Adrenocortical carcinoma: a case report and literature review


ABSTRACT

Patient is a 43-year-old man with oncologic genetic load: mother presented with breast cancer, father with prostate cancer, and sister with ovarian cancer. Patient has ten-year progression of high blood pressure controlled with angiotensin-converting enzyme inhibitor. Present illness of one-year progression, patient presented with diffuse postprandial abdominal pain with peaks of intensity in the epigastrium and right hypochondrium accompanied with vomiting. Patient was initially treated for peptic acid disease with no success. Physical examination did not produce relevant information. In studying pain, right adrenal mass was detected. Laboratory tests were normal. Ultrasound imaging revealed 9.9 x 6.8 cm right heterogeneous adrenal mass that was confirmed with tomography and magnetic resonance studies. Histopathological result of adrenal mass reported right adrenal carcinoma.

Keywords: Incidentaloma, adrenal mass, adrenal carcinoma, Mexico.

RESUMEN

Presentamos el caso de paciente masculino de 43 años de edad, con carga genética oncológica. Madre con cáncer de mama, padre con cáncer de próstata, hermana con cáncer de ovario. Portador de hipertensión arterial de 10 años de evolución, controlado con inhibidor de la enzima convertidora de angiotensina. Padecimiento actual de un año de evolución, con dolor abdominal posprandial en epigástrico e hipocondrio derecho, difuso con picos de dolor intensos acompañados de vómito. Tratado inicialmente como una enfermedad ácido péptica, sin éxito. Exploración física sin datos relevantes. En su estudio del dolor, se detectó masa suprarrenal derecha. Exámenes de laboratorio normales. Gabinete: ecografía con presencia de masa suprarrenal derecha heterogénea de 9.9 cm por 6.8 cm. Confirmamos con tomografía y resonancia magnética. El resultado histopatológico de la masa suprarrenal señaló carcinoma suprarrenal derecho.

Palabras clave: Incidentaloma, masa suprarrenal, carcinoma suprarrenal, México.
INTRODUCTION

Adrenal carcinoma is an aggressive malignant neoplasia with poor prognosis. It is a rare tumor that represents 0.02% of all neoplasias. Global incidence is 0.5-2 per every 1,000,000 inhabitants and adrenal incidentaloma incidence is 2-3%. Non-functioning tumor is predominant in men in the fourth and seventh decades of life. Etiology is unknown. The majority of cases are incidental diagnoses of advanced stage disease that metastasizes precociously due to its tendency to invade vascular structures.

Fundamental understanding of adrenal gland physiology, from the initial description by Eustachius in 1563, has been advanced through current biochemical analysis of adrenal gland secretory products and precise imaging techniques. The adrenal glands and their division into cortex and medulla were not recognized until the work of Addison in 1855 when he observed their indispensable function in patients that died from adrenal destruction secondary to tuberculosis. Shortly thereafter, he carried out bilateral adrenalectomy in animals and foresaw that these glands were essential for life. Adrenal cortex hyperactivity was not documented until 1912. A definitive report came out in 1932 on 11 patients with basophilic adenoma of the pituitary gland that described the now classic Cushing’s syndrome. Later, forms of adrenocortical hypertension, congenital adrenal hyperplasia, adrenal carcinoma, and other adrenal disorders were described.

CASE PRESENTATION

Patient is a forty-three-year-old man referred to the urology service by the gastroenterology department. His oncological genetic load included mother with breast cancer, father with prostate cancer, and sister with ovarian cancer. Non-pathological past history included smoking and social drinking without reaching inebriation. He presented with high blood pressure of 10-156 mm Hg, weight 107 Kg, and height 184 cm. There were no other relevant data. Right adrenal mass was detected through ultrasound. Laboratory work-up including full blood count, blood chemistry, serum electrolytes, liver function tests, cortisol, aldosterone, normetanephrines, total metanephrines, and urine metanephrines were all within normal ranges. Ultrasound revealed a 9.9 x 6.8 cm right heterogeneous adrenal mass that was confirmed with tomography and magnetic resonance (MR) studies (Figures 1, 2, 3 and 4).

Treatment: Diagnosis of right adrenal mass was made from clinical and radiological findings. Laparoscopic adrenalectomy was carried out and an approximate 10 cm well-encapsulated adrenal tumor with no macroscopic evidence of local invasion was found. Patient was released 24 hours after surgery in good clinical condition.

Histopathological result of macroscopic aspect stated: 9 x 7 x 5 cm well-encapsulated nodular specimen that weighed 261 g and presented with congestive areas. Microscopically it was graded according to the Weiss criteria (0-9) with a score of 5.

Patient is completely asymptomatic with good progression at 3-month postoperative follow-up.

Adrenal carcinoma: Adrenal carcinoma is an infrequent tumor and the majority of reports in the international literature are case reports. Diagnosis is based on biochemical aspects of the hormonal syndrome and on imaging techniques.

Adrenal incidentalomas have a prevalence of 2.3% in autopsy and 0.5-2% in abdominal tomography. A reduced number of adrenal tumors are functioning and an even lower number (1%) are malignant. Adrenal lesions often go clinically unnoticed because they are asymptomatic. Findings and diagnoses have increased greatly thanks to ultrasonography (US) and computed tomography (CT). These diagnostic techniques are available in most hospitals, even though other diagnostic tools are sometimes at hand. Adrenal carcinoma incidence rate is reported to be <0.03% in regard to all adrenal incidentalomas from 1.5-6 cm in diameter. Adrenal carcinoma is a malignant tumor representing 0.02% of all malignant neoplasias in the United States’ with an incidence of 1 case per every 1.7 million inhabitants per year. Adrenal carcinoma in children barely reaches 0.002% incidence. In some studies described in the literature, mean diagnostic age is 50-60 years, but in the majority of published series presentation age is higher in men than in women. The majority of adrenal tumors are sporadic and unilateral but 2-6% are bilateral and are associated with Li-Fraumeni syndrome, Type 1 multiple endocrine neoplasia, Beckwith-Wiedemann syndrome, and Carney complex, principally in children.

Functioning tumors are more frequent in women and the most frequent adrenal hyperfunction symptoms in order of frequency are Cushing’s syndrome and virilization. Non-functioning tumors predominate in men and usually manifest as general syndrome or abdominal mass.
Adrenal carcinoma has a bimodal age distribution with an incidence increase in children under five years of age and in adults in the fourth and fifth decades of life. Adrenal carcinoma shows no racial predilection and there is an approximate 4:3 woman to man ratio. Men tend to be older and have poorer prognosis. Adults generally present with advanced stage disease and 5-year survival rates are discouraging and vary from 16-38%.

Complete resection continues to be the best opportunity for cure even though recurrence rate is still elevated and estimated at 70-80%.\textsuperscript{12} Etiology is unknown. Chromosome heterozygosity in the 11p, 13q, and 17p chromosomes may play a role and abnormalities in p53 have been found.\textsuperscript{13}

Adrenal gland anatomy: The two adrenal glands are retroperitoneal organs found inside the perinephric fat at the anterosuperior and medial surface of the kidneys. They can be up to 5 cm long and 3 cm wide and are 1 cm thick. Each gland weighs approximately 5 g. In contrast, at birth the adrenal gland is large (5-10 g) due to the fetal adrenal cortex that can play an important role in embryogenesis of the fetus and in homeostasis. The fetal adrenal cortex involutes quickly during the first six weeks of infancy due to apoptotic cell death at the moment of fetal birth. Both glands are flattened on their anterior sides with a thick and thin central, medial, and lateral crest.

The right adrenal gland is on top of the kidney posterolateral to the inferior vena cava. The anterior surface is in immediate contact with the inferior and posterior surface of the liver. The inferior vena cava is medial; the posterior surface of both adrenal glands is in contact with the posterior part of the diaphragm. The left renal artery is often found on a deeper plane in relation to the suprarenal vein. The left adrenal gland is on the upper pole of the kidney with its anterior and medial surface behind the splenic artery and the pancreas. The anterior surface of the left adrenal gland can be exposed by the rest of the retroperitoneal structures and by the spleen. The adrenal gland has a blood supply of 6-7 mL per minute. Right vein drainage usually exits the vertex of the gland and enters in the posterior surface of the inferior vena cava; this trajectory is brief and fragile and is the most common source of bothersome bleeding during right adrenalectomy. The left vein empties directly into the left renal vein about 3 cm from the inferior vena cava and often in front of the gonadal vein.\textsuperscript{14-16}

Adrenal embryology: The adrenal cortex arises from the mesoderm and the adrenal medulla from the neuroectoderm. During the fifth week of development, mesothelial cells proliferate and invade the mesenchyme. These cells form the fetal adrenal cortex and a type of cell is mesonephric in origin. The finding of ectopic or aberrant adrenal tissue can generally be explained by the intimate developmental relation of the
gonads, kidney, and adrenal glands. Ectopic tissue is found in 2.7% of inguinal examinations in boys and none is detected in girls. Microscopic study of the adrenal cortex is divided into three zones: zona glomerulosa, zona fasciculata, and zona reticularis. The zona glomerulosa is less prominent in humans than in other species and is the production site of aldosterone. The zona fasciculata produces glucocorticoids and the zona reticularis produces androgens. The adrenal medulla produces estrogens and also produces adrenaline and noradrenaline in the presence of glucocorticoids. In addition there is morphological evidence of a close chromaffin-cortical cell interaction suggesting a possible paracrine role of the adrenal cortex in neuroregulation.

Adrenal gland physiology: The adrenal gland can be thought of functionally as two organs, the cortex and the medulla. Each has its particular physiology and its own secretory products derived from hormonal activation.

Adrenal cortex: The adrenal cortex produces a series of steroid hormones that carry out a series of actions, including salt retention, metabolic homeostasis, and sexual development.

The zona glomerulosa is the only source of principal mineralocorticoids such as aldosterone that regulates the absorption of sodium in the kidney, intestine, sweat glands, and salivary glands. The other zones can produce and secrete cortisol, the principal glucocorticoid in humans, and the principal androgens, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione. The initial step in the formation of these hormones is pregnenolone production.

The excess of one or various steroid products results in the signs and symptoms of Cushing’s syndrome, primary hyperaldosteronism (Conn’s syndrome), or adrenal carcinoma. Corticosteroid release regulation involves a complex interaction among the hypothalamus, the pituitary gland, and the adrenal gland.

Corticotropin-releasing hormone (CRH) is synthesized in the hypothalamus and is taken to the anterior pituitary gland in the blood. CRH is a lineal
peptide of 41 amino acids that stimulates the release of adrenocorticotropic hormone (ACTH). And finally, ACTH secretion is mutually related to the level of circulating cortisol. Adrenal androgen production in the zona reticularis and zona fasciculata is also under the influence of ACTH. In contrast, regarding adrenal glucocorticoids and androgens, the principal physiological control in aldosterone secretion is angiotensin II. ACTH control is secondary.

The release of renin and the formation of angiotensin II condition aldosterone secretion resulting in sodium retention in an attempt to restore kidney perfusion. In contrast, if there is sodium retention renin secretion is suppressed, aldosterone secretion drops, and urinary sodium is increased.

A second less potent aldosterone-releasing stimulus is potassium.17,18

**Hormonal actions:** Glucocorticoids are essential for life even after mineralocorticoid substitution. Glucocorticoids have a wide variety of effects on cellular metabolism including the accumulation of glycogen in the liver and muscles, increase in gluconeogenesis, the deterioration of peripheral glucose utilization, muscular atrophy and myopathy, immune inflammation-mediated osteopenia, and many interactions with other hormones.

Aldosterone represents 95% of mineralocorticoid adrenal activity and maintains the sodium/potassium balance. Active sites include the kidney, intestine, salivary glands and sweat glands. In all sites the effect is to stimulate sodium reabsorption and to increase potassium and hydrogen secretion through Na+-K+-ATPase activation in the membrane.19

**Metabolism:** In practice, 80% of cortisol is bound to corticosteroid-binding globulin, 10-15% is bound to serum albumin, and 7-10% is free. Elevated serum concentrations of testosterone and DHEA are characteristic of adrenal tumors and can cause hirsutism in women.20

**Adrenal medulla:** The adrenal medulla is composed of large chromaffin cells that principally secrete epinephrine, but also norepinephrine and dopamine. The phenylethanolamine N-methyltransferase enzyme (PNMT) that catalyzes norepinephrine methylation to epinephrine is almost exclusively localized in the adrenal medulla. If there is an excess of either norepinephrine or epinephrine production the lesion is almost always inside the adrenal gland and not in other chromaffin tissue sites. Studies on healthy humans indicate that in plasma dopamine represents 13% of free catecholamine, 14% of epinephrine, and 73% of norepinephrine.

Preganglionic sympathetic nerve stimulation during stress, pain, cold, heat, asphyxia, hypotension, hypoglycemia, and sodium depletion increases catecholamine release.21

**Catecholamine metabolism:** Catecholamines are rapidly eliminated from circulation with a half-life in plasma of less than 20 seconds. Catecholamines are degraded by the action of catechol-O-methyltransferase and monoamine oxidase or with the enzyme from the process degradation. The principal metabolite in urine is vanillylmandelic acid accompanied with metanephrines, normetanephrines, and their derivatives that often are measured in the evaluation of patients with pheochromocytomas.22

**Catecholamine actions:** Circulating catecholamines act in different organs with specific receptors, conditioning the diversity of symptoms that patients with pheochromocytomas are exposed to. In addition different tumors can produce different quantities of norepinephrine, epinephrine, or dopamine.

**Clinical symptoms:** Adrenal carcinoma symptoms can be grouped into three categories: a) symptoms due to the adrenal mass itself b) symptoms due to locoregional or distant dissemination or both, and c) endocrine symptoms of hyperfunction with active or inactive hormone overproduction. Approximately 60% of adrenal carcinomas are functioning tumors,23 although various steroid hormones produced are released by organic lesions. The most common are cortisol hormone, aldosterone, and sexual hormones, conditioning well-defined clinical syndromes. The majority of adrenal carcinomas can secrete various hormones and can change secretion according to size, growth rate, and histological differentiation.

Adrenal carcinoma has a common clinical presentation: glucocorticoid excess seen in about 45% of cases or a mixture of Cushing’s syndrome and virilization syndrome with glucocorticoid and androgen excess seen in 25% of cases.24,26

In Cushing’s syndrome there is a complex group of functioning symptoms derived from tumors with excess cortisol. Symptoms vary but the majority of patients have body trunk obesity, a round face, and thinning in the arms and legs. The skin becomes thin and fragile with frequent ecchymosis. Stretch marks can appear on the abdomen, thighs, buttocks, arms, and chest. Many patients present with fatigue, proximal muscle weakness, osteoporosis, high blood pressure, and glucose intolerance. Manifestations of irritability, anxiety, and depression can be frequent. Women normally present with hirsutism, dysmenorrhea, or amenorrhea, and rarely clitoromegaly. In men a decrease in fertility or absence of libido is frequent. Virilization tends to be more marked in Cushing’s syndrome. In adrenocortical cancer (ACC) there is virilization in women and feminization in men manifesting as gynecomastia, testicular atrophy, and low sperm count; feminization
has been observed in patients with androstenedione-secreting tumors converted peripherally to estrogens.24

There is a wide range of differential diagnoses that includes Cushing’s syndrome and virilization syndrome. The majority of patients with non-functioning carcinomas present with signs and symptoms related to tumor growth such as abdominal pain or flank pain or a feeling of fullness. Adrenal masses are often found incidentally by means of imaging studies carried out for different purposes.

Clinical classification: Adrenal carcinoma has been subclassified in a practical manner in accordance with its capacity to produce adrenal hormones. The majority of tumors segregate multiple compounds. A review of 62 patients with functioning tumors showed that 53% had Cushing’s syndrome, 21% had virilization alone, 10% had Cushing’s syndrome and virilization, 8% had feminization, and 5% had hyperaldosteronism.26

Incidental finding of adrenal masses: Adrenocortical carcinoma (ACC) represents 2% of tumors under 4 cm, 6% of tumors that are 4.1-6.0 cm and 25% of tumors that are over 6.0 cm. Malignant tumors tend to be larger than 6 cm. Consequently, solid adrenal lesions over 6 cm should be considered malignant until proven otherwise through exploration and adrenalectomy.

Follow-up of patients presenting with smaller nodules reveals that 5-25% of those nodules increase in size by at least 1 cm in a varying period of time. Malignancy risk is 1 in 1000 and up to 20% of patients can develop hormonal hyperfunction, especially if the tumor is larger than 3 cm.27,28

All patients with solid adrenal masses should undergo biochemical evaluation. Evaluation, including urinary and plasma metanephrine determination, is recommended to rule out pheochromocytoma. Steroid suppression is also recommended to rule out Cushing’s syndrome and serum potassium, plasma renin activity, and aldosterone proportion should be measured in high blood pressure patients.

Due to the probability that solid non-functioning lesions larger than 6 cm are malignant, they should be removed. Computed axial tomography can underestimate the size of adrenal gland lesion and therefore surgical exploration is suggested when the lesion is larger than 5 cm in CT or MR.

There is discrepancy among various authors in regard to carrying out surgical intervention or maintaining the more conservative watchful waiting in lesions of 4.0 cm (±1). Other authors include tumor elimination in smaller lesions (3 and 4 cm), in patients under 50 years of age, proposing surgery especially in the younger patients.28

Diagnosis, evaluation, and preoperative management: Careful endocrine evaluation before surgery is essential in adrenal carcinoma. Hormonal secretion pattern can signal a lesion’s potential malignancy and can affect surgical strategy. Autonomous cortisol secretion by the tumor is associated with risk of postoperative adrenal failure. Endocrine management is important in establishing tumor markers for recurrent tumor follow-up. Imaging studies using CT, MR and more recently positron emission tomography (PET-FDG) to observe adrenal mass size and appearance have been used to distinguish between benign and malignant lesions. None of these imaging techniques is specific for adrenal carcinoma but each modality is complementary to the others.

Adrenal mass size, measured by CT or MR, continues to be one of the best indicators of potential malignancy. Adrenal masses larger than 6 cm are highly suspicious of malignancy and should be surgically removed. Adrenal masses that are smaller than 3 cm have less malignant potential and can be left under follow-up observation. Tumors between 3 and 6 cm are the most challenging.

MR sensitivity for benign and malignant tumor differentiation varies from 81-89% and specificity is from 92-99%. A useful characteristic of MR is that it can identify tumor invasion in the inferior vena cava (IVC) enabling better surgical planning.29,30

Fine needle aspiration is only carried out if surgical approach is not possible and diagnosis cannot be made with CT or MR imaging.

11C-metomidate-PET is a new adrenal gland imaging method. Adrenal metomidate binds to 11-b-hydroxylase making it a potentially useful tool for distinguishing adrenocortical lesions from others. This method is available in the majority of research centers, especially in Europe.31-34 It is important to correct electrolyte abnormalities that can be the result of endocrinologically active adrenal tumor. In particular, in aldosteronoma, hypokalemia can make potassium repletion and potassium-saving diuretic administration necessary. High blood pressure should also be treated before surgery. In pheochromocytoma α-adrenergic blockers should be initiated two weeks before surgery. Phenoxybenzamine (10-40 mg 4 times a day, maximum 300 mg/day) is used, beginning gradually with a 10-20 mg dose twice a day. Some patients with tachycardia can benefit from concurrent β-blocker administration. As an alternative, selective α1-blockers such as prazosin or doxazosin can be used. Intraoperatively, high blood pressure should be treated with nitroprusside or a short action β-blocker such as esmolol. Volume repletion is important for preventing hypotension secondary to vasoconstriction loss after pheochromocytoma elimination. In patients with Cushing’s syndrome, both electrolyte abnormalities and hyperglycemia must be corrected before surgery. These patients can...
benefit from adrenolytic agents such as mitotane or aminoglutethimide.36

Mechanical intestinal preparation is useful for open surgery or transperitoneal laparoscopy. Intestinal preparation is not necessary in retroperitoneal surgery. All patients should receive appropriate preoperative antibiotics.

**Surgical treatment:** Complete surgical resection is the only potentially curative treatment for ACC. Other published studies have reported that 5-year survival rates vary from 32-48% with a mean survival of 2 years in patients that underwent complete resection compared with mean survival of less than 1 year for patients that underwent incomplete resection. 36,37 The presence of IVC invasion should be considered to be tumor extension rather than metastatic disease. In such cases surgical procedure should be more aggressive, attempting to completely eliminate intravascular lesion. Total tumor excision indication in patients with stage III and IV disease continues to be controversial. Palliative surgical treatment does not influence survival in these patients. Tumor invasion into the celiac trunk axis, aorta, or proximal to the superior mesenteric artery represents clear evidence of locally non-resectable tumor. 38

**Open adrenalectomy:** Open adrenalectomy can be carried out through either transperitoneal or retroperitoneal approach at the transperitoneal, subcostal, or thoracoabdominal midline. Advantages of transperitoneal approach are better exposure of and excellent access to larger tumors. The principal disadvantages are prolonged postoperative intestinal paresis and difficult exposure in the morbidly obese patient. Retroperitoneal approach provides the same results except in postoperative intestinal paresis and can result in shorter hospital stay. Open surgery is recommended when there is any suspicion or certainty of adrenocortical malignancy to facilitate maximum exposure for complete surgical resection and to minimize tumor dissemination risk.

**Laparoscopic adrenalectomy:** Due to high rate of local recurrence and intraperitoneal diffusion, laparoscopic adrenalectomy should be reserved for resection of presumed benign cortical tumors (<3 cm).39,40 However, if CT indicates that there is no local invasion and the lesion is not excessively large, laparoscopic adrenalectomy is possible. Suprarenal vein or vena cava abnormality is an absolute contraindication for laparoscopic surgery. Currently laparoscopic adrenal surgery is considered to provide excellent results and has become the criterion standard.

**Robotic adrenalectomy:** Robotic surgery is becoming more widely used in this type of surgery and with good results, with the disadvantage of its high cost. 41

**Radiofrequency ablation:** Radiofrequency ablation has been used for the successful treatment of adrenal lesions, especially adrenal metastases or ACC metastasis. 42

**Cryoablation:** Clinical experience with this resource has been quite limited. Experiments on dogs have confirmed it as effective treatment for the adrenal gland. 43

**Radiotherapy:** Radiotherapy has been considered ineffective by the majority of experts as adrenal carcinoma treatment. It is limited to palliative treatment of non-resectable tumor or to metastatic disease with poor results. 44,45

**Chemotherapy:** Mitotane is the only medication approved by the FDA for adrenal carcinoma treatment. It was developed in 1960 as the insecticide DDT. It affects the adrenal cortex causing necrosis. It has a cytotoxic effect on adrenocortical cells producing focal degeneration of the zona fasciculata and particularly the zona reticularis, while changes in the zona glomerulosa are relatively slight. Antitumor activity is produced at a plasmatic concentration of 14 mg/L or higher but toxic secondary effects occur at a level above 22 mg/L.

There are frequent reversible adverse effects in the gastrointestinal system or the central nervous system. Concomitant glucocorticoid administration is recommended. Mitotane has been used in adjuvant fixation after curative therapy or complete surgical resection. Average objective response rate of the tumor to mitotane is approximately 32%. 44

**Cytotoxic chemotherapy:** Experience with cytotoxic chemotherapy is limited. It has not been adequately evaluated due to the rareness of the disease. Cisplatin-based chemotherapy is active in ACC. Various chemotherapeutic regimens have been combined with mitotane and there has been a response rate of 49% with mitotane-doxorubicin-etoposide-cisplatin, but also significant toxicity. Response rate of cisplatin-based chemotherapy is 20-30%. The combination of mitotane-streptozotocin has a 36% objective response rate. 46

In 1977 the United States Department of Health and Human Services and the Surveillance, Epidemiology and End Results (SEER) Program created a classification, modified by Sullivan in 1978, considering four stages:

1. **Localized disease:** Tumor that after extirpation is confined to the adrenal gland and does not manifest metastasis. Less than 5% of adrenal carcinoma is in this category.
2. **Regional disease:** Tumor affecting contiguous tissues and neighboring organs including lymph nodes, but with no metastasis. Between 20% and 30% of tumors belong to this group.
3. Distant disease: Tumors that are metastasized when diagnosed. This group makes up 40-60% of tumors.

4. Recurrent disease: Appearance of local recurrence or distant dissemination after theoretically curative primary tumor resection. Metastasis: Except for testosterone-secreting tumors, ACCs are very malignant and present with local as well as hematematic dissemination and have low survival rates. The most common metastatic sites are the lungs, liver, and lymph nodes. Autopsy studies revealed 132 cases of metastases to the lungs (60%), liver (50%), lymph nodes (48%), bone (24%), pleura and heart (10%). In addition these tumors frequently extend directly into adjacent structures, especially the kidney, and can involve the vena cava or the splenic vein.

Prognosis: The majority of patients present with advanced stage disease. In almost 70% of adrenal carcinoma cases there has been disease propagation beyond the adrenal gland at the time of diagnosis. Approximately 32% of patients are diagnosed with stage I and II disease and 68% with stage III and IV.

Complete resection offers curative opportunity in patients with locally advanced tumors and resectable disease. Local recurrence or metastasis after radical resection occurs in 80% of patients. Other series report that overall survival rate was higher in patients that responded to mitotane.

Compilation of adequate studies for correlating population size or validating any given prognostic factor (molecular or clinical) among patients has been limited due to the rareness of the disease. In addition, distant metastasis, advanced age (>45 years) and incomplete resection were determining factors for survival (Table 1).

Histopathological diagnosis: Pathological diagnosis should be carried out by experts. Benign and malignant adrenal tumor differentiation is difficult and is based on macroscopic and microscopic characteristics.

Macroscopic: Weight, hemorrhage, tumor capsule invasion, and vascular invasion are evaluated. Weiss score is the most widely used classification method for microscopic characteristics suggestive of malignant tumor and enumerates nine histological criteria:

1. High mitosis rate (>5 per 50 high field).
2. Atypical mitoses.
3. Venous invasion.
4. High nuclear grade (Fuhrman III to IV).
5. Absence of cells with clear cytoplasm (<25% of cells).
6. Diffuse growth pattern (more than a third of the tumor).

7. Necrosis.
8. Sinusoidal invasion.

Three or more of these aspects are necessary for adrenal carcinoma diagnosis. Additional information obtained from immunohistochemistry is also important. Various studies have shown the value of the Ki67 stain in differentiating benign lesions from malignant lesions. Melan-A (MART-1) is a gene that encodes an antigen recognized by cytotoxic T cells. Although MART-1 has been said to be restricted in its expression for melanocytes, researchers at Memorial Sloan-Kettering Cancer Center have reported that it has diagnostic potential that is applicable to ACC. Once melanoma is ruled out, immunoreactivity for A103 (a MART-1 antibody) rules out any other possibility of cancer that can enter into adrenal carcinoma differential diagnosis.
Other markers such as D11, inhibin-alpha, Melan-A and chromogranin-A help define whether the tumor is adrenocortical or rule out an originating tumor. New markers (LOH in 17p13, with IGF-2 overexpression, cyclin E) have been proposed to separate malignant adrenal gland lesions from benign ones.  

International epidemiology: In regard to adrenal gland carcinoma there is no objective information available in the archives of the World Health Organization (WHO). It is obvious that this pathology is not among the primary causes of disease. The international literature states that incidence is 1 case per 1.7 million individuals. It is generally reported in adults with a mean age of 44 years and is in a potentially malignant and aggressive reproductive stage with a 5-year survival rate of about 40%.

National epidemiology: There is no information on this pathology in the Epidemiology Division of the Mexican Health Department (Dirección General de Epidemiología de la Secretaría de Salud de México). In Mexico only sporadic cases have been reported and the present article was developed using the international references cited in the bibliography.

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