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Outcomes of Adults with Ewing's Sarcoma Family of Tumors (ESFT) of the Kidney: A Single Institution Experience

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Abstract

Background—Ewing's sarcoma family of tumors (ESFT) of the kidney are exceedingly rare. Given the rarity of this neoplasm and the complexity associated with its management, information regarding treatment and outcome is warranted.

Methods—We conducted a retrospective study of patients with ESFT of the kidney who were treated at MDACC between 1/1/2001 and 1/1/2011. Descriptive statistics were used.

Results—Thirteen patients were identified. (Median age 33 years; male:female 11:2). Common presenting symptoms were back pain, flank pain and hematuria. Six patients had metastatic disease at presentation. Initial diagnostic biopsy was performed in six patients. Immunohistochemistry showed strong positivity for CD99 (mic2) and cytogenetic analysis demonstrated evidence of EWSR1 fusion gene in eight cases. Nine patients underwent nephrectomy. Frequently used chemotherapy regimens consisted of vincristine, doxorubicin, and ifosfamide. Median overall survival (OS) was 17.2 months. Three patients were alive at the time of analysis, at 2 years, 7 years and 11 years from diagnosis (the latter without evidence of disease).

Conclusion—Renal ESFT carry a guarded prognosis with limited response to therapy and short median OS. For patients with metastatic disease, diagnostic biopsy and sarcoma-based chemotherapy regimens are recommended as upfront therapeutic strategy. The role of nephrectomy in the metastatic setting is unclear. Future studies with novel therapies are needed.

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Keywords

ESFT; PNET; extraskeletal Ewing's sarcoma; kidney tumors; cytoreductive nephrectomy; chemotherapy

Introduction

Renal cell carcinoma (RCC) is the most common type of kidney cancer accounting for 80–85% of all cases. RCC primarily arises from the renal cortex with the clear cell subtype being the most common. While other malignant tumors such as transitional cell carcinoma (TCC) of the renal pelvis, and collecting duct carcinoma are well known, extraosseous neuroectodermal neoplasms including Ewing's sarcoma family of tumors (ESFT) arising in the kidney present diagnostic and therapeutic challenges, given the rarity of these tumors.

Renal ESFT are aggressive tumors and often difficult to differentiate clinically and radiologically from RCC and TCC of the renal pelvis and hence are frequently misdiagnosed. ESFT includes Ewing's sarcoma, primitive neuroectodermal tumor (PNET), and Askin tumor. They are small round cell tumors that typically arise in bone, soft tissue and chest wall. ESFT of genitourinary tract are rare and were first described by Seemayer et al. in 1975 and tend to occur most often in young adults (1). These tumors are characterized by t(11;22) (q24;q12), EWS-FLI-1 fusion gene, which is integral to the diagnosis.(2) Renal ESFT can be pathologically confused with other small round cell tumors arising from the kidney, such as small cell carcinoma, Wilm's tumor, monophasic synovial sarcoma and lymphoma. Given the rarity of this diagnosis and the complexity associated with management of these tumors, information regarding treatment modalities and outcome of patients with renal ESFT is limited thus prompting our retrospective study. Herein, we present a case series of adult patients with renal ESFT who were treated at our institution and summarize the clinical characteristics, treatment modalities and outcomes.

Patients and Methods

Following Institutional Review Board approval, a retrospective study of the clinical and pathological records of adult patients seen and treated at MDACC from 1/1/2001 to 1/1/2011 was conducted. The pathological specimens were reviewed by a dedicated sarcoma pathologist. All cases of confirmed ESFT were included in this review, and non renal cell cancers (carcinoid tumors of kidney and small cell carcinoma of kidney) were excluded. Radiographic studies were reviewed with particular attention to the presence of tumor thrombus in major vessels. Overall survival (OS) was determined from diagnosis to death secondary to ESFT as well as other causes. Data collected at baseline included demographics (age, race, gender), past medical history, prognostic variables, nephrectomy, systemic therapy with treatment data (i.e. initiation and discontinuation dates of therapy), last available date of follow-up or date of death.

Results

Thirteen cases with Renal ESFT were identified including one case which we previously reported (3) now with further follow up information. There were 11 males and 2 females. The median age at diagnosis was 33 years (range 31–45 years). Eight patients were non-smokers. The most common presenting symptoms were back pain/flank pain (53.8%), abdominal pain (23%) and hematuria (23%); one patient presented with left testicular swelling and two other patients presented with abdominal mass. Two of the 13 patients were anemic at diagnosis but 1 of these 2 patients had an underlying CKD. The tumor size ranged from 7 to 16.2 cm. The radiological appearance of a renal mass extending into the renal vessels similar to renal cell carcinoma was noted in 65% of our cases. The tumor was more frequently seen arising from the left kidney, although no particular site predominance has been reported in the literature. The radiological appearance of the renal mass had no specific characteristics to distinguish it from RCC, except where the tumor was noted to arise from renal hilum or was central/medullary in nature which is atypical for RCC. The presence of extensive metastases and atypical appearance of renal mass prompted a biopsy instead of upfront nephrectomy in six cases. Five of the 13 cases were noted to have a tumor thrombus in the major vessels.

On review of the pathology, the gross appearance of tumor was noted to vary from tan-yellow to grayish-white with areas of necrosis and hemorrhage in three cases. Twelve cases were described as small round blue cell tumor with abundant round cells and minimal cytoplasm. The immunohistochemical profile showed strong positivity for CD99 in 11 of 13 patients. Tumors were negative for chromogranin, synaptophysin, WF-1, desmin and vimentin. Cytogenetic analysis for EWSR1 transcript was performed in 10 of 13 cases and eight of them were noted to be positive for EWSR1(q22;q12) gene rearrangement. Two cases were negative for the EWSR1 gene rearrangement, however the morphology in conjunction with the immunohistochemical profile (strong and diffuse CD 99 reactivity) were thought to be consistent with ESFT, and hence these patients were categorized as renal ESFT. Table 1 summarizes the demographic, radiographic, clinical and immunohistochemical features of the 13 cases.

Six patients had metastases at initial presentation. The most common sites of metastases were the retroperitoneum and lungs. All six patients underwent a diagnostic biopsy initially, and five of them received upfront systemic chemotherapy consisting of the combination of VAI (vincristine, doxorubicin, ifosfamide) alternating with the EP regimen (cisplatin-etoposide) (4, 5). Two of these six patients with metastases at presentation underwent nephrectomy: one had pre-surgical chemotherapy followed by cytoreductive nephrectomy while the other patient who had disease limited to kidney and the ipsilateral adrenal gland underwent upfront left radical nephrectomy with left adrenalectomy followed by adjuvant chemotherapy.

The remaining seven patients who did not have metastases at presentation underwent nephrectomy and were diagnosed with renal ESFT histologically following the nephrectomy. All of these seven patients received adjuvant chemotherapy consisting mostly of VAI alternating with EP with irinotecan used as a salvage agent after relapse. The median

number of systemic chemotherapy regimens administered was 2 (range, 1–5) and the median total time on systemic chemotherapy was 11.2 months (range, 3.5–29.8). Table 2 summarizes the treatment modalities including nephrectomy, systemic chemotherapy, and the outcome of each of the 13 patients.

Ten of the 13 patients have died and the OS was 17.2 months (6.5–112.8). One patient who presented with metastatic disease in July 2003 (3) and received chemotherapy only is alive with no evidence of disease while the other patient who underwent nephrectomy followed by adjuvant chemotherapy is alive with no evidence of disease 2 years since diagnosis.

Discussion

Neuroectodermal tumors of the kidney, though rare, are a distinct clinicopathological entity and are poorly differentiated round cell tumors traditionally defined by their primitive neural features such as rosette formation at the light microscopic level and secretory granule formation at the ultrastructural level (6).ESFT arises from bone in >80% of cases, especially in children, and arises less frequently from extraskeletal sites (7). ESFT of bone is the second most common primary bone malignancy occurring in the flat and long bones, and presents with localized pain and swelling. Extraskeletal ESFT occurs more commonly in young adults, compared to skeletal Ewing's, which tends to occur in young children and adolescents. The most common site of extraskeletal ESFT is the trunk. Tumors in this location tend to have an insidious onset, and a delayed diagnosis; and are frequently large at presentation (8).

ESFT has a propensity for the kidney and retroperitoneum. Originating from the cells of primitive neuroectoderm, renal ESFT may be the result of embryonic neural crest cells migrating into the kidneys thereby undergoing tumorgenesis. Approximately 75% of renal ESFT's tend to occur in young adults similar to our case series. Of note, our study population included adult patients only (age range 31 to 45 years), while the Zollner et al review included pediatric and adult patients (age range 11 to 59.8 years).(9). Immunoreactivity for CD99 (mic2) (10) is present in the vast majority of ESFT, as was noted in our series (11 out of 13 patients in our series were positive for CD99). Molecularly, ESFT is characterized by translocations and fusions of the EWSR1 gene with a number of the ETS family of genes. EWSR1-ETS fusion protein is believed to be pivotal to the tumorigenesis of ESFT and the tumor phenotype (11). The most frequent translocation is t (11;22) (q24;12) which results from fusion of the 5' end of the EWSR1 to the 3' of FLI-1 and accounts for >85% of all translocations. Molecular confirmation of gene rearrangement is widely considered to be integral to the diagnosis of ESFT as the immunohistochemical and histological features of ESFT overlap with other small round blue cell tumors that may occur in the kidney, such as desmoplastic small blue round cell tumor and synovial sarcoma. Although helpful for the diagnosis, the absence of EWSR1 gene rearrangement does not entirely exclude the diagnosis of ESFT, especially if the clinical and morphological features are highly suggestive of the diagnosis. In our series, cytogenetic analysis was performed in 10 out of 13 cases and eight of them demonstrated the presence of EWSR1 fusion gene rearrangement.

The presence of a vascular tumor thrombus has been cited as a distinctive feature of renal ESFT/PNET, and was noted in 56.2% of the cases reported by Zollner et al. as compared to 38.4% in our study and has been linked to a higher rate of pulmonary metastases, although our patients showed equal predilection for lung metastases regardless of the presence of a tumor thrombus. Six (46%) of our patients had an initial diagnostic biopsy performed, as compared to 33.3% in a recent literature review (12). We believe many patients with renal ESFT do not undergo initial biopsy prior to nephrectomy, due to similar presentation to renal cell carcinoma, thereby precluding the delivery of upfront systemic chemotherapy. The standard treatment of non-metastatic renal ESFT has been widely accepted as nephrectomy with neoadjuvant and adjuvant chemotherapy (13). However chemotherapy alone may be sufficient to produce long term survival in patients with metastatic disease, with durable complete remissions and potential cure in a few patients, as we previously reported (3). The majority of patients (94.1%) in the Zollner et al review received local therapy with surgery or radiotherapy, or both, with 37.5% of patients having metastatic disease at diagnosis. In contrast, only 69% of patients in our series underwent surgery and no patients received radiation, with 46.1% of patients having metastatic disease at presentation. This highlights the importance of chemotherapy and no local therapy in the treatment of metastatic ESFT.

Subclinical metastatic disease is present in 80%–90% of ESFT of the bone, with overt metastases occurring in less than 25% of cases, however renal ESFT tends to present with overt metastases more frequently (14) as we noted in our series. In a large series of 182 patients with ESFT/PNET, the 5-year OS rate was reported to be 41%, and the median OS for patients without metastatic disease was 61 months as compared to 14 months for patients with metastatic disease at presentation (15). Another study (16) of 16 ESFT patients reported a median OS of 15 months in five patients with metastatic disease. Results from our retrospective study showing a median OS of 17.2 months are consistent with those reported in the literature.

Conclusion

ESFTs of the kidney are exceedingly rare and can be clinically confused with RCC and may show histological overlap with other small round cell tumors. Ancillary studies including immunohistochemistry play an important role in differentiating them from other tumors. Our case series emphasizes the importance of performing a diagnostic biopsy in atypical renal masses, prior to nephrectomy, especially in patients with metastatic disease. An important goal is to avoid unnecessary surgery, as nephrectomy would delay and may even preclude the delivery of effective systemic chemotherapy, such as high-dose ifosfamide. Our data highlight the effective role of chemotherapy in achieving durable complete remission and potential cure without the need for nephrectomy in a few patients with ESFT even if they have metastatic disease. However, novel more effective therapies for ESFT are still needed.

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Table 1

Clinical, Pathological and Immunohistochemical features of ESFT

Case	Age, years	Sex	Smoking History	Presenting symptoms	Radiographic Findings (Site/Tumor thrombus)	Size, cm	Sites of Metastases	Pathologic Findings	CD99/ PAS Positive	FISH result	Biopsy for diagnosis
1	31	F	N	Abd mass	R/Yes	12.5	None	SRBCT, hemorrhage, necrosis,	+	neg	-
2	32	F	N	Flank pain/ hematuria	L/Yes	11	Lung retroperitoneum	SRBCT, minimal cytoplasm	+	neg	+
3	51	M	Y	R flank pain/ hematuria	R/No	13	Lung, liver, retroperitoneum, supraclavicular LNs	SRBCT, fibrosis	+	N/A	+
4	41	M	N	R flankpain/ fever/ wt loss	R/No	12	Bone, brain, retroperitoneum	SRBCT, rare pseudorossettes	+	FISH pos	+
5	34	M	Y	L testicular swelling	L/Yes	14	Lung and adrenal	SRBCT, fibrosis, rosette formation	+	FISH pos	+
6	44	M	Y	Abd pain	L/No	16.2	Retroperitoneum	SRBCT, necrosis	-	FISH pos PCR neg	+
7	31	M	Y	R kidney mass	R/No	Unknown	Lung, eyes, retroperitoneum, pulmonary vasculature	primitive high grade neoplasm	+	FISH pos	-
8	23	M	Y	Back pain, n/v	L/No	9	Lung	SRBCT	+	FISH pos	-
9	46	M		L flank pain	L/Yes	9	Retroperitoneum	SRBCT, undifferentiated	+	N/A	-
10	22	M	Y	Abd pain	L/No	7.2	Lung, retroperitoneum	SRBCT	+	PCR pos	-
11	25	M	Y	Flank pain/ hematuria	L/No	18	Lung	SRBCT, undifferentiated	+	N/A	-
12	20	M	Y	Flank pain/ nausea	R/No	7.7	Lung	SRBCT, necrosis	-	FISH pos	+
13	35	M	N	Hematuria	L/Yes	16	None	SRBCT, extending into renal vein, pelvis	+	FISH pos	-

Case	Age, years	Sex	Smoking History	Presenting symptoms	Radiographic Findings (Site/Tumor thrombus)	Size, cm	Sites of Metastases	Pathologic Findings	CD99/ PAS Positive	FISH result	Biopsy for diagnosis
								and perirenal adipose tissue			

R=right, L=left, FISH=Flourescent in-situ hybridization, PCR=Polymerase chain reaction, pos=positive, neg=negative, SRBCT=small round blue cell tumor, Abd=abdomen, wt=weight, N/A=not available

Table 2

Treatment and Follow-up Data

Case	Nephrectomy	Upfront Therapy	Treatment (Neoadjuvant/adjuvant)		Time between diagnosis and last follow-up, months	Dead	NED at last f/up
1	+	Adjuvant chemo, no RT	**1**	Dox 25 mg/m2 IV daily days 1–3 + ifos 2 gm/m2 IV daily days 1–4 alternating with	112.8	−	+
			2	Cis 20 mg/m2 IV daily days 1–5+ etop 80 mg/m2 IV daily days 1–5 × 15 weeks			
2	+	pre-surgical chemo, cytoreductive nephrectomy, post-op chemo, no RT	**1**	Etop IV and cis IV every 3 weeks × 2 cycles	10.9	+	−
			2	Etop 50 mg PO twice daily × 1 week then 1 week off			
			3	Paclitaxel 100 mg/m2 IV and cis 25 mg/m2 IV every 2 weeks × 2 cycles			
			4	Actinomycin-D 0.5 mg IV daily days 3–5, cyclophos 500 mg IV on day 5, and etop 100 mg/m2 IV daily days 1–5 × 3 cycles			
			5	Cis 35 mg/m2 IV, gem 600 mg/m2 IV, ifos 1000 mg/m2 IV every 2 weeks			
3	−	upfront chemo, no RT	**1**	Etop 133 mg/m2 IV daily days 1–3 and cis 33 mg/m2 IV daily days 1–3 alternating with	89.1	−	−
			2	Ifos 2000 mg/m2 IV daily days 1–4 and dox 25 mg/m2 IV daily days 1–4 every 3 weeks × 6 cycles			
			3	Vinc 2 mg IV X 1 dose, dox 25 mg/m2 IV daily days 1–3, ifos 1000 mg/m2 IV daily days 1–4 every 3 weeks × 3 cycles			
			4	Etop 100 mg po daily × 3 weeks, then 1 week off; then etop 100 mg po daily × 2 weeks, then 2 weeks off			
4	−	upfront chemo, no RT	**1**	Cyclophos IV, dox IV, vinc IV × 3 cycles	11	+	−
			2	Ifos IV, etop IV × 2 cycles			
			3	Cyclophos IV, dox IV, vinc IV × 1 cycle			
5	+	Adjuvant chemo, no RT	1) Dox 25 mg/m2 IV daily days 1–3, ifos 2500 mg/m2 IV daily days 1–3 every 3 weeks × 3 cycles		6.5	+	−
6	−	upfront chemo	2) Vinc 2 mg IV × 1 dose, dox 75 mg/m2 IV, cyclophos 1200 mg/m2 IV × 4 cycles Irino 16 mg/m2 IV daily days 1–5 and 8–13 × one cycle		9.1	+	−
7	+	adjuvant chemo	**1**	Carbo IV, gem IV	33.9	+	−
			2	Cis IV, gem IV, ifos IV			
8	+	adjuvant chemo	**1**	Vinc 2 mg IV × 1 dose, dox 25 mg/m2 IV daily days 1–3, ifos 2000 mg/m2 IV daily days 1–5 every 3 weeks × 6 cycles	27.4	+	−

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Case	Nephrectomy	Upfront Therapy	Treatment (Neoadjuvant/adjuvant)		Time between diagnosis and last follow-up, months	Dead	NED at last f/up
			2	Ifos 2500 mg/m2 IV daily × 5 days × 5 cycles			
			3	Irino 20 mg/m2 IV daily days 1–5 and 8–12 every 3 weeks × 2.5 cycles			
9	+	adjuvant chemo	**1**	Vinc 2 mg IV, dox 75 mg/m2 IV, cyclophos 1200 mg/m2 IV × 6 cycles	93.6	+	−
			2	Irino 16 mg/m2 IV daily days 1–5 and 8–12 every 4 weeks × 6 cycles			
			3	Gem IV, docetax IV × 4 cycles			
			4	Temsirolimus 25 mg IV, IGF-1 receptor antibody × 3 cycles			
10	+	adjuvant chemo	**1**	Vinc 2 mg IV, dox 75 mg/m2 IV, cyclophos 1250 mg/m2 IV × 4 cycles	17.2	+	−
			2	Vinc 2 mg IV, dox 75 mg/m2 IV, ifos 10 gram/m2 IV × 3 cycles			
11	+	adjuvant chemo	**1**	Vinc IV, dox IV, and cyclophos IV × 4 cycles	17.2	+	−
			2	Ifos 2000 mg/m2 IV every 12 hours × 7 doses × 2 cycles			
			3	Etop 100 mg PO daily × 3 weeks then 1 week off × 3 cycles			
			4	5-fluoro 4 gram/m2 IV continuous infusion over 4 days and interferon 10 million units SC daily × 5 days every 2 weeks			
12	−	upfront chemo	**1**	Vinc 2 mg IV × 1 dose, ifos 2500 mg/m2 IV daily days 1–4, dox 25 mg/m2 IV daily days 1–3 × 6 cycles	20.6	+	−
			2	Etop 100 mg/m2 IV daily days 1–5, cis 20 mg/m2 IV daily days 1–5 × 4 cycles			
			3	Etop 100 mg po daily × 3 weeks then 1 week off			
			4	Vinc 2 mg iv × 1 dose, irino 12 mg/m2 IV daily days 1–5 and 8–12, temozol 100 mg/m2 PO daily days 1–5 every 3 weeks × 4 cycles			
			5	Dox 75 mg/m2 IV and dexraz IV × 2 cycles			
			6	Etop 100 mg/m2 IV daily days 1–4 every			
13	+	adjuvant chemo	**1**	Vinc IV, dox IV, cyclophos IV × 8 cycles	25.5	−	+
			2	Vinc IV, irino IV, temozol PO × 6 cycles			

NED = No evidence of disease; f/u = follow-up; IV=intravenous; PO=oral; Carbo=carboplatin, cis=cisplatin, cyclophos=cyclophosphamide, dexraz=dexrazoxane, dox=doxorubicin, etop=etoposide, 5-fluoro=5-fluorouracil, gem=gemcitabine, ifos=ifosphamide, irino=irinotecan, temozol=temozolamide, vinc=vincristine

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