A Rare Case of a High-Grade Non-Functioning Oncocytic Type Adrenal Cortical Carcinoma: Case Report

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Abstract. Adrenal cortical carcinoma (ACC) is a rare malignancy, and oncocytic ACC (OAC) is a rare histopathologic variant of ACC, with <70 cases documented worldwide as of 2021. This is a case of a 64-year-old female initially presenting with epigastric-to-periumbilical pain, left flank pain, nausea, vomiting, and bloatedness. Computed tomography (CT) urogram revealed a 12.2 x 12.7 x 15 cm left adrenal mass, with pulmonary metastases on chest CT. The patient was clinically and biochemically unremarkable based on the hormonal panel. Left thoracoabdominal adrenalectomy was done, and the left adrenal mass was identified as a high-grade non-functioning OAC on histopathology and immunohistochemistry. The patient showed clinical improvement on chemotherapy with etoposide, cisplatin, doxorubicin (EDP), without mitotane, due to local unavailability. In conclusion, while EDP + mitotane is the standard therapy for metastatic cases, EDP alone showed promising outcomes in improving quality of life and resolving paraneoplastic neuropathy in the absence of mitotane. To date and to the best of our knowledge, this is the first documented case of non-functioning OAC in the Philippines.
DS-related Kaposi sarcoma (KS) progresses rapidly with early mucosal and systemic involvement. Early diagnosis and treatment are crucial as they significantly impact the outcome. This is a case of disseminated cutaneous and gastrointestinal KS in a 24-year-old Filipino male living with HIV, presenting with hyperpigmented violaceous subcutaneous nodules, odynophagia, progressive dysphagia, and symptomatic anemia. Capsule endoscopy demonstrated utility in diagnosing gastrointestinal KS lesions, highlighting its crucial role when conventional upper endoscopy was challenging due to oropharyngeal involvement. Diagnostic limitations, mainly the unavailability of human herpesvirus-8 (HHV-8) immunohistochemical stain, were addressed through high clinical suspicion. Multidisciplinary approach including chemotherapy with liposomal doxorubicin, radiotherapy, and supportive care eventually yielded good clinical response. This case emphasizes the importance of early diagnosis, timely intervention, and long-term surveillance in achieving favorable outcomes for patients with KS despite some diagnostic limitations.

Keywords. *Oncocytic, Adrenal cortical carcinoma, Abdominal pain, Non-functioning, Case report*

Introduction

Adrenal cortical carcinoma (ACC) is a rare malignancy with an incidence of 0.7 to 2.0 per million population per year, comprising only around 43% non-functioning type. Oncocytic adrenocortical carcinoma (OAC) is a rare histopathologic variant of ACC, with <70 cases documented worldwide as of 2021.[1,2]

Case

A 65-year-old Filipino woman, Eastern Cooperative Oncology Group (ECOG) 2, was admitted in our institution due to a 3-month history of boring epigastric pain radiating to the periumbilical area. This was accompanied by left-flank pain, nausea, vomiting, bloatedness, and early satiety. She was normotensive with no prior history of weight gain/loss, palpitations, hyperglycemia, insomnia, mood changes, nor anxiety. She had a 5 pack-year smoking history and a brother with testicular cancer. Physical examination was unremarkable, with no features suggestive of endocrine abnormality.

CT Urogram revealed a 12.2 x 12.7 x 15 cm left suprarenal mass (Figure 1). Hormonal evaluation revealed normal serum cortisol, aldosterone, total metanephrine, urine vanillylmandelic acid, metanephrine, and normetanephrine. CBC revealed normocytic, normochromic anemia (Table 1).

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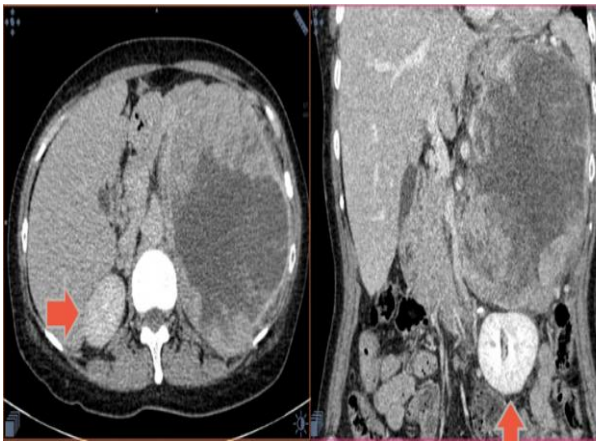

Figure 1. CT urogram: Large, heterogeneously enhancing necrotic mass in the left suprarenal region with vascularities at the periphery. The mass displaces the left kidney inferiorly, the stomach medially, and the pancreatic body and tail superiorly. The left renal hilar vessels were also displaced posteromedially.

Table 1. Hormonal panel, blood chemistry, and complete blood count

	Result	Ref. value
Urine VMA	6.27	0.6–13.6 µg/24 hours
Urine metanephrine	67	24–96 µg/24 hours
Urine normetanephrine	155	75–375 µg/24 hours
Urine total metanephrine	222	<1300 µg/24 hours
Serum aldosterone	173	67–335 pg/mL
Morning cortisol	288.9	<497 nmol/L
Blood chemistry		
BUN	11	
Crea	0.63	
eGFR	94.79	
Na	142	
K	5.1	
Ca	8.6	
Alb	4.01	
Mg	2.46	
FBS	89	
CBC		
WBC	7.5	
Neut%	0.72	
Lymph%	0.21	
Mono%	0.05	
Eo%	0.02	
Baso%		
RBC count	4.03	
Hgb	111	
Hct	0.35	
MCV	85.8	
MCH	1.7	
MCHC	322	
Platelets	368	

Chest CT scan revealed multiple non-calcified pulmonary nodules suggestive of metastases and pleural effusion on the left lung, approximately 150–200 cc. Left thoracoabdominal adrenalectomy was done. Intraoperatively, a 20 x 18 cm mass at the left suprarenal area without any grossly normal-looking left adrenal gland was identified. There were good planes of demarcation between the mass and the pancreatic tail, spleen, splenic flexure of the colon, and left kidney (Figure 2).

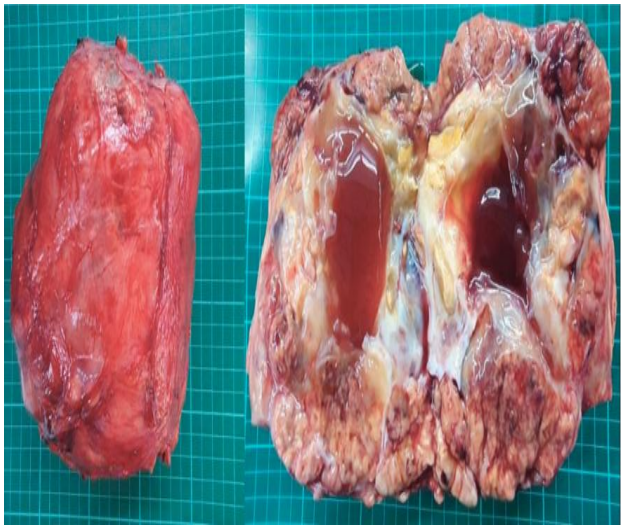

Figure 2: Specimen sent for histopathology. 16 x 14 x 8.3 cm left adrenal mass weighing 1.25 kg, surrounded by scanty adipose tissues. The tumor is soft to firm, ovoid, and solid, with several areas of pale

Histopathologic examination revealed high-grade OAC (Figure 3). On immunohistochemistry, the tumor was negative for chromogranin and cytokeratin and was positive for synaptophysin and Melan-A (Figure 4).

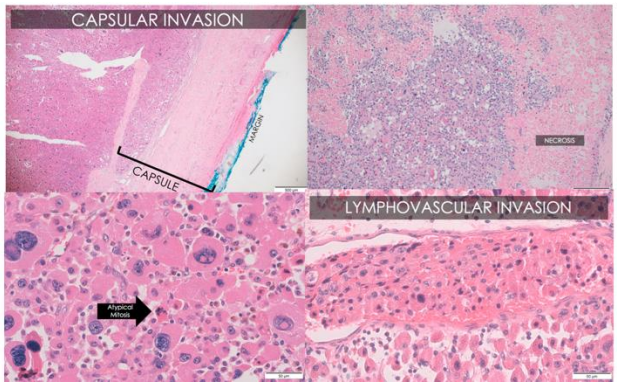

Figure 3: Oncocytic cells with round to severely pleomorphic, hyperchromatic nuclei, with one to multiple nucleoli and abundant eosinophilic cytoplasm. Several mitotic figures and foci of necrosis are also seen with lymphovascular invasion.

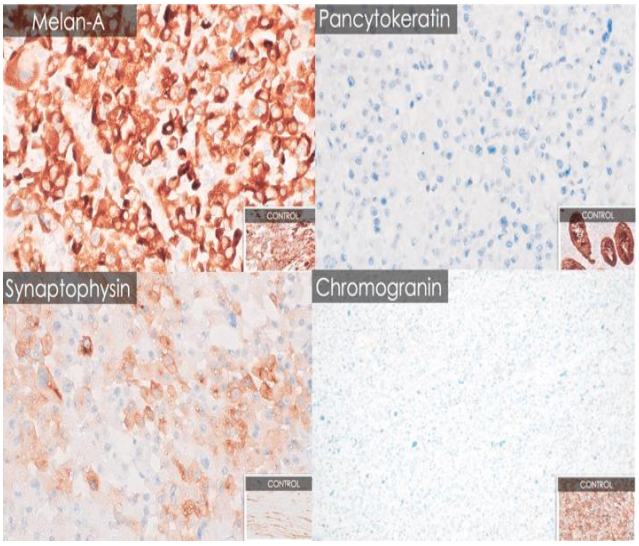

Figure 4. Immunohistochemistry: 80% of adrenal cortical carcinomas are positive for synaptophysin, and Melan-A is positive in adrenal cortical tumors. Negativity in pancytokeratin ruled out a possible metastatic renal cell carcinoma. Negativity in chromogranin ruled out pheochromocytoma.

Postoperatively, the patient underwent chemotherapy with etoposide 100 mg/m²/day intravenous infusion administered on days 1–3, doxorubicin 40 mg/m² on day 1, and cisplatin 40 mg/m² on days 1–2 of each chemotherapy cycle (etoposide, cisplatin, doxorubicin [EDP]) upon the recommendation of the multidisciplinary board. She was not able to receive mitotane, since it was not readily available at our setting. The patient completed four cycles of chemotherapy, experiencing Grade 1–2 hematologic toxicity, melanonychia, and alopecia. She noted improvement in appetite and in her performance status (ECOG 0). On re-evaluation positron emission tomography/computed tomography (CT) scan, there was resolution of left pleural effusion; however, there was overall increase in size but no increase in number of the non-calcified pulmonary nodules scattered throughout both lungs (at least 10 in the right and 8 in the left).

By multidisciplinary board, patient was to continue chemotherapy; however, patient had COVID-19 infection, causing a month's delay in the treatment. She then experienced tolerable morning stiffness and intermittent pins and needles on both upper and lower extremities, causing difficulty in doing household chores. On physical examination, there were no signs suggestive of cerebrovascular disease or motor weakness, and sensory examination was also intact. Work-ups showed normal electrolyte and glucose levels. She then underwent her fifth cycle of chemotherapy, with noted resolution of her symptoms thereafter and was able to resume work. Currently, the plan for the patient is to maximize dose of doxorubicin for EDP, and subsequently to receive etoposide, cisplatin (EP), followed by re-evaluation scans after eight cycles.

Discussion

ACC is a rare aggressive "orphan malignancy" that originates in the adrenal cortex**.** It has an estimated incidence of 0.7 to 2.0 per million population per year.[1] Around 60% are functioning, which usually presents earlier with hormonal manifestations such as Cushing's syndrome, virilization, feminization, or hyperaldosteronism. Only around 43% are non-functioning tumors, which pose a diagnostic challenge because they are usually diagnosed incidentally or due to mass effect, as seen in our patient. [2]

OAC is a rare histopathologic variant of ACC. This was first documented in 1986, with <70 cases documented as of 2021.[3] It is composed entirely or predominantly (>75%) of oncocytic cells with abundant cytoplasmic mitochondria. Functioning tumors are more common in non-oncocytic ACC, in contrast with OAC wherein only 30–40% are functioning. A few case reports suggest that Lynch syndrome may predispose patients to OAC.[4,5] Our patient's family history of testicular cancer may be significant since Lynch syndrome was also associated with urologic or genitourinary malignancy, according to some studies.[6]

The only definitive criteria for malignancy regardless of the type are distant metastasis or local angioinvasion. The most common metastatic site is the lungs, which was primarily seen in our patient. Other common sites of metastasis include lymph nodes, liver, bone, and inferior vena cava. For the differentiation of benign from malignant adrenal masses, unenhanced CT scan of the adrenals is the procedure of choice. Many adrenocortical adenomas are lipid rich and thus present with low attenuation values or densities. A homogenous adrenal mass with a smooth border and an attenuation value <10 Hounsfield units on unenhanced CT is very likely to be benign adenoma.[7] On delayed contrast-enhanced CT, adenomas typically exhibit rapid contrast medium washout, whereas non-adenomas have delayed contras

material washout 10 minutes after administration of contrast.[8]

The Weiss system for malignancy is usually used in non-conventional ACC, but it is not applicable in OAC, since at least three parameters (eosinophilic cytoplasm, high nuclear grade, and diffuse architecture) are intrinsically present in this tumor type. Hence, the modified scoring Lin-Weiss-Bisceglia (LWB) system is used for OAC. The European Network for the Study of Adrenal Tumors is one of the staging systems used for adrenal cortical carcinoma utilizing the tumor size, nodal involvement and metastases.[9] The presence of lung metastases signifies a stage IV malignancy in our patient. Radical resection is the only potential curative treatment.

The goal of treatments for our patient were to prevent progression and provide relief of symptoms. Regardless of the type, mitotane is the adjuvant chemotherapy of choice. Based on NCCN guidelines, the preferred regimen for metastatic ACC includes the EDP-M regimen: etoposide, doxorubicin, cisplatin/carboplatin mitotane. However, mitotane is not available in the Philippines.

A study by Kapoor et al, explored the role of systemic chemotherapy in adult ACC.[10] The agents compared in metastatic adrenal cortical carcinoma with palliative intent were EDP versus EP. There was no significant difference in the progression-free survival between both arms: 6 months for EP and 7 months for EDP, but a longer median overall survival was observed in the EDP arm than the EP arm (20.9 months versus 13 months, respectively). Hence, we opted to start this patient with the EDP protocol.

OAC carries a significant risk of local recurrence, distant metastasis, and mortality. Approximately 30% of patients with OAC experience adverse outcomes, underscoring the need for vigilant monitoring and management.[11]

In retrospect, one of the pertinent symptoms the patient experienced was peripheral neuropathy, characterized by pins and needles, and intermittent morning stiffness, causing difficulty doing household chores. Physical examination and laboratory evaluation results were normal, and the cumulative dose of cisplatin given was at 260 mg/m^2 in four cycles. Peripheral neuropathy associated with platinum agents is usually seen at 350 mg/m^2, and our patient received only lower doses. Also, after each cycle of EDP, there were no complains of neuropathies. It was only after her delay in the treatment that she experienced these symptoms. After the fifth cycle, patient was able to resume work and noted resolution of stiffness and neuropathies. We therefore surmise that she had a paraneoplastic neuropathy, fulfilling a definitive criterion for paraneoplastic syndrome. As of today, there are no current retrospective studies as to the response of OAC to systemic treatment without mitotane; there are also no current reports for any documented paraneoplastic syndrome on this type of ACC. In this case, EDP gave a better quality of life and notable improvement of symptoms in our patient.

To date and to the best of our knowledge, this is the first documented case of non-functioning OAC in the Philippines. Previous literature from the country only describes an oncocytic adrenocortical neoplasm with uncertain malignant potential,[12] which was not specifically categorized as carcinoma, along with other cases of functioning ACC.[13,14]

Conclusion

ACC is a rare aggressive malignancy; moreover, OAC is a rare histopathologic variant of ACC. Histopathologic diagnosis is the gold standard, and immunohistochemistry plays an important role. Complete surgical resection is the only potential curative treatment for ACC. EDP + mitotane is the adjuvant chemotherapy of choice for metastatic ACC. Despite the unavailability of mitotane in the Philippines, EDP provided a promising outcome in terms of quality of life in this patient, as well as the resolution of the paraneoplastic neuropathy syndrome.

Consent for Publication

Informed consent was obtained from the patient.

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