



Paratesticular sarcomas: our case series

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ABSTRACT

Objective: Paratesticular tumors, which comprise a heterogeneous group of entities, are often described in case reports in the literature. In this study, we present histomorphological, immunohistochemical and clinical features of six cases with paratesticular sarcoma.

Material and methods: Six cases with paratesticular sarcoma diagnosed in our hospital between 1997 and 2012 were included in this study. Information regarding treatment modalities, tumor recurrence, metastasis, and survival were obtained from archival patient records. Hematoxylin-eosin sections of the cases were examined, and immunohistochemical analyses were performed for markers including smooth muscle actin, desmin, Ki67, CD34, S100 and myogenin. Percentage of staining in five high-power fields were counted to document Ki67 and p53 nuclear positivity rates.

Results: Of the 6 paratesticular sarcoma cases, 3 were rhabdomyosarcomas, 2 leiomyosarcomas and 1 liposarcoma. The case with sclerotic-type liposarcoma showed two recurrences during the 15-year follow-up period. Two cases with the diagnosis of leiomyosarcoma presented with lung metastases at the time of diagnosis, and 1 patient died of the disease at 7th month. Of the 3 cases with rhabdomyosarcomas, 2 patients were lost to postoperative follow up. The other patient presented with liver and prevertebral metastasis at the 3rd month and died of the disease in the 14th month. The Ki67 proliferation index was significantly higher for one case with rhabdomyosarcoma, and 2 cases with leiomyosarcoma. Differences in p53 expression were not statistically significant between the cases.

Conclusion: Paratesticular tumors belong to a heterogeneous group of tumors that can follow different clinical courses. This study showed that the most important features in determining prognosis are histopathological subtype and tumor grade.

Key words: Leiomyosarcoma; liposarcoma; paratesticular; rhabdomyosarcoma.

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Introduction

Most of the scrotal masses are neoplastic testicular masses. Some of the scrotal masses are extratesticular neoplasias, and develop from paratesticular tissues. Paratestiküler region has a complex anatomy, and contains epididymal, and testicular appendages as spermatic cord, testicular tunicas, epididymis, and vestigial remnants. Therefore neoplasia originating from this region comprise a heterogenous group of tumors.^[1] Herein, six cases diagnosed as paratesticular sarcoma whose clinical follow-up records can be accessed were presented with their histomorphological, and immunohistochemical (IHC) properties.

Material and methods

A total of six cases diagnosed as paratesticular tumors between 1997-2012 in Tepecik Training and Research Hospital were included in the study. Data concerning age of the patients, and tumor sizes were retrieved from archival pathology reports. Information about patients' complaints, treatment approach, tumoral recurrence, and survival rates were derived from clinical data. We couldn't obtain information about recurrence, metastasis, and survival of two patients who had lost to postoperative follow-up.

Hematoxylin-eosin (HE) stained slides of the cases in archive files were re-evaluated, and

appropriate paraffin blocks representing tumor were picked out. From blocks chosen for IHC, 5 μ sections were prepared and placed on glass slides. All preparations were treated with IHC markers including smooth muscle actin (SMA), (DAKO, IR611), desmin (DAKO, IR606), p53 (DAKO, IR616), Ki-67 (DAKO, IR626), CD34 (DAKO, IR632), S100 (DAKO, IR504) and myogenin (DAKO, IR067). All IHC analyses were done using Dako Autostainer Link 48 automatic immunohistochemical staining device, and preprepared Dako Flex antibodies using Envision Flex system.

For the evaluation of positivity for smooth muscle actin, desmin, and S100 markers cytoplasmic staining, for CD 34 markers membranous staining, and for myogenin, Ki-67, and p53 markers nuclear staining methods were used.

Percent of tumor cells stained with Ki67, and p53 was numerically calculated under at least 5 high power fields.

Results

All patients included in our study were consulted to our hospital with painless scrotal mass. In a patient with pulmonary metastases, as an additional finding coughing was observed. Mean age of the cases was 39.5 (min: 16, max: 67) years, and mean tumor size was 7 cm (min: 5, max: 10). All cases underwent inguinal orchiectomy with high ligation. Two cases with distant organ metastases, also underwent postoperative chemotherapy (CT). Information about recurrences, metastases, and survival times of the patients are summarized in Table 1.

Six patients included in the study after histomorphological, and immunohistochemical analyses were diagnosed as rhabdomyosarcoma (RMS) (n=3), leiomyosarcoma (LMS) (n=2), and liposarcoma (n=1). On HE stained sections of a case with well-

differentiated, sclerotic type LPS, sparsely scattered bizarre stromal cells in a large, and loose collagenous stroma, in addition to smaller number of interspersed mature adipocytes were observed. (Figure 1). Atypical stromal cells did not stain with DKA, CD34, S100, and myogenin, while some of them stained with desmin. Ki67 proliferation index was 1%, and p53 expression percentage was 10 percent (Table 2).

On HE stained sections of the case #3 with the diagnosis of leiomyosarcoma, intersecting bundles of spindle cells with eosinophilic cytoplasm having hardly defined borders were observed (Figure 2). In this nonnecrotic tumor, 5 mitoses/10BBA were counted. Ki67 proliferation index was 40.5, and p53 expression ratio was 5 percent.

On HE stained sections of the case (case #5) with the diagnosis of LMS, in addition to patchy areas resembling those of the abovementioned case, myxoid changes in the tumor, related microcystic areas, and dedifferentiated areas containing bulky pleomorphic cells with large cytoplasm, and also multinuclear cells were observed. Necrotic foci, and lymphovascular thrombi were also seen. In the tumor, 9 mitoses/10BBA were counted, while Ki67 proliferation index was 40%, and p53 expression ratio was 30 percent. In both cases, tumor was diffusely (+) stained with DKA, and desmin, while tumor cells were distinctly negative for CD34, S100 and myogenin (Table 2).

On sections of two cases (#4, and #6) diagnosed as embryonal RMS with similar histological appearance hypo-, and hypercellular areas separated by fibrous bands in a loose myxoid stroma attracted our attention. On hypercellular areas, cells with constricted cytoplasm with central oval nuclei, and on the periphery more distinctly differentiated spindle cells with occasionally striated eosinophilic cytoplasm in more hypocellular areas were seen (Figure 3). In case #3, tumor was stained

Table 1. Patients' data related to diagnosis, age, tumor size, and recurrence, metastases, and survival

Patients	Diagnosis	Age	Tumor diameter	Complaint at presentation	Treatment	Recurrence	Metastasis	Survival
Patient #1	LPS	35	6	Scrotal swelling	IOHL	3 years-1 recurrence 12 years 2 recurrences	None	Right (15 years)
Patient #2	RMS	16	5	Scrotal swelling	IOHL	None	hepatic, prevertebral	DSD (14 months)
Patient #3	LMS	42	10	Scrotal swelling, coughing	IOHL+CT	None	hepatic, pulmonary, paraaortic lymph node	Right (one month)
Patient #4	RMS	67	6	Scrotal swelling	IOHL	Lost to follow-up	Lost to follow-up	Lost to follow-up
Patient #5	LMS	58	9	Scrotal swelling	IOHL+ CT	None	Pulmonary	DSD (7 months)
Patient #6	RMS	19	6	Scrotal swelling	IOHL	Lost to follow-up	Lost to follow-up	Lost to follow-up

LPS: liposarcoma; RMS: rhabdomyosarcoma; IOHL: inguinal orchiectomy with high ligation; CT: chemotherapy; DSD: disease-specific death

positively with desmin, and myogenin, while it was negative for DKA, CD34, and S100. Ki67 proliferation index of the tumor was 70%, and its p53 expression ratio was 10 percent. IHC evaluation of the case #4 revealed a tumor mass negative for all markers (Table 2).

In this case with histomorphological characteristics compatible with embryonal RMS, negativity for HSC markers was thought to stem from issues related to tissue surveillance, and detection.

On tissue sections of case #2 where embryonal, and alveolar RMS histological subtypes were seen in combination, predominantly layers of atypical cells with round/oval nuclei with indistinct cytoplasm, and more markedly differentiated areas of cells with eosinophilic cytoplasm dispersed focally on a more loosely myxoid background were detected. Tumor cells yielded focal reaction with desmin, and diffuse positive reaction with myogenin, while they didn't stain with CD34, S100, and DKA.

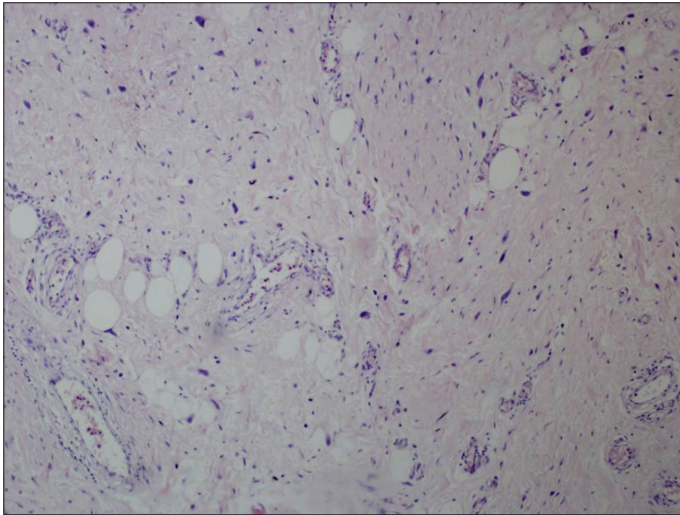


Figure 1. Bizarre stromal cells dispersed individually in a loose collagenous stroma, and interspersed mature adipocytes (HE x200)

Ki67 proliferation index of the tumor was 10%, and its p53 expression ratio was evaluated as 10 percent (Table 2).

Discussion

Paratesticular region was a complex anatomic region histogenetically consisting of epithelial, mesothelial, and mesenchymal components. Therefore, neoplasms developed in this region belong to a heterogenous group of tumors which demonstrate different behavioural patterns.^[1] It is not possible to detect precise origin of the paratesticular tumors. However these tumors have been thought to originate from spermatic cord in 90% of the cases.^[1]

In most cases with paratesticular tumors, patients complain of painful or painless scrotal masses.^[1-3] Therefore these tumors can not be discriminated from testicular tumors. Common complaint of our cases was painless scrotal mass. In one patient, coughing secondary to pulmonary metastasis accompanied painless mass.

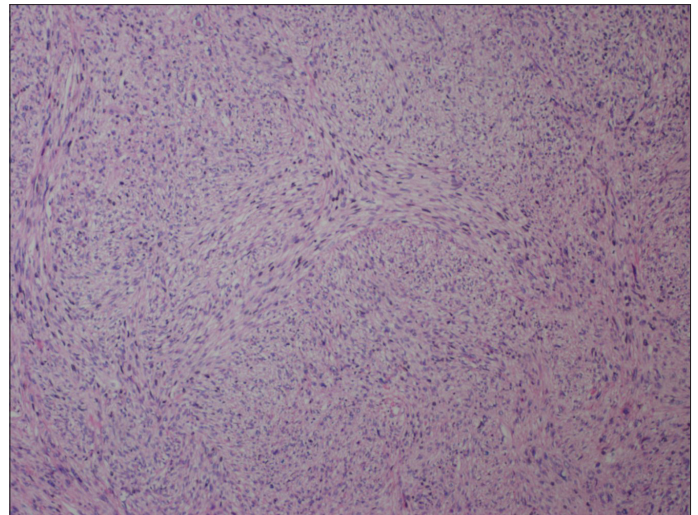


Figure 2. Intersecting spindle-shaped tumor cells with hardly seen cytoplasmic borders (HE x200)

Table 2. The results of staining with IHC markers including smooth muscle cell actin, desmin, p53, S100, Ki67, and myogenin

Patients	Diagnosis	SMA	Desmin	p53 (%)	CD34	S100	Ki-67 (%)	Myogenin
Patient #1	LPS	-	focal +	10	-	-	1	-
Patient #2	RMS	-	focal +	10	-	-	10	+
Patient #3	LMS	+	+	5	-	-	40	-
Patient #4	RMS	-	-	5	-	-	1	*
Patient #5	LMS	+	+	30	-	-	40	-
Patient #6	RMS	-	+	10	-	-	70	+

LPS: liposarcoma; RMS: rhabdomyosarcoma; LMS: leiomyosarcoma; SMA: smooth muscle actin; (*) In sections prepared from paraffin blocks sent for consultation optimal staining could not be achieved.

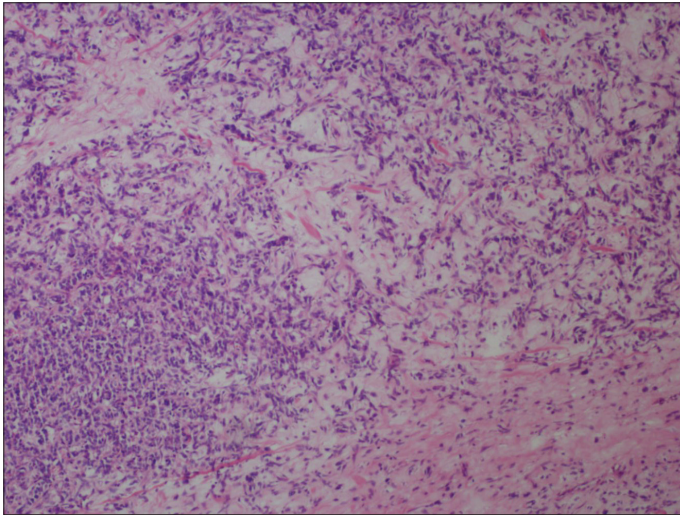


Figure 3. Hypo-, and hypercellular areas consisting of cells with round, oval nuclei, and indistinct cytoplasm on a myxoid stroma, and individually interspersed better differentiated cells with eosinophilic cytoplasm (HE x200)

Rarely seen paratesticular tumors which are cited in the literature as anecdotal reports consist mostly of (70%) benign, and malignant (30%) neoplasms. Most frequently observed benign tumors are lipomas, adenomatoid tumors, and myomas.^[1]

Most of the malignant tumors consist of soft tissue masses, and malignant paratesticular tumors reported in many series consist of LMS (32%), RMS (24%), and LPS (20%) in order of decreasing frequency.^[1] LMS constitutes nearly 5-10% of all soft tissue tumors, and comprises approximately 30% of paratesticular sarcomas observed in adults.^[1,4] Generally, incidence of these tumors peak at 6.-7. decades of life.^[1] Paratesticular tumors reported in the literature, most frequently originate from spermatic cord, testicular tunica, epididymis, and scrotum.^[5] Macroscopically tumor forms a solid, gray-white nodular mass. Histologically, tumor can be seen in a large spectrum varying from well-differentiated LMS to pleomorphic undifferentiated LMS where smooth muscle differentiation can be detected using IHC methods.^[1] It metastasizes into retroperitoneal lymph nodes through lymphatic drainage, and into lungs through hematogenous route.^[6] In most of the cases, immunohistochemically, tumor cells stain positively with DKA, desmin, and h-caldesmon. With keratin, epithelial membrane antigen, CD34, and S100, focal positive reaction can be observed. Diagnosis is made using morphological methods, and immunohistochemical markers.^[4]

In our series, in two cases with LMS aged 42, and 58 years, tumor cells yielded diffuse positive reaction with IHC markers actin, and desmin, and negative reaction with CD34 and S100.

In both of our cases pulmonary metastases were detected at the time of diagnosis. In one of these cases metastases were also observed in the liver, and paraaortic lymph nodes. In this patient widespread metastases were detected, and 3 cycles of VAC (vincristine, adriamycin, cyclophosphamide) + IMET (ifosfamide, etoposide) treatment were applied in the clinic of medical oncology. During follow-up period, disease progression was detected in the patient who then received 7 cycles of docetaxel, and gemcitabine therapy. The patient who demonstrated partial response is still under our surveillance. Since our other case with diagnosis of LMS referred to another medical center for treatment, we have no idea about his CT protocol.

Liposarcomas constitute nearly 20% of paratesticular sarcomas. These tumors can develop from adipose tissue surrounding spermatic cord or from malignant transformation of preexisting lipoma.^[1] These rarely seen tumors are usually reported as anecdotal case reports or as a component of a large-scale case series. In a retrospective evaluation published by Montgomery and Fisher related to a series of 30 cases with paratesticular LPS, the authors indicated that most of them originated from spermatic cord (76%) followed by testicular tunica (20%), and epididymis.^[3] Mean age of the patients, and tumor diameter were documented as 63 (41-87) years, and 11.7 cm (3-30 cm), respectively. In the same study, the following histological types were observed in order of decreasing frequency: well-differentiated (19/30), dedifferentiated (10/30), and myxoid /round cell LPS (1/30).^[3]

Sclerotic subtype of LPS which is defined as one of 4 subtypes of LPS are frequently seen in tumors arising from retroperitoneal, and paratesticular tissue.^[7] Pleomorphic subtype is more rarely seen, however recurrences and/or metastases are more frequent in this group.^[1,8] Well-differentiated LPS grows slowly, but it recurs if incompletely excised.^[1]

Our case of LPS with a sclerosing subtype was in his young adulthood (age, 35), and he had a tumor with a diameter of 6 cm. It was totally excised, and this histologically well-differentiated LPS was included in the follow-up program without treatment by our urooncology team. His local recurrences which developed at 3., and 12, years of his follow-up period were managed surgically, and during 15 years of his monitorization any metastatic lesion was not detected. The clinical course of this entity is in concordance with literature findings.

Paratesticular RMS constitutes nearly 7% of RMS, and it is the most frequently observed soft tissue sarcoma in the pediatric age group.^[9] Paratesticular RMS comprises of nearly 80% of paratesticular tumors seen in males under 21 years of age, and

approximately 24% of those encountered in adulthood.^[1] Tumor develops from spermatic cord, epididymis, and mesenchymal components of testicular tunica, and forms a painless scrotal mass.^[10,11] However in adolescents, and young adults, alveolar subtype has been more frequently reported. Pleomorphic RMS which is the rarest histological type, is frequently encountered in adults. Histological types more frequently seen in adults (alveolar, and pleomorphic subtypes) have a poorer prognosis when compared with embryonal RMS.^[1,10] IHC markers of MyoD1, and myogenin have higher degrees of specificity, and sensitivity. Apart from these, markers such as S100, neurofilament, α -cell markers can yield aberrant positive reaction. SMA, and neuron specific enolase positivity have been also reported (10, and 30%, respectively).^[12]

In our study, two cases were less than 21 years of age, and the third patient was in advanced age group. Histologically embryonal subtypes were detected in two cases aged 10, and 67 years, respectively. In our 16-year-old case, both alveolar, and embryonal subtypes were seen in combination.

In our series, two of our RMS cases were referred to our center for the establishment of diagnosis, but their further treatment was maintained in centers which planned their treatment protocol. Therefore we couldn't obtain details of their treatment, and follow-up. Diagnosis of one case with RMS which was referred to us from an external center had not been made conclusively using IHC markers (possibly due to detection, and follow-up artifacts) at that institute. We considered this case as an embryonal tumor, and the patient was followed up accordingly. At 3. month hepatic metastases were detected, and application of VAC + Imet treatment protocol was decided for this patient. However we couldn't obtain his detailed CT program implemented in another center, but he died at 11. month of his treatment from a disease-specific cause.

Treatment of paratesticular sarcomas is primarily surgical (inguinal orchiectomy with high ligation of the spermatic cord). Since sarcomas generally tend to infiltrate surrounding tissue, it is very hard to excise the tumor completely. After orchiectomy local inguinal, and scrotal recurrence rates have been reported as 25-37 percent. However, decrease in local recurrence risk has been reported with regional adjuvant radiotherapy and/or surgery applied after orchiectomy.^[1]

Though, the role of adjuvant chemotherapy is not clear-cut in adult cases with paratesticular sarcomas, in pediatric cases with paratesticular RMS, it has been reportedly associated with longer survival times.^[1]

In the treatment of paratesticular sarcomas, application of retroperitoneal lymph node dissection (RPLND) is controversial. In the literature, RPLND has been recommended in the treatment of the cases with RMS, but it not advised for the management of patients with LMS. In LPS, its benefit is doubtful.^[1]

In conclusion, paratesticular tumors belong to a heterogenous group of tumors which demonstrate different behavioural patterns. Definitive treatment protocols for these rarely seen tumors are not available yet. In all the cases in this small series clinical progression correlated with histological subtype, and the most important factor influential on tumor prognosis in cases with paratesticular sarcoma were observed to be histological subtype, and stage of the tumor.

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