Giant adrenocortical carcinoma with 27-month disease-free survival by surgical resection alone: A case report

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Background. Adrenocortical cancer (ACC) is a rare disease with an estimated incidence of 1-2/million/year. The tumour stage and completeness of surgical resection have the biggest impact on survival. Whereas stage I-II patients survive in 55-64% of cases, only 0-5% of patients with stage IV disease are still alive at 5 years. A median survival of 33 months can be expected after curative surgery. Incomplete surgery leads to a significant drop in survival.

Method. We present a 40-year-old man who underwent a technically demanding complete surgical excision of a giant (26 cm, 2372 g) ACC and experienced a 27-month disease-free survival without any systemic treatment. Detailed description of the surgical anatomy in relation to tumour size and patient body constitution is provided. The surgical strategy and exposure pitfalls under such extreme circumstances are discussed.

Conclusion. To achieve R0 resection in locally advanced disease, en bloc resection with neighbouring organs is widely recommended. Giant tumours may however pose a technical challenge due to space constraints.

Key words: adrenocortical carcinoma, adrenal tumour, surgical resection, disease-free survival

INTRODUCTION

Adrenocortical cancer (ACC) is a rare disease with a dismal prognosis 1-3. Most ACCs are of sporadic origin, but the tumour may be a part of several congenital or familiar diseases 4-5. The tumour presents as an overt clinical syndrome of hormonal hypersecretion or symptomatic abdominal mass 5-6. The stage of the tumour and completeness of the surgical intervention are the main determinants of outcome 4-7. Prognosis is highly stage dependent and over the years several staging systems have been proposed. Currently, the ENSAT (European Network for the Study of Adrenal Tumours) classification (2008) is commonly used 8. Tumour size 5 cm defines stages I and II with a 5 years survival rate 84% and 63% respectively. Stage III tumour is either locally spread or any size tumour with positive lymph nodes. Five-year survival for stage III patients is 51% (ref. 9). Stage IV ACC invades neighbouring organs or has fixed positive lymphnodes or distant metastases. For this stage, survival drops to 15% at 1 year 10. Complete surgical excision is achieved in 70-85% of cases and these patients have a median survival up to 74 months 6-7. Incomplete resection on the other hand, shrinks the median survival to 6-27 months 11-13. It is important to know that most patients surviving at 5 years are not cured but alive with the disease and 85% of patients resected for cure will develop recurrence or distant metastases 6,14. Other factors negatively influencing the outcome are size of the tumour (more than 12 cm), high mitotic activity, necrosis, high expression of Ki-67 and TP53 gene mutation positivity 15-17. Surgical excision represents the mainstay of treatment and is indicated even in selected patients with stage IV disease 6,18,19. Specific treatment with the adrenolytic agent mitotan is widely discussed elsewhere. Although considered as a reference treatment with a response rate of 30%, the drug has serious side-effects, which may limit its use in some patients. Plasma concentration has to be monitored closely as there is a narrow therapeutic range 6,9,19. Two combinations of mitotan and cytotoxic agents were studied recently. These are the Berruti protocol with etoposid, doxorubicin, cisplatin (EDP) in combination with mitotan and a combination of streptozocin with mitotan. EDP plus mitotan was found to be superior to mitotan plus streptozocin in the FIRM-ACT study group randomized study published this year. Median survival to progression for the EDP plus mitotan group was longer. However overall survival was not significantly different (14.2 vs. 12 months) (ref. 20). Overall, systemic treatment of ACC is unsatisfactory to date 19.

CASE REPORT

A 40-year-old, obese (BMI 32.7 kg.m⁻²), Caucasian man was admitted to ICU in October 2009 after 14 days of respiratory distress. The patient’s history included the
death of his father due to pulmonary embolism, apendec-
tomy in the past, hypertension and alcohol abuse medical-
tly treated. Brochoscopy was negative, echocardiography 
showed right ventricular dilatation and pulmonary hyper-
tension, computerized tomographic angiography (CTA) 
scans revealed massive pulmonary embolism (Fig. 1). 
Anticoagulant treatment was started and the patient’s 
condition improved. A giant right hypochondrium tumour 
with severe right kidney and inferior vena cava (VCI) dis-
placement was shown to be an underlaying cause of em-
bolism (Fig. 2). An inferior vena cava filter placement 
procedure was discussed with both interventional radi-
ologist and vascular surgeon, but was considered techni-
cally not feasible due to VCI angulation. Patient went on 
with anticoagulant treatment and further investigations 
were carried out. Neuron specific enolase (NSE) level 
of 97.8 ug/L was positive and a diagnosis of suprarenal 
gland adenoma was suggested based on percutaneous 
biopsy. Being aware of the high risk that adrenal gland 
carcinoma might be in fact involved, distant metastases 
were excluded and surgical exploration was planned. The 
overall condition of the patient allowed for planed sur-
gery not sooner than 01.2010. Due to the patient’s body 
constitution, thoracophrenolaparotomy had to be made 
to approach the tumour. Even this wide exposure did not 
enable handling the tumour conveniently. Every effort 
was made to deliberate the right kidney without sacrificing 
its vasculature. Here, especially the right renal vein pres-
ervation was demanding due to extensive distortion and pressure from the tumour (Fig. 3). Several collateral veins draining to the right renal vein had to be secured. After right kidney mobilization, displaced VCI was carefully detached from the tumour, without any direct involvement found. The most problematic part of the excision turned out to be the right hepatic lobe and retrohepatic VCI detachment. The option of liver hanging maneuver with en bloc right hepatectomy was considered, but this was abandoned (this will be discussed later). Right lobe detachment was complicated by 4000 mL of blood loss due to venous collateral hemorrhage, which was hard to control despite suprarenal VCI clamping. Due to the size of the tumour, the right suprarenal vein could not be approached until the very end of the dissection. The tumour was excised without capsule violence and R0 resection was achieved (Fig. 4). Tumour met Weiss and van Slooten ACC criteria, with several negative prognostic factors: high nuclear grade 3-4, intratumoral necrosis, vascular invasion, tumour capsule infiltration, mitotic activity 7/50 HPF, Ki 67 positivity (12%) (Fig. 5 and 6). No residual VCI thrombosis during the surgery was found and no direct damage to the vessel occurred. Despite this a caval filter for infrarenal incomplete thrombosis was inserted postoperatively and excessive manipulation with VCI could be responsible for this. Neither in the postoperative, nor in the follow-up period did any pulmonary embolism attack occur. The patient was discharged after prolonged wound healing period with vacuum-assisted healing device.

The medical oncologist and endocrinologist followed the patient for the next 27 months. No adjuvant treatment was initiated. The patient had repeated Positron Emission Tomography Computed Tomography (PET/CT) scanning to diagnose disease recurrence early. In March 2012 scanning revealed pathological 18-fluorodeoxyglucose (FDG) accumulation in the interaortocaval lymph nodes as a sign of disease progression. In June 2012 an attempt at radical extirpation was made, but confluent malignant lymphnodes with invasion to retroperitoneal structures were found and further excision abandoned. To time, the patient survived 36-month with surgical excision of primary tumour alone.

**DISCUSSION**

Several issues concerning surgical startegy and adjuvant therapy need to be discussed. First, the option of en bloc right hepatectomy. In large tumours, there is a universally accepted approach of en bloc resection of ACC with neighbouring organs, demonstrated by several authors. This ensures not only R0 resection in case of questionable local tumour infiltration, but it also prevents blood loss from pathological collateral vessels. Elimination of the blood loss and tumour cell seeding is of paramount importance in ACC excision. En bloc resection with right kidney and right hepatic lobe in case of right sided lesion may in fact be technically easier and oncologically safer. According to the literature, the average tumour size at the time of surgery is 800 g, or 12 cm in diameter. Giant tumours, such as was the case here, impose specific operating field constraints. Under extreme conditions, such as a patient with high BMI and 2372 g tumour (26x16x13 cm), thoracophrenolaparotomy is done to expose the field adequately. Bearing in mind, that the right lobe detachment/resection is going to be the most demanding and risky part of excision, we detached the right kidney, all lateral aspects of the tumour and retroperitoneal fat, secured VCI above the renal veins. The tumour was left attached to the right lobe and retrohepatic VCI only, with no option of early right suprarenal vein division. To that point virtually no blood loss was encountered. The option of liver hanging maneuver with en bloc right hepatectomy was considered but this was abandoned because the retrohepatic VCI course was distorted and the risk of uncontrolled hemorrhage was high. An anterior approach could be used without liver hanging and this option we judged repeatedly during the procedure, but the space we were able to create in the operating field we did not consider adequate for safe parenchymal transection with an anticipation of the hardest part in

**Fig. 5.** Adrenal carcinoma, hematoxylin and eosin stain (200x). Area of necrosis.

**Fig. 6.** Adrenal carcinoma, hematoxylin and eosin stain (200x). Capsular invasion.
the very end of the dissection. The risk of uncontrolled hemorrhage without prior liver hanging we evaluated as unacceptable. Not doing this however, resulted in extremely high blood loss which we were trying to avoid in the first instance. Retrospectively, we admit that the decision not to resect the right lobe en bloc with the tumour was not right. In the light of our negative experience under such extreme circumstances liver hanging maneuver with prior suprahilar-intrapericardial and suprarenal VCI control probably could minimize the blood loss as described by Japanese authors in cases where VCI resection was necessary\(^\text{20}\). We achieved R0 without tumour capsule violation without en bloc liver resection, but at the price of a considerable blood loss.

Thrombosis of VCI and consequent pulmonary embolism as a first tumour presence symptom we considered to be malignant (i.e. tumour embolism). As no direct tumour infiltration to VCI was found, anticoagulant treatment led to complete resolution of the thrombus and no thrombosis was found at the time of operation, we found tumour pressure and severe VCI dislocation to be a cause of thromboembolism rather than malignant nature of the disease in this particular case. Even if we had not noticed any direct damage to VCI during the dissection, manipulation with the vessel was excessive and could lead to formation of small infrarenal thrombus in the postoperative period.

Systemic treatment of ACC is unsatisfactory to date. In our particular case, systemic adjuvant treatment was abandoned both due to patient non-compliance (alcohol abuse) and prolonged wound healing. As the lymph node disease progression in June 2012 was found inoperable, the patient was offered palliative radiotherapy. This modality had technical limits given by the immediate presence of radiosensitive tissues in the past. These days the issue is revisited and the use of conformal radiotherapy or intensity-modulated radiation therapy (IMRT) made radiotherapy valuable option in a palliative setting\(^\text{21}\).

CONCLUSION

Surgical excision of ACC should be offered to every fit patient in stage I-III and carefully considered for selected patients with stage IV disease. Resection of large ACC can be a technical challenge. Wide exposure and en bloc resection should be considered in cases of locally advanced disease. Vascular control should be attempted in any case where massive blood loss can be expected. Not doing so may result in life threatening blood loss and uncontrolled intraoperative hemorrhage. Our (negative) experience supports general recommendation to resect the lesion en bloc whenever there is a close relationship to neighbouring organs. This might be true regardless of extreme operating space constraints in giant tumours. Even in cases when systematic therapy with mitotan is contraindicated, radical surgery alone may lead to considerable survival benefit.

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REFERENCES


