

Renal primitive neuroectodermal tumour: Case series and brief review

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Abstract

Renal primitive neuroectodermal tumor is a rare malignancy. These tumours rarely present with caval involvement. We report 2 cases of primitive neuroectodermal tumours (PNETs) with inferior vena cava involvement. The initial presentation and outcomes differed significantly. The diagnosis was confirmed using histologic and pathologic analysis. We present a brief literature review and an outline of typical clinical and pathologic features of renal PNETs.

Case 1

A 17-year-old previously healthy male presented to the emergency department at the Health Sciences Centre with a 2-month history of persistent cough, 10-lb weight loss and 1 month of abdominal bloating. The patient also described an episode of gross hematuria after exercising. Physical exam revealed a non tender abdomen with fullness in the left upper quadrant. Initial blood work showed a creatinine (Cr 93) and mild anemia (Hgb 98). The patient's international normalization rate (INR) (1.8) and lactic acid dehydrogenase (LDH) (530) were elevated; however, all other liver function tests were normal.

A computerized tomography (CT) chest and abdomen were performed for further workup. We noted a large left renal mass measuring 14 × 11 cm with tumour thrombus extending to the infrahepatic inferior vena cava (IVC) with multiple regional metastatic lymph nodes, as well as lung metastasis (Fig. 1). A bone scan revealed no osseous metastatic involvement.

The patient underwent left radical nephrectomy, IVC tumour thrombectomy and retroperitoneal lymphadenectomy. The pathology revealed a 14.8 × 14 × 12-cm tumour

involving the entire left kidney, contained within Gerota's fascia and negative surgical margins. Two out of 11 lymph nodes were positive for malignancy. Initial immunohistochemistry showed tumour cells positive for vimentin, CD99, CD56 and p53 and negative for CD45, WT1, desmin and MyoD1. This suggested a poorly differentiated sarcoma or Ewing's family tumour. Molecular test by reverse transcriptase was performed and was positive for EWSR1-FLI1, which confirmed the diagnosis of Ewing's sarcoma/primitive neuroectodermal tumour (PNET).

The patient is now 12 months post-surgery and has received 12 cycles of chemotherapy on an alternating regimen of cyclophosphamide, adriamycin and vincristine (CAV) interchanged with ifosfamide/etoposide every 2 weeks. The patient has had a dramatic response to chemotherapy with regression of pulmonary metastases. Unfortunately, the patient has developed ifosfamide-induced Fanconi syndrome and nephrotoxicity. His serum creatinine is 630 and he may require dialysis.

Case 2

A 31-year-old male with a medical history of hypertension, recent diagnosis of deep vein thrombosis of the leg and reactive airway disease presented to a walk-in clinic with several weeks of general malaise, flank pain and gross hematuria. The patient had also experienced leg pain and cramping along with shortness of breath. An abdominal ultrasound revealed a renal mass and a Doppler ultrasound of the right lower extremity confirmed a deep venous thrombus involving the right lower extremity with nearly completely occlusive thrombus.

Physical examination revealed a palpable mass in the right upper quadrant with no associated tenderness. No palpable lymphadenopathy or peripheral edema was found. Bloodwork revealed a normocytic anemia (Hgb 111) and an elevated serum creatinine (Cr 127). Alkaline phosphatase



Fig. 1a. Computed tomography axial view showing left renal mass with extension of tumour into renal vein and vena cava.

tase (ALP 178), Gamma-glutamyl transpeptidase (GGT 492), and LDH (384) were all elevated. INR was elevated at 1.6. Several imaging studies were ordered to evaluate the extent of metastatic disease and for surgical planning. A CT abdomen demonstrated a 17 × 13-cm right renal mass with tumour thrombus extending to the intrahepatic cava and inferiorly to both common iliacs. Subsequent magnetic resonant imaging (MRI) of the abdomen and pelvis showed the renal mass with the tumour extending up the IVC and contralaterally into the left renal vein orifice. Extensive bland tumour thrombus was present within the cava and iliac veins below the tumour. No hepatic metastases were seen. The chest x-ray was unremarkable, however a CT thorax revealed small clusters of branching nodular opacities in the right lung. No evidence of pulmonary embolus was seen. Bone scan was negative for skeletal metastases.

The patient was admitted to hospital for urgent surgery and anticoagulation. An open right radical nephrectomy, caval thrombectomy, resection of the vena cava and retroperitoneal lymph node dissection were preformed. The IVC was tied off at its bifurcation and the renal and suprarenal cava resected en block with the mass. Bland thrombus was removed from the proximal cava prior to ligation. Intraoperative inspection of the gallbladder revealed acute on chronic inflammation with cholelithiasis. A cholecystectomy was performed as well. The patient tolerated the surgery quite well after an estimated blood loss of 5 L requiring hematologic support.

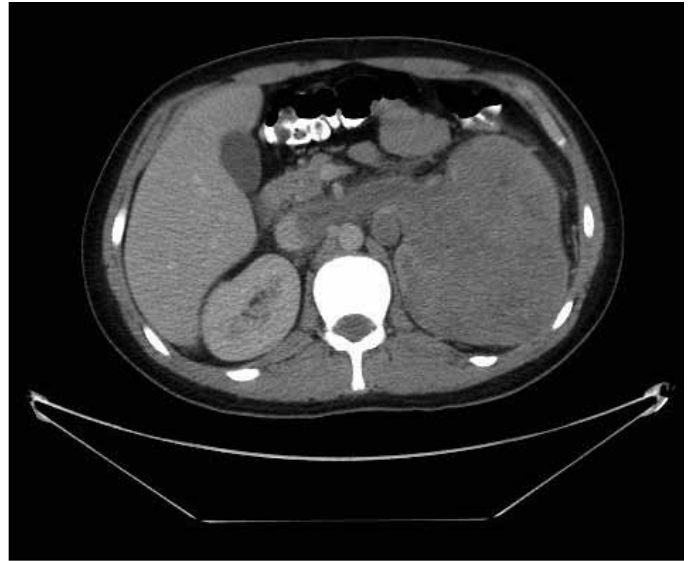


Fig. 1b. Computed tomography coronal view showing left renal mass with extension of tumour into renal vein and vena cava.

Pathology revealed a 17-cm tumour involving the right kidney with renal capsule and peri-renal fat involvement along with renal vein and vena cava invasion. There were no positive lymph nodes and no involvement of Gerota's fascia. Tumour cells were strongly positive for vimentin, focal positivity for CD99, BCL-2, NSE, focal weakly positive for Synaptophysin, CD 56, S-100, but negative for WT1, actin, chromogranin, CK7, CK20, p53, CD10, EMA, inhibin, and CD 45. Molecular tests were performed and showed positivity for EWSR1-FLI1 by reverse transcriptase protein:creatinine ratio. These findings confirmed the diagnosis of Ewing's sarcoma/PNET.

The patient was referred to medical oncology and adjuvant chemotherapy of 6 cycles of CAV (cyclophosphamide, adriamycin, and vincristine), alternating with 6 cycles of VP-16 ifosamide. Consultation with radiation oncology was also obtained; however radiation was not offered. Imaging after the initiation of chemotherapy showed pulmonary, hepatic, and abdominal lymphadenopathy consistent with metastases. After completion of this chemotherapeutic regimen, the patient had unfortunately continued disease progression and was switched to gemcitabine/docetaxel. Palliative care started 1 year after surgery and the patient died of the disease shortly thereafter.

Discussion

PNETs are small round cell tumours that arise from cells of the primitive ectoderm and comprise 1% of all sarcomas. These tumours are part of the Ewing's sarcoma/PNET family of tumours and exhibit neuroepithelial differentiation. Their location is typically in the trunk or axial skeleton as a bone or soft tissue mass, and rarely in the genitourinary system.

The first report of renal PNET was by Seemayer and colleagues and to date there have been few reports.^{1,2-7} There are even fewer cases of renal PNET with extension into the IVC.⁸⁻¹¹ PNETs are characterized by an aggressive clinical course and poor prognosis. The mean patient survival is about 10 months.¹² The first patient we presented not only had IVC extension, but also showed remarkable response to treatment. This patient has survived 12 months to date and has had a dramatic response to treatment. The second patient also had renal vein involvement; however invasion into the vena cava was also noted along with bland tumour thrombus extending bilaterally to the iliac veins. To the best of our knowledge, there have only been 2 other case reports of caval thrombectomy in patients with PNET.¹³

Renal PNETs typically occur in young adults. Patients with renal PNET present with non-specific symptoms which may include malaise, fever, flank pain, hematuria, night sweats, and dyspnea. Serum biochemistry values may show elevated LDH, glutaminoxaloacetic transaminase, glutamic-pyruvic transaminase, and creatinine.¹³ These tumours have various different macroscopic presentations. Gross inspection reveals a lobular shape with either dark brown, yellow, or gray-white areas of necrosis or hemorrhage.¹³ The histologic hallmark of PNET is formation of Homer-Wright rosettes or pseudorosettes involving hyperchromatic cells. Several immune markers may be detected which include neuron-specific enolase (NSE), vimentin, synaptophysin and S-100. The immune marker CD-99 is present in virtually all tumours.¹³ The most common genetic mutation in PNETs is t(11;22)(q24;q12) and the second most common being t(21;22)(q22;q12).¹⁴ Molecular testing is helpful in situations with a confusing immunohistochemical profile. The diagnosis of renal PNET must include tumour morphology, immunostaining profile and occasionally genetic mutations.

Treatment may be a combination of surgery, chemotherapy and radiotherapy.^{12,13} Renal PNET is treated with similar chemotherapeutic agents used with Ewing's sarcoma given their biologic similarities. The typical chemotherapeutic agents used are vincristine, dactinomycin, adriamycin, cyclophosphamide, ifosamide and etoposide.¹⁵ The addition of ifosfamide and etoposide has been shown to improve overall survival in patients with non-metastatic skeletal Ewing's sarcoma.¹⁶ Neoadjuvant chemotherapy can improve surgical outcomes and potentially avoid adjuvant radiotherapy, which is often reserved for patients with positive margins after resection or involvement of Gerota's fascia.^{17,18}

Conclusion

These 2 case reports are unique as there have only been a few published case reports of renal PNETs with caval involvement. Both patients had varying clinical presenta-

tions and outcomes. Renal PNETs are rare tumours with a poor prognosis. These cases outline the difficulty in diagnosis, management, and variation in natural history. Unique histologic features, immunostaining profile, and genetic features are important in making the histologic diagnosis. Our report shows that a multidisciplinary approach is essential in the management of renal PNET, and some patients may respond more favourably than previously thought.

Competing interests: Dr. Krocak, Dr. Sharda and Dr. Al-Essawi all declare no competing financial or personal interests. Dr. Drachenberg has attended Advisory Boards for Astellas and Janssen and has been a speaker for Amgen and Actavis (formerly Watson). He has also been an investigator in clinical trials run by Cancer Care Manitoba (CCMB).

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