

## Adult type granulosa cell tumor of the testis: Radiological evaluation and review of the literature

### *Erişkin tip granuloza hücreli testis tümörü: Radyolojik değerlendirme ve literatürün gözden geçirilmesi*

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#### ABSTRACT

A testicular granulosa cell tumor of the adult type is very rare. Isolated case reports and small series have been published in the English literature. Here, we analyze an incidentally discovered testicular granulosa cell tumor in a 29-year-old man to discuss the radiological evaluation of this entity and review the literature.

**Key words:** Adult; granulosa cell tumor; testis.

#### ÖZET

Erişkin tip granuloza hücreli testis tümörü çok enderdir. İngilizce literatürde izole olgu raporları ve küçük seriler yayınlanmıştır. Burada, 29 yaşında bir erkekte tesadüfen keşfedilmiş bir granuloza hücreli testis tümörü olgusunu incelemekte, bu olgunun radyolojik değerlendirmesini tartışmakta ve literatürü gözden geçirmektediriz.

**Anahtar kelimeler:** Erişkin; granuloza hücreli tümör; testis.

#### Introduction

Granulosa cell tumor (GCT) of the testis is a subtype of testicular sex cord stromal tumors and is divided into adult and juvenile types. Testicular GCT (TGCT) of the adult type is very rare, and only a small number of cases have been reported. It is generally considered to be a slow growing neoplasm, but it can have a low metastatic potential, metastasizing many years after the initial diagnosis. A follow-up protocol for these patients is necessary because of its unpredictability. However, small number of reported cases represent a serious limitation towards the establishment of such a follow-up program.

#### Case presentation

A 29-year-old man presented with a painless right testicular swelling. The patient did not report any congenital problems of testicular development, such as cryptorchidism. There was no history of testicular trauma, systemic or sexually transmitted diseases, urinary symptoms or erectile dysfunction. The right testis was hard and swollen on palpation, and

physical examination revealed the enlargement of both breasts.

Ultrasonography of the testes showed a 2.5x2 cm mass with sharply defined and slightly lobulated borders occupying the inferior pole of the right testis (Figure 1a). The lesion presented with a hypoechoic echotexture along with linear hyperechoic foci and small, scattered areas of calcification. Increased vascularity was registered mainly at the periphery of the lesion on color (Figure 1b) and power Doppler (Figure 1c) images. However, at the center of the lesion, only one or two abnormal neoplastic vessels extended radially from the periphery all the way to the center of the neoplasm (Figure 1c). This vascular pattern raised the possibility of malignancy. On real-time elastography, the entire lesion presented with a stiff pattern without strain (Figure 2a, b), which along with a maximum strain ratio of 4.32 (Figure 2c), is considered to be a characteristic feature of malignancy. There was a small reactive hydrocele between the two layers of tunica vaginalis on the right side. Left scrotal examination revealed a normal testis.

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**Submitted:**  
16.06.2013

**Accepted:**  
26.08.2013

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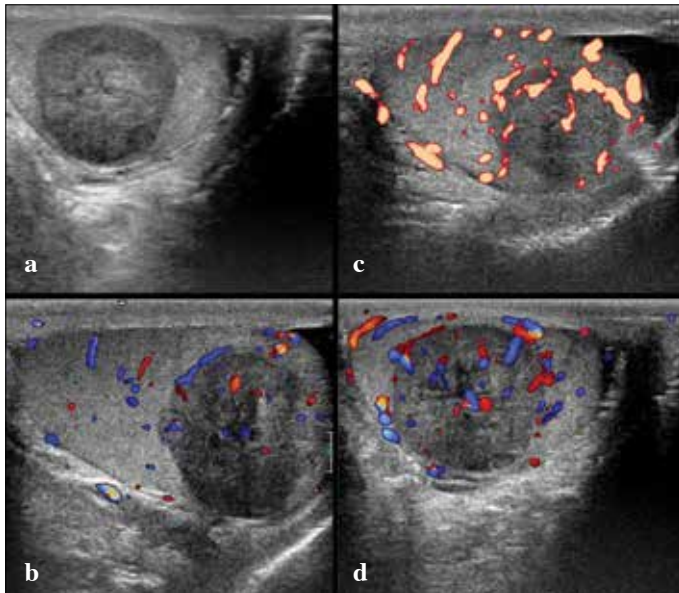


Figure 1. A sagittal B-mode (a) sonogram showing a hypoechoic lesion with few internal echoes at the inferior pole of the testis. Color Doppler (b) and power Doppler (c) sagittal sonograms demonstrating the increased peripheral and decreased central vascularity within the lesion

Serum levels of alpha-fetoprotein, human chorionic gonadotropin, lactate dehydrogenase, and placental alkaline phosphatase were all within the normal ranges.

Computed tomography of the abdomen and chest did not reveal any evidence of retroperitoneal lymph node enlargement or metastatic disease.

Inguinal exploration and radical orchiectomy were performed without any complication.

The macroscopic view of the cut surface area of the specimen showed a solid, well-defined, white intratesticular tumor, with an average diameter of 2 cm (Figure 3).

Histopathological examination of the lesion showed increased cellularity with solid cell formations within a layer of connective tissue. These malignant cells had ovoid-to-elongated nuclei with distinct longitudinal nuclear grooves ("coffee bean" appearance) (Figure 4a). Additionally, longitudinal adenoid formations of the rete testis were trapped within the tumor mass. The tumor was confined to the testis, without any invasion to the spermatic cord or the epididymis.

Immunohistochemical staining of the solid tumor cell formations demonstrated strong positivity for vimentin and a-inhibin (Figure 4b), and negativity for calretinin. Furthermore, the adenoid formations within the lesion were positive for cytokeratins

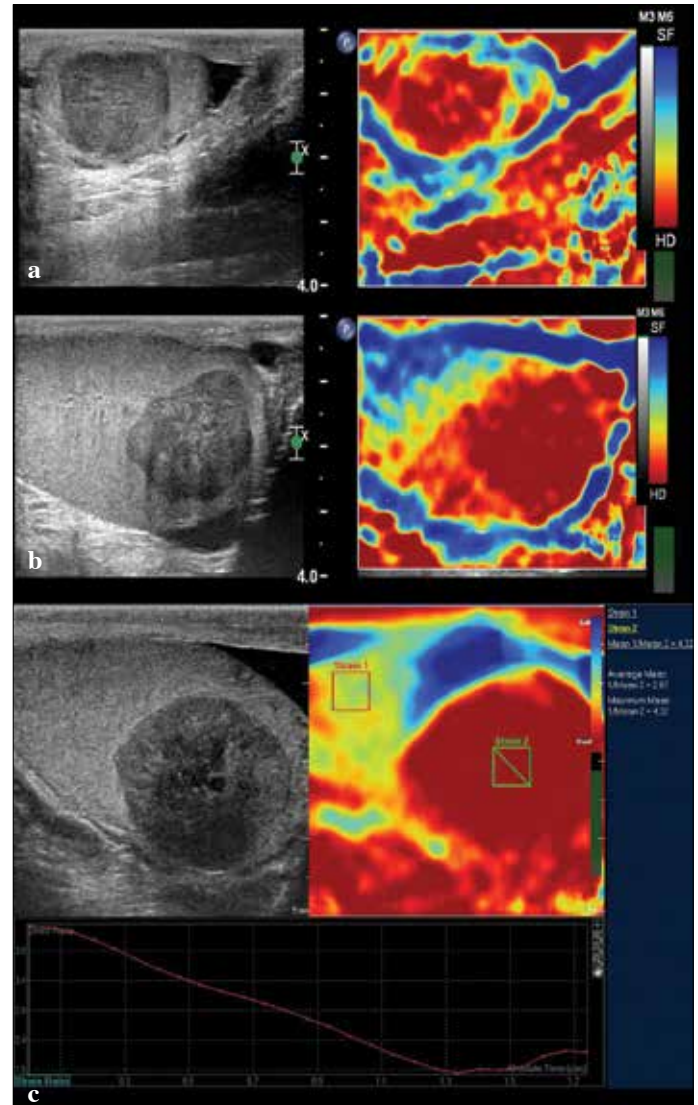


Figure 2. Sonoelastography (a, b) demonstrates the stiffness of the entire lesion. The strain ratio was 4.32 (c)

AE1/AE3 and CK7. The stroma surrounding the tumor expressed strong positivity for actin of the smooth muscle fibers.

At the one-year follow-up, the CT and MRI showed no lymph node involvement or metastatic disease, and all laboratory tests were normal. The only finding upon physical examination was persistent gynecomastia.

## Discussion

Granulosa cell tumor is a sex-cord stromal tumor, which occurs more commonly in the ovary. Testicular sex cord stromal tumors contain epithelial elements of the sex cord (granulosa cell tumors and Sertoli cell tumors), as well as elements of

mesenchymal or stromal origin (theca cell tumors and Leydig cell tumors). These tumors are very rare and account for 4-6% of all testicular neoplasms.<sup>[1]</sup>

TGCTs are classified into juvenile and adult types. Juvenile GCTs are rare, but are the most frequent congenital testicular neoplasms occurring in infants younger than 6 months of age.<sup>[2]</sup> There is a connection of this subtype with cytogenetic abnormalities. It is considered to be benign, as there have been no case reports of metastatic disease.

The adult type of GCTs is the least common among the sex cord stromal tumors and is seen at any of the post-pubertal age groups ranging from 16 to 76 years (mean age: 44 years).<sup>[2]</sup> Although

they are generally thought to behave in a benign manner, cases of metastatic disease have been reported. Hence, the clinical course of these tumors is difficult to predict. Accordingly, they are characterized as slow growing neoplasms, which may metastasize to distant sites years after the initial diagnosis.<sup>[3]</sup>

Granulosa cell tumor mainly affects white males, and they usually present as a painless testicular mass<sup>[4]</sup>. Many of the reported cases have been discovered incidentally or during a routine scrotal examination. In 1952, Laskowski documented the first case of an adult TGCT in a 35-year-old man with a history of cryptorchidism<sup>[5]</sup>. Gynecomastia is present in 25% of cases<sup>[4,6,7]</sup> due to hormonal abnormalities, such as estrogen hypersecretion or chromosomal anomalies.



Figure 3. A macroscopic view of the testis showing a well-encapsulated, white-colored tumor with slightly lobulated margins

Ultrasonography is usually the first diagnostic procedure performed in patients with testicular enlargement and shows intra- or extratesticular location of the abnormality. In contrast, the use of primarily color, but occasionally gray-scale Doppler sonography, demonstrates the characteristics of the individual lesions and may help distinguish a neoplastic lesion from a benign testicular mass.<sup>[8,9]</sup> In our case, the ultrasonographic findings of a slightly lobulated, well-defined, hypoechoic intratesticular mass with few internal echoes, scattered calcifications, increased peripheral and low central vascularity led to a high suspicion of malignancy, and constituted a strong indication for orchiectomy. Previously, Mitra et al.<sup>[10]</sup> considered these findings typical for adult TGCTs and stated that the increased vascularity within the tumor, as demonstrated on color Doppler sonography, helped them make the decision for the surgical excision of the testis.

It is mandatory to state that these ultrasonographic features are not specific for adult TGCTs and may be seen in other primary or secondary testicular neoplasms. Similar characteristics detec-

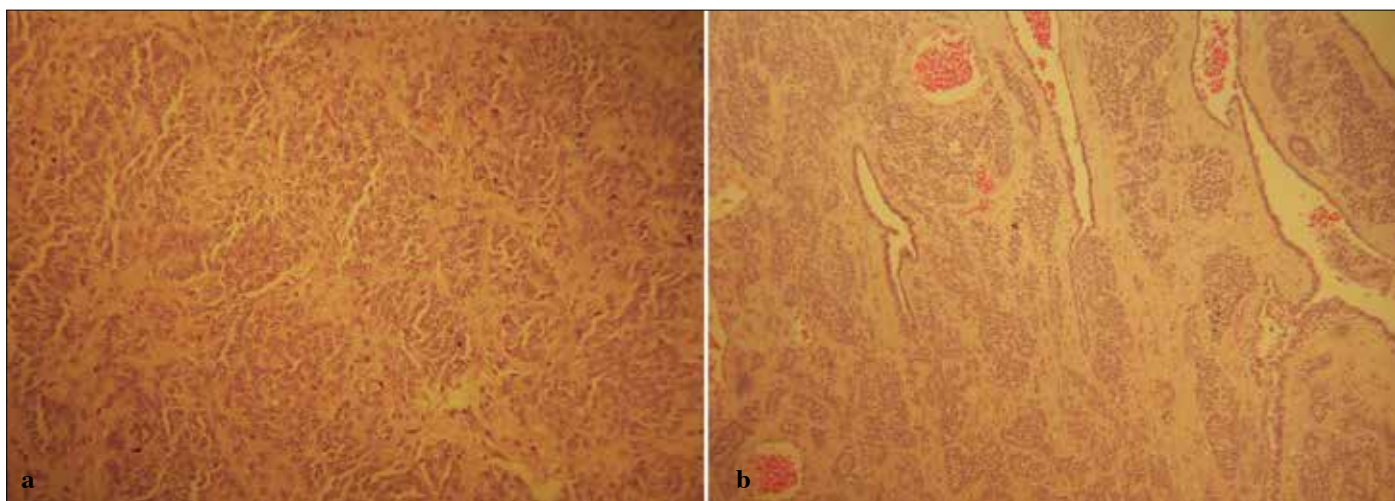


Figure 4. Histology with E-H reveals the characteristic granulosa cells with "coffee-bean" nuclei (a). Immunohistochemically, the tumor was positive for inhibin (b)



ted by B-mode ultrasonography have been reported for testicular lymphomas, which often present as a focal intratesticular mass.<sup>[9,11,12]</sup> However, in our case, the vascular pattern of the neoplasm differed from that of typical cases of focal testicular lymphoma, which present with strikingly increased vascularity of the entire lesion. In contrast, the color Doppler and power Doppler sonographic findings in our patient were that of increased peripheral and decreased central vascularity, and resembled those of a plasmablastic lymphoma.<sup>[12]</sup>

These are not the only ultrasonographic patterns that have been described for these tumors. Although ultrasonographic examination results have not been documented in all published reports, the available ultrasonographic findings clearly show that adult TGCTs can have various appearances. Specifically, the neoplasm may be heterogeneous with solid and cystic components<sup>[13-15]</sup> with ill-defined borders<sup>[16]</sup> or present with a discrete hypoechoic echotexture.<sup>[1]</sup>

Finally, the juvenile type of TGCT has a “Swiss cheese” appearance, with solid and cystic areas.<sup>[1]</sup>

Real-time sonoelastography is a non-invasive technique that evaluates the elasticity and the mechanical characteristics of biological tissue through its compression and displacement (strain), representing a “new method” of palpation.<sup>[17,18]</sup> The lack of strain, that is, the hardness of the testicular lesions, is an indicator of malignancy, while the presence of strain implies increased elasticity and usually characterizes benign lesions.<sup>[17-20]</sup> Because the value of B-mode and Doppler sonography is limited for the assessment of small testicular nodules and pseudonodules, sonoelastography is useful mainly in these cases.<sup>[17]</sup> A vast majority of larger lesions display clinical and ultrasonographic properties that indicate malignancy. In such cases, sonoelastography has a confirmative role in their diagnosis.<sup>[17]</sup> As such, we should always implement this method, along with conventional ultrasonography<sup>[19]</sup>, although we should keep in mind that the proper interpretation of the elastographic findings is only possible if we take into consideration all the available clinical, laboratory and imaging data.<sup>[18]</sup> In our patient, real-time sonoelastography showed stiffness of the entire lesion, with a maximum strain ratio of 4.32, indicating malignancy.

The macroscopic appearance of the adult-type TGCT may vary from a yellow to a gray-white solid mass and cystic components may also be present. The borders of the neoplasm are usually sharply defined, and the presence of a fibrous pseudocapsule has been described in some cases. In our case, the tumor was white and solid, without any cystic areas.

The histology of these tumors may reveal variable patterns. Microscopically, they may be arranged in a gyriform, macrofollicular, microfollicular, trabecular, solid, pseudosarcomatous or insular pattern. In the microfollicular presentation, the cells

may exhibit pseudo-acinar patterns surrounding nuclear fragments (Call-Exner bodies). Typically, neoplastic cells have oval nuclei with a longitudinal groove, in a so-called “coffee bean” appearance.<sup>[6]</sup> They usually do not invade the tunica albuginea. Intrusion of neoplastic cells between the seminiferous tubules at the periphery of the tumor<sup>[21]</sup> or the minimal invasion of the testicular parenchyma have also been reported.<sup>[3]</sup> Lymphovascular invasion or hemorrhage is rarely observed. In our case, there was infiltration of the rete testis, which was similar to the case reported by Matoška et al.<sup>[7]</sup>

Immunohistochemistry is important for the discrimination of adult type TGCTs from other testicular neoplasms that may resemble them histopathologically, such as malignant lymphoma and germ cell tumors. The panel of immunohistochemical tests usually demonstrates the presence of strong immunoreactivity for vimentin and inhibin, as was the case in our patient, as well as for smooth muscle actin and in most cases, for calretinin. Variable results have been reported for cytokeratin expression, while epithelial membrane antigen (EMA)<sup>[4]</sup> and placental alkaline phosphatase have been reported to be negative. Estrogen and progesterone receptors may be expressed in these neoplasms.<sup>[14]</sup> Immunostaining with mullerian inhibiting substance may be useful in distinguishing between granulosa cell and Leydig cell tumors.<sup>[14]</sup>

The differential diagnosis of adult type GCT includes unclassified sex cord-stromal tumor, lymphoma, metastatic carcinoma with spindle cell differentiation, primary sarcoma, carcinoid tumors and metastatic melanoma.<sup>[15,22,23]</sup>

The ovarian counterpart of this tumor is more aggressive and has a worse prognosis. The clinical behavior of testicular GCTs is generally thought to be benign, although cases of malignancy have been reported. From the 30 reported cases of these tumors, including all previously reported cases and the current case, 6 patients had metastatic disease.<sup>[23]</sup> The most common site of metastasis was the retroperitoneal lymph nodes. Additionally, hepatic, lung and bone metastases have been also described.<sup>[3]</sup>

Jimenez-Quintero et al.<sup>[4]</sup> reviewed 52 cases of testicular sex-cord-stromal tumors, of which there were 7 cases of adult type GCTs. They found that many malignant tumors were larger than 7.0 cm and presented with lymphovascular invasion, tumor necrosis, and hemorrhage. They indicated that these characteristics might help predict the danger for metastasis in these tumors. Based on all reported cases of adult TGCTs, Hanson et al.<sup>[3]</sup> reported that only a tumor size greater than 5.0 cm was statistically associated with malignancy. A larger number of cases are necessary to determine the metastatic potential of these neoplasms.

The lack of a follow-up protocol in these patients is due to the unpredictable biological and clinical behavior of these tumors. The fact that these slow growing neoplasms have the potential

to cause distant metastases many years after the initial diagnosis necessitates the long-term follow-up of these patients.

Adult-type granulosa cell tumor is a very rare testicular tumor. The ultrasonographic characteristics of this entity raise a high index of suspicion for malignancy but display low specificity because other more common neoplasms, such as the focal testicular lymphoma, present with similar features. All the reported cases of this tumor were treated with orchiectomy, and the diagnosis was made on the basis of histopathologic and immunohistochemical findings. Although this tumor is associated with a good prognosis and a long survival, long-term follow-up should be implemented due to its metastatic potential, which may occur a long time after its initial presentation.

**Informed Consent:** Written informed consent was obtained from patient who participated in this case.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - I.T.; Design - I.T., C.M.; Supervision - I.T., E.P.; Materials - I.T., C.M., A.S., S.P., E.P.; Data Collection and/or Processing - C.M., A.S.; Analysis and/or Interpretation - C.M., A.S.; Literature Review - C.M., E.P.K.; Writer - C.M.; Critical Review - E.P.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Hasta Onamı:** Yazılı hasta onamı bu olguya katılan hastadan alınmıştır.

**Hakem Değerlendirmesi:** Dış bağımsız.

**Yazar Katkıları:** Fikir - I.T.; Tasarım - I.T., C.M.; Denetleme - I.T., E.P.; Malzemeler - I.T., C.M., A.S., S.P., E.P.; Veri toplanması ve/veya işleme - C.M., A.S.; Analiz ve/veya yorum - C.M., A.S.; Literatür taraması - C.M., E.P.K.; Yazıyı yazan - C.M.; Eleştirel İnceleme - E.P.K.

**Çıkar Çatışması:** Yazarlar çıkar çatışması bildirmemişlerdir.

**Finansal Destek:** Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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