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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