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Metastatic Extraosseous Ewing's Sarcoma (EES)/ Primitive Neuroectodermal Tumor (PNET) of the Kidney: 8-Year Durable Response After Induction and Maintenance Chemotherapy

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Keywords

Chemotherapy; Cytoreductive nephrectomy; Renal mass

Introduction

Primitive neuroectodermal tumors of the kidney (extraosseous Ewing's sarcoma [EES]/ primitive neuroectodermal tumor [PNET]) are classified within the Ewing's sarcoma family of tumors (ESFT), which include EES and Askin's tumor of the chest wall. ESFT share a common translocation, t(11;22) and (q24;q12), and often express the EWS-FLI1 fusion transcript by polymerase chain reaction testing.¹ The vast majority of cases occur in children and young adults, with patients over the age of 40 years representing a very small fraction of cases. The most common ESFT primary sites are bone and soft tissues, but cases arising from the kidneys, breasts, ureter, bladder, testes, seminal vesicles, ovaries, and lungs have been reported.^{2,3} Primary EES/PNET of the kidney are very rare, with few cases reported in the literature and no available randomized trials to guide treatment strategies.

We report a patient who presented with metastatic EES/PNET of the kidney, was treated with chemotherapy alone without local therapy, and achieved a durable clinical remission that has lasted longer than 8 years.

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Disclosure

All authors have no conflicts of interest.

Case Report

A 50-year-old Caucasian man presented with right flank pain and an episode of gross hematuria. Evaluation in July 2003 revealed a palpable abdominal mass and a palpable left supraclavicular lymph node. Computed tomography (CT) scans demonstrated a 15.9×10.6 cm mass in the right kidney (Figure 1A), appearing to originate from the renal hilum, with involvement of the renal fat and renal vessels, diffuse intrathoracic and abdominal lymphadenopathy, bilobar liver hypodensities, and numerous punctuate lesions in both lungs. Laboratory data showed hemoglobin 10.6 g/dL, serum lactate dehydrogenase 1814 IU/L (3 times upper limit normal), and normal serum calcium level. Bone scan and magnetic resonance imaging of the brain were normal. Bone marrow aspirate/biopsy and positron emission tomography were not recommended for routine staging work-up at the time of diagnosis and initiation of treatment and were not done.

The location of the main portion of the tumor, appearing to arise from the renal hilum, was unusual for renal cell carcinoma. An incisional biopsy of the left supraclavicular lymph node and a core biopsy of the renal mass were performed to rule out other malignancies in the differential diagnosis such as upper tract transitional cell carcinoma, collecting duct carcinoma, lymphoma of the kidney, or EES/ PNET of the kidney. This information was essential to obtain before considering treatment options, which would have included cytoreductive nephrectomy, if the pathology showed renal cell carcinoma. Pathology from both the kidney and the lymph node was similar and demonstrated a high-grade small blue round cell tumor with a prominent fibrotic background (Figure 2A). The tumor cells were positive for CD56 and CD99 and negative for pancytokeratin, MOC-31, chromogranin, and synaptophysin. A periodic acid schiff (PAS) stain performed on the lymph node biopsy demonstrated large amounts of intracytoplasmic glycogen in the neoplastic cells. Fluorescence in situ hybridization studies performed on interphase nuclei in paraffin-embedded sections of the lymph node biopsy revealed a clonal population of cells with rearrangement of the *EWSR1* (22q12) locus (Figure 2B), which supported the diagnosis of EES/PNET.

Chemotherapy was initiated with 3-week cycles of etoposide 133 mg/m^2 daily for 3 consecutive days and cisplatin 33 mg/m^2 daily for 3 consecutive days alternating with ifosfamide 2 g/m^2 per day for 4 days and doxorubicin 25 mg/m^2 per day for 3 days. After a total of 6 cycles (3 of each regimen); restaging showed decrease in the size of the right renal mass to $5 \text{ cm} \times 3.2 \text{ cm}$, with stable hypodense liver lesions, and minimal residual lymphadenopathy. He then received three 21-day cycles of vincristine 2 mg, doxorubicin 75 mg/m^2 by continuous infusion over 72 hours, and ifosfamide 2 g/m^2 daily for 5 days, with further reduction in the size of the renal tumor and stable liver hypodensities. Subsequently, he received oral etoposide for 15 months as maintenance therapy, and has been in clinical remission for more than 8 years. Recent CT imaging shows an atrophic right kidney with residual stranding (Figure 1B). Due to the continued response to chemotherapy and eventual disappearance of the primary tumor in the kidney and all the enlarged infra- and supradiaphragmatic lymph nodes, the patient did not undergo radiation or nephrectomy. We did not test for the differential function of the right kidney, however any potential functionality was preserved by avoiding radiation and surgery in this case.

Discussion

The most commonly used treatment regimens for ESFT include various combinations of vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide, and cisplatin and are well described in the literature.⁴⁻⁸ Miser et al described ESFT to be chemoradiosensitive tumors in a 1987 publication describing the outcome of 8 patients with metastatic disease who underwent combined modality treatment with chemotherapy and radiation, with 50% complete remission rate at 30 months.⁹ Two studies of 59 and 182 patients with ESFT treated with chemotherapy showed 5-year overall survival (OS) rates of 38% and 41%, respectively.^{10,11} One patient with renal EES/PNET was treated with surgery, radiation, cytokine therapy, and high dose chemotherapy with autologous stem cell transplant was reported and was alive at 34 months.¹²

Primary EES/PNET of the kidney are very rare, with few cases reported in the literature and no available randomized trials to guide treatment strategies.¹³⁻¹⁷ Casella et al¹⁸ reported 2 patients with metastatic EES/PNET of the kidney who were treated with cytoreductive nephrectomy and polychemotherapy regimens, followed by high-dose chemotherapy and autologous stem cell transplant. Thyaviahally et al reported a single-institution experience of 16 patients with primary EES/PNET of the kidney, who were treated with chemotherapy and radical nephrectomy, with few patients also receiving radiation. The median OS for 11 patients with disease confined to the kidney was 60 months, with 36% 5-year disease-free survival; however, for the 5 patients with metastatic disease, the median OS was 15 months. One case series reported on 4 patients with nonmetastatic EES/PNET of the kidney and 3 patients with meta-static EES/PNET of the kidney. The 4 patients with localized disease at presentation were treated with nephrectomy; 1 relapsed quickly and received salvage chemotherapy, while the other 3 received adjuvant chemotherapy. Only 1 patient did not relapse and was alive at 149 months. The 3 patients who presented with metastatic disease (all with metastasis to both the liver and lymph nodes) were treated with chemotherapy, without local therapy, with patients surviving 13.1, 26.5, and 62 months.¹⁹

Our case report illustrates the importance of obtaining a biopsy of a kidney tumor that appears atypical for renal cell carcinoma, and promptly initiating upfront combination chemotherapy, if the diagnosis of EES/PNET of the kidney is confirmed. Long-term disease-free survival can be achieved with chemotherapy alone. The role of cytoreductive nephrectomy (CN) is not defined in this patient population. It is our view that CN may not be necessary in the management of patients with metastatic EES/PNET of the kidney, may expose the patient to unnecessary major surgery, and may limit the ability to administer intensive chemotherapy regimens such as high-dose ifosfamide.

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Clinical Practice Points

- Extraosseous Ewing's sarcomas (EES)/primitive neuroectodermal tumors (PNET) of the kidney are rare.
- They are classified within the Ewing's sarcoma family of tumors (ESFT) and include those arising from the kidney.
- We report a patient who presented with metastatic EES/PNET of the kidney, was treated with chemotherapy without local therapy, and achieved a durable clinical remission that has lasted longer than 8 years.
- This case report illustrates the importance of obtaining a biopsy of a kidney tumor that appears atypical for renal cell cancer and promptly initiating upfront combination chemotherapy, if the diagnosis of EES/PNET is confirmed.
- The role of cytoreductive nephrectomy (CN) is not defined in this patient population.
- We believe that long-term disease-free survival can be achieved with chemotherapy alone.
- CN may not be necessary in the management of patients with metastatic EES/PNET of the kidney, and may limit the ability to administer intensive chemotherapy regimens such as high-dose ifosfamide.

Figure 1.
Computed Tomography Scans of the Abdomen Before (A) and After (B) Treatment

Figure 2.

Histology and Fluorescence in Situ Hybridization of Surgical Specimen (A) Lymph Node Biopsy Demonstrating Involvement by a High-Grade Small Round Cell Tumor. Inset: Tumor Cells Were High Grade With a High N:C Ratio and Abundant Necrosis. A PAS Stain Demonstrated the Presence of Intracytoplasmic Glycogen (Not Shown). (B) Fluorescence in Situ Hybridization Studies Performed With an Abbott Molecular *EWSR1* Breakapart Probe Demonstrated Rearrangement of the *EWSR1* Locus, Thus Supporting the Diagnosis of Ewing's Sarcoma/Primitive Neuroectodermal Tumor