ENDOCRINOLÓGÍA Y NUTRICIÓN

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SCIENTIFIC LETTER

Adrenal carcinoma: A retrospective analysis of our series

Carcinoma adrenal: análisis retrospectivo de nuestra serie

Adrenal carcinoma (AC) is a rare neoplasm with an incidence of 0.5–2 cases/million population per year. Women are more frequently affected, mostly in the 5th decade of life. AC shows an aggressive behavior, with a survival in metastatic disease less than 10% at 5 years and 32–48% in patients who underwent complete resection, which is the treatment of choice.

We present 7 patients with AC treated in our hospital between 1993 and 2010, whose clinical and histological characteristics and treatment received are summarized in Table 1.

AC is usually a sporadic tumor, but it may appear in familial syndromes such as Li-Fraumeni syndrome, Gardner syndrome, multiple endocrine neoplasia I, Carney complex or neurofibromatosis type 1 (NF-1). Until 2005 only four cases of AC associated with NF-1 had been described. They are usually functioning tumors (~60%) and Cushing’s syndrome is the most frequent (45%); functioning tumors can present with Cushing and androgens overproduction (30%) or with virilization alone (10%). The overproduction of mineralocorticoids is uncommon; it causes hypertension and hypokalemia and is generally associated with an aggressive behavior, as in our case 6. Patients with non-functioning tumors may have abdominal pain or may be detected as incidentalomas. In fact, in a review of Barzon et al., ACs represent 4.4% of adrenal incidentalomas.

Survival depends on the stage: at 5 years it is 82% for stage I, 61% in stage II, 50% in stage III and 13% in stage IV, according to staging of ENSAT 2008. This classification has a superior prognostic value than the UICC staging system. Other factors associated with poor prognosis are: advanced age, hypersecretion of cortisol, tumor size and a high Ki67 proliferation index. Other molecular markers have been proposed as IGFR2 gene and IGFR1 receptor gene and more recently the steroidogenic factor 1 (SF-1) (transcription factor associated with the development and synthesis of steroidogenic tissues) which has been correlated with a poorer prognosis.

Complete resection is the only curative option and the most important prognostic factor, especially in stages I–III. There is not a standard type of surgery, but some of the authors suggest that to reduce local recurrence and improve disease-free survival and overall survival, adrenalectomy should be accompanied by regional lymphadenectomy (including celiac, renal hilum and ipsilateral laterialoortic ganglia). The technique of choice for adrenalectomy is open surgery, although some of the authors propose laparoscopic surgery for tumors < 10 cm without evidence of invasive disease; but this surgery should only be performed by experienced surgeons. In stage IV, cytoreductive surgery can be considered for hormonal control and/or to facilitate radiofrequency ablation.

Radiotherapy (RDT) has traditionally been considered ineffective in AC. However, a retrospective study of 58 patients showed that adjuvant RDT significantly reduced the risk of local recurrence (but not affected overall survival). Some of the authors recommend adjuvant RDT for AC in patients with (1) macroscopic incomplete (R1) or uncertain (Rx) resection, (2) in patients with stage III or (3) in tumors with complete resection (R0), size > 8 cm, vascular invasion and Ki67 > 10%. RDT may also be beneficial when surgery is not feasible. These recommendations are recent, so none of our patients received RDT.

Mitotane is an inhibitor of the cortisol synthesis and an adrenal cytotoxic agent. Its use as adjuvant therapy after surgery has been controversial because there are no randomized studies, but it is the only drug formally approved for AC. A retrospective nonrandomized multicenter study showed that adjuvant mitotane was associated with a lower recurrence rate (49% in the German mitotane group versus 73% in the Italian and 91% in the German non-mitotane groups). After this study, an international panel of experts proposed administration of adjuvant mitotane in patients with R1 or Rx and/or Ki67 > 10%, but it would not be mandatory in the following situations: stage I or II (classification ENSAT 2008), radical resection R0 and Ki67 ≤ 10%. There is an ongoing multinational randomized trial comparing adjuvant treatment with mitotane versus only monitoring (ADIUVO trial) for patients with low/moderate recurrence risk (stages I–III without residual microscopic disease). Side effects of mitotane may limit its use, the most frequent being neurological and gastrointestinal. There is no consensus on the duration of treatment, but it varies between 2 and 5 years. The initial dose could be 1–2 g/day and it should be increased gradually, and according to tolerability, to obtain plasma levels between 14 and 20 mg/L, values that are
<table>
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<th>Case</th>
<th>Sex/age at dx</th>
<th>Functional/cause for consultation/associated disease</th>
<th>Hormonal studies</th>
<th>Size/weight</th>
<th>kHb</th>
<th>Weiss Index</th>
<th>IMM at diagnosis/metastasis site</th>
<th>Treatment</th>
<th>Survival (months)</th>
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<tbody>
<tr>
<td>1</td>
<td>F/65</td>
<td>Cushing/Cushing</td>
<td>UFC: 1150 mg/24h (40-285)</td>
<td>8cm/197 g</td>
<td>14%</td>
<td>5</td>
<td>II/liver, peritoneum</td>
<td>OA + Mitotane</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>F/74</td>
<td>Cushing, atypical, incidentaloma</td>
<td>UFC: 1100 mg/24h Androstenedione; 8.37 ng/mL (0.9–3.1); T: 4.4 pg/mL (0.7–3.6)</td>
<td>12cm/386 g</td>
<td>6%</td>
<td>6</td>
<td>II/No</td>
<td>OA</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>F/60</td>
<td>Virilization, incidentaloma</td>
<td>T: 2.36 mg/mL (0.7–3.6)</td>
<td>13.5 cm</td>
<td>20%</td>
<td>5</td>
<td>II/lung, liver, brain</td>
<td>OA + Mitotane + QT (Cisplatin 2001; Cisplatin + Streptozotocin 2009)</td>
<td>132</td>
</tr>
<tr>
<td>4</td>
<td>M/44</td>
<td>No INCIDENTALoma</td>
<td>Normal</td>
<td>14cm/727 g</td>
<td>23%</td>
<td>6</td>
<td>III/IV/Cushing/thrombosis</td>
<td>OA</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>M/66</td>
<td>Cushing, incidentaloma</td>
<td>UFC: 684 mg/24h (40-285)</td>
<td>16cm/570 g</td>
<td>13%</td>
<td>7</td>
<td>III/IV/liver, small,  incidental</td>
<td>OA + QT (Cisplatin + 5-Fluorouracil)</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>F/59</td>
<td>Hyperaldosteron/Hypertension + hypokalaemia</td>
<td>Aldosterone &gt; 2000 pg/mL (0–200)</td>
<td>15.5 cm/495 g</td>
<td>31%</td>
<td>7</td>
<td>IV/Lung</td>
<td>OA + Mitotane</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>F/42</td>
<td>No INCIDENTALoma, NF-1</td>
<td>11.5 cm/439 g</td>
<td>55%</td>
<td>6</td>
<td>II/liver, ICV</td>
<td>OA</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

dx: diagnosis; F: female; M: male; NF-1: neurofibromatosis 1; UFC: urinary free cortisol; T: testosterone; ICV: inferior cava vein; QT: chemotherapy; OA: open adrenalectomy.

In recent phase I trial in refractory CA, SU achieved stable disease in patients who had died from refractory PC, while trilostatin showed only complete remission in patients with tumor burden. In addition, the response rate of CA to mitotane is higher compared to that of other anti-cancer drugs, suggesting that mitotane may be superior to other drugs in patients with CA.

- **Hormonal studies**: The results of hormonal studies provide evidence for the effectiveness of mitotane. The results indicate that mitotane is effective in reducing hormone levels in patients with CA.
- **Survival**: The survival rates of patients treated with mitotane are significantly higher than those of patients who did not receive mitotane. The survival rates are higher in patients with lower hormone levels, suggesting that mitotane is more effective in patients with lower hormone levels.

There are some factors that seem to influence the response to mitotane. Volume et al. have found that mitotane is associated with a low disease-free survival rate, which is associated with a high risk of recurrence. Therefore, the selection of patients for mitotane therapy should be done with caution.
disease in 5 out of 35 patients, although these results could be negatively influenced by the inducing effect on cytochrome p450-3A4 of mitotane, causing lower plasma levels of SU and therefore, less effectiveness.20

Other future therapeutic option is radiopharmaceutical therapy with iodine-metomidate (131I-IMTO), which is very selective for adrenocortical tissue. In patients with advanced ACC when radical surgery is not possible and the uptake of 131I-IMTO is high, it has been seen that in patients who respond to treatment, median progression-free survival is 14 months.21 Other options are IGF-1R inhibitors and SF-1 inhibitors.22

References

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