Intratesticular Mucinous Cystadenoma

Immunohistochemical Comparison With Ovarian and Colonic Tissue

Teresa M. Alasio, MD; James Borin, MD; Kevia Taylor, MD; Natan Bar-Chama, MD; Pamela D. Unger, MD

• We report a case of a primary intratesticular mucinous cystadenoma in an asymptomatic 39-year-old man. The mass was found incidentally during a consultation for infertility. Pathologic examination of the orchiectomy specimen revealed a unilocular cyst lined with bland mucinous epithelium and mucinous extravasation, consistent with a diagnosis of mucinous cystadenoma. Foci of bone were also found in association with extensive chronic inflammation. Immunohistochemical stains performed showed immunoreactivity for cytokeratin 7, and nonreactivity for cytokeratin 20, CA125, chromogranin, and synaptophysin. The immunohistochemical staining patterns of the present case are compared with those of known mucinous cystadenomas of the ovary and nonneoplastic colonic mucosa. The histogenesis of this entity is discussed in light of the literature and the immunohistochemical findings in this rare case.

(*Arch Pathol Lab Med.* 2005;129:399–402)

A handful of case reports of mucinous testicular tumors have appeared in the literature in the past 50 years, making the report of such tumors a relatively rare occurrence.[1–6] Although all of these reports have speculated on the histogenesis of these tumors, doubt and controversy persist. The general consensus among these authors supports a mullerian origin, but there is argument as to whether mesothelial inclusions or germ cell derivations play a role.

We report a case of intratesticular mucinous cystadenoma and discuss the histogenesis of this tumor as compared with similar ovarian tumors and histologic samples from the lower intestinal tract in light of immunohistochemical reactivity.

REPORT OF A CASE

A 39-year-old man presented to a private urologist with a right testicular mass of unknown duration; the mass was found incidentally on evaluation for infertility. He had no risk factors for testicular cancer, such as cryptorchidism. He had no significant prior medical history and took no medications. The patient was otherwise in good health. Physical examination was unremarkable, except for induration of the right testicle, which was not associated with pain or fever. Tumor markers, including α-fetoprotein, β-human chorionic gonadotropin, and lactate dehydrogenase were all within normal limits.

Ultrasound examination revealed a predominantly hypoechoic and heterogenous mass that almost replaced the entire right testicle (Figure 1). Small echogenic areas were noted within the mass, suggestive of calcifications. Multiple punctate echogenic foci within the normal portion of the right testicular parenchyma were identified. This finding was also observed in the contralateral testicle, which was consistent with a diagnosis of testicular microlithiasis. No focal mass was noted within the left testicle. Color flow imaging of the venous plexus was performed bilaterally and showed no evidence of varicocele.

A staging computed tomographic scan with contrast of chest, abdomen, and pelvis demonstrated multiple foci of mildly enlarged, partially calcified lymph nodes in the thorax, which were not typical of metastatic disease. There was no retroperitoneal lymphadenopathy.

Right radical orchiectomy was performed. No evidence of recurrence was evident at the 1-year follow-up examination. Markers remained negative and computed tomographic scans of the chest at 4 and 8 months after surgery were unchanged.

MATERIALS AND METHODS

To evaluate the immunoreactivity for low-molecular-weight cytokeratins and neuroendocrine markers, we performed immunohistochemical studies on deparaffinized tissue sections for the testicular mucinous tumor described. For comparison, the same studies were performed on an additional 22 selected cases of ovarian and lower gastrointestinal tract tissues from the surgical pathology files of the Mount Sinai Hospital, New York, NY. These selected cases included 10 cases of ovarian mucinous cystadenoma (9 endocervical type, 1 intestinal type), 1 case of atypical proliferating mucinous ovarian tumor, 9 cases of nonneoplastic colonic mucosa, 1 case of pseudomyxoma appendices, and 1 case of appendiceal mucinous villous adenoma. Immunoreactivity for cytokeratin (CK) 7 (Dako Corporation, Carpinteria, Calif), CK20 (Dako), CA 125 (Dako), synaptophysin (BioGenex, San Ramon, Calif), and chromogranin (BioGenex) was evaluated in all cases. Immunohistochemical stains were performed on paraffin-embedded tissue sections as per institutional protocol for all antibodies.

PATHOLOGIC FINDINGS

The orchiectomy specimen consisted of a 3.0 × 2.5 × 3.09-cm testicle with a grossly normal tunica albuginea and epididymis and an 8-cm-long segment of spermatic cord attached. The testis was nearly entirely replaced by a thin-walled unilocular cystic mass measuring 2.0 cm in

Accepted for publication September 29, 2004.

From the Departments of Pathology (Drs Alasio, Taylor, and Unger) and Urology (Drs Borin and Bar-Chama), The Mount Sinai Hospital, New York, NY.

Presented as a poster at the annual meeting of the American Society for Clinical Pathology, New Orleans, La, September 2003.

The authors have no relevant financial interest in the products or companies described in this article.

Reprints: Teresa M. Alasio, MD, Department of Pathology, New York University School of Medicine, 550 First Ave, New York, NY 10016 (e-mail: teresa01@med.nyu.edu).

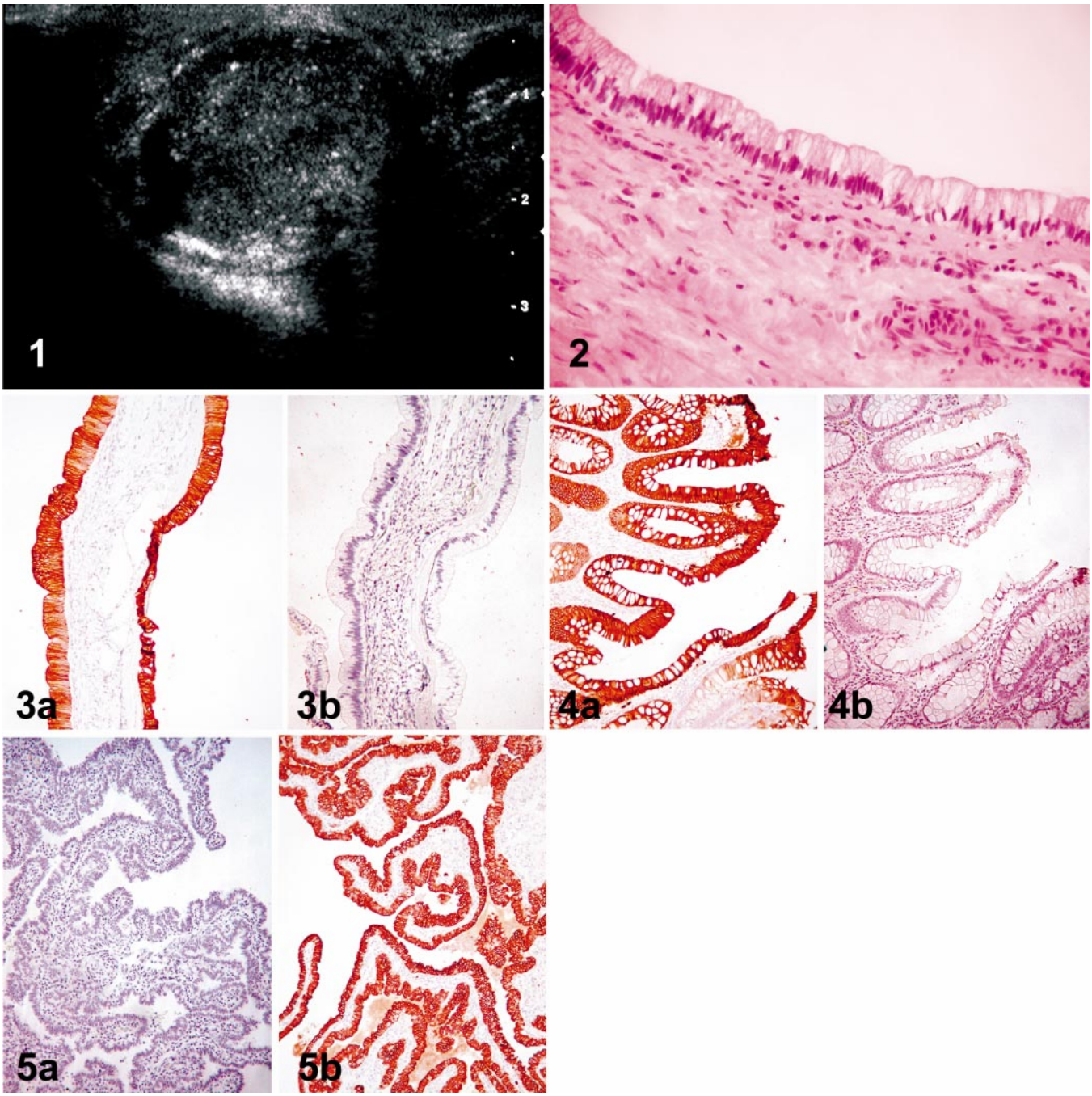

Figure 1. *Ultrasound showing right intratesticular mass.*

Figure 2. *Cyst wall showing benign mucinous epithelium (hematoxylin-eosin, original magnification ×40).*

Figure 3. *Testicular tumor epithelium showing positive cytokeratin (CK) 20 immunoreactivity (a) and negative CK7 immunoreactivity (b) (original magnification ×10).*

Figure 4. *Colonic epithelium showing positive CK20 immunoreactivity (a) and negative CK7 immunoreactivity (b) (original magnification ×10).*

Figure 5. *Ovarian mucinous cystadenoma epithelium showing negative CK20 immunoreactivity (a) and positive CK7 immunoreactivity (b) (original magnification ×10).*

greatest dimension. The inner lining of the cyst wall was hemorrhagic and variegated. The cyst contained a small amount of whitish mucoid material. A 1.0-cm portion of normal-appearing testicular parenchyma was located at the superior pole of the specimen. The tissue was fixed in 10% neutral buffered formalin and embedded in paraffin for histologic sections stained with hematoxylin-eosin.

Microscopic examination of hematoxylin-eosin–stained sections showed the unilocular cyst was lined with bland mucinous epithelium with focal areas of stratification (Figure 2). No mitotic figures were identified within the epithelium. The solid part of the tumor showed a fibromyxoid stroma with focally cellular areas. Numerous degenerative and reactive features were identified, including

Comparison of Immunohistochemical Findings of the Present Case With Selected Cases of Ovarian and Lower Gastrointestinal Tract Tissues*

Tissue	Diagnosis	No. of Cases	Cytokeratin 20	Cytokeratin 7	Synaptophysin	Chromogranin	CA 125
Testicular	Intratesticular mucinous cystadenoma	1	+	−	−	+†	−
Ovary	Mucinous cystadenoma, endocervial type	9	+† (1), + (2), − (6)	+	−	+†	−
Ovary	Atypical proliferating mucinous tumor	1	+†	+	+†	+†	−
Ovary	Mucinous cystadenoma, intestinal type	1	+	+	+	+	−
Appendix	Mucinous villous adenoma	1	+	+	−	+†	−
Appendix	Pseudomyxoma appendices	1	++	−	+	+	−
Colon	Normal colon	1	+	−	+†	+†	−
Colon	Diverticulosis	1	+	+†	+†	+†	−
Colon	Diverticulitis	3	+ (3)	+† (1), − (2)	+† (2), − (1)	+† (3)	− (3)
Colon	Adenocarcinoma	4	+ (4)	− (4)	+† (2), − (2)	+, +† (3)	− (4)

* + indicates positive; −, negative. Numbers in parentheses indicate number of cases.
† Focal immunoreactivity.

cholesterol clefts, mucinous extravasation, benign multinucleated giant cells, and extensive infiltration of lymphocytes, plasma cells, and hemosiderin-laden macrophages. Focal areas of ossification were present, and areas of bone formation were located adjacent to the cyst and found primarily in association with chronic inflammation. There was no connection between the borders of the cyst and the channels of the rete testis, which was compressed, but otherwise unremarkable. The nonneoplastic testicular parenchyma showed atrophic changes and rare Walthard nests in paratesticular soft tissue.

RESULTS

The immunoreactivity of the low-molecular-weight cytokeratins, CK7 and CK20, CA 125, synaptophysin, and chromogranin was assessed in 23 cases, including the testicular tumor described herein. Only those cases showing greater than 5% epithelial cell positivity were regarded as positive. Focal positivity was determined as less than 10% cell positivity. Results are summarized in the Table.

The present case was positive for CK20 (Figure 3, a) and was focally positive for chromogranin. The testicular case was negative for CK7 (Figure 3, b). All cases of the lower gastrointestinal tract, including appendiceal neoplasms, were positive for CK20 (Figure 4, a) and were at least focally positive for chromogranin. The lower gastrointestinal tract cases were all negative for CK7 (Figure 4, b). Of the 11 ovarian cases, 4 were focally positive for CK20; nearly 95% of the ovarian tissue examined was negative for CK20 (Figure 5, a). One case of ovarian tissue was positive for CK20 (mucinous cystadenoma, intestinal type). All ovarian cases and 1 appendiceal case were positive for CK7 (Figure 5, b), while 2 cases of normal colon were focally positive for CK7. Five colon cases and 4 ovarian cases were focally positive for synaptophysin, while 1 appendix case (pseudomyxoma appendices) was positive. The testicular case was negative for synaptophysin. All cases were negative for CA 125. These immunohistochemical findings support a gastrointestinal profile for this case.

COMMENT

Cystic mucinous neoplasms of the testicle, both benign and malignant forms, have only sporadic representation in the literature.[1–6] Kellert[2] described the first case in 1959; that case involved an ovarian-type pseudomucinous cystadenoma in the scrotum. Kellert attributed the origins of the tumor to persistent mullerian duct remnants. A later report by Young and Scully[1] described 4 cases of testicular and paratesticular tumors. The authors discussed these tumors in terms of the mullerian-type epithelium that occurs in the vicinity of the testis and epididymis.

According to a review by Sundarasivarao,[7] mullerian epithelium is found at the epididymotesticular junction, as well as in the peritoneal folds between the lower end of the border of the epididymis. A persistent duct may also be distended with mucoid material, an expression of the inherent mucosecretory capability of the mullerian epithelium. In this respect, adenomatous tumors of the epididymis arise from mullerian vestiges.

Nistal et al[3] described a case of bilateral mucinous cystadenocarcinoma of the testis and epididymis. In that case, a mesothelial origin of the neoplasm was postulated, citing tubular connections between the mesothelium covering the tunica albuginea and seminiferous tubules, which are implicated in testicular disorders, as well as in the normal testis. However, the authors also suggested that their case may have originated directly in the mullerian remnants that are known to be present within the epididymis itself, or between it and the testis. Although the suggestion of an intestinal origin of the cystadenocarcinoma was briefly described, the likelihood that their case represented a metastatic lesion was not considered. Likewise, Elbadawi et al[4] reported a case of intratesticular papillary mucinous cystadenocarcinoma in a 60-year-old man, citing mullerian remnants as the likely culprit in its histogenesis.

Recently, Mesia et al[5] described a case of ossified intratesticular mucinous tumor of low malignant potential. Because rare foci of mature bone were found in the nonfibrosed cyst wall, a teratoma could not be ruled out. Most

of the bone identified in this case was located in fibrotic areas, supporting the presence of metaplastic change, which is similar to the ovarian counterpart. The immunohistochemical staining pattern was positive for CK20 and negative for CK7 and chromogranin. The article was inconclusive on the etiology of the tumor.

A relatively recent case report of multiloculated mucinous cystadenoma of the testicle was published by Nokubi et al.[6] The authors identified goblet cells and intestinal differentiation, and suggested that this tumor may represent a monodermal teratoma. The authors concluded that although mesothelial origin was not completely excluded, the location of the tumor (intratesticular) and the intestinal differentiation seen were in line with germ cell derivation.

Immunohistochemical stains using antibodies to CK7 and CK20 have often been cited to differentiate between ovarian and colonic neoplasms. Three reports addressing this topic have appeared in the literature in recent years. First, Shen et al[8] evaluated the origin of pseudomyxoma peritonei in 15 cases using CK7 and CK20 antibodies. They demonstrated nearly universal immunoreactivity for CK20 in tissues derived from the peritoneum, ovary, appendix, and pancreas, but only selective immunoreactivity for CK7 in ovarian-derived tumors. They concluded the pseudomyxoma peritonei was unlikely of appendiceal origin if the lesions were immunoreactive for CK7.

Chu et al[9] performed immunohistochemical stains for CK7 and CK20 on 435 cases to evaluate their expression in various epithelial neoplasms. Interestingly, virtually all cases of ovarian adenocarcinoma (as well as breast, endometrial, thyroid, and salivary gland tumors) were $CK7^{+}/CK20^{-}$. In contrast, virtually all cases of colorectal carcinoma were $CK7^{-}/CK20^{+}$.

In a study by Cathro and Stoler,[10] mucinous ovarian neoplasms stained positively for CK7 and more often were negative for CK20, while nongynecologic neoplasms, in particular lower gastrointestinal tumors, were consistently $CK20^{+}/CK7^{-}$. They concluded that this differential staining of mucinous tumors using CK7 and CK20 was useful for predicting the site of origin in the case of metastatic lesions in which the site of the primary tumor is otherwise unknown.

The most recent series, collected by Ulbright and Young,[11] described 9 cases of primary mucinous tumors of the testis and paratestis. Two cases from this series described as mucinous cystadenoma were both paratesticular, unlike the intratesticular cases described herein. These 2 cases were also characterized as testicular counterparts to ovarian mucinous tumors, for which the histologic findings could represent a form of neometaplasia of the epithelium, rather than supporting a germ cell origin. This type of phenomenon is known to occur in ovarian mucinous tumors, in which transformation of the normal ovarian surface epithelium results in the development of mucinous forms with gastrointestinal features.[12]

By comparing the immunohistochemical profile of the mucinous epithelium of our case with the profiles of ovarian mucinous and normal colonic mucinous neoplasms, we believe that we have ruled out the link between our tumor and its ovarian counterpart. Based on previous studies involving the expression of CK7 and CK20 in ovarian and intestinal neoplasms, we performed our own comparison to find a correlation between our testicular mucinous tumor and these tissues. Previous reports have demonstrated the expression of CK7 in ovarian neoplasms, while intestinal neoplasms are consistently CK7 negative.[8–10] Furthermore, ovarian neoplasms can be either negative or positive for CK20, while intestinal neoplasms are consistently CK20 positive. To a large extent, our findings correlate with the evidence found in the literature. However, we did note 2 cases of colon showing CK7 positivity, albeit focal. Our testicular tumor was strongly positive for CK20 (Figure 3, a), which was identical to the immunoreactivity found in colonic epithelium, and was unequivocally negative for CK7 (Figure 3, b). Additional cases will have to be evaluated in order to clarify the histogenesis of these unusual neoplasms.

We present a case of testicular mucinous cystadenoma identified in an asymptomatic, 39-year-old, otherwise healthy man. Microscopic examination revealed a benign mucinous neoplasm with metaplastic bone formation and extensive chronic inflammation. Immunohistochemical studies showed immunoreactivity for CK20; an absence of reactivity for CK7, CA 125, and synaptophysin; and focal reactivity for chromogranin. This is the same pattern of immunohistochemical staining that has been observed in neoplasms that occur in the lower gastrointestinal tract and is opposite to that of ovarian neoplasms. In our own comparative assessment, the testicular neoplasm described in the current case report exhibited the same immunohistochemical pattern of reactivity as normal colonic tissues. A literature review reveals an extensive controversy regarding the origins of the rare tumors, mostly surrounding mullerian versus germ cell derivations. While our study does not resolve this controversy, we believe that this evidence classifies this tumor as a testicular mucinous cystadenoma with gastrointestinal features, comparable to a gastrointestinal monodermal teratoma.

References

1. Young RH, Scully RE. Testicular and paratesticular tumors and tumor-like lesions of ovarian common epithelial and mullerian types: a report of 4 cases and review of the literature. *Am J Clin Pathol.* 1986;86:146–152.
2. Kellert E. An ovarian type pseudomucinous cystadenoma in the scrotum. *Cancer.* 1959;12:187–190.
3. Nistal M, Revestido R, Paniagua R. Bilateral mucinous cystadenocarcinoma of the testis and epididymis. *Arch Pathol Lab Med.* 1992;116:1360–1363.
4. Elbadawi A, Batchavarov MM, Linke CA. Intratesticular papillary mucinous cystadenocarcinoma. *Urology.* 1979;14:280–284.
5. Mesia L, Georgsson S, Zuretti A. Ossified intratesticular mucinous tumor. *Arch Pathol Lab Med.* 1999;123:244–246.
6. Nokubi M, Kawai T, Mitsu S, Ishikawa S, Morinaga S. Mucinous cystadenoma of the testis. *Pathol Int.* 2002;52:648–652.
7. Sundarasivarao D. The mullerian vestiges and benign epithelial tumors of the epididymis. *J Pathol Bacteriol.* 1952;66:417–431.
8. Shen DH, Ng TY, Khoo US, Xue WE, Cheung AN. Pseudomyxoma peritonei: a heterogeneous disease. *Int J Gynaecol Obstet.* 1998;62:173–182.
9. Chu P, Wu E, Weiss LM. Cytokeratin 7 and cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases. *Mod Pathol.* 2000;13:962–972.
10. Cathro H, Stoler M. Expression of cytokeratins 7 and 20 in ovarian neoplasia. *Am J Clin Pathol.* 2002;117:944–951.
11. Ulbright TM, Young RH. Primary mucinous tumors of the testis and paratestis: a report of 9 cases. *Am J Surg Pathol.* 2003;27:1221–1228.
12. Scully RE, Young RH, Clement PB. *Tumors of the Ovary, Maldeveloped Gonads, Fallopian Tube, and Broad Ligament.* Washington, DC: Armed Forces Institute of Pathology; 1998. *Atlas of Tumor Pathology*; 3rd series, fascicle 23.