Spontaneously metachronous ruptures of adrenocortical carcinoma and its contralateral adrenal metastasis

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Abstract Adrenocortical carcinomas (ACCs) are rare neoplasms. In spite of its rarity, ACCs are the second most lethal endocrine cancer after anaplastic thyroid carcinomas. Currently, the only chance for a cure is an early diagnosis and a radical surgical resection. We present the case of a previously unreported bilateral adrenal hemorrhage occurring in a 59-year-old Caucasian male who was admitted to our surgical division with the diagnosis of a right retroperitoneal spontaneous hemorrhage. Imaging revealed a 10-cm ruptured right adrenal mass with no other abdominal lesions, endocrine screening results were normal, and a right adrenalectomy was performed. Pathology revealed a ruptured ACC. The postoperative period was uneventful and the patient was discharged. While recovering, 3 weeks after the operation, the patient showed the same symptoms on the contralateral side. Imaging once again revealed a retroperitoneal hemorrhage due to a 5-cm ruptured left adrenal mass. Endocrine screening showed a frank peripheral hypercortisolism and imaging showed a huge metastatic dissemination to the liver, lungs, and retroperitoneal space. An urgent left adrenalectomy was performed and pathology showed a metastatic ruptured ACC. The patient was placed in substitutive therapy but never recovered and died of penta lobar pneumonia on postoperative day 31. An extensive review of the current literature on the issue was performed. ACC is confirmed to be a lethal cancer. Rupture is the rarest clinical presentation

and appears to be caused by the tumor's growth rate more than the tumor dimensions itself. The use of endocrine screening on such hemodynamically unstable patients is questionable.

Keywords Adrenocortical carcinoma · Spontaneous rupture · Retroperitoneal hemorrhage · Endocrine cancer · Metastatic adrenal carcinoma

Introduction

Adrenocortical carcinomas (ACCs) are rare neoplasms. Autopsy series report an overall incidence of 2.5 cases per million [1]. ACCs account for about 0.2 % of all cancer-related deaths [2]. In spite of its rarity, ACCs are the second most lethal endocrine cancer after anaplastic thyroid carcinomas [3]. Currently, the only chance for a cure is an early diagnosis with a radical surgical resection [3, 4]. Nonetheless, the prognosis is very poor with a UICC/ENSAT (European Network for the Study of Adrenal Tumors) stage-adjusted 5-year survival rate of 82 % for stage I patients, 61 % for stage II, 50 % for stage III, and 13 % for stage IV. Diagnosis may be difficult sometimes and the pathologic response is based upon the Weiss criteria (Table 1). Sporadic forms are the wide majority of cases, but in a few instances, ACC may rise in the setting of rare hereditary forms as Li–Fraumeni syndrome, Beckwith–Wiedemann syndrome, MEN 1, Carney complex, and congenital adrenal hyperplasia. Diagnosis is often occasional or driven by endocrine symptoms (mostly Cushing syndrome) in about half of the cases [4] or by non-specific symptoms due to the local tumor growth or invasion of adjacent organs. One rare presenting symptom of an ACC is a spontaneous retroperitoneal hemorrhage, but the

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Table 1 Weiss criteria for definition of adrenal mass malignancy. The lesion should meet at least three criteria to be claimed as malignant

1. Nuclear grade III or IV based on criteria of Fuhrman
2. >5 mitotic figures/50 HPF (40× objective), counting 10 random fields in area of greatest number of mitotic figures on 5 slides with greatest number of mitoses
3. Presence of atypical mitotic figures (abnormal distribution of chromosomes or excessive number of mitotic spindles)
4. Clear or vacuolated cells comprising 25 % or less of tumor
5. Diffuse architecture (more than 1/3 of tumor forms patternless sheets of cells; trabecular, cord, columnar, alveolar or nesting is not considered to be diffuse)
6. Microscopic necrosis
7. Venous invasion (veins must have smooth muscle in wall; tumor cell clusters or sheets forming polypoid projections into vessel lumen or polypoid tumor thrombi covered by endothelial layer)
8. Sinusoidal invasion (sinusoid is endothelial lined vessel in adrenal gland with little supportive tissue; consider only sinusoids within tumor)
9. Capsular invasion (nests or cords of tumor extending into or through the capsule with a stromal reaction); either incomplete or complete

incidence of this particular presentation is almost anecdotal in the worldwide literature. Here, we present the case of a young adult Caucasian male who experienced a metachronous bilateral retroperitoneal hemorrhage due to a primary ACC on both adrenal glands. To our knowledge, this is the first report on this particular presentation of a metachronous bilateral ACC.

Case Report

On January 21, 2011, a 59-year-old Caucasian male was admitted to our surgical division with the diagnosis of a retroperitoneal right spontaneous hemorrhage. The patient's past medical history was irrelevant. The patient referred to a previous two-week history of continuous pain in the right lumbar area treated by analgesics. He described, 2 h before his referral, the sudden onset of progressively increasing pain localized in the upper right abdomen and of an overwhelming dizziness with some limited altered mental status. Upon admission in the emergency setting, hemodynamics were stable, arterial blood pressure (ABP) was 100/75 mmHg, heart rate (HR) was 98 bpm, respiratory rate (RR) was 18 breaths per minute, and peripheral O₂ saturation was 97 %. Signs of hypovolemic shock reverted after rapid crystalloid infusion. On physical examination, only a moderate tenderness in the right abdomen was noted. Blood tests were consistent with a mild anemia, and the platelet count was $136.000 \times 10^9/L$. The bedside ultrasound examination showed a small amount of free fluid in the Morrison area with a 10-cm mass in the subdiaphragmatic right space. A contrast-enhanced CT scan of the abdomen showed a retroperitoneal hemorrhage originating from a huge right adrenal mass (Figure 1), no lesions were detected elsewhere, particularly in the contralateral adrenal region. As the patient's hemodynamics remained stable, we performed a complete adrenal function screening resulting in: normal medullary

adrenal function, normal aldosterone and renin blood levels in either the upright or recumbent position, normal adrenocorticotrophic hormone (ACTH) with a moderately increased cortisol level at 8 a.m. [722.4 nmol/L (n.v. 119–618)], and dehydroepiandrosterone (DHEA) was threefold the normal level. In the same afternoon, the patient again showed signs of hypovolemia and underwent emergent surgery via a transverse laparotomy. During the surgical exploration, a huge fractured mass grossly well capsulated and with no signs of local invasion was found in the right adrenal gland. A right adrenalectomy was performed along with the hemorrhagic-fatty tissue surrounding the gland; a nodal sampling of the ipsilateral renal pedicle completed the procedure. The duration of the operation was 90 min with a total estimated blood loss of 3 liters. The patient recovered uneventfully showing no postoperative signs of adrenal insufficiency and was discharged on postoperative day 10 without any need for replacement therapy. Pathology of the specimen showed a ruptured G₃ T₃N₀M₀ ACC according to the ENSAT staging system. The most common architectural pattern was that of patternless sheets of cells interrupted by a fine sinusoidal network and/or separated by broad fibrous bands dividing the tumor into prominent lobules. The cells had varying sizes and eosinophilic or bubbly clear cytoplasm. The nuclei were hyperchromatic, atypical, and with coarse chromatin. A high mitotic activity with a frequent atypical figure was observed (Figure 2). The tumor infiltrated the capsule and invaded the veins and sinusoids (Figure 3). Ki-67 (clone MIB-1) was expressed in 70 % of the cells (Figure 4) that also positively stained for AE1 and AE3 cytokeratins (clone AE1–AE3) and vimentin (clone V-9). Staining for Melan A (clone HMB45), chromogranin A, EMA (clone GP1.4), and CEA (clone II-7) were negative as were the sampled lymph nodes examined.

Cortical adrenal function tests obtained on postoperative day 18 were all in the normal range. The patient was then scheduled for a complete postoperative re-staging.

Fig. 1 Right ruptured adrenal mass with surrounding hemorrhage. Note the absence of liver mets and the *normal left adrenal gland*

Fig. 2 Hematoxylin-Eosin of the *right* adrenal mass (original magnification $\times 40$)

While recovering and waiting for a total body PET-CT, the patient presented again at the emergency department complaining of the same symptoms on the contralateral side. At presentation, hemodynamics were normal (ABP: 120/80 mmHg, HR: 84 bpm, RR: 14/min, and peripheral O_2 saturation: 99 %). Surprisingly, an urgent contrast-enhanced CT scan showed a left upper retroperitoneal hemorrhage arising from a left adrenal mass that was not present on the previous CT scan (28 days earlier).

Moreover, a gross retroperitoneal recurrence was seen in the right adrenal space together with multiple lung and liver masses that were strongly suspicious for metastases (Figure 5). Upon readmission, the adrenal function tests showed elevated serum cortisol levels with a complete suppression of ACTH secretion on both samples taken at 8 h and 18 h, and mineralocorticoid function was normal. The patient was then kept under strict clinical observation but a continuous, slow decline of the hematocrit suggested further surgery was needed. The patient underwent a left adrenalectomy via a widening of the previous incision together with a liver mass biopsy. A 5-cm maximum diameter adrenal mass was removed together with the surrounding fatty and hemorrhagic tissue. The duration of the operation was 240 min with an estimated blood loss of 2.5 liters. The gross appearance of the removed mass was of a yellowish-gray friable mass with a fractured capsule showing an active intra-mass hemorrhage. Pathology of the specimen confirmed that the mass had the same immunostaining features of the previously removed right ACC. Postoperative cortisol levels remained more than threefold greater than the normal values with complete ACTH suppression. On postoperative day 9, the patient developed sudden respiratory distress syndrome due to the onset of bilateral pneumonia with septic shock. He was

Fig. 3 Hematoxylin-Eosin stain: note the nuclear pleomorphism and mitotic figures, often atypical and 3b) capsular and vascular invasion

Fig. 4 Ki67 immunostaining of *right* adrenal mass (original magnification 40×)

intensively treated in the ICU but died on postoperative day 31. A postmortem examination showed a wide metastatic dissemination from the ACC into the liver and retroperitoneum, and a penta lobar pneumonia as the cause of the death.

Discussion

Adrenal spontaneous hemorrhage is a rare condition presenting in various clinical settings and showing features ranging from self-limiting events to life-threatening conditions with hemorrhagic shock. Causes of the adrenal glands' spontaneous bleeding are classified according to their etiology as follows: iatrogenic (anticoagulation excess, long-term use of NSAIDs [non-steroidal anti-inflammatory drugs], and adrenal biopsies); septic

(Waterhouse–Friderichsen syndrome); neoplastic (adrenal cysts, myelolipomas, pheochromocytoma, and hemangioma); plus a variety of miscellaneous conditions frequently complicating other diseases or pregnancy. An intratumoral hemorrhage is a common finding in the ACC setting; a paper from Harrison and colleagues report that a hemorrhage occurs in 50 % of ACC surgical specimens [5], however, an overt retroperitoneal hemorrhage due to an ACC is extremely infrequent.

Spontaneous rupture of an ACC is considered anecdotal since, in an extensive review of the literature, we have been able to retrieve only 15 previously described cases [6–17] (Table 2). The present case being the 16th and, to our knowledge, the very first report of a spontaneous rupture of the primary cancer and a short-term rupture of the contralateral metachronous metastasis. Most of the reported cases presented in an emergency setting with only one case [15] treated by deferred resection after a mild, self-limiting hemorrhage. In such a setting, priority has to be given to the control of the bleeding more than to the study of the tumor's metabolic pathways. Since one of the crucial points in assessing the nature of adrenal masses is their functional status [18], in this particular subset of patients one must consider the presence and severity of hemorrhagic shock at presentation. Our patient presented in class II shock with a good volemic response to a rapid saline infusion and a prolonged stability at the first presentation; at the second presentation, the patient was in a class I shock. This allowed us to perform a CT scan and a 24-hour endocrine screening; in both cases, surgery was decided due to signs of bleeding reprise or persistence even if at a low rate. In other reported cases, the presenting hemodynamic features have not been clearly reported. However,

Fig. 5 CT scan at patient's second presentation 28 days after first hemorrhage

one [15] study reported an urgent laparotomy that may be interpreted as the consequence of hemodynamic instability and in another case, the patient was previously examined for a nonfunctioning adrenal mass and had initially declined the operation [11]. Our patient did not have any personal history of hypertension, diabetes mellitus, sexual function impairment, psychiatric disorders, nor did he present with skin striae, buffalo lump, or “moon face”. At the first presentation, the adrenal function assessment showed no increase in cortisol, ACTH, aldosterone or metanephrines, only DHEAs were threefold the normal levels, and this is consistent with the diagnosis [19]. At the second presentation, the patient showed an increase in serum cortisol levels at both the 6 a.m. and 6 p.m. measurements with a constant suppression of ACTH secretion. This is consistent with adrenal hypercortisolism and this condition remained after surgery. A similar case has previously been described in a case report by Kasperlik-Zaluska and colleagues [12], interestingly, they describe the onset of hypercortisolism together with the spread of metastatic disease. Certainly, the endocrine assessment at presentation was not complete, we feel that a dexamethasone suppression test would have ruled out

hypercortisolism, but suppression tests can take a long time that bleeding patients do not always have. Alternatively, one may question the reliability of tests acquired during or soon after a huge volume replacement. The timing of the operation, in this particular subset of patients, depends mostly upon the severity of the bleeding more than on the tumor features themselves. There have been some reports on bleeding control by transarterial embolization, but these procedures were on benign lesions or pheochromocytomas [20, 21]. These authors state that achieving hemodynamic stability through endovascular bleeding control may allow a surgeon better recognition of the endocrine function and, thereafter, a better preparation of the surgical removal of the tumor with a decreased risk of morbidity [21]. It is also true that a standard surgical approach to ACC is still to be determined [22]. In our patient, at his first presentation, the right adrenal was removed together with all the surrounding retroperitoneal fatty tissue since the mass did not adhere to the adjacent structures. In the second presentation, even if we already knew the nature of the mass, we performed a limited operation due to the huge metastatic spread of the tumor; the spread included the lung and bilobar liver metastases, and local recurrence into the right

Table 2 Overview of previously reported cases of ruptured ACC

Author/year	Patient's sex/age	Tumor side	Functional status	Max diameter (cm)	Treatment	Outcome
O'Kane et al. [6]	M/52	Left	Nonfunctioning	NR. Liver metastases	Urgent adrenalectomy	NR
Leung et al. [7]	M/5	Right	Nonfunctioning	9	Urgent adrenalectomy	CT- no short term recurrence
Liguori et al. [8]	F/39	Left	Nonfunctioning	13	Urgent adrenalectomy	NR
Bussani et al. [9]	F/39	Left	Nonfunctioning	13	Urgent adrenalectomy	2 years DOD (personal communication)
Stamoulis et al. [10]	M/41	Left	Nonfunctioning	8	Urgent adrenalectomy	Adjuvant CT-
Suyama et al. [11]	17/F	Right	Nonfunctioning	15	Ipsilateral nephrectomy	Multisite metastases at 7 months
Kasperlik-Zaluska et al. [12]	F/12	Right	Not known—cortisol secretion in follow-up	10	Urgent Adrenalectomy	Alive 48 month (No adjuvant therapy) DOD 30 months
	F/49	Right	Nonfunctioning	6	Urgent adrenalectomy	DOD 24 months
	F/21	Right	Slight cortisol increase	10	Urgent adrenalectomy	DOD 5 months
	F/65	Left	Nonfunctioning	11	Urgent adrenalectomy	DOD 6 months
Lu et al. [13]	M/46	Right	Nonfunctioning	14	Urgent adrenalectomy	No adjuvant therapy Local recurrence plus hepatic metastases at 4 month
Chung et al. [14]	F/36	Left	Cortisol secreting	12	Adrenalectomy	Local recurrence (Chemotherapy)
Sakata et al. [15]	F/79	Left	Nonfunctioning	NR	Delayed (2 months) Adrenalectomy/nephrectomy	DOD 11 months
Symeonidis et al. [16]	F/35	Left	Not defined	9	Urgent adrenalectomy	NR
Jagtap et al. [17]	M/45	Right	Nonfunctioning	15	Urgent adrenalectomy	NR
Present case	M/49	Right/left	Nonfunctioning(?)/Cortisol secreting	10/5	Urgent adrenalectomy (right first, left 22 days later)	DOD 2 months

NR not reported, DOD dead of disease

renal space. Other authors reporting on the issue also performed a radical adrenalectomy. Only in the case described by Sakata and colleagues [15] was a nephrectomy coupled with an ipsilateral adrenalectomy, but was also the only planned operation done after self-control of the bleeding. Metastatic spread is common in ACCs since even radically resected patients develop metastatic disease within 2 years [23]. What surprised us was the rapidity of the tumor growth. At the first CT scan, the left adrenal was completely normal, however, at 28 days, the CT showed a bleeding mass measuring 5 cm. Such a growth rate may be, in our opinion, responsible for the rupture rather than, as previously suggested [13], the tumor dimension itself. The mean maximum diameter of a ruptured lesion is, according to reported data, 10.4 cm. This dimension completely overlaps the mean diameter reported by Gratian et al. on a series of 2,765 patients with ACC and no rupture [24]. Moreover, an intratumoral hemorrhage is a frequent finding in the pathology of an ACC [5, 25], but seems not to affect the risk of a rupture. The only other available case of rupture of a previously assessed adrenal mass is the one reported by Suyama et al. [11]. This group diagnosed a 13 × 9 cm mass in the right adrenal gland and the patient declined an operation; one year later, the patient was readmitted in an emergency setting showing a rupture of the mass that had grown to 15 × 12 cm. Even in this case, one may postulate that more than the dimension itself, the rupture was elicited by the tumor growth. The appearance of late onset hypercortisolism has been previously reported [12], similar to our patient, there were no signs of hypercortisolism. However, our case did show clinical hypercortisolism at the second presentation, together with a widespread metastasization of the tumor, probably depending above all on the total mass of neoplastic tissue. We hypothesize that these are tumors with a low rate of cortisol secretion that needs a large amount of tumor mass to reach clinical significance. Moreover, none of the 15 described patients presented with the typical somatic changes of hypercortisolism. Our opinion is that, since the physical changes may take several months to be evident, rapidly growing tumors preferably present with mass symptoms or rupture.

Only nine papers have reported on the patient's survival and/or onset of metastatic disease; for reported papers, the mean overall survival time was 17.4 months (range: 2–48 months) and only one patient was deemed disease free at 48 months after surgery. Overall, a 4-year survival rate in the nine reported cases was 11 %, in three cases adjuvant chemotherapy was given, but the only reported long-term survivor did not receive any adjuvant therapy. These data on survival, even if potentially biased by a type III error due to the heterogeneous and limited sample size, appear to be more in the range of overall survival for stage

IV disease than in that reported for stage III disease according to the ENSAT guidelines.

Conclusion

An adrenocortical carcinoma is a rare tumor that is often fatal. Very little is known about its biology and pathology. The most frequent clinical presentation is that of hypercortisolism that occurs in about 60 % of patients, the remaining patients complain of mass symptoms or no symptoms at all. Spontaneous rupture of an ACC is an extremely rare event and almost never presents with signs of acute abdomen and hemorrhagic shock. A differential diagnosis is often very difficult since urgent or emergent laparotomies are required in almost all cases. At present, no specific causes for spontaneous rupture have been identified; however, from reported cases, the tumor diameter seems not to affect the risk of rupture by itself. We postulate that a rupture may be the consequence of a rapidly growing tumor, but, of course, we are unable to confirm this. Based on the rarity of the situation, this issue is unlikely to be addressed until each case is reported, preferably with the most reliable data possible.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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