Case Report

Adult-Type Granulosa Cell Tumor of the Testis: A Report of a Case and a Discussion of the Literature

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Case Report

Adult-Type Granulosa Cell Tumor of the Testis: A Report of a Case and a Discussion of the Literature.

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Abstract: Testicular granulosa cell tumors (TGCTs) are rare tumors of sex cord-stromal origin. TGCTs can be classified into the adult type and the juvenile type. The adult type is extremely rare with only 93 known cases reported in the literature. We, herein, present a report of a case of a 30 year old male patient who presented with a testicular mass, underwent radical inguinal orchiectomy and the pathology examination revealed an adult type granulosa tumor. We additionally review the literature to summarize the scientific knowledge of an entity barely described worldwide.

Keywords: testis; granulosa-cell tumor; adult – type; sex cord-stromal tumor of testis; testicular cancer

Introduction

Testicular granulosa cell tumors (TGCTs) are rare tumors of sex cord-stromal tissue. They originate from epithelial elements of the sex cords. The mechanism underpinning the development of TGCTs remains poorly understood due to the rarity of these cases. They comprise granulosa cells and stromal components are generally low-grade malignancies, manifested by indolent growth and a low risk of metastasis [1]. GCTs are more frequently discovered in the ovaries, where the adult type is more prevalent. On the other hand, the juvenile type, despite being uncommon, predominates in the testis [2]. Men with juvenile tGCT never had documented metastatic disease [2]. On the other hand, men with adult GCT can have metastatic disease (10% to 13% of all documented cases) [2, 3]. These tumors appear to be slow-growing neoplasm with the potential to metastasize to distant sites years after initial diagnosis. There have been cases described that during the follow up were diagnosed with distant sited metastases even 10 years after the first radical surgical treatment, though appearing with no progression in this whole period. As a result, men who have undergone orchiectomy require extended follow-up because of the delayed metastatic potential of these tumors [4]. Due to the rarity of tGCT, there are several unanswered questions regarding the optimal management of patients with localized or metastatic tGCT. The aim of the present case report is to document a case of an adult type GCT and to commit an updated summary of the international literature concerning the reported cases of adult type of granulosa cell tumor of the testis, so a very infrequent oddity to be reminded and a tumor that both urologists and oncologists should have in mind.

Case Presentation

A male patient, age 30 years old, was admitted to our outpatient private office from an internal medicine department with a swelling in the left testis that was at first noticed two years ago and was growing slowly. The patient did not show any disturbance or anxiety due to the slow growth of the testis and he only decided to visit a doctor when the testis changed texture in self-examination. By the time of the examination left testis was enlarged, hard to palpation. The medical history revealed no trauma or signs of inflammation or any other known disease. We performed blood tests and

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radiological control. Blood tests revealed no indication of inflammation (urine culture was negative and C - reactive protein was within normal values). A-fp (A – fetoprotein), β- hg (β-choric gonadotropin) and LDH (lactate dehydrogenase) values found to be within normal range. Initially, we performed a scrotum ultrasound, which revealed a hypoechoic - solid mass of 3,8 cm diameter suspicious of malignancy. A scrotum magnetic resonance imaging confirmed the suspicion of malignancy, showing a mass with septum which was enhancing the intravenous paramagnetic contrast agent. The rest of the imaging control with CT scan of chest, abdomen and brain revealed no sites of metastatic disease or any other pathology.

According to the European Association Guidelines 2022 edition update, radical inguinal orchiectomy was proposed to the patient and he agreed.

We performed a radical inguinal orchiectomy and the left testis with its components was removed lege artis and was sent for pathology examination. The patient had a normal postoperative course with no complications according to the Clavien – Dindo score noticed. The pathology report revealed a tumor with septa consisting of large elongated cells with large grooved nuclei, inhibin positive, proposing an adult type testis granulosa tumor with a diameter of 3.8 cm, inhibin positive. Moreover, the presence of Call-Exner bodies helped to underline the diagnosis of adult type granullosa cell tumor of testis. There was a proliferation rate of mitosis lower than 3/10 hpf. The other components of the testis, rete testis, the tunica albuginea, the epididymis or the vans deferens were free of the disease. Serum inhibin type B measured in the patient right after the operation and one month later showed a decrease from 32 pg/dL to 4 pg/dL. Nevertheless, Inhibin type A did not show the same downward trend. One month after the surgery was at 10pg/dL and 6 months after the surgery was at 16pg/dL. At this timepoint we conducted a new screening with CT scan of the chest, abdomen and brain, which did not reveal any metastatic sites. 9 months after the surgery, we performed a new laboratory control and was revealed an Inhibin type A at 90 pg/dL. We conducted a FDG-PET/CT. It revealed no site of recurrence or any distant metastases or lymph nodes. Next follow up is planned to take place in 3 months' time with new serum markers and any imaging tests needed.

Discussion

Histologically, about 90% of all testicular neoplasms comprise germ cell tumors (GCTs) while the remainder involves sex cord gonadal stromal tumors, malignant lymphomas, secondary tumors, and other very rare new growths.

Testicular granulosa cell tumors are rare neoplasms. They are sex cord stromal tumors of the testicles (SCSTs). SCSTs show differentiation towards Leydig cells, Sertoli cells, and/or other types of sex cord-stromal cells (eg, granulosa cells) [5]. Compared to germ cell tumors (GCTs), SCSTs are substantially less frequent, making up fewer than 5% of all testicular neoplasms in adults. Among the gonadal stromal tumors, Leydig cell tumors and Sertoli cell tumors are the most common subtypes encompassing 1-2% and 0.5%, respectively, of all testis tumors. However, prepubertal men have SCSTs at a somewhat higher rate [6].

Granulosa cell tumors resemble ovarian granulosa cell tumors morphologically and are classified into adult and juvenile types, just as granulosa cell cancers in the ovary. The first documentation of an AGCT is credited to Laskowski in 1952.

The adult form is more prevalent in the ovaries, where GCTs are more frequently detected. On the other hand, the adult form is less common and the juvenile type, despite being rare, predominates in the testis [2].

Some studies have suggested that the formation of granulosa cell tumors is associated with sex chromosome abnormalities and aberrant gonadal development. It has been shown that infants with mixed gonadal dysgenesis or intersexual disorder develop juvenile-type GCTs (59). Regarding to the adult type, the expression of FOXL2 gene is supposed to play a leading role in the growth. *FOXL2*, a granulosa cell-expressed gene, regulates granulosa cell fate and ovarian function. A missense mutation of *FOXL2* is vital in the pathogenesis of adult-type ovarian GCTs (60). With regard to its contribution to GCT development, studies have shown that this mutation impairs the capability

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of growth differentiation factor 9, an oncocyte-produced protein, in promoting follistatin transcription in the presence of SMAD3. This may lead to increased cell proliferation due to unopposed activin signaling. In addition, *FOXL2* mutation also reduces apoptosis and increases the induction of aromatase (CYP19), which promotes estrogen synthesis (61).

Using the PUBMED database and manually scanning the reference lists of earlier studies, only 93 examples of adult type GCTs in testis could be found in the literature (Table 1). Not every case report had specific information about every clinical trait. As a result, numerous clinical aspects have to be examined using varied sample sizes.

The juvenile variety of granulosa cell tumor is the most prevalent (though uncommon) testicular tumor in infancy and is only infrequently encountered in adults. Granulosa cell tumors of the juvenile type don't exhibit the usual Call-Exner body development, have a tendency to have a little bit more cytoplasm, or have the pronounced grooving of the adult variety. The cells are instead grouped in solid sheets, nests, or nodules and frequently form ectatic areas filled with eosinophilic or basophilic material that resemble enormous follicles [7]. Infants under six months old are the age group when these tumors are most frequently found [8].

Although malignant behavior has rarely been described, adult-type granulosa cell tumors of the testicles tend to grow slowly and have a good prognosis [2, 9].

The adult type of granulosa cell tumor shares the same histologic characteristics as ovarian granulosa cell tumors. Known as typical Call-Exner body formation, the cells are organized to form solid sheets and microfollicular structures and feature elongated, grooved nuclei and little cytoplasm [9].

In our patient the pathology review revealed neoplasm tumor with septa consisting of large cells with large elongated grooved nuclei, inhibin positive, proposing an adult type testis granulosa tumor with a diameter of 3.8 cm, inhibin positive. Also the presence of Call-Exner bodies helped to underline the diagnosis of adult type granullosa cell tumor of testis.

The age of the present patient is 30 years which is clearly lower than the median age of 43.2 years and even lower than the inter quartile range (26 -55 years) as observed in the literature survey.

From our review the median tumor size at the diagnosis was 3,2 cm. Our patient at the time of diagnosis presented with a tumor of 3,8 cm in the largest dimension. Regarding laterality of AGCT, our patient presented with a left sided tumor which corresponds to the findings in the majority of cases of the survey where 46 (50% of cases) had left sided tumors as opposed to 37 (40% of cases) right sided tumors. For 10 (10% of cases) patients there are no side location information.

Our analysis of the literature revealed that the painless scrotal lump or enlargement is the most typical presenting symptom in patients with adult tGCTs. Overall, like with testicular germ cell tumors, a palpable mass is likely the typical presenting sign of AGCT [3,10]. Gynecomastia and other endocrine-related symptoms are uncommon in these patients, however occurrences of the aforementioned symptoms in patients with adult-type GCTs have been documented. More specifically, gynecomastia or other endocrine symptoms were observed in 9 of the 93 reported instances (9% of reported cases). This symptom is not specific for AGCT because it is frequently observed in Leydig cell tumors and sometimes also in beta-human chorionic gonadotropin secreting germ cell tumors [11].

Metastatic disease was never observed in men with juvenile tGCT but in men with adult tGCT [2,3]. Primary site of metastasis is represented by the retroperitoneal lymph nodes, but other sites including lungs, liver, bone and inguinal lymph nodes can also be affected [2]. In our review the average of metastatic patients was 12 of the 93 reported cases (13% of all reported cases were metastatic). Crogg et al in a recent analysis of the literature defined some predictive factors for metastases, Predictive variables for metastatic disease included tumor size, angiolymphatic invasion and presence of gynecomastia (62). Our patient was not metastatic at the initial staging, despite the increased level of Inhibin type A. We proceed a thorough follow up with control of Inhibin type A, which revealed a remarkable upward trend (from 10 pg/dL to 90 pg/dL within 3 months). We performed a FDG-PET/CT, which revealed no site of distant metastases. Till the time this report is

being written, the patient remains 9 months after the initial radical surgical treatment with no recurrence and under strict follow up.

Conclusions

In conclusion, in this case presentation we report a case of adult type of germ cell tumor of testis and we committed a summary of all reported cases in the international medical literature. This is a very rare entity in adult men with specific histopathological characteristics, specific clinical characteristics and in most cases a benign clinical behavior. Nevertheless, there are some cases with metastatic disease even many years after the initial diagnosis, a fact that underlines the need of a proper oncological follow up and a detailed staging even in tumors that predominantly have a benign clinical behavior.

TGCTs: Testicular granulosa cell tumors

AGCT: Adult granulosa cell tumor

CT: computed tomography

LDH: lactate dehydrogenase

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