Complete Response of Metastasized Adrenal Cortical Carcinoma With o,p‘-DDD

Case Report and Literature Review

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This study concerns the history of a male patient with hormone-producing adrenal cortical carcinoma. Six months after resection of the primary tumor, lymph node metastases were detected and treatment with o,p‘-DDD [1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane] (Lysodren/mitotane) was started. After 2 years, a complete histologically proven response was confirmed at laparotomy and is still sustained 2 years after the discontinuation of treatment. As a consequence of insufficient steroid replacement the patient suffered bouts of adrenal insufficiency. After 1 year of treatment, the measurement of the plasma levels of o,p‘-DDD showed an accumulation of the drug. At that time, progressive major central nervous system toxicity occurred, which proved to be reversible on discontinuation of the treatment.


ADRENAL CORTICAL CARCINOMA (ACC) is an extremely rare tumor with a reported incidence of about two cases per 1,000,000 of the population per year. In general, the prognosis is very poor once the tumor has metastasized. Since its clinical introduction in 1960, o,p‘-DDD [1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane] (Lysodren/mitotane) has proven to be effective for the treatment of patients with metastasized ACC. In two studies, the response rate was 35% and 61%, and the median duration of response was 7 and 6 months, respectively. In 107 patients studied by Lubitz and associates the effect of this drug on the duration of survival was reported to be 8.4 months (median, 5 months). Macfarlane reported a mean duration of survival of 2.9 months from the time of diagnosis in 20 untreated inoperable cases of ACC. In the literature, we found seven patients with advanced ACC in whom a complete response had been achieved with o,p‘-DDD. None of these complete responses had been proven by biopsy specimens. In two patients, treatment with o,p‘-DDD was discontinued, and no evidence of disease was found in the following 17 and 13 months, respectively. In another patient, who had been treated by a short course of o,p‘-DDD and 5-fluorouracil, the findings at autopsy 9 years later did not provide microscopic evidence of ACC.

The toxicity of o,p‘-DDD is severe and the effects have been observed in 87% of patients, mainly nausea and vomiting (79%), central nervous system (CNS) depression (49%), and skin rash (15%). In addition, side effects resulting from the required steroid replacement further complicate treatment with o,p‘-DDD.

In the current study we report a patient with a histologically documented complete response of metastasized ACC following treatment with o,p‘-DDD. The review of the clinical course and the measurement of plasma levels of the drug indicate another approach to using o,p‘-DDD and minimizing its toxicity.

Case Report

In March 1977, a 45-year-old man was referred to our hospital because of a large tumor mass (10 × 16 cm) in the left side of the abdomen. There were no paraneoplastic symptoms indicating hormone production. Routine hematologic and biochemical examinations were unremarkable except for an elevated erythrocyte sedimentation rate (ESR) of 62 mm and an lactate dehydrogenase (LDH) level of 595 U/l. Urinary 24-hour excretion showed an increased steroid excretion (Table 1) which did not change under adrenocorticotropic hormone (ACTH) stimulation and was not suppressed by dexamethasone, a finding which is consistent with the diagnostic ACC. Radiologic investigations revealed a large lesion localized in the retroperitoneal lumbar region above the left kidney. Angiographic examination showed

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TABLE 1. Biochemical Data for Surgical Treatment of Adrenal Cortical Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Normal values</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR &lt; 7 mm</td>
<td></td>
<td>62</td>
<td>40</td>
<td>96</td>
</tr>
<tr>
<td>LDH &lt; 175 U/l</td>
<td></td>
<td>595</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td>Cortisol (9 am)</td>
<td>200-700 μmol/l</td>
<td>350</td>
<td></td>
<td>210</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-hydroxycorticoids</td>
<td>20-70 μmol/24 h</td>
<td>215</td>
<td>23</td>
<td>43</td>
</tr>
<tr>
<td>Etiocolanolate</td>
<td>10-50 μmol/24 h</td>
<td>94</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Androsterone</td>
<td>10-45 μmol/24 h</td>
<td>142</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Dehydroepiandrosterone</td>
<td>0-30 μmol/24 h</td>
<td>350</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>&lt;8 μmol/24 h</td>
<td>20</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Tetrahydro-S</td>
<td>&lt;1 μmol/24 h</td>
<td>60</td>
<td></td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

A: data just before surgery; B: postoperative data; C: data at diagnosis of metastases.

an avascular tumor and echographic examination indicated that this mass had a solid structure. There was increased uptake of Ga-67 citrate. Uptake of 6-β-iodomethyl-nor cholesterol was normal in the right adrenal gland and absent in the left gland.

At laparotomy, a tumor mass with a diameter of 20 cm and originating from the left adrenal gland was resected radically, and there were no apparent metastases.

The diagnosis ACC was confirmed at histologic examination. In cross section, the tumor showed a brownish-red discoloration with areas of hemorrhage and necrosis. The histologic findings included pleomorphic cells, having hyperchromatic nuclei with nucleoli and a foamy, occasionally vacuolated, cytoplasm in a fibrous stroma. Mitotic activity was about 3 per high power field (×500). There was invasion of the vessels and of the capsule. The section margins were free of tumor (Fig. 1).

Postoperatively, the ESR dropped to 40 mm, and LDH and steroid excretion returned to normal levels (Table 1) but in December 1977, the ESR rose again to 96 mm (Table 1). A Ga-67 citrate scan revealed an increased uptake adjacent to the right kidney (Fig. 2). A computerized tomography (CT) scan showed a mass in this area (Fig. 3).

In March 1978, a diagnostic laparotomy was performed. In the right paralumbar region there was a nonresectable large round mass of retroperitoneal lymph nodes with a diameter of 10 cm. Histologic examination of a biopsy specimen confirmed

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**Fig. 1.** Histologic pattern of ACC. Pleomorphic cells with hyperchromatic nuclei and foamy cytoplasm in a fibrous stroma (H & E, original magnification 3.2 × 10). Inset: original magnification 3.2 × 40.

**Fig. 2.** In the right upper part of the abdomen a Ga-67 citrate scan shows high uptake in the right paralumbar region below the liver.
the diagnosis ACC, the tumor cells showing round to oval nuclei, prominent nucleoli, and abundant granular cytoplasm, similar to the findings in the primary tumor (Fig. 4).

Treatment was started with o,p'-DDD in a low dose which was increased to 6 g daily until plasma levels reached 15 to 20 μg/ml. Oral glucocorticoid replacement consisted of cortisoneacetate 37.5 mg/day. Six months later a Ga-67 citrate scan and a CT scan showed a complete regression of the mass.

However, the toxicity of o,p'-DDD was severe. Initially, bouts of adrenal insufficiency were prevented by increasing the dose of hydrocortisone to 50 mg/day and by the addition of the mineralocorticoid desoxycortone 25 mg intramuscularly weekly. After a year of treatment, the patient became depressed, his speech was slurred, and he had an ataxic gait. There proved to be no cerebral metastases. His electroencephalogram (EEG) showed a diffuse low-voltage pattern consistent with drug toxicity. During this period, plasma levels of o,p'-DDD were in the range of 20 to 34 μg/ml. Because of the progressive CNS toxicity, the treatment was discontinued in May 1980. A laparotomy to remove residual tumor tissue was negative, as were intraoperative biopsy results. After o,p'-DDD was withdrawn the patient’s condition improved, as did the EEG. The plasma half-life of o,p'-DDD was 55 to 60 days. In December 1980, traces of o,p'-DDD could still be detected in the patient’s plasma. The steroid dose was reduced to 37.5 mg hydrocortisone, and desoxycortone was discontinued. At the moment, after a 3-year o,p'-DDD-free interval, the patient is alive and able to work. There are no signs of tumor recurrence, as shown by a recent Ga-67 citrate scan and a CT scan.

Discussion

Valuable diagnostic procedures for the detection of ACC are radiologic examinations, including echography and CT scanning, and determination of serum and urinary hormone levels. After removal of the primary tumor the search for metastases can be difficult. In our patient, Ga-67 scanning appeared to be helpful, uptake occurring in both the primary tumor and the lymph node metastases. This diagnostic procedure has been reported to be valuable for the detection of pulmonary carcinoma, hepatoma, and some stages of lymphomas. In other neoplasms, the sensitivity has been known to be less than 70%. We are not aware of its sensitivity for the localization of ACC. Urinary steroid excretion was increased before resection of the primary tumor. In our patient, ACC metastases did not appear to produce excess amounts of steroids, but this may be related to the relatively small tumor volume at that time.
Because of its high fat solubility, o,p'-DDD is deposited in subcutaneous fat and in the liver, brain, and both normal and malignant adrenal tissue and the drug can be measured in the plasma. The use of a fat-containing vehicle results in a much higher plasma level after an oral dose and probably in fewer gastrointestinal side effects. In the initial studies on o,p'-DDD in metastasized ACC the recommended daily dose was 8 to 10 g/day, which may produce severe toxicity. However, Hogan and associates have reported objective responses in two patients at doses of 5 and 6 g/day which gave a plasma level of 10 µg/ml. In our patient an o,p'-DDD dose of 6 g/day was effective with plasma levels of 15 to 20 µg/ml. The optimal plasma level necessary to achieve objective tumor response is not known yet. After 1 year of treatment, the regimen resulted in increasing plasma levels up to 34 µg/ml. Another manifestation of accumulation of o,p'-DDD was the late occurrence of CNS toxicity. As proven through the results in our patient, the toxic effects of o,p'-DDD are reversible after discontinuation of the drug.

Long-term administration of o,p'-DDD at doses higher than 3 g/day results in adrenal cortical atrophy. Early in the therapy, there is a need for both glucocorticoid and mineralocorticoid replacement. O,p'-DDD also alters the peripheral metabolism of cortisol which is accompanied by increased excretion of 6-ß-hydroxycortisol. Stimulation of the metabolism of cortisol seems to be related to induction of the liver microsomal enzymes. In selected cases, such as our patient, the glucocorticoid dose should be increased.

Several months after discontinuation of the treatment with o,p'-DDD, traces of the drug can still be detected in the blood. This makes it necessary to continue steroid replacement, and, on reduction of the dosage, to watch keenly for signs of adrenal insufficiency.

Further investigation is needed to establish effective o,p'-DDD plasma levels for the treatment of advanced ACC.

Progressive toxicity might be prevented by lowering the dose of o,p'-DDD, in order to maintain the same plasma levels in case of long-term administration.

REFERENCES


