Metastatic Adrenal Cortical Carcinoma: Biochemical Changes Accompanying Clinical Regression During Therapy with o,p'-DDD

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A 7-year-old girl with a six-month history of increasing virilism, growth, and acne excreted supranormal amounts of urinary 17-ketosteroids (87.6 mg/24 h). ACTH stimulation and dexamethasone suppression studies indicated adrenal tumor. A large left adrenal carcinoma was removed. Metastases were not observed. Postoperatively, 24-h urinary ketosteroids remained supranormal (16 mg). Sudden fever, cough, and hemoptysis precipitated hospitalization 42 months later. Bilateral lung metastases, a mass in the right upper quadrant, virilism, advanced bone age, and supranormal 24-h urinary ketosteroids (166 mg) and hydroxysteroids (16 mg) were found. The patient received 240 g of o,p'-dichlorodiphenyl-dichloroethane (o,p'-DDD), whereupon the abdominal mass and lung lesions regressed and 24-h urinary ketosteroids and hydroxysteroids decreased. Since this treatment (which ended April, 1968) the patient has been maintained at home on 7.5 g o,p'-DDD/day and replacement therapy with 9-{\alpha}-fluorohydrocortisone and cortisone acetate. Almost all signs and symptoms have disappeared and urinary steroids are normal.

Experience with adrenal cortical carcinoma at the Memorial Hospital during 1935–1967 consists of 34 cases (1), four of whom were diagnosed before the age of 20; none was cured. Although rare, the tumor has a metastatic biosynthetic potential and consequent overt endocrine manifestations that make it susceptible to study by clinical and biochemical methods. The selective adrenolytic effect of o,p'-dichlorodiphenyl-dichloroethane (o,p'-DDD) affords a unique example of an agent active against a tissue and its secretory activity (2–5). This paper documents biochemical alterations and other laboratory and clinical manifestations in a child who shows unusual and prolonged tumor response to continuous treatment with o,p'-DDD.

Methods and Materials

During the first three months of therapy, the 24-h excretion of 17-ketosteroids and 17,21-dihydroxyprogesterone in the urine was measured one to three times weekly. The 17,21-dihydroxyprogesterone were measured by the method of Silber and Porter (6), and the 17-ketosteroids by a modification of the method of Zimmerman (7).

The o,p'-DDD was supplied by the National Cancer Institute in the form of 500-mg white uncoated tablets (now available from Calbiochem, La Jolla, Calif. 92037, as "Lysodren.")

Case Report

In November 1964, TW, a 7-year-old girl, was seen. She had a six-month history of gradually increasing signs of virilization (pubic and axillary hair, clitoral hypertrophy), rapid growth, weight gain, acne, and a deep voice. A mass was detected in the left flank on physical examination. Her skeletal age was 11 years.

Two 24-h urine specimens contained respectively, 64.8 and 87.6 mg of 17-ketosteroids (normal, 3–5 mg/24 h) and 8.2 and 10.2 mg 17,21-dihydroxyprogesterone (normal, 4–11 mg/24 h). After ACTH stimulation, the urinary ketosteroids increased to 112.6 mg and 113.4 mg/24 h, but 17,21-dihydroxyprogesterone remained at 8.2 mg and 7.4 mg/24 h.

Dexamethasone, 0.5 mg four times daily for four days, partially suppressed steroid secretion (28.8 mg ketosteroids and 14.6 mg 17,21-dihydroxyprogesterone), indicating autonomous adrenal gland activity. Biochemical and pertinent clinical data are summarized in Figure 1.

Adrenal carcinoma was diagnosed, and on June 17, 1965, both adrenal glands were surgically explored. A large left adrenal tumor was found, which required removal of the spleen in order to excise the tumor, which was attached to no other

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1 This paper is the second in the new "Case Report" category. The first appeared, together with the Editors' guidelines, in our September issue—Editor.

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1 Presented at the May 1969 meeting of the Society of Pediatric Research.
surrounding structures. No obvious metastases were seen. Immediately after surgery the patient was given postoperative steroid replacement for several days. Her acne and signs of masculinization remained. Excretion of urinary 17-ketosteroids decreased to 14.5 mg and 16.0 mg/24 h, but was still abnormal.

She was examined at three-month intervals for one year, and every six months thereafter, until November 1967. "Menstrual" periods occurred in January and August of that year. She was hospitalized again in January 1968, after two months of progressive pharyngitis, cough, fever, and, finally, episodes of hemoptysis.

A chest radiograph at that time showed bilateral lung infiltrates (Figure 2). She was excreting 77 mg of urinary 17-ketosteroids per 24 h, hemoglobin was 15.6 g/100 mg and her hematocrit was 49. Although her chronological age was now 9 years and 10 months, her skeletal age was 15. Marked virilism and a mass in the right upper quadrant were noted, and she was transferred to Memorial Hospital, where she received 1–10 g of o,p'-DDD and 10 mg of prednisone each day for 12 weeks. Acute papular eruption over her face and thorax, vertigo, pruritus, recurrent nausea, somnolence, lethargy, and occasional vomiting—all chemotherapeutic side effects—prompted modification of drug administration. Her hemoglobin values ranged from 13–19.2 g/100 ml (median, 15.2) during this period.

By March 1968, 250 g of o,p'-DDD had been administered. When prednisone was inadvertently omitted for about two weeks, the patient became pale, lethargic, and dizzy; she vomited, had a rapid, thready pulse, and was hypotensive (90/40 mm Hg). Serum electrolyte concentrations were: Na+, 131 mmol/liter; Cl–, 88 mmol/liter; and K+, 5.6 mmol/liter. Acute adrenal insufficiency was diagnosed. She responded dramatically to infusion of physiological saline (8.5 g of NaCl per liter) containing 4 mg dexamethasone and to the intramuscular administration of 50 mg of hydrocortisone.

At this time, the size of the lung metastases and of the right upper quadrant mass decreased noticeably, as did the severity of her acne. Urinary 17-ketosteroids and 17,21-dihydroxy corticoids decreased progressively to normal amounts, but hemoglobin and hematocrit remained supranormal. Replacement therapy with cortisone acetate, 37.5 mg/day, and continued therapy with o,p'-DDD, 7.5 g/day, and oral 9-α-fluorohydrocortisone to correct hypernatremia, appeared to stabilize the patient adequately and she continued on these medications at home. Since then, occasional increases in cortisone acetate have been necessary during intercurrent infections. By radiographs, pulmonary metastases continued to regress, so that by May 18, 1971, only scar tissue apparently remains in the right middle lung field (Figure 2). Her acne has cleared, but her deep voice remains.

After 42 months of therapy, the patient continues to tolerate o,p'-DDD, without symptomatic side effect.

Examination and review of anatomic and functional systems most likely to be affected by chronic o,p'-DDD administration indicated the following:

- Serial electroencephalograms, dating from 1968, changed to normal from bilateral cerebral dysfunction.
- I.Q., as measured by the Wechsler Intelli-
gence Scale for Children and by Rorschach Tests, is 82, the range of dull normal.

- There is a disproportionate concern with bodily functions, especially the gastrointestinal tract.

- Although her deep voice persists, no problems of sexual identification are noted. Female secondary sexual characteristics (breasts, pubic, and axillary hair) are developing normally.

- Menstrual periods occur irregularly.

- Values for serial pituitary gonadotropin assays remain below 52 mouse units/24 h and within the range of pubertal normal.

- Thyroid function, judged by T₃ uptake, is within normal limits.

- Borderline low-normal pulmonary function studies, recorded in 1968, have persisted. The patient's initially abnormally elevated hemoglobin returned to normal.

The patient currently is taking 7.5 g of o,p'-DDD by mouth each day, and is receiving steroid replacement. She functions adequately in her school and participates fully in social activities.

**Comments**

Clinically recognizable metastatic disease may appear two to three years after diagnosis and surgical excision. In addition to chest radiographs and blood counts, follow-up procedures for the diagnosis of metastatic disease should include serial assays of urinary 17-ketosteroids, 17,21-dihydroxy-corticoids, or other secretory steroid products characteristic of the primary tumor.

Although it has been suggested that steroid replacement be administered after appearance of signs of adrenocortical insufficiency or when urinary corticoid excretion is low (2), we postulate that it is safer to administer replacement therapy concomitant with o,p'-DDD because the time of onset of tumor lysis and residual adrenal cortical tissue lysis may vary. The administration of maintenance glucocorticoid therapy in an incompletely adrenalectomized patient may cause overdosage effects.

9-α-Fluorohydrocortisone replacement is indicated when there are signs of mineralocorticoid deficiency. Once the tumor has regressed and reversible endocrinologic symptoms have abated, chemotherapeutic maintenance is the major problem. If the models of acute leukemia and Wilms' tumor are any indication, maintenance is required for 2–8 years. If o,p'-DDD therapy is stopped we suggest monthly serial study for a period equal to the time interval between diagnosis and appearance of metastases. Serial study intervals could be prolonged afterwards.

The toxicity ensuing from prolonged administration of o,p'-DDD in this one patient does not appear to be significant. This patient has taken over 9 kg of drug during 42 months without discernible side effects.

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**References**