folia medica

Folia Medica 67(1)
DOI: 10.3897/folmed.67.e130505

Case Report

Adrenocortical carcinoma with dual androgen and cortisol secretion

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Received: 25 June 2024 ♦ **Accepted:** 23 September 2024 ♦ **Published:** 26 February 2025

Citation: Kalfoutzou A, Petroulakis P, Mylonakis A, Restemi A, Chaleplidis N, Anagnou E, Tsikalakis G, Tsantopoulos M, Mostratou E. Adrenocortical carcinoma with dual androgen and cortisol secretion. Folia Med (Plovdiv) 2025;67(1): e130505. doi: 10.3897/folmed.67.e130505.

Abstract

Adrenocortical carcinoma (ACC) is a rare endocrine cancer that originates in the adrenal cortex, known for its capacity to produce hormones such as cortisol, aldosterone, estrogens, or androgens. These hormonal imbalances lead to a diverse array of clinical manifestations. This case report describes a middle-aged male patient presenting with a dual-hormone secreting ACC, characterized by the secretion of both androgens and cortisol. This hormonal profile resulted in Cushing syndrome along with symptoms of androgen excess, including bilateral lower limb edema, prolonged fatigue, and altered mental status. An extensive diagnostic evaluation, including clinical assessments, laboratory tests and imaging revealed the presence of an adrenal mass and lung metastases. Imaging-guided biopsy confirmed diagnosis of ACC with simultaneous androgen and cortisol secretion. This report enriches the sparse literature on dual-secreting ACC, highlighting the complexities in its diagnosis and management.

Keywords

adrenocortical carcinoma, adrenal cortex hormones, Cushing syndrome

Introduction

Adrenocortical carcinoma (ACC) is an extremely rare malignancy, with an annual incidence of 0.7 to 2 cases per million people globally.[1-3] It develops from one of the three zones of the adrenal cortex: glomerulosa, fasciculata, or reticularis.[4] More than two thirds of these tumors are functional, leading to an excess production of hormones such as cortisol, aldosterone, estrogen or androgens.[5] Clinical presentation varies depending on the specific hormones being overproduced, with the most prevalent manifestations including Cushing syndrome, virilization, feminization, hypertension or electrolyte disorders.[4,7] Diagnosis relies on histopathologic examination; however, there are no pathognomonic cellular features.[6] Pathology usually reveals areas of diffuse architecture, comprising of large cells with an eosinophilic cytoplasm.[8] The Weiss criteria for malignancy aid in definitive diagnosis of ACC and distinction from benign adrenal tumors.[9] This report presents the case of a middle-aged male patient who presented with altered mental status, fatigue, and bilateral lower extremity edema for two weeks and was diagnosed with dual androgen- and cortisol-secreting ACC.

Case Presentation

A 62-year-old Caucasian male patient presented with bilateral lower limb edema, fatigue, and episodes of blurred vision for the past two weeks. His past medical history was significant for alcohol abuse and arterial hypertension. The patient was a non-smoker and reported no recent travel or illicit drug use. His family history was unremarkable.

Clinical examination revealed an ill-appearing, agitated patient exhibiting a moon face, truncal obesity, and bilateral pitting edema of the lower limbs. There was no buffalo hump, striae or skin bruising. Auscultation revealed prolonged expiration, and there was mild tenderness upon palpation of the left abdominal region. Neurologic examination revealed no abnormal findings; the patient was well-oriented in time and space, and his Glasgow Coma Scale (GCS) score was 15/15. His vital signs were within normal limits, except for a slightly decreased oxygen saturation ($SatO_2$: 91%) and an elevated arterial blood pressure (165/70 mmHg).

The complete blood count revealed a marginally elevated white blood cell (WBC) count with neutrophilia, slightly decreased levels of hemoglobin and hematocrit, and a modestly increased red blood cell (RBC) count **(Table 1)**. *Biochemical analyses indicated mild hyperglycemia, pronounced hypokalemia, and elevated liver function tests (LFT)* **(Table 1)**. *The electrocardiogram (ECG) showed no significant abnormalities or acute changes attributable to the hypokalemia. As part of the investigation for lower limb edema, echocardiographic evaluation revealed a mildly reduced systolic function with an ejection fraction of 50%, diffuse hypokinesis, and grade I diastolic dysfunction.*

The persistence of hyperglycemia, hypokalemia, hypertension, and the patient's cushingoid appearance warranted further laboratory investigations to assess the pituitary-adrenal axis. These evaluations revealed elevated serum and 24-hour urine free cortisol levels and normal adrenocorticotropic hormone (ACTH) levels **(Table 2)**. *Importantly, cortisol levels failed to suppress following a low-dose dexamethasone suppression test, indicating an ACTH-independent mechanism of cortisol overproduction* **(Table 2)**. *Additionally, markedly elevated serum concentrations of androgens were observed* **(Table 2)**.

A chest X-ray revealed multiple coin-like white nodules in both lungs **(Fig. 1A)**. *Computed tomography (CT) scans of the brain, chest and abdomen with intravenous contrast identified a lesion measuring 97×64 mm in the left adrenal gland with an unenhanced attenuation of 36 Hounsfield Units (HU), suggestive of a primary tumor* **(Fig. 1B)**, *along with multiple lung lesions suspicious for metastases* **(Fig. 2)**. *The adrenal lesion demonstrated significant contrast enhancement and exhibited delayed washout following administration of intravenous contrast.*

A biopsy of the adrenal lesion was performed under ultrasonographic guidance. Histopathological examination revealed diffuse architecture encompassing small to medium-sized cells with an eosinophilic cytoplasm, as well as areas of focal necrosis ***(Fig. 3A)***. *Significant nuclear polymorphism and a high mitotic rate of more than 5 mitoses per 50 high power fields (HPF) after phospho-histone H3 immunostaining (PHH3) were observed* ***(Fig. 3B)***, *alongside a Ki-67 proliferation index of 25%* ***(Fig. 4A).*** *The cells exhibited positive staining for Steroidogenic Factor 1 (SF1)* ***(Fig. 4B)***, *Melan-A, inhibin, and vimentin, while showing negative staining for cytokeratin (CK AE1/AE3) and S100.*

The patient's hospital course was marked by refractory hypertension and hypokalemia, resistant to intravenous potassium replacement, potassium-sparing diuretics and calcium channel blockers. Additionally, the patient experienced episodes of rage and agitation, requiring management with intravenous thiamine and lorazepam.

Table 1. Laboratory examinations of the patient upon admission

Laboratory examination	Patient's values	Normal range
White blood count	**10.4**	**4–10 K/μL**
Neutrophils	**9**	**1.5–7 K/μL**
Red blood count	**3.96**	**4.2–6 M/μL**
Hemoglobin	14.2	14–18 g/dL
Hematocrit	42.7	42–52 %
Platelets	223	150–400 K/μL
Blood urea nitrogen	54	15–54 mg/dL
Creatinine	1.28	07–1.3 mg/dL
Glucose	**144**	75–110 mg/dL
AST	**88**	**5–40 IU/L**
ALT	**222**	**5–45 IU/L**
G-GT	**500**	**10–75 IU/L**
Sodium	136	135–145 mEq/L
Potassium	**2.6**	**3.5–5.3 mEq/L**

AST: aspartate aminotransferase, ALT: alanine aminotransferase; G-GT: gamma-glutamyl transferase

Table 2 . Hormone profile of the patient during hospitalization

Laboratory Examination	Patient's values	Normal ranges
Serum free cortisol	**34.6**	4.8-19.46 µg/dL
Low-dose dexamethasone suppression test	**Positive (22.8)**	<1.8 µg/dL
ACTH	4.6	<40 pg/mL
Renin	19.3	2–20 pg/mL
Aldosterone	120.1	29–160 pg/mL
Testosterone	**1367**	**127–1020 ng/dL**
SHBG	13.8	13.5–71.4 nmol/L
DHEA	**1219**	**48.6–361.8 µg/dL**
D4-androstenedione	**9.91**	**0.62–3.12 pg/mL**
24-hour urine free cortisol	**684**	20–90 µg
Urine metanephrines	261.12	100–800 mg/24 h
Urine VMA	3.2	1.8–6.7 mg/24 h

SHBG: sex hormone binding globulin; VMA: vanillylmandelic acid

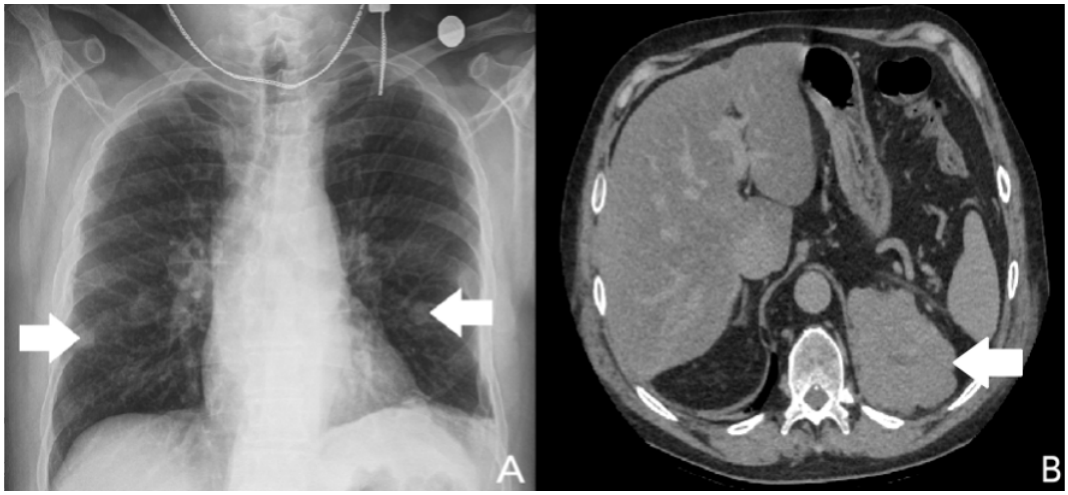

Figure 1. Chest X-ray demonstrating multiple coin-like nodules in both lungs, suggestive of metastatic lesions (white arrows, panel A). Axial CT scan of the abdomen with intravenous contrast displaying a heterogeneous lesion measuring 97×46 mm in the left suprarenal lesion (white arrow, panel B).

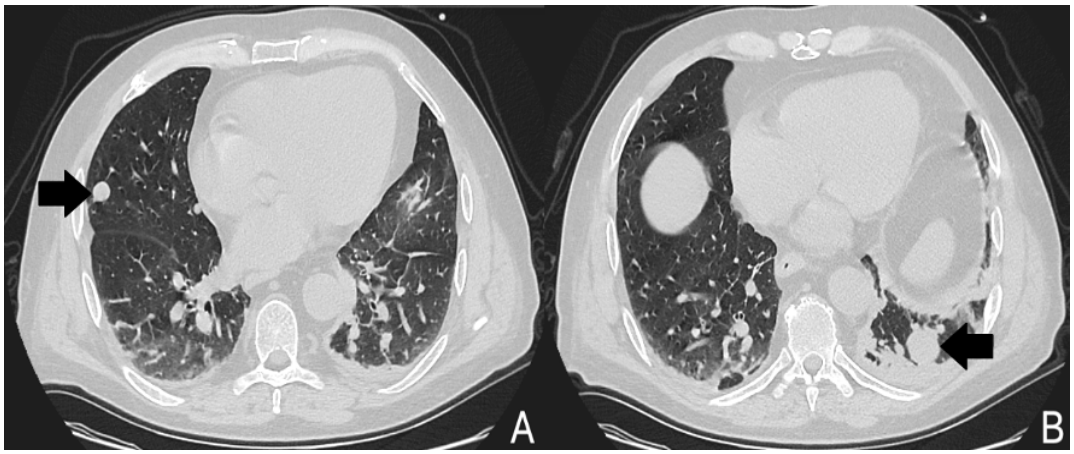

Figure 2. Axial CT scan of the chest displaying bilateral pulmonary nodules (indicated by black arrows in panels A and B), highly indicative of metastatic lesions, along with a minor left-sided pleural effusion.

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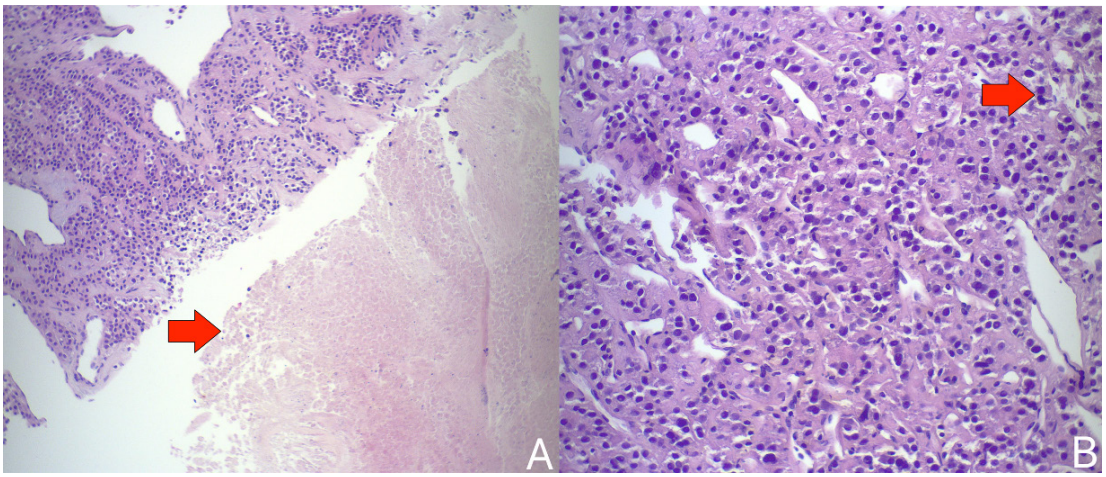

Figure 3. Histopathological examination reveals cells exhibiting significant nuclear pleomorphism, high nuclear grade, and an eosinophilic cytoplasm. The specimen displays areas of diffuse architecture and focal necrosis (red arrow, panel A) (Hematoxylin-eosin stain, ×10 magnification). Mitotic figures are observed at a rate of >5 per 50 high power fields, with one example highlighted by a red arrow in panel B (Hematoxylin-eosin stain, ×10 magnification).

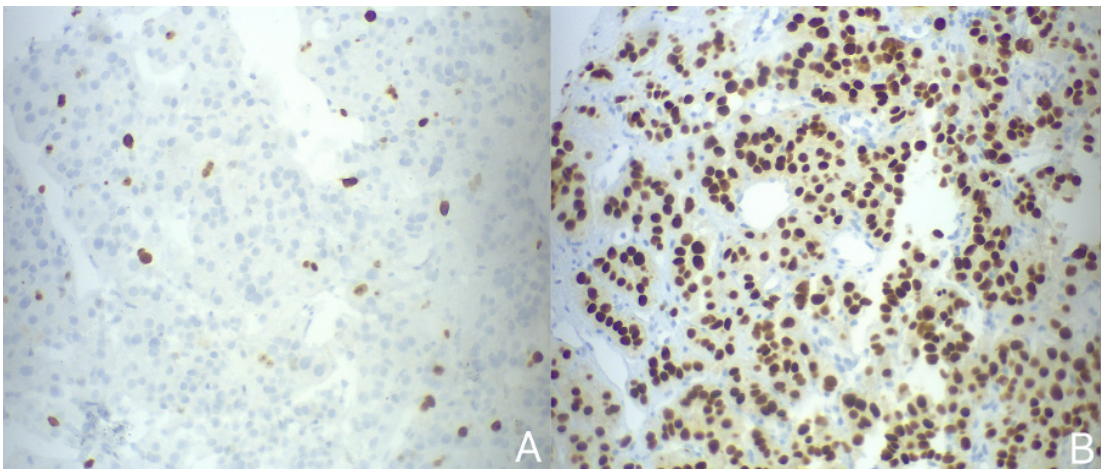

Figure 4. The proliferation index, as indicated by Ki-67 staining, is measured at 25% (panel A, ×20 magnification). Nuclear stain for Steroidogenic Factor 1 (SF1) is positive on the tumor cells (panel B, ×20 magnification).

The case was reviewed by a Multidisciplinary Tumor Board (MDT), where the tumor was deemed unresectable and chemotherapy in combination with mitotane was decided. Regrettably, the patient opted for discharge against medical advice for ongoing hospitalization and prompt initiation of therapy, and he passed away one month following his discharge.

Discussion

Adrenocortical carcinoma (ACC), an uncommon form of cancer that develops from any of the three zones of the adrenal cortex, presents with an annual incidence rate of 0.7-2 cases per million individuals worldwide.[1,3] It comprises 0.05%–0.2% of all cancer cases and accounts for 0.3% of all adrenal gland tumors.[5,10] ACC typically shows a bimodal distribution in age at onset, occurring primarily in the 1st and during the 4th to 5th decades of life, with a female predominance (2.5:1).[11] Familial cases are diagnosed earlier and are often associated with genetic syndromes, including congenital adrenal hyperplasia, multiple endocrine neoplasia type 1 (MEN 1), Li-Fraumeni, familial adenomatous polyposis (FAP), Beckwith-Wiedemann syndrome, type 1 neurofibromatosis, and Lynch syndrome, among others.[4,8,11]

Clinical presentation of functioning adrenocortical carcinoma is often subtle and may not become apparent until advanced stages. Manifestations depend on the specific hormone that is overproduced; thus, patients may exhibit classic CS due to hypercortisolism, hyperglycemia, hypertension, and hypokalemia due to hyperaldosteronism, or a broad spectrum of symptoms stemming from the altered metabolism of androgens or estrogens, including mood disturbances, weight changes, and abnormal body hair distribution.[12] Conversely, non-functioning tumors may be-

come apparent through abdominal pressure symptoms.[6] Symptoms related to metastases, including involvement of the lungs, bones, and lymph nodes, can occur with all types of adrenal gland tumors.[6] Our case presented with features of a Cushingoid phenotype, and further investigation revealed refractory hypertension and hypokalemia. The patient's altered mental state upon admission and subsequent agitation during hospitalization could be attributed to the excess production of cortisol or androgens, or to alcohol withdrawal syndrome.

Laboratory examinations vary according to the hormonal profile of the tumor. As per the blood differential, elevated white blood cell count, typically with a predominance of neutrophils and a reduction in lymphocytes, is a common finding.[13] Androgen overproduction often leads to erythrocytosis, characterized by increases in hematocrit, hemoglobin, and red blood cell (RBC) count.[13] Conversely, excess glucocorticoids, which can impact androgen levels by typically lowering testosterone, may result in decreased hemoglobin, hematocrit, and RBC.[13] In the classic Cushing syndrome, serum cortisol levels are characteristically elevated, with normal adrenocorticotropic hormone (ACTH) levels, and an inability to suppress cortisol levels with low doses of dexamethasone is observed.[14] Hyperaldosteronism is indicated by elevated aldosterone levels with low or normal renin levels, whereas increased levels of testosterone, dehydroepiandrosterone (DHEA), and D4-androstenedione suggest excess androgen production. [10,14] In our case, there was a slight elevation in WBC with a neutrophil predominance, and slightly decreased RBC, likely due to hypercortisolism. Biochemical tests indicated hyperglycemia and hypokalemia, while the hormonal profile consisted of elevated cortisol and androgen levels, and an absence of suppression following low-dose dexamethasone administration. The patient's elevated liver function tests were attributed to his chronic alcohol abuse.

Imaging studies such as CT, Magnetic Resonance Imaging (MRI) or Fluorodeoxyglucose Positron Emission Tomography (FDG PET) scans are able to localize the primary adrenal tumor.[14] ACC typically appears as a large heterogenous mass measuring >4 cm with irregular margins and an unenhanced attenuation of >10 HU on the CT scan.[14] On CT and MRI scans with intravenous contrast, adrenocortical carcinoma typically presents with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, with marked contrast enhancement and slow washout.[15] Ultrasound provides limited diagnostic value in assessing an adrenal mass.[15]

Definitive diagnosis is dependent on histopathological examination, with ongoing debate regarding the choice between biopsy and complete surgical excision for diagnostic confirmation.[6] In cases of suspected adrenal malignancy without known metastases, en bloc removal is the preferred method for histopathological confirmation, whereas tissue biopsy from a metastatic site is preferred in cases of advanced disease, due to the potential risk of capsule rupture associated with adrenal biopsy.[16] A systematic review by Bancos et al. concluded that adrenal biopsy should only be performed in carefully selected cases where the result could potentially alter patient management, and only after excluding pheochromocytoma in order to avoid a fatal catecholamine storm.[17]

Histopathologically, the differential diagnosis of adrenocortical carcinoma from other adrenal tumors is based on the Weiss criteria for malignancy, which include the following: a nuclear grade of Fuhrman III or higher, a mitotic rate exceeding 5 per 50 high-power fields (HPF), presence of atypical mitoses, less than 25% clear cells, diffuse architectural pattern in at least 1/3 of the specimen, evidence of necrosis, venous invasion, sinusoidal invasion, and capsular invasion.[9] A diagnosis of adrenocortical carcinoma is strongly considered if the surgical specimen meets at least three out of these nine criteria.[9] Immunohistochemistry typically demonstrates positive staining for vimentin, melan A, calretinin, inhibin, and SF-1, along with negative staining for epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA).[4] Phospho-histone 3 (PHH3) immunostaining is a reliable marker of proliferation in ACC with a low mitotic index.[9] In our case, although we analyzed a core biopsy specimen rather than a surgical specimen, the observed cellular characteristics were highly suggestive of malignancy.

Differential diagnosis of ACC includes other benign or malignant lesions of the adrenal glands, namely cyst, myelolipoma, pheochromocytoma, adrenal adenoma, or metastasis from a primary malignancy, most commonly of the lung.[14] Despite their rarity, entities such as lymphoma, angiosarcoma, ganglioneuroma or adenomatoid tumor of the adrenal gland should also be considered during the diagnostic process.[18,19] Given the poor prognosis of ACC, the presence of an enlarging adrenal mass - whether or not associated with hormone overproduction – warrants comprehensive evaluation to rule out malignancy.[1,5]

Approximately half of patients present with locally advanced or metastatic disease at diagnosis.[3,20] The overall prognosis is poor, with an estimated overall survival not exceeding 15 months for patients with metastatic disease.[3] Hypercortisolism is an independent poor prognostic factor, whereas the combined hypersecretion of cortisol and androgens bears unknown prognostic significance.[5,10] Adrenalectomy is the first option for localized tumors.[10] Treatment options for metastatic disease are limited, with the regimen comprising etoposide, doxorubicin, and cisplatin (EDP), either with or without mitotane, being the primary therapeutic choice.[21] For second-line therapies, strategies such as gemcitabine-based combinations, mitotane as either monotherapy or in conjunction with pembrolizumab, and etoposide in combination with cyclophosphamide, have been explored, all with unsatisfactory response rates.[3] Multikinase inhibitors (MKIs), such as lenvatinib, and somatostatin analogs are currently being investigated as potential treatments.[22,23] Recently, image-guided locoregional treatments (IGLT), including chemoembolization, radioembolization, transarterial embolization or ther-

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mal ablation, have gained interest, especially in patients with advanced disease, focusing on tumor debulking and symptom palliation.[24]

To our knowledge, there are 30 cases of multiple hormone secretion by ACC documented in literature.[5,7,10,12,25,26] Among these, 27 cases involve the simultaneous secretion of cortisol and aldosterone[7,10,12,25], one case is associated with the co-secretion of aldosterone, cortisol, and estrogens[27], and another case details the concurrent overproduction of cortisol, androgens, and aldosterone[5]. This case represents a dual androgen- and cortisol- secreting adrenocortical carcinoma, which has been documented in up to 46.7% of cases of ACC, hoping to shed light in this rarely reported, yet multifaceted clinical entity.

Limitations of this case include the absence of a whole surgical specimen biopsy of the adrenal gland, which precluded the application of the Weiss criteria for definitive diagnosis. Furthermore, no molecular testing was performed, which could have provided valuable insights into the genetic and molecular characteristics of the tumor, potentially guiding targeted therapeutic strategies. The lack of molecular testing also means that any potential hereditary or syndromic associations were not explored, which could have implications for the patient's family and future management of similar cases.

Conclusion

In conclusion, due to the rarity and its atypical clinical and pathologic features, ACC diagnosis is often delayed. Specifically the diagnosis of dual-hormone secreting ACC poses a significant challenge, requiring a high index of clinical suspicion, meticulous diagnostic evaluation and collaborative efforts among different specialties. The necessity of expert centers remains paramount, ensuring patients' benefit from specialized knowledge and advanced treatment options. Furthermore, the incorporation of molecular insights into the pathogenesis of ACC holds promise for identifying novel therapeutic targets, potentially improving outcomes for this type of cancer with a historically dismal prognosis.

Declaration of interest

The authors have no disclosures related to this report and no competing interests to declare.

Sponsorship

The authors received no public or commercial funding in relation with this work.

Patient consent for publication

The patient provided an informed consent for the publication of this case report.

Author contribution

A.K. and E.A. wrote the first draft of the manuscript. A.R., N.C., and M.T. performed the pathology studies and figures. P.P., G.T. and E.M. performed the initial investigation and follow-up of the patient. AM performed the additional investigation and management of the patient and coordinated the case report. All authors reviewed and approved the final version of the manuscript.

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