CASE REPORT

Favourable prognosis in metastatic adrenal carcinoma: An unexpected outcome

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Abstract

The case of a 45-year-old male patient diagnosed with European Network for the Study of Adrenal Tumours (ENSAT) criteria, stage IV adrenocortical carcinoma (ACC) with unexpectedly prolonged survival is being reported. The patient underwent resection of stage IV ACC and despite suboptimal adherence to postoperative mitotane and chemotherapy, had a prolonged survival spanning almost seven years. The possible reasons for such an outcome are discussed. ACC is a rare tumour with stage 4 disease known to be associated with a particularly grim prognosis. A low grade on histology (mitotic index 11-12 per 50 HPF) was likely responsible for the prolonged survival of our patient. Low grade disease may predict extended survival in stage IV ACC.

Keywords: adrenal cancers, Adrenal cortex diseases, Adrenal gland diseases, Adrenal gland neoplasms.

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Introduction

Adrenocortical carcinoma (ACC) is a rare, aggressive neoplasm with limited therapeutic options. Tumour stage is the most important prognostic factor, with the presence of metastasis being a particularly strong predictor of poor prognosis.[1] However, the prognosis is not uniform within a given tumour stage. Factors such as tumour grade,[2] completeness of resection,[3] older age,[4] and presence of hypercortisolism[5] are independent prognostic determinants. Adrenocortical tumours with a mitotic rate >20 per 50 high power field (HPF) are classed as high grade, while those with a mitotic rate <20 per 50 HPF are considered low grade.[6] Median survival of ACC patients ranges from 3-4 years, with estimated five-year survival being lowest in stage 4 disease ranging from 0% to 28%.[1]

Case Report

The case of a 45-year-old male patient, a known case of hypertension and non-ischaemic cardiomyopathy, presenting to Aga Khan University Hospital, Karachi in May 2012 with a gradual increase in abdominal girth over 2-3 months accompanied by weight loss is described. Examination revealed a large mass occupying the left upper outer quadrant of the abdomen. Abdominal purple striae and axillary acanthosis nigricans were also seen.

Computed tomography of the abdomen revealed a huge mass originating from the left adrenal gland with multiple nodules in bilateral lung fields and pleura. Lab workup showed 24-hour urinary vanillylmandelic acid of 3.1 mg/24 h (normal, ≤6 mg/24 h); overnight dexamethasone suppression test gave a result of 23.30 µg/dl (normal, 4.3-22.4 µg/dl); 24-hour urinary cortisol was 5429 µg/24 hours (normal, 36-137 µg/24 hours) and fasting blood glucose 77 mg/dl (normal, 65-100 mg/dl).

Ketoconazole was given pre-operatively, and hydrocortisone was given during and after surgery. The patient underwent en bloc surgical excision of the mass measuring 32 x 22 x 17cm. Histology showed nests of polygonal cells having abundant eosinophilic cytoplasm and moderate atypia with 11-12 mitoses per 50 HPF (Figure-1). Capsular and vascular invasion by tumour cells was seen along with extensive foci of necrosis (Figure-2 through 4), focal calcification and myxoid change. Immunohistochemical staining was reactive for synaptophysin, melan A, cytokeratin CAM 5.2 and inhibin. The histopathologic picture was given a score of 5 on the Weiss scoring system, which classifies a score of ≥3 as being consistent with malignant adrenocortical carcinoma.[7] Based on the above, a diagnosis of stage IV

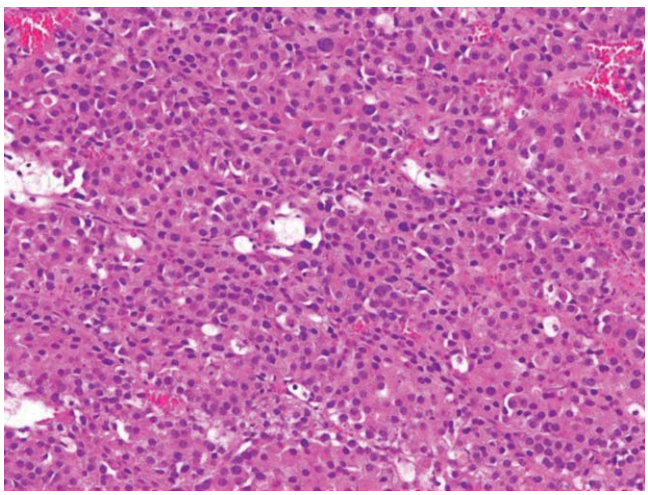

Figure-1: Histologic section of adrenal carcinoma (haematoxylin and eosin, x100). Nests of polygonal cells with abundant eosinophilic cytoplasm and moderate atypia.

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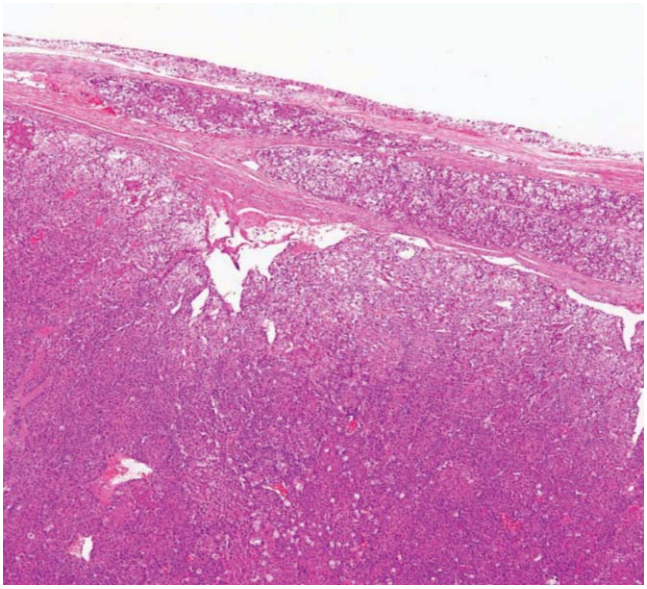

Figure-2: Histologic section of adrenocortical carcinoma (haematoxylin and eosin, x4) showing capsular invasion by tumour cells.

ACC was made.

Due to the non-availability of the medication, there was a delay of two weeks in starting and maintaining recommended doses of mitotane. Taking the medication for a total of 26 months postoperatively, the patient maintained a dose of 2g/day to 3.5g/day during the bulk of therapy; however, mitotane levels were not measured. A week after surgery, the patient's 8 AM serum cortisol levels decreased to 3.10 µg/dl (normal, 4.3-22.4 µg/dl) for which dose of hydrocortisone was adjusted accordingly. Serum renin and aldosterone levels done at 4 months postoperatively were 130.1 IU/ml (normal, 4.4-46.1 uIU/ml) and 24.24 ng/dl (normal, 2.52-39.2 ng/dl)

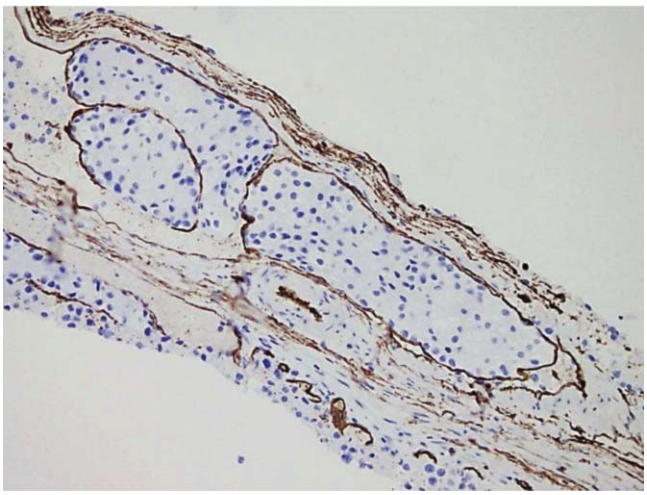

Figure-3: Immunostaining of adrenocortical carcinoma (CD34, x200) showing vascular invasion by tumour cells.

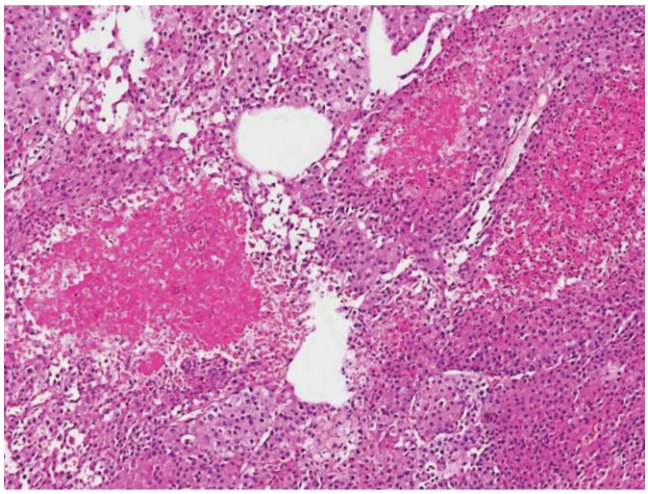

Figure-4: Histologic section of adrenocortical carcinoma (haematoxylin and eosin, x8) showing focal necrosis of tumour.

respectively. Computed tomography scan done five months postoperatively showed stable disease. Later a new hepatic metastatic lesion was observed on the 12-month scan with the progression of pulmonary and hepatic lesions on subsequent scans. Addition of chemotherapy with cisplatin and etoposide (doxorubicin was omitted due to cardiac comorbidity) to the regimen which lead to a reduction in the number of hepatic and pulmonary lesions. Despite this encouraging initial response, monitoring ultrasound scan after completion of chemotherapy showed interval progression of the hepatic lesions. Second-line chemotherapy was planned. However, the patient did not come for follow up for almost five years and stopped taking all medications. Computed tomography at that time showed an increase in the number and size of pulmonary metastatic lesions. However, the hepatic lesions remained stable and there was no evidence of disease recurrence at the site of surgery. Six years and 11 months after diagnosis, the patient expired due to cardiogenic shock.

Discussion

We report the case of a patient with Stage 4 ACC whose clinical course defied the predicted prognosis. Features of the case that favoured a poor prognosis are due to the presence of distant metastases, autonomous cortisol secretion, and histologic features of focal necrosis, venous and capsular invasion by tumour cells.[2] However, the mitotic rate of 11-12 per 50 HPF would classify the tumour as low grade.

Our patient presented with stage 4 ACC with unresectable extra-abdominal metastases; therefore, the aim of therapy was complete resection of the adrenal mass followed by long-term control of the

metastatic lesions. This was achieved with some success as there was no recurrence at the site of surgery, presumably due to an R0 resection, although this was not explicitly reported in the histopathology report. Completeness of resection is a known independent prognostic factor for ACC.[3]

Postoperatively, mitotane monotherapy was initially started to address residual disease taking patient preference for avoidance of chemotherapy into account. Based on clinical experience and low-quality evidence, adjuvant mitotane is recommended to treat advanced ACC which has a high risk of recurrence.[1] Treatment with mitotane is ideally titrated to achieve therapeutic mitotane levels of 14-20 µg/ml.[1] Our approach was to increase the dose of mitotane over two weeks to the highest tolerated dose; however, the lack of availability of the drug hindered the patient from adhering to the advised dose. As mitotane levels were not measured, it is uncertain if the patient achieved recommended therapeutic blood levels. Therapeutic blood levels of mitotane have been documented with doses as low as 1-2 g/day[8] thus, it is possible that the administration of adjuvant mitotane played a significant role in slowing down the progression of the disease.

Our patient was off all medications for almost four years, the greater part of the documented survival. During this period, he developed only a slight increase in the number and size of pulmonary metastases with hepatic lesions remaining stable. Thus, the stage 4 ACC tumour afflicting our patient progressed quite indolently even without treatment. This is likely due, in large part, to the mitotic index <20 per 50 HPF. This claim is substantiated by the fact that a mitotic rate <20 per 50 HPF was the only known prognostic factor in relative agreement to the observed prognosis of unexpectedly prolonged survival despite suboptimal adherence to therapy and inconsistent follow-up. However, there are factors that affect prognosis that remain unknown in our patient, such as genetic mutations and molecular signatures.

A few case reports have reported of stage 4 ACC with prolonged survival.[9-15] Most of these reports do not mention tumour grade; however, in those that do mention, most patients had low-grade disease on histology. An analysis of 124 patients examining predictors of outcome in ACC found mitotic index, presence of distant metastases at presentation and adjacent organ invasion, to be independent predictors of survival. Among these, only the mitotic index predicted survival across all tumour stages.[2] A retrospective review of 91 patients with ACC compared low-grade to high-grade tumours within each of the 4 stages of ACC. A statistically significant difference in time to recurrence and survival was seen within stage 2 tumours when comparing low-grade to high-grade tumours. Patients having low-grade tumours survived longer and had recurrence later. The authors of that study proposed a modification to the ENSAT staging system that incorporated tumour grade.[16]

Conclusion

This case report indicates that low tumour grade most likely contributed to prolonged survival of our patient and may be a predictor of prolonged prognosis in stage 4 ACC. As such, it adds to the case for including histological grade in prognostication and therapeutic decision-making of adrenocortical carcinoma.

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Conflict of Interest: None to declare.

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