A Case of Adult Granulosa Cell Tumor of the Testis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient:	**Female, 22**
Final Diagnosis:	**Testis granulosa cell tumor**
Symptoms:	**Pain in testicles • swelling of epididymides • tenderness of epididymiides**
Medication:	**—**
Clinical Procedure:	**—**
Specialty:	**Urology**

Objective: **Rare disease**

Background: Adult granulosa cell tumors of the testis (AGCTT) are classified as sex cord-stromal tumors. Only 31 cases have been reported. Typical presentation includes a slowly enlarging, painless testicular mass. Associated findings are gynecomastia, decreased libido, and erectile dysfunction. Immunohistochemistry can be used to confirm the diagnosis.

Case Rrport: A 22-year-old male presented with complaint of mild pain in both testicles. A testicular ultrasound revealed a 4.0×3.8×4.6 mm hypoechoic lesion within the left testicle. Serum tumor markers (STM) included lactate dehydrogenase (LDH) measuring 146 IU/L (98–192), serum alpha-1-fetoprotein (AFP), 2.89 ng/mL (0–9), and plasma beta human chorionic gonadotropin (Beta HCG) measuring less than 0.50 mIU/mL (<0.50–2.67). Computed tomography (CT) of the abdomen and pelvis with oral and intravenous contrast was normal. A radical orchiectomy was recommended but the patient refused. He agreed to surveillance with imaging and serum tumor markers (STM). The patient's testicular ultrasound showed the mass to be stable in size and STMs remained negative. The patient agreed to an orchiectomy 9 months after his diagnosis. This case is the first reported with c-kit-positive immunohistochemistry. His post-operative course has been unremarkable.

Conclusions: AGCTT is a rare tumor and information regarding its presentation, gross and microscopic morphology, and immunohistochemical characteristics is lacking. This report provides an update of the immunohistochemical findings and adds to the available data concerning this tumor. Based on the results of this case, future reports that include c-kit immunohistochemistry would be beneficial to evaluate its utility in diagnosing AGCTT.

MeSH Keywords: **Granulosa Cell Tumor • Immunohistochemistry • Inhibins • Testicular Neoplasms • Vimentin**

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Background

Granulosa cell tumors (GCT) are classified as sex cord-stromal tumors of the gonads. Other tumor types included in this class are thecomas, fibromas, Sertoli, Leydig, and Sertoli-Leydig cell tumors [1]. GCTs are divided into 2 different types: juvenile and adult [2]. The juvenile type is one of the most common testis neoplasms occurring in the first 6 months of life [3]. The adult type is very rare and occurs over a broad age range. Only 31 cases of adult GCT of the testis (AGCTT) have been reported to date [2]. A number of clinical, morphological, and immunohistochemical characteristics have emerged through various studies that assist in diagnosing AGCTT. In over one-half of cases, the clinical presentation is one of slow, painless enlargement over a variable period of time [4–6]. The average age of diagnosis is 47 years and ranges from 12 to 77 years [4,7]. Gynecomastia, decreased libido, and erectile dysfunction may also be present [5,7]. Gross morphologic analysis of AGCTT cells typically shows a solid, well-circumscribed, lobular mass that may have a fibrous pseudocapsule. Microscopically, AGCTTs typically show round cells with pale-to-eosinophilic, scant cytoplasm and round or oval nuclei with a characteristic "coffee-bean" nuclear groove, fine chromatin, and inconspicuous nucleoli [6,8]. Rarely, theca cells may be visualized surrounding the testicular parenchyma along with Leydig cell hyperplasia and Sertoli cell nodules. Call-Exner bodies, while not essential, are very often present and aid in differentiating AGCTT from the juvenile type [5,6,9,10]. Growth patterns are variable and include solid, microfollicular, gyriform, insular, trabecular, or pseudosarcomatous [6,11]. The mitotic rate is highly variable and ranges from less than 1 to 50 mitoses per high-power field (HPF) [7]. Immunohistochemical analysis, while not essential, can be helpful in establishing the diagnosis in more ambiguous cases [12]. AGCTTs typically exhibit immunopositivity to vimentin, inhibin, smooth muscle actin (SMA), MIC2 (CD99), and calretinin. A positive reaction with pancytokeratin antibodies or S100 may be seen in some cases. A negative immunohistochemical response is typically seen with epithelial membrane antigen (EMA) and placental alkaline phosphatase (PLAP). Many other immunohistochemical tests have been used in a small number of cases or are underreported, making analysis difficult (Table 1) [6,7,10]. While the AGCTTs are distinctly uncommon and most often benign, slow growing, and non-functioning, they do have the potential for distant metastases that lead to poor outcomes [4,12]. Patients with metastasis to regional lymph nodes typically have a relatively long survival period; however, patients that have distant metastasis exhibit rapid disease progression with death occurring a few months to a few years after metastases have occurred [12]. Metastasis has been reported most commonly to the retroperitoneal lymph nodes, but lung, liver, and bone metastases have also been noted [10,12,13]. The most recent evidence indicates that approximately 20%

of cases of AGCTTs are malignant; however, due to the very limited number of cases, factors predictive of malignancy have yet to be well defined. Early research failed to reliably identify factors predictive of malignancy, but Jimenez-Quintero et al. suggested that size greater 7.0 cm, presence of lymphovascular invasion, hemorrhage, and necrosis might be indicative of malignancy because these characteristics were present in the malignant cases they identified [5,11]. More recently, Hansen and Ambaye evaluated patient age, laterality, presence of gynecomastia, tumor size, and presence of mitoses and necrosis in an attempt to determine valid variables for prediction of malignancy. Of the variables analyzed, only tumor size greater than 5.0 cm achieved statistical significance [5]. Initial management of a suspected AGCTT is radical orchiectomy [2,14]. Retroperitoneal lymph node dissection should be considered in cases with pathology suggestive of malignant features or if small-volume metastatic disease is present. If performed, it should immediately follow orchiectomy. Patients with widespread, unresectable metastatic disease have a very poor prognosis because these tumors are not amenable to chemotherapy or radiotherapy [6]. In cases believed to have low malignant potential, ultrasound of the abdomen and testis, coupled with clinical examination, may be sufficient [11]. With larger tumors or tumors deemed to be aggressive, more extensive follow-up may be warranted. One suggested follow-up regimen consists of abdominal and testicular ultrasound coupled with chest x-ray alternated with CT of the abdomen and pelvis at 6-month intervals. The duration of follow-up is not well-defined; however, as noted above, metastasis has been discovered more than 10 years after treatment, so long-term follow-up is mandatory [6]. Further analysis is necessary to identify factors that can reliably predict tumor behavior.

Case Report

A 22-year-old male presented with complaint of mild pain in both testicles. He denied dysuria, urethral discharge, back pain, abdominal pain, or recent illness. He denied personal or family history of genitourinary disease. Past medical history was not significant. The patient denied previous abdominal or genitourinary surgeries. The patient quit smoking in 2012 and had a 3 pack-year history. Vital signs were within normal limits. Physical exam was remarkable for tenderness and swelling in both epididymides; however, no masses or tenderness were noted on palpation of the testicles. Other pertinent findings included the absence of cervical, supraclavicular, or inguinal lymphadenopathy, gynecomastia, urethral discharge, or scrotal swelling. Abdominal examination revealed no masses or tenderness. Urinalysis showed no blood, leukocytes, or protein and was negative for nitrite and leukocyte esterase. A testicular ultrasound revealed a 4.0×3.8×4.6 mm hypoechoic lesion within the anterior aspect of the left testicle. Serum

Table 1. Immunohistochemistry in 32 cases adult granulosa cell tumor of the testis.

Antibody	Number of cases	Positive	Negative	Current case
Pancytokeratin	13	3	10	Negative
Vimentin	18	18	0	Positive
EMA	15	2	13	Negative
Inhibin	13	11	2	Positive
SMA	6	6	0	Positive
S100	6	2	4	Not performed
PLAP	8	0	8	Negative
Desmin	3	2	1	Not performed
MIC2 (CD99)	6	6	0	Positive
Calretinin	6	6	0	Positive
ER/PR	3	1	2	Not performed
Chromogranin	2	0	2	Negative
Synaptophysin	2	0	2	Negative
c-kit (CD117)	3	1	2	Positive
CD30	2	0	2	Not performed
Beta HCG	2	0	2	
LCA (CD45)	4	0	4	
AFP	4	0	4	
CD3	2	0	2	
CD5	2	0	2	
CD20	2	0	2	
CD79a	2	0	2	
CD21	2	0	2	
CD35	2	0	2	
CD10	2	0	2	
Desmoplakin	1	0	1	
Melan-A	1	1	0	
LMW Cytokeratin	7	3	4	

AFP – alpha-fetoprotein; Beta-HCG – beta human chorionic gonadotropin; EMA – epithelial membrane antigen; ER/PR – estrogen receptor/progesterone receptor; LCA – leukocyte common antigen; LMW – low molecular weight; PLAP – placental alkaline phosphatase; SMA – smooth muscle actin. Number of cases and positive and negative totals include results obtained in the current case.

tumor markers (STM) included lactate dehydrogenase (LDH) measuring 146 IU/L (98–192), serum Alpha-1-fetoprotein (AFP), 2.89 ng/mL (0–9), and plasma beta human chorionic gonadotropin (Beta HCG) measuring less than 0.50 mIU/mL (<0.50–2.67). CT of the abdomen and pelvis with oral and intravenous contrast revealed no abnormal findings, including retroperitoneal lymphadenopathy. A radical orchiectomy was strongly recommended, but the patient refused. The patient agreed to surveillance with imaging and STMs. During surveillance, STMs remained negative and the patient's testicular ultrasounds showed the mass to be generally stable in size, increasing only 1 mm in size at its largest dimension over
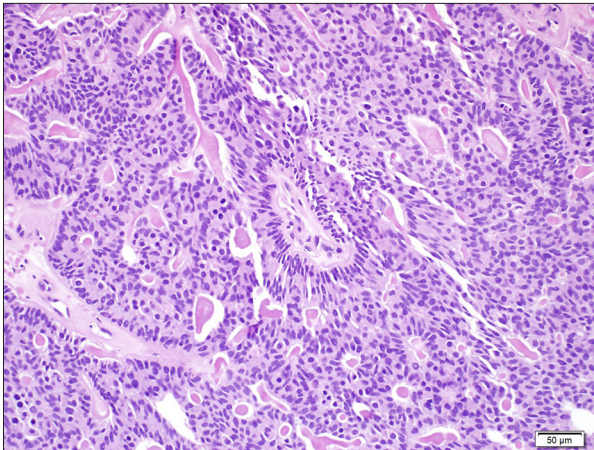
Figure 1. Hematoxylin and eosin staining at 20× magnification showed granulosa cell composition in a primarily microfollicular pattern and Call-Exner bodies.
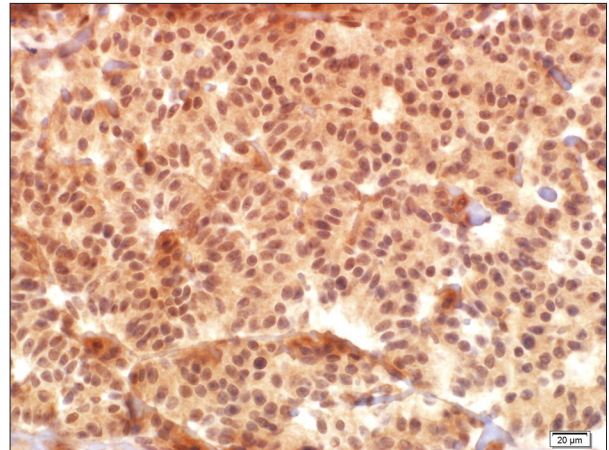

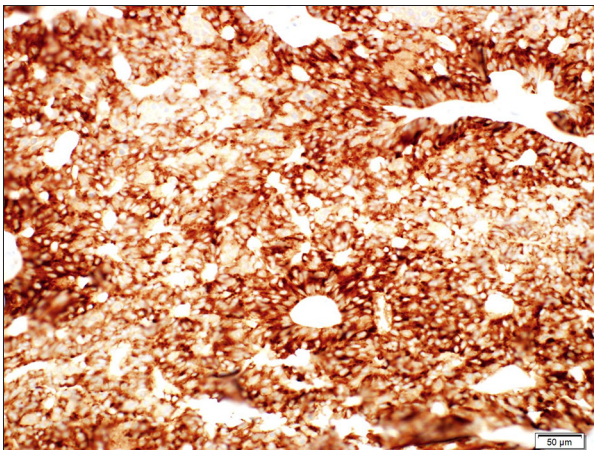**Figure 3.** Calretinin staining at 40× magnification showed strong cytoplasmic staining.

Figure 2. Inhibin staining at 20× magnification showed strong cytoplasmic staining.
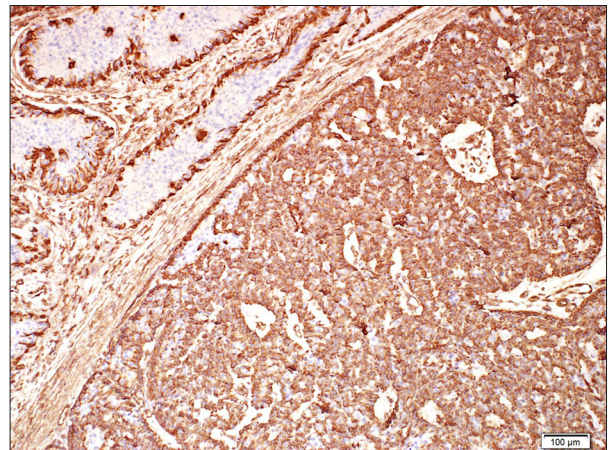

Figure 4. Vimentin staining at 10× magnification.

a 9-month period. This change is negligible given variability among sonographers. The patient agreed to an orchiectomy approximately 9 months after his initial diagnosis. Radical orchiectomy was performed with no complications. The surgical specimen consisted of the left testis, weighing 69 grams and measuring 4.8×3.5×2.9 cm. Sectioning of the testis revealed an irregularly-shaped tan-white lesion with a firm cut surface in the otherwise unremarkable fleshy, beige testicular parenchyma. The lesion measured 0.6 cm in its greatest dimension and was enveloped in a thin capsule No invasion of the surrounding tissue was noted. There was no evidence of hemorrhage or necrosis and there was no gross involvement of the tunica albuginea. Routine hematoxylin- and eosin-stained tissue sections revealed the lesion to be composed of granulosa cells in a predominantly microfollicular pattern, although trabecular and insular patterns were present. The microfollicles were filled with eosinophilic secretions characteristic of Call-Exner bodies. The surrounding granulosa cell nuclei

were generally oval in shape with occasional nuclear grooves. Scattered mitotic figures were present without appreciable atypia. Consistent with the gross impression, the lesion had a thin fibrous capsule and was non-infiltrative. Figure 1 illustrates the major morphologic findings. Immunohistochemical stains were performed with appropriately reactive controls (Ventana, Tucson AZ). The tumor cells showed strong membrane and cytoplasmic staining for inhibin, as demonstrated in Figure 2. The cells also showed strong cytoplasmic staining for calretinin (Figure 3). Other antigens that were positive included vimentin (Figure 4), MIC2 (CD99), SMA, and c-kit. Ki-67 revealed a mitotic index of approximately 10%. Other negative immunohistochemical stains included chromogranin, synaptophysin, PLAP, EMA, and pancytokeratin. Given the histopathologic findings, as well as the immunohistochemistry, the patient was diagnosed with AGCTT. To date, post-operative surveillance including ultrasound and clinical examinations have been unremarkable.

Discussion

AGCTT is rarely encountered; therefore, other more common diagnoses need to be eliminated before the diagnosis can be made. AGCTT can be differentiated from juvenile GCTT by the presence of Call-Exner bodies or "coffee-bean" nuclei in the former [9]. Additionally, juvenile GCTT is usually diagnosed in patients aged 4 years and younger, but it has been diagnosed in adults [8]. Yolk sac tumors are usually positive for PLAP, cytokeratin, and AFP, whereas AGCTT is usually negative for these immunohistochemical tests. Hematopoietic malignancies, though they may share some histologic similarities with AGCTT, can be differentiated by the presence of leukocyte common antigen (LCA, CD45). Metastatic carcinoma is usually positive for cytokeratin. Carcinoid tumors, whether primary or metastatic, are typically positive for synaptophysin, chromogranin, and cytokeratin [9,15]. Sertoli-Leydig cell tumors are usually positive for pancytokeratin [9]. Although not required for diagnosis, the immunohistochemical staining profile of AGCTTs can help confirm the diagnosis in equivocal cases. As noted in Table 1, vimentin, SMA, MIC2, calretinin, and inhibin are consistently positive, but EMA, pancytokeratin, and PLAP are typically negative. To the best of our knowledge, this case is the first to demonstrate c-kit positive immunohistochemistry. Excluding this finding, the typical immunohistochemical profile presented in other reports was supported. It was suggested in a previous report that inhibin may be an equivocal tumor marker; however, the most recent reports, including this case, have demonstrated inhibin

positivity [2,7]. Overall, inhibin has been used in 13 cases and it has demonstrated positivity in 11 cases. More data from additional cases are required to refine the immunohistochemical profile and resolve the inconsistencies.

Conclusions

AGCTT is a rare tumor and information regarding its clinical presentation, gross and microscopic morphology, and immunohistochemical characteristics are lacking. This report provides an update of the most current immunohistochemical findings and adds to the available data concerning this tumor. The immunohistochemical profile needs further elucidation as many of the markers have been utilized in only a few cases. Based on the results of this case, future reports that include c-kit immunohistochemical staining would be beneficial to evaluate its usefulness in diagnosing AGCTT.

Disclosures

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