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Case Report

Non-functioning adrenocortical carcinoma requiring radical nephrectomy-case report with review of literature

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ABSTRACT

Adrenocortical carcinoma (ACC) is rare malignancy of the adrenal gland and is the second most aggressive endocrine malignant disease after anaplastic thyroid carcinoma. These tumours can be detected very late as majority are non-functional, i.e., does not secrete any hormones, and only present with vague symptoms. Surgical management of such tumours can be challenging as it can invade the surrounding structures making it very difficult for resection. This is a case of a 61-year male with a large non-functioning adrenal tumour which appeared to be separate from the kidney in the radiological imaging but was found stuck to the renal parenchyma posing a dilemma for the operating team.

Keywords: Non-functional, Adreno-cortical carcinoma, Anaplastic, Aggressive

INTRODUCTION

Adrenocortical carcinoma (ACC) is an aggressive endocrine malignancy with an incidence of 0.5-2 cases per million population.[1] These tumors can be functional or nonfunctional based on the hormones that are secreted. Functional adrenocortical carcinoma presents at a relatively earlier stage with the hormonal manifestations such as virilization, feminization, or the Cushing's syndrome. However, non-functional tumors pose a diagnostic challenge because they are either diagnosed incidentally due to the mass effect or present as the metastatic disease in the late stage.

This is a case of a 61 year male patient with a giant non-functional adrenocortical carcinoma presenting with vague abdominal symptoms, with a misleading radiological imaging which showed the tumour separate from the renal capsule, but intra-op found to be adhered to the kidney leading to performing a radical nephrectomy with the adrenalectomy.

CASE REPORT

Sixty-one-year-old male patient presented with complaints of abdomen pain in the left lumbar region and left hypochondrium radiating to the left back. Pain was mild, dull aching, continuous with no specific aggravating or relieving factors. On examination, patient was vitally stable with per-abdomen exam findings of a single 9×5 cm mass felt involving the left hypochondrium and left lumbar regions, not moving with respiration, non-tender with plane of swelling retroperitoneal and non-ballotable on palpation. There was fullness felt in left renal angle.

Contrast-enhanced-computed-tomography (CECT) of abdomen revealed a 9×5 cm mass arising from the left adrenal gland. The mass crossed the midline and compressed the stomach, spleen with minimal abutment to the pancreatic tail. The mass appeared free from the renal capsule with a clear plane of demarcation as shown in the figures.

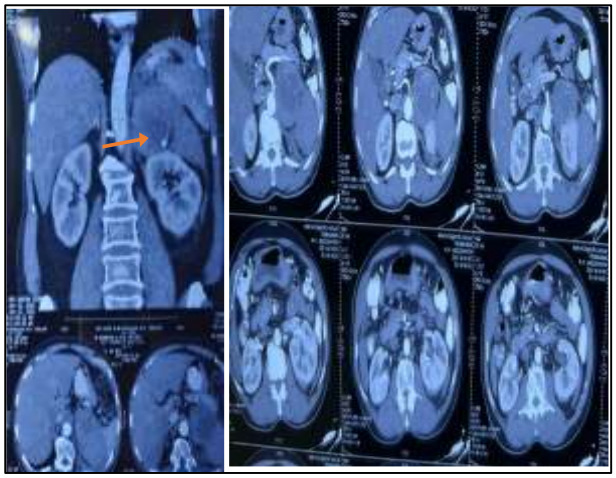

Figure 1: CECT of clear plane of demarcation marked in red arrow.

A functional endocrine workup was done, plasma-adrenaline- 31.6 pg/ml (Normal<100) and plasma-noradrenaline 243.6 (Normal<600 pg/ml), 8 am serum-cortisol-233 (Normal 136-635 nmol/L), serum aldosterone-7 ng/l (Normal 2-9 ng/l); confirming it to be non-functional tumour. Metastatic workup done- CT scans of head and chest with bone scan showing no metastasis.

Patient was planned for an open left adrenalectomy through anterior approach with sparing of the kidney as there was a plane of demarcation in scans. Intraoperatively with midline laparotomy, the adrenal mass was exposed after medial reflection of descending colon and was found abutting the spleen, stomach and tail of pancreas. There was no plane of separation from upper pole of left kidney as shown in image. The mass was firmly adherent to the kidney and there was also torrential bleeding intraoperatively while dissecting. Hence radical nephrectomy was performed with due informed consent.

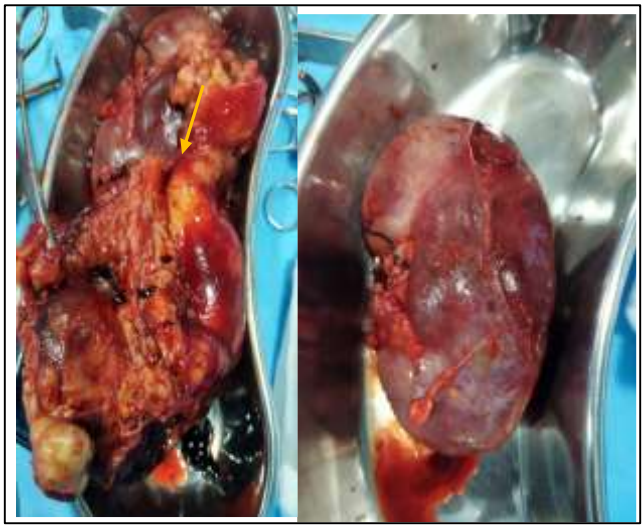

Figure 2: Intra-op specimen of anterior and posterior surfaces of kidney, with the yellow arrow marking mass.

The postoperative recovery was uneventful. The drain was removed on postoperative day 4, and the patient was discharged on postoperative day 6. He was followed up 4 weeks postoperatively with no complications.

Histological examination showed a 1.23 kg en-bloc left radical nephrectomy specimen that measured 18×16.5×10.0-cm. Opening of the specimen revealed a huge mass arising from the left adrenal gland measuring 11×6×4 cm which was tan yellow. Histopathology revealed infiltrative neoplasm composed of epithelioid and focal spindle shaped cells in sheets d trabeculae with extensive areas of necrosis and increased mitosis.

Weiss criteria shows 6/9 confirming ACC. Immunohistochemistry showed positive staining for synaptophysin as shown in Table 1.

Table 1: Detailed Weiss criteria and immunohistochemistry finding of this patient.

Criteria	Present/absent	Score	Max score
Nuclear grade III or IV(Fuhrman)	Present	1	1
>5 mitotic figures/50 high power fields	Present	1	1
Atypical mitotic figures	Present	1	1
Clear or vacuolated cells<25% tumour	Present	1	1
Diffuse architecture (>33% of tumour)	Present	1	1
Necrosis	Present	1	1
Venous invasion (of smooth muscle walled vessels)	Absent	0	1
Sinusoidal invasion	Absent	0	1
Capsular invasion	Absent	0	1
Total score		6	9
Weiss criteria: score ≥ 3for adrenal cortical carcinoma			
Immunohistochemistry			
IHC marker	Interpretation		
Synaptophysin	Positive		
Chromogranin-A	Negative		
Ki67	Positive in 40% of lesional cells		

As per histopathology R0 resection was done. Hence pathological stage is pT3, pN0 (no nodes were found) and M0.

Since Ki-67 was 40% it was termed high risk localised ACC and mitotane adjuvant therapy was given. Dose was started as 1g twice daily for 1 week and gradually increased every week to 6g/ day and was given for 6 weeks. Apart from nausea and minimal vertigo, no other side effects were told by patient.

DISCUSSION

Adrenal cortical carcinoma (ACC) is the most common primary cancer in the adrenal gland and the second most common malignant endocrine tumour after anaplastic thyroid carcinoma.[2,3] It is more common in females like other endocrine tumours with male to female ratio of approximately 1 to 1.4.[4] Some series demonstrate a bimodal age distribution with peaks in the paediatric group and middle age group, however recent data show that there is a steady increase of ACC with increased age peaking at the sixth and seventh decades.[1] About 5-10% ACC are associated with many hereditary syndromes like multiple endocrine neoplasia type 1 (MEN1), approximately 20 cases reported, Lynch syndrome (mismatch repair genes) approximately 10 cases, Li-Fraumeni syndrome (TP53, more than 10 cases) and neurofibromatosis type 1 (NF1, approximately 10 cases).[5-9]

ACC most commonly arises from left adrenal (left to RR=1.2 to 1). Bilateral ACC is uncommon (only 1% accounted).[4] Ectopic ACCs arise from ectopic adrenal rests in the retroperitoneum, ovary, spinal region, liver and abdominal wall.[10-14] Functional ACC constitute 50% of the incidence of ACC, out of which half present with clinical features of cortisol excess.[15] Sex hormone secreting tumours constitute 20% of cases which predominantly secrete androgens. Aldosterone secreting ACC are accounted for 8% of cases and mixed hormone production in15% to 25% of functioning ACCs.[16]

Non-functioning ACCs commonly present with abdominal mass, abdominal pain and other constitutional symptoms of malignancy. They can also present with paraneoplastic symptoms like hypoglycaemia (secondary to insulin growth factor 2 [IGF2] production) and clinical manifestations related to ACTH production. Other rare manifestations include cancer related thrombotic microangiopathy and retroperitoneal hemorrhage.[17-19]

The following are the histological variants of ACC-conventional, oncocytic, myxoid and sarcomatoid. Table 2 describes the characteristics of the different types of ACC.[20]

Table 2: Types of ACC and characteristics.

Characteristics	Conventional		Oncocytic	Myxoid	Sarcomatoid
	Adult	Paediatric			
Number of cases	~8000	~200	56	47	28
Mean age (in years)	47 to 55	5 (median=4)	48	48	56
Most common age group (decade) (in years)	Sixth/Seventh	First (<5)	Fourth	Fifth	Sixth/seventh
Male to female	1 to 1.4	1 to 2	1 to 1.1	1 to 1	1 to 1.3
Functioning	Half	85%	Half	57%	11%
Most common hormone produced	Cortisol	Sex hormones	Sex hormones	Cortisol	-
Laterality	left adrenal	left adrenal	left adrenal	left adrenal	right adrenal
Left to right ratio	1.2 to 1	1.4 to 1	1.6 to 1	1.5 to 1	1 to 1.4
Bilateral	1%	-	None	None	7% (n=2)
Size (median/ maximum) (mm)	100-120/280	95/200	10/285	100/300	127/240
Weight (median [range]) (gm)	528 (38-4000)	276 (20-1046)	552 (50-5720)	450 (38.5-3200)	620 (20-6500)
Metastases (%)	1/3rd (26 to 35)	31	13	68	75
Median survival (months)	17-35	-	60	29	7

On macroscopic examination, ACC is often yellow to tan colour. On cut sections there is heterogenous appearance due to areas of necrosis and hemorrhage. As of recent literature, largest non-functioning ACC reported in 39-year-old women from Greece with max diameter of the 236 mm.[21] The largest functioning (androgen-secreting) ACC with max dimension of 230 mm noted in 48-year-old Canadian woman.[22] On microscopic exam, ACC often has eosinophilic cytoplasm with thick fibrous bands and capsules, areas of necrosis with the prominent mitotic figures. Based on mitotic frequency, it can be subdivided into low grade or the high grade-dividing line is between-20 and>20 mitosis per 50 high power fields/10 mm^2.

The pathological parameters of ACC can be assessed using the Weiss Criteria established in 1984.[23] According to this system, ACC could be diagnosed on at least three of the 9 histological features-high nuclear grade (Fuhrman III or IV), high mitotic rate (>5 mitoses per 50 high power field), atypical mitotic figures, <25% clear cells, diffuse architecture, tumour confluent necrosis, venous invasion, sinusoidal invasion, and capsular invasion. A newer system in 2015 is the Helsinki score, which is diagnostic and prognostic and relies on the mitotic rate, necrosis and Ki-67 index. Score>8.5 is pathognomic of ACC.[24]

As of imaging for ACC, there is no current gold standard imaging which can characterise a localised mass as ACC. In unenhanced CT, any mass <10HU suggests benign; with contrast, an absolute washout >50% suggest benign.[25] In MRI there are three main characteristics which are helpful in diagnosing ACC-isointense to hypointense signal on T1-weighted images, a hyperintense signal on T2 and an heterogeneous signal drop on chemical shift. In functional imaging, ACC shows high uptake to 18F-fluorodeoxyglucose (FDG), with a cutoff of >1.45 standardised uptake value (SUV).[26] In our case although the CT image showed an organ localised ACC, the patient had to undergo a radical nephrectomy as there was no clear plane of the demarcation.

Staging of ACC is based on the tumour-node-metastasis (TNM) proposed by ENSAT classification as demonstrated in Table 3.[27]

Table 3: ENSAT stage.

Stages	Class
I	T1, N0, M0
II	T2, N0, M0
III	T3-T4, N1
IV	T1-T4, N0-N1, M1

T1-tumor<5 cm; T2-tumor >5 cm; T3-histologically proven tumor invasion of surrounding tissue; T4-tumor invasion of adjacent organs/venous tumor thrombus in vena cava/ renal vein, N0-negative lymph nodes; N1- positive lymph nodes. M0-absence of distant metastases; M1-presence of distant metastases.

In our case the tumour was found involving the ipsilateral kidney, hence it is T3, with no nodes found N0 and no metastasis M0, suggesting stage III. Hence it is considered as localised ACC i.e., ACC amenable to resection for which R0 resection is the treatment of choice as depicted in the algorithm shown in Figure 4. The resection can be done by open or laparoscopic method. However, for T3 tumours open adrenelectomy is considered better surgical approach.

Five-year stage-dependent survival rate is 66-82% for stage I, 58-64% for stage II, 24-50% for stage III and 0-17% for stageIV.[28]

Our patient falls in the category of high-risk localised ACC, hence mitotane adjuvant therapy was given. Mitotane is a derivate of dichlorodiphenyltrichloroethane (DDT), with adrenolytic and citotoxic activity inhibiting several enzymes in the adrenocortical steroidogenensis pathway like CYP11A1 and CYP11B1. It also induces the cytochrome P450 enzyme groups leading to lowering of blood levels of many drugs like steroids, anti-hypertensives, antibiotics, etc. For metastatic ACC, mitotane is the only approved drug of choice used in combination with etoposide- cisplatin-doxorubicine (EDP). Local treatment modalities, such as radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) can be considered for metastatic ACC or ACC recurrence only when open debulking cannot be possible.

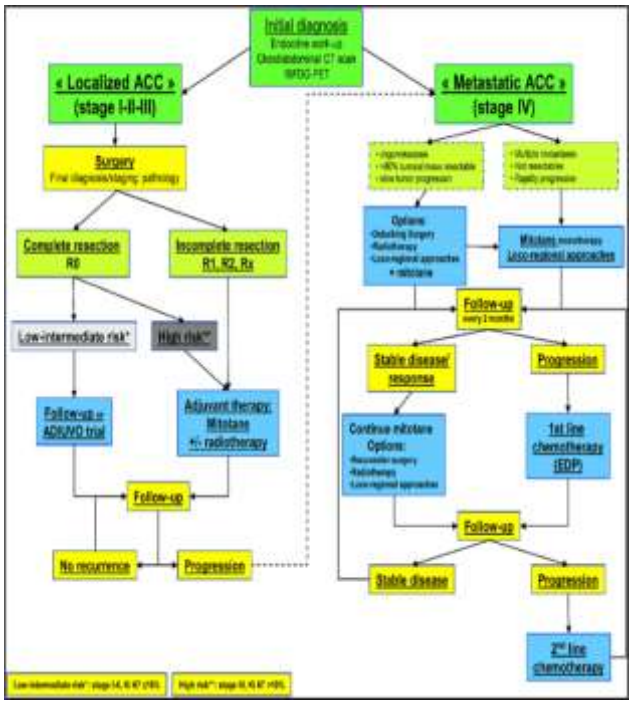

Figure 2: ACC management.

R0- completeresection; R1-microscopic incomplete resection; R2-macroscopic incomplete.

CONCLUSION

ACC is an aggressive malignancy especially with a very delayed onset of presentation. Effective evaluation and management are the key for a good survival. Although traditional imaging can predict the exact anatomy of the tumour i.e., whether it is organ confined or infiltrating to adjacent structure, the surgeon and patient must be prepared for a radical debulking surgery if warranted intra-op. With new advancements in targeted therapy, the survival rates are currently increasing for ACC.

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