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Case Report

Paratesticular Rhabdomyosarcoma: Diagnostic and Therapeutic Advances Through a Case Report

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Abstract

Paratesticular rhabdomyosarcoma (PRMS), a rare and aggressive urogenital tumor, presents significant challenges. The embryonal subtype is the most frequently encountered. Treatment often requires a multimodality approach, combining surgery, chemotherapy, and radiation therapy, to improve patient outcomes. The treatment regimen is based on following principles: local control of the primary site with radical orchiectomy and assessment of local control and distant sites. Further treatment is directed according to disease stage, histology, and age of the patient. The goal of treatment is to achieve cure or maximum tumor control while minimizing toxicity. We report an observation of a paratesticular rhabdomyosarcoma in a 16-year-old patient. We discuss diagnostic and therapeutic modalities based on data from the literature. With the changing landscape in the management of paratesticular rhabomyosarcoma, significant improvement is evident in the oncologic outcomes. With advancements in the management of PRMS, significant improvements in oncologic outcomes have been observed. Further progress in genomic testing will enable the personalization of treatment regimens based on individual patient risk factors, ultimately minimizing long-term side effects.

Keywords: rhabdomyosarcoma; Paratesticular; embryonal variant; chemotherapy, surgery

Introduction

Paratesticular rhabdomyosarcoma (RMS) is a rare and aggressive malignant mesenchymal tumor originating from connective tissues [1]. The urogenital tract is the most common site of involvement. Paratesticular localization accounts for approximately 7% to 10% of all RMS cases [1-3]. The disease typically presents in two age peaks: early childhood (2-5 years) and adolescence [4]. The embryonal variant is the most common histological subtype and carries a poor prognosis [2,5]. Clinical presentation is nonspecific, Scrotal ultrasonography is the initial imaging modality of choice, which reveals a solid heterogeneous extratesticular mass, and the diagnosis is confirmed by histopathological examination of the orchiectomy specimen [4-6]. Traditionally, radiotherapy or surgery has been used to treat RMS. Chemotherapy's introduction in the 1950s significantly improved overall survival and illness control. Management is multidisciplinary, combining surgery, chemotherapy, and radiotherapy, with treatment plans tailored to the clinical stage and prognostic group [5].We report a case of embryonal paratesticular rhabdomyosarcoma (P-RMS) in a young patient and discuss the clinical and therapeutic aspects of this disease in our context, supported by a literature review.

Case Presentation

A 16-year-old boy with no significant medical history presented with a one-month history of right scrotal enlargement. Physical examination revealed a firm, painless, and enlarged right testis without associated signs of inflammation. Initial scrotal ultrasound demonstrated multiple solid masses infiltrating the tunica vaginalis.

Tumor markers, including alpha-fetoprotein, lactate dehydrogenase (LDH), and human chorionic gonadotropin (hCG), were within normal limits. An inguinal orchiectomy with high ligation of the spermatic cord was performed. Histopathological examination with immunohistochemistry revealed an embryonal rhabdomyosarcoma with spindle cells infiltrating the epididymis and base of the cord, with positive staining for actin, desmin, and myogenin (Figure 01).

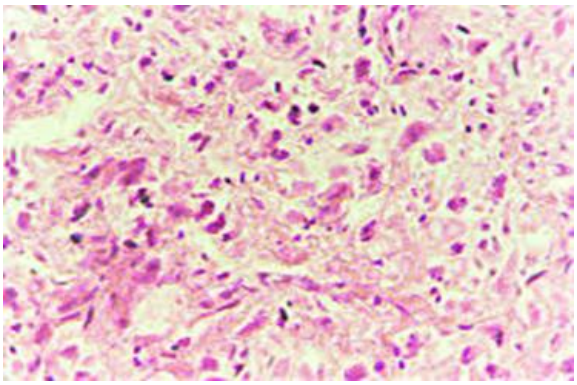

Figure 1: Histopathological aspect of the tumor process on hématoxyline-éosine stain (Cellular proliferation composed of round, oval, or sometimes elongated cells with eosinophilic cytoplasm and irregular hyperchromatic nuclei reminiscent of rhabdomyoblasts, suggesting a rhabdomyosarcoma. Photo credit: Dr Sarah ZEROUAL).

A computed tomography (CT) scan of the chest, abdomen, and pelvis, performed for staging, revealed bilateral pulmonary nodules, as well as intra-abdominal and inguinal lymph node involvement. The tumor was staged as IV according to the Intergroup Rhabdomyosarcoma Study (IRS) classification.

The patient was initiated on a multi-agent chemotherapy regimen (IVA protocol) consisting of ifosfamide, vincristine, and actinomycin D. A follow-up CT scan after the third cycle of chemotherapy demonstrated a partial response of the pulmonary and nodal lesions. However, a subsequent CT scan after three additional cycles showed progressive disease with an increase in the size and number of pulmonary nodules, along with the development of cough and dyspnea. A salvage chemotherapy regimen with cyclophosphamide and etoposide was initiated. Unfortunately, the patient developed Fournier's gangrene and succumbed during emergency surgery.

Discussion

Paratesticular rhabdomyosarcoma (PT-RMS) represents 7-10% of all RMS tumors arising in the genitourinary tract, making it the third most common site after the prostate and bladder. The disease exhibits a bimodal age distribution, with peaks occurring in early childhood (1-5 years) and adolescence (16 years) [1-6].The most frequent presenting symptom of PT-RMS is a scrotal mass, accounting for 85% of cases, consistent with the typical presentation described in the literature [7-8]. Other less common presenting symptoms include trauma or bruising (8%) and hydrocele or hernia (6%). Physical examination often reveals a palpable mass, although a hydrocele may mask the underlying testicular tumor in 15-20% of cases. Differential diagnoses to consider include testicular torsion, hydrocele, epididymo-orchitis, inguinal hernia, and mumps orchitis. However, the paratesticular nature of these tumors can be challenging to determine on physical examination alone. The rapid, often painless growth of PT-RMS contributes to early local invasion and a high risk of distant metastasis [9]. Metastatic spread most commonly involves the retroperitoneal lymph nodes, lungs, liver, and bones [9]. Unfortunately, there are no specific tumor markers to aid in the diagnosis of PT-RMS. The definitive diagnosis relies on the histopathological examination of the tissue obtained from an inguinal orchiectomy [10].

Histologically, three types of rhabdomyosarcoma exist: embryonal, the most common (97% of cases) with a poor prognosis due to frequent nodal involvement at diagnosis, as seen in our patient who presented with pulmonary and nodal metastases at initial evaluation; alveolar, and pleomorphic [11-15].

•**Embryonal RMS:** The most common subtype, accounting for approximately 80% of cases. It is characterized by its expression of skeletal muscle markers and is thought to arise from muscle progenitor cells or through trans-differentiation of mesenchymal tissue (Figure 2).

•**Alveolar RMS:** Associated with a worse prognosis, especially those with PAX7 or PAX3 gene fusions. However, a significant proportion of alveolar RMS cases lack these fusions.

•**Spindle Cell and Sclerosing RMS:** Rare subtypes with overlapping histological features.

Histological examination remains the gold standard for diagnosis and classification. While gene fusions, particularly PAX7/FOXO1 and PAX3/FOXO1, have been used for risk stratification, their prognostic significance is still being investigated. The International Classification of Rhabdomyosarcoma (ICR) has refined the classification system, leading to a more accurate assessment of tumor behavior and prognosis [15-16].

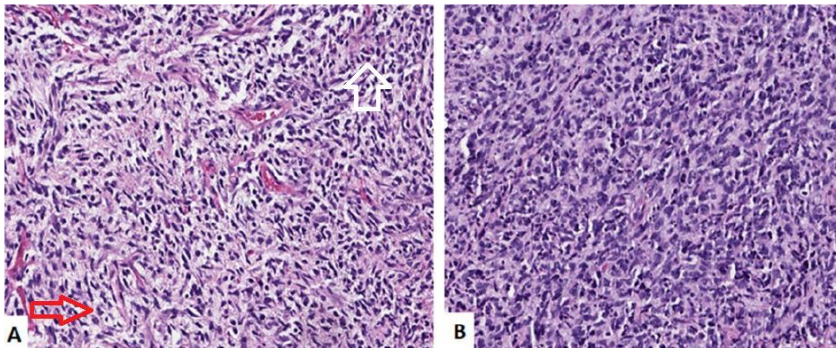

Figure 2: Histopathological appearance of Embryonal Rhabdomyosarcoma [15].

A. Low power image showing cellular neoplasm with hyper (white arrow) and hypocellular (red arrow) areas. (H&E, 200x) B. High power image showing primitive spindle cells with scattered rhabdomyoblasts. (H&E, 400x).

Discovery of a scrotal mass will be complemented by a systematic testicular ultrasound. It shows a mass with a heterogeneous echotexture, with inguinoscrotal extension in 80% of cases [17]. Echo-Doppler reveals a hypervascular appearance of the tumor mass and specifies its extratesticular location [17]. Conventional CT scan has been used for evaluation of the retroperitoneum and current recommendations are that all patient sunder go thin cut(5mm for age<10 years, 7mm for age > 10 years) abdominal or pelvic CT with double contrast to identify regional retroperitoneal lymph node in volvement for staging purposes [18-19].The locoregional extension assessment can be completed by an MRI. MRI is a high-performance imaging modality, using surface coils; the tumor appears homogeneous on T1-weighted images and heterogeneous on T2-weighted images with a signal intensity similar to the normal testis. Due to the hypointensity of the tunica albuginea on T2-weighted images, the mass is clearly separated from the testis [16-17]. For the assessment of distant metastases, a thoraco-abdominopelvic computed tomography (CT) scan allows the detection of deep lymph node involvement, especially the lumbaraortic and pelvic nodes, as well as hepatic and pulmonary metastases. The assessment of distant metastases also includes a bone scan [9,18].

18F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/CT has been studied as a more sensitive tool in staging and restaging of patients with RMS. Tateishi and colleagues compared the sensitivity of FDG PET/CT to that from conventional imaging (CI) (whole body CT, bone scan, and MRI) of the primary site. They demonstrated that using PET/CT, M stage was correctly assigned in 89% of patients compared with 63% when CI was used. There was also improved accuracy with nodal metastases being identified in 86% of patients undergoing PET/CT compared with 54% undergoing CI [20].The classification of RMS malignancies is unique and can be confusing due to the 2 different prognostic systems used by the IRSG during their clinical trials. Risk stratification relies on both a pretreatment (Tumor-node-metastasis [TNM]) staging system and a surgical or pathologic clinical grouping system based on the extent of disease following initial surgery [18]. Therefore, during IRS-I/II, patients were separated into prognostic categories, referred to as "groups," based on the extent of disease remaining after primary surgical intervention. (Table 1).

I	**Localized disease, completely resected**	
	A	Confined to the organ or muscle or origin
	B	Infiltration outside organ or muscle or origin; regional nodes not involved
II	**Total gross resection with evidence of regional spread**	
	A	Grossly resected tumors with "microscopic" residual tumor
	B	Regional disease completely resected with regional nodes involved, tumor extension into adjacent organs, or both.
III	**Incomplete resection or biopsy with gross residual disease remaining**	
	A	Localized or locally extensive tumor, gross residual disease after biopsy only
	B	Localized or locally extensive tumor, gross residual disease after "major' resection (>50% debulking)
IV	**Any size primary tumor, with or without regional lymph node involvement, with distant metastases irrespective of surgical approach to the primary tumor**	

Table 1: TNM Pretreatment Staging System (IRSG) [18]

With the advent of multimodal therapy, a pretreatment TNM staging system was introduced for IRS-III. This system considers tumor size, invasiveness, nodal status, and distant metastases. Additionally, tumor location (favorable or unfavorable) was identified as a significant prognostic factor (Table 2).The IRS-IV study combined stage, group, and histological subtype to classify patients into low, intermediate, and high-risk categories, guiding treatment decisions (Table 3). PT-RMS can be either stage I or IV given its location as a favorable primary site. Risk stratification was introduced during IRS-V, in which the study combined stage, group, and histological subtype to place patients into different therapeutic protocols according to risk of recurrence (Table 4).

Classification	**Description**
Tumor	
T1	Confined to anatomical site of origin
a	<5 cm in diameter
b	≥5 cm in diameter
T2	Extension or fixation to surrounding tissue
a	<5 cm in diameter
b	≥5 cm in diameter
Regional lymph nodes	
N0	Regional lymph nodes not clinically involved
N1	Regional lymph nodes clinically involved by neoplasm
Nx	Clinical status of regional lymph nodes unknown (especially with sites that preclude lymph node evaluation)
Metastasis	
M0	No distant metastasis
M1	Metastasis present

Table 2: Clinical grouping for patients with rhabdomyosarcoma [18]

Stage	Sites	T	Tumors Size	N	M
Favorable					
I	Orbit	T1 or T2	a or b	N0 or N1 or N2	M0
	Head and neck (excluding parameningeal)				
	GU-non bladder or non-prostate				
II	Bladder or prostate	T1 or T2	b	N0 or Nx	M0
	Extremity				
	Head and neck parameningeal				
	Other (including trunk, retroperitoneum, etc.)				
Unfavorable					
III	Bladder or prostate	T1 or T2	a b	N1 N0 or N1 or Nx	M0
	Extremity				
	Head and neck parameningeal				
	Other (including trunk, retroperitoneum, etc.)				
Metastasis					
IV	All	T1 or T2	a or b	N0 or N1	M1

Table 3: Soft Tissue Sarcoma Committee of the Children's Oncology Group: pretreatment staging system

Risk group	Histology	Stage	Group
Low risk	Embryonal	1	I, II, III
	Embryonal	2, 3	I, II
	Embryonal	2, 3	III
Intermediate risk	Alveolar	1, 2, 3	I, II, III
High risk	Embryonal or alveolar	4	IV

Table 4: Soft Tissue Sarcoma Committee of the Children's Oncology Group: rhabdomyosarcoma risk group classification [18]

Multimodal treatment with systemic chemotherapy in conjunction with either surgery, RT, or both is used to maximize tumor control. Before using effective chemo- therapy agents, surgical intervention alone produced approximately a 50% 2-year relapse-free survival [19,21].

Treatment guidelines for the surgical management of PT-RMS, including primary inguinal orchidectomy, pretreatment re-excision (PRE), management of large tumors, trans-scrotal excision, scrotal violation, hemi-scrotectomy (HS), testicular transposition and retroperitoneal lymph node assessment and management [22].

Use of retroperitoneal lymph node dissection (RPLND) of RPLND in PT-RMS is controversial and has evolved over the past 20 years. Approximately 25% of patients with PT-RMS are found to have retroperitoneal lymph node disease at presentation [18]. Historically, RPLND was recommended for all patients with localized renal tumors, but recent studies have shown that this approach may lead to overtreatment in certain cases.

Adolescent male patients and those with primary tumors exceeding 7 cm are at heightened risk of retroperitoneal lymph node (RPLN) metastasis [19]. Current treatment guidelines advocate for RPLND in all adolescent boys and younger boys with suspicious lymph nodes on CT scans [22-24]. Additionally, RPLND is indicated for patients with confirmed RPLN metastasis, except in cases of excessively large lymph nodes. For low-risk patients with concerning imaging findings, PET/CT scans can aid in identifying true metastatic disease, thereby preventing unnecessary surgery [25]. While RPLND is a valuable tool, it carries potential risks, including bowel obstruction, retrograde ejaculation, and lymphedema. Therefore, treatment decisions should be tailored to individual patient characteristics, imaging findings, and risk assessment. Ongoing research endeavors to refine treatment strategies to optimize outcomes while minimizing adverse effects [25-28].

The primary objectives of chemotherapy in this context are to enhance overall survival and diminish the likelihood of disease recurrence. Multiple chemotherapy regimens have been investigated, including VAC, IVA, and VIE (consisting of vincristine, actinomycin D, etoposide or ifosfamide, and cyclophosphamide) [29]. Among these, the VAC regimen is the most widely adopted. In cases of tumor resistance or progression, additional agents such as doxorubicin, cisplatin, and bleomycin may be incorporated into the treatment plan [30].

Treatment with alkylating agents like cyclophosphamide and ifosfamide has been shown to affect fertility by depletion of the germinal epithelium. It has been shown that depletion of the germ cell epithelium is dose dependent [31]. Complete surgical resection as primary or salvage treatment is not always feasible and radiation therapy (RT) has assumed a major role in the management of RMS [18]. In contrast with other primary sites, up to 82% of PT-RMS are diagnosed in a localized stage and able to be completely resected [14,32].

RT has been primarily used as a salvage treatment for nodal extension or in cases of incomplete surgical resection [32]. Its role in treating locally advanced or nodal disease remains controversial. While the Children's Oncology Group (COG) recommends RT for patients with group II-III disease, the Société Internationale d'Oncologie Pédiatrique (SIOP) reserves RT for patients with poor response to systemic therapy or incomplete resection [33-34]. Both groups, however, have achieved similar 5-year overall survival (OS) and failure-free survival (FFS) rates. This suggests that the necessity of RT following RPLND in patients with pathologically confirmed nodal disease may be questionable [35].

For patients with advanced stage disease in the retroperitoneum, the extent of RT depends on the completeness of post-chemotherapy RPLND. Patients with complete resection receive a lower dose of RT (41.4 Gy) compared to those with incomplete resection (50.4 Gy) [36].

While RT has shown benefit in improving FFS for patients with alveolar histology, it does not appear to provide additional benefit for patients with embryonal variants or other poor prognostic factors [18].

While the introduction of radiation therapy (RT) in treating pediatric rhabdomyosarcoma (RMS) has significantly improved survival rates, it's not without substantial side effects. Hughes et al. conducted a retrospective review of long-term side effects in 18 patients who received multimodal therapy, including systemic chemotherapy, RT, and retroperitoneal lymph node dissection (RPLND), for group II and III RMS. The 5-year failure-free survival (FFS) and overall survival (OS) for this cohort were 80% and 87%, respectively. Among the 18 patients, two succumbed to complications arising from RT: one due to severe intestinal adhesion disease, and the other due to recurrent pericardial effusions and subsequent congestive heart failure following chest RT. One patient developed biliary stenosis necessitating choledochojejunostomy, and two experienced hypogonadism and infertility. Furthermore, all patients who received RT exhibited height deficits compared to untreated patients. [36].

Despite these challenges, advancements in RT techniques, such as intensity-modulated radiation therapy (IMRT) and proton beam therapy, offer promise in reducing toxicity while maintaining therapeutic efficacy. These technologies allow for precise dose delivery to the tumor while minimizing exposure to surrounding healthy tissues.

Conclusion

Paratesticular rhabdomyosarcoma, while a rare malignancy, presents as an urgent diagnostic and therapeutic challenge, particularly in children and young adults. Early diagnosis, accurate staging, and a standardized treatment regimen involving surgery, multi-agent chemotherapy, and radiotherapy have significantly improved outcomes. Long-term follow-up is essential to detect potential recurrences. The introduction of multi-agent chemotherapy has dramatically transformed the prognosis for patients with paratesticular rhabdomyosarcoma, with 3-year overall survival rates reaching 95%. Ongoing advancements in genomic testing and imaging technologies offer promising opportunities to further personalize treatment strategies, optimizing both cancer control and minimizing long-term side effects.

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