LEYDIG CELL (INTERSTITIAL CELL) TUMOR
(OVERVIEW AND CASE REPORT)

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SUMMARY
Leydig cell tumors are usually benign in nature, originating from testicular mesenchyme. Endocrinologic manifestations may precede the tumoral mass. Since there are no clear cut differences between the histopathologic appearance of benign and malignant tumors and differential diagnosis can be made only by the presence of metastases, a close follow-up is essential in these tumors.

Key words: Leydig cell, benign and malignant tumors

INTRODUCTION
Leydig cell tumors are the most common type of sex chord mesenchyme lesions and constitute 1.2% to 3% of all testicular neoplasms (1,2,3,4).

Approximately one fourth have been reported before puberty (4), but the majority of cases are between 20-60 years (4).

Histologic features are well described (5, 6), however the ultrastructure of benign and malignant interstitial cell tumors is indistinguishable from normal cells and there are no reliable criteria for making a judgement about malignancy.

Leydig cell tumors are often associated with excess sex steroid production, although clinical symptoms of endocrine disturbance are less commonly reported (6), yet endocrinologic manifestations may occur before a palpable mass in the testis is noticed.

Virilizing types of congenital adrenocortical hyperplasia, Klinefelter’s syndrome, and other feminizing testicular disorders should be considered in differential diagnosis (4).

In this paper we report two similar cases displaying the characteristics of this type of tumor and review the current literature on the aspect.

CASE REPORT: (1)
A 30-year-old male patient was admitted to Marmara University Hospital, Department of Urology, with the complaints of pain and lump in the left testicle. The pain had begun 2.5 months before the admission when he noticed a mass in his testis at the same time. The severity of the pain had improved with antibiotics and analgesics prescribed by a doctor, but the lump persisted.

On physical examination, the patient had a left testicular mass nearly 5 cm in diameter. He was normal otherwise. There were no manifestation of an endocrinologic abnormality. Serum levels of AFP, Beta-HCG, and also biochemical and hematologic tests were in normal limits. With the diagnosis of a testicular tumor, an immediate left sided inguinal orchiectomy was performed. His postoperative period was uneventful.

Macroscopic examination of the surgical specimen revealed an orange colored tumor, which was 2.5 cm in diameter and extending to tunica albuginea. In microscopic examination, there were neoplastic cells with large, pale, granular cytoplasm, some of them having vacuoles and Reinke crystals. Cells were producing solid masses in a fibrous stroma. The nuclei were small and rounded, displaying mild pleomorphism (Fig. 1, 2). Immunoperoxidase staining of the paraffin embedded tissue slides yielded negative re-
Fig. 1: Macroscopic appearance of the tumor.

Fig. 2: Microscopic appearance of the tumor.
sults for AFP and Beta-HCG. The tumor with a small necrotic area, was found to be extending to the tunica albuginea. There was no invasion at the surgical margins. With these histologic findings a diagnosis of Leydig cell tumor was intituted.

After the operation the serum levels of FSH, LH, estrogen, testosterone, AFP and Beta-HCG were found to be in normal limits. The chest X-ray, retroperitoneal ultrasonography, and whole body CT scanning examination of the patient revealed normal findings.

As a result, the patient was regarded as having localised disease treated by complete excision of the tumor, and he was entered the surveillance program with monthly follow-ups.

CASE REPORT: (2)
A 32-year-old male patient was admitted to our department because of gynecomastia. His complaints had begun in December 1987, when he first noticed a painful left sided gynecomastia. He had been examined by a physician and in laboratory examinations performed elsewhere serum estradiol level was found to be elevated (patient value: 52 pg/mL, normal value: 6-44 pg/mL) and Beta-HCG in normal limits. With these findings a thorough physical examination was repeated and a left sided testicular mass was found which also escaped the attention of the patient. A diagnosis of testicular tumor led to left inguinal orchectomy.

In macroscopic examination of the surgical specimen there was a well circumscribed, yellow-orange colored, firm lobular tumor in the testis with a diameter of 2 cm. Microscopic examination of the tissue revealed neoplastic cells forming cords and alveolar structures in a stroma which was rich in blood vessels. Tumor cells had round nuclei with large eosinophilic cytoplasms. Some of these cells had double nuclei. There was no invasion at the surgical margins.

With these histologic findings a diagnosis of Leydig cell tumor was instituted.

After the operation the serum levels of estradiol, testosterone, AFP and Beta-HCG were all found in normal limits. Even though it has shown regression to some extent the gynecomastia of the patient had persisted. The chest X-ray, excretory urography, and abdominal ultrasonography of the patient revealed normal findings. Therefore this patient was also regarded as having localised disease and taken into the surveillance program.

DISCUSSION
Leydig cells, which are located between the seminiferous tubules develop embryologically from mesenchyme derived from the posterior urogenital ridge and possibly also from coelomic epithelial cells which do not become incorporated in to the tubules (7,8).

The tumors originating from Leydig cells are usually seen between the second and the sixth decade (4), and account for nearly 20% of childhood testis tumors (9).

The tumors are generally small, yellow to brown in color, and well circumscribed. They rarely exhibit hemorrhage and necrosis (4). Microscopically the tumor consists of relatively uniform polygonal cells, producing cords or sheets, with large amounts of eosinophilic granular cytoplasm and nuclei which often contain prominent nucleoli (6). There may be lipid vacuoles, brownish pigmentation and occasional Reinke crystals in the cytoplasm. None of these histologic features appear to be related to malignant potential. Large size, extensive necrosis, marked cellular pleomorphism with bizarre cell forms with atypical nuclei, numerous and atypical mitoses, invasion of vascular and lymphatic channels, extension of the tumor in to the spermatic cord and invasion of the capsule are the prominent features suggestive of malignancy (4, 6, 10-12). Yet there may be considerable overlap between the microscopic features in benign and malignant tumors. Consequently the presence of metastases remains to be the only reliable criteria for malignancy (6). Only 7% to 10% of Leydig cell tumors do metastasize and the metastatic form of this type of tumor occur exclusively in adults (3, 5, 13). Like other testicular tumors malignant lesions may involve retroperitoneal lymph nodes, lungs, bone, liver, kidney and other organs. The most important observation in case of malignancy is almost nonexistance in prepubertal age group (4). Bilateral tumors are also reported in the literature (14).

Leydig cell tumors may be either feminizing or virilizing functionally (15, 16).

When the androgen producing type of tumor occurs in a prepubertal boy, precocious development of penis, beard, and muscles occur along with accelerated linear growth (17). An increased testosterone production is usually demonstrable and urinary 17-ketosteroid output may or may not be elevated (4). Leydig cell tumors that produce feminization are found only
in adult males. Symptoms such as impotence and gynecomastia may occur. Elevation of urinary and plasma estrogens in this type of tumor is relatively common (4).

Evidences of endocrinologic abnormalities due to the tumor may be encountered before a lump in the testis is found.

The similar embryological origin of interstitial cells and adrenocortical cells, and also the occurrence of adrenal rests in the testis may complicate the differential diagnosis. Klinefelter's syndrome, and other feminizing testicular disorders and virilizing types of congenital adrenocortical hyperplasia must be ruled out accordingly in the diagnosis of Leydig cell tumors.

The treatment of this type of tumors is primarily surgical (18). These tumors, in case of malignancy are generally refractory to radiotherapy (11, 19-25) and conventional chemotherapy (3, 10, 12, 18-20, 25). Because of the histologic and biochemical similarities between Leydig cells and adrenal cortical cells, chemotherapy with o,p'DDD(mitotane), which is an adrenolytic agent, have been used for metastatic disease (16, 18, 21, 26). A variety of chemotherapeutic agents including Cis-platinum, vinblastine, bleomycin, cyclophosphamide, doxorubicin and vincristin have been utilised with unpromising results (4). Trials of endocrine therapy based on experimental evidence of estrogen receptors in mouse Leydig cell tumors, have been performed with some benefit (27). Inhibition of mitochondrial protein synthesis with arrest of in vivo growth of solid Leydig cell tumors in rats by oxytetracycline has also been reported (28). Lonidamine, a powerful antispermatogenic agent and selective inhibitor of aerobic glycolysis (29) has been suggested to suppress the Leydig cell function and reduce plasma testosterone levels. Yet very few patients had subjective improvement and no patient had any objective response to lonidamine (6). Retroperitoneal lymph node dissection has been recommended as routine in patients whose Leydig cell tumors appear histologically or biochemically malignant.

The prognosis of Leydig cell tumors is good because of their generally benign nature. The persistence of virilizing of feminizing features following orchietomy is not necessarily an indication of malignancy, since these changes are irreversible to some extent. What seems to be the most important factor in this of particular group of tumors is the late occurrence metastasis, which may emerge after a long latent period, as much as 9 years (6). This calls for a close surveillance with great patient compliance for a long period. The average survival time in case of malignancy is about 2-3 years (4), where the patient is cured by radical orchietomy in benign tumors.

REFERENCES

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