Case Report

Multi-Target Approach to Metastatic Adrenal Cell Carcinoma

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Abstract

Adrenal cell carcinoma is a rare tumor and more than 70% of patients present with advanced stages. Adrenal cell carcinoma is an aggressive tumor with a poor prognosis. Surgical intervention is the gold standard treatment and mitotane is the only drug approved for the treatment of adrenal cell carcinoma. Until recently in 2012, the etoposide, doxorubicin, cisplatin plus mitotane are approved as first-line therapy based on response rate and progression-free survival.

This case illustrates a case of advanced adrenal cell carcinoma in a young girl who presented with huge adrenal mass with inferior vena cava thrombosis and pulmonary embolism. Multi-approach of therapy was used to control the tumor size and metastasis. Therefore, it may prolong her survival rate for up to 5 years and 4 months.

Keywords: Advanced adrenal cell carcinoma, mitotane, radiofrequency ablation, Sorafenib, surgical resection

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Introduction

Adrenal cell carcinoma (ACC) is a rare tumor with annual incidence of 0.7 – 2.0 per million populations.[1] ACC occurs more often on the left than right side, and is more common in women than in men.[2,3] Surgery has been the mainstay treatment for ACC regardless of staging, if resection is feasible.[4] Despite complete resection of primary tumor, up to 80% – 85% of patients subsequently developed local recurrence or metastasis.[4] Previous studies reported 5 years survival vary from 32% – 48% with a mean survival of 2 years in patient underwent complete resection compared with a mean survival of less 1 year in those who had incomplete resection.[5,6] In this report, we present a young girl who was diagnosed with advanced ACC in 2008 and survived for more than 5 years with aggressive multi-approach treatment, involving two major surgeries, radiofrequency ablation (RFA), mitotane and thyroxine kinase inhibitor.

Case Report

A 17-year-old girl with a 2-week history of progressively worsening shortness of breath was admitted in October 2008. Urgent CT-thorax was requested in view of suspicion for acute PE. The CT pulmonary angiogram and the abdomen confirmed the presence of PE, which originated from inferior vena cava (IVC) thrombosis as a result of tumor infiltration from a huge left adrenal mass measuring 10 × 12 × 15 cm (Figures 1). Anticoagulation therapy was initiated. A tru-cut biopsy of the mass was performed and its histopathological examination (HPE) was consistent with ACC. She was commenced on mitotane, which could only be titrated up to 1.5 g daily limited by a derangement in her liver enzymes. Despite a month of mitotane therapy, CT scan evaluation showed progressive disease in which the tumor increased in size with extension of the tumor thrombus into the right atrium. Following comprehensive multidisciplinary teams (medical & surgical endocrinology and cardiothoracic) discussions between the patient and family, she was subjected to laparotomy with cardiopulmonary bypass during which she had a left adrenalectomy with right atrium and IVC thrombectomy. HPE of the adrenal mass, cava and right atrium thrombi confirmed ACC. Post-operatively, mitotane and warfarin was recommenced. Mitotane was slowly titrated up to 4.5 g/day within 3 months.

Nine months after the initial surgery, the 18-FDG-PET-CT scan showed an evidence of residual disease at the primary site and IVC. A month later, repeated surgery was performed to remove the recurrence in the primary tumor bed. In April 2010, a repeated 18-FDG-PET-CT scan showed a reduction of activity in the primary disease site, but with new foci of activity in the right adrenal and liver. She underwent several RFA to tackle her liver metastasis. A few months later, repeated imaging revealed that the pre-existing liver lesion, which was targeted during RFA remained stable. However, they are a few new liver lesions. In 2011, Sorafenib, a tyrosine kinase inhibitor, was added. Throughout the course of her treatment, she had six monthly PET-CT scans, which showed the size of the tumor and metastases remained the same with no new lesions (Figures 2 and 3). Due to financial constraints, the patient only received Sorafenib for 2 years, after which she was on mitotane, warfarin and hydrocortisone. Otherwise, she remained active and able to complete her college education. In 2012, she refused further RFA or chemotherapy as a treatment option. She passed away in March 2014.

Discussion

ACC is an aggressive tumor and about 40% are non-functioning.[7] Up to 70% of patients with ACC presents at an advanced tumor

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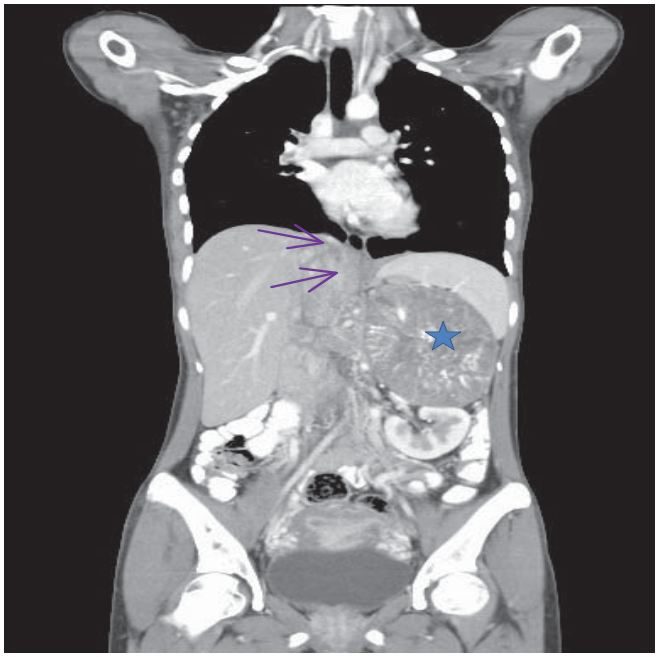

Figure 1. Coronal image of contrast-enhanced CT at diagnosis depicting a large well-circumscribed, heterogenously enhancing left suprarenal mass (5-pointed star), pushing the left kidney inferiorly. There is also tumor thrombus within the left renal vein (dotted line) extending into-& along- the infradiaphragmatic inferior vena cava (purple arrow)

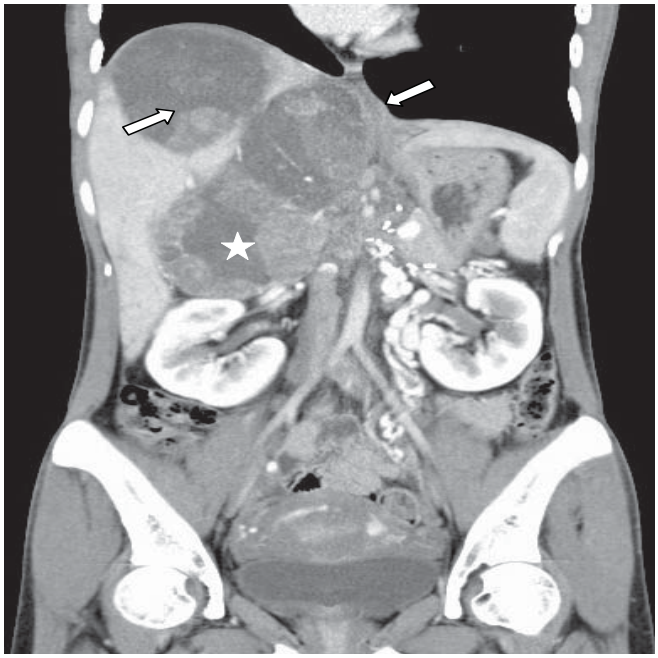

Figure 2. Coronal image of contrast-enhanced CT 1 year later demonstrating multiple well-circumscribed lesions in the right suprarenal (5-pointed star), and two of the liver metastases within segment VIII and segment IV (white, block arrows). The lesions are generally solid with necrotic/cystic areas within. Surgical clips from previous surgery are seen in the left suprarenal surgical bed which is free of tumor recurrence.

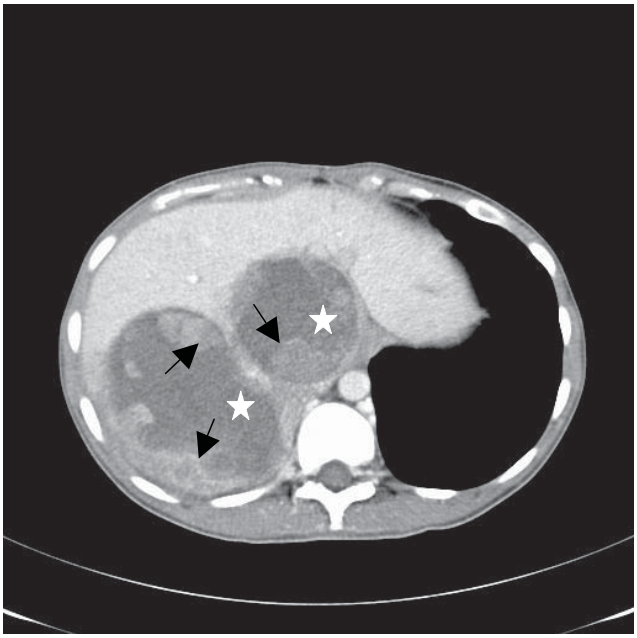

Figure 3. Axial image of contrast-enhanced CT demonstrating two of the liver metastases within segment VIII and segment IVa which contain necrotic/cystic areas (5-pointed star) and solid intraluminal projections (black arrows). The necrotic component increased with each RFA & TACE injections signifying partial success of treatment.

stage.[4] About one third of ACC metastasis to the lung followed by lymph nodes, liver and bone. There have been only a few reported cases of direct invasion to IVC and right atrium.

Our patient presented at an advanced stage of ACC with pulmonary embolism due to local extension of the tumor. The ACC had extended into the pulmonary vessels and invaded into the right atrium. On its own, the multi-organ involvement in this patient was a powerful predictor of adverse prognosis. In the previous 3 multi-centric studies, 5 years survival of patients with Stage IV ACC ranges from 0 to 13%.[8] The presence of both multi-organ involvement and high mitotic count in the primary tumor predicts a survival of approximately 9 months.[8]

Extensive surgery was undertaken in this patient to remove as much tumor as possible with the sole aim of reducing tumor bulk. In our adjuvant therapy with mitotane, we were limited by the lack of access to measurements of mitotane levels or its metabolites to guide us in achieving the optimum therapeutic dose. Thus, we hoped by reducing tumor bulk, the mitotane and Sorafenib will be more effective in prolonging survival.

Surgery remains the gold standard for the treatment of ACC, followed by mitotane and or chemotherapy regardless of staging. Despite surgery and mitotane, most patients have disease progression. Previous studies have reported that the only effective treatment that would increase the median survival rate for recurrence and metastasis is reoperation.[9] It is recommended that the surgery not only to primary tumor or local recurrence but also to metastatic foci in the liver as well as the lung. The appearance of inoperable liver lesions after the reoperation led us to consider alternative approaches to surgery, RFA. These was considered as it was minimally invasive and a safe treatment option for those who had multiple surgical or inoperable tumors.[10] Previous studies showed that RFA is a well-tolerated procedure, effective and safe treatment for benign bone tumor, malignant primary and metastases liver tumors, renal cell carcinoma (RCA), ACC or metastatic adrenal neoplasm.[10]

Sorafenib is an anti-angiogenic and anti-proliferative agent, which has been proven to show improvement in overall survival in patients with advanced RCA and hepatoma. At the time of its initiation in this patient, the use of Sorafenib in particular and thyroxine kinase in general, has not been established for ACC. There was one case report by Butler, et al. who described sustained radiological and biochemical remission in their patient with stage IV ACC after receiving Sorafenib for 32 months.[11] A recently published study by Quinkler, et al. involving advanced ACC treated with Erlonitib and Gemcitabine showed very limited to no activity or response.[12]

In the earlier stage, the treatment strategies for ACC are based on the retrospective study or small trial only until the result of a large prospective study (FIRM-ACT) been announced in 2012.[13] This study showed a response rate and progression free survival significantly better in patients who received EDP with mitotane rather than streptozocin plus mitotane.[13] However, there were no significant differences in overall survival or serious adverse events.[13]

The role of radiotherapy in ACC is only well defined in metastatic disease, especially in bone or unrespectable bulky tumor in the abdomen.[14] German adrenocortical carcinoma registry showed 57% of advanced disease patients' responses to radiotherapy and Dutch registry revealed advanced ACC could be radiosensitive.[15,16]

In conclusion, the treatment of stage IV ACC has often yielded disappointing results in terms of survival prolongation. The extension of this patient's survival beyond 5 years after the diagnosis of her advanced ACC was achieved by combining multiple treatment approaches. Reducing the overall tumor burden by extensive surgery with aggressive reoperation and targeted approach to metastatic lesions lead to a better control of tumors by the combination of mitotane and Sorafenib.

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References

1. Huang CJ, Wang TH, Lo YH, Hou KT, Won JGS, Jap TS, et al. Adrenocortical carcinoma initially presenting with hypokalemia and hypertension mimicking hyperaldosteronism: a case report. *BMC Research Notes.* 2013; 6: 405.
2. Fassnacht M, Libé R, Kroiss M, Allolio B. Adrenocortical carcinoma: A clinician's update. *Nature Reviews Endocrinology.* 2011; 7: 323 – 335.
3. Berruti A, Baudin E, Gelderblom H, Haak HR, Porpiglia F, Fassnacht M, et al. Adrenal cancer: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol,* 2012; 23 (Suppl 7): vii131 – vii138.
4. Meyer A, Behrend M. 32-year survival with metastatic adrenal cortical carcinoma--update of a case report. *Anticancer Res.* 2007; 27: 1045 – 1046.
5. Icard P, Chapuis Y, Andreassian B, Bernard A, Proye C. Adrenocortical carcinoma in surgically treated patients: a retrospective study on 156 cases by the French Association of Endocrine Surgery. *Surgery.* 1992; 112: 972 – 979; discussion 979.
6. Crucitti F, Bellantone R, Ferrante A, Boscherini M, Crucitti P. The Italian registry for adrenal cortical carcinoma: Analysis of a multiinstitutional series of 129 patients. The ACC Italian Registry Study Group. *Surgery.* 1996; 119: 161 – 170.
7. van Ditzhuijsen CIM, van de Weijer R, Haak HR. Adrenocortical carcinoma. *Neth J Med.* 2007; 65: 55 – 60.
8. Baudin E, Leboulleux S, Al Ghuzlan A, Chougnet C, Young J, Deandreis D, et al. Therapeutic management of advanced adrenocortical carcinoma: what do we know in 2011? *Hormones & Cancer.* 2011; 2: 363 – 371.
9. Sakamoto K, Ariyoshi A, Okazaki M. Metastatic adrenocortical carcinoma treated by repeated resection: a case report of long-term survival over 18 years. *Int J Urol.* 1995; 2: 50 – 52.
10. Wood BJ, Abraham J, Hvizda JL, Alexander HR, Fojo T. Radiofrequency ablation of adrenal tumors and adrenocortical carcinoma metastases. *Cancer.* 2003; 97: 554 – 560.
11. Butler C, Butler WM, Rizvi AA. Sustained remission with the kinase inhibitor sorafenib in stage IV metastatic adrenocortical carcinoma. *Endocr Pract.* 2010; 16: 441 – 445.
12. Quinkler M, Hahner S, Wortmann S, Johanssen S, Adam P, Ritter C, et al. Treatment of advanced adrenocortical carcinoma with erlotinib plus gemcitabine. *J Clin Endocrinol Metab.* 2008; 93: 2057 – 2062.
13. Fassnacht M, Terzolo M, Allolio B, Baudin E, Haak H, Berruti A, et al. Combination chemotherapy in advanced adrenocortical carcinoma. *N Engl J Med.* 2012; 366: 2189 – 2197.
14. Lebastchi AH, Kunstman JW, Carling T. Adrenocortical carcinoma: Current therapeutic state-of-the-art. *Journal of Oncology.* 2012; 2012: 234726.
15. Polat B, Fassnacht M, Pfreundner L, Guckenberger M, Bratengeier K, Johanssen S, et al. Radiotherapy in adrenocortical carcinoma. *Cancer.* 2009; 115: 2816 – 2823.
16. Hermsen IGC, Groenen YE, Dercksen MW, Theuws J, Haak HR. Response to radiation therapy in adrenocortical carcinoma. *J Endocrinol Invest.* 2010; 33: 712 – 714.