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Primary Renal Rhabdomyosarcoma in an Adolescent With Tumor Thrombosis in the Inferior Vena Cava and Right Atrium

A Case Report and Review of the Literature

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Abstract: Although the second peak of the age distribution of rhabdomyosarcoma (RMS) is at adolescence, renal RMS is extremely rare at this age group. This tumor is indistinguishable from other renal tumors based on clinical and imaging findings, and the diagnosis relies on histology and immunohistochemical staining. We report a unique case of adolescent renal RMS associated with tumor thrombus extending into the inferior vena cava (IVC) and right atrium.

An 18-year-old female adolescent presented with shortness of breath and palpitations, associated with right flank discomfort, and hematuria. A pleomorphic-type renal RMS with Budd–Chiari syndrome and arrhythmia induced by IVC and RA thrombosis was diagnosed. Despite complete tumor resection, the patient developed multiple lung metastases a month after surgery. Chemotherapy was recommended, but the patient declined. She died within a year of the initial operation.

Adolescent renal RMS is rare and associated with poor outcome. Early aggressive multimodal therapy seems to be appropriate, in particular, in the presence of tumor thrombosis.

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Abbreviations: CT = computed tomography, EKG = electrocardiography, HMB-45 = human melanoma black-45, INI-1 = nuclear integrase interactor-1, IVC = inferior vena cava, MyoD1 = myogenic differentiation-1, RA = right atrium, RCC = renal cell carcinoma, RMS = rhabdomyosarcoma, RS = sarcomeric

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actin, RV = right ventricle, SC = smooth muscle, WHO = World Health Organization, WT-1 = Wilm's tumor-1.

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children, with the second peak of bimodal age distribution at adolescence.^{1–3} The head and neck, genitourinary system, trunk, and extremities are most commonly involved.² RMS in the genitourinary system represents ~25% of all adolescent cases of RMS; but only 1 case of renal RMS has been reported.^{3,4} The prognosis of RMS is poorer in adolescents than in other age groups, so these tumors should probably be treated as a distinct entity.^{1,5–8} The rarity of adolescent renal RMS has impeded research and prevented advances in the diagnosis and treatment of this cancer. We present a case of an adolescent with a renal RMS presenting with tumor thrombosis extending into the inferior vena cava (IVC) and right atrium (RA) and review the literature.

CONSENT

The patient's father signed the necessary documents to consent to the use of her data for teaching and publication.

TABLE 1. Significant Abnormal Laboratory Data

Laboratory Studies	Data	
Hematological profile	WBC	12990 μ L
	RBC	3.8×10^6 μ L
	Hemoglobin	9.7 gm/dL
	Hematocrit	29.3 %
Liver function profile	AST	46 IU/L
	Total bilirubin	2.35 mg/dL
	LDH	371 U/L
	Albumin	2.9 g/dL
Inflammation profile	CRP	6.12 mg/L
Coagulation profile	PT	21.4 seconds
	INR	1.82
	D-dimer	3723.06 ng/mL
	Urinalysis	RBC
	Occult blood	3+
	Protein	30 mg/dL

AST = aspartate aminotransferase, CRP = C-reactive protein, HPF = high-power field, INR = International Normalized Ratio, LDH = lactate dehydrogenase, PT = prothrombin time, RBC = red blood cell count, WBC = white blood cell count.

CASE REPORT

An 18-year-old female presented with shortness of breath and palpitations. Her associated symptoms included right flank discomfort, abdominal pain, fatigue, 2 episodes of hematuria, and nocturia without oliguria. Physical examination revealed no specific abnormalities except for some engorged superficial veins on the abdominal wall. Her heart rate ranged from 45 to 116 beats/min, but the blood pressure was normal. Electrocardiography (EKG) revealed no abnormalities. The platelet count, blood urea nitrogen, serum creatinine, and electrolytes were within normal limits. Significantly abnormal laboratory data are described in Table 1.

An abdominal ultrasonography showed a 6-cm heterogeneous echogenic mass in the right kidney. On a subsequent computed tomography (CT) scan, the lesion demonstrated heterogeneous enhancement following the intravenous injection of iodinated contrast media (Figure 1). A tumor thrombus was seen extending from the right renal vein into the IVC to the left renal vein, to the RA, cranially, and to the level of the confluence of the common iliac veins, caudally. The liver demonstrated

heterogeneous enhancement showing a nutmeg pattern. Ascites and enlarged retroperitoneal lymph nodes were also noted. Echocardiography confirmed a large thrombus in the RA that protruded into the right ventricle (RV) during systole. A chest CT, bone scintigraphy, and bone marrow aspiration revealed no evidence of lung or osseous metastases.

The patient was taken to the operating room and during surgery markedly engorged collateral veins were noted in the retroperitoneum. The presence of tumor thrombus in the renal veins, IVC, and RA was confirmed. Cava wall involvement was observed. The renal pelvis and ureter were intact. A right atriotomy, thrombectomy of the IVC with partial wall resection and reconstruction, radical nephrectomy, and retroperitoneal lymph node dissection were performed. Hepatic congestion resolved after the thrombus was removed.

Pathological examination demonstrated a 7.6-cm multi-lobulated mass, originating from the right kidney (Figure 2). Surgical margins were tumor free. The tumor was composed of ovoid and pleomorphic tumor cells with hyperchromatic, bizarre nuclei, and eosinophilic cytoplasm (Figure 3A).

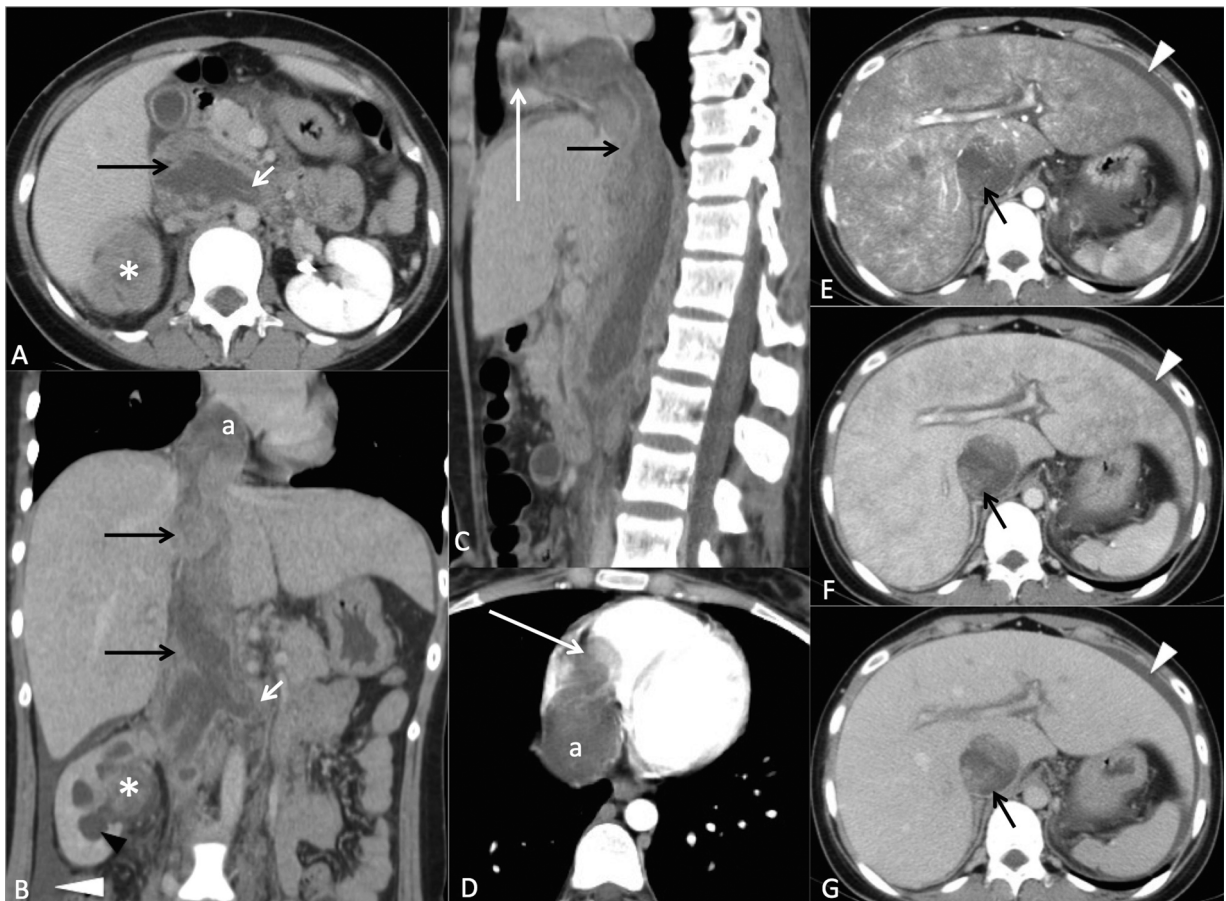


FIGURE 1. Axial (A), coronal (B), and sagittal (C) sections from abdominal contrast-enhanced computed tomography indicating a heterogeneously enhanced mass in the right kidney (*) with venous thrombosis extending into the right renal vein (not shown) via the inferior vena cava (black arrows) into the right atrium (a) and left renal vein (short white arrow). Enhanced soft tissue components within the engorged inferior vena cava represent tumor thrombi. Hydronephrosis of the right kidney (black arrowheads) and ascites (white arrowheads) were also noted. Axial sections (D) and sagittal sections (C) of the heart revealed a tumor thrombus protruding into the right ventricle (long white arrows). Axial sections in arterial (E), portal (F), and delayed venous phases (G) of contrast-enhanced computed tomography revealed mottled liver enhancement with periportal edema related to hepatic venous outflow obstruction.

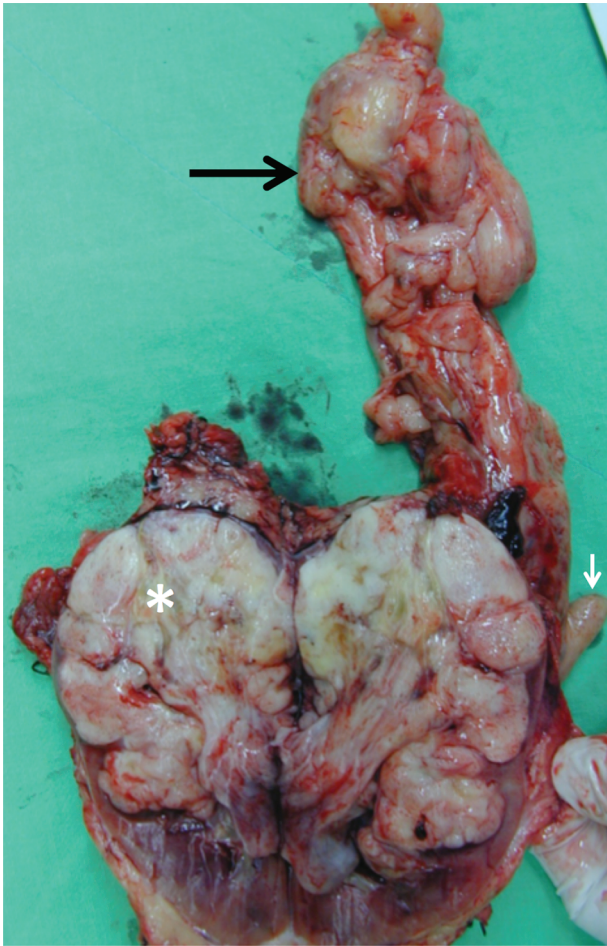


FIGURE 2. Tumor gross pathology. Radical nephrectomy specimen reveals a multilobulated, whitish mass (*) in the upper to middle poles of the right kidney. Tumor thrombus is observed the inferior vena cava (black arrow) and left renal vein (white arrow).

Abundant giant tumoral cells were observed within a myxoid background with focal tumor necrosis and hemorrhage. Neither blastemal nor epithelial components were detected. All dissected lymph nodes were negative for malignancy.

The tumor demonstrated positive cytoplasmic staining for vimentin, desmin, Wilm's tumor-1 (WT-1), and myogenic differentiation-1 (MyoD1), and retention of nuclear integrase interactor-1 (INI-1) staining (Figure 3). Cytokeratin, renal cell carcinoma (RCC), human melanoma black-45 (HMB-45), smooth muscle actin, and sarcomeric actin were all negative. Based on the surgical and pathological findings, a pleomorphic RMS with Budd–Chiari syndrome induced by IVC and RA thrombosis was diagnosed.

The patient had an uneventful postoperative recovery. Adjuvant chemotherapy was recommended, but the patient declined further treatment. A chest radiograph and a chest CT scan obtained a month after surgery showed multiple lung metastases. Chemotherapy was again recommended, again declined. The patient opted for seeking a second opinion elsewhere and died within a year of the initial operation.

METHODS

Immunohistochemistry

The tissue sections were dewaxed with xylene and rehydrated with decreasing ethanol concentrations ending with distilled water. The following primary antibodies were used: vimentin (cat no: NCL-L-VIM-572, Leica Microsystems, clone SRL 33), desmin (cat no: M076029, Dako Corporation, clone D33), Wilm's tumor-1 (WT-1) (cat no: NCL-L-WT1-562, Leica Microsystems, clone WT49), myogenic differentiation-1 (MyoD1) (cat no: M351201, Dako Corporation, clone 5.8A), nuclear integrase interactor-1 (INI-1) (cat no: Z2177, ZETA, clone 25), Cytokeratin (cat no: NCL-AE1/AE3, Leica Microsystems, clone AE1/AE3), renal cell carcinoma (RCC) (cat no: NCL-RCC, Leica Microsystems, clone 66.4.C2), human melanoma black-45 (HMB-45) (cat no: NCL-L-HMB45, Leica Microsystems, clone HMB45), smooth muscle actin (cat no: NCL-L-MSA-594, Leica Microsystems, clone SC28), and sarcomeric actin (cat no: NCL-MYOTILIN, Leica Microsystems, clone RS034). All tissue sections were autoclaved (TM-327; Tomin Medical Equipment Co., Ltd., Taipei, Taiwan, ROC) in a Tris buffer (pH=9.0) for 20 minutes. After cooling to room temperature, all the tissue sections were incubated with 3% H₂O₂ for 15 minutes so as to block endogenous peroxidase activity. Subsequently, the tissue sections were incubated with primary antibodies for various intervals (8–16 hours) at room temperature. The biotinylated secondary antibody and the streptavidin–peroxidase conjugate (Universal LSAB2 kit; DakoCytomation) were then used according to the manufacturer's instructions. 3',3'-Diaminobenzidine (DakoCytomation) was used as a peroxidase substrate for developing the brown color and, subsequently, hematoxylin (Merck Ltd., Taipei, Taiwan, ROC) was used as a counterstain. The negative control was prepared using normal mouse serum instead of the primary antibody.

Literature Review

We searched the MEDLINE database for publications of human research in English, without publication date limits, up to March 2015, utilizing the indexed search terms “rhabdomyosarcoma” AND “kidney” or “renal” in “All Fields.” The references of collected articles were used to identify further relevant publications.

DISCUSSION

RMS is divided in 4 histopathologic subtypes: embryonal, spindle cell/sclerosing, alveolar, and pleomorphic types.⁹ The embryonal type of RMS usually occurs in children and usually affects the head and neck region, and the genitourinary tract, with a better prognosis. Alveolar RMS usually affects adolescents and young adults, whereas the other 2 subtypes usually affect adults in the head and neck, extremities or trunk and have poor prognoses.^{9,10} Renal RMS in adolescents is very rare, with 1 previous case of an embryonal type reported in the literature. Our patient presented with a pleomorphic type, which is typically seen in adults.³

The clinical presentation and laboratory results reflect the immune reactions to the cancer and the extent of tumor. Systemic signs and symptoms, pain, and a palpable mass are common.¹¹ The presence of arrhythmia and nocturia in our case is unusual, though, and may be explained by the extension of tumor thrombus into the RA and, during systole, to the RV. This

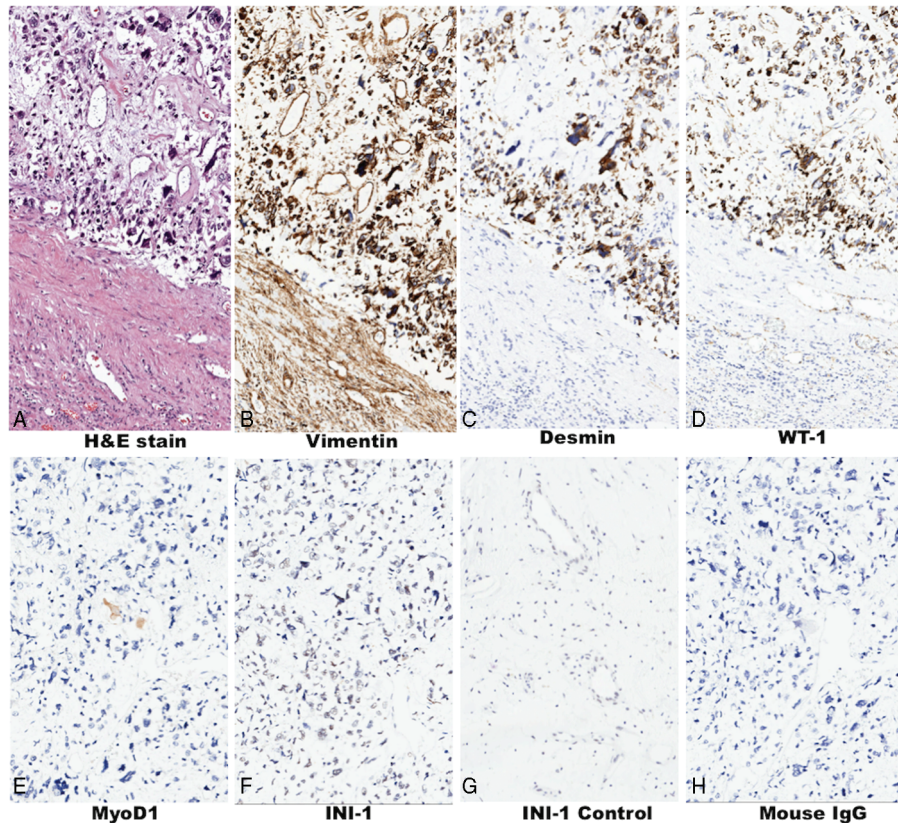


FIGURE 3. Tumor histology and immunophenotype. The upper portion in pictures A to D is tumor part and the lower portion is adjacent normal tissue. Pleomorphic tumor cells with bizarre nuclei are in a loosely textured background (A) (hematoxylin–eosin stain; original magnification $\times 200$). Immunohistochemical staining shows cytoplasmic positivity for vimentin (B), desmin (C), WT-1 (D), and MyoD1 (E). Nuclear INI-1 staining is demonstrated (F). Nuclear staining for INI-1 of vascular endothelium in brain is used as a positive control (G). Mouse IgG is used as a negative control (H) (B–L, original magnification $\times 200$). INI-1 = nuclear integrase interactor-1, MyoD1 = myogenic differentiation-1.

could have led to hypovolemia and stimulation of baroreceptor reflexes, leading to increased heart rate, peripheral arterial resistance, and retention of fluid through the renin–angiotensin system.¹² When the patient was laying down at night, the venous return increased, the heart rate reduced, and the retained fluid was excreted.¹² Clinicians should identify any underlying causes of arrhythmia in adolescents, as patients of this age have greater compensatory mechanisms for maintaining blood pressure. Anemia, leukocytosis, and elevated C-reactive protein are due to tumor-related inflammation. Pancytopenia may be found if the bone marrow is involved.¹³ Coagulopathy, abnormal liver, and renal function may be seen with thrombosis of the IVC. Our patient had extensive IVC thrombosis, but the well-established collateral circulation preserved her renal function.

Imaging features of renal RMS are indistinguishable from RCC or other sarcomas, but provides useful information for surgical planning, particularly in cases with venous thrombosis extending into IVC and heart.^{14,15} The diagnosis of a primary renal sarcoma, therefore, is based on histological and immunohistochemical results, and should fully fit the criteria proposed by Grignon et al.¹¹ Vimentin and myogenic regulatory proteins, such as desmin and MyoD1, are typically positive in cases of RMS.^{16–18} MyoD1 is a myogenic transcriptional regulator found in the cell nucleus and a specific marker for RMS. However, because of transactivation of myogenin, a proportion of pleomorphic RMS cases demonstrate only

cytoplasmic MyoD1 expression.^{19–21} Cytoplasmic MyoD1 staining is less specific for RMS and could also be seen in angiomyolipoma, perivascular epithelioid cell tumor, neuroblastoma, and Ewing's sarcoma because of cross reaction with undetermined proteins in the cytoplasm.^{22,23} Additional stains are obtained to differentiate RMS from other malignancies, for example, rhabdoid tumors, sarcomatoid RCC, angiomyolipoma, and Wilm's tumor.^{24–26}

No treatment guidelines for renal RMS have been established. Nephrectomy is usually the main treatment,²⁴ followed by adjuvant chemotherapy with vincristine, dactinomycin, and cyclophosphamide (VAC). Radiation therapy may be utilized for residual tumor and localized recurrences.^{7,8}

The impact of vascular invasion on the prognosis of patients with RMS is unknown.^{2,27,28} However, the rapid development of lung metastases in this case, in spite of the complete resection of the primary tumor, suggests these patients may have a higher risk for poor outcomes and could benefit from early aggressive multimodal therapy.

CONCLUSIONS

Adolescent renal RMS is a rare tumor with diverse clinical presentations and outcomes. The histologic subtype is either embryonic or pleomorphic. Currently, there is a lack of knowledge and consensus regarding the treatment of adolescent renal

RMS. Renal RMS with IVC thrombosis seems to require aggressive treatment, and multimodal therapy may play an important role. Further studies on the molecular biology and most efficacious treatments of renal RMS, with particular consideration of adolescent cases, are required to improve clinical outcomes. As this is a case-report, our conclusions are based only on data derived from this particular patient and the limited available literature. Any extrapolations must take into account this limitation.

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