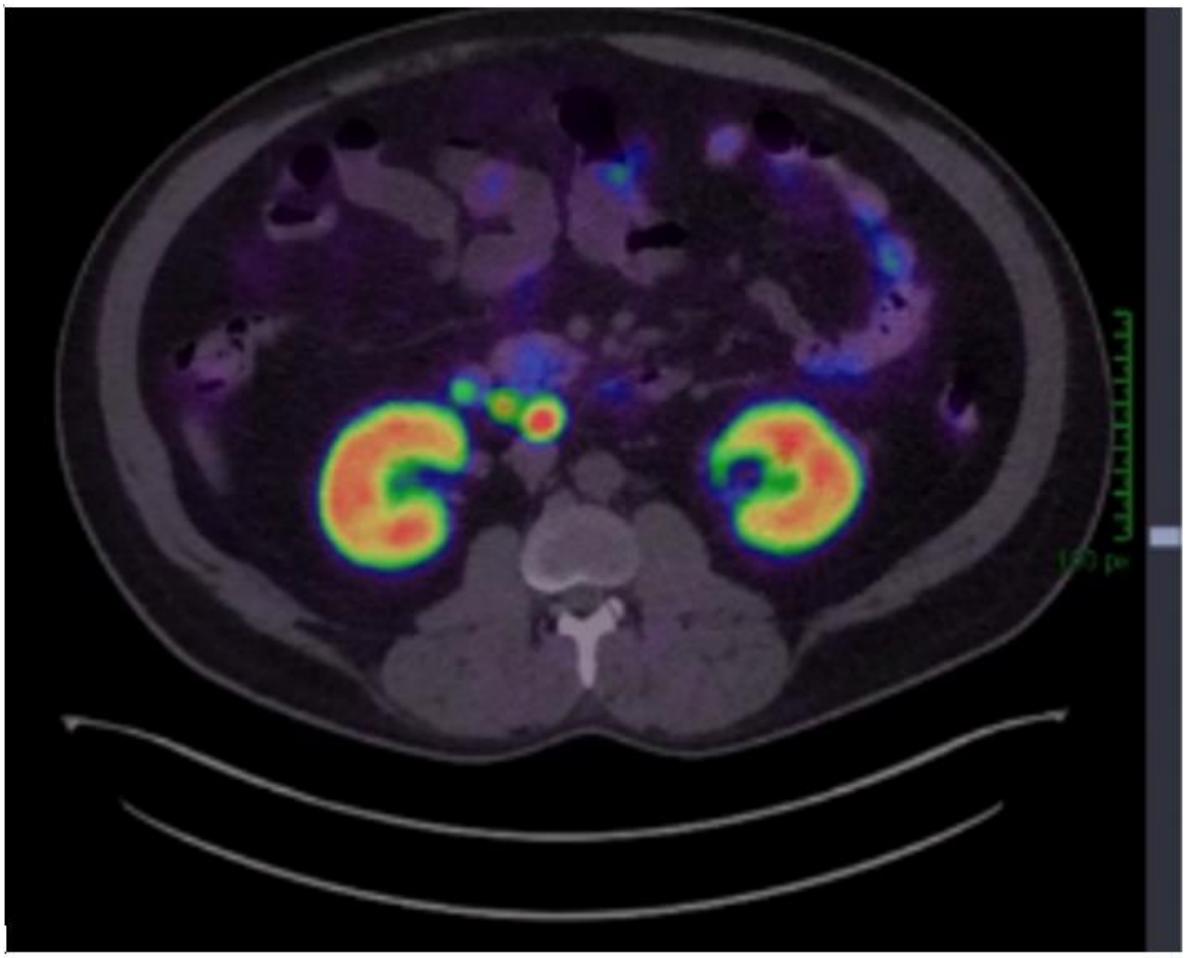


Figure 1: DOTATATE-PET study showing two avid peripancreatic, pre-caval lymph nodes.

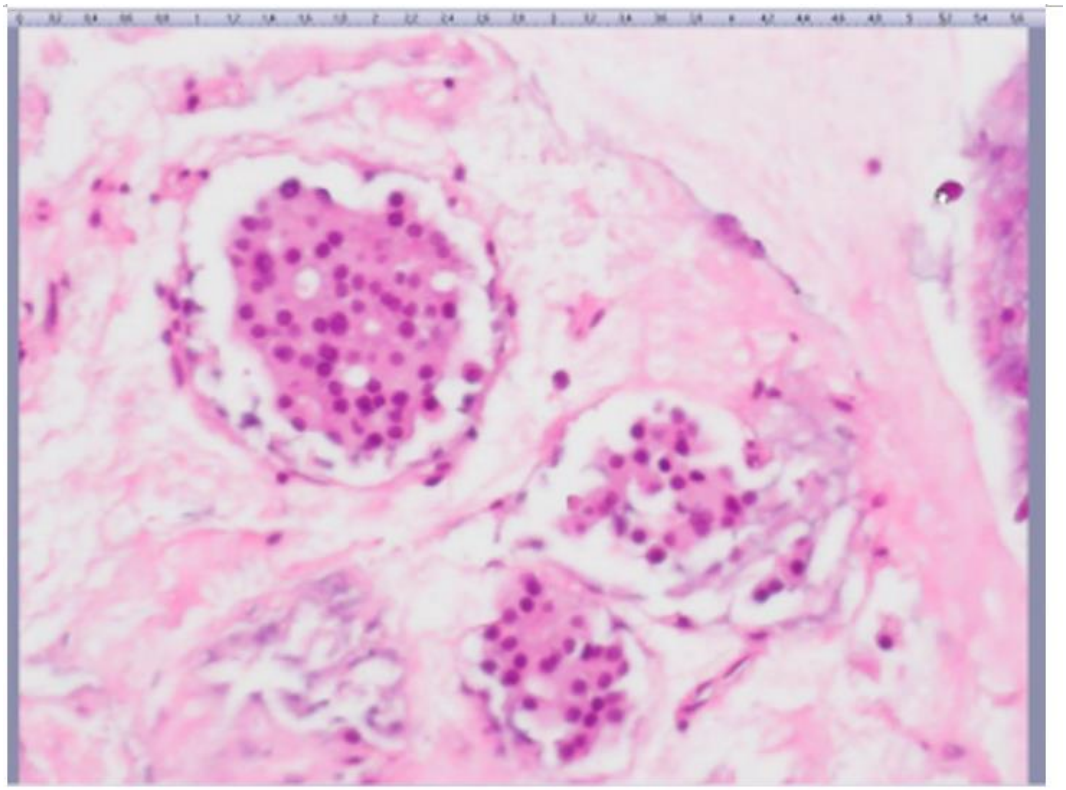
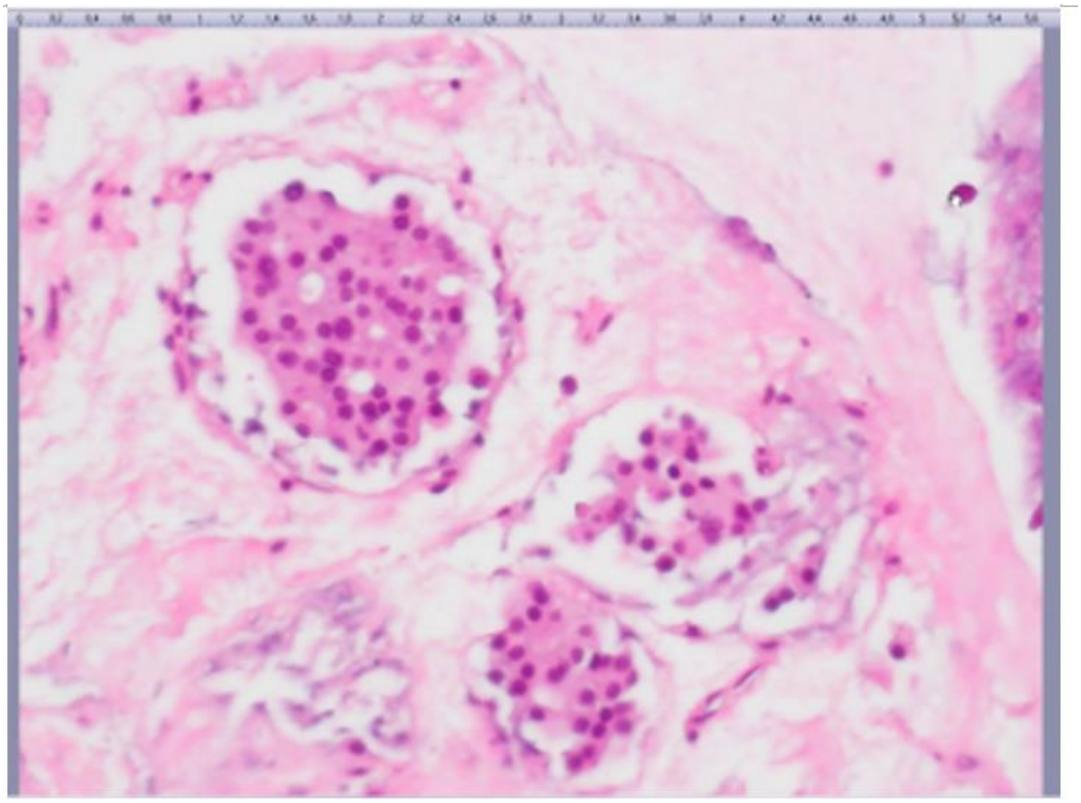


Figure 2: Histological staining of lymph node fine needle aspirate, containing rounded neuroendocrine cells.



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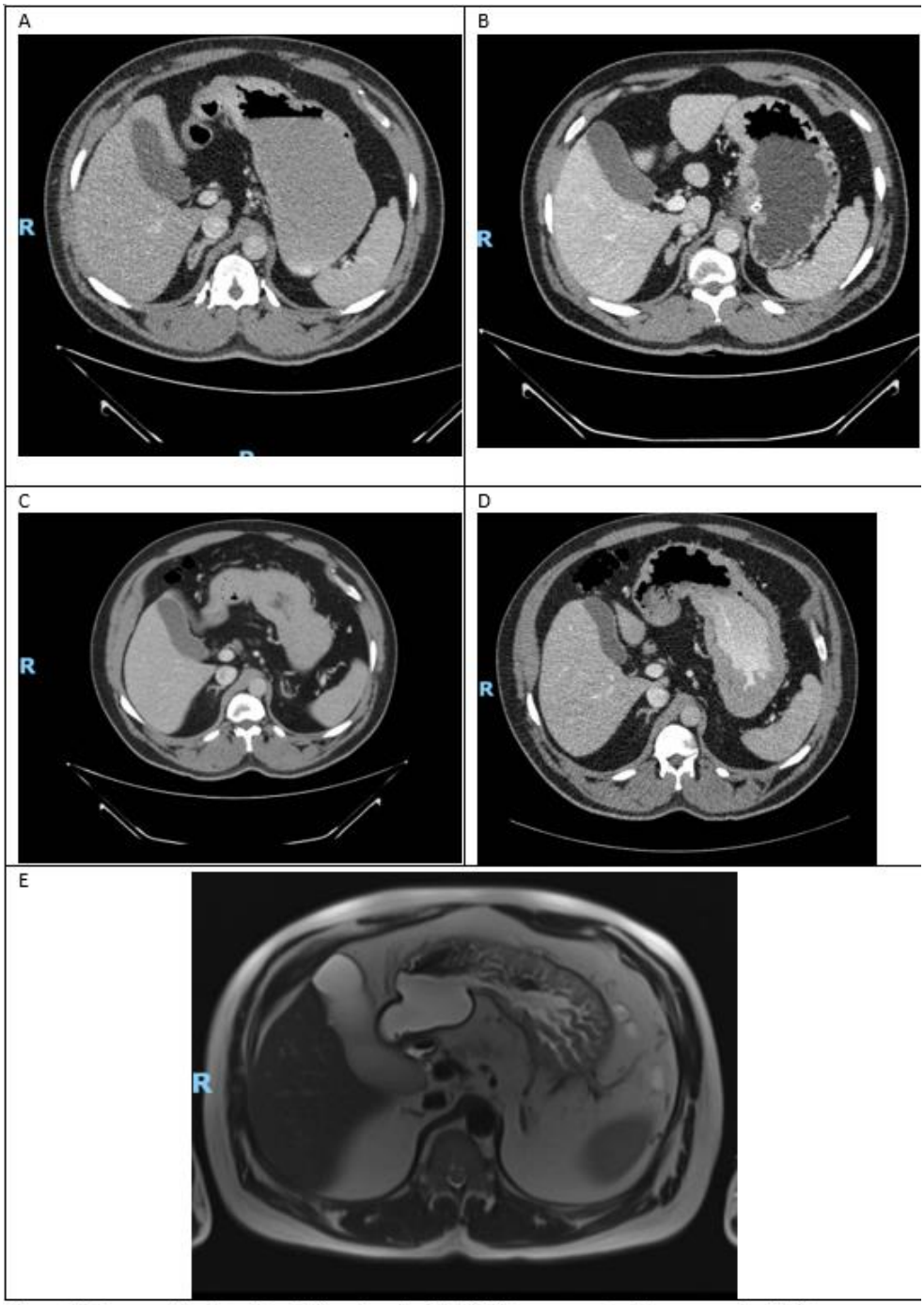

Figure 3: Progression of gastric thickening. A – 6/8/2017 on computed tomography (CT). B – 24/11/2018 on CT. C – 29/11/2020 on CT. D – 9/3/2022 on CT. E – 27/5/2022 on magnetic resonance, T2 weighted.

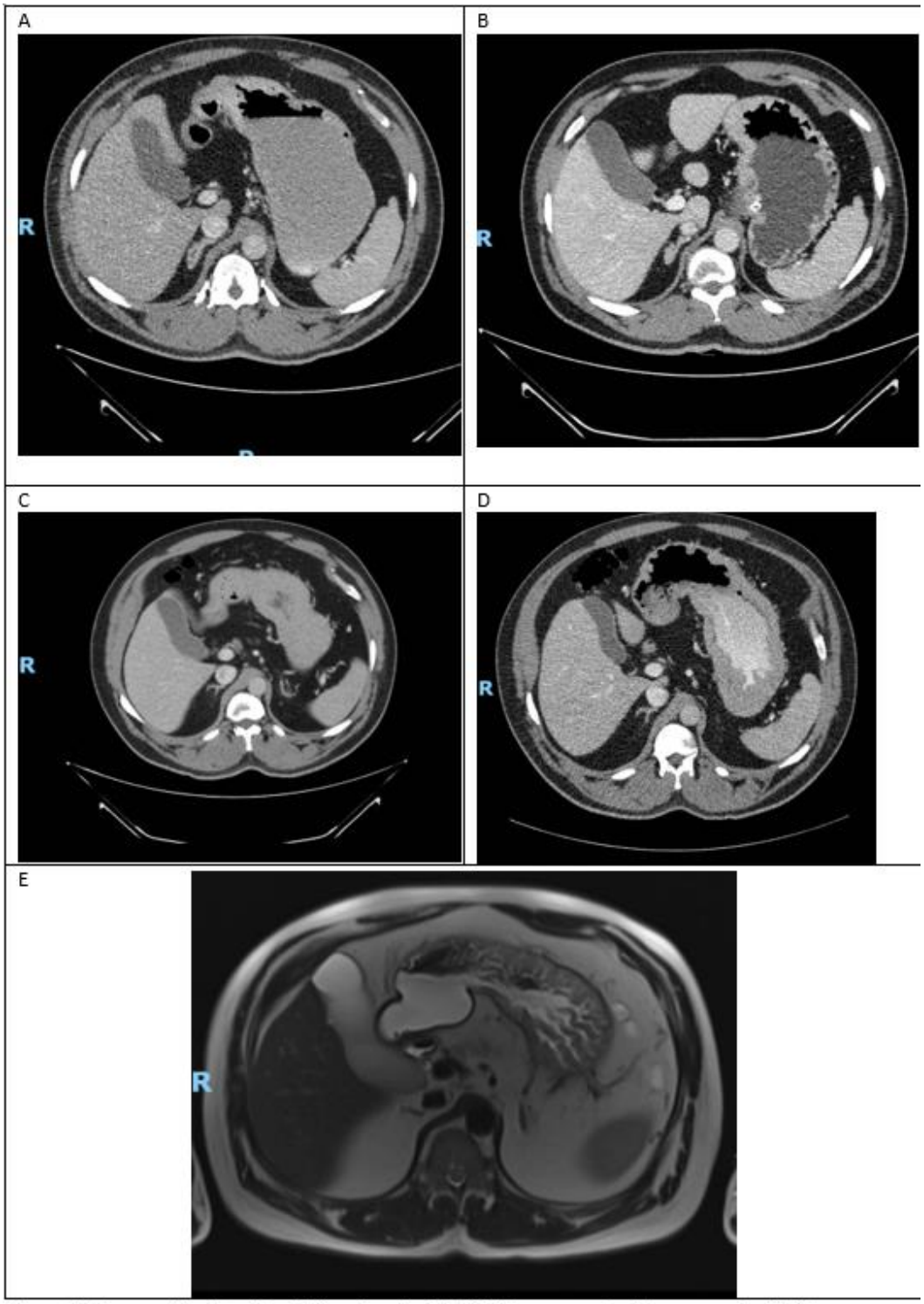

Figure 3: Progression of gastric thickening. A – 6/8/2017 on computed tomography (CT). B – 24/11/2018 on CT. C – 29/11/2020 on CT. D – 9/3/2022 on CT. E – 27/5/2022 on magnetic resonance, T2 weighted.

Date	CGA [27-94 mcg/L]	Gastrin [5-55 pmol/L]	Competing effects (on continuous nizatidine)
6/8/2017	1230		Pantoprazole – 1 dose 2 hours prior
5/11/2017	3410		Pantoprazole – for 1 week
23/3/2022	>15,200		Pantoprazole, octreotide and AKI (Cr 172)
30/3		1476	Pantoprazole – for 1 week
28/4		8121	Pantoprazole – for 3 weeks
29/4	12,780		Pantoprazole for 3 weeks and AKI (Cr 270)
12/5	352		Pantoprazole – 1 and 11 days prior Octreotide – for 1 week
27/5	456	128	Off pantoprazole – 16 days, Cr stable (132) On octreotide
2/6	965	406	Off pantoprazole, on octreotide
14/6	1198	255	Off pantoprazole, on octreotide

Table 1: Chromogranin A (CGA) and gastrin levels on continuous nizatidine, with pantoprazole between 15-20 and 24-29 March, 11-28 April, 1 May then 11 May. Octreotide between 15-20 March, 4 May to 14 June then lanreotide thereafter.

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The incognito polyjuice potion

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A 57-year-old male presented following one-week of nausea, diarrhoea, poor appetite, and reduced urine output. His medical history included atrial fibrillation (AF) treated with dabigatran and digoxin, hypertension on cilazapril, asthma/obstructive airway disease with moderate pulmonary hypertension, stage 3 chronic kidney disease thought secondary to hypertension, untreated seropositive rheumatoid arthritis (RA), gout on allopurinol, and chronic hepatitis B treated with entecavir. He previously drank alcohol in excess but denied consumption over the last few months.

On admission, he appeared unwell and was slow to respond. He was bradycardic and hypotensive with a heart rate (HR) of 39/minute and blood pressure of 70/50mmHg respectively. He was afebrile, with normal oxygen saturations and a respiratory rate of 12/minute. Examination findings were notable for cold peripheries and a widespread hyperpigmented rash.

Laboratory findings demonstrated severe acute kidney injury (AKI). His creatinine was 800 umol/L from a baseline of 140 umol/L, with a clear urine specimen. He had a metabolic acidosis with a pH of 7.22, bicarbonate of 16 mmol/L, CO2 of 5.3 kPa, base excess of -11 mmol/L, and a normal lactate of 1.9 mmol/L. He was hyponatremic (sodium 121 mmol/L), hyperkalemic (potassium 6.6 mmol/L), and normoglycemic. He had a mildly raised CRP of 30 mg/L, but with normal white blood cells and neutrophils. His liver functions tests were normal, apart from hypoalbuminemia (albumin of 26 g/L). An electrocardiogram showed slow AF with a HR of 39/minute. The initial working diagnosis was gastrointestinal illness leading to pre-renal AKI. The bradycardia was likely secondary to digoxin toxicity in the setting of reduced renal clearance.

The patient was treated with aggressive fluid resuscitation, atropine, adrenaline, and Digibind. Despite this, he remained hypotensive and was transferred to the intensive care unit for vasopressors and urgent dialysis. Due to increasing Noradrenaline and Adrenaline requirements, a screening cortisol was sent.

The 6am cortisol returned unusually low at 46 nmol/L, during a period of the patient being critically unwell. Adrenocorticotrophic hormone (ACTH) was suppressed at 1 pmol/L. Stress-dose hydrocortisone was commenced with a reduction in vasopressor requirements. On endocrinology review, the patient reported fatigue over a 4-month period resulting in loss of employment. He denied change to his weight. He denied glucocorticoid use in all forms, apart from Seretide 125/25mg for asthma, which he took sporadically. He initially denied use of over-the-counter and herbal supplements.

On endocrinology review, widespread hyperpigmentation was noted, including involvement of the buccal mucosa, upper and lower limbs, and torso. Notably, the hyperpigmentation spared the palmar creases and soles. He had facial fullness from bilateral parotid gland enlargement, thought secondary to previous alcohol excess. There were no other features of chronic liver disease on examination.

The patient was again questioned regarding supplement use and finally disclosed consumption of 3-4 capsules a day of the supplement *'Nhan Sam Tuyet Lien Truy Phong Hoan',* to ease arthralgias.

On review of the supplement's printed ingredient list, no glucocorticoids were disclosed. The supplement was sent for analysis, with dexamethasone traces detected. A dexamethasone level was retrospectively performed via liquid chromatography tandem mass spectrometry (LC-MS/MS) on the patient's serum samples collected at time of hospital admission. This returned elevated at 11.8 nmol/L, suggesting recent dexamethasone consumption. A punch-biopsy of the hyperpigmented lesion on his upper limbs showed cutaneous hyperpigmentation, initially thought secondary to Addison's disease, and prior to the availability of the ACTH result. However, dermatological follow up as an outpatient found new tense blisters at the same sites of hyperpigmentation, with repeat biopsy demonstrating bullous pemphigoid. The patient had normal aldosterone (438 pmol/L) and renin levels (34 mu/L). Adrenal antibodies also returned negative at <40.

A further three patients, consuming the same supplement, have presented with isolated adrenal insufficiency (AI) to Middlemore Hospital over a two-year period- i) a 67-year-old female with delirium, life-threatening hyponatremia (sodium of 109 mmol/L), and an undetectable serum cortisol after discontinuing the supplement for 3 weeks; ii) a 61-year-old male with fatigue, early morning cortisol of 19 nmol/L, but paradoxically Cushingoid-appearing with moon-facies and a prominent dorsocervical fat pad; and iii) a 67-year-old female with weight gain, deterioration in hypertension and glycaemic control, with a low morning cortisol and a detectable serum dexamethasone level. All patients were taking between 1-4 capsules of the supplement daily, for at least 6 months, prior to hospital admission.

Discussion:

The manufacturing of over-the-counter supplements are not regulated and may contain harmful substances. In each of the four cases presented, the patients were taking the supplement to ease arthralgias. Laboratory analysis of the supplement found traces of Dexamethasone, Chlorphenamine and Frusemide, which was not disclosed on the printed ingredients label (1, 2).

This case series highlights the range of presentations in the patient with unbeknownst glucocorticoid consumption. The first patient had a life-threatening adrenal crisis, precipitated by gastrointestinal illness. His personal history of autoimmunity and the curious presentation with widespread hyperpigmentation, hyponatremia and hyperkalemia, were initially concerning for primary AI. However, his ACTH later returned low-normal, his aldosterone production was intact, and adrenal antibodies were negative.

Subsequent outpatient review with the dermatological service and the presence of new, tense blisters led to a revision of the dermatological diagnosis to bullous pemphigoid following repeat biopsy. His initial hyperkalemia was likely related to the AKI.

The second patient with severe, symptomatic hyponatremia, developed adrenal insufficiency following withdrawal of the glucocorticoid-containing supplement. This highlights the important role of cortisol in sodium homeostasis. Cortisol has an inhibitory role on vasopressin secretion, and cortisol deficiency can lead to inappropriate increase in vasopressin, with resultant water retention and hyponatremia(3).

Paradoxically, two patients on the supplement presented with Cushing's syndrome and an undetectable cortisol from glucocorticoid-induced AI. Exogenous Cushing's, either iatrogenic or from surreptitious consumption, is the most common form of hypercortisolism(4). With sustained glucocorticoid exposure, this can lead to adrenal atrophy and persistent suppression of the hypothalamic-pituitary-adrenocortical (HPA) axis, which becomes apparent when the offending agent is ceased(5).

The four patients presented in this case series highlight an important supplement for Endocrinologists to be aware of. The supplement and each patient's presentation were notified to New Zealand's medical regulatory body Medsafe, with the last presentation notified in June this year(6). Medsafe has released an alert last month (July 2022) advising against consumption of the supplement and a notification to health practitioners regarding the supplement's active ingredients(1). In Australia, the Therapeutic Goods Administration released safety advisory communications in January 2022 declaring the supplement illegal to be manufactured, imported, or advertised in Australia(2). It does however remain purchasable online.

Learning points:

- Long-term glucocorticoid consumption can lead to both adrenal insufficiency and Cushing's syndrome
- Always take a thorough medication history, including the use of alternative and complimentary medicines. This is crucial in the patient with a clinical phenotype that contradicts the biochemical investigations.
- The active ingredient in supplements may not be evident from those listed on packaging. If there is suspicion of surreptitious glucocorticoid consumption, biochemical assessment of a potentially causative substance should be considered.

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Mitochondrial disease and preconception care

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Case study

J.E is a 30 year old female, who was previously well in childhood. In 2014, she started experiencing migraines, bowel symptoms and lethargy. She was of short stature (height 152cm) and low-normal BMI (weight 43kg BMI 18kg/m2).

In 2018, she was noted to have an incidental high random glucose of 10.6 mmol/L, and diabetes was confirmed with an oral glucose tolerance test (OGTT Baseline 10.6mmol/L;1hr 21.2mmol/L;2hr 24.7 mmol/L). Her diabetes was well controlled on metformin alone, with HbA1c 5.8% (40mmol/mol) 3 months after medication commencement. Screening for type 1 diabetes antibodies and MODY was negative. J.E. developed sensorineural hearing loss one year following diagnosis of diabetes.

Notable family history includes mother and maternal grandmother with hearing impairment. Her maternal grandfather passed away at age 38 from myocardial infarction, and her maternal great aunt has type 2 diabetes.

Given her multisystem involvement with diabetes, hearing loss, short stature, migraines and gut motility issues, she was referred for genetic testing for mitochondrial disease. Genetic testing confirmed that there was a pathogenic mutation in mitochondrial DNA m.3243A>G, commonly seen in Maternally Inherited Diabetes and Deafness (MIDD) and Mitochondrial Encephalopathy with Lactic acidosis and Stroke-like episodes (MELAS). She was prescribed supplements including CoQ10, B1, B2 and arginine. Screening echocardiogram and ophthalmology review were unremarkable.

In 2020, metformin was ceased due to theoretical risk of lactic acidosis and gliclazide MR 30mg BD was introduced. Glycaemic control remained satisfactory with HbA1c 6.7% (50mmol/mol). Due to her planning pregnancy, gliclazide was replaced with insulin in 2021 (HbA1c 5.8%;40mmol/mol on Optisulin 7 units pre-bed and Novorapid 4 units with dinner only).

She has been counselled by genetics regarding the risk of mitochondrial disease in her offspring**.** Despite regular menses, she has not successfully conceived after 6 months of actively trying for pregnancy.

In mid 2022, she was referred to the renal team for investigation of sub-nephrotic range proteinuria with preserved eGFR, first noted in Sept 2020 (urine ACR 260 in Sept 2020, and urine ACR 110, eGFR 82 in April 2022). The extent of the proteinuria was out of keeping with her well-controlled diabetes with no other microvascular complications. Kidney biopsy confirmed focal segmental glomerulosclerosis and interstitial nephritis, with abnormal mitochondria seen on electron microscopy, diagnostic of mitochondrial nephropathy.

Discussion

Mitochondrial dysfunction results in reduced ATP production from oxidative phosphorylation, as well as oxidative stress from reactive oxygen species. In the pancreatic beta-cell, there is reduced glucose mediated insulin secretion[1] and apoptosis of pancreatic beta cell mass over time[2]. Mitochondrial diabetes makes up 3% of all diabetes cases, with the most common being MELAS/MIDD[2].

Most patients with MELAS and MIDD have the mitochondrial DNA (mtDNA) mutation m.3243A>G in the MT-TL1 gene for $tRNA^{leu}$, ultimately leading to reduced activities of complex 1 and 4 of the mitochondrial respiratory chain[2]. MIDD and MELAS represent two identifiable phenotypes within a spectrum of disease. MIDD presents with sensorineural hearing loss in 75% of the patients, typically in early adulthood, and frequently preceding the diagnosis of diabetes[2]. Other manifestations include cardiomyopathy, myopathy, nephropathy, gastrointestinal dysmotility, macular retinal dystrophy, and other endocrinopathies including short stature from GH deficiency, hypothalamic hypogonadism and secondary hypothyroidism[2,4]. In addition to these manifestations, MELAS patients also have neurological manifestations such as stroke-like episodes at a young age, hemianopia or cortical blindness, seizures, dementia or ataxia[2]. However, even in the absence of MELAS, brain imaging abnormalities are seen in >50% of MIDD patients. Reduced mitochondrial oxidative phosphorylation and early use of the anaerobic glycolytic pathway for energy production also predisposes to lactic acidosis[2]. The m.3243A>G mutation is not generally associated with fertility issues, except in the minority of patients with hypogonadotropic hypogonadism[5].

Diabetes in MIDD usually presents insidiously, but ketoacidosis can occur in ~8% [2]. Penetrance of diabetes is high (estimated as over 85%) in patients with the m.3243A>G mutation. Patients commonly develop diabetes in their 30s to 40s and tend to have low BMI[2]. Patients with higher mtDNA mutation burden present with diabetes at a younger age[4]. There are no formal studies looking at the safety or adverse events of novel diabetes medications in mitochondrial diabetes. Case reports have demonstrated the successful use of sulfonylureas, DPP4-inhibitors, SGLT-2 inhibitors and GLP-1 agonists [1]. Metformin is generally avoided given the theoretical risk of lactic acidosis. Given progressive insulin deficiency, there is inevitable progression to insulin requirement, which is more rapid compared to type 2 diabetes[3].

Various combinations of antioxidants and vitamins have been trialed in mitochondrial disease, with minimal data to support improvements in outcomes, including coenzyme Q, riboflavin, thiamine, folic acid, alpha-lipoic acid, vitamin E, creatine and carnitine[9]. Coenyzme Q acts as an electron carrier in the mitochondria respiratory chain and may reduce progression of hearing loss and diabetes in patients with the m.3243A>G mutation[6]. L-arginine may improve stroke like episodes in MELAS[9].

Mutations in mtDNA are maternally inherited, such as in MIDD/MELAS. In disease states, mtDNA mutation may be present in only a portion of the mtDNA – this can be quantified as the heteroplasmy load. While individuals with higher heteroplasmy levels tend to have higher disease burden, age-adjusted blood heteroplasmy levels only account from 25-27% of variance in disease burden, suggesting that other factors such as nuclear genetic variation, environmental influences and epigenetics also affect the phenotype[7]. The m.3243 A>G mutation at lower heteroplasmy causes MIDD, and at higher levels may cause MELAS[9].

For maternally inherited mtDNA mutations, it can be difficult to predict the phenotype in offspring, making genetic counselling challenging. During oocyte production, only a small number of maternal mtDNA molecules are transferred into each oocyte – this can lead to a random shift of mtDNA mutational load between generations, resulting in significant phenotypic variability within families[9]. Prenatal diagnosis and pre-implantation genetic diagnosis have both been used to reduce the risk of affected offspring, by selecting for pregnancies below a certain heteroplasmy threshold. These reproductive techniques would only be suitable for women who are able to make oocytes with heteroplasmy below the threshold, and is unlikely to be successful in highly affected individuals with high heteroplasmy load[9]. A heteroplasmy threshold of <18% has been proposed for embryo transfer in pre-

implantation genetic diagnosis, however noting that for the m.3243A>G mutation, physical manifestations of disease can occur at very low heteroplasmy levels below this threshold[8].

Maeve's law was passed in Australia in March 2022, which will allow mitochondrial donation techniques to be used. It involves transferring maternal nuclear DNA (from the affected woman) to a donated oocyte with normal mtDNA from which nuclear DNA has been removed, popularly coined as the "three-parent baby" [9]. This will allow highly affected women the chance of having a baby unaffected by mitochondrial disease.

Take home messages

- Consider mitochondrial disease in a patient with diabetes with other multi-systemic manifestations.
- Mitochondrial diabetes is phenotypically different from type 1 or type 2 diabetes. Patients tend to have a low BMI and diabetes commonly presents insidiously at age 30s-40s. Although most oral hypoglycaemic agents can be used (except metformin given risk of lactic acidosis), there is often a more rapid progression to insulin requirement.
- Preconception care includes genetic counselling and consideration of assisted reproductive techniques such as prenatal diagnosis, pre-implantation genetic diagnosis and mitochondrial donation

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