Journal of the ASEAN Federation of Endocrine Societies

CASE REPORT

An Unusual Case of Adrenocortical Carcinoma with Multiple Facets

Jie En Tan,[1] Florence Hui Sieng Tan,[1] Yueh Chien Kuan,[1] Pei Lin Chan,[1] Yusuf Yusri[2]

[1]*Endocrine Unit, Department of Medicine, Sarawak General Hospital, Ministry of Health, Malaysia*
[2]*Pathology Department, Sarawak General Hospital, Ministry of Health, Malaysia*

Abstract

Adrenocortical carcinoma (ACC) is a rare malignant tumour from the adrenal cortex. Half of the cases are functional, with ACTH-independent autonomous cortisol production being the most common. It is rare for ACC to present with markedly elevated metanephrine levels, characteristic of pheochromocytoma. We report a case of a large functioning adrenal tumour with overlapping biochemical features of ACC and pheochromocytoma. Biopsy confirmed the histopathological diagnosis of metastatic ACC.

Key words: adrenocortical carcinoma, pheochromocytoma, urine fractionated metanephrines

INTRODUCTION

Adrenocortical carcinoma (ACC) and pheochromocytoma are both rare tumours with incidence ranging from 0.7 to 2.0 per million per year for ACC and 2 to 8 per million per year in combined cases of pheochromocytoma and paraganglioma (PPGL).[1,2] It is often difficult to differentiate ACC from pheochromocytoma based on imaging alone. ACC and pheochromocytoma share common radiological characteristics such as large size, high attenuation values on unenhanced CT and inhomogeneity with areas of haemorrhage or necrosis with or without calcifications, which makes diagnosis challenging. A comprehensive endocrine work-up is helpful to differentiate one entity from another. This is important as the management and prognosis of the two diseases differ. One distinguishing feature is that pheochromocytomas secrete catecholamines, whereas most ACCs, if functioning, can secrete various adrenocortical hormones, including cortisol, sex steroids or rarely mineralocorticoids. Cortisol excess in functioning ACC is usually non-ACTH dependent, whereas pheochromocytoma can be associated with ACTH-dependent Cushing or ectopic ACTH syndrome (EAS). Pheochromocytoma must be ruled out in the initial evaluation of an adrenal mass to prevent a potentially life-threatening pheochromocytoma crisis before undertaking any invasive procedure. Furthermore, autonomous cortisol secretion from a functioning ACC or ectopic ACTH secretion from pheochromocytoma will require steroid replacement perioperatively during resection to prevent adrenal crisis.

We herein report a case of a large adrenal tumour with an elevated normetanephrine level but with concurrent androgen excess and ACTH-dependent subclinical Cushing syndrome, in which the diagnosis was finally clinched through tissue biopsy.

CASE

A 49-year-old Malay female with no known medical illness presented with a two-month history of abdominal pain and distension associated with nausea, vomiting and unintentional weight loss. She had been married for 25 years but remained nulliparous. At the time of presentation, she was amenorrhoeic for almost a year. She denied paroxysmal symptoms and had no significant family history of neuroendocrine tumours or solid organ tumours. She did not appear Cushingoid or hirsute. On examination, she had a normal BMI of 22 kg/m^2 (height 1.46 m, weight 47.9 kg), blood pressure was 141/76 mm Hg, and pulse rate was 97 beats per minute. Physical examination was significant for hepatomegaly.

Her initial bedside ultrasound showed multiple liver masses. A multiphase CT scan of the liver was subsequently done (Figure 1A), which revealed multiple heterogeneous masses in the right liver lobe with necrotic components, the largest in segment VII/VIII, measuring 9.3 x 10.3 x 10.4 cm. Another liver mass in segment V/VI measuring 8.9 x 9.2 x 8.5 cm, associated with the capsular breach and surrounding perihepatic hemoperitoneum suggestive of tumoral rupture. A large heterogenous, lobulated left

eISSN 2308-118x (Online)
Printed in the Philippines

Received: April 23, 2024. Accepted: May 29, 2024.
Published online first: September 3, 2024.
https://doi.org/10.15605/jafes.039.02.16

Corresponding author: Jie En Tan, MD
Endocrinology Trainee, Sarawak General Hospital
Jalan Hospital, 93586 Kuching, Sarawak
Tel. No.: +6082-276666
Fax No.: +6082-242751
E-mail: sgh@moh.gov.my
ORCiD: https://orcid.org/0009-0005-2290-0987

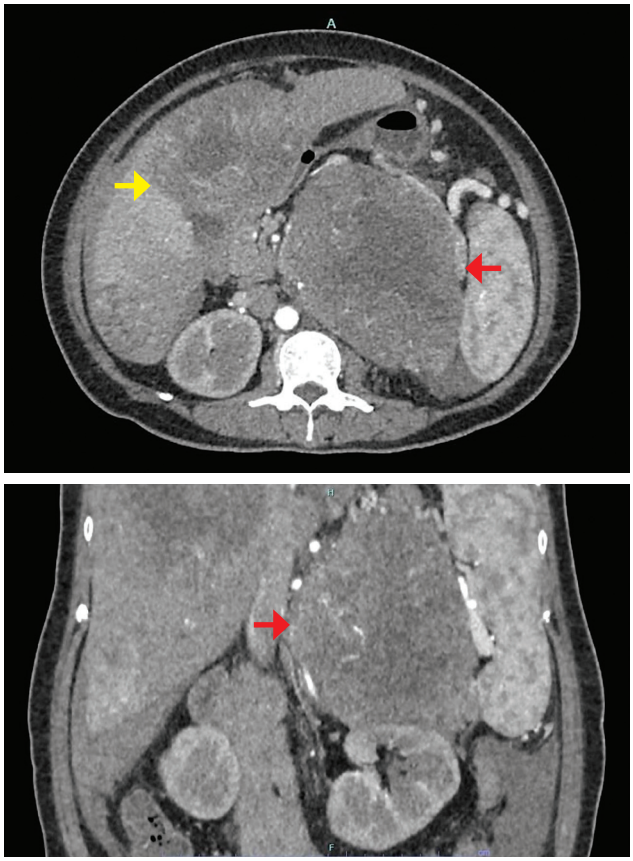

Figure 1. (A) Large heterogenous left adrenal mass *(red arrow)* with central hypodensity and multiple heterogenous masses *(yellow arrow)* in the right liver lobe (CT Abdomen axial view in arterial phase). **(B)** Left adrenal mass *(red arrow)* displaced the left kidney with no clear fat plane and abuts the spleen (CT abdomen coronal view in arterial phase).

suprarenal mass was visualized, measuring 9.9 x 12.7 x 13.5 cm with hypodense areas, which may represent a necrotic component (CT attenuation values: 39 HU on plain, 61 HU on arterial phase, 60 HU on portovenous phase and 59HU on delayed phase). The suprarenal mass showed some patchy arterial enhancement, displaced the left kidney with no clear fat plane and abutted the spleen (Figure 1B) . The right adrenal gland and pancreas appeared normal. Based on the imaging characteristics of the adrenal lesion, adrenocortical carcinoma was highly possible, but pheochromocytoma could not be ruled out.

Her subsequent hormonal workup revealed a basal 8 a.m. serum cortisol of 491 nmol/L, which was not suppressible with an overnight 1 mg dexamethasone suppression test (cortisol 474 nmol/L) or 48-hours, 2 mg/day low-dose dexamethasone suppression test (cortisol 508 nmol/L). Her DHEA-S level was markedly elevated at >27.1 micromol/L (reference range: 0.96-6.95), and her testosterone was 5.120 nmol/L (reference range: 0.29-1.67) with suppressed gonadotropins. The excess of both the cortisol and sex steroid hormones was consistent with the suspicion of a functioning ACC. Unexpectedly, ACTH levels were non-suppressed at 6.2 pmol/L and repeatedly within

Table 1. 24-hour urine metanephrines

Laboratory parameters	Value	Unit	Reference
Urine volume	0.97	L	
Urine PH	2.00		
Urine creatinine	8.83	mmol/24 h	
Normetanephrine	6.30	µmol/day	0.00 - 2.13
Metanephrine	0.40	µmol/day	0.00 - 1.62
3-methoxytyramine	1.80	µmol/day	0.10 - 1.79

the normal range, 5.4 pmol/L (normal 1.6-13.9) using the Roche Elecsys electrochemiluminescence immunoassay (ECLIA) method, suggesting ACTH-dependent Cushing syndrome. Adding to the diagnostic dilemma, her 24-hour urine metanephrine by liquid chromatography with an electrochemical detection method showed elevated normetanephrine levels three times above the upper reference limit (Table 1). The sample collection was strictly done under careful instructions, ensuring the absence of interfering drugs and significant physiological stress. Other than an elevated LDH 1287 U/L (reference range: 135-214) and ALP 601 U/L (reference range: 35-104), other blood parameters such as complete blood count, blood glucose, renal profile, electrolytes, including corrected calcium and liver function, were within normal limits.

Given the raised urine normetanephrine level and inability to rule out pheochromocytoma, she was started on an alpha-blocker, terazosin 1 mg ON. With up-titration of terazosin to 3 mg ON, she achieved normotension (systolic BP ranged 118-130 mm Hg, diastolic BP 53-69 mm Hg). A beta blocker was added later, maintaining her heart rate between 84 to 91 beats per minute without tachycardia. CT of the neck and thorax was done to look for extra-adrenal tumours or paragangliomas, but no suspicious lesions were detected. Similarly, MIBG scintigraphy did not show any MIBG-avid disease. A multidisciplinary team discussion concluded with the decision to do a biopsy of the adrenal and liver lesions for a likely inoperable disease and the need for histopathological diagnosis for oncologic planning. The diagnosis of metastatic adrenocortical carcinoma was still highly probable at the time of discussion due to the biochemically confirmed nature of mixed hormonal hypersecretion of both cortisol and androgen of the tumour. The biopsy was done after the adrenergic blockade.

Her liver and adrenal mass biopsy results later confirmed the histopathological diagnosis of metastatic adrenocortical carcinoma (Figures 2A and B), with immunohistochemical staining showing diffuse strong positivity for synaptophysin and inhibin (Figure 3) and focal positivity for Melan A. The cells stained negative for Chromogranin A, ruling out pheochromocytoma. ACTH staining was not available locally. Limited by the small tissue sample, the pathologist could not provide further information to prognosticate based on the Weiss score, Ki67 index or nodal status. She was ENSAT stage IV, nevertheless, due to the evidence of liver metastasis. As her disease was advanced and complete resection was not possible, she was offered mitotane with chemotherapy (etoposide/carboplatin).

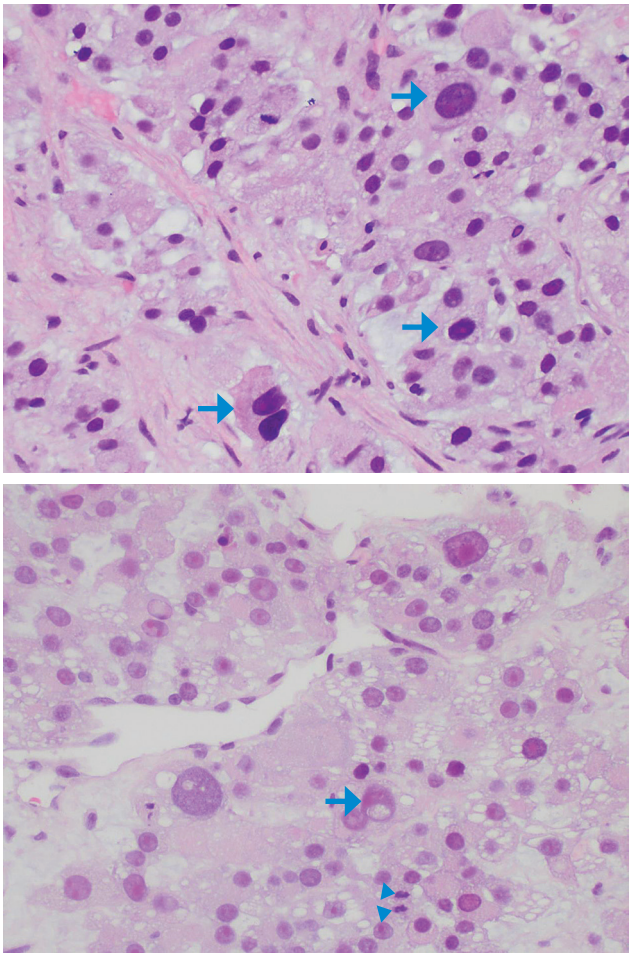

Figure 2. (A) Tumour exhibits large cells displaying large round pleomorphic hyperchromatic nuclei, prominent eosinophilic nucleoli and abundant granular cytoplasm (H&E, 40x). **(B)** Frequent intranuclear inclusions *(blue arrow)* and mitoses *(blue arrow heads)* (H&E, 40x).

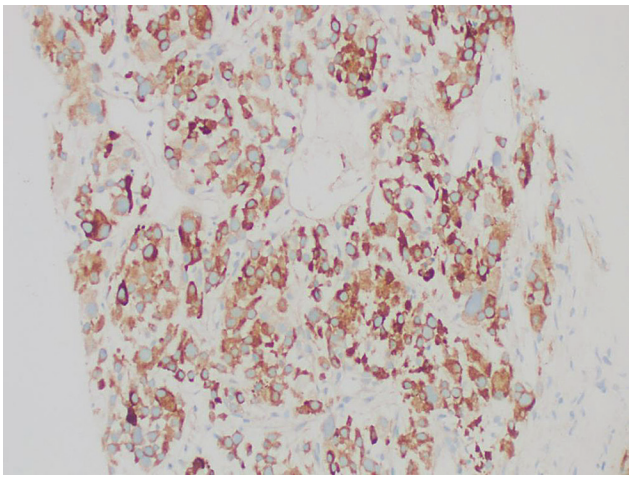

Figure 3. Synaptophysin and Inhibin stain with strong diffuse positivity (20x).

DISCUSSION

It is uncommon for ACC to present with markedly elevated metanephrine levels and even more unusual for the same disease entity to show ACTH-dependent Cushing syndrome (CS) with androgen excess.

Plasma free or urine fractionated metanephrines have high diagnostic sensitivity and specificity. Patients who tested positive should be followed up appropriately, considering both clinical presentation and degree of metanephrine elevation.[3] The isolated elevation of urine normetanephrine 3-fold above the upper limit was significant. However, the MIBG scan, pathological findings and immunohistochemical staining have ruled out the definitive diagnosis of pheochromocytoma. Therefore, the increased level of 24-hour urinary normetanephrine may be a false positive in this case. False positive biochemical test results for pheochromocytoma are common and present particular problems because of the low prevalence of the disease.[4] The diagnostic cut-offs for most 24-hour urinary fractionated metanephrine assays are based on normal ranges derived from a normotensive volunteer reference group, which can result in a high rate of false-positive results.[5] For this reason, tests should be repeated to confirm the results.[6]

A literature review revealed several possible similar cases of adrenal cortical tumours with increased metanephrines and catecholamine levels, labeling them as metanephrine-producing adrenocortical carcinoma[7] and so-called pseudo-pheochromocytoma.[8]

The unsuppressed ACTH level was an unexpected finding in this case. If the plasma ACTH concentration is above 20 pg/mL (4.4 pmol/L) in a patient with sustained hypercortisolism, one can assume that cortisol secretion is ACTH-dependent (i.e., due to pituitary disease or ectopic ACTH or corticotropin-releasing hormone [CRH] secretion). However, patients with ACTH-independent causes of Cushing syndrome who have cyclic or mild hypercortisolism (and consequently lack suppression of normal corticotrophs) may have normal ACTH values, falsely indicating an ACTH-dependent condition.[9]

Of note is that ACTH immunoassays are vulnerable to assay interference, which gives rise to discordant biochemical results from the clinical pictures. ACTH assays are also burdened by high variability and often fail to identify patients with suppressed ACTH secretion correctly.[10] Based on the results of an Italian multicentre study, it was found that plasma ACTH concentrations were detectable in 58% of patients with ACTH-independent CS, and 28% fell within the normal range among this group of patients using the radioactive immunoassay (RIA) or immunoradiometric assay (IRMA) method.[11] Another multi-center study conducted by Giraldi et al. found that 40% of plasma ACTH measurements fell into the normal range using chemiluminescent immunometric assay (CLS) and IRMA in patients whose ACTH secretion should

be suppressed. This raises the question of whether this phenomenon could be due to technical problems or if the pathophysiology of glucocorticoid negative feedback and secondary adrenal insufficiency should be revisited.[10] In this case, plasma ACTH was measured using the newer electrochemiluminescence ACTH immunoassay (Roche Diagnostics). Although rarely reported with the newer ECLIA method, it is worthwhile to exclude assay interference when encountering biochemical results discordant with the clinical presentation. Communication with the pathologists on further steps to eliminate analytical errors would be useful in identifying the mechanism of CS in this case.

Dilrukshi et al., described a case of ACC-associated aberrant ACTH production in which the tumour cells expressed granular cytoplasmic positivity for ACTH, having a plasma ACTH level of 40.3 pg/ml (8.87 pmol/L).[12] Law A et al., also reported 2 cases of functioning ACCs with unsuppressed ACTH concentrations despite having glucocorticoid excess. Both cases showed no stainable ACTH with anti-ACTH antibody on histology, and the exact pathophysiology was unknown.[13]

Rarely, ACC can be associated with multiple endocrine neoplasia type 1 (MEN1). Hypercortisolism in the context of MEN1 can result from pituitary, adrenal or thymic neuroendocrine tumours and can therefore reflect either ACTH-dependent or ACTH-independent pathophysiologies.[14] The incidence of ACC is approximately 1% in MEN1 patients and 13% in MEN1 patients with adrenal tumours larger than 1 cm.[15] The diagnosis of MEN1 is less likely in this case given that the patient was normocalcemic, which makes primary hyperparathyroidism unlikely, and the pancreas was normal on imaging. However, an MRI of the pituitary may help rule out a pituitary adenoma, especially in cases of ACTH-dependent CS. A high-dose dexamethasone suppression test and CRH stimulation test may be helpful in the work-up of unsuppressed ACTH levels, as was seen in this case . Cases of subclinical CS with ectopic ACTH have been described in mixed corticomedullary tumour (MCMT) of the adrenal gland by Kimura et al., MCMT is an extremely rare tumour characterized by an admixture of steroidogenic cells and chromaffin cells in a single tumour mass, producing adrenocortical hormones and catecholamines.[16] As surgical resection was not done in this case, there remain unanswered questions if the biopsy samples are fully representative of the underlying disease aetiology.

An adrenal biopsy is generally not recommended for suspected ACCs due to the risk of tumour dissemination and significant risks, such as haemorrhage. Exceptions are conditions where the disease is inoperable, and confirmation of diagnosis is needed for oncologic management, as part of a clinical trial or suspected metastasis from an extra-adrenal malignancy.[17] The presence of metastatic disease in this case precluded surgery, and histological proof was pertinent to distinguish ACC from pheochromocytoma with certainty as management would differ depending on the disease aetiology. MIBG scintigraphy, despite being the gold-standard diagnostic tool for pheochromocytoma, can be negative in poorly differentiated or metastatic pheochromocytomas.[18] A retrospective review on transcutaneous adrenal biopsy done in Stage I to III ACCs showed that biopsy did not significantly affect patient outcomes in terms of recurrence-free or overall survival but may only be helpful in the right setting.[19]

CONCLUSION

The myriad biochemical features of ACC, some of which overlap with pheochromocytoma, can make it challenging for clinicians to arrive at an accurate diagnosis. Close collaboration of a multidisciplinary team comprising of endocrinologists, pathologists, radiologists, endocrine surgeons and oncologists is needed to facilitate accurate diagnosis and appropriate management in such unique cases with multiple adrenocortical hormone excess with markedly elevated metanephrines.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
JET: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **FHST:** Validation, Writing – review and editing, Supervision; **YCK:** Validation, Writing – review and editing, Supervision; **PLC:** Writing – review and editing, Supervision; **YY:** Investigation, Resources.

Author Disclosure
The authors declared no conflict of interest.

Data Availability Statement
No datasets were generated or analyzed for this study.

Funding Source
None.

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