Seeking a basic solution for a complex case of periostitis

Michael Bennett[1, 2], **Jerry Greenfield**[1, 3, 2], **Jackie Center**[1, 3, 2]

1. Department of Endocrinology, St Vincent's Hospital , Darlinghurst, NSW, Australia

2. University of New South Wales, Sydney, NSW, Australia

3. Garvan Institute of Medical Research, Darlinghurst, NSW, Australia

CASE

A 68-year-old woman presented to the emergency department with a four-month history of progressive lower limb weakness and lethargy associated with multiple small and large joint pains, worst in the bilateral shoulders, hips, elbows, and hands. She had lost 12 kilograms (17% body weight) over 12 months, and was no longer able to mobilise or perform her activities of daily living without assistance.

Her medical history included a single left lung transplant in August 2018 for pulmonary fibrosis and emphysema. Transplantation was complicated by *Lomentospora prolificans* colonisation with mycetoma formation in the right lung requiring long-term treatment with voriconazole and terbinafine. She was diagnosed with osteoporosis in August 2017 (femoral neck T-score -3.0SD) and had been receiving denosumab 60mg six monthly since diagnosis. She had no history of fragility fracture. She was diagnosed with type two diabetes and primary hypothyroidism in 2011, which were well controlled.

Her regular medications included: immunosuppressants (tacrolimus, mycophenolate, and prednisone 7.5mg daily), antimicrobials (azithromycin, trimethoprim/sulfamethoxazole, valganciclovir, terbinafine, and voriconazole 300mg TDS), colecalciferol, levothyroxine, and metformin. She had ceased calcium supplements one-month prior on the advice of her transplant team.

Initial investigations (Table 1) revealed hypophosphataemia (0.58 mmol/L) and secondary hyperparathyroidism (PTH 25.6 pmol/L, corrected calcium 2.30 mmol/L), normal 25-hydroxyvitamin D, renal function and magnesium. Despite treatment with denosumab her bone turnover markers were unsuppressed (P1NP 104 ug/L, CTX 307 ng/L). Voriconazole concentration was supratherapeutic (6.2 mg/L, target 3-4mg/L). 24-hour urine collection demonstrated renal calcium conservation and phosphate wasting.

Table 1: Initial investigations including serum (left) and urine (right) results

Parameter	2/5/20	8/5/20	20/5/20	Reference
Creatinine		72		45-90 umol/L
eGFR		74		>60 mL/min/1.73m^2
Urea		7.3		3.5-8 mmol/L
Corrected calcium		2.30		2.1-2.6 mmol/L
Phosphate		0.58		0.7-1.5 mmol/L
PTH	25.6			2-9 pmol/L
25(OH)vit D		65		50-150 nmol/L
1,25$(OH)_2$vit D			93	60-200 pmol/L
Albumin		28		33-48 g/L
ALP		107		30-110 U/L
GGT		70		0-35 U/L
AST		17		0-30 U/L
ALT		6		0-35 U/L
CTX		307		50-800 ng/L
P1NP		104		8-84 ug/L
FGF23		189		23.2-95.4 ng/L
Voriconazole	6.2 mg/L on 15/5/20			

24h Urine	7/5/20	Reference
Volume	1.459	L
Calcium conc	0.4	mmol/L
Calcium excr	0.6	2.5-8 mmol/day
Phosphate conc	20.7	mmol/L
Phosphate excr	30.2	mmol/day
Creatinine conc	3.3	mmol/L
Creatinine excr	4.4	mmol/day
TmP/GFR	0.116	0.8-1.35 mmol/L

Urine metabolic screen (03/7/20): no abnormality
Urine glucose: 0

Skeletal x-rays showed widespread ill-defined calcific deposits consistent with thick periosteal reactions in the hands, forearms, shoulders, and hips (Image 1 and 2). Radionuclide bone scan demonstrated multiple areas of abnormal tracer uptake corresponding to radiological areas of periosteal new bone formation (Image 3). FDG-PET, DOTATATE-PET, and sestamibi parathyroid scintigraphy were normal (Image 3).

Image 1: X-ray images of right hand, left shoulder, hips and pelvis, right elbow, and lumbar spine

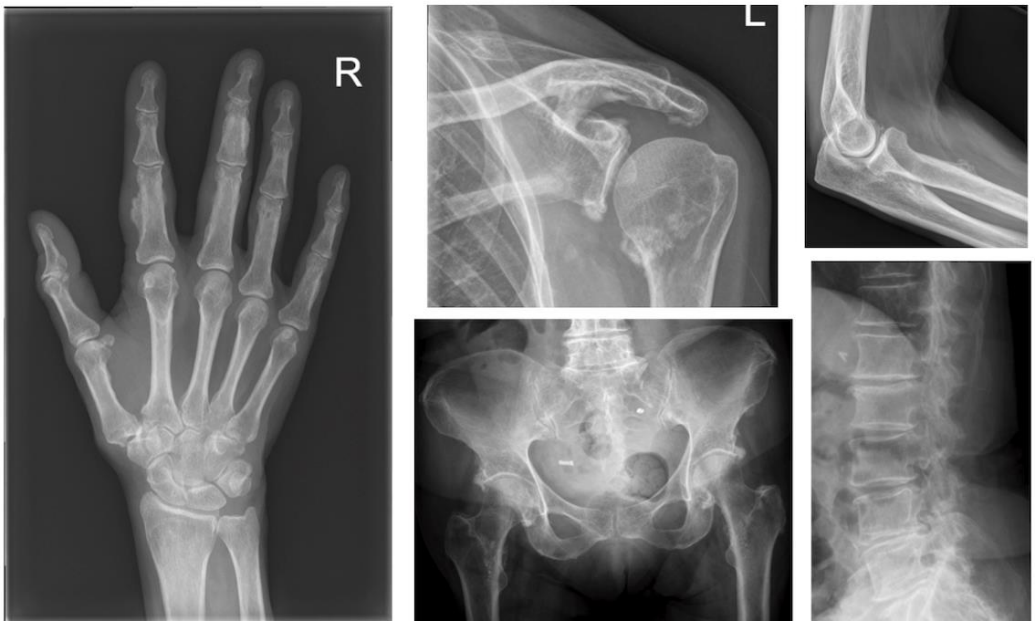
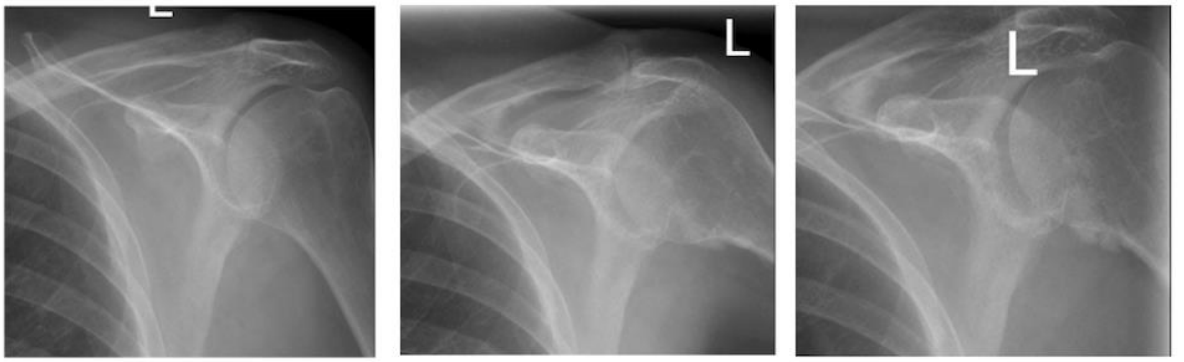
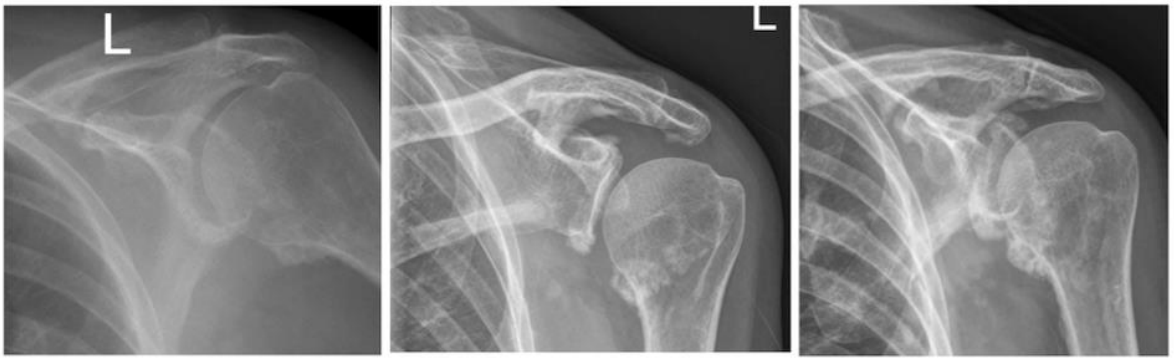


Image 2: Evolution of radiological changes in the left shoulder

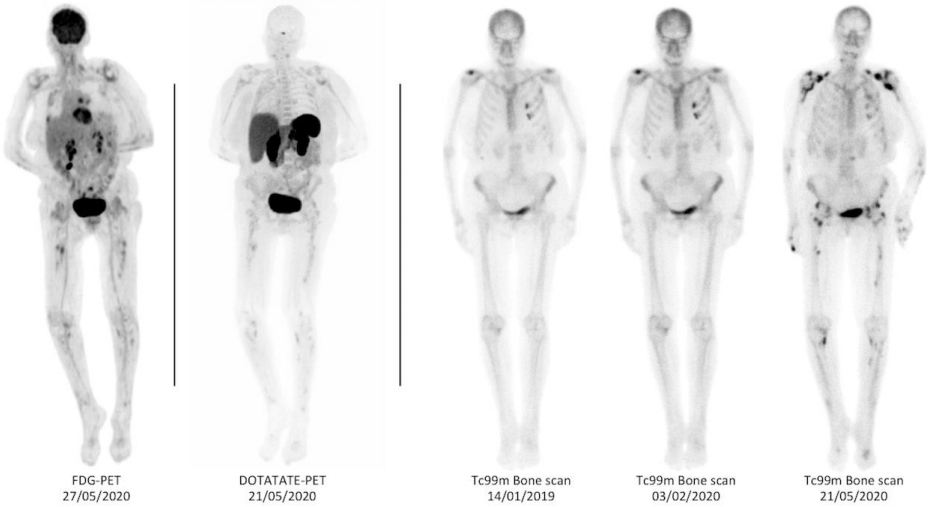


07/01/2019 31/10/19 15/11/19



22/01/2020 04/02/2020 18/05/2020

Image 3: Nuclear medicine studies (left to right): FDG-PET, DOTATATE-PET, and serial Tc99m Bone scans



DXA demonstrated normal T-scores in the lumbar spine and osteopenic T-scores in the right femoral neck (-2.0SD). Right total hip bone density had increased 25% over 3 years.

The emergence of widespread nodular periostitis and secondary hyperparathyroidism after transplantation suggested an acquired cause. The skeletal distribution and lack of digital clubbing argued against hypertrophic pulmonary osteoarthropathy. Imaging studies did not indicate a malignant source.

Voriconazole-related periostitis was suspected secondary to fluoride toxicity. This was confirmed by a plasma fluoride concentration (31 nmol/L, reference range 0.5-1.5 nmol/L).

Denosumab was ceased and calcium and calcitriol were commenced. *Lomentospora* was isolated from bronchoalveolar washings that was sensitive only to combination voriconazole and terbinafine. Access was sought to a novel orotomide antifungal (F901318) that was undergoing phase III clinic trials and was effective against *Lomentosporta*, however the manufacturer declined. To promote fluoride excretion, sodium bicarbonate was commenced for urinary alkalinisation (target pH >7.5).

Over the next five weeks, serum fluoride concentration slowly reduced to a nadir of 13 umol/L (Figure 2). With intensive rehabilitation her weight increased 3.6kg and mobility improved so that she was able to stand unassisted and mobilise with a four wheeled walker prior to discharge (Table 2).

Graph 1: Plasma fluoride concentration and voriconazole dose versus time

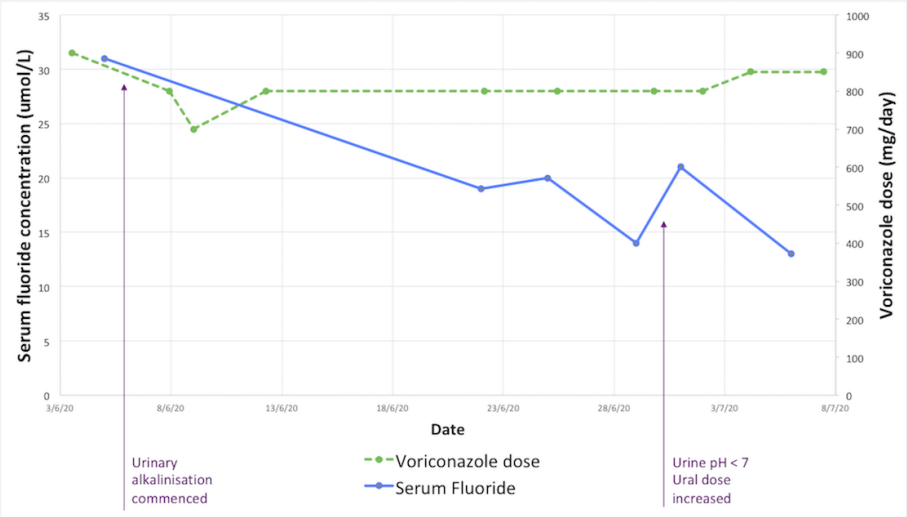


Table 2: Progress following calcium and calcitriol treatment and urinary alkalinisation

Parameter	6/7/20	4/6/20	2/5/20	Reference
Creatinine	67	74	69	45-90 umol/L
eGFR	81	72	78	>60 mL/min/1.73m²
Corrected calcium	2.45	2.41	2.19	2.1-2.6 mmol/L
Phosphate	0.93	0.91	0.55	0.7-1.5 mmol/L
PTH	6.2	7.7	25.6	2-9 pmol/L
ALP	208	254	103	30-110 U/L
Voroconazole	1.0	3.4	0.4	mg/L
Calcium dose	500mg	500mg	Nil	/day
Phosphate dose	Nil	Nil	1000mg	/day
Voriconazole dose	850mg	900mg	1200mg	/day
Calcitriol dose	0.5mcg			/day
Mobility: STS	Standby assist	Moderate assist	Full assist	
Mobility: walking	Independent 4WW	Standby assist with 4WW	Full assist	
Weight	62.5	61	58.7	kg

Four weeks later, she was readmitted with deteriorating respiratory function, acute kidney injury and skeletal pain. After careful consideration and discussion with her treating physicians and family she decided to discontinue active treatment and receive terminal care. She died of respiratory failure six days later.

LITERATURE REVIEW

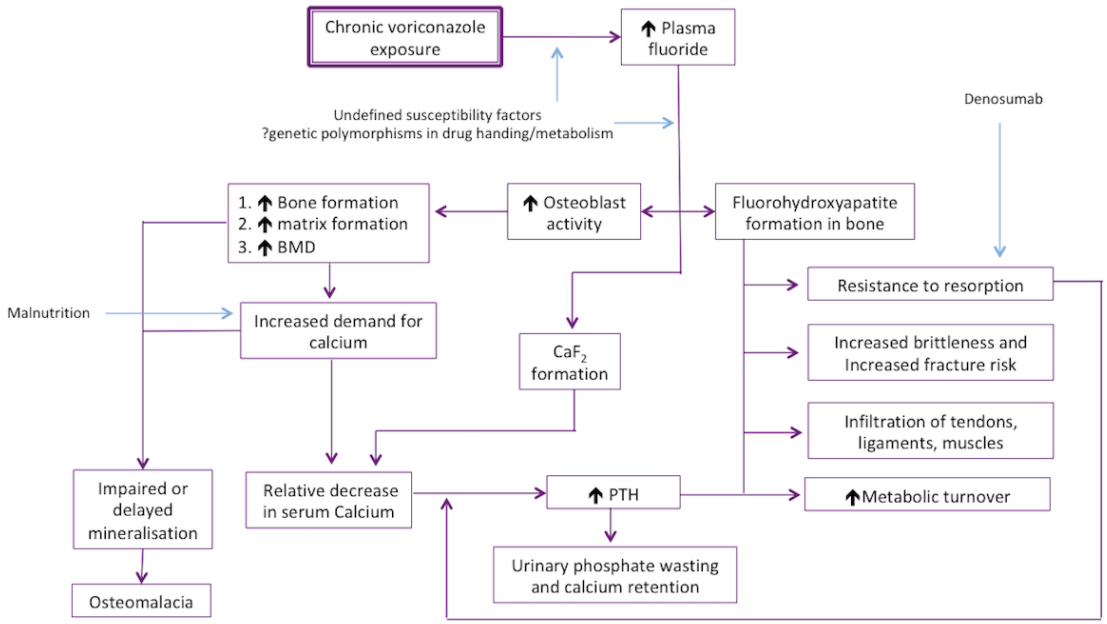
Voriconazole is a broad-spectrum triazole antifungal agent with activity against *Lomentospora*, *Aspergillus*, *Candida*, and *Fusarium* species(1). It is widely used in the post-transplant setting where fungal colonisation and invasive fungal infections are common. Since the first description of the condition among a series of lung transplant recipients in 2009, several other case series' have been published(2-6).

The condition is characterised by diffuse, irregular, periostitis and exostosis on x-ray, raised ALP, generalised bone and joint pain, and multifocal uptake on radionuclide bone scintigraphy(3). The clinical features are indistinguishable from subacute fluoride intoxication, which lead authors to conclude that these conditions have a

common aetiology. This theory is supported by several observations: (a) significantly elevated plasma fluoride concentrations are universally observed among cases, (b) each voriconazole molecule contains three fluoride atoms and five precent of the dose is metabolised to fluorine, and (c) discontinuation of voriconazole results in a rapid normalisation of serum fluoride concentration that coincides with resolution of clinical and radiological features(3-5).

Excess fluoride exposure has deleterious cellular, mineral, matrix, and hormonal effects on bone (Image 4). Fluoride ions have a similar size and electrical charge to hydroxide ions but greater affinity for calcium(7). They replace hydroxide ions within the hydroxyapatite lattice forming fluoroapatite(8). This alters the physical and mechanical properties of the lattice increasing stability and density but making it brittle and more resistant to resorption(7, 8). Increased skeletal demand for calcium combined with resistance to resorption results in secondary hyperparathyroidism, which may lead to urinary phosphate wasting(8). Fluoride also has anabolic effects, stimulating osteoblasts to make excess new, poor quality, unmineralised bone (osteomalacia)(8). Furthermore, it accumulates most readily in the periosteal and endosteal regions of bone, explaining the pronounced radiological changes in these areas(9).

Image 4: Proposed pathophysiological model incorporating case-specific factors (denosumab & malnutiriton)



While the incidence of voriconazole-related periostitis is unknown, a retrospective review of 242 haematopoietic stem cell recipients receiving voriconazole at the Mayo Clinic found 32 (13.2%) patients had serum fluoride measurement performed to investigate musculoskeletal pain, of which 29 (93%) were elevated(10). Pain associated with voriconazole use was observed in 15.3% of patients after one year of treatment and 35.7% of patients after two years of treatment(10). No significant association between serum voriconazole concentration and plasma fluoride was observed(10).

Those who develop periostitis have significantly higher serum fluoride and ALP and cumulative voriconazole doses, compared with those who do not develop skeletal disease(4). Mean serum fluoride concentrations >8 umol/L are associated with skeletal toxicity and elevated fluoride concentrations with bony pain in the setting of voriconazole use is highly suggestive of periosotitis(3, 4) .

Pharmacogenomic variation in drug metabolising enzymes (particularly CYP2C19) is thought to account for individual susceptibility to this adverse effect(1, 3). Despite fluoride being predominantly renally excreted, renal function was shown not to predict serum fluoride levels among transplant patients taking voriconazole(3).

Discontinuation of voriconazole is the only curative treatment for voriconazole-related periosotitis. In a series of ten cases, all experienced normalisation of ALP and resolution of symptoms within two months of cessation(3). In cases where cessation is not possible, supportive care involves analgesia, correction of malnutrition, and treatment of hyperparathyroidism with calcium and calcitriol. As fluoride absorption, distribution, and excretion are pH-dependent, and not homeostatically regulated, we attempted urinary alkalinisation to increase free fluoride excretion(9). While this appeared to reduce serum fluoride concentrations in the short term, the long-term efficacy of this approach in preventing disease progression requires further investigation.

LEARNING POINTS

1. Chronic voriconazole exposure is associated with skeletal toxicity in a subset of individuals.
2. Clinical features include: diffuse, irregular periostitis and exostosis on x-ray, raised ALP, generalised bone and joint pain, and multifocal uptake on radionuclide bone scintigraphy.
3. All reported cases have been associated with high serum fluoride concentrations.
4. Discontinuation of voriconazole results in normalisation of serum fluoride concentration and resolution of signs and symptoms.
5. If it is not possible to cease voriconazole, supportive therapy involves calcium and calcitriol supplementation and correction of any malnutrition.
6. Urinary alkalinisation may increase fluoride excretion, although further studies are required.

REFERENCES

1. Scholz I, Oberwittler H, Riedel KD, Burhenne J, Weiss J, Haefeli WE, et al. Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to CYP2C19 genotype. British journal of clinical pharmacology. 2009;68(6):906-15.
2. Ayub A, Kenney CV, McKiernan FE. Multifocal nodular periostitis associated with prolonged voriconazole therapy in a lung transplant recipient. JCR: Journal of Clinical Rheumatology. 2011;17(2):73-5.
3. Wermers RA, Cooper K, Razonable RR, Deziel PJ, Whitford GM, Kremers WK, et al. Fluoride excess and periostitis in transplant patients receiving long-term voriconazole therapy. Clinical Infectious Diseases. 2011;52(5):604-11.
4. Moon WJ, Scheller EL, Suneja A, Livermore JA, Malani AN, Moudgal V, et al. Plasma fluoride level as a predictor of voriconazole-induced periostitis in patients with skeletal pain. Clinical Infectious Diseases. 2014;59(9):1237-45.
5. Chen L, Mulligan ME. Medication-induced periostitis in lung transplant patients: periostitis deformans revisited. Skeletal radiology. 2011;40(2):143-8.
6. Wang T, Wang T, Altman R, Eshaghian P, Lynch III J, Ross D, et al. Periostitis secondary to prolonged voriconazole therapy in lung transplant recipients. American Journal of Transplantation. 2009;9(12):2845-50.
7. Johnston NR, Strobel SA. Principles of fluoride toxicity and the cellular response: a review. Archives of Toxicology. 2020:1-19.
8. Teotia S, Teotia M, Singh K, editors. Highlights of forty years of research on endemic skeletal fluorosis in India. 4th International workshop on fluorosis Prevention and Defluoridation of water; 2004.
9. Buzalaf MAR, Whitford GM. Fluoride metabolism. Fluoride and the oral environment. 22: Karger Publishers; 2011. p. 20-36.
10. Barajas MR, McCullough KB, Merten JA, Dierkhising RA, Bartoo GT, Hashmi SK, et al. Correlation of pain and fluoride concentration in allogeneic hematopoietic stem cell transplant recipients on voriconazole. Biology of Blood and Marrow Transplantation. 2016;22(3):579-83.

Ectopic Anti-Diuretic Hormone Secretion in a Patient with Metastatic Neuroendocrine Tumour Presenting with Hyponatraemia

Rebecca Foskey[1], Emma Boehm[2], Andra Desra[3], Cherie Chiang[1, 3], John Wentworth[1]

1. Diabetes & Endocrinology, Royal Melbourne Hospital, Melbourne, VIC, Australia

2. Endocrinology and Diabetes, Western Health, Sunshine, Victoria, Australia

3. Department of Internal Medicine, Peter MacCallum Cancer Institute, Parkville, VIC, Australia

A 45-year-old male presented to the emergency department with acute malaise and fatigue. He had a past medical history of depression, anxiety and childhood bladder surgery for atonic bladder and was not prescribed any regular medications. He was clinically euvolaemic and his serum sodium was 121 mmol/L. Full blood examination, liver function tests, other electrolytes, creatinine, urea and tests for secondary causes of hyponatraemia were normal. Paired serum and urine osmolality were 252 mOsm/kg and 261 mOsm/kg respectively, with urine sodium 143 mmol/L. CT brain was unremarkable and a CT chest revealed occasional intraparenchymal knots and subpleural lung nodules which were classified as low risk and not in need for further investigation according to Fleischner lung nodule guidelines.

A diagnosis of idiopathic syndrome of inappropriate ADH (SIADH) was made and the patient was treated with a 750 mL fluid restriction which, over the subsequent year, maintained serum sodium between 128 and 134 mmol/L.

Fifteen months after the initial presentation with hyponatraemia, the patient presented to his general practitioner with back pain after a bicycle accident. Imaging revealed extensive lytic lesions throughout the humerus and spine, with widespread lymphadenopathy above and below the diaphragm. On GATATE PET scan, the spinal metastases were intensely avid but there was no significant uptake in the lymphadenopathy. Conversely, FDG PET revealed uptake in both the osseous metastases and the lymphadenopathy. Neither scan showed any focal avidity to suggest the location of a primary tumour. An excisional lymph node biopsy was performed. Histology revealed a Grade 3 metastatic neuroendocrine tumour of unknown primary, with Ki67 20.4% (<1/10 mitoses/HPF), strong and diffuse staining for synaptophysin and chromogranin, and focal but weak positive staining for cytokeratin AE1 and AE3. A research-grade polyclonal antibody raised against the first 100 amino acids of the vasopressin-neurophysin 2-copeptin precursor identified nests of immunoreactive tumour cells, confirming their ability to produce ADH prohormone. Copeptin concentrations in stored serum samples were dramatically elevated (>5000 pmol/L; no reference range for hyponatraemia; for non-water deprived, non-fasting adults normal <16.3 pmol/L), suggesting the efficiency of prohormone processing to ADH and copeptin by the tumour was very low.

The NET was initially treated with external beam radiotherapy to the spine, carboplatin/etoposide and zoledronic acid. Disease progression prompted a change to second line capecitabine/temozolamide in addition to a left femoral internal fixation for prophylaxis against pathological fracture.

The fluid load associated with this procedure precipitated severe symptomatic hyponatraemia (nadir sodium 113 mmol/L), treated with intravenous 3% saline and 500mL fluid restriction. The sodium concentration become progressively more difficult to maintain over subsequent months despite adherence to the fluid restriction. Further hospital admissions for hyponatraemia were precipitated by pain crises related to bony metastases. FOLFIRI chemotherapy and nivolumab monotherapy were trialled to halt disease progression without effect and daily tolvaptan was prescribed to maintain a safe sodium concentration.

Discussion

Hyponatraemia, defined as a serum sodium of less than 135mmol/L, is a common finding in the inpatient oncology setting, with one centre reporting a prevalence of 47% among inpatients with a diagnosis of cancer[1]. SIADH is the most common cause of euvolaemic, hypo-osmolar hyponatraemia. Inappropriate hypothalamic production and release of ADH from the posterior pituitary can occur as a result of numerous non-malignant and malignant disorders[2].

Paraneoplastic SIADH is due to ectopic secretion of ADH from tumour cells. The persistent unregulated expression of ADH in paraneoplastic SIADH leads to excessive dilution of free sodium, the primary aetiology of the observed hyponatraemia. SIADH has been reported in 11-15% of patients with small cell lung carcinoma and 3% of patients with head and neck cancer[3-4]. However, the condition is rare in non-small cell neuroendocrine tumours. There are only two other reported cases of paraneoplastic SIADH in these tumours confirmed by either elevated serum ADH or positive ADH immunohistochemistry staining of tumour specimen[5,6].

Historically, confirmation of ectopic ADH secretion has been challenging because ADH has a short half-life and readily degrades ex vivo[7]. The advent of copeptin sandwich immunoassay circumvents these issues. Copeptin is the more stable 39-amino-acid protein cleaved from the c-terminal end of pre-provasopressin released in stoichiometric equivalence with ADH[7,8].

Our report describes a male in his fifth decade initially diagnosed with idiopathic SIADH with a subsequent revision of the diagnosis after investigations revealed a slowly progressive neuroendocrine tumour of unclear primary that stained positive for the vasopressin-neurophysin 2-copeptin prohormone. The striking elevation in copeptin suggests his circulating ADH levels were also extremely high, which would explain the refractory nature of his SIADH. Had this degree of copeptin elevation been measured when he first developed hyponatraemia, it may have prompted more extensive investigation for occult tumour by PET scanning. Instead, the patient's disease progressed and his prognosis was poor at the time of diagnosis. As his symptoms worsened, the prescription of tolvaptan improved his quality of life by allowing a more permissive fluid restriction and reducing the severity of hyponatraemia during pain or periods of relative fluid loading, such as during surgery.

This case is novel given it is the first report of a patient with confirmed ectopic ADH secretion from a non-small cell neuroendocrine tumour with both positive ADH immunohistochemistry and elevated copeptin.

The implications of this clinical experience are numerous. Firstly, syndrome of inappropriate ADH should only be labelled "idiopathic" after extensive investigation. Our findings suggest that a serum copeptin level should now be considered for inclusion in this workup, particularly in young patients without significant comorbidities. There is value in making this diagnosis as it prognosticates for the persistence of the individual patient's predisposition to hyponatraemia. It provides impetus for early exploration of other treatment modalities, such as urea or tolvaptan, to relieve the burden of strict fluid balance and potentially prevent hospital admission with relapse[9,10]. Finally, in this setting copeptin could be used alongside PET imagining as a marker for tumour differentiation. This is an area that requires further study.

1. Fenske W, Sandner B, Christ-Crain M. A copeptin-based classification of the osmoregulatory defects in the syndrome of inappropriate antidiuresis. Best Pract Res Clin Endocrinol Metab. 2016;30(2):219-233. doi:10.1016/j.beem.2016.02.013
2. Doshi SM, Shah P, Lei X, Lahoti A, Salahudeen AK. Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. Am J Kidney Dis. 2012;59(2):222-228. doi:10.1053/j.ajkd.2011.08.029
3. Sorensen, J. B., M. K. Andersen, and H. H. Hansen. 1995. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease. J. Intern. Med. 238:97–110.
4. Talmi, Y. P., H. T. Hoffman, and B. F. McCabe. 1992. Syndrome of inappropriate secretion of arginine vasopressin in patients with cancer of the head and neck. Ann. Otol. Rhinol. Laryngol. 101:946–949.
5. Yarmohammadi H, Erinjeri JP, Brown KT. Embolization of metastatic neuroendocrine tumor resulting in clinical manifestations of syndrome of inappropriate secretion of antidiuretic hormone. J Vasc Interv Radiol. 2015;26(4):533-537. doi:10.1016/j.jvir.2014.11.032
6. Alshaikh OM, Yoon JY, Chan BA, et al. Pancreatic Neuroendocrine Tumor Producing Insulin and Vasopressin. Endocr Pathol. 2018;29(1):15-20. doi:10.1007/s12022-017-9492-5
7. Morgenthaler NG, Struck J, Alonso C, Bergmann A. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem. 2006;52(1):112-119. doi:10.1373/clinchem.2005.060038
8. Morgenthaler NG, Müller B, Struck J, Bergmann A, Redl H, Christ-Crain M. Copeptin, a stable peptide of the arginine vasopressin precursor, is elevated in hemorrhagic and septic shock. Shock. 2007;28(2):219-226. doi:10.1097/SHK.0b013e318033e5da
9. Nervo A, D'Angelo V, Rosso D, et al. Urea in cancer patients with chronic SIAD-induced hyponatremia: Old drug, new evidence. Clin Endocrinol (Oxf). 2019;90(6):842-848. doi:10.1111/cen.13966
10. Kai K, Tominaga N, Koitabashi K, Ichikawa D, Shibagaki Y. Tolvaptan corrects hyponatremia and relieves the burden of fluid/dietary restriction and hospitalization in hyponatremic patients with terminal lung cancer: a report of two cases. CEN Case Rep. 2019;8(2):112-118. doi:10.1007/s13730-019-00375-7

3

Adult-onset hypophosphatasia diagnosed after bilateral atypical femoral fractures after antiresorptive therapy

Annabelle M Warren[2, 1], Peter R Ebeling[3, 4], Vivian Grill[5], Ego Seeman[2, 6], Shoshana Sztal-Mazer[7, 1]

1. Department of Endocrinology, The Alfred Hospital, Melbourne, VIC, Australia

2. Department of Endocrinology, The Austin Hospital, Heidelberg, VIC, Australia

3. Department of Medicine, Monash University, Clayton, VIC, Australia

4. Department of Endocrinology, Monash Health, Clayton, VIC, Australia

5. Department of Endocrinology, Western Health, Sunshine, VIC, Australia

6. Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia

7. Women's Health Research Program, School of Public Health and Preventative Medicine, Monash University, Melbourne, VIC, Australia

Introduction

Hypophosphatasia (HPP) is a rare but under-recognised genetic defect of bone mineralisation often misdiagnosed as osteoporosis. Patients with hypophosphatasia can present with fragility fractures and have an increased risk of atypical femoral fracture (AFF) after bisphosphonate therapy. We diagnosed a case of adult onset hypophosphatasia in a 40-year-old woman presenting with bilateral atypical femoral fractures after 4 years of denosumab therapy. A low serum alkaline phosphatase (ALP) level is an important clue in the diagnosis of hypophosphatasia. Clinicians should be aware that hypophosphatasia can be misdiagnosed as antiresorptive therapy-related AFF and that both bisphosphonates and denosumab are contraindicated in this condition.

Case

A 40-year-old female from rural Victoria was referred to the Alfred Hospital metabolic bone clinic after sustaining bilateral AFFs 10 months prior. At the time of referral, she was mobilising with crutches and required a wheelchair over longer distances.

Her first fracture was sustained in 2005 at the age of 25 when she suffered left navicula, 3rd and 5th metatarsal fractures after a fall from standing height. She experienced delayed fracture healing for many years and a diagnosis of complex regional pain syndrome was made. On assessment of her delayed healing, a computed tomography (CT) scan of her foot was performed in 2013, which reported radiographic osteopenia, later confirmed on Dual Energy X-ray Absorptiometry (DXA). At that time the patient was commenced on a weekly oral bisphosphonate by her general practitioner but experienced gastrointestinal intolerance and ceased after 4 months. Denosumab was commenced in 2014, which she received regularly every 6 months for 4 years.

Notable past history included a seizure at the age of 28 for which she was prescribed sodium valproate. She denied any developmental or pubertal delay, early dental loss or any periodontal pathology, or family history of fractures.

In December 2018, aged 39, the patient sustained bilateral atypical femoral fractures after a fall from standing height. A symptomatic complete right femoral diaphyseal fracture was surgically fixed on 28 December 2018. The pre-operative x-ray showed features of an AFF with beaking of the lateral femoral periosteum at the fracture site. Imaging of the contralateral left femur demonstrated a nondisplaced asymptomatic partial AFF which was conservatively managed. Both fractures fulfilled 2014 ASBMR criteria for AFF. Denosumab was discontinued with no further doses administered after June 2018. DXA in February 2019 showed bone mineral density (BMD) at the lumbar spine 1.150 g/cm2 (T score +0.8, Z score +0.9) and left total hip BMD 0.730 g/cm2 (T score -1.7, Z score -1.4). (Z score represents number of standard deviations below age-and sex-matched mean).

Upon presentation to our bone clinic in October 2019, the patient's height was 153.1 cm and weight 69.2 kg, with body mass index 29.5 kg/m^2. She did not have obvious craniofacial abnormality.

Investigation in October 2019: Serum calcium 2.31 mmol/L (2.10 – 2.60), parathyroid hormone 2.9 pmol/L (1.1 – 6.0) and renal function (eGFR > 90 mL/min/1.73m^2) were normal. Serum phosphate was just above the upper limit of normal 1.55mmol/L (0.75-1.50. Serum alkaline phosphatase (ALP) was low at 11 U/L (30 – 110) which, on further review, had also been apparent in 2016 when it was 7 U/L (30 to 120) whilst the patient was on denosumab. Carboxy-terminal collagen crosslinks (CTX) were low at 127 ng/L (150-800) and *N*-terminal propeptide of type I procollagen (P1NP) was normal at 32 mcg/L (15-70). The serum 25-hydroxyvitamin D was sufficient at 96 nmol/L (50-100). Vitamin B6 (pyridoxine) was extremely elevated >2000 nmol/L (35 – 110). Cranial X-ray showed no evidence of craniosynostosis. Repeat femoral X-rays revealed non-union of the right AFF and near completion of the left AFF with the exception of an intact medial cortex. Knee and hip imaging demonstrated mild degenerative arthrosis of the left hip.

The clinical history, low ALP and elevated vitamin B6 supported a diagnosis of hypophosphatasia. ALPL gene testing performed by Sydney Children's Hospital Network Genetic Service revealed two pathogenic heterozygous ALPL variants (c.526G>A; 881 A>C), confirming the diagnosis of recessive hypophosphatasia.

In February 2020, 18 months of subcutaneous teriparatide 20mcg daily therapy was commenced via the Alfred Hospital's individual patient usage program. Compassionate use of asfotase alpha enzyme therapy will be sought in the future. Since commencement of teriparatide, there have been no further fractures but the patient continues to require a gait aid to mobilise. Serial femoral X-Rays are planned to monitor fracture healing.

Discussion

Hypophosphatasia is a rare genetic disorder affecting mineralisation of bone due to a defect in the ALPL gene leading to deficiency of alkaline phosphatase (ALP), causing osteomalacia. There is a wide spectrum of phenotypic presentation with a severe childhood-onset form occurring in approximately 1/100,000 births manifesting skeletal deformity and even neonatal death. Less severe forms detected in adulthood are more frequent, up to 1/2500, and are increasingly being recognised in

adults misdiagnosed with osteoporosis (1). Other manifestations include delayed fracture healing, stress fractures, pyrophosphate arthropathy and vitamin B6-responsive seizures. Epilepsy occurs as ALP also plays a role in vitamin B6 metabolism, with ALP deficiency leading to reduced neuronal production of inhibitory GABA neurotransmitter, and accumulation in serum of its activated vitamin B6 precursor.

There are four previously-reported cases of AFF following bisphosphonate use in patients with hypophosphatasia (2), and an increased risk of AFF is also thought possible with denosumab (3). In support we identified two further cases of AFF in hypophosphatasia following denosumab treatment from the literature, one of whom had also received bisphosphonate therapy (4, 5). Our patient's short four-month course of bisphosphonate therapy and 4-year interval between bisphosphonate exposure and fractures would suggest denosumab as the greater contributor in her case.

Hypophosphatasia caused impaired bone mineralisation and osteomalacia as reduced tissue non-specific ALP (TNSALP) impairs hydroxyapatite crystal deposition, leading to accumulation of the inhibitory substrate inorganic pyrophosphate (PPi). In healthy bone, microscopic cracks that may predispose to fracture are resorbed by osteoclasts through targeted bone remodelling. Denosumab inhibits RANK ligand which is responsible for osteoclast recruitment and action. Impaired resorption of damaged bone coupled with the predisposition for impaired mineralisation of new bone is thought to explain increased risk for AFF in patients with hypophosphatasia using antiresoprtive therapy (2).

Targeted enzyme therapy with asfotasfe alfa is optimal treatment for hypophosphatasia, and has been shown to promote fracture healing in patients with hypophosphatasia (6). Access to Asfostase alfa is limited as its cost is prohibitive (>$1 million AUD per year). Teriparatide may be an alternative treatment that has not been observed to increase fracture and may theoretically improve healing while halting ongoing fracture propagation, but does not provide a sustained response in hypophosphatasia (7). Preliminary results suggest antisclerostin therapy may have a role (8).

Clinicians should be alert to the possible diagnosis of HPP in patients with fragility fractures and low serum ALP. In addition, both bisphosphates and denosumab can increase the risk of AFF in these patients and are therefore contraindicated. Hypophosphatasia is one of several monogenic bone diseases that can result in AFF (9).

1. Mornet E, Yvard A, Taillandier A, Fauvert D, Simon-Bouy B. A molecular-based estimation of the prevalence of hypophosphatasia in the European population. Ann Hum Genet. 2011;75(3):439-45.
2. Marini F, Brandi ML. Atypical femur fractures: a distinctive tract of adult hypophosphatasia. Clin Cases Miner Bone Metab. 2017;14(3):324-8.
3. Shapiro JR, Lewiecki EM. Hypophosphatasia in Adults: Clinical Assessment and Treatment Considerations. J Bone Miner Res. 2017;32(10):1977-80.
4. Lefever E, Witters P, Gielen E, Vanclooster A, Meersseman W, Morava E, et al. Hypophosphatasia in Adults: Clinical Spectrum and Its Association With Genetics and Metabolic Substrates. J Clin Densitom. 2018.
5. Magdaleno AL, Singh S, Venkataraman S, Perilli GA, Lee YY. Adult-Onset Hypophosphatasia: Before and After Treatment with Asfotase Alfa. AACE Clin Case Rep. 2019;5(6):e344-e8.
6. Klidaras P, Severt J, Aggers D, Payne J, Miller PD, Ing SW. Fracture Healing in Two Adult Patients With Hypophosphatasia After Asfotase Alfa Therapy. JBMR Plus. 2018;2(5):304-7.
7. Gagnon C, Sims NA, Mumm S, McAuley SA, Jung C, Poulton IJ, et al. Lack of sustained response to teriparatide in a patient with adult hypophosphatasia. J Clin Endocrinol Metab. 2010;95(3):1007-12.
8. Seefried L, Baumann J, Hemsley S, Hofmann C, Kunstmann E, Kiese B, et al. Efficacy of anti-sclerostin monoclonal antibody BPS804 in adult patients with hypophosphatasia. J Clin Invest. 2017;127(6):2148-58.
9. Nguyen HH, van de Laarschot DM, Verkerk AJMH, Milat F, Zillikens MC, Ebeling PR. Genetic Risk Factors for Atypical Femoral Fractures (AFFs): A Systematic Review. JBMR Plus. 2018;2(1):1-11.

A novel approach to the treatment of ectopic ACTH-dependant Cushing's

Kate Flentje[1, 2], Anna Cunliffe[1], Anindita Chakrabarti[1, 3], Adam Roberts[1, 2, 4]

1. University Hospital Geelong, East Geelong, Victoria, Australia

2. Barwon Endocrinology, Geelong, Victoria, Australia

3. Geelong Endocrinology and Diabetes, Geelong, Victoria, Australia

4. Epworth Geelong, Geelong, Victoria, Australia

Case Presentation

BC is a 75 year old man on chemotherapy for metastatic prostate small cell carcinoma who presented with profound hypokalaemia , hypertension and new onset hyperglycaemia. Very high cortisol levels were associated with non-specific cushingoid features including generalised weakness and debility, lower limb oedema, central adiposity and low mood. ACTH was also found to be very high raising suspicion of a paraneoplastic cause in the absence of a pituitary tumour. Metastatic deposits were widespread and included liver, lung, and skeletal involvement.

His background medical conditions also included hypertension, hyperlipidaemia and atrial fibrillation. There was no personal or family history of endocrine disorders. Regular medications included atorvastatin 20mg daily, apixaban 5mg twice daily, bicalutamide 50mg daily, and 4 monthly doses of leuprorelin. He was on carboplatin and etoposide chemotherapy. He had no drug allergies.

Investigations

Initial investigations showed hypokalaemia with a metabolic alkalosis and hyperglycaemia.

Table 1. Baseline haematology and biochemistry

Analyte	Result	Reference range
Hb (g/L)	130	125-175
WCC	**3.1 x10(9)/L**	4.0-11.0
Na (mmol/L)	142	135-145
K (mmol/L)	**2.4**	3.5-5.0
Bicarb mmol/L)	**37**	20-32
Glucose (mmol/L)	**18.1**	4.0-7.9
PSA	0.09	<6.51
ALP (U/L)	90	35-110
GGT (U/L)	**141**	5-50
AST (U/L)	36	10-40
ALT (U/L)	58	5-40
Albumin (g/L)	29	34-45

Further endocrine evaluation revealed the following:

Table 2: Baseline endocrine biochemistry

Analyte	Result	Reference range
Cortisol AM (nmol/L)	**1141**	133-537
Cortisol PM (nmol/L)	**1150**	68-327
24hr urinary free cortisol (nmol/d)	**10,653**	<130
Plasma ACTH (pmol/L)	**58**	1.6-13.9
Aldosterone (pmol/L)	**68**	100-950
Renin (mU/L)	32	3.3-41
ARR (pmol/L /mU/L)	2	<70
TSH (mU/L)	**0.11**	0.5-6.0
FT4 (pmol/L)	19.8	11.0-22.0
GH (ug/L)	0.2	
IGF-1 (nmol/L)	11	7-28
Prolactin (mIU/L)	377	90-400
Testosterone (nmol/L)	**1.7**	19-76
SHBG (nmol/L)	**15**	19-76
Free Testosterone (pmol/L)	**56**	130/570

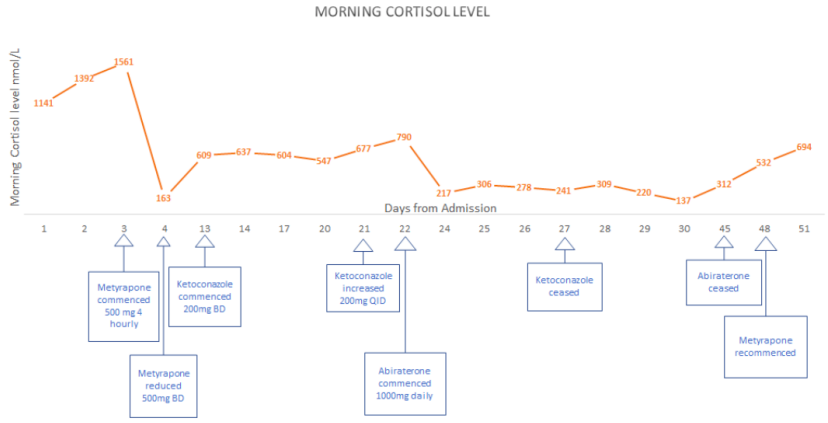


Figure 1: Timeline of treatments and morning cortisol level trend

The patient was immediately commenced on cortisol blocking therapy. Ketoconazole was not immediately available so treatment was initiated with metyrapone 500mg every four hours, the less preferred option due to patient expense. A repeat morning cortisol level within 24 hours of therapy was dramatically reduced at 163nmol/L. Shortly thereafter, E. coli urosepsis lead to an ICU admission for haemodynamic support, metyrapone dosing was subsequently reduced to 500mg twice daily and he was commenced on IV hydrocortisone under a block-and-replacement rationale.

When it became available metyrapone was replaced with ketoconazole 200mg twice daily. Hydrocortisone was changed to tapering doses of prednisolone. Pantoprazole was started for acid suppression and spironolactone was instituted to counteract mineralocorticoid excess and potassium deficits. As the patient improved, ketoconazole was incremented over a fortnight to 200mg six hourly, with monitoring for hepatotoxicity. However, morning cortisol levels remained elevated, from 575-790nmol/L.

At this time there was a discussion between the treating oncologist and endocrinologist about alternative treatment options. The novel idea of abiraterone, a CYP17 inhibitor used to treat metastatic prostate cancer, was put forth with potential dual benefit in treatment for cancer and hypercortisolaemia. Abiraterone was commenced at 1000mg daily and the following morning a cortisol level of 217nmol/L indicated good effect. Ketoconazole was able to be ceased.

Repeat morning cortisol level, five days later, demonstrated a decrease to 167nmol/L and was associated with a significant postural drop. Dexamethasone 2mg daily was commenced to treat potential adrenal insufficiency. He continued to improve and was weaned off potassium infusions. His blood pressure stabilised, blood glucose levels normalised without the need for insulin and he was able to be transferred to rehabilitation.

One week later routine monitoring showed recurrent hypercortisolism with a morning cortisol of 694nmol/L, an ACTH of 109pmol/L, with associated worsening hypertension and hypokalaemia. Liver function tests were deranged requiring cessation of abiraterone. Due to disease progression, BC was transferred to palliative care and passed away two months after initial diagnosis of CS.

Discussion:

This case demonstrates the treatment challenges of this disease as well as the novel use of an established oncology therapy for ACTH dependent Cushing's syndrome. The following points will form the basis of discussion:

1. Prostate small cell cancer is a rare cause of Cushing's syndrome. CS due to ectopic production of ACTH is associated with a large range of tumours including small cell lung cancer and bronchial carcinoid most commonly. Prostate cancer-causing CS is rare with less than 30 cases published worldwide1.

2. Suppressed aldosterone despite apparent mineralocorticoid excess in this case may be accounted for by: Profound hypercortisolism resulting in overwhelmed capacity of 11B-HSD2 enzyme which usually protects renal tubular mineralocorticoid receptors from cortisol2; Excessive mineralocorticoid receptor stimulation and downregulation of aldosterone[2;] Direct inhibition of 11B-HSD2 by ACTH,2 and/or Downregulation of the renin-angiotensin pathway as the patient was receiving intravenous potassium with normal saline at the time of blood collection.

3. Treatment of hypercortisolism associated with ectopic ACTH secretion includes resection of the primary tumour and nodes as first line therapy3. Second line therapies include bilateral adrenalectomy as well as medical therapies3. No optimal order of medications has been established for the management of severe hypercortisolism[3]. Potential therapies include metyrapone and ketoconazole which were used in this case for their quick onset of action. These medications work at different sites of the steroid synthesis pathway (figure 1). Ketoconazole is no longer registered for use in Australia but is available via the special access scheme. Treatment requires close monitoring for severe hepatitis and drug-drug interactions. Furthermore, absorption requires an acidic environment which may be the cause of treatment failure in our patient who was taking concurrent pantoprazole.

4. The mechanism of action of these adrenal blocking therapies warrants consideration. Metyrapone and ketoconazole inhibit multiple steps in cortisol biosynthesis (figure 2). Both agents have similar efficacy measured in retrospective multicenter trials, ranging from 53-88% for ketoconazole5 and 43-76% for metyrapone6. Other options include mitotane which is generally reserved for treatment of adrenocortical cancer and has toxic side effects, etomidate which is only available in an intravenous formulation and mifepristone, a glucocorticoid receptor antagonist. This agent is difficult to monitor and prohibitively expensive for prolonged use in Australia. A recent phase III trial of osilodrostat (LC1699 in figure 1), an inhibitor of CYP11B1 showed this is an effective new treatment option for endogenous Cushing's disease with 86% complete response at 34 weeks7, however this is not yet available for use in Australia. Close monitoring is required with all agents to assess efficacy of adrenal blockade, detect hypoadrenalism and toxicities.

5. Abiraterone as a novel treatment. It irreversibly inhibits CYP17 (17 alpha hydroxylase) which is required for glucocorticoid and androgen biosynthesis. It is commonly used to treat relapsed and metastatic prostate cancer, in addition to standard androgen deprivation therapy, with improved progression free survival8. In prostate cancer it is usually administered with glucocorticoid to overcome hypocortisolaemia and to suppress pit-ACTH mediated mineralocorticoid production. In this case,

abiraterone was used to ameliorate hypercortisolism and block androgen production in the management of his prostate cancer. To our knowledge, this is the first time abiraterone has been used for this dual purpose.

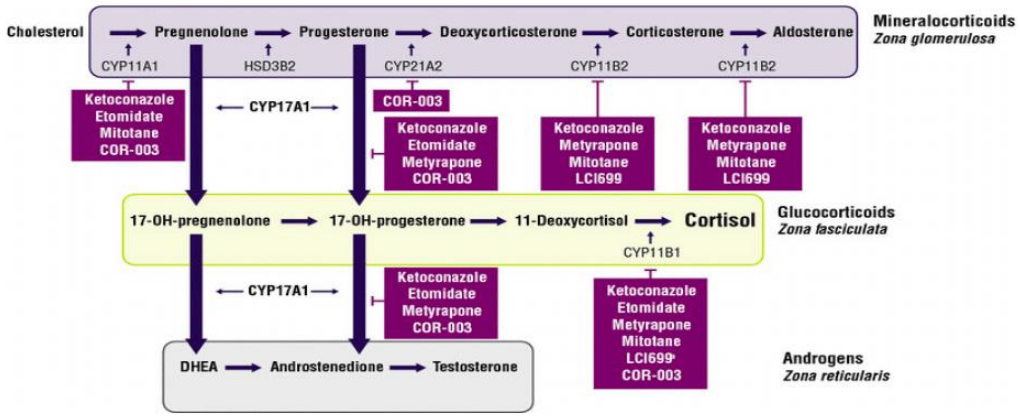


Figure 2: Steroid synthesis pathway and sites of steroidogenesis inhibitor action4.

Key Learning Points:

- ACTH dependant Cushing's syndrome in dedifferentiated prostate small cell cancer is very rare
- While surgery is the preferred treatment for ectopic ACTH secretion, medical therapies for inoperable cases is limited and determining best therapy can be difficult
- Abiraterone could become a novel treatment option for paraneoplastic ACTH secretion in prostate cancer associated hypercortisolaemia offering dual inhibition of androgen and steroid production

1. Elston et al. Severe Cushing's syndrome due to small cell prostate carcinoma: a case and review of literature. Endocrine Connections, 2017, R80–R86
2. Torpy, D. J., Mullen, N., Ilias, I., & Nieman, L. K. (2002). Association of hypertension and hypokalemia with Cushing's syndrome caused by ectopic ACTH secretion: A series of 58 cases. Annals of the New York Academy of Sciences, 970, 134–144. https://doi.org/10.1111/j.1749-6632.2002.tb04419.x.
3. Nieman et al Guidelines on Cushing's Syndrome Treatment J Clin Endocrinol Metab. August 2015, 100(8): 2807-2831
4. Fleseriu, Maria & Castinetti, Frederic. (2016). Updates on the role of adrenal steroidogenesis inhibitors in Cushing's syndrome: a focus on novel therapies. Pituitary. 19. 10.1007/s11102-016-0742-1
5. Castinetti F et al, (2014) Ketoconazole in Cushing's disease: is it worth a try? J Clin Endocrinol Metab 99:1623–1630
6. Daniel E et al. (2015) Effectiveness of metyrapone in treating Cushing's syndrome: a retrospective multicenter study in 195 patients. J Clin Endocrinol Metab 100:4146–4154
7. Pivonello et al (2020) Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. Lancet Diabetes and Endocrinology, Volume 8, Issue 9, p748-761 748-761
8. James, N. D.,et al. (2017). Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. New England Journal of Medicine, 377(4), 338–351. https://doi.org/10.1056/NEJMoa1702900