



Review Article

Clear cell carcinoma of testis: A review

Michelle Lin, Hazel Awalt, Alberto G. Ayala, Jae Y. Ro*

Department of Pathology and Genomic Medicine, Weill Medical College of Cornell University, Houston, TX, United States of America

ARTICLE INFO

Keywords:

Ovarian-type
Mullerian tumors
Clear cell tumors
Molecular pathology
Targeted treatment

ABSTRACT

Clear cell Mullerian-type adenocarcinoma of the testis is an exceedingly rare entity, and its histogenesis and clinical behavior are still poorly understood. We discuss three cases of clear cell carcinoma of the testis, compiled from a review of the literature and our personal experience. Microscopically, the tumors closely resembled clear cell carcinoma of the ovary, displaying papillae lined by clear cells with areas of hobnailing. The reported immunophenotypic features were also similar to that of ovarian tumors, as positivity for epithelial markers (CK7, CAM5.2, AE1/AE3, EMA) and Mullerian markers (PAX8, CA125) with negativity for estrogen and progesterone receptors have been observed. The pathogenesis of testicular clear cell carcinoma is still poorly understood, with reported cases displaying evidence of both mesothelial and Mullerian origin. In addition, molecular characterization of testicular clear cell carcinomas has yet to be accomplished; however, studies performed on ovarian clear cell carcinomas may provide insight to the origin, biologic behavior, and potential therapeutic modalities for this obscure, aggressive malignancy.

1. Introduction

Ovarian-type surface epithelial tumors may rarely occur in the testis. Serous tumors are the most frequently reported and best characterized, with about 60 cases described in the literature [1,2]. In contrast, clear cell tumors of the testis are the least common subtype, with very little information published about this entity [1,2]. We provide a review of cases of clear cell carcinoma arising from the testicular region and describe salient clinical and histopathologic characteristics. We also discuss important considerations in the differential diagnosis, theories of pathogenesis, and potential trajectories for molecular analysis and therapy.

2. Review of cases

The first case of clear cell carcinoma of the testis was reported in 1954 by Teilum et al. and described a 44-year-old male who presented with left-sided scrotal swelling, followed one month later by cervical lymphadenopathy, dysphagia, and hemoptysis, with a chest X-ray showed secondary pulmonary deposits (Table 1) [3]. An orchiectomy was performed, revealing a hemorrhagic tumor occupying the upper two-thirds of the testis with extension into the epididymis [3]. Microscopically, the tumor was composed of papillary structures lined by cuboidal cells with variable amounts of cytoplasmic clearing [3]. The

patient received a course of radiation with reported resolution of symptoms five months following surgery [3].

In 2004, Tulunay et al. reported a second case from a 43-year-old male who presented with a painful testicular mass, in addition to abdominal pain, weight loss, hemoptysis, and inguinal lymphadenopathy; computed tomography showed multiple pulmonary lesions and enlarged paratracheal lymph nodes [4]. An orchiectomy was performed and gross examination showed near-complete replacement of the testicular parenchyma with multiloculated cystic structures containing numerous papillary excrescences, as well as a papillary tumor located on the tunica vaginalis [4]. On microscopic exam, papillae lined by clear cells with a hobnailed appearance were seen; occasional psammoma bodies and focal hyalinization of the papillary fibrovascular cores were also present [4]. Immunohistochemically, the tumor cells displayed positivity for cytokeratin (CK) 7, epithelial membrane antigen (EMA), and CA125; and they were negative for CK20, calretinin, estrogen receptor (ER), and progesterone receptor (PR) [4]. Interestingly, a separate paratesticular mass was identified microscopically, composed of atrophic endometrial-type glands and stroma; this lesion was not recognized on initial gross examination [4]. Unfortunately, the tumor progressed extremely rapidly and the patient died two weeks after the orchiectomy [4].

A third case of clear cell carcinoma of the testis arose in a 71-year-old male presenting with a 1-month history of right-sided hydrocele,

* Corresponding author at: Department of Pathology and Genomic Medicine, Weill Medical College of Cornell University, 6565 Fannin Street, Houston, TX, United States of America.

E-mail address: jaero@houstonmethodist.org (J.Y. Ro).

<https://doi.org/10.1016/j.anndiagpath.2019.03.002>

Table 1
Clinical and pathologic characteristics of testicular clear cell carcinoma cases.

	Case 1 (Teilum et al.)	Case 2 (Tulunay et al.)	Case 3 (current case)
Age	44	43	71
Clinical presentation	Scrotal swelling, cervical lymphadenopathy, dysphagia, hemoptysis	Painful testicular mass, abdominal pain, weight loss, hemoptysis, lymphadenopathy	Painless scrotal swelling, hydrocele
Location of tumor	Testicular parenchyma	Tunica vaginalis, with extension into the testicular parenchyma	Tunica vaginalis
Immunoprofile	Not performed	- CK7 +, CK20-, EMA + - CA125 +, ER-, PR- - Calretinin-	- CK7 +, CK20-, EMA +, CAM5.2 + - PAX8 +, WT-1 + (focal), CA19-9 + (focal) - ER-, PR-, AR + - Calretinin-, D2-40-
Metastasis	Pulmonary metastases	Pulmonary and lymph node metastases	None
Clinical course	Resolution of symptoms following radiation therapy	Death two weeks after orchiectomy	Follow-up not available



Fig. 1. Clear cell adenocarcinoma arising from tunica vaginalis, showing a layer of fibromuscular tissue with a surface exophytic proliferation.

previously diagnosed as epididymo-orchitis but unresponsive to oral antibiotics. Scrotal ultrasound showed a large complex right hydrocele with accompanying enlargement of the right epididymis; no evidence of intratesticular mass was seen. A hydrocelectomy was performed. Gross examination showed a 5×4 cm fibromembranous saccular structure, with a 2.4×1.8 cm slightly nodular mass located on the surface. Microscopic examination showed a layer of fibromuscular tissue, compatible with hydrocele sac, with an exophytic surface neoplastic proliferation (Fig. 1) composed of papillary structures lined by cells with abundant eosinophilic to clear cytoplasm and focally prominent nucleoli (Fig. 2A, B). Mild cytologic atypia and occasional mitotic figures, with up to 3 mitoses per 10 high-power fields, were seen (Fig. 2C). The tumor showed invasion of the underlying fibrous wall up to 0.2 cm (Fig. 2D). Immunohistochemical studies showed positivity for EMA and CAM5.2, and focal positivity for CK7 in the tumor cells. In addition, nuclear expression of PAX8 and androgen receptor (AR) as well as focal expression of CA19-9 and WT-1 were observed (Fig. 3A, B). Stains for CK20, calretinin, D2-40, ER, and PR were negative. Finally, Ki-67 studies showed a high proliferative index, with up to 40% staining of the tumor cells (Fig. 3C).

3. Discussion

Ovarian-type epithelial tumors of the testis are very rare, with approximately 100 cases reported in the literature; they are estimated to comprise 5–7% of non-germ cell testicular tumors [1,2,5]. Serous tumors are the most commonly reported, followed by (in descending order of frequency) mucinous, Brenner, endometrioid, and clear cell tumors [1,2]. While these tumors are histologically similar to their

ovarian namesakes, in some cases, they display distinct clinical associations and immunohistochemical characteristics, and also warrant a unique approach to the differential diagnosis. In addition, due to their rarity, their clinical behavior and overall prognostication in comparison to ovarian tumors is still not well understood.

The pathogenesis of ovarian-type epithelial tumors of the testis has still not been fully elucidated, and several theories have been proposed for their histologic origin. One of the more widely propounded theories states that ovarian-type tumors arise from Mullerian remnants in the testicular region, including the appendix testis (a Mullerian vestige located at the upper pole of the testis); rests of Mullerian epithelium are also found in the connective tissue between the testis and epididymis and in the spermatic cord [1,6]. As many tumors are found in the paratestis, particularly the testiculo-epididymal groove, this theory would sufficiently explain the histogenesis of these tumors [6,7]. Another possible origin of ovarian-type neoplasms in the testis is via Mullerian metaplasia of mesothelium lining the tunica vaginalis, which is consistent with the large proportion of tumors arising from the tunica vaginalis [6,7]. As the mesothelium of the ovary is widely believed to undergo Mullerian metaplasia to differentiate into surface epithelial neoplasms, it is not unreasonable to surmise that the mesothelium of the tunica vaginalis has a similar capacity. The pathogenesis of intratesticular tumors is less clear, but they have been hypothesized to develop from entrapped Mullerian or mesothelial inclusions within the testicular parenchyma [6,7].

Clear cell carcinoma is the least common of the ovarian-type epithelial tumors encountered in the testis [1,2]. Morphologically, clear cell carcinoma of the testis resembles its ovarian counterpart, with all three reported cases displaying papillary structures lined by cuboidal to columnar cells with cytoplasmic clearing and focal hobnailing. The immunohistochemical profile also resembles that of ovarian clear cell carcinoma, as reported cases have shown expression of epithelial markers (CK7, EMA, and CAM5.2) and markers of Mullerian differentiation (including PAX8 and CA125) as well as high Ki-67 proliferation index (up to 40%) [3,4]. The differential diagnosis of clear cell adenocarcinoma is broad and includes other entities which may display clear cell change with papillary architecture. Malignant mesothelioma of the tunica vaginalis is often characterized by a papillary growth pattern and may uncommonly exhibit cells with cytoplasmic clearing, and thus may resemble clear cell adenocarcinoma histologically; however, on immunohistochemistry mesothelioma displays expression of the mesothelial markers calretinin and D240, while clear cell carcinoma (and other ovarian epithelial-type tumors) do not [7]. Serous carcinomas may also display clear cell change, mimicking clear cell carcinoma, but typically more numerous psammoma bodies and characteristic stratification with cellular budding and tufting are seen [7]. One final consideration in the differential diagnosis is metastatic carcinoma, especially renal cell carcinoma. Usually, clinical history and imaging can facilitate the exclusion of possible metastasis; in the case of renal

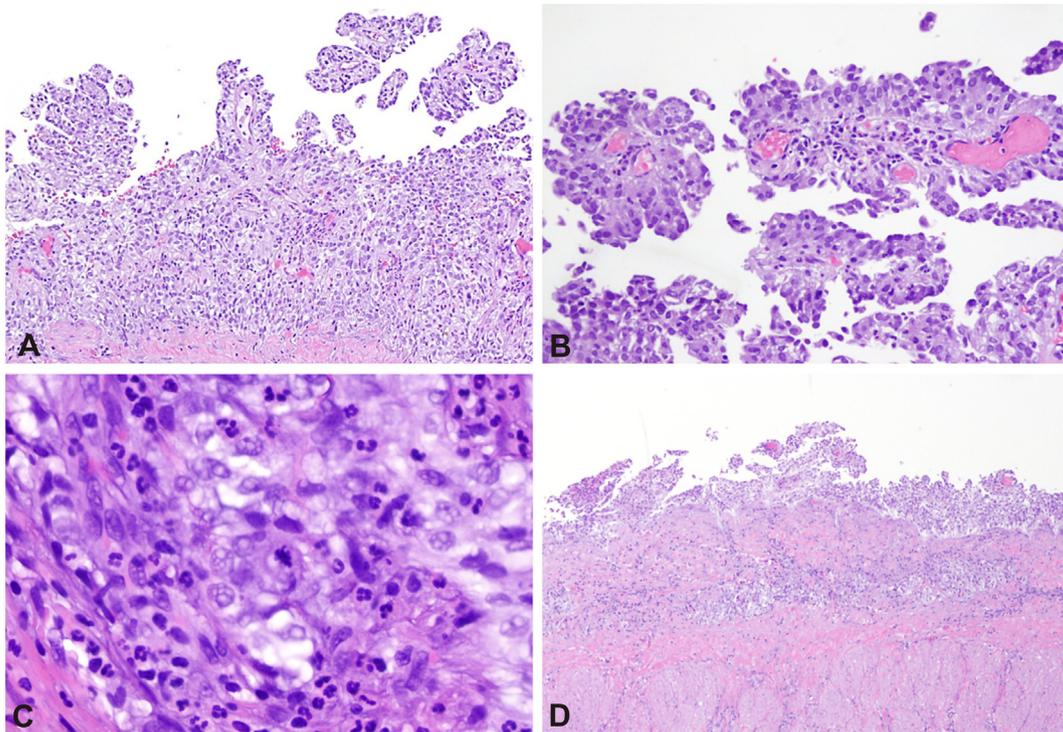


Fig. 2. (A) The neoplasm is composed of papillary structures lined by cells with clear to eosinophilic cytoplasm. (B) The cells display mild cytologic atypia, focal hobnailing, and variably prominent nucleoli. (C) Occasional atypical mitotic figures were identified. (D) Superficial invasion of the underlying fibromuscular wall was seen.

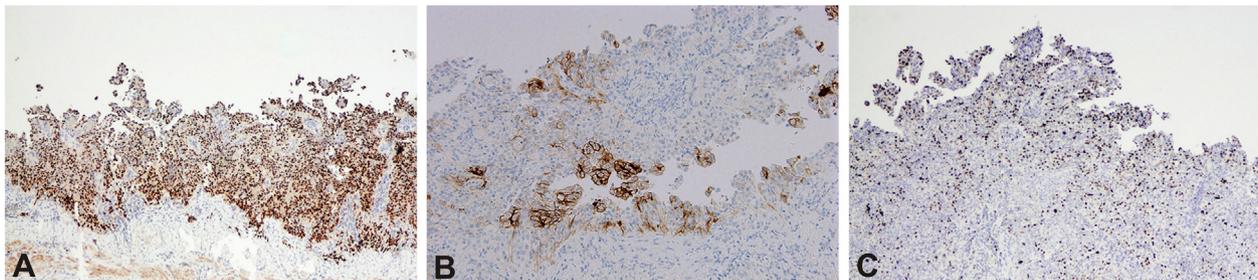


Fig. 3. (A) Diffuse positivity for PAX8. (B) Focal positivity for CA19-9. (C) High proliferation index highlighted by Ki-67.

cell carcinoma, differences in the immunoprofile (CK7-negative, RCC-positive) also can guide the diagnosis [7].

There is evidence to support that clear cell carcinomas of the testis may originate from either mesothelium or Mullerian epithelium. Two of the three cases describe tumors arising from the tunica vaginalis, which is consistent with mesothelial origin. However, the immunoprofile of testicular clear cell tumors (PAX8-positive, CA125-positive, calretinin-negative, and D240-negative) suggests derivation from Mullerian tissue. In addition, the case reported by Tulunay et al. also displayed an atrophic uterus-like structure composed of endometrial glands, which was hypothesized to originate from paratesticular Mullerian remnants [4]. As the tumor showed continuity with this uterus-like structure, it is possible that the tumor was also derived from foci of Mullerian epithelium in the testicular region. Furthermore, ovarian clear cell carcinomas, which display a strong association with endometriosis, are generally regarded to arise from endometrial tissue from retrograde menstruation in endometriosis, therefore lending further support to the pathogenesis of testicular clear cell carcinomas (which display analogous histologic and immunophenotypic characteristics) from Mullerian, rather than mesothelial, tissue [8,9].

Molecular analysis of testicular clear cell carcinomas has heretofore not been performed; however, the molecular characteristics of ovarian

clear cell carcinomas have been recently characterized. Unlike the more well-studied serous carcinomas of the ovary (which typically show KRAS or BRAF mutations if low-grade or p53 mutations if high-grade), clear cell carcinomas have been shown to harbor mutations in the PIK3CA and ARID1A genes [10,11,12]. The PIK3CA gene encodes a subunit of the PI3K protein, a part of the PI3K/AKT/mTOR intracellular signaling pathway which has been linked to the pathogenesis of many different types of cancers [11]. The ARID1A gene encodes BAF250a, a subunit of the SWI-SNF chromatin remodeling complex involved in multiple facets of the regulation of gene expression [12]. ARID1A deletions have been shown to cause aberrant activation of the PI3K/AKT/mTOR pathways and have been implicated in many cancers; thus the gene has been hypothesized to act as a tumor suppressor [12]. Decreased ARID1A expression has also been associated with chemoresistance in patients with ovarian clear cell carcinoma [13,14]. Investigations of therapies targeting the altered signaling involved in these mutations (particularly the mTOR inhibitors everolimus and temsirolimus) have shown some promising initial results; however, no phase III trials have been reported [15]. Experience with treatment for testicular clear cell carcinoma is woefully sparse, with only one case reportedly improving with radiation therapy, as described above [3]. Nevertheless, the molecular abnormalities and therapeutic strategies

studied in ovarian clear cell carcinoma will help guide future studies on the biological and molecular characterization of testicular clear cell carcinoma, and potentially help to establish the optimal therapies for this rare, clinically aggressive entity.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

- [1] Amin MB. Selected other problematic testicular and paratesticular lesions: rete testis neoplasms and pseudotumors, mesothelial lesions and secondary tumors. *Modern Pathol* 2005;18:S131. <https://doi.org/10.1038/modpathol.3800314>.
- [2] Lin MS, Ayala AG, Ro JY. Ovarian-type tumors (Mullerian tumors) of testis: clinicopathologic findings with recent advances. *Ann Urol Oncol* 2019. <https://doi.org/10.32948/auo.2019.03.07>. [in press].
- [3] Teilum G. Special tumors of the ovary and testis. In: Teilum G, editor. *Comparative pathology and histological identification*. Philadelphia: JB Lippincott; 1976. p. 466–9.
- [4] Tulunay Ö, Göğüş Ç, Baltacı S, Bulut Ş. Clear cell adenocarcinoma of the tunica vaginalis of the testis with an adjacent uterus-like tissue. *Pathol Int* 2004;54:641–7. <https://doi.org/10.1111/j.1440-1827.2004.01675.x>.
- [5] Talmon GA, Johannson SL. Serous cystadenoma of the epididymis. *Urology* 2007;70:372–7. <https://doi.org/10.1016/j.urology.2007.04.010>.
- [6] Young RH, Scully RE. Testicular and paratesticular tumors and tumor-like lesions of ovarian common epithelial and mullerian types: a report of four cases and review of the literature. *Am J Clin Pathol* 1986;86:146–52. <https://doi.org/10.1093/ajcp/86.2.146>.
- [7] McClure RF, Keeney GL, Sebo TJ, Cheville JC. Serous borderline tumor of the paratestis: a report of seven cases. *Am J Surg Pathol* 2001;25:373–8. <https://doi.org/10.1097/00000478-200103000-00012>.
- [8] Kurman RJ, Shih IM. The origin and pathogenesis of epithelial ovarian cancer—a proposed unifying theory. *Am J Surg Pathol* 2010;34:433. <https://doi.org/10.1097/pas.0b013e3181cf3d79>.
- [9] Zhao C, Wu LS, Barner R. Pathogenesis of ovarian clear cell adenofibroma, atypical proliferative (borderline) tumor, and carcinoma: clinicopathologic features of tumors with endometriosis or adenofibromatous components support two related pathways of tumor development. *J Cancer* 2011;2:94. <https://doi.org/10.7150/jca.2.94>.
- [10] Vang R, Shih IM, Kurman RJ. Ovarian low-grade and high-grade serous carcinoma: pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. *Adv Anat Pathol* 2009;16:267. <https://doi.org/10.1097/pap.0b013e3181b4fffa>.
- [11] Kuo KT, Mao TL, Jones S, Veras E, Ayhan A, Wang TL, et al. Frequent activating mutations of PIK3CA in ovarian clear cell carcinoma. *Am J Pathol* 2009;174:1597–601. <https://doi.org/10.2353/ajpath.2009.081000>.
- [12] Takeda T, Banno K, Okawa R, Yanokura M, Iijima M, Irie-Kunitomi H, et al. ARID1A gene mutation in ovarian and endometrial cancers. *Oncol Rep* 2016;35:607–13. <https://doi.org/10.3892/or.2015.4421>.
- [13] Yokoyama Y, Matsushita Y, Shigeto T, Futagami M, Mizunuma H. Decreased ARID1A expression is correlated with chemoresistance in epithelial ovarian cancer. *J Gynecol Oncol* 2014;25:58–63. <https://doi.org/10.3802/jgo.2014.25.1.58>.
- [14] Katagiri A, Nakayama K, Rahman MT, Rahman M, Katagiri H, Nakayama N, et al. Loss of ARID1A expression is related to shorter progression-free survival and chemoresistance in ovarian clear cell carcinoma. *Modern Pathol* 2012;25:282. <https://doi.org/10.1038/modpathol.2011.161>.
- [15] Gasparri ML, Bardhi E, Ruscito I, Papadia A, Farooqi AA, Marchetti C, et al. PI3K/AKT/mTOR pathway in ovarian cancer treatment: are we on the right track? *Geburtshilfe Frauenheilkunde* 2017;77:1095–103. <https://doi.org/10.1055/s-0043-118907>.