Malignant Mesothelioma of the Tunica Vaginalis Testis:

Report of First Case with Preoperative Diagnosis

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The cytologic, histologic and ultrastructural features of a malignant carcinomatous mesothelioma of the tunica vaginalis testis in a 30-year old patient are described. This is the first such case with preoperative diagnosis by cytologic examination of hydrocele fluid and the second with documented history of exposure to asbestos. The identity of the tumor was confirmed by a positive immunoperoxidase reaction directed against mesothelial cells. A review of the previously described ten cases is presented.
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MALIGNANT MESOTHELIOMA of the tunica vaginalis testis is an uncommon tumor of which only ten well-documented examples could be found in the literature. In all previously recorded instances the diagnosis was established postoperatively and appeared to have been unexpected. For this reason, it was thought worthwhile to report a case of this tumor with a preoperative diagnosis established by cytologic evaluation of the hydrocele fluid. The identity of the tumor could be confirmed by immunohistologic and ultrastructural findings. The young patient's prior exposure to asbestos is of epidemiologic interest.

Case Report

The patient was a 30-year old man who presented with painless right scrotal swelling, first observed three weeks earlier. He had no other symptoms and suffered no recent trauma to his testicles. On physical examination, the positive findings were confined to the right scrotum. There was a small hydrocele with a mildly indurated right epididymis. Twenty milliliters of clear hydrocele fluid were aspirated through a 21-gauge needle and submitted for cytologic examination. After aspiration, a slight epididymal nodularity was noted and the patient was placed on antibiotic therapy with a presumptive diagnosis of epididymitis. Cytologic examination of the hydrocele fluid revealed malignant carcinomatous mesothelioma.

The patient was readmitted two weeks later for surgery, at which time the fluid had reaccumulated. On admission, except for the scrotal lesion, there were no abnormal physical, biochemical, or roentgenographic findings. The patient's right scrotal compartment was explored through an inguinal incision. The testicle and surrounding hydrocele sac were easily mobilized; the outer portion of the tunica was smooth and glistening. Upon opening the sac, multiple small yellow nodules were noted on both visceral and parietal surfaces of the tunica. Frozen section of the tunica vaginalis confirmed the cytologic diagnosis and a right radical orchiectomy was performed.

Because of the diagnosis of malignant mesothelioma, a detailed occupational history was obtained. For a period of eight years, until two years prior to admission, the patient was a pipefitter at an oil refinery. His work involved placing thick asbestos insulation around large pipe lines, straddling the pipes and their insulation in the process.

The patient was seen again 4½ months postoperatively. At that time, the physical examination was unremarkable and his right scrotal wound was well healed. Intravenous pyelogram and abdominal computed tomography (CT) were negative for metastatic disease. There was no evidence of retroperitoneal lymph node enlargement. Six months postoperatively, the patient was well and without clinical evidence of disease.

Laboratory Findings

Cytology

Fluid from the right hydrocele was received prefixed in an equal volume of 50% ethanol. Four smears were prepared from the sediment of the centrifuged specimen

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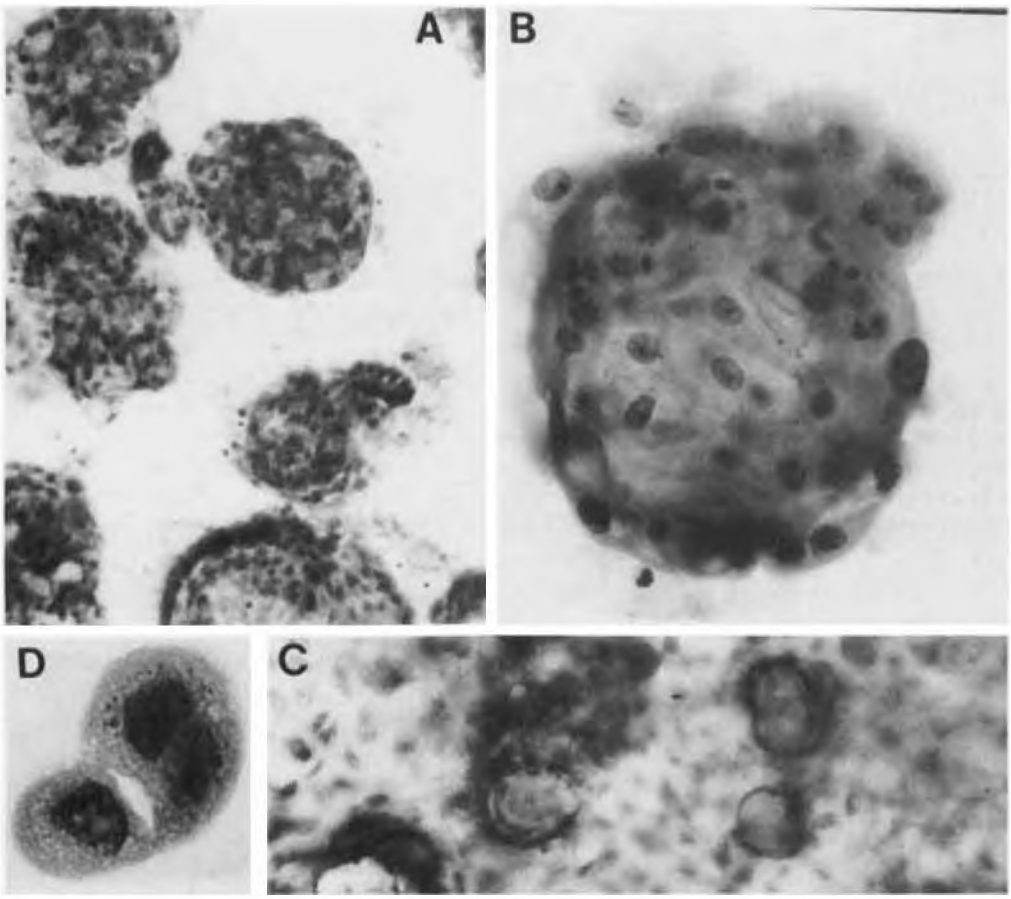

FIG. 1. Hydrocele fluid cytology. A. Low power view of spherical clusters of cells (×140) B. Close-up of a mulberry-shaped cell cluster. Note several enlarged and hyperchromatic nuclei at the periphery of the cluster (×350). C. Calcified structures (psammoma bodies) within a cell cluster (×350). D. Two malignant cells separated from each other by a clear space ("window") (×560). (A, B, C—Papanicolaou stain; D—cell-block, H & E.)

and stained by the Papanicolaou technique. Cellular material was abundant and was predominantly composed of three-dimensional, essentially spherical or "mulberry-shaped" clusters of cells. These clusters ranged from small round balls made up of four to five cells each to very large papillary structures with complex budding arrangements (Fig. 1A).

The cells within the large clusters had a distinctive arrangement. The peripheral cells and their nuclei were generally flattened, and were oriented in a circular fashion around the core of the cluster (Fig. 1B).

Within some of the larger structures as well as lying free in the background were numerous round, lamellated calcifications resembling psammoma bodies (Fig. 1C). The background was otherwise clear except for a rare mesothelial cell, occurring singly and in small clusters (Fig. 1D).

The cytoplasm of the tumor cells was generally abundant and eosinophilic and the cell borders were well defined. Many cells displayed cytoplasmic vacuoles, occasionally with peripheral displacement of the nucleus resulting in a signet ring appearance.

The nuclei showed a wide range of atypism. Most cells had a single, centrally placed nucleus, but occasionally binucleated cells were noted. In general, the nuclei were of moderate size, round or oval, with a smooth nuclear membrane. However, even within the same clusters, some nuclei were markedly enlarged with drastic alteration of the nucleocytoplasmic ratio (Fig. 1B). The chromatin pattern was predominantly finely granular but rare, irregularly shaped, coarsely granular, hence hyperchromatic nuclei were also seen (Figs. 1B and 1D). Some cells had from one to three very small chromocenters while others had one or two large, reddish, round nucleoli. No mitotic figures were observed.

A paraffin-embedded cell block was also prepared from residual fluid sediment, and the sections were stained with hematoxylin and eosin. The findings were essentially identical to those described above. Mucicarmine and alcian blue stains performed on the cell block were negative for mucin. Neither the smears nor the cell block contained asbestos bodies. The diagnosis of malignant carcinomatous mesothelioma was rendered on the strength of the microscopic findings.

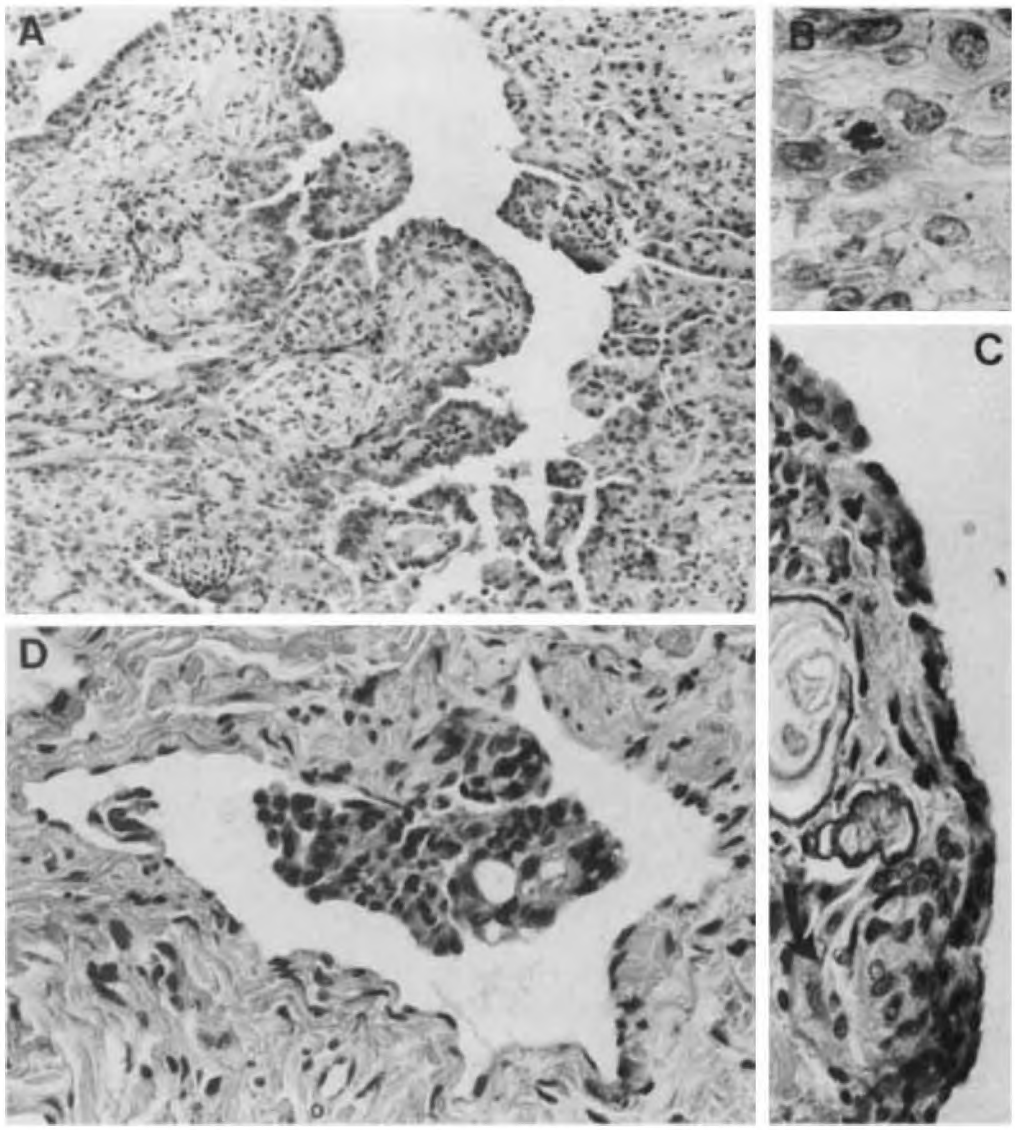

FIG. 2. Histologic appearance of malignant mesothelioma. A. Low power view showing exophytic, papillary proliferations protruding into the lumen of the tunica vaginalis (×140). B. Detail of the tumor with an abnormal mitotic figure (×560) C. Gradual transition between normal mesothelial cells and tumor. Note superficial extension of the tumor into the connective tissue stroma (*arrow*) (×350). D. Plug of tumor in a lymphatic vessel (H & E, ×350).

Surgical Pathology

Yellow tumor nodules measuring 0.3–0.5 cm in diameter were located on the parietal and visceral surfaces of the tunica vaginalis, the surface of the epididymis, and the base of the segment of the spermatic cord. The epididymis and the testis appeared normal and there was no gross evidence of invasion by tumor.

On microscopic examination, each of the multiple tumor nodules was composed of sheets of densely packed, large cells, forming exophytic, papillary proliferations (Fig. 2A), which were usually attached to the wall of the tunica by only a single, narrow connective tissue pedicle. The tumor was composed of cells bearing strong resemblance to normal mesothelial cells except for moderate variability in size (Fig. 2A). The nuclei were fairly uniform, yet infrequent abnormal mitotic figures were observed (Fig. 2B). The mesothelial surface of the tunica showed gradual transitions between normal mesothelium and tumor (Fig. 2C). Numerous psammoma bodies were present within the tumor. Mucicarmine and alcian blue stains were negative for mucin. Periodic acid-Schiff (PAS) stain disclosed positively staining cytoplasmic granules which disappeared with prior diastase digestion, indicating the presence of glycogen. The vacuoles seen in many cells did not react with any of the histochemical stains, including colloidal iron.

Invasion by tumor cells was observed in the connective tissue pedicles supporting papillary structures. Su-

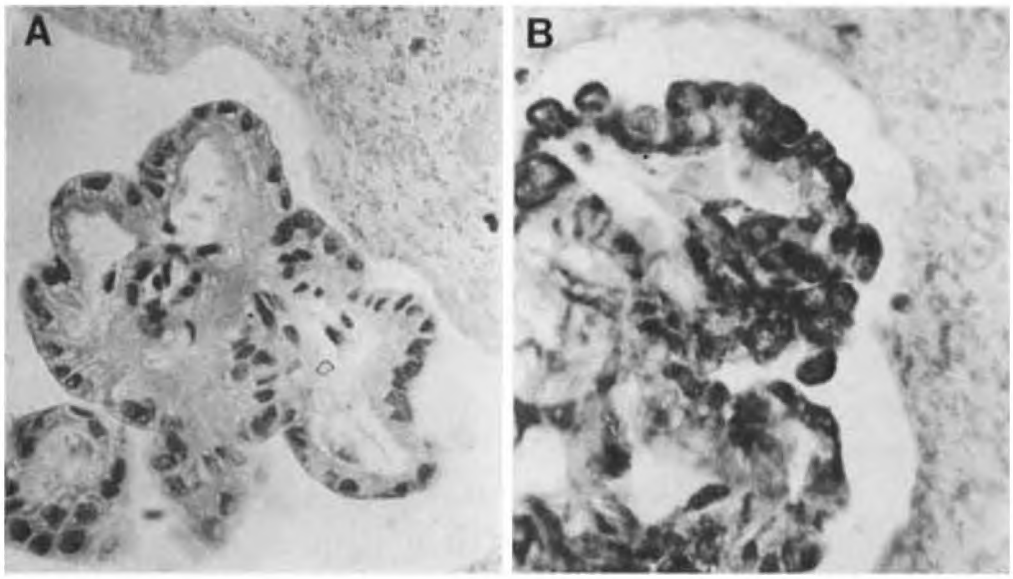

FIG. 3. Immunoperoxidase reaction performed on cell-block of hydrocele fluid. A. Negative control (see text) (~ ×350). B. There is a strong positive reaction for mesothelial cell antigens. (~ ×500).

perficial invasion of the wall of the tunica vaginalis (Fig. 2C) and the presence of a plug of tumor in one lymphatic were also noted (Fig. 2D). The epididymis itself, as well as the testis, were not invaded by tumor and both appeared normal. No asbestos bodies or asbestos fibers were found following digestion of 1.3 g of tumor tissue with household bleach.

Immunoperoxidase Reaction

A paraffin-embedded cell block of the fluid was sent to one of us (G.S.) for immunoperoxidase staining. Antiserum to mesothelial cells was prepared and absorbed according to the protocol described earlier.[1] An additional absorption with the homogenates of formalin-fixed colonic and breast carcinomas was carried out prior to immunoperoxidase staining. Immunoperoxidase staining was done according to the method of Pinkus and Said.[2] Normal rabbit serum, absorbed in parallel with the antimesothelial cell serum, and rabbit antihuman IgG were used as negative controls (Fig. 3A). The antimesothelial cell serum had been evaluated for its specificity by immunoperoxidase staining of non-mesotheliomatous tumors.[3]

The tumor cells in the cell block exhibited strong positive reaction for mesothelial cell antigen(s) (Fig. 3B).

Electron Microscopy

Fresh tumor tissue was minced into 1-mm fragments and fixed in phosphate-buffered 5% glutaraldehyde. Following postfixation in chromate buffer, the sections were rinsed, dehydrated in graded alcohols and embedded in Epon. Selected ultrathin sections were mounted on copper grids, stained with uranyl acetate and lead citrate, and examined with a Siemens 101 electron microscope.

The tumor cells were generally large and polygonal, with abundant cytoplasm; occasional cells were dark and more spindle-shaped. Many slender microvilli of variable length and configuration were present on free surfaces of the cells (Fig. 4A) and within the cleft-like spaces which occurred between cells. Remnants of glycocalix were observed on the surface of the microvilli (Fig. 4B) Numerous well-developed desmosomes between tumor cells were observed (Fig. 4A). Occasional cells were accompanied by partial basement membranes.

The cytoplasm contained large, round to oval mitochondria in a perinuclear location. The Golgi apparatus was generally inconspicuous. The rough endoplasmic reticulum was fragmented in some cells, while in others it formed undulating tubules which partially surrounded mitochondria. Some of the cells contained sparse, peripherally located, smooth vesicles as well as dark, dense bodies. The latter were probably lipid or lysosomal bodies. Numerous tonofilaments and scattered aggregates of glycogen were present in many of the cells.

The nuclei were large and pale, of irregular contour, with angular, shallow or deep indentations (Fig. 4A). The chromatin was aggregated at the nuclear membrane and around the well-developed nucleoli. The ultrastructural appearance was consistent with an epithelial tumor of mesothelial origin.

Discussion

The normal tunica vaginalis testis is an extension of the peritoneum, normally lined by a single layer of mesothelial cells. Primary malignant mesothelioma of

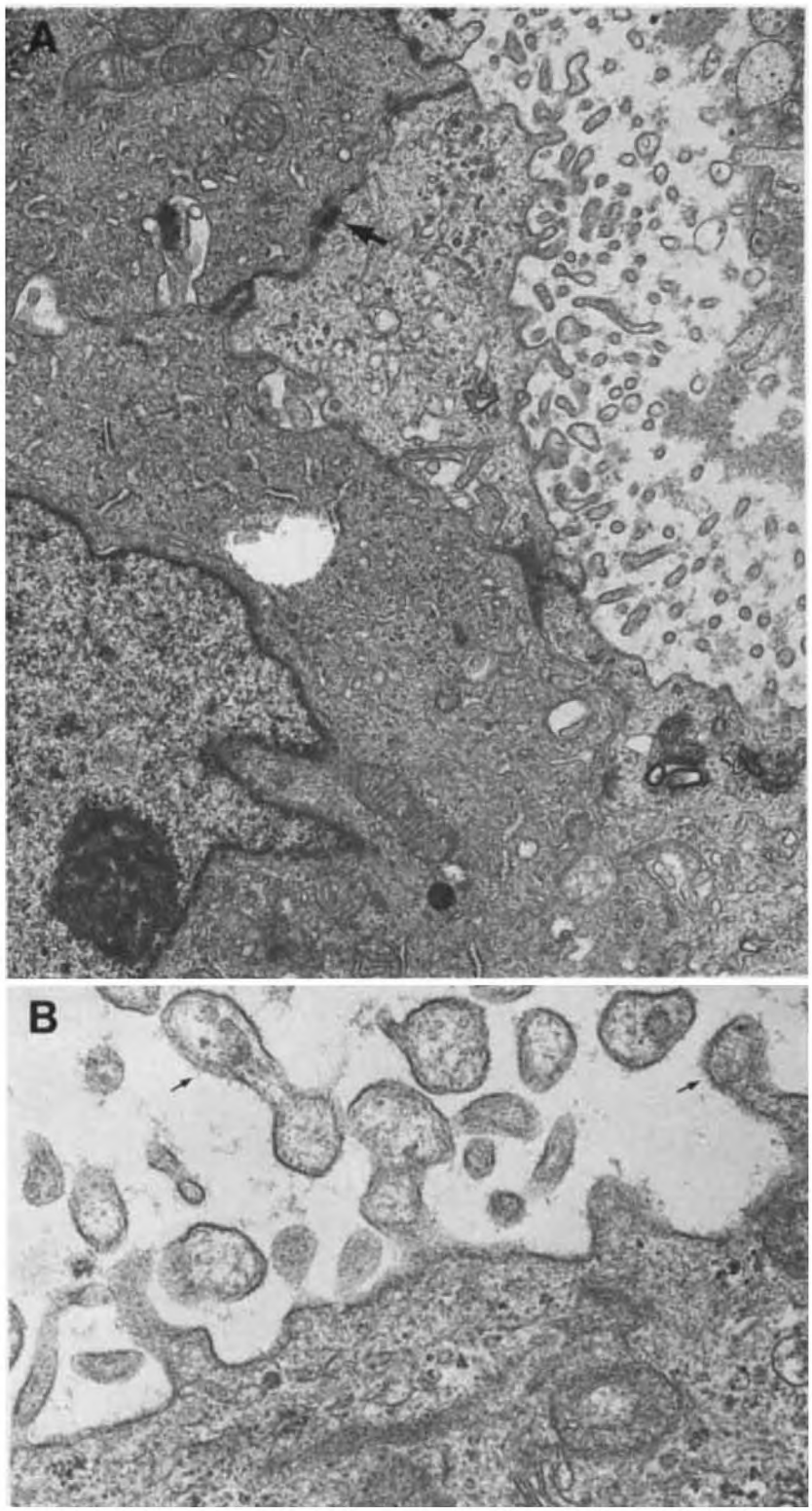

FIG. 4. Electron micrographs of tumor. A. Numerous microvilli of variable length and configuration cover the outer surface of the cells. Several well-developed desmosomes bind the tumor cells (*arrow*). Note the irregularly shaped nucleus (×12,400). B. Detail of cell surface. Remnants of glycocalix are attached to the irregular microvilli (*small arrows*) (×40,000).

the tunica vaginalis is an uncommon tumor, analogous to the malignant mesothelioma of the pleura or the peritoneum.[4-6]

Malignant mesothelioma can be of three histologic types: carcinomatous, fibrosarcomatous, and mixed.[7] The differential diagnosis of carcinomatous mesothelioma comprises mesothelial hyperplasia either spontaneous or secondary to inflammatory processes,[4,7-9] and metastatic adenocarcinomas either from distant or adjacent sites.[10]

TABLE 1. Case Summaries

Cases and Ref.#	Age/clinical presentation	History of asbestos exposure	Hospital course		Survival after diagnosis
			Procedures	Findings	
1[33]	21/R scrotal lump for 5 yr. with recent enlargement	NS	R scrotal exploration, excision of one of multiple nodules within TVT, followed by R orchiectomy and excision of scrotal skin.	Papillary adenocarcinoma, well differentiated and infiltrating. Superficially invasive papillary adenocarcinoma of appendix testis, with MET to TVT. Small hydrocele. Testis & epididymis neg.	Alive & well—15 mo.
2[32]	70/NS	NS	NS	MPM of TVT.	Dead—16 mo. METs
3[32]	78/NS	NS	NS	MPM of TVT.	Dead—3¾ yr. METs
4[8]	56/R hydrocele	NS	Multiple aspirations over 2 yr. period, followed by R orchiectomy & hemiscrotectomy. Radiotherapy for metastatic disease.	Hydrocele fluid not examined MPM of TVT with invasion of vessels. Testis neg.	Dead—5 yr. with disseminated disease.
5[8]	72/R hydrocele	None	Aspiration, 2 yr. later R hydrocelectomy. 5 mo. later R orchiectomy, retroperitoneal lymphadenectomy. 3 yr. later: Bx of groin LN.	Hydrocele fluid not examined. Superficially invasive tumor of TVT. Diffuse MPM of TVT with invasion of testis, epididymis & cremaster muscle. One of 21 LN's with MET. Metastasis to one LN.	Alive—5 yr. with METs.
6[37]	23/R hydrocele for 4 mo.	NS	Aspiration. 1 mo. later: R scrotal hydrocelectomy for rapid reaccumulation of fluid. 1 mo. later: exploratory laparotomy, R inguinal orchiectomy, hemiscrotectomy. 1 mo. later: R inguinal lymphadenectomy.	Hycrocele fluid not examined. MPM of TVT, infiltrating. Grossly neg laparotomy. MPM of TVT overlying epididymis. Tumor involving scrotal scar, site of previous hydrocelectomy. Epididymis & testis neg. 15 LNs neg.	Alive—3 mo.

7[34]	60/L hydrocele swelling for 1 yr.	NS	L hydrocelectomy, L orchiectomy. 2 wk. later: bilateral lower limb lymphangiography. Laparotomy & para-aortic LN Bx. Radiotherapy to inguinal, para-aortic, mediastinal & L supraclavicular LN.	MPM of TVT, superficially invasive. Testis & epididymis neg. Enlarged para-aortic LNs. METs in LNs.	Alive & well—12 mo.
8[35]	68/R hydrocele for 5 mo.	40 yr. exposure, pipe-fitter	Chest x-ray R orchiectomy. 20 mo. later: chest x-ray Mediastinoscopy & Bx mediastinal mass.	Suggestion of pleural thickening. Slight mediastinal shift to the R. MPM of TVT with superficial invasion of epididymis & testis; LN METs. Marked mediastinal shift to the R, thickening of pleurae, large mediastinal mass. METs in LNs	Dead—20 mo. with METs
9[16]	35/L scrotal swelling for 2½ mo.	None	L orchiectomy, radiotherapy.	20 ml hydrocele fluid. Malignant fibrous mesothelioma of TVT with invasion of spermatic cord. Slight invasion of testis.	Alive & well—1½ mo.
10[36]	77/hydrocele & hematocele for 6 wk. with recent rapid enlargement.	None	L inguinal orchiectomy 8 mo. later: cholecystectomy for cholecystitis, excision of para-aortic LN	MPM of TVT with superficial invasion. Testis & epididymis neg. MET in para-aortic LN.	Dead—12 mo. with METs at PM.
11 Present case	30/R hydrocele for 3 wk.	8 yr. exposure, pipe-fitter.	Aspiration. R inguinal orchiectomy.	MPM of TVT (cytology) Superficially invasive MPM of TVT. Testis & epididymis neg.	Alive & well—6 mo.

Abbreviations: R = right; L = left; yr. = years; mo. = months; wk. = weeks; NS = not specified; TVT = tunica vaginalis testis; MPM = malignant papillary mesothelioma; Bx = biopsy; MET = metastasis; LN = lymph node; neg = negative for tumor; PM = postmortem examination.

The conclusion that we were indeed dealing with a malignant mesothelioma of the tunica vaginalis testis and not with a benign proliferative process affecting the mesothelium was based on several considerations. The cytologic presentation was characteristic and fully compatible with malignant carcinomatous mesotheliomas of other sites such as the pleura, peritoneum and pericardium.[4,5,7,11-15] There was evidence of stromal and, more importantly, lymphatic invasion (Fig. 2D).

The presence of abundant microvilli of variable length and irregular configuration on the surfaces of the tumor cells demonstrated by electron microscopy (Fig. 4A) was also strongly supportive of the diagnosis of malignant mesothelioma.[6,16,17] Benign mesothelium is characterized by regularly spaced, relatively short microvilli.[7] The rapid reaccumulation of fluid two weeks after the initial tap of the "hydrocele" has also been recorded in other malignant tumors of tunica vaginalis and has been considered an important clinical indication of a malignant process.[18] Other ultrastructural findings, such as the presence of glycogen, tonofilaments, desmosomes, and the perinuclear location of mitochondria, while not specific, were entirely consistent with observations recorded in other cases of malignant carcinomatous mesothelioma.[17] On the other hand, the presence of calcified psammoma bodies does not necessarily indicate a malignant process: such structures may be observed in malignant mesotheliomas[6,7,16] but also in benign proliferative processes of the mesothelium.[14]

The mesothelial derivation of the tumor could be confirmed by immunoperoxidase reaction, using antibodies with previously documented high degree of specificity for mesothelial cells in fluids.[1]

We undertook a review of the literature on the subject of malignant mesothelioma of the tunica vaginalis testis using the following arbitrary criteria: there should be no evidence of adenocarcinoma elsewhere; the tumor should not be mucicarmine-positive;[4,11,14,19-21] there should be *in situ* changes within the epithelium lining the tunica vaginalis in the surgical material. Specifically excluded were cases of adenomatoid tumors and other clearly benign tumors,[22-28] tumors of probable epididymal origin,[29-31] and mucin-positive tumors.[22,31] Using the above criteria, there were only ten previously described cases,[13,16,32-37] that we considered as bona fide malignant mesotheliomas of the tunica vaginalis. The ten case histories and the present case are summarized in Table 1.

The ages of the patients were from 21 to 78 years. Seven of the nine cases for which there was adequate description presented with a unilateral hydrocele. The other two cases (Cases 1 and 9) presented with scrotal lumps, wherein fluid-filled cavities were observed on pathologic examination. It is of interest that a very small amount of fluid was present in Case 9 of sarcomatous mesothelioma. Contrary to carcinomatous mesotheliomas, such tumors are generally not associated with significant accumulation of fluid.[7]

The relationship of mesotheliomas to asbestos exposure is well established for pleural and peritoneal tumors.[38-42] In reference to the cases of malignant mesotheliomas of tunica vaginalis testis, the occupational history was sought in five. Two (Case 8, and this case) provided positive histories of asbestos exposure. Case 8[35] also had a mesothelioma in the thoracic cavity, possibly of pleural origin. To our knowledge, the shortest interval reported between the first exposure to asbestos and the development of mesothelioma is 13 years.[40] A more usual period is from 20 to 40 years.[38,43] Our patient gave a history of initial asbestos exposure dating back only ten years. This probably does not negate a causal relationship. Since the space surrounding the testis is relatively small and easily palpated, it is possible that tumor growth and abnormal fluid accumulation may be observed earlier within the scrotum than within the pleural or peritoneal cavities. Another interesting facet to our patient's occupational history is that he straddled large asbestos-lined pipes. The possibility of exposure through scrotal skin should not necessarily be discounted.

In terms of diagnostic procedures, it is important to note that cytologic examination of hydrocele fluid was not recorded in any of the previously reported cases, even those in which aspirations were performed (Cases 4–6). The efficacy of cytologic evaluation of hydrocele fluids has not been established. However, there is a report on record in which the diagnosis of a malignant testicular tumor was made, based on the cytologic examination of the hydrocele fluid.[7] As stated in a large review, "the presence of a hydrocele in association with a paratesticular tumor is usually an indication that the tumor is malignant".[15] Failure to perform a cytologic examination of hydrocele fluid may lull the urologist into believing that he is dealing with a benign process. He may either withhold treatment for a long period of time (Cases 4 and 5) or perform a trans-scrotal hydrocelectomy when a radical orchiectomy through an inguinal approach would have been the procedure of choice. Surgical violation of the scrotal skin may lead to tumor implantation into the incision site as recorded in Case 6. Hemiscrotectomy appears to be the procedure of choice if prior trans-scrotal hydrocelectomy was undertaken.

As with malignant mesothelioma of the pleura or peritoneum, distant spread of mesothelioma of the tunica vaginalis is usually via lymphatics (Cases 5, 7, and 8). Consequently, once the diagnosis is seriously entertained, preoperative evaluation of the para-aortic and

iliac lymph nodes by lymphangiography and/or computed tomographic scan appears indicated.

Malignant mesothelioma confined to the tunica vaginalis may lend itself to complete surgical extirpation, contrary to mesotheliomas of the pleura, pericardium or peritoneum. Therefore, early diagnosis by cytologic examination of hydrocele fluid may prove to be of major therapeutic and prognostic advantage.

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