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Leydig Cell Tumors of the Testis: A Case Report

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Introduction

Approximately 5-6% of all testis tumors are non-germ cell tumors. Included in this group are sex cord/gonadal stromal tumors, most originating from Leydig or Sertoli cells, mixed tumors, and tumors of mesenchymal or hematopoietic origin [1]. Leydig cell tumors are rare, and represent 1–3% of all testicular tumor in adults and 4% in prepubertal children [2]. They are bilateral in only 3–9% of cases, and a metachronous occurrence is extremely rare [3].

This kind of tumor is mostly benign. However, approximately 10% of the cases, and uniquely in adults [2], demonstrates malignant behaviour, presenting with metastatic disease.

In children, the peak incidence is between the ages of 5 and 10 years and owing to autonomous production of testosterone, the tumors lead to precocious puberty, producing masculinization [2]. In adults, they manifest between 30 and 35 years of age, in the form of feminization, consisting of unilateral or bilateral gynecomastia, diminution of the libido, impotence and contralateral testicular atrophy [4].

The preoperative diagnosis of this histological type of tumor is very difficult; however, a hypoechoic ultrasound image associated with hormonal disorders and tumor markers (alphafoetoprotein [AFP], gonadotropic chorionic beta hormone [B-HCG], lactate dehydrogenase [LDH]) should cause suspicion of such tumors.

Case report

A 40 year old Moroccan man with no notable pathological antecedents, the course of puberty phases having been without abnormalities, had a secondary sterility of 5 years with oligospermia and since 08 months a progressive increase in testicular volume left, all evolving in a context of conservation of the general state. On clinical examination, the left testicle was tumor-like, enlarged, painless, and tense, with a negative transilumination test; the right testicle was of normal size and consistency, the general examination found a patient in good general condition with a masculine morphotype and well developed primary and secondary

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ABSTRACT

Leydig cell tumors (LCTs) represent less than 3% of all testis tumors; they concern the interstitial tissue of the testis and occur at any age. They are part of the group of tumors called "sex cords and stroma" with Sertoli cell tumors. Only 7 to 10% of these tumors are malignant and are almost always seen in adults. We report a case found in a 40-year-old adult with a left testis tumor treated with orchiectomy. The diagnosis of malignancy may be difficult to establish and may be beyond histopathological examination, hence the importance of regular long-term follow-up.

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sexual characteristics.No other sign, including gynecomastia or swelling of superficial lymph nodes was observed. Scrotal ultrasonography revealed a non-homogenous hypoechogenic tumoral mass in the left testis (Figure 1). Tumor markers such as alpha-fetoprotein (AFP) and β -human chorionic gonadotropin (β -hCG) were negative, and hormonal investigations were normal.

Ultrasonography of the scrotal contents revealed a large 9.5 cm diameter left testicle of hypovascularized multinodular heterogeneous echostructure (figure 1).



Figure 1. Ultrasound appearance of the tumor: several avascular hypoechogenic nodules.

Left inguinal orchiectomy was performed. On the orchidectomy piece weighing 102 g, macroscopic examination revealed a testicular tumor measuring $7 \times 5 \times 4$ cm, multinodular in appearance, firm in consistency and beige in color (figure 2).

Histologically, it is a tumor proliferation of nodular architecture made of nodule separated by fibrous septa. These nodules consist of cells with abundant granular cytoplasm and nucleated ovoid nuclei sometimes grooved. Leydigal hypertrophy is noted in an oedematous testicular parenchyma without recognizable seminiferous tubules. There is no vascular embolization, there is no infiltration of the vaginal or albuginea and spermatic cord. The presence of multiple an is okaryotic hyper chromatic nuclei and the high mitotic index

However, heterogeneou adults [2], of 40 mitoses / 10 fields remains a very important criterion of malignancy.

The postoperative course was simple, and the evolution after 6 months of recession is good without appearance of tumor recurrence





Figure 2. pathologic aspect of leydig cell tumor: A / Microscopic aspect of leydigal hypertrophy with globular cytoplasm cells and ovoid nuclei.

B . Macroscopic aspect of orchiectomy surgical specimen. Discussion

Normal Leydig cells are located in the peritubular spaces of the testis and secrete testosterone under the influence of LH. This testosterone diffuses both to the capillaries present in the interstitial spaces (endocrine function) and to the seminiferous tubes where it is captured by Sertoli cells (paracrine function). A small portion of the testosterone is flavored with estradiol within the cells of Leydig. LCTs occur in approximately 75% of adults and 25% of children. They are part of the group of tumors called "sex cords and stroma" with Sertoli cell tumors.[5]

In the last few years the incidence of LCTs seemed to increase well above the literature predictions (14.7% of all testicular tumors removed). One possible explanation for this phenomenon is the increasing use of better ultrasound technology and the subsequent in creased detection of small nodules that have not been found in historical series [1].

In adults, the usual mode of revelation is most often signs of hypogonadism secondary to hyperestrogenemia due to this aromatase activity of Leydig cells: bilateral and often asymmetrical gynecomastia, present in 31% of cases in the series of Conkey [6], 40% of cases in the Kalfon experiment [7], and may precede by several years the clinical appearance of the tumor, erectile insufficiency with often a drop in libido, infertility with oligo- or azoospermia. This is the case found in our patient.

The origin of Leydig cell tumors is not clearly defined. Some authors have reported in Leydig tumors in adult a somatic activating mutation in the guanine nucleotide binding protein a gene, which may result in tumor development, leading to overexpression on the inhibin alpha subunit and hyperactivity of the testosterone biosynthetic pathway [8].

Alterations in local stimuli include müllerian-duct inhibitory factor, inhibin, growth factors, and temperature, may also create favourable conditions for tumorigenesis [1].

Although these tumors arise at any age, they affect mostly men between 20-60 years old. In our case the tumor was unilateral in left testis and our patient belongs to the age group with the highest incidence.

At the exam, the tumor presents as a hard and painless intratesticular swelling. Sometimes, it is a scrotal ultrasound discovery of which one third of the no palpable testicular tumors correspond to LCTs [9], in the form of a homogeneous hypoechoic nodule [10]. Ten to 15% of these forms of the adult are malignant forms, especially in the elderly. In children, LCTs are relatively rare and correspond to 4% of the 98 testicular tumors collected by Pohl [11]. Paediatric forms are therefore androgen-secreting and are manifested by an early pseudo puberty isosexual occurring around the age of 5 to 9 years.

Except for the testicular tumor mass present in all cases, other signs and symptoms may be present in different degrees (pain in the testis, enlargement of a testicle, heaviness in the scrotum, and gynecomastia). Azoospermia and infertility are uncommon and, if exist they are reversible after removal of the tumor [12].

First imaging examination to be requested, can detect tumors not exceeding 3 to 6 mm in the form of homogeneous hypoechoic nodules [12], Ultrasound of scrotum is very useful to confirm the diagnosis of testicular tumor , but it cannot differentiate between a benign and a malignant tumor [13]. In our case scrotal ultrasonography has revealed a nonhomogenous hypoechogenic tumoral mass in the left testis. On color and power Doppler sonography, the lesions can have various patterns of increased vascularity. Increased peripheral blood flow in a behaviour or circumferential fashion, along with limited or absent central vascularisation, has been reported as the most frequent type by some study groups. [14]

The differential diagnosis is often difficult with seminomas with close ultrasound characteristics. Ultrasound allows the contralateral testicle to be explored and evidence of occult bilateral involvement. Cryptorchidism is also, like germline tumors, considered a risk factor. [4]

In patients with LCTs the blood tests for tumor markers (AFP, HCG, and LDH) are negative. The most common hormones secreted by LCTs are testosterone and estrogens. In most cases, adults have non functional testicular masses. The usual hormonal profile in adults is: normal or low testosteroneemia; normal estradiol, or increased; T/E2 ratio collapsed (<85); The elevation of serum estradiol levels leads to a negative feedback control of gonadotropin depletion, which explains the frequency of azoospermia due to inhibition of spermatogenesis according to an endocrine mechanism (decrease of gonadotropins), but also paracrine (local elevation). Estradiol). This is the case explained in our patient. In the atypical forms, two endocrine tests are very strongly suggestive of the diagnosis: during the administration of HCG, one observes a very exaggerated ascent of estradiol, and during the

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administration of Gn-RH a weak response of FSH and a normal response of LH are obtained[15].

The pathological exam and immunohistochemical straining are essential for the diagnosis and for the next steps in treatment. The testicular tumor can be multinodular or uninodular with a size between 1 and 10 cm and a rarely encapsulated lobulate appearance. The tumor is brownish yellow. Microscopically, the tumor is composed of large hexagonal cells with granular eosinophilic cytoplasm containing 40% of Reinke crystalloids [15]. The nucleus is small, round and nucleated. LCTs are small volume tumors, consisting solely of monomorphic Leydig cells, with rare cytonuclear abnormalities. They must be distinguished from nodules of leydigal hyperplasia, characterized by the persistence, within ranges of Leydig cells, of seminiferous tubes, which most often contain only Sertoli cells. Such lesions have been described initially in patients with Klinefelter syndrome with elevated endogenous LH levels, or in patients who have received HCG injections, or who have a germ cell tumor producing HCG.

The differential diagnosis of LCTs mainly concerns bilateral forms. It is mainly found in children and young adults in palpable or non-palpable forms with testicular tumors induced by HCS whose origin is subject to discussion: intratesticular adrenal vestiges, Leydig cells or pluripotent cells. These tumors are bilateral in 83% of cases and regress in 75% of cases under steroids [16].

While benign, LCTs have malignant potential in about 10% of cases with metastatic forms, particular to the lymph nodes, especially the retroperitoneal and inguinal nodes (70%), liver (45%), lungs (40%), and bone (25%) [17]. the metastatic type occurs exclusively in adults and is more common in older patients with an average age of more than 40 years. The risk of malignancy in the undescended testis is 4 to 10 times higher than that in the general population but the most common type of testicular cancer occurring in undescended testes is seminoma [18]. There is no clear limit between benign and malignant tumors, but there are presumptive criteria for malignancy that are defined by: advanced age, the presence of a disturbed hormonal balance in an asymptomatic patient the absence of hormonal decay in post-orchiectomy, tumor size greater than 5 cm, existence of peritumoral vascular emboli, invasion of surrounding structures, necrosis and mitotic index greater than three mitoses / ten fields, absence of Reinke crystals, nuclear polymorphism, p53 level> 50%, MIB-I> 20%, aneuploidy in flow cytometry [16].

The use of fine needle aspiration for diagnosis may be an alternative to more invasive biopsy procedures in the preoperative diagnosis of this rare testicular tumor [19].

Orchiectomy is the initial treatment for LCTs, with or without removal of nearby lymph nodes (lymphadenec tomy). Some authors suggest a more conservative therapy. Testis sparing surgery has proved to be a feasible and safe choice and could be regarded as first-line therapy in cases of benign, small (under 25 mm),unifocal and peripheral testicular tumors which are limited to the organ (without infiltration of the rete testis) and young men [20,21]. Testis-sparing surgery can preserve the patient's fertility, and eliminates the long-term need for a hormone replacement, without compromising the patient's longterm survival. Partial resection should therefore only be used in patients with one testis, and who either wish to preserve their fertility and/or refuse to use androgen hormone replacement therapy. [20].

Enucleation or lumpectomy is an attractive technique for well-selected patients with good cancer control despite the small number of retrospective series reported. Indications are limited to patients with bilateral testicular tumors, as well as patients with a single testicular tumor, and to tumor-associated hypofertility patients whose size is less than 25 mm, requiring a histologist experienced for performing an extemporaneous examination, sections made after clamping the spermatic pedicle and locating the lesion clinically or on ultrasound [21].

Although orchiectomy is curative in approximately 90% of cases, the remaining patients can develop refractory metastases to chemotherapy and radiation. Radical orchiectomy remains in use if malignancy is suspected [20].Inguinal orchiectomy. This behaviour is recommended because of the absence of formal histological criteria of benignity and the absence of effective catch-up treatment in case of malignancy.

The evolution after the orchiectomy is usually as follows [4]: oestradiolemia is normalized in 24 hours, testosterone is normalized in about ten days, contralateral testicular volume which is reduced normalizes in 30 days, gonadotrophins and spermatogenesis takes several months to normalize, gynecomastia usually regresses in the first year after orchiectomy.

Some authors like De Jong et al. Reported the possibility of fertility conservation despite unilateral orchiectomy associated with contralateral lumpectomy for a bilateral LCTs. However, it offers the advantage of keeping the body diagram, especially as infertility is a more frequent reason for the discovery of this type of tumor, but the price of this therapeutic attitude is an extremely close monitoring in order to detect recurrence and the appearance of metastases [22].

The treatment of malignant forms is not codified, no protocol having proved its effectiveness. It uses ganglionic muscle surgery, chemotherapy (cisplatin, vinblastine, bleomycin, cyclophosphamide) and radiotherapy. The median survival would be about three years. Metastases are primarily retroperitoneal lymph nodes, then pulmonary, osseous and hepatic, and can occur several years after orchiectomy [18].

The monitoring of LCTs is the only sure and essential way to monitor the possible occurrence of metastases, since there are not until now certain tools to decide on the benignity or malignancy of these tumors. The pace and duration of surveillance are still controversial because of the small number of series produced in this direction. The progression of the disease is rarely diagnosed by clinical symptoms or hormonal disorders of the disease; imaging is the best way for the diagnosis of metastases.

Carmignani et al. [23] recommend that surveillance be continued for 10 to 15 years after surgery, as there is always a risk of late metastasis, with a clinical and hormonal TAP scanner during the first two years, then every year for 10 to 15 years.

Conclusion

LCTs are quite rare tumors of the testis. They occur most often in adults with signs of hypogonadism and in children with early pseudopuberty. The exploration of fertility disorders in humans and the advent of ultrasound have increased the mode of revelation of these tumors. The main diagnostic difficulty is the distinction between malignant and benign forms. Inguinal orchiectomy is the gold standard treatment; however, there is a trend towards Testis-sparing surgery, but at the cost of longterm metastasis and surveillance.

Conflict of Interests

The authors declare no conflict of interest.

Authors Contribution

All authors mentioned have contributed to the development of this manuscript. All authors also declare to have read and approved the final manuscript.

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