Elevated secretion of androstenedione in a patient with a Leydig cell tumour

P. Boulanger1, M. Somma2, S. Chevalier1, G. Bleau1, K. D. Roberts1 and A. Chapdelaine1

Endocrine Laboratory1, Maisonneuve-Rosemont Hospital Research Centre, Endocrinology Service2, Notre-Dame Hospital
Department of Medicine and of Biochemistry, University of Montreal, Canada

Abstract. In this study, we report the case of a 48-year-old man with a well-encapsulated Leydig cell tumour, azoospermia, decreased libido and impotence. The basal peripheral blood levels of testosterone, dihydrotestosterone, 5α-androstane-3α,17β-diol and oestradiol were normal and oestrone was moderately increased. In contrast, androstenedione was extremely elevated at 521 ng/dl (normal: 88 ± 60 ng/dl). Upon hCG stimulation, plasma testosterone increased 2.1-fold while androstenedione increased 1.4-fold. Plasma LH and FSH were also elevated and their response to LRH was exaggerated. At the time of surgery the levels of androstenedione in the spermatic vein plasma, as well as in the testicular tumour were elevated. In contrast, testosterone levels in the spermatic vein blood were decreased indicating a partial deficiency of 17β-hydroxysteroid dehydrogenase in the tumoural tissue. A follow-up study revealed that the contralateral testis did not respond to hCG although the sex steroid concentrations in the peripheral plasma were within normal limits. Plasma gonadotrophins remained elevated. These results demonstrate that this Leydig cell tumour secreted high amounts of androstenedione into the blood and that the contralateral testis exhibited an impaired androgenic function.

Interstitial cell tumours of the testis are rare and represent less than three per cent of all testicular tumours (Guinet 1979). These tumours are well delineated and encapsulated while the resulting clinical manifestations are heterogeneous. In young males, the tumour is usually associated with precocious puberty (Turner et al. 1976). In adults, the clinical picture and steroid levels are variable. Thus, 10 to 30% of the patients have signs of feminization (Gabrilove et al. 1975) with gynaecomastia and elevated oestrogens (Shimp et al. 1977) associated with normal or low androgen levels (Selvaggi et al. 1973) and azoospermia while most of the patients are clinically normal. Few studies have been reported in the literature with regard to the concentration of androgens and oestrogens in the peripheral and spermatic vein blood as well as in the neoplastic tissue. The aim of this study was to measure steroid levels within the tissue and in the plasma of a patient with a Leydig cell tumour. The response to LRH and hCG before and after surgical removal of the tumour was also investigated.

Materials and Methods

Case report

A 48 year-old man was seen for decreased libido and impotence. Physical examination revealed a painful right testis measuring 3.5 × 3.0 cm. According to the patient, the left testis has always been atrophic and measured 1 × 1 cm, and the volume of the right testis had progressively increased over the last 7 years. There was no history of previous testicular damage or undescended testis. The volume of the ejaculate was normal (1.8 cm) but spermatozoa were absent. All other secondary sexual characteristics and peripheral karyotype were normal and no gynaecomastia was observed. A unilateral testicular biopsy was performed on the right side and 1 month later, the right testis was removed and the macroscopic examination revealed a tumour of 2 × 2.5 cm in diameter.
Measurement of steroid concentrations

Several androgens and oestrogens in the peripheral and spermatic vein plasma and in the tumour were measured by radioimmunoassay following chromatography on Celite: ethylene glycol columns. The sensitivity, cross-reactivity and inter- and intra-assay variability of the androgen radioimmunoassays have been published previously (Boulanger et al. 1982). Plasma oestrone (E₁) and oestradiol (E₂) were measured with antisera obtained from Endocrine Science (Tarzana, CA). Serum LH, FSH and prolactin were measured using double antibody techniques (Bio-RIA, Montreal, Canada).

The testis containing the tumour was dissected into two fractions: one consisted of conjunctive-vascular tissue obtained from the periphery of the gland and the second portion was tissue obtained from the Leydig cell tumour. Three explants of approximately 0.5 g were obtained from each fraction and homogenized with a Polytron apparatus (Brinkman Instruments, Westbury, N.Y.) in bi-distilled water and extracted with ether (Fisher Scientific Montreal, Canada). Radioactive tracers (New England Nuclear, Boston, MA) were added for calculation of procedural losses and the results are expressed as the means of these three determinations.

Dynamic studies

These studies were performed before and after removal of the tumour. To assess pituitary gonadotrophin reserve, the responses of FSH and LH to LRH were measured following the iv administration of 100 µg of the releasing hormone. Chorionic gonadotrophin stimulation of the testis was performed by im administration of A.P.L. (Ayerst Laboratories, Montréal Canada) 5000 U/ day for 4 (before surgery) and 3 (after surgery) consecutive days; daily blood samples were obtained for plasma hormone assays.

Results

Optical microscopy revealed a uniform proliferation of cells with acidophilic cytoplasm but no mitosis or any other sign of malignancy were observed. Electron microscopy revealed an ultra-structure similar to normal Leydig cells but an absence of crystalloids of Reinke (Fig. 1). Table 1 illustrates the plasma hormone levels both in the normal male and in the basal state of the patient. Testosterone (T), dihydrotestosterone (DHT), 5α-androstane-3α,17β-diol, oestradiol and prolactin were normal. Oestrone, LH and FSH were moderately elevated. In contrast, androstenedione (Δ4) in the patient’s plasma was 6.6-fold higher than normal. The results of a gonadotrophin stimula-
Table 1.
Plasma hormone concentrations in a patient with an interstitial cell tumour.

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Normal values*</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androstenedione (ng/dl)</td>
<td>88 ± 60</td>
<td>521</td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>372 ± 130</td>
<td>379</td>
</tr>
<tr>
<td>Dihydrotestosterone (ng/dl)</td>
<td>35 ± 17</td>
<td>40</td>
</tr>
<tr>
<td>5α-androstane-3α,17β-diol (ng/dl)</td>
<td>14 ± 6</td>
<td>26</td>
</tr>
<tr>
<td>Oestrone (pg/ml)</td>
<td>20 ± 7</td>
<td>51</td>
</tr>
<tr>
<td>Oestradiol (pg/ml)</td>
<td>22 ± 11</td>
<td>27</td>
</tr>
<tr>
<td>LH (mU/ml)</td>
<td>6–30</td>
<td>56</td>
</tr>
<tr>
<td>FSH (mU/ml)</td>
<td>5–25</td>
<td>52</td>
</tr>
<tr>
<td>Prolactin (ng/ml)</td>
<td>0–20</td>
<td>8.9</td>
</tr>
</tbody>
</table>

*The normal values for steroid (mean ± sd) and protein (normal range) hormones were obtained from men between 25 and 45 years old.

Fig. 2.
Gonadotrophin stimulation test before surgery (solid line) and 10 months after surgery (dashed line). APL: 5000 U/day.

Fig. 3.
LRH stimulation test before (LH o—o), FSH □—□) and 10 months after surgery (LH •—•), FSH ■—■).

During the 4 day treatment period, T and Δ4 increased and the testosterone response was somewhat greater with a 2.1-fold increase over the basal value compared to 1.4-fold for androstenedione. The increase in plasma DHT was detectable only at day 4, at the end of the treatment.

In Fig. 3, the plasma LH and FSH response to LRH is illustrated. In addition to elevated basal LH and FSH values, the LH response to LRH is exaggerated and at 15 min plasma LH was 11.7-fold higher than the basal value.

Sex steroid concentrations in the peripheral vein, in blood from the spermatic vein, in the tumoural tissue and in the tissue from the periphery of the tumour are presented in Table 2. In the spermatic vein, Δ4 and T concentrations were 30920 ng/dl and 1909 ng/dl, respectively. When steroid levels in the tumour were compared to those observed in the peripheral testicular tissue, androstenedione concentrations were found to be 17-fold higher.

LRH and hCG stimulation tests were performed 10 months following ablation of the tumour. The basal levels of LH and FSH were still higher than normal (60 and 53 mU/ml, respectively) and the response to LRH was the same magnitude as the
response obtained prior to surgery (Fig. 3). Stimulation with hCG did not result in any increase in androgen concentrations indicating that the contralateral testis did not respond to gonadotrophins 10 months after surgery (Fig. 2).

Twenty-eight months after surgery, the sex steroid levels including androstenedione were all normal. Levels of LH (59 mU/ml) and FSH (64 mU/ml) remained elevated.

**Discussion**

Of the few cases of Leydig cell tumours that have been reported in the literature, the histological findings have been more frequently documented than the endocrine parameters. Furthermore, the distinction between an adenoma and a well differentiated carcinoma can be a problem for the histopathologist. In the present case, both the optical and electron microscopic findings are similar to those reported previously for those cases of benign interstitial cell tumours and there was no evidence for the presence of the crystalloids of Reinke (Beals et al. 1965; Kay et al. 1975). More than 2 years post-operatively, the patient remains free of metastases.

In reported cases of both benign adenoma and carcinoma of the interstitial cells, the clinical manifestations and endocrine profiles are variable and the source of elevated circulating sex steroids has not always been delineated. In general, in cases with gynaecomastia, serum testosterone levels were found to be below normal (Herwig & Vinson 1978; Weill et al. 1978) while the oestrogen levels were elevated (Selvaggi et al. 1973; Weill et al. 1978). The elevated circulating oestrogens can suppress the pituitary gonadotrophins and lead to the atrophy of the non-neoplastic testicle, impaired spermatogenesis and decreased testosterone secretion (Selvaggi et al. 1973). In some carcinomas, the hormonal pattern can closely resemble that seen in patients with virilizing adrenal carcinoma (Lipsett et al. 1966) with elevated androgens, oestrogens and 17-hydroxyprogesterone. In others, such as the patient described by Davis et al. (1980), the pattern resembles that seen in patients with congenital absence of 17-hydroxysteroid dehydrogenase with markedly elevated serum levels of Δ4, elevated LH and E1 levels and low T.
Our normal plasma androgens levels, as well as the levels found in the non-tumoural testicular tissue are in the same range as the published data (Hammond et al. 1977, 1978; Fiorelli et al. 1976; De la Torre et al. 1982). In our patient, the concentration of plasma androstenedione was more than 6-fold higher than the levels found in normal males. The testicular tumour was very likely to be the source of the circulating androstenedione since its level within the tumour was extremely elevated compared to the level measured in non-tumoural tissue. Moreover, it was higher in the spermatic vein compared to the reported values reported for normal men by Fiorelli et al. (1976), Hammond et al. (1977), Laatikainen et al. (1971) and Weinstein et al. (1974). On the other hand, the testosterone level in the tumoural tissue was similar to the concentration found in the non-tumoural testicular tissue. In the spermatic vein the testosterone level was lower than the reported values (Fiorelli et al. 1976; Hammond et al. 1977; Laatikainen et al. 1971; Weinstein et al. 1974), while its concentration in peripheral plasma was at the lower limit of normal. It is conceivable that the tumoural tissue had a partial deficiency of 17β-hydroxysteroid dehydrogenase as described by Davis et al. (1980) and that part of the circulating testosterone originates either from the peripheral conversion of a high circulating androstenedione level (Wegienka & Kolb 1967) or from the non-tumoural testicular tissue and the contralateral testis in response to the high level of LH. In favour of the latter hypothesis, the plasma level of testosterone is normal after surgery while the plasma concentration of androstenedione has decreased 2.5-fold. Sharma et al. (1967) have also reported such a patient with a virilizing interstitial cell tumour and a defect in 17β-hydroxysteroid dehydrogenase as demonstrated in vitro.

Plasma dihydrotestosterone levels were found to be in the normal range in the periphery while they were below normal in the spermatic vein (Fiorelli et al. 1976). 5α-androstane-3α,17β-diol concentrations were slightly increased in the plasma (Kinouchi & Horton 1974) and normal in the tumour and spermatic vein (Moneti et al. 1980).

Peripheral plasma oestrone levels were moderately elevated compared to our normal values which are lower than the published data (Purvis et al. 1975). These somewhat higher plasma oestrone levels could be, at least in part, the result of the peripheral aromatization of increased concentrations of circulating androstenedione since normal levels were measured within the tumour as well as in the spermatic vein, and since plasma levels of oestrone returned to normal after surgery. The fact that plasma levels of oestradiol were normal and remained unchanged after surgery indicate that the tumour did not contribute significantly to this circulating oestrogen. From our data, it is not possible to determine which fraction of the elevated oestradiol levels found in the right spermatic vein (Martikainen et al. 1982) is derived from the tumour or the testicular tissue surrounding the tumour. The peripheral ratios of testosterone vs oestradiol were greater than 100, which could explain the absence of gynaecomastia (Gabrilove et al. 1975).

The tumour was not completely autonomous since an increase in the plasma levels of Δ4 and T were seen upon gonadotrophin stimulation while, 10 months following ablation of the tumour, the contralateral testis failed to respond to hCG stimulation and remained soft and atrophic.

In view of the results obtained after surgery, namely the increase in the basal levels of LH in the presence of normal steroid levels, the lack of response to hCG and the exaggerated LRH response, it would appear that the remaining testis presents an impaired function of the Leydig cell. This defect in conjunction with elevated plasma oestrone, could also be partly responsible for the elevated level of LH seen before surgery.

Acknowledgments

We wish to thank Dr. E. Schick, Department of Surgery, Notre-Dame Hospital for supplying the testicular tumour. We are also grateful to Dr. F. Paquin, Department of Pathology, Notre-Dame Hospital for the microscopic evaluation. The secretarial assistance of Mrs. M. Boire is gratefully acknowledged. (This study was supported by the Medical Research Council of Canada [PG-14]).

References


Received on December 5th, 1983.