ESA CLINICAL WEEKEND 2021

Virtual Meeting   20 & 21 NOVEMBER 2021

Full Case Studies

esa
endocrine society of australia

ANZBMS
Early Career
Investigator Committee

Two for the price of one: juxtaposed glandular tissue.

William Yu[1], Christopher Rowe[1]

1. Endocrinology & Diabetes, John Hunter Hospital, Hunter New England Local Health District, Newcastle, New South Wales, Australia

PM is a 77-year-old gentleman who presented with increasing thoracic back pain in April 2019*. His medical history included paroxysmal atrial fibrillation on aspirin and osteoarthritis. PM was discovered to have a prostate-specific antigen (PSA) of 490μg/L (reference range < 7.5) and was subsequently diagnosed with Gleason 5+4=9 prostatic adenocarcinoma. His initial CT showed prostatomegaly, sclerotic bone lesions, retroperitoneal lymphadenopathy, visceral lung lesions and a left adrenal lesion measuring 68 x 45 x 45mm with elevated pre-contrast density (20-30 Hounsfield). A clinical diagnosis of metastatic prostate cancer was made.

PM had treatment initiated from May 2019 with fractionated radiotherapy to his T9 vertebral body and androgen deprivation therapy (ADT) with leuprorelin (GnRH analogue) and cyproterone acetate (androgen receptor antagonist). There was reduction in his PSA to 120μg/L by July 2019. As part of safety screening, testosterone was discovered to be elevated at 21.5nmol/L (reference range 8 - 30) with undetectable LH and FSH. There was no prior testosterone for comparison.

Leuprorelin was changed to triptorelin considering presumed disease progression. Testosterone remained elevated at 23nmol/L and PSA 98μg/L. Repeat staging CT showed growth in the left adrenal mass to 78 x 50mm and local extension towards the posterior surface of the stomach. Other sites of metastatic disease were stable.

He was first reviewed by his treating Endocrinologist in September 2019. Suspicion was raised of synchronous functional left adrenal mass given evidence of gonadotropin-independent testosterone release and change in mass size. There was no clinical evidence of androgen or cortisol excess. He appeared eugonadal which was thought to be unusual on ADT. 24-hour urinary free cortisol was 159nmol/L (reference range < 270). An adrenal hormonal panel confirmed elevated testosterone over two separate assays, elevated DHEA-S 13μmol/L (reference < 10), elevated androstenedione 28nmol/L (reference range 2.1 – 11), cortisol 437nmol/L with ACTH 0.6nmol/L (reference range 1 – 10), and failure to suppress post-1mg dexamethasone cortisol of 363nmol/L (reference range < 50). Plasma metanephrines and normetanephrines were negative.

To confirm suspicion of androgen-secreting adrenocortical carcinoma (ACC), he underwent a fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scan which demonstrated highly avid radiopharmaceutical uptake in this adrenal lesion with attenuated uptake in other identified prostatic metastases. A prostate-specific membrane antigen (PSMA)-PET scan showed moderate uptake in the adrenal lesion and avid uptake in skeletal metastases as expected.

The presumed ACC was thought to be localised to the adrenal bed based on the disparities between FDG-PET and PSMA-PET findings. The high lethality of untreated ACC and clinical suspicion of metastatic prostate cancer being driven by dysregulated androgen secretion by the ACC prompted the decision to proceed to surgery. PM underwent a left adrenalectomy in October 2019. Surgical notes described tumour budding at time of removal but with clear macroscopic margins. Post-surgery, the patient was placed on hydrocortisone replacement at 20mg mane, 10mg midi, and 10mg 2pm.

Histological examination showed a pT3 high-grade adrenocortical carcinoma 80mm in maximal length, invading peri-vesical fat but with clear resection margins. The lesion was grade pT3NxMx, Ki-67 40%. Stage III ACC was diagnosed. There were several foci of metastatic prostatic adenocarcinoma within the ACC parenchyma (Figure 2). These were confirmed with immunohistochemical staining with synaptophysin and inhibin staining positively on the ACC (Figure 2C) and PSA staining on the foci of metastatic prostate adenocarcinoma. Multi-disciplinary team consensus was prioritisation of ACC treatment and mitotane therapy as well as adrenal bed radiation was recommended.

Cyproterone was ceased and GnRH based ADT (triptorelin) was continued in November 2019 given metastatic hormone sensitive state was presumably restored. Mitotane was initiated in November 2019 with initial doses of 500mg BD for a week followed by sequential uptitration using serum levels to 3g BD. His hydrocortisone dosing was increased following initiation of mitotane with increasing symptoms of hydrocortisone insufficiency up to 30mg mane, 20mg midi, and 10mg 2pm. His post-surgery tests showed a 24-hour urinary free cortisol of 199nmol/day (ref range < 270), testosterone < 0.4nmol/L, DHEA-S 0.9μmol/L, and PSA 30μg/L.

In June 2020, there was a brief cessation of mitotane therapy to allow for excision of 3x nodular BCCs. In July 2020, there was cessation of mitotane for 1 month following admission with a pulmonary embolus. In October 2020, bone scan for back pain demonstrated a new vertebral L3 lesion. This was treated with radiotherapy as a symptomatic prostate cancer metastasis. The scan also showed resolution of other known bony metastatic disease. In November 2020, FDG-PET scan demonstrated multiple new hypermetabolic thoracic and abdominal nodes, as well as liver and bony metastases. Blood tests demonstrated a resurgence in androgens including testosterone 7.3nmol/L, DHEA-S 15.8μmol/L, and androstenedione 55.0nmol/L. Triplet chemotherapy of cisplatin, doxorubicin and etoposide was considered but declined due to deteriorating physiological reserve and a decision to continue with best supportive care was made.

Discussion:

Current state of the art metastatic prostate cancer therapy employs an arsenal of therapies that target different parts of the sex hormone axis including anti-androgen therapy (enzalutamide), cyp-17 inhibitors (abiraterone), GnRH antagonist/agonists (degarelix, leuprolide), and surgical castration. Initial GnRH agonist/antagonist failure is exceedingly rare. LH elevation can suggest dose omission as the cause for GnRH agonist/antagonist failure. On occasion, anti-drug antibodies and rapid metabolism of the drug can result in therapy failure(1). Castrate resistant prostate cancer (CRPC) that metastasise (mCRPC) show intratumoural levels of testosterone/dihydrotestosterone which are similar to hormone naïve patients despite undergoing biochemical castration(2), suggestive of loss of feedback inhibition. The proposed mechanisms are (i) upregulation of direct testosterone biosynthesis via AKR1C3, (ii) tumoural conversion of adrenal androgens to testosterone & dihydrotestosterone, (iii) and bypass of testosterone following the alternate conversion pathway of androstenedione to 5α-androstenedione and subsequently dihydrotestosterone(3).

Adrenocortical carcinoma as a cause for GnRH agonist/antagonist failure is postulated. ACC is a rare clinical entity and even rarer still to be described synchronously with metastatic prostate cancer. The recommendation is open adrenalectomy with en-bloc resection of involved organs, with an experience adrenal surgeon. There is some signal for improved outcome with routine lymphadenectomy but not systematic unilateral total nephrectomy (4). The rate of distant metastases within 2 years is predicted by staging: Stage 1, 26%; Stage 2, 46%; Stage 3, 63%(5). Ki-67 and mitotic count informs prognosis and adjuvant therapy is recommended. The coexistence of Li-Fraumeni syndrome (incidence of 4%), Beckwith-Wiedemann syndrome or Carney complex should be considered.

Mitotane therapy remains a key component of ACC treatment(6) and its mechanism remains non-definitive. The side effects are noteworthy: adrenolytic therapy, rapid cytotoxicity, neurotoxicity including ataxia, gastrointestinal effects including hepatic failure, bleeding diathesis and CYP3A4 inducer. The mechanism of adrenolysis is presumptively mediated by glucocorticoid clearance, CBG increase, SHBG increase and inhibition of 11-β-hydroxylase activity. It is noteworthy that there is estrogenic activity and occasionally fT4 decline.

Take Home Messages:
- Failure to achieve castration with ADT is rare and should prompt careful review to identify the underlying cause.
- All adrenal lesions should be evaluated for hormone production, as well as assessed for risk of (primary or secondary) malignancy.
- Adrenocortical carcinomas are commonly functional and can secrete steroid hormones or their precursors (androgens, progestogens, glucocorticoids and mineralocorticoids).
- In this case, a co-incident, androgen-producing adrenocortical carcinoma was the cause of failure of testosterone suppression from androgen deprivation therapy as treatment for metastatic prostate cancer.
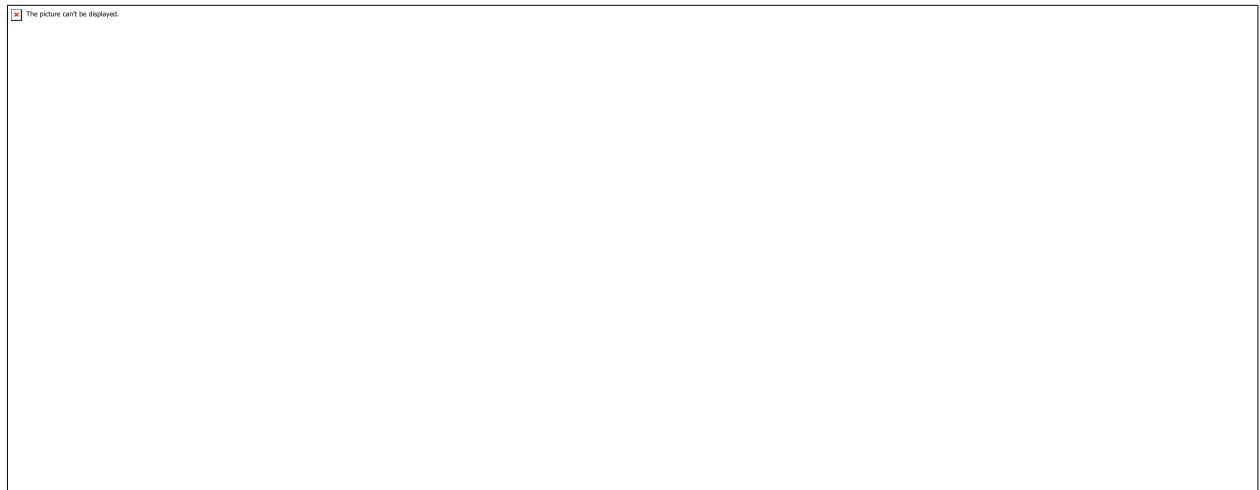
*Dates shifted

1. Jorion JL. Idiopathic resistance to luteinizing hormone-releasing hormone analogue in a patient with prostatic carcinoma. J Urol. 1992;148(5):1539-40.
2. Montgomery RB, Mostaghel EA, Vessella R, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res. 2008;68(11):4447-4454. doi:10.1158/0008-5472.CAN-08-0249
3. Chandrasekar T, Yang JC, Gao AC, Evans CP. Mechanisms of resistance in castration-resistant prostate cancer (CRPC). Transl Androl Urol. 2015 Jun;4(3):365-80. doi: 10.3978/j.issn.2223-4683.2015.05.02. PMID: 26814148; PMCID: PMC4708226.
4. Libé R. (2015). Adrenocortical carcinoma (ACC): diagnosis, prognosis, and treatment. Frontiers in cell and developmental biology, 3, 45. https://doi.org/10.3389/fcell.2015.00045
5. Icard P, Goudet P, Charpenay C, Andreassian B, Carnaille B, Chapuis Y, Cougard P, Henry JF, Proye C. Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. World J Surg. 2001 Jul;25(7):891-7. doi: 10.1007/s00268-001-0047-y. PMID: 11572030.
6. Lacroix A, Hammer GD. (2020). Treatment of adrenocortical carcinoma. In J. A. Melin (Ed.), UpToDate. Retrieved July 30, 2021, from https://www.uptodate.com/contents/treatment-of-adrenocortical-carcinoma

Secondary hyperaldosteronism due to reninoma of the kidney: a rare cause of severe hypertension

<u>Annabelle G Hayes</u>[1], Mahesh M Umapathysivam[1], James M McNeil[1], Michael Stowasser[2, 3], David J Torpy[1, 4]

1. Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, SA, Australia

2. Endocrine Hypertension Research Centre, University of Queensland Diamantina Institute, Greenslopes and Princess Alexandra Hospitals, Brisbane, QLD, Australia

3. Discipline of Medicine, University of Adelaide, Adelaide, SA, Australia

4. University of Adelaide, South Australia, Australia

A 35-year-old woman was referred with a seven year history of hypertension and hypokalaemia. Mean 24-hr blood pressure was 168/118mmHg and she was subsequently treated with Olmesartan 20mg daily. This controlled her blood pressure well to 120/60mmHg. On referral, she was considering pregnancy and Olmesartan is teratogenic .

Her medical history included depression and anxiety managed with Escitalopram 20mg daily and Quetiapine 100mg daily. There was no family history of hypertension or endocrinopathies.

Upon changing her Olmesartan to Prazosin 5mg tds to allow investigation for secondary causes of hypertension, she became symptomatic with headache, flushing and weakness. The systolic blood pressure rose to over 200mmHg, serum potassium fell to 3.1mmol/L (ref range). This occurred again when transitioned to Diltiazem 180mg daily for confirmatory testing, resulting in an emergency department presentation with headache, chest tightness, palpitations, hypertension and hypokalaemia to 2.5mmol/L. Hypokalaemia, hypertension and symptoms rapidly recovered on restarting Olmesartan, demonstrating exquisite sensitivity to angiotensin receptor blockade.

Direct renin concentration (DRC) was elevated to 10-fold upper limit of normal (ULN) but serum aldosterone was normal while taking Olmesartan. When Olmestartan was held, DRC remained 10-fold ULN but aldosterone rose to 2 to 4-fold ULN and hypokalaemia ensued.   (Table 1).

Tests for hypercortisolism and catecholamine excess were negative. Echocardiogram did not demonstrate coarctation of the aorta or changes of hypertensive cardiomyopathy, but albuminuria suggested early hypertensive nephropathy.

Imaging with renal tract ultrasound and CT angiogram showed normal renal arteries with no evidence of renal artery stenosis nor fibromuscular dysplasia. A 1.1cm partially cystic, right renal cortical lesion was noted, considered a simple cortical cyst. Follow up MRI demonstrated hypointense T1 signal and hyperintense T2 signal compared to the surrounding renal parenchyma. An enhancing internal septum was noted and a CT with portal venous contrast showed nodularity of the wall of the cystic lesion (Figure 1).

The biochemical and clinical picture therefore indicated hyperreninaemia with resultant secondary hyperaldosteronism. This nodular, septated cyst was the likely culprit lesion but functionality was required to confirm this prior to resection. Renal vein sampling of renin would lateralise autonomous production to the side of the tumour although confers only 56% reliability without adequate preparation and technique (1).

Renal vein sampling (RVS) was conducted, with care to avoid recrudescent severe hypertension and hypokalaemia. Olmesartan was stopped 2 weeks before RVS.   The patient was admitted 6 days prior to RVS for bed rest, final antihypertensive titration and salt deprivation. Prior to renal vein sampling, blood pressure was controlled on Verapamil 240mg CR daily, Hydralazine 50mg QID, Prazosin 5mg QID, Methyldopa 250mg BD and Slow K 4 tablets QID (9.6g daily) to a mean blood pressure of 150/95mmHg and serum potassium 4.1mmol/L.

Renal vein renin sampling was undertaken using the technique outlined by Wolley et al. (2) sampling before and 20 minutes after IV enalaprilat to stimulate renin production emphasising lateralisation after salt deprivation and careful recumbency.

Renin production was lateralised to the right with a right to left ratio of 1.9 before enalaprilat and 2.0 after enalaprilat, confirming the complex right renal cyst as a functional renin-producing tumour (Table 2). The patient is currently awaiting partial nephrectomy.

This case illustrates a possibly curable, rare form of secondary hypertension where a more likely diagnosis would be renal artery fibromuscular dysplasia and where an effort to achieve surgical cure was needed as the available medical treatments are unsafe or not known to be safe in pregnancy.

Discussion

Fewer than 200 cases of renin producing tumours (reninomas or juxtaglomerular cell tumours) have been described in the literature since their discovery in 1967 by Robertson (2, 3). These tumours have a tendency to occur in young women, present with headache, hypertension and hypokalaemia and demonstrate extreme sensitivity to angiotensin blockade through either angiotensin converting enzyme inhibition or angiotensin receptor blockade (2-4). Hypertension is typically severe with median reported blood pressure 201/130 mmHg and hypokalaemia present in over 80% of cases (1).

The patient's excellent response to angiotensin II receptor blockade normalised the blood pressure and potassium through reduction in angiotensin II's vasoconstrictive and sympathomimetic effects and blockade of stimulation of serum aldosterone.

Imaging has high sensitivity for detection of reninomas but heterogeneity in appearance confers low specificity. Most tumours are isodense on CT imaging with little contrast enhancement. MR imaging with T1 weighting appears more consistent than T2 weighted imaging demonstrating isointense signal while iso, hyper or hypointense signal on T2 weighted sequences (1, 5). A peripheral thin rim "pseudocapsule" was noted in over half studied cases (5).

While reninomas can occur in a wide demographic, their occurrence in women of childbearing age presents a management dilemma. Our patient was planning pregnancy and demonstrably her hypertension due to a renin producing tumour was difficult to control on four agents without the use of an ACEi or ARB, which are contraindicated in pregnancy due to teratogenicity (6). Furthermore, pregnancy is a physiologic state of hyperaldosteronism with increased oestrogen driven hepatic angiotensinogen providing additional substrate for the renin enzyme and angiotensin I production (7). Previous cases of renin producing tumours during pregnancy have therefore unsurprisingly seen poor maternal and foetal outcomes (8).

Reninomas are commonly cured with resection, typically resulting in normotension and normokalaemia without continuation of pharmacologic agents (1, 2, 4). We await the outcome of surgical resection in the coming weeks.

Take Home Messages

1. Reninoma is a rare case of secondary hypertension due to renin producing tumour, typically presenting in young females. Diagnosis requires a high index of suspicion.
2. Due to hyperstimulation of renin-angiotensin-aldosterone system, hypertension due to a reninoma is exquisitely sensitive to angiotensin receptor blockade or angiotensin converting enzyme inhibition. However, these agents are contraindicated in pregnancy
3. Reninomas may be found on CT with high sensitivity but renal vein sampling is required to confirm renin hypersecretion prior to surgical resection
4. Preparation with low salt diet and ACEi blockade should be taken to increase likelihood of lateralisation of the renal vein renin sampling

1. Wong L, Hsu TH, Perlroth MG, Hofmann LV, Haynes CM, Katznelson L. Reninoma: case report and literature review. J Hypertens. 2008;26(2):368-73.
2. Wolley M, Gordon RD, Stowasser M. Reninoma: the importance of renal vein renin ratios for lateralisation and diagnosis. Am J Nephrol. 2014;39(1):16-9.
3. Mezoued M, Habouchi MA, Azzoug S, Mokkedem K, Meskine D. Juxtaglomerular Cell Cause of Secondary Hypertension in an Adolescent. Acta Endocrinol (Buchar). 2020;16(3):359-61.
4. Inam R, Gandhi J, Joshi G, Smith NL, Khan SA. Juxtaglomerular Cell Tumor: Reviewing a Cryptic Cause of Surgically Correctable Hypertension. Curr Urol. 2019;13(1):7-12.
5. Faucon AL, Bourillon C, Grataloup C, Baron S, Bernadet-Monrozies P, Vidal-Petiot E, et al. Usefulness of Magnetic Resonance Imaging in the Diagnosis of Juxtaglomerular Cell Tumors: A Report of 10 Cases and Review of the Literature. Am J Kidney Dis. 2019;73(4):566-71.
6. Martin U, Foreman MA, Travis JC, Casson D, Coleman JJ. Use of ACE inhibitors and ARBs in hypertensive women of childbearing age. J Clin Pharm Ther. 2008;33(5):507-11.
7. Irani RA, Xia Y. Renin Angiotensin Signaling in Normal Pregnancy and Preeclampsia. Seminars in Nephrology. 2011;31(1):47-58.
8. Diker-Cohen T, Abraham SB, Rauschecker M, Papadakis GZ, Munir KM, Brown E, et al. Reninoma presenting in pregnancy. J Clin Endocrinol Metab. 2014;99(8):2625-6.

Primary Bilateral Macronodular Adrenal Hyperplasia - No longer a rare entity?

Soong Zheng Ng[1]

1. Department of Endocrinology, Cairns Hospital, Cairns, QLD, Australia

Ms SB, a 60-year-old female, was reviewed in our Endocrinology Clinic in September 2016 for bilateral adrenal incidentalomas which were identified during imaging for vertebral fractures. This was on a background of osteoporosis with multiple vertebral fractures, chronic back pain, untreated hypertension, depression, left hydroureter, and dental decay. She was a smoker of 50-pack-year history and drank 2-3 standard units of alcohol per day. Her medications included pregabalin, baclofen, opioids, benzodiazepines, antidepressants and denosumab.

She did not have proximal myopathy, Cushingoid facies, fat pads, bruising or striae. Weight was 62.7kg.

Imaging:

On Computed Tomography (CT), the left adrenal lesion measured 24x23mm with a density of -4.5 Hounsfield Units (HU). The right adrenal lesion measured 16.6x11mm with a density of -3.1 HU.

CT July 2017 showed an increase in size of the left adrenal lesion (25x31mm) and no change in the right adrenal lesion.

CT November 2018 did not show any significant change in size or characteristics of bilateral adrenal lesions.
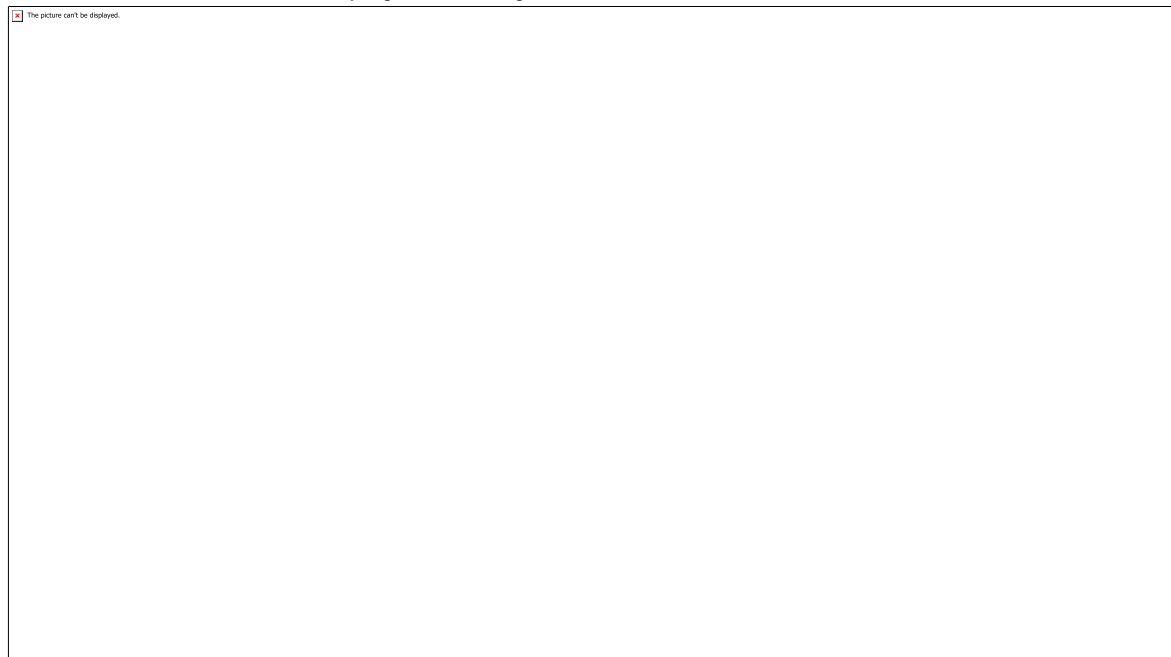
Functional assessment (summarized in Fig. 2):

Initial assessment showed normal 24-hour plasma metanephrines, elevated aldosterone-renin ratio (ARR) and an elevated 24-hour urine free cortisol (UFC). Overnight 1mg dexamethasone suppression test (DST) showed a failure to suppress cortisol. Repeat ARR was normal.

In July-August 2017, 24-hour UFC was normal and overnight 1mg DST was normal. These tests were repeated 4 months later showing a normal 24-hour UFC and non-suppressed overnight 1mg DST.

By November 2018, Ms SB had gained 8kg of weight. Biochemical testing continued to show non-suppressed overnight 1mg DST, but normal midnight salivary cortisol and 24-hour UFC.

Morning serum ACTH was consistently low-normal or suppressed.

Shortly after this clinic visit, the suspicion of Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH) as the diagnosis was raised due to the presence of bilateral adrenal nodules with consistently abnormal response to overnight 1mg DST. Magnetic Resonance Imaging (MRI) in February 2019 showed bilateral adrenal lesions with irregular enhancement. There was no evidence of fat contained overtly within the lesions.

Dynamic testing was performed to identify aberrant receptors by stimulation testing, as well as confirm exaggerated cortisol response to exogenous ACTH. For our patient, the test protocol was developed by the Endocrine Unit at Princess Alexandra Hospital, Brisbane, and consisted of baseline cortisol and ACTH levels (morning, late afternoon, midnight), DHEA-S levels, bone turnover markers, and genetic testing; followed by a mixed meal test with cortisol and ACTH levels every 30 minutes for 180 minutes. Subsequently, a 250mcg Short Synacthen Test (SST) was performed. The testing was completed by IV infusion of arginine vasopressin (AVP) at 1.01IU/70kg with cortisol and ACTH levels at -15, 0, 15, 30, 45, 60, 90 and 120 minutes.

The results were consistent with a diagnosis of PBMAH.

After multidisciplinary team discussion with Ms SB, the decision was made to proceed with left adrenalectomy (as the left adrenal lesion was the largest), which was performed in November 2019. Histopathology showed a single unencapsulated nodular expansion of adrenal cortical cells resembling normal zona fasciculata, favouring nodular cortical hyperplasia. Ms SB was commenced on oral hydrocortisone post-operatively. An SST performed 18 months after adrenalectomy showed a normal morning serum ACTH with satisfactory response to Synacthen, and hydrocortisone was gradually weaned.

Discussion:

Bilateral adrenal incidentalomas represent approximately 15% of adrenal incidentalomas[1], and differential diagnosis includes PBMAH.

The prevalence of PBMAH is uncertain.[2] PBMAH is a condition that was initially characterized by massively enlarged adrenal glands with multiple macronodules (>10mm) causing distortion of normal adrenal configuration. However, with increasing use of cross-sectional imaging (CT/MRI), less impressive bilateral adrenal enlargement is often recognized, most commonly as one discrete macronodule on each adrenal.[2] Although it is an uncommon cause of endogenous Cushing's Syndrome, the most common endocrinological dysfunction in PBMAH is autonomous cortisol secretion. This usually presents as an abnormal response to dexamethasone suppression testing with normal urinary free cortisol.[3] Plasma ACTH and DHEA-S is usually low or suppressed.

The pathogenesis for PBMAH is complex, with aberrant hormone receptors as the primary driver for autonomous cortisol production. In one case series of PBMAH, at least 85 percent of the cases had at least one aberrant cortisol response to seven provocative tests and one inhibitory (octreotide) test.[3] Of these, the V1-vasopressin receptor (V1-AVPR) is the most common aberrant stimulator of cortisol production. Other aberrant receptors include those for gastric inhibitory polypeptide (GIP), beta-adrenergic agonists, luteinising hormone (LH), human chorionic gonadotrophin (hCG), and serotonin (5-HT4).[4] This aberrancy stimulates adrenal cortical cells outside of the normal cortisol-mediated feedback, leading to hyperplasia.

Cortisol secretion in PBMAH is also partially regulated by intra-adrenal ACTH, which is secreted independent of dexamethasone and corticotropin-releasing hormone (CRH) control.[5] ACTH is secreted in response to aberrant hormonal triggers and further potentiates cortisol production via the MC2R receptor.

The majority of PBMAH cases were previously thought to be sporadic, however, several genetic abnormalities have now been detected. Of these, Armadillo repeat containing 5 (ARMC5) inactivation has been most common (approximately 25 percent of apparently sporadic cases).[6] ARMC5 is likely to be a tumour suppressor gene and follows a 'two-hit' model of tumorigenesis. An

initial ARMC5 germline mutation is followed by a somatic mutation leading to inactivation of ARMC5 and subsequent proliferation of affected cells.[7] Further identification of genotype-phenotype correlation may be useful to aid early diagnosis.

The decision for treatment of PBMAH should be individualised, as it remains controversial in patients with mild cortisol excess. The treatment of PBMAH is mainly surgical. In the past, bilateral adrenalectomy was the preferred treatment option, however, this led to inevitable adrenal insufficiency requiring lifelong corticosteroid replacement. In recent years, unilateral adrenalectomy (of the adrenal with largest mass / largest nodule) has emerged as an alternative, with high rates of remission of hypercortisolism and low rates of adrenal insufficiency.[8] European Society of Endocrinology and the Endocrine Society guidelines recommend bilateral adrenalectomy for Cushing's Syndrome in PBMAH, with consideration of selective unilateral adrenalectomy in milder cases, utilizing an individualised approach.[9]

Pharmacological treatment options for PBMAH are limited but growing. PBMAH expressing aberrant beta-adrenergic receptors have shown response to non-selective beta-blockers such as propranolol. PBMAH expressing LH/hCG receptors may respond to GnRH agonists, and GIP receptor-mediated cortisol secretion responds transiently to somatostatin inhibition. There are limited options for targeted pharmacological therapy of vasopressin and serotonin receptor mediated cortisol secretion. The identification and role of ACTH (MC2R) antagonists is currently being explored. Inhibitors of adrenal steroidogenesis such as ketoconazole and metyrapone can be used in cases of severe Cushings' Syndrome as an adjunct leading to adrenalectomy.[10]

Learning points:

- PBMAH should be suspected when a patient presents with bilateral adrenal incidentalomas and autonomous cortisol secretion (non-suppressed overnight 1mg DST).
- Aberrant receptors, intra-adrenal ACTH production and genetic mutations all have a role in pathogenesis of PBMAH.
- Diagnosis of PBMAH is via a combination of characteristic imaging and dynamic testing to confirm aberrant cortisol production.
- Treatment of PBMAH is primarily surgical, and unilateral adrenalectomy of the largest adrenal / nodule may be considered over bilateral adrenalectomy.
- Pharmacological therapy of PBMAH is limited but new options for targeted therapy are currently being explored.

1. Bourdeau I, El Ghorayeb N, Gagnon N, Lacroix A. MANAGEMENT OF ENDOCRINE DISEASE: Differential diagnosis, investigation and therapy of bilateral adrenal incidentalomas. Eur J Endocrinol. 2018 Aug;179(2):R57-R67. doi: 10.1530/EJE-18-0296. Epub 2018 May 10. PMID: 29748231.
2. Vassiliadi DA, Tsagarakis S. Diagnosis and management of primary bilateral macronodular adrenal hyperplasia. Endocr Relat Cancer. 2019 Oct 1;26(10):R567-R581. doi: 10.1530/ERC-19-0240. PMID: 32053747.
3. Libé R, Coste J, Guignat L, Tissier F, Lefebvre H, Barrande G, Ajzenberg C, Tauveron I, Clauser E, Dousset B, Bertagna X, Bertherat J, Groussin L. Aberrant cortisol regulations in bilateral macronodular adrenal hyperplasia: a frequent finding in a prospective study of 32 patients with overt or subclinical Cushing's syndrome. Eur J Endocrinol. 2010 Jul;163(1):129-38. doi: 10.1530/EJE-10-0195. Epub 2010 Apr 8. PMID: 20378721.
4. Lacroix A, Ndiaye N, Tremblay J, Hamet P. Ectopic and abnormal hormone receptors in adrenal Cushing's syndrome. Endocr Rev. 2001 Feb;22(1):75-110. doi: 10.1210/edrv.22.1.0420. PMID: 11159817.
5. Louiset E, Duparc C, Young J, Renouf S, Tetsi Nomigni M, Boutelet I, Libé R, Bram Z, Groussin L, Caron P, Tabarin A, Grunenberger F, Christin-Maitre S, Bertagna X, Kuhn JM, Anouar Y, Bertherat J, Lefebvre H. Intraadrenal corticotropin in bilateral macronodular adrenal hyperplasia. N Engl J Med. 2013 Nov 28;369(22):2115-25. doi: 10.1056/NEJMoa1215245. PMID: 24283225.
6. Assié G, Libé R, Espiard S, Rizk-Rabin M, Guimier A, Luscap W, Barreau O, Lefèvre L, Sibony M, Guignat L, Rodriguez S, Perlemoine K, René-Corail F, Letourneur F, Trabulsi B, Poussier A, Chabbert-Buffet N, Borson-Chazot F, Groussin L, Bertagna X, Stratakis CA, Ragazzon B, Bertherat J. ARMC5 mutations in macronodular adrenal hyperplasia with Cushing's syndrome. N Engl J Med. 2013 Nov 28;369(22):2105-14. doi: 10.1056/NEJMoa1304603. PMID: 24283224; PMCID: PMC4727443.
7. Correa R, Zilbermint M, Berthon A, Espiard S, Batsis M, Papadakis GZ, Xekouki P, Lodish MB, Bertherat J, Faucz FR, Stratakis CA. The ARMC5 gene shows extensive genetic variance in primary macronodular adrenocortical hyperplasia. Eur J Endocrinol. 2015 Oct;173(4):435-40. doi: 10.1530/EJE-15-0205. Epub 2015 Jul 10. PMID: 26162405; PMCID: PMC4572515.
8. Meloche-Dumas L, Mercier F, Lacroix A. Role of unilateral adrenalectomy in bilateral adrenal hyperplasias with Cushing's syndrome. Best Pract Res Clin Endocrinol Metab. 2021 Mar;35(2):101486. doi: 10.1016/j.beem.2021.101486. Epub 2021 Jan 13. PMID: 33637447.
9. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A; Endocrine Society. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015 Aug;100(8):2807-31. doi: 10.1210/jc.2015-1818. Epub 2015 Jul 29. PMID: 26222757; PMCID: PMC4525003.
10. Feelders RA, Newell-Price J, Pivonello R, Nieman LK, Hofland LJ, Lacroix A. Advances in the medical treatment of Cushing's syndrome. Lancet Diabetes Endocrinol. 2019 Apr;7(4):300-312. doi: 10.1016/S2213-8587(18)30155-4. Epub 2018 Jul 20. PMID: 30033041.

Crohn-ic hypophosphataemia

Kate Hawke[1], Syndia Lazarus[1]

1. Department of Diabetes and Endocrinology, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia

Introduction

Phosphaturic mesenchymal tumours (PMT) cause tumour-induced osteomalacia (TIO) through secretion of phosphatonins, principally fibroblast growth factor 23 (FGF23) (1). FGF23 decreases tubular phosphate reabsorption and circulating phosphate levels.

We present the case of a 37-year-old man with TIO on a background of active Crohn disease, with resolution following successful resection of a PMT.

Case report

A 37-year-old man was referred to endocrinology outpatients regarding insufficiency fractures and chronic hypophosphataemia, on a background of ileocolonic Crohn disease.

He reported difficulty walking for two years due to weakness and bilateral foot pain, and was mobilising in a wheelchair. Fractures of L1 and L2 were identified following a fall one year prior and he had lost 6cm in height. Recent investigations for foot pain included an MRI demonstrating a calcaneal fracture. Hypophosphataemia was present intermittently for four years and persisted despite recent oral supplementation.

He had required three bowel resections for Crohn disease over a 20 year course, further complicated by enterocutaneous fistula. Initial treatment was with azathioprine monotherapy, though adherence had been variable. He had participated in a two-year etrolizumab trial but withdrew just prior to presentation due to persistent disease, with a plan to transition to infliximab. His cumulative corticosteroid exposure was minimal. Other history included Vitamin D deficiency, iron deficiency anaemia and gastric ulcers. Apart from the recent vertebral and calcaneal fractures, there was no personal or family history of low-trauma fracture, short stature, limb deformities, delayed dentition or dental abscesses.

Current daily medications were azathioprine 100mg, cholecalciferol 4000IU, calcium carbonate 600mg, elemental phosphorous 1000mg, naproxen 500mg, pantoprazole 40mg, multivitamin and paracetamol/codeine 1000/30mg. Over two years, four intravenous iron infusions had been administered (Figure 1). He had adverse drug reactions to intravenous iron polymaltose and ferric carboxymaltose.

He was a married Information Technology professional with no children, and a lifelong non-smoker. Past hobbies included martial arts, which had never resulted in fractures.

He presented in a wheelchair. His weight was 105kg and height 191.6cm, with body mass index 28.5kg/cm^2. There was lower limb proximal weakness. There were no clinical features of Cushing's syndrome. There was diffuse tenderness over the feet bilaterally.

Biochemistry at initial endocrinology assessment (Table 1) demonstrated a plasma phosphate of 0.52mmol/L (reference range 0.75 – 1.10). Alkaline phosphatase (ALP) was persistently raised in the absence of other liver function abnormalities. There had been a recent normalisation of 25-hydroxy-vitamin D level with cholecalciferol replacement. CRP was 20mg/L (< 5).
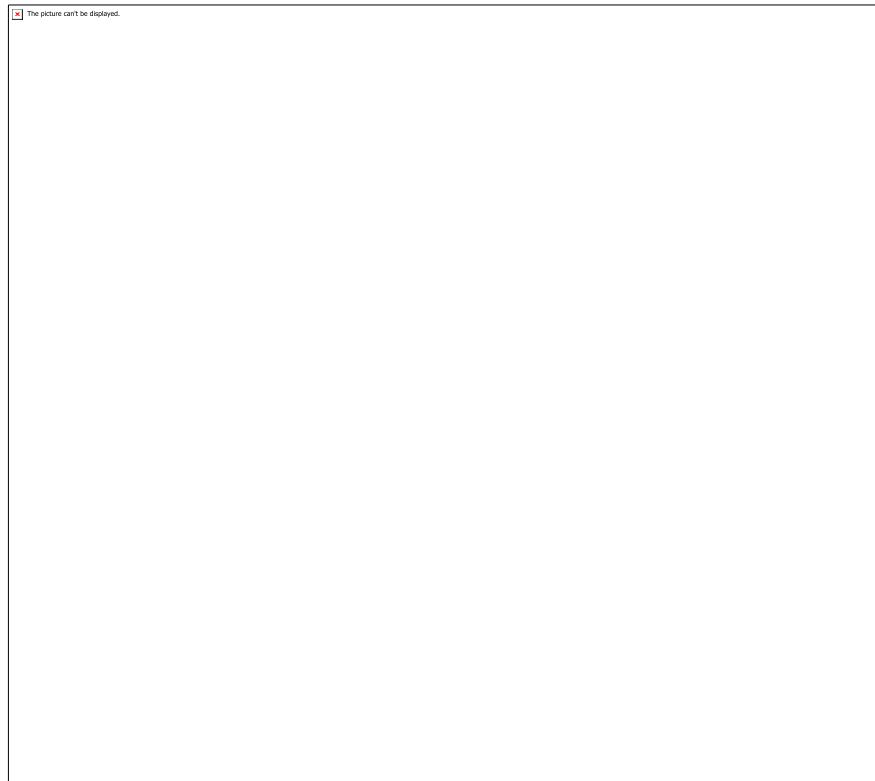
Fasting urine phosphate was 50.1mmol/L with urine creatinine 25.9mmol/L. The calculated tubular reabsorption of phosphate (TmP/GFR) was low at 0.42mmol/L (1 – 1.30). Plasma FGF23 level was inappropriately elevated at 101ng/L (23-95). 1,25-dihydroxyvitamin D was low at 30 nmol/L. Serum phosphate had seemingly dropped in the two months after his first iron infusion, however, his nadir level of 0.31 mmol/L had occurred prior to receiving any iron infusions. (Figure 1).

Dual energy x-ray absorptiometry showed low bone mass, with Z score -3.3 at the lumbar spine and -3.8 at the left femoral neck. Bone scintigraphy (Figure 2) was consistent with osteomalacia. MRI foot demonstrated a left calcaneal fracture traversing 50% of the depth of the calcaneal tuberosity, and a suspected fracture of the medial cuneiform.
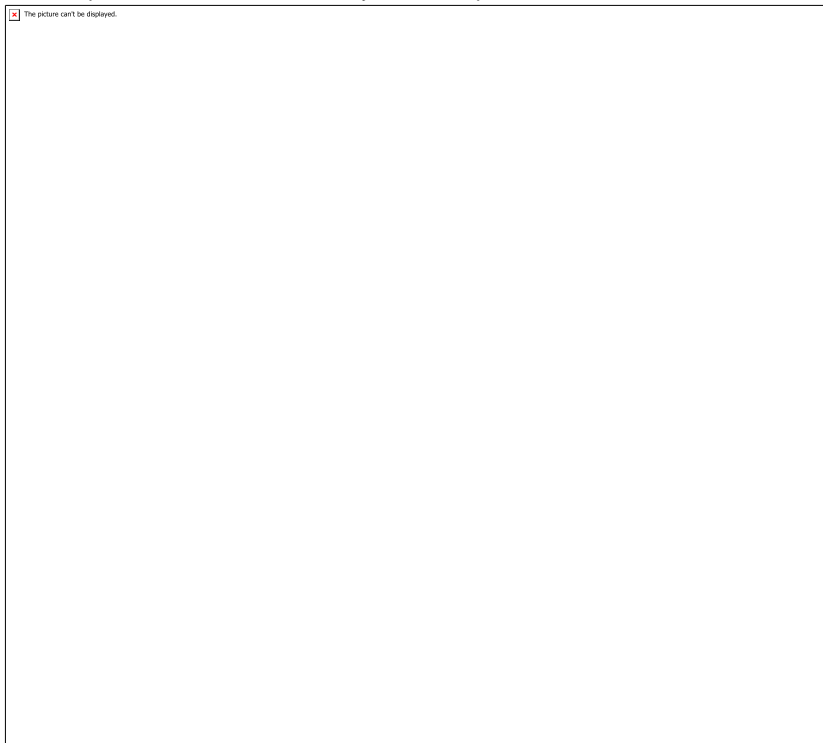
DOTATATE PET scan (Figure 3) showed an avid soft tissue nodule posterior to the right knee, measuring 10 x 15mm. The patient proceeded to an uncomplicated excision of the lesion.

Histopathology demonstrated a highly vascular lesion with spindle cells in short fascicles (Figure 4). Immunohistochemistry for FGF23 was positive (Figure 5). The final histopathological diagnosis was PMT.

Following surgery, FGF23 levels dramatically decreased and plasma phosphate levels completely normalised (Table 1). The bone pain improved and the patient was mobilising with no aid.

Discussion

The possible aetiologies for hypophosphataemia in patients with active Crohn disease are multiple. Firstly, malnourished patients with chronic diarrhoea are at risk for hypophosphataemia due to malabsorption of phosphate and Vitamin D, especially in the presence of secondary hyperparathyroidism, which limits renal tubular phosphate reabsorption. Secondly, FGF23-mediated hypophosphataemia is a well-described side effect of intravenous iron preparations (3). Ferric carboxymaltose administration in IBD patients is associated with a 57% incidence of moderate-to-severe hypophosphataemia two weeks after infusion, with the time to spontaneous normalisation ranging from one to six months (3). In our case, the lack of responsiveness of hypophosphataemia to supplementation of Vitamin D and phosphorous, as well as the time course distinct from iron infusions, warranted consideration of an alternative cause, leading to the diagnosis of TIO due to a phosphaturic mesenchymal tumour.

In TIO, the chronic hypophosphataemia induced by ectopic FGF23 secretion leads to suboptimal supply of phosphate to bone and subsequent reduced rate of osteoid mineralization, resulting in osteomalacia (1). Understanding of the tumorigenesis of the underlying PMTs has progressed in recent years, suggesting a central role for an autocrine/paracrine loop between fibroblast growth factors and FGFR1, driven by fusion proteins (4). However, the relevance of FGF23's association with inflammatory markers to the pathogenesis of TIO is unclear.

Crohn disease is a chronic inflammatory bowel disease (IBD). Available medical therapies are directed against immune signalling pathways including the mediators TNF-α, IL-12/23 and integrin α4β7 (2). An association between FGF23 levels and inflammation has been established. In chronic kidney disease, FGF23 correlates directly with IL-6, CRP, and TNF-α levels, independent of renal function and mineral metabolism measures (5). Possible explanations include FGF23 directly stimulating inflammation by inducing cytokines, or pro-inflammatory effects from FGF23-mediated suppression of 1,25-dihydroxyvitamin D (5). Conversely, inflammation may stimulate production of FGF23, due to its direct bone resorptive effects (6). FGF23 levels are higher among children with IBD during flares and among psoriasis patients compared to controls (7, 8). Thus, TIO may affect the severity of Crohn disease, or conversely Crohn disease may increase FGF23 secretion in TIO, as has been postulated in a previous case report of psoriasis and TIO (9). A further aspect of our patient's case is the long history of immunosuppression. Immunosuppressive therapy is a risk factor for a wide variety of malignancies, including rare tumours (10), though to our knowledge there is no specific data on TIO incidence in immunosuppressed patients.

Conclusion

We presented the case of a young man with TIO in the setting of active Crohn disease on immunosuppressive therapy.

Take home messages

- Differential diagnoses for hypophosphataemia in patients with Crohn disease include nutritional causes and iron infusion-induced.
- If the time course and response to phosphate supplementation are not as expected for these diagnoses, less common causes such as TIO should be considered.
- While there is an association between FGF23 levels and inflammatory markers, the possible links between TIO and inflammatory disorders are not known.

1. Minisola S, Peacock M, Fukumoto S, Cipriani C, Pepe J, Tella SH, et al. Tumour-induced osteomalacia. Nature Reviews Disease Primers. 2017;3(1):17044.
2. Cushing K, Higgins PDR. Management of Crohn Disease: A Review. JAMA : the journal of the American Medical Association. 2021;325(1):69-80.
3. Detlie TE, Lindstrøm JC, Jahnsen ME, Finnes E, Zoller H, Moum B, et al. Incidence of hypophosphatemia in patients with inflammatory bowel disease treated with ferric carboxymaltose or iron isomaltoside. Aliment Pharmacol Ther. 2019;50(4):397-406.
4. Lee JC, Su SY, Changou CA, Yang RS, Tsai KS, Collins MT, et al. Characterization of FN1-FGFR1 and novel FN1-FGF1 fusion genes in a large series of phosphaturic mesenchymal tumors. Mod Pathol. 2016;29(11):1335-46.
5. Munoz Mendoza J, Isakova T, Ricardo AC, Xie H, Navaneethan SD, Anderson AH, et al. Fibroblast growth factor 23 and Inflammation in CKD. Clin J Am Soc Nephrol. 2012;7(7):1155-62.
6. Dai JC, He P, Chen X, Greenfield EM. TNFalpha and PTH utilize distinct mechanisms to induce IL-6 and RANKL expression with markedly different kinetics. Bone. 2006;38(4):509-20.
7. El-Hodhod MA, Hamdy AM, Abbas AA, Moftah SG, Ramadan AA. Fibroblast growth factor 23 contributes to diminished bone mineral density in childhood inflammatory bowel disease. BMC Gastroenterol. 2012;12:44.
8. Okan G, Baki AM, Yorulmaz E, Doğru-Abbasoğlu S, Vural P. Fibroblast Growth Factor 23 and Placental Growth Factor in Patients with Psoriasis and their Relation to Disease Severity. Ann Clin Lab Sci. 2016;46(2):174-9.
9. Akbari M, Larijani B, Sharghi S, Jalili A, Sajjadi-Jazi SM. Is there any link between tumor-induced osteomalacia and psoriasis? A case report. J Diabetes Metab Disord. 2017;16:34.
10. D'Arcy ME, Castenson D, Lynch CF, Kahn AR, Morton LM, Shiels MS, et al. Risk of Rare Cancers Among Solid Organ Transplant Recipients. J Natl Cancer Inst. 2021;113(2):199-207.

A Rare Case of Hypocalcaemia

<u>Bon Hyang Lee</u>[1], Kathy Wu[1, 2, 3, 4, 5], Daniel Chen[1, 3]

1. St Vincent's Hospital Sydney, Darlinghurst, NSW, Australia
2. Clinical Genomics, St Vincent's Hospital, Sydney, New South Wales, Australia
3. Garvan Institute of Medical Research, Sydney, New South Wales, Australia
4. School of Medicine, University of New South Wales, Sydney, New South Wales, Australia
5. Discipline of Genetic Medicine, University of Sydney, Sydney, New South Wales, Australia

Case Description

A 44-year-old male presented with a long-standing history of hypocalcaemia with elevated parathyroid hormone (PTH) levels. He required regular calcium and calcitriol to maintain normocalcaemia. His other background history included antibody-negative hypothyroidism on thyroxine replacement and obesity. Despite normal calcium (2.49mmol/L) and phosphate (1.17mmol/L), he had persistently elevated PTH of 17 pmol/L. 24-hour urinary calcium was normal at 4.5mmol/24h. There was no evidence of gonadotropin or somatotropin excess. He had normal vitamin D and renal function, excluding secondary hyperparathyroidism. His diagnosis was most consistent with pseudohypoparathyroidism (PHP).

On examination, he was 174cm tall, above mid-parental height and weighed 105kg with a body mass index of 34.7kg/m2. Blood pressure was 140/100mmHg. He did not have overt features of Albright hereditary osteodystrophy. He did not have facial dysostosis. Neck ultrasound was unremarkable, and the brain CT did not reveal basal ganglia calcification.

His initial presentation was with facial and carpal spasms at age 27. At that time, he had low calcium of 1.64 mmol/L, high phosphate of 1.62 mmol/L with elevated PTH of 54 pmol/L (1-7 pmol/L) with low 24-hour urinary calcium of 0.87 mmol/24h (1.2-10 mmol/24h). Secondary causes of hyperparathyroidism were excluded, and he was diagnosed with PHP. He started regular calcium and calcitriol replacement, maintained normal calcium levels with persistently elevated PTH above 15 pmol/L (1.5-9.9). Within a few years, he developed subclinical hypothyroidism with elevated TSH between 4.6 and 7 mIU/L (0.4-4).

He is one of two sons born to non-consanguineous parents. His mother had hypothyroidism, and his father died at age 70 with bowel cancer. He has a well 38-year-old brother. He is married with a 1-year-old daughter who is well. There was no known family history of abnormal calcium homeostasis.

Molecular testing confirmed a pathogenic variant, a heterozygous deletion of exons 5 to 7 within the *STX16* gene, supporting the diagnosis of PHP type1b. A high-density array comparative genomic hybridisation (aCGH) confirmed the deletion with breakpoints in intron 4 and exon 7, of approximately 2.3kb in size.

Discussion

PHP is a rare genetic disorder characterised by hypocalcaemia, hyperphosphataemia secondary to PTH resistance. The estimated prevalence of PHP is between 0.34 to 1.1 in 100,000[1]. There are different classical subtypes, and the main subtypes characteristics are summarised in Table 1.

Table 1: Characteristics of the Main Subtypes of Pseudohypoparathyroidism and Hypoparathyroidism.

	PHP type1A	PHP type1B	PPHP	Hypoparathyroidism
Calcium	↓	↓	-	↓
Phosphate	↑	↑	-	↑
PTH	↑	↑	-	↓
24-hr urinary calcium	-	-	-	↑
AHO	+	+/-	+	-
Other Hormone resistance	Multiple THS, Gn, GHRH	TSH	-	-
GNAS mutation	Maternal inactivating mutations	Imprinting dysregulation	Paternal inactivating mutations	-

PHP pseudohypoparathyroidism, PPHP pseudopseudohypoparathyrodisim, AHO Albright Hereditary Osteodystrophy, TSH thyroid-stimulating hormone, Gn gonadotropin, GNRH growth hormone-releasing hormone.

Normocalciuria is a distinct feature of PHP due to a selective PTH resistance in the proximal renal tubule with intact PTH action in the renal distal tubule[2]. Normally, PTH inhibits phosphate reabsorption in the proximal tubule and increases calcium reabsorption in the distal tubule. In PHP, PTH resistance in the proximal renal tubule causes hyperphosphataemia, which reduces active vitamin D levels with resultant hypocalcaemia. Due to intact PTH action in the renal distal tubule with preserved anti-calciuric effect, patients with PHP maintain normocalciuria[3]. Thus, complications including nephrocalcinosis and nephrolithiasis are rare[4]. Hypoparathyroidism has similar serum biochemical features to PHP, but due to the impaired PTH action in both proximal and distal tubules, hypercalciuria and related complications are commonly seen.

PHP type 1b usually presents with isolated PTH resistance but can present with TSH resistance, defined by raised serum TSH level, in the absence of antithyroid antibodies with normal thyroid ultrasonography [5]. TSH resistance in PHP1b is generally mild

compared with PHP type 1a with minimally elevated TSH and thyroxine levels that are normal or slightly low[3]. A study by Liu et al.[6] showed that in the thyroid, most *GNAS* gene product (~72%) is generated from the maternal allele and the rest from the paternal allele. In PHP type 1b, it is postulated that there is an imprinting defect in the exon 1A region, a negative regulatory element of the *GNAS* gene, upstream of the *GNAS* locus. As a result of the mutation, this region becomes non-methylated in both parental alleles, with *GNAS* gene products equivalent to having two functional paternal alleles. This may explain the milder presentation of TSH resistance in PHP type 1b, compared to type 1a with mutations in the maternal *GNAS* allele, but more noticeable TSH resistance than pseudopseudohypoparathyroidism where a full maternal *GNAS* allele is at function. The age of diagnosis of TSH resistance in PHP type 1b occur between 2 and 48 years with TSH levels between 2.6 to 8.9 mU/L (0.3-4.2)[5]. Our patient was diagnosed with subclinical hypothyroidism at age 26 with only mildly elevated TSH. Given that his thyroid antibodies were negative in the absence of goitre, this suggests TSH resistance associated with PHP type 1b.

PHP is an imprinting genetic disease caused by genetic or epigenetic mutations in the *GNAS* locus on chromosome 20q13.3, which encodes the alpha subunit of the stimulatory G-protein required for the PTH signalling pathway. Most PHP type 1b is de novo, but 10–15% of cases are inherited as autosomal dominant (AD) disorders[1]. The established genetic mechanisms of PHP type 1b include an inactivating *GNAS* pathogenic variant or a genetic alteration in the imprinting regulatory elements in the *GNAS* complex locus or the nearby gene, *STX16*, preventing proper maternal imprint of the *GNAS* complex locus. Heterozygous 3-kb deletion of *STX16*, which encodes syntaxin 16, is the most frequent mutation found in AD PHP type 1b [7]. *STX16* microdeletion is postulated to disrupt a putative cis-acting control element required for methylation at exon 1A of the *GNAS* gene, and that this epigenetic defect underlies the pathogenesis of PHP Ib[8].

Patients with autosomal dominant PHP type 1b will only manifest symptoms if it is maternally inherited, as paternally inherited allele is silenced. The offspring of affected males will not develop clinical symptoms of PHP type 1b, but each offspring will be at a 50% chance of inheriting the genetic mutation. In our patient, while we do not expect the proband's daughter to develop clinical symptoms if the daughter has inherited the mutation, she will be at risk of having affected children with symptomatic PHP type 1b in the future. Preimplantation Genetic Diagnosis (PGD) may be considered as a reproductive option for the family.

Without apparent clinical features and in the absence of family history, diagnosis can be challenging and may be delayed for many years. Once clinical suspicion exists, molecular testing with appropriate genetic counselling should be offered to confirm the diagnosis and inform more accurate screening and reproductive implications.

Take-Home Messages

- PHP type 1b is characterised by PTH resistance which manifests as hypocalcaemia and hyperphosphataemia, usually in the absence of AHO features. Mild TSH resistance is commonly associated with PTH type 1b.
- Normocalciuria is a distinct feature of PHP due to a selective PTH resistance in the proximal renal tubule with intact PTH action in the renal distal tubule.
- Most PHP type 1b is de novo but 10-15% have maternally inherited mutations in the maternally imprinted *GNAS* gene or *STX16* gene. The symptoms will only manifest if the mutation is maternally inherited.
- Genetic testing/confirmation is important for accurate diagnosis and counselling due to overlapping phenotypes between PHP subtypes.

References

1. Mantovani, G., et al., Diagnosis and management of pseudohypoparathyroidism and related disorders: first international Consensus Statement. Nat Rev Endocrinol, 2018. 14(8): p. 476-500.
2. Stone, M.D., et al., The renal response to exogenous parathyroid hormone in treated pseudohypoparathyroidism. Bone, 1993. 14(5): p. 727-35.
3. Mantovani, G., Clinical review: Pseudohypoparathyroidism: diagnosis and treatment. J Clin Endocrinol Metab, 2011. 96(10): p. 3020-30.
4. Mantovani, G., et al., Recommendations for Diagnosis and Treatment of Pseudohypoparathyroidism and Related Disorders: An Updated Practical Tool for Physicians and Patients. Horm Res Paediatr, 2020. 93(3): p. 182-196.
5. Mantovani, G., et al., Genetic analysis and evaluation of resistance to thyrotropin and growth hormone-releasing hormone in pseudohypoparathyroidism type Ib. J Clin Endocrinol Metab, 2007. 92(9): p. 3738-42.
6. Liu, J., B. Erlichman, and L.S. Weinstein, The stimulatory G protein alpha-subunit Gs alpha is imprinted in human thyroid glands: implications for thyroid function in pseudohypoparathyroidism types 1A and 1B. J Clin Endocrinol Metab, 2003. 88(9): p. 4336-41.
7. Juppner, H., Molecular Definition of Pseudohypoparathyroidism Variants. J Clin Endocrinol Metab, 2021. 106(6): p. 1541-1552.
8. Linglart, A., et al., A novel STX16 deletion in autosomal dominant pseudohypoparathyroidism type Ib redefines the boundaries of a cis-acting imprinting control element of GNAS. Am J Hum Genet, 2005. 76(5): p. 804-14.

Rebound hypercalcaemia post-denosumab cessation: an emerging phenomenon?

Ray Wang[1], Debra Renouf[1]

1. Peninsula Health, Frankston, VIC, Australia

Hypercalcaemia in patients with malignancy can occur due to a variety of reasons, most commonly tumour cell secretion of parathyroid hormone-related peptide (PTHrP) or osteolytic bony metastases with pathological bone resorption, and rarely due to 1,25(OH) vitamin D hypersecretion (Stewart 2005). Amongst patients with bony metastatic disease, denosumab, a monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL), has established benefit in delaying or preventing skeletal related events (SRE) (Uchida 2020). Unlike bisphosphonates which are retained in the skeleton leading to a sustained antiresorptive effect, denosumab is rapidly cleared from the circulation leading to a post-discontinuation rebound effect of excessive bone resorption and multiple vertebral fracture risk (Anastasilakis 2021).

We present the case of a patient who experienced a rarely described rebound hypercalcaemia response after cessation of long-term denosumab therapy for the prevention of SRE in metastatic breast cancer.

Case

A 49-year-old woman presented with recurrent symptomatic PTH-independent hypercalcaemia. She was a long-term survivor after resected glioblastoma multiforme treated with adjuvant chemoradiotherapy, as well as oligometastatic breast cancer (ER/PR positive), having underwent bilateral mastectomy in 2012 prior with radiotherapy for an isolated left 5th rib metastasis and subsequent hormonal therapy initially with tamoxifen and then later on with anastrozole. To reduce the risk of skeletal related events, she was treated with denosumab 120mg every 4 weeks from August 2013 to October 2015, and then every 3 months until March 2020 (total of 42 doses).

She then had three presentations to hospital with symptomatic hypercalcaemia requiring inpatient treatment. The first presentation occurred 8 months after the last dose of denosumab, with symptomatic hypercalcaemia with a corrected calcium 3.29 mmol/L, phosphate 1.00 mmol/L, suppressed PTH 0.8 pmol/L (N: 1.5-7.0), and 25(OH) Vitamin D level of 75 nmol/L. She was administered 60mg IV pamidronate with resolution of hypercalcaemia, though experienced transient hypocalcaemia. She presented to hospital a second time 10 months after last dose of denosumab with corrected calcium 3.52 mmol/L, phosphate 1.44 mmol/L, and was treated with 30mg IV pamidronate with resolution of hypercalcaemia. A 1,25(OH) Vitamin D level was 14 pmol/L (N:50-190). She then presented to hospital a third time 11 months after last dose of denosumab with corrected calcium 3.01 mmol/L, phosphate 1.58 mmol/L and was treated with 4mg IV zoledronic acid with sustained resolution of hypercalcaemia thereafter.

Over the course of these admissions, numerous investigations were performed to look for possible recurrent malignancy or alternate aetiologies for PTH-independent hypercalaemia. Serum ACE, protein electrophoresis, serum free light chains, CA 15-3, CA 125 and CEA were normal. Brain MRI, CT of the chest/abdomen/pelvis, whole body bone scintigraphy and FDG PET scan did not reveal any active malignancy, nor rebound vertebral fractures, and simply demonstrated stable appearances of the previously irradiated left 5th rib lesion without significant tracer uptake on bone scintigraphy or FDG PET. A bone density scan performed just prior to the zoledronic acid reported T scores of 0.0 at the lumbar spine, -1.1 at the femoral neck, and -1.0 at the total hip. Bone turnover markers (BTM) 2 months after zoledronic acid showed P1NP of 93 ug/L and CTX 971 ng/L, and 3 months after zoledronic acid were P1NP 136 ug/L and CTX 1101 ng/L. Given the absence of evidence of active malignancy or osteolytic bone lesions, together with the markedly elevated BTM despite 3 doses of IV bisphosphonates, we diagnosed her with PTH-independent hypercalcaemia related to a rebound effect post-denosumab cessation.

Discussion

This is only the fourth case report in the literature of an adult with rebound hypercalcaemia post-denosumab cessation, without alternative confounding factors that could be driving the hypercalcaemia. In the literature, there are 32 cases reported to date of post-denosumab cessation hypercalaemia (summarised in Camponovo 2020; also Maugars 2020), however the majority of cases (n=21) have been reported in the paediatric population where higher baseline bone turnover may be a predisposing factor for these cases to be more prone to rebound hypercalcaemia. Additionally, amongst the 11 adult cases there are 8 with additional driving factors for hypercalcaemia (5 GCTB with its over-expression of RANKL [Uday 2018, Chawla 2019], 2 with osteoporosis and concomitant hyperparathyroidism [Camponovo 2020, Maugars 2020], and one with breast cancer and concomitant severe thyrotoxicosis [Uchida 2020]), leaving only 3 other cases with true rebound hypercalcaemia.

The first, a 54-year-old woman (Roux 2019) with breast cancer treated with denosumab 120mg for 5.5 years, experienced hypercalcaemia 6 months after cessation with calcium 3.10 mmol/L. No evidence of malignancy recurrence was found and treatment with 4 doses of pamidronate eventually led to biochemical resolution though ongoing elevated CTX 669 ng/L. The other two cases occurred after osteoporosis treatment. One, a 67-year-old woman (Koldjaer Solling 2016) treated with denosumab 60mg 6-monthly for 10 years, experienced hypercalcaemia 6 months after cessation with calcium 3.1 mmol/L, effectively managed with oral alendronate. The other, a 77-year-old woman (Tjelum 2018) with hypercalcaemia 6 months after cessation, was managed with rehydration alone, though denosumab duration and hypercalcaemia severity are not specified.

The rebound effect seen after denosumab cessation results in dramatic increases of bone turnover markers, often even exceeding pre-treatment levels, with an increased risk of multiple vertebral fractures (Anastasilakis 2021). Whilst the exact pathway behind this rebound effect remains undefined, proposed mechanisms include sudden activation of an expanded pool of osteoclast precursors, as well as an elevated RANKL:OPG ratio after denosumab is cleared from the circulation (Anastasilakis 2021) (McClung 2016), leading to marked bone resorption after denosumab's inhibitory effect on RANKL wears off. There is some evidence to suggest duration of denosumab treatment may impact the magnitude of the rebound effect, with some studies demonstrating longer exposure to denosumab being associated with greater number and earlier onset of vertebral fractures, together with greater BMD loss (Anastasilakis 2021). Transition to an alternate antiresorptive agent is currently recommended after denosumab cessation to minimise rebound bone loss (Anastasilakis 2021), although the optimal timing of this transition remains unclear and is an area of ongoing research.

Rebound hypercalcaemia post-denosumab cessation is a rare but potentially serious complication that few clinicians are aware of. We recommend transitioning to bisphosphonate therapy upon cessation of denosumab, and in any patients who are not transitioned, that clinicians consider assessing calcium levels starting 4-6 months after denosumab cessation to assess for possible hypercalcaemia, especially in those with a longer duration of treatment. In those who develop rebound hypercalcaemia, bisphosphonate treatment is suggested, and in some cases repeated dosing may be required in the first 12 months after denosumab cessation.

Learning Points

- Hypercalcaemia may occur due to a variety of reasons in patients with malignancy
- Denosumab withdrawal is associated with a rebound phenomenon characterised by markedly raised bone turnover markers and multiple vertebral fractures, as well as potentially hypercalcaemia
- In patients in whom denosumab is being ceased, treatment should generally be transitioned to bisphosphonate therapy, although the optimal regime and timing of this requires further research

1. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med. 2005 Jan 27;352(4):373-9. doi: 10.1056/NEJMcp042806. PMID: 15673803.
2. Uchida T, Yamaguchi H, Kushima C, Yonekawa T, Nakazato M. Elevated levels of circulating fibroblast growth factor 23 with hypercalcemia following discontinuation of denosumab. Endocr J. 2020 Jan 28;67(1):31-35. doi: 10.1507/endocrj.EJ19-0198. Epub 2019 Sep 13. PMID: 31527321.
3. Anastasilakis AD, Makras P, Yavropoulou MP, Tabacco G, Naciu AM, Palermo A. Denosumab Discontinuation and the Rebound Phenomenon: A Narrative Review. J Clin Med. 2021 Jan 4;10(1):152. doi: 10.3390/jcm10010152. PMID: 33406802; PMCID: PMC7796169.
4. Camponovo C, Aubry-Rozier B, Lamy O, Gonzalez Rodriguez E. Hypercalcemia upon denosumab withdrawal in primary hyperparathyroidism: a case report and literature review. Osteoporos Int. 2020 Dec;31(12):2485-2491. doi: 10.1007/s00198-020-05676-7. Epub 2020 Oct 15. PMID: 33057735; PMCID: PMC7661408.
5. Maugars Y, Guillot P, Glémarec J, Berthelot JM, Le Goff B, Darrieutort-Laffite C. Long-term follow up after denosumab treatment for osteoporosis - rebound associated with hypercalcemia, parathyroid hyperplasia, severe bone mineral density loss, and multiple fractures: a case report. J Med Case Rep. 2020 Aug 11;14(1):130. doi: 10.1186/s13256-020-02401-0. PMID: 32792004; PMCID: PMC7427054.
6. Roux S, Massicotte MH, Huot Daneault A, Brazeau-Lamontagne L, Dufresne J. Acute hypercalcemia and excessive bone resorption following anti-RANKL withdrawal: Case report and brief literature review. Bone. 2019 Mar;120:482-486. doi: 10.1016/j.bone.2018.12.012. Epub 2018 Dec 17. PMID: 30572144.
7. Uday S, Gaston CL, Rogers L, Parry M, Joffe J, Pearson J, Sutton D, Grimer R, Högler W. Osteonecrosis of the Jaw and Rebound Hypercalcemia in Young People Treated With Denosumab for Giant Cell Tumor of Bone. J Clin Endocrinol Metab. 2018 Feb 1;103(2):596-603. doi: 10.1210/jc.2017-02025. PMID: 29211870.
8. Chawla S, Blay JY, Rutkowski P, Le Cesne A, Reichardt P, Gelderblom H, Grimer RJ, Choy E, Skubitz K, Seeger L, Schuetze SM, Henshaw R, Dai T, Jandial D, Palmerini E. Denosumab in patients with giant-cell tumour of bone: a multicentre, open-label, phase 2 study. Lancet Oncol. 2019 Dec;20(12):1719-1729. doi: 10.1016/S1470-2045(19)30663-1. Epub 2019 Nov 6. PMID: 31704134.
9. Koldkjær Sølling AS, Harsløf T, Kaal A, Rejnmark L, Langdahl B. Hypercalcemia after discontinuation of long-term denosumab treatment. Osteoporos Int. 2016 Jul;27(7):2383-2386. doi: 10.1007/s00198-016-3535-5. Epub 2016 Apr 20. PMID: 27098536.
10. Tjelum L, Eiken P. [Multiple vertebral fractures after denosumab discontinuation]. Ugeskr Laeger. 2018 Nov 5;180(45):V12170948. Danish. PMID: 30404716.

To Continue or Pause Bone Protection in A Patient with Metastatic Breast Cancer Who Suffered an Atypical Femoral Fracture

<u>Ushank Ranasinghe</u>[1], Sridhar Chitturi[1]

1. Royal Darwin Hospital, Darwin, NT, Australia

A 58-year-old female (AO) presented with a fracture involving the right proximal femur following a mechanical fall while walking in October 2020. The patient has a history of metastatic breast cancer which was diagnosed in 2013 with multiple bony metastases, including two deposits in the proximal right femur (lesser trochanter and proximal diaphysis). AO had a left mastectomy with lymph node dissection followed by radiotherapy and declined chemotherapy but has been on letrozole (aromatase inhibitor) and Goserelin (GnRH agonist) since January 2014. Around the same time, she started Denosumab to prevent malignancy-associated skeletal-related events (SREs) and continued 120mg every three months until January 2020, at which time it was changed to four monthly injections. Additionally, the patient had bone scans every 4-6 months, which showed primarily stable disease with interval reduction in osteoblastic activity. However, in August 2017, a small new focus of increased uptake was noted in the lateral left proximal femur, thought to be a new metastatic deposit.

In October 2020, the patient's right proximal femoral fracture was managed with a long gamma nail. A CT scan of the right hip and femur revealed irregular cortical thickening along the lateral margin of the proximal fracture component as well as cortical buttressing. The patient could weight-bear but continued to experience pain along the left thigh while walking. A re-review of the X-rays from the time of initial fracture revealed an incomplete atypical fracture along the lateral margin of the left proximal femur (Figure 1). There were concerns about a pathological process, given the patient's history of breast cancer, and in January 2021 a prophylactic gamma nail was inserted but bone fragments did not show signs of metastatic disease. A second surgery involving an intramedullary nail exchange with bone graft was done in April 2021 for poor fracture healing, and the left femoral fracture line was visible with callus formation on the most recent X-ray taken in July 2021.

AO was referred for an endocrinological opinion given the delayed/non-healing of her left femoral fracture. The Dual Energy X-ray Absorptiometry (DEXA) showed the average BMD of the lumbar spine (L2-4) to be 1.386g/cm (T-score 1.1) and the radial distal 1/3rd 1.007g/cm (T-score 1.3). The bone turnover markers were elevated (CTX 1866 ng/L [0-399], P1NP 210 ug/L [15-75]) with normal 25-Hydroxy Vitamin D (98 nmol/L) as well as electrolytes (corrected calcium 2.55mmol/L, magnesium 0.85mmol/L, phosphate 1.34 mmol/L).

The patient is now mobilising without any aids albeit experiencing some discomfort across the hips with prolonged walking and hopes to return to work as a gaming attendant in a local casino upon approval by the surgical team. Regarding Denosumab, it was last administered in October 2020. The repeat bone scan did not show any new metastatic bone lesions, and the patient has not had any new SREs either.

Discussion

Bone is a common site of cancer metastasis, and some cancers have very high rates of skeletal involvement, including multiple myeloma (95%), prostate cancer (85%) and breast cancer (70%) [1]. Bone metastases most frequently affect the axial skeleton and often cause complications termed as skeletal-related events (SREs) such as pathological fractures, spinal cord compression (SCC) and hypercalcaemia.

Amongst these cancers, breast cancer has the highest incidence of SREs. The proliferating tumour cells in the bone produce a range of cytokines and growth factors that increase osteoblast production by the receptor activator of nuclear factor kappa B ligand (RANKL), resulting in the activation of osteoclasts and disturbing the coupling of bone formation and bone resorption. Meanwhile, bone-derived growth factors stimulate the proliferation of the tumour cell population and thus create a self-sustaining vicious cycle between cancer cells and the bone microenvironment [2]. Furthermore, bone loss is also accelerated by breast cancer treatment.

SREs are associated with loss of mobility, reduced quality of life, increased health care expenditure and bleaker survival rates. Cancer society guidelines suggest the frequent use of antiresorptive treatment to reduce SREs (Figure 2) [3]. Denosumab is the preferred treatment for prevention of SREs in metastatic breast cancer. However, with advancement of oncology treatments and increased survival rates of patients with metastatic breast cancer, the cumulative dose exposure of Denosumab has increased. The prolonged use of Denosumab can cause severe treatment-related adverse events such as osteonecrosis of the jaw and atypical fractures.

An Atypical Femoral Fracture (AFF), defined as a stress-type fracture originating in the femur's lateral shaft, is a well-known complication of antiresorptive treatment [4]. The pathogenesis of AFF is poorly understood and proposed mechanisms suggest that, in genetically predisposed individuals with variance in limb geometry (varus deformity), disturbance to targeted remodelling by antiresorptive therapy results in unrepair of accumulation of microdamage leading to stress fractures [5]. Although most reported cases of AFF are seen with bisphosphonates, there is now emerging evidence of AFF associated with prolonged use of Denosumab.

There is greater uncertainty of managing AFF and no reported RCTs of treatment in patients following AFF. Most society guidelines recommend discontinuation of antiresorptive treatment and monitoring of the healing process. Non-healing AFFs are managed either with anabolic agents or surgery (Figure 3) [6]. In patients with metastatic cancer, discontinuation of antiresorptive treatment can be challenging (drug holiday) and the use of anabolic agents is not considered.

With improved survival rates of breast cancer patients, the frequency and duration of antiresorptive exposure have increased along with consequent adverse events. Antiresorptive therapy de-escalation studies do not show a difference between 4-weekly and 12-weekly Denosumab use in causing SREs. However, no studies observing longer drug holidays (>12 weeks) are available [7]. An inevitable risk arising from the discontinuation of Denosumab is the possible occurrence of rebound vertebral fractures, and this risk is markedly more apparent in patients suffering from breast cancer with bone metastases as these patients are already at a higher risk of vertebral fractures than the average population [8].

In such cases, we would advocate an approach that guides antiresorptive therapy by means of a multidisciplinary team involving an oncologist, endocrinologist, and radiologist. Patients at higher risk of developing SREs (presenting with clinical stage of the

disease, older age, early menopause, or osteolytic lesions on imaging) would benefit from frequent administration of Denosumab. On the contrary, patients evincing a lower risk of SREs with signs of tumour regression (evidence of sclerosis) and no new bone lesions could be considered for longer drug holidays. Moreover, the use of a potent bisphosphonate prescribed at Denosumab discontinuation could diminish the risk of rebound vertebral fractures. However, in the setting of a non-healing fracture as in our patient, it remains a clinical conundrum.

Key Points

- Patients with bone metastases are given frequent high-dose antiresorptive treatment to prevent skeletal-related events (SREs).
- Breast cancer treatment has improved patient survival rates, effectuating prolonged exposure to antiresorptive treatment, and associated adverse events such as Atypical Femoral Fractures (AFF).
- We propose a rational approach for de-escalation of antiresorptive treatment, guided by an MDT to identify patients with low risk of SREs to reduce the risk of AFFs.
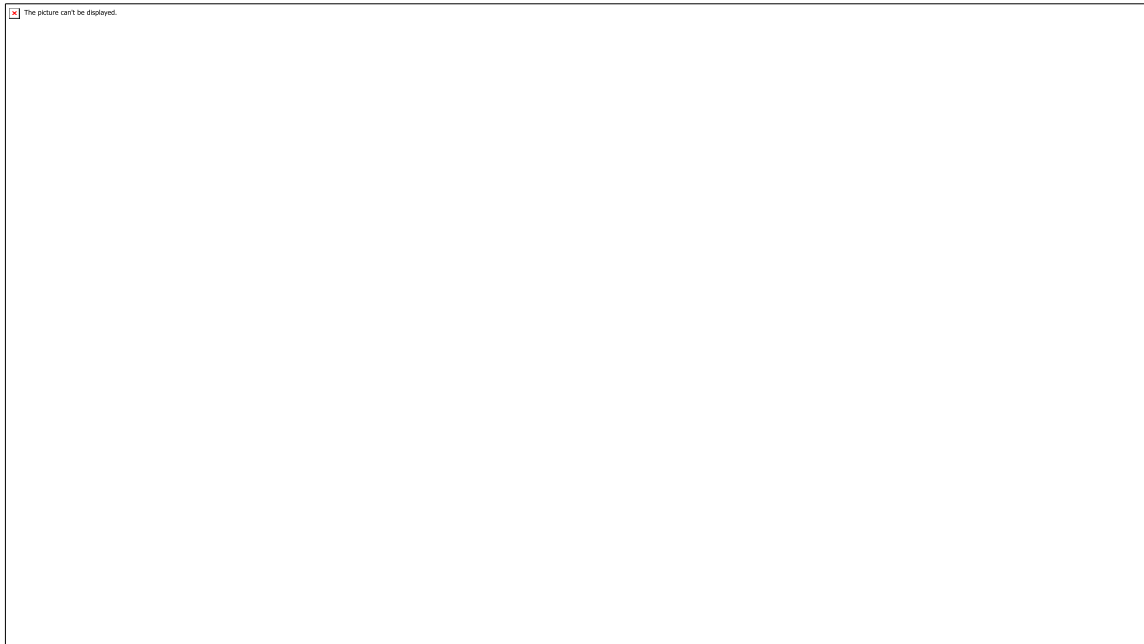
The picture can't be displayed.

1. 1. Macedo, F., et al., (2017). Bone metastases: an overview. Oncology Reviews, 11(1), 321
2. 2. Shupp, A.B., et al., (2018). Cancer metastases to bone: concepts, mechanisms and interactions with bone osteoblasts. Cancers, 10(6), 182
3. 3. Coleman, R., et al., (2020). Bone health in cancer: ESMO clinical practice guidelines. Annals of Oncology, 31(12), 1650-1663

4. 4. Tile, L. & Cheung, A.M. (2020). Atypical Femur Fractures: current understanding and approach to management. Therapeutic Advances in Musculoskeletal Disease, 12, 1759720X20916983-1759720X20916983

5. 5. Ramchand, S.K. & Seeman, E. (2020). Reduced bone modeling and unbalanced bone remodeling: targets for antiresorptive and anabolic therapy. Handbook of Experimental Pharmacology, 262, 423-450

6. 6. Van de Laarschot, D.M., et al., (2020). Medical management of patients after Atypical Femur Fractures: a systematic review and recommendations from the European Calcified Tissue Society. The Journal of Clinical Endocrinology & Metabolism, 105(5), 1682-1699

7. 7. Abousaud, A.I., et al., (2020). Safety and efficacy of extended dosing intervals of Denosumab in patients with solid cancers and bone metastases: a retrospective study. Therapeautic Advances in Medical Oncology, 12, 1758835920982859

8. 8. Body, J.-J., (2011). Increased fracture rate in women with breast cancer: a review of the hidden risk. BMC cancer, 11, 384

Tumour-induced osteomalacia – An elusive search for an FGF23-secreting tumour

Alexandra Matthews[1], Ashim K Sinha[1]

1. Endocrinology, Cairns Hospital, Cairns , Queensland, Australia

Case

A 35 year-old Filipino mother of three presented in 2017 with nausea, significant weakness and musculoskeletal pain. There was a background history of previous pulmonary tuberculosis that was treated in 2014 with twelve months of anti-tuberculous medication in the Phillipines. The patient had been wheelchair-bound for three years prior to presentation in the context of progressive pelvic pain and proximal weakness over the course of five years, which had been previously diagnosed as Pott's Disease of the sacrum. The chronic pain was affecting multiple sites, including the pelvis, back and chest wall, resulting in opioid dependence and a reported reduction in body height. This was in stark contrast to the patient's young adult life where she previously trained with the Philippine Olympic swimming team. On examination, body weight was low at 34kg with a body mass index of 14kg/m². There was severe proximal myopathy and evidence of multiple fractures clinically, including rib and vertebral.

Biochemistry revealed severe hypophosphataemia at 0.28mmol/L (0.75-1.50), with an elevated alkaline phosphatase of 336 U/L (30-110), low 1,25-dihydroxyvitamin D ($1,25(OH)_2$ D) at 22pmol/L (48-190) and normal albumin-adjusted serum calcium at 2.18mmol/L (2.10-2.60). Renal phosphate wasting was evident with a high urinary phosphate excretion and low calculated tubular phosphate reabsorption at 42%. Serum fibroblast growth factor 23 (FGF23) was elevated at 172ng/L (23-95).

Computed tomography (CT) revealed severely dysplastic proximal femoral bones and bilateral fractures of the inferior pubic rami. A skeletal survey demonstrated extensive fractures, including a fracture of the left acromion and scapula, five rib fractures, bilateral sub-capital femoral fractures and widespread crush fractures throughout the thoracic and lumbar spine. Symptoms significantly improved after commencement of phosphate and vitamin D supplementation. Within weeks of the hospital admission, the patient was no longer requiring a wheelchair.

There was no family history of bone disorders and no personal history of childhood Rickett's. The working diagnosis was tumour-induced osteomalacia and the focus turned to attempting to localise an FGF23-secreting tumour. A DOTATATE PET/CT performed in late 2017 did not show a potential mesenchymal tumour. Magnetic resonance imaging (MRI) of the head, hands and feet was also unrevealing. A repeat 68Ga-DOTATATE-PET–CT performed twelve months following the initial scan again did not reveal a tumour. Genetic testing done in late 2018 for congenital hypophosphataemic conditions identified no pathogenic sequence variation in multiple genes tested.

In October 2019, whole body venous sampling study for FGF23 was performed in an attempt to localise a tumour. This study found a slight gradient towards the right leg with an elevated FGF23 in the right common iliac vein compared to the left, although FGF23 levels were high throughout the body (see Table 1). Subsequently, an MRI of the right lower limb was performed and showed a possible focus in the right mid-thigh posterior to the femur, however, the patient had difficulty tolerating the examination and subsequent ultrasound of the region did not show any focal lesion. A plan was made for annual 68Ga-DOTATATE-PET–CT scans to find a causative lesion.

More recently, a 68Ga-DOTATATE-PET–CT performed earlier this year has revealed a focus of mild DOTATATE avidity in the midshaft of the right humerus. A subsequent MRI has shown a T2 hyperintense lesion in the midshaft of the right humerus measuring 30mm, entirely intramedullary and reported as potentially consistent with a benign disease process such as fibrous dysplasia (see Figure 1). The patient has recently had serum FGF23 levels collected from the left and right arms, with the hope that the right arm might show an elevated FGF23 level in comparison to the left to suggest that we have found the causative lesion. These results are not yet available.

The patient remains on phosphate replacement, calcitriol and Cinacalcet and this is maintaining phosphate in the low normal range. There is ongoing titration of the phosphate supplementation to try to minimise gastrointestinal disturbance.

Discussion

Tumour-induced osteomalacia (TIO) is a rare paraneoplastic syndrome caused by mesenchymal tumoural production of FGF23. TIO results in the hallmark biochemical features of hypophosphataemia (due to renal phosphate wasting), elevated ALP, low to low normal $1,25(OH)_2$ D and inappropriately normal, or elevated, FGF23.[1] Chronic hypophosphataemia ultimately results in osteomalacia in adults and Rickett's in children.[2] TIO is a rare condition with less than 1000 cases reported in the literature and data around the true prevalence is not available.[1]

This case highlights the difficult and often delayed diagnosis of TIO. Patients usually present with progressive musculoskeletal pain and muscle weakness with insufficiency fractures often found on imaging. The average time between onset of symptoms and diagnosis has been reported as ranging from 2.5 to 28 years.[2] The diagnostic challenge is partly due to the diagnosis being one of exclusion and additionally, the tumour, which can be located anywhere in the body (soft tissue or bone), is often small and extremely difficult to localise. The important first step in a patient presenting with hypophosphataemia is calculating the tubular phosphate reabsorption (TPR) to establish if renal phosphate wasting is present (see Figure 2). This is calculated based on the phosphate and creatinine levels in both serum and urine.[4]

The imaging modality of choice for tumour localisation in TIO is 68Ga-DOTATATE-PET–CT, due to the mesenchymal tumoural expression of somatostatin receptors. MRI should also be performed given its superiority over CT at characterising soft tissue and bone. The mesenchymal tumours are found slightly more often in bone than soft tissue, and frequently in craniofacial bones or extremities, emphasising the importance of whole body imaging.[5] Targeted venous sampling for FGF23 is a sensitive and specific technique to confirm that an identified lesion is responsible for excess FGF23, whereas whole body venous sampling (that was previously advocated for) appears to be ineffective at tumour localisation.[6]

Surgical removal of the tumour is the only definitive management for TIO. When surgery is not possible (e.g. tumour is unable to be localised or complete resection is not possible), an option for medical management is Burosumab, a fully human monoclonal antibody against FGF23. This is a newer treatment that was first approved for use in children and adults with X-linked hypophosphataemia (XLH) in 2018 after studies showed significant improvement in quality of life and reduction in number of fractures and pseudofractures.[6,7,8] More recently, a study has specifically looked at the use of Burosumab for TIO in a small cohort

of patients and has demonstrated similar benefits to those with XLH.[9] Burosumab has been considered as a treatment option for this patient but was not able to be accessed due to prohibitive cost.

This case highlights the challenges in diagnosis and management of TIO. We are hoping that the upcoming investigations might be revealing as to the underlying causative lesion.

Take Home Messages
1. Tumour-induced osteomalacia (TIO) is rare and should be considered in patients with chronic hypophosphataemia, low 1,25-dihydroxyvitamin D and renal phosphate wasting.
2. Localisation of a causative lesion in TIO can be very challenging.
3. DOTATATE-PET/CT and MRI are the best imaging modalities for localisation of an FGF23-secreting tumour.
4. The only definitive management for TIO is complete surgical resection.
5. Burosumab is a new monoclonal antibody against FGF23 that can be used in TIO cases where surgical resection is not possible or tumour localisation is unsuccessful.
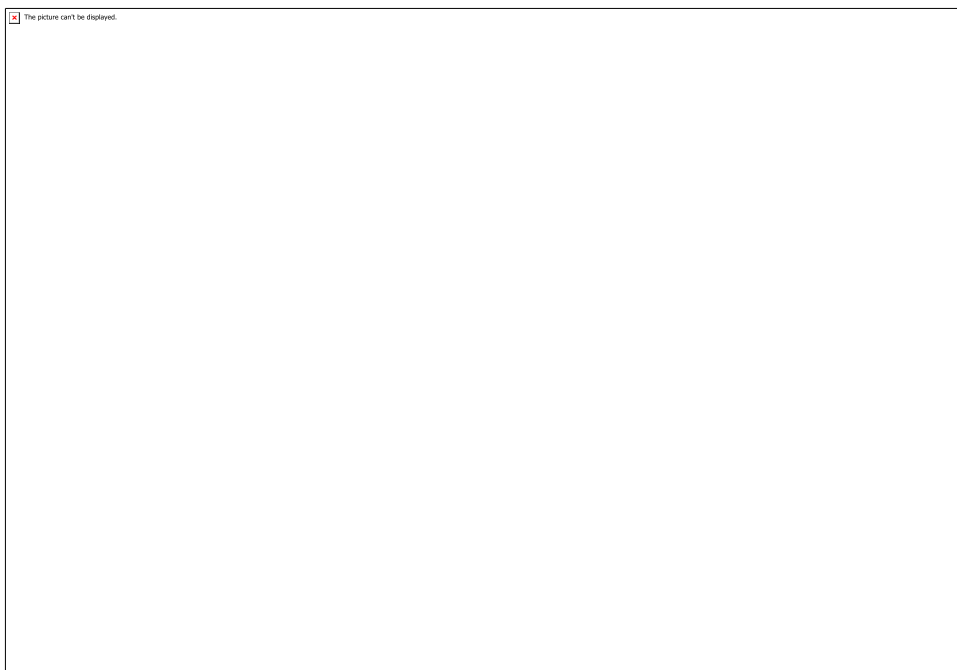
1. Florenzano, Pablo, Hartley, Iris R, Jimenez, Macarena, Roszko, Kelly, Gafni, Rachel I, & Collins, Michael T. (2021). Tumor-Induced Osteomalacia. Calcified Tissue International, 108(1), 128–142. https://doi.org/10.1007/s00223-020-00691-6

2. Minisola, Salvatore, Peacock, Munro, Fukumoto, Seijii, Cipriani, Cristiana, Pepe, Jessica, Tella, Sri Harsha, & Collins, Michael T. (2017). Tumour-induced osteomalacia. Nature Reviews. Disease Primers, 3(1), 17044–17044. https://doi.org/10.1038/nrdp.2017.44

3. Chong, William H, Andreopoulou, Panagiota, Chen, Clara C, Reynolds, James, Guthrie, Lori, Kelly, Marilyn, Gafni, Rachel I, Bhattacharyya, Nisan, Boyce, Alison M, El-Maouche, Diala, Crespo, Diana Ovejero, Sherry, Richard, Chang, Richard, Wodajo, Felasfa M, Kletter, Gad B, Dwyer, Andrew, & Collins, Michael T. (2013). Tumor localization and biochemical response to cure in tumor-induced osteomalacia. Journal of Bone and Mineral Research, 28(6), 1386–1398. https://doi.org/10.1002/jbmr.1881

4. Kurpas, Anna, Supeł, Karolina, Idzikowska, Karolina, & Zielińska, Marzenna. (2021). FGF23: A Review of Its Role in Mineral Metabolism and Renal and Cardiovascular Disease. Disease Markers, 2021, 1–12. https://doi.org/10.1155/2021/8821292

5. Rayamajhi, Sampanna Jung, Yeh, Randy, Wong, Tony, Dumeer, Shifali, Mittal, Bhagwant Rai, Remotti, Fabrizio, Chikeka, Ijeuru, & Reddy, Arun K. (2019). Tumor-induced osteomalacia – Current imaging modalities and a systematic approach for tumor localization. Clinical Imaging, 56, 114–123. https://doi.org/10.1016/j.clinimag.2019.04.007

6. Athonvarangkul, Diana, & Insogna, Karl L. (2021). New Therapies for Hypophosphatemia-Related to FGF23 Excess. Calcified Tissue International, 108(1), 143–157. https://doi.org/10.1007/s00223-020-00705-3

7. Collins, Michael. (2018). Burosumab: At Long Last, an Effective Treatment for FGF23-Associated Hypophosphatemia. Journal of Bone and Mineral Research, 33(8), 1381–1382. https://doi.org/10.1002/jbmr.3544

8. Insogna, Karl L, Briot, Karine, Imel, Erik A, Kamenický, Peter, Ruppe, Mary D, Portale, Anthony A, Weber, Thomas, Pitukcheewanont, Pisit, Cheong, Hae Il, Jan de Beur, Suzanne, Imanishi, Yasuo, Ito, Nobuaki, Lachmann, Robin H, Tanaka, Hiroyuki, Perwad, Farzana, Zhang, Lin, Chen, Chao-Yin, Theodore-Oklota, Christina, Mealiffe, Matt, … Carpenter, Thomas O. (2018). A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial Evaluating the Efficacy of Burosumab, an Anti-FGF23 Antibody, in Adults With X-Linked Hypophosphatemia: Week 24 Primary Analysis. Journal of Bone and Mineral Research, 33(8), 1383–1393. https://doi.org/10.1002/jbmr.3475

9. Jan de Beur, Suzanne M, Miller, Paul D, Weber, Thomas J, Peacock, Munro, Insogna, Karl, Kumar, Rajiv, Rauch, Frank, Luca, Diana, Cimms, Tricia, Roberts, Mary Scott, San Martin, Javier, & Carpenter, Thomas O. (2021). Burosumab for the Treatment of Tumor-Induced Osteomalacia. Journal of Bone and Mineral Research, 36(4), 627–635. https://doi.org/10.1002/jbmr.4233

Parathyroid carcinoma: diagnosis and follow-up of a rare malignancy

<u>Jessica Deitch</u>[1], **Deepak Dutta**[1, 2]
1. Department of Endocrinology and Diabetes, Western Health, Sunshine, Victoria, Australia
2. Department of Endocrinology and Diabetes, Peninsula Health, Frankston, Victoria, Australia

Case presentation

A 46-year-old male is eight years post diagnosis and management of parathyroid carcinoma (PC) and is undergoing close outpatient follow-up to monitor for recurrence.

The patient initially presented to hospital in 2013 with a two month history of myalgias, back pain and lethargy with unintentional 5kg weight loss over six months. Medical history included chronic kidney disease stage 3 diagnosed in 2012 with the cause not investigated, Vitamin D deficiency and childhood hepatitis A infection. He was taking no medications or supplements aside from intermittent diclofenac. Family history was significant with his maternal aunt and maternal grandmother having renal calculi and his maternal first cousin having a parathyroidectomy in their 20's for primary hyperparathyroidism (PHPT). There was no family history of jaw tumours. He is of Indian ethnicity, lives with his wife and son and is a non-smoker. No other first degree relatives live in Australia.

Initial investigations revealed severe hypercalcaemia with a dramatically elevated parathyroid hormone (PTH) of 343pmol/L, significant renal impairment and elevated alkaline phosphatase (ALP) (Table 1). He received a single dose of pamidronate 45mg. Pre-operative neck ultrasound and sestamibi imaging identified a 3.1cm right inferior parathyroid lesion (Figure 1). Renal ultrasound demonstrated bilateral nephrocalcinosis. X-ray imaging identified multiple brown tumours and osteopaenic bones (Figure 2). The presentation and investigations prompted suspicion pre-operatively for PC.

In October 2013 the patient underwent a focused parathyroidectomy which was converted to a right hemithyroidectomy and right central neck dissection following identification of an enlarged firm parathyroid gland and concern intraoperatively for malignancy. Histopathology confirmed a parathyroid carcinoma with presence of an unequivocal invasive pattern of growth with immunohistochemistry negative for parafibromin and positive for PGP9.5. Ki67 showed a proliferative index of 2%. The excision margin was 0.1mm with no metastatic tumour identified in the right level VI neck dissection. Post-operative calcium normalised and PTH decreased.

The patient's case was discussed in numerous endocrine cancer multi-disciplinary meetings. He was referred to a familial cancer clinic however declined genetic testing. Baseline DXA revealed severe osteoporosis (Table 2). Phaeochromocytoma and paraganglioma screening, including CT and MIBG imaging, were negative. This CT imaging depicted the previously recognised Brown tumours (Figure 2). Calcium and PTH were measured three monthly for the first year with a plan for six monthly ongoing. Routine neck imaging with ultrasound was planned to assess for recurrence.

The patient's course has been complicated by severe osteoporosis and end stage renal failure secondary to nephrocalcinosis. Following operative management he remained eucalcaemic however, with worsening renal function, the PTH level elevated in keeping with tertiary hyperparathyroidism (Table 3). A 99mTc Sestamibi was repeated in 2016 and did not show any residual parathyroid tissue in the right thyroid bed nor focal abnormalities related to the left hemithyroid. Concurrent neck ultrasound and CT imaging did not detect any changes. The patient commenced peritoneal dialysis in January 2016 and received a deceased donor renal transplant in February 2018.

The patient continues to be reviewed regularly by endocrinology and nephrology. Yearly neck ultrasounds show a subcentimetre lymph node, unchanged over the last two years. Serum calcium levels remain normal. PTH has remained mildly elevated since transplant with a normal vitamin D (Table 4). Serial DXA has demonstrated improvement in bone mineral density following PC surgery and transplant however severe osteoporosis remains an ongoing concern (Table 2). There is no fracture history. The transplanted kidney has excellent function three years post-transplant (Table 4).

Discussion

Parathyroid carcinoma (PC) is a rare malignancy, with estimated incidence 0.015 per 100,000 population, making up 1% of PHPT cases.[1] Increasing incidence has been noted internationally, however it is unclear whether this reflects improvement in diagnosis with increased PHPT operative management or a true incidence increase.[2, 3, 4, 5] PC occurs sporadically or in the context of familial endocrine malignancy syndromes.[1] As an uncommon cancer, case series and retrospective cohort studies guide current knowledge of PC.

PC can be a challenging diagnosis as it cannot be made pre-operatively. Patients typically present with severe symptoms of PHPT; approximately 50% present with both renal and skeletal complications.[1] PC should be considered pre-operatively with severely deranged biochemistry (elevated serum calcium, PTH and ALP levels)[2, 6] and pre-operative imaging showing a tumour larger than 3cm.[1]

Definitive diagnosis of PC is confirmed by surgical histopathology specimens.[7] Operative management remains the only curative treatment. Where PC is suspected, en bloc resection of adherent tissues should be considered.[6, 7] Extended surgery including prophylactic lymph node dissection is controversial as there is insufficient evidence to prove an overall survival benefit.[2, 7] In the presence of secondary or tertiary hyperparathyroidism stricter histopathological criteria may be used to determine a PC diagnosis as associated parathyroid gland atypical features may mimic carcinoma.[7] Markers which may assist with PC diagnosis include

loss of nuclear expression of parafibromin, overexpression of Protein Gene Product 9.5 (PGP9.5), Cyclin D1 and retinoblastoma loss of expression.[7]

Prognosis and recurrence rates are highly variable and there are no consensus clinical or pathological staging systems in place to formally guide follow-up.[1, 7] Overall survival rates are 76-85% at 5 year and 49-77% at 10 year follow-up.[1] Prognostic factors have been mostly derived from longitudinal single-institution studies and small case series. The best outcomes are seen in patients with complete tumour resection at initial operation. Negative factors for survival include older age, distant metastases, higher calcium level at recurrence, number of local recurrences, simple parathyroidectomy at initial surgery, incomplete tumour resection, tumour DNA aneuploidy, presence of CDC73 mutation and loss of parafibromin expression.[1, 2, 8, 9]

Although there are no guidelines to suggest ideal PC follow-up methods and intervals, it has been suggested that patients are followed-up life-long due to recurrence risk after operative management. After initial surgical management, restoration of normal calcium levels indicates successful removal of hyperfunctioning tissue. Presence of lymph node and distant metastases at time of diagnosis are uncommon however recurrence rates are high with 50% of patients having recurrences two to five years after diagnosis. Recurrences have been described up to 23 years after initial surgery, presenting with elevated calcium or PTH levels. Regional recurrence is most common. Distant metastases, most commonly lungs and liver metastases, occur in up to 25% of patients during follow-up. Follow-up should include serial measurements of serum calcium and PTH and ultrasound surveillance. Should hypercalcaemia develop, localisation studies should be performed to identify recurrent sites and guide surgical resection. Although reports exists, there is currently no evidence to recommend radiotherapy or chemotherapy for PC. Medical management of hypercalcaemia may be required in the case of recurrences which are not amenable to operative management.[1, 9, 10]

Take home messages
- PC diagnosis cannot be made pre-operatively however a significantly elevated calcium, PTH and parathyroid lesion larger than 3cm should prompt pre-operative suspicion for malignancy.
- PC is a rare malignancy with an increasing incidence rate and reasonable overall survival but high recurrence rates.
- There are no consensus guidelines to guide follow-up of these patients however, reassessment with biochemistry and neck imaging should be life-long to screen for recurrence.
- Further assessment of prognostic factors and disease progression post initial operative treatment in multi-centre settings are required to guide higher quality evidence based guidelines for management, staging and follow-up.
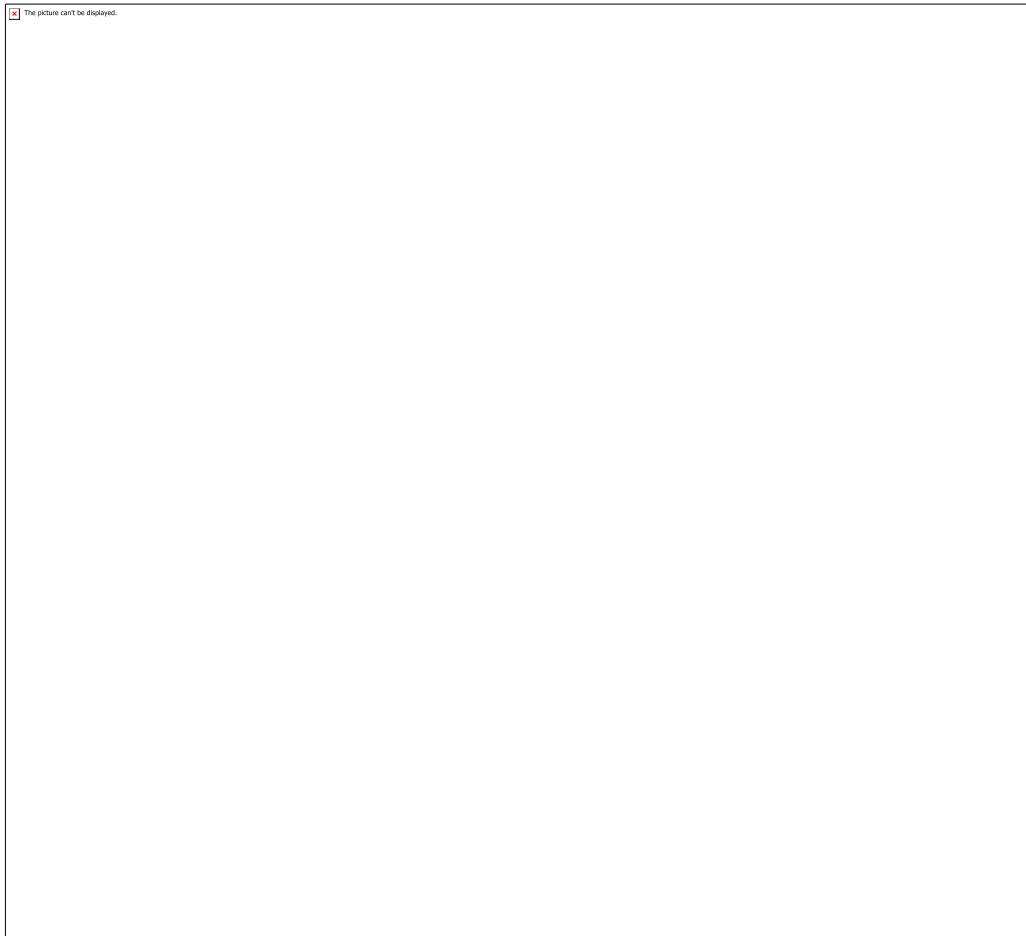
The picture can't be displayed.

1. Ferraro V, Sgaramella LI, Meo GI et al. Current concepts in parathyroid carcinoma: a single centre experience. BMC Endocr Disord. 2019, 19(Suppl 1):46
2. Lenschow C, Schragle S, Kircher S et al. Clinical presentation, treatment and outcome of parathyroid carcinoma. Results of the NEKAR retrospective international multicentre study. Ann Surg. 2020 Jul 7. doi:10.1097/SLA.0000000000004144
3. Kong SH, Kim JH, Park MY et al. Epidemiology and prognosis of parathyroid carcinoma: real-world data using nationwide cohort. J Cancer Res Clin Oncol. 2021 Feb. doi:10.1007/s00432-021-03576-9
4. Ryhanen EM, Leijon H, Metso S et al. A nationwide study on parathyroid carcinoma. Acta Oncologica. 2017;57(7):991-1003
5. Sadler C, Gow KW, Beierle EA et al. Parathyroid carcinoma in more than 1000 patients: a population-level analysis. J Surg. 2014, 156(6):1622-1630
6. Wilhelm SM, Wang TS, Ruan DT et al. The American Association of Endocrine Surgeons Guidelines for definitive management of primary hyperparathyroidism. JAMA Surg. 2015;151(10):959-968
7. Williams MD, DeLellis RA, Erickson LA et al. Pathology data set for reporting parathyroid carcinoma and atypical parathyroid neoplasm: recommendations from the International Collaboration on Cancer Reporting. Hum Pathol. 2021;110:73-82
8. Zhu R, Wang Z, Hu Y. Prognostic role of parafibromin staining and CDC73 mutation in patients with parathyroid carcinoma: a systematic review and meta-analysis based on individual patient data. Clin Endocrinol (Oxf). 2020;92:295-302
9. Liu R, Gao L, Xia Y et al. Locoregional recurrence of parathyroid carcinoma: how to identify this rare but fatal condition using ultrasonography. Endocr J. 2021 May 8. doi:10.1507/endocrj.EJ21-0124
10. Medas F, Erdas E, Loi G et al. Controversies in the management of parathyroid carcinoma: a case series and review of the literature. Int J Surg. 2016; S94-98

Two patients with acromegaly and medullary thyroid cancer: pure coincidence or MEN 1.5?

Shejil Kumar[1], Terry Diamond[1]

1. Endocrinology Department, St George Public Hospital, SYDNEY, New South Wales, Australia

CASE 1

A 70-year-old man referred for 5-year history of progressive flushing was subsequently diagnosed with both medullary thyroid cancer (MTC) and acromegaly, on a background of type 2 diabetes, hypertension and obesity.

Regarding MTC, he had elevated serum calcitonin concentration (132 pmol/L) and ^{68}Ga-DOTATATE-avid left thyroid lobe and adjacent nodule. He underwent total thyroidectomy and central neck dissection with histopathology confirming 8mm focus of MTC in the left thyroid lobe and 7/17 lymph nodes. Calcitonin levels markedly reduced post-thyroidectomy but remained elevated between 10-11 pmol/L (Figure 1). Venous sampling revealed step-up in plasma calcitonin in the left mid- and lower jugular vein (Table 1), lateralising residual MTC to the left. Left lateral neck dissection yielded 1/24 positive lymph nodes with subsequent decline in calcitonin levels which have remained non-suppressed (3-4 pmol/L) for 18-months post-dissection and is being closely monitored in the absence of symptoms or ^{68}Ga-DOTATATE-avidity.

Regarding acromegaly, phenotypic features included prominent nasopharyngeal folds and supraorbital ridges. Serum insulin-like growth-factor (IGF)-1 was elevated (66 nmol/L) however MRI pituitary scans were unable to identify pituitary adenoma (Figure 2). Initial management with long-acting octreotide controlled IGF-1 levels down to 25 nmol/L, before rising to 72 nmol/L six months later. Inferior petrosal sinus sampling revealed right-sided lateralisation in growth hormone (GH) concentrations (Table 2). He then underwent right-sided sella clearance with subsequent IGF-1 normalisation to 28 nmol/L (Figure 3). Histopathology confirmed somatotroph adenoma with positive staining for Pit-1, GH and prolactin (in scattered cells).

He lacked evidence of other multiple endocrine neoplasia (MEN)-1- or MEN-2-related tumours. CT abdomen demonstrated 12mm right adrenal nodule, although plasma metanephrines and normetanephrines were normal. No pancreatic lesion was identified. Serum calcium and parathyroid hormone (PTH) concentrations were normal. Family history was unremarkable.

Tumour DNA from MTC sample was heterozygous for the pathogenic variant p.(Cys634Trp) in exon 11 of the rearranged during transfection (RET) gene, which was not found in tumour DNA from somatotroph adenoma. No pathogenic germline variants in RET or menin genes were identified in peripheral blood.

CASE 2

A 38-year-old woman had a distant history of MTC. Left thyroid nodule biopsy results were suspicious for MTC with associated elevated serum calcitonin concentrations. Total thyroidectomy and histopathology confirmed left-sided MTC, and serum calcitonin levels have since remained undetectable.

Ten years later, she suffered accidental head-strike on furniture. CT Brain performed for persistent headache incidentally detected pituitary macroadenoma. MRI pituitary scan confirmed 20mm x 17mm pituitary macroadenoma with optic chiasmal compression without cavernous sinus invasion (Figure 4). Further history revealed 2-years of headaches, increasing ring and shoe size and prior carpal tunnel release. Examination demonstrated enlarged hands and feet, coarse facial features, skin tags and seborrhoea with intact visual fields. Pituitary panel was significant for elevated IGF-1 concentration (113 nmol/L, normal-range 11-37 nmol/L). She underwent uncomplicated pituitary adenoma resection. Histopathology confirmed somatotroph adenoma with positive staining for Pit-1, GH and prolactin (in scattered cells). Post-operatively, IGF-1 levels declined to 24 nmol/L and MRI pituitary scan showed decompression of optic chiasm.

Plasma metanephrines and normetanephrines, calcium and PTH were within normal limits. She has no family history of MEN-1- or MEN-2-associated tumours. Genetic analyses of peripheral blood and somatotroph adenoma tissue are pending.

DISCUSSION

Acromegaly is a rare clinical syndrome of GH and IGF-1 excess predominantly caused by GH-producing somatotroph pituitary adenoma, manifesting with phenotypical changes in appearance, headaches and cardiometabolic/osteoarticular complications. Several candidate genes have been identified. Hereditary acromegaly is most commonly a manifestation of familial isolated pituitary adenoma caused by AIP mutation, or part of a syndrome e.g. MEN-1, MEN-4, Carney complex. MEN-1 is characterised by primary hyperparathyroidism (PHPT) (>95%), pancreatic neuroendocrine neoplasms (60%) and pituitary adenomas (30-40%). MEN-1 is heritable through autosomal dominant inactivating heterozygous mutations in tumour suppressor gene encoding menin (chromosome 11q13). Acromegaly occurs in 10% of MEN-1 and is more commonly macroadenoma, early onset, locally invasive and treatment-resistant compared to sporadic cases. MEN-4 is more recently described in a small proportion of patients with MEN-1 phenotype without MEN-1 mutation but presence of loss-of-function mutation in CDKN1B (chromosome 12q13). GHoma is the most common pituitary tumour associated with MEN-4 (1).

MTC arises from parafollicular C cells and accounts for <5% of thyroid cancers. Cases can be familial (25%) or sporadic (75%) with mutations in RET proto-oncogene (chromosome 10q11.2) accounting for the vast majority. MEN-2, MEN-3 and familial MTC are heritable syndromes associated with autosomal dominant germline activating RET mutations. MEN-2 is associated with MTC (>95%), phaeochromocytoma (50%) and PHPT (20-30%), whilst MEN-3 differs by absence of PHPT and presence of mucosal neuromas, marfanoid habitus and intestinal ganglioneuromas. RET is a membrane-bound tyrosine kinase receptor which drives cell growth and differentiation (2).

Few patients have been described with phenotypic MEN-1 and MEN-2 overlap who underwent genetic testing for both menin and RET mutations (Table 3) (3-11). Three patients harboured both MEN-1 and MEN-2 mutations, five had isolated MEN-1 or MEN-2, whilst one patient had familial MEN-1 with loss of heterozygosity in the menin gene from MTC tissue, suggesting MTC was a possible manifestation of MEN-1.

Acromegaly is associated with goitre and predisposition to papillary and follicular thyroid cancers. However only one case has been reported, to our knowledge, of co-existent acromegaly and MTC (9). A 40-year-old man with familial MEN-2 was positive for germline RET mutation and negative for germline menin mutation. Acromegaly was considered sporadic and coincident with MEN-2 however somatotroph adenoma tissue was not investigated for RET mutation. Despite lack of clinical evidence, a potential link exists between acromegaly and MEN-2 (12). Normal somatotrophs express RET (receptor), GDNF (RET ligand) and GFRA1

(RET co-receptor) and are dependent on GDNF activating RET and facilitating expression of Pit-1 transcription factor and GH secretion, whilst absence of GDNF promotes p53 accumulation and apoptosis (Figure 5). Limited in-vitro evidence suggests this survival pathway is strongly expressed in GHomas and hence activating RET mutations may theoretically predispose patients to acromegaly and MTC.

Hypotheses for co-existent acromegaly and MTC are summarised in Figure 6. Germline MEN-1 mutation was not identified in case 1. The RET mutation found in MTC tissue was absent in peripheral blood, suggesting a somatic RET mutation, i.e. sporadic MTC rather than familial MTC or MEN-2. Delineating between sporadic or genetic acromegaly would require further genetic testing e.g. for AIP or CDKN1B mutations. Genetic testing in case 2 will initially focus on MEN-1, MEN-2 and AIP mutations before performing clinical exome sequencing.

TAKE-HOME MESSAGES
- Venous sampling is an important diagnostic tool in localising secretory tumours.
- Few MEN-1 and MEN-2 overlap cases have been described, mostly explained by familial co-occurrence of both mutations or presence of isolated MEN-1 or MEN-2 syndrome with somatic unrelated tumours.
- Co-existence of acromegaly and medullary thyroid cancer is rare with various potential explanations which should be investigated.
- RET may have an important role in regulation of pituitary somatotroph survival and apoptosis.
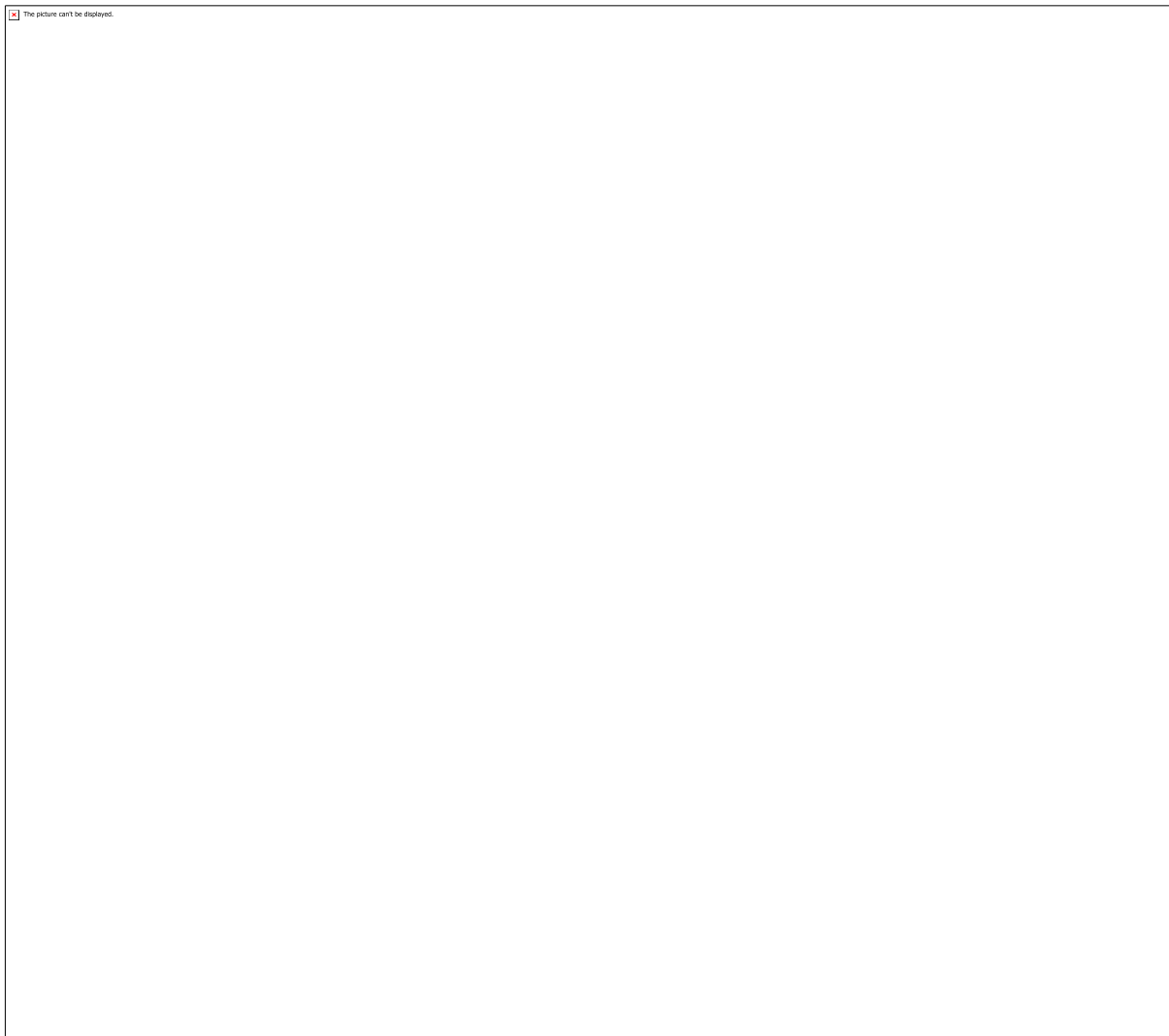
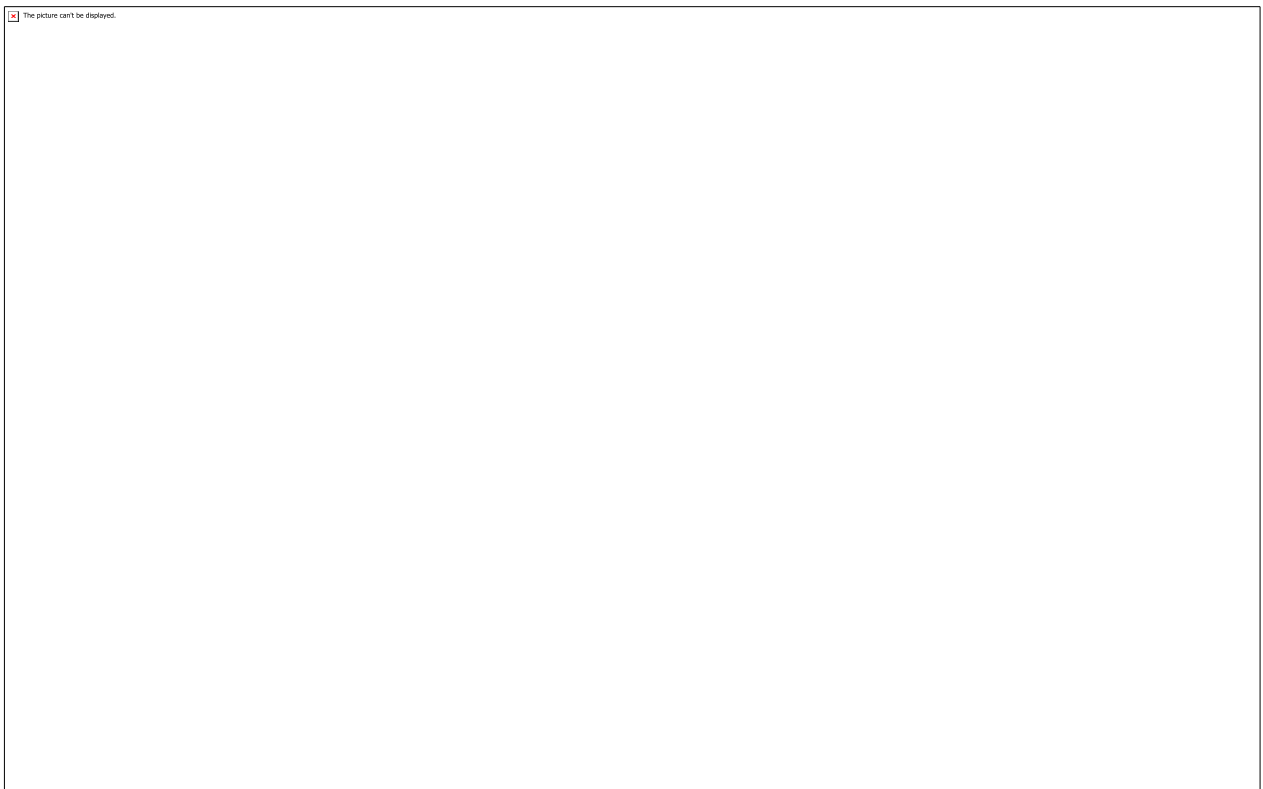1. Boguslawska A, Korbonits M. Genetics of Acromegaly and Gigantism. J Clin Med. 2021;10(7):1377.
2. Larouche V, Akirov A, Thomas CM, et al. A primer on the genetics of medullary thyroid cancer. Curr Oncol. 2019;26(6):389-394.
3. Friziero A, Da Dalt G, Piotto A, et al. Medullary Thyroid Carcinoma in a Patient with MEN1 Syndrome. Case Report and Literature Review. Onco Targets Ther. 2020;13:7599-7603.
4. Brown SJ, Riconda DL, Zheng F, et al. Features of Multiple Endocrine Neoplasia Type 1 and 2A in a Patient with Both RET and MEN1 Germline Mutations. J Endocr Soc. 2020;4(4):bvaa020.
5. Cetani F, Pardi E, Berardi V, et al. Incidental occurrence of metastatic medullary thyroid carcinoma in a patient with multiple endocrine neoplasia type 1 carrying germline MEN1 and somatic RET mutations. J Surg Oncol. 2017;116(8):1197-1199.

6. Aranda VGB, Porta MM, Martinez D, et al. Medullary thyroid carcinoma as a manifestation of the loss of heterozygosity in a patient with MEN1. Endocrinol Nutr. 2016;63(7):371-373.
7. Naziat A, Karavitaki N, Thakker R, et al. Confusing genes: a patient with MEN2A and Cushing's disease. Clin Endocrinol (Oxf.). 2013; 78(6):966-968.
8. Mastroianno S, Torlontano M, Scillitani A, et al. Coexistence of multiple endocrine neoplasia type 1 and type 2 in a large Italian family. Endocrine. 2011;40(3):481-485.
9. Saito T, Miura D, Taguchi M, et al. Coincidence of multiple endocrine neoplasia type 2A with acromegaly. Am J Med Sci. 2010;340(4):329-331.
10. Frank-Raue K, Rondot S, Hoeppner W, et al. Coincidence of multiple endocrine neoplasia types 1 and 2: mutations in the RET protooncogene and MEN1 tumor suppressor gene in a family presenting with recurrent primary hyperparathyroidism. J Clin Endocrinol Metab. 2005;90(7):4063-4067.
11. Brauer VFH, Scholz GH, Neumann S, et al. RET germline mutation in codon 791 in a family representing 3 generations from age 5 to 70 years: should thyroidectomy be performed? Endocr Pract. 2004;10(1):5-9.
12. Chenlo M, Rodriguez-Gomez IA, Serramito R, et al. Unmasking a new prognostic marker and therapeutic target from the GDNF-RET-PIT1/p14ARF/p53 pathway in acromegaly. EBioMedicine. 2019;43:537-552.

Between a rock and a hard place – a challenging case of Cushing's disease

Lucy Collins[1], Angeline Shen[1], Spiros Fourlanos[1]

1. Department of Diabetes and Endocrinology, Royal Melbourne Hospital, Melbourne, Victoria, Australia

Case presentation

Mr CB is a 67-year-old gentleman who presented in June 2015 with weight gain and hypertension. Investigations confirmed the diagnosis of Cushing's disease (CD) (Table 1) with evidence of a pituitary tumour on MRI (Figure 1). He underwent trans-sphenoidal resection (TSR) in June 2016. Biochemistry and MRI imaging (Figure 2) 10 months following first TSR suggested recurrent disease and so he underwent second TSR in June 2017. Despite this, he continued to show biochemical and clinical evidence of active CD and so was commenced on adrenal blockade with ketoconazole 800mg BD and subsequent hydrocortisone 20mg mane, 10mg nocte following hospitalisation for an adrenal crisis. Adjuvant stereotactic radiosurgery (40 Gy) was undertaken in March 2018. During this time, hydrocortisone was changed to dexamethasone to aid the interpretation of his underlying endogenous cortisol axis. This likely precipitated a second adrenal crisis, and in April 2018, with worsening liver function, ketoconazole was changed to metyrapone, 500mg BD. Ongoing up-titration of his metyrapone was required due to evidence of active CD. Metabolically, osteoporosis was treated with zoledronic acid and teriparatide.

In February 2021 he was admitted to hospital due to concerns of worsening CD control (Figure 3). Clinically, he had sustained new vertebral fractures despite teriparatide commenced in June 2019. Profound weight gain, peripheral oedema, poor wound healing and easy bruising over recent months was reported. His biochemistry confirmed deteriorating hypercortisolaemia; cortisol of 591 (reference range, 100-540 nmol/L) despite metyrapone and dexamethasone, elevated midnight salivary cortisol of 20 (reference range, < 8 nmol/L) and 24-hour urinary cortisol excretion (UFC) of 167 (reference range, < 130 nmol/d). MRI imaging displayed no evidence of recurrence of his pituitary adenoma or residual disease, and discussion with neurosurgical colleagues confirmed no further resectable adenoma. Meanwhile, his dexamethasone was ceased and diuresis implemented. Semaglutide was commenced, and up-titrated over 1-2 months, assisting in weight loss of 20kg. Metyrapone was up-titrated to 2000mg BD.

In June 2021 he developed an extensive carotid dissection and was found to have unique cerebral anatomy, in that his entire right hemisphere was supplied by the anterior circulation due to a foetal vertebral artery. Dual anti-platelet therapy was commenced. There was great concern from neurology with regards to the risk of re-dissection given his underlying anatomy.

Unfortunately, his 24-hour UFC continues to rise with evidence of hypercortisolaemia despite maximum medical therapy. MDM meetings were held with input from neurosurgery, endocrine surgery, neurology and endocrinology and decision made to proceed with bilateral adrenalectomy, with consideration of a pause in his dual anti-platelet therapy. The patient was informed of the risk, and is now consented and awaiting bilateral adrenalectomy.

Discussion

Cushing's disease is rare and often challenging to diagnose. It has an overall prevalence of 2-3 per million, and is the 3rd most common type of functional pituitary adenoma. Due to the hypercortisolaemic state, patients suffer from a range of metabolic complications, including diabetes mellitus, hypertension and hypercholesterolaemia. Mortality studies have also demonstrated an increased risk of death, in particular amongst those with active and persistent disease (1).

Consequently, a major treatment goal in the management of CD is achieving biochemical remission, defined as normal serum cortisol, 24-hour UFC, salivary cortisol and 1mg dexamethasone-suppression test < 50 nmol/L. Surgery remains the treatment of choice as it allows rapid correction of hypercortisolaemia with minimal peri-operative risks. Long-term remission rates are between 70-80%, with disease relapse in up to 35% of patients, predominantly within 5 years following surgery (2). Predictors of recurrence include undetectable adenoma on preoperative MRI, high immunopositivity for Ki-67, invasion of the tumour beyond the sella and unsuppressed cortisol post-operatively (3).

Diagnosis of recurrence is comparable to the initial diagnostic process. No formal consensus exists as to how recurrence should be monitored, and what screening test is best for diagnosis. Late-night salivary cortisol has been suggested as a more sensitive diagnostic test compared with 24-hour UFC (3). This can be explained by the fact that circadian rhythm alterations are the first sign of hypothalamus-pituitary-adrenal axis dysfunction and precede defects in both negative feedback (investigated by DST) and hypercortisolaemia (screened by 24-hour UFC) (4).

Treatment options following recurrence and in persistent CD include second TSR, radiation therapy, medical therapy and bilateral adrenalectomy. A second TSR is currently first-line therapy, however significant variability in rates of remission (38-90%) are reported. A second TSR may be more complicated due to the presence of scar tissue in the pituitary (2).

Radiation therapy can be delivered as conventional radiotherapy or stereotactic radiosurgery. The main disadvantages include prolonged time to remission, with medical therapy required in the interim, and rates of recurrence. A meta-analysis reported recurrence rates following conventional radiotherapy of 26%, and following stereotactic radiosurgery, 32% (3). In addition, hypopituitarism is common, affecting over one-third of patients following radiation therapy (3).

The three main tenets of medical therapy include steroidogenesis inhibitors, such as ketoconazole and metyrapone, glucocorticoid receptor blockade with mifepristone, and newer agents, pasireotide, osilodrostat and levoketoconazole. Pasireotide, a somatostatin analogue that targets four of the five somatostatin receptors, with particular affinity for subtype 5, has shown promise in the treatment of corticotrophin adenomas. Reductions in 24-hour UFC, serum and salivary cortisol levels have

been reported, however side effects including increased blood glucose and glycated haemoglobin levels were noted (5). Osilodrostat and levoketoconazole have showed promising results in phase III trials (6, 7).

Bilateral adrenalectomy is regarded as the final option. Whilst offering immediate cure, the main concerns are the risk of Nelson's syndrome post-operatively and permanent adrenal insufficiency. Nelson's syndrome has been reported in 21% of patients after median follow-up time of 61 months post adrenalectomy (8). The occurrence of Nelson's syndrome is related to higher pre-treatment urinary cortisol level, young age at diagnosis, larger tumour size at diagnosis and the presence of pituitary adenoma at previous pituitary surgery (8). Recently, a retroperitoneal surgical approach has markedly reduced perioperative complications, operative and recovery time (9). Nevertheless, surgery remains challenging, as these patients are often morbidly obese.

Lastly, the association between hypercortisolism and arterial dissection is rare, and has only been reported in a small number of case reports. Prolonged exposure to excessive cortisol is associated with multiple cardiovascular risk factors, including hypertension, alteration of the arterial wall, hypercholesterolaemia, impaired glucose tolerance and hypercoagulability. There is certainly a plausible pathophysiological link between hypercortisolism and arterial dissection (10).

In conclusion, Mr CB has persistent CD following his second TSR, providing diagnostic and management challenge. A key focus of CD management is achievement of biochemical remission. There is increasing evidence that a multi-modal approach is required to manage disease recurrence and/or relapsing disease.

Take-home points
1. CD is associated with high mortality risks when left untreated, and even with treatment the mortality rate does not return to that of the general population, highlighting the damage prolonged hypercortisolaemia pose on individuals with the condition.
2. Recurrence is seen in up to 35% of CD post initial surgery, mostly within 5 years.
3. Remission rate with repeated surgery is poor, < 30% in most case series, and adjuvant therapy, including radiotherapy and/or medical therapy needs to be considered early amongst those with active disease.
4. Newer agents, including pasireotide, osilodrostat and levoketoconazole have shown good clinical results with fewer side effects.

The picture can't be displayed.

1. van Haalen, F., Broersen, L., Jorgensen, J., Pereira, A. and Dekkers, O., 2015. MANAGEMENT OF ENDOCRINE DISEASE: Mortality remains increased in Cushing's disease despite biochemical remission: a systematic review and meta-analysis. European Journal of Endocrinology, 172(4), pp.R143-R149.
2. Braun, L., Rubinstein, G., Zopp, S., Vogel, F., Schmid-Tannwald, C., Escudero, M., Honegger, J., Ladurner, R. and Reincke, M., 2020. Recurrence after pituitary surgery in adult Cushing's disease: a systematic review on diagnosis and treatment. Endocrine, 70(2), pp.218-231.
3. Ragnarsson, O., 2020. Cushing's syndrome – Disease monitoring: Recurrence, surveillance with biomarkers or imaging studies. Best Practice & Research Clinical Endocrinology & Metabolism, 34(2), p.101382
4. Hinojosa-Amaya, J., Varlamov, E., McCartney, S. and Fleseriu, M., 2019. Hypercortisolemia Recurrence in Cushing's Disease; a Diagnostic Challenge. Frontiers in Endocrinology, 10.
5. Colao, A., Petersenn, S., Newell-Price, J., Findling, J., Gu, F., Maldonado, M., Schoenherr, U., Dipl.-Biol., Mills, D., Salgado, L. and Biller, B., 2012. A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease. New England Journal of Medicine, 366(10), pp.914-924.
6. Pivonello, R., Fleseriu, M., Newell-Price, J., Bertagna, X., Findling, J., Shimatsu, A., Gu, F., Auchus, R., Leelawattana, R., Lee, E., Kim, J., Lacroix, A., Laplanche, A., O'Connell, P., Tauchmanova, L., Pedroncelli, A. and Biller, B., 2020. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. The Lancet Diabetes & Endocrinology, 8(9), pp.748-761.
7. Fleseriu, M., Pivonello, R., Elenkova, A., Salvatori, R., Auchus, R., Feelders, R., Geer, E., Greenman, Y., Witek, P., Cohen, F., Biller, B., 2020. Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): A phase 3, multicentre, open-label, single-arm trial. Yearbook of Paediatric Endocrinology
8. Ritzel, K., Beuschlein, F., Mickisch, A., Osswald, A., Schneider, H., Schopohl, J. and Reincke, M., 2013. Outcome of Bilateral Adrenalectomy in Cushing's Syndrome: A Systematic Review. The Journal of Clinical Endocrinology & Metabolism, 98(10), pp.3939-3948.
9. Raffaelli, M., Brunaud, L., De Crea, C., Hoche, G., Oragano, L., Bresler, L., Bellantone, R. and Lombardi, C., 2013. Synchronous Bilateral Adrenalectomy for Cushing's Syndrome: Laparoscopic Versus Posterior Retroperitoneoscopic Versus Robotic Approach. World Journal of Surgery, 38(3), pp.709-715.
10. Ilie, I., Vouillarmet, J., Decaussin-Petrucci, M., Jeannin-Mayer, S., Lifante, J., Thivolet, C. and Marchand, L., 2019. Bilateral vertebral artery dissection revealing Cushing's syndrome. Annales d'Endocrinologie, 80(1), pp.67-69.

Pituitary puzzles a rare case of hypophysitis

Lauren C Burrage[1]**, Kate Hawke**[1]**, Daniel Mazzoni**[1]**, Sumant Kevat**[1]**, Jennifer Gillespie**[1]**, Jason Papacostas**[1]**, Donald McLeod**[1]

1. Department of Endocrinology and Diabetes, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia

Case

A 40-year-old female presented with one month of headaches, nausea, polyuria, and polydipsia of six to eight litres per day. Posterior and anterior hypopituitarism were diagnosed (table 1 for initial pituitary profile and table 2 for water deprivation test). Pituitary magnetic resonance imaging (MRI) demonstrated an unusual sellar mass with suprasellar extension and thickening of the pituitary infundibulum (Figure 1). Visual fields were normal. She was commenced on physiological glucocorticoid replacement, desmopressin, and thyroxine. Fluorodeoxyglucose–positron emission tomography (FDG-PET) revealed non-specific irregularity of the vertebral arteries. Computed tomography (CT)-angiogram was initially reported as normal, but a second opinion identified vasculitis of the vertebral arteries with no other sites of disease. Anti-neutrophil cytoplasmic antibodies against enzyme proteinase-3 (PR-3-ANCA) were elevated with a titre of 63mU/L (reference range <20mU/L). Serum angiotensin-converting enzyme was also elevated at 130U/L but CT chest showed only tiny non-specific calcified granulomas without other features of sarcoidosis. Renal function and urinalysis were normal. Due to the lack of other confirmed sites of disease, the patient underwent pituitary biopsy. Frank purulent material under pressure met the surgeon on breaching the pituitary fossa. Histology could only confirm a non-specific hypophysitis. Microbiology was negative (including standard culture, fungi, acid-fast bacilli), as was QuantiFERON-Gold, HIV serology, syphilis serology, cryptococcal antigen, and Whipple's serology. Two-week course of intravenous vancomycin and ceftriaxone yielded no improvement. Histology on repeat pituitary biopsy three months after presentation identified a necrotising granulomatous inflammatory process, consistent with granulomatous polyangiitis (GPA). Serum IgG4 was mildly elevated; tissue staining was negative. PR-3-ANCA peaked at 118mU/L. Due to the absence of life-threatening disease, rheumatology commenced the patient on maintenance methotrexate (MTX) 10mg weekly, increasing to 20mg. Repeat MRI pituitary two months later showed improvement of the pituitary stalk thickening and the pituitary gland had reduced in size (Figure 2). PR-3-ANCA improved to 83mU/L and the patient's desmopressin requirement reduced by 30%. Three months after commencing MTX, the patient developed worsening headaches, ear pain, and conductive hearing loss. The patient completed a short course of 50mg prednisolone. At the time of writing, the patient is on 15mg of prednisolone and remains under close surveillance.
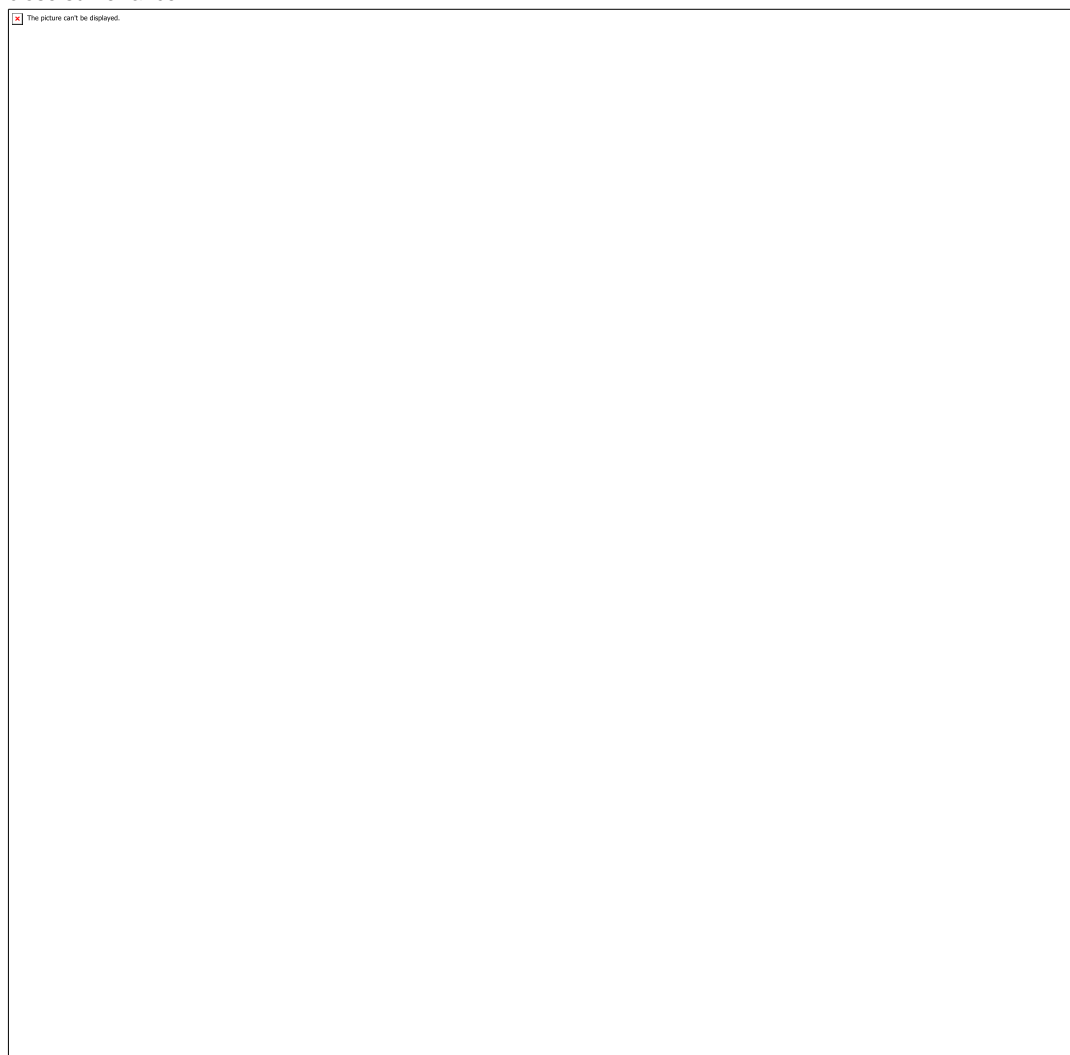
Discussion

Hypophysitis is an inflammatory process of the pituitary gland and an important cause of pituitary dysfunction. Hypophysitis may be due to primary autoimmune hypophysitis or secondary causes including infection, infiltration, autoimmune systemic diseases, and immunotherapy.[1,2] GPA is a multi-system necrotising vasculitis affecting small to medium vessels with an annual incidence of 10 cases per million people per year.[3] It presents between 35-55 years of age and affects men and women equally.[3] GPA typically affects the upper airways, lungs, and kidneys and is strongly associated with PR-3-ANCA elevation.[1]

Central nervous system dysfunction occurs in 7-11% of patients with GPA.[1] However, pituitary involvement is rare. It was first described in 1953 and has been documented in 1% of GPA cases, with less than 100 cases reported in the literature.[4] The underlying pathogenesis may be due to direct extension of granulomas from contiguous sites of disease, vasculitis of pituitary vessels, or de novo development of granulomas in the pituitary.[5,6] The median age at diagnosis of pituitary dysfunction is 38 years.[5,7] Women appear to be more commonly affected and may have worse outcomes with higher prevalence of headache, hypopituitarism, and visual defects.[1,5,7]

Symptoms of pituitary dysfunction are often non-specific and may cause a delay in diagnosis. If hypophysitis is the initial presentation, the diagnosis of GPA can be delayed for up to twelve months.[1] Conversely, if patients present with other manifestations of GPA, the diagnosis is made within two months.[1] A review of 74 patients with pituitary involvement of GPA from 1953 to 2019 found pituitary dysfunction was the initial manifestation in 46%, with 42% having pituitary dysfunction as the sole clinical manifestation.[1] In contrast, another case series reported that 35% of patients had pituitary dysfunction at the time of GPA diagnosis, but only 4% had isolated pituitary involvement.[7] Other case series have reported that pituitary dysfunction is rarely present initially and is instead diagnosed 10 -14 months after the diagnosis of GPA, with a range from 2 months to 15 years.[2,5,6,8] Notably, pituitary dysfunction can develop even when systemic disease is in remission.[1,8]

Diabetes insipidus (DI) is the most common pituitary manifestation of GPA, occurring in up to 88% of cases.[1] Hypogonadism is the second most common, although some studies have reported it more frequently than DI.[5,9] This may represent an over-estimation as multiple other factors, including treatment with cyclophosphamide, cause hypothalamic-pituitary-gonadotroph axis suppression. Central hypothyroidism has been quoted in 50-54% and secondary adrenal insufficiency (AI) in 12-48%.[5,8,9] The

prevalence of AI is likely to be underestimated as patients treated with high-dose glucocorticoids will not undergo hypothalamic-pituitary-adrenal axis evaluation. Growth hormone deficiency is uncommonly described but this may be due to less frequent diagnostic evaluation. The most common radiological finding is a sellar mass, often with peripheral enhancement and a central cystic component, with abnormal pituitary stalk thickness in 41-62%.[1,2,6,9] Pituitary biopsy is reserved for patients lacking systemic disease manifestations without a clear diagnosis, where there is no safer site to biopsy.[2]

Given the paucity of data, optimal treatment has not been established but often includes induction immunosuppression followed by maintenance treatment. De Parisot et al. reviewed nine cases of pituitary GPA from the French Vasculitis Study Group and performed a literature review of forty-two other cases.[5] 69% were treated with high-dose glucocorticoids and cyclophosphamide, with remission achieved in 57%.[5] The Mayo Clinic's experience was that 75% of patients were treated with cyclophosphamide induction and 66% achieved remission.[9] Other treatment modalities reported in the literature include biologic agents (rituximab, infliximab) or immunosuppressants such as azathioprine and MTX.[1,7] From small numbers, these alternative agents have been associated with higher rates of relapse.[7] Rituximab is shown to be more effective in relapsing GPA,[10] but there is limited experience in patients with pituitary involvement.[6,9] Surgery is reserved for patients with symptoms of mass effect.[1]

Recovery of pituitary function is rare, even in the setting of disease remission and radiologic resolution. Persistence of hormonal pituitary deficiencies is described in 48-86% of cases, suggesting that early granulomatous infiltration causes irreversible damage.[1,5,7] However, the one exception may be DI with some case reports demonstrating resolution.[2,5] The Mayo Clinic case series reported that DI resolved in 4 out of 6 patients but the outcome of anterior pituitary function was less favourable.[9] There is not yet enough data to correlate recovery of pituitary dysfunction with earlier diagnosis or specific treatment.

In summary, our patient has GPA which presented with isolated pituitary involvement and was confirmed on pituitary biopsy. She was not treated with induction immunosuppression but has improved with MTX. Pituitary dysfunction is persistent, but her desmopressin requirement is reducing.

Learning points from this case include:

- GPA should be considered in patients with DI and hypophysitis of unclear aetiology.
- Pituitary biopsy may be required for diagnosis, especially in the absence of systemic disease.
- Persistent pituitary dysfunction is common despite disease remission, but DI has been reported to resolve in small case series.

1. 1. Vega-Beyhart A, Medina-Rangel IR, Hinojosa-Azaola A, Fernandez-Barrio M, Vargas-Castro AS, Garcia-Inciarte L, et al. Pituitary dysfunction in granulomatosis with polyangiitis. Clin Rheumatol. 2020 39(2):595-606.
2. 2. How Hong E, Shalid A, Gatt D, Deepak S, Bahl A. Primary pituitary granulomatosis with polyangiitis and the role of pituitary biopsy, case report and literature review. Br J Neurosurg. 2021 doi: 10.1080/02688697.2021.1878345. Epub ahead of print.
3. 3. Comarmond C and Cacoub P. Granulomatosis with polyangiitis (Wegener): clinical aspects and treatment. Autoimmun Rev. 2014 13(11):1121-1125.
4. 4. Ahlstrom CG, Liedholm K, Truedsson E. Respirato-renal type of polyarteritis nodosa. Acta Med Scand. 1953 144(5):323-332.
5. 5. De Parisot A, Puechal X, Langrand C, Raverot G, Gil H, Perard L, Le Guenno G et al. Pituitary involvement in granulomatous with polyangiitis: report of 9 patients and review of the literature. Medicine. 2015 94(16);e748.
6. 6. Esposito D, Trimpou P, Giugliano D, Dehlin M, Ragnarsson O. Pituitary dysfunction in granulomatosis with polyangiitis. Pituitary. 2017 20(5):594-601.
7. 7. Yong TY, Li JYZ, Amato L, Mahadevan K, Phillips PJ, Coates PS, Coates TH. Pituitary involvement in Wegener's granulomatosis. Pituitary. 2008 11(1):77-84.
8. 8. Gu Y, Sun X, Peng M, Zhang T, Shi J, Mao J. Pituitary involvement in patients with granulomatosis with polyangiitis: case series and literature review. Rheumatol Int. 2019 39(8):1467-1476.
9. 9. Kapoor E, Cartin-Ceba R, Specks U, Leavitt J, Erickson B, Erickson D. Pituitary dysfunction in granulomatosis with polyangiitis: the Mayo Clinic experience. J Clin Endocrinol Metab. 2014 99(11):3988-3994.
10. 10. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffam GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010 363(3):221-232.

Pregnancy and non-classical congenital adrenal hyperplasia

Elisabeth Ng[1], Peter Fuller[1, 2], Carolyn Allan[1, 2, 3]

1. Department of Endocrinology, Monash Health, Clayton, Victoria, Australia

2. Hudson Institute of Medical Research, Clayton, Victoria, Australia

3. Department of Obstetrics & Gynaecology, Monash University, Clayton, Victoria, Australia

Case

A 28-year-old female with non-classical congenital adrenal hyperplasia (NC-CAH) was referred to an Endocrine Pregnancy Clinic after two first trimester miscarriages following spontaneously conceived pregnancies.

Her history of NC-CAH was explored: she was born with normal external genitalia and presented at age 7 with precocious puberty and an advanced bone age of 10 years. Baseline 17-hydroxyprogesterone (17-OHP) level was elevated at 8.6 nmol/L and urinary pregnanetriol was markedly elevated at 4.5 µmol/L (0-0.04). Treatment with hydrocortisone led to normalisation of urinary pregnanetriol levels. Genetic testing identified homozygosity for a CYP21A2 gene pathogenic variant (Val281Leu). She was treated with oral hydrocortisone in three divided doses from the age of 8, and she grew and gained weight normally to a height of 154 cm and a weight of 48 kg (BMI 20.2kg/m2). She underwent menarche at age 12 and established regular menstrual cycles. Renin was assessed intermittently and was never elevated.

At the age of 17 care was transferred from paediatric to adult endocrinology, and she saw various endocrinologists infrequently until the age of 25. During this period, hydrocortisone dosing was adjusted to twice-daily (daily dose 14mg). Secondary amenorrhoea from age 22 to 24 was attributed to weight loss down to 35 kg in the context of disordered eating. The oral contraceptive pill (OCP) was introduced for oestrogen replacement and contraception. With multidisciplinary input including psychology and dietetics, she regained weight back to her baseline.

Family planning started after marriage at the age of 25 years. She and her partner are of Ashkenazi Jewish descent, her partner with mixed Caucasian heritage. Neither had a known family history of CAH or NC-CAH. The couple consulted a Genetics service and the risk of paternal carriage for a 21-hydroxylase gene mutation was estimated to be 1 in 58. Their risk of having a child with a form of CAH due to 21-hydroxylase deficiency (21-OHD) was estimated to be 1 in 116 for each pregnancy. This degree of risk did not qualify for hospital funding and self-funded options were provided. These options were deemed too costly, and her husband eventually had genetic testing with an alternative provider. A 'preconception screen' was undertaken, unaccompanied by counselling, providing a reassuring result. Retrospective review of this panel indicated an absence of screening for a pathogenic variant in the CYP21A2 gene.

The patient stopped the OCP shortly after marriage and menses resumed spontaneously. Spontaneous pregnancy occurred at the age of 27, with a preceding 17-OHP level of 30.2 nmol/L (not timed in cycle). A miscarriage occurred at six weeks' gestation. A second miscarriage occurred at eight weeks' gestation after a second pregnancy five months later. A 17-OHP level before this pregnancy was 14.2 nmol/L (not timed in cycle). Investigations following the second miscarriage are shown in Table 1.

One month later she again conceived spontaneously and upon confirmation, her hydrocortisone dose was increased to 12mg mane and 8mg in the evening, from 8mg and 6mg, respectively. She received close antenatal monitoring, with clinical assessment of glucocorticoid replacement adequacy. Her blood pressure remained stable in the range of 105-115 mmHg systolic, and 65-75 mmHg diastolic, with no nausea or vomiting. Relevant blood tests measured during pregnancy are shown in Table 2, acknowledging the limitations of cortisol level assessment in pregnancy.

During this current pregnancy her husband's genetic profile was revisited and testing repeated, fortunately indicating no clinically significant CYP21A2 variant.

She is due in October 2021; progress and the outcome of this pregnancy will be followed.

Discussion

21-OHD is the most common form of CAH[1] and presents variably, where the classic forms are often classed as 'salt-wasting' or 'simple virilising' (non-salt-wasting), while NC-CAH may be asymptomatic or present with features of hyperandrogenism and subfertility. The latter presentation may mimic polycystic ovarian syndrome (PCOS) and distinguishing between the two disease entities is critical given the differing management and genetic implications for offspring.[2] NC-CAH has been found in 1.5-6.8% of presentations with androgen excess,[3] with an estimated worldwide prevalence of NC-CAH among hyperandrogenic women being 4.2%.[4]

Treatment in NC-CAH should follow an individualised approach and is not always indicated. Glucocorticoid therapy may be indicated for 1) accelerated growth velocity with advanced bone maturation, 2) infertility, or 3) hyperandrogenism unresponsive to steroid-sparing options.[5] There is preserved aldosterone synthesis and cortisol production in NC-CAH due to residual 21-OH activity.[1]

Pre-pregnancy

Infertility is a presenting symptom in ~13% of symptomatic patients with NC-CAH.[6] Pregnancy rates in women with NC-CAH presenting with infertility or hyperandrogenemia, range between 65-95% in various studies. Spontaneous miscarriage rates are higher in women with CAH and NC-CAH,[2] and these rates fall with glucocorticoid treatment.[7, 8] Androgen levels are higher in women with recurrent miscarriages, compared to normal fertile controls,[8] and contribute to this outcome by impairing endometrial development and priming. NC-CAH features hyperandrogenism; use of glucocorticoids suppresses hypothalamic CRH and pituitary ACTH, thereby reducing adrenal androgen production.

Pre-conception assessment and planning is important in the care of a woman with NC-CAH (Table 3). The role of glucocorticoids should be discussed if recurrent miscarriages have been an issue. Genetic counselling is important and it is known that genotype-phenotype discordance can result in an offspring with classic CAH despite maternal NC-CAH.[7] Cortisol production is typically adequate in NC-CAH but the multiple indications for glucocorticoid therapy may result in exogenous HPA-axis suppression. Pre-pregnancy evaluation allows planning for stress cortisol dosing during late pregnancy and labour.

Management in pregnancy

Considerations for the management of CAH in pregnancy are described in Table 4. Multidisciplinary collaboration is important, as is early screening for gestational diabetes given an increased risk.[5, 7] NC-CAH in non-pregnant individuals is monitored with 17-OHP, androstenedione, and testosterone levels, with the goal of normalising the latter two, and achieving a 17-OHP level 2-3 times the upper limit of normal to avoid overtreatment. These values rise physiologically in pregnancy[9] and a lack of standardised pregnancy-specific ranges makes biochemical monitoring challenging.

Summary

This 28-year-old female with NC-CAH commenced hydrocortisone at age 8 for accelerated bone age and this was continued into adulthood, with the opportunity to reassess its role limited by inconsistent engagement with any one clinician. She has iatrogenic adrenal suppression, with no previous adrenal crisis. She had two early miscarriages with elevated 17-OHP levels beforehand. An increase in her cortisol dosing early in her third pregnancy may or may not have contributed to successful carriage of the pregnancy to date. Monitoring in pregnancy was performed with clinical evaluation.

Take home messages

- Pregnancy rates in NC-CAH are similar to the general population but higher rates of miscarriage may result in overall lower fertility rates.
- Given the phenotypic overlap between PCOS and NC-CAH, exclusion of the latter is important in the common presentation of irregular menses and hirsutism, given the differing management and genetic implications.
- Glucocorticoids have a role in NC-CAH in children with early pubarche and advanced bone maturation; and in women with infertility or clinical hyperandrogenism unresponsive to the OCP or antiandrogens. Re-evaluation of the indication for glucocorticoid therapy should be considered at various life stages.
- A pre-pregnancy assessment involves evaluating fertility history, cortisol reserve, and both partners CYP21A2 gene status.
- Genetic counselling pre-conception is critical for the couple to address risks and discuss potential interventions where an embryo may possibly have CAH.
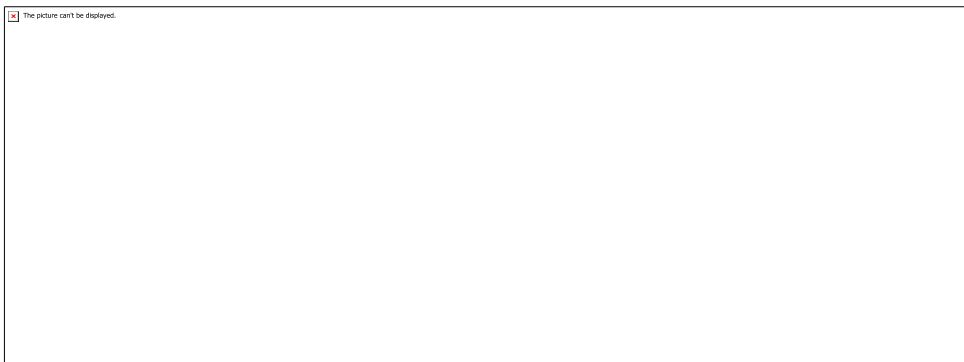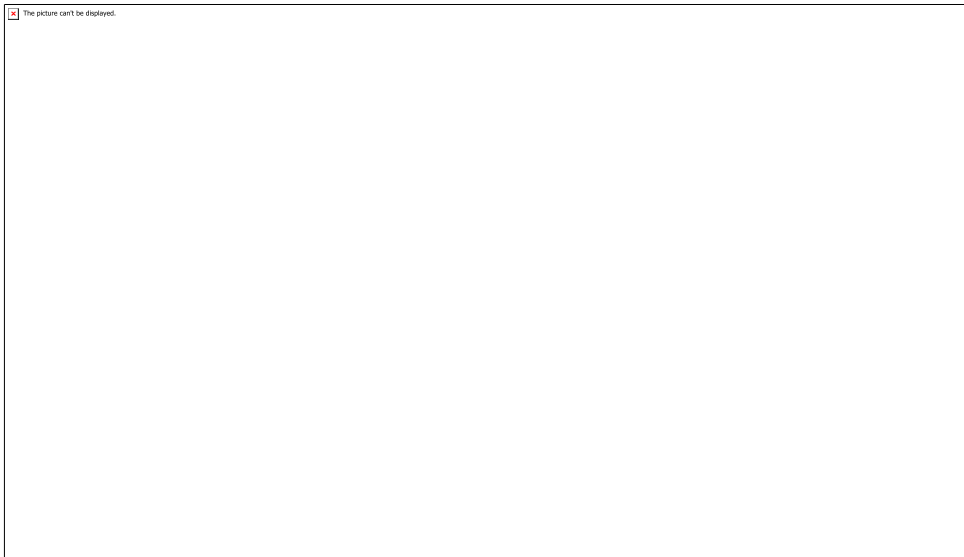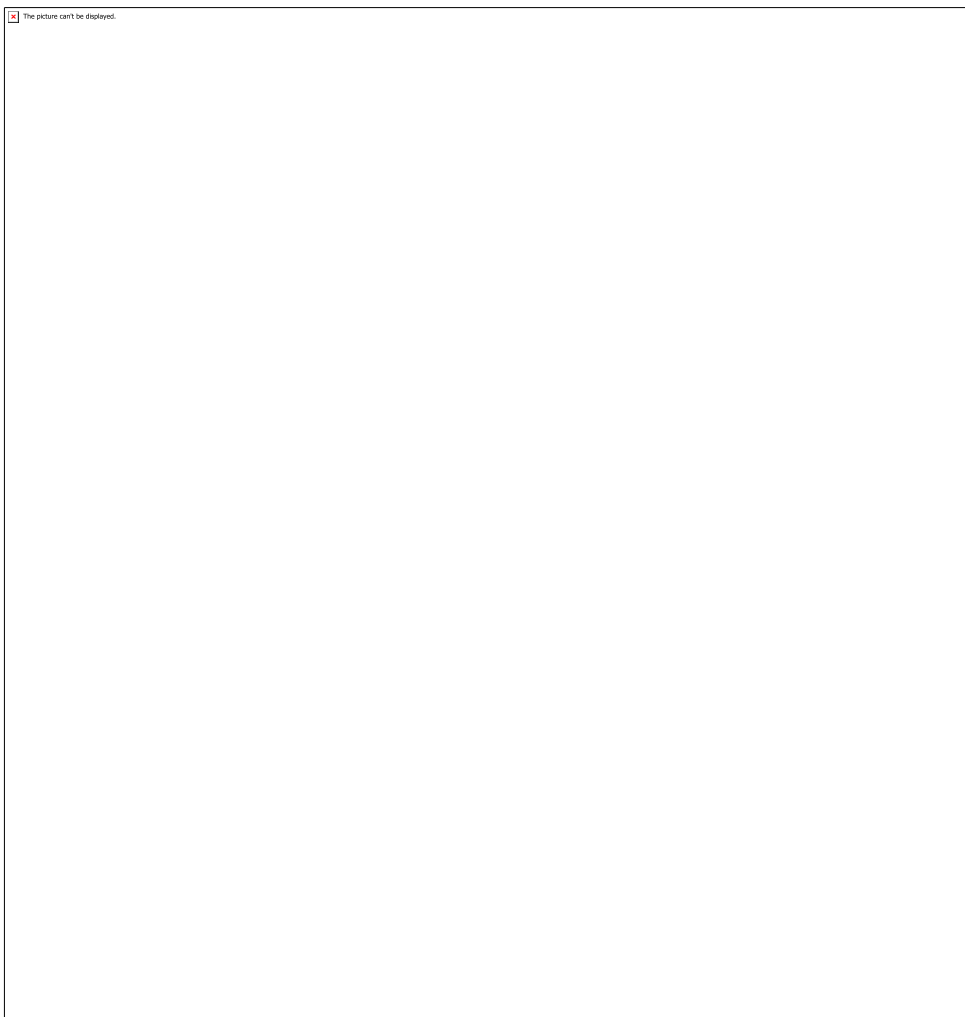
1. Speiser PW, White PC. Congenital adrenal hyperplasia. N Engl J Med. 2003;349(8):776-88.
2. Chatziaggelou A, Sakkas EG, Votino R, Papagianni M, Mastorakos G. Assisted Reproduction in Congenital Adrenal Hyperplasia. Front Endocrinol (Lausanne). 2019;10:723.
3. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013;98(12):4565-92.
4. Carmina E, Dewailly D, Escobar-Morreale HF, Kelestimur F, Moran C, Oberfield S, et al. Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency revisited: an update with a special focus on adolescent and adult women. Hum Reprod Update. 2017;23(5):580-99.
5. Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society* clinical practice guideline. J Clin Endocrinol Metab. 2018;103(11):4043-88.

6. Reichman DE, White PC, New MI, Rosenwaks Z. Fertility in patients with congenital adrenal hyperplasia. Fertil Steril. 2014;101(2):301-9.
7. Falhammar H, Nordenström A. Nonclassic congenital adrenal hyperplasia due to 21-hydroxylase deficiency: clinical presentation, diagnosis, treatment, and outcome. Endocrine. 2015;50(1):32-50.
8. Okon MA, Laird SM, Tuckerman EM, Li TC. Serum androgen levels in women who have recurrent miscarriages and their correlation with markers of endometrial function. Fertil Steril. 1998;69(4):682-90.
9. Jung C, Ho JT, Torpy DJ, Rogers A, Doogue M, Lewis JG, et al. A longitudinal study of plasma and urinary cortisol in pregnancy and postpartum. J Clin Endocrinol Metab. 2011;96(5):1533-40.
10. Reisch N. Pregnancy in congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. 2019;48(3):619-41.

Time of the monthly rash

<u>Lauren Tyack</u>[1], John Walsh[1], Bronwyn Stuckey[1]

1. Sir Charles Gairdner Hospital, Nedlands, WA, Australia

Case presentation

Mrs JMW, A 46 year old female was referred to endocrinology in 2017 for management of recurrent erythema multiforme major (EMM) which appeared to be tightly linked to her menstrual cycle.

Her medical history includes type two diabetes mellitus, morbid obesity (BMI 56), obstructive sleep apnoea, hypertension, hypercholesterolaemia, and IgA/IgM deficiencies causing recurrent chest infections. She is a previous smoker and consumes minimal quantities of alcohol on rare occasions. She lives with her husband and four children. She had previously worked part time as a cleaner.

She had been seen in immunology, dermatology and infectious diseases clinics for EMM since 2016. EMM eruptions were characterised by erythema multiforme targetoid skin lesions, oral mucosal ulcers, conjunctival erythema and nasal crusting. It was thought that this was in part explained by Herpes Simplex Virus (HSV) reactivation as there was partial response to oral valaciclovir. HSV serology was positive for HSV type 1 IgG, and negative for HSV type 2 IgG. During an acute eruption, swabs for viral PCR were taken from tongue and lip lesions. These were negative for all Herpes viruses.

Further history revealed that the onset of EMM was indeed menstrual related, in keeping with catamenial dermatosis. She would experience lip tingling the day prior to menses, and on day 1 of her cycle she experienced an eruption of targetoid lesions affecting arms, hands and feet, as well as mouth ulcers and conjunctival erythema. New lesions appeared on each day of menses, with final lesions appearing on the final day before resolving (see figure 3). Her cycles had started to become longer and irregular, making it difficult to predict the onset of EMM which was debilitating for the patient.

With regards to reproductive history, menarche was at 13 years. Her menstrual cycle was mostly irregular. She is G5P4; after a termination of pregnancy at age 17, she fell pregnant with her four children at age 23, 24, 29 and 30. She breastfed each child for approximately one month. She took the oral contraceptive pill for several months at one stage in her twenties, however did not tolerate this due to nausea. Otherwise, she used barrier contraception. Her menstrual cycles became regular at age 45 after she lost 35kg. This coincided with the onset of recurrent EMM. However, her cycles had become longer and less regular in 2018.

With regards to weight history, she recalls being normal size compared to her peers as a child and teenager. She started to gain weight at age 18 and became progressively heavier with each pregnancy. She was her heaviest at 185kg in 2016. At this time, she sought help from her general practitioner and successfully lost 35kg using Optifast meal replacement drinks. When she resumed a normal diet, she gained weight again and plateaued at around 178kg.

Biochemistry from 5 December 2017 demonstrated oestradiol 300pmol/L, progesterone 33nmol/L, LH 1.9 U/L and FSH 2 U/L. These results are consistent with a luteal phase, however the patient does not recall where she was in her menstrual cycle at this time, nor if she had EMM.

She was counselled regarding several options with regards to EMM:

- Do nothing and wait for menopause,
- use GnRH analogue therapy to suppress gonadotropins and ovarian steroids until age 50,
- trial transdermal oestrogen patch towards end of menstrual cycle as it is plausible that the EMM is triggered by oestrogen withdrawal (however, this option would be difficult to time due to irregular cycles).

Ultimately, the patient elected to use a GnRH analogue. She was prescribed Zoladex (goserelin) depot therapy commencing April 2018. She was commenced on 3.6 mg every month for three months. This was well-tolerated, so she was given 10.8 mg every three months. She became amenorrhoeic and had no further recurrence of EMM. This added further confidence in the diagnosis of a catamenial dermatosis. In October 2018, her infectious diseases physician ceased the valaciclovir due to no further clinical need. In terms of side effects, she experienced mild vasomotor symptoms which did not affect her quality of life. She was not prescribed add-back oestrogen therapy. With regards to bone health, she had no history of fractures. Serial bone mineral density scans performed which showed normal bone density.

She was seen in clinic in April 2021. At this point, she was 50 years old and her last dose of goserelin had been administered in August 2020, eight months prior. She had remained amenorrhoeic and free of EMM. On review of biochemistry ordered by her general practitioner, it was noted that HbA1c was 12.6%. Diabetes treatment involved only metformin and gliclazide. As she was not being seen by another endocrinologist, we recommended she consider a GLP-1 analogue and provided a prescription for dulaglutide 1.5 mg weekly.

We reviewed her via telephone consult in July 2021. Again, she remains amenorrhoeic with no recurrence of EMM. She also reported 20 kg of weight loss since she had last been seen. Review of her biochemistry revealed HbA1c 6.1%, undetectable oestradiol, LH 0.3 U/L and FSH 2 U/L. Hypogonadotropic hypogonadism is not consistent with menopause, however in the context of recent significant weight loss, it was thought that the hypothalamic gonadal axis may be disrupted. Further, it is possible that there was an accumulation of goserelin after more than two years of therapy. We will continue to review her to assess for recurrence. Mrs JMW represents a case of catamenial EMM where treatment with GnRHa was successful.

Literature review

Menstrual cycle-related dermatoses are rarely reported. The most frequently reported is autoimmune progesterone dermatitis (AIPD) which occurs in the luteal phase.[1] Autoimmune estrogen dermatitis (AEPD) in the follicular phase is less common.[1] A systematic review found 19 cases of EMM AIPD and 1 case of AIED EMM (figure 2).[1] There were no catamenial cases of EMM reported. One case reported exposure to uterine prostaglandins as a trigger for a non-EMM catamenial skin eruption.[2] Another reported oestrogen withdrawal in catamenial anaphylaxis which was successfully treated with an oestrogen patch prior to menstruation.[3] Catamenial conditions are thought to be triggered by oestrogen withdrawal towards the end of the follicular phase,

such as is seen in menstrual migraine.[4] Diagnosis is made on history and is supported by successful proof of concept treatment.[4,5] A wide range of treatment for menstrual cycle-related dermatoses has been reported. Milder dermatoses have treated with antihistamines and glucocorticoids.[1,4] Suppression of ovulation by the oral contraceptive pill, GnRH analogues, tamoxifen and oophorectomy have been reported.[1] For catamenial conditions specifically, exogenous oestrogen replacement towards the end of the menstrual cycle where oestrogen levels decline has been successful.[4,5]

Take home messages

- Menstrual cycle-related dermatoses are rarely reported in the literature; true prevalence is unknown and mechanisms are poorly understood.
- There have been no reported cases of EMM in the menstrual phase.
- A history of recurrent cutaneous eruptions in women of childbearing age should be considered in the context of the menstrual cycle.
- The diagnosis is largely clinical.
- The most common of the catamenial dermatoses is AIPD. Oestrogen exposure, oestrogen withdrawal, and uterine PGs have also been reported as triggers.

The picture can't be displayed.
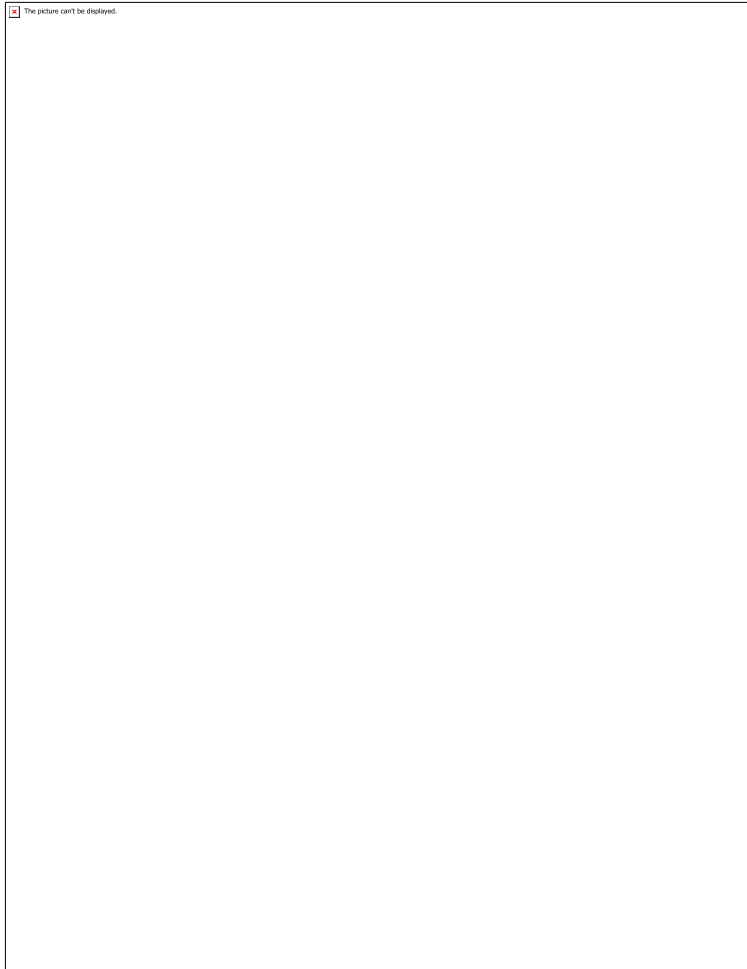
1. Zachary C, Fackler N, Juhasz M, Pham C, Mesinkovska NA. Catamenial dermatoses associated with autoimmune, inflammatory, and systemic diseases: A systematic review,. Int J Womens Dermatol. 2019 Oct 25;5(5):361-367.
2. Verdolini R, Atkar R, Clayton N, Hasan R, Stefanato CM. Catamenial dermatoses: has anyone ever considered prostaglandins? Clin Exp Dermatol. 2014 Jun;39(4):509-12.
3. Klinken K, Stuckey B, McLean-Tooke A. A Case of Catamenial Anaphylaxis. Int Med J. 2015 Sept 45(Suppl. 4):26.
4. Bernstein JA. Progestogen Sensitization: a Unique Female Presentation of Anaphylaxis. Curr Allergy Asthma Rep. 2020 Jan 28;20(1):4.
5. Burns K, Stuckey B. Periodic allergy. Abstracts. Clin Endocrinol (Suppl. 1) 2017;86:41.

Primary amenorrhea, patchy puberty, and now pregnancy planning - "incidental" primary amenorrhea in a woman referred with papillary thyroid cancer

Aditi Nevgi[1], Amanda Vincent[1]

1. Endocrinology, Monash Health, Clayton, Victoria, Australia

Patient Case

Sarah, a 31 year old radiographer, had undergone a total thyroidectomy for a self-diagnosed Papillary Thyroid Cancer (PTC) (which she had detected herself when demonstrating ultrasonography on her own neck)! On review by endocrinologists in the Thyroid Cancer Clinic, her history of primary amenorrhea came to light.

Sarah reported onset of early secondary sexual characteristics at approximately 15 of age, with meagre pubic and axillary hair development. She also reported a late growth spurt ate age 14, to 170cm, despite a short family. However she had never undergone menarche. On review of this with a GP in her late teenage years, she was told to "wait and see". She then travelled overseas for much of her 20s without further assessment. She had no menopausal symptoms.

Past medical history included: low-trauma wrist fractures (aged 14, 15 and 24), and mild asthma

Medications: Caltrate 2 BD, Thyroxine 100 mcg daily, Ventolin PRN.

Relevant family history included osteoporosis, and Type 2 Diabetes Mellitus. Her one brother had normal pubertal development.

On examination, she was of Asian heritage. Height 170cm, BMI 26. Breast development consistent with Tanner Stage II. She had sparse axillary hair. No virilisation. Short 4th metacarpal. BP 120/85. Pelvic examination was not performed.

Preliminary investigations:
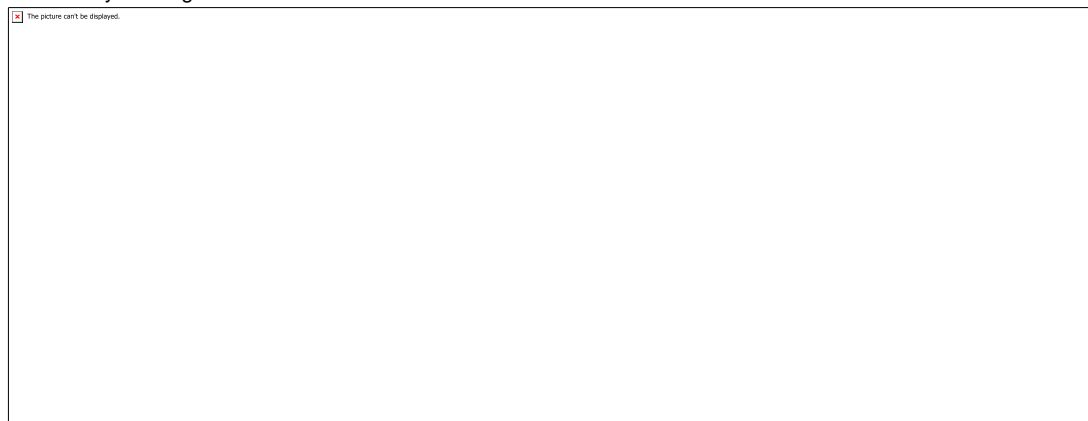
The investigations indicated hypogonadotropic hypogonadism. The Karyotype was 46XX, with no evidence of mosaicism (confidence interval 95%), excluding Turner's Syndrome.

Further questioning then revealed that she was a lifelong sufferer of anosmia, having been unable to smell anything since birth.

Our postulated diagnosis was thus Kallman's Syndrome.

Further imaging:
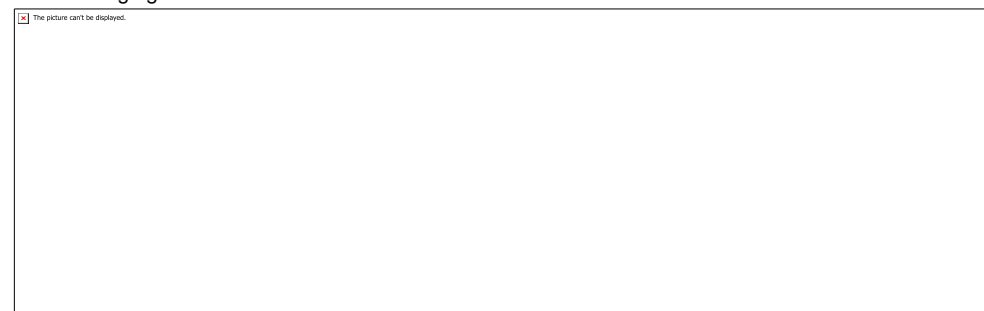
This seemed consistent with the diagnosis of Kallman's. Nevertheless, we note her MRI pituitary provided us with a differential diagnosis:

The rest of her pituitary profile was normal, however isolated gonadotrophin deficiency from the Rathke's Cyst remained a differential. This would not, however, explain her anosmia.

Therefore, our final diagnosis was that of Kallman's, with oestrogen deficiency causing atrophic uterus and low bone density.

Pubertal induction therapy was commenced, using low-dose transdermal oestrogen. The dose of oestrogen was titrated upwards and response monitored via breast examination and pelvic ultrasound (uterine size and endometrial thickness). Progestogen was added two years later when endometrium 4.6mm as combined sequential hormone replacement therapy (HRT), Estalis sequi 50/140, with regular withdrawal bleeds.

She also had a slight increase in breast size.

Her repeat DEXA scan conducted 2 years later showed significant benefit:
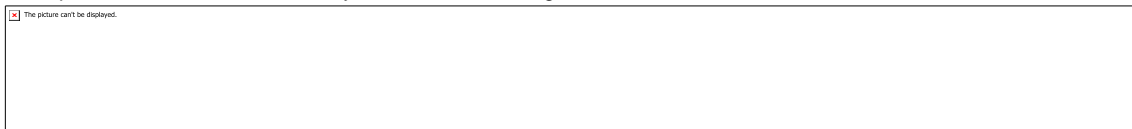
Furthermore her bone turnover markers were low on oestrogen therapy:

Thyroxine was continued, with no recurrence of PTC.

In 2020, aged 35, she noted that she was considering her future fertility and she wished to try for pregnancy in the future.

For this reason, her gynaecologist had her HRT temporarily withheld in order to assess her underlying fertility status. Her biochemistry revealed the following:

Of note her AMH level was low-normal. HRT was recommenced hereafter.

She is awaiting genetic testing for Kallman's Syndrome, to be completed in the next few months.

Overall, Sarah remains currently well.

Discussion

This case highlights the problems of delayed diagnosis of primary amenorrhoea, Kallman's syndrome as a rare cause, and management considerations in a young women with hypogonadotrophic hypogonadism.


Kallman's Syndrome

Kallman's Syndrome (KS), a genetic disorder causing hypogonadotrophic hypogonadism, presents with anosmia and delayed or absent puberty. Over 25 possible causative genes are identified. The incidence is about 1 in 150,000 in females.

Pathophysiology of KS is impaired in utero development of the olfactory bulbs and migration of GnRH neurones to the hypothalamus resulting in impaired or absent GnRH secretion. Sarah's clinical presentation of primary amenorrhoea and anosmia, serum gonadotrophin levels and MRI findings are consistent with this.

Diagnosis

The diagnosis of KS usually made clinically, with findings of congenital hypogonadotropic hypogonadism and anosmia.
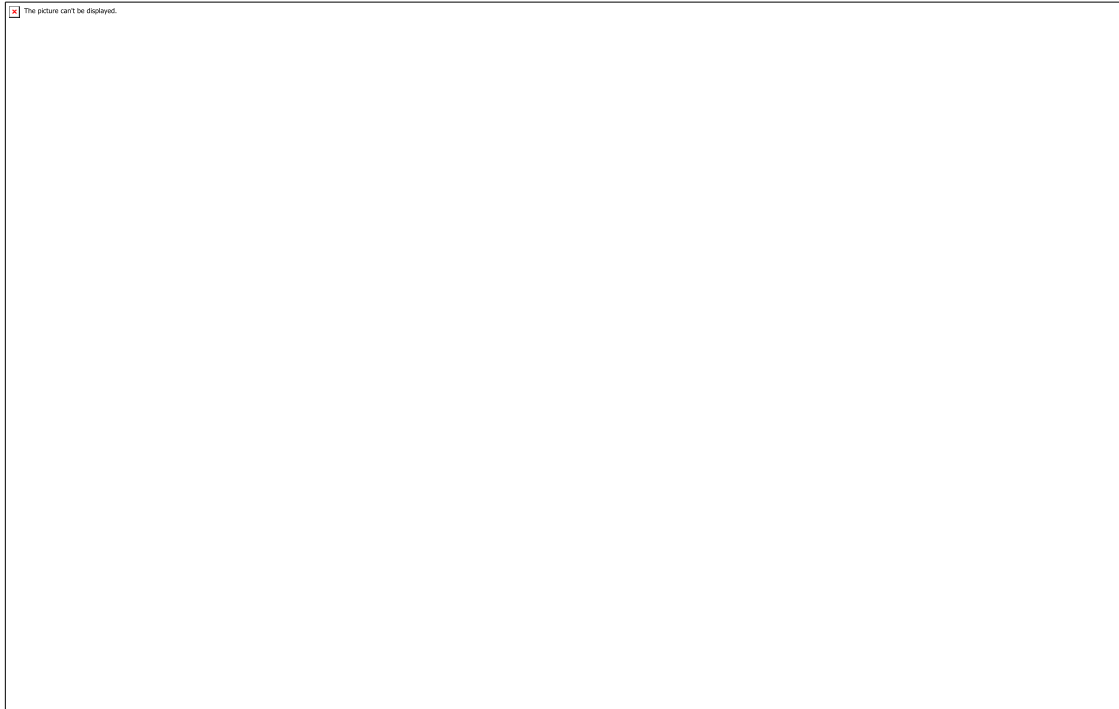
A genetic cause can be identified in only approximately 50% of cases; therefore this contributes to but is not required for the diagnosis. If a gene is found, however, it would provide prognostication for Sarah in regards to future pregnancies, as most cases are monogenic and autosomal dominant, meaning her child would have 50% chance of having Kallman's syndrome themselves.

MRI of the olfactory bulbs can be considered, but is not diagnostic, as there is heterogeneity in the appearance of olfactory bulbs in Kallman's Syndrome.

Assessment of gonadal status via ultrasound, and bone health via DEXA, is important.

Treatment

Treatment hinges on developing the sex organs and secondary sexual characteristics. Pubertal induction is required in those with primary amenorrhoea, initially with oestrogen alone and then addition of a progestogen. Hormone replacement therapy (HRT) should be continued until the usual age of menopause in women.

Oestrogen will also help with anabolic bone development.

HRT will not induce ovulation.

Fertility management, in the setting of longstanding Hypogonadotropic Hypogonadism

a. Fertility optimisation

Infertility in Kallman's Syndrome is due to immaturation of the follicles, and thus anovuation. There is no evidence for a decreased follicular reserve in patients with KS. Therefore, with treatment, the reproductive prognosis is good.

Pubertal induction and ongoing oestrogen will induce uterine growth, further optimising fertility. Sarah's initial pelvic ultrasound revealed a small atrophic uterus; however, oestrogen therapy promoted uterine growth and endometrial thickening.

b. The role of AMH

AMH, secreted by primordial follicles, is used as a marker of ovarian reserve.

Sarah's AMH level was the bottom 10th centile for her age. However, it must be emphasized that studies, such as that published by Bry-Gauillard, have shown that hypogonadotropic hypogonadal women still respond well to ovarian induction despite this. Therefore, AMH levels in hypogonadotropic hypogonadism, whilst reassuring if high, should *not* be used to tell women that their chances of fertility are poor if the AMH is low. Rather, it would be expected to be low in hypogonadotropic women, but should improve well once pulsatile GnRH or FSH is given.

c. Fertility induction

Ovulation induction in hypogonadotropic hypogonadism can be stimulated either with pulsatile GnRH therapy, or with FSH and hCG/LH therapy. There is a risk of ovarian hyperstimulation, and thus multiple pregnancies.

The risk of ovarian hyperstimulation is higher with FSH / LH stimulation, than with GnRH. Using pulsatile GnRH, the pituitary is triggered to make its own FSH / LH, levels of which then fall into normal range. Therefore the risk of overstimulation is far lower. In Sarah, however, given the presence of the Rathke's Cleft Cyst (of unknown clinical significance), FSH and LH/HCG stimulation may be preferred.

The success of this has been shown to be about 70% at 6 months of treatment, with a 20% chance of multiple pregnancies.

TAKE-HOME MESSAGES
- Primary amenorrhoea present at age 13 years (without breast development) or at age 15 years (with breast development) requires investigation
- Kallman's Syndrome is a rare cause of hypogonadotrophic hypogonadism associated with anosmia.
- Treatment involves pubertal induction and ongoing hormone replacement therapy
- Fertility is possible with ovulation induction in women with Kallman's Syndrome.

1. Boehm, U, et al. (2015). European Consensus Statement on congenital hypogonadotropic hypogonadism – pathogenesis, diagnosis and treatment. Nature Rev Endo. [online] 11, 547 – 564. Available at https://www.nature.com/articles/nrendo.2015.112 [Accessed July 2021].
2. Acien, P, et al. (2020). Disorders of Sex Development: Classification, Review, and Impact on Fertility. J of Clin Med. [online] 9(11), 3555. Available at https://www.mdpi.com/2077-0383/9/11/3555/htm [Accessed July 2021].
3. AMH fertility test. (2019). Sullivan Nicolaides Pathology. [online] Available at: https://www.snp.com.au/media/Multisite11187/amh-fertility-test-2019.pdf [Accessed July 2021].
4. Mitchell AL, Dwyer A, Pitteloud N, Quinton R. (2011) Genetic basis and variable phenotypic expression of Kallmann syndrome: towards a unifying theory. Trends Endocrinol Metab. 22(7):249-58.
5. Costa-Barbosa, FA, et al. (2013) Prioritizing genetic testing in patients with Kallmann syndrome using clinical phenotypes. J Clin Endocrinol Metab. 98(5):943-53.
6. Young J, Rey R, et al. (1999) Antimüllerian hormone in patients with hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 84(8):2696-9.

7. Ankarberg-Lindgren C, Kriström B, Norjavaara E. (2014) Physiological Estrogen Replacement Therapy for Puberty Induction in Girls: A Clinical Observational Study. Horm Res Paediatr. 81:239-244.
8. Schoot, DC, et al. (1994). Recombinant human follicle-stimulating hormone and ovarian response in gonadotrophin-deficient women. Human Reproduction, 9(7), 1237–1242
9. Forni, PE, Wray, S. (2015) GnRH, anosmia and hypogonadotropic hypogonadism – Where are we?, Frontiers in Neuroendoc, 36, 165-177.
10. Bry-Gauillard, H, et al. (2017). Anti-Mullerian Hormone and Ovarian Morphology in Women With Isolated Hypogonadotropic Hypogonadism/Kallmann Syndrome: Effects of Recombinant Human FSH. J Clin Endocrinol Metab, 102(4):1102–1111.