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Thyroid cancer on overdrive: an unexpected pit stop (127087)

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Case presentation

A 45-year-old female, from home with husband and child, ECOG 0, presented to her GP with right-sided chest pain on a background of morbid obesity, hypertension and no regular medications. Imaging revealed a pathological rib fracture and innumerable lung nodules, which were FDG-avid along with a 22mm thyroid nodule and lytic bony lesions (Figure 1). The patient was referred to the thyroid multidisciplinary team after multiple non-diagnostic biopsies (2x thyroid FNA, 1x thyroid core biopsy, 1x EBUS). A diagnosis of metastatic follicular thyroid cancer was ultimately established by biopsy of the rib lesion 4 months after initial presentation. Total thyroidectomy was performed 4 weeks later (Table 1), followed by commencement of levothyroxine 100µg and referral for radioiodine ablation (RAI).

Table 1. Total thyroidectomy pathology & staging

Feature	Finding
Size of lesion	20mm
Tissue	Poorly differentiated follicular
Margins	Positive anterior margin
Vascular invasion	Present
Lymph nodes	Nil involvement
BRAF	Negative
nRAS	Variant detected
TNM staging	T1N0M1
AJCC staging	Stage II
ATA risk classification	High-risk

On assessment by the nuclear medicine team, new-onset bitemporal hemianopia was noted. The patient underwent CT re-staging revealing a sellar lesion, not evident on the prior FDG-PET, along with effacement of the spinal theca by a known T10 vertebral lytic lesion. RAI was deferred pending admission under the endocrine team. Further assessment demonstrated otherwise intact neurological function, anterior hypopituitarism with presumed ‘stalk effect’ hyperprolactinaemia, and adequate thyroid hormone replacement (Table 2). Baseline MRI characterised a 22mm sellar/suprasellar lesion, compressing the optic chiasm, and excluded cord

compression (Figure 2). She was started on hydrocortisone 10mg BD and transferred to a tertiary pituitary centre.

Table 2. Pituitary panel pre- and post-transsphenoidal resection.

Hormone	Preoperative levels (0900hrs)	After 2x transsphenoidal resections	Reference range
Cortisol (nmol/L)	**51** nmol/L	**663** (on hydrocortisone)	133-540 nmol/L
ACTH (ng/L)	22 ng/L	**<3**	7-60 ng/L
Prolactin (mIU/L)	**2926** mIU/L	**<20**	90-630 mIU/L
FSH (IU/L)	2 IU/L	**<1**	2-12 IU/L
LH (IU/L)	**<0.3** IU/L	**<0.3**	1-100 IU/L
Oestradiol (pmol/L	**<40** pmol/L	N/A	100-1100 pmol/L
TSH (mIU/L)	**0.02** mIU/L	**<0.01**	0.5-4.5 mIU/L
FT4 (pmol/L)	16 pmol/L	**>99**	10-20 pmol/L
FT3 (pmol/L)	3.5 pmol/L	**8.2**	3.1-5.4 pmol/L
IGF-1 (nmol/L)	**5** nmol/L	**2**	9-33 nmol/L
Sodium (mmol/L)	138	**146**	135-140

Within a span of 4 days, the patient underwent transsphenoidal resection of the sellar/suprasellar lesion, repeat surgery due to residual sellar disease radiologically (haemodynamic compromise on attempted resection of disease adherent to the optic chiasm prevented full surgical clearance), and single-fraction radiotherapy to the T10 lesion. The bitemporal hemianopia resolved. The second surgery was complicated by arginine vasopressin deficiency requiring desmopressin 200µg BD. Histopathology demonstrated well-differentiated follicular thyroid tissue, confirming the suspected but extremely rare diagnosis of thyroid cancer sellar metastasis.

Unexpectedly, 1 day following the second operation, the patient developed asymptomatic but biochemically severe thyrotoxicosis, persisting till discharge (Table 3). Levothyroxine was withheld, hydrocortisone increased to 20mg mane and 10mg midday, and close outpatient follow-up planned. Unfortunately, the patient was re-admitted within 24 hours of discharge with vomiting, polyuria and confusion associated with haemodynamic compromise. Her abnormal observations and polyuria resolved with parenteral steroids and desmopressin, though she remained intermittently nauseous and confused and had new mixed hepatocellular/cholestatic biochemical derangement. Postoperative infection and pulmonary embolism were excluded. Further investigation of the thyrotoxicosis was undertaken including: exclusion of assay interference, and a lack of pertechnetate uptake on whole-body functional imaging (albeit <6 weeks post-radiocontrast exposure) as well as thyroid autoantibodies (Table 3). The impression was of symptomatic hyperfunctioning metastases, potentially provoked by iodinated radiocontrast administration preoperatively. Prednisolone, propylthiouracil and propranolol were initiated, and later tapered when euthyroid (Table

3.). Her symptoms resolved, and levothyroxine restarted with hypothyroidism, without recurrence of thyrotoxicosis.

Table 3. Timeline of investigation and management of hyperthyroidism in days post-1st transsphenoidal resection

Test / intervention (reference range, units)	D -1	D1	D3	D15	D22	D40	D46	D52
FT4 (10-20, pmol/L)		19	**>99**	**>99**	**85**	14	**9**	10
FT3 (3.1-5.4, pmol/L)		3.5	**8.2**	**36.1**	**13.8**	**3.0**	**2.5**	**2.2**
TSH (0.5-4.5, mIU/L		**0.02**	**<0.01**					
Propylthiouracil				150mg TDS	100mg BD	50mg TDS		Ceased
Prednisolone				40mg OD	15mg OD	10mg OD		Ceased
Propranolol				40mg TDS	20mg TDS			20mg OD
Levothyroxine	100 µg OD		Held				50 µg daily	
Other tests / intervention	Contrast-enhanced CT Brain	Transsphenoidal resection (D0 & D2) Radiotherapy to T10 lesion (D1)	• Negative assay interference studies • (-) thyroid receptor and thyroid peroxidase antibodies • Nil residual thyroid on ultrasound • No significant pertechnetate uptake on whole body imaging					

Systemic treatment was revisited. RAI was deferred due to the potential for inducing tumour expansion. Noting this and the patient's risk factors for radioiodine-refractory disease (FDG-avidity, poorly differentiated primary tumour, follicular cell type, vascular invasion, large primary tumour size and metastatic disease) (1), lenvatinib was initiated. Lenvatinib has been tolerated with transient treatment interruptions, stable disease radiologically, and improved disease burden biochemically (thyroglobulin 165 µg/L from baseline 4669 µg/L [0-76 µg/L] with thyroglobulin antibody titres of 16 and 25 IU/mL respectively) over the past 6 months.

Figure 1. FDG-PET/CT images demonstrating a 22mm FDG-avid right-sided thyroid lesion (A). Whole-body FDG-PET demonstrating avid lesions in the lungs, thyroid gland and thoracolumbar spine (B). CT chest demonstrated innumerable lung metastases (C).

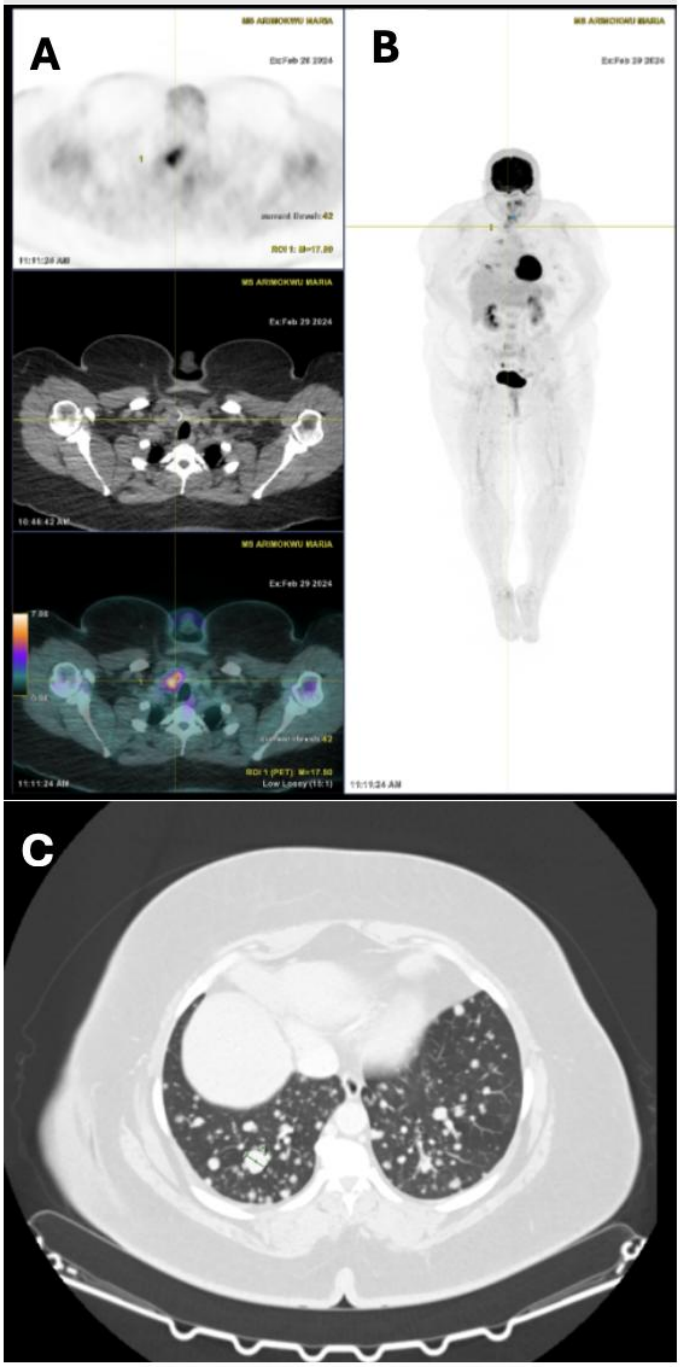
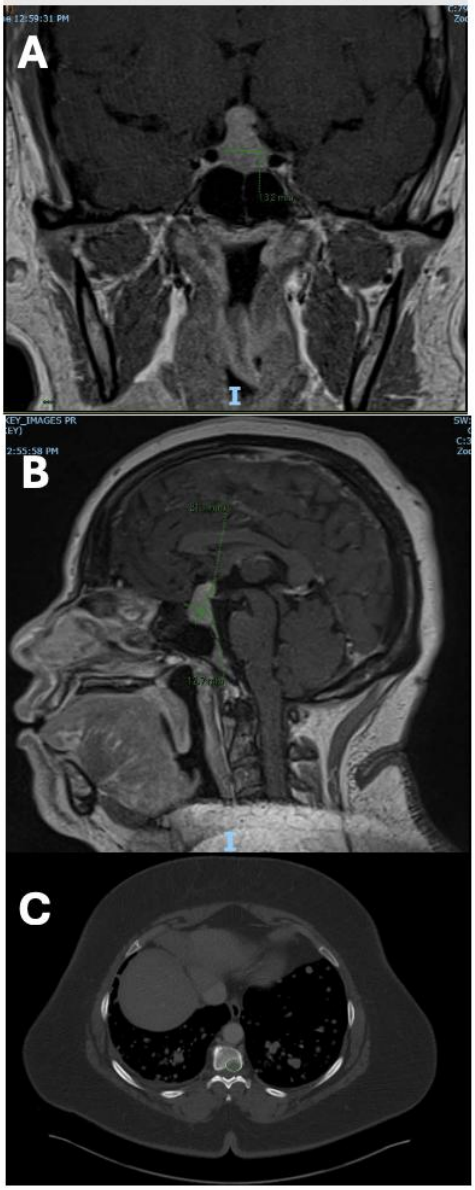


Figure 2. Pituitary MRI (A & B) demonstrated a 21x12x13mm solid contrast-enhancing lesion with sellar and suprasellar components, intermediate T1 and T2 signal, Knosp grade 2 right-sided cavernous sinus invasion and optic chiasmal compression. A small degree of sellar expansion was seen, relative to the size of the mass. Encroachment on the spinal dura by the T10 vertebral lytic lesion, without cord compression is demonstrated on spinal MRI (C).



Discussion

There are several noteworthy considerations raised by this case of aggressive follicular thyroid cancer complicated by sellar metastasis, panhypopituitarism and thyrotoxicosis.

Prognostication of follicular thyroid cancer

Differentiated thyroid cancer (DTC) typically has a benign trajectory. Even after metastatic spread, DTC is classified as stage II by the American Joint Committee on Cancer Staging when age <55-years-old, which predicts 85-95% 10-year survival (2). A worse outcome in our case was likely with consideration of poor prognostic factors including FDG-avidity, aggressive histological classification, vascular invasion and metastatic disease. The latter, specifically at diagnosis, is the most significant predictor of 10-year survival in follicular thyroid cancer, regardless of age, suggestive of 41% 10-year survival (3). Pituitary metastasis, as seen in our case, is extremely rare, being reported in <30 cases worldwide, but appears to predict a further reduction in median survival to ~12 months (4). Prognostication is of vital importance in patient counselling and clarifying the urgency of investigation and treatment - as demonstrated in our case where sellar metastasis occurred 6 months post-presentation.

Thyrotoxicosis in the setting of thyroid cancer

Thyrotoxicosis is not typically associated with thyroid cancer. However, 2% of DTC are hyperfunctioning (5). The reported cases are generally associated with large tumour size or metastatic disease. A much greater proportion of hyperfunctioning DTC, relative to non-functional, are follicular (5).

The mechanisms of thyrotoxicosis are varied. Hyperfunctioning primary tumours or distant metastases have been demonstrated on functional imaging, theorised to reflect somatic mutations in the *TSHR* or *PRKAR1A* genes, or in association with TSH-receptor autoantibodies (5). In our case, the tumour was not initially hyperfunctioning. Pertechnetate was not taken up by the metastases (albeit recent iodine exposure may have suppressed uptake), nor were thyroid autoantibodies detected. Cancer cell death and thyroid hormone release was considered, but our patient's cancer treatment at that time was limited to transsphenoidal surgery for the sellar mass and external-beam radiotherapy for a single vertebral lesion, making this unlikely. Instead, we suspected thyrotoxicosis due to radiocontrast-mediated iodine excess, with hyperthyroidism caused by escape from the Wolff-Chaikoff effect and the Jod-Basedow effect. Isolated case reports similarly report patients with severe thyrotoxicosis 3-5 days after iodinated radiocontrast in previously euthyroid patients with DTC and bony metastases, who then responded to combined therapy with thionamides, corticosteroids and beta-blockade (6, 7).

The decision not to pursue RAI

RAI is the primary treatment modality for metastatic DTC. It is typically highly effective and selective when administered after TSH stimulation (1). DTC metastases are known to have less functional sodium-iodide symporters (NIS), requiring preceding TSH stimulation to upregulate NIS (8), which can be achieved via levothyroxine withdrawal or recombinant TSH administration (8).

The decision to omit RAI was not without controversy. There is little, albeit emerging, evidence for the use of tyrosine kinase inhibitor therapy without preceding RAI (9). The characteristics of our case, particularly the sellar metastasis, profoundly impacted her suitability for RAI. Firstly, levothyroxine withdrawal could not be relied upon for TSH stimulation due to panhypopituitarism. Secondly, recombinant TSH and RAI could induce transient tumour expansion (10). Although steroid cover may attenuate this risk, CNS metastasis is a precaution for treatment – in our case there was a risk of compromise to the optic chiasm and spinal cord. Thirdly, the patient had numerous risk factors for radioiodine-refractory disease - RAI may have been futile. Finally, the onset of therapeutic effect following RAI is delayed. The patient's malignancy was rapidly progressing, and prompt treatment was necessary.

Take home messages

- Metastasis at presentation of follicular thyroid cancer portends a poor prognosis, informing patient counselling and management.
- Thyrotoxicosis is a rare complication of DTC that may arise due to intrinsic tumour hypersecretion, TSH-receptor antibodies or thyroid cancer destruction, with possible interactions from iodinated radiocontrast and DTC treatments, necessitating comprehensive workup.
- Sellar metastasis is an extremely rare complication of DTC that warrants expert multidisciplinary input to navigate the limited evidence base of management.

1. 1. Wang Y, Lu X, Liu H. Current status of the prediction for radio-iodine refractory thyroid cancer: a narrative review. Front Endocrinol (Lausanne). 2024;15:1433553.
2. 2. Ghaznavi SA, Ganly I, Shaha AR, English C, Wills J, Tuttle RM. Using the American Thyroid Association Risk-Stratification System to Refine and Individualize the American Joint Committee on Cancer Eighth Edition Disease-Specific Survival Estimates in Differentiated Thyroid Cancer. Thyroid. 2018;28(10):1293-300.
3. 3. Wu MH, Lee YY, Lu YL, Lin SF. Risk Factors and Prognosis for Metastatic Follicular Thyroid Cancer. Front Endocrinol (Lausanne). 2022;13:791826.

4. 4. Ilerhunmwuwa NP, Wasifuddin M, Perry J, Hakobyan N, Inyang L, Zavgorodneva Z, Gasparyan L, Tahir M. Pituitary Metastases From Differentiated Thyroid Cancers: A Systematic Review. World J Oncol. 2023;14(3):165-73.

5. 5. Liu J, Wang Y, Da D, Zheng M. Hyperfunctioning thyroid carcinoma: A systematic review. Mol Clin Oncol. 2019;11(6):535-50.

6. 6. Basida B, Zalavadiya N, Ismail R, Krayem H. Weathering the Storm: Thyroid Storm Precipitated by Radioiodine Contrast in Metastatic Thyroid Carcinoma. Cureus. 2021;13(3):e14219.

7. 7. Lorberboym M, Mechanick JI. Accelerated Thyrotoxicosis Induced by Iodinated Contrast Media in Metastatic Differentiated Thyroid Carcinoma. Journal of Nuclear Medicine. 1996;37(9):1532-5.

8. 8. Avram AM, Giovanella L, Greenspan B, Lawson SA, Luster M, Van Nostrand D, Peacock JG, Ovčariček PP, Silberstein E, Tulchinsky M, Verburg FA, Vrachimis A. SNMMI Procedure Standard/EANM Practice Guideline for Nuclear Medicine Evaluation and Therapy of Differentiated Thyroid Cancer: Abbreviated Version. Journal of Nuclear Medicine. 2022;63(6):15N-35N.

9. 9. Dickerson K, Milas M, Metzger R, Tomeh C, Shellenberger T, Ahmad I, Hebert M, Nasr C, Nelson JA, Westfall E, Eisen R, Niu J. Neoadjuvant systemic therapy for inoperable differentiated thyroid cancers: Impact on tumor resectability. Surgery. 2025;177:108836.

10. 10. Klubo-Gwiezdzinska J, Burman KD, Van Nostrand D, Mete M, Jonklaas J, Wartofsky L. Potential use of recombinant human thyrotropin in the treatment of distant metastases in patients with differentiated thyroid cancer. Endocr Pract. 2013;19(1):139-48.

RETaliation: Acquired resistance in a MEN2A Phaeochromocytoma (127049)

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A 70-year-old male with genetically confirmed Multiple Endocrine Neoplasia type 2A (MEN2A) presented with treatment-refractory metastatic phaeochromocytoma. His initial diagnosis was established in the 1970s following laparotomy for abdominal pain, leading to bilateral adrenalectomy in 1978. He subsequently underwent total thyroidectomy in 1980 for medullary thyroid carcinoma, with further surgery in 1991. Genetic testing confirmed a germline *RET* mutation p.Cys634Phe.

The patient remained clinically stable for over a decade until 1991, when he developed symptomatic recurrence involving the left suprarenal region, aortocaval lymph nodes, and small pancreatic and pulmonary metastases. Surgical resection was not pursued due to multifocal disease, and biopsy was avoided due to catecholaminergic crisis risk. He was treated with MIBG therapy, receiving two courses with the second in June 2016.

He later re-presented with pulsatile headaches and paroxysmal hypertension (SBP >200 mmHg). Between November 2017 and June 2018, he underwent four cycles of 177Lu-DOTATATE peptide receptor radionuclide therapy (PRRT), achieving partial biochemical and radiographic response. However, within a year, biochemical markers rose again (Table 1), and he developed severe thoracic back pain from a destructive T6 vertebral lesion requiring palliative radiotherapy.

In September 2019, he was commenced on selpercatinib (160 mg twice daily) as part of the LIBRETTO-001 trial [1]. Selpercatinib is a highly selective RET kinase inhibitor developed for RET-altered malignancies including MTC and RET fusion-positive solid tumours. Within days of treatment initiation, his thoracic back pain improved. He has a confirmed partial response with 8.3 months duration. Plasma normetanephrine decreased dramatically from >9,999 pmol/L to 1,190 pmol/L and metanephrine from 906 pmol/L to >50 pmol/L (Figure 1, Table 1). Radiologically, a partial response was confirmed with the aortocaval mass reducing from 50mm to 28 mm (Figure 2).

He remained on selpercatinib with good clinical benefit for approximately 20 months. At this point, imaging demonstrated disease progression, although therapy was continued with informed consent due to ongoing symptomatic improvement. After 18 months, he developed grade 2 diarrhoea, associated with hypoalbuminemia and peripheral oedema. Colonoscopy and biopsy were consistent with selpercatinib-induced

enteropathy. Steroid therapy was initiated, and the selpercatinib dose was reduced to 80 mg twice daily. Despite a good response to the steroids, he had a hospital admission for new-onset atrial fibrillation with rapid ventricular response in the context of electrolyte disturbance.

At 30 months of therapy, plasma normetanephrine levels again began to rise (Table 1). By month 35, significant radiographic disease progression was evident, with new hepatic metastases and bony lesions in T9, T11, and T12; as well as significantly raised normetanephrine. Cell-free DNA analysis revealed an acquired *RET* p.Gly810Ser solvent front mutation, a known mechanism of resistance to selpercatinib [2]. As a result, selpercatinib was ceased, and transition to CAPTEM (capecitabine and temozolomide) chemotherapy was planned. Unfortunately, the patient deteriorated rapidly and died two months after discontinuation of targeted therapy.

Phaeochromocytomas occur in 20-50% of MEN2 patients; they are the index tumour in 5-10% MEN2 cases. They are bilateral in up to 50% cases, and can be associated with striking catecholaminergic features although typically have a low metastatic potential [3]. Metastatic phaeochromocytoma in MEN2A is rare, with reported incidence below 5% [4], but it is associated with significant morbidity and poor prognosis with 5-year survival rates of 40-60% depending on tumour burden and location [5]. Management is particularly challenging in the absence of resectable disease.

Current management of metastatic phaeochromocytoma follows a multimodal approach. This can involve MIBG radiotherapy when tumours demonstrate adequate uptake, achieving disease control in 60-70% of patients though complete responses are rare (10-15%) [6]. PRRT with 177Lu-DOTATATE can also be as an effective option for somatostatin receptor-positive lesions, with systematic reviews demonstrating objective response rates of 25% and disease control rates of 84% in metastatic phaeochromocytoma/paraganglioma, though median progression-free survival remains limited to 29-40 months [7].

The emergence of RET-targeted therapies has reshaped the landscape for RET-altered tumours. Multi-kinase inhibitors such as sunitinib and cabozantinib, and more recently, highly selective RET inhibitors like selpercatinib, have demonstrated efficacy in medullary thyroid carcinoma and have emerging roles in phaeochromocytoma [5, 8].

Selective RET inhibitors offer advantages over multi-kinase inhibitors like vandetanib and cabozantinib, which demonstrate modest activity but significant off-target toxicities. The LIBRETTO-001 trial established selpercatinib's efficacy across RET-altered solid tumours, demonstrating overall response rates of 64% in RET-mutant medullary thyroid carcinoma with median duration of response not reached at 24 months [5]. While phaeochromocytoma patients comprised a small subset of only 6 patients, 4 showed partial response and 2 had stable disease with treatment duration

ranging between 9.2 to >56.4 months [1]. Common adverse events of any grade include hypertension (82%), diarrhoea (51%), and elevated liver enzymes (51%), with grade 3-4 events occur in approximately 30% of patients [9]. In this case, selpercatinib resulted in an extended partial response in a patient previously treated with both MIBG and PRRT.

However, acquired resistance remains a significant limitation. Documented mechanisms include either on-target secondary *RET* mutations — particularly solvent front mutations such as G810R/S/C which cause steric hindrance to selpercatinib and pralsetinib binding; or bypass resistance such as *MET* or *FGFR1* amplification, fusion events, tumour suppressor loss or mutations in downstream effectors such as *NRAS*. These alterations enable tumours to bypass RET inhibition, sustaining oncogenic signalling through alternative pathways [2]. Median time to resistance development ranges from 12-24 months across different tumour types. In this patient, a *RET* G810S mutation was identified via cell-free DNA sample, consistent with on-target resistance-driven disease progression.

Cell-free DNA offers a non-invasive modality for molecular profiling in patients unsuitable for repeat biopsy [10]. Its utility in detecting resistance mutations such as RET G810S is increasingly recognised, allowing timely treatment adaptation.

Following resistance to selective RET inhibitors, therapeutic options remain limited. On-target *RET* mutations also inhibit binding of multikinase inhibitors such as vandetanib or cabozantinib. PRRT offers a disease control strategy for somatostatin receptor–expressing lesions. However, rapidly progressive or heterogeneous disease may show poor responses. Other available strategies include MIBG therapy, the cyclophosphamide-vincristine-dacarbazine (CVD) regime, and investigational agents under clinical trial protocols.

Despite advances, the outlook for patients with treatment-refractory metastatic phaeochromocytoma remains poor. A personalised, multidisciplinary approach and enrolment in clinical trials continue to play pivotal roles in care.

Take-home messages:

- Metastatic phaeochromocytoma in MEN2A is rare and can follow an aggressive course requiring multimodal therapy.
- Selpercatinib, a selective RET inhibitor, can achieve substantial biochemical and radiographic responses in RET-mutant disease.
- Resistance to RET inhibition can occur via solvent front mutations such as G810S, detectable through circulating tumour DNA.
- Liquid biopsy (cfDNA) is a valuable, non-invasive method for identifying mechanisms of resistance and guiding further treatment.

- Long-term selpercatinib use may be complicated by adverse effects such as enteropathy, requiring dose adjustment or cessation.
- Further research is needed to define effective therapies after resistance to selective RET inhibition emerges.

Table 1 - Changes in catecholamine metabolites during response and resistance to selpercatinib.

	Normetanephrine (pmol/L)	**Metanephrine** (pmol/L)
Baseline Sept 2019	>9999 (NR < 1080)	755 (NR <447)
Post-selpercatinib May 2020 (8m on therapy)	1720 (NR < 1280)	65 (NR <447)
Radiological Progression June 2021 (20m on therapy)	1430 (NR <1310)	75 (NR<447)
Emergence of Resistance March 2022 (30m on therapy)	3700 (NR < 1350)	95 (NR <447)
Cessation of therapy *Oct 2022* (37m on therapy)	93,410 (NR <1080)	1150 (NR <447)

NR: normal range.

Figure 1 - Effect of selpercatinib on normetanephrine and metanephrine over the first 6 months of therapy.

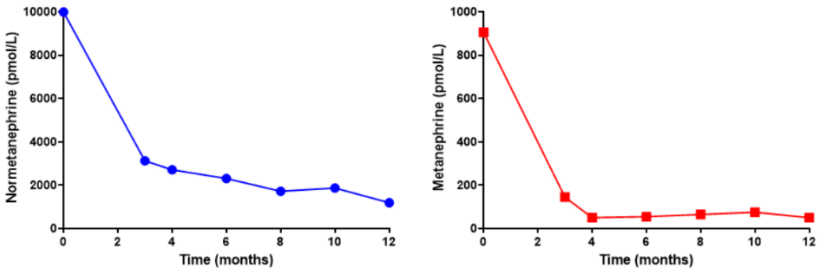
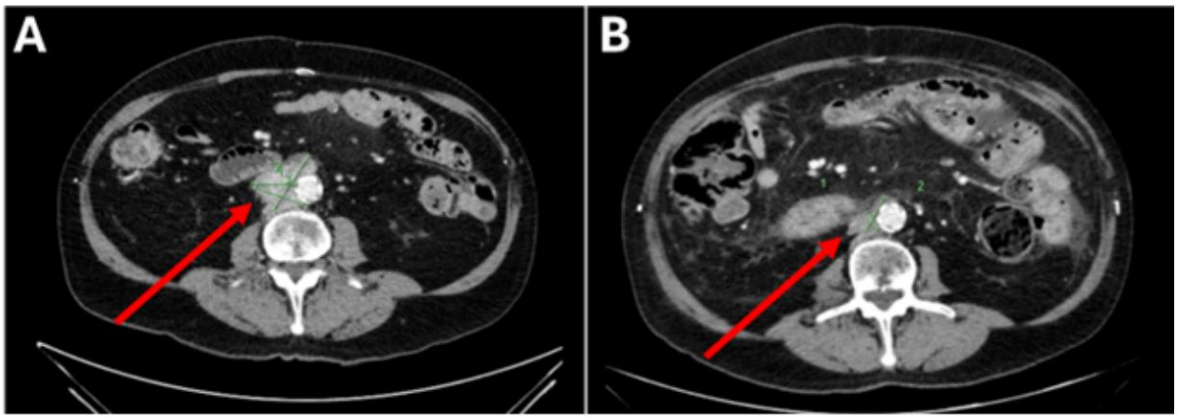


Figure 2- CT images at baseline (A) and after 14 months of treatment with selpercatinib (B). There is reduction of the aortocaval mass from 50x38 mm to 28x14mm.



1. Deschler-Baier, B., et al., Clinical Activity of Selpercatinib in RET-mutant Pheochromocytoma. J Clin Endocrinol Metab, 2025. 110(3): p. e600-e606
2. Clifton-Bligh, R.J., Mechanisms of resistance to RET-directed therapies. Endocr Relat Cancer, 2025. 32(2).
3. Gild, M.L., et al., Pheochromocytoma in MEN2. Recent Results Cancer Res, 2025. 223: p. 211-235.
4. Casanova, S., et al., Phaeochromocytoma in multiple endocrine neoplasia type 2 A: survey of 100 cases. Clin Endocrinol (Oxf), 1993. 38(5): p. 531-7.
5. Wirth, L.J., et al., Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. N Engl J Med, 2020. 383(9): p. 825-835.
6. van Hulsteijn, L.T., et al., (131)I-MIBG therapy for malignant paraganglioma and phaeochromocytoma: systematic review and meta-analysis. Clin Endocrinol (Oxf), 2014. 80(4): p. 487-501.
7. Satapathy, S., B.R. Mittal, and A. Bhansali, 'Peptide receptor radionuclide therapy in the management of advanced pheochromocytoma and paraganglioma: A systematic review and meta-analysis'. Clin Endocrinol (Oxf), 2019. 91(6): p. 718-727.
8. Wang, K., et al., Targeted Therapies in Pheochromocytoma and Paraganglioma. J Clin Endocrinol Metab, 2022. 107(11): p. 2963-2972.
9. Hadoux, J., et al., Phase 3 Trial of Selpercatinib in Advanced RET-Mutant Medullary Thyroid Cancer. N Engl J Med, 2023. 389(20): p. 1851-1861.
10. Stewart, C.M., et al., The value of cell-free DNA for molecular pathology. J Pathol, 2018. 244(5): p. 616-627.

A Rare Case of Ovarian Hyperthecosis in a 28-Year-Old Woman with PCOS and Severe Hyperandrogenism: Diagnostic Approach and Fertility Considerations (127242)

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Case presentation:

Mrs XY is a 28year old female from home with husband who presented for pre-conception planning in the setting of significant obesity and previously diagnosed polycystic ovary syndrome (PCOS). At the age of 22, she was diagnosed with PCOS by her general practitioner (GP) and endocrinologist. Pelvic ultrasound and biochemical investigations were performed under the care of both clinicians, but she was lost to follow-up until she presented to with metromenorrhagia.

Regarding her gynaecological history, menarche occurred during her early teenage years. Since then, she had experienced irregular menstrual cycles. To regulate her cycles, she commenced the combined oral contraceptive pill, which she used for approximately three years, during which she gained significant weight. She typically had 6 to 10 menstrual episodes per year, ranging from heavy bleeding to occasional spotting. Norethisterone was prescribed at one stage as a progesterone challenge to induce menstruation. The patient expressed a desire to conceive in the future. She and her partner had previously used condoms as contraception, prior to the insertion of the Mirena IUD. They plan to attempt conception within the next 1–2 years.

On examination, her BMI was significantly elevated at 55 kg/m^2. Blood pressure was 120/68 mmHg. She had thin, white striae on the flanks and thighs but no overt signs suggestive of Cushing's syndrome. Acanthosis nigricans was present in the neck folds and axillae. Her self-reported Ferriman-Gallwey score was 18–20, consistent with severe hirsutism. No androphonia or clitoromegaly was noted.

Investigations	Patient's results			Normal reference range
Year	2022	2024	2025	
Karyotype			46 XX	
LH (U/L) FSH (U/L)	5.1 3.5		8.2 4	2-100 2-20
Testosterone (nmol/L)	**10.2**	**10.5**	6.48	0.5 - 2.0
Androstenedione(nmol/L)		**11.2**		0.91-7.48
SHBG (nmol/L)		83	65	25-90
DHEAS (umol/L)	1.6	2.4		1.8-9.2
Oestradiol(pmol/L)	430	501	368	>200
Progesterone(nmol/L)	<0.5		< 0.5	0.2-46.3
TSH (mIU/L)			1.36	
EUC, LFT			normal	
HbA1c (%)	5.1		5.2	
Insulin (mU/L)			82.2(Glucose 4.6mmol/L)	0.0-12.0
ACTH ng/L	5		12	7-60
Dex. Suppression test (nmol/L)		25		<59
Prolactin			410 mIU/L	90-630

Location		Time of Sample	Testosterone nmol/L	DHEAS umol/L	ACTH ng/L	Cortisol nmol/L	Androstenedione nmol/L	Oestradiol pmol/L	Progesterone nmol/L	Ratios	Ratios
Peripheral	1	1321	6.92	1.6	12	163	8.24	444	0.8		
Peripheral	2	1322	6.83	1.6	12	162	7.35	419	0.6		
Left Adrenal	1	1306	6.26	1.8		295	13.69			1.80982	
Left Adrenal	2	1307	6.27	1.8		328	15.34			2.02469	
Left Adrenal	3	1336	11.1	2.7		3535	93.4			21.821	
Left Adrenal	4	1338	11.8	2.9		3817	108.2			23.5617	
Right Adrenal	1	1356	6.84	1.6		176	7.96			1.07975	
Right Adrenal	2	1358	7.32	1.6		194	12.89			1.19018	
Left Ovarian	1	1301	>51.00	1.9			>400	7717			17.38063
Left Ovarian	2	1303	>51.00	1.9			>400	9278			20.8964
Right Ovarian	1	1317	>51.00	1.8			>400	6136			14.64439
Right Ovarian	2	1378	>51.00	1.9			>400	6479			15.46301

CT 2020	Normal adrenal glands.
US pelvis 2018	Unremarkable examination, although the ovaries were not able to be visualised.
US pelvis 2024	IUCD noted, reduced diagnostic ability. No obvious adnexal mass or cyst on the limited views on either side
Hysteroscopy 24	Increased endometrial thickness. Proliferative pattern endometrium with changes suggestive of benign endometrial polyp
CT 2023	Normal adrenals and ovaries

Diagnostic Considerations

The markedly elevated serum testosterone level, peaking at 10 nmol/L, was deemed inconsistent with PCOS alone and prompted further investigation. An adrenal source was excluded with normal adrenal morphology on imaging, suppressed ACTH, and normal DHEAS levels. Sex chromosome abnormalities were ruled out by a normal female karyotype. A short Synacthen test showed a 17-hydroxyprogesterone level of <9.8 nmol/L at 60 minutes, making congenital adrenal hyperplasia (CAH) unlikely. Cushing's syndrome was less likely given absence of typical Cushing's features, normal 24-hour urinary free cortisol, DST and normal midnight salivary cortisol. At this stage, ovarian hyperthecosis emerged as the leading diagnosis. However, the possibility of a small ovarian or adrenal neoplasm could not be entirely excluded. Therefore, ovarian venous sampling was performed. Elevated testosterone levels were detected in samples from both ovaries without lateralisation, leading to a diagnosis of bilateral ovarian hyperthecosis.

Literature review:

Ovarian hyperthecosis (OHT) is a rare but important cause of severe hyperandrogenism, typically reported in postmenopausal women. However, a limited number of cases have documented its occurrence in premenopausal women, where it often mimics virilising ovarian neoplasms due to the severity of clinical features and biochemical abnormalities.

Pathophysiology :

Intrafollicular theca cells in the ovary express LH receptors, which, when stimulated by circulating pituitary LH, produce androgens such as testosterone and precursors (DHEA, A4). These are transferred to granulosa cells, which, under FSH stimulation, convert testosterone into oestradiol via aromatase activity.

In OHT, however, theca cells undergo aberrant differentiation into luteinised theca cells that are dispersed throughout the ovarian stroma. These ectopic cells produce androgens independently of granulosa cell regulation, resulting in elevated systemic testosterone(1).

Clinical Presentation in Premenopausal Women

While classically described in postmenopausal women, OHT can rarely present in premenopausal individuals. To our knowledge, this is the first reported case of premenopausal OHT in Australia. Clinical features may include severe hirsutism, acne, clitoromegaly, temporal balding, and, in some cases, secondary amenorrhoea. Most patients demonstrate insulin resistance, and the condition is often considered a severe phenotype along the PCOS spectrum. Serum testosterone levels typically exceed those seen in PCOS, necessitating evaluation for androgen-secreting tumours(1,2).

Diagnostic Challenges

Differentiating OHT from other causes of hyperandrogenism is critical. In the premenopausal group other causes such as PCOS, non-classic congenital adrenal hyperplasia, and androgen-secreting tumours must be ruled out through clinical, biochemical, and radiological assessments. In OHT, imaging studies may reveal bilaterally enlarged ovaries with increased stromal echogenicity but typically lack discrete tumour masses. In many cases, like the one discussed here, the ovaries can appear normal on radiological imaging. Serum testosterone levels are markedly elevated, while DHEA-S levels, usually adrenal in origin, remain within normal limits. Androstenedione, the precursor of testosterone is also elevated in most cases (3).

Dynamic endocrine testing can be useful for diagnostic clarification. A reduction of more than 50% in serum testosterone following administration of a gonadotrophin-releasing hormone (GnRH) analogue supports the diagnosis of LH-dependent hyperandrogenism, which favours OHT over tumour-related aetiologies. Venous sampling of ovarian and adrenal sources, though invasive, may be necessary in equivocal cases and can demonstrate bilateral androgen production without lateralisation—a finding characteristic of OHT (2,3).

Histological confirmation via ovarian biopsy remains the gold standard, revealing nests of luteinised theca cells dispersed throughout the stroma.

Management Strategies

There is no consensus on managing OHT in premenopausal women due to its rarity. Treatment goals focus on reducing androgen production and controlling symptoms. In postmenopausal women, bilateral oophorectomy is curative. In younger women, fertility preservation is a key consideration. In the few case reports documented in literature, treatment primarily involved GnRH analogue with either OCP or HRT with or without an anti-androgen such as Spironolactone (1,2,4, 5). No cases to date have documented successful conception in women with OHT, and this remains an area requiring further research.

GnRH analogues, such as goserelin effectively suppress pituitary gonadotrophins and thus reduce LH-mediated androgen synthesis. In reported cases, significant biochemical and clinical improvement was achieved within a few months of initiating therapy. Combined oral contraceptives (COCs) have also been utilised, particularly when GnRH analogues are culturally or personally unacceptable. COCs may offer partial suppression of gonadotrophins and aid in the control of hyperandrogenic symptoms. Anti-androgens such as cyproterone acetate or spironolactone have been reported as adjunctive options, though clinical experience remains limited.

In our case, the patient was commenced on Tirzepatide and Metformin for weight loss and insulin resistance management. In addition, she was started on GnRH analogue with oestradiol patches (with Mirena IUD) to good effect, with a plan to continue this for 6 months and review prior to considering pregnancy.

Conclusion

Ovarian hyperthecosis, while predominantly reported in postmenopausal women, should be considered in premenopausal women presenting with severe hyperandrogenism and virilisation. Differentiation from androgen-secreting tumours and PCOS is essential and relies on a combination of hormonal assays, imaging, dynamic suppression testing, and histopathological confirmation. Medical management with GnRH analogues and/or COCs presents a viable, non-surgical treatment option in younger patients. Increased clinical awareness and further case documentation are necessary to inform evidence-based practice in this rare condition. Navigating fertility in this age group remains an ongoing challenge.

Key Learning Points

- Virilisation in premenopausal women warrants thorough evaluation to identify biochemical hyperandrogenism and determine its source.
- OHT is characterised by LH-dependent androgen secretion from ectopic luteinised theca cells in the ovarian stroma.
- A >50% suppression in testosterone following a single dose of a GnRH analogue supports the diagnosis of OHT.
- Ovarian and adrenal venous sampling may assist in confirming the diagnosis when imaging is inconclusive.
- OHT must be distinguished from PCOS and neoplastic causes due to differences in management and prognosis.
- Medical therapy is often effective in premenopausal women however navigating fertility in this age group remains an ongoing challenge.

A Brittle Balance - Navigating Bone Health in Bariatric Surgery (127084)

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We present a case of a young woman with severe clinical obesity and low bone mineral density (BMD) scheduled for sleeve gastrectomy (SG). This case illustrates a complex management dilemma involving skeletal protection, where the intervention itself exacerbates bone loss. Her management was further complicated by mobility restrictions, nutritional deficits, and uncertainty around anti-resorptive therapies in younger women. This case underscores the need for individualized musculoskeletal risk assessment and highlights a critical gap in current bariatric guidelines for bone health in younger, high-risk populations.

Case Report

A 31-year-old pre-menopausal woman with severe clinical obesity (BMI 51.4kg/m^2) was referred for multidisciplinary bariatric surgery assessment. Her obesity developed in the context of chronic immobility following extensive childhood burn injuries, resulting in bilateral forefoot amputations, multiple skin grafts, and ongoing wound care. Her mobility was severely restricted, and she could only walk short distances, relying on a scooter for longer ambulation.

She lost 10kg weight following 1-year treatment with Semaglutide, dietary and behavioural interventions, but continued to have bilateral lower limb lymphoedema, recurrent cellulitis, and chronic, non-healing wounds. Other obesity-associated comorbidities include OSA, MASLD, anxiety and depression. She did not smoke or consume alcohol and had regular menses with menarche at age 13-years.

On examination, she had gross central adiposity and marked bilateral lower limb muscle atrophy. Bilateral foot examination revealed deformities with superficial wounds **(Figure 1)**. Dietary calcium intake was 1300mg/day. Her calcium level was 2.32mmol/L, vitamin D level of 59nmol/L but parathyroid hormone (PTH) level and bone turnover markers were pending at the time of writing. Other laboratory investigations were summarized in **Table 1.** Abdominal ultrasound confirmed hepatomegaly (188mm) and moderate hepatic steatosis. Dual-energy X-ray absorptiometry (DXA) revealed preserved lumbar spine BMD but significantly reduced femoral neck and total hip BMD for her age and sex **(Table 2)**. She had no prior fragility fractures but was at high falls risk.

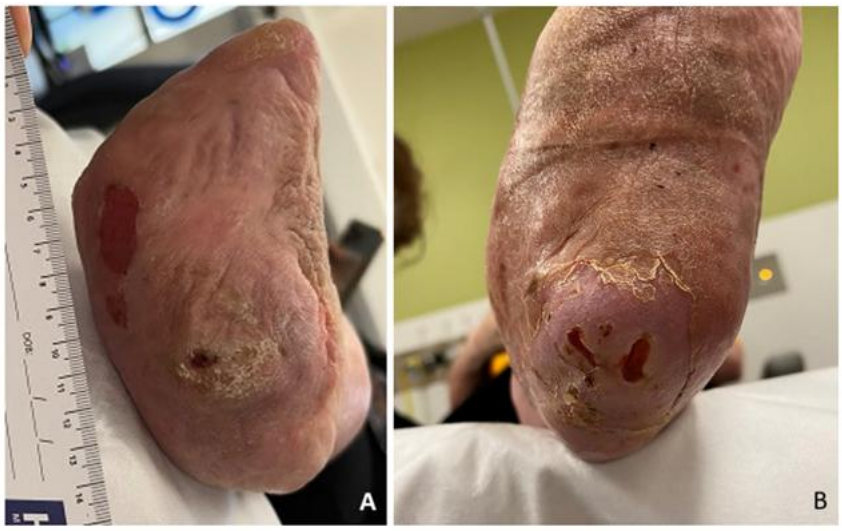

Figure 1. Bilateral forefoot amputation and deformity. (A) Right foot with two superficial wounds over the lateral aspect of foot, and one heel wound with surrounding callus. (B) Left foot with two superficial heel wounds.

Investigation	Results
Glycated haemoglobin (HbA1c)	5.5%
Fasting blood glucose	5.0 mmol/L
Calcium level	2.32 mmol/L
Magnesium level	0.92 mmol/L
Phosphate level	1.07 mmol/L
Creatinine	51 umol/L
eGFR	>90 mL/min/1.73m^2
Vitamin D level	59 nmol/L
Parathyroid hormone (PTH)	Pending
C-terminal telopeptide of type 1 collagen (CTX)	Pending
Procollagen type 1 N-terminal propeptide (P1NP)	Pending
Albumin	36 g/L
Alkaline Phosphatase (ALP)	81 U/L
Thyroid stimulating hormone (TSH)	1.7 mIU/L
Free thyroxine (T4)	14 pmol/L
Free triiodothyronine (T3)	5.0 pmol/L

Table 1. Laboratory investigation results.

Scan Region	Bone mineral density (g/cm^2)	T-score	Z-score
Lumbar spine (L1-L4)	1.294	0.9	-0.2
Femoral neck	0.853	-1.1	-1.9
Total hip	0.869	-1.1	-2.0
Radius 33%	0.714	0.0	0.0

Table 2. Bone mineral density via dual-energy X-ray absorptiometry (DXA).

Following multidisciplinary team discussions, she commenced a supervised, graded physical activity program under physiotherapy guidance at the gym 3-to-4 times per week. Resistance training was however limited by lower limb deformities and chronic wounds, which also precluded hydrotherapy.

Pre-operative nutritional optimisation included oral calcium, vitamin D, and a very low energy diet (VLED) with increased protein targets of 80–100g/day. Because most bone loss occurs in the 12-to 24-month period after bariatric surgery, a single pre-operative dose of intravenous Zoledronic acid was proposed but this was complicated by her pre-menopausal status, and desire for pregnancy 2-years post-surgery.

Discussion

Bariatric procedures consistently reduce BMD and increase PTH and bone turnover markers, independent of vitamin D status [1]. The mechanisms for this are multifaceted, including micro- and macro-nutrient malabsorption, mechanical unloading, muscle loss, increased falls risk, and changes in gut hormones and adipokines secretion [1]. Current evidence consistently demonstrates that bariatric surgery, regardless of procedure type, leads to BMD reductions at the hip and femoral neck [1]. Post-surgery, total hip BMD decreases by 3–5% at 6-months and up to 10.5% by 12-months, with femoral neck BMD declining 5–12% within 1-year [2]. Fracture risk is also increased, even in younger patients undergoing restrictive bariatric procedures. In a 12-year nationwide cohort study, individuals (mean age 31.8-years) who underwent predominantly restrictive surgeries had a 1.21-fold higher overall fracture risk compared to matched controls [3].

Whilst current guidelines recommend routine pre-operative screening for osteoporosis with DXA in post-menopausal women and men above 50-years, screening for pre-menopausal women and men below 50-years were only recommended if there was history of fragility fractures, or risk factors including endocrinopathies, chronic liver, kidney or inflammatory disease, or corticosteroid-use [2,4]. Conversely, the French guidelines do recommend pre-operative BMD screening in all patients undergoing malabsorptive bariatric procedures such as Roux-en-Y gastric bypass (RYGB) or biliopancreatic diversion, but this was not inclusive to restrictive procedures like SG or adjustable gastric banding [5].

These recommendations may overlook high-risk individuals outside the typical screening thresholds. Our patient, who is pre-menopausal without prior fragility fractures, but with chronic immobility and significant falls risk, would not have qualified for pre-operative DXA screening under current recommendations. Nonetheless, she demonstrated significantly low BMD at the femoral neck and total hip. Her reduced bone density was likely multifactorial. She was unlikely to have achieved peak BMD and had ongoing immobility, lack of weight bearing and muscle atrophy. Her risks of bone loss were further compounded by nutritional insufficiency and limited participation in resistance training—each of which is independently associated with adverse skeletal outcomes post-operatively [1]. These skeletal stressors are not explicitly addressed in existing algorithms, underscoring a gap in guideline applicability to patients with complex physical disabilities preparing for bariatric surgery.

The optimal strategy to protect bone following bariatric surgery remains unclear. All major guidelines emphasize the importance of calcium and vitamin D repletion, along with adequate protein intake and resistance training to support bone and muscle health [2,4,5]. Evidence for anti-resorptive therapies is limited and there are no studies evaluating anti-resorptive therapy use specifically in pre-menopausal women undergoing bariatric surgery. Zoledronic acid (ZOL) showed some promise in small studies. A pilot study demonstrated temporary suppression of bone turnover markers and preservation of spinal trabecular volumetric BMD, but not hip BMD, after a single ZOL dose prior to RYGB [6]. The ZABAS trial corroborated ZOL's effect in mitigating spine and hip BMD losses when given pre-operatively in patients undergoing RYGB or SG, although significant bone loss still occurred at the hip [7]. Risedronate may also attenuate BMD loss after SG. The WE RISE pilot trial reported improvements in lumbar spine and femoral neck BMD, though hip BMD was still reduced [8]. For Denosumab, preliminary results from a randomized controlled trial revealed preservation of BMD at the spine, femoral neck, and hip in older adults undergoing RYGB or SG. These findings suggest Denosumab may be a promising alternative, though full publication of the results is pending [9].

Current guidelines differ in recommendations for anti-osteoporosis therapy following bariatric surgery. The American Society for Metabolic and Bariatric Surgery (ASMBS) position statement do not address the use of anti-resorptive therapies [4]. The French guidelines recommend intravenous ZOL as first-line therapy for patients with fragility fractures, or those at risk of falls with a T-score < –2.0, or with non-severe fractures and T-score < –1.0 [5]. The European Calcified Tissue Society (ECTS) recommends ZOL as first-line therapy for post-menopausal women and men over 50-years with fragility fractures, or those with a T-score < –2.0, and Denosumab considered as second-line [2]. However, for pre-menopausal women and men under 50-years, none of the major guidelines make definitive pharmacologic recommendations, and consistently defer to specialist referral, highlighting a significant gap in evidence and guidance for this

subgroup. Furthermore, although it was recommended that bisphosphonate therapy should be avoided in women planning pregnancy within the next 12-months, the optimal interval between treatment and conception remains uncertain [10].

Conclusion/Key points

- Current guidelines may overlook high-risk bariatric candidates who fall outside traditional DXA screening criteria, such as younger patients with significant immobility or physical disability.
- Zoledronic acid and Denosumab potentially attenuates BMD loss post-bariatric surgery in small studies. However, in pre-menopausal women, applicability remains uncertain and current guidelines defer to specialist input rather than offer definitive recommendations
- Multidisciplinary care is essential in managing skeletal risk in bariatric candidates with complex physical comorbidities.

1. Mele C, Caputo M, Ferrero A, et al. Bone Response to Weight Loss Following Bariatric Surgery. Front Endocrinol (Lausanne). 2022;13:921353. Published 2022 Jul 7. doi:10.3389/fendo.2022.921353
2. Paccou J, Tsourdi E, Meier C, et al. Bariatric surgery and skeletal health: A narrative review and position statement for management by the European Calcified Tissue Society (ECTS). Bone. 2022;154:116236. doi:10.1016/j.bone.2021.116236
3. Lu CW, Chang YK, Chang HH, et al. Fracture Risk After Bariatric Surgery: A 12-Year Nationwide Cohort Study. Medicine (Baltimore). 2015;94(48):e2087. doi:10.1097/MD.0000000000002087
4. Kim J, Nimeri A, Khorgami Z, et al. Metabolic bone changes after bariatric surgery: 2020 update, American Society for Metabolic and Bariatric Surgery Clinical Issues Committee position statement. Surg Obes Relat Dis. 2021;17(1):1-8. doi:10.1016/j.soard.2020.09.031
5. Paccou J, Genser L, Lespessailles É, et al. French recommendations on the prevention and treatment of osteoporosis secondary to bariatric surgery. Joint Bone Spine. 2022;89(6):105443. doi:10.1016/j.jbspin.2022.105443
6. Liu Y, Côté MM, Cheney MC, et al. Zoledronic acid for prevention of bone loss in patients receiving bariatric surgery. Bone Rep. 2021;14:100760. Published 2021 Mar 2. doi:10.1016/j.bonr.2021.100760
7. Gam S, Lysdahlgaard S, Gram B, et al. Zoledronic acid increases spine bone mass and prevents hip bone loss after bariatric surgery: a randomized placebo-

controlled study. Obesity (Silver Spring). 2025;33(4):659-670. doi:10.1002/oby.24214

8. Beavers KM, Beavers DP, Fernandez AZ, et al. Risedronate use to attenuate bone loss following sleeve gastrectomy: Results from a pilot randomized controlled trial. Clin Obes. 2021;11(6):e12487. doi:10.1111/cob.12487
9. Schafer AL. Denosumab increases bone mass in post-menopausal women and older men undergoing bariatric surgery: a randomized controlled trial. Annual meeting. J Bone Miner Res. 2024.
10. Pepe J, Body JJ, Hadji P, et al. Osteoporosis in Premenopausal Women: A Clinical Narrative Review by the ECTS and the IOF [published correction appears in J Clin Endocrinol Metab. 2021 Mar 25;106(4):e1931. doi: 10.1210/clinem/dgaa947.]. J Clin Endocrinol Metab. 2020;105(8):dgaa306. doi:10.1210/clinem/dgaa306

Riding the cortisol coaster: a case of cyclical Cushing's syndrome unmasked during obesity workup (127128)

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Case Summary

A 47-year-old woman was referred for multidisciplinary bariatric surgery evaluation. Her weight was 101kg (BMI 41 kg/m^2, class III obesity). Comorbidities included type 2 diabetes, hypertension, polycystic ovarian syndrome (PCOS), dyslipidaemia, obstructive sleep apnoea (on CPAP), depression, anxiety and familial cavernoma syndrome. Interestingly in 2014, she had hyperprolactinaemia (prolactin 920 mIU/L; RR < 370) and a 10×8 mm pituitary adenoma. Cabergoline was commenced to assist with conception of her third child, which was complicated by intrauterine growth restriction and pre-eclampsia.

Her medications included atorvastatin, fenofibrate, ezetimibe, ramipril, metformin, Ryzodeg, empagliflozin, semaglutide, and venlafaxine. Following lifestyle and dietary intervention, she achieved 12kg of weight loss.

Initial biochemical workup revealed elevated ACTH (125 ng/L) and cortisol (590 nmol/L), with raised 24-hour urinary free cortisol (UFC: 321 nmol/day) and a non-suppressible 1mg dexamethasone suppression test (DST: 335 nmol/L). Late-night salivary cortisol (LNSC), collected during the UFC period, was normal (9 nmol/L), suggesting diurnal rhythm was maintained. BMD showed osteopaenia, and liver ultrasound demonstrated metabolic-associated steatotic liver disease.

She reported episodic sweating, fluctuating glycaemia and labile mood. Examination revealed moon facies, dorsocervical fat pad, wide red striae, and proximal myopathy—features consistent with Cushing's syndrome (CS).

The pituitary adenoma was unchanged on repeat MRI (Figure 1). CT showed bulky calcified adrenals without discrete lesions. Given discordant results and intermittent symptoms, cyclical ACTH-dependent CS was suspected.

Clinical challenges with our case

Serial UFCs were initially pursued, assuming diurnal rhythm was intact (Figure 2). Multiple inferior petrosal sinus sampling (IPSS) attempts failed due to phase switching. Retrospective review revealed that the original paired UFC and LNSC (elevated UFC, normal LNSC) were actually concordant, collected during an 'off' phase. LC-MS/MS UFC metabolite analysis identified elevated 20α-dihydrocortisone during true 'on'

phases, even when UFC collection errors occured (Table 1). This highlighted novel insights into cortisol metabolism pathways during hypercortisolism.

LNSC was then used to detect 'on' phases. Ultimately, IPSS was performed during a biochemically confirmed 'on' phase (UFC 178 nmol/24h, elevated LNSC), confirming a central ACTH source. A PET scan was negative for ectopic sources. She is now awaiting pituitary surgery.

Discussion

Recognising Secondary Obesity

Secondary obesity is uncommon but important to consider, particularly before bariatric surgery. Endocrine causes include CS, hypothyroidism, PCOS, growth hormone deficiency and hypothalamic pathology (1). Identifying and treating underlying conditions can optimise weight loss outcomes and avoid inappropriate surgery.

Relevance to Bariatric Surgery

In patients considered for bariatric surgery, CS may be under-recognised due to overlapping features with obesity and metabolic syndrome. A recent case series found 65% of patients with CS were diagnosed only after bariatric surgery (2). Delayed diagnosis carries significant surgical risk: impaired wound healing, venous thromboembolism, increased infection rates, post-surgical bone loss and muscle atrophy (2).

Cyclical Cushing's Syndrome

Cyclical CS is a rare form of endogenous hypercortisolism characterised by intermittent peaks and troughs in cortisol levels. These cycles can range from days to years. Approximately 14–18% of CS cases are cyclical, with pituitary adenomas accounting for ~80%, followed by ectopic ACTH and adrenal sources (3). There is no universal diagnostic definition, but recent proposals suggest at least two cortisol peaks and one trough to meet criteria for cyclicity(4). Symptoms may fluctuate or persist between phases depending on cycle frequency.

Diagnosis is complicated by episodic cortisol excess. UFC and LNSC are preferred screening tools, requiring repeated sampling. Hair cortisol may aid long-term exposure assessment (such an assay is in development locally). ACTH levels are similarly variable and should be interpreted cautiously. During peak phases, ACTH may be elevated in ACTH-dependent disease; however, normal or low levels may be seen during troughs (5).

IPSS is the gold standard for localisation and must be timed during a biochemically confirmed 'on' phase to maintain diagnostic accuracy. Performing IPSS during an 'off'

phase risks false results and can misdirect surgery (5). In our case, IPSS was delayed due to phase shifts, highlighting the need for flexible, monitored planning.

Interpreting Biochemical Testing in Cyclical Cushing's Syndrome

Biochemical testing in cyclical CS requires nuanced interpretation given the episodic nature of cortisol excess and assays limitations.

24-hour UFC is a standard screening tool, reflecting unbound cortisol filtered by the kidneys. However, its diagnostic performance can be compromised in cyclical CS and by several assay-related factors (6):

- Analytical interference: Most immunoassays cross-react with cortisol metabolites such as tetrahydrocortisol (THF) and tetrahydrocortisone (THE), leading to falsely elevated UFC results, particularly in individuals with altered or enhanced cortisol metabolism. Tandem mass spectrometry (LC-MS/MS) provides greater specificity and is emerging as a superior modality in complex cases, however there are pitfalls even with analysis. In South Australia at SA Pathology, it was identified that 20α/20β-dihydrocortisone caused interference on LC-MS/MS, falsely elevating UFC due to the metabolites having the same molecular weight and similar structure to cortisol (Figure 3). New methods now isolate cortisol accurately.
- Intra-individual variability: UFC values fluctuate even in stable CS, and this variability is amplified in cyclical disease, necessitating multiple timed collections.
- Physiological factors: High fluid intake, incomplete collections, and renal impairment reduce accuracy.

LNSC detects loss of diurnal cortisol suppression and is especially valuable in cyclical CS (6). It is minimally invasive, patient-friendly, and amenable to serial home sampling. If measured by LC-MS/MS, LNSCs are also susceptible to 20α/20β-dihydrocortisone interference (7).

The 1mg DST, although widely used, is less reliable in cyclical CS. Cortisol suppression may occur during a trough phase. Furthermore, dexamethasone absorption or metabolism variability (e.g. in patients taking enzyme-inducing medications or with obesity) can also cause false-positive results (6). SA Pathology very recently began measuring serum dexamethasone concentration alongside the 1mg DST. This allows confirmation of adequate absorption and plasma levels at the time of testing, reducing false interpretations due to pharmacokinetic variability. This practice is particularly useful in patients with suspected non-suppression or borderline results. This was not available for our case.

Cortisol Metabolism

Cortisol is inactivated to cortisone by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) and reactivated by 11β-HSD1 (8). It is further metabolised by 5α-/5β-reductases into tetrahydro-metabolites (THF, allo-THF, THE). Obesity or hepatic dysfunction may skew this, affecting UFC assays and interpretation. Our case identified that 20α-dihydrocortisone, a metabolite not routinely included in cortisol metabolism pathway depictions, was markedly elevated during hypercortisoaemic states. This metabolite has not previously been described in this context and may represent a novel biomarker (Figure 3).

Accurate diagnosis in cyclical CS depends on test timing, serial sampling, analytical method quality and clinical context. Our case offers early insights into ACTH-driven cortisol metabolism, with elevated 20α-dihydrocortisone as a potential biomarker.

Take Home Messages

1. Consider secondary causes, including Cushing's syndrome, in obesity assessment.
2. Cyclical Cushing's syndrome presents diagnostic challenges; a single negative test does not exclude the condition; serial testing is required.
3. Correct sample collection and robust lab analysis are vital for diagnostic accuracy.
4. Confirming an 'on' phase is essential before localisation testing (IPSS).
5. Cortisol metabolites may offer insights into cortisol metabolism in hypercortisolaemic states and aid diagnosis.

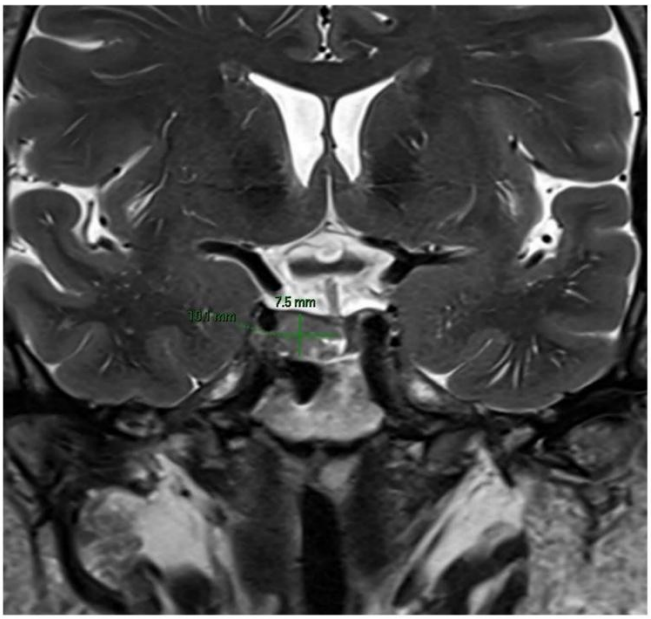
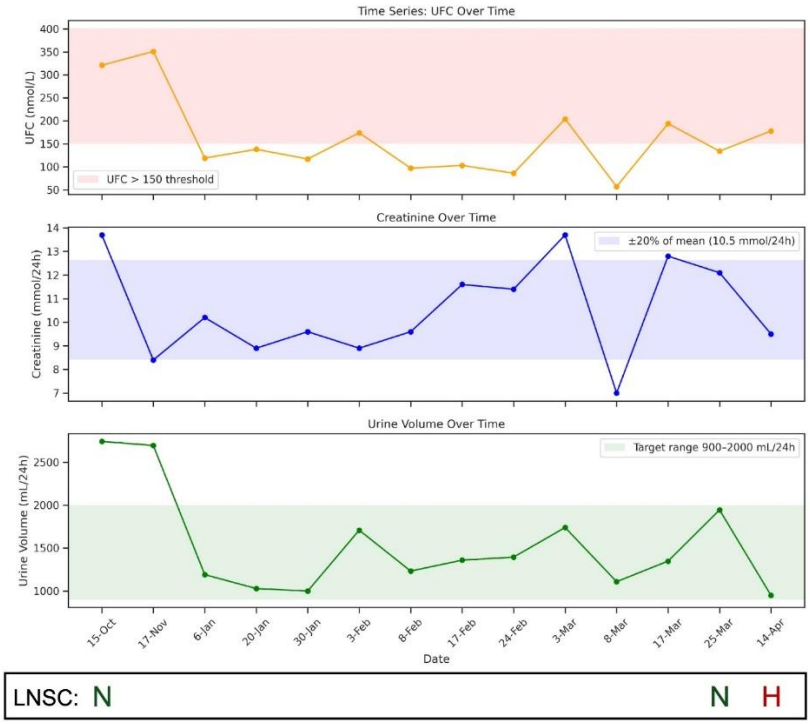


Figure 1: MRI pituitary (2025)
10x8mm right-sided pituitary adenoma



LNSC: N N H

Figure 2: Urinary free cortisol (UFC) over time
With concurrent late night salivary cortisol (LNSC) results: N = normal, H = elevated

Date	Volume (ml)	20α (nmol/L)	20β (nmol/L)	α/β ratio	24h cortisol (nmol/24h)	24h cortisone (nmol/24h)	Creatinine excretion (mmol/24h)	Cyclical CS Phase
15/10/24	2744	98	33	2.97	321	895	13.7	Off*
17/11/24	2697	68	16	4.25	351	844	8.4	On
3/2/25	1709	100	20	5.00	174	299	8.9	On
8/2/25	1232	39	22	1.77	97	241	9.6	Off
3/3/25	1740	66	39	1.69	204	433	13.7	Off*
8/3/25	1108	28	16	1.75	57	156	7.0	Off
14/4/25	948	244	32	7.63	178	193	9.5	On

Table 1: Cortisol and metabolite levels in 24-hour urine samples
20α = 20α-dihydrocortisone, 20β = 20β-dihydrocortisone. CS= Cushing's syndrome. Red = high results
*Reported as positive UFC results; however, discordant 20α-dihydrocortisone levels along with high urinary volumes or creatinine excretion confirmed these UFCs were false-positives.

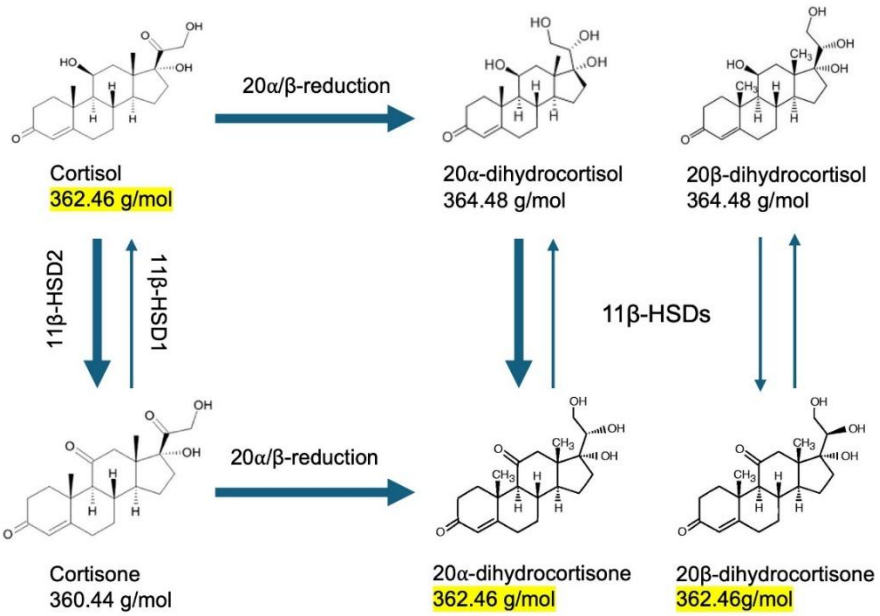


Figure 3: 20α/β-reduction metabolism pathways of cortisol
Cortisol has the same molecular weight as 20α-dihydrocortisone and 20β-dihydrocortisone (highlighted). HSD = hydroxysteroid dehydrogenase.

1. Rubino F, Cummings DE, Eckel RH, Cohen RV, Wilding JPH, Brown WA, et al. Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol. 2025;13(3):221-62.
2. Ahmed SF, Mahmood SW, Ismaeil DA, Baba HO, Salih KM, Tahir SH, et al. Challenges of Cushing's syndrome and bariatric surgery: a case report with literature review. Journal of Surgical Case Reports. 2025;2025(6).
3. Gadelha M, Gatto F, Wildemberg LE, Fleseriu M. Cushing's syndrome. Lancet. 2023;402(10418):2237-52.
4. Nowak E, Vogel F, Albani A, Braun L, Rubinstein G, Zopp S, et al. Diagnostic challenges in cyclic Cushing's syndrome: a systematic review. Lancet Diabetes Endocrinol. 2023;11(8):593-606.

5. Ferriere A, Nunes M-L, Tabarin A. Approach to the Patient With Cyclical Cushing Syndrome. The Journal of Clinical Endocrinology & Metabolism. 2024.
6. Nieman LK, Biller BMK, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2008;93(5):1526-40.
7. Israelsson M, Brattsand R, Brattsand G. 20α- and 20β-dihydrocortisone may interfere in LC-MS/MS determination of cortisol in saliva and urine. Ann Clin Biochem. 2018;55(3):341-7.
8. Schiffer L, Barnard L, Baranowski ES, Gilligan LC, Taylor AE, Arlt W, et al. Human steroid biosynthesis, metabolism and excretion are differentially reflected by serum and urine steroid metabolomes: A comprehensive review. J Steroid Biochem Mol Biol. 2019;194:105439.

Multisystem mystery a case of erdheim chester disease (127024)

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Case Summary

We present a case of a 37-year-old male from Samoa who was transferred for further evaluation of a three-week history of bilateral proptosis, conjunctival injection, intermittent subject fevers, and two-days of declining visual acuity of his left eye. Past medical history consisted of hypertension managed with perindopril, with no history of malignancy or autoimmune disease.

On presentation, examination revealed a visual acuity was 6/6 (right eye) and 6/9 (left eye), proptosis was measured at 25mm (right) and 28mm (left), with unrestricted eye movements. Due to concern for orbital compartment syndrome, he underwent a lateral canthotomy and cantholysis. Further investigation with cerebral imaging (Computed Tomography Scan [CT] and Magnetic Resonance Imaging [MRI]) revealed bilateral orbital masses with features suggestive of an infiltrative process. The patient's visual acuity deteriorated further overnight and on the advice of ophthalmology was commenced on 3 days of intravenous methylprednisolone which stabilised his vision.

To further determine the extent of the disease, the patient underwent a whole-body CT. This revealed perivascular soft tissue thickening around the abdominal aorta, superior mesenteric artery branches and bilateral carotid bifurcations, and extensive retroperitoneal and mesenteric soft tissue infiltration involving both renal hila with consequent severe bilateral hydronephrosis.

In the setting of bilateral hydronephrosis and routine bloods indicating an acute kidney injury (estimated Glomerular Filtration Rate 33 mL/min/1.73 m^2, with a baseline >90 mL/min/1.73 m^2), the patient underwent bilateral ureteric stent insertion. Post decompression, he developed marked polyuria, initially attributed to post-obstructive diuresis. However, persistent polyuria (2000mL per hour) and the development of new hypernatraemia (serum sodium 149 mmol/L) with urine sodium 43 mmol/L and urine osmolality 105 mOsm/kg, prompted concern for arginine vasopressin deficiency (AVP-D) or resistance (AVP-R). Notably, previous MRI imaging showed no hypothalamic or pituitary abnormalities however this was not a dedicated pituitary sequence. A trial of 1 mcg subcutaneous desmopressin resulted in a decline in urine output and normalisation of sodium, therefore the patient was continued on oral desmopressin, initially dosed at 100 mcg four times daily, with strict fluid and sodium monitoring.

Further history at this time found that the patient had been drinking up to 24L per day with constant thirst and associated polyuria for 12 months preceding this admission, resulting in concern for AVP-D or AVP-R, possibly in the setting of an infiltrative disease

process. Desmopressin therapy was further titrated in response to urine output, fluid balance and sodium levels, initially using oral formulations. There was difficulty titrating his desmopressin during his inpatient admission with ongoing polyuria, fluctuating sodium and the development of a gastroenteritis illness while an inpatient, further complicating his fluid balance (Figure 1). When stable, he was transitioned to an intranasal spray 20 mcg intranasal desmopressin twice daily.

To determine the aetiology of the extensive soft tissue deposits, the patient underwent paraaortic soft tissue density core biopsy. However, this biopsy revealed reactive changes only, and resultantly, a peri-orbital biopsy was conducted which revealed lipid-laden foamy histiocytes with surrounding fibrosis, strongly positive for BRAFV600E and a diagnosis of Erdheim-Chester Disease was confirmed (Figure 2). Haematology was involved in the management process and targeted therapy with BRAF inhibitors (e.g. vemurafenib) was considered, subject to funding and availability.

A pituitary panel showed parameters all within normal limits except for cortisol level which was in low in the setting of concurrent treatment with methylprednisolone and a new testosterone deficiency with normal LH and FSH (Table 1). A dedicated MRI pituitary was performed which revealed an empty sella and absence of the normal post pituitary signal. Discussions were held with the patient regarding his testosterone deficiency and he was commenced on Human Chorionic Gonadotrophin injections and discharged on 1500 units twice weekly until fertility completed with the plan to then transition to testosterone replacement.

Discussion

Erdheim-Chester Disease (ECD) is a rare, clonal, non-Langerhans-cell histiocytosis. It was first described in 1930, and as of 2020 only 1500 cases have been reported.[1] ECD is derived from mononuclear phagocyte lineage, typically associated with somatic mutation in the BRAF gene (particularly the V600E mutation) or other components of the Mitogen-activated protein kinase (MAPK) signalling pathway.[2] These mutations lead to cell proliferation and survival, resulting in an overproduction of histiocytes, histiocytic infiltration and fibrosis of multiple organ systems. While ECD can occur in childhood, it is extremely rare with less than 20 reported cases.[3] ECD is more common in adults with a 3:1 male predominance.[4]

The skeletal system is most frequently affected, with multifocal sclerotic lesions of long bones, but histiocytic infiltration of extra-osseous tissues may occur and more than half of cases of ECD result in a multi-system disease including cardiovascular system, central nervous system, retroperitoneum, skin, orbits and testicular infiltration.[4] The cardiovascular and respiratory systems are commonly involved and there may be pericardial, peri-aortic, pleural and coronary artery infiltration.[4] Additionally, ECD can manifest with retro-orbital lesions resulting in bilateral and symmetrical exophthalmos,

retroperitoneal fibrosis complicated by bilateral hydronephrosis, and endocrinopathies.[5] The most common endocrinopathy is AVP-D occurring in 25% of patients due to infiltration of the hypothalamic or pituitary, and can often be the first manifestation of ECD.[6] This can also lead to other hormonal disruptions such as hyperprolactinaemia or gonadotropin deficiency.[6]

The aetiology of ECD is unknown, however it is hypothesised to involve an exaggerated T-helper type 1 (Th1) immune response. In one study, untreated ECD patients demonstrated Th1-predominant inflammation with elevated serum levels of interleukin-6, interferon-α, and monocyte chemoattractant protein-1.[7] Further histological studies have confirmed the presence of interferon-γ-expressing Th1 lymphocytes within ECD lesions.[8] To date, no infectious aetiology or other environmental cause for ECD has been identified, and there is no evidence that ECD is inherited.

Diagnosis of ECD is relies on distinctive histopathologic findings. Biopsy specimens typically demonstrate foamy or lipid-laden $CD68^{+}CD1a^{-}$ histiocytes admixed with reactive inflammatory cells and/or fibrosis.[1] Immunohistochemistry demonstrates CD68-positive, CD1a-negative histiocytes, which distinguishes ECD from Langerhans cell histiocytosis.[9] However, unclear biopsy, delayed biopsy or erroneous diagnosis can make the diagnosis of EDC challenging.

There is currently no definitive cure for ECD however the discovery of MAPK/ERK mutations has led to targeted therapeutic treatments. Two targeted agents have been approved by the United States Food and Drug Administration for the treatment of ECD including Vemurafenib and cobimetinib.[10] Vemurafenib is a selective BRAF inhibitor and cobimetinib is a MEK1/2 inhibitor. Recent studies have shown that targeted therapies, particularly those aimed at BRAF and MEK pathway, have been effective in preventing disease progression. This has highlighted the importance of molecular testing in suspected cases.[1]

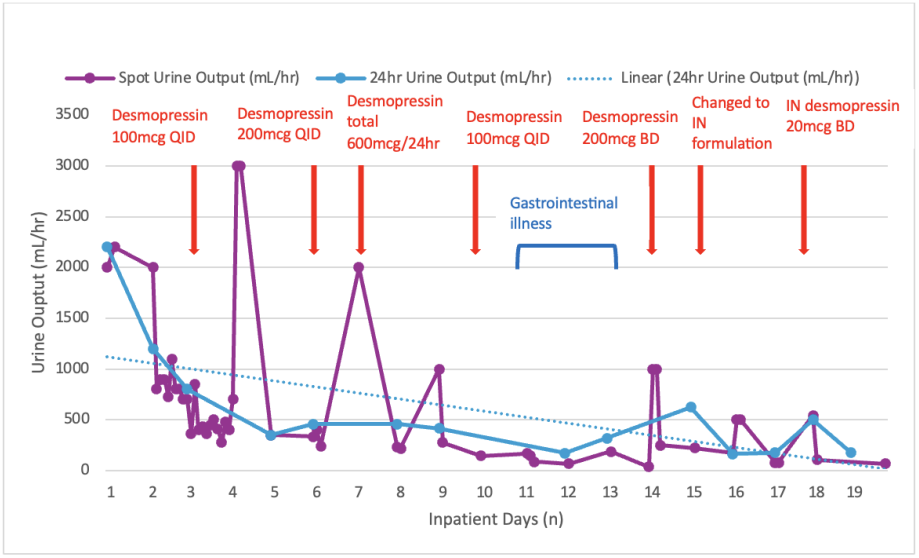
The incidence of ECD is expected to increase with increasing awareness and improved diagnostics, and with the advent of targeted therapies this will hopefully lead to improved prognosis for individuals with ECD.[1]

Learning objectives

1. Recognising the rare causes of AVP-D, particularly when AVP-D can often be the first manifestation of infiltrative processes.
2. Appreciating the importance of early molecular testing. Not all ECD patients have BRAF V600E mutations, other pathways may be involved and broader genomic profiling to guide therapy may be required.
3. Exploring the role of targeted therapies in histiocytic disorders.

4. While targeted therapies have improved outcomes, long-term data on efficacy, relapse rates, and toxicity are limited.

Figure 1. Daily 24-hour vs Spot Urine Output Over Time



QID: four times a day; BD: twice a day; hr: hour; IN: intranasal

Figure 2. Histopathology consistent with a diagnosis of Erdheim Chester Disease

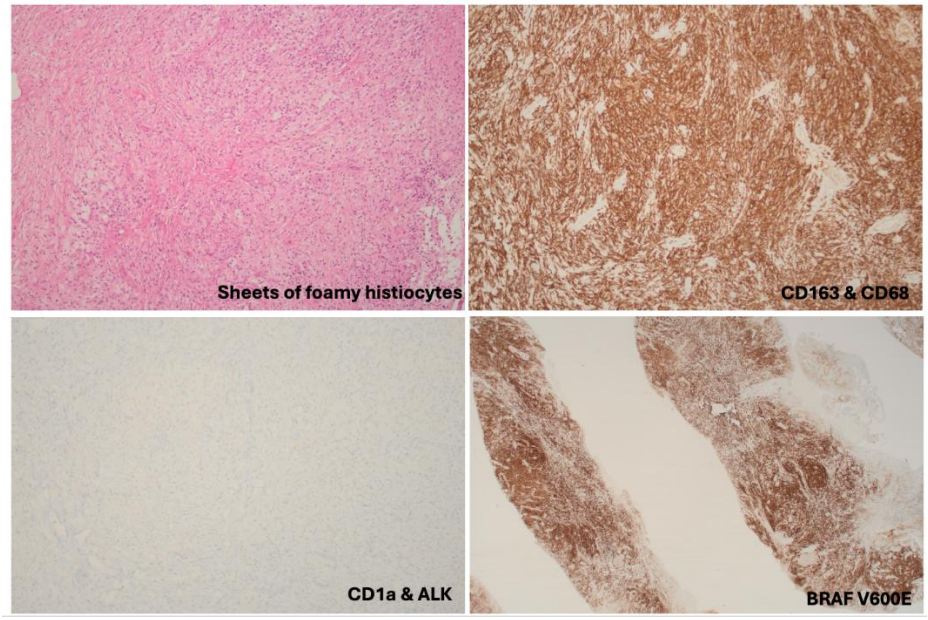


Table 1. Pituitary Panel

Hormone	Result	Reference Range
Cortisol	<28	100-535 nmol/L
TSH	0.74	0.35-4.94 mU/L
fT4	3.1	9.0-19.0 pmol/L
fT3	16	3.2-5.3 pmol/L
Prolactin	284	73-410 mU/L
LH	7.4	0.6-12.0 unit/L
FSH	5.6	1.0-12.0 unit/L
Testosterone	2.4	8.0-20.0 nmol/L
IGF-1	20.6	13.8-30.9 nmol/L

TSH: Thyroid-Stimulating Hormone; fT4: free thyroxine; fT3: free triiodothyronine; LH: Luteinising Hormone; FSH: Follicle-Stimulating Hormone; IGF-1: Insulin-like Growth Factor 1

1. Haroche J, Cohen-Aubart F, Amoura Z. Erdheim-Chester disease. Blood. 2020;135(16):1311-8.
2. Milne P, Bigley V, Bacon CM, Néel A, McGovern N, Bomken S, et al. Hematopoietic origin of Langerhans cell histiocytosis and Erdheim-Chester disease in adults. Blood. 2017;130(2):167-75.
3. Tran TA, Fabre M, Pariente D, Craiu I, Haroche J, Charlotte F, et al. Erdheim-Chester disease in childhood: a challenging diagnosis and treatment. J Pediatr Hematol Oncol. 2009;31(10):782-6.
4. Cohen-Aubart F, Emile JF, Carrat F, Helias-Rodzewicz Z, Taly V, Charlotte F, et al. Phenotypes and survival in Erdheim-Chester disease: Results from a 165-patient cohort. Am J Hematol. 2018;93(5):E114-e7.
5. Yelfimov DA, Lightner DJ, Tollefson MK. Urologic manifestations of Erdheim-Chester disease. Urology. 2014;84(1):218-21.
6. Courtillot C, Laugier Robiolle S, Cohen Aubart F, Leban M, Renard-Penna R, Drier A, et al. Endocrine Manifestations in a Monocentric Cohort of 64 Patients With Erdheim-Chester Disease. J Clin Endocrinol Metab. 2016;101(1):305-13.
7. Arnaud L, Gorochov G, Charlotte F, Lvovschi V, Parizot C, Larsen M, et al. Systemic perturbation of cytokine and chemokine networks in Erdheim-Chester disease: a single-center series of 37 patients. Blood. 2011;117(10):2783-90.
8. Stoppacciaro A, Ferrarini M, Salmaggi C, Colarossi C, Praderio L, Tresoldi M, et al. Immunohistochemical evidence of a cytokine and chemokine network in three patients with Erdheim-Chester disease: implications for pathogenesis. Arthritis Rheum. 2006;54(12):4018-22.
9. Mazor RD, Manevich-Mazor M, Shoenfeld Y. Erdheim-Chester Disease: a comprehensive review of the literature. Orphanet J Rare Dis. 2013;8:137.
10. Gulyás A, Pinczés LI, Mátyus J, Végh E, Bedekovics J, Tóth J, et al. Case report: Targeted treatment strategies for Erdheim-Chester disease. Front Oncol. 2024;14:1305518.

When an adrenalectomy improves glycaemia (127256)

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Mr SB is a 75-year-old male of Indian ethnicity with a background of longstanding type 2 diabetes. He presented with worsening glycaemia requiring escalation in his diabetes management, with associated fatigue and unintentional weight loss of 10 kg over the past several years. A type 1 diabetes screen was unremarkable, and a computed tomography (CT) of his abdomen was performed to assess for pancreatic pathology. Unexpectedly, large bilateral adrenal nodules measuring 4.6 cm on the right (40 HU, 16% washout) and two adrenal nodules on the left measuring 1.2 cm (32 HU, 16% washout) and 2 cm (37 HU, 2% washout) were detected (Figure 1A). Imaging characteristics were not consistent with an adenoma, and a subsequent fluorodeoxyglucose-positron emission tomography (FDG-PET) revealed intense uptake bilaterally in the adrenals without significant uptake elsewhere (Figure 1B). With concerns for primary adrenal malignancy, the patient underwent a right sided adrenalectomy after consultation at a surgical-endocrine multidisciplinary meeting. A hormone panel pre-operatively was consistent with a non-functioning adrenal lesion (Table 1). An isolated elevation in 3-methoxytyramine was felt to be secondary to dopamine agonist therapy for his Parkinson's disease.

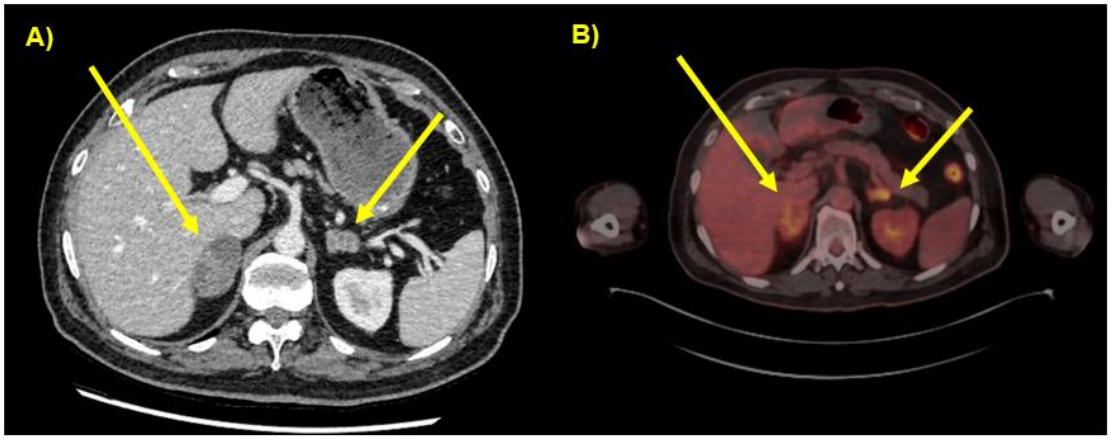

Figure 1. A) CT abdomen axial slice with arrows demonstrating bilateral adrenal masses. These demonstrated elevated Hounsfield Units and delayed contrast washout. B) FDG-PET axial slice with arrows demonstrating avid uptake in the adrenals bilaterally (SUVmax 5.3 right, 6.7 left).

Hormone	Result	Reference range
Cortisol (baseline; 11.20 am)	347 nmol/L	170-500 nmol/L
ACTH (baseline; 11.20 am)	9.3 pmol/L	1.6-13.9 pmol/L
Cortisol (post-dexamethasone 1 mg)	42 nmol/L	<50 nmol/L
Testosterone	12.1 nmol/L	6.7-25.7 nmol/L
DHEAS	0.6 umol/L	0.4-3.3 umol/L
Androstenedione	1.0 nmol/L	nmol/L
17-hydroxyprogesterone	1.9 nmol/L	1.7-6.0 nmol/L
Oestradiol	80 pmol/L	18-159 pmol/L
Aldosterone	545 pmol/L	60-980 pmol/L
Renin activity	1919 fmol/L/sec	130-2350 fmol/L/sec
Metanephrines (plasma)	60	<447
Normetanephrines (plasma)	744	<1080
3-methoxytyramine (plasma)	1937	<100

Histopathology of the right adrenal gland revealed extensive necrotising granulomatous inflammation with intracellular yeast-like organisms with morphological features suggestive of *Histoplasma*. *Histoplasma* serology and blood culture were negative, and a fungal culture of the adrenal specimen is ongoing. Immunosuppression screen was negative. Itraconazole was commenced under guidance of Infectious Diseases team. Post-operative cortisol levels have been normal (498 nmol/L). Glycaemia also significantly improved with treatment for histoplasmosis, with the patient being able to cease insulin therapy completely.

In retrospect, our patient had experienced episodes of systemic symptoms over the past two decades of unclear aetiology despite extensive investigations, and these events may have reflected relapsing-remitting histoplasmosis. High risk exposures in his travel history included his birthplace in India, South Africa, as well as caving activities on the east coast of Australia.

Discussion

Histoplasma capsulatum is a dimorphic fungus that is a rare cause for adrenal masses and primary adrenal insufficiency, representing <1% of adrenal lesions [1]. Infection occurs after inhalation of spores from soil or bat/bird guano, and histoplasmosis can result in localised respiratory disease, or chronic disseminated disease which presents with systemic features and possible multi-organ involvement. 95% of patients after exposure are asymptomatic, and chronic disseminated disease may present years to decades later. Rarely, there may be long asymptomatic periods that are interrupted by symptomatic relapses [2].

Adrenal involvement occurs in 80% of chronic disseminated cases and the adrenals may be the only organ involved in half of cases. Tropism for the adrenal gland by *Histoplasma* appears to be due to cortisol production in the adrenal cortex and a relative absence of reticuloendothelial phagocytes [3]. Bilateral adrenal enlargement is common with adrenal histoplasmosis, although adrenal insufficiency due to *Histoplasma* is not universal, with estimates ranging from 40% [4], to 85% [5] in an Australian review of cases. Higher rates of insufficiency in Australia have been hypothesised to be due to delays in diagnosis. Adrenal insufficiency is irreversible, and can occur during treatment in up to 30%, which is not thought to be related to the effects of itraconazole at the therapeutic doses used [6].

Histoplasma is endemic in many countries across the Americas, southern Africa, and South-East Asia, including the Indian subcontinent [2]. In Australia, locally acquired cases have been observed in most states, although the majority have occurred on the eastern coast from northern New South Wales to Queensland [7]. Traditional immunosuppressive factors such as human immunodeficiency virus, transplant patients, and use of TNF-α inhibitors have been associated with an increased risk for developing acute and chronic histoplasmosis. Diabetes is increasingly recognised as a risk factor for developing chronic disseminated histoplasmosis, and has been over-represented in case series of adrenal histoplasmosis [3, 8].

Diagnostic work up and management

Diagnosis of adrenal histoplasmosis can be challenging, particularly as cases of isolated adrenal infection may mimic primary adrenal malignancy which needs to be investigated in a time-sensitive manner. Fine needle aspiration or adrenal biopsy can be considered for adrenal masses suspicious for extra-adrenal malignancy, lymphoma, sarcoma, or infiltrative or infectious processes [9], although a biopsy should be avoided in lesions likely to represent phaeochromocytoma or adrenocortical carcinoma. Case series in countries with higher endemicity of *Histoplasma* have shown successful diagnoses of histoplasmosis through adrenal biopsy, thereby obviating the need for adrenal surgery [3, 8]. However, how this practice may translate to Australia where the pre-test probability of histoplasmosis is lower remains unclear. Notably, bilateral primary adrenal malignancy (albeit rare) remains a more prevalent diagnosis than adrenal histoplasmosis [1].

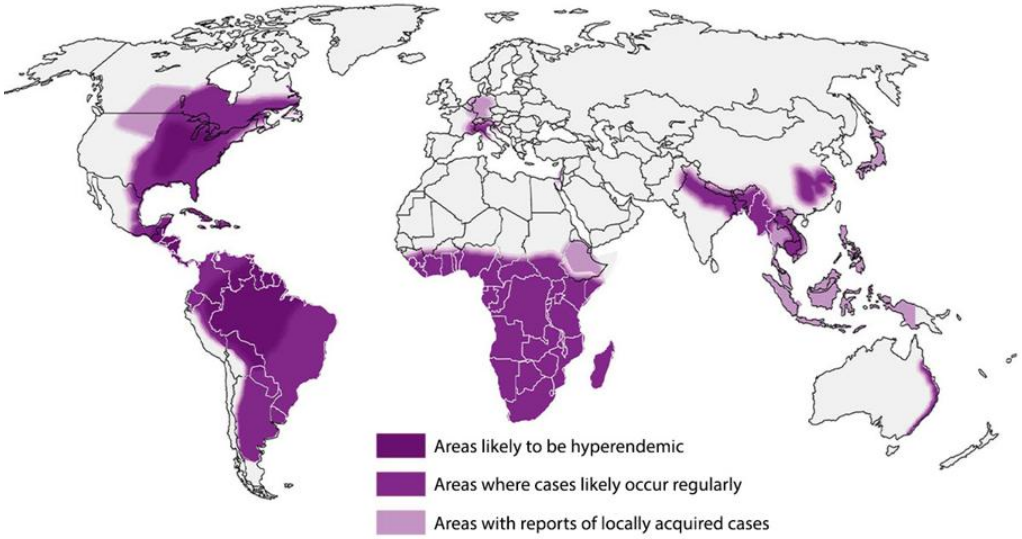

Figure 2. Locations of documented Histoplasma infection [2]

Serology to demonstrate previous exposure may help support a diagnosis of histoplasmosis, with rates of diagnostic sensitivity reported up to 75% [10]. However, sensitivity may be lower in immunocompromised patients, whilst sensitivity has been shown to be as low as 28% in Australia [7]. The cause for its low sensitivity in Australia remains unclear. Antigen testing of serum and/or urine has been shown to reach sensitivities of 75% in immunocompetent patients and 95% in immunocompromised patients [11], although availability is scarce with only one centre in the United States currently offering this test. Fungal blood cultures have a 65% sensitivity for histoplasmosis [10], although rates of positive blood culture in isolated adrenal histoplasmosis are unknown.

Imaging studies do not reliably differentiate *Histoplasma* from other causes of bilateral adrenal masses, with CT often demonstrating large nodules with central hypodensity

and peripheral rim enhancement [3]. Functional imaging studies such as FDG-PET can confirm the extent of the disease, but are unable to differentiate between neoplasms and infection.

Management for histoplasmosis is primarily with itraconazole for at least one year, although amphotericin B should be used as the initial agent in severe cases. Monitoring for treatment response is difficult due to issues with accessibility of antigen testing. Rather, clinical symptoms alongside serial imaging and evidence of therapeutic itraconazole levels can be used as surrogates of treatment response.

Take home messages

- Adrenal histoplasmosis should be considered as a differential diagnosis for patients presenting with bilateral adrenal masses in the context of an appropriate travel history.
- Investigations may include serology, fungal blood cultures or adrenal biopsy; however, diagnosis remains challenging considering the potentially time-sensitive nature of working up suspicious lesions, and the low sensitivity or lack of availability of tests.
- Assessing for adrenal insufficiency at diagnosis and during treatment remains important, although adrenal insufficiency is not universal.

1. 1. Vassiliadi DA, Delivanis DA, Papalou O, Tsagarakis S. Approach to the Patient With Bilateral Adrenal Masses. J Clin Endocrinol Metab. 2024;109(8):2136-2148. doi:10.1210/clinem/dgae164
2. 2. Histoplasmosis. Centers for Disease Control and Prevention (CDC). Accessed May 24, 2025. https://www.cdc.gov/histoplasmosis/index.html
3. 3. Nacher M, Alsibai KD, Valdes A, et al. HIV-Associated Disseminated Histoplasmosis and Rare Adrenal Involvement: Evidence of Absence or Absence of Evidence. Front Cell Infect Microbiol. 2021;11:619459. Published 2021 Mar 15. doi:10.3389/fcimb.2021.619459
4. 4. Koene RJ, Catanese J, Sarosi GA. Adrenal hypofunction from histoplasmosis: a literature review from 1971 to 2012 [published correction appears in Infection. 2015 Jun;43(3):387. doi: 10.1007/s15010-015-0767-9.]. Infection. 2013;41(4):757-759. doi:10.1007/s15010-013-0486-z
5. 5. McLeod DSA, Mortimer RH, Perry-Keene DA, et al. Histoplasmosis in Australia: report of 16 cases and literature review. Medicine (Baltimore). 2011;90(1):61-68. doi:10.1097/MD.0b013e318206e499
6. 6. Singh M, Chandy DD, Bharani T, et al. Clinical outcomes and cortical reserve in adrenal histoplasmosis-A retrospective follow-up study of 40 patients. Clin Endocrinol (Oxf). 2019;90(4):534-541. doi:10.1111/cen.13935

7. 7. Vorasayun T, Pengkhum P, Thavaraputta S, et al. Adrenal Histoplasmosis and Tuberculosis: Clinical Presentations and a High Prevalence of Adrenal Insufficiency. Clin Endocrinol (Oxf). Published online April 9, 2025. doi:10.1111/cen.15246

8. 8. Fassnacht M, Tsagarakis S, Terzolo M, et al. European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2023;189(1):G1-G42. doi:10.1093/ejendo/lvad066

9. 9. Assi MA, Sandid MS, Baddour LM, Roberts GD, Walker RC. Systemic histoplasmosis: a 15-year retrospective institutional review of 111 patients. Medicine (Baltimore). 2007;86(3):162-169. doi:10.1097/md.0b013e3180679130

10. 10. Hage CA, Ribes JA, Wengenack NL, et al. A multicenter evaluation of tests for diagnosis of histoplasmosis [published correction appears in Clin Infect Dis. 2012 Feb 1;54(3):454]. Clin Infect Dis. 2011;53(5):448-454. doi:10.1093/cid/cir435

An unexpected glycaemic shift post total pancreatectomy with islet autotransplantation (TPIAT) (127219)

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Case Presentation

A 20-year-old Nunga female presented with pancreatitis at age 10 years with subsequent episodes of recurrent pancreatitis. She was later diagnosed with familial pancreatitis due to a pathogenic *PRSS1* variant (R122H), in the cationic trypsinogen pathway (Family pedigree in Figure 1).

She progressed to develop chronic pancreatitis, complicated by debilitating pain. Following that, she underwent TPIAT at age 17, where she received 489,000 islet equivalents (IEQ)/kg.

Preoperative endocrine testing indicated intact beta cell function, normal C-peptide and glucose level (Table 1). A 75-gram glucose tolerance test was normal.

Postoperatively, tight glycaemic control was achieved with insulin infusion and she was transitioned to an insulin pump. Her post-transplant C-peptide was 410 pmol/L (300-1600) with concomitant glucose 6.1 mmol/L.

Six months post-TPIAT, she was switched from insulin to just sitagliptin 100mg daily monotherapy for mild hyperglycaemia, with hbA1c of 6.9% with normal C-peptide level. Sitagliptin was discontinued twenty months post-TPIAT.

Thirty months following TPIAT, she presented with new onset hyperglycaemic symptoms. Blood glucose levels were 20-29 mmol/L, with rising HbA1c, shown in Table 1. Her C-peptide was inappropriately normal at 752 pmol/L (366 -1466) with concomitant hyperglycaemias (glucose 15 -20 mmol/L).

Given the sudden and severe deterioration in beta cell function well at over 2 years since TPIAT, pancreatic autoantibodies were tested. Her Glutamic Acid Antibody (GADA) titre at 1732 IU/ml (normal <9.9), confirming type 1 diabetes post TPIAT. Lymphocytotoxic antibodies (LCTAbs) were negative, indicating no evidence of newly formed anti-HLA antibodies and suggesting low risk of early antibody-mediated

graft rejection. Hyperglycaemia was controlled with continuous subcutaneous insulin infusion and continuous glucose monitoring.

Discussion

Hereditary pancreatitis

Chronic pancreatitis (CP) is a progressive disease marked by irreversible pancreatic inflammation, leading to loss of both exocrine and endocrine function (1). Around 1–4% of cases are genetic, often presenting before age 10 (1). The most common genetic variants causing hereditary pancreatitis affect the trypsinogen activation pathway (2). Hereditary pancreatitis commonly involves variants in the trypsinogen activation pathway. *PRSS1* variants cause premature trypsin activation and pancreatic autodigestion, while *SPINK1* variants impair trypsin inhibition, increasing susceptibility. Other genes implicated include *CFTR, CTRC*, and *CPA1* (2).Although these genes don't directly cause cancer, they create a pro-inflammatory environment that raises the risk of pancreatic adenocarcinoma (Standardised Incidence Ratio 59–87). Genetic testing aids in identifying individuals at risk of CP, type 3c diabetes, and pancreatic cancer, allowing for timely interventions to preserve islet function and improve TPIAT outcomes (1,3).

Hereditary pancreatitis is significantly more prevalent among Indigenous South Australians, with *PRSS1* variant rates up to 70 times higher than in non-Indigenous populations. This may be due to founder effects, genetic bottlenecks, or pseudogene variations, though the exact cause remains unclear (2).

TPIAT

Total pancreatectomy with islet autotransplantation (TPIAT) is an established surgical treatment for patients with refractory chronic pancreatitis with severe intractable pain who have failed other therapies (4). Before the advent of TPIAT, surgical options often resulted in the development of pancreatogenic diabetes (4). TPIAT involves removal of chronically inflamed exocrine pancreas, the source of intractable pain and a known precursor for pancreatic adenocarcinoma while preserving endocrine function through autologous islet transplantation into the liver. Unlike allograft pancreas transplants, islet autotransplants (IATs) offer greater long-term durability, nearly 50% of autograft recipients remain insulin independent at 5 years (5).

Post-TPIAT glycemic outcomes are strongly influenced by transplanted islet mass, with larger islet equivalents associated with improved islet function and higher rates of insulin independence. Higher preoperative fasting and stimulated C-peptide levels have also been linked to better glycemic control after transplantation (5,6).

Late onset hyperglycaemia post TPIAT

Late-onset hyperglycaemia after TPIAT may result from islet graft exhaustion, pancreatogenic diabetes, comorbid type 2 diabetes or insulin resistance, medications, or autoimmunity. In this case, inappropriately low C-peptide despite marked hyperglycaemia suggests inadequate insulin secretion. Given her prolonged period of insulin independence, early graft failure is less likely. Insulin resistance also appears unlikely given her BMI and absence of contributory medications.

As islet autoantibodies were not assessed preoperatively, one possible explanation for the development of autoimmune diabetes post-TPIAT is unrecognised pre-existing autoimmunity, i.e. latent type 1 diabetes. Patients may already have positive GADA pre-TPIAT but has not manifested as overt diabetes. In a cohort of 350 TPIAT recipients, 9 were found to be GADA-positive prior to surgery despite normoglycaemia (HbA1c <5.7%) (7). None achieved insulin independence post-transplant, and two with high GADA titres (>250 IU/mL) experienced early graft failure despite a high islet yield. These findings suggest that pre-transplant GADA positivity may predict autoimmune islet destruction, even in the absence of overt diabetes, highlighting the importance of routine preoperative screening (7).

Although rare, the reported prevalence of autoimmune diabetes post TPIAT is approximately 0.2%, which is comparable to the background prevalence of T1DM in the general population (4). While most patients with recurrent pancreatitis who develop diabetes exhibit pancreatogenic diabetes, emerging evidence suggests that the prevalence of autoimmune diabetes may be higher in this group compared to the general population, confirmed by the detection of islet-autoantibodies (8,9). Chronic pancreatic inflammation may trigger neoepitope formation and immune activation, leading to loss of tolerance in genetically susceptible individuals (8, 9). While our patient had no personal or family history of autoimmunity, she carried the HLA-DRB1*03:04. The broader DRB103 group is a known risk factor for development of autoimmune diabetes but the data on the *03:04 subtype are inconclusive (10). Thus, these findings support the hypothesis that persistent inflammation and possibly underlying genetic predisposition are the more plausible driver of autoimmune diabetes. In other words, this patient would have developed type 1 diabetes irrespective of TPIAT.

Another possibility is that autoimmune diabetes develops only after TPIAT, as demonstrated in a previously reported case of new onset type 1 diabetes occurring post-TPIAT in a patient who was tested negative for GADA preoperatively and subsequently became positive (4). It has been proposed that the intraportal islet infusion may itself trigger autoimmunity by exposing the immune system to β-cell antigens released during the early phase of islet loss following transplantation. Whether the TPIAT procedure accelerates immunologic β-cell destruction through enhanced

antigen exposure remains unclear. The main difference is GADA status was not assessed preoperatively in our case (Table 2). Without preexisting antibody status, it remains uncertain whether autoimmunity was preexisting or truly induced by the surgical intervention.

Take away points:

1. Hereditary pancreatitis (HP) often presents in childhood and is linked to *PRSS1* variant, which are significantly more prevalent among indigenous South Australians — making genetic testing especially important in Indigenous patients with recurrent pancreatitis, which is profoundly underappreciated.

2. Total pancreatectomy with islet auto-transplantation (TPIAT) is a key treatment for symptomatic hereditary pancreatitis offering pain relief, prevents obligate development of pancreatogenic diabetes and HP-related adenocarcinoma of pancreas and achieving long-term insulin independence in selected patients.

3. Autoimmune diabetes following TPIAT is rare and may result from chronic pancreatic inflammation rather than the TPIAT itself. However, the possibility that TPIAT could trigger or accelerate autoimmunity through increased antigen exposure cannot be excluded without preoperative autoantibody assessment. Therefore, while not yet formalized in official guidelines, islet autoantibodies screening prior to TPIAT should be considered in clinical practice to identify patients at risk of autoimmune diabetes.

Table 1: Investigation results

	Pre-transplant	Day 0 post transplant	6 months post-transplant	30 weeks post transplant
Glycated hemoglobin (hbA1c), mmol/mol (%)	37 (5.5)	Not checked	51.9 (6.9)	121 (13.2)
Random blood glucose level (mmol/L)	6.8	6.1	7.5	27
C-peptide (normal range > 70 pmol/L)	327	410	341	752
Diabetes Antibodies	Not checked	Not checked	Not checked	Positive

Figure 1: Family pedigree of the patient (indicated by arrow)

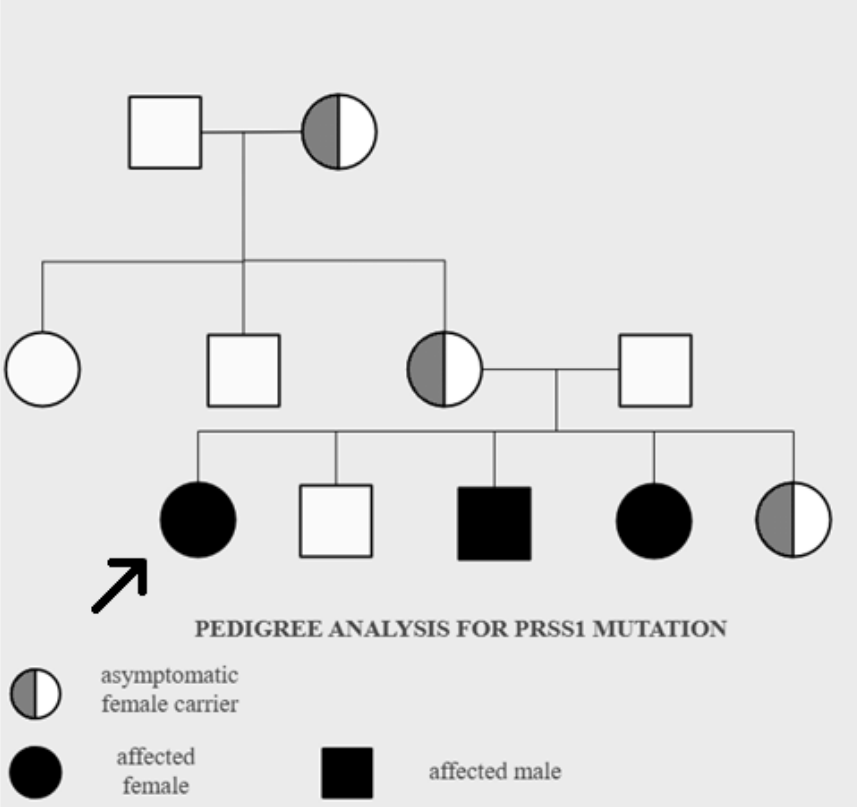

Table 2 The documented case of autoimmune-mediated T1DM following TPIAT

Study (Year)	Patient Characteristics	Pre-op Autoantibodies (GADA titre in IU/ml) [normal range 0.0-5.0]	Post-op Autoantibodies (GADA titre in IU/ml) [normal range 0.0-5.0]	Time to insulin independence post TP-IAT	Time to T1DM Onset
Our patient	**20 yo F**	**Negative**	**Positive (1732)**	**Within 6 months**	**30 months**
Bellin et al., 2015[20]	43 yo F	Negative	Positive (524)	Within 6 months	Within 1 year
Kizigul et al[19]	39 yo F	Positive (48.7)	Positive (46.5)	NR	3 months

F= female, M= male; NR = not reported

1. Bampton TJ, Chen JW, Brown A, Barnett MI, Coates PT, Palmer LJ. Epidemiology and burden of adult chronic pancreatitis in South Australia: a 20-year data linkage study. BMJ Open. 2025;15(3):e089297. doi:10.1136/bmjopen-2024-089297 Yadav D, Timmons L, Benson JT, et al. Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. Am J Gastroenterol 2011;106:2192–9.
2. Wu D, Bampton TJ, Scott HS, et al. The clinical and genetic features of hereditary pancreatitis in South Australia. Med J Aust. 2022;216(11):578–582. doi:10.5694/mja2.51517
3. Shelton, C. A., et al. (2018). "Hereditary Pancreatitis in the United States: Survival and Rates of Pancreatic Cancer." American Journal of Gastroenterology 113(9): 1376-1384.
4. Bellin MD, Moran A, Wilhelm JJ, et al. Development of autoimmune-mediated β-cell failure after total pancreatectomy with autologous islet transplantation. Am J Transplant. 2015;15(4):1044-1052. doi:10.1111/ajt.13216.
5. Sutherland DE, Gruessner AC, Carlson AM, et al. Islet autotransplant outcomes after total pancreatectomy: a contrast to islet allograft outcomes. Transplantation. 2008;86(12):1799-1802. doi:10.1097/TP.0b013e31819143ec
6. Chinnakotla S, Beilman GJ, Dunn TB, et al. Factors predicting outcomes after a total pancreatectomy and islet autotransplantation: lessons learned from over 500 cases. Ann Surg. 2015;262(4):610-622.

7. Kizilgul M, Wilhelm JJ, Dunn TB, et al. The prognostic significance of glutamic acid decarboxylase antibodies in patients with chronic pancreatitis undergoing total pancreatectomy with islet autotransplantation. Diabetes Metab. 2019;45(3):301-305. doi:10.1016/j.diabet.2018.01.001.

8. Kharoud HK, Mettler T, Freeman ML, et al. Type 1 diabetes mellitus in patients with recurrent acute and chronic pancreatitis: a case series. Pancreatology. 2022;22(4):553–556. doi:10.1016/j.pan.2022.03.003.

9. James EA, Pietropaolo M, Mamula MJ. Immune recognition of beta-cells: neoepitopes as key players in the loss of tolerance. Diabetes. 2018;67(6):1035-1042. doi:10.2337/dbi17-0010

10. Noble JA. Fifty years of HLA-associated type 1 diabetes risk: history, current knowledge, and future directions. Front Immunol. 2021;12:689582. doi:10.3389/fimmu.2021.689582

The Weight for a Genetic Link: A Case of Childhood Obesity (127231)

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Case Summary

RT is a 24-year-old male with a suspected form of monogenic obesity presenting with morbid obesity since infancy, Arginine vasopressin (AVP) deficiency and hypogonadotrophic hypogonadism. Other past medical history includes bilateral Duane's Syndrome, Wolff-Parkinson-White syndrome (WPW), Migraines and a right ankle fracture complicated by osteomyelitis.

Obesity onset was evident at birth when he crossed from the 25th to the 75th percentile by 6 months. By age 5 he had a body mass index (BMI) of 30.1 kg/m^2 associated with symptoms of hyperphagia. Various diets were trialled in childhood, however followed by rebound weight gain after cessation. Pharmacological approaches such as Metformin and Semaglutide showed minimal benefit. A trial of Phentermine had to be ceased due to risk for arrhythmia with his WPW syndrome, for which he had an elective ablation for in 2018. There is no family history of obesity, and there were no delays in developmental milestones.

AVP deficiency was diagnosed at the age of 4 on a water deprivation test after he presented with polyuria and polydipsia since age 2. Pituitary screen completed did not demonstrated any significant abnormalities (Table 1). He was initially commenced on intranasal desmopressin then transitioned to oral tablets at the age of 11, current doses are 300 microg mane and 600 microg nocte.

Lab (unit)	2002	2003	2005	2015	2024	2025	Reference Ranges
Na mmol/L		138	142	140	143	140	135-145
IGF-1 U/mL	0.07						0.34 – 1.42
IGF-1 nmol/L					11.2	12	13 – 39
GH mcg/L					<0.1		<5.0
PTH mIU/L	1.0						1.0 – 6.0
Adj Ca mmol/L	2.56					2.59	2.10 – 2.60
Cortisol nmol/L	385			163	253	251	145 – 619
ACTH pmol/L	11.3					9.7	1.6 – 13.9
Prolactin mIU/L	481				147	234	45 – 375
FSH IU/L	0.5			2	2	3	1 – 10
LH IU/L	<0.3			4	3	3	1 – 10
Total T nmol/L					1.0	3.0	10.0 – 35.0
Leptin ng/ml		23.4				142	2.0 – 5.6
TSH mIU/L			0.76		2.10	1.57	0.50 – 4.00
FT4 pmol/L			9.9		12.0	12.2	10 – 23.0

Table 1

On subsequent, pituitary panel in 2024 demonstrated a Total testosterone level of 1.0 mmol/L (Ref 5.0 – 28.0), Follicular stimulating hormone (FSH) of 2 IU/L (Ref 2 – 18) and Luteinising hormone (LH) of 3 IU/L (Ref <6) demonstrated hypogonadotrophic hypogonadism. He was commenced on Testogel and 2 months later he remained hypogonadal and was transitioned to Reandron 1000 mg. 7 weeks after his 1st dose of Reandron his Total testosterone was 1.2 mmol/L, FSH 2 IU/L and LH 3 IU/L. There were nine-week intervals between his first, second and third dose. 6 weeks after his 3rd dose his Total testosterone was 3.0 mmol/L, FSH 3 IU/L and LH 3 IU/L. His dosing interval has been reduced to 6-weekly with follow up investigations to come. Androgen investigations are summarised on Table 2. The remainder of his pituitary panel was otherwise normal (Table 1). Karyotype was 46 XY and negative for Prader Willi and Fragile X syndrome. Leptin level were raised since childhood (Table 1).

Laboratory (unit)	20/05/24	02/08/24	18/11/24 (7 weeks post 1st dose)	21/03/25 (6 weeks post 3rd dose)	Ref Range
Total Testosterone (nmol/L)	1.0	1.5	1.2	3.0	6.0 – 28.0
SHBG (nmol/L)		19	18		15 – 50
Free Testosterone (pmol/L)		36	29		200 – 600
FSH (IU/L)	2	2	2	3	2 – 18
LH (IU/L)	3	4	3	3	< 6
Prolactin (mIU/L)	147	128			45 – 375
Estradiol LCMS (pmol/L)				93	40-160

Table 2

On examination, he has red hair with distinct dysmorphic facies including a vertical indentation from the central hairline involving the superior half of his forehead, as well as indentations above both his eyebrows. His has a BMI of 79.1 kg/m^2, bilateral gynaecomastia and non-pitting oedema. There are no abdominal striae, and olfactory sensation is intact. Patient has self-assessed Tanner stage 2 for genital development and pubic hair. Testicular volume on ultrasound demonstrated bilateral small testes (right testis 18 x 22 x 40 mm measuring 8.3 cc and left testis 21 x 28 x 44 mm measuring 13.3 cc).

Pituitary magnetic resonance imaging (MRI) demonstrates an absent posterior pituitary bright spot with no abnormal mass lesion in the hypothalamus or pituitary axis (Figure 1).

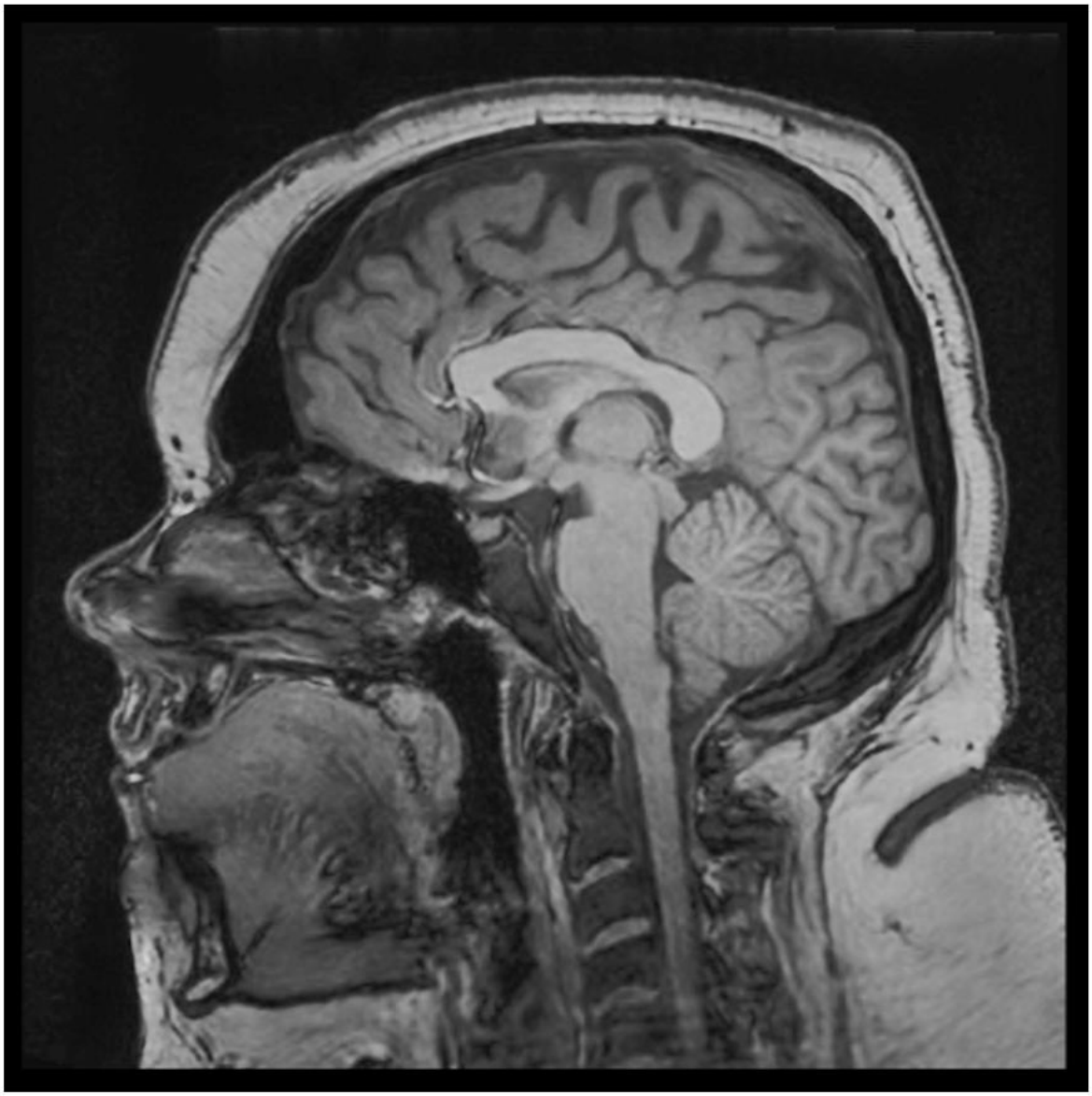

Figure 1

Given his two pituitary abnormalities and hyperphagia we are highly suspicious of monogenic form of obesity. He had a genetic testing completed in 2003 and they are currently reanalysing the data to see if they can identify a pathogenic gene mutation to explain his escalating obesity.

Discussion

Australian Institute of Health and Welfare reported 32% of adults living with obesity and 8.1% of children living with obesity in Australia (1). Prevalence of monogenic obesity is estimated at ~5% in individuals living with Obesity (2). Monogenic Obesity is caused by single gene mutations which lead to impaired satiety signalling via the melanocortin-4 receptor. It is characterised by appetite dysregulation manifesting as hyperphagia, with severe treatment resistant obesity which often presents in childhood.

The leptin melanocortin pathway involves leptin, which activates the Pro-opiomelanocortin (POMC) anorexigenic neuron and downregulates the Agouti-related protein (AgRP) orexigenic neuron. POMC is cleaved by Proprotein Convertase 1/3 (PCSK1) enzyme which forms Melanocyte stimulating hormone type α (α-MSH) which activates the Melanocortin receptor type 4 (MC4R) which induces satiety signals. Conversely, AgRP inhibits MC4R which reduces these satiety signals. Monogenic obesity is the result of single gene mutations affecting various aspects of this pathway for example PCSK1 mutation leading to dysfunction of the enzyme (2).

Management of monogenic obesity has a unique challenge due to the insatiable hunger and early onset in childhood. Lifestyle modifications with restrictive diet guided by a dietitian and physiotherapist are the foundations of management. It is recommended to enact these early with parental involvement to control access to food (2).

GLP1 agonists in hypothalamic obesity and a MC4R mutation have demonstrated modest benefit (summarised in Table 3). The ECHO study demonstrated a significant difference in fat mass of -3.1 kg and waist circumference of -3.5 cm between Exenatide treatment and placebo (3). The CRANIOEXE study demonstrated significant difference in weight of -3.1 kg and reduction in hunger score between patient treated with Exenatide and placebo (4). Luraglutide demonstrated no significant difference in weight loss, waist circumference or BMI in a cohort of patients living with obesity with and without MC4R mutation (5). This demonstrated a preserved efficacy of GLP1 agonist in patients with monogenic obesity. Further studies in other forms of monogenic obesity and studies with newer forms of GLP1 agonists, such as Semaglutide, would be beneficial to further investigate the role of GLP1 agonist in this cohort of patients.

Study		Baseline characteristics		Results
ECHO *Roth et al.* Double blind multicentre RCT 10–25-year-olds with hypothalamic injury following intracranial tumour and obesity 36 weeks	ExQW: GLP1-RA Exenatide 2mg (n = 23) Placebo (n = 19)	ExQW: • Age: 16.9 years • Male 39% Female 61% • Weight: 95.1kg • Waist circumference (WC): 112.8 cm • BMI 35.8 kg/m^2 • Fat mass	Placebo: • Age 16.9 years • Male 39% Female 61% • Weight 103.7 kg • WC: 119.7 cm • BMI: 39.2 kg/m^2 • Fat mass	BMI % change: No significant difference • ExQW: -1.7 ± 0.8% • Placebo: -3.5 ± 0.9% Fat mass: Treatment effect -3.1 ± 1.4kg • ExQW: -1.5 ± 0.9 kg • Placebo: -4.6 ± 1.0 kg WC: Treatment effect -3.5 cm • ExQW: -0.1 ± 0.7 cm • Placebo: -3.6 ± 0.7 cm
CRANIOEXE ***Gatta-Cherifi et al.*** Double blind multicentre RCT 18-75-year-olds with BMI > 30 kg/m^2 with weight gain following therapy for craniopharyngioma 26 weeks	Exenatide 5mcg BD 4 weeks then 10mcg BD 22 weeks (n = 20) Placebo (n = 20)	Exenatide: • Age: 40.4 years • Male 60% Female 40% • Obesity Class: I 60%, 2 10% and III 30%	Placebo: • Age: 40.4 years • Male 55% Female 45% • Obesity Class: I 53%, II 10% and III 37%	Weight: Difference -3.1kg • Exenatide: -3.8 kg • Placebo: -1.6 kg Hunger score: Difference -2.3 • Exenatide: -1.6 ± 3.5 • Placebo: -0.1 ± 3.6 *Three factor Eating Questionnaire (TFEQ)*
Iepsen et al. Matched cohort study Liraglutide given 16 weeks	MC4R mutation (n = 14) Mutation free (n = 28)	MC4R: • Age: 32.8 ± 13.5 • Male 54% Female 46% • Weight: 122.4 ± 24.9 kg • WC: 110.6 ± 3.5 cm • BMI: 37.5 ± 6.8 kg/m^2	Mutation free: • Age: 42.8 ± 10.2 • Male 57% Female 43% • Weight: 112.6 ± 18.9 kg • WC: 114.5 ± 2.7 cm • BMI: 36.8 ± 4.8 kg/m^2	Weight: No significant difference • MC4R: -6.8 ± 1.8 kg • No mutation: -6.1 ± 1.2 kg WC: No significant difference • MC4R: -5.4 ± 1.5 cm • No mutation: -6.5 ± 1.7 cm BMI: No significant difference • MC4R: -2.0 ± 0.5 kg/m^2 • No mutation: -2.0 ± 0.4 kg/m^2

Table 3

Setmelanotide is a selective MC4R agonist which activates the MC4R to release satiety signals. Two randomised control trials have been conducted, and both show promising results in patients with monogenic forms of obesity (6,7) (summarised in Table 4). Development of agents targeting them leptin-melanocortin pathway may lead to effective personalised therapy.

Study	Baseline characteristics		Results
Clément et al. Single-arm, open-label, multicentre phase 3 trial Setmelanotide 1.0 mg for adults and 0.5 mg for children → ↑ by 0.5mg weekly until individualised therapeutic dos 52 weeks treatment	POMC (n = 10) • Age: 18.4 • Male 50% Female 50% • Weight: 118.7 kg • WC 118.9 cm • BMI: 40.4 kg/m^2 • Hunger score 8.1/11	LEPR (n = 11) • Age: 23.7 • Male 27% Female 73% • Weight: 133.3 kg • WC: 127.3 cm • BMI 48.2 kg/m^2 • Hunger score 7.0/11	POMC • Weight: -25.6% • WC: -14.9% • BMI -27.8% • Hunger score: -27.1% LEPR • Weight: -12.5% • WC: -7.2% • BMI -13.1% • Hunger score: -43.7%
Collet et al. Phase 1b trial Double blinded RCT MC4R Heterozygote carrier (n = 8) Obese controls (n = 8) Setmelanotide 0.01mg/kg/day 29 days treatment	MC4R (Age: 22-57) Setmelanotide (n = 6) • Weight: 130.46 ± 22.96 kg • WC: 132.8 ± 18.1 cm Placebo (n = 2) • Weight: 101.75 ± 21.71 kg • WC: 112.3 ± 13.1 cm	Obese controls (Age 19-53) Setmelanotide (n = 5) • Weight: 97.86 ± 17.18 kg • WC: 107.2 ± 8.9 cm Placebo (n = 3) • Weight: 98.26 ± 7.99 kg • WC: 112.3 ± 12.4 cm	Weight: Setmelanotide vs placebo • MC4R: -2.63 kg • Control: -3.97 kg WC: Setmelanotide vs placebo • MC4R: -5.08 cm • Control: -2.47 cm

Table 4

There is uncertainty surround the sustained long term benefit of bariatric surgery (summarised in Table 5). Cooiman et al. in 2020 demonstrated relatively similar weight loss over 24 months between patients with no mutations and patients found to have monogenic mutations on genetic analysis, except for MC4R mutations which demonstrated significantly less weight loss (8). However, a multicentre case-control study demonstrated significant weight regain of 12.8% in the patients with MC4R mutation compared to 7.8% in patients without mutations 60 months post a Roux-en-Y Bypass (RYGB) and similar discrepancies post sleeve gastrectomy (SG) (9). Campos et al. demonstrated lower nadir of 32.1% in those with monogenic mutations compared to those without which had a nadir of 35.8% (10).

Study	Baseline characteristics		Results
Cooiman et al. 2020 Retrospective cohort study 1041 patients Bariatric surgery F/U 24 months	Mutation (n = 30) • Age 44.1 ± 11.7 • Male 30% Female 70% • BMI 48.3 ± 9.9 kg/m^2 MC4R (n = 11) POMC (n = 12) PCSK1 (n = 5) PTEN (n = 1) SIM1 (n = 1)	No mutations (n = 827) • Age 46.3 ± 11.3 • Male 22% Female 78% • BMI 45.6 ± 8 kg/m^2	RYGB: No significant difference for MC4R, POMC and PCSK1 SG: • MC4R: Significantly less weight loss • POMC: No significant difference for Revision RYGB: No significant difference for MC4R and SIM1
Cooiman et al. 2022 Multicentre case-control study MC4R pathogenic variants 2:1 match Follow up (F/U) 60 months	Roux-en-Y: RYGB (n = 57) MC4R (n = 19) • Age 42.3 | Male 26% Female 74% • Weight 134.2 kg | BMI 47.3 kg/m^2 Controls (n = 38) • Age 41.8 | Male 26% Female 74% • Weight 135.7 kg | BMI 48.4 kg/m^2	Sleeve Gastrectomy: SG (n = 24) MC4R (n = 8) • Age 39.5 | Male 25% Female 75% • Weight: 146.3 kg | BMI: 50.9 kg/m^2 Controls (n = 16) • Age 37.5 | Male 25% Female 75% • Weight: 141.9 kg | BMI: 49.1 kg/m^2	RYGB: All reach >25% total weight loss • MC4R: 12.8% weight regained at 60 mo • Controls: 7.9% weight regained at 60 mo SG: • MC4R: 2/8 cases achieved >25% weight loss. 2/8 cases had >15% weight regain at 60 mo • Controls: All reached >25% weight loss. Regained 6.3%
Campos et al. Retrospective case control RYGB: 150 patients F/U 15 years	Mutations • Age 49.6 • Male 22% Female 78% • Weight 125.6 kg • BMI 45.3 kg/m^2	No mutations • Age 51.3 • Male 21% Female 79% • Weight 126.3 kg • BMI 45.7 kg/m^2	• Similar in the first 6 months of follow up • Nadir: 32.1% vs 36.8% • 5 years: -22.6% vs -26.7% • 10 years: -15.6% vs -25.9% • 15 years: -16.6% vs 28.7%

Table 5

Learning Points

1. Monogenic obesity is a rare form of obesity caused by a single gene mutation which affects various parts of the leptin-melanocortin pathway
2. Management requires a highly involved multidisciplinary team approach
3. GLP1 agonist show promise in the management of monogenic obesity
4. Novel therapies that target the leptin melanocortin pathway has demonstrated successful weight loss and patient precision therapy should be explored
5. Due to hyperphagia bariatric surgery may have limited utility patients tend to loss less weight than their mutation free counterparts and regain weight faster in the long term

The calm before the storm: three decades post adrenalectomy (127239)

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Case Report

A 16-year-old girl first presented in 1987 with psychosis and cushingoid appearance. Initial assessment confirmed ACTH-dependent Cushing's syndrome with CT pituitary revealing a normal size pituitary gland with an area of low attenuation, consistent with a microadenoma. Inferior petrosal sinus sampling confirmed Cushing's disease. After initial stabilisation with metyrapone and then ketoconazole, she underwent two hypophysectomies but remained hypercortisolaemic. The patient therefore proceeded to bilateral adrenalectomy for definitive treatment of her cortisol excess, with adjuvant external beam radiotherapy (50.4Gy/28 fractions) to the pituitary gland to mitigate the risk of corticotroph tumour progression (CTP; formerly, Nelson's syndrome). She subsequently developed panhypopituitarism and was commenced on hormonal replacement, along with fludrocortisone for primary adrenal insufficiency. After 20 years of stable endocrine surveillance, she was discharged from follow-up in 2007.

In 2019, 12 years since her last endocrine review, the patient briefly returned to endocrinology outpatients for evaluation of presyncope. Notably, there were no signs of Cushing's recurrence and MRI confirmed the absence of a pituitary mass. (Fig 1).

Soon after, in 2020, she was diagnosed with stage IVa lung adenocarcinoma, managed with surveillance only per patient preference given lack of subsidised therapies and disease stability on follow-up imaging.

Between 2023 and 2024, serial lung cancer surveillance CT revealed new sellar expansion, prompting dedicated MRI which revealed an 18x17x20 mm sellar/suprasellar mass displacing the optic chiasm (Fig 2). On endocrine review, now 36 years from initial presentation, she was strikingly hyperpigmented (Fig 3) and had headaches. ACTH was markedly elevated at >1750 ng/L (7-60 ng/L). Neuro-ophthalmological assessment was normal.

The patient was diagnosed with CTP and proceeded to transsphenoidal resection, with immediate postoperative ACTH decline to 341 ng/L. Histopathology demonstrated a T-PIT- and ACTH-positive corticotrophinoma with high Ki67 index (10%). Somatic sequencing revealed *MEN1* and *ATRX* frameshift variants, and *CDK4*amplification;

germline testing to determine if the *MEN1* variant is germline is pending. ACTH rose again to 603 ng/L, leading to fractionated stereotactic radiosurgery (25Gy/5 fractions).

Concurrently, the patient was diagnosed with metastatic melanoma and commenced pembrolizumab. After 3 months of pembrolizumab (just 2 weeks following radiotherapy completion), ACTH declined to a nadir of 220 ng/L (Fig 4), with symptomatic improvement and reduced hyperpigmentation. Close clinical, biochemical and radiological surveillance is ongoing.

Discussion

This case demonstrates the risk of very delayed onset of CTP despite use of adjuvant radiotherapy and scrupulous, extended surveillance. Current guidelines provide limited recommendations for monitoring beyond 10–20 years post-bilateral adrenalectomy (1). However, as clinical outcomes and survival rates improve for Cushing's disease patients, lifelong vigilance remains essential. The case also highlights issues around the assessment and management of aggressive pituitary tumours (APTs), including the emerging roles of immunotherapy and somatic genetic testing.

Corticotroph tumour progression surveillance post bilateral adrenalectomy

Cushing's disease (CD) arises from autonomous ACTH secretion by pituitary corticotrophinomas, leading to hypercortisolism. While transsphenoidal surgery remains the first-line treatment, recurrence occurs in 10–30% of cases (1,2). Bilateral adrenalectomy (BADX) is a definitive treatment for hypercortisolism when surgical interventions and medical therapies fail, but it carries the lifelong risk of CTP. Consensus recommendations define radiological tumour progression as the primary criterion for CTP diagnosis, with progressive rise in plasma ACTH and hyperpigmentation considered secondary, non-mandatory criteria (1). Mean time interval from BADX to CTP is 5.3 years with incidence up to 53%, but it has been reported up to 39 years after BADX (1). The mechanism of very late onset CTP is unknown but might relate to accumulating genetic defects in residual microscopic disease, eventually leading to rapid tumour proliferation. While standard surveillance protocols recommend MRI 3 months post-BADX and annually for the first 3 years, long-term surveillance intervals vary (suggested MRI every 2–4 years) (1). However, there has been a significant reduction in mortality from CD, as demonstrated by a 71% reduction in proportion of deaths over time in CD patients when comparing pre vs post year 2000 (2), meaning larger proportions of patients are at risk of late relapse. Given the lifelong risk of CTP, a practical long-term surveillance strategy may be annual clinical assessment for hyperpigmentation and visual field deficits alongside ACTH measurement, with MRI pituitary every 2-4 years or sooner if clinically indicated.

Emerging therapies for aggressive pituitary tumours

CTP falls within the umbrella term of APTs which are characterised by rapid growth and resistance to standard therapy, with corticotroph tumours comprising 45% of all APTs (3). Management strategies include surgical resection, radiotherapy, and medical therapy tailored to tumour subtype. (4). The first-line chemotherapeutic agent for APTs and pituitary carcinoma (PC) is temozolomide, demonstrating radiological response in 64% of patients, with 2-year overall survival up to 84%. Nonetheless, disease progression following temozolomide occurs in up to 29% of cases, highlighting the need for alternative strategies (4). Emerging options include immune checkpoint inhibitors (ICI), which have shown partial radiological responses in 24% of patients with prior treatment failure (4). As of the latest 2025 APT/PC guidelines, ICIs are now suggested for consideration in PC with disease progression after temozolomide. The case presented herein is notably the fourth reported case of CTP with an evident treatment response to ICI (5, 6). Other treatment options include bevacizumab, an anti-VEGF monoclonal antibody, but this has shown limited effectiveness with most cases experiencing disease progression, as well as combined treatment modalities such as temozolomide with concurrent radiotherapy (4). Multidisciplinary decision-making and consideration of clinical trials are essential in APT management given the limited evidence and lack of comparative studies.

Somatic testing of pituitary tumours

Somatic genetic testing has the potential to provide diagnostic and therapeutic stratification of APTs. While no genetic alterations currently offer established targets for APT therapy, somatic testing may provide prognostic information and inform therapeutic escalation. Somatic variants in *TP53* and *ATRX* are particularly associated with aggressive corticotrophinoma (7), while *SF3B1* variants are enriched in metastatic prolactinomas (8). Notably, these variants are often present before radiotherapy and metastatic spread, suggesting utility in early risk stratification. For patients exhibiting tumour progression despite conventional therapies, somatic testing also offers the possibility – albeit rare – of identifying genetic variations predictive of specific treatment responses. For example, mismatch repair deficiency and high tumour mutational burden predict favourable ICI response in non-pituitary tumours. Variants detected on somatic testing that may plausibly be germline (e.g., the *MEN1* variant in this case) should be considered for germline DNA sequencing to guide overall healthcare of the individual and their relatives. Whilst the role of somatic testing remains under investigation in the pituitary setting, it shows promise in the management of APTs, offering the potential for early identification of high-risk patients and future incorporation into precision therapeutic interventions.

Take home messages

- CTP is common following bilateral adrenalectomy for Cushing's disease, supporting a strategy of lifelong surveillance with annual clinical and biochemical assessment and periodic MR imaging
- Management of APTs typically involves a multimodal approach, with immune checkpoint inhibitors an emerging option when conventional therapies are ineffective.
- The role of somatic testing in pituitary tumours is evolving and may be considered on an individualised basis to predict tumour aggressiveness and potential treatment avenues in APTs

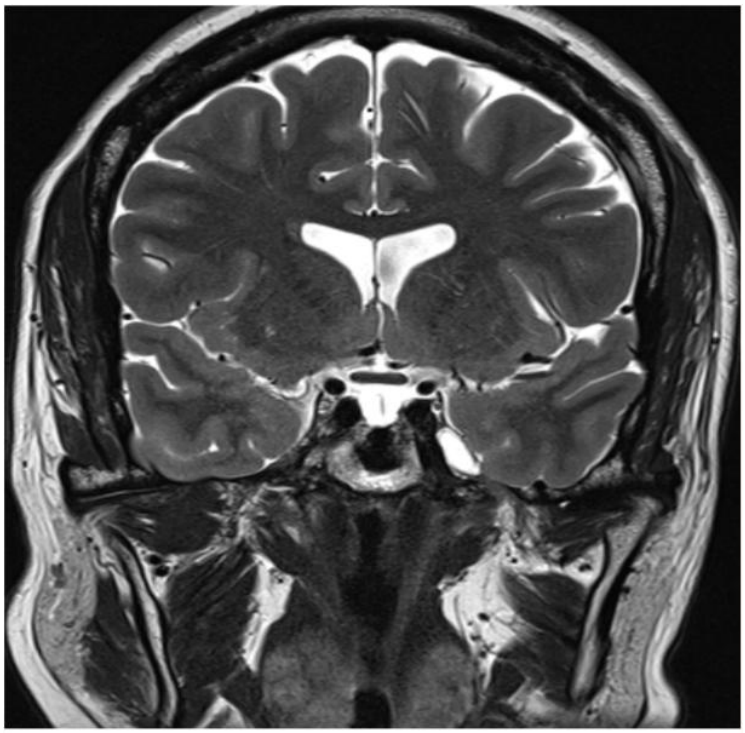

Figure 1: MR Head (9/1/19) – No pituitary mass evident

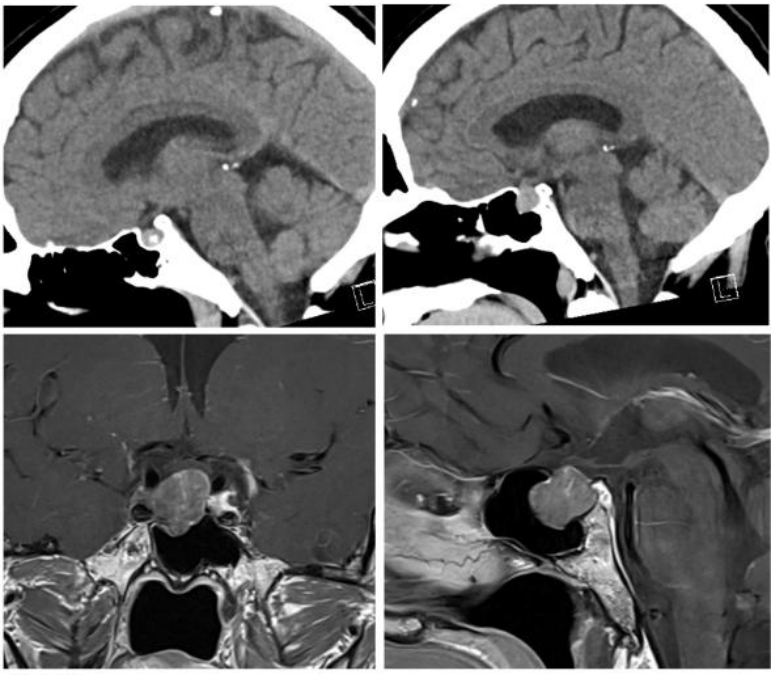

Figure 2:
(A) CT Head (8/6/23) – Pituitary gland enlargement, measuring 9x10 mm
(B) CT Head (5/6/24) - Enlarging lobular pituitary mass, now 16x12 mm, bulging through the anterior cortex into the sphenoid sinus
(C) , (D) MR Head (22/6/24) - Enlarging pituitary mass expanding the sella and extending into the suprasellar region and lateral aspect of the right cavernous sinus, 18x17x20mm in diameter. The optic chiasm drapes over the lesion.

Figure 3: Patient appearance in 2019 (left) compared to hyperpigmentation seen in 2024 (right)

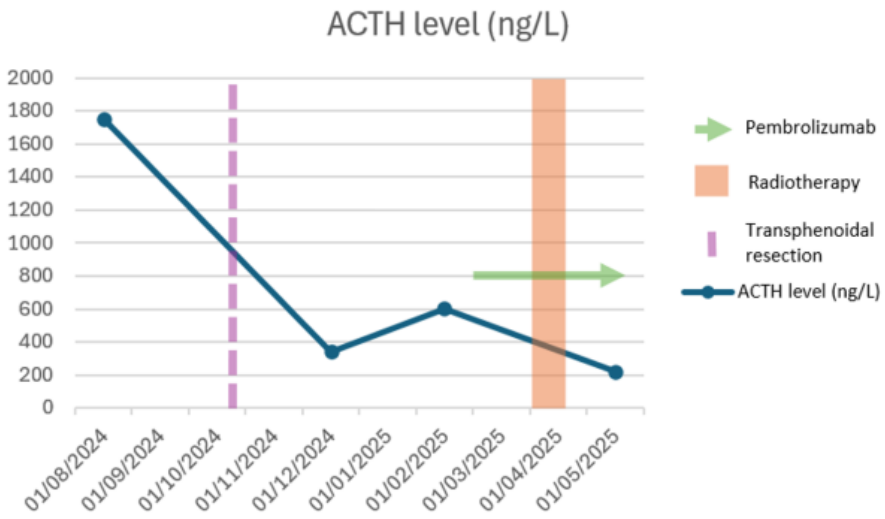

Figure 4: ACTH levels dropping post pituitary resection but then beginning to rise again. Further drop of ACTH 3 months after commencing pembrolizumab and 2 weeks post completion of radiotherapy.

1. 1. Reincke M, Albani A, Assie G, Bancos I, Brue T, Buchfelder M, et al. Corticotroph tumor progression after bilateral adrenalectomy (Nelson's syndrome): systematic review and expert consensus recommendations. Eur J Endocrinol. 2021;184(3):P1-p16.
2. 2. Limumpornpetch P, Morgan AW, Tiganescu A, Baxter PD, Nyawira Nyaga V, Pujades-Rodriguez M, et al. The Effect of Endogenous Cushing Syndrome on All-cause and Cause-specific Mortality. J Clin Endocrinol Metab. 2022;107(8):2377-88.
3. 3. McCormack A, Dekkers OM, Petersenn S, Popovic V, Trouillas J, Raverot G, et al. Treatment of aggressive pituitary tumours and carcinomas: results of a

European Society of Endocrinology (ESE) survey 2016. Eur J Endocrinol. 2018;178(3):265-76.

4. 4. Raverot G, Burman P, Abreu AP, Heaney AP, van Hulsteijn L, Lin AL, et al. Revised European Society of Endocrinology Clinical Practice Guideline for the management of aggressive pituitary tumours and pituitary carcinomas. Eur J Endocrinol. 2025;192(6):R45-r78.
5. 5. Sol B, de Filette JMK, Awada G, Raeymaeckers S, Aspeslagh S, Andreescu CE, et al. Immune checkpoint inhibitor therapy for ACTH-secreting pituitary carcinoma: a new emerging treatment? Eur J Endocrinol. 2021;184(1):K1-k5.
6. 6. Park JY, Choi W, Ram Hong A, Yoon JH, Kim HK, Kang HC. THU018 Remarkable Response Of ACTH-secreting Pituitary Carcinoma To Immune Checkpoint Inhibitors: A Case Report. J Endocr Soc. 2023;7(Suppl 1).
7. 7. Casar-Borota O, Boldt HB, Engström BE, Andersen MS, Baussart B, Bengtsson D, et al. Corticotroph Aggressive Pituitary Tumors and Carcinomas Frequently Harbor ATRX Mutations. J Clin Endocrinol Metab. 2021;106(4):1183-94.
8. 8. Li C, Xie W, Rosenblum JS, Zhou J, Guo J, Miao Y, et al. Somatic SF3B1 hotspot mutation in prolactinomas. Nat Commun. 2020;11(1):2506.

Decision: Oral Presentation

Managing pregnancy in mccune albright syndrome (127244)

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Table 1. Results of relevant biochemical testing

Test	Result	Reference Range
Mid-cycle oestradiol	101 pmol/L	150 – 1500 pmol/L
Mid-cycle LH	9.2 IU/L	4.0 – 22.5 IU/L
Mid-cycle FSH	4.7 IU/L	15 – 100 IU/L
Prolactin	5167 mIU/L	8.0 – 500 mIU/L
IGF-1	98 nmol/L	14 – 46 nmol/L
GH nadir after 75 g oral glucose tolerance test	4.3 ng/L	<1.0 ug/L
Morning cortisol	346 nmol/L	170 – 500 nmol/L
TSH	2.5 mIU/L	0.5 – 4.0 mIU/L
Free T4	13.4 pmol/L	9.0 - 19 pmol/L

Abbreviations: LH, luteinising hormone; FSH, follicle-stimulating hormone; IGF-1, insulin-like growth factor-1; GH, growth hormone; TSH, thyroid stimulating hormone.

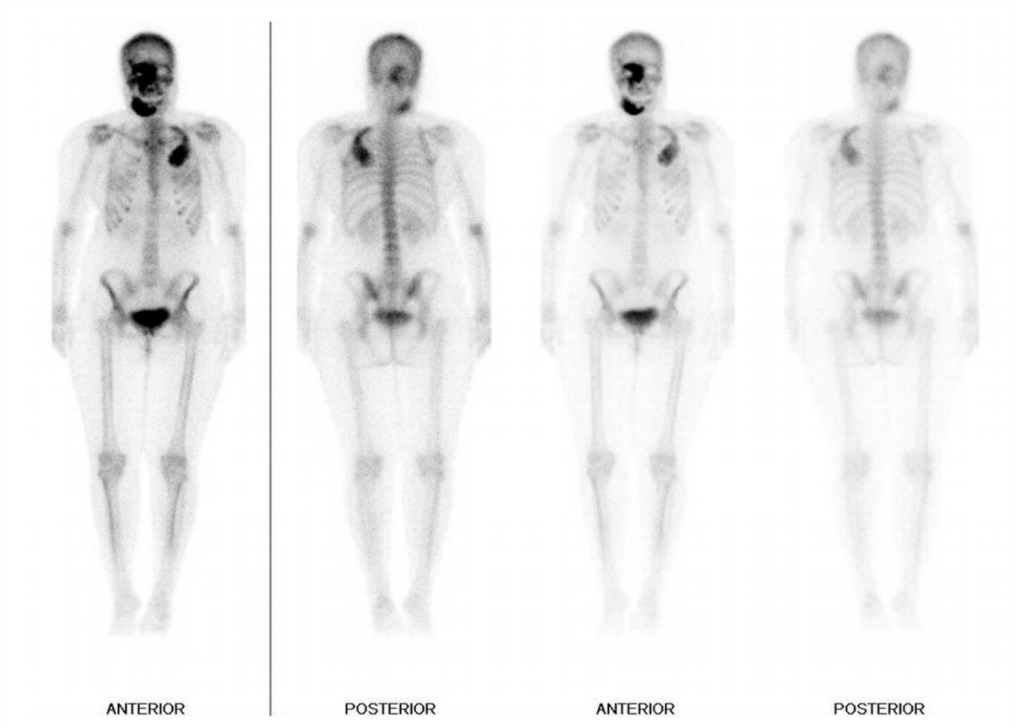

Figure 1. Whole-body bone scan findings at initial diagnosis consistent with polyostotic fibrous dysplasia with expansion and hyperaemia involving the right medial orbit (thought to be the sphenoid bone) and skull base, right mandible, and left superior rib.

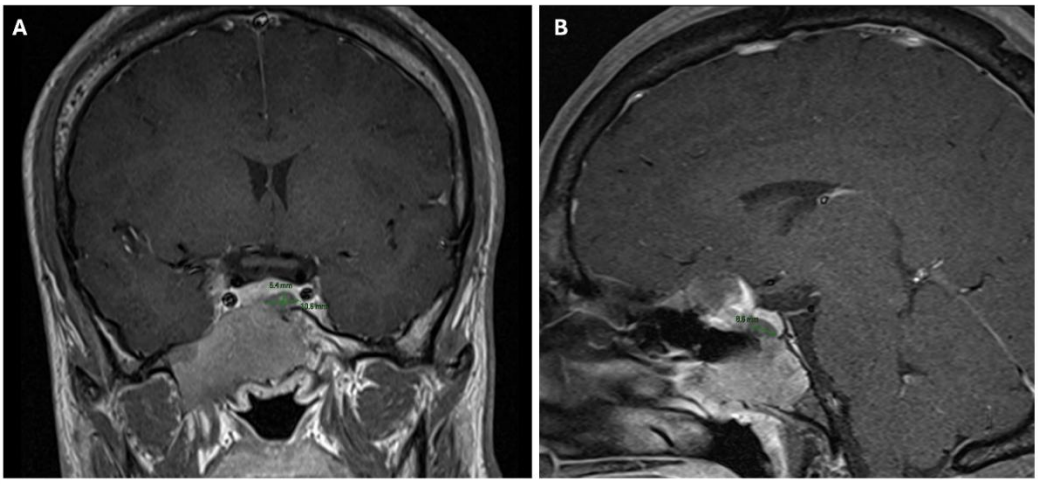

Figure 2. T1-weighted images of pituitary MRI at initial diagnosis. (A) coronal view showing T1-hypoenhancing 5.4 x 10.8 mm lesion. (B) Sagittal view of T1-hypoenhancing lesion with anterior-posterior diameter of 8.6 mm.

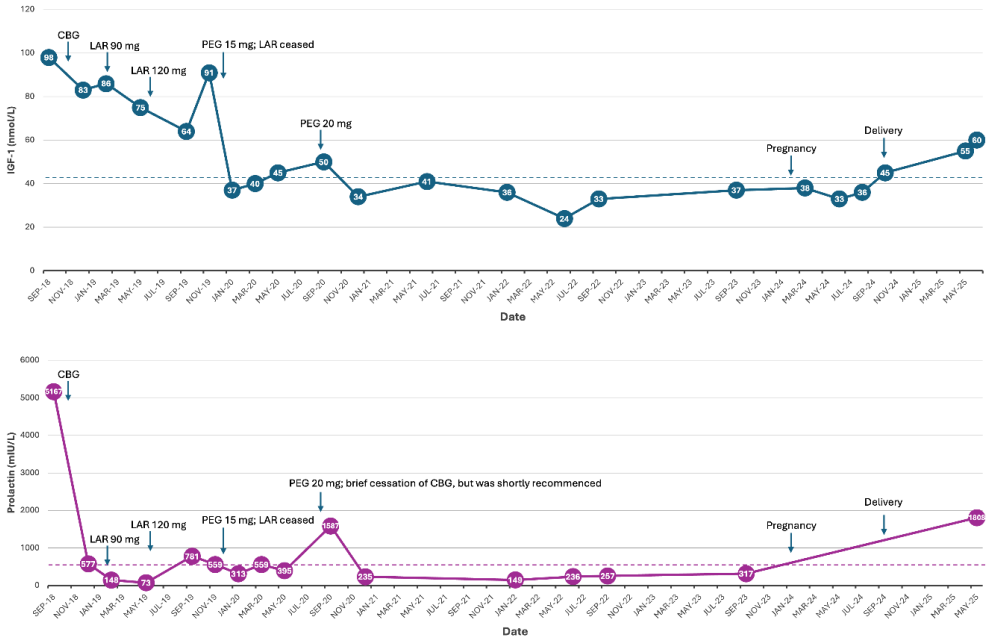

Figure 3. The measured levels of IGF-1 and prolactin from the initial diagnosis of McCune-Albright syndrome to the present day. The dotted line represents the upper limit of the normal range for each test (43 nmol/L for IGF-1 and 560 mIU/L for prolactin, respectively).

Abbreviations: CBG, cabergoline; LAR, lanreotide; PEG, pegvisomant.

This case report aims to educate the audience regarding McCune Albright syndrome (MAS), a rare genetic disorder associated with several endocrinopathies. It highlights the physiologic changes in the growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis and their implications for the diagnosis and monitoring of acromegaly during pregnancy. It discusses how the management of acromegaly in pregnant women with MAS might differ from those with pituitary adenoma.

Case

A 26-year-old woman presented with an eight-month history of oligomenorrhea without galactorrhea nor history of precocious puberty. On examination, there was expansion of the mandible. She had no bony pain or skin lesions. A diagnosis of MAS was based on the presence of polyostotic fibrous dysplasia involving the right medial orbit and skull base, right mandible, and left superior rib as seen on whole body bone scan (Fig 1); GH excess evidenced by elevated IGF-1, with lack of GH suppression following a 75mg glucose tolerance test; and hyperprolactinaemia(Table 1).

Magnetic resonance imaging (MRI) demonstrated a prominent pituitary gland with a 10.6×5.4×8.6mm T1-hypoenhancing lesion on the left, consistent with an adenoma(Fig 2A and 2B). There was extensive craniofacial fibrous dysplasia involving the right frontal, sphenoid, and mandibular bones, causing obliteration of the right sphenoid sinus, narrowing of the superior orbital fissure, and optic nerve compression within the right optic canal. Formal ophthalmology assessment showed pallor of the right optic disc, right temporal scotoma and axial proptosis.

Cabergoline was initiated and up-titrated to 1mg twice weekly, leading to normalisation of prolactin and return of regular menstrual cycles, but no change in IGF-1. Lanreotide was trialled, but did not normalise IGF-1 despite dose escalation to 120mg every 28 days. She was subsequently switched to pegvisomant, achieving IGF-1 normalisation at a dose of 20mg daily(Fig. 3). Treatment was associated with a gradual improvement in visual fields. Annual MRIs showed stable fibrous dysplasia and a slight reduction in pituitary adenoma size.

At age 31 years the patient conceived and cabergoline was discontinued. However, pegvisomant was continued during pregnancy to prevent expansion of craniofacial FD and visual compromise. During her pregnancy, she did not develop hypertension or gestational diabetes. Second-trimester morphology scans and subsequent growth scans (4-weekly) showed normal fetal development within the 40th-50th percentile. IGF-1 remained within the age-adjusted normal range throughout the pregnancy(Fig. 3). At 40 weeks' gestation, she had a spontaneous vaginal delivery of a healthy female infant weighing 3235g and measuring 50.5cm. Cabergoline was not resumed postpartum to facilitate breastfeeding. The patient's clinical findings remained stable at follow-up.

Discussion

MAS is a rare genetic disorder that arises from postzygotic gain-of-function mutations of the GNAS gene, resulting in mosaic activation of the α subunit of the G_s protein(1,2). It is defined as the combination of either fibrous dysplasia (FD) of the bone with one or more extra-skeletal features, or two or more extra-skeletal features, including café-au-lait skin macules, hyperfunctioning endocrinopathies (gonadotrophin-independent sex

steroid production, non-autoimmune hyperthyroidism, GH excess, or neonatal adrenal hypercortisolism) and intramuscular myxomas (1). The clinical phenotype of MAS is dependent on the number, cell type and viability of clones that arise from the mutated pluripotent cell(2).

In osteoprogenitor cells, constitutive G_s alpha subunit signalling leads to impaired differentiation and functioning, resulting in fibro-osseous tissue(2). FD is classified as monostotic or polyostotic depending on the number of skeletal sites involved, and clinical sequelae are dependent on location (1,2). Fibroblast growth factor-23 (FGF-23) overproduction is another feature of FD, although the development of hypophosphatemia is dependent on the degree of FGF-23 elevation, which correlates to FD burden (2). FD involving the craniofacial skeleton can cause compression of the optic or vestibulocochlear nerve, resulting in vision or hearing loss.

The pituitary is involved in 10-15% cases of MAS and approximately 85% of those with pituitary involvement experience combined GH and prolactin excess. Importantly, expansion of craniofacial FD can occur due to GH excess(2). Affected somatomammotrophs are usually spread diffusely throughout the pituitary, and surgical cure is generally only achieved with total hypophysectomy, even in cases where pituitary imaging suggests focal adenoma(2). As such, medical management with somatostatin analogues (SSAs) or GH receptor antagonists (pegvisomant) are first-line in patients with growth hormone excess in MAS. Cabergoline may also be utilised, particularly in the case of GH and prolactin co-secretion(1).

Data regarding pregnancy outcomes in patients with MAS are limited to small retrospective observational studies and case reports(3). While there have been case reports of skeletal complications during pregnancy, including increased FD-related bone pain, aneurysmal bone cysts, and malignant transformation of FD lesions, a retrospective cohort study comprising 14 pregnancies found no consistent association between pregnancy and FD-related bone pain or skeletal morbidity(3).

Pregnancy causes physiological changes in the GH/IGF-1 axis (Fig 3). By the fifth week of gestation, the placenta produces increasing amounts of GH, resulting in suppression of pituitary GH production in non-acromegalic patients(5). During the second half of pregnancy, placental GH is the main form of GH, stimulating increased production of IGF-1, above the age specific reference range for non-pregnant women(4). In women with acromegaly, high oestrogen concentrations from the placenta cause GH resistance, which may initially reduce IGF-1(4).Placental growth hormone increases, as in non-acromegalic patients, however the somatotropinoma continues to produce GH autonomously, and combined with placental GH, leads to an increase in IGF-1. Hence, an increase in IGF-1 does not necessarily reflect a change in pituitary GH. GH assays cannot distinguish between placental and pituitary GH. As such, biochemical

monitoring of acromegaly through IGF-1 levels during pregnancy is generally not recommended(6).

Clinical practice guidelines advising on the management of acromegaly during pregnancy are based on outcomes for patients with pituitary adenoma. Guidelines recommend that long-acting SSAs and pegvisomant should be stopped approximately two months prior to attempts to conceive; short-acting octreotide may be used until conception(6). It is recommended that medical therapy be administered only for tumour and headache control, though very few patients with GH-secreting tumours have been reported to have had enlargement of their tumours during pregnancy(4). However, in patients with MAS, the potential for GH-driven expansion of craniofacial FD could result in increased facial deformity and functional impairment. Safety data for the use of SSAs during pregnancy are limited to case reports. No malformations have been found in the children of these women, however decrease in uterine artery blood flow with short-acting octreotide has been reported(6). Similarly, safety data for Pegvisomant exposure during pregnancy are very limited, but no complications have been reported(6). In this patient, pegvisomant was safely continued, likely preventing ocular complications related to GH-driven FD expansion, achieving favourable maternal and fetal outcomes.

Learning Points

1. MAS is defined as the combination of either FD of the bone with one or more extra-skeletal features, or two or more extra-skeletal features (café-au-lait skin macules, hyperfunctioning endocrinopathies or intramuscular myxomas).
2. Pregnancy causes changes in GH and IGF-1 levels that impact the diagnosis and monitoring of patients with acromegaly.
3. While treatment is stopped during pregnancy in most patients with a GH-secreting pituitary adenoma, management of GH excess in MAS should be individualised because of the potential for GH-driven FD expansion, particularly in the craniofacial skeleton.
4. Although data on pegvisomant use in pregnancy and breastfeeding are limited, existing reports indicate it may be safe in selected cases to prevent FD-associated complications.

1. Javaid, M.K., Boyce, A., Appelman-Dijkstra, N., Ong, J., Defabianis, P., Offiah, A., Arundel, P., Shaw, N., Pos, V.D., Underhil, A., Portero, D., Heral, L., Heegaard, A.-M., Masi, L., Monsell, F., Stanton, R., Dijkstra, P.D.S., Brandi, M.L., Chapurlat, R. and Hamdy, N.A.T. (2019). Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium. Orphanet Journal of Rare Diseases, 14(1).

2. Boyce, A.M. and Collins, M.T. (2020). Fibrous Dysplasia/McCune-Albright Syndrome: A Rare, Mosaic Disease of Gαs Activation. Endocrine Reviews, [online] 41(2), p.bnz011.

3. Boyce, A.M., Casey, R.K., Ovejero Crespo, D., Murdock, C.M., Estrada, A., Guthrie, L.C., Brillante, B.A., Gomez-Lobo, V., Nieman, L.K. and Collins, M.T. (2019). Gynecologic and reproductive outcomes in fibrous dysplasia/McCune-Albright syndrome. Orphanet Journal of Rare Diseases, 14(1).

4. Muhammad, A., Neggers, S.J. and van der Lely, A.J. (2016). Pregnancy and acromegaly. Pituitary, 20(1), pp.179–184.

5. Luger, A., Broersen, L.H.A., Biermasz, N.R., Biller, B.M.K., Buchfelder, M., Chanson, P., Jorgensen, J.O.L., Kelestimur, F., Llahana, S., Maiter, D., Mintziori, G., Petraglia, F., Verkauskiene, R., Webb, S.M. and Dekkers, O.M. (2021). ESE Clinical Practice Guideline on functioning and nonfunctioning pituitary adenomas in pregnancy. European Journal of Endocrinology, [online] 185(3), pp.G1–G33.

6. Katznelson, L., Laws, E.R., Melmed, S., Molitch, M.E., Murad, M.H., Utz, A. and Wass, J.A.H. (2014). Acromegaly: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism, [online] 99(11), pp.3933–3951.

Aromatase deficiency; a rare cause of growth in adulthood (127173)

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Case Summary

A 25-year-old man presented to the ED after left finger fracture from a sporting injury requiring surgical management. It was noted on x-ray that the growth plates in the hand were unfused (Figure 1), and he was referred for further work up.

His history was significant for albinism and previous appendicectomy. He was taking no regular medications and did not use recreational drugs. He reported normal adrenarche with puberty starting at age 15 with development of normal male sexual characteristics and shaving daily. Libido and sexual function were reported as normal with daily morning erections. There was no family history of endocrinopathy or ambiguous genitalia in female relatives.

On examination, he was 197cm tall with an arm span of 197cm and weight of 99.7kg. He was over 30 cm taller than his mid parental height of 160 cm and noted to have grown 25 cm since the age of 19. There were no clinical features of growth hormone excess. Testicular examination noted normal testicular volume of greater than 25 ml bilaterally. He had sparse axillary and pubic hair with no gynecomastia.

X-ray imaging of his left wrist indicated skeletal age of 15 years despite chronological age of 25 (Figure 2). Additional x-rays identified partial fusion of left knee distal femoral and proximal tibial and fibular epiphyses (Figure 3a), partial fusion of left radial olecranon and medial epicondylar epiphyses and united capitellar and trochlear epiphyses of the left elbow (Figure 3b). He had partial fusion of the hip joints at the superior femoral capital epiphyses and greater and lesser trochanter epiphyses (Figure 3c).

Morning serum testosterone was 63.4nmol/L (10 - 27.6 nmol/L), oestradiol <10 pmol/L (40 – 60pmol/L), and SHBG 58nmol/L, FSH 16 IU/L (0-10IU/L) and LH 5 IU/L (0-10IU/L). These results were persistent on repeat testing with Immunoassay and LCMS (Table 1). His pituitary and other androgenic hormone levels were within normal limits. He showed evidence of elevated bone turnover with CTX 1558 and P1NP 286 with normal calcium PTH, ALP, vitamin D and renal function (Table 1). Bone density was severely low, particularly in wrist and lumbar spine with Z-score of -3.2 and -2.1 respectively.

Chromosomal analysis was 46XY and semen analysis showed normal sperm count of 153 million with normal motility and form (Table 1).

Clinical diagnosis of aromatase deficiency was made, and he was referred for genetic screening. Genetic microarray and gene panel returned homozygous deletion in chromosome region 15q21.2 a pathogenic variant known to be associated with autosomal recessive aromatase deficiency. The patient was commenced on low dose transdermal oestradiol via patch twice a week with slow dose titration to limit side effects aiming to achieve serum oestradiol levels in the upper range of normal for men.

He is planned to have repeat radiography imaging at 9 months post treatment initiation to monitor growth plate closure, this will be due in September 2025.

Literature Review

Aromatase deficiency is a rare syndrome of abnormal growth in adults with a documented 8 cases in the literature since 1998 (1). Oestradiol is synthesized from testosterone by the action of aromatase, or CYP19A1, a type II cytochrome CYP450 enzyme that catalyses the conversion of C19 androgens to C18 oestrogens (2). Germline loss-of-function variants in chromosome 15q21, the gene encoding aromatase, result in aromatase deficiency (3). Gonadal steroid hormones are critically important in establishing peak bone mass for both sexes. In females, aromatase deficiency presents clinically as ambiguous genitalia in infancy and progressive virilization during puberty, however in males, presentation can be delayed as pubertal development is normal. Fertility is variably affected on review of case reports available in the literature (2). The underlying mechanisms for this have not been fully elucidated; however, it has been described that oestrogen replacement does not appear to improve fertility in these cases (2,8).

There is delayed closure of epiphysial plates in both sexes and therefore continued growth in young adulthood which is often the first sign of medical investigation in young men. In both sexes osteopenia is present concluding the vital role of oestrogen in skeletal maturation and bone density (4).

Oestrogen affects the growth plates in a biphasic manner, with relative low levels of oestrogen increasing the cartilage growth and relative higher concentration of oestrogen promoting mineralisation of the cartilage and growth arrest (5). Animal studies and published case reports have shown improvement in clinical outcomes including bone plate closure and improvement in bone density with replacement of oestrogen (4,6). Case report data have indicated improvement in bone mineral density with replacement of oestrogen in the order of 1 standard deviation and most pronounced in the first year of treatment (2,7). It is reported that bone maturation and closure of epiphysial plates with oestrogen replacement occurs after 6-9 months of therapy and then should be continued lifelong to prevent bone loss and to mitigate the risk of cardiovascular disease (1).

Key Points

- Aromatase deficiency in men is a rare cause of growth in adulthood, however due to normal pubertal development diagnosis is often delayed.
- Aromatase deficiency should be among the diagnostic considerations in young adult men with unfused epiphyses or bone age significantly delayed compared with chronologic age.
- Hand and wrist radiography, measurement of serum oestradiol, testosterone and luteinizing hormone should be used to diagnose the condition clinically and then should be confirmed with genetic testing.
- Men diagnosed with aromatase deficiency should receive oestradiol therapy for completion of bone maturation. Long term treatment with oestradiol with the therapeutic aim for oestradiol levels within the normal range for males should be continued lifelong to improve their bone mass and reduce risk of metabolic dysfunction
- Men with aromatase deficiency appear to be variably affected by fertility and oestrogen replacement does not appear to improve fertility in these cases.

Table 1: Biochemistry			
	Initial testing at diagnosis	Following 5 months of treatment	Reference Range
Testosterone	Immunoassay > 52.0	Immunoassay 45.1	10 – 35 nmol/L
	LCMS 63.4	LCMS n/a	10 - 27.6 nmol/L
SHBG	58	46	13 – 71 nmol/L
FSH	16	12	1 – 10 IU/L
LH	5	5	1 – 10 IU/L
Oestradiol	Immunoassay <100pmol/L	Immunoassay 130	<146 pmol/L
	LCMS <10pmol/L	LCMS n/a	10 – 130 pmol/L
CTX	1240	1547	100 – 600 ng/L
P1NP	295	523	15 -80 ug/L
CorCa	2.49	2.35	2.15 – 2.65 mmol/L
PTH	3.5	-	2.0 – 8.5 pmol/L
ALP	198	280	30 – 110 units/L
25-0H-Vit D	44	82	>50 nmol/L
DHT	2.67	-	0.4 – 2.5 nmol/L
Androstenedione	3.2	-	1.2 – 4.7 nmol/L
Progesterone	1.0	-	1.2 – 4.8nmol/L
DHEAS	4.2	-	2.3 – 18.7 nmol/L
bHCG	< 2	-	<2 IU/L
ACTH	2.1	-	1.6 – 13.9 pmol/L
Cortisol	275	-	145 – 619 nmol/L
Prolactin	122	-	45 – 375 mIU/L
Growth Hormone	<1	-	0 – 7 mIU/L
IGF-1	14	-	12 – 25 nmol/L
TSH	1.08	-	0.5 – 4.0 mIU/L
T4	16.3	-	10.0 – 23.0 pmol/L
Semen Analysis	Volume of ejaculate 3.5ml Sperm concentration: 153 mil Motility: 72% Progressive motility: 67% Morphology: 7% normal forms	-	>1.5ml >15 mil >40% >32% >4%

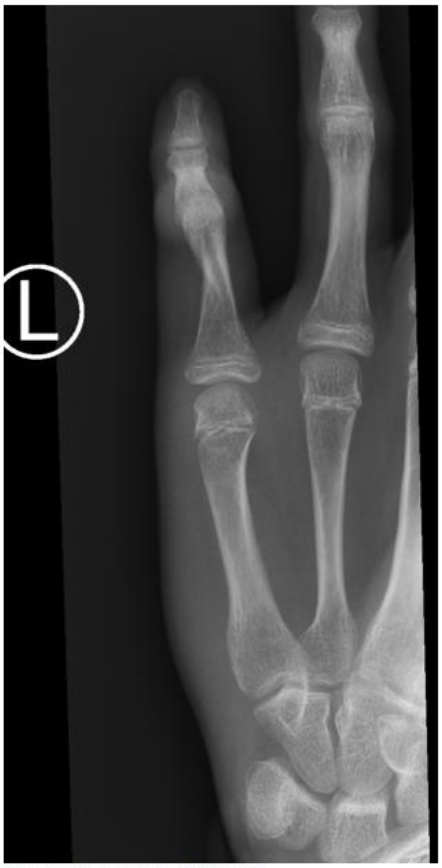

Figure 1: x-ray Left Hand

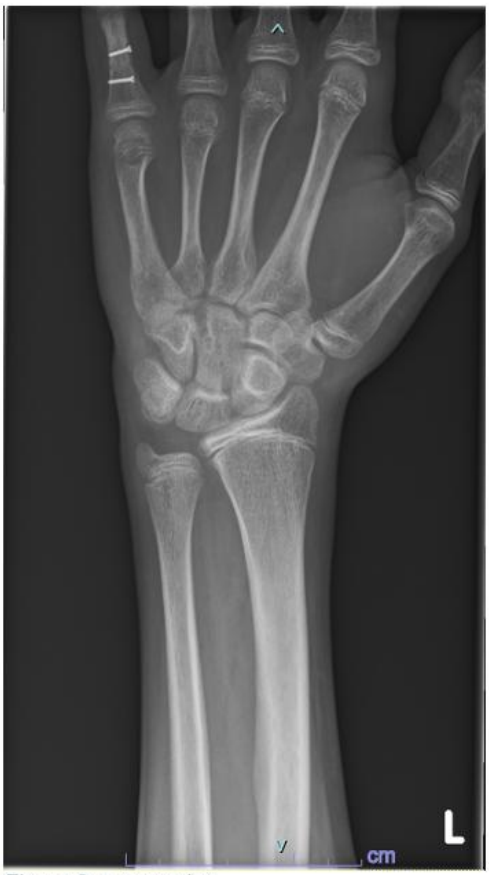

Figure 2: x-ray wrist

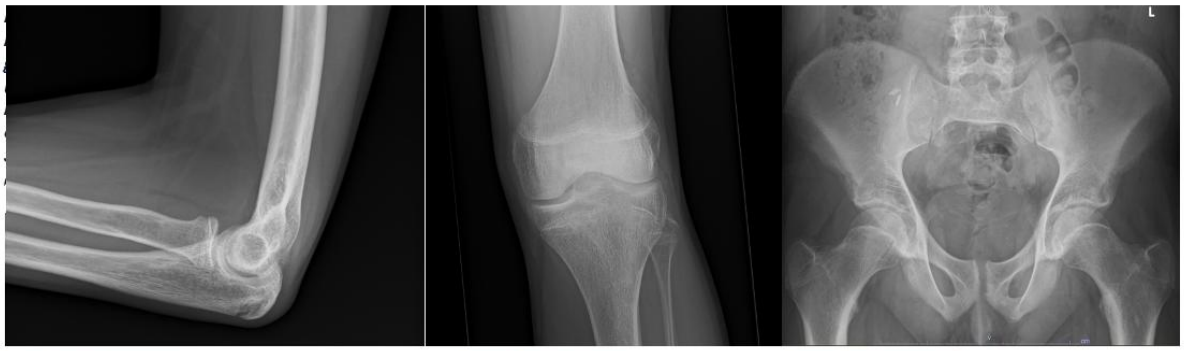

Figure 3a: x-ray elbow

Figure 3b: x-ray knee

Figure 3c: x-ray pelvis

1. 1. Rochira, V., Carani, C. Aromatase deficiency in men: a clinical perspective. Nat Rev Endocrinol 5, 559–568 (2009). https://doi.org/10.1038/nrendo.2009.176
2. 2. Miedlich SU, Karamooz N, Hammes SR. Aromatase deficiency in a male patient - Case report and review of the literature. Bone. 2016 Dec;93:181-186. doi: 10.1016/j.bone.2016.09.024. Epub 2016 Sep 29. PMID: 27693882
3. 3. Fukami M, Ogata T. Congenital disorders of estrogen biosynthesis and action. Best Pract Res Clin Endocrinol Metab. 2022 Jan;36(1):101580. doi: 10.1016/j.beem.2021.101580. Epub 2021 Sep 13. PMID: 34538723.

4. 4. Carani C, Qin K, Simoni M, Faustini-Fustini M, Serpente S, Boyd J, Korach KS, Simpson ER. Effect of testosterone and estradiol in a man with aromatase deficiency. N Engl J Med. 1997 Jul 10;337(2):91-5. doi: 10.1056/NEJM199707103370204. PMID: 9211678.

5. 5. Cutler, G. B. Jr. The role of estrogen in bone growth and maturation during childhood and adolescence. J. Steroid Biochem. Mol. Biol. 61,141–144 (1997).

6. 6. Simpson ER, Clyne C, Rubin G, Boon WC, Robertson K, Britt K, Speed C, Jones M. Aromatase--a brief overview. Annu Rev Physiol. 2002;64:93-127. doi: 10.1146/annurev.physiol.64.081601.142703. PMID: 11826265.

7. 7. Bilezikian JP, Morishima A, Bell J, Grumbach MM. Increased bone mass as a result of estrogen therapy in a man with aromatase deficiency. N Engl J Med. 1998 Aug 27;339(9):599-603. doi: 10.1056/NEJM199808273390905. PMID: 9718379.

8. 8. Rochira V, Granata AR, Madeo B, Zirilli L, Rossi G, Carani C. Estrogens in males: what have we learned in the last 10 years? Asian J Androl. 2005 Mar;7(1):3-20. doi: 10.1111/j.1745-7262.2005.00018.x. PMID: 15685347.

ESA CLINICAL WEEKEND 2026

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