There are few cases of ectopic ACTH from prostate cancer (Mostly from small cell cancer) but we rarely found any cases that is histologically confirmed as prostatic adenocarcinoma with neuroendocrine differentiation secreting clinically significant level of ACTH. Here we will depict such a case in a 61-year-old gentleman.

Case Report

A 61-year-old, community ambulant, known diabetic and hypertensive gentleman was diagnosed with metastatic prostate carcinoma (Bone, para rectal lymph node, liver, lung) on December 2018 when he presented with lower urinary tract symptoms. Trans Rectal Ultrasound guided biopsy (TRUS) revealed acinar adenocarcinoma (Fig 1) Gleason (5+4). One week after diagnosis, he was referred to emergency department from his GP for severe hypokalaemia of 2.4 mmol/L when he presented with generalized weakness. It was his second visit to his GP. Initially he consulted same GP for weakness and found to have low K of 3.3 and was managed with oral potassium tablet. He did not have any history of taking over the counter or traditional medication. On examination, he was not cushingoid but noted to have ecchymosis of the left forearm measuring about 5 cm. His ECG showed a long QTc and widespread T wave inversion.

Fig 1: Prostatic adenocarcinoma with perineural invasion (White arrow).

ECTOPIC CUSHING’S SYNDROME FROM PROSTATIC ADENOCARCINOMA: A RARE CLINICAL ENTITY

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Abstract
A 61-year-old man known to have metastatic prostate adenocarcinoma was seen at Changi General Hospital, Singapore, because of severe hypokalaemia due to ACTH dependent Cushing’s syndrome. He underwent a Dotate PET CT which showed increased DOTA-NOC-avidity in the right side of the prostate gland. Subsequent immunohistochemical staining of prostate biopsy sample documented ACTH, synaptophysin and CD 56 positivity. He was suggested medical management for prostate cancer complicated by Cushing’s syndrome. Unfortunately, Cushing’s syndrome was not controlled and the patient’s clinical condition progressively worsened. Subsequently, he developed fatal sepsis due to immunocompromised state. This case report describes a case of Cushing’s syndrome due to metastatic adenocarcinoma of the prostate, a tumour with very few therapeutic options and negative prognosis.

Key words
Ectopic Cushing’s; Prostate Adenocarcinoma; Sepsis.

Introduction
Cushing’s syndrome is the clinical manifestation that results from excessive level of circulating steroid¹. Among all the causes of Cushing’s syndrome, ectopic ACTH production is responsible for 10–12% of the cases². The commonest tumour types responsible for ectopic ACTH production are those with neuroendocrine features and 50% of them are due to small cell lung carcinoma.

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Initially, for the workup of persistent and severe hypokalaemia following investigations were performed:

- 24-hour urine K: 86 mmol/day (Normal range: 25-125 mmol/day)
- 8 am cortisol: 1229 nmol/L (Normal range: 180-620 nmol/L).

In view of high 8 am Cortisol further evaluation was done:

- 24-hour free urine cortisol: 20475 nmol/L (Normal range: 0-560 nmol/24 hour)
- 8 am ACTH: 57.4 pmol/L (Normal range: 2.2-13.3 pmol/L)
- 1mg Overnight Dexamethasone Suppression Test (ONDST): 1327 nmol/L (Normal range: <50 nmol/L)
- Low dose dexamethasone suppression test: 1447 nmol/L (Normal range: <50 nmol/L)
- 8mg high dose dexamethasone suppression test: 1424 nmol/L (Using 1229 nmol/L as baseline) (Normal range: reduction of serum cortisol by greater than 50%)
- MRI Pituitary: No pituitary lesion is seen.

In view of suspected ACTH dependent Cushing’s syndrome patient was offered inferior petrosal sinus sampling but he declined as it was an invasive test.

Subsequently, he underwent a Dotate PET CT which showed mild grade increased DOTA-NOC-avidity in the right side of the prostate gland (Fig 2).

As a result, we requested for immunohistochemical studies on previous prostate specimen. It showed focal weak synaptophysin (Fig 3) and CD 56 positivity in left base tumour measuring less than 1 mm. Focal convincing ACTH immunohistochemical staining was also noted in this tiny focus of tumour which might be the source of endogenous ACTH production. Features of small cell carcinoma were not seen.

![Fig 3: Prostatic adenocarcinoma with cytoplasmic synaptophysin staining in tumour cells.](image)

He was managed as prostate cancer (Adenocarcinoma) associated with ectopic ACTH secretion and was commenced on ketoconazole, IV and oral potassium replacement. The case was presented at our neuroendocrine tumour board. Urologist excluded prostate resection as it was considered too dangerous for the patient. After discussion with oncologist it was decided that in view of poor prognosis he should be managed medically. Ketoconazole was administered with an up-titrating dose of 400 mg/twice daily (Started at 200 mg/twice daily) for 3 weeks. Unfortunately, after 3 weeks of treatment, no significant clinical benefit was seen. Rather, patient deteriorated rapidly. On fourth week, he developed a glucocorticoid induced psychosis followed by sepsis due to severe immunosuppression and unfortunately died within one week.

**Discussion**

Prostatic adenocarcinoma is the most common prostate cancer in men. If prostatic adenocarcinomas have scattered foci of neuroendocrine immunohistochemical expression, they are termed as prostatic adenocarcinoma with neuroendocrine differentiation. Routine H&E stain is unable to recognize neuroendocrine features. For that reason, the neuroendocrine immunostains such as
chromogranin or synaptophysin is used to highlight the neuroendocrine cells. If H&E staining shows fine eosinophilic granules and nuclei with “salt and pepper” chromatin on prostate biopsy sample, neuroendocrine differentiation is suggested and should be confirmed by immunohistochemical stains. There are differing opinion regarding whether neuroendocrine differentiation in primary prostatic adenocarcinoma worsens prognosis. It can be an insignificant prognostic finding or an independent negative effect on prognosis3-11.

Ectopic ACTH production is responsible for 10–12% of all endogenous Cushing’s syndrome12. Half of all ectopic ACTH secretion is due to small cell lung carcinoma13. Carcinoid tumours are also very common (Thymic carcinoid 15%, pancreatic endocrine tumours, including pancreatic carcinoids, 10%; bronchial carcinoid 10%)14-18. Cushing’s syndrome due to adenocarcinoma of the prostate is an extremely rare entity.

Patients often do not manifest central weight gain despite often extremely high cortisol level due to the underlying malignant process and associated cachexia. Facial plethora, proximal muscle weakness, bruising without an obvious trauma are specific physical finding19. Other features are hypertension, hypokalaemia, metabolic alkalosis (Overwhelming of the 11B-hydroxysteroid dehydrogenase enzyme, resulting in exposure of the mineralocorticoid receptor to high circulating glucocorticoids) glucose intolerance, susceptibility to infection, thin skin, poor wound healing, and steroid-associated mood disturbance. On investigation, ACTH levels may be extremely high and in 90% of ectopic ACTH-secreting tumours, high-dose dexamethasone testing (2mg 6 hourly) shows a failure of cortisol levels to drop to 50% of baseline values due to a lack of any normal physiological feedback upon ACTH production. As some carcinoid tumours may behave indistinguishably from pituitary-dependent ACTH production, Corticotrophin Releasing Hormone (CRH) testing and/or inferior petrosal sinus sampling may be necessary to distinguish these conditions. Regarding finding out the source of ectopic ACTH-producing tumours, it can be extremely difficult to localize and may require multiple modalities of imaging such as Dotate PET CT, DOTANOC PET/CT. Ambrosini et al and Naswa et al published the role of Ga-68 DOTANOC PET/CT in initial staging20,21. They found sensitivity in the range of 78–92% and specificity of 92.5–98% for detection of neuroendocrine tumours. In terms of management, excision of the underlying tumour with neuroendocrine differentiation and/or bilateral adrenalectomy with glucocorticoid and mineralocorticoid replacement is an option if disease is at initial stage. Other options include medical management using metyrapone and/or ketoconazole, although very high doses may be needed. Here multidisciplinary team meeting involving endocrinologist, oncologist, surgeon pathologist and radiologist is crucial.

**Limitation**

Since it is a single center retrospective study involving a single case and is not chosen from representative population samples we cannot generate information on rates, ratios, incidences or prevalences of this rare clinical entity of Ectopic Cushing’s Syndrome from Prostatic Carcinoma. The general issues with these kind of case studies are that:

- They cannot lead to conclusions regarding causality.
- The individual studied may be atypical of the larger population.
- Researchers try to ensure that their studies are generalizable; that is, applicable to similar circumstances because of the predictable outcomes of repeated tests.
- The volume of data, together with the time restrictions in place, impacted on the depth of analysis that was possible within the available resources.

**Conclusion**

Prostate adenocarcinoma evolving into an ACTH-secreting neuroendocrine phenotype is a rare entity that is associated with high risk for infections, refractory hypokalaemia, and poor survival. Further clinical and pathological characterization is needed to ensure early recognition and appropriate treatment interventions for these patients.

**Recommendations**

Randomized Controlled Trials from multi-center institutions need to be done to rule out observer bias, determine possible relationships between the cause and effect and to provide us with a more accurate perspective to determine population statistics (rate, prevalence, incidence etc.) of the case in question. Furthermore, it has been suggested that venous sampling of the IPS, with
or without CRH stimulation, is the most accurate way to establish the diagnosis of CD. Although this is an invasive procedure and its success rate and complications depend on operator skill and experience, it is the most direct way of demonstrating pituitary hypersecretion of ACTH and thus identifying the patients who will benefit from pituitary surgery. In this case we did not receive the consent from the patient for performing the inferior petrosal sinus sampling due to the invasive procedure otherwise it could have guided us towards the prognosis.

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Contribution of authors
RHC - Conception, design, critical revision & final approval.
SRC - Design, critical revision & final approval.
TT - Citing references, manuscript writing & final approval.
MMA - Citing references, manuscript writing & final approval.

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All the authors declared no competing interests.

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