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Primary intratesticular rhabdomyosarcoma: A case report and literature review

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Abstract. Rhabdomyosarcoma (RMS) that primarily occurs in the testes is particularly rare, with only retrospective studies and sporadic cases reported in the literature. The present study describes the case of a large, primary intratesticular RMS (ITRMS) that was treated with a radical inguinal orchiectomy (RIO) and a regimen of chemotherapy. The study also presents a review of the literature regarding primary ITRMSs, aiming to elucidate the clinical characteristics and optimal treatment of the disease. A 14-year-old male presented with a 1-year history of a slow-growing, painless, left scrotal mass. Magnetic resonance imaging identified a mass in the left scrotum with mixed signal intensity; no abnormal signals were identified in the right testicle and retroperitoneal lymph node. An X-ray of the chest demonstrated no evidence of metastasis. Subsequent to this, a left RIO was performed. Histopathological and immunohistochemical examination confirmed the final diagnosis of embryonal ITRMS. At 21 days post-surgery, an ^{18}F-fluorodeoxyglucose-positron emission tomography-computed tomography (FDG-PET-CT) scan identified widespread metastatic lesions in the lungs, local lymph nodes and bones, presenting as increased glucose metabolism nodules. Subsequently, the patient received six sequential cycles of adjunct chemotherapy. The patient is alive with disease in October 2015. The case described is noteworthy as it is an example of ITRMS, in which the patient received successful treatment. However, multidisciplinary treatment may further improve the outcome of the disease.

Introduction

Rhabdomyosarcoma (RMS), originating from the mesenchymal cells, is the most common soft-tissue sarcoma in children and adolescents, with an annual incidence of 4-7 cases per million children aged ≤15 years (1). Intratesticular sarcoma only accounts for 1% of testicular tumors and the majority are germ cell tumors. Intratesticular RMS (ITRMS), a rare sarcoma of the testes, develops rapidly and primarily presents as a painless scrotal mass for <6 months before diagnosis. A radical inguinal orchiectomy (RIO), followed by adjuvant chemotherapy, is currently the recommended treatment for ITRMS. The occurrence of distant metastasis is the main cause for unsuccessful treatment. The present study describes a large primary ITRMS, measuring 17x11x11 cm, presenting in an adolescent. Widespread metastasis of the mass was detected by ^{18}F-fluorodeoxyglucose-positron emission tomography-computed tomography (FDG-PET-CT) 3 weeks after the RIO. According to our limited knowledge, the use of FDG-PET-CT has been reported only once previously to determine a clinical stage and evaluate the treatment efficacy of ITRMS (2). The ITRMS described in the present case underwent distant metastasis within a shorter time period than those cases reported in the literature (2-12). In order to improve our understanding regarding the clinic characteristics of ITRMS, the current study presents a notable case and reviews the available literature of primary ITRMS from the 1960s onwards (2-12). The patient provided full written informed consent.

Case report

A 14-year-old male was referred to the Department of Urology at a Chenzhou No. 1 People's Hospital (Chenzhou, China) in January 2014, presenting with a 1-year history of a slow-growing, painless, left scrotal mass, which had rapidly become swollen and painful following incidental trauma to the scrotum. Initially, an incision in the scrotum was performed for drainage. Magnetic resonance imaging, performed 3 weeks later, detected a mass in the left scrotum demonstrating mixed signal intensity; no abnormal signal was identified in the right testicle or retroperitoneal lymph node (RPLN) (Fig. 1). Several tumor marker levels, including those of serum α-fetoprotein (AFP), β-human chorionic gonadotropin (β-HCG) and lactate dehydrogenase (LDH), were all within the normal ranges. An X-ray of the chest demonstrated no evidence of metastasis. Subsequently, a left RIO was performed, with the left testis demonstrating a 17x11x11-cm, whitish malignant tumor, exhibiting necrosis and liquidation. Histologically, viable tumor cells, primarily round and spindle cells, were identified to contain eccentric nuclei

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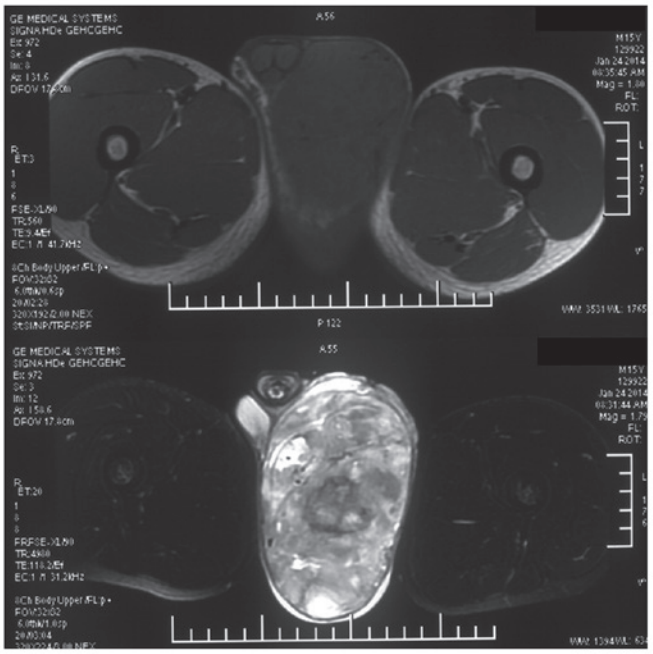

Figure 1. Magnetic resonance imaging scan demonstrating a left scrotal mass with a mixed signal, consisting of isointensity on T1-weighted images and high signal on T2-weighted images, with no abnormal signal identified in the right testicle and epididymis.

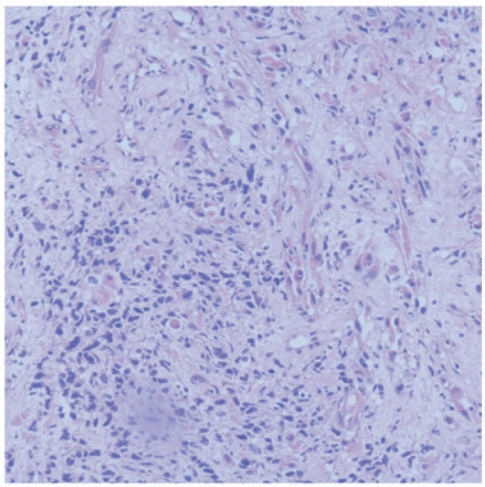

Figure 2. Histological section in which viable tumor cells, primarily round and spindle cells, were identified to contain eccentric nuclei and deeply eosinophilic cytoplasm. Hematoxylin and eosin staining; magnification, x100.

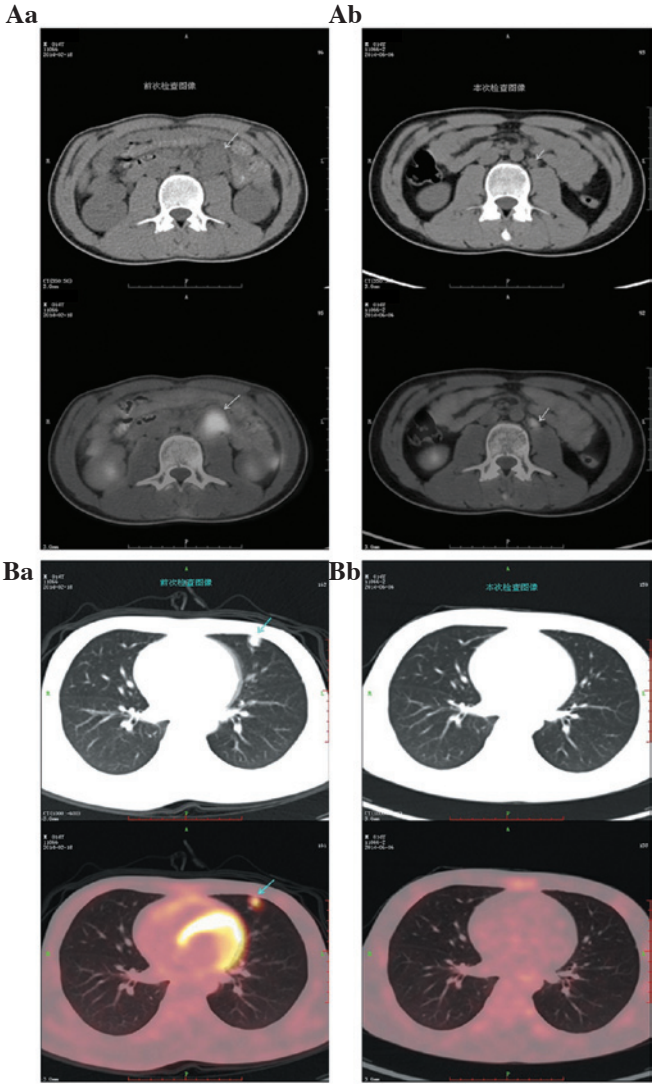

Figure 3. Positron emission tomography/computed tomography scans demonstrating complete remission of the pulmonary lesion and partial remission of the retroperitoneal lesion in response to chemotherapy. (Aa) Arrows indicate retroperitoneal lymphodonus metastasis in pre-chemotherapy. (Ab) Arrows indicate retroperitoneal lymphodonus metastasis in post-chemotherapy. (Ba) Arrows indicate the pulmomary lesion in pre-chemotherapy. (Bb) Post-chemotherapy in the pulmonary lesion.

and deeply eosinophilic cytoplasm (Fig. 2). The left epididymis was involved macroscopically and microscopically. However, the margin of excision was free from tumor cells. Immunohistochemically, the viable tumor cells stained positively for vimentin, desmin, smooth muscle actin, myogenin, cluster of differentiation (CD)99, CD34 (focally), Ki-67 (70%) and myogenic differentiation 1, with no staining for octamer-binding transcription factor 4 and placental alkaline phosphatase. Finally, the diagnosis of embryonal ITRMS was confirmed. A total of 21 days after surgery, FDG-PET-CT scanning identified widespread metastatic lesions in the lungs, local lymph nodes and bones, presenting as increased glucose metabolism nodules. The effected bones included the 5th thoracic vertebrae, 7th thoracic vertebrae and left caput femoris; The affected lymph nodes located in the left groin, peri-Iliaca vessels and peri-aorta region. The case was therefore classified as stage IV, group IV, with an intermediate risk, according to the Intergroup Rhabdomyosarcoma Study Group (IRSG) staging and grouping system (9). The patient was administered six sequential 3-week cycles of adjunct chemotherapy (2,000 mg ifosfamide and 40 mg cisplatin on day 1-3, and 120 mg epirubicin on day 1, every 3 weeks). Complete remission (CR) was achieved in the pulmonary lesions, and partial remission (PR) in the bone and lymph node lesions, as evaluated by FDG-PET-CT (Fig. 3).

The patient finished treatment in September 2014 after the sixth cycle of chemotherapy and an evaluation of FDG-PET-CT in May 2015 demonstrated progressive disease in the bones and local lymphnodes and new metastases in the anterior mediastinum and left abdominal cavity. The patient was alive at the latest follow-up in October 2015.

Table I. Characteristics of patients with intratesticular RMS.

First author/s, year (ref.)	Age, years	MH, months	SPT, cm	HT	Location	Surgery	IRSG	Chemotherapy and response	Outcome, last follow-up in months
Liu *et al*, 2011 (2)	23	NS	10	eRMS	RPLN	RIO + FNAB	III	CR	Alive with pelvic LN, 51
	17	NS	6	eRMS	RPLN	RIO + RPLND	II	CR	Alive, 19
	23	NS	5	pRMS	None	RIO + RPLND	I	NA	Alive, 22
	20	NS	10	eRMS	RPLN + lung	RIO + RPLND+RPL	IV	PR	Alive, 36
	19	NS	8	eRMS	LSN, lung + bone	RIO	IV	PR	Lost to follow-up with residual tumor, 26
	21	NS	12	eRMS	RPLN	RIO + RPLND	II	CR	Alive, 12
Kumar *et al*, 1994 (3)	41	3	NS	eRMS	None	RIO + FNAB	I	NA	NS
	5	1	NS	eRMS	None	RIO + FNAB	I	NA	NS
Banfield and Brookstein, 1995 (4)	26	5	15	uRMS	None	RIO	I	NA	Alive, 8
Alexander, 1968 (5)	2.5	3	NS	pRMS	None	RIO	NS	NA	Alive, 96
	0.25	1	NS	aRMS	None	RIO	NS	NA	Alive, 60
Nasit *et al*, 2013 (6)	2	2	5	pRMS	None	RIO	I	PD	Multi-metastasis, 16; succumbed, 20
Thompson *et al*, 1997 (7)	31	24	7	eRMS	None	RIO + RPLND	I	PD	Multi-metastasis, 16; succumbed, 18
Chung *et al*, 2007 (8)	0.75	9	3.7	eRMS	None	RIO	I	CR	Alive, 24
Kelly *et al*, 2011 (9)	33	2	11	eRMS	None	RIO	I	NA	Alive, 3
Terrier-Lacombe *et al*, 1990 (10)	21	NS	7	eRMS	None	RIO + RPLND + LILND	I	PR	Multi-metastasis, 17 alive, 20
Jungling and Culp, 1975 (11)	17	3	NS	eRMS	None	RIO + RPLND	I	CR	Lung metastasis; alive, 96
Erbay *et al*, 2004 (12)	20	1	4.6	eRMS	None	RIO	I	CR	Alive, 24
Present study	14	12	14	eRMS	None	RIO	IV	PR	Alive, 8

MH, medical history; SPT, (mean) size of primary tumor; location, location of metastases; HT, histological type; IRSG, Intergroup Rhabdomyosarcoma Study Group; NS, not stated; RMS, rhabdomyosarcoma, uRMS, undetermined RMS; pRMS, pleomorphic RMS; eRMS, embryonic RMS; aRMS, alveolar RMS; RIO, radical inguinal orchiectomy; RPLND, retroperitoneal lymph node dissection; LSN, left supraclavicular nodes; FNAB, fine-needle aspiration biopsy; RPL, right pulmonary lobectomy; LILND, left inguinal lymph node dissection; CR, complete remission; PR, partial remission; PD, progressive disease; NA, not available.

Discussion

The origin of ITRMS remains uncertain. Primary ITRMS should be differentiated from germ cell tumors with a sarcomatous component, other intratesticular spindle cell sarcomas and paratesticular RMS. Teratoma of the testes, cryptorchidism, trauma or exogenous maternal estrogen (*in utero*) may be associated with its development (4,7,10). Immunohistochemical markers are critical to exclude other intratesticular spindle cell sarcomas and germ cell tumors that also present with rhabdomyoblastic differentiation. Rhabdomyosarcoma exhibit positivity for smooth muscle actin, muscle-specific actin, S-100, and vimentin and negative for cytokeratine on immunohistochemical staining (12). Scrotal ultrasound and abdominal computed tomography imaging may be used to determine a intatesticular or paratesticular pathology (13).

RMS occurs predominantly in the head and neck, the genitourinary tract and the extremities. RMS of the bladder and paratesticular organs accounts for the majority of such tumors located in the genitourinary tract system, while they are rarely identified in the testes. Only 18 cases describing primary ITRMSs and 6 cases reporting metastatic ITRMSs are currently documented in the literature (2-12,14-18). These primary and metastatic ITRMSs typically affected only a single testis, with the exception of a single case with bilateral testicular involvement of metastatic ITRMS (14). Metastatic ITRMSs are secondary to RMSs of the extremities and maxillary sinus, with all cases presenting as alveolar type (14-18).

The clinical features of the present case, amongst 18 other cases of primary ITRMS sourced from the literature, are summarized in Table I (2-12). The median age of the patients at presentation was 20 years (range, 3 months to 41 years). All patients presented with a single, slow-growing, painless testicular mass. A total of 9 tumors developed in the left testis and 10 occurred in the right. The median medical history of the 12 patients with such data was 3 months (range, 1-24 months), prior to seeking medical advice. The median size of the primary tumors of the relevant 14 cases was 7.5 cm (range, 3.7-15 cm). For the histological subtypes, embryonal RMS accounted for 73.7% (14/19) of cases, pleomorphic RMS for 15.8% (3/19) of cases and alveolar RMS for 5.3% (1/19) of cases, while 1 case presented with undetermined RMS. Among them, 2 patients were diagnosed initially by fine-needle aspiration biopsy (FNAB) of the testis, confirmed by post-RIO histological sections. To determine staging information, FNAB was performed on the RPLN of 1 patient in whom there was difficulty in performing a complete excision. During the initial imaging investigations prior to RIO, 4 patients presented with evidence of RPLN metastasis and 2 patients with distant metastasis. Furthermore, 5 cases developed a novel metastatic lesion, with locations that included the lungs, the bones, the chest cavity or the local lymph nodes, ranging from 3 weeks to 17 months after RIO was conducted. RIO was mandatory in all patients in the present cohort as the initial treatment, and a total of 12 cases received post-RIO adjunctive chemotherapy. CR was observed in 50% (6/12) of cases, PR in 33.3% (4/12) of cases and disease progression in 16.7% (2/12) of cases. Retroperitoneal lymph node dissection (RPLND) was performed in 3 patients presenting with RPLN metastasis and in 4 patients without evidence of metastasis for staging (2,11). The median duration of follow-up of the 17 cases with data was 22 months (range, 3-96 months), including 1 patient who was lost to follow-up 26 months after RIO, and 2 patients who succumbed at 18 and 20 months, respectively, following RIO, who presented with distant metastasis. A further 14 patients were reported as alive when the corresponding literature was published, with 11 cases described as disease-free and 3 patients living with RPLN or distant metastasis.

Unlike other germ cell tumors that develop in the testes, tumor markers in ITRMS, including AFP, β-HCG and LDH, are typically within the normal ranges. An exception to this in the present literature review was AFP, which was slightly elevated in 2 cases that developed teratoma (4,10). Ultrasound is the most prevalently used imaging technique to examine the testicular mass and adjacent organ. Gross appearance, histopathology and immunohistochemical staining may aid the final diagnosis and distinguish ITRMS from paratesticular or spermatic cord RMS (19). ITRMS is a highly aggressive tumor that may be present with early metastasis (6). X-ray or CT of the chest and abdominopelvic cavity are typically performed to identify whether metastasis has occurred. As a novel iconography approach, PET-CT not only presents detailed functional and metabolic molecular information, but also provides a precise, anatomical localization of lesions (20). PET-CT is widely used to investigate various types of tumors, but has rarely been reported in the evaluation of metastatic lesions of ITRMS (21). The technique may be more sensitive for minimal metastatic lesions and may have a potential impact on tumor staging and treatment planning.

Multidisciplinary treatment approaches have greatly improved the prognosis of RMS (22). RIO, as an initial treatment of ITRMS, is mandatory for all patients, and may therefore serve an important role in the pathological diagnosis and treatment of the disease. RIO, followed by chemotherapy, appears to be the optimal treatment for ITRMS (2). Chemotherapy is generally effective in treating RMS, and the recommended chemotherapy regimen for the treatment of IRSG is VAC, consisting of vincristine, actinomycin D and cyclophosphamide (9). In the present literature review, 6 cases chose the VAC regimen and 4 cases chose the VA regimen (2,6,8,10,11). Numerous chemotherapeutic agents have been tested in clinical trials. Controversy remains over whether RPLND should be performed as a routine staging procedure following RIO, or as an initial treatment (2). However, it may serve a role in debunking disease when positive nodes persist following chemotherapy. Regarding RMS, radiotherapy is recommended for patients presenting with an unresectable tumor, a post-operative residual tumor, local recurrence, distant metastasis and an unfavorable histology, including alveolar RMS (2). However, as chemotherapy is generally effective in treating patients with RMS, the concept of radiotherapy use has been partially modified and it is recommended on an individual basis (2,9). In adult RMS of the prostate or bladder, adjuvant radiotherapy is not regarded as necessary when the patient has undergone complete surgical resection and chemotherapy (23,24). In the present literature review, no patients received radiotherapy for the treatment of primary ITRMS.

Multiple factors have been demonstrated to affect the prognosis of RMS; these primarily consist of the histological subtype, patient age, tumor size, resectability, lymph nodal involvement and local recurrence (9). There is limited long-term data available regarding the prognosis of ITRMS; the disease is typically believed to present with a poor prognosis, however, it is not as poor as the prognosis associated with paratesticular RMS (25).

Despite ITRMS occurring in rare instances, clinicians should be aware of this possibility, with prompt investigation required of any unilateral, painless, testicular mass. ITRMS is extremely aggressive and develops rapidly, with metastasis often occurring within a 2-year period (2). Therefore, an early diagnosis and the regular monitoring of metastatic lesions are key factors that may improve patient prognosis. PET-CT is a sensitive tool for accurately determining the response to therapy, particularly the occurrence of CR (2,9). Multidisciplinary treatment, specifically RIO followed by chemotherapy, serves a significant role in the treatment of ITRMS (8). The patient described in the current study presented with a large primary ITRMS, underwent a full evaluation, received the appropriate treatment and subsequently achieved a positive prognosis. This case demonstrates that primary ITRMS has an improved prognosis when compared with RMS located at other sites, and that multidisciplinary treatment may further improve the patient outcome. However, future prospective studies are required in order to acquire an increased understanding of this rare disease.

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