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CASE REPORT

Adrenocortical carcinoma in a patient presenting with recurrent pulmonary emboli

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Adrenocortical carcinomas are rare malignancies with a clinically heterogeneous presentation. These tumours can be detected incidentally on imaging, where biochemical evaluation is required to assess tumour functionality. This case describes a patient presenting with recurrent pulmonary emboli and an incidental finding of an adrenal mass. Biochemistry revealed hypercortisolism, plus elevated androgen and oestrogen levels despite only mild clinical features of hypercortisolism. Histology confirmed a high-grade adrenocortical carcinoma.

Keywords: adrenal incidentaloma, adrenocortical carcinoma, pulmonary embolism

Introduction

An adrenal incidentaloma is a clinically unapparent adrenal mass larger than 1 cm, detected on imaging for purposes other than underlying adrenal disease.[1] This definition excludes patients undergoing screening and surveillance imaging for underlying hereditary syndromes (e.g. multiple endocrine neoplasia 2, or Von Hippel Lindau disease) or with extra-adrenal malignancies.[2,3] The prevalence of adrenal incidentalomas varies depending on the data source, such as autopsy, surgery, or radiological series.[1] Thus, the true prevalence is challenging to determine. It has been reported that adrenal tumours are discovered in 5–7% of patients undergoing abdominal imaging, where approximately 75% are then found to be benign non-functional cortical adenomas. Importantly, disorders such as phaeochromocytoma and other functional tumours, primary adrenal carcinomas, and metastases to the adrenal glands need to be excluded.[2,4] This case describes a patient presenting with recurrent pulmonary emboli (PE), where the underlying cause was due to an underlying adrenal tumour.

Case description

A 40-year-old female with a background medical history of hypertension and dyslipidaemia presented with progressive dyspnoea and pleuritic chest pain in April 2023. She was a previous smoker with a 20-pack-year smoking history. In 2016, she had a similar presentation, where a computed tomography pulmonary angiogram (CTPA) confirmed bilateral pulmonary emboli, with no other pathology documented on the radiology report. Oral contraceptive use was identified as the most likely risk factor for the emboli at the time, and she was discharged to complete six months of anticoagulation with warfarin.

A CTPA was again performed on this admission due to the working diagnosis of recurrent PE. The imaging demonstrated bilateral pulmonary emboli with features of pulmonary hypertension. Of note, the partially imaged abdomen revealed a large right-sided adrenal mass, which was reported to have increased in size compared with the partially imaged adrenal gland in 2016. Subsequently, an abdominal CT was performed, which revealed a large ($104 \times 97 \times 92$ mm) heterogeneous suprarenal mass on the right (Figure 1). Hounsfield units and washout could not be performed due to the heterogeneity and size of the lesion. Radiologically, the mass was suggestive of a phaeochromocytoma with a differential diagnosis of adrenocortical carcinoma. This prompted a referral to the Endocrinology Department for further evaluation.

On enquiry, the patient reported a background history of weight gain (approximately 5 kg over four months), hair loss and oligomenorrhea. There was no significant family history of note. Antihypertensive medication included atenolol, amlodipine, losartan, doxazosin, and indapamide, though her blood pressure control was noted to be poor despite these multiple agents. The patient denied prescribed and over-the-counter exogenous steroid use. On clinical examination, the patient weighed 126 kg, with a height of 168 cm and an elevated BMI of 44.6. Abdominal striae were noted, but no other overt clinical features of hypercortisolism were found. Hirsutism was present but no evidence of virilisation.

Investigations

Table 1 depicts the biochemical profile. The endocrine assessment of the adrenal mass revealed elevated androgen levels and a significantly elevated oestradiol concentration with appropriately low follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels. An early morning serum cortisol level was elevated (Table 1), and this was confirmed by a midnight serum cortisol measurement of 255 nmol/l. Additionally, a 24-hour urinary cortisol excretion test was performed, and hypercortisolism was demonstrated. A short dexamethasone suppression test was performed, which failed to suppress, with a serum cortisol of 219 nmol/l. Similarly, the prolonged dexamethasone test failed to suppress, with serum cortisol of 265 nmol/l on day 1, 209 nmol/l on day 2, and 189 nmol/l on day 3. The adrenocorticotropic hormone (ACTH) level was low,

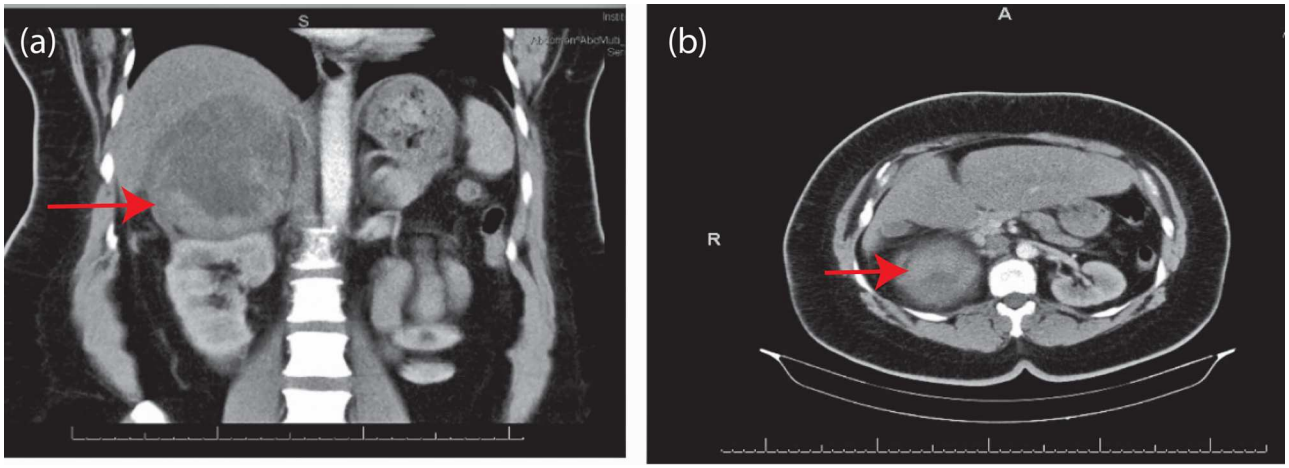

Figure 1: Abdominal CT. (A) Coronal view; (B) axial view.

which was in keeping with cortisol production from an adrenal or ectopic origin. The patient was noted to have normal aldosterone and low renin levels, with an increased aldosterone:renin ratio. No hypokalaemia was noted on biochemistry during admission. Lastly, the urine normetanephrines were increased. The patient had a normal fasting plasma glucose measurement with an HbA1C level of 5.4%, which was not diagnostic of diabetes mellitus. Dual-energy X-ray absorptiometry (DEXA) scan was normal.

Biochemical investigations were performed at ISO 15189:2012-accredited laboratories within the National Health Laboratory Services (NHLS) in South Africa.

Outcome and follow-up

A right adrenalectomy and nephrectomy were performed in July 2023. Histology confirmed high-grade adrenocortical carcinoma (ACC), with immunohistochemistry staining showing Ki-67 at 14%, with clear tumour margins and a pT2NxMx staging. Biochemistry after surgery demonstrated a marked improvement in sex hormone concentrations. A staging 18^{F}-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) was performed one month after surgery (Figure 2). This revealed no evidence of local residual tumour and no nodal or distant metastases. The patient was subsequently referred for neoadjuvant radiation and is currently still being followed up at the Oncology clinic at Tygerberg Hospital. At present, the patient reports no ongoing symptoms and has lost approximately 10 kg since her presentation.

Discussion

This case describes a patient presenting with recurrent PE due to an underlying ACC. Due to the advancement of radiological imaging, the detection of adrenal incidentalomas has increased. The European Society of Endocrinology, in collaboration with the European Network for the Study of Adrenal Tumours, introduced updated recommendations in the 2022 clinical practice guideline for the management of adrenal incidentalomas. The guideline recommends that all adrenal incidentalomas undergo imaging to assess whether the mass is homogeneous and lipid-rich (benign), with non-contrast CT as the preferred initial imaging modality. Notably, the revised recommendations state that adrenal incidentalomas larger than 4 cm, with heterogeneous features and HU > 20, should be evaluated by a multidisciplinary team. In the present case, the patient was discussed at the multidisciplinary meeting involving Radiology, Endocrinology and Endocrine Surgery. Additionally, the guideline emphasises that these lesions need comprehensive staging prior to surgery, including a thoracic CT, with or without FDG-PET/CT.[5] This staging was not performed preoperatively in this patient; however, post-surgical FDG-PET/CT revealed no evidence of local or distant metastases.

The finding of the adrenal mass at the index presentation in 2016 was not added to the formal CTPA report and, regrettably, further biochemical and radiological evaluation was not performed at that stage. The radiology report can influence referrals for adrenal incidentalomas, where the language used in the report, whether it suggests follow-up or indicates a diagnosis, can impact patient referral.[3,6] A study by Watari et al. aimed to identify the factors influencing referrals for adrenal incidentalomas. They reviewed the imaging characteristics of 246 adrenal nodules. Among these, 12 nodules (4.9%) were described as benign, and none of these were referred for follow-up. The study also found that follow-up recommendations in the radiology report resulted in outpatient referrals being five times more likely.[6]

The assessment of an adrenal incidentaloma aims to determine whether it is functional and/or malignant. This relies on a thorough clinical evaluation, radiological findings, and biochemical testing. The laboratory testing, guided by the clinical findings, can involve screening for catecholamine, glucocorticoid, mineralocorticoid, and androgen excess.[1,2,4] This patient interestingly had relatively mild clinical symptoms of glucocorticoid excess despite the overt biochemical findings and duration of the abdominal mass being present. This may be suggestive that mild autonomous cortisol secretion (MACS) was present. MACS is characterised by biochemical hypercortisolism without the classic clinical features of Cushing's syndrome. It has been reported that up to 5–30% of adrenal incidentalomas are associated with MACS.[7] Patients with MACS are at increased risk of developing hypertension, dyslipidaemia, obesity, osteopenia, osteoporosis, and glucose intolerance compared with those with non-functional tumours.[2] Thus, screening for these coexisting conditions should be performed.

Adrenocortical carcinoma (ACC) is a rare malignancy arising from the adrenal cortex, with an estimated worldwide incidence of approximately 1–2 cases per million population per year.[1] It is an aggressive malignancy, with a 5-year survival of 16–45%, depending on the clinical staging at diagnosis.[8] ACCs have a

Table 1: Laboratory investigations

Item	May 2023	July 2023	Reference interval
Sodium	141		136–145 mmol/l
Potassium	4.1		3.5–5.1 mmol/l
Urea	3.9		2.1–7.1 mmol/l
Creatinine	65		49–90 µmol/l
eGFR (CKD-EPI)	102		ml/min/1.73m^2
HbA1C	5.4%		
FSH	< 0.1		Follicular phase: 2.5–12.5 IU/l Ovulation phase: 4.7–21.5 IU/l Luteal phase: 1.7–7.7 IU/l Postmenopausal: 25.8–134.8 IU/l
LH	< 0.1		Follicular phase: 2.4–12.6 IU/l Ovulation phase: 14.0–95.6 IU/l Luteal phase: 1.0–11.4 IU/l Postmenopausal: 7.7–58.5 IU/l
Oestradiol	3660	60	Follicular phase: 45 854 IU/l Ovulation phase: 151 1461 IU/l Luteal phase: 82 1251 IU/l Postmenopausal: < 18–505 IU/l
Testosterone	14.1	<0.1	0.3–1.7 nmol/l
SHBG	220.8		32.4–128.0 nmol/l
Free androgen index	6.4		0.3–5.6
DHEAS	20.3	1.0	1.7–9.2 µmol/l
Serum cortisol	656	488	133–537 nmol/l (06:00–10:00) 68–327 nmol/l (16:00–20:00)
dU cortisol	137		10–124 nmol/24 h
ACTH	0.7		1.6–13.9 pmol/l
dU metanephrine	281		152–913 nmol/24 h
dU normetanephrine	2794		650–2462 nmol/ 24 h
Aldosterone	160		Supine: < 443 pmol/l Upright: 111–859 pmol/l
Renin	1.2		Supine: 2.8–39.9 mIU/l Upright: 4.4–46.1 mIU/l
Aldosterone:renin	133.3		> 5 pmol/mIU

Abbreviations: ACTH: adrenocorticotropic hormone; DHEAS: dehydroepiandrosterone sulphate; FSH: follicle stimulating hormone, LH: luteinising hormone, SHBG: sex hormone binding globulin.

heterogeneous clinical presentation. Approximately 60% present with an overproduction of glucocorticoids with features of Cushing's syndrome and/or androgen excess, evidenced by virilisation. Biochemical evidence of hypersecretion from two adrenal zones, as noted in this patient, is more suggestive of an ACC.[1] The remainder of cases typically present with symptoms related to the abdominal mass or may be detected as an incidental finding on imaging.[8,9] The prevalence of ACC is 2–12% of incidentally diagnosed tumours.[10] ACC often occurs sporadically; however, it is also associated with familial tumour syndromes such as multiple endocrine neoplasia type 1 (MEN-1). This syndrome is characterised by neoplasia of the pituitary gland, parathyroid gland, and neuroendocrine tissue of the gastro-entero-pancreatic organ system.[11] The clinical features that suggest an underlying hereditary syndrome with increased susceptibility to ACC include a childhood diagnosis, bilateral ACC, and affected family members.[11] This patient had no clinical suspicion of an underlying hereditary syndrome, and no further genetic testing was performed.

The European Society of Endocrinology Clinical Practice Guidelines recommends that all patients with suspected ACC have a detailed hormonal assessment performed to identify glucocorticoid, sex hormone, mineralocorticoid, and adrenocortical steroid hormone precursor hormone excess.[12] The proposed laboratory evaluation is presented in Table 2. The investigation of these patients also includes radiological imaging; however, conventional imaging may not always differentiate a phaeochromocytoma from an ACC. The predominant imaging techniques include CT, magnetic resonance imaging (MRI), and FDG-PET/CT. MRI and CT are mainly used to identify benign lesions, whereas FDG-PET/CT is utilised to detect malignant disease.[12] The finding of Hounsfield units ≤ 10 in an unenhanced CT is one of the best criteria for diagnosing a benign tumour (e.g. adenoma).[13] In the present case, this measurement could not be performed due to the heterogeneity of the lesion, which is more suggestive of an ACC, as these lesions typically show an inhomogeneous appearance on CT scans.[13]

The initial CT scan was suggestive of a possible underlying phaeochromocytoma in the current case. Other than underlying hypertension, no overt clinical findings were evident. Approximately 1.5–14% of adrenal incidentalomas are found to be pheochromocytomas.[2] It is recommended that all patients undergo biochemical screening for an underlying phaeochromocytoma, as these tumours may be clinically silent and can induce life-threatening crises.[13] There was an increase in the urinary normetanephrine result; however, this test is susceptible to false positives. Medication, including beta blockers, which were prescribed to this patient, may have caused a falsely elevated result.[14]

Excess cortisol and sex hormones are associated with an increased risk of venous thromboembolism.[15] This is the likely underlying cause of recurrent PE in the present case. The early morning cortisol, 24-hour urinary cortisol, and failure to suppress both short and long dexamethasone suppression tests in this patient indicated glucocorticoid excess. It has been reported that patients with Cushing's syndrome have a 10-fold increased risk of developing venous thromboembolism. The underlying mechanism is related to increased hypercoagulability from increased production of procoagulant factors and impaired fibrinolysis.[16]

During the endocrine evaluation, a significantly elevated level of oestradiol was noted. 17β-oestradiol (E2) is a steroid hormone synthesised from cholesterol. It is the most potent form of oestrogen produced by the ovaries.[17] Elevated concentrations of oestrogens can be observed in virilising tumours due to the peripheral conversion of androstenedione. It has been suggested that increased aromatase activity in ACC tumour cells may contribute to elevated oestrogen synthesis.[18] Oestrogen-secreting ACCs are exceedingly rare in adults and account for 1–2% of ACCs. They are more prevalent in men, who present with feminising features.[18] Oestrogen is known to impact multiple homeostatic factors and lead to an increased risk of venous thromboembolism.[19] Elevated circulating oestrogen was likely an additional contributing risk factor to the development of recurrent PE in the presented case.

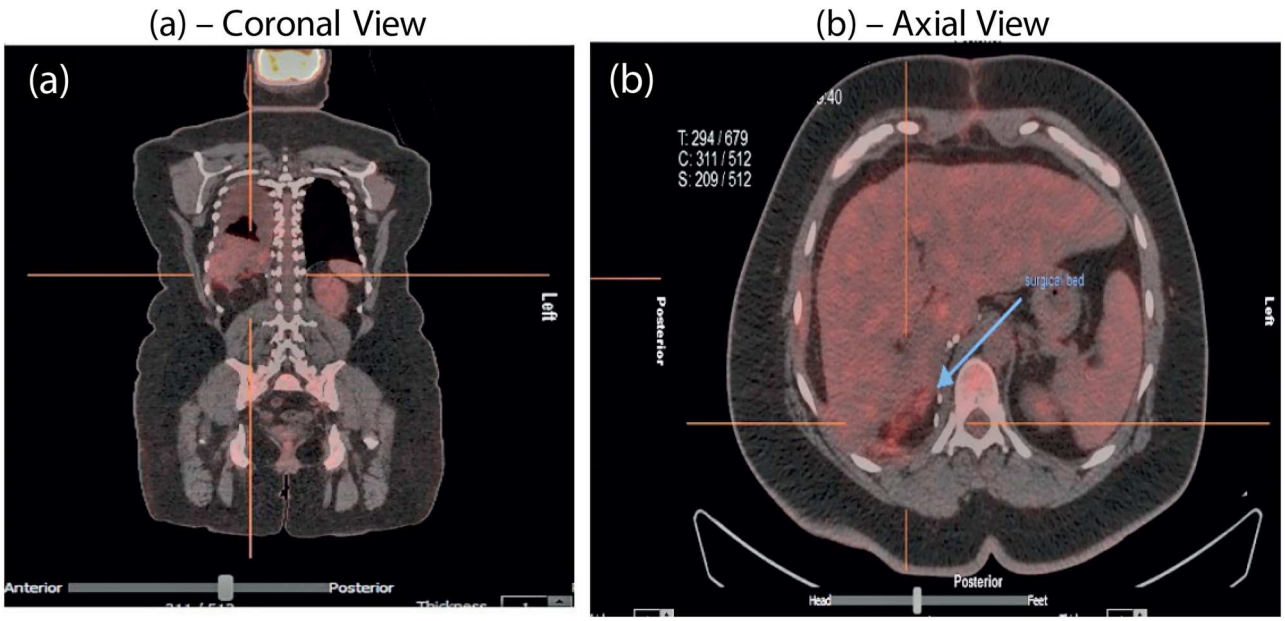

Figure 2: 18^{F}-fluorodeoxygludose PET/CT. (A) Coronal view; (B) axial view.

A case report by Yokoyama et al. described a case of an oestrogen-secreting adrenocortical carcinoma. They reported a 68-year-old post-menopausal woman presenting with vaginal bleeding. Imaging revealed a left adrenal tumour with elevated serum oestradiol and testosterone. They performed immunohistochemical analysis and demonstrated that the tumour expressed P450arom, which enabled the conversion of androgens to oestrogen.[20] Further immunohistochemical analysis was not performed in the presented case to assess P450arom expression. Thus, it is challenging to delineate whether the underlying oestrogen elevation is due to increased peripheral conversion of androgens or secretion of oestrogen from the tumour itself.

In this case, the low renin with normal aldosterone may be secondary due to the hypercortisolism. Glucocorticoids can bind both mineralocorticoid and glucocorticoid receptors. At physiological cortisol concentrations, binding to the mineralocorticoid receptor is inhibited by the enzyme 11-hydroxysteroid dehydrogenase type 2 (11-HSD2), which converts cortisol to inactive cortisone.[21] However, with excess cortisol, the ability of 11-HSD2 to convert cortisol to cortisone is impaired. Thus, the excess cortisol can bind to the mineralocorticoid receptor and mimic the action of aldosterone. The resultant blood volume expansion suppresses renin excretion and contributes to hypertension in Cushing's syndrome.[21] Primary hyperaldosteronism is rare in cases of ACC and, if present, is often accompanied by severe hypokalaemia. The hypokalaemia observed in ACC is more often a result of hypercortisolism via the above-described mechanism.[12]

Table 2: Diagnostic evaluation in patients with suspected or proven ACC[12]

Glucocorticoid excess	1 mg dexamethasone suppression test or free cortisol in 24-hour urine Basal plasma ACTH
Sex steroids and steroid precursors	DHEA-S 17-hydroxyprogesterone Androstenedione Testosterone (only in women) 17β-oestradiol (only in men and postmenopausal women) 11-Deoxycortisol
Mineralocorticoid excess	Potassium Aldosterone:renin ratio (only in patients with arterial hypertension and/or hypokalaemia)
Exclusion of a phaeochromocytoma	Fractionated metanephrines in 24-hour urine or free plasma-metanephrines CT or MRI of the abdomen and pelvis Chest CT FDG-PET/CT Bone or brain imaging (when skeletal or cerebral metastases are suspected)

This patient was diagnosed with stage 2 disease, based on the adrenal tumour size of more than 5 cm in the absence of lymph node involvement, which has a reported 5-year survival ranging from 19–54%.[22] Immunohistochemical staining in this case further revealed an elevated Ki-67 of 14%. Ki-67 is a nuclear DNA-binding protein present during the cell cycle's G_1, S, and G_2 phases but absent in the G_0 phase, suggesting its role as a marker of cell proliferation in various cancers.[22,23] Ki-67 is utilised in tumour grading as a marker of tumour proliferation.[23] In the grading of ACC, the Ki-67 index is evaluated, where ACC typically exhibits a Ki-67 level of $\geq 5\%$.[24] Malignancies with a high Ki-67 index often have a poor prognosis. A Ki-67 index greater than 10%, irrespective of primary resection status, indicates an intermediate risk of recurrence of ACC ranging from 30% to 70%.[22,23] Given the disease stage with an elevated Ki-67 index, this underscores the necessity for regular follow-up and monitoring for recurrence in this patient.

In the index case, the patient was initiated on postoperative hydrocortisone. The European Society of Endocrinology Clinical Practice Guidelines on the management of ACC in adults, in collaboration with the European Network for the Study of Adrenal Tumours, recommends perioperative hydrocortisone replacement for all patients with hypercortisolism undergoing surgery for ACC, as adrenal insufficiency may occur following the removal of the adrenal source of cortisol production. Additionally, the guideline suggests offering mitotane to patients at high risk of recurrence, including those with stage

III disease, an R1 resection, or a Ki-67 index > 10%.[12] Mitotane primarily targets the adrenal cortex by inhibiting steroidogenic enzymes in mitochondria and inducing endoplasmic reticulum stress, impairing steroidogenesis and cell destruction.[22] In the present case, mitotane was not prescribed.

Conclusion

This case describes a patient with a rare diagnosis of ACC who presented with recurrent pulmonary emboli. Despite the presence of an adrenal mass on the initial imaging at the index presentation in 2016, the lack of follow-up recommendations in the radiology report may have caused delayed evaluation and management. As demonstrated in this patient, few clinical signs of hypercortisolism were present despite the biochemical evidence. Thus, this case further emphasises the importance of a comprehensive biochemical and radiological evaluation in cases of adrenal incidentaloma, as these may present with subtle clinical signs.

Ethical statement

Informed patient consent was obtained for the use of anonymised patient information. Ethical approval for this case report was granted by the Stellenbosch University Health Research Ethics Committee (Ref: C24/09/031).

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