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Long-term recurrence-free survival of adrenocortical cancer extending into the inferior vena cava and right atrium

Case report and literature review

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Abstract

Context: Adrenocortical cancer (ACC) is rare but frequently fatal malignancy. Tumor extension into the inferior vena cava signifies an advanced stage (stage III) of the disease and is frequently associated with high risk of recurrence and short-term survival.

Objective: To present the surgical and medical management of an unusual case of ACC with IVC invasion up to the right atrium. He has the longest reported tumor-free survival of such a situation. We also reviewed and summarized the literature of similar cases.

Patient: We present a 15-year old boy who presented with an 11 cm ACC extending into the IVC up to the right atrium and causing the Budd Chiari syndrome. He had complete surgical excision under cardiopulmonary bypass of a large ACC followed by Mitotane adjunctive therapy for 5 years. He is alive and free of any clinical or radiological signs of recurrence 98 months after surgery. This is the longest tumor-free survival reported in the literature of similar cases.

Conclusion: Significant invasion of the IVC up to the right atrium by ACC should not preclude surgery with the intent of complete resection. Cardiopulmonary bypass significantly aids this surgical procedure and Mitotane therapy should be instituted postoperatively. Long-term free-survival is possible in such a situation.

Lessons: our patient and the literature review strongly suggest that complete surgical extirpation is the primary choice for patients with ACC invading the IVC, including those reaching the right atrium.

Abbreviations: ACC = adrenocortical cancer, ACTH = adrenocorticotrophic hormone, CPB = cardiopulmonary bypass, CT = computed tomography, DHEA = dihydroepiandrosterone, FDG = F-18-flurodeoxyglucose, IVC = inferior vena cava, PET = positron emission tomography.

Keywords: adrenal gland, adrenocortical cancer, inferior vena cava, right atrium

1. Introduction

Adrenocortical carcinoma (ACC) is a rare malignancy occurring in 1 or 2 cases per million population.[1,2] ACC can develop at any age but it has a bimodal age distribution, with disease peaks before the age of 5 years and around the fifth decade of life.[3,4] About 60% to 70% of the tumors are functional secreting cortisol, androgens, or sometimes mineralocorticoids and presenting with corresponding clinical syndromes.[5] Although most commonly sporadic, ACC can be a manifestation of familial syndromes such as Li Fraumeni syndrome, Beckwith–Weidmann syndrome, multiple endocrine syndrome type1, Lynch syndrome, and familial polyposis coli.[6]

Although rare, ACC is often a fatal disease. The 5-year survival rate ranges from 15% to 35%.[5,7] Surgery remains the primary modality of therapy but recurrence is common, occurring in 20% to 85% of patients.[5,7] The best results are in those with stage I and II disease (ACC limited to the adrenal gland).[5,7–9] For patients with stage III (locally invasive) or IV (distant metastasis), cure is very rare and death usually occurs in the first 24 months after diagnosis.[5,7–9] Invasion of inferior vena cava is not uncommon and is usually associated with high rate of persistent and metastatic disease.[10] Patients with this situation have already major vascular invasion and are at a very high risk of widespread distant metastases and death.[11] We report a young man with high grade ACC invading the inferior vena cava (IVC) all the way to the right atrium and causing Budd Chiari syndrome. Although initially deemed inoperable, resection of the tumor was achieved under the cardiopulmonary bypass (CPB) procedure followed by Mitotane adjuvant therapy. Surprisingly, the patient continued to do well and free of disease without evidence of local or distant metastasis 8 years after the initial surgery. To our knowledge, this is the longest recurrence-free survival of stage III ACC invading the IVC up to the level of the right atrium. In this report, we describe the presentation and management of this patient and review the literature on ACC with extension to IVC and right atrium.

2. Case report

After obtaining an Institutional Review Board approval and an informed consent, we report a 15-year old boy, not known to

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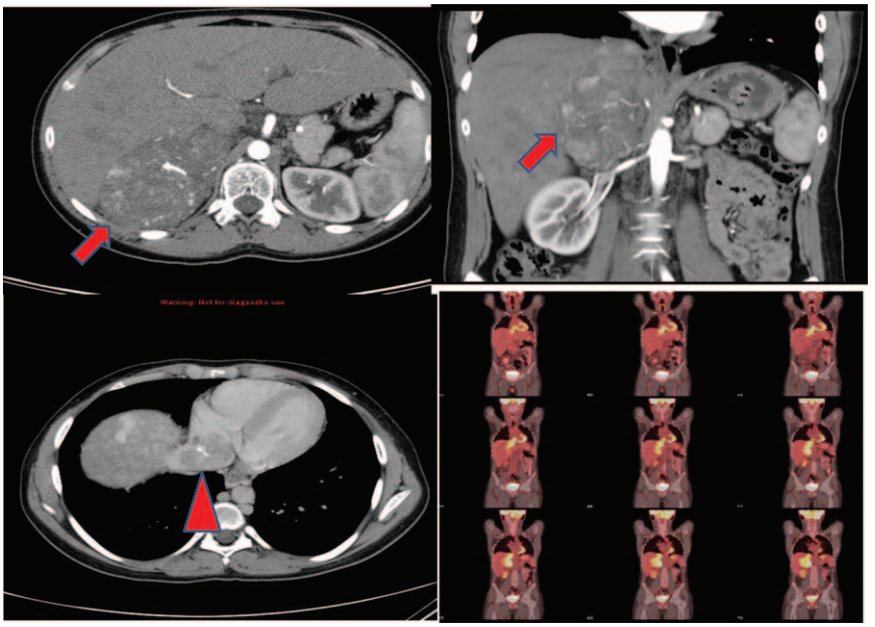

Figure 1. Axial and coronal cuts of a contrast-enhancing CT scan of the abdomen and chest showing a large heterogeneous mass (arrows) extending from the right adrenal region through the IVC behind the liver and reaching the right atrium (arrowhead) showing a mass of 10.9 × 8.1 × 9.2 cm. Serial cuts of 18-flurodeeoxyglucose PET/CT scans (right lower panel) are showing an intense uptake and extension of the same mass seen on CT scan. CT = computed tomography, IVC = inferior vena cava, PET = positron emission tomography.

have any medical illness presented in April 2008 with right abdominal pain for 6 months. The pain was dull in nature, gradually increasing, not radiating with no aggravating or relieving factors and not associated with any gastrointestinal or urinary symptoms. There was history of intentional weight loss of 10 kg by dieting and exercise. He had no history of sweating, palpitation, headache, fever, flushing, or night sweats. No history of high blood pressure or diabetes mellitus, obesity, skin, or facial changes. Family history was unremarkable with no history of cancer or high blood pressure. An abdominal computed tomography (CT) revealed a huge heterogeneously enhancing right adrenal mass measuring 10.9 × 8.1 × 9.2 cm and extending through the IVC up to the right atrium (Fig. 1). 18-FDG PET/CT whole body scan showed an intense FDG uptake in the same mass that is seen on CT scan (Fig. 1). There was marked hepatomegaly and mild ascites but no evidence of metastases in other organs, particularly the liver, lungs, and the contralateral adrenal gland.

On examination, the patient looked well, not pale or jaundiced. He had no Cushingoid features and his blood pressure was 119/81 mm Hg. He had scanty facial and upper lip hair but normal axillary and pubic hair and mild gynecomastia. Skin, chest, cardiovascular, and neurological examinations were unremarkable. Abdominal examination revealed marked hepatomegaly but no splenomegaly.

Investigation showed 24-hour urine free cortisol of 699 nmol (normal range 100–379). Morning cortisol post 1 mg dexamethasone suppression test: 543 nmol/L (<138). ACTH <1 ng/L (5–60). S. Testosterone 5.74 nmol/L (0.98–38). S. DHEA 7.49 umol/L (3.61–15). S. Estradiol: 215 pmol/L (28–156). Right adrenal mass core needle biopsy under CT guidance showed cells with features of adrenocortical neoplasm. The patient had tumor embolization pre surgery in order to decrease vascularity of the tumor and the risk of bleeding during surgery. He was prepared with Hydrocortisone 100 mg before surgery. A combined cardiac and general surgery was done under CPB. Through a bilateral subcostal laparotomy, an attempt was made to remove the tumor. However, this was difficult due to the huge congested liver obscuring the tumor. The patient was then placed on CPB with hypothermia, the right atrium was opened, and the IVC thrombus was broken just at the level of hepatic veins and pulled up through the right atrium. The liver immediately shrank due to relief of the hepatic vein obstruction. The adrenocortical tumor and the remaining part of the IVC thrombus were then dissected and removed through the laparotomy opening. The patient was kept intubated for 24 hours in the intensive care unit. He had a smooth postoperative course and discharged home on Mitotane and oral Hydrocortisone at the 7th postoperative day. The histopathological examination of the resected tumor reported ACC with tumor necrosis, mitosis, and vascular invasion (Fig. 2). There was thick capsule around the tumor including the part that was invading the IVC and right atrium (Fig. 2). The Weiss score was 9 and Auber score was 7. The patient was maintained on Mitotane 2 to 3 g daily although his compliance was not always good. He was also on hydrocortisone 15-5-5 mg daily and Florinef 0.1 mg daily. Repeated abdominal and chest CT scans every 6–12 months, and MRI abdomen and several whole body PET CT scans showed no local recurrence or distant metastasis. The patient continued to do well clinically and biochemically until now with a total follow-up period of 98 months.

3. Discussion

In this report, we presented an unusual case of a highly invasive ACC that had extended into the IVC up to the right atrium. Such a situation indicates severe intravascular invasion and is expected to be associated with hematogeneous spread of tumor cells and seeding of other organs. This implies that any surgical procedure would be only of palliative value. Considering the frequently poor overall prognosis of ACC even in cases with much less

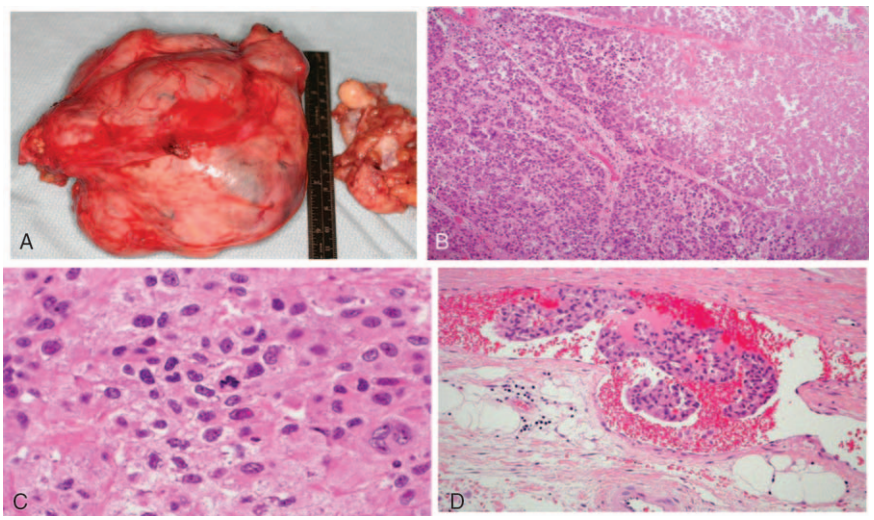

Figure 2. Pathological examination of the mass shows the gross pathology of the tumor (A), low power magnification of H&E stained section showing sheets of uniform cells with areas of necrosis and hemorrhage (B), higher magnification section of an H&E stained section showing mitosis and necrosis (C), and a low magnification section showing a thick tumor capsule with vascular invasion (D). H&E = hematoxylin and eosin.

spread, it was inconceivable that surgery that this patient had would result in long-term disease-free survival. Although Mitotane was initiated immediately after surgery and continued until now, it was not expected to have a significant impact in this grossly invasive ACC. Mitotane had been recommended as adjunctive therapy in patients with R0 disease where there is suspicion of microscopic residual disease and for patients with definite residual (R1) or distant metastases.[6,12] Its use in patients with complete resection is based on a large retrospective study showing that resected AAC is less likely to recur when treated with adjuvant mitotane therapy following adrenalectomy.[6,12] This issue remains controversial and an ongoing trial is being conducted to address this question in a more controlled prospective design (Clinicaltrials.gov, NCT00777244). It is possible that the good course that this patient had can be partially explained by the fact that the ACC, although large and of high grade, was contained by its thick capsule which may have prevented spillage of tumor cells in the blood stream with secondary seeding in other distant sites and partially explained by the use of mitotane. Although the tumor mass was filling up the IVC and causing the Budd Chiari syndrome, there was no pre or post-operative evidence of liver or other distant metastasis suggesting that this is more of a local extension of the tumor rather than local or intravascular invasion.

A number of cases of ACC with IVC invasion/spread have been reported.[10,13–21] Ohwada et al[19] reported results of combined liver and IVC surgery in 6 ACC patients with extension to the IVC and liver extension/metastasis. Although complete gross resection was achieved in all patients without mortality, 3 patients (50%) had recurrence within 8.1 months. The mean recurrence-free survival period was 20.1 ± 7.7 months. The 5-year disease-free survival rate was 16.7%.[19] Chiche et al[10] reported a case series of 15 patients with ACC and IVC extension of variable extent including 7 with suprahepatic IVC extension, of whom 4 to the right atrium. Seven of these cases had concurrent distant metastases. The surgical approach used included thrombectomy in 13 patients, partial resection with direct closure in 1 patient and total resection with IVC replacement in 1 patient. CPB was used in 6 of these cases including 3 with right atrial extension. Two patients died in the immediate postoperative period, whereas 10 other patients died 4 to 31 months after surgery due to metastases. Three patients were still alive at 24, 25, and 45 months after surgery including 2 who had right atrial thrombus.[10] In the same report, the authors reviewed 106 cases of ACC with variable degrees of IVC extension reported in the literature during the period 1972–2006. Different surgical approaches were used to treat those patients but thoracoabdominal approach and throbectomy was frequently used. The extent of tumor extension varied between infrahepatic, retrohepatic, and suprahepatic but the latter was the most frequent, probably due to reporting bias. The outcome was reported in 65 cases and was analyzed and reported as follows: "Seven patients died before or during the postoperative period. Twenty-four patients died during follow-up after a mean survival time of 13.2 ± 13.6 months (range 2–60 months) and a median survival time of 9 months. Ten of these patients (43%) survived at least 12 months. Thirty-four patients were alive with metastasis or no evidence of recurrence after a mean follow-up of 23.1 ± 20.4 months (range 1–80 months). Twelve of these patients (35%) survived at least 24 months."[10]

To further analyze this situation, we looked specifically at all cases of right atrial extension in that report and those subsequently reported in the literature until July 2016 including our patient (Table 1). A total of 42 patients with ACC with IVC invasion reaching the right atrium were reported between 1972 and 2016. Analysis of these cases revealed that there were 30 females and 12 males with a median age of 38.5 years (range 1.7–77) and interquartile range of 26.7–52.3 years. Thirty-four (81%) of those tumors occurred in the right adrenal gland and 8 (19%) occurred in the left side. Thoracoabdominal surgery (median sternolaparotomy in 9 patients or lateral thoracolaparotomy in 11 patients) was performed in 20 patients, subcoastal laparotomy in 1 case, subcostal laparotomy with mid sterneotomy in 6 cases, thoracotomy alone in 1 patient, and median laparotomy alone in 1 patient. Three patients had no surgery and another patient received chemotherapy only. In 10 patients who had surgery, the procedure type was not mentioned. At the time of reporting of these cases, 19 cases died, 15 cases alive, and in 8 cases, the status was not mentioned. Of those 19 cases who died, 3 died preoperatively and 1 before surgery. The other 15 cases

Table 1

All cases of ACC with IVC extension up to the right atrium that were reported between 1972 and 2016.

Study	No. of cases	Sex	Age, y	Tumor side	Status at time of reporting	Duration after surgery, mo
Chiche et al[10]	32	25F:7M	40	25R/7L	11 alive, 15 dead, 6 not mentioned	13 (1–60)
Annamaria et al[13]	1	F	51	Right	Alive	12
Mezhir et al[18]	1	M	34	Right	Alive	6
Hisham et al[22]	1	M	43	Left	Dead	12
Patil et al[23]	1	F	30	Right	Not mentioned	
Wang et al[20]	1	M	33	Right	Dead	18
Levin et al[17]	1	F	1.7	Right	Dead	1.25
Kumar et al[16]	1	F	40	Right	Died in the postoperative period	1
Péterffy A et al[24]	1	F	47	Right	Alive	12
Kim et al[25]	1	M	34	Right	Alive	8
Alghulayqah et al (current)	1	M	15	Right	Alive	98
Total	42	30F:12M	38.5	34R:8L	19 dead, 16 alive, 7 not mentioned	12 (1–98)

died at a median duration of 9 months after surgery (range 1–60). The median survival time for the 15 patients who were alive at the time of reporting was 14 months (range 1–98). Our patient has the longest survival of 98 months. Not only that he is alive at 98 months, but he is also free of residual or metastatic disease!

In conclusion, our patient and the literature review strongly suggest that complete surgical extirpation is the primary choice for the patients with ACC invading the IVC, including those reaching the right atrium. The surgical removal should be as much as possible en bloc to minimize tumor cell spillage. CBP significantly aids the surgical procedure. Postoperative long-term mitotane therapy is a very important part of the management of those cases.

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