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Review

Adrenocortical carcinoma: What the surgeon needs to know. Case report and literature review

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ABSTRACT

Adrenocortical carcinoma is a rare and aggressive cancer and its prognosis is frequently unsatisfactory. Due to its rarity there's a lack of prospective randomized studies. Without experience in the approach of this kind of tumor, managing becomes challenging and, moreover, we have only few recommendations, based on weak evidence. We report a case that has some peculiarities and is an excellent food for thought. Then we deal with a literature review to highlight and summarize most significant aspects of epidemiology, clinic, diagnosis, therapy and prognosis in an exquisitely surgical point of view.

1. Introduction

Primary carcinoma of the adrenal cortex (Adrenocortical Carcinoma, ACC) is a rare and highly aggressive cancer with a frequently dismal prognosis. It affects worldwide approximately 1–2 new patients per million people a year [1–10], accounting for 0.2% of cancer-related deaths in the United States [7,8]. Due to the high and increasing incidence of benign adrenal lesions and incidentalomas, differential diagnosis becomes essential but it's not ever clear preoperatively [5,11]. With respect to the ability of hormone production, ACCs can be functioning or non-functioning tumors [12,13]. The rarity of the disease and its dismal prognosis require a multidisciplinary approach to improve results [12]. Indeed diagnosis is often delayed, many patients present at advanced stages and the tumor is quite unresponsive to chemotherapy [14–25]. Recurrences, both local and metastatic, are reported in up to 85% of patients after resection [26,27], and overall the prognosis remains poor, with a 5-year survival rate of 16%–47% [1,5,24,28]. Radical surgical resection, avoiding tumor rupture, remains the mainstay of therapy and the most important prognostic factor [14–29]. The very low incidence of the disease has precluded several statistically significant studies that would be needed to improve the management of patients with ACCs. In fact most of recommendations are derived from retrospective series or expert opinions, whereas only few of them are based on prospective clinical trials [1–29]. In order to emphasize several issues of differential diagnosis and treatment, we describe the peculiar case of a 53-old-man with a gigantic ACC that we operated with excellent results; in addition, we report the results of our literature review to summarize all the existing knowledge of surgical interest on this topic.

2. Case report

A 53-year-old man was found to have a large mass in the left upper abdomen. He was 177 cm tall and weighed 90 kg. He had always been healthy but, during the last 3 months, he was complaining dull, vague abdominal pain localized to the left quadrants. He didn't report colicky pain, nor nausea, vomiting, fever, weight loss. Vital signs were normal. Abdominal inspection highlighted a large swelling amid left quadrants and the palpation revealed a huge lump of around 20 cm × 20 cm, that started from the left hypochondrium and exceeded the transverse umbilical line. It was smooth, firm-to-hard in consistency and was not moving with respiration. Ultrasonography showed left kidney caudally and medially displaced by a large, roundish, hypo-isoechoic solid mass at the upper pole of the left kidney. The chest radiograph did not reveal any abnormality. CT scan showed a gross solid mass with inhomogeneous density, 21 × 18 cm, closely adjacent to the pancreas' tail, inseparable from the psoas muscle. There were no

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signs of lymphadenopathy or metastasis. The radiologist concluded that it was a renal heteroplasia. Functioning of both kidneys was normal on intravenous urography. We measured levels of adrenal hormones (glucocorticoids, mineralocorticoids, sexual steroids and steroid precursors, catecholamines, metanephrines) and all were normal. Bone scintigraphy was performed to exclude skeletal metastases and it was negative. A fine needle biopsy was performed and it just identified malignant cells but didn't raise the suspicion of adrenal origin's mass. The case was further discussed in a multidisciplinary team meeting comprising urologists, radiologists, and oncologists: the diagnosis of renal heteroplasia was considered as the most likely. The patient signed a consent for radical left nephrectomy and underwent it. We performed a laparotomy, using a large median anterior approach. Peroperatively the lesion appeared as a single mass, strongly adherent to the upper pole of left kidney, without any cleavage plan. Histopathology confirmed the diagnosis of non-functional ACC of 24 × 21 × 19 cm. It showed few mitosis (2–3 × 30 HPF). Left kidney measured 14 × 10 × 8 cm and its parenchyma was free from cancer. The patient's postoperative course was complicated by acute renal failure but it was successfully controlled by drugs. He was discharged on the 30th postoperative day in good conditions. The medical oncologist, radiologist and endocrinologist followed the patient for the next 60 months. No adjuvant treatment was initiated. He has been regularly followed-up and now, after 14 years, he's alive and well. The case described is shown for his own peculiarities because, normally, the prognosis is much more ominous, especially with so advanced cancers. This underlines the importance of mitotic index and, more generally, the aggressiveness of the tumor, which, in the case we described, were certainly not very high.

3. Literature review

3.1. Materials and methods

A literature search, using the Medline/PubMed database for full-length papers, was performed up to 31 January 2014. Entry terms were: adrenal cancer, adrenocortical carcinoma, treatment, surgery, laparoscopy, staging and prognosis. Out of the retrieved records, those pertinent to the objective of the present review were selected. The corresponding full-length articles were examined carefully and those articles with clinical relevance were considered for analysis. Review articles and the most recent guidelines and consensus reports on management of adrenal incidentalomas and ACC by the European Network for the Study of Adrenal Tumours (ENSAT), American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons, were also analyzed and critically reviewed.

3.2. Epidemiology

ACC is a rare solid tumor [6,24]. The exact incidence is difficult to determine and most authors estimate an incidence of 1–2 per million population [1,5,24,30]. In contrast, adrenal incidentalomas have a prevalence of at least 3% in a population >50 yr of age (ACC constitute <5% of all adrenal incidentalomas) [31–35]. However, ACC prevalence depends on the size of the tumor, accounting for 2% of lesions <4 cm, 6% of lesions 4–6 cm, and 25% of lesions >6 cm [36]. ACC affects women more commonly than men with a ratio of 1.5:1 [1,25,37–41]. Females with ACC are more likely to have functional tumors. Men with ACC tend to have functional tumors before the age of 20 years and non-functional tumors after the age of 40 years [3,13,14]. Some reports indicate a bimodal age distribution, with a first peak in childhood (<5 years) and a second higher peak in the fourth and fifth decades [3,11,13,24,39,40]. In adults, the mean age of diagnosis is 45 years [24]. The incidence of ACC is 10–15 times higher in children in southern Brazil, which is related to an inherited germline p53 mutation [42,43]. Indeed, while ACC most frequently arises sporadically and without known pathogenesis, it has been also associated with a number of familial tumor syndromes, including multiple endocrine neoplasia type 1 or MEN-1 (mutation of the MEN1 tumor suppressor at 11q13), Li-Fraumeni syndrome (p53 mutation on 17p13), Beck-with–Wiedemann syndrome (alterations of gene clusters on 11p15.5 and 15q11–13), and Carney complex (mutation of PRKAR1A gene at 17q23–24 or mutations at 2p16) [44,45].

3.3. Clinical presentation

ACC can be asymptomatic or can present with symptoms of hormone excess or complaints referable to the mass [3,11]. Generally ACC present an immature steroidogenesis and almost all of these tumors exhibit hormonal precursor excess but, approximately, 60% of all ACC patients will present with hormone-related signs and symptoms (so-called “functional tumors”) [3,11]. Around 60% of cases of functional tumors present with signs and symptoms of Cushing's syndrome that most commonly is rapidly progressing [39,45,46]. Indeed rapid course of illness is highly suspicious of ACC or should suggest ectopic ACTH secretion by a malignant neoplasm. Classic signs of Cushing's syndrome are truncal obesity, facial plethora, rounded “moon” facies, thinning of skin, easy bruising, muscle weakness, supraclavicular fat pads, menstrual irregularity, hypertension, glucose intolerance up to frank diabetes mellitus, osteoporosis with fractures, renal calculi and psychiatric disturbances. Androgen-secreting ACCs in women may present with virilization and associated hirsutism, deepening of the voice, breast atrophy, male pattern baldness, acne, androgenetic effluvium, clitoral hypertrophy, oligomenorrhea, and altered libido. These androgen-related signs and symptoms can, sometimes, coexist with Cushing's syndrome while, most commonly, they don't. Also in this case, the rapid development of the symptoms should suggest ACC-related androgen excess, instead of more common reasons, like polycystic ovary syndrome. Estrogen-secreting adrenal tumors are less frequent (5–10% of male patients), but if present are almost pathognomonic for ACC. These tumors may result in feminization with gynecomastia, breast tenderness, decreased libido, and testicular atrophy. Symptoms of isolated mineralocorticoid (aldosterone) excess with severe hypertension and hypokalemia are rare (2–5% of all functional tumors) [47,48]. Patients with a non-functional ACC usually present with symptoms related to local mass: abdominal discomfort, nausea, vomiting, abdominal fullness, indigestion, back pain. In these cases, the tumors are mostly larger than 10 cm in diameter. Non-specific symptoms such as fever, weight loss, and loss of appetite are less typical in patients with ACC.

3.4. Diagnosis

The initial evaluation of all patients with adrenal tumors >1 cm should determine whether the tumor is functional or not and should define the extent of disease [49,50]. In 2006 standards for diagnostic procedures in patients with suspected or established ACC have been proposed by the ACC working group of the European Network for the Study of Adrenal Tumors (ENSAT) and endorsed by colleagues outside of Europe [51]. They may be useful to outline the diagnostic iter although the evidence level is low. Endocrine assessment prior to surgery is mandatory, for all patients with suspected ACC, as it is for all adrenal tumors and the pattern of secretion is useful for more than simply establishing the adrenocortical origin of the tumor [49,50]. Endocrine assessment is

essential to establish the adrenocortical origin of the tumor but, moreover, hormones may serve as tumor markers during follow-up. Furthermore we must consider that an excess of cortisol, if undiagnosed, may lead to adrenal insufficiency after surgery. Finally the steroid pattern is very important because, in general, co-secretion of different steroids may be highly suspicious for ACC [28,45]. Table 1 shows recommendation of the ACC working group of the European Network for the Study of Adrenal Tumors (ENSAT) for the hormonal workup of patients with suspected or proven adrenocortical carcinoma. Following these hormonal investigations only a minority of ACCs are hormonally inactive. Using gas chromatography/mass spectroscopy (GC/MS) for sophisticated urinary steroid analysis, hormonal activity can be demonstrated in almost all cases (more than 95%) of ACC [52]. However, due to low efficiency of intratumoral steroidogenesis or the exclusive secretion of steroid precursors, tumors may appear clinically as hormonally inactive. Careful search for abnormal adrenal steroid secretion reveals increased hormone production in up to 80% ACCs, even in tumors that may appear clinically as non-functional [45,46]. In these cases it is important to search for the precursor steroid and avoid to inappropriately classify a tumor as non-functional or, worst, to misdiagnose a tumor of the adrenal region as an ACC. In all patients with adrenal tumors, a pheochromocytoma has to be excluded prior to surgery or any other invasive procedure by determination of metanephrines in plasma or urine. Nowadays, because of more frequent and improved abdominal imaging, an increasing percentage of ACC is discovered incidentally [35,48,53,54]. Size and appearance on radiologic imaging studies are fundamental to distinguish benign and malignant lesions. For differential diagnosis of an adrenal mass, computerized tomography (CT) and magnetic resonance imaging (MRI) are currently equally effective [55–57]. Surely size is the strongest predictor of malignancy. Only 2% of tumors <4 cm are found to be ACC, while 6% of tumors 4 < 6 cm, and 25% of tumors >6 cm [34,58]. In fact, according to the NIH consensus of 2002, patients with tumors >6 cm should be treated surgically [36]. Identification of smaller ACCs can be challenging and, when a small lump is found, imaging follow-up is mandatory to detect early modifications. Various radiologic techniques are employed, in addition to size, to discriminate between benign and malignant lesions, as unenhanced density characteristics (Hounsfield units, HU) [59] or intravenous contrast wash-out characteristics [60–62]. Each radiologist, according to his own experience, could use the methods he considers most appropriate. CT and MRI are also fundamental for determining resectability and relationships to adjacent structures. Probably MRI is the best method to determine invasion into adjacent organs and into the inferior vena cava. 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), especially when used in combination with CT, may be useful in patients with suspected ACC [63–65] but it raises several issues of differential diagnosis with adenomas or phaeochromocytomas [57,64]. There is no agreement on the appropriateness of fine needle biopsy. Some authors argue that, given the risk of needle-track metastasis [55,56], a biopsy should be performed only in case of inoperability to target the medical therapy or in patients with a history of cancer, a suspect adrenal metastasis and no other signs of metastatic disease. Accuracy in distinction of adenomas versus metastasis is quite high (90%) but it's not the same in distinguishing between adenoma versus carcinoma of adrenal gland [67]. Furthermore, due to the high false negative rate, a benign cytologic diagnosis does not rule out malignancy. However, a biopsy without prior exclusion of a phaeochromocytoma constitutes malpractice [68,69]. It should be noted that on the patient of our case-report we performed a biopsy because we suspected, preoperatively, that the lump was belonging to the kidney.

3.5. Staging

TNM is the classic method of staging tumors and it is used as well in the case of ACC. Staging prior to surgery is indispensable for excluding distant metastases. About 30% of patients have metastasis at the onset and lung and liver are the most frequent sites. Radical surgical resection, when can be achieved, remains the mainstay of therapy and the most important prognostic factor [14–29] therefore it is mandatory to know preoperatively whether distant metastasis are present or not. To achieve a good staging several systems have been proposed. In 2004, the Union Internationale Contre Cancer (UICC) and the World Health Organization (WHO) published a staging system [70] but it had some prognostic limitations, especially between stages III and IV. Thus ENSAT, in 2008, proposed a revised TNM classification [71] that was confirmed, in 2010, in an independent cohort from the United States [72]. The ENSAT staging system is superior to other proposed staging systems in predicting clinical outcome of patients with ACC. In this staging system, stage III is defined by tumor infiltration in surrounding tissue or tumor thrombus in vena cava/renal vein or positive lymph nodes, whereas stage IV is defined only by the presence of distant metastasis. Table 2 shows differences between these staging systems. Preoperatively, CT of the chest and abdomen is mandatory to find out distant metastases. MRI could be used but cannot substitute for a chest CT for small lung lesions. FDG-PET may detect distant metastases not apparent on CT or MRI [73,74]. If there

Table 1
Recommended diagnostic work-up for ACC.

Hormonal work-up in patients with suspected or proven adrenocortical carcinoma (ACC) recommendations of the ACC working group of the European Network for the study of adrenal tumors (ENSAT)	
Glucocorticoid excess (minimum three of four tests)	- Dexamethasone suppression test (1 mg, 23:00 h) - Excretion of free urinary cortisol (24-h urine) - Basal cortisol (serum) - Basal ACTH (plasma)
Sexual steroids and steroid precursors	- DHEA-S (serum) - 17-OH-progesterone (serum) - Androstenedione (serum) - Testosterone (serum) - 17b-estradiol (serum, only in men and postmenopausal women)
Mineralocorticoid excess	- Potassium (serum) - Aldosterone/renin ratio (only in patients with arterial hypertension and/or hypokalaemia)
Exclusion of a phaeochromocytoma (minimum one of three tests)	- Catecholamine excretion (24-h urine) - Metanephrine excretion (24-h urine) - Meta- and normetanephrines (plasma)

ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulfate.

Table 2
Staging systems' comparison for ACC.

UICC/WHO 2004	STAGE	ENSAT 2008
T1, N0, M0	I	T1, N0, M0
T2, N0, M0	II	T2, N0, M0
T1-2, N1, M0	III	T1-2, N1, M0
T3, N0, M0		T3-4, N0-1, M0
T3, N1, M0	IV	Any M1
T4, N0-1, M0		
Any M1		

UICC = Union Internationale contre le cancer.
WHO = World Health Organisation.
ENSAT = European Network for the Study of Adrenal Tumours.
T1 = tumor ≤5 cm; T2 = tumor >5 cm; T3 = tumor infiltration in surrounding tissue; T4 = tumor invasion in adjacent organs (ENSAT = also venous tumor thrombus in vena cava or renal vein); N0 = no positive lymph nodes; M0 = no distant metastases; N1 = positive lymph nodes; M1 = presence of distant metastasis.

is clinical evidence for bone metastases a bone scintigraphy may settle the question, while, in suspected brain lesions cerebral imaging is required.

3.6. Therapy

In patients with localized adrenal tumor, suspicious for ACC, surgical resection should be considered. Suspicious features to consider are: tumors size >4 cm, functional tumor, radiologic suspicious characteristics (see above). Local invasion and lymph node involvement are very evocative. Complete resection is the only curative option for localized ACC and should be pursued aggressively by a qualified oncologic surgeon [75]. A margin-free complete resection (R0 resection), as well as leaving the adrenal capsule intact during resection, are crucial for achieving long-term cure [1,49]. Routine removal of the adjacent kidney is not necessary, thus, for tumors not invading the kidney, the surgeon should perform a kidney-sparing adrenalectomy [76]. For tumors invading surrounding tissue or organs, concomitant resection of kidney, liver, spleen, pancreas, stomach, colon and wall of the vena cava should be considered [66] even if, in primary ACCs, it is quite infrequent that the tumor invades the liver or adjacent kidney. Obviously this is not always predictable during surgery, as in our case in which the tumor was strongly adherent to the kidney, such as to look like a single mass, although histological examination has then denied the spread to the renal parenchyma. For large, right-sided lesions, the inferior vena cava (IVC) is often involved with tumor. The presence of a tumor-thrombus in the inferior vena cava or the renal vein is compatible with complete tumor resection [5,77]. If tumor extraction is not feasible, the infrarenal IVC can generally be resected without replacement. Managing of a tumor involving the suprahepatic IVC, right atrium, or superior vena cava (SVC) could be very challenging. Although is known that ACCs often spread via lymphatic drainage, the importance of regional lymph nodes resection has always been underestimated. A recent study suggests that locoregional lymphadenectomy reduces risk for tumor recurrence [79]. Open surgery is still the standard for all patients with resectable ACC and it is the required procedure for tumors >10 cm and for all invasive tumors [78]. We recommend a wide anterior approach which allows access to sites of potential invasion and metastatic spread and to regional lymph nodes. Some argue that postoperative steroid administration is necessary since it is difficult to predict whether the contralateral adrenal gland will be able to compensate for. In fact it's an old concept that adrenal insufficiency is a major cause of postoperative morbidity and mortality [99]. Over the last two decades, laparoscopy has emerged as the preferred approach to the adrenal. The role of laparoscopic adrenalectomy (LA) in suspected cases of adrenal malignancies is a matter of debate. There were, in the past, some disastrous experiences [80,81] in terms of oncologic results but several contemporary reports now suggest that laparoscopy can be performed with oncologic outcomes equivalent to open surgery [82–84]. We think that laparoscopy is a feasible option for tumors <10 cm and without evidence of invasive disease but only when performed by a trained laparoscopic surgeon with experience in ACC [85–87]. In cases of metastatic disease, surgery is still the first-choice treatment, when complete resection of the primary tumor and all metastases is feasible and particularly in patients with endocrinopathy in which debulking can alleviate symptoms. At times, limited hepatic resections, omental and peritoneal debulking, and pulmonary metastasectomy should be considered. For larger tumors or when one plans a pulmonary metastasectomy, a thoracoabdominal approach may be necessary. Liver metastases can be treated with partial hepatectomies. An alternative to surgery of liver metastases <5 cm is radiofrequency ablation [88]. Reoperations are feasible for local recurrence or single metastases but we think that it should be considered if sufficient time (at least 6 month) have elapsed since the intervention and if the new lesions seem to be completely excised [89,90]. Some authors argue that repeated radical resections seem to improve survival [89,90] but the extent of benefit is difficult to determine due to lack of randomized trials [22,91–93]. Adjuvant therapy is recommended for most patients because of high recurrence rates, even after radical resection [26,27]. In a large recent retrospective study, adjuvant mitotane prolonged disease-free survival (DFS) and overall survival (OS) in comparison to two independent control groups [94]. Radiation therapy has shown his usefulness in several scenarios, i.e. to control local recurrence risk (especially in R1-R2 resections) or, with palliative intent, in the treatment of unresectable lesions or to control local symptoms [38,95–97]. The role of cytotoxic chemotherapy is continuously under investigation. The recommended first-line cytotoxic treatment regimens are etoposide, doxorubicin, cisplatin plus mitotane [98], or streptozotocin plus mitotane [92]. In most patients mitotane abolish steroid secretion but, since uncontrolled hormone secretion might worsen significantly quality of life and may even be life threatening, sometimes additional measures are required to control endocrine symptoms, such as adrenostatic drugs (metyrapone, etomidate). About follow-up, it's repeated every 3 months for the first two years, including abdominal CT or MRI and hormonal markers, and kept on for at least 10 yr.

3.7. Prognosis

Tumor stage is still one of the best available prognostic factors with a 5-year survival of 84% for stage I, 63% for stage II, 51% for stage III and 15% for stage IV [28]. Overall 5-year survival, after complete resection, in different series has ranged between 16% and 47%, while the median survival is less than one year in case of incomplete resection [6,38,71,82,103]. Large tumor size (diameter >12 cm) has been associated with inferior survival even after complete resection [27]. In addition, the mitotic rate and other histologic and immunohistologic parameters (i.e. tumor necroses, atypical mitotic figures, Ki67 index, mutated TP53, etc.) have high prognostic value [27,100–102]. As we have already said, patient we have described had a very low mitotic rate, despite huge dimension and, in our opinion, this was a crucial aspect of his extraordinarily good prognosis.

4. Conclusions

Adrenocortical carcinoma is a rare and difficult to cure cancer. Despite the studies, many of which are still ongoing, and

continuous efforts, unfortunately, the prognosis remains unacceptably poor. In order to approach the treatment of this cancer a multidisciplinary team is required. However, current knowledge leads to believe that we can achieve more and more encouraging results. New prospective trials investigating the role of laparoscopic surgery and the value of lymphadenectomy are mandatory. As emphasized in this review, to get the best results, a sound knowledge and a previous experience of this disease are needed and patients should always be sent in high-volume referral centers. Scientific collaboration between these centers will lead to future improvements.

Conflicts of interest

All Authors have no conflict of interests.

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Ethical approval

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Author contribution

Giacomo Benassai: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Vincenzo Desiato: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Gianluca Benassai: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Tommaso Bianco: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Luigi Sivero: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Rita Compagna: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Gabriele Vigliotti: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Gennaro Limite: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

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