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Malignant Mesothelioma of the Tunica Vaginalis Testis: Outcomes Following Surgical Management beyond Radical Orchiectomy

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Abstract

Objective—To describe clinical management and outcomes of a cohort of patients with malignant mesothelioma of the tunica vaginalis testis (MMTVT) who received treatments beyond radical orchiectomy.

Methods—Patients with confirmed MMTVT at a single tertiary-care institution were identified. Treatments, pathologic outcomes, and survival were recorded. Prognostic variables associated with survival were analyzed with a Cox proportional hazards model and Kaplan-Meier curves.

Results—Overall, 15 patients were included. Initial presentation was a scrotal mass in 7/15(47%) and hydrocele in 5/15(33%). Clinical staging revealed enlarged nodes in 5/15(33%) patients.

Radical Orchiectomy was the initial treatment in 5/15(33%). Positive surgical margins were found in 6/14(43%) radical orchiectomies, and associated with worse survival ($p=0.007$). The most frequent histologic subtype was epithelioid, associated with better survival ($p=0.048$).

Additional surgeries were performed in 12/15(80%). Pathologic examination revealed MMTVT in 6/12(50%) hemiscrotectomies; 7/8(88%) retroperitoneal lymph node dissections; 1/7(14%) pelvic lymph node dissections; and 10/10(100%) groin dissections. Five patients received adjuvant chemotherapy. Two also received adjuvant radiation therapy. Three patients with lymph node involvement remain NED over 6 years after diagnosis.

After a median follow-up of 3.5 years (IQR 1.2 – 7.2) five patients have died, all of MMTVT; median overall survival has not been reached. Common sites of relapse were lungs (5/7) and groin (3/7).

Conclusions—The pattern of metastatic spread of MMTVT is predominantly lymphatic. Nodes in the retroperitoneum and the groin are commonly involved. Prognosis is poor, but there may be a

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role for aggressive surgical resection including hemiscrotectomy, inguinal and retroperitoneal lymph nodes.

Keywords

Mesothelioma; Surgical Procedures; Operative; Treatment outcomes

INTRODUCTION

Malignant Mesothelioma of the Tunica Vaginalis Testis (MMTVT) is a rare neoplasm of mesenchymal origin that arises from the serous lining that covers the testis or epididymis (visceral lamina) or the, spermatic cord and internal wall of the scrotum (parietal lamina). It represents less than 5% of all malignant mesotheliomas, which more frequently arise from the mesothelial lining of the pleural or peritoneal cavities [1]. MMTVT was originally described by Barbera in 1957[2]. Since then, only case reports and a few small case series have been published, comprising less than 300 patients in total. As such, there is scarce evidence regarding prognostic factors and treatment of this disease, and therapeutic principles are frequently extrapolated from management of pleural or peritoneal malignant mesothelioma.

MMTVT usually presents between ages 55 and 75, and is less frequent among younger patients. This disease poses a diagnostic challenge and usually goes unrecognized as it lacks specific clinical features, and can mimic common inguinal or scrotal diseases such as a hydrocele or an inguinal hernia. Patients usually undergo procedures such as hydrocelectomy, inguinal hernia repair or scrotal exploration, where intraoperative findings including thickening, multifocal nodules or friable papillary fronds on the tunica vaginalis suggest the diagnosis [3–4]. A few prognostic factors have been described, including age at diagnosis[5], presence of metastasis at diagnosis [5], and asbestos exposure (which has an established role in the pathogenesis of MMTVT)[6–7]. MMTVT usually has an aggressive behavior, with a median survival after diagnosis ranging between 18 and 23 months. There is a paucity of curative treatments for MMTVT other than surgery, which remains the mainstay of management. There is a lack of consensus regarding management beyond radical orchiectomy, which is typically not curative [4].

We aimed to describe characteristic and outcomes of a cohort of patients with MMTVT managed mostly with aggressive surgical resections at a single tertiary care institution.

METHODS

Patient Cohort

Following IRB approval, we performed a retrospective review of our prospectively collected database. All patients with pathologically confirmed MMTVT over a 17-year period (1997 – 2014) were included. We recorded staging, pathologic outcomes, additional surgical and non-surgical treatments, recurrence and survival. Patients were usually staged with CT scans, and all underwent radical orchiectomy except for one who was lost to follow-up. All outside pathology was reviewed in-house by dedicated genitourinary pathologists.

Statistical analysis

To describe survival, Kaplan Meier curves were constructed for the entire cohort, and by stage, surgical margin status at orchiectomy, and histologic subtype. To assess the predictive value of these variables, we used a multivariable Cox proportional hazards model with robust variance estimates. Laterality was evaluated with a binomial probability test. Significance (α) was set at the 5% threshold. All analyses were conducted using Stata 12.0 (StataCorp, College Station, TX, USA).

RESULTS

Patient characteristics at presentation

Overall, 15 patients with pathologically confirmed MMTVT were included. Patient characteristics are described in Table 1. Left side was more common in this cohort (80%, p -value=0.03). Median age at diagnosis was 62 years, however distribution of age at diagnosis was bimodal, with a peak at 65 years, and a smaller peak at 39 years (Supplementary Fig. 1). These two groups appeared to have a significantly different prognosis (Supplementary Fig. 2). Age as a continuous variable was inversely associated with cancer-specific survival in the Cox proportional hazards model (p -value < 0.001). Asbestos exposure was recorded in 2/15(13%) patients. Initial presentation was a scrotal mass (usually with a cystic component) in 7/15(47%), a hydrocele in 5/15 (33%), and an inguinal mass in 3/15 (20%) patients. All patients received initial surgical treatment in the community and were subsequently referred to MSKCC. Two thirds of the patients initially underwent a surgical procedure other than radical orchiectomy. These included hydrocelectomy in 4 patients, scrotal exploration in 3, inguinal hernia repair in 2, and inguinal exploration in 1 patient. Suboptimal surgical technique including scrotal violation or opening the cavity of the tunica vaginalis with potential tumor spillage was identified in 11/15 (73%) patients. Clinical staging at diagnosis revealed enlarged lymph nodes (>1 cm) in the retroperitoneum in 3/15(20%), and in the groin in 2/15(13%); 1 patient (7%) presented with peritoneal carcinomatosis at diagnosis. Diagnosis of MMTVT was suspected preoperatively in only 1 patient, who underwent a testicular MRI (Fig. 1).

Pathologic outcomes at Radical Orchiectomy

Pathology reports of radical orchiectomy specimens were available for review in 14/15(93%) patients; however radical orchiectomy was the initial treatment in only 5/15(33%), of which 4 were performed at our institution. Pathologic outcomes at orchiectomy are described in Table 1. Average tumor size ($\pm$ SD) was 4.5 ± 2.8 cm, although in several cases there were multiple nodules rather than a discrete tumor. Lymphovascular invasion was identified in 2 patients. All specimens evaluated with immunohistochemistry were positive for Calretinin ($n=13$); WT-1 ($n=9$); and AE-1/AE-3 ($n=10$). Positive surgical margins were found in 6/14(43%) of all radical orchiectomy specimens, and were associated with worse cancer specific survival (Fig. 2). The most frequent histologic subtype was epithelioid, which was associated with better survival (Fig. 3).

Additional surgical treatments and pathologic outcomes

Surgical treatment beyond radical orchiectomy was performed in 12/15(80%) of patients; pathologic findings of these procedures are described on Supplementary Table 1. Twelve patients (80%) underwent hemiscrotectomy; 8 patients underwent retroperitoneal lymph node dissection (RPLND); 6 patients underwent groin dissection (of which two patients underwent repeat groin dissections, for a total of 10 procedures); and 7 patients underwent pelvic lymph node dissection (PLND). Pathologic examination revealed residual tumor in 6/12(50%) hemiscrotectomy specimens. The limits of RPLND dissection were full bilateral template in 7/8(88%), and unilateral template in 1/8 (13%) patient. Median number (IQR) of resected nodes at RPLND was 45(39–58). Pathologic examination revealed positive nodes in 7/8(88%) patients undergoing RPLND, the median (range) number of involved nodes was 4(1–18). The primary area of testicular lymphatic drainage (landing zone; paraaortic for left-sided tumors; interaortocaval or paracaval for right side tumors) was involved in all patients with retroperitoneal lymph node metastases. Pathologic examination revealed positive nodes in 1/7(14%) patient undergoing PLND; this patient also had extensive RPLND involvement. All patients undergoing groin dissections had clinical evidence of a suspicious mass in the groin. Pathologic examination revealed malignancy in 10/10(100%) groin dissection specimens, involving either the spermatic cord or lymph nodes.

Adjuvant treatments

Five patients received adjuvant chemotherapy (Pemetrexed + Cisplatin), 4 of them completed 4 cycles, and one required substitution of Cisplatin by Carboplatin because of renal toxicity. Of patients who received chemotherapy, 2 also received adjuvant radiation therapy to the groin.

Progression and survival

After a median followup of 3.5 years (IQR 1.2 – 7.2 years), 7 patients experienced disease progression; the most common sites of relapse were lungs (5/7), groin (3/7), and peritoneal carcinomatosis (2/7). Five patients have died, all from metastatic MMTVT; median overall survival has not been reached. Survival for the entire cohort and by clinical stage is illustrated in Supplementary Figures 3 and 4. Of note, 2 patients with confirmed metastatic lymph node involvement of the retroperitoneum remain free of disease 8 and 6 years after RPLND, PLND and hemiscrotectomy, without adjuvant treatments. Prognostic factors in the multivariable model are shown on Supplementary Table 2.

DISCUSSION

We present the first single institution series of MMTVT, which involved aggressive surgical management, alone or in combination with a recent adjuvant chemotherapy regimen. Outcomes for this cohort were better than previously reported; median overall survival has not been reached after a median followup of 42 months; compared to a median overall survival of 18 to 23 months in previously published series [5–6]. We confirmed the prognostic value of age at diagnosis, and observed a bimodal distribution consistent with a previous systematic review [5]. We identified surgical margin status at radical orchiectomy, and histologic subtype as prognostic factors. In concordance with our findings, non-

epithelioid subtypes are also associated with a worse prognosis among malignant pleural mesotheliomas [8] and malignant peritoneal mesotheliomas [9]. Prevalence of asbestos exposure was lower than previously reported. In our cohort most metastatic sites involved lymph nodes. Furthermore, aggressive surgical resection including RPLND, PLND and hemiscrotectomy resulted in prolonged remissions in 2 patients with confirmed retroperitoneal lymph node involvement, who remain with no evidence of disease after 6 and 8 years without further treatment. These findings support a predominantly lymphatic pattern of metastatic spread. Finally, in this cohort, left-side tumors were more frequent, which contrasts with previous reports.

The largest study focusing on MMTVT was published by Plas et al in 1998 [5], and represents a systematic review including 73 published case reports and one of their own. In that study, the authors performed a univariate Cox regression model and determined that age 60 and presence of metastasis at diagnosis were associated with worse survival, although the multivariable analysis did not determine any significant findings. In our cohort, age at diagnosis (analyzed as a continuous variable) was associated with decreased survival in the multivariable Cox regression model. Overall and cancer-specific survival were equal in our cohort since all five deaths were caused by MMTVT, which supports the observation of a worse prognosis in older patients. In line with the study by Plas et al [5], we also found a bimodal distribution of age at diagnosis with a peak at 65 and another at 39 years old. Prognosis appears to be significantly different for both groups; we observed no events (deaths) in the younger group.

Preoperative diagnosis was infrequent in our series, in line with previously reported series [5]. MMTVT should be suspected in older men presenting with a hydrocele or cystic paratesticular mass with parietal vegetations, especially if the internal wall shows high vascularity on Doppler examination [3]. MRI appears to be helpful in that regard, providing preoperative diagnosis in the single cases it was used.

Asbestos exposure is a well known risk factor for the development of Mesothelioma in any location. A study by Mensi et al describing a cohort of 13 patients with MMTVT registered in the Lombardy Mesothelioma Registry investigated asbestos exposure in a standardized fashion, and documented exposure in 8/12 patients. We found a lower prevalence of asbestos exposure than previously reported; however this variable was not documented in a standardized fashion in medical records, so it may be under-reported in our study.

The pattern of metastatic spread is one of the relevant findings of our study. There were two major sites of lymph node involvement: the retroperitoneum and the groin. This could possibly be explained by different lymphatic drainage routes of the visceral lamina and the parietal lamina of the tunica vaginalis; the former to the retroperitoneum (mimicking germ cell tumor spread), and the latter to the groin (mimicking penile cancer spread). However, 5/6 patients who with pathologic evidence of inguinal lymph node involvement had either a scrotal violation during the primary treatment, or a positive surgical margin at radical orchiectomy, so a iatrogenic alteration of the normal lymphatic drainage cannot be excluded. It is also possible that inguinal lymph node involvement was caused by spread along the spermatic cord and not necessarily through lymphatic vessels. Nevertheless, all patients who

progressed developed retroperitoneal and/or inguinal lymph node metastases before visceral or peritoneal metastases.

Three patients with pathological evidence of lymph node involvement remain NED after 6 to 8 years after diagnosis. Aggressive surgical resection alone was curative in 2 of these patients (who ordinarily would have been considered incurable), while the other received adjuvant chemotherapy. RPLND was performed in 5 clinical stage I patients, and metastatic malignant mesothelioma was found in all of them, emphasizing the limitations of clinical staging. In contrast, pelvic lymph nodes were compromised infrequently. All patients undergoing groin dissection had suspicious groin masses at the time of the procedure, so we have no data regarding groin dissection in patients with clinically negative groin. We believe these findings can inform surgical planning.

Although this cohort is very small, it represents the largest single-institution series presented to date. Our study provides outcome data of patients undergoing aggressive surgical resections beyond radical orchiectomy, including RPLND, PLND, ILND and hemiscrotectomy, and the use of a recent chemotherapy combination for mesothelioma (Pemetrexed + Cisplatin) with proven efficacy in pleural mesothelioma [10]. Outcomes of these treatments for MMTVT have not been previously published to our knowledge.

Two major limitations of this study are its retrospective nature and the small sample size. Unfortunately these are impossible to overcome given the very low incidence of MMTVT; even at our tertiary care institution MMTVT was diagnosed less than once a year. The wide confidence intervals in the proportional hazards model reflect the low power of the study. Nevertheless highly significant p-values were calculated for age at diagnosis and PSM using robust variance estimators, which may decrease the type II error when dealing with heteroscedasticity. Although we consider our data as low level evidence, it is unlikely a better level of evidence will be available for this disease anytime soon. The generalizability of our findings is also limited because these patients were treated at a tertiary care facility by highly experienced surgeons. Also, selection bias precludes efficacy analyses for surgical procedures or chemotherapy; as such we didn't attempt to determine whether aggressive surgical resection or combination chemotherapy is associated with a clinical benefit. Nevertheless we believe our data provides incremental knowledge regarding the pattern of metastatic spread, and surgical management of MMTVT, beyond radical orchiectomy which is seldom curative by itself [4]. Given the rarity of this entity it seems unlikely that it could be the subject of a prospective clinical trial, so management will be based on retrospective data and extrapolated data derived from mesothelioma in other locations.

CONCLUSIONS

Urologists should have a suspicion of MMTVT in patients with papillary fronds, multifocal nodules, or thickened tunica vaginalis. In these cases a scrotal MRI may provide a preoperative diagnosis. The pattern of metastatic spread of MMTVT is predominantly lymphatic. The most commonly involved nodes are in the retroperitoneum and the groin. Prognosis is poor, but there may be a role for aggressive surgical resection including

hemiscrotectomy, groin and retroperitoneal lymph node dissections, and adjuvant combination chemotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Radiologic studies of patients diagnosed with MMTVT. MRI study T1 weighted image (top left), and T2 weighted image (Top right). Ultrasound and Doppler study (bottom). Images show multifocal nodules/papillary fronds on the tunica vaginalis, and the tunica vaginalis wall shows high vascularity on Doppler.

Figure 2.
Kaplan Meier Survival curves according to surgical margin status

Figure 3.
Kaplan Meier Survival curves according to histologic type

Table 1

Patient characteristics, initial treatment and pathologic outcomes at radical orchiectomy

	N=15
Age at Diagnosis (years)	62 (39 – 66)
Laterality	
Left	12 (80%)
Right	3 (20%)
Asbestos exposure	2 (13%)
Presentation	
Scrotal mass	7 (47%)
Hydrocele	5 (33%)
Inguinal mass	3 (20%)
Clinical N staging	
cN0	10 (67%)
cN1	5 (33%)
Clinical M staging	
cM0	14 (93%)
cM1	1 (7%)
Initial Surgical Treatment	
Radical Orchiectomy	5 (33%)
Hydrocelectomy	4 (27%)
Scrotal exploration	3 (20%)
Inguinal hernia repair	2 (13%)
Inguinal exploration	1 (7%)
Tumor size in cm (n=13)	4.5 (2.8 – 5.5)
Surgical Margin Status at Radical Orchiectomy (n=14)	
Positive	6 (43%)
Negative	8 (57%)
Histologic type	
Epithelioid	8 (53%)
Biphasic	4 (27%)
Not specified	3 (20%)

Statistics are presented as median (IQR) or frequency (percent).