Endocrinology, Diabetes & Metabolism CASE REPORTS

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Ectopic adrenocorticotrophic hormone syndrome secondary to treatment-related neuroendocrine differentiation of metastatic castrate-resistant prostate cancer

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Summary

A 64-year-old man with progressive metastatic castrate-resistant prostate adenocarcinoma presented with recurrent fluid overload, severe hypokalaemia with metabolic alkalosis and loss of glycaemic control. Clinical features were facial plethora, skin bruising and proximal myopathy. Plasma adrenocorticotrophic hormone (ACTH), serum cortisol and 24-h urinary cortisol levels were elevated. Low-dose dexamethasone failed to suppress cortisol. Pituitary MRI was normal and ^{68}Gallium-DOTATATE PET–CT scan showed only features of metastatic prostate cancer. He was diagnosed with ectopic ACTH syndrome secondary to treatment-related neuroendocrine prostate cancer differentiation. Medical management was limited by clinical deterioration, accessibility of medications and cancer progression. Ketoconazole and cabergoline were utilised, but cortisol remained uncontrolled. He succumbed 5 months following diagnosis. Treatment-related neuroendocrine differentiation of prostate adenocarcinoma is a rare cause of ectopic ACTH syndrome.

Learning points

- Neuroendocrine differentiation following prostate adenocarcinoma treatment with androgen deprivation has been described.
- Ectopic adrenocorticotrophic hormone (ACTH) syndrome should be considered where patients with metastatic prostate cancer develop acute electrolyte disturbance or fluid overload.
- Ketoconazole interferes with adrenal and gonadal steroidogenesis and can be used in ectopic ACTH syndrome, but the impact may be insufficient. Inhibition of gonadal steroidogenesis is favourable in prostate cancer.
- More data are required to evaluate the use of cabergoline in ectopic ACTH syndrome.
- Ectopic ACTH syndrome requires prompt management and is challenging in the face of metastatic cancer.

Background

The incidence of neuroendocrine differentiation of primary prostate cancer is less than 1% (1) but 25–30% in metastatic castrate-resistant prostate cancer and increases with the use of androgen deprivation therapy (2). Treatment-related neuroendocrine prostate cancer is associated with survival of less than 12 months (1, 3) There are approximately 30 reported cases of ectopic adrenocorticotrophic hormone (ACTH) syndrome (EAS) secondary to neuroendocrine prostate cancer (3).

Case presentation

This 64-year-old Caucasian man had a background of obesity (BMI: 44.2 kg/m^2), gout, hypertension and osteoarthritis, requiring treatment with colchicine 500 µg and amlodipine 5 mg. He was diagnosed with prostate adenocarcinoma with metastatic disease to the bone, liver and retroperitoneal lymph nodes in August 2018. Initial investigations were prompted by a leucoerythroblastic blood film and subsequent bone marrow immunohistochemistry was strongly positive

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for NKX3.1. Prostate-specific antigen (PSA) level was 5773 µg/L (reference range <4.51 µg/L). Six cycles of docetaxel with degarelix were administered prior to leuprorelin 4 mg s.c. 6 monthly and there was resolution of retroperitoneal lymphadenopathy and one liver metastasis with minor reduction of another liver metastasis. Bone disease remained stable. Given the prostate cancer was castrate-resistant, abiraterone 500 mg daily was added to leuprorelin. Initial prednisolone 10 mg daily was followed by dexamethasone 0.5 mg. After 3 years, imaging showed locally progressive disease in the prostate bed and a potentially new sacral lesion. PSA level increased within 5 months from 3.7 to 12 µg/L.

One month later, he presented with fluid overload with 15 kg weight gain, exertional dyspnoea, significant hypokalaemia (2.3 mmol/L), metabolic alkalosis (venous pH 7.57, bicarb 48 mmol/L, pCO_2 52 mmHg), systolic hypertension 180 mmHg, atrial fibrillation and new type 2 diabetes (HbA1c 6.8%). Imaging revealed no adrenal lesion. He received fluid restriction, spironolactone, frusemide, potassium replacement and apixaban. Abiraterone was ceased due to potential secondary hyperaldosteronism despite the steroid therapy. He re-presented within weeks with fluid overload, hyperosmolar symptoms, facial plethora, skin bruising and proximal myopathy. HbA1c increased to 9.7% and PSA to 107.86 µg/L.

Investigations

Plasma ACTH was 372 pg/mL (reference range <46 pg/mL) with corresponding serum cortisol 1099 nmol/L (reference range 110–550 nmol/L). The 24-h urinary cortisol excretion (immunoassay) was 3678 nmol (reference range 200–1000 nmol). Morning serum cortisol level was elevated at 1453 nmol/L following a 1 mg dexamethasone suppression test. The pituitary had a normal appearance on MRI.

Treatment

In January 2022, a diagnosis of ectopic ACTH syndrome was made with endocrinology input. Metyrapone was not readily accessible and ketoconazole was commenced at 200 mg three times daily (Figure 1). Metformin and insulin were used for glycaemic control. Apixaban was converted to warfarin due to potential drug interaction with ketoconazole. The patient was then lost to follow-up.

Outcome and Follow-Up

He was re-admitted from March to April 2022 with fluid overload, hypokalaemia and international normalised ratio (INR) lability, with the latter leading to trepidation regarding overly rapid increases in ketoconazole doses in addition to the possibility of reduced gut absorption given his fluid status. PSA level was 90.42 µg/L. Further anti-cancer therapy apart from androgen deprivation therapy was deemed unsuitable due to a prolonged reduced performance score.

A ^{68}Gallium-DOTATATE PET–CT scan confirmed neuroendocrine differentiation of prostate cancer with patchy DOTATATE uptake in the prostate bed. Nodal (pelvic and retroperitoneal lymphadenopathy), skeletal (sacrum, bilateral hemipelvis, right femur) and pulmonary DOTATATE-avid metastases were detected, which had not been detected in previous studies (Figs. 2, 3 and 4).

Two months later, he presented with significant hypotension (systolic blood pressure 70 mmHg) that stabilised with fluid resuscitation and brief antibiotic coverage. No cause was identified; however, he had persisting acute kidney injury, hypokalaemia (2.7 mmol/L) with persistent metabolic alkalosis and haematuria secondary to supratherapeutic INR. Cabergoline 0.5 mg oral daily was added based on case report evidence

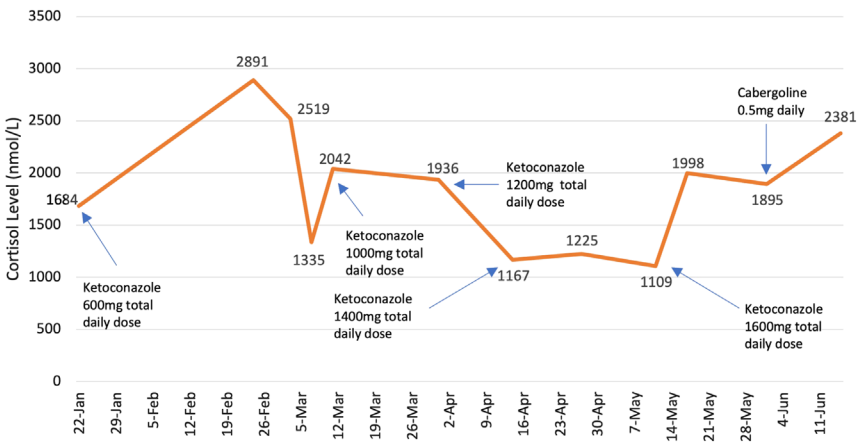

Figure 1
Serum cortisol trends over time with ketoconazole and cabergoline.

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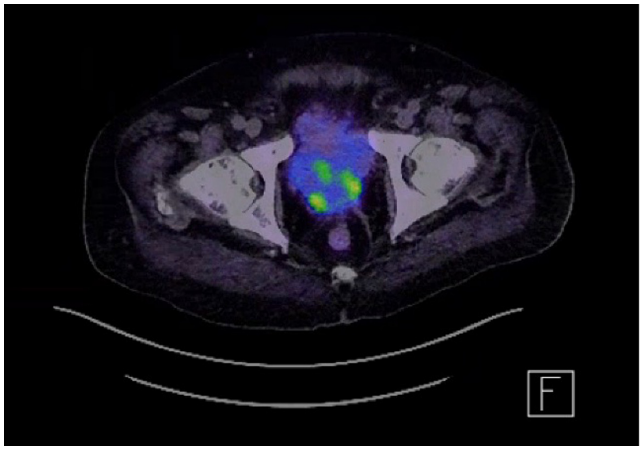

Figure 2
^{68}Gallium-DOTATATE PET–CT image showing avidity in the prostate bed.

whilst a financial subsidy application for metyrapone was underway, but he died from progressive cancer symptoms within 2 weeks in June 2022.

His biochemical progress with ketoconazole and cabergoline is depicted in Figure 1.

Discussion

In this case, neuroendocrine differentiation of castrate-resistant prostate cancer with EAS was an aggressive disease process with significant associated morbidity.

Achieving a diagnosis of EAS requires clinical suspicion. Diagnosis may be challenging in the presence of cancer progression, heart failure or exogenous glucocorticoid use. Acute electrolyte disturbance or fluid overload should alert the clinician to the possibility of EAS in the appropriate clinical context. In the setting of known primary prostate cancer and hypercortisolism symptoms, ^{68}Gallium-DOTATATE PET-CT scan confirmed our biochemical diagnosis.

Second-line dynamic tests for challenging cases of ACTH-dependent hypercortisolism can include corticotropin-releasing hormone test, high-dose dexamethasone suppression test and bilateral inferior petrosal sinus sampling (4). Localisation of EAS should be initially performed with conventional imaging (CT or MRI) (4). ^{68}Gallium-DOTATATE PET assists with the localisation of EAS, with 65% localisation of previously occult ectopic ACTH-secreting primary or metastatic tumours when combined with CT (5). A prospective study comparing the diagnostic value of ^{68}Gallium-DOTATATE PET/CT and ^{18}F-Flurodeoxyglucose PET/CT showed a higher detection rate for ectopic ACTH-secreting tumours with ^{68}Gallium-DOTATATE PET/CT (75% vs 60%), with

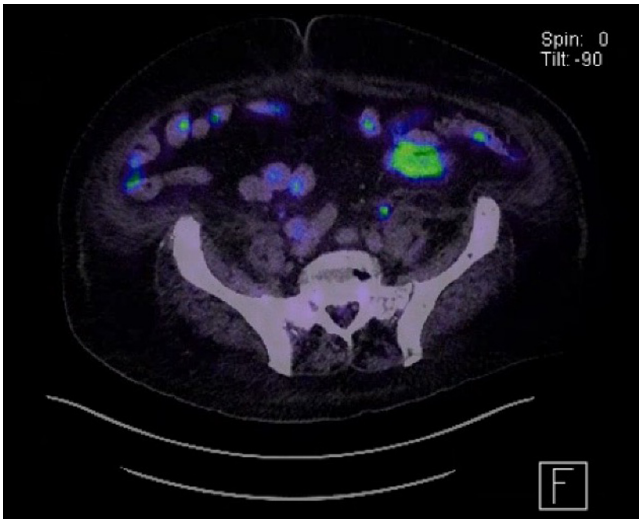

Figure 3
^{68}Gallium-DOTATATE PET–CT image showing avidity in retroperitoneal lymph nodes as well as sacrum.

a 90% localisation rate with both modalities combined (6). False positive results can occur and necessitate careful interpretation.

The management of EAS includes histological diagnosis and treatment of underlying malignancy, in addition to management of cortisol-related sequelae. Therapeutic strategies require consideration of the clinical context (7). A histological diagnosis was not pursued in this case as it would not have altered clinical management; however, the PSA elevation, hormone studies and radiographic results suggest a combination of prostate adenocarcinoma and neuroendocrine cells. This patient's poor performance

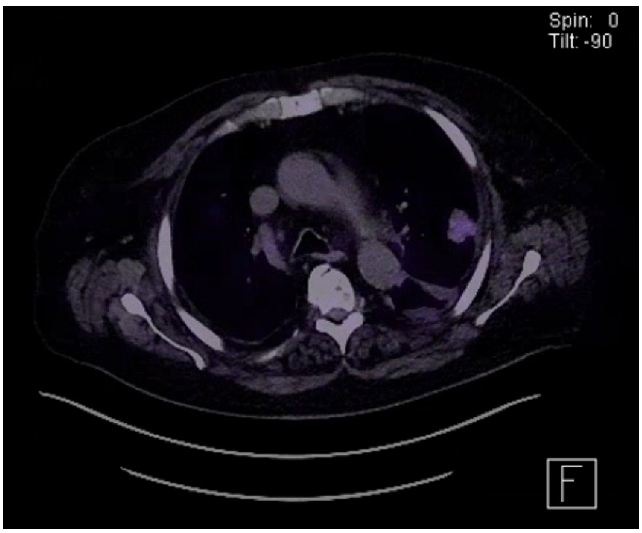

Figure 4
^{68}Gallium-DOTATATE PET–CT image showing mild avidity in the lung.

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status and prognosis precluded the use of platinum-based chemotherapy (1) or bilateral surgical adrenalectomy. Medical therapy for his hypercortisolism was the most suitable option.

Ketoconazole is a steroidogenesis inhibitor that acts on cytochrome P450 steroidogenic enzymes: 17a-hydroxylase, 20,22-desmolase, 11b-hydroxylase, 17,20-desmolase and 18-hydroxylase (8). It interferes with gonadal steroidogenesis (8) and its use in prostate cancer has continued since the 1980s. Ketoconazole acts within days to reduce cortisol levels and is inexpensive; however, its use is limited by potential hepatotoxicity. In a limited case series of nine patients with EAS, ketoconazole monotherapy led to eucortisolism (cortisol 150–300 nmol/L) in four cases (9). In this case, we were unable to achieve this with ketoconazole monotherapy, despite attaining maximum total daily dose of 1600 mg, emphasising the challenge with medical monotherapy for EAS. Dosage titration was also impacted by periods of clinically significant INR lability; however, in retrospect, more rapid dose escalation could have been achieved with more frequent titration whilst in the outpatient setting.

Another more commonly used rapid-acting steroidogenesis inhibitor is metyrapone, an 11-hydroxylase inhibitor (7). In a case series of 14 patients using combination therapy with ketoconazole and metyrapone, eucortisolism was achieved in 73% of cases (10). Metyrapone use can lead to accumulation of deoxycortisone and androstenedione, which can lead to hypokalaemia and hirsutism, and cortisol monitoring requires highly specific immunoassays, liquid chromatography–mass spectrometry or gas chromatography–mass spectrometry due to 11-deoxycortisol test interference (7). Its high cost in Australia was a limiting factor for initial use in this case. Due to its synergistic effect with ketoconazole, metyrapone at an initial dose of 750 mg TDS would have been the preferred second-line agent to achieve a target serum cortisol level of 150–300 nmol/L.

Cabergoline, a dopamine agonist, was used as a second agent in this case whilst pursuing metyrapone funding. Use has been described in combination treatment with somatostatin analogues and steroidogenesis inhibitors (7). In a small case series of eight patients with EAS, two cases achieved eucortisolism when treated with combination cabergoline and a steroidogenesis inhibitor (including ketoconazole) (11). Cabergoline and somatostatin analogues are not recommended as first-line agents (7). Our limited use of cabergoline as a second-line agent did not yield any discernible biochemical improvement.

Other agents described in the treatment of EAS are etomidate, an i.v. medication with rapid-acting cortisol-lowering properties, mitotane, a slower-acting medication with adrenolytic properties and many side effects, and lastly, mifepristone, which provides rapid blockade of glucocorticoid receptor activation (7). Cortisol results cannot be used to guide treatment with mifepristone use as it antagonises the binding of cortisol to its nuclear receptor without inhibiting cortisol biosynthesis. Mifepristone can lead to hypokalaemia (7). Osilodrostat, an 11b-hydroxylase inhibitor initially approved for the treatment of Cushing's disease, has been shown to be effective (monotherapy and combination therapy), well tolerated and safe in the treatment of EAS in case reports and a phase 2 trial (12, 13, 14).

Advancement in nuclear medicine has seen the emergence of peptide receptor radionuclide therapy with ^{177}Lutetium-DOTATATE as a therapeutic option for unresectable neuroendocrine tumours, amongst other systemic treatment strategies such as somatostatin analogues, chemotherapy and targeted therapies. Localised therapies include embolisation and ablation. ^{177}Lutetium-DOTATATE trials have predominantly studied pancreatic and gastrointestinal neuroendocrine tumours (15, 16, 17). ^{177}Lutetium-prostate-specific membrane antigen radioligand therapy has also been shown to be safe and effective for patients with metastatic castrate-resistant prostate cancer refractory to standard treatment (18).

Our case emphasises castrate-resistant prostate cancer with treatment-related neuroendocrine differentiation as a cause of ectopic ACTH syndrome. EAS is aggressive and requires prompt recognition and management with endocrinology involvement. Medical management of EAS remains challenging in the face of advanced malignant states with limited oncological therapeutic options. If utilised, ketoconazole titration should be undertaken once to twice weekly and maximal doses may be required.

Declaration of interest
There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of the patient's clinical details and clinical images was obtained from a relative of the patient.

Author contribution statement
All co-authors participated in the delivery of clinical care for the patient and contributed to the manuscript.

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