



# ADENOMATOID TUMORS OF THE TESTIS: REPORT OF A CASE WITH A FOCUS ON HISTOGENESIS, CLINICO-PATHOLOGIC CHARACTERISTICS AND DIFFERENTIAL DIAGNOSES OF THESE RARE NEOPLASMS

L. ALESSANDRINI<sup>1</sup>, F. ITALIA<sup>3</sup>, T. PERIN<sup>1,2</sup>, A. LLESHI<sup>4</sup>, V. CANZONIERI<sup>1,2</sup>

<sup>1</sup>Division of Pathology, CRO Aviano National Cancer Institute, Aviano (PN) Italy;

<sup>2</sup>CRO-Biobank, CRO Aviano National Cancer Institute, Pordenone, Italy.

<sup>3</sup>Oncopath Lab, Florida, SR, Italy.

<sup>4</sup>Medical Oncology A, CRO Aviano National Cancer Institute, Aviano (PN), Italy.

**ABSTRACT** – Adenomatoid tumors (ATs) are relatively uncommon benign tumors usually arising in the paratesticular area. Among different theories proposed for its histogenesis, the most favored one seems to be the mesothelial origin, supported by different immunohistochemical and ultrastructural studies. As a consequence of the variety of morphologic patterns observed for ATs, the differential diagnosis of these tumors is quite extensive, ranging from benign to malignant tumors of both epithelial and stromal origin. These tumors represent a diagnostic challenge due to their clinical signs similar to those of other testicular neoplasms and ultrasonography nonspecific findings. The importance of a correct diagnosis implies avoidance of unnecessary orchiectomy, thereby maintaining endogenous testosterone production and fertility potential at its fullest. Clinical outcome is excellent in all cases, with no published relapses, and follow-up by postoperative ultrasound is sufficient.

We report a case of AT occurring in the tunica albuginea of the right testis in a 48-year-old man, referred to our Institute for a diagnostic revision. A brief review of the literature is also addressed, with a focus on histogenesis, clinico-pathologic characteristics and differential diagnoses of these rare neoplasms.

## INTRODUCTION

ATs are relatively uncommon benign tumors usually occurring in the male and female genital tracts. The term adenomatoid tumor was first introduced by Golden and Ash in 1945<sup>1</sup> to describe a group of benign tumors of the urogenital tract, with a glandular pattern and unknown histogenesis. Adenomatoid tumors are the most common paratesticular neoplasms and account for approximately 30% of all paratesticular masses<sup>2</sup>. The great majority of tumors in men arise in the epididymis (about 77%), the testis sheath or tunica albuginea (about 22%), and rarely in the spermatic cord (about 1%). Extragenital adenomatoid tumors are rare and have been found in the adrenal glands, heart, mesentery, lymph nodes, and pleura<sup>3</sup>. Occasionally, they grow into tes-

ticular parenchyma<sup>4,5</sup>. Pediatric cases are considered very rare with only few reported cases<sup>5,6</sup>. The Authors present a case of AT occurring in the tunica albuginea of a 48-year-old man, referred to our Institute for a diagnostic revision. A brief review of the current literature is also addressed, with a focus on clinico-pathologic specific characteristic, histogenesis and differential diagnoses of these tumors.

## CASE REPORT

A 48-year-old man with a diagnosis of adenomatoid tumor of the testis was referred in September 2015 to our Institute for a second diagnostic opinion. His clinical history started 5 months before, when he presented a gradual increase in size of the

scrotum unassociated with pain or other symptoms. His physical examination was unremarkable, except for an approximately 1.5 cm nontender intratesticular mass. Scrotal ultrasonography revealed a hypoechoic mass of the right testis, measuring 1.5 x 1 x 0.8 cm. However, serum tumor markers including alpha-fetoprotein and beta-human chorionic gonadotropin were within normal limits. The patient subsequently underwent testis-sparing surgery, as preoperative imaging and clinical data were suggestive of a benign lesion. Formalin-fixed, paraffin-embedded tissue samples were obtained, and 4-micron sections were stained with hematoxylin and eosin. 2.5-micron sections were cut and immunohistochemical analysis was performed in an automated system (Benchmark-XT/Benchmark-ULTRA, Ventana, Tucson, AZ, USA). The following primary antibodies were used: Pankeratin (AE1/AE3/pCk26, pre-diluted, Ventana, Tucson, AZ, USA), Calretinin (SP65, prediluted, Ventana), vimentin (V9, prediluted, Ventana). Color was developed with 3,3'-diaminobenzidine (DAB) and slides were counterstained with Meyer's hematoxylin. Appropriate positive and negative controls run concurrently.

Postoperative histopathologic examination of the mass demonstrated a well-demarcated vaguely nodular lesion measuring 1 cm in maximum diameter, composed of irregularly arranged tubules and gland-like structures with eosinophilic cells, embedded in a fibrous stroma containing lymphoid aggregates (Figure 1 A,B). Immunohistochemical staining showed a diffuse and strong positivity in neoplastic cells for Calretinin, Pancytokeratins and Vimentin (Figure 2 A-C).

Two pathologists revised the case in our Institute and diagnosis was confirmed.

There was no history of testicular tumor or any other tumor in the family. At 3 months follow-up examination, the patient was asymptomatic, and scrotal ultrasound scan showed no evidence of local recurrence.

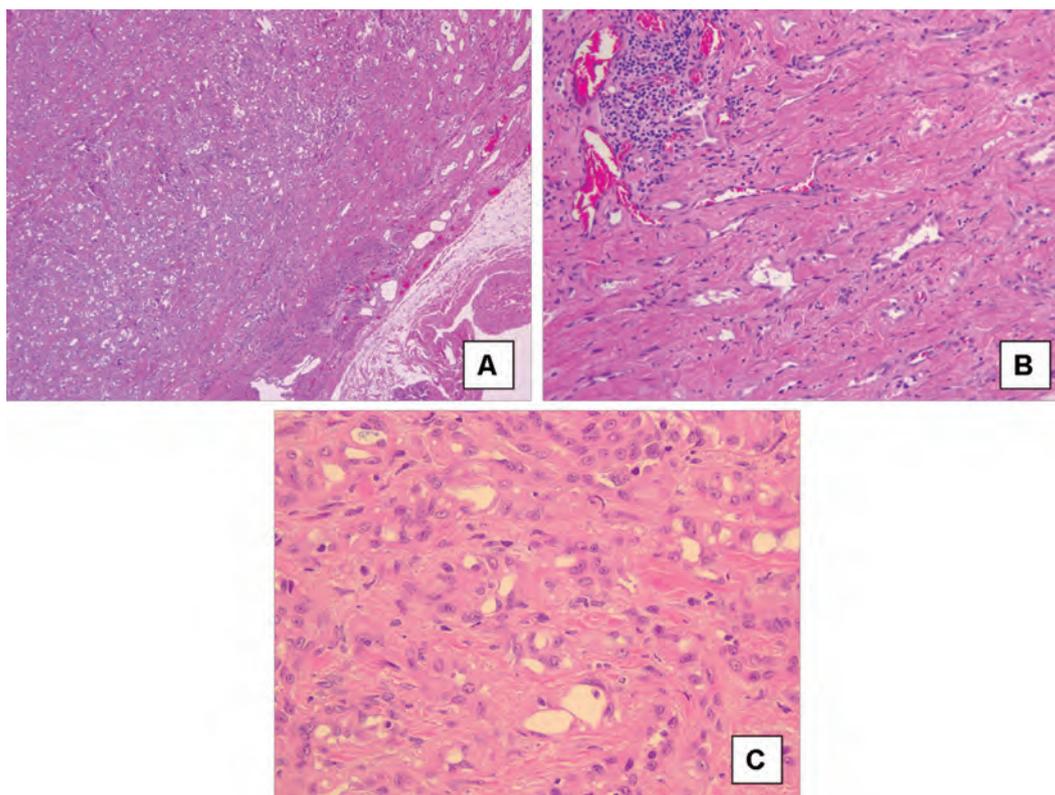
## DISCUSSION

Adenomatoid tumors are rare and benign tumors of the male and female genital tract, whose histogenesis has been a source of controversy for years. In early studies AT was thought to be derived from mesonephric (Wolffian) remnants due to its apparent localization exclusively within the genital tract<sup>7</sup>. Conversely a paramesonephric (Mullerian) origin has also been proposed for ATs because of an observed continuity of Fallopian tube or appendix testis epithelium with adjacent tumour acini<sup>8</sup>. The first hypothesis of a mesothelial origin for adenomatoid tumour was pro-

posed by Masson et al<sup>9</sup> and subsequently supported by reported cases of ATs at extragenital sites covered by serosal membrane<sup>3</sup>. Mesothelial origin of ATs has been confirmed by ultrastructural and immunohistochemical studies of both male and female genital tract tumors. On transmission electron microscopy, this tumor typically shows features in common with mesothelial cells, that is prominent desmosomes, and long microvilli on the luminal surface of tumor acini and on the surface of intercellular canaliculi<sup>10</sup>. The ultrastructural similarity between adenomatoid tumour, mesothelial cells and epithelioid mesothelioma has been observed and confirmed in several studies<sup>11,12</sup>. The similarity of ultrastructural features of adenomatoid tumour and epididymal duct cells has also been noted and it has been suggested that adenomatoid tumour is derived from coelomic cells as they differentiate towards genital epithelium<sup>13</sup>. For what concerns immunohistochemistry, AT, as well as mesothelial cells, universally express vimentin and cytokeratin AE1/AE3, while cytokeratin 34 $\beta$ E12 expression is seen in 25% of cases<sup>14</sup>. Epithelial membrane antigen is present in both the cytoplasm and cell membrane of tumor cells<sup>14</sup>. Thrombomodulin is all expressed on the surface of microvilli of the acinar component of the tumor, while staining is seen in occasional cells in the cords of the solid component. Both solid and acinar areas are strongly positive for calretinin<sup>15,16</sup>. Markers expressed in a variety of carcinomas such as Leu M1, AUA-1, CA19.9, Ber-EP4, CEA, HEA-125, B72.3, MOC-31, and LEA.135 are all negative, as are markers of endothelial cells (CD34 and factor VIII). Negative expression of p53 is consistent with the benign nature of these tumors<sup>14</sup>.

In the present case, tumor cells were positive for Calretinin, Cytokeratins and Vimentin, according to literature data.

Macro and microscopic features of ATs could be of help to identify the lesion. During gross examination, it is usually clear that the neoplasm is paratesticular or juxtatesticular. Very rarely the testicular parenchymal involvement is so extensive to give the gross impression of a "bona fide" testicular neoplasm. Their size is up to about 7 cm with the majority being in the range of 3-5 cm. The tumor is grossly well circumscribed and oval to crescent-shaped. It is typically white and firm on cut surface. ATs have a plethora of microscopic appearances represented by three basic patterns: tubules, cords, and small nests lined by or formed of cells that are cuboidal with moderate to occasionally abundant eosinophilic, amphophilic or vacuolated cytoplasm. Severe atypia and mitoses are usually absent<sup>17-19</sup>. An irregular disposition of tubules, cords and nests within a prominent fibrous stroma may suggest infiltration and bring into consideration diverse entities such as malignant mesothelioma and secondary carcinoma<sup>20</sup>. AT, al-



**Figure 1.** *A*, Vaguely nodular lesion composed of haphazardly arranged tubules and gland-like structures (Hematoxylin & eosin, 25x original magnification). *B*, The lesion displays distorted tubules and glands in a fibrous stroma; a small lymphocyte aggregate is identifiable on top left corner (Hematoxylin& eosin, 100x original magnification). *C*, Higher magnification shows gland-like structures lined by bland cells. Mitoses are absent (Hematoxylin& eosin, 400x original magnification).

though grossly circumscribed, often infiltrates microscopically between the testicular tubules, a finding that should not be misinterpreted as evidence of malignancy. A helpful microscopic low-power clue to the diagnosis of AT in many cases is the presence of prominent lymphoid aggregates, particularly towards the periphery of the neoplasm<sup>20</sup>.

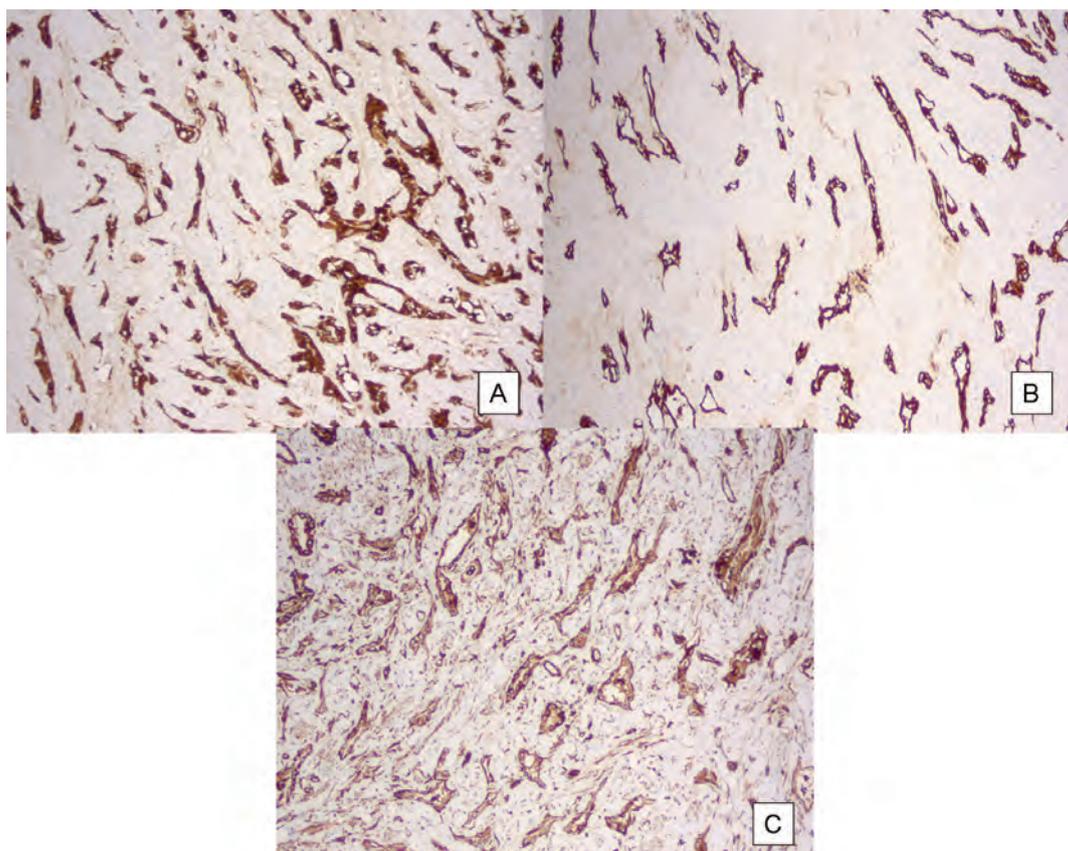
As a consequence of the variety of morphologic patterns observed for AT, the differential diagnosis of these tumors is quite extensive, ranging from benign to malignant tumors of both epithelial and stromal origin, including carcinoma of the rete testis, embryonal carcinoma, yolk sac tumor, metastatic carcinoma, epithelioid haemangioma and malignant mesothelioma<sup>21</sup>. Adenocarcinoma of the rete testis could be easily recognized due to the presence of an infiltrative growth pattern and marked nuclear pleomorphism. In difficult cases, an appropriate immunohistochemical panel of markers<sup>14</sup> may confirm the diagnosis. Yolk sac tumors showing either a microcystic or polyvesicular vitelline pattern may be differentiated from AT by Alpha-fetoprotein (AFP) immunopositivity, although this marker is not very sensitive and not universally positive in yolk sac tumors. Moreover, yolk sac tumors do not exhibit the typical stroma of AT and usually have a much

greater degree of nuclear pleomorphism. The absence of staining of epithelial markers is of utility in excluding carcinomas and germ cell tumors from the differential diagnosis, while negativity of vascular markers (CD34, factor VIII) excludes a diagnosis of epithelioid haemangioma. The diagnosis of mesothelioma could not rely only on immunohistochemistry, as both neoplasms share most mesothelial differentiation markers. Absence of severe cytologic atypia and of high mitotic rate along with lack of infiltrative pattern of growth are all features favoring a diagnosis of AT.

Adenomatoid tumors show a predilection for white males they appear mostly in the third to fifth decades, with a mean age of 36 years<sup>22</sup>. They present either as an incidental finding or a slow

growing scrotal mass being asymptomatic for several years. Enlargement is usually painless with normal scrotal skin and surrounding adnexa<sup>22</sup>. ATs are usually small in size and rarely exceed 2 cm<sup>3</sup> (range is 0.5-5.0 cm). On ultrasonography they typically appear as hyperechoic and homogeneous, although they may also be hypoechoic.

Orchiectomy has traditionally been the gold standard for the treatment of testicular tumors. According to recent favorable reports, testis-sparing



**Figure 2.** Immunohistochemical stainings of the lesion showed in Figure 1. Tubules and gland-like structures are intensely positive for (A) Calretinin, (B) Pancytokeratin and (C) Vimentin. (A-C: 100x original magnification).

surgery has become a concrete option in the treatment of benign testicular tumors<sup>15</sup>. In doubtful cases, intraoperative frozen sections have been documented to be a reliable tool for discriminating between benign and malignant tumors<sup>17</sup>; therefore, this technique can be used whenever testis-sparing surgery is considered.

### Conclusions

AT is a benign lesion with clinical signs similar to other testicular neoplasms and ultrasonography nonspecific findings, consistent with isoechoic, hypoechoic, or hyperechoic nodules. Normal levels of preoperative serum tumor markers combined with intraoperative histologic examination, when indicated, can prevent unnecessary orchiectomy, thereby maintaining endogenous testosterone production and fertility potential at its fullest [19]. Clinical outcome is excellent in all cases, with no published relapses and follow-up by postoperative ultrasound is sufficient.

### CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

### REFERENCES

1. Golden A, Ash JE. Adenomatoid tumors of the genital tract. *Am J Pathol* 1945; 21: 63-79.
2. EBLE JN SG, EPSTEIN JI, SESTERHENN IA. World Health Organization Classification of Tumors. Pathology and Genetics of Tumour of the Urinary System: IACR Press; Lyon, 2004.
3. ISOTALO PA, KEENEY GL, SEBO TJ, RIEHLE DL, CHEVILLE JC. Adenomatoid tumor of the adrenal gland: a clinicopathologic study of five cases and review of the literature. *Am J Surg Pathol* 2003; 27: 969-977.
5. ALEXIEV BA, XU LF, HEATH JE, TWADDELL WS, PHELAN MW. Adenomatoid tumor of the testis with intratesticular growth: a case report and review of the literature. *Int J Surgical Pathol* 2011; 19: 838-842.
5. EVANS K. Rapidly growing adenomatoid tumor extending into testicular parenchyma mimics testicular carcinoma. *Urology* 2004; 64: 589e12-589e.13.
6. Liu W, Wu RD, Yu QH. Adenomatoid tumor of the testis in a child. *J Pediatr Surg* 2011; 46: E15-E17.

7. CODNERE JT, FLYNN JE. Adenomatoid tumors of epididymis: report of 3 cases. *J Urol* 1946; 56: 448-453.
8. SUNDARAVARAO D. The Müllerian vestiges and benign epithelial tumours of the epididymis. *J Pathol Bacteriol* 1953; 66: 417-432.
9. MASSON R, RIOPELLE JL, SIMARD LC. Le Mésotéliome bénin de la sphère génitale. *Rev Can Biol* 1942; 1: 720-751.
10. MARCUS JB, LYNN JA. Ultrastructural comparison of an adenomatoid tumor, lymphangioma, hemangioma and mesothelioma. *Cancer* 1970; 25: 171-175.
11. TAXY JB, BATTIFORA H, OYASU R. Adenomatoid tumours: a light microscopic, histochemical and ultrastructural study. *Cancer* 1974; 34: 306-316.
12. MORRIS JA, OATES K, STAFF WG. Scanning electron microscopy of adenomatoid tumours. *Br J Urol* 1986; 58: 183-187.
13. SÖDERSTRÖM KO. Origin of adenomatoid tumor. A comparison between the structure of adenomatoid tumor and epididymal duct cells. *Cancer* 1982; 49: 2349-2357.
14. DELAHUNT B, EBLE JN, KING D, BETHWAITE PB, NACEY JN AND THORNTON A. Immunohistochemical evidence for mesothelial origin of paratesticular adenomatoid tumour. *Histopathology* 2000; 36: 109-115.
15. NAGATA S, AISHIMA S, FUKUZAWA K, TAKAGI H, YONEMASU H, IWASHITA Y, KINOSHITA T AND WAKASUGI K. Adenomatoid tumour of the liver. *J Clin Pathol* 2008; 61: 777-780.
16. SCHWARTZ EJ AND LONGACRE TA. Adenomatoid tumors of the female and male genital tracts express WT1. *Int J Gynecol Pathol* 2004; 23: 123-128.
17. ULBRIGHT TM, AMIN MB, YOUNG RH. Tumors of the Testis, Adnexa, Spermatic Cord, and Scrotum, 3rd Series, Fascicle 25. Armed Forces Institute of Pathology: Washington, DC, 1999.
18. SRIGLEY JR, HARTWICK RW. Tumors and cysts of the paratesticular region. *Pathol Annu* 1990; 25(Part 2): 51-108.
19. PEREZ-ORDONEZ B, SRIGLEY JR. Mesothelial lesions of the paratesticular region. *Semin Diagn Pathol* 2000; 17: 294-306.
20. AMIN MB. Selected other problematic testicular and paratesticular lesions: rete testis neoplasms and pseudotumors, mesothelial lesion and secondary tumors. *Mod Pathol* 2005; 18: S131-S145.
21. SANGOI AR, MCKENNEY JK, SCHWARTZ EJ, ROUSE RV AND LONGACRE TA. Adenomatoid tumors of the female and male genital tracts: a clinicopathological and immunohistochemical study of 44 cases. *Mod Pathol* 2009; 22: 1228-1235.
22. AMIN W, PARWANI AV. Adenomatoid tumors of the testis. *Clin Med Pathol* 2009; 2: 17-22.