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ECTOPIC ACTH SYNDROME PRESENTING AS REFRACTORY HYPOKALEMIA IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER WITH NEUROENDOCRINE TRANSFORMATION

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ABSTRACT

Ectopic adrenocorticotropic hormone (ACTH) syndrome resulting from neuroendocrine transformation of prostate adenocarcinoma may present with refractory hypokalemia as an initial manifestation. Because hypokalemia is often attributed to other more common aetiologies, the diagnosis is often overlooked, leading to delayed management. A 62-year-old man with metastatic castration-resistant prostate cancer (mCRPC) with neuroendocrine transformation presented with persistent hypokalemia. He later developed severe hypokalemia, metabolic alkalosis, and hypertension with disease progression. Endocrine workup revealed markedly elevated cortisol, no suppression on low dose dexamethasone testing, and elevated ACTH. Imaging showed no pituitary or adrenal lesions but demonstrated progression of metastatic disease. These findings supported ectopic ACTH secretion secondary to neuroendocrine transformation. Before initiation of the appropriate treatment, he developed supraventricular tachycardia, hypotension, pulmonary edema, and died. This case underscores the importance of considering paraneoplastic endocrine syndromes, such as ectopic ACTH secretion, in patients with malignancies and unexplained or refractory electrolyte disturbances—particularly in the context of neuroendocrine transformation.

KEYWORDS

Neuroendocrine neoplasm, ectopic ACTH syndrome, hypokalemia, prostate cancer

LEARNING POINTS

- Neuroendocrine transformation of prostate cancer is a rare but clinically significant cause of ectopic adrenocorticotropic hormone (ACTH) syndrome.
- A high index of suspicion for ectopic ACTH syndrome is warranted in patients with prostate cancer with unexplained or refractory hypokalemia, especially in known or suspected neuroendocrine transformation.

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INTRODUCTION

Prostate adenocarcinoma is the most common malignancy in men. Although most cases are driven by androgen, prolonged exposure to androgen deprivation therapy can result in neuroendocrine transformation, an aggressive malignancy with poor prognosis and unique paraneoplastic syndrome such as ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS).

Given the rarity of EAS in neuroendocrine prostate cancer and hypokalemia is often initially attributed to more common causes, the diagnosis and treatment are often delayed. We report a case of EAS in neuroendocrine prostate cancer that presented with refractory hypokalemia which led to delayed management. This case highlights the importance of early recognition of this uncommon but clinically significant paraneoplastic syndrome.

CASE DESCRIPTION

A 62-year-old male presented with persistent mild-to-moderate hypokalemia on routine oncology follow-up for metastatic castration-resistant prostate cancer (mCRPC) diagnosed 2 years prior. His initial pathology had revealed high-grade adenocarcinoma of the prostate, with a Gleason score of 9 (4+5), and metastatic involvement of the right femur, left iliac bone, and liver. He underwent sequential treatment with androgen deprivation therapy (ADT), darolutamide and docetaxel, followed by cabazitaxel, along with denosumab and palliative radiation therapy to symptomatic bone lesions. Approximately 1 year into his treatment of his prostate cancer, histological neuroendocrine transformation was detected after a pathological fracture requiring surgical fixation. He was subsequently treated with 6 cycles of cisplatin and etoposide followed by cyclophosphamide on biochemical and radiographic progression. His past medical history was notable for a resected T1 colonic adenocarcinoma with negative margins and Barrett's oesophagus. He was not taking diuretics, and his home medications included potassium and magnesium supplements.

Over the course of 8 months, the patient's serum potassium continued to fall to between 2.6 and 3.5 mmol/l, despite ongoing oral potassium and magnesium supplementation. During this period, he remained asymptomatic and denied any weakness, palpitations, syncope, nausea and vomiting, diarrhoea, or hypertension. After a further reduction in his serum potassium to 2 mmol/l, he was prompted to present to the emergency department.

At presentation, his blood pressure was elevated at 173/76 mmHg, and his blood gas was consistent with a metabolic alkalosis. An electrocardiogram revealed a prolonged QTc interval of 525 milliseconds without associated T-wave abnormalities or ST-segment changes. The patient was admitted under internal medicine for further investigations. Urine studies revealed a urine potassium-to-creatinine ratio of 5.22 and a urine chloride level of 97 mmol/l, suggesting renal potassium and chloride wasting. These findings raised concern for endocrinological pathology. This prompted measurement of serum aldosterone and renin levels, cortisol, imaging of adrenal glands and brain, and further processing of his prior pathology samples.

Differential diagnosis included primary hyperaldosteronism, Cushing syndrome, and congenital renal tubular disorders such as Bartter or Gitelman syndromes.

Aldosterone and renin levels were measured in both the supine and upright positions. Aldosterone remained low at 100 pmol/l in both positions *(Table 1)*, well below the diagnostic threshold for primary hyperaldosteronism, and, therefore, this diagnosis was excluded. Given the context of malignancy, paraneoplastic Cushing syndrome was considered, and an endocrine workup was initiated *(Table 2)*. The findings were consistent with an ACTH-dependent Cushing syndrome.

Imaging studies further assisted with identifying the potential source of ACTH. A contrast-enhanced computed tomography scan of the chest/abdomen/pelvis demonstrated normal bilateral adrenal glands with progression of metastases, evidenced by increased adenopathy and liver metastases. Magnetic resonance imaging of the brain did not reveal any pituitary adenomas or other abnormalities. ACTH stain of the tumour biopsy was also performed, although the result was negative. The absence of pituitary or adrenal gland abnormalities in the context of a known history of neuroendocrine transformation of prostate cancer supported a diagnosis of paraneoplastic ectopic ACTH secretion from mCRPC.

The patient was treated with potassium and magnesium supplementation. Electrolyte management was challenging due to the progressive malignant disease. Adrenal steroidogenesis inhibitors such as ketoconazole were

Test	Supine	Upright
Aldosterone (pmol/l)	100	100
Renin (ng/l)	4.3	1.5

Table 1. *Aldosterone and renin testing.*

Test	Result	Interpretation
24-hour urine free cortisol (nmol/day)	6423	Elevated (<275)
1 mg dexamethasone suppression test (nmol/l)	AM cortisol: 2000	Not suppressed
ACTH (pmol/l)	50	Elevated: ACTH-dependent Cushing syndrome

Table 2. *Cushing syndrome investigations.*
Abbreviations: ACTH, adrenocorticotropic hormone.

briefly initiated. The patient's clinical course further deteriorated with the development of supraventricular tachycardia, hypotension, and pulmonary oedema, which subsequently led to his demise.

DISCUSSION

This case underscores the importance of early investigation of persistent hypokalemia in patients with advanced malignancy, particularly those with known neuroendocrine differentiation[1]. EAS is a rare paraneoplastic disorder characterized by ACTH secretion from non-pituitary tumours such as small cell lung carcinoma with proopiomelanocortin gene expression which normally expressed in the pituitary gland. While small cell lung carcinoma is the most commonly reported source, prostate cancer with neuroendocrine differentiation has also been implicated in the literature[2]. Treatment-related prostatic neuroendocrine carcinoma arises as a consequence of intensification of anti-androgen therapy in patients with prostate adenocarcinoma, where cells consequently loss TP53 and RB1 leading to loss of androgen receptor dependence[3]. It accounts for approximately 10-15% of cases of castration-resistant prostate cancer and is associated with aggressive clinical behaviour and poor prognosis[4].

Hypokalemia occurs more frequently in Cushing syndrome due to ectopic ACTH secretion rather than in other forms of the disease[5]. Cortisol, which has mineralocorticoid activity, is normally inactivated by conversion to cortisone by 11-beta hydroxysteroid dehydrogenase. In ectopic ACTH Cushing syndrome, the marked hypercortisolism saturates the 11-beta hydroxysteroid dehydrogenase and reduces its ability to convert cortisol. Additionally, the excess levels of ACTH suppress 11-beta hydroxysteroid dehydrogenase activity, further limiting the conversion of cortisol to cortisone[6]. As a result, excess cortisol can bind to mineralocorticoid receptor and leads to hypokalemia, which is often refractory to potassium supplementation as is seen in our case, without source control[7].

In our case, the mild but refractory hypokalemia was the earliest clue to an underlying endocrine disturbance. Approximately 70% of patients manifest hypokalemia when diagnosed with EAS[8]. It often presents with subtle or atypical features, and patients may lack the classical signs of Cushing syndrome, particularly in the context of rapid disease progression or catabolic states. In this case, no cushingoid features were observed, and the patient developed rapid and severe hypokalemia coinciding with progression of metastatic disease. ACTH tissue staining is diagnostic for ectopic Cushing syndrome, but the sensitivity is low based on other studies[9,10].

These findings underscore the importance of maintaining a high index of suspicion of EAS in the context of refractory electrolyte imbalances in patients with a history of malignancy. Early recognition of this paraneoplastic syndrome is essential, as timely diagnosis can significantly impact both prognosis and therapeutic decision-making in patients with advanced prostate cancer.

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