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Original contribution

Mesothelioma of the tunica vaginalis testis☆,☆☆

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Summary Malignant mesothelioma (MM) arising from the serosal membranes of the tunica vaginalis testis (TVT) is rare. Most examples in the published medical literature are individual case reports. This study presents the clinicopathological findings of mesothelioma of the TVT in one of the largest series to date. Individuals with mesothelioma of the TVT were identified from a database of more than 4000 mesothelioma cases, and their clinicopathological features were recorded. Eighteen men with MM and 2 with well-differentiated papillary mesothelioma of the TVT were identified, which represented 0.6% of males with mesothelioma in study population. The median age at diagnosis was 72 years (range, 32-85 years). A neoplasm was not suspected preoperatively in 12 of the 17 (71%) men whose clinical presentation was known, 7 of whom presented with hydrocele and 5 with inguinal hernia. The other 5 had a clinically recognized mass. Seven of the men underwent herniorrhaphy; 7, radical orchiectomy; 3, hydrocelectomy; and 3, paratesticular mass biopsy or excision as the initial diagnostic procedure. Twelve of the MM cases were epithelioid and 6 were biphasic. Among the 6 men with MM who had ≥6 months of follow-up, 1 was alive with no evidence of disease at 6 months, and 5 were known to have died of disease 8-74 months (median = 31.5 months) following diagnosis. Three men with MM had received either chemotherapy or radiation therapy. Of the 2 men initially diagnosed with well-differentiated papillary mesothelioma, 1 was alive without evidence of disease 5 years after diagnosis, while the other had findings more compatible with MM with peritoneal involvement 2 years following initial diagnosis. In 15 of the 18 cases of MM (83%), there was documented occupational or paraoccupational exposure to asbestos, the average duration of which was 33 years (range, 2-46 years). Information regarding the presence or absence of pleural plaques was available in 5 of the MM cases, and pleural plaques had been found in 4. Lung tissue was not available for fiber analysis in any of the cases. One additional case originally diagnosed at another institution as MM of the TVT was reclassified as adenocarcinoma following performance of additional immunohistochemical testing. TVT is a rare site of MM, the diagnosis of which is often unsuspected preoperatively. Like its counterparts at other serosal sites, MM of the TVT is an aggressive tumor with a poor prognosis that evidence would suggest is etiologically associated with asbestos in at least some cases.

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1. Introduction

The tunica vaginalis testis (TVT) is subject to the same spectrum of mesothelial lesions as the peritoneum with which it has an embryologic connection. By far, the most common mesothelial lesion of the TVT is reactive mesothelial hyperplasia, which can occasionally be so florid as to cause diagnostic confusion with malignancy [1]. Rarely, the TVT is the site of well-differentiated papillary mesothelioma (WDPM) or malignant mesothelioma (MM). Examples of these number only in the hundreds in the published medical literature, mainly as individual case reports and small case series. The purpose of this study is to detail the clinicopathological characteristics of mesotheliomas of the TVT using a large consultation database to provide one of the most comprehensive series to date.

2. Materials and methods

A retrospective search of a database compiled by one of the authors (V. L. R.) containing more than 4000 mesotheliomas received in professional and medicolegal consultation from 1982 to the present time was undertaken to identify tumors arising in the TVT. Cases were excluded if the initial diagnosis of mesothelioma had been made at a site other than the TVT. The diagnosis of mesothelioma was based upon histologic and immunohistochemical features, in accordance with the World Health Organization classification, along with characteristic macroscopic findings, as determined by imaging findings and observations made at the time of surgical exploration [2]. Information regarding age, clinical presentation, presence or absence of pleural plaques and asbestosis, asbestos exposure history, macroscopic features, histologic type of mesothelioma, immunohistochemical findings, treatment, and survival was recorded for each case when available. A 2-sided, 2-sample median test was used to compare the median age of men with mesothelioma of the TVT and men with mesothelioma of either the pleura or peritoneum. Statistical analysis was performed using SAS Version 9 statistical software (SAS Institute, Cary, NC). Statistical significance was based on $\alpha = .05$. This study was approved by the Duke University Institutional Review Board.

3. Results

Eighteen men with MM and 2 with WDPM of the TVT whose cases were reviewed in consultation between the years of 1987 and 2017 were identified from a database containing 3589 men with mesothelioma. These represented 0.6% of all males with mesothelioma in the database. The clinicopathological findings of all 20 cases are summarized in Table 1. One of the WDPM cases (WDPM case 1) was originally reported in a previously published study, since which time additional clinical information has become available [3].

The median age at the time of diagnosis for men with mesothelioma of the TVT was 72 years (range, 32-85 years), which was similar to men in the study database with mesothelioma of the pleura ($P = .65$) but significantly older than men with mesothelioma of the peritoneum ($P = .007$). The clinical presentation was known in 17 men, only 5 (29%) of whom were suspected to have a neoplastic process prior to surgery. The most common presenting features were hydrocele (n = 7); groin, paratesticular, or testicular mass with associated scrotal pain and/or swelling (n = 5); or inguinal hernia (n = 5). Several men had signs and/or symptoms months to years prior to diagnosis. One man (MM case 1) had undergone hydrocele drainage 1 year prior to the diagnosis of MM, whereas another (MM case 18) underwent hydrocelectomy 2 years earlier. Two other men (MM cases 10 and 11) had longstanding presumed hydrocele for 5 or more years. Two of the men presumed to have inguinal hernia had undergone ipsilateral inguinal herniorrhaphy, one at 3 years prior to the diagnosis of MM (MM case 3) and another (MM case 13) twice at 30 years and 6 years prior to his MM diagnosis. Another man (MM case 5) had a history of ascites with atypical epithelial cells on peritoneal biopsy that was presumed to represent tuberculous peritonitis 2 years prior to presenting with signs and symptoms that were attributed to inguinal hernia. Preoperative imaging information was available in 7 of the men. Two of the men had undergone preoperative computed tomography of the abdomen and pelvis (MM cases 5 and 9), and 6 had undergone scrotal/testicular ultrasound (MM cases 1, 3, 9, 11, 15, and 18), which disclosed hydrocele in 5 cases and an array of other findings. The types of specimens in which the diagnosis of mesothelioma was initially established were as follows: herniorrhaphy (n = 7), radical orchiectomy (n = 7), hydrocelectomy (n = 3), and paratesticular mass biopsy or excision (n = 3). Three of the men who had not undergone radical orchiectomy initially (MM cases 1, 12 and 18) did so shortly after their diagnosis of MM. Operative findings ranged from gritty excrescences and nodules or masses up to 5 cm in greatest dimension to rindlike thickening of the TVT.

Of the 18 MM cases, 12 were epithelioid (Fig. 1) and 6 were biphasic (Fig. 2). Among the epithelioid MMs, the most common growth pattern was tubular, which predominated in 5 cases. Four cases were predominantly tubulopapillary, whereas another 2 cases exhibited a prominent papillary pattern. Most epithelioid cases also contained areas of sheets, nests, and/or infiltrating cords surrounded by desmoplastic stroma, which was the predominant appearance in 1 case. Two epithelioid cases featured wispy basophilic secretions (MM cases 3 and 7). One epithelioid case showed focally myxoid stroma as well as foci resembling WDPM (MM case 6). At least focal stromal invasion was present in all of the epithelioid cases. The biphasic cases demonstrated an epithelioid

Table 1 Clinicopathological features of mesotheliomas of the TVT

Case	Age	Neoplasm clinically suspected	Prior genitourinary history	Clinical presentation	Preoperative imaging	Diagnostic specimen	Operative findings	Histologic type	Adjuvant therapy	Outcome	Asbestos exposure history	Cumulative asbestos exposure (y)	Pleural plaques
MM1	80	N	Hydrocele	Hydrocele	Hydrocele with internal debris	Hydrocelectomy	Polypoid projections	Bi	ND	ND	Laborer, dressmaker	42	ND
MM2	66	N	ND	Inguinal hernia	ND	Herniorrhaphy	Roughening and nodules	Bi	ND	ND	ND	ND	ND
MM3	84	Y	Herniorrhaphy	Groin mass	Hydrocele, subcutaneous nodule at herniorrhaphy scar site	Paratesticular mass excision	Mass	Epi	Radiation	ND	US Navy, auto mechanic	46	ND
MM4	65	N	ND	Inguinal hernia	ND	Herniorrhaphy	Mass	Bi	Chemotherapy	DOD	Construction worker	20	N
MM5	72	N	ND	Inguinal hernia	Ascites extending into scrotum	Herniorrhaphy	Nodules	Epi	ND	DOD 50 mo	Oil refinery worker	46	ND
MM6	64	Y	ND	Groin mass	ND	Paratesticular mass biopsy	Mass	Epi	ND	ND	Laborer, vermiculite insulation manufacturing	2	ND
MM7	81	ND	ND	ND	ND	Herniorrhaphy	Nodules	Epi	ND	DOD 8 mo	Insulation manufacturing	ND	Y
MM8	73	Y	ND	Scrotal mass	ND	Radical orchiectomy	Nodularity and thickening	Epi	ND	ND	Auto mechanic, welder	ND	ND
MM9	82	N	ND	Hydrocele	Hydrocele, vascular mass at lower testicular pole	Radical orchiectomy	Gritty excrescence and nodules	Epi	Chemotherapy	ND	Shipyard worker, trucker, construction worker	39	ND

MM10	66	N	Hydrocele	Hydrocele	ND	Hydrocelectomy	ND	Epi	ND	ND	US Navy, railroad worker	44	Y
MM11	73	Y	Hydrocele	Testicular mass	Scrotal mass	Radical orchiectomy	Shaggy and granular mass	Epi	ND	ND	Millwright, construction worker	40	Y
MM12	72	Y	ND	Testicular mass	ND	Paratesticular nodule biopsy	Nodule	Epi	ND	ANED 6 mo	Mechanic, maintenance worker	33	ND
MM13	72	N	Herniorrhaphy	Inguinal hernia	ND	Herniorrhaphy	Nodules	Bi	ND	ND	ND	ND	ND
MM14	78	ND	ND	ND	ND	Radical orchiectomy	Nodule	Bi	N	DOD 74 mo	Crane operator	ND	ND
MM15	85	N	ND	Hydrocele	Hydrocele with internal debris	Radical orchiectomy	ND	Epi	ND	DOD 13 mo	Electrician, auto mechanic	23	ND
MM16	69	N	ND	Hydrocele	ND	Radical orchiectomy	Mulitlocular cystic mass	Bi	N	ND	US Navy shipyard worker	15	Y
MM17	60	ND	ND	ND	ND	Radical orchiectomy	Multiple nodules	Epi	ND	ND	ND	ND	ND
MM18	54	N	Hydrocele	Hydrocele	Hydrocele, enlarged heterogenous epididymis	Hydrocelectomy	ND	Epi	ND	ND	Carpenter/ construction, service station attendant	41	ND
WDPM1	32	N	Hydrocele	Hydrocele	ND	Herniorrhaphy	ND	WDPM	ND	AWD 24 mo	Household contact of oil refinery workers (father and grandfather)	10	N
WDPM2	61	N	ND	Inguinal hernia	ND	Herniorrhaphy	ND	WDPM	ND	ANED 60 mo	Merchant Marine seaman	ND	ND

Abbreviations: ANED, alive with no evidence of disease; AWD, alive with disease; Bi, biphasic; DOD, died of disease; Epi, epithelioid; ND, not determined.

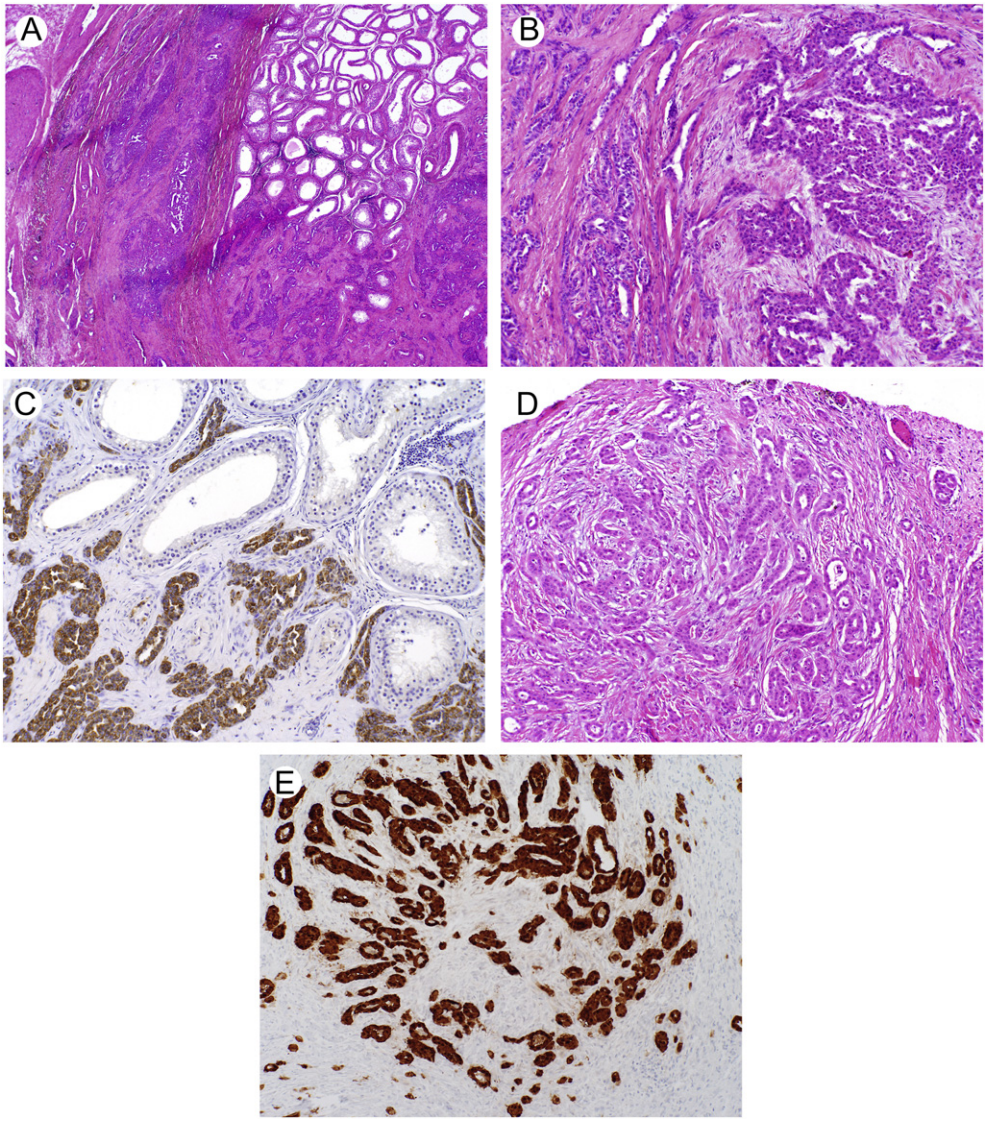

Fig. 1 Epithelial variants of MM of the TVT. A, Low-power view shows epithelial malignancy (left) invading into testis (right). B, Higher-power magnification shows tubular and lacelike patterns of growth. C, Immunostain for cytokeratins highlights invasion of keratin-positive tumor cells into the seminiferous tubules. The tumor also stained positive for calretinin, cytokeratins 5/6, WT-1, and D2-40. D, Tubular epithelial malignancy in a myxoid stroma. E, The tumor cells stain positively for calretinin in a nuclear and cytoplasmic distribution. The tumor cells also stained positively for cytokeratins 5/6, WT-1, and D2-40 (A-C, MM case 8; D and E, MM case 10; A, original magnification ×20; B-E, ×100).

component showing the spectrum of patterns described above, along with an infiltrating sarcomatoid component of cytologically malignant spindle cells with variable degrees of pleomorphism. The 2 cases of WDPM featured a single layer of cytologically bland cuboidal mesothelial cells that lined fibrovascular to myxoid-appearing cores and lacked stromal invasion. Focal psammomatous calcifications were noted in 1 of the 2 WDPM cases.

Immunohistochemical evaluation had been performed in 18 of the 20 cases, the results of which are summarized in Table 2. A panel of at least 2 mesothelium-associated markers and at least 2 markers typically expressed in carcinomas had been applied in most of the MM cases, in accordance with current consensus recommendations [4]. However, several cases had been initially evaluated prior to the routine use of immunohistochemistry and/or before some immunohistochemical antibodies were commercially available, and the paraffin blocks were no longer available for additional testing. Staining results were supportive of the diagnoses. In the few cases with aberrant staining for carcinoma-associated markers, expression was usually focal and was accompanied by robust staining for 1 or more mesothelium-associated markers.

Clinical records were limited with respect to postoperative treatment and survival. Follow-up information of ≥6 months was available for 6 of the MM cases and both cases of WDPM. Three men with MM had received either chemotherapy or radiotherapy. One man with MM was alive with no evidence of disease at 6 months after diagnosis. All of the other 5 men with

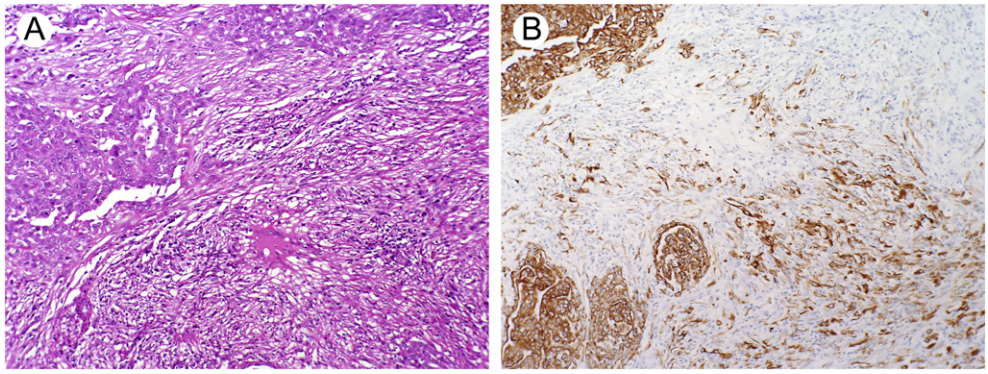

Fig. 2 Biphasic variant of MM of the TVT. A, Biphasic morphology with epithelial component (top and left) and sarcomatoid component (bottom and right). B, Immunostain for cytokeratins highlighting epithelial (left) and sarcomatoid elements (right). The tumor also stained positively for calretinin, cytokeratins 5/6, WT-1, and D2-40 (MM case 16; ×100).

MM who had adequate follow-up were known to have died of disease. The length of survival following initial diagnosis, which was known in 4 of the men with MM who died, was 8-74 months (median = 31.5 months). One of the men with WDPM was alive with no evidence of disease 5 years after diagnosis, whereas the other had subsequent findings more compatible with MM and evidence of peritoneal involvement 2 years after initial diagnosis.

A history of occupational or paraoccupational exposure to asbestos had been documented in 15 of the 18 (83%) cases of MM, as well as in both cases of WDPM. The average cumulative duration of asbestos exposure was 33 years (range, 2-46 years). Autopsy slides from 1 of the cases (MM case 4) reviewed at the time of initial consultation showed several asbestos bodies without evidence of asbestosis on a hematoxylin and eosin–stained section of lung tissue. The paraffin block of lung tissue was not available for fiber analysis in this case. Adequate lung tissue was also not available in the other 19 cases to perform fiber analysis and/or assess for the presence or absence of asbestos bodies or histologic asbestosis. None of the cases had a documented radiographic diagnosis of asbestosis. Information regarding the presence or absence of pleural plaques was available in 5 of the MM cases, and pleural plaques were radiographically apparent in 4 of them. Pleural plaques were not noted in 1 of the 2 WPDM cases, and information regarding pleural plaques was not available in the other case.

One additional case identified in the database search conducted for this study that bears mentioning is an adenocarcinoma that had been originally diagnosed as MM of the TVT at the treating institution. The diagnostic specimen was an

Table 2 Immunohistochemical staining results of mesotheliomas of the TVT

Case	Pan-CK	Calretinin	CK5/6	D2-40	WT-1	HBME-1	CEA	MOC-31	BerEp4	B72.3	Leu-M1	TTF-1
MM1	+					–	–			–	–	
MM2	+						–				–	
MM3	+	+			+			–	–			
MM4	+	+					–	–		–		
MM5	+	+	–				–			–	–	–
MM6	+	+				+	–				–	
MM7	+	+				+	–				–	
MM8	+	+	–	+	+				–	–		
MM9	+	+	+	+	+				+			
MM10	+	+	+	+	+				f, w	–		
MM11		+	+	+	+		–	–	–			
MM12		+	+		+		–	f	f	–		–
MM13												
MM14		+	+	+	+		–				–	
MM15	+	+	+	+	+				–	–		
MM16	+	+	+	+	+				+	–		
MM17												
MM18	+	+	–	+	+		–			–		
WDPM1	+	+				+						
WDPM2	+	+	+				–			–	–	

Abbreviations: f, focal staining; w, weak intensity staining.

orchiectomy from a 67-year-old patient with a 1-month history of testicular swelling and discomfort. The tumor was composed of polygonal epithelioid cells with vesicular nuclei, prominent nucleoli, and a moderate amount of eosinophilic cytoplasm arranged in sheets, papillary structures, and tubules that featured wispy basophilic secretions. In addition to staining for pan-cytokeratins, the tumor was positive for LeuM1 and EMA (Fig. 3). There was focal weak positivity for WT-1, but the tumor was negative for calretinin, D2-40, CK 5/6, BerEp4, B72.3, CD30, α-fetoprotein, and carcinoembryonic antigen (CEA).

4. Discussion

Achieving more than a modicum of understanding about mesothelioma of the TVT has been constrained by the rarity of this disease. Barbera and Rubino are generally credited with the first report of mesothelioma of the TVT in the medical literature, which in all likelihood represented WDPM based on their photomicrographic depictions [5]. In the ensuing 6 decades, there has been a dearth of case series of mesothelioma of the TVT. To our knowledge, the largest published series of MM of the TVT have been from Winstanley et al (18 cases), Recabal et al (15 cases), Mensi et al (13 cases), Perez-Ordonez et al (13 cases), Jones et al (11 cases), An et al (7 cases), and Antman et al (6 cases) (Table 3) [6-12]. In the series with 18 cases, 20 tumors were initially examined, 2 of which were excluded because of immunohistochemical staining results inconsistent with MM [6]. Although an exhaustive review of other previously reported cases of MM of the TVT is beyond the scope of this study, additional cases reported through 2009 have been comprehensively reviewed in a prior publication [13]. The present study includes 18 cases of MM of the TVT, equaling the largest previously published series of which we are aware [6].

The findings in this study affirm that mesotheliomas of the TVT are indeed uncommon, accounting for less than 1% of all mesotheliomas. Similar to men with mesotheliomas of the pleura, mesotheliomas of the TVT occur predominantly, although not exclusively, in the sixth to eighth decades of life. The youngest man in the current series was a 32 years old, but cases have been reported in boys as young as 7 years old [14]. A somewhat surprising finding in this study, given their embryologic connection, is that peritoneal mesotheliomas in males occurred at a younger age as compared to mesotheliomas of the TVT. The reason for this age disparity is unknown.

Mesotheliomas of the TVT are routinely mistaken clinically for far more common benign entities, such as hydrocele or inguinal hernia. Initial conservative management in some cases has resulted in delayed diagnosis. At surgery, however, the macroscopic appearance typically connotes a neoplastic process, with most cases showing studding, nodularity, excrescences, and/or irregular thickening of the TVT. As with other serosal sites, most cases of MM of the TVT are

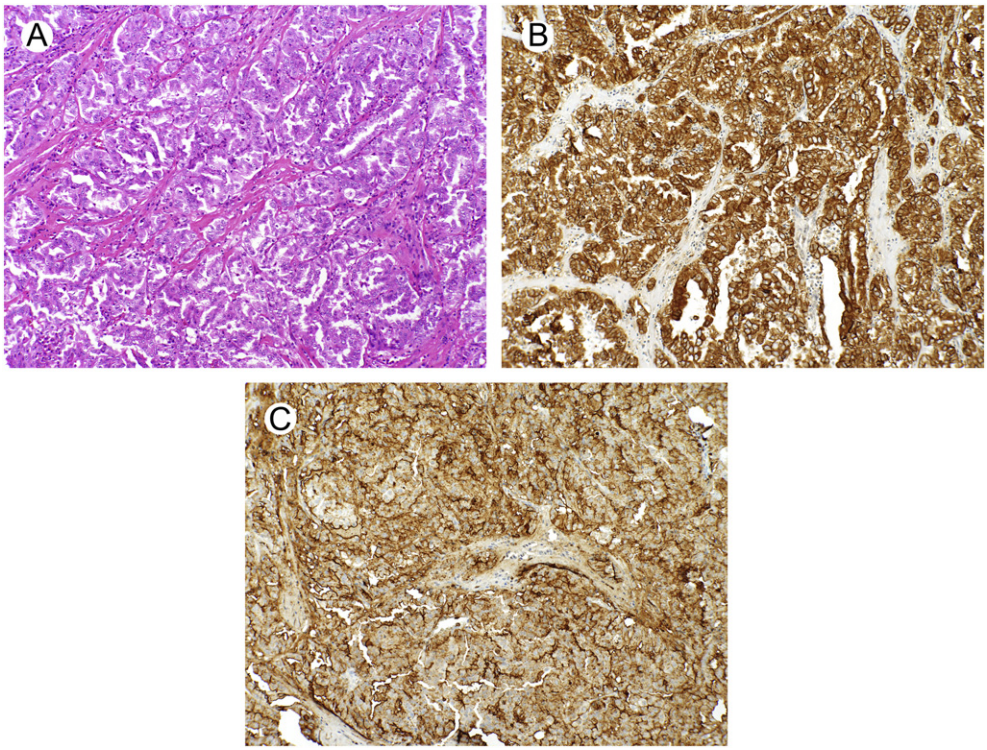

Fig. 3 Paratesticular adenocarcinoma. A, Epithelial malignancy with lacelike growth pattern. B, The tumor cells stain diffusely and strongly positive for cytokeratins. C, The tumor cells also stain diffusely positive for CD15 in a predominately membranous pattern. The tumor cells stained focally and weakly positive for WT-1 and were negative for calretinin, cytokeratins 5/6, and D2-40 (×100).

Table 3 Summary of published series of MM of the TVT

Study	No. of cases	Median age (y) (range)	Commonest clinical presentation	Asbestos exposure	Histologic type	Died of disease
Antman et al, 1984 [12]	6	55 (23-73)	Testicular/scrotal mass 4/6 (67%)	4/6 (67%)	5 Epi 1 NS	3/6 (50%)
Jones et al, 1995 [10]	11	58 (12-76)	Hydrocele 7/11 (64%)	1/5 (20%)	5 Epi 6 Bi	3/7 (43%)
Perez et al, 1998 [9]	13	64 [a] (31-84)	Hydrocele 8/13 (62%)	3/13 (23%)	10 Epi [b] 3 Bi 1 Sarc	2/10 (20%)
Winstanley et al, 2006 [6]	18	59 (45-79)	Hydrocele 9/14 (64%)	1/8 (13%)	15 Epi 3 Bi	3/13 (23%)
Mensi et al, 2012 [8]	13	69 (34-99)	Hydrocele 8/13 (62%)	8/12 (67%)	7 Epi 2 Bi 3 Sarc 1 NS	11/13 (85%)
An et al, 2017 [11]	7	67 (43-85)	Hydrocele 4/7 (57%)	2/7 (29%)	3 Epi 2 Bi 2 NS	1/6 (17%)
Recabal et al, 2017 [7]	15	62 (39-66)	Scrotal mass 7/15 (47%)	2/15 (13%)	8 Epi 4 Bi 3 NS	5/15 (33%)
Present study	18	72 (54-85)	Hydrocele 7/17 (41%)	15/18 (83%)	12 Epi 6 Bi	5/7 (71%)

Abbreviations: NS, not specified; Sarc, sarcomatoid.
[a] Mean (median not provided).
[b] Total number of cases discordant with number based on histologic types.

epithelioid, often exhibiting a tubulopapillary architecture. No purely sarcomatoid examples were seen in the present study. Sarcomatoid MM of the TVT has been only rarely reported in the last 25 years [8,9].

Meaningful conclusions regarding the most appropriate treatment of MM of the TVT were unable to be drawn from this study. The rarity of these tumors has hampered the development of specific management guidelines. Some investigators have proposed radical orchiectomy as affording the best chance for long-term recurrence-free survival [15]. It remains unclear whether adjuvant chemotherapy and/or radiotherapy is beneficial [11,15,16]. What is clear is that, like its counterparts in the pleura, pericardium, and peritoneum, MM of the TVT generally pursues an aggressive clinical course. More than 70% of men with MM in the present study who had adequate clinical follow-up died of disease an average of 31.5 months following initial diagnosis. It is difficult to compare outcomes among published series of MM of the TVT because of limited follow-up data. One prior series reported a median survival of only 20 months [8]. There are, however, notable exceptions. No recurrences were observed in 6 of 7 men with MM of the TVT in another previous series [11]. Cases are also on record as having a remarkably indolent course, including a man who was alive without evidence of disease 10 years after the diagnosis of MM of the TVT and 2 who did not experience recurrence for 15 or more years [10,12,17].

Much remains to be elucidated about factors that influence the outcome of MM of the TVT. An epithelioid histology appears to confer better survival, and one study suggested that a younger age at diagnosis portends a more favorable prognosis [7,15]. Interestingly, the longest survivor in the present study was diagnosed at the age of 78 years with a biphasic MM.

WDPM of the TVT is distinctly more heterogeneous in its behavior than MM, in part perhaps because not all reports have used the same definitional criteria. In a recent study that scrutinized the pathologic findings of 24 cases reported as WDPM of the TVT up to that time, only 8 were deemed "true" examples of WDPM of the TVT by the authors, which they defined as having a papillary or tubular-papillary structure lined by a single row of cuboidal cells with bland nuclear cytology, low mitotic activity, and absent stromal invasion [18]. No recurrences were observed in 6 of the 8 cases for which follow-up information was available, although only 1 had greater than 36 months of follow-up [5,18-24]. Nonetheless, there appear to be rare cases of WDPM of the TVT that do not follow a stereotypically benign/indolent course, as evidenced by 1 of the cases in the present study. The possibility of inadequate sampling of invasive foci exists for cases that appear to represent WDPM histologically yet demonstrate aggressive behavior. As with MM of the TVT, treatment guidelines for WDPM of the TVT are lacking. However, given they do not always behave in a benign manner, long-term follow-up would appear warranted.

Several mesotheliomas of the TVT that do not fit neatly into either the category of WDPM or MM have been described [22,25]. The designation of *mesothelioma of the TVT with uncertain malignant potential* has been proposed for tumors that are more complex than classic WDP, but are not overtly histologically malignant [22]. Under this proposal, which has not yet been formally recognized by the World Health Organization, the term *WDPM* is restricted to localized solitary tumors exhibiting exclusively papillary architecture in which the papillae are lined by a single layer of bland cuboidal cells. To date, 9 cases of mesothelioma of the TVT with uncertain malignant potential have been reported, all of which exhibited indolent behavior [22,25]. Long-term follow-up was not available in every case, limiting the robustness of conclusions and treatment recommendations that can be made regarding the prognosis of tumors that fall along the morphologic continuum between WDPM and MM.

A limitation of this study is the potential bias toward asbestos-related TVT MM being overrepresented due to the medicolegal consultative nature of the database from which cases were identified. If Helsinki criteria were to be applied, 4 of the 18 (22%) cases of MM of the TVT in the present study would be attributable to asbestos based on the presence of pleural plaques [26]. However, the role of asbestos in the development of MM of the TVT remains controversial. Because of the rarity of this disease, there have been no formal epidemiological studies supporting asbestos causation. That being said, 15 of the 18 men with MM (83%) in the present study had a documented history of either employment in occupations where there was a likelihood of asbestos exposure or paraoccupational exposure, as did the 2 with WDPM [27]. The percentage of cases with known asbestos exposure in other published series has ranged from 13% to 67% [6-12]. The potential for the prevalence of asbestos exposure in men with MM of the TVT to have been underestimated in some of these series exists because of incomplete exposure information. The most detailed examination of asbestos exposure among previously published series evaluated cases from the Italian Mesothelioma Registry over a 10-year period and found that two thirds of men with MM of the TVT for whom extensive histories were available had documented asbestos exposure [8]. Although there was insufficient lung tissue available in any of the cases in the present study for fiber analysis, based on their occupational histories, some of the men had the potential to have been exposed to sizable amounts of commercial forms of amphibole asbestos [27].

The mechanisms by which asbestos may exert a carcinogenic effect on the mesothelium of the TVT remain uncertain. The presence of an accompanying inguinal hernia would allow direct communication with the peritoneum. Asbestos has been postulated to gain direct access to the peritoneum via transdiaphragmatic migration of inhaled fibers passing from the lungs through the pleura and/or penetration of ingested fibers through the wall of the gastrointestinal tract [28]. Lymphatic and hematogenous routes of dissemination have also been proposed [29,30].

A number of nonasbestos factors have been implicated in the development of MM, including radiation [31]. We are not aware of any published cases of MM of the TVT in which radiation was specifically invoked, nor did any of the cases in the present study have a known history of prior radiation. Chronic serosal irritation/inflammation has been postulated to be an inciting factor in MM of other serosal sites [32-35]. Whether it can be considered an etiologic factor in MM of the TVT is unclear. There have been several reports of MM of the TVT arising in the setting of longstanding hydrocele, prior ipsilateral testicular trauma, or preceded by multiple hernia repairs and even a case developing on the same side in a man who had a recurrent epididymal adenomatoid tumor excised over a decade earlier [12,36-38]. In the present study, 1 of the men had a remote history of prior ipsilateral herniorrhaphy.

As illustrated by a case of adenocarcinoma initially mistaken for MM of the TVT in the present study, mesotheliomas of the TVT can be challenging to diagnose. The application of immunohistochemistry can be quite useful in this regard. However, as no single immunohistochemical stain is entirely sensitive and specific, using a panel that includes both mesothelial and carcinoma-associated markers is prudent [4]. The main nonmesothelial neoplasms that are differential considerations of MM of the TVT are likewise uncommon. Adenocarcinoma of the rete testis can exhibit a papillary or tubulopapillary architecture and stain positively for some mesothelial-associated markers, such as calretinin, CK 5/6, and WT-1 [39]. However, adenocarcinoma of the rete testis also expresses carcinoma-associated markers such as BerEp4 and MOC-31, is centered on the testicular hilum rather than the TVT, and has a tendency to exhibit more slitlike branched tubules and greater nuclear pleomorphism than MM. Paratesticular serous tumors resembling epithelial-type tumors of the ovary can also show some morphologic overlap with mesotheliomas of the TVT but are more likely to display tumor budding, psammomatous calcifications, positivity for carcinoma-associated markers such as BerEp4 and CEA, and negative staining for mesothelial-associated markers [40]. Paratesticular ovarian epithelial-type serous tumors are reported to be less likely associated with large hydroceles than MM [41]. Papillary or tubulopapillary growth can also be seen in adenocarcinoma of the epididymis, but the tumor cells are negative for mesothelial markers, usually more columnar than those seen in MM, and have a propensity to display cytoplasmic clearing [42]. Both primary testicular germ cell tumors, in particular, embryonal carcinoma and yolk sac tumor, and metastases to the testis from a variety of extragonadal sites can infiltrate paratesticular structures, causing diagnostic confusion in limited samples. Knowledge of the anatomic distribution of disease and thorough immunohistochemical evaluation can assist in this distinction [43].

The anatomic distribution of disease is also critical for separating MM of the TVT from MM originating in nearby sites. Very rare examples of primary MM of the testis, spermatic cord, and epididymis have been reported [44-46]. Other mesothelial lesions from which MM of the TVT must be distinguished

include adenomatoid tumor and reactive mesothelial hyperplasia. MM occasionally features a prominent adenomatoid growth pattern in which flattened/attenuated cells line tubules that sometimes form lacelike arrangements. The macroscopic appearance and invasion of adjacent structures, such as the subtunical connective tissue, spermatic cord, testicular parenchyma, epididymis, or scrotum, aid in diagnosis [47]. Additionally, in contrast to MM, adenomatoid tumors are typically solitary, well-demarcated lesions that tend to arise from the lower pole of the epididymis. Reactive mesothelial hyperplasia is more commonly observed in hernia sacs but can occasionally be prominent enough in hydroceles as to simulate a neoplastic mesothelial proliferation [1]. Reactive mesothelial hyperplasia lacks the bland papillae with fibrovascular cores that characterize WDPM. No formal cutoff has been established for separating reactive and malignant mesothelial processes based on the thickness of the proliferation. More useful is the presence of a zonal distribution in reactive mesothelial hyperplasia, in which the greatest degree of cellularity is near the luminal surface and is abruptly demarcated from underlying typically fibrotic tissue [48,49]. Layering of linear arrays of mesothelial cells is also a feature of reactive mesothelial processes and may be evident in hydroceles with organizing hematocele.

5. Conclusions

The present study ties the largest previously published study of MM of the TVT in terms of the number of cases reported [6]. Not infrequently, MM of the TVT is misinterpreted clinically as a commoner benign entity, such as hydrocele, belying the generally aggressive nature of this rare neoplasm. The operative impression, however, is usually not banal. Typical macroscopic findings include studding, nodularity, and/or irregular thickening of the TVT. Most cases are epithelioid with tubular and tubulopapillary patterns predominating. Criteria for attribution have not been established, but evidence of asbestos exposure in the form of pleural plaques has been found in some cases of MM of the TVT.

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References

[1] Lee S, Illei PB, Han JS, Epstein JI. Florid mesothelial hyperplasia of the tunica vaginalis mimicking malignant mesothelioma: a clinicopathologic study of 12 cases. Am J Surg Pathol 2014;38:54-9.

[2] Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG, editors. WHO classification of tumours of lung pleura, thymus and heart. Lyon: IARC; 2015.

[3] Butnor KJ, Sporn TA, Hammar SP, Roggli VL. Well-differentiated papillary mesothelioma. Am J Surg Pathol 2001;25:1304-9.

[4] Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma 2017 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 2018;142:89-108.

[5] Barbera V, Rubino M. Papillary mesothelioma of the tunica vaginalis. Cancer 1957;10:183-9.

[6] Winstanley AM, Landon G, Berney D, Minhas S, Fisher C, Parkinson MC. The immunohistochemical profile of malignant mesotheliomas of the tunica vaginalis: a study of 20 cases. Am J Surg Pathol 2006;30:1-6.

[7] Recabal P, Rosenzweig B, Bazzi WM, Carver BS, Sheinfeld J. Malignant mesothelioma of the tunica vaginalis testis: outcomes following surgical management beyond radical orchiectomy. Urology 2017;107:166-70.

[8] Mensi C, Pellegatta M, Sieno C, Consonni D, Riboldi L, Bertazzi PA. Mesothelioma of tunica vaginalis testis and asbestos exposure. BJU Int 2012;110:533-7.

[9] Perez-Ordonez B, Srigley JR, Thomas MJ, Hartwick RWJ, Mccaughey WTE. Malignant mesothelioma of the tunica vaginalis. A clinicopathologic study of 13 cases. Arch Anat Cytol Pathol 1998;46:430.

[10] Jones MA, Young RH, Scully RE. Malignant mesothelioma of the tunica vaginalis. A clinicopathologic analysis of 11 cases with review of the literature. Am J Surg Pathol 1995;19:815-25.

[11] An JY, Kim D, Tanakchi S, et al. Clinical features and outcomes of tunica vaginalis mesothelioma: a case series from the National Institutes of Health. Clin Genitourin Cancer 2017;15:e871-5.

[12] Antman K, Cohen S, Dimitrov NV, Green M, Muggia F. Malignant mesothelioma of the tunica vaginalis testis. J Clin Oncol 1984;2:447-51.

[13] Bisceglia M, Dor DB, Carosi I, Vairo M, Pasquinelli G. Paratesticular mesothelioma. Report of a case with comprehensive review of literature. Adv Anat Pathol 2010;17:53-70.

[14] Stein N, Henkes D. Mesothelioma of the testicle in a child. J Urol 1986;135:794.

[15] Plas E, Riedl CR, Pfluger H. Malignant mesothelioma of the tunica vaginalis testis: review of the literature and assessment of prognostic parameters. Cancer 1998;83:2437-46.

[16] da Fonseca LG, Marques DF, Takahashi TK, Aguiar FN, Ravanini JN, Saragiotto DF. Malignant paratesticular mesothelioma. Autops Case Rep 2014;4:45-51.

[17] Harmse JL, Evans AT, Windsor PM. Malignant mesothelioma of the tunica vaginalis: a case with an unusually indolent course following radical orchidectomy and radiotherapy. Br J Radiol 1999;72:502-4.

[18] Tan WK, Tan MY, Tan WS, et al. Well-differentiated papillary mesothelioma of the tunica vaginalis: case report and systematic review of literature. Clin Genitourin Cancer 2016;14:e435-9.

[19] Fujii Y, Masuda M, Hirokawa M, Matsushita K, Asakura S. A case of benign mesothelioma of the tunica vaginalis testis. Hinyokika Kiyo 1993;39:89-92.

[20] Chollet Y, Hauser P, Da Silva T, et al. Well-differentiated papillary mesothelioma of the tunica vaginalis testis: imaging on Tc-99m heat-denatured red blood cell scintigraphy. Clin Nucl Med 2008;33:282-4.

[21] Fukunaga M. Well-differentiated papillary mesothelioma of the tunica vaginalis: a case report with aspirate cytologic, immunohistochemical, and ultrastructural studies. Pathol Res Pract 2010;206:105-9.

[22] Brimo F, Illei PB, Epstein JI. Mesothelioma of the tunica vaginalis: a series of eight cases with uncertain malignant potential. Mod Pathol 2010;23:1165-72.

[23] Mak CW, Cheng TC, Chuang SS, Wu RH, Chou CK, Chang JM. Malignant mesothelioma of the tunica vaginalis testis. Br J Radiol 2004;77:780-1.

[24] Manganiello M, Cassalman C, Dugan J, Bennett N. Scrotal mesothelioma. Can J Urol 2014;21:7163-5.

[25] Trpkov K, Barr R, Kulaga A, Yilmaz A. Mesothelioma of tunica vaginalis of "uncertain malignant potential"—an evolving concept: case report and review of the literature. Diagn Pathol 2011;6:78.
[26] Wolff H, Vehmas T, Oksa P, Rantanen J, Vainio H. Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: recommendations. Scand J Work Environ Health 2015;41:5-15.
[27] Roggli VL, Sharma A, Butnor KJ, Sporn T, Vollmer RT. Malignant mesothelioma and occupational exposure to asbestos: a clinicopathological correlation of 1445 cases. Ultrastruct Pathol 2002;26:55-65.
[28] Enticknap JB, Smither WJ. Peritoneal tumours in asbestosis. Br J Ind Med 1964;21:20-31.
[29] Becklake MR. Asbestos-related diseases of the lung and other organs: their epidemiology and implications for clinical practice. Am Rev Respir Dis 1976;114:187-227.
[30] Hillerdal G. The pathogenesis of pleural plaques and pulmonary asbestosis: possibilities and impossibilities. Eur J Respir Dis 1980;61:129-38.
[31] Li X, Brownlee NA, Sporn TA, Mahar A, Roggli VL. Malignant (diffuse) mesothelioma in patients with hematologic malignancies: a clinicopathologic study of 45 cases. Arch Pathol Lab Med 2015;139:1129-36.
[32] Butnor KJ, Rueckert J, Pavlisko EN, Sporn TA, Roggli VL. Malignant peritoneal mesothelioma in patients with endometriosis. J Clin Pathol 2018;71:971-4.
[33] Butnor KJ, Pavlisko EN, Sporn TA, Roggli VL. Malignant peritoneal mesothelioma and Crohn disease. J Clin Pathol 2017;70:228-32.
[34] Hillerdal G, Berg J. Malignant mesothelioma secondary to chronic inflammation and old scars. Two new cases and review of the literature. Cancer 1985;55:1968-72.
[35] Riddell RH, Goodman MJ, Moossa AR. Peritoneal malignant mesothelioma in a patient with recurrent peritonitis. Cancer 1981;48:134-9.
[36] Gkentzis A, Sawalem K, Husain J. An unusual case of paratesticular mesothelioma on the site of previously excised epididymal adenomatoid tumour. Int J Surg Case Rep 2013;4:460-2.
[37] Amin R. Malignant mesothelioma of the tunica vaginalis testis—an indolent course. Brit J Radiol 1995;68:1025-7.
[38] Gurdal M, Erol A. Malignant mesothelioma of tunica vaginalis testis associated with long-lasting hydrocele: could hydrocele be an etiological factor? Int Urol Nephrol 2001;32:687-9.
[39] Al-Obaidy KI, Idrees MT, Grignon DJ, Ulbright TM. Adenocarcinoma of the rete testis: clinicopathologic and immunohistochemical characterization of 6 cases and review of the literature. Am J Surg Pathol 2019;43:670-81.
[40] Anchala PR, Dhir R, Parwani AV, Zynger DL. Immunohistochemical profile of paratesticular serous papillary adenocarcinoma and tunica vaginalis facilitates distinction from malignant mesothelioma. Int J Surg Pathol 2011;19:692-8.
[41] Perez-Ordonez B, Srigley JR. Mesothelial lesions of the paratesticular region. Semin Diagn Pathol 2000;17:294-306.
[42] Jones MA, Young RH, Scully RE. Adenocarcinoma of the epididymis: a report of four cases and review of the literature. Am J Surg Pathol 1997;21:1474-80.
[43] Ulbright TM, Young RH. Metastatic carcinoma to the testis: a clinicopathologic analysis of 26 nonincidental cases with emphasis on deceptive features. Am J Surg Pathol 2008;32:1683-93.
[44] D'Antonio A, Mastella F, Colucci A, Silvestre G. Malignant mesothelioma of spermatic cord in an elderly man with a history of asbestos exposure. Urology 2016;87:e1-3.
[45] Robinson JC, DeFranco JN, Hollowell CM. Malignant mesothelioma of the epididymis: a case report. Curr Urol 2014;7:217-8.
[46] Attanoos RL, Gibbs AR. Primary malignant gonadal mesotheliomas and asbestos. Histopathology 2000;37:150-9.
[47] Yang LH, Yu JH, Xu HT, et al. Mesothelioma of the tunica vaginalis testis with prominent adenomatoid features: a case report. Int J Clin Exp Pathol 2014;7:7082-7.
[48] Churg A. Paratesticular mesothelial proliferations. Semin Diagn Pathol 2003;20:272-8.
[49] Amin MB. Selected other problematic testicular and paratesticular lesions: rete testis neoplasms and pseudotumors, mesothelial lesions and secondary tumors. Mod Pathol 2005; 18 Suppl 2, S131–145.