Malignant mesothelioma of the tunica vaginalis testis: A case report

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Abstract. Malignant mesothelioma of the tunica vaginalis testis (MMTVT) is a rare pathological entity. The present report describes the case of a patient who presented with insidious-onset right lower abdominal pain and was diagnosed via histopathological examination following a radical right orchidectomy. After 7 months, the patient developed a palpable mass along the spermatic cord, which prompted a laparoscopic retroperitoneal lymph node dissection combined with an inguinal tumor resection. Adjuvant chemotherapy with pemetrexed and cisplatin was administered thereafter. At 9 months after the initial surgery, a groin mass was surgically excised, with pathology revealing fibroinflammatory changes. The patient remained under close surveillance without evidence of recurrence. Radiation therapy was initiated at 13 months post-surgery but was temporarily discontinued due to adverse effects. Given the current absence of standardized treatment guidelines for MMTVT, radical surgical resection combined with adjuvant radiotherapy or chemotherapy remains the mainstay of therapy, with the inguinal approach being the most commonly employed technique. Given the validated efficacy of immunotherapy in certain rare diseases and pleural mesothelioma, it may represent a promising therapeutic alternative for MMTVT patients whose pathological immunohistochemistry meets eligibility criteria and who have failed standard adjuvant radiotherapy and chemotherapy.

Introduction

Malignant mesothelioma (MM) is a rare neoplasm originating from mesothelial cells that line serosal surfaces, including the pleura, peritoneum, pericardium and tunica vaginalis testis (TVT). MM accounts for <1% of all malignancies (1) and is generally associated with a poor prognosis (2). Although the pleura is the most commonly affected site, MM primarily arising from the TVT is exceedingly rare (3). Both entities share an origin from the embryonic mesoderm (4) and exhibit three main histological subtypes: Epithelioid, sarcomatoid and biphasic (5,6). As a phenotypic variant of MM, MMTVT constitutes <1% of all mesotheliomas (7,8) and represents 0.3-5% of MMs (9). Since its first description in 1957, <300 cases have been reported globally (10), with only 41 cases documented in the Chinese literature based on a search of the China National Knowledge Infrastructure (https://www.cnki.net) and Wanfang (https://www.wanfangdata.com.cn) databases. The epidemiological characteristics and risk factors of MMTVT remain poorly defined. Although asbestos exposure is a well-established risk factor for MM (11), its association with the pathogenesis of MMTVT has not been conclusively established (12). Non-specific clinical presentations, such as hydrocele and scrotal pain (13), along with the lack of specific imaging features on computed tomography (CT) or magnetic resonance imaging (MRI) (14,15), often lead to diagnostic challenges and suboptimal surgical management. Radical surgery remains the cornerstone of treatment (16), yet the efficacy of adjuvant chemotherapy or radiotherapy remains uncertain (13). Consequently, novel targeted agents and immunotherapeutic strategies that have demonstrated efficacy in malignant pleural mesothelioma may offer potential avenues for optimizing the management of MMTVT.

Case report

A 71-year-old man presented to the General Surgery Outpatient Clinic of Suzhou Municipal Hospital Affiliated to Nanjing Medical University (Suzhou, China) in August 2024 with a complaint of recurrent dull pain in the right lower abdomen for half a month. The past medical history was unremarkable. A physical examination revealed mild deep tenderness in the right lower abdomen without rebound tenderness or guarding. Enlarged lymph nodes were palpable bilaterally in the inguinal regions.

An ultrasound scan performed subsequently showed an enlarged right testis with internal linear echoes and bilateral inguinal lymphadenopathy, more prominent on the right side

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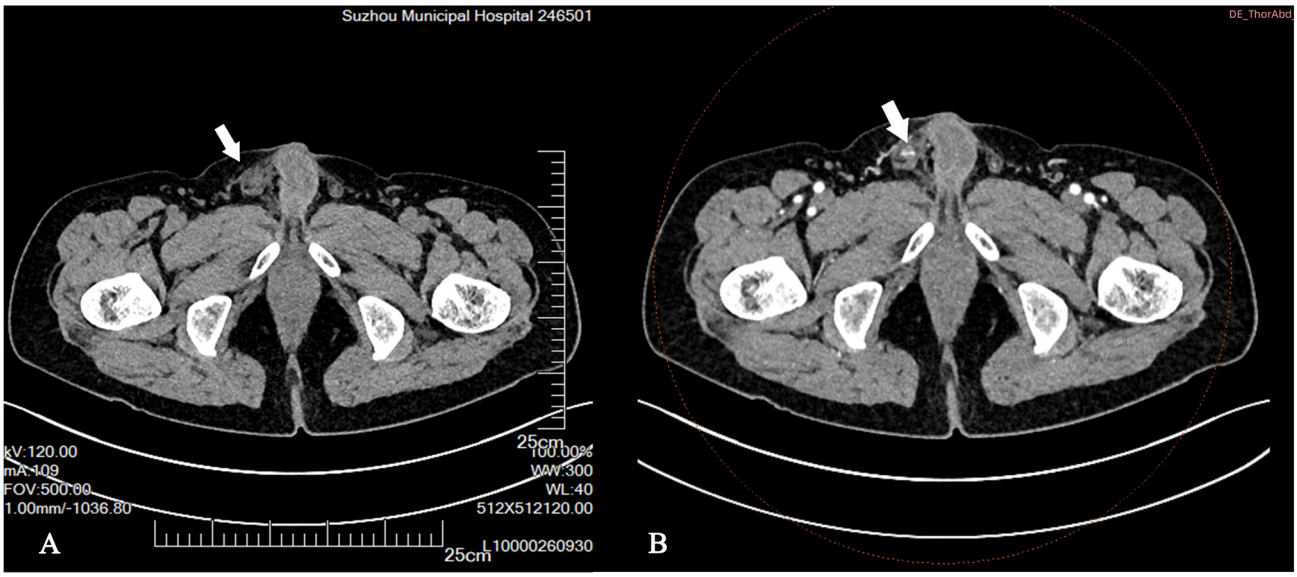

Figure 1. (A) Non-contrast and (B) arterial-phase contrast-enhanced computed tomography demonstrating right testicular enlargement with heterogeneous enhancement and cystic components, accompanied by an enlarged lymph node adjacent to the right external iliac artery.

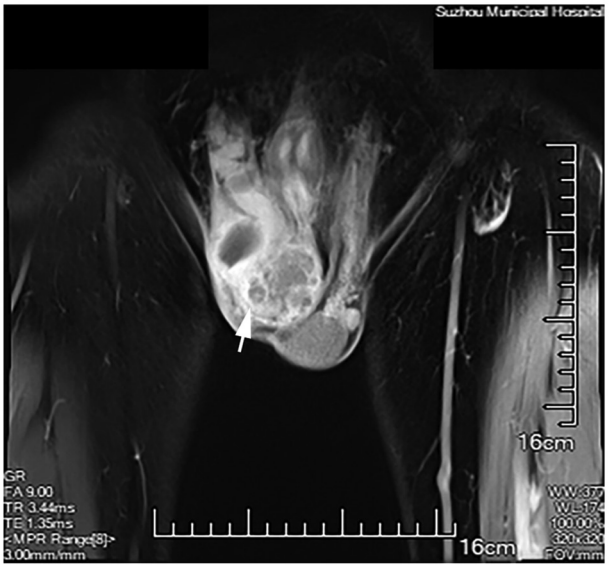

Figure 2. Contrast-enhanced magnetic resonance imaging of the testes demonstrates a right epididymal lesion with associated testicular compression.

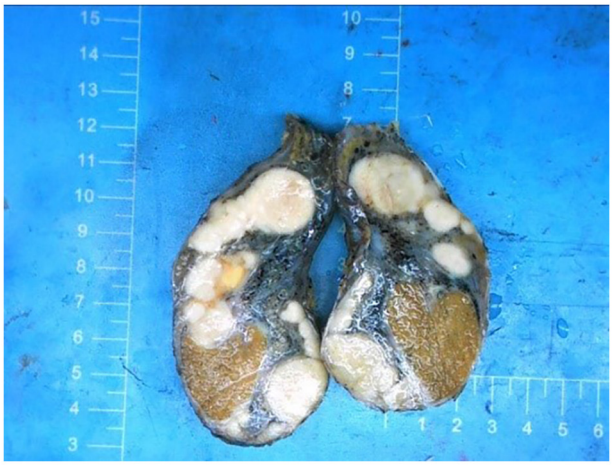

Figure 3. Gross specimen measuring 9.5x6.0x4.7 cm demonstrating multinodular and lobulated architecture with grayish-white solid cut surfaces and a firm consistency.

(Fig. S1). Non-contrast and contrast-enhanced CT scans performed on the same day confirmed an enlarged right testis with heterogeneous enhancement and cystic changes, along with enlarged lymph nodes adjacent to the right external iliac artery (Fig. 1A and B). Enhanced scrotal MRI 3 days later revealed a lesion in the right epididymis causing compression of the testis (Fig. 2).

The patient was subsequently transferred to the Department of Urology of Suzhou Municipal Hospital Affiliated to Nanjing Medical University. A physical examination showed redness and swelling of the right scrotum with a slightly elevated local temperature. The epididymis was enlarged and tender, with poorly defined borders from the testis. No significant abnormalities were noted on the left side. A preliminary diagnosis of right epididymitis was made. A follow-up ultrasound scan indicated thickening of the right scrotal wall, localized fluid collection within the right tunica vaginalis cavity containing heterogeneous internal echoes, and inflammatory changes in the epididymis and surrounding tissues (Fig. S2).

In September 2024, the patient underwent a right epididymo-orchidectomy under general anesthesia. Intraoperatively, significant epididymal enlargement was noted, particularly in the head of the epididymis, with severe adhesions to the testis. As an epididymectomy alone was deemed insufficient for complete resection, a combined epididymo-orchidectomy was performed.

The pathological report described a gross specimen measuring 9.5x6.0x4.7 cm. The cut surface was grayish-white, solid, of medium consistency, and exhibited a multinodular and lobulated appearance (Fig. 3). No tumor involvement was identified at the surgical margins.

All specimens were fixed within 30 min post-resection in 4% neutral buffered formalin at room temperature for 24 h,

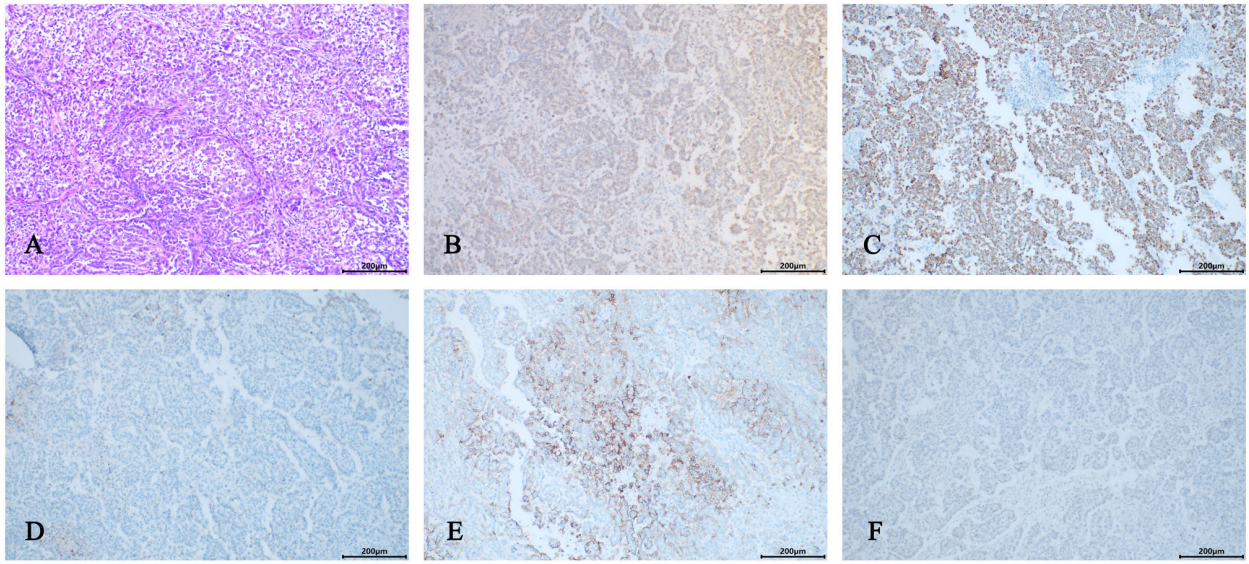

Figure 4. (A) Tumor cells exhibit cuboidal, polygonal or flattened morphology, with abundant cytoplasm that is predominantly eosinophilic but may appear vacuolated. Nuclei show regular contours and often contain visible nucleoli. Multiple morphological variants are present, including tubulopapillary, micropapillary, solid, clear cell, deciduoid, signet-ring cell-like rhabdoid, and pleomorphic patterns (hematoxylin and eosin; magnification, x20). (B) Calretinin immunohistochemical staining of tumor tissue (magnification, x10). (C) Cytokeratin 5/6 immunohistochemical staining of tumor tissue (magnification, x10). (D) Podoplanin immunohistochemical staining of tumor tissue (magnification, x10). (E) Epithelial membrane antigen immunohistochemical staining of tumor tissue (magnification, x10). (F) Wilms' tumor-1 immunohistochemical staining of tumor tissue (magnification, x10).

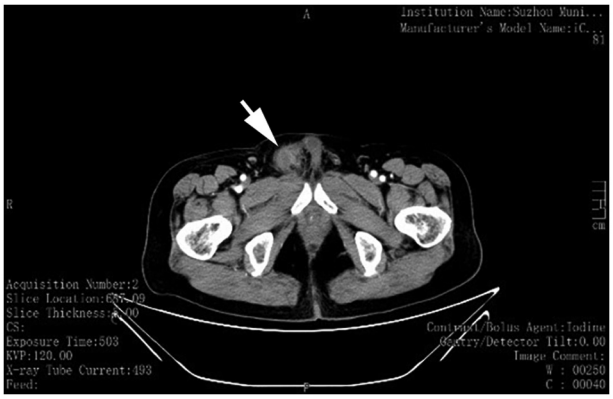

Figure 5. Contrast-enhanced abdominopelvic computed tomography demonstrates postsurgical alterations in the right scrotal region, with a soft-tissue density along the spermatic cord suggestive of recurrence, accompanied by sclerotic iliac bone lesions.

followed by gross examination, routine dehydration, clearing and paraffin embedding. From each paraffin block, 4-μm thick sections were cut using a microtome for hematoxylin and eosin (H&E) staining. After deparaffinization in xylene and rehydration through a graded ethanol series, the sections were stained with hematoxylin at room temperature for 5 min, rinsed in running tap water, differentiated with 1% acid-alcohol, counterstained with eosin at room temperature for 3 min, dehydrated through ethanol, cleared in xylene and finally mounted with a resinous mounting medium. Histological examination was performed under an Olympus BX53 upright light microscope. H&E staining revealed that the tumor was composed of cells with cuboidal, polygonal or flattened morphology (Fig. 4A; scale bar, 200 μm; magnification, x20). The cytoplasm was abundant and predominantly eosinophilic, but occasionally vacuolated. Nuclei were relatively regular, often featuring discernible nucleoli. Various morphological patterns were observed, including tubulopapillary, micropapillary, solid, clear cell, deciduoid, signet-ring cell-like, rhabdoid and pleomorphic variants.

Immunohistochemical staining was performed on 4-μm thick sections of formalin-fixed, paraffin-embedded tissue using a fully automated immunostainer (Roche BenchMark ULTRA PLUS; Roche Diagnostics GmbH). All staining procedures followed the standardized protocols of the instrument. Briefly, after preheating, dewaxing with EZ Prep solution and antigen retrieval (incubation in Cell Conditioner #1 at 95˚C for 8 min), endogenous peroxidase activity was blocked using the instrument-matched inhibitor (UV INHIBITOR). Subsequently, the sections were incubated with specific primary antibodies at 37˚C for 32 min. All primary antibodies were applied at ready-to-use concentrations and included: Calretinin, cytokeratin (CK)5/6, AE1/AE3, vimentin, CK7, p53, Ki-67, β-catenin, epithelial membrane antigen (EMA), podoplanin (D2-40), Wilms' tumor 1 (WT-1), spalt-like transcription factor 4 (SALL4), placental alkaline phosphatase (PLAP), S-100, α-inhibin, carcinoembryonic antigen (CEA), CD30, α-fetoprotein (AFP), CD117, CD99, melanoma markers, P504s (AMACR), GATA binding protein 3 (GATA3), CK20, EpCAM, programmed death-ligand 1 (PD-L1) and VEGF (Table I). Following primary antibody incubation, the sections were sequentially incubated with a horseradish peroxidase (HRP)-labeled polymer secondary antibody (UV HRP UNIV MULT) at 36˚C for 8 min and the chromogenic substrate (UV DAB and UV DAB H_2O_2) at room temperature for 8 min. The reaction product was enhanced with copper ions (UV COPPER) to optimize the signal. Finally, the sections were counterstained with hematoxylin (Hematoxylin II), blued (Bluing Reagent), washed, dehydrated, cleared, and mounted with a synthetic resin. Immunohistochemical results showed positivity for calretinin,

Table I. Markers, catalog numbers, clones and suppliers used in immunohistochemical analysis.

Protein	Catalog number	Clone	Supplier
Calretinin	GT200904	Poly	Gene Tech Co., Ltd.
EMA	GM061302	E29	Gene Tech Co., Ltd.
D2-40	GM361902	D2-40	Gene Tech Co., Ltd.
CK5/6	GM723707	EP24&EP67	Gene Tech Co., Ltd.
WT1	GM356104	6F-H2	Gene Tech Co., Ltd.
AE1/3	GM351502	AE1/3	Gene Tech Co., Ltd.
SALL4	ZM-0393	6E3	Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.
Vimentin	GM072504	V9	Gene Tech Co., Ltd.
PLAP	GM719102	8A9	Gene Tech Co., Ltd.
CK7	GM701807	OV-TL 12/30	Gene Tech Co., Ltd.
S100	GT224902	4C4.9	Gene Tech Co., Ltd.
P53	GM700107	DO-7	Gene Tech Co., Ltd.
α-inhibin	GT230202	EP378	Gene Tech Co., Ltd.
Ki67	GT209407	GM027	Gene Tech Co., Ltd.
CEA	GT210802	COL-1	Gene Tech Co., Ltd.
β-catenin	GT211902	EP35	Gene Tech Co., Ltd.
CD30	GT213902	JCM182	Gene Tech Co., Ltd.
AFP	GA000802	Poly	Gene Tech Co., Ltd.
CD117	ZA-0523	EP10	Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.
CD79	GT212302	EP8	Gene Tech Co., Ltd.
P504S	GT200102	13H4	Gene Tech Co., Ltd.
GATA3	ZA-0661	OTIR4F2	Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.
CK20	GT204202	Ks208	Gene Tech Co., Ltd.
EPCAM	GM080402	MOC-31	Gene Tech Co., Ltd.
PD-L1	GT228004	ZR3	Gene Tech Co., Ltd.
VEGF	GT217004	VG1	Gene Tech Co., Ltd.
GPC-3	GT206802	1G12	Gene Tech Co., Ltd.
Oct3-4	GT207202	C10	Gene Tech Co., Ltd.
SOX-2	ZA-0571	EP103	Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.
AR	GM356202	EP120	Gene Tech Co., Ltd.
P40	GT233807	GR006	Gene Tech Co., Ltd.
Ber-Ep4	ZM-0099	Ber-Ep4	Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.
P16	GT233002	GM501	Gene Tech Co., Ltd.
Syn	GT206504	SP11	Gene Tech Co., Ltd.
CgA	GT211404	GM306	Gene Tech Co., Ltd.
CD56	GT200504	123C3	Gene Tech Co., Ltd.

CK5/6, AE1/AE3, vimentin, CK7, p53 (wild-type pattern), Ki-67 (hotspot 35%) and β-catenin (membranous), partial positivity for EMA, and negativity for D2-40, WT-1, SALL4, PLAP, S-100, α-inhibin, CEA, CD30, AFP, CD117, CD99, melanoma markers, P504s, GATA3, CK20, MOC31, PD-L1 (Fig. S3) and VEGF (Fig. S4) (Figs. 4B-F and S5). Based on morphological features and immunohistochemical results, a diagnosis of MM (epithelioid type) was rendered. The patient received no further treatment postoperatively.

The patient was readmitted in April 2025 due to the presence of a right spermatic cord mass for 5 days, accompanied by localized fever and progressive enlargement over the preceding day. No abdominal pain, nausea, vomiting, hematuria, dysuria, urinary frequency or urgency was reported. Laboratory investigations revealed a mildly elevated cytokeratin fragment CYFRA 21-1 level of 7.53 ng/ml (normal range, <3.3 ng/ml), while other tumor markers, including AFP (1.14 ng/ml; normal range, <20 ng/ml), were within normal limits. An abdominal

and pelvic non-contrast and contrast-enhanced CT scan performed 3 days later showed post-operative changes in the right testicular region and a soft-tissue density within the right spermatic cord, suggestive of recurrence. Additionally, dense opacities were noted in both iliac bones (Fig. 5).

After another 2 days, the patient underwent a laparoscopic right retroperitoneal lymph node dissection combined with a resection of a right inguinal mass under general anesthesia. Intraoperatively, a hard mass ~3 cm in diameter was identified at the distal stump of the right spermatic cord. The proximal spermatic cord was transected near the peritoneum, and the mass was dissected along its margins. Lymphatic dissection commenced over the surface of the right common iliac artery, extending superiorly to the origin of the right renal artery from the abdominal aorta. The lymphatic tissues overlying the sheath of the common iliac vein were opened and dissected towards the inferior vena cava (IVC). A thorough lymphadenectomy was performed in the interaortocaval region and between the right ureter and the IVC, with ligation of the internal spermatic vein. Finally, lymph nodes surrounding the right external iliac vessels were dissected. Pathology results indicated paratesticular mesothelioma at the right spermatic cord stump, with areas of necrotic change. The resection margins were free of tumor involvement. Metastatic tumor was identified in the lymph nodes as follows: Right spermatic cord stump adipose tissue (0/10), obturator (0/9), interaortocaval (1/6), right internal inguinal ring (2/2) and paracaval (1/6). Immunohistochemical analysis of the specimens was performed using the previously described protocol. Details regarding each marker, including clone numbers and suppliers are summarized in Table I. The results demonstrated positivity for AE1/AE3, EMA, calretinin, D2-40, CK7, CK5/6, WT1 (focal) and β-catenin (membranous), along with a Ki-67 proliferation index of 40%. Stains for inhibin-α, CD117, CD30, glypican-3, octamer binding transcription factor 3-4, SALL-4, SOX2, PLAP, androgen receptor, p40, Ber-Ep4, p16, synaptophysin, chromogranin A and CD56 were negative, while desmin showed focal positivity (Fig. S6).

The patient subsequently received six cycles of first-line AP regimen chemotherapy (600 mg/m^2 pemetrexed on day 1 + 30 mg/m^2 cisplatin on days 1-3), administered every 21 days between May and September 2025. Prophylactic administration of varying doses of efbemalenograstim was implemented following each cycle to maintain neutrophil counts, and the patient was discharged after each session without reporting any notable treatment-related discomfort. In June 2025, the patient was re-admitted due to the emergence of an inguinal mass. Surgical excision was performed the following day, during which the mass was noted to be soft in consistency and well-circumscribed. Histopathological examination of the resected specimen revealed fibroconnective tissue with features of microvascular proliferation, inflammatory cell infiltration, fat necrosis and a multinucleated giant cell reaction, consistent with a fibroinflammatory process rather than tumor recurrence. Restaging CT scans performed after the 2nd (Fig. S7) and 4th cycles of chemotherapy demonstrated stable disease, indicating no evidence of progression. A follow-up contrast-enhanced MRI study conducted in October 2025 confirmed the absence of local recurrence or distant metastasis.

The patient commenced adjuvant radiotherapy in October 2025. The target volume encompassed the pelvic regional lymphatic drainage basin plus the right epididymis and spermatic cord region, planned for a total dose of 45 Gy in 25 fractions. However, after receiving 15 fractions (by November 2025), the treatment course was interrupted due to the development of pancytopenia on routine blood testing, accompanied by patient-reported epigastric discomfort and erythema in the right inguinal region. Radiotherapy was consequently suspended, and appropriate supportive care was initiated. The patient has been scheduled for regular follow-up visits every 3 months thereafter. At the most recent assessment, the patient remains well with no complaints of discomfort.

Discussion

Testicular mesothelioma typically occurs in men aged 55 to 75 years (17). The median age at diagnosis is 62 years [interquartile range (IQR), 44-73 years] (13) and incidence increases with age, being 18.6 times higher in men >80 years compared with those <50 years (7). While asbestos exposure is strongly associated with malignant pleural mesothelioma, accounting for up to 80% of cases (2), its role in the pathogenesis of testicular mesothelioma remains unclear (18). In a review of 223 cases, Bisceglia *et al* (12) found that only 30-40% were associated with asbestos exposure. Similarly, the patient in the present report, who worked in wool carpet production, had no history of asbestos exposure.

Patients with testicular mesothelioma have a generally poor prognosis that strongly correlates with the presence of metastasis. Huang *et al* (19) reported a median overall survival (OS) time of 71.5 months for 4 patients without metastasis. By contrast, Grogg *et al* (13) found that among 84 patients with metastatic disease, the median survival time was only 18 months (IQR, 7-43 months), underscoring the critical importance of early detection and treatment. Furthermore, the overall recurrence rate (including both local recurrence and widespread metastasis) is 52.5%, with >60% of recurrences occurring within the first 2 years of follow-up (20).

The majority of patients with testicular mesothelioma are incidentally identified during hydrocelectomy (21). The majority of patients present with a painless testicular mass/swelling or hydrocele (244/259; 94%), followed by scrotal pain (40/259; 15%), which may be accompanied by orchitis or epididymitis (13,22). Due to these non-specific manifestations, most cases are not correctly diagnosed preoperatively (23). Common clinical misdiagnoses include hydrocele, testicular tumors and epididymitis (24). Additionally, routine serum tumor markers (e.g., AFP, β-human chorionic gonadotropin and lactate dehydrogenase) are typically normal. However, positive PD-L1 expression has been reported (19), suggesting a potential role for immunotherapy. By contrast, in the present case, immunohistochemistry of the primary tumor showed negative staining for PD-L1, indicating that immune checkpoint blockade may not be a suitable therapeutic option for this specific patient.

A preoperative diagnosis of MMTVT based on imaging findings is challenging. Ultrasound can be used for the initial screening. In the epithelioid subtype, ultrasonography may reveal a solid lesion in the head of the epididymis and hypoechoic fluid collection within the scrotum, containing fine floating internal echoes (25). The tunica vaginalis appears irregularly thickened, with multiple nodular

protrusions of varying sizes demonstrating high or slightly hyperechoic signals on its wall, corresponding to intra-tunical deposits (26,27). Doppler evaluation may show scant (28) or abundant (23) internal blood flow, which may be associated with the papillary nodules on the parietal layer of the tunica vaginalis seen in pathological specimens. CT offers low specificity for diagnosing this condition (15), but is valuable for assessing metastasis and staging (29). MRI findings are also non-specific (14), typically demonstrating a heterogeneous intratesticular mass that may contain partially calcified tumor tissue (30). On contrast-enhanced scans, the tumor often shows marked heterogeneous enhancement. The presence of a hydrocele with enhancing wall nodules, particularly in a hypervascular lesion, should raise suspicion for MMTVT (31).

Mesothelial tumors are categorized into benign or potentially premalignant lesions and malignant mesotheliomas. The former group includes adenomatoid tumors, well-differentiated papillary mesothelial tumors and mesothelioma *in situ*. MM is further subdivided into three principal subtypes: Epithelioid, sarcomatoid and biphasic (32). In a review of 275 cases of MTVT reported up to January 2019 (13), 227 out of 275 (83%) cases were classified as MM. The histopathological distribution among these malignant cases was as follows: Epithelioid (130/227; 57%), sarcomatoid (4/227; 2%), biphasic (53/227; 23%) and unspecified subtype (40/227; 18%).

The immunohistochemical profile of MMTVT is similar to that of other mesotheliomas (33). Tumor cells typically show positive reactivity for calretinin, EMA, thrombomodulin, CK7, WT-1 and D2-40, while expression of CK5/6 can be variable (34). Given that the morphological features of epithelioid mesothelioma on H&E staining closely resemble those of adenocarcinoma, immunohistochemical studies are essential for the differential diagnosis. Among the various markers, calretinin is considered the most reliable for distinguishing mesothelioma from adenocarcinoma, as it is consistently negative in adenocarcinomas. This marker demonstrates both high sensitivity and specificity for mesothelioma (21). Notably, D2-40 and WT1 constitute pivotal diagnostic markers (35,36), with D2-40 demonstrating superior sensitivity in confirming epithelioid mesothelioma (37). In the present patient, immunohistochemical analysis of the primary tumor specimen showed negativity for both D2-40 and WT-1. It is noteworthy that additional sampling and re-testing from different areas of the same primary specimen consistently yielded negative results for these markers (Figs. S8 and 9). By contrast, the recurrent lesion exhibited a divergent immunoprofile, with positive staining for D2-40 and focal positivity for WT1. This discrepancy, wherein the primary tumor cells lacked expression of D2-40 and WT-1 while the recurrence acquired it, may be attributable to one or a combination of the following factors: i) Intratumoral heterogeneity in the expression of D2-40 and WT-1 within this malignant mesothelioma; ii) selective survival and proliferation of residual tumor cells post-surgery that were double-positive for D2-40 and WT-1; iii) phenotypic transformation of tumor cells during the recurrence process; or iv) technical artifacts such as sampling variation or other unforeseen factors. This phenomenon finds support in the literature, as Wang and Liu (38) similarly reported a case of epithelioid testicular MM that was D2-40 negative, and Yang *et al* (39) documented a patient with epithelioid testicular MM exhibiting WT-1 negativity.

In MMTVT, electron microscopic examination reveals that tumor cells are interconnected by desmosomes and junctional complexes, forming luminal spaces lined by long, slender microvilli with a characteristic length-to-diameter ratio typically >10 (9). Yuan *et al* (40) observed similar ultrastructural features in MMTVT tumor cells and noted abundant cytoplasmic intermediate filaments, including tonofilaments, along with a moderate amount of glycogen within the cytoplasm. The presence of these electron microscopic features serves as a definitive diagnostic criterion, playing a pivotal role in the pathological distinction of MMTVT from histological mimics, such as adenocarcinoma.

For patients with MMTVT, the most common surgical indications are a rapidly enlarging hydrocele or suspicion of testicular tumor (20). For localized MMTVT, radical inguinal orchidectomy is the treatment of choice, while inguinal lymph node dissection is warranted when signs of lymph node metastasis are present (41). For advanced or recurrent disease, radical resection combined with adjuvant chemotherapy and/or radiotherapy is recommended (23). Primary radical inguinal orchidectomy with partial scrotal resection and retroperitoneal lymph node dissection has also been proposed (13,23). It is noteworthy that the inguinal approach is preferred as it allows early control of the testicular vascular and lymphatic supply, effectively reducing the risk of tumor dissemination via the blood and lymphatics during surgery, thereby potentially lowering the local recurrence rate (42). Furthermore, cisplatin and doxorubicin have been suggested for chemotherapy (43). In a previous study focusing on MMTVT patients who underwent lymph node dissection, of the 9 patients who received adjuvant chemotherapy or chemoradiotherapy, 5 (56%) developed local and/or metastatic recurrence. Similarly, among 11 patients who underwent radiotherapy targeting the scrotum, as well as the retroperitoneal and inguinal lymph nodes (maximum dose 55-60.5 Gy), 6 (55%) experienced recurrence, suggesting that the efficacy achieved with radiotherapy may be comparable to that of chemotherapy (13).

Since 2004, platinum-pemetrexed chemotherapy has remained the first-line standard for unresectable mesothelioma, without approved second- or third-line regimens (44). Bevacizumab targeting vascular endothelial growth factor combined with cisplatin-pemetrexed demonstrated significant median overall survival time improvements in the phase III MAPS trial for malignant pleural mesothelioma when compared with platinum-pemetrexed alone (45). Leveraging a shared molecular pathogenesis, pleural mesothelioma therapies may offer clinical utility for MMTVT. A phase II trial evaluating amatuximab (anti-mesothelin monoclonal antibody) with cisplatin-pemetrexed in unresectable malignant pleural mesothelioma achieved a median OS time of 14.8 months, surpassing historical controls (13.3 months) (46). The phase III CONFIRM trial established the superiority of nivolumab over a placebo in patients with recurrent mesothelioma, demonstrating improved progression-free survival (median PFS, 3.0 vs. 1.8 months; HR, 0.67; P=0.0012) and OS (median, 10.2 vs. 6.9 months; HR, 0.69; P=0.0090) times (47). Furthermore, the CheckMate 743 trial demonstrated that nivolumab plus ipilimumab, compared with platinum-pemetrexed chemotherapy, significantly prolonged overall survival time (median OS time, 18.1 vs. 14.1 months) and resulted in a higher 2-year OS rate (41 vs. 27%), subsequently leading to approvals by the US Food and Drug Administration and the European Medicines Agency (48). Mishra *et al* (49) reported

a case of metastatic testicular mesothelioma in which the patient underwent a left orchiectomy followed by immunotherapy with ipilimumab and nivolumab. After 6 months of treatment, the patient exhibited a partial response, with reduction in size of known pleural nodules and effusion. In the present case, however, immunohistochemistry of the primary tumor showed negative staining for both PD-L1 and VEGF, suggesting a potentially lower likelihood of clinical benefit from corresponding targeted antibodies. Notably, in rare tumors, clinical trials have reported efficacy of immunotherapy in certain subtypes, including biliary tract cancer, neuroendocrine tumors, carcinoma of unknown primary and pancreatic acinar carcinoma (50-54). Collectively, these findings indicate that immunotherapy holds promise in the treatment of malignant testicular mesothelioma.

The present report shares the inherent limitations common to single-case descriptions: i) The small sample size precludes statistical analysis and limits the ability to draw definitive conclusions regarding treatment efficacy or prognostic factors. ii) The surgical, chemotherapeutic and radiotherapy regimens were tailored to this specific patient and may not represent an optimized or standardized strategy. iii) The follow-up period in this case is relatively short, and long-term outcomes remain to be observed. Furthermore, this study has the following additional shortcomings: i) The proposed treatment suggestions lack supporting mechanistic data, comparative genomic evidence or specific treatment response information from this patient. ii) There is an absence of further ultrastructural studies. iii) The study lacks key ancillary tests that are now crucial in mesothelioma diagnosis, such as BAP1 immunohistochemistry (55), assessment of methylthioadenosine phosphorylase deletion (56), cyclin dependent kinase inhibitor 2A fluorescence *in situ* hybridization (57) or next-generation sequencing (58). This, to some extent, limits the referential value of this case within the modern diagnostic and classificatory framework for mesothelioma. Future studies could address these limitations as potential research directions.

In conclusion, MMTVT is an extremely rare and highly aggressive neoplasm characterized by non-specific clinical presentations, with a definitive diagnosis relying on a pathological examination. In suspected cases, a comprehensive imaging evaluation is essential for the differential diagnosis and the detection of metastasis. The disease is prone to local invasion and distant spread, and patients generally have a short overall survival time. Therefore, an early diagnosis and radical surgery via an inguinal approach are critical. When lymph node metastasis is identified, lymph node dissection should be performed, and postoperative adjuvant chemotherapy or radiotherapy should be considered to improve outcomes. Meanwhile, novel targeted therapeutic strategies may hold potential benefit. Furthermore, long-term and regular follow-up surveillance is necessary for these patients.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YCL designed the study, drafted the initial manuscript, collated research data, created original figures and flowcharts, and revised key academic content. JJM assisted in editing the manuscript and contributed to the examination and analysis of pathology slides. ZRF and LH were responsible for the selection, critical evaluation and analytical annotation of clinical imaging data. ZZ played a key role in the examination and analysis of pathology slides. JPD and JJX provided administrative support and contributed to the study design. YCQ, XHS, and JQH analyzed patient data and assisted in editing the discussion section. JJX performed the surgical procedure on the patient. YCL, JJM, ZRF, ZZ, LH, JPD, XHS, JQH, YCQ and JJX confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent for publication was obtained directly from the patient.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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