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Research Article

Clinical and Pathological Features of Ewing Sacoma Family Tumors in Uro-oncology: A Single-Institute Experience

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Abstract

Objectives: Genitourinary Ewing Sarcoma Family Tumors (ESFT) are rare and very aggressive tumors. We aimed to demonstrate the clinical features and prognosis of 6 genitourinary ESFT patients from a single institute from Turkey.

Methods: A total of 6 cases of genitourinary ESFT (3 renal, 2 bladder and 1 adrenal) treated at our department were reviewed retrospectively and data considered with the literature.

Results: Half of the patients in our cohort consisted of women and the median age of the cohort was 39 years at presentation. Median follow-up time was 46.3 (range; 3.6-103.2) months and median overall survival was 25 months. Half of patients were diagnosed at metastatic stage. Four cases were undergone radical surgery, while the remaining cases were performed diagnostic biopsy due to metastatic disease. Five cases received adjuvant or palliative chemotherapy, while one case (patient 5) rejected to receive chemotherapy.

Conclusion: ESFT is rare among urologic malignancies, it is often overlooked for differential diagnosis preoperatively and mortality is high despite multimodal treatment. We suggest that ESFT should be kept in mind as a rare differential diagnosis of all genitourinary tumors in advanced stage disease of young patients and large primary tumor especially if renal origin is involved.

Keywords: Ewing sarcoma family tumors, genitorinary tract, immunohistochemistry, treatment

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The Ewing sarcoma family tumors (ESFT) is consisted of primitive neuroectodermal tumors (PNETs), extraosseous Ewing's sarcoma (ES), Askin's tumor (PNET of the chest wall) and Ewing's sarcoma of bone.[1] ESFT most often develops in almost any bone or soft tissue but the most common site is in a flat or long bone and patients typically present localized pain and swelling.[2] Moreover, genitourinary localization of ESFT is extremely rare.[3] Unfortunately, 25-50% of the patients admitted are in metastatic stage at the time of diagnosis. Although oncological management has improved in recent years, treatment success rates are still not good enough (5-year survival rate 45% to 55%).[4, 5] The presentation is nonspecific and radiological findings are not distinctive.[6–9] Histopathology confirmed by cytogenetics studies and immunohistochemistry (IHC) are important components of diagnostic process.[7, 8] As a result of new advances in IHC and molecular pathology, the differential diagnosis of these tumors can be done easily and that caused increased interesting case reports over the last few years. Since the first description of renal ESFT case in 1975 by Seemayer et al.,[10] more than 150 cases of genitourinary ESFT mostly renal, have been reported worldwide.

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There is no detailed clinicopathologic report available on ESFT in adult uro-oncology literature from Turkey. We described 3 renal, 2 bladder and 1 adrenal ESFT patients treated in our institution and reviewed the literature.

Methods

Patients

Six cases of genitourinary ESFT (3 renal, 2 bladder and 1 adrenal) at advanced stage were treated at our institution and followed up to the present day. Pediatric ESFT cases were not included in this study. Data about clinical (history, physical examination, clinical outcome, treatment options), biochemical (liver and renal function tests) and radiological findings (computed tomography scans of the abdomen, thorax and pelvis) were evaluated from medical records. In addition, histopathologic features of the study subjects, which were determined by HE staining, IHC stainingand fluorescence in situ hybridization (FISH) were retrospectively recorded. Signed informed consents for pathological assessment and oncological treatments were obtained from all patients This study protocol was reviewed and approved by the Institutional Review Board of our institute (IRB registration 13/09/2019-182683) and conducted in accordance with the precepts established by the Helsinki Declaration.

Statistical Analysis

The study was closed in July 2019 and as of this date statistical analyzes were performed. Overall survival was defined as the time from diagnosis to the date of death from the disease or the last known alive. Survival curves and estimates were obtained by the Kaplan Meier method.

Results

Our cohort consisted of 6 (3 female and 3 male) patients and the median age was 39 (15-61 years). Median follow-up time was 46.3 (range; 3.6-103.2) months. Table 1 demonstres the clinical features of the study subjects. All of the patients were suffered from abdominal pain;furthermore two cases had a palpable abdominal mass and two cases had macroscopic hematuria. Half of patients were metastatic at diagnosis. Three renal ESFT patients had localized, locally advanced and metastatic disease (bone), while adrenal ESFT patient had metastatic disease (bone, liver and lung) and other two bladder ESFT patients had localized and metastatic disease (liver). The renal ESFT patient with metastasic disease also had renal vein thrombosis extending into the inferior vena cava. All patients had heterogeneously contrast enhanced, exophytic, spiculated and central necrotic mass lesions on the CT scan.

The tumors ranged from 5.4-19.5 cm in size (median, 11.5

Table 1. Clinical and follow-up data of the cases of the present study

Case no.	Age (years)	Sex	Origin of Tumor	Size (cm)	Metastasis at Diagnosis	Diagnostic Biopsy	Presentation	Surgery	Adjuvant Treatment	Recurrence Progression	Fllow-up Duration (mo)	Status at Last Follow-up
1	41	M	Kidney (left)	12	No	No	Palpable abdominal mass, left flank pain	Radical nephrectomy	VACx5; VDCx1; IEx6	None	68	AWOD
2	37	M	Kidney (right)	19.5	Yes (bone)	Yes	Palpable abdominal mass, right flank pain	None	VACx6; IEx6	Progression	25	DOD
3	29	M	Kidney (right)	11	No	No	Right flank pain	Radical nephrectomy	VACx6; IEx6+ Radiotherapy to tumor bed and renal hilus	None	103	AWOD
4	48	F	Bladder	5.4	No	Yes	Hematuria	Complete TUR-BT	VACx3+ IEx2+ Local radiotherapy+ VACx1+ IEx2	None	76	AWOD
5	61	F	Bladder	6.8	Yes (liver)	Yes	Hematuria, abdominal pain	None	None		4	DOD
6	15	F	Adrenal (right)	15.8	Yes (liver, lung, bone)	Yes	Abdominal pain, right flank pain	Adrenalectomy	VACx5; IEx5	Progression	11	DOD

AWD: alive with disease; AWOD: alive without disease; DOD: died of disease; F: female; IE: ifosfamide and etoposide; M: male; VAC: vincristine, adriamycin and cyclophosphamide; VD: Cvincristine, dactinomycin and cyclophosphamide; TUR-BT: Transurethral Resection of Bladder Tumor.

cm) but especially renal ESFT cases had very large tumors (11, 12 and 19.5 cm, respectively). Four cases received radical surgery, while the remaining cases were underwent diagnostic biopsy due to metastatic disease. There were neither death nor major intra-nor-post-operative any complications. Five cases received adjuvant or palliative chemotherapy, while one case (patient 5) rejected to receive chemotherapy. Two cases (patients 3 and 4) had radiotherapy to the tumor bed after complete surgery and chemotherapy (Table 1).

All patients had histopathological examinations and IHC were performed to confirm the diagnosis. The FISH result was only present in one case of bladder ESFT and it ultimately belonged to a laboratory outside our institution and the result was negative. On histopathology, ESFTs typically exhibit uniform, small, blue and round cells with hyperchromatic and scant cytoplasm could be seen in only 3 ESFT cases (2 renal and 1 adrenal). All had positive staining with CD99. Partial IHC findings are demonstrated in Table 2.

Median follow-up of 6 patients was 46.5 months and ranged from 4 to 103 months. Three patients were still alive without disease while three patients died of disease at 4th, 11th and 25th months, respectively due to metastatic disease progression (Table 1). Five patients were treated with combination chemotherapy using vincristine, adriamycin, cyclophosphamide (VAC) alternating with ifosfamide and etoposide (IE) every 21 days for a total of 17 cycles.[11] When the cumulative dose of doxorubicin reached 375 mg/m^2, switched to dactinomycin at 1.25 mg/m^2.

For the entire cohort, the median OS was 25 months and 3-year survival rate was 50%. The survival rate of 18 month was 33% and 100% for metastatic and non-metastatic disease, respectively. The median OS was 11 months (95% CI 0-22.2) in metastatic patients, whereas the median OS was not reached in the non-metastatic patients ($p<0.05$, Fig. 1).

Table 2. Staining of immunohistochemical markers

Case no.	CD99	Vim	NSE	Chr	Syn	S-100	CD56	CKs
1	+	+	+	-	-	+	-	-
2	+	n/a	n/a	-	-	n/a	-	-
3	+	+	n/a	n/a	n/a	n/a	n/a	-
4	+	n/a	-	-	-	n/a	-	-
5	+	+	-	-	-	-	-	-
6	+	n/a	+	-	-	n/a	n/a	-

Vim; vimentin; NSE; neuron-specific enolase; Chr; chromogranin; Syn; synaptophysin; CKs; cytokeratin.

Discussion

Although ESFT is a very rare tumor originating in the genitourinary tract, it has been recognized more frequently as a result of new advances in IHC and cytogentic studies. In our study, we demonstrated pathological and characteristics of 6 cases of primary ESFT (3 renal, 2 bladder and 1 adrenal) and reviewed the literature in this often overlooked entity. Our findings was compatible with literature including a high rate of metastatic stage and young age. In our study, these tumors typically manifested in adolescents and young adults (median age 39 years) except for one 61-year-old patient. These findings were also comparable to previously reported findings[12] where mean age at diagnosis was 27 years (range 3-78). In concordance with the reported aggressive behavior of this tumor, all our cases presented at an advanced stage. Half of them had distant metastasis which included metastases to liver, lungs and bones. Other investigators had also reported high rates (50–60%) of distant metastases at the time of presentation.[9, 12–14] But interestingly, both our series and literature showed that genitourinary ESFT presented more frequent-

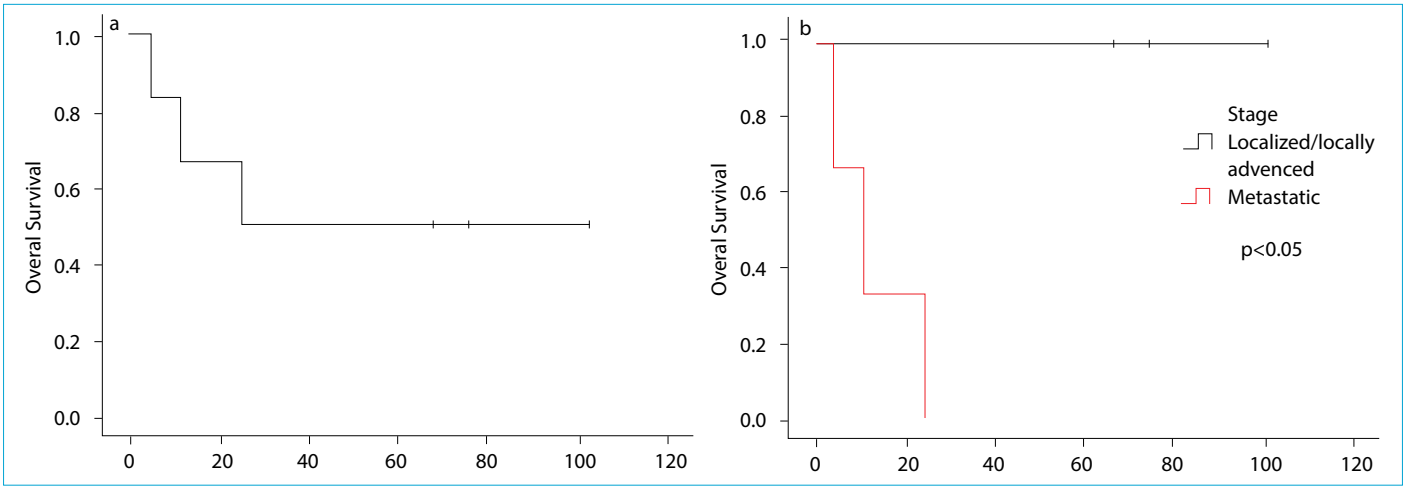

Figure 1. (a) overall survival of the entire cohort. **(b)** overall survival according to the metastatic status.

ly with metastases than other bone or soft tissue ESFT (44% in our series versus approximately 25% reported for all ESFTs[15]) and presented at an older age (in our series 39 years) compared with other sites of primary ESFT (median age 12 years).[16]

Contrary to other studies,[9, 13, 14] male predominance (literature 2:1 vs 1:1 in our study) and presence of concomitant renal vein thrombosis (literature 83.3 % vs 33.3% in our study) especially in renal ESFT cases were not present in our study. The most likely cause is that the gender trend is not accurately reflected due to the small number of cases.

While renal ESFT mainly affects adolescents and young adults, patients with bladder ESFT were older. Interestingly, although an association between bladder ESFT and immunosuppressive status had been shown in the literature, two patients in our series had no history of immunosuppressive status. So, our bladder ESFT cases did not support the hypothesis that an impaired immunological mechanism might be an etiologic factor in the occurence of bladder ESFT. Adrenal ESFT is also a very rare occurrence and only occasional case reports are found in the literature.[17, 18] In our study, a young female with metastatic adrenal ESFT (liver, lung and bone) showed a good clinical response with VAC/IE chemotherapy. However, her disease progressed and died at 11th month.

Histopathological findings are the most important element in the diagnosis of ESFT. It is crucial that all diagnostic stainings should be performed in order to determine the diagnosis correctly and to exclude multiple differential diagnoses such as rhabdomyosarcoma, Wilms' tumor, carcinoid, lymphoma, neuroblastoma, small cell variant of osteosarcoma, clear cell sarcoma of the kidney, small cell anaplastic neuroendocrine carcinoma, desmoplastic small round cell tumor and nephroblastoma.[19]

The typical histopathologic finding of a small, round and blue tumor cells forming pseudorosettes and classic rosettes is a hint of ESFT;[8, 19] however molecular and/or immunohistochemical pathological assessment are need to confirm the diagnosis. Remarkably, overexpression of CD99 as a surface membrane protein is a unique and universal feature for ESFTs, since other renal tumors such as clear cell carcinomas, nephroblastomas, and neuroblastomas do not express CD99.[8] All of our cases had been confirmed by IHC and/or presence of Homer-Wright rosette formation. The 'Homer-Wright rosette' formation was seen in half of the tumors in our study, and IHC analysis revealed that 100% and 50% of cases were positive for CD99 and vimentin, respectively (Table 2). Furthermore, all of the cases were negative for CK.

Genitourinary ESFT is an extremely rare tumor. Studies with consisting of large number of patients are rare due to the low incidence and unfortunately no randomized studies have been published so far. This explains the conflicts and contradictions in treatment approaches in published studies. Therapeutic strategies are often based on conventional cytotoxic chemotherapy regimens used for osseous Ewing's sarcoma. Furthermore, in disease management, there is a still need to determine a standardized approach in order to prevent the disease recurrence and prolong survival.

Successful treatment requires multimodal approaches (radical surgery, multidrug chemotherapy and radiotherapy).Surgery is an important tool for local control and is often performed as the first line of treatment. However, even in the majority of patients with apparently localized disease, additional chemotherapy is required because of the presence of undetectable micrometastatic disease and should be used in most cases. ESFT is sensitive both chemotherapy and radiotherapy. Chemotherapy independent of the disease stage should be considered for adjuvant or palliative purposes. In cases of insufficient resection, positive margin or recurrence of the tumor, radiotherapy should be applied.[20]

Patients with localized ESFTs have a 5-year disease-free survival rate of approximately 60% to 70%.[11] Despite aggressive treatment, the prognosis of patients with metastatic disease is poor. For metastatic ESFTs, the overall survival rate has been 20%.[21] In our analysis, the median OS was 25 months for entire cohort and consistent with literature.[13, 22]

We operated upon two cases of renal ESFT/EWS as suspected cases of renal cell carcinoma (RCC), and ESFT/EWS was not considered in the differential diagnosis before surgery. If we knew diagnosis of ESFT/EWS before nephrectomy, we could offer a neo-adjuvant chemotherapy regimen with VAC/IE. But after surgery, approximately 1 year adjuvant VAC/IE chemotherapy regimen was given to these patients and also 50.4Gy radiotherapy was given one of them due to metastatic renal hilar lympadenopathy. These patients are still alive without disease. The other renal ESFT patient was metastatic at the time of diagnosis and his tumor in the right kidney infiltrated the renal vein and had extension in the vena cava inferior (Fig. 2). So, palliative VAC/IE chemotherapy was given and good clinical results were obtained at the beginning and the patient's complaints improved significantly. Unfortunately, after 25 months from diagnosis, patient died due to disease progression. One patient with bladder ESFT was diagnosed with complete TUR-BT and VAC/IE chemotherapy regimen was started. In addition, radiotherapy was administered with concurrent IE to the local lesion. This patient is currently being followed without any sign of The other bladder ESFT patient had

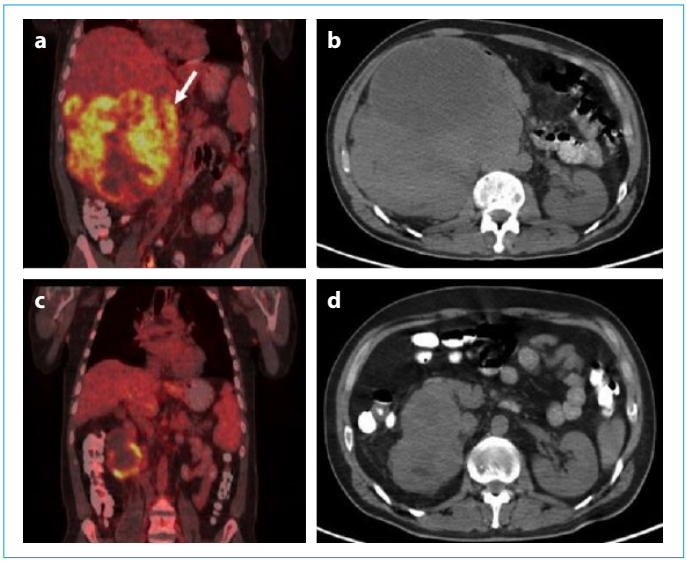

Figure 2. Radiologic features of renal Ewing sarcoma family tumor (ESFT) (Case 2) before **(a, b)** and after **(c, d)** chemotherapy. A poorly defined, centrally necrotic, large heterogeneous tumor on the lateral side of the right kidney is seen in PET-CT iamges **(a, b)**. Infiltration of renal vein and vena cava by tumor is seen in A (white arrow). Tumor shrinkage and disappearance of tumor in vena cava after chemotherapy **(c, d)**.

metastatic disease at the time of diagnosis and she refused chemotherapy and died 4 months after diagnosis.

The present study had some important limitations. Due to its retrospective nature and small number of patients, the statistical comparison of treatment results were inconclusive.

To our knowledge, this is the largest report on genitourinary ESFT from Turkey with a focus on treatment approach and we believe that multimodal treatment had an important impact on survival.

Conclusion

This case series highlight many aspects of this aggressive tumor from a developing country perspective. Because ESFT is rare among urologic malignancies, it is often overlooked for differential diagnosis preoperatively and mortality is high despite multimodal treatment. We suggest that ESFT should be included as a differential diagnosis of all genitourinary tumors in young patients with advanced stage disease and large primary tumor especially if renal origin is involved. Patients with Stage IV disease at the time of diagnosis should be evaluated for diagnostic biopsy prior to definitive local treatments.

It is crucial to assess ESFT patients in prospective randomized trials to collect more details about the disease biology and investigate the more efficient options of different therapeutic approaches.

Disclosures

Ethics Committee Approval: The Ethics Committee of Istanbul University, Institute of Oncology provided the ethics committee approval for this study (13/09/2019-182683).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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