

Adrenocortical Carcinoma With Cushing's Syndrome and Extensive Tumor Thrombosis of the Inferior Vena Cava in a 30-Year-Old Filipino Female

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Abstract

Adrenocortical carcinoma (ACC) is a rare and aggressive neoplasm with poor prognosis. We report a case of a 30-year-old female who presented with profound classic features of an adrenocorticotrophic hormone (ACTH)-independent Cushing's syndrome (CS) and a large adrenal mass with massive venous tumor thrombosis of the entire inferior vena cava (IVC), left renal and adrenal veins confirmed by imaging. Adrenal biopsy histopathology and immunohistochemistry confirmed ACC. Systemic palliative chemotherapy was administered. This rare case presents a unique and atypical presentation of an extensive tumor thrombosis of IVC. With the advanced stage at diagnosis, aggressive nature and poor prognosis of the disease, there is still a need to determine viable therapeutic options for metastatic ACC associated with venous invasion.

Key words: Cushing's syndrome, adrenocortical carcinoma, inferior vena cava thrombosis

INTRODUCTION

ACC is a rare endocrine neoplasm with an incidence of one to two per million of the population.¹ It has a bimodal age distribution with a peak in early childhood and a second peak in the fifth decade of life.¹⁻³ While patients often present with symptoms of hormone hypersecretion, they may also present with abdominal pain or a palpable mass.¹ Forty to sixty percent of patients manifest with symptoms and signs of excess cortisol (50%), sex hormones (20%), aldosterone (8%) and mixed hormones (15 to 25%).⁴ ACC can also present as an incidentally-discovered non-functioning mass (incidentaloma).¹ ACC is an aggressive tumor that may have early-onset metastasis to the lung, lymph nodes, liver and bone.⁵ Extension to the adrenal vein, renal vein or IVC occurs in 15-25% of patients.⁵ Venous tumor thrombosis in the IVC is rare, usually occurring in right-sided adrenal masses. Surgery is the only curative therapy. The five-year survival of patients with complete resection is 32% to 48%. However, this rate drops to 5 to 10% for metastatic cases.⁵ We report the case of a patient with ACC who presented as classic CS complicated by a thrombus extension to the left renal vein, left adrenal vein and IVC, and was treated with an adrenolytic drug and combination chemotherapy.

CASE

A 30-year-old female presented with a one-year history of menstrual irregularity with associated moon facies, acne, easy bruising, wide, purplish striae and hirsutism. The day before admission, the patient had severe persistent flank pain that prompted admission. The patient is multi-gravid [G2P2 (2002)], with menarche at age 10 years. She denied any vices or intake of exogenous steroids. She had an unremarkable family history. On admission, she was in pain, with elevated blood pressure (160/100 mm Hg) and normal heart rate (96 beats per minute). She had moon facies, facial plethora, severe hirsutism, acne, and dorsocervical and supraclavicular fat pads. Her abdomen was asymmetric, with diffuse wide, purplish striae and a palpable mass at the left side (Figures 1A and 1B). Ecchymoses were noted on the extremities (Figure 1C).

Hormonal evaluation revealed a non-suppressed cortisol after a 1 mg dexamethasone test [22.6 µg/dL, normal value (NV) <1.8µg/dL], an elevated 24-hour urine free cortisol (314.19 µg/24 hours, NV 22 to 243 µg/24 hours) and a normal ACTH (8.46 pg/mL, NV 5 to 46 pg/mL), confirming an ACTH-independent Cushing's syndrome. Further tests revealed increased dehydroepiandrosterone-sulphate

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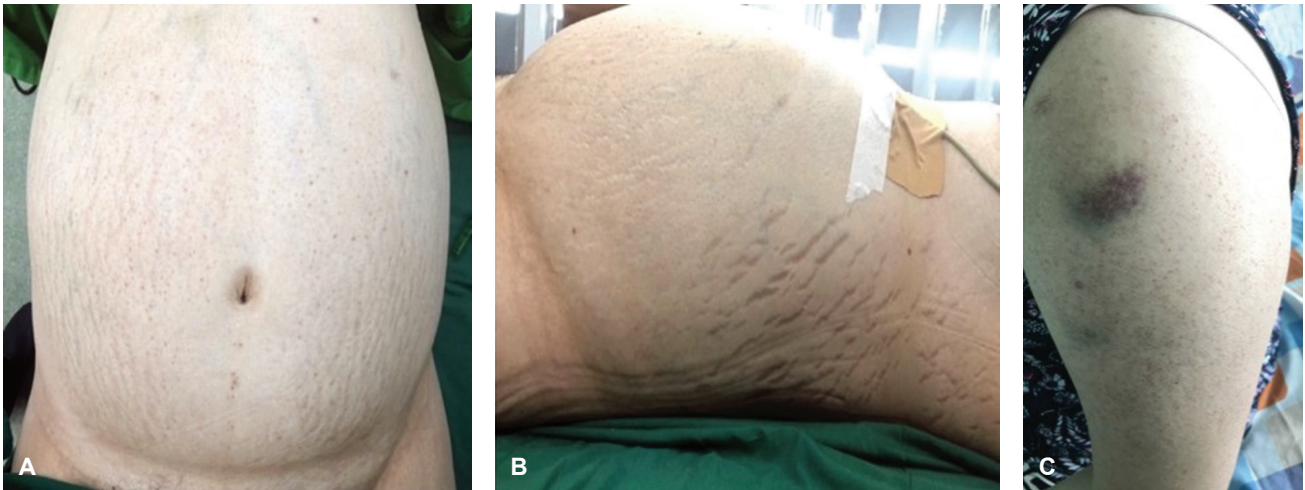


Figure 1. Physical findings included (A) globular asymmetric abdomen with (B) wide violaceous striae and (C) ecchymoses.

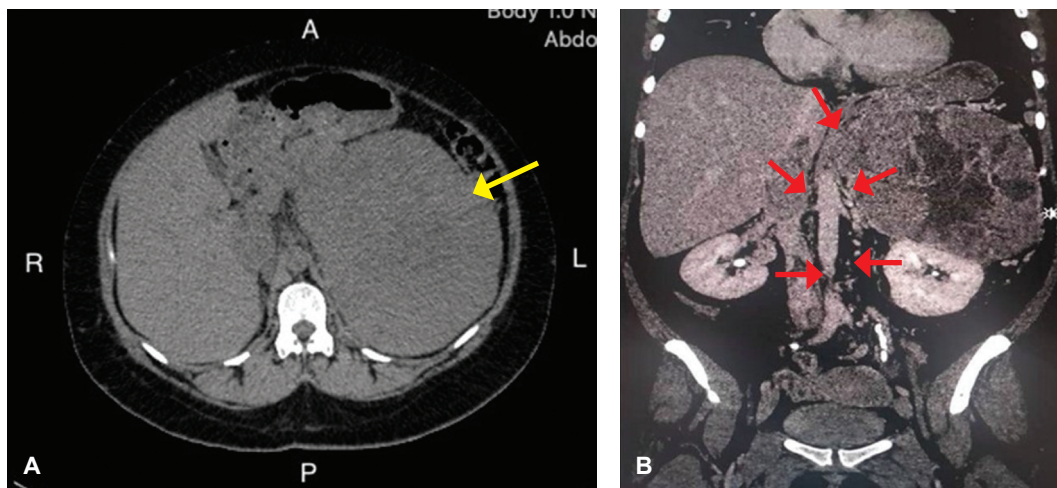


Figure 2. Computerized tomography prior to treatment. (A) Plain scan of the whole abdomen showed a heterogeneously large left adrenal mass measuring 19 cm x 14.4 cm x 14 cm in its greatest and perpendicular dimensions (yellow arrow); (B) angiography of the aorta showed the extent of the tumor at different aortic segments: aortic root mid-ascending, proximal arch, mid-descending, distal descending, suprarenal abdominal and infrarenal abdominal. Enlargement of the inferior vena cava with intraluminal filling defects was seen along its entire course from T11 to the bifurcation of common iliac veins, as well as in the left renal, left common iliac, and left ovarian veins (red arrows). The stomach and spleen were also displaced.

(DHEA-S) (1,402 $\mu\text{g/dL}$, NV 95.80 to 511 $\mu\text{g/dL}$) and an elevated 24-hour urine metanephrines (2.61 mg/24 hours, NV 0 to 1.0 mg/24 hours). Serum aldosterone, plasma renin activity and aldosterone/renin ratio (ARR) were within the normal reference range (Table 1). The patient had normocytic normochromic anemia with thrombocytosis, normokalemia, hyponatremia and hyperlipidemia. Abdominal computed tomography (CT) revealed a large, heterogeneously enhancing left adrenal mass measuring 19 cm x 14.4 cm x 14 cm, displacing the stomach and spleen (Figure 2A). Deep vein thrombosis was seen involving the IVC, left renal vein, and its suprarenal and ovarian tributaries due to tumor invasion by the adrenal mass. A CT angiography study showed that the mass had a venous connection from the IVC at the level of L2. The IVC was enlarged with an intraluminal filling defect along the entire course of the IVC from the level of T11 down to the

bifurcation of common iliac veins, including the left renal vein, left common iliac, and left ovarian vein (Figure 2B).

The patient was medicated with verapamil 180 mg once daily (OD) and terazosin 5 mg OD for hypertension, enoxaparin 30 mg subcutaneous injection OD, and atorvastatin 40 mg OD for hyperlipidemia. The planned treatment was radical resection of the left adrenal neoplasm and adjacent organs with possible cardiopulmonary bypass, segmentectomy of the IVC and reconstruction with vascular prosthesis. The involvement of the IVC and extensive vascular tumor invasion made the operative plan technically difficult and risky, carrying a poor surgical prognosis. After a family conference to discuss alternative options for treatment, the patient, family and medical team decided on adjuvant chemotherapy with pretreatment open biopsy and palliative care.

Table 1. Diagnostic work-up based on recommendations of the ACC Working Group of the ENSAT³

Hormone study	Result	Reference value
Glucocorticoid		
8AM Cortisol after 1 mg overnight dexamethasone suppression test, µg/dL	22.6	<1.8
ACTH, pg/mL	8.46	5-46
24-hour urine free cortisol, µg/24 hours	314.19	22-243
Sex steroid		
DHEAS, µg/dL	1,402	95.80-511
Mineralocorticoid		
Aldosterone, ng/dL	13.27	3.78-23.30
PRA, ng/mL/hr	1.79	0.3-1.90
Aldosterone/renin ratio, ng/dL/ng/mL/hr	7.413	
Metanephrines and catecholamines		
24-hr urine metanephrines, mg/24 hours	2.61	0- 1.0

ENSAT - European Network for the Study of Adrenal Tumors

She was prepared preoperatively for the biopsy with terazosin to achieve adequate alpha blockade, increased oral fluids and liberal salt intake. A large and firm left adrenal mass with hypervascularity was noted on open biopsy (Figure 3). Microscopically, the specimen showed diffuse sheets of cells having eosinophilic cytoplasm with clear cells comprising <25% of the field. (Figure 4). Focal areas showed highly pleomorphic tumor cells and mitosis in less than 5 per 50 high power fields (hpf) with no atypical mitotic figures. There were areas with hemorrhage and necrosis, with no lymphovascular invasion (Figure 4). The immunohistochemistry panel of the biopsy sample revealed positive results for melan A, inhibin, vimentin and synaptophysin, which favored a diagnosis of adrenal malignancy. Chromogranin, a marker for neuroendocrine differentiation and a test to rule out pheochromocytoma, was negative. Ki-67, an indicator of poor prognosis, was estimated at 30% (Figure 5). The final pathologic diagnosis was ACC Stage 4.

The patient was started on ketoconazole 200 mg every 8 hours to suppress adrenal cortisol production. Medical oncology service recommended palliative chemotherapy using etoposide, doxorubicin, and cisplatin combined with mitotane. Due to the unavailability of mitotane at the onset, the combination of cisplatin plus etoposide was given. The patient tolerated the initial cycle of chemotherapy and continued the rest of the chemotherapy sessions on an outpatient basis.

On the third month of follow-up, a repeat abdominal CT scan with contrast showed stable disease (Figure 6A). Follow-up tests including CBC, electrolytes, liver enzymes, bilirubin and alkaline phosphatase were all within normal range. On the fourth month of follow-up, she was given mitotane 2 g daily in four divided doses. An incremental increase of the daily dose by 1 gram every 1 to 2 weeks was given if without untoward side effects. Cisplatin and etoposide were also given in combination with mitotane for the next three months. She had bouts of nausea and vomiting which were relieved by ice chips and proton pump inhibitors. Subsequent blood tests (CBC, AST, ALT, FT4 and TSH, cortisol and lipid profile) were all normal.

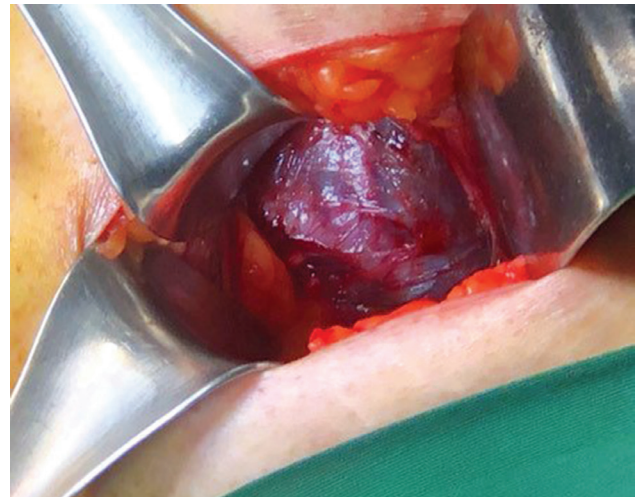


Figure 3. Open biopsy showing a large and firm left adrenal mass with hypervascularity.

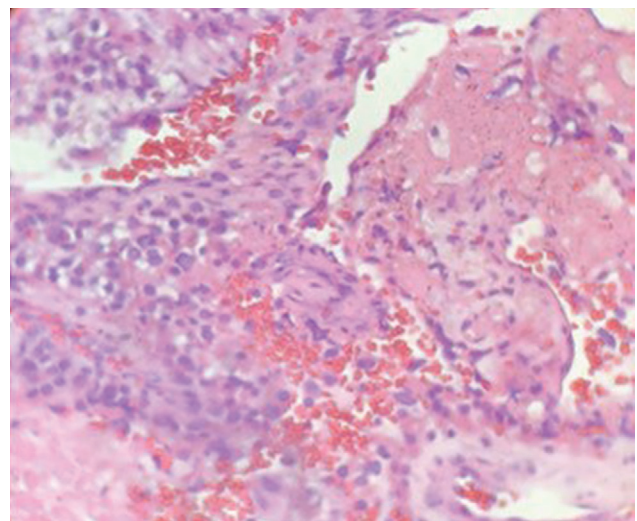


Figure 4. Histopathologic examination showed diffuse sheets of cells containing eosinophilic cytoplasm, <25% clear cells, focal areas with highly pleomorphic tumor cells, mitosis in less than 5 per 50 hpf and no atypical mitotic figures. Hemorrhage and necrosis without lympho-vascular invasion were also observed. (H&E, 200x).

Eight months post-chemotherapy, a surveillance abdominal CT scan showed progressive disease (Figure 6B). The patient continued with chemotherapy for another two months using the combination of doxorubicin and mitotane. Unfortunately, the patient's condition gradually deteriorated with persistent complaints of severe flank pain while on home palliative care.

DISCUSSION

ACC is a rare endocrine malignancy. An associated venous tumor thrombosis to the IVC is much rarer. There are only two cases of ACC with overt Cushing's syndrome and tumor thrombus invasion to the IVC documented in the literature.^{6,10} In a literature review of 44 cases of ACC with tumor thrombus extending to the IVC, only 26

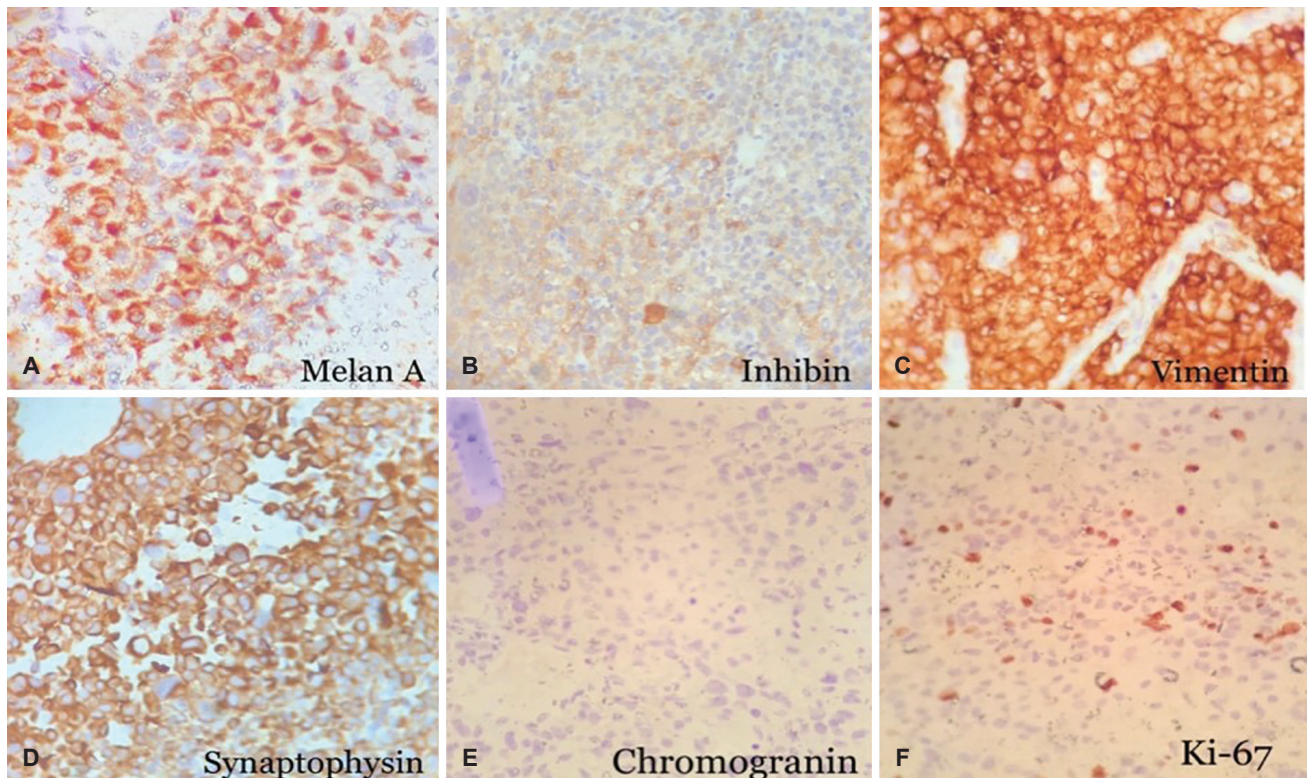


Figure 5. Immunohistochemical staining for was positive for (A) Melan A, (B) Inhibin, (C) Vimentin and (D) Synaptophysin and negative for (E) Chromogranin, (F) Ki-67 positivity was seen in 30% of neoplastic cells.

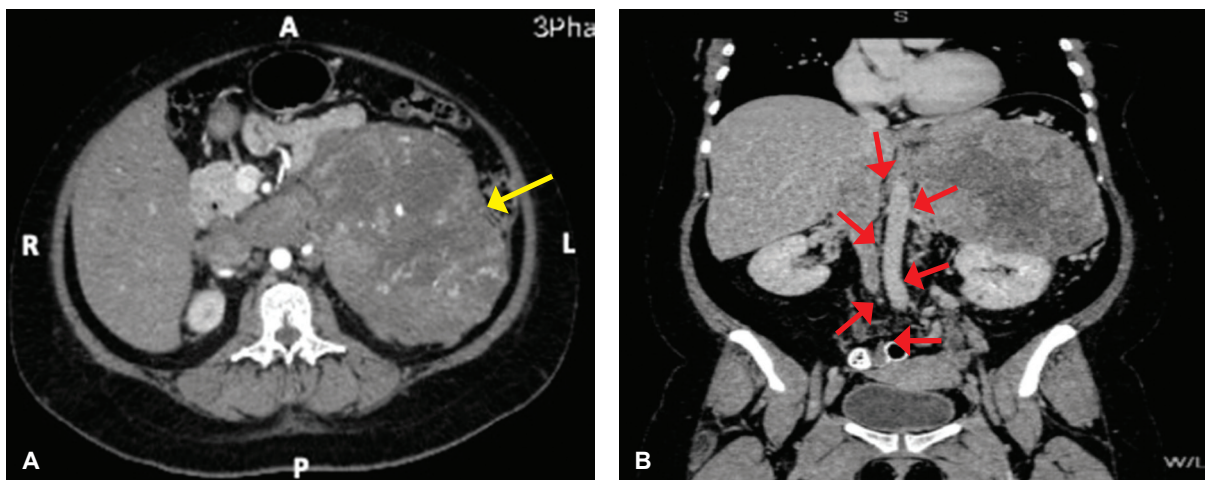


Figure 6. Computerized tomography of the abdomen with intravenous contrast after treatment. (A) Sagittal view taken three months after treatment. There was no interval change in the left adrenal mass size (yellow arrow), with tumor thrombus involving the inferior vena cava (IVC) and left renal, left adrenal and bilateral common iliac veins. (B) Coronal view taken six months after treatment. The left adrenal mass was found be slightly increased in size, abutting the spleen and pancreas, with probable invasion of the adjacent left kidney. Similar findings of tumor thrombus involving the IVC and left renal, left adrenal and both common iliac veins were also seen (red arrows).

were functioning tumors with a few manifesting virilization, heterosexual pseudo-precocious puberty or occult hypercortisolism demonstrable only with hormonal testing.⁶⁻¹⁰ ACC is predominantly right-sided (32 right-versus 12 left-sided), usually large (range 1.8 to 25.5 cm, median 11.0 cm), with no apparent gender predominance half of cases occurring in men.⁶⁻¹⁰ Tumor thrombosis, which may grow into the IVC, was more commonly found in right- compared to left-sided tumors. Chiche and

colleagues documented a left-sided ACC which extended into the IVC through the renal vein, similar to our case.⁷ Half of the cases also had an extension to the right atrium.^{6,9}

ACC is often diagnosed late and already in advanced stages, as exemplified by our case. A large tumor burden and potential hormonal functionality highly impact the disease process. CS in the setting of ACC has a negative prognostic factor because the excessive cortisol has immune

suppressive effects which favor the further growth of the tumor and its metastases.¹¹ Adrenal cortical neoplasms may also be associated with findings that simulate pheochromocytoma (pseudo-pheochromocytoma).¹² These tumors may have neuroendocrine features which may explain the significant increase in the 24-hour urine metanephrines. The elevated DHEAS causes features of virilization and contributes to its aggressive course.

The European Network for the Study of Adrenal Tumors (ENSAT) published the standard diagnostic procedures for ACC.^{2,13} After localization of the lesion with ACTH, appropriate imaging should be requested. In patients with low or normal ACTH, CT scan of the adrenals can evaluate the tumor size, malignant potential, intravascular extension and presence of metastases. Adrenal adenomas are usually <4 cm with Hounsfield (HU) density of <10 and >50% washouts after intravenous (IV) contrast, while ACC is heterogeneous with high pre-contrast density >10 HU and washout of <50% after IV contrast.^{2,4} The risk for ACC increases with tumor size >6 cm.² An adrenal biopsy should only be considered in selected cases in which the tumor is considered inoperable.¹²

The Modified Weiss Scoring system is used for pathologic diagnosis.¹⁴ It is composed of nine items, with three items each referring to tumor architecture, cell nuclei and the presence of any type of invasion). A Weiss score ≥ 3 defines an ACC.¹⁴ An important prognostic parameter is Ki-67. As a marker of cell proliferation, it can define the diagnosis and prognosis of ACC in both localized and metastatic disease. A Ki-67 of $\geq 5\%$ is usually seen in ACC. The patient's Ki-67 of 30% confirmed the tumor's aggressiveness. Meanwhile, tumor staging, such as the TNM classification, is used to assess prognosis in ACC.^{2,12} Stage I and II are strictly localized tumors with a size of ≤ 5 or >5 cm, respectively. Stage III is characterized by infiltration to the surrounding tissue, positive regional lymph nodes or a tumor thrombus in the vena cava and/or renal vein. Stage IV is defined by the presence of distant metastasis.^{2,15}

Complete surgical resection of the tumor mass is the cornerstone of treatment in all patients with localized and locally advanced disease, even in cases with tumor thrombus invasion. Surgery becomes more complex and carries a higher morbidity and mortality rate the higher the tumor thrombus extends. A margin-free complete resection provides the only means to achieve long-term survival.^{2,6-15} The presence of a tumor thrombus in the IVC and the renal vein is compatible with complete tumor resection and may need a cardiac bypass technique.⁶ Unfortunately, there is no data for radical surgery with tumor thrombus invasion in the Philippines. Although invasive surgery is the only therapeutic option, Kim et al., reported a case of a large ACC with thrombus extension to the right atrium where despite the patient's refusal to undergo surgery, the tumor regressed spontaneously during follow-up.¹⁵ The median survival post-surgery for metastatic and nonmetastatic

cases with tumor invasion of the IVC was eight months.¹³ A three-month survival only after surgery was noted in one case because of metastatic disease which showed that systemic chemotherapy is a better alternative than radical surgery.¹⁰ There are no randomized controlled trials on the treatment of ACC with invasion to the IVC.

Our current knowledge is based on case reports and expert opinion due to the low incidence of ACC and the rare site for tumor invasion and extension. The infiltrative, expansile tumor thrombus extended from the left renal and adrenal veins to the entire course of the IVC. With only a 3.6 cm thrombus-free zone of the IVC before the right atrium and an area that is totally occluded, all these findings made surgery technically difficult and risky. Even with the utmost precaution, there was a high risk for pulmonary embolism, stroke and myocardial infarction.

The European Society of Clinical Endocrinology Clinical Practice Guidelines suggest against adrenal surgery in case of widespread metastatic disease, and recommend either mitotane monotherapy or combined mitotane, etoposide, doxorubicin and cisplatin depending on prognostic parameters.¹² Mitotane is the most effective and frequently used chemotherapeutic agent in metastatic adrenal carcinoma. A study revealed that mitotane in ACC provided a response rate of 48.6%, and longer median progression-free survival.¹⁶ When mitotane is used together with drugs such as cisplatin, doxorubicin, and etoposide, the combination may produce a clinical response rate of about 50% even in advanced cases.^{2,16} Treatment is 1 to 2 grams daily to be adjusted based on tolerance and attainment of therapeutic plasma levels. However, a study on mitotane alone in metastatic, unresectable, or incomplete resection cases have demonstrated a lower response rate and a lower survival rate.¹⁶

CONCLUSION

Our case illustrates that early diagnosis is crucial for preventing complications (such as extensive tumor invasion) and timely surgical treatment. Palliative care and chemotherapy remain as important treatment options for patients with ACC. Given the advanced stage upon diagnosis, aggressive nature and poor prognosis of the disease, there is a need to determine other viable therapeutic options for metastatic ACC associated with venous invasion.

Ethical Consideration

Patient consent was obtained before the submission of the manuscript. The patient's family requested that facial features not be published.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Contribution Statement

KA, MHG, JMC and RA conceived the idea; validated the data; conducted the research; provided the study materials; prepared the original draft; reviewed and edited the manuscript.

Author Disclosure

The authors declared no conflict of interest.

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