MALIGNANT LEYDIG CELL TUMOR OF THE TESTIS IN COMPLETE REMISSION ON o,p'-DICHLORODIPHENYL-DICHLOROETHANE

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ABSTRACT

A 56-year-old patient is described who presented with retroperitoneal lymph node metastases 2 years after resection of a Leydig cell tumor of the left testis. The patient did not suffer from endocrinological imbalance. Surgical removal of the metastases alleviated abdominal symptoms for 1 year. o,p'-Dichlorodiphenyl-dichloroethane (o,p'-DDD) treatment was started at the time of recurrence of the retroperitoneal mass and the appearance of a hepatic metastasis. Tumors were remarkably responsive to o,p'-DDD, since 2 complete remissions could be obtained for extended periods. The o,p'-DDD was tolerated reasonably well and serum levels of 15 to 20 mg./l. were sustained for many months. Unfortunately, the patient could not be cured with this effective treatment.

KEY WORDS: testicular neoplasms, Leydig cell tumor, DDD, mitotane

Leydig cell tumors (interstitial cell tumors) are rare and account for less than 3% of all testicular neoplasms. Leydig cell tumors have no preference for a particular age group; they have been found in 2-year-old boys and in men up to 90 years old. The clinical course is usually benign but about 10% of the cases have been associated with metastases and ultimate death.¹ Patients with malignancy invariably belong to the older age group.²

The most common initial manifestation of a Leydig cell tumor is a testicular swelling with or without a palpable mass.¹ Extratesticular manifestations generally consist of endocrinopathy as a result of Leydig cell hyperplasia or proliferation. In approximately 20% of the patients concurrent gynecomastia can be found.^{3,4} In prepubertal patients isosexual virilization has been observed. At a young age feminizing symptoms are occasionally superimposed on the virilism.³

To date less than 50 patients have been reported with a malignant Leydig cell tumor of the testis.^{1,4-6} Generally, response to radiotherapy and conventional chemotherapy is poor. Two patients on treatment with o,p'-dichlorodiphenyl-dichloroethane (o,p'-DDD) have demonstrated a temporary regres-

sion of disease.^{7,8} We describe a middle-aged man with a Leydig cell tumor of the testis metastasized to the retroperitoneal lymph nodes and liver. The patient experienced a remarkable response to o,p'-DDD and was alive for 7 years after onset of the disease.

CASE REPORT

A 56-year-old man underwent orchiectomy of the left testis elsewhere in December 1983 because of a painless mass. Diagnostic tests revealed no other symptoms or lesions. The tumor measured 6.3 × 4.5 × 4.0 cm., and was composed of solid sheets and nests of cells (fig. 1, A). Tumor cells had an abundance of eosinophilic, finely granular cytoplasm and round to oval nuclei. The nuclei showed a fine chromatin structure and a few central nucleoli were prominent. The mitotic rate was 3 to 5 per high power field. Invasion into the capsule and into small blood vessels could be detected easily. The histological pattern agreed with a Leydig cell tumor of the testis, although crystalloids of Reinke were not found.

In September 1985 computerized tomography (CT) was performed because of abdominal pain. Lymph node enlargement (7 cm. in diameter) adjacent to the left kidney was completely removed. Tumor cells similar to those found in the primary tumor had completely replaced the lymphoid tissue (fig. 1, B). Occasionally, crystalloids of Reinke could be detected. Unfor-

FIG. 1. A, histological section from left testis shows infiltration by Leydig cell tumor. H & E, ×40. B, lymph node completely replaced by Leydig cell tumor cells. H & E, reduced from ×250.

FIG. 2. Metastases from malignant Leydig cell tumor of testis responding to o,p'-DDD as visualized on abdominal CT scans. Lymph node enlargement between hilus of left kidney and aortic artery (A), and hepatic metastasis (B) in December 1986. Remarkable regression of enlarged lymph nodes (C) and liver lesion (D) on o,p'-DDD treatment in Spring 1987. New hypodense lesion in right liver lobe in March 1988 (E) had disappeared after o,p'-DDD by August 1988 (F).

tunately, followup CT revealed a retroperitoneal recurrence in November 1986. At laparotomy the tumor could not be removed because it was fixed around the aorta and inferior vena cava, and attached to the psoas muscle. Multiple biopsies confirmed the diagnosis of metastases from a malignant Leydig cell tumor of the testis.

In December the patient was referred to our hospital for further treatment. Upon physical examination there were no enlarged breasts or palpable lesions. Laboratory data, such as serum lactic dehydrogenase, β -human chorionic gonadotropin, α -fetoprotein and carcinoembryonic antigen were within normal limits. Serum testosterone and dihydroepiandrosterone were not elevated. Daily urinary excretion of 17-hydroxysteroids, pregnanetriol, pregnanediol, ethiocholanolone, androstosterone and dehydroepiandrosterone was unremarkable. A

chest x-ray and a nuclear bone scan were normal. CT of the abdomen showed the large recurrence between the left renal and aortic arteries (fig. 2, A). Also, a lesion was found in the right liver lobe (fig. 2, B) suggestive of metastasis. A 131 iodine-cholesterol scan showed no uptake in the tumor.

Treatment with o,p'-DDD was started orally at a daily dose of 4 gm. escalating with 2 gm. every 3 days up to 10 gm. Simultaneously, cortisone acetate supplementation was given to prevent adrenal insufficiency. However, within 3 weeks of treatment ascitic fluid production was evident and o,p'-DDD was discontinued presuming progressive disease. Paracentesis revealed 3.5 l. chylous fluid without malignant cells. The fluid contained 58 mmol./l. triglycerides and 4.5 mmol./l. cholesterol, while serum values were 2.7 and 8.9 mmol./l., respectively. Surprisingly, the o,p'-DDD concentration in ascites was 160 mg./l., while in serum this level had only reached 4.9 mg./l.

FIG. 3. o,p'-DDD treatment of malignant Leydig cell tumor of testis. Upper panel shows o,p'-DDD serum levels (mg./l.) and lower panel shows o,p'-DDD daily doses (gm.). From June 1987 to March 1988 treatment was discontinued and from August 1988 to May 1989 dose was reduced because of complete remission.

In February 1987 followup CT showed remarkable regression of the retroperitoneal tumor (fig. 2, C) with no evidence of ascites, while the hepatic lesion had decreased in size (fig. 2, D). Treatment with o,p'-DDD was resumed at a dose of 10 gm. daily. At this maximum tolerated dose the patient experienced fatigue, poor appetite and diarrhea. Because serum o,p'-DDD levels increased gradually to 15 to 20 mg./l. (fig. 3) doses were lowered to limit toxic side effects. In April only a minimal para-aortic mass was left, which was reason to attempt another surgical resection. At laparotomy in June no lesions could be found and the surgical specimens from previously affected areas were histologically proved to be negative for tumor cells. Because complete remission had been obtained with o,p'-DDD this treatment was discontinued.

Until March 1988 the patient felt well. At that time CT revealed recurrent disease, which was, as previously, localized next to the left kidney but another metastasis was visible in the right liver lobe (fig. 2, E). Again, upon o,p'-DDD a complete remission could be obtained with doses as low as 6 gm. daily (serum levels of 15 to 20 mg./l.) as demonstrated by CT in August (fig. 2, F). In an attempt to minimize toxicity from o,p'-DDD and to retain the antitumor effects, the daily dose was lowered to 3 gm. resulting in serum levels of approximately 5 mg./l. However, multiple hepatic metastases were evident in May 1989. Upon increment of the o,p'-DDD dose stable disease could be obtained for 1 year. In July 1990 progression was inevitable, because of which o,p'-DDD was discontinued. Because the patient was still in excellent clinical condition a phase I clinical trial with suramin was initiated. In September he died suddenly at home. An autopsy was not performed.

DISCUSSION

For a long period it was believed that the clinical and pathological features of a Leydig cell tumor of the testis could not be related to prognosis, that is metastasis formation. Kim et al compared a number of variables between clinically benign and malignant tumors.¹ They found that tumors with a malignant behavior generally had a diameter of 5 cm. or greater, an infiltrative margin, lymphatic or vascular invasion, necrosis, a mitotic rate of more than 3 per 10 high power fields and grade 2 or grade 3 nuclear atypia. Metastases were detected either immediately in the postoperative period or even up to 8 years after the primary diagnosis.¹ The most common sites reported were retroperitoneal and inguinal lymph nodes (72%), lungs (43%), liver (28%) and bone (28%).⁵ Our patient had a primary tumor with various characteristics suggesting malignancy. Indeed, retroperitoneal lymph node enlargement occurred as the initial manifestation of metastatic disease. Dissection at the time of overt metastases unfortunately offered no cure for the patient. Thus, early retroperitoneal lymph node dissection fol-

lowing excision of a primary tumor with malignant features should be considered.⁶

At the time metastases of a Leydig cell tumor are detected the majority of patients will die within 24 months.⁵ Radiotherapy has only a small therapeutic role and effects are limited to pain relief. Also, no standard cytostatic agents have proved to be of major benefit. Of 8 patients reported 2 have responded to o,p'-DDD.⁵⁻⁸ Abelson et al described a patient with liver and peritoneal metastases from a Leydig cell tumor resulting in hepatomegaly, ascitic fluid and elevation of urinary 17-ketosteroids.⁷ In this patient o,p'-DDD induced a decrease in liver size, lessening of ascites production and reduction of 17-ketosteroid excretion for 18 months. Azer and Braunstein reported on a patient with multiple metastases from a Leydig cell tumor associated with hypertension, hypokalemic alkalosis and an elevated serum concentration of desoxycorticosterone.⁸ With o,p'-DDD pulmonary lesions disappeared, hypertension lessened and hypokalemic alkalosis resolved for 6 months. Our patient demonstrates that metastases from a Leydig cell tumor may respond well to o,p'-DDD treatment. The drug was able to induce a complete remission on 2 separate occasions. Survival time from the detection of lymph node metastases was 5 years. Our patient received o,p'-DDD for slightly less than 3 years and up to a total dose of 6 kg.

o,p'-DDD (mitotane) is an isomer of the insecticide p,p'-DDD and a chemical congener of the insecticide dichlorodiphenyl trichloroethane (DDT).⁹ The drug causes severe atrophy of the adrenal cortex and interferes with steroid production. Clinical studies with o,p'-DDD in inoperable or metastasized adrenocortical carcinoma have shown an objective response rate of 34 to 61% and significant suppression of steroid secretion in 70 to 85% of the patients. Complete responses can be obtained as has been previously reported by our group.¹⁰ Pathological and hormonal similarities to adrenocortical carcinoma have been arguments to administer the drug to patients with a malignant Leydig cell tumor of the testis.⁷ Obviously, corticosteroid supplementation is necessary in case of long-term administration of o,p'-DDD.

The administration of o,p'-DDD should be monitored by the measurement of serum levels. The drug is highly fat soluble, and is deposited in adipose tissue, liver, brain and adrenal cortex. Gastrointestinal side effects may be lessened by giving o,p'-DDD in a fat-containing vehicle, which also improves resorption.¹¹ The optimal serum level to achieve objective tumor response in adrenocortical carcinoma is not yet known but it is presumed to be greater than 14 mg./l.¹² Such levels will only be reached after a 6-week period, starting with o,p'-DDD at a small dose with rapid escalation to a dose of 8 to 10 gm. per day. Further increase of serum levels to greater than 30 mg./l. should be avoided to prevent intolerable neurotoxicity. In our patient a 30-fold higher concentration of o,p'-DDD in chylous ascites was found compared to the serum level. Response to treatment occurred at serum levels of 15 to 20 mg./l. sustained with daily doses of 6 to 8 gm. o,p'-DDD.

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