

## Original Article

# Case Report: Adjuvant Therapy with a High Dose of Mitotane for Adrenocortical Carcinoma in a 4-year-old Boy

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**Abstract.** This report concerns control of adrenocortical carcinoma in a 4-yr-old boy by adjuvant mitotane therapy. He presented precocious puberty and was diagnosed with adrenocortical carcinoma. He underwent surgical resection, and adjuvant mitotane therapy was initiated, leading to a final dose of 5.0 g/day. Despite monitoring of the plasma mitotane level, encephalopathy developed 5 mo after initiation. Although he recovered from the encephalopathy, careful follow-up of his growth and development is necessary. On the other hand, he has been free of recurrence and metastases for 3 yr since discontinuation of mitotane. A high dose of mitotane is potentially effective as an adjuvant chemotherapy for adrenocortical carcinoma, although optimal and safe usage needs to be established for children.

**Key words:** adrenocortical carcinoma, adjuvant therapy, mitotane, encephalopathy

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## Introduction

Adrenocortical carcinoma is a rare malignant tumor, especially in children. It has a poor prognosis, and the only curative therapy is complete resection by surgery (1–3). Mitotane (o,p'-DDD) has been widely used as an adjuvant chemotherapy in adults, and the importance of monitoring the plasma level has been emphasized (4–6). However, its efficacy is controversial, and the optimal therapy for children remains to be

established. Its narrow therapeutic range easily leads to several side effects and makes the therapy difficult (4, 6, 7). We herein report a 4-yr-old boy with adrenocortical carcinoma that was controlled by adjuvant therapy with a high dose of mitotane.

## Case Report

The patient was a 4-yr-old boy born to nonconsanguineous parents. He has a strong familial history of carcinoma on his mother's side: mother, hemangioblastoma and breast cancer; grandmother, liver and breast cancer; great-grandfather, gastric cancer; and great-grandmother, renal cancer. He was admitted for evaluation of precocious puberty with

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**Table 1** Endocrinological data

LH	2.2 mIU/ml (0–0.4, 0.8–4.2*)
FSH	3.4 mIU/ml (0.6–3.0, 2.9–10.8*)
Testosterone	2.5 ng/ml (0.3–1.3)
ACTH	76 pg/ml (9.1–27.3)
Cortisol	12.3 $\mu$ g/dl (6.4–18)
DHEA-S	1500 ng/ml (59–87)
Androstenedione	0.87 ng/ml (0.12–0.18)
Urinary 17-OHCS	1.22 mg/day (0.96–1.94)
Urinary 17-KS	1.26 mg/day (0.12–0.3)
LH-RH stimulation test	
Peak LH	20.3 mIU/ml (0.4–6.0, 18.2–38.0*)
Peak FSH	8.3 mIU/ml (6.2–15.6, 5.8–22.3*)

Values in parentheses are reference ranges for the patient's age or pubertal age\*. DHEA-S, dehydroepiandrosterone sulfate; 17-OHCS, 17-hydroxycorticosteroid; 17-KS, 17-ketosteroid.

acceleration of growth rate and maturation of external genitalia. His height was 116.9 cm (+3.62 SD), and his body weight was 23.6 kg (body mass index, 17.3 kg/m<sup>2</sup>). His Tanner stages were G2 and PH2, and each of his testicles was 8 ml in volume. No other abnormalities, such as cushingoid symptoms and hemihypertrophy, were found. The results of blood count and blood chemistry evaluation were all within normal ranges. Although his familial history reminded us of *p53* gene mutation, genetic analysis was not performed because informed consent was not obtained. The endocrinological data are shown in Table 1. His LH, FSH and testosterone levels were elevated compared with his age's reference. Although his dehydroepiandrosterone sulfate (DHEA-S), androstenedione and urinary 17-ketosteroid (17-KS) levels were increased, his cortisol and urinary 17-hydroxycorticosteroid (17-OHCS) levels were normal. The peaks of LH and FSH by LH-RH stimulation were at pubertal levels. His bone age was 11 years. Magnetic resonance imaging (MRI) showed a 2 × 3 cm mass in the left adrenal gland, and <sup>131</sup>I-adosterol scintigraphy showed increased uptake there. No metastases were found based on radiological findings. An operation was performed based on the diagnosis of left androgen-secreting

adrenocortical tumor. The tumor, which was 2 × 2.1 × 2.6 cm in size with focal necrosis and hemorrhage, was totally removed, and the pathological diagnosis was adrenocortical carcinoma.

Mitotane therapy was initiated as an adjuvant chemotherapy because the capsule and surgical margin were microscopically invaded by the carcinoma cells. We began with 0.5 g/day and increased the dose gradually by 0.5 g/1–2 weeks while monitoring the plasma level, up to 5.0 g/day (plasma level, 13.43  $\mu$ g/ml, 3 mo after initiation). Leuprorelin acetate was also administered because an LH-RH test after the surgery still showed a response at the pubertal level (LH, 20.9 mIU/ml; FSH, 6.6 mIU/ml), suggesting secondary central precocious puberty. Hydrocortisone replacement was also initiated for treatment of adrenal insufficiency caused by mitotane.

Five months after initiation of mitotane, the patient became anorexic and his steps while walking became unsteady. These symptoms progressively worsened, and he began to have difficulty walking and speaking. He was apathetic to his surroundings and showed memory disturbance. His gait was unstable due to moderate spastic quadriplegia and ataxia. A

head MRI revealed mild cerebral and cerebellar atrophy, and electroencephalography showed diffuse slowing of background activity. Thus, encephalopathy developed due to the increased level of mitotane (34.55  $\mu\text{g/ml}$ , 6 mo after initiation). We discontinued mitotane and administered a high dose of hydrocortisone for adrenal crisis. The plasma mitotane level gradually decreased, and the neurological symptoms improved. It took 6 mo for the mitotane to disappear from the plasma and for clinical recovery from the encephalopathy.

No signs of tumor recurrence have been observed for 3 yr since discontinuation of mitotane. All neurological abnormalities found after initiation of mitotane, including memory disturbance and motor disability, are no longer present, thereby enabling him to preschool and play with similarly aged children without problems.

### Discussion

Adrenocortical carcinoma is a rare disease with poor prognosis, especially in children. The efficacy of anti-cancer drugs cannot be expected, and the only effective treatment is complete resection (1–3). Although its efficacy is controversial, mitotane is widely used in adults for this disease, and its efficacy for prolonging recurrence-free survival has recently been reported (8). According to a report that recruited 254 pediatric patients with adrenocortical tumors, our patient is classified into stage III based on the possibility of a residual tumor identified by microscopic examination, which indicates a poor 5-yr event-free survival prognosis (2). Although he required adjuvant chemotherapy, anti-cancer drugs and genetic factors, such as *p53* gene mutation, are presumed to be related to the occurrence of the second cancer (9). Therefore, we chose to use mitotane as the adjuvant chemotherapy.

There has been limited use of mitotane in children, and its usage remains to be established.

Even in adults, a wide range of doses is used depending on the individual. Monitoring of the plasma level is emphasized to exploit its therapeutic effects and to avoid its toxic effects. Mitotane therapy at low plasma levels is known to be meaningless, and its level should be more than 14  $\mu\text{g/ml}$  (4–6). A high dose of mitotane was reported to successfully treat a 14-yr-old patient with adrenocortical carcinoma and extensive pulmonary metastases (10). Therefore, we gradually increased the mitotane dose to achieve the therapeutic range with plasma level monitoring.

On the other hand, several side effects of mitotane are known, especially due to its narrow therapeutic range. A mitotane level of more than 20  $\mu\text{g/ml}$  is associated with neurological toxicity (4, 6). In our patient, encephalopathy appeared after 5 mo despite monthly monitoring of the plasma level after determination of the dose. This might have been caused by gradual accumulation of lipid-soluble mitotane (11) after we determined the therapeutic dose. Therefore, for effective and safe treatment with mitotane, close monitoring of the plasma level is necessary even after the dose has been determined. However, the mitotane assay is not performed regularly for clinical use. In fact, it took 1–2 weeks to obtain the mitotane level data, and encephalopathy developed before we noticed the high level of mitotane. The mitotane assay should be more readily available so that the dose can be adjusted immediately according to the plasma level in order to obtain better effects with less toxicity.

The toxicity of mitotane has been reported to be reversible after discontinuation of the drug in adults (4, 7). Because its toxicity is reversible, a high dose of mitotane is recommended to control the disease. However, complete recovery in developing pediatric patients is questionable, and long-term follow-up is needed. De Leon *et al.* reported a 15-yr outcome in an infant with metastatic adrenocortical carcinoma (12). The patient showed long-term recovery from the toxic

effects of mitotane, such as growth arrest and developmental delay. They concluded that long-term disease-free survival should justify use of mitotane therapy for adrenocortical carcinoma with an extremely poor prognosis. On the other hand, Nagasaki *et al.* reported a case of adrenocortical carcinoma in a 3-yr-old child with *p53* gene mutation (13). They did not administer an adjuvant chemotherapy, and multiple lung metastases and a single liver metastasis were found 5 mo after surgery. Therefore, they suggested postoperative adjuvant chemotherapy for pediatric patients at high risk, even if macroscopic total surgical removal is performed. It took 6 mo for our patient to achieve clinical recovery from the encephalopathy, whereas he has had no signs of recurrence and metastasis for 3 yr since discontinuation of mitotane. The high concentration of mitotane may have prevented later recurrence and metastasis. We believe that our use of mitotane was also justified considering the poor prognosis and possibility of *p53* gene mutation in our patient.

In conclusion, we report a case of adrenocortical carcinoma in a child. Although encephalopathy, which appeared reversible, developed and long-term follow-up of his growth, brain function and development is needed, adjuvant mitotane therapy was potentially effective for the cancer itself. Adrenocortical carcinoma requires further investigation in children, especially concerning effective and safe adjuvant chemotherapies.

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