Adult granulosa cell tumor of the testicle

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We report a rare case of adult granulosa cell tumor of the testis in a 68-year-old man. A case and literature review of the associated clinical features, histopathological characteristics and immunochemistry are presented. The tumor is typically slow growing but has a higher risk of malignancy when > 5 cm. Our patient was disease-free 18 months following a right radical orchiectomy.

Key Words: testicular tumors, sex cord tumors, granulosa cell tumors

Introduction

Testicular granulosa cell tumors are rare sex cord stromal tumors. They are histologically related to ovarian granulosa cell tumors and, like these, can be divided into adult and juvenile types. While adult granulosa cell tumors represent approximately 3% of ovarian neoplasms, adult granulosa cell tumors of the testes (AGCTT) are exceedingly rare with only 30 reported cases.[1] Average age at diagnosis is 47 years and most present with painless testicular swelling over a period of months to years. Some have associated features of endocrine disturbance including gynecomastia, low libido and erectile dysfunction.[1-4]

It has been proposed that these tumors have limited malignant potential[5] but seven of reported cases (~ 20%) had metastases at presentation or developed them subsequently. Diagnosis of AGCTT is based upon characteristic histologic findings following radical orchiectomy. Metastatic disease has been found in retroperitoneal and inguinal lymph nodes, lungs and liver. Biological behavior is unpredictable and metastases may occur long after initial diagnosis and can progress rapidly.[3,4,6-9] Therapeutic regimens have been used to manage metastatic disease with varying degrees of success.

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Case report

A 68-year-old man was referred with a 1 year history of a slowly growing, painless right testicular mass without associated lymphadenopathy. Serum alpha-feto-protein (AFP) and human chorionic gonadotropin (βHCG) were negative. There was no evidence of gynecomastia or other endocrine disturbance.

Right radical orchiectomy was performed. Grossly, the tumor was non-encapsulated, homogeneous, white-tan in color and measured 1.5 cm in maximum dimension. It abutted, but did not penetrate the tunica albuginea. Microscopically, there were sheets of cells organized in a trabecular pattern with scanty cytoplasm and grooved nuclei, Figure 1a, 1b. Mitotic count was 1/20 HPF. There was no necrosis, hemorrhage nor lymphovascular invasion and paratesticular tissues were not involved. Immunohistochemical stains revealed positive staining with vimentin, calretinin, CD99 and Melan A. PLAP, CD30, AFP, βHCG, inhibin and EMA immunostains were negative.

Studies were performed that showed no evidence of metastatic disease at presentation or 3, 6, 12 and 18 months follow up.

Discussion

The differential diagnosis for a testicular mass that is morphologically similar to AGCTT includes germ cell tumors, metastatic carcinoma, neuroendocrine tumors and non-Hodgkin's lymphoma. Characteristic microscopic features of AGCTT include Call-Exner

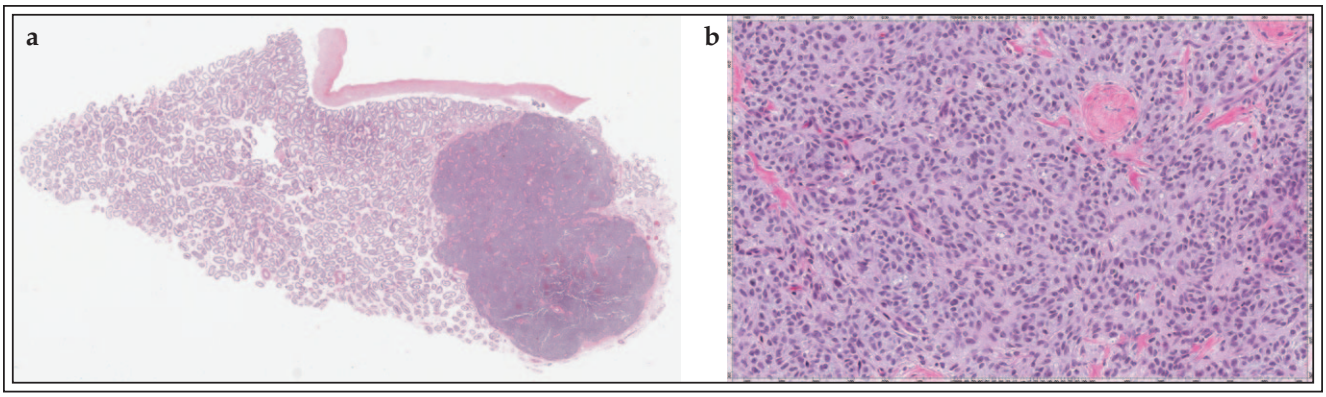

Figure 1. a) Low power image showing well-circumscribed nodule in testes. **b)** Tumor showing trabecular growth pattern and coffee-bean shaped nuclei (H&E 200X).

bodies and "coffee-bean" or grooved nuclei. Cellular arrangement can be trabecular, insular, macrofollicular, microfollicular or gyriform. The mitotic rate is variable ranging from < 1 to 50/HPF.[7] The morphologic features of our case are consistent with the histological characteristics of AGCTT.

The unique immunohistochemical profile of AGCTT also helps rule out other mimickers. Inhibin, M1C2 and calretinin are frequently positive.[8] Lymphoma, usually stains positively with CD45 while neuroendocrine tumours frequently stain positively with synaptophysin and chromogrannin.[8] MIC2 (CD99), although positive in AGCTT, is nonspecific and stains a number of tumors positively including many sarcomas, leukemias, lymphomas and certain carcinomas. We demonstrate that inhibin may be an equivocal marker in AGCTT.

Table 1 updates the summary of immunohistochemistry reported in AGCTT.[8] Vimentin, MIC2, SMA, cytokeratin and calretinin have always been positive in the AGCT stained. However, with the exception of vimenten (which has been used on 13 tumors) the remaining markers have been employed on small numbers of tumors (between 2 and 4). EMA, PLAP, ER/PR, chromogranin, synaptophysin, c-kit, CD30, βHCG, LCA and AFP have been invariably negative. There is one reported case of an AGCTT that tested positive for ER/PR.[11] Remaining markers have shown variable staining results. Our case represents only the second case where a AGCTT has been negative for inhibin.

AGCTT tends to be extremely slow growing with symptoms manifesting over a period of years. Initial management of all reported cases was radical orchiectomy and there is no evidence to support additional therapy if disease is clinically confined to the testicle. Although it demonstrates limited

TABLE1. **Summary of reported immunohistochemistry of adult granulosa cell tumors**

Antibody	Positive	Negative
Pancytokeratin	3/11	8/11
Vimentin	16/16	0/16
EMA	2/14	12/14
Inhibin	9/11	2/11
SMA	4/4	0/4
S100	2/6	4/6
PLAP	0/6	6/6
Desmin	2/3	1/3
MIC2	4/4	0/4
LMW cytokeratin	3/7	4/7
Calretinin	4/4	0/4
ER/PR	1/2	½
Chromogranin	0/1	1/1
Synaptophysin	0/1	0/1
c-kit	0/1	0/1
CD30	0/2	2/2
βHCG	0/2	2/2
LCA	0/4	4/4
AFP	0/3	3/3
CD3	0/2	2/2
CD5	0/2	2/2
CD20	0/2	2/2
CD79a	0/2	2/2
CD21	0/2	2/2
CD35	0/2	2/2
CD10	0/2	2/2
CD99	1/1	0/1
Desmoplakin	0/1	1/1
Melan-A	1/1	0/1

metastatic potential, 7 of 28 reported cases had definite spread.[3,4,6,7,9,10] The rarity of these lesions has prevented the development of standard management protocols for the management of metastatic or recurrent AGCTT. Chemotherapy and radiation are often used with variable responses.[4,7,9,10]

Of the cases reported with metastases, four had metastatic disease at the time of diagnosis;[4,7,9,10] three of these had disease in the retroperitoneal lymph nodes[4,7,10] and one had bilateral pulmonary metastases.[9] Two of these individuals went on to develop late metastases in the inguinal lymph nodes[7] and the other extensive peritoneal and retroperitoneal disease.[10] The three remaining individuals presented with late metastases.[3,6,7] Patient 1 was found to have widespread metastases 5 months after initial surgery.[3] Patient 3 had metastases in the ipsilateral tibia 60 months after initial surgery.[6] Patient 4 had disease in the liver and retroperitoneal lymph nodes 121 months post orchiectomy.[7]

Establishing definite predictors of malignancy has proven challenging because of the small number of reported cases. In a series of seven cases of AGCTT, two presented with definite metastases; size greater than 7 cm, lymphovascular invasion, necrosis and hemorrhage correlated with malignancy but none of the variables was statistically significant.[7] A review of all reported cases of metastatic AGCTT correlated the following variables with the presence of metastatic disease: age, location (right versus left), gynecomastia, size, presence of mitoses, and necrosis; only size greater than 5 cm was statistically significant ($p = 0.02$).[8] Although definitive guidelines are not possible because of the limited data, patients with tumors greater than 5 cm should be reassessed every 3 months for the first year, every 6 months for the second year and annually thereafter; those with smaller tumors can be seen less frequently.

Our case further characterizes AGCTT with regards to its clinical presentation, histopathological characteristics and immunohistochemistry. □

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