Leydig Cell Tumors of the Testis

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ABSTRACT

Leydig cell tumors represent approximately one to three percent of all testicular tumors. Whereas in experimental animals predisposing conditions include administration of chemical carcinogens, hormones and heavy metals, environmental or endogenous factors in man are presently unrecognized. Leydig cell tumors do not show preferential lateralization or tendency for bilaterality. The symptoms are related to the local effects or to hormones released into the systemic circulation. Laboratory findings are variable, depending on endocrinological activity. Typical tumors rarely exceed five cm in diameter, are brown on cross section and are composed of polyhedral cells with acidophilic, granular cytoplasm. Ultrastructurally, neoplastic Leydig cells resemble normal Leydig cells. Surgical ablation is curative for benign Leydig cell tumors.

Testicular interstitial (Leydig) cell tumors are relatively rare and account for a small portion of all testicular neoplasms.10,16 Although the tumors originate from cells that synthesize and secrete androgenic hormones under physiological conditions, the neoplasm may present with virilization, feminization or no obvious endocrine symptoms.3,10,15 Owing to the unpredictable hormonal activity of neoplastic Leydig cells, there are no generally applicable diagnostic tests, and in practice, each case has to be evaluated individually. Owing to the scarcity of Leydig cell tumors, even large institutions have limited experience with this type of neoplasm. The present authors have, therefore, reviewed cases of Leydig cell tumors from the literature and have critically evaluated and summarized those clinical, laboratory and morphologic findings of practical value. Our experience with five cases, two of which were previously reported,2 is also summarized.

Incidence

Leydig cell tumors represent approximately one to three percent of all testicu-
lar tumors. This incidence was reported from various parts of the world, suggesting no geographic difference in the occurrence of this tumor. In a review of 612 testicular tumors in children, Giebink and Ruymann found 51 Leydig cell tumors.

Age

Leydig cell tumors occur more often in adults than in children. Approximately two-thirds of all Leydig cell tumors recorded in the literature were discovered in postpubertal patients, whereas the remaining third was found in children. Although most tumors in adults occur between 25 and 35 years, peak incidence of prepubertal cases is between one and five years of age.

Predisposing Conditions

Leydig cell tumors develop in experimental animals subsequent to administration of chemical carcinogens, hormones or heavy metals such as cadmium. Although the older literature lists X-irradiation as a reliable procedure for induction of Leydig cell tumors in rats, recent experiments have failed to confirm these claims. Leydig cell tumors develop spontaneously in aging rats of certain strains.

No environmental or endogenous factors are known to predispose to the development of Leydig cell tumors in man. Although it is known that plutonium is preferentially deposited in or near the interstitial cells of the testis, no cases of Leydig cell tumors have been related to exposure to any radioactive substance or to prolonged irradiation. On the basis of a Leydig cell tumor described in a patient with clinical evidence of chronic lead intoxication, Medras et al have speculated about the relationship between the neoplastic proliferation of Leydig cells and lead or lead induced porphyria. No additional cases of testicular neoplasms were reported in patients exhibiting signs of heavy metal intoxication that would corroborate these speculations.

Cryptorchid testes often contain foci of Leydig cell hyperplasia, but the tumors do not appear to be more common in undescended than in scrotal testes.

Hormonally active testicular tumors are relatively common in patients with congenital adrenal hyperplasia. These lesions have been considered to represent either Leydig cell tumors or tumors of adrenal rests. Although hormonally active tumors appear morphologically indistinguishable from Leydig cell neoplasms, functionally they resemble adrenal cortical cells and, therefore, most likely represent adrenal rests located in the scrotum.

Localization

Leydig cell tumors do not show significant predilection for either the right or the left testis, although somewhat more tumors were reported on the right side. Of the 151 tumors reviewed by Hugues and Caron, 73 (48.3 percent) were in the right and 61 (40.4 percent) in the left testicle. Seven tumors (4.6 percent) were bilateral and three (2 percent) were paratesticular. Symington and Cameron reviewed 43 cases from the British Testicular Tumor Panel and Registry material and reported that 20 tumors were right-sided and 16 left-sided. One tumor was bilateral and, in six cases, the side involved was not recorded. Thus, Leydig cell tumors do not appear to show preferential lateralization or a tendency for bilaterality.

The existence of paratesticular Leydig cell tumors has been questioned, primarily because of conflicting views as to whether or not the extratesticular endocrine cells in the scrotum represent ectopic adrenal tissue or Leydig cells. Ultrastructural findings of Peters indicate that cells with eosinophilic cytoplasm found in the funiculus spermaticus repre-
sent well differentiated Leydig cells. Hence, tumors may conceivably develop from ectopic Leydig cells.

Symptoms

Symptoms caused by Leydig cell tumors are related either to the local effects of the growing neoplasm or to the hormones released into the systemic circulation. Of the 85 patients with benign Leydig cell tumors reviewed by Hugues and Caron,\(^7\) 42.6 percent presented with gynecomastia, 41.2 percent had complaints related to the enlargement of the testis, 9 percent complained of loss of libido and 8.8 percent had experienced scrotal pain. Childhood Leydig cell tumors often cause precocious puberty and virilization.\(^1)\) Patients with malignant Leydig cell tumors frequently develop systemic metastases.\(^12\) Average survival of patients with malignant tumors is 42 ± 5.7 months from the time of diagnosis.\(^7\) Range of longevity is from 42 days after diagnosis of Leydig cell carcinoma to 17 years after removal of the primary tumor.

Laboratory Findings

Laboratory findings vary from one case to another.\(^3,5,7\) Virilizing tumors usually secrete predominantly androgenic hormones and feminizing tumors predominantly estrogens. The endocrinologically inactive tumors cause few, if any, alterations in the hormonal status of the tumor bearing host. In patients with gynecomastia and loss of libido, plasma and urinalysis will usually show increased amounts of total estrogens, estrone \(E_1\), estradiol \(E_2\), estriol \(E_3\), progandiol and pregnanetriol. 17-Ketosteroid excretion in urine was normal in 15 patients with feminization reviewed by Gabrilove et al.\(^3\) Excretion of 17-OH steroids in urine is usually normal in feminized patients. Plasma levels of testosterone may be significantly decreased. Gabrilove et al.\(^3\) have suggested that gynecomastia develops in these patients primarily because of an imbalance between circulating androgens and estrogens.

In precociously virilized boys with Leydig cell tumors, urinary 17-ketosteroids are excreted in urine in large amounts.\(^7\) Plasma levels of testosterone, androstenedione and 17-OH progesterone may be elevated to normal adult values or higher. Large amounts of 17-ketosteroids excreted in the urine or high levels of estrogens in the plasma and urine without concomitant gynecomastia are considered by Gabrilove et al.\(^3\) to be suggestive of Leydig cell carcinoma.

Analysis of testicular effluent blood may aid in localization of hormonally active tumors not palpable owing to central location or small size.\(^3\) Stimulation by infusion of HCG is occasionally performed to distinguish autonomously secreting, HCG independent, Leydig cell tumors from Leydig cell hyperplasia. Adrenal cortical hyperplasia and adrenal rests localized in the scrotum may be distinguished from Leydig cell tumors with a dexamethasone inhibition test.\(^13\)

Pathology

Leydig cell tumors vary in size and shape.\(^1,10\) In general, malignant tumors are larger than benign tumors. The size of the tumor does not appear to be related to its endocrine activity. Most tumors are well demarcated from the testicular tissue. Only a few of the tumors reviewed by Dalgaard and Hesselberg\(^1\) exceeded five cm in diameter and none of the acceptable cases showed areas of necrosis, hemorrhage or cyst formation. Typical tumors are brown, brown-yellow or dark brown on cross section. They are composed of polyhedral cells with abundant acidophilic, granular cytoplasm and lipid granules. Reinke’s crystals are found in less than half of all tumors.\(^7\) Approximately 10 percent of all Leydig cell tumors are malignant.\(^7\) Distinction of be-
nign from malignant tumors cannot be made on histologic examination, and metastasis is the only definite indicator of malignancy.

Testicular tissue surrounding the tumor may show compression atrophy in non-functional tumors, and either arrest of spermatogenesis, hypospermatogenesis or aspermatogenesis in estrogen producing tumors. Premature maturation of seminiferous tubules occurs in prepubertal boys with virilizing tumors.

**Ultrastructural Findings**

Neoplastic Leydig cells resemble normal Leydig cells. Like the normal Leydig cells, the tumor cells have abundant smooth endoplasmic reticulum, well developed rough endoplasmic reticulum, large numbers of mitochondria with vesicular cristae, microbodies and lipid droplets. In contrast to normal cells, neoplastic cells have prominent and often multiple nucleoli with a complex nucleolomema and irregularly undulating nuclear membranes. The cytoplasm of tumor cells usually contains fewer lipofuscin granules, paracrystalline inclusions and Reinke crystals than normal Leydig cells. In addition, neoplastic cells often show prominent whorls of rough and smooth endoplasmic reticulum. Virilizing tumors do not differ ultrastructurally from feminizing neoplasms, and hormonally active tumors are ultrastructurally better differentiated than the inactive tumors.

**Treatment**

Whereas surgical ablation of the tumor or semicastration is curative for benign Leydig cell tumors, there is no effective therapy for malignant lesions. Removal of tumors usually leads to regression of endocrine symptoms, although gynecomastia and hormonal imbalance may occasionally persist for prolonged periods, even without evidence of remaining or recurrent neoplastic disease.

**Illustrative Clinical Material**

Our clinical experience with Leydig cell tumors is based on the study of five cases. Two cases were previously reported. Pertinent clinical and pathologic findings are tabulated in table I.

All patients were adults. Four patients had benign tumors, whereas one tumor was malignant. Three tumors originated from the right testis and one from the left testis. The site of origin in the fifth case could not be definitely established, although it is presumed that the tumor

**TABLE I**

Clinico-pathologic Findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Years</th>
<th>Tumor Size</th>
<th>Benign (B)</th>
<th>Malignant (M)</th>
<th>Location</th>
<th>Duration</th>
<th>Local</th>
<th>Endocrine</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>5 x 5 x 4.5</td>
<td>B</td>
<td></td>
<td>Right testis</td>
<td>18 months</td>
<td>+</td>
<td>-</td>
<td>Electron microscopy</td>
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<tr>
<td>2</td>
<td>45</td>
<td>2.5 x 5 x 3</td>
<td>B</td>
<td></td>
<td>Right testis</td>
<td>5 years</td>
<td>+</td>
<td>+</td>
<td>Electron microscopy (gynecomastia)</td>
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<tr>
<td>3</td>
<td>34</td>
<td>3</td>
<td>B</td>
<td></td>
<td>Left testis</td>
<td>3 months</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>81</td>
<td>-</td>
<td>B</td>
<td></td>
<td>Right testis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>6</td>
<td>M</td>
<td></td>
<td>Left inguinal canal</td>
<td>2 1/2 months</td>
<td>-</td>
<td>-</td>
<td>Died 1 year after removal of primary tumor. Metastases in lung, liver, kidneys, right adrenal gland, abdominal lymph nodes and bones</td>
</tr>
</tbody>
</table>
Figure 1. Hormonally active tumor from patient No. 1. Tumor is composed of well differentiated cells. Note the well developed rough endoplasmic reticulum, mitochondria, lipid droplets ($\times 6,300$).

Figure 2. Hormonally active tumor from patient No. 1. Cells contain whorls of smooth endoplasmic reticulum apposed to mitochondria with vesicular cristae. Smooth endoplasmic reticulum (SER) is well developed ($\times 9,800$).
arose from a cryptorchid testis located in the inguinal canal. One tumor presented with gynecomastia, whereas the remaining four were hormonally inactive. Histologically, all five tumors displayed the appearance typical of Leydig cell neoplasms, and the malignant tumor did not differ historically from benign lesions. Two tumors were examined by electron microscopy.

In the patient with gynecomastia, tumor cells were well differentiated and contained abundant smooth endoplasmic reticulum and stacks of rough endoplasmic reticulum (figure 1). Whorls of smooth and rough endoplasmic reticulum were also seen (figure 2). Smooth endoplasmic reticulum was often dilated. Mitochondria were large and numerous and had vesicular cristae. Lipid was present in some cells in the form of membrane bound and nonmembrane bound droplets. In the patient with hormonally inactive tumor, the cells were less differentiated and contained less endoplasmic reticulum, fewer mitochondria and more free ribosomes than the functionally active tumor (figure 3).

Acknowledgment

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References

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