Giant Adrenocortical Carcinoma: A Case Report and Review of the Relevant Literature

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Patient: Female, 63-year-old
Final Diagnosis: Adrenal cortical carcinoma
Symptoms: Abdominal pain and discomfort
Medication: —
Clinical Procedure: Excision of the recurrent mass along with the tail of the pancreas and a small part of the left lobe of the liver • extended open surgical excision of the mass with an esophago-jejunal anastomosis and a side to side jejuno-jejunal anastomosis
Specialty: Endocrinology and Metabolic • Oncology • Surgery
Objective: Rare disease
Background: Adrenocortical carcinomas are rare and aggressive tumors often diagnosed as incidentalomas. The malignancy can present with abnormal hormone secretion or the tumor may be non-functioning and present as a palpable mass causing discomfort. Here, we present a case of an adrenal cortical carcinoma originally identified as an incidentaloma.
Case Report: A 63-year-old woman presented with abdominal pain and discomfort. A large abdominal mass, occupying the left upper and lower quadrant, was palpated. Imaging revealed a mass occupying the left abdomen between the stomach and the spleen, applying pressure on the pylorus, duodenum, splenic vessels, and pancreas. The mass size was 21.2×13×14.6 cm. Hormonal investigations were normal. Surgical exploration was performed, and the tumor was excised. Pathological analysis revealed an adrenocortical carcinoma and the patient underwent adjuvant chemotherapy. Twelve months later, the carcinoma recurred. The patient underwent a second operation in which the recurrent mass was excised along with the tail of the pancreas and a small part of the left lobe of the liver. The postoperative period was uneventful, and the patient was discharged home on the 7th postoperative day. No further adjuvant therapy was applied. The patient remains disease-free 18 months after the reoperation.
Conclusions: Giant adrenocortical carcinomas, although rare, pose a challenge to the surgical team both diagnostically and therapeutically. Surgical excision with the appropriate oncologic support can guarantee excellent outcomes.
Keywords: Adrenal Gland Neoplasms • Adrenocortical Carcinoma • Case Reports • Incidental Findings • Mitotane

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Background

Adrenocortical carcinomas (ACC) are rare and frequently aggressive tumors. Their worldwide incidence is estimated at 2 per million cases annually in the USA, affecting women more frequently than men [1]. The 5-year survival rate varies from 15% to 84% and is directly correlated with the stage of the cancer at presentation [2]. ACCs can be divided in 2 groups: functioning (hormone-producing) and non-functioning tumors [3].

The clinical presentation depends on the size, location, and hormonal production status. A large tumor can be the cause of abdominal pain and discomfort to the patient due to a mass effect. The patient might also present with generalized symptoms such as weight loss, malaise, and dyspnea [4].

The cornerstone therapy has always been complete surgical removal of the tumor and adjacent organs. Adjuvant chemotherapy with mitotane and cytotoxic factors can be used for functional adrenal carcinomas according to the stage of the disease and the status of the patient [5].

Here, we present the case of a patient with a large abdominal mass that turned out to be ACC and the patient underwent a radical surgical resection.

Case Report

A 63-year-old woman was referred from the gastroenterology clinic of our hospital to our unit with a giant solid mass in the upper abdomen of unknown origin. Her initial symptoms were abdominal pain and discomfort. Her past medical history included type II diabetes mellitus treated with metformin and a history of hysterectomy for uterine fibroids. On examination, a large abdominal mass was palpated occupying mostly the left upper and lower abdominal quadrant. Upper gastrointestinal endoscopy was normal. After investigation with CT and MRI abdominal scans (Figures 1, 2, respectively), a mass was found occupying the left abdomen, located between the stomach and the spleen. The mass was shown to originate from the left paranephric space extending to the greater curvature of the stomach, applying pressure to the pylorus, duodenum and splenic vessels, as well as being in direct contact with the pancreas (Figure 1). Due to the size (21.2×13×14.6 cm) and location of the mass, an adrenocortical carcinoma was suspected. After biochemical studies, no hormonal abnormalities were discovered (serum cortisol level: 188 ng/ml, normal reference range: 50-230 ng/mL), dehydroepiandrosterone level: 67 μg/dl (normal reference range: 45-270 μg/mL), plasma...
fractioned metanephrines 31 pg/mL (normal reference range: 12-60 pg/mL), plasma fractioned normetanephrines 75 pg/mL (normal reference range: 18-111 pg/mL), and aldosterone-to-renin ratio of <20 (normal reference range: 20-40).

The patient underwent an extended open surgical excision of the mass along with the stomach that was attached to it (Figure 3). An esophago-jejunal anastomosis and a side-to-side jejuno-jejunal anastomosis were performed. Resection margins were clear of residual mass, confirmed by frozen section study. Due to the duration of the operation (3.5 hours) and the co-morbidities of the patient (diabetes mellitus, obesity) she was transferred to the Intensive Care Unit (ICU) for postoperative resuscitation and remained there for the first 24 hours. In the immediate postoperative period, she developed a lower respiratory tract infection that was treated successfully with intravenous antibiotics. Otherwise, her postoperative period was uneventful and she was discharged home on the 22nd day.

The histology exam revealed that the mass was an adrenal cortical neoplasm (WHO 2004 Classification-tumors of endocrine organs) with the following immunochemistry profile: vimentin (+), CD56 (+), synaptophysin (+), melan-A (+/-), calretinin (+/-), CD138 (+). The modified Weiss score system incorporates the
| Author               | Age | Sex | Presentation                          | Laboratory studies | Tumor size (cm) | Site | Histological findings | Immunohistochemical studies |
|----------------------|-----|-----|---------------------------------------|--------------------|----------------|------|-----------------------|-----------------------------|
| Alastrue Vidal et al | 45  | F   | Virilization                          | Elevated: T, DHEA-S | 16.2           | R    | ACC                   | N/R                         |
| Alastrue Vidal et al | 50  | F   | Virilization                          | Elevated: T, DHEA-S | 20.3           | R    | ACC                   | N/R                         |
| Almarzouq et al      | 30  | F   | Abdominal pain, weight loss           | Normal             | 20             | L    | ACC                   | Vimentin(+), Synaptophysin(+) |
| Bacaibasa et al      | 65  | M   | Caval compression syndrome, abdominal pain | N/R                | 35             | R    | ACC                   | Vimentin(+), Synaptophysin(+), Melan-A(+), Calretinin(+), Ki-67(+) (14%) |
| Bagchi et al         | 35  | F   | Altered menstrual symptoms           | Elevated: serum cortisol, norepinephrine, dopamine | 21             | L    | ACC                   | N/R                         |
| Benassai et al       | 53  | M   | Palpable mass on the L flank          | Normal             | 24             | L    | ACC                   | N/R                         |
| Brown and Bacal      | 64  | M   | Abdominal distention                  | Normal             | 19             | R    | ACC                   | N/R                         |
| Chentli et al        | 34  | F   | Cushing                               | Elevated: Serum GLC, E2, T, 17OH P, CA125, Decreased: ACTH, K+, Hb | 14.5 | R ovary | ACC | Inhibin-A(+), Melan-A(+), Sf1(+) |
| Chung et al          | 36  | F   | Incidental finding                    | Normal             | 12             | L    | ACC                   | Vimentin(+), CD56(+), Inhibin-A(+), Melan-A(+) |
| Coli et al           | 75  | F   | Abdominal pain                        | N/R                | 15             | L    | Sarcomatoid ACC       | MNF-116(+), Vimentin(+), Desmin(+), Actin(+), H-Caldesmon(+), Myogenin(+), HMB-45(+) |
| Fancellu et al       | 41  | M   | Feminization                          | Elevated: E2, Cortisol, ACTH Decreased: T, Gonadotropins | 27             | L    | ACC                   | Melan-A(+), Synaptophysin(+) |
| Fernandez et al      | 64  | F   | Abdominal pain                        | N/R                | 12             | R    | ACC                   | N/R                         |
| Fimmano et al        | 61  | M   | N/R                                   | N/R                | 24             | R    | ACC                   | N/R                         |
| Fulawka et al        | 27  | M   | Non-specific                          | N/R                | 22             | L    | ACC                   | Vimentin(+), Inhibin(+), Synaptophysin(+), Bcl-2(+), Calretinin(+) |
| Ghorayeb et al       | 50  | M   | Palpable mass on the L flank          | Elevated: DHEA     | 18             | L    | ACC                   | Ki-67(+) (12%), IGF-2(+), β-Catenin(+) |
| Habibi et al         | 38  | F   | Abdominal pain, palpable mass         | Normal             | 22             | L    | ACC                   | Ki-67(+) (15-20%)            |
| Hatano et al         | 60  | M   | Feminization                          | Elevated: E2, Preg, P, DOC, 17OH-P, DHEA-S Decreased: T, LH, FSH | 13             | R    | ACC                   | Ki-67(+) (18%), Sf1(+)       |
Table 1 continued. Giant ACCs reported in the literature [3-5,7,10-19].

| Author          | Age | Sex | Presentation                              | Laboratory studies | Tumor size (cm) | Site | Histological findings | Immunohistochemical studies                        |
|-----------------|-----|-----|-------------------------------------------|--------------------|-----------------|------|----------------------|-----------------------------------------------|
| Hoang et al     | 39  | M   | Ascites, abdominal mass                   | N/R                | 14              | R    | ACC                  | Cytokeratin(+), Vimentin(+), Synaptophysin(+) |
| Hoang et al     | 53  | F   | Abdominal pain                           | N/R                | 17              | L    | ACC                  | Cytokeratin(+), Vimentin(+), Synaptophysin(+) |
| Hoang et al     | 58  | M   | 1 year History of rapidly enlarging adrenal mass | N/R                | 13              | R    | ACC                  | Cytokeratin(+), Vimentin(+), Synaptophysin(+) |
| Hsieh et al     | 82  | F   | Primary hyperaldosteronism                | Elevated: ALDO, Decreased: Plasma renin activity | 13              | L    | Myxoid ACC           | Synaptophysin(+), Melan-A(+), Vimentin(+)     |
| Kalra et al     | 34  | M   | Incidental finding                       | Normal             | 16              | L    | ACC                  | Inhibin-A(+), Melan-A(+)                       |
| Kashiwagi et al | 47  | F   | Lower back pain                          | Decreased: Hb      | 13.5            | L    | ACC                  | N/R                                          |
| Khan et al      | 40  | M   | Incidental finding                       | Normal             | 30              | R    | ACC                  | N/R                                          |
| Kovecsi et al   | 71  | M   | Weight loss, epigastric pain              | Normal             | 13              | R    | ACC                  | Vimentin(+), Synaptophysin(+), NSE(+), Ki-67(+) (30%) |
| Kunieda et al   | 52  | M   | Weight loss, palpable mass                | Elevated: Cortisol, S, DHEA-S, 17-KS Decreased: ACTH | 29              | R    | ACC                  | N/R                                          |
| Lee et al       | 61  | M   | Right flank pain                         | VMA                | 12              | R    | Sarcomatoid ACC      | Cytokeratin(+), Vimentin(+), NSE(+)           |
| Lee et al       | 21  | M   | R flank pain, palpable mass               | N/R                | 21              | R    | ACC                  | N/R                                          |
| Meshikhes et al | 20  | M   | R flank pain, palpable mass               | Normal             | 24              | L    | ACC                  | Vimentin(+), Synaptophysin(+), Cytokeratin(+) |
| Ohwada et al    | 47  | F   | Incidental finding                       | Normal             | 18              | R    | ACC                  | N/R                                          |
| Ohwada et al    | 68  | M   | Incidental finding                       | Normal             | 16              | R    | ACC                  | N/R                                          |
| Ohwada et al    | 62  | M   | Weight loss, bilateral Lower extremities edema | Normal             | 20              | R    | ACC                  | N/R                                          |
| Ohwada et al    | 43  | F   | Cushing                                  | Elevated: 17-OHCS, 17-KS, DHEA-S | 15              | R    | ACC                  | N/R                                          |
| Onkar and Shilpi| 47  | M   | Non-specific                             | Normal             | 22              | L    | ACC                  | N/R                                          |
| Permana et al   | 21  | F   | Virilization                             | Elevated: T, DHEA-S, E2, Morning Cortisol Decreased: LH, FSH, | 15.6            | R    | ACC                  | NSE(+) , HEPI(+) , CD56(+)                     |
### Table 1 continued. Giant ACCs reported in the literature [3-5,7,10-19].

| Author            | Age | Sex | Presentation               | Laboratory studies | Tumor size (cm) | Site | Histological findings | Immunohistochemical studies |
|-------------------|-----|-----|-----------------------------|--------------------|-----------------|------|-----------------------|----------------------------|
| Reyes et al       | 42  | F   | Right flank pain            | Normal             | 12              | R    | ACC                   | N/R                        |
| Saeger et al      | 53  | F   | Incidental finding          | N/R                | 13              | R    | Sarcomatoid ACC       | β-Catenin(+), Vimentin(+), Synaptophysin(+), Desmin(+), SF1(+), Melan-A(+), Ki-67(+) (60%) |
| Sasaki et al      | 45  | M   | Epigastric pain, weight loss | Normal             | 17              | L    | Sarcomatoid ACC       | Synaptophysin(+), Melan-A(+), Vimentin(+), Calretinin(+), Desmin(+), Myogenin(+), Myoglobin(+) |
| Souto et al       | 54  | F   | Cushing                     | Elevated: DHEA-S, AE, 17OH-P, T, Urinary free cortisol decreased: LH | 21              | L    | ACC                   | Ki-67(+) (20%)              |
| Straka et al      | 40  | M   | PE                           | NSE                | 26              | R    | ACC                   | Ki-67(+) (12%)              |
| Sung et al        | 48  | F   | Palpable mass               | N/R                | 19              | R    | Myxoid ACC            | Ki-67(+) (4%)               |
| Sung et al        | 59  | F   | Incidental finding          | N/R                | 12.5            | L    | Myxoid ACC            | Ki-67(+) (5%)               |
| Sung et al        | 48  | F   | Non-specific                | N/R                | 16              | R    | Myxoid ACC            | Ki-67(+) (18%)              |
| Sung et al        | 51  | M   | Non-specific                | N/R                | 15              | R    | Sarcomatoid ACC       | Ki-67(+) (12%)              |
| Tseng et al       | 56  | M   | AKI, PE                     | Normal             | 24              | R    | ACC                   | Melan-A(+)                  |
| Uruc et al        | 48  | F   | Abdominal pain              | Elevated: T, DHEA-S | 23              | L    | ACC                   | Vimentin(+), Synaptophysin(+), Cytokeratin(+), Ki-67(+) (13%) |
| Veron Esquivel et al | 39 | F   | HTN, HypoK, metabolic alkalosis | Elevated: ALDO, renin, cortisol, T, AE | 13              | R    | ACC                   | N/R                        |
| Wei et al         | 53  | F   | Palpable mass               | Elevated: T, P     | 12              | L    | ACC                   | N/R                        |
| Wilkinson et al   | 64  | F   | Abdominal pain              | Normal             | 12              | L    | ACC                   | N/R                        |
| Wolf et al        | 46  | M   | Feminization, varicocele L  | Elevated: P2, E, 17-OHCS, 17-KS | 17              | L    | ACC                   | N/R                        |
| Yavascaoglu et al | 51  | M   | L flank pain, weight loss, bilateral leg edema | Normal            | 18              | L    | ACC                   | N/R                        |
| Yeh et al         | 53  | F   | Virilization                | Elevated: T, DHEA-S, AE | 12              | R    | ACC                   | N/R                        |

**ACC** – adrenocortical carcinoma; **VMA** – vanilmandelic acid; **NSE** – neuron specific enolase; **N/R** – not reported; **ALDO** – aldosterone; **AE** – androstenedione; **T** – testosterone; **E** – estrogens; **P2** – pregnadiol; **17-OHCS** – 17-hydroxycorticosteroids; **17-KS** – 17-Ketosteroids; **AKI** – acute kidney injury; **PE** – pulmonary edema; **SF1** – steroidogenic factor 1; **DHEA-S** – dehydroepiandrostenedione-sulfate; **IGF-2** – insulin-like growth factor 2; **GLC** – glucose; **P** – progesterone; **ACTH** – adrenocorticotropic hormone; **Hb** – hemoglobin; **Preg** – pregnenolone; **DOC** – deoxycorticosterone; **17OH-P** – 17-hydroxyprogesterone; **LH** – luteinizing hormone; **FSH** – follicle stimulating hormone, S – 11-Deoxycortisol.
following criteria: 1) mitotic rate >5 per 50 high-power fields, 2) cytoplasm (clear cells comprising 25% or less of the tumor), 3) abnormal mitoses, 4) necrosis, and 5) capsular invasion. According to the system, each of these criteria is differently weighted and a score of 3 or more suggests malignancy [6]. In our patient, the modified Weiss score system of 6, size of 20 cm in diameter, and the ki-67 proliferation index of 5-7% were all suggestive of carcinoma. The patient underwent adjuvant chemotherapy postoperatively with mitotane treatment.

Despite adjuvant therapy, she presented with a cystic lesion 1 year after the operation. A CT-guided core biopsy was performed, which revealed recurrent adrenocortical carcinoma (Figure 4). The recurrence was located posterior lateral to the esophagojejunal anastomosis (Figure 5A). She underwent a second operation in which the recurrent mass was excised along with the tail of the pancreas and a small part of the left lobe of the liver (Figure 5B). The postoperative period was uneventful, and the patient discharged home on the 7th postoperative day. No further adjuvant therapy was applied. The patient undergoes follow-up with CT scan every 6 months, which revealed no recurrence 1.5 year after the reoperation, and no metastasis was observed.

**Discussion**

Adrenal cortical carcinoma (ACC) is an uncommon malignant endocrine neoplasm. ACC accounts for 0.02% of all cancers reported annually in the United States. It has an estimated incidence of 0.02 to 0.2 cases per million population per year [7]. The clinical presentation of adrenal cortical tumors depends on their size and hormonal status. Many non-functioning adrenal tumors are incidental findings and not always related to the patient’s clinical presentation, and are therefore called incidentalomas [8].

Less than 2% of incidentalomas under 4 cm in size are primary adrenal carcinomas, while the risk for adrenal carcinoma increases to 25% in adrenal masses greater than 6 cm. The sensitivity and specificity for cutoffs of 4 cm are 98% and 59%, respectively [9,10]. Our patient presented with an abdominal mass of 21.2×13×14.6 cm, which rarely has an adrenal origin.

After thorough review of the literature, cases of adrenal carcinomas larger than 12 cm were documented (Table 1) [3-5,7,11-20]. The mean size of these tumors was 18 cm. The largest tumor, reported by Bacalbasa et al, was 35 cm [21]. The size of the tumor we resected was at the 74th percentile of the normal distribution curve. The tumor appears to be larger than the mean tumor size reported in the literature (Figure 6). The clinical manifestation of ACCs depends on their hormone-producing status. Non-functioning tumors can present with unspecific symptoms like abdominal pain, malaise, hematuria, and weight loss or no symptoms at all (incidental findings). Functioning tumors have a varied presentation, including Cushing’s syndrome, virilization, and feminization [8]. Our patient had non-specific symptoms, none of which were associated with hormone production (abdominal pain, discomfort, palpable abdominal mass). Blood hormonal levels where within normal levels. The imaging studies that are most commonly and effectively used for the differential diagnosis between the types of adrenal masses are non-contrast CT, MRI, and adrenal scintigraphy [5].

The laboratory tests used for the differential diagnosis for adrenal masses depends on the clinical signs of hormonal production. In cases of obvious endocrine symptomatology there are a number of measurements that indicate the functionality of the mass. Dexamethasone suppression test and 24-hour urine cortisol sample are used in the presence of Cushing’s syndrome, while plasma estradiol or estrone is measured when feminization is present [5,8]. When an adrenal lesion is incidentally found, appropriate laboratory tests to be performed are electrolyte levels measurement in the presence of hypertension to rule out hyperaldosteronism, urinary metanephrines and catecholamines levels to exclude pheochromocytoma, and estrogen or androgen levels where relevant symptoms exist [8]. Our patient underwent an abdominal CT and MRI scan, in which the mass was found, and a full blood biochemical work-up including cortisol, aldosterone, renin, metanephrines, normetanephrines, and dehydroepiandrosterone level measurement.

Radical surgical resection is suggested for all patients presenting with adrenal tumor (stage I, II, or III disease), while achieving an R0 excision remains the most important prognostic factor for survival. Laparoscopic adrenalectomy is an option for experienced surgeons and masses <6 cm, whereas open adrenalectomy remains the suggested option for larger masses, signs of local invasion, or if carcinoma/malignancy is suspected [22].

Table 1

| Tumor size (cm) | Frequency |
|----------------|-----------|
| 10             | 1         |
| 15             | 2         |
| 20             | 3         |
| 25             | 4         |
| 30             | 5         |
| 35             | 6         |
| 40             | 7         |

**Figure 6.** The size of the tumor we resected was at the 74th percentile of the normal distribution curve. The tumor appears to be larger than the mean tumor size reported in the literature.
We performed an extended surgical excision of the tumor along with the stomach that was attached to it and completed the operation with the appropriate anastomosis (esophageal-jejunal anastomosis and a side-to-side jejuno-jejunal anastomosis). Radical resection is also the criterion standard strategy for recurrence. Similarly, the attached organs such as the left liver lobe and the tail of the pancreas were excised along with the recurrent mass. Our patient needed a second operation 1 year later due to recurrence, but she remains cancer free to date.

Mitotane, as a single agent or in combination with other cytotoxic drugs, is the current standard treatment for advanced ACCs [23]. Treatment regimens in ACC are mitotane monotherapy, EDPM (etoposide, doxorubicin, cisplatin plus mitotane), or streptozotocin plus mitotane. However, time to progression was observed to be significantly better in patients treated with mitotane [20]. In our case, despite open radical excision and adjuvant chemotherapy with mitotane, adrenocortical carcinoma reoccurred after 1 year.

Recently, gene expression profiling has improved our understanding of the oncogenesis of ACC and helped identify potential new targets for treatment [20]. New avenues for ACC therapy have been opened by studies investigating the biological and molecular bases of this disease [23]. Several pathways have been identified in the tumorigenesis of ACC. IGF-2, mTOR, EGFR, and VEGF are overexpressed in ACC [23]. In vitro and in vivo studies have been performed to identify potential targeted therapies for ACC [20]. Those include IGF-1 receptor antagonists, β-catenin antagonists, SF-1 (steroidogenic factor 1) inverse agonists, and mTOR antagonists. PPARγ and estrogen receptors have also been identified as potential markers for ACC tumor-genesis [23].

Conclusions

Non-functioning adrenal incidentalomas are rare and present with vague symptoms such as dull abdominal pain, nausea, and discomfort. Their size is a strong indicator of their malignant potential. Masses larger than 6 cm have increased risk being carcinomas. The criterion standard treatment for adenocortical carcinomas is open radical excision with adjuvant chemotherapy, although the recurrence rate and disease-free survival remain unsatisfactory.

Conflict of Interest

None.

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