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Adrenocortical Carcinoma: Case Series Reports and Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Adrenocortical carcinoma (ACC) is a rare endocrine malignancy that arises from the adrenal cortex. ACC is a significantly aggressive tumor with an elevated rate of recurrence.
Objectives: the core objectives of our study are to summarize our current practice regarding the management of ACC, to assert the challenges in the diagnosis and management of cases of ACC and to illustrate the clinical outcomes post-surgery.
Design: Retrospective analysis of five cases presented with features of ACC and had adrenalectomy during the period between 2014 and 2020.
Methods: retrospective review of all patients' data including age, clinical presentation, radiological findings, hormonal profile, operative management, adjuvant treatment, complications, follow up and survival.
Results: The average age was 53.8 ± 8.41years of age. Females were more affected than males. Three cases presented with functioning ACC, while two cases had non-functioning ACC. The average tumor size was 12 cm. All the 5 tumors weighted more than 100g. Four cases had metastasis; two cases presented with metastatic disease and two patients developed metastasis on follow-up post-operatively.
Conclusion: ACC is an extremely aggressive malignant tumor with poor outcomes. Early diagnosis, localized disease and clear surgical margins provide the primary treatment for stages I to Ⅲ.

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Keywords: adrenocortical carcinoma; survival; recurrence; chemotherapy; mitotane.

1. INTRODUCTION

1.1 Background

Adrenocortical carcinoma (ACC) is a rare and highly malignant neoplasm with an estimated annual incidence of one to two cases per a million individuals [1]. The age distribution is bimodal with the first peak in childhood and the second peak in the 4th to the 5th decade [2,3]. Women are more affected than men, at a ratio of 1.5:1. Although most cases are sporadic; however, ACC may arise in association with hereditary syndromes, such as multiple endocrine neoplasia-1, Lynch syndrome, familial adenomatous polyposis coli, and Li-Fraumeni syndrome [4]. The overall prognosis is poor; estimates of 5-year survival range from 30% to 50%; metastatic disease is associated with a median survival of less than 1 year [5].

Complete surgical resection represents the only curative treatment for ACC, which can be achieved only in tumors with no extensive regional or distant dissemination. In patients with metastatic disease, medical therapies such as Mitotane or platinum-based chemotherapy regimens, offer limited efficacy [6]. In terms of overall survival, the benefit of other treatment modalities like trans-arterial chemoembolization, radiofrequency ablation or radiotherapy, has been poorly evaluated [7].

The clinical outcomes of the disease are heterogeneous due to the variable tumor biology, disease presentations, and management options. Tumor size and extension, regional lymph node involvement and distant metastasis (TNM classification) remain the key elements in ACC staging. Adrenocortical tumors in children tend to be less aggressive with better clinical outcomes after complete surgical resection compared to ACC in adults [8]. Cortisol-secreting ACC has a worse prognosis with higher recurrence rates and worse survival compared to non-cortisol-producing ACCs [9]. Ki67 proliferation index is another clinically valuable marker with deep association with the disease prognosis [10]; patients with Ki67 of ≥ 20% had overall survival about 9.4 months compared to overall survival of 53.2 months in patients with Ki67 < 10% [11].

1.2 Objective

The aims of this study are to illustrate the challenges of diagnosis, surgical management options of ACC cases, and to evaluate the outcomes after surgery. In addition, we briefly reviewed the available literature on the same topic.

2. METHODS

In this review, we retrospectively followed the course of management of five patients, who were diagnosed with adrenocortical carcinomas in our general surgical department, during the period from 2011 to 2021. Data were obtained from our hospital recording system. Preoperative assessment included history taking, physical examination, hormonal analysis and imaging studies (CT/MRI). Every separate case was discussed at an endocrine MDT meeting involving an endocrine surgeon, endocrinologist, anesthetist, radiologist and pathologist. Our findings were compared to the available literature.

2.1 Case Presentation

Five cases of ACC were operated in our general surgical department. Four of them were females and one male. The mean age was 53.8 ± 8.41 years of age. Two of them presented with incidental finding of adrenal mass on abdominal CT which has been requested for the evaluation of another medical condition. The other three cases had clinical manifestations such as abdominal swelling, weight loss, night sweating, loin pain, facial hair gross and change of sweat smells.

Hormonal assessment of all patients included: ACTH, plasma cortisol, plasma metanephrines, aldosterone, renin, angiotensin, DHEAS, androstendione, testosterone, 17 OH progesterone, Dexamethasone suppression test and 24hr urinary cortisol. However, only two of them presented with a high plasma cortisol level > 650 nmol/L.

The mean size of the tumor on MSCT abdomen was 12 ± 6.2 cm. The smallest tumor was 50 x 43 x 44mm and the largest one was about 20cm. In one case, the abdominal CT revealed a tumor with mixed soft tissue attenuation, with extension around the left renal artery, with a left para-aortic lymph node and the tumor was abutting the celiac axis and superior mesenteric artery. While in another case there was a solitary lung nodule suspicious for metastasis from a 20-cm left adrenal mass. The other 3 cases had localized

disease. All the five cases had left sided ACC. (Figs 1-4)

Three of our cases underwent open radical nephrectomy including adrenalectomy, nephrectomy, splenectomy + lymph node dissection ± distal pancreatectomy; one of them was discovered to have a solitary hepatic metastasis intra-operatively and underwent metastatectomy in the same session. Two cases with a localized disease; one had open adrenalectomy, and the other one had a laparoscopic surgery.

On histology, one case was diagnosed as adrenocortical carcinoma staging pT3 N1, Pn1, V1 with infiltration of the tumor to the SMA, the second case's diagnosis was consistent with adrenocortical carcinoma with oncocytic and sarcomatoid components staging pT2N0 (0/10) , while the third case had adrenal cortical carcinoma staging pT3 N0 M1 R0. The fourth case was diagnosed as oncocytic adrenal cortical carcinoma with TNM stage of pT2 pNX RX, and the fifth case was diagnosed as adrenocortical carcinoma staging pT2 pNX R0. We found also that patients with high Ki67 Proliferation Index were associated with more aggressive disease. Four of our patients who had an aggressive tumor course; including 2 cases of recurrence, one mortality and one metastatic tumor, had a Ki67 Proliferation Index more than 10%.

Complications were related to the tumor behavior. Pancreatic leakage was reported in one case that underwent distal pancreatectomy. Two cases had recurrent disease; one patient declined Mitotane therapy and had a recurrent disease at the port site of the initial surgery, and the 2nd case had a widespread metastatic disease, despite Mitotane therapy. One patient who had a metastatic adrenal tumor to the lung and underwent radical adrenalectomy; however, during the operation a small liver metastatic nodule was found and had metastatectomy of this nodule during the same session, this patient had wedge excision of the lung metastatic lesion after 6 months and no recurrence was detected in 5 years of follow-up. One mortality was reported giving the aggressive tumor behavior with infiltration to the SMA, with postoperative bleeding, DIC and death. (Table 3).

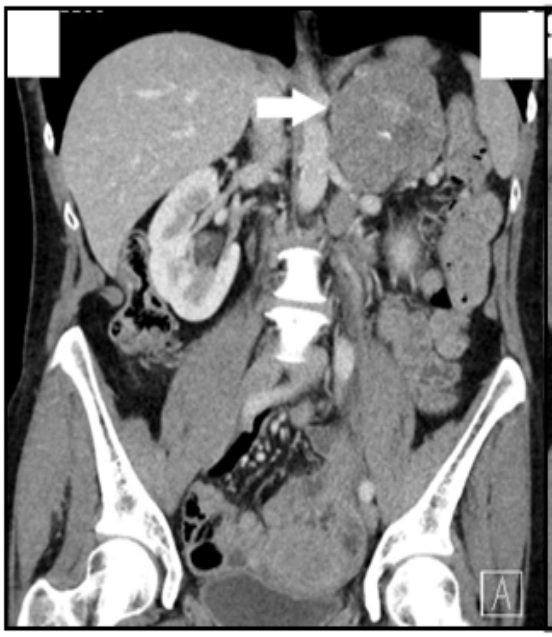

Fig. 1. MSCT abdomen showing large irregular predominantly hypodense mass in the left adrenal measuring 82mm in addition to a left para-aortic lymph node 19×14mm

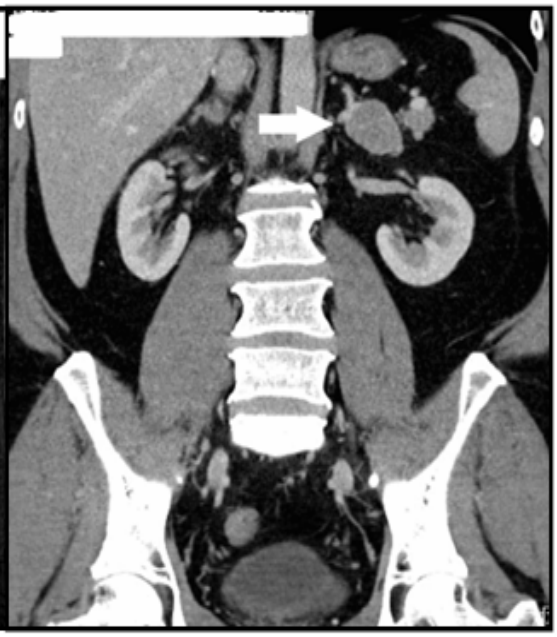

Fig. 2. MSCT abdomen showing 35×32×33mm fairly homogenous left adrenal nodule with preserved fat planes, measuring: 30HU on pre-contrast, 59HUon PV images, 38HU on 15m washout images

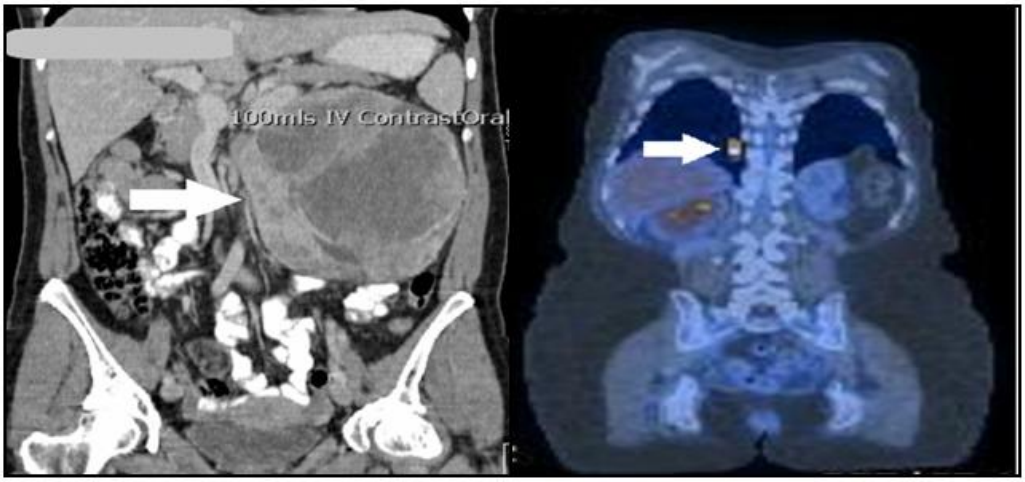

Fig. 3. MSCT abdomen showing a well-defined heterogeneous 15.6×11.7×16.8 cm left retro-peritoneal adrenal mass displacing the lower pole of the left kidney with no direct kidney connection

Fig. 4. PET-CT showing a metastatic smoothly marginated 14mm right lower lobe subpleural pulmonary nodule intensively FDG avid, secondary to left adrenal carcinoma

2.2 Literature Review

2.2.1 Epidemiology

Adrenocortical carcinoma is a rare solid tumor [12]; however, it is difficult to determine the exact incidence. In addition, adrenal incidentalomas have a prevalence of about 3% in a population > 50 years of age [13]. In adults, it is estimated that the mean age of diagnosis is 45 years [14]. Although most cases of ACC are sporadic and with no known pathogenesis, it has been also associated with a number of familial tumor syndromes, including multiple endocrine neoplasia type 1 (mutation of the MEN1 tumor suppressor at 11q13), Li- Fraumeni syndrome (p53 mutation on 17p13), Beckwithe-Wiedemann syndrome (alterations of gene clusters on 11p15.5 and 15q11e13), Carney complex (mutation of PRKAR1A gene at 17q23e24 or mutations at 2p16) and Familial adenomatous polyposis; (Gardner's syndrome; germline inactivating mutations of the APC gene) [15,16].

3. RESULTS

Functioning ACC (approximately 60% of cases) often presents with signs and symptoms of adrenal steroid hormone excess. Cushing's syndrome (CS) with or without virilization is the most frequent presentation in case of functioning ACC [17], including rapid development of muscle weakness, skin atrophy, hyperglycaemia, hypertension and psychiatric manifestations. Androgen excess in women leads to hirsutism, male pattern baldness, deep voice, breast atrophy and menstrual abnormalities. Oestrogen-secreting ACCs in males usually present with gynaecomastia and testicular atrophy, in women breast tenderness and irregular menstrual bleeding may occur [18].

Cases of ACC associated with Aldosterone hypersecretion are rare and may present with hypokalaemia and hypertension. In children, adrenal sex steroid excess is common and may lead to virilization and precocious pseudo-puberty [19].

Patients with a non-functioning ACC usually present with symptoms related to the local mass effect like abdominal fullness, pain, indigestion, nausea and vomiting [20]. In a minority of patients, weight loss, low-grade fever and weakness +/- distant metastasis, may also occur [21].

3.1 Diagnosis

3.1.1 Hormonal evaluation

Hormonal evaluation is mandatory for all patients with suspected ACC, including the following:

- Low dose dexamethasone suppression test; 24 h urinary free cortisol excretion;

CRH-test in case of subclinical Cushing's syndrome.
- Baseline serum DHEAS, 17α-OH progesterone
- Baseline serum 17α-oestradiol (in men)
- Baseline serum testosterone, androstendione (in virilizing tumours)
- Random serum aldosterone + plasma renin activity (only in patients with hypokalaemia and hypertension)
- 24h urinary catecholamine excretion or plasma metanephrines (for exclusion of phaeochromocytoma).

The presence of an adrenal lesion with an elevated serum dehydroepiandrosterone sulphate (DHEAS) levels suggests an ACC, as benign adrenocortical tumors often exhibit low DHEAS concentrations [22]. In addition, elevated serum 17 β-oestradiol is a typical marker of oestrogen-secreting ACC in men [23]. Evaluation for adrenal Cushing's syndrome is essential as cortisol hypersecretion is the most common hormone excess in ACC.

Aldosterone-secreting ACCs are rare and usually present with hypokalemia and very high serum aldosterone concentration. Aldosterone-secreting tumors smaller than 4 cm with only moderately elevated aldosterone levels are suggestive of a benign adenoma.

3.1.2 Imaging

The size of the adrenal mass, as measured by computed tomography (CT) or magnetic resonance imaging (MRI) remains one of the best indicators of malignancy. Typical CT features suggestive of ACC include inhomogeneous appearance, irregular margins, calcifications and local invasion or extension into the adjacent structures ± distant metastasis. MRI is equally as effective as CT in distinguishing malignant from benign lesions [24]. ACCs are typically iso-intense to liver on T1 and show intermediate to increased intensity on T2. MRI has sensitivity and specificity for differentiation of benign and malignant adrenal masses reaching about 89% and 99%, respectively [25].

18 F-fluorideoxyglucose positron emission tomography (18 F-FDG–PET) has demonstrated good performance in differentiating malignant form benign adrenal lesion [26]. Moreover, FDG–PET can be used to detect metastatic disease.

Fine-needle aspiration (FNA)/ core cut biopsy is not recommended to establish the diagnosis of ACC due to the risk of complications (up to 12%) [27], risk of needle tract metastases [28], and its controversial diagnostic value.

3.1.3 Staging

The differentiation between benign and malignant adrenocortical tumors may be not easy. Tumor weight is important, as most adenomas weigh between 20 and 50 g, while most malignant cortical tumors weigh more than 100 g [29]. Typical histopathological markers of malignancy include a high number of mitoses, atypical mitoses, vessel or capsule invasion and necrosis. However, no single marker is diagnostic of ACC. A Ki-67 staining index of more than 5% in adrenocortical tumors is suggestive of an ACC. Other tumor markers include steroidogenic factor-1 [SF-1], tumor protein P53, insulin-like growth factor (IGF) 2, cyclin E, reticulin [30].The marker D11 is useful, as it is positive in almost all cortical but negative in medullary adrenal tumors. To identify a pheochromocytoma or a neuroendocrine carcinoma, chromogranin A is the best marker. The tumors are classified into four grades according to the criteria in Table 1.

Tumor staging is essential to predict the outcome. Although the TNM (tumor, node, and metastasis) system from the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (IUCC) was introduced in 2004, the European Network for the Study of Adrenal Tumors (ENSAT) classification has emerged as a more accurate predictor of cancer-specific mortality risk. Although the two systems classify stage I and II tumors identically, ENSAT stage III tumors are defined by the presence of positive lymph nodes, infiltration of peri-adrenal tissue +/- the adjacent structures or venous thrombus; stage IV includes patients with distant metastasis only. Table 2.

3.2 Therapy

3.2.1 Surgery

Surgical resection carries the best chance for the cure in patients with localized ACC [31]. Open adrenalectomy is generally the favored approach in ACC cases, although with careful patient selection, laparoscopic approach has been proposed as an alternative approach in some studies [32]. However, evidence from other studies suggests higher rates and shorter time to develop loco-regional and peritoneal recurrence, and worse overall survival following laparoscopic

Table 1. Criteria for tumor grading

Grade	Mitosis	Necrosis	Atypical Mitosis
1	< 5/50 HPF	-	-
2	5-20 /50 HPF	+	+
3	21-50/50 HPF	+	+
4	>50/50 HPF	+	+

Table 2. TNM classification of adrenocortical carcinoma with comparison of AJCC/UICC/WHO and ENSAT classification systems

Staging Criteria		
T1	Tumor ≤ 5cm, no invasion	
T2	Tumor > 5 cm, no invasion	
T3	Tumor any size, locally invading to but not involving the adjacent organs	
T4	Tumor any size, locally invading the adjacent organs	
N0	No regional positive lymph nodes	
N1	Positive regional lymph nodes	
M0	No distant metastatic disease	
M1	Distant metastatic disease	
Stage	AJCC/UICC/WHO	ENSAT
I	T1, N0, M0	T1, N0, M0
II	T2, N0, M0	T2, N0, M0
III	T3, N0, M0 or T1-2, N1, M0	T3-4, N0, M0 T1-4, N1, M0
IV	T4, N0, M0 or T3, N1, M0 or T1-4, N0-1, M1	Any M1

Table 3. Characteristics of our 5 cases of ACC

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	55	65	58	46	45
Sex	F	F	M	F	F
Clinical presentation	3 months nonspecific abdominal symptoms as nausea, loin pain, abdominal bloating, facial her gross, change of sweat smell	Incidental finding on staging CT after hystrectomy operation	CT detected enlarging adrenal mass on follow up for a potential pancreatic lesion	Painless left hypochondrial swelling	Unintentional weight loss and night sweating
CT finding and tumor size	Lt renal mass 82 mm, of mixed soft tissue attenuation, extension around the left renal artery, 19×14mm left paraaortic lymph node post to Lt RV, , The tumor also abutting the celiac axis and superior mesenteric artery	Lt adrenal mass 9×10cm, abutting Lt kidney, tail of pancreas and spleen. ?? Mets?? Lt adrenal tumor	Enlarging left adrenal mass on follow up CT for a potential pancreatic lesion, new dimensions 50 x 43 x 44 mm	Well-defined 16.8 cm left-sided retroperitoneal mass which is displacing the lower pole of the left kidney	20cm Lt upper quadrant mass, displacing left kidney, spleen, pancreas with solitary lung nodule suggestive of Mets
Operation	Left Adrenalectomy, nephrectomy and splenectomy + Paraaortic LN dissection.	Left Adrenalectomy, Nephrectomy, Splenectomy + distal Pancreatectomy	Laparoscopic left adrenalectomy	Open left adrenalectomy	left adrenalectomy en block left nephrectomy, splenectomy and resection of solitary hepatic Mets in left lobe
Histopatholgy	Adrenocortical carcinoma.	Adrenocortical carcinoma with oncocytic and sarcomatoid components.	Oncocytic adrenal cortical carcinoma	Adrenal cortical carcinoma	Adrenal cortical carcinoma
Mitotic Figures	20/10HPF	13/ 10 HPF.	6/50 HPF	15/50 HPF	11MF/5HPF
Ki67 Proliferation Index	>90%	>5%	10%	14.5%	Variable
Stage	pT3 N1, Pn1, V1	pT2N0 (0/10)	pT2 pNX RX	pT2 pNX R0	pT3 N0 M1 R0
Complication	Bleeding, DIC, death		Port site recurrence	Multiple metastasis after one year	Pancreatic fistula
Mitotane therapy		Yes	Declined	Yes	Yes

resection [33]. Thus, open surgery is preferable in case of large adrenal mass with suspected malignancy.

There is no agreement regarding the optimal extent of regional lymph node resection during primary resection of ACC [34], although removal of at least five regional lymph nodes was associated with reductions in the risk of tumor recurrence and disease related mortality [35].

3.2.2 Adjuvant therapy

Although the rate of recurrence of ACC after surgery by experienced surgeons in high volume centers is low [36]; however, the overall risk of recurrence remains high approaching 60–70%, requiring the use of adjuvant therapies after surgical resection.

3.2.2.1 Mitotane

It is anadrenolytic compound with specific activity on the adrenal cortex [37]. Mitotane is hydroxylated in the mitochondria at the β-carbon and further transformed into an acylchloride. It has been reported that the active metabolites cause toxicity by oxygen activation with superoxide formation or by covalent binding to specific proteins [38].

3.2.2.2 Chemotherapy

Etoposide, doxorubicin, and cisplatin (EDP)-Mitotane regimen is considered the standard chemotherapy in advanced ACC. EDP-Mitotane use was associated with longer progression-free survival (5.5 months); however, up to 58% of patients receiving EDP-M had serious adverse events [39]. GEM-based chemotherapy (gemcitabine + capecitabine) is well-tolerated, but with moderate effect against advanced ACC. This can be used with or without Mitotane [40].

3.2.2.3 Radiation therapy

Radiotherapy has been associated with reduced likelihood of recurrence and prolonged time to recurrence with some survival benefits [38]. Radiotherapy could be used as an alternative to systemic therapy or surgery in highly selected patients with oligo-metastases who are not good candidates for surgery or systemic therapy [41].

3.2.2.4 Targeted therapy

To date, no specific tyrosine kinase inhibitor is approved in treating advanced ACC [42].The Wnt/β-catenin signaling pathway is an important pathway in the development of many tissues and many organs including the adrenal gland. Genetic alteration involving activation of Wnt/β-catenin occurs frequently in ACCs. In vitro studies to block the Wnt/b-catenin signaling in ACC cell line have shown increased apoptosis and impairment of adrenal steroidogenesis [43].

3.2.2.5 Radiofrequency ablation

Percutaneous image-guided radiofrequency ablation (RFA) is appealing as minimally invasive, locally effective treatment choice, in patients who are not good candidates for reoperation [44]. Studies have shown that RFA can potentially result in effective, short-term local control of primary ACC in case of tumors less than 5 cm in size [45].

3.3 Follow-up

Close follow-up is of vital importance in ACC to detect recurrence at a time when surgical intervention is still possible. Follow- up using CT should be performed every 3–4 months during the first 2 years after complete tumor removal. Intervals may then increase with disease-free time from surgery. In functioning tumors, hormonal marker (e.g. DHEAS) may rise again after surgery long before tumor tissue becomes detectable by imaging techniques.

4. DISCUSSION

Adrenocortical carcinomas are rare and lethal neoplasm with the incidence of about 1 to 2 cases per million individuals [1]. An adrenocortical carcinomas more often occurring in woman than in men [46], we had similar results in our study. ACC occurs with increased frequency in association with other genetic syndromes like Beckwith-Wiedmann syndrome and Li-Fraumani syndrome; however, most of the tumors are sporadic [47]. All the five cases in our study were sporadic. Adrenocortical carcinomas are usually diagnosed late; two of our cases had advanced disease during diagnosis, one with hepato-pulmonary metastasis and one with infiltration of the superior mesenteric artery. Other studies reported similar findings [48]. In addition, the average tumor size on diagnosis in our study was 12cm, similar to other studies [49].

About 60% of adrenocortical carcinomas are functional hormonal syndrome including feminization or cortisol excess syndrome and 40% are non-functional. The diagnosis of

adrenocortical carcinoma depends on clinical, hormonal work-up and imaging studies. CT scan is considered the imaging of choice to assess adrenal masses. The differentiation between benign and malignant adrenal masses is difficult. Macroscopically, a weight of more than 100g, grossly lobulated cut surfaces, necrotic areas, calcifications and intra-tumoral hemorrhage can predict the presence of malignancy. The microscopic features include a high nuclear grade, mitotic rate more than 5/50 HPF, atypical mitotic figures, necrosis, invasion of venous structures, and capsular invasion.

The most common site for distant metastasis is the liver (48-85%), the lungs (39-60%), lymph nodes (7-29%), and bones (7-13%) [49]. One case in our study had metastatic disease in the liver and lung, one case had recurrence at port site and one case had multiple metastases.

Surgery is still the only chance for the cure for ACC. However, aggressive behavior of this cancer limits the cure rate. Medical therapy with Mitotane plays an important role as adjuvant therapy and in cases in which surgery is not suitable, or in patients with metastatic adrenocortical carcinomas. Adrenocortical carcinomas are relatively radio-resistant; therefore, radiotherapy is usually reserved for palliating bone metastasis and for unrespectable local recurrence [50].Two cases in our study had metastatic disease from the start, and 2 cases had recurrence within one year. In general, the prognosis of adrenocortical carcinomas is poor; however, it is estimated that patients with stage I and II have a similar prognosis which is significantly better than that for stage III and IV patients [51].Three of our patients had T2 disease with a better overall prognosis than the other 2 patients who had T3 disease. In general, the 5-year survival of 84% for stage I, 63% for stage II, 51% for stage III and 15% for stage IV [52].

5. CONCLUSION

Adrenocortical carcinoma is a rare and highly aggressive tumor with a poor prognosis. Early diagnosis and radical surgery with clear margins provide the only cure for ACC patients. More data is needed for better understanding of the tumor behavior and characteristics.

CONSENT

Not applicable.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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