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Atypical clinical presentation of oncocytic adrenocortical carcinoma with decompensated metabolic syndrome and psychotic outbreak

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SUMMARY

Adrenal incidentalomas, mostly adrenal adenomas, affect 3%–10% of the global population. Adrenocortical carcinoma (ACC) is rare, with an incidence of 0.7–2 cases per million. Adrenocortical oncocytic neoplasms (ACONs) account for about 10% of ACC cases, often discovered incidentally, with 17–34% being functionally active.

We report a case of a woman in her 60s with treatment-resistant hypertension, diabetes and psychotic delirium. Imaging revealed a 6 cm left adrenal mass with marginally elevated metanephrines. Laparoscopic adrenalectomy was performed. Histology confirmed ACON. Positive margins necessitated adjuvant chemotherapy and radiotherapy. Postoperatively, psychiatric symptoms and hypertension resolved, indicating the tumour's secretory nature.

This case highlights the diverse ACONs hormonal secretions, leading to complex clinical presentations, including metabolic and psychiatric symptoms. ACONs secretory nature may not be reflected in standard hormonal panels.

ACONs challenging diagnosis and management emphasise the need for a multidisciplinary approach and further research.

BACKGROUND

The fortuitous discovery of an adrenal mass is defined as an adrenal incidentaloma, which is very common, affecting 3%–10% of the global population, with most cases presenting as adrenal adenomas.[1] In contrast, adrenocortical carcinoma (ACC) is a rare disease, with an estimated incidence of 0.7–2 cases per million annually.[2] Adrenocortical oncocytic neoplasms (ACONs), constituting about 10% of the ACCs,[3] are typically incidentally detected and literature regarding this pathology remains limited. Indeed, the hormonal activity of the ACONs is unclear: a systematic review by Kanitra *et al* found that 34% of ACONs were hormonally functional,[4] which is in contrast with the results (17%) of Mearini *et al*'s systematic review.[5] These tumours predominantly affect females (66%) with an average age of 44 years and a median size of 80 mm, often larger than other adrenal tumours. Most ACONs are left adrenal gland tumours (64%).[4] The 5 years survival rate for malignant ACONs is reported to be 47%, with a recurrence rate of 16%, 80% of which occur within the first 5 years.[4] Here, we present the case of an ACON with an unusual presentation, discovered in the context of a decompensated metabolic syndrome and psychotic outbreak.

CASE PRESENTATION

We present the case of a woman in her 60s who was admitted due to decompensated metabolic syndrome. She exhibited symptoms of refractory arterial hypertension accompanied by dizziness, headache, asthenia and a weight gain of 20 kg within a span of 6 months. Despite maximal antihypertensive therapy (amlodipine 10 mg, lisinopril 20 mg, métoprolol 50 mg, aldactone 25 mg, all PO), her systolic blood pressure remained around 160 mm Hg. The investigation revealed an onset of type 2 diabetes, requiring insulin immediately, and mixed hyperlipidaemia associated with hypokalaemia and hypernatraemia. While hospitalised under geriatric care, she experienced a psychotic breakdown, characterised by persecutory delirium, non-critical visual hallucinations and mistrust of contacts associated with anxiety, particularly fear of transmitting SARS-CoV2 as she believed herself to be the origin of the pandemic. She was initially treated, after the exclusion of a cerebral lesion, with haloperidol (1 mg three times per day Per Os (PO)) and clomethiazole (192 mg two times per day PO as needed). Due to extreme agitation involving self-harm, she was transferred to a psychogeriatric unit. During her stay, she received care through a multidisciplinary approach that encompassed a hypostimulant framework, psychiatric and psychotherapeutic treatment. Behavioural disorders improved, but delusions persisted and were associated with disabling anxiety and a tendency towards social withdrawal.

Liver tests were abnormal with gamma-glutamyltranspeptidase levels at 1749 U/L, total bilirubin at 17.3 µmol/L, ALAT 118 U/L, ASAT 85 U/L, alkaline phosphatase 74 U/L, as well as hypernatraemia at 149 mmol/L. Calcaemia and ammonia levels were normal, at 2.31 mmol/L and 36 µmol/L respectively.

Concurrently, she experienced dysuria without fever, asthenia, and intermittent sweating, prompting her readmission to an internal medicine department for further investigation.

Her medical history is relevant for hypertension, morbid obesity and unstaged heart failure. She did not use alcohol, tobacco or other substances. She had a surgical history of appendicectomy 10 years earlier and two C-sections 40 years ago. Prior to admission, her medications included olmesartan 20/25 mg,

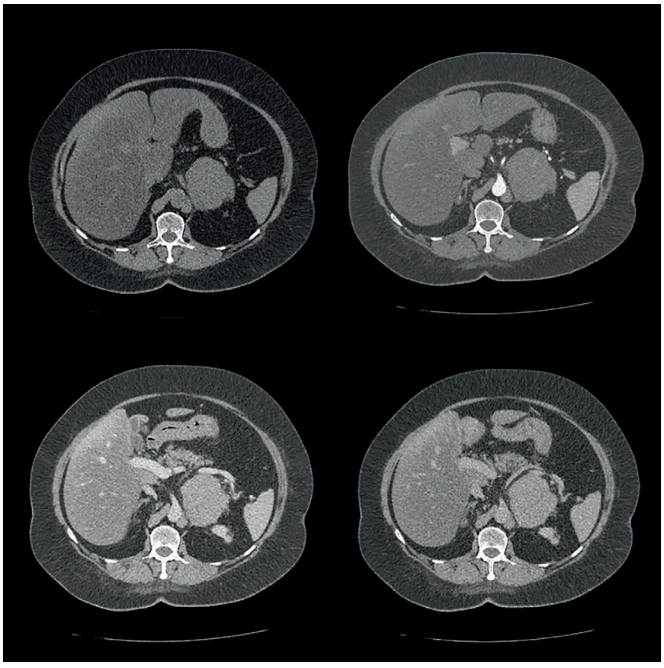

Figure 1 CT of the abdomen with adrenal protocol showing a bilobed left adrenal mass of 8×5 cm and 1.8×2.2 cm, vascularised and without calcifications, measuring 32 Hounsfiled units (HU) in native, 56 HU in arterial, 76 HU in the portal and 62 HU in the late, delayed phase. Steatotic hepatomegaly with bumpy hepatic contours associated.

hydrochlorothiazide 10 mg, verapamil 120 mg, acetylsalicylic acid 100 mg and bezafibrate 400 mg, all PO. Neither she nor her family have a history of psychiatric disorders, and her family has no notable diseases.

Initial physical examination revealed a blood pressure of 189/105 mm Hg, a heart rate of 104/min, oxygen saturation of 99% on room air, and a temperature of 37.1°. Her body mass index was 46.7 kg/m^2.

She was alert and fully oriented to name, place, time and purpose. She had anxiety. She had regular tachycardia, normal heart sounds, clear bilateral chest auscultation and a distended abdomen with mild epigastric tenderness. She had bilateral lower limb oedemas up to knee level. Skin examination was unremarkable.

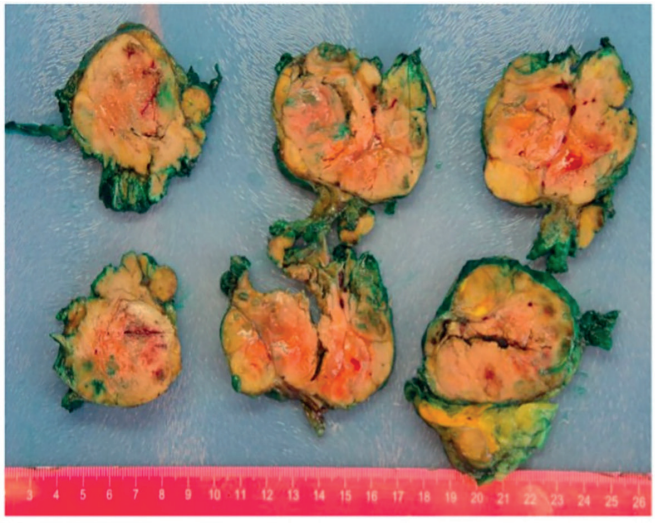

Figure 2 Macroscopic aspect of the left adrenal showing a 12×8.5×6.8 cm bilobed mass, with green ink added for histological analysis to verify resection margins, positive in this case.

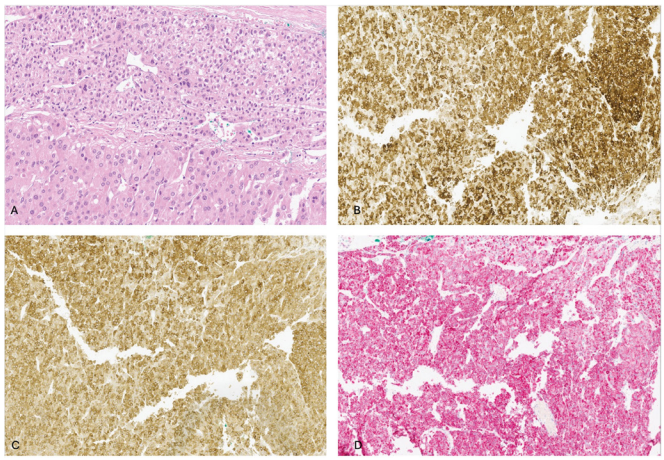

Figure 3 The microscopic appearance was consistent with adrenocortical carcinoma, with 5/9 Weiss criteria and two major and three minor Lin-Weiss-Bisceglia criteria: >5 mitoses per 50 high power fields (11) with atypical mitosis, and for minor criteria, a larger size >10 cm (12), with capsular invasion and necrosis.[6] H&E staining (A), Immunohistochemical staining with inhibin (B), synaptophysin (C) and melan A (D).

INVESTIGATIONS

Urine analysis revealed proteinuria, ketonuria, urobilinogen and haematuria. Hepatitis A-B-C-E, HIV, EBV, CMV serology and a complete autoimmune panel were negative. Aldosterone renin ratio was normal (0.003) with renin 27.8 mUl/L and aldosterone 0.08 nmol/L.

Further functional assessments including estradiol (333 pmol/L), progesterone (0.39 nmol/L), 17-OH-progesterone (14.1 nmol/L), androstenedione (11.5 nmol/L), DHEAS (9.17 (0.26–6.68 µmol/L) and cortisoluria (53 nmol/24 hours) were normal. Only DHEAS (9.17 µmol/L) and urinary catecholamines, including metanephrine (1283 nmol/24 hours), normetanephrine (4218 nmol/24 hours), methoxytyramine (2107 nmol/24 hours), were marginally increased. ACTH, GnRH, LH and FSH were not assessed.

Following initial evaluation, an ultrasound was performed, revealing a large bilobed retropancreatic mass facing the left kidney and para-aortic region. Subsequent abdominal CT imaging (figure 1) confirmed the bilobed left adrenal mass, measuring 8×5 cm and 1.8×2.2 cm, which was vascularised without calcifications. The CT scan ruled out the presence of any locoregional or distant spreading of the disease.

DIFFERENTIAL DIAGNOSIS

Regarding the liver test abnormalities, we ruled out haemochromatosis due to the absence of significant hyperferritinaemia, as well as viral causes with negative hepatitis serologies. Autoimmune conditions, such as primary biliary cirrhosis, primary cholangitis and autoimmune hepatitis, were also excluded following a negative autoimmune work-up. A liver biopsy confirmed histological evidence of NASH, consistent with an unbalanced metabolic syndrome likely related to diabetes and dyslipidaemia.

The differential diagnosis initially included a secretory adenoma, but this was deemed unlikely based on radiological findings and normal renin, aldosterone and cortisol levels. Although the imaging did not reveal a primary neoplasm, a neoplastic origin (either primary or secondary) could not be completely ruled out. A pheochromocytoma was also considered, supported by radiological features and

elevated urinary metanephrines, suggesting the secretion of catecholamine precursors. No other causes for the elevated urinary catecholamines were identified.

TREATMENT

Prior to the intervention, the patient was medically managed with haloperidol (1 mg PO three times per day) and clomethiazole (192 mg PO two times per day as needed) for psychiatric decompensation; metformin 500 mg PO three times per day, linagliptin 5 mg PO and insulin glargine 30U SC for diabetes; metoprolol 50 mg, spironolactone 25 mg, lisinopril 20 mg and doxazosine 4 mg all PO for hypertension.

Due to a marginal increase in plasmatic and urinary metanephrines, with subsequent normalisation of her blood pressure, she was treated as if it was a pheochromocytoma with doxazosin.

This case was discussed during our institution's tumour board meeting, and we opted for surgery as the first course of action. She underwent laparoscopic left adrenalectomy without encountering intraoperative complications. The patient required adrenergic support until postoperative day four. Additionally, all antihypertensive therapies were discontinued except for the beta-blocker. Due to the circumstances caused by the pandemic, she was transferred to another clinic and subsequently discharged home.

OUTCOME AND FOLLOW-UP

Subsequent histology results revealed an oncocytic adrenocortical carcinoma, staged as pT2 pN0 R1, with incomplete resection on the non-peritonealised side (R1). The mass fulfilled the Lin-Weiss-Bisceglia criteria for malignant ACONs (figures 2 and 3). Tumour cells were positive for synaptophysin, inhibin, calretinin, Melan-A and CD56, which confirmed the adrenal origin of the mass, but negative for chromogranin, protein S100, KWS, HepPar1, AFP, TTF1, CK7, CK20, HMB45, SOX10, thyroglobulin and PAX8, consistent with a non-secreting mass. The Ki67 proliferation index was 10%.

CT of the abdomen 2 months later showed the post-resection status of the left adrenal carcinoma, with a fleshy infiltrative appearance measuring 2.8×2 cm bordering the pancreatic tail, the left renal medial side, and the coeliac trunk, suspected to be a tumour remnant. Nodular thickening of the peritoneum at the level of the left paracolic gutter evokes the beginning of dissemination requiring monitoring in the context.

Adjuvant chemotherapy with mitotane was initiated alongside concomitant radiotherapy targeted at the resection area. Glucocorticoid replacement therapy was introduced to prevent adrenal insufficiency. The patient recovered fully from her psychiatric condition.

DISCUSSION

In our case, the diagnosis of ACON was atypical, as only 17%–34% of ACONs are functional.[4] The tumour was identified in the context of a fully decompensated metabolic syndrome and psychotic decompensation. In contrast, 55% of patients with ACC present with symptoms related to adrenocortical hypersecretion, typically hypercortisolism combined with hyperandrogenism, while 30%–40% have symptoms due to tumour volume, and the remaining 10% are discovered incidentally.[2]

To our knowledge, this is the first ACON case described in the literature with such an atypical clinical presentation. The psychotic presentation of ACC has been described but, on a cortisol-secreting ACC as a part of Cushing's syndrome.

Imaging plays a crucial role in distinguishing benign from potentially malignant adrenal masses. While CT and MRI cannot definitively identify ACONs, they can raise suspicion. Inhomogeneous lesions larger than 4 cm or with a density of >20 Hounsfield units on CT are considered at higher risk of malignancy, making surgery the preferred treatment option. In our case, imaging indicated malignancy, though it is not always reliable for differentiating subtypes of malignant tumours.[4]

Histological analysis remains the gold standard for diagnosing ACON. The Lin-Weiss-Bisceglia classification system, established in 2004, has replaced the original Weiss criteria. According to this system, ACONs are classified as malignant if they meet at least one primary criterion (eg, a mitotic rate of more than 50 mitoses per 50 high-power fields, atypical mitoses or venous invasion).[4] Tumours with only minor criteria, such as size larger than 10 cm, necrosis, sinusoidal or capsular invasion, are considered of uncertain malignant potential.[6] If neither primary nor minor criteria are present, the tumour is classified as an oncocytic adrenal cortical adenoma.[4]

The European Network for the Study of Adrenal Tumours staging system is used to assess tumour stage.[7] Surgical management should aim for complete resection without rupture of the adrenal capsule.[8] For tumours larger than 6 cm, the European Society of Endocrinology recommends open adrenalectomy by an experienced adrenal surgeon. This threshold, also applied to suspected pheochromocytomas,[9] is somewhat arbitrary, and the surgeon's experience is crucial in the decision-making process.[7] In our case, we performed left laparoscopic adrenalectomy via a transabdominal approach, which may have contributed to the R1 status of our resection.[10]

ACONs are a rare entity, typically only diagnosed through histological examination. In most cases, they are non-secretory, with 68% of these tumours being non-functional, which often leads to delayed diagnosis and treatment.[7] One limitation in our case was the delay in operative management due to an atypical presentation, including psychotic decompensation and metabolic syndrome, initially raising suspicion of Cushing's syndrome caused by pheochromocytoma. This challenge was further compounded by the SARS-CoV-2 pandemic, which limited access to critical diagnostic tests like PET-CT, making timely diagnosis even more difficult.

Additionally, we could not conclusively determine whether the tumour was a pure non-secreting ACON. The clinical presentation resembled Cushing's syndrome, and hypokalaemia could be attributed to vasospasm from secondary hyperaldosteronism. Due to the patient's ongoing use of antihypertensive medications (β-blockers, spironolactone, calcium channel blockers and ACE inhibitors), we were unable to definitively assess the tumour's aldosterone secretion. This may have affected the aldosterone-renin ratio, leading to a potentially false-negative assessment.[11] A dexamethasone suppression test, which is recommended for evaluating Cushing-like syndromes, was not performed due to the patient's psychiatric condition.[7] While a glucocorticoid precursor secreted by the tumour could explain the symptoms, we were unable to measure this. It is also important to note that standard hormonal panels may not fully exclude the secretory nature of adrenal masses, and steroid precursor analysis should be considered when clinical suspicion is high.[12] In our case, we hypothesise that the tumour was secreting metanephrines, as evidenced by the fact that most of the antihypertensive therapy could be discontinued following surgical removal of the tumour. This suggests that the tumour's secretion of metanephrines was likely contributing to the patient's hypertensive state.

The rarity of ACONs and the limited available evidence underscores the importance of a multidisciplinary approach to optimise patient care.[13] As ACONs are a subtype of ACC, their clinical management generally follows the guidelines for ACC, particularly when considering the resection of tumours suspected to be malignant or hormone-secreting.

Due to the uncommon nature of ACONs, there is no standardised follow-up protocol. Accurate classification requires the expertise of a skilled pathologist, as the disease course can vary significantly. While oncocytomas and oncocytic neoplasms of uncertain malignant

potential tend to have favourable prognoses, Bottazzi *et al* have shown that ACONs carry a higher risk of local recurrence (5.1%), metastasis (3.7%), and mortality (30%).[8] This highlights the necessity of long-term follow-up to detect disease progression.[14]

The follow-up of ACONs can be compared with other rare and aggressive adrenal neoplasms, such as leiomyosarcomas. Managing these conditions involves considering multiple factors—such as the patient's age, sex, tumour size and extent of disease—to develop individualised monitoring strategies.[14] This comprehensive approach is crucial to ensure appropriate long-term surveillance and optimise outcomes for patients with such rare tumours.

This case report underscores the critical importance of thoroughly evaluating adrenal incidentalomas, especially in the presence of metabolic disorders or unexplained hypertension. Prompt evaluation of patients with atypical symptoms, as observed in this case, in specialised facilities for comprehensive work-up and management is imperative to ensure accurate diagnosis and timely treatment tailored to individual patient needs.

Patient's perspective

My blood pressure was too high, and I remember not being able to take it at home. So I went to see a substitute doctor because my GP was on holiday. As I explained to him, I could see in his eyes that he was making fun of me a little. Then he didn't succeed either. He gave me some medicine and then he still couldn't measure my blood pressure, so he referred me to an emergency. After that, I don't remember much, except that I wondered what I was doing in a psychiatric hospital. It was a difficult time and my son told me that he didn't recognise me in my behaviour. Then I met my surgeon, whom I trusted straight away. I thought I had a lump of fat, but he was able to tell me the diagnosis in a human way, always with a word of comfort. Then the operation went well, and I was soon back home with nursing help and physiotherapy sessions at home. I was followed up by my oncologist, endocrinologist and surgeon, which reassured me and helped me get outside. Indeed, I was afraid of going out and contracting covid again. Now, I only go out when I need to, because I'm not as resistant as I used to be, and I get tired quicker.

As I fully recovered from my psychiatric episode, I didn't need any psychiatric follow-up, and psychotherapy was never an option. Finally, I've always been well surrounded by my husband, my son and the Lord. Without my faith and the Lord, I wouldn't be here.

Learning points

- The variable clinical presentation and lack of sensitivity and specificity of preoperative diagnostic modalities like imaging in an aggressive malignancy make adrenocortical oncocytic neoplasms a considerable challenge for clinicians.
- A complete biological work-up, including a hormonal panel as well as steroid precursors in case of high clinical suspicion, is essential to establish an optimal treatment plan.
- The best management care is a complete resection.
- There are still no solid recommendations for adrenocortical oncocytic neoplasm management, making this entity an exciting topic for future research.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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