Does Renal Mass with Venous Thrombosis always Indicate Renal Cell Carcinoma? A Case Series

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Intravascular tumor extension in the major renal veins or their tributaries, as a rare but important clinical entity that can change the disease stage, prognosis, and approach to treatment. There is limited literature on the obstruction of renal vein and IVC by tumor thrombus in other types of renal tumors that are not of RCC type. We presented four different renal tumor cases with the presence of gross renal vein or IVC thrombosis.
Although the incidence of renal vein and IVC tumor thrombus might be suggestive of (often diagnosed as) RCC, the possibility of other non-RCC renal tumors should be included in the differential diagnosis.

Keywords: nephrectomy; renal cell carcinoma; thrombus; venous thrombosis/surgery

INTRODUCTION

Renal vein tumor thrombosis describes the presence of intravascular tumor extension in the major renal veins or their tributaries, as a rare but important clinical entity that can change the disease stage, prognosis, and approach to treatment [(1,2)]. Various symptoms such as flank pain, flank tenderness, microscopic or gross hematuria, varicocele, lower extremity swelling, deterioration of renal function, proteinuria, and pulmonary embolism have been reported for tumor thrombus; however, most patients with tumor thrombus are asymptomatic[(3,4)].

Imaging modalities, such as ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) are the most accurate tools for detecting the presence of tumor thrombosis, evaluating the extension of the tumor, and differentiating it from the bland thrombus. However, differentiation and diagnosis of the exact type of renal tumors with tumor thrombosis might be challenging or might lead to misdiagnosis[(5,6)]. Histopathological evaluations and immunohistochemistry (IHC) are useful for the final diagnosis of the tumor type, and surgery is known as the primary potential treatment for renal vein tumor thrombosis in the absence of lymph node involvement and distant metastasis[(7)]. The propagation of tumor thrombus into the renal vein or the inferior vena cava (IVC) is a well-known manifestation of malignancies, including primary renal cell carcinoma (RCC), Wilms tumor, adrenal cortical carcinoma (ACC), and hepatocellular carcinoma (HCC)[(8,9)]. However, there is limited literature on the obstruction of renal vein and IVC by tumor thrombus in other types of renal tumors that are not of RCC type.
In this study, we presented four different renal tumor cases, including oncocytoma, leiomyosarcoma, urothelial carcinoma and Primitive Neuroectodermal Tumor (PNET), with the presence of gross renal vein or IVC thrombosis.

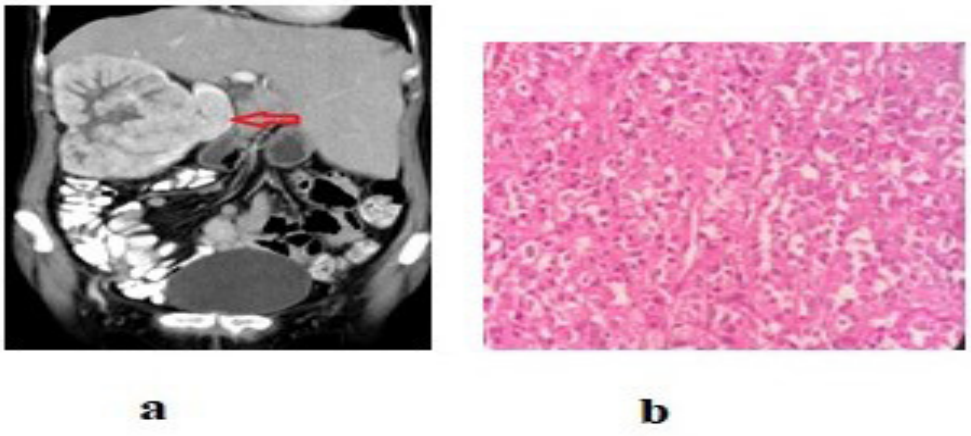

Figure 1(a): Right renal mass with vein thrombosis.1**(b)** Oncocytoma: Polygonal neoplastic large cells with eosinophilic granular cytoplasm (H & E stained).

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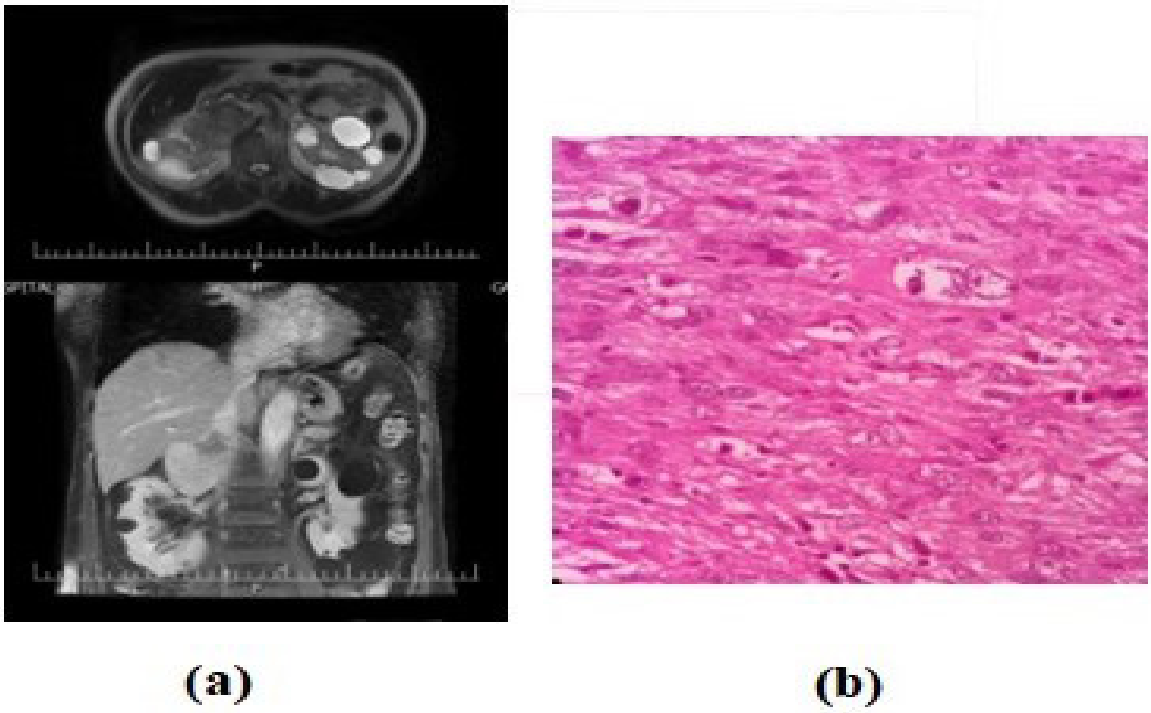

Figure 2(a).MRI: Tumor thrombus extended IVC near the atrium. **2(b)** Renal leiomyosarcoma: Spindle-shaped cells with atypical large pleomorphic nucleus (H & E stained).

CASE PRESENTATION

Patient 1

A 61-year-old woman with right side flank pain, pallor, and no previous/familial medical history was referred to the urology ward. On clinical examination, vital signs were stable; the abdomen was fine and had no palpable mass or organomegaly. Laboratory studies showed normal renal and liver function tests and hemoglobin 12.3 g/dl (normal range 12-15.5). Urine analysis did not reveal hematuria and pyuria. Ultrasonography (US) imaging revealed a large heteroechoic solid mass involving the right kidney, and the left kidney was normal. Contrast-enhanced CT scan showed a 10×11.5×13 cm heterogeneously enhancing lesion arising from the

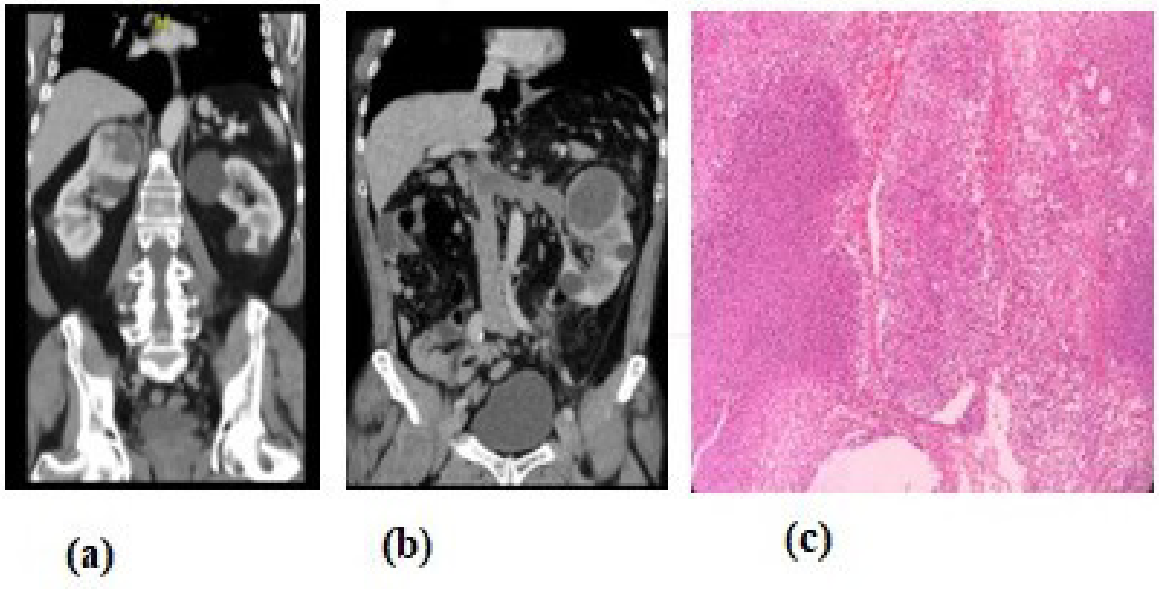

Figure 3(a). CT scan: Multiple cysts on both kidneys and heteroechoic solid mass in right kidney. **3(b)** CT scan: Left renal mass, renal vein thrombosis with extension to IVC. **3(c)** High grade urothelial carcinoma (H&E stained).

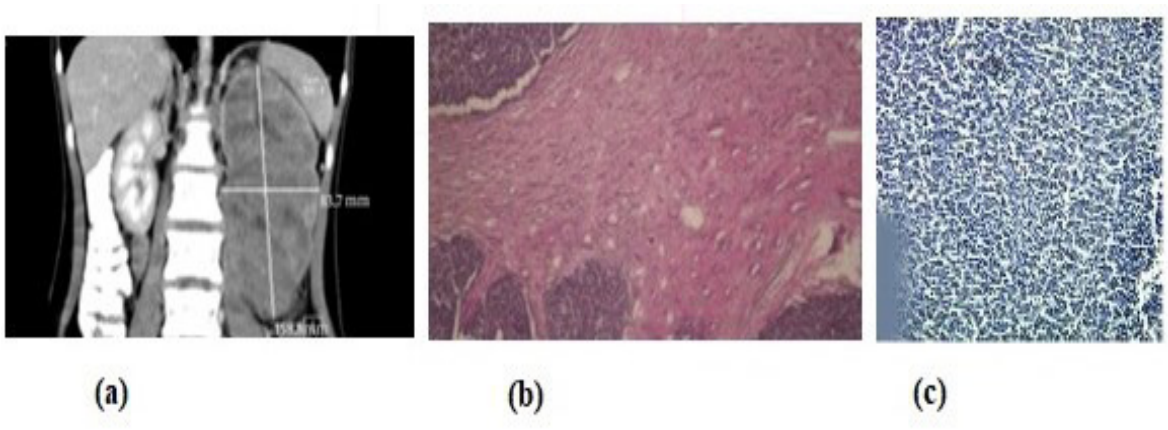

Figure 4(a) CT scan: Solid mass in the left kidney. **4(b)** PNET: Intrarenal tumor consists of solid sheets with intervening fibrous strands (H&E), **4(c)**: Calretinin

upper pole of the right kidney with a central scar, and revealed the presence of a tumor thrombus in the right renal vein with extension into the IVC. According to the Mayo Clinic grading system, tumor thrombus level 1 (**Figure1a**), the existing symptoms and paraclinical test results were suggestive of renal cell carcinoma. The patient underwent open radical nephrectomy via an anterior subcostal incision providing exposure for tumor thrombectomy. After the exposure of the renal veins, it was possible to gently palpate the tumor in the right renal vein and adjacent IVC. Nephrectomy was performed following the early ligation of the renal artery. The tumor thrombus was extracted after local control of the IVC and renal vein with a patch of IVC resected. Once the kidney and the thrombosis were removed, closure of cavotomy was done with 5-0 Prolene running suture.

In microscopic evaluations, well circumscribed lesion with polygonal neoplastic large cells with eosinophilic granular cytoplasm, round vesicular nuclei (sometimes double nuclei) without prominent mitosis, necrosis, or sarcomatoid component in the background of hyalinized stroma were observed.

IHC analyses were performed and data were consistent with the diagnosis of oncocytoma (**Figure1b**).

Patient 2

A 38-year-old woman was referred with right side flank pain, weakness, lethargy, and a history of hypertension. On clinical examination, she was pale with slight lower extremities pitting edema, the vital signs were stable, and the abdomen was soft with no organomegaly. On laboratory examinations, the urine, renal, and liver function tests were in the normal range. The hematocrit was 31.8%, and hemoglobin was 9.8 g/dL (normal range 12-15.5).

Based on the results of US and CT, both kidneys contained multiple cysts; however, the right kidney was enlarged and had a heteroechoic solid mass measuring 9×4×8 cm arising from the upper pole. A large tumor thrombus extended into the renal vein and IVC up to the hepatic vein and near the atrium, IVC tumor thrombus level 4. MRI confirmed the results, and the clinical diagnosis was RCC (**Figure 2a**).

The patient was a candidate for open right radical nephrectomy, adrenalectomy, and thrombectomy, in the open heart surgery operation room. Following the general anesthesia, the patient underwent a midline incision. After renal artery ligation, thoracotomy was performed. Cardiopulmonary bypass and total circulating arrest were performed. By controlling the IVC, the tumor thrombus that was extended near the right atrium completely resected through the longitudinal cavotomy, renal vein was resected. Nephrectomy and adrenalectomy were done and IVC was repaired and the patient was off pump. In microscopic evaluations, a homogenous mass consisted of spindle-shaped cells with atypical large pleomorphic nucleus and acidophilic cytoplasm with highly mitotic rate and focal necrosis. Degenerative vascular wall changes were present without tumoral involvement. Remnant of adrenal tissue was seen adjacent to the tumor. Based on histopathological and IHC findings, the final diagnosis was renal leiomyosarcoma (**Figure 2b**).

Patient 3

A 69-year-old non-smoking man referred to the urology ward with microscopic (Mic) hematuria (RBC 10-12). CT scan revealed a heterodense solid mass in the upper pole of the right kidney. There were multiple cysts with Bosniak I on both kidneys; however, only one Bosniak IIF cyst was observed in the left kidney (**Figure 3a**). He underwent a radical nephrectomy of the right side kidney. The histopathological diagnosis was clear cell RCC grade II (T1b N0M0). Six months after nephrectomy, liver and renal function tests were in normal limit, but urine analysis revealed microscopic hematuria (RBC 15-16).

The US and CT revealed the presence of a solid mass in the left kidney, which corresponded with the left renal cyst with Bosniak IIF in the first imaging finding. There was also renal vein thrombosis with extension to IVC, IVC tumor thrombus level 1 (**Figure 3b**).

There were no signs of tumor metastasis. The preoperative diagnosis was RCC, and the patient was again a candidate for nephrectomy.

Under general anesthesia and midline incision, the left renal vein was exposed. The left renal artery was ligated, and the IVC was controlled proximally and distally. The renal vein tumor thrombus of renal vein was totally resected with an IVC patch. The IVC was repaired with prolene 5/0.

Histopatholgical evaluations showed a cystic beige-colored mass with extensive necrosis. The neoplastic proliferation of elongated cells with nucleated nuclei, acidophil cytoplasm, and papillary pattern, extended to the connective tissue, sinus fat, and renal vein wall invasion were apparent. Based on the morphologic findings, the diagnosis was high-grade urothelial carcinoma in the renal pyelocaliceal system and renal vein tumor thrombosis (**Figure 3c**).

Patient 4

A 14-year-old girl referred to the urology ward because of chronic flank pain in the left side. Clinical examination revealed a huge, mobile mass in the left upper quadrant of abdomen. There were no other signs and symptoms. A spiral CT scan with oral and intravenous contrast also showed a huge solid mass (158*92*83 mm) in the left kidney with renal vein thrombosis (**Figure4a**).

Color doppler ultrasonography revealed high resistance of renal vessel flow in the left main renal vein suggesting venous thrombosis (IVC tumor thrombus level 1). HRCT of thorax showed multiple sub-pleural nodules in both lungs, which was suggestive of metastases.

The patient underwent laparotomy. The left renal artery was dissected and meticulously separated from renal vein and ligatured, and then the left radical nephrectomy was completed with renal vein and IVC patch resection.

Histopathologic examination showed sheets of small blue round cells with round nuclei, fine chromatin, and scant clear to slightly eosinophilic cytoplasm with numerous mitotic figures. Immunostaining for myogenin, desmin, CD45, and other lymphoid markers were negative; however, strong immunoreactivity for CD99 (O13, MIC2) was seen (**Figure 4(b,c)**. These data are consistent with the diagnosis of PNET.

DISCUSSION

The tendency of some tumor cells to spread to the venous system and IVC is not well understood. Tumor thrombus of the renal vein and IVC is not frequently observed in kidney tumors; however, almost 4% to 10% of the RCCs reveal renal vein thrombus, which is rarely seen in non-RCC renal tumors[10]. The incidence of tumor thrombus can affect the staging of cancer and change the treatment strategy. In some cases, thrombosis of the renal vein has non-specific symptoms and clinical manifestation to be diagnosed early and might be detected following the presence of severe complications. There is no specific laboratory test for detecting renal vein thrombus, and imaging is the primary diagnostic tool.

From March 2015 until January 2020, 572 patients with renal mass underwent open and laparoscopic nephrectomy surgeries. Of these, about 18 patients were diagnosed with venous thrombosis before surgery and underwent open radical nephrectomy and thrombectomy. We presented four different rare tumors with renal and IVC tumor thrombosis including oncocytoma and renal urothelial carcinoma, leiomyosarcoma and PNET. The presented cases did not have any significant changes in laboratory findings; only one patient with urothelial carcinoma had microscopic hematuria in laboratory results.

We performed different imaging modalities such as US, CT, and MRI for the four cases. The imaging techniques are noninvasive approaches with 100% sensitivity and specificity in detecting the incidence of the renal vein or IVC tumor thrombosis and clarifying the extent of the thrombus; however, they were not able to distinguish the exact kidney tumor type in any of the cases, and several histopathological evaluations were required. In all four cases, imaging findings revealed a hyper-echoic kidney mass characterized as the early phase of the renal vein thrombosis in 90% of the reported cases[11].

Renal oncocytoma accounts for 3%-7% of kidney tumors and is a common benign renal epithelial neoplasm; however, huge oncocytoma with thrombus increases the risk of hematogenous metastasis[12]. Based on the larger studies on oncocytoma, the incidence of renal vein thrombosis is less than 2% in these cases. In the study of Wobker et al., grossly visible tumor thrombus was reported in only two of the twenty-two oncocytoma, and the diagnosis was made only by H&E staining alone, not the IHC[14]. In the study of Hess et al., among the 324 patients diagnosed with oncocytoma from 1977 to 1990, tumor extension to vascular structures was grossly suspected in only five patients (1.5%). In all their patients, the final diagnosis was made following the histopathological analysis with a panel of immunochemical stains[13].

Similar to our patient, other presented cases of oncocytoma associated with renal vein thrombus had difficulties in distinguishing large oncocytomas from RCC via imaging modalities[12,14,15]. Based on the literature, oncocytic papillary RCC (PRCC), succinate dehydrogenase (SDH)-deficient RCC, eosinophilic, solid and cystic RCC (E SC RCC, and eosinophilic variant of ChRCC might be the differential diagnosis of oncocytoma[16].

Primary renal sarcomas are aggressive sarcomas with poor prognosis. They constitute lower than 1% of kidney malignancies; however, renal leiomyosarcomas as the most common type, account for almost 50% of all the renal sarcomas[17]. Renal leiomyosarcoma is more common in women than men, with increased risk by age. Renal leiomyosarcoma patients have clinical presentations similar to the RCCs, including flank pain, hematuria, and abdominal mass; therefore, the exact diagnosis is usually based on histopathological examination and IHC[18].

Leiomyosarcoma should be differentiated from the sarcomatoid variant of renal cell carcinoma, leiomyoma, and epithelioid angiomyolipoma following histological evaluations[15]. The origin of the lesions in our cases was from intrarenal blood vessels with the highest diameter of 7 cm. The presence of renal vein and IVC thrombosis is rarely reported in cases with leiomyosarcoma of renal origin. In two similar case reports, the renal vein thrombosis was observed in cases with renal leiomyosarcoma, and the differential diagnosis was malignant renal mass, likely RCC, by imaging evaluations[19,20].

Renal urothelial cell carcinoma (UC) accounts for lower than 10% of the renal carcinomas, which is usually symptomatic. The incidence of renal vein and IVC tumor thrombus in UC is almost 4%-7%[21]. There is little evidence regarding the macroscopic renal vein thrombus in UC of the kidney with a low number of reported cases. Our case also had persistent microscopic hematuria, no lower extremity edema, and the history of right radical nephrectomy due to clear cell renal carcinoma. In

this case, the presence of UC arising from renal calyceal with extensions to the renal vein was misdiagnosed as RCC in the preoperative differential diagnosis through imaging techniques of US and CT. In a series of 102 patients from 1990 to 2010 with renal TCC, only five patients revealed venous tumor thrombus (two had IVC involvement) with no gross hematuria[22]. Performing CT, MRI, and contrast-enhanced ultrasonography are accurate in detecting the tumor thrombus and estimating the size and position of the tumor thrombosis [23, 24]. Similar to previous reports, we performed nephrectomy with thrombectomy as the primary surgery strategy in the treatment of UC with renal vein tumor thrombus. In one similar study, the presence of infiltrative renal mass with venous involvement and maintaining the reniform shape of the kidney were proposed as possible indications of the TCC[25].

Peripheral neuroectodermal tumor (PNET) is a rare clinical condition and poorly differentiated neoplasm with neuroectodermal origin, first described in the 1990's. Since then, most features of this neoplasm have been presented through case reports, and there are few original articles in this context[26,27]. Based on the literature reviewed, fewer than 100 cases of PNET of kidney have been reported to date. However, the presence of venous thrombosis is not very common in this rare condition. This neoplasm mostly occurs in young males aged between 13 and 18 years[26,28].

Final diagnosis of renal PNET, confirmed by histopathological and immunohistochemical

Studies of the nephrectomy specimen reveal a small blue round cell tumor with diffuse membranous positivity for CD99[29]. The differential diagnosis of renal small round blue cell tumor includes Neuroblastoma, Alveolar rhabdomyosarcoma, Lymphoblastic lymphoma, and blastemal Wilm's tumor[30]. These tumors are high grade and their characterization without immunohistochemistry is often difficult. Therefore, immunohistochemical examination is necessary for the diagnosis of these tumors[31].

CONCLUSIONS

Although the incidence of renal vein and IVC tumor thrombus might be suggestive of (often diagnosed as) RCC, the possibility of other non-RCC renal tumors should be included in the differential diagnosis. More precise preoperative and intraoperative evaluations are needed to lead to correct diagnosis and decision making for effective treatment.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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