

Severe Acute Kidney Injury With Significant Uremia in an Infant Found to Have Inferior Vena Cava, Bilateral Renal Vein, and Bilateral Renal Artery Thromboses

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Background: Common neonatal etiologies of acute kidney injury (AKI) include renal vein and inferior vena cava thromboses, maternal use of nonsteroidal antiinflammatory drugs, and congenital renal disease. The incidence of renal vein thrombosis is estimated to be 0.5 per 1,000 neonatal intensive care unit admissions, with approximately half of cases extending to the inferior vena cava and with unilateral disease being significantly more common than bilateral. Data on abdominal venous thromboembolism in pediatric patients are limited, and the clinical presentation of renal vein thrombosis can vary, although most patients have at least one of the three cardinal signs: hematuria, thrombocytopenia, or abdominal mass.

Case Report: We present the case of a 5-month-old female transferred to our pediatric intensive care unit from an outside hospital with AKI and significant uremia (creatinine 6.01 mg/dL, blood urea nitrogen >200 mg/dL) secondary to inferior vena cava, bilateral renal vein, and bilateral renal artery thromboses. The patient was started on a heparin drip and subsequently underwent mechanical thrombectomy of her inferior vena cava and right renal vein in addition to site-directed tissue plasminogen activator to her renal veins, renal arteries, and inferior vena cava. Following the procedure, she developed severe coagulopathy and became hemodynamically labile. The coagulopathy was corrected, but further anticoagulation to prevent further thrombus propagation was not sustainable in the face of ongoing bleeding and hemodynamic instability, so the decision to withdraw mechanical support was made.

Conclusion: Because of the varied presentations of renal vein thrombosis and because prompt intervention significantly improves survival and renal outcomes, a high index of suspicion is warranted when risk factors and any of the three cardinal features of renal vein thrombosis are present.

Keywords: Acute kidney injury, anuria, intensive care–neonatal, intensive care–pediatric, thrombosis–venous, uremia

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INTRODUCTION

The definition of pediatric acute kidney injury (AKI) published in 2012 by the Kidney Disease: Improving Global Outcomes (KDIGO) work group is an increase in serum creatinine of at least 0.3 mg/dL within 48 hours, or an increase in serum creatinine to 1.5 times the patient's baseline either known or assumed to be within the prior 7 days, or urine output <0.5 mL/kg/hr for 6 hours.^{1,2} For infants in industrialized countries, intrinsic renal disease (glomerulonephritis, hemolytic-uremic syndrome, toxin/drug-mediated acute tubular necrosis) is the leading cause of AKI, although AKI related to surgery, organ and tissue transplantation, and severe infection is also frequently seen in hospitalized infants.^{3,4} Cases in the literature describing neonates with

AKI and significant uremia have varied etiologies, including renal vein and inferior vena cava thromboses (blood urea nitrogen [BUN] to 37.52 mg/dL, creatinine to 2.1 mg/dL)⁵; maternal use of nonsteroidal antiinflammatory drugs, including indomethacin (BUN >140 mg/dL and creatinine to 7.1 mg/dL in one case)⁶ and diclofenac (BUN to 85 mg/dL and creatinine of 2.3 mg/dL in one case)⁷; and congenital glomerular sclerosis (BUN to 115 mg/dL and creatinine to 8.2 mg/dL in one case).⁸ In general, beyond the neonatal period, the features of AKI and uremia in children become similar to those of adults.³

Data about abdominal venous thromboembolism in pediatric patients are limited, and current diagnosis and management guidelines rely heavily on extrapolation from adult

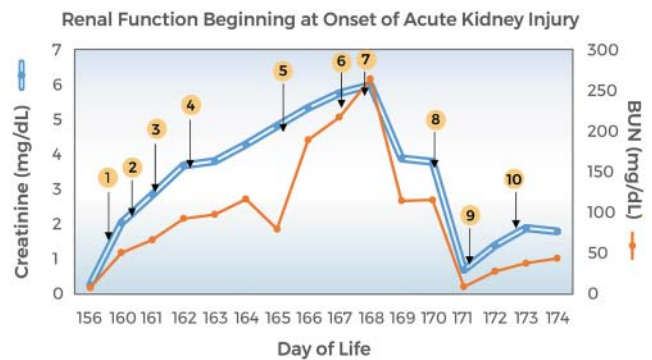
studies.⁹⁻¹¹ Maternal risk factors specifically for renal vein thrombosis include diabetes, hypertension, amphetamine use, and polyhydramnios.^{9,12} Neonate risk factors include perinatal asphyxia, respiratory distress, sepsis, hypotension, dehydration, inherited thrombophilia, use of central venous and umbilical catheters, and congenital heart disease.^{9,12} While approximately 90% of venous thromboembolisms in neonates are associated with central venous catheters, the majority of renal vein thromboses are non-catheter-related.^{10,13} The three cardinal features of renal vein thrombosis are hematuria (either microscopic or macroscopic), a palpable abdominal mass, and thrombocytopenia, although a classic presentation with all three is rare.^{12,14} Renal function at presentation can vary,^{5,9,13,15} and changes in blood pressure may only occur later in the disease course.^{13,16} Aortic and renal artery thromboses are strongly associated with umbilical artery catheter placement and commonly present with oliguric renal failure, hypertension, and hematuria.¹⁷

We present the case of a 5-month-old female transferred to our pediatric intensive care unit (PICU) with severe AKI and significant uremia (creatinine 6.01 mg/dL, BUN >200 mg/dL) secondary to inferior vena cava, bilateral renal vein, and bilateral renal artery thromboses associated with a right femoral Broviac line.

CASE REPORT

A 5-month-old preterm female was transferred to our PICU from an outside hospital neonatal intensive care unit (NICU). She was born at 24 weeks' gestational age via vaginal delivery for incompetent cervix, preterm labor, and prolonged rupture of membranes. She weighed 710 grams at birth and was 30.5 inches long; her head circumference was 21.5 inches. Her family history was negative for hereditary thrombophilias. She was intubated and mechanically ventilated shortly after delivery because of respiratory distress. The outside hospital records report that she was hypothermic with labile blood pressures and oxygen saturations and required bag-valve-mask ventilation on multiple occasions to correct hypoxemia. Umbilical arterial and venous catheters were placed shortly after birth and were removed prior to transfer, although the exact date is not known. After multiple failed attempts to maintain venous access using peripheral and peripherally inserted central catheter (PICC) lines, the patient received a left femoral Broviac line (Figure 1, arrow 1) that remained in place after transfer to our facility. On the same day the Broviac line was placed, the patient became thrombocytopenic, with platelets dropping from 439,000/ μ L to 79,000/ μ L.

Eight days prior to transfer, the patient's creatinine was noted to have increased from 0.3 to 2.0 mg/dL in a 4-day period (Figure 1, arrow 2). Renal ultrasound (Figure 1, arrow 2) demonstrated echogenic kidneys with flow documented bilaterally and increased resistive indices on the left side. The patient's records indicate that these findings were attributed at the time to renal insufficiency. She was intermittently treated with hydrochlorothiazide and Lasix (furosemide) before being transitioned to a Bumex (bumetanide) drip. One week prior to transfer, the patient was first noted to be oliguric and hyperkalemic, with a serum potassium of 10.7 mEq/L (Figure 1, arrow 3). Six days prior to transfer, the patient was noted to be anuric (Figure 1, arrow 4). Renal ultrasound 4 days prior to transfer (Figure 1, arrow 5) demonstrated



- 1 First documented decline in platelet count (439,000 → 79,000/ μ L) on day of life 158; Broviac line placed
- 2 First renal ultrasound: echogenic kidneys visualized, documented flow in both kidneys, increased resistive indices on the left side
- 3 First documented oliguria; hyperkalemia (potassium 10.7 mEq/L)
- 4 Anuria documented; intermittent scant hematuria
- 5 Second renal ultrasound + abdominal ultrasound: dampened arterial waveforms, renal arteries and veins still patent bilaterally
- 6 Third renal ultrasound + abdominal ultrasound: echogenic kidneys with almost complete obliteration of flow through the renal veins, increased echogenicity
- 7 Patient transfer to our hospital; initiation of SLED/SCUF (sustained low-efficiency dialysis/slow continuous ultrafiltration); abdominal ultrasound showed extension of inferior vena cava thrombus to the left renal vein; initiation of heparin drip
- 8 First cardiac catheterization procedure with inferior vena cava mechanical thrombectomy and angioplasty, inferior vena cava Possis rheolytic aspiration thrombectomy, right renal vein mechanical thrombectomy and angioplasty, site-directed TPA to both renal veins, and McNamara catheter placement
- 9 Second cardiac catheterization procedure with directed TPA administration to both renal arteries; Broviac line removed
- 10 Coagulopathy noted

Figure 1. Patient's timeline with renal function data.

dampened renal artery waveforms but patent venous and arterial systems. One day prior to transfer, a third renal ultrasound (Figure 1, arrow 6) demonstrated almost complete obliteration of the renal venous flow, increased echogenicity of the inferior vena cava suggesting venous thrombus, and high resistive flow in the renal arteries.

Upon admission to our hospital, the patient was hypertensive with blood pressures to 129/70 mmHg, but vital signs were otherwise stable. She was noted to be listless on physical examination, with bilateral lower limb swelling and pitting edema. Nephrology was immediately consulted, and the patient was placed on sustained low-efficiency dialysis/slow continuous ultrafiltration (SLED/SCUF) for ultrafiltration and clearance. Abdominal ultrasound demonstrated an occlusive thrombus within the inferior vena cava, as well as markedly decreased perfusion to both kidneys (Figure 1, arrow 7). Renal ultrasound demonstrated extension of the inferior vena cava thrombus to a nearly occluded left renal vein, while the right renal vein appeared to be patent (Figure 1, arrow 7). The patient was started on a heparin drip at 20 units/kg/hr. The patient's protein C, protein S, and antithrombin III levels were tested and found to be within normal limits.

The following day, the patient underwent cardiac catheterization to further evaluate the venous occlusions seen on ultrasound and was found to have inferior vena cava and bilateral renal vein occlusion (Figure 1, arrow 8, and Figure 2). She underwent inferior vena cava mechanical thrombectomy and angioplasty, inferior vena cava Angiojet rheolytic thrombectomy (Possis Medical Inc.), and right renal vein

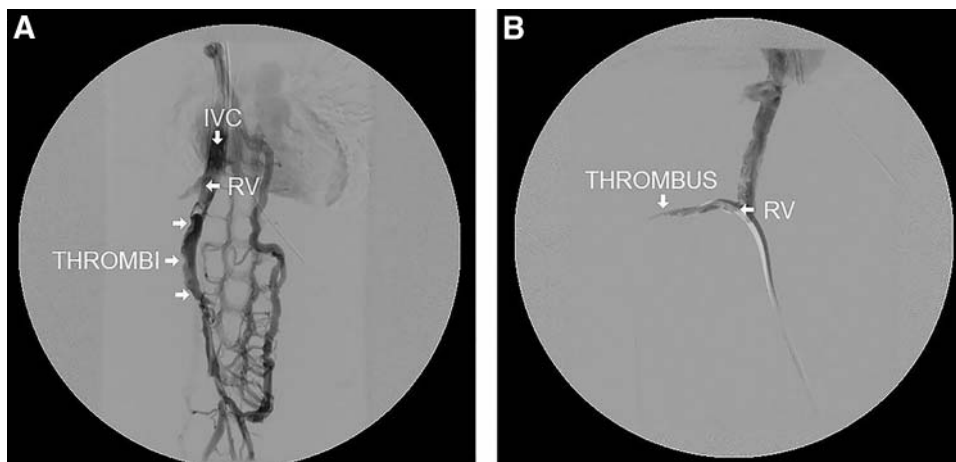


Figure 2. Angiography of the (A) inferior vena cava (IVC) (downward arrow) and right renal vein (RV) (leftward arrow) prior to angioplasty. Note the stenosis of the right RV and thrombi visible along the IVC. Angiography of the (B) RV (leftward arrow) shows significant thrombotic occlusion (downward arrow).

mechanical thrombectomy and angioplasty. She was administered site-directed tissue plasminogen activator (TPA) to both renal veins. The result of these procedures was improved patency of the patient's inferior vena cava with some flow demonstrated through the right renal vein but significant clot burden remaining in both renal veins (Figure 3). Extensive collateral circulation to the portal system was also noted at this time (Figure 4), and angiography of the innominate vein indicated possible subclavian stenosis with collateral circulation to the internal jugular vein (Figure 5). In a further attempt to resolve the remaining clot burden, a McNamara catheter (Medtronic) was placed, and upon arrival back in the PICU, the patient received an additional 0.014 mg/kg/hr TPA over 12 hours through the catheter with concurrent low-dose heparin administration at 10 units/kg/hr. When the patient returned to the catheter laboratory

the following day for evaluation of her renal arteries (Figure 1, arrow 9 and Figure 6), she was found to have extensive thrombi in her renal arteries bilaterally and underwent directed TPA administration to both renal arteries. Repeat angiography continued to show diminished flow through the renal arteries, with limited perfusion to the renal parenchyma and no return of contrast to the renal veins (Figure 7). She was continued on a heparin drip starting again at 20 units/kg/hr and subsequently titrated to maintain an anti-Xa level of 0.3-0.7 IU/mL. The highest dose of heparin she received was 34 units/kg/hr. Throughout her hospitalization, the patient received continuous renal replacement therapy.

During the next 24 hours (Figure 1, arrow 10), the patient developed severe coagulopathy from multiple sites, including her nose, mouth, arterial line, and dialysis catheter. She became hemodynamically unstable, requiring

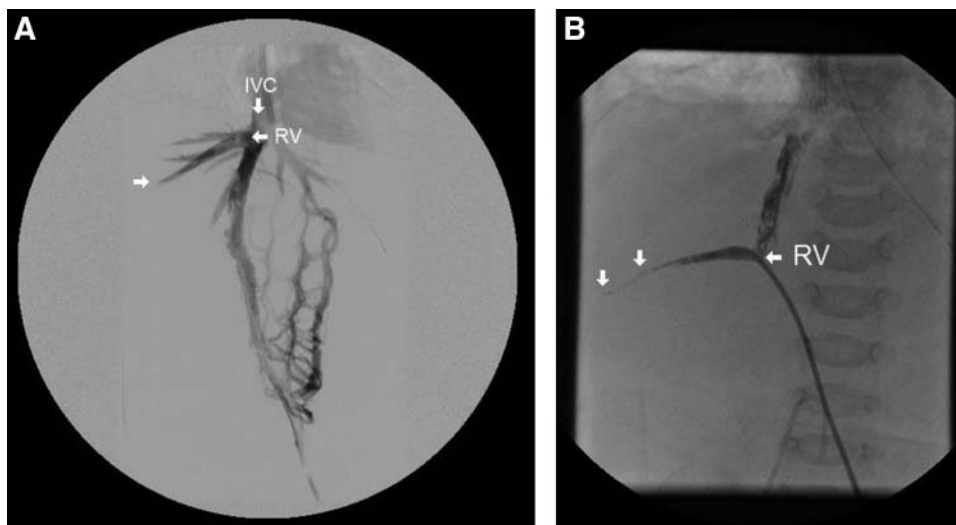


Figure 3. Angiography of the inferior vena cava (IVC) (downward arrow) and right renal vein (RV) (leftward arrow) following angioplasty. Note the slightly improved flow through the right RV (rightward arrow in view A, downward arrow in view B).

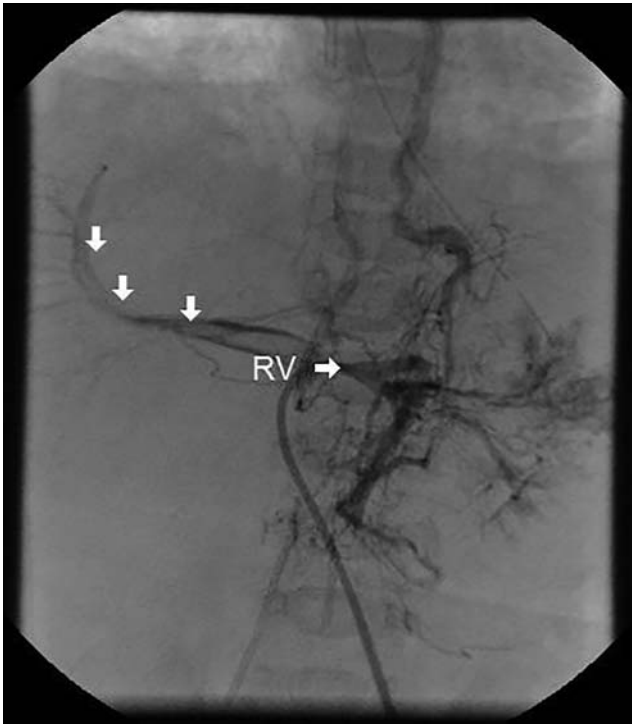


Figure 4. Angiography of the left renal vein (RV) (rightward arrow) shows collateral circulation to the portal system (downward arrows).



Figure 5. Angiography of the innominate vein (IV) (downward arrow) shows possible stenosis of the left subclavian vein (upward arrow) and collateral circulation to the internal jugular vein (rightward arrow).



Figure 6. Arteriogram of the abdominal aorta shows that bilateral renal arteries are not patent.

administration of an epinephrine drip at 0.02 mg/kg per minute. Even with correction of her coagulopathy, she continued to have sanguineous output from multiple sites and remained hemodynamically labile, requiring continued administration of epinephrine. Because of her persistent coagulopathy and hemodynamic lability, anticoagulants could not be administered to resolve the remaining clot burden. After a conversation with the family, the decision was made to withdraw mechanical support. The patient died comfortably, surrounded by her family.

DISCUSSION

The incidence of renal vein thrombosis is unclear, as large-scale epidemiologic studies have not been conducted¹⁴; however, international registry data estimate that renal vein thrombosis occurs in approximately 0.5 per 1,000 NICU admissions.¹⁸ Neonates have a significantly higher incidence of renal vein thrombosis than older children, possibly because of decreased levels of natural anticoagulants (eg, antithrombin, proteins C and S) and plasminogen, small vessel diameter, low renal perfusion pressure, and the double intracapillary network in the neonatal kidney.^{9,13} Renal vein thrombosis is also more commonly seen in males than females, unilateral thrombosis is significantly more common than bilateral, and left-sided thrombosis is more common than right.¹⁴ Approximately 7.3% of patients present in utero, 67.1% within the first 3 days of life, and 25.6% more than 3 days postnatally.¹³ Extension of the thrombus into the inferior vena cava is seen in approximately half of reported cases.¹³ In our literature review, we found no other cases of simultaneous bilateral renal vein, renal artery, and inferior vena cava thromboses from any cause in an infant or neonate,^{5,15,16,19,20} or any cases of AKI in an infant or neonate with a BUN >200 mg/dL.^{5-8,16}

Clinically, the presentation of renal vein thrombosis can be highly variable, and prompt diagnosis and treatment can

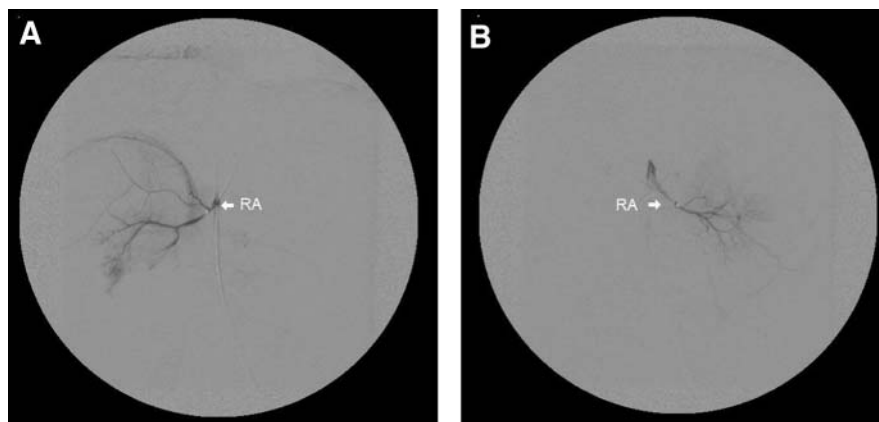


Figure 7. Arteriogram of the (A) right renal artery (RA) (leftward arrow) and the (B) left RA (rightward arrow) following tissue plasminogen activator administration. Note minimal flow through the right RA.

have a significant impact on mortality and long-term renal function.¹² As stated earlier, the three cardinal features of renal vein thrombosis are hematuria (macroscopic or microscopic), a palpable abdominal or flank mass, and thrombocytopenia; all three may not be seen at presentation, but most patients have at least one.^{5,12-15,17} Because a classic presentation is rare, Zigman et al recommended that a patient with any of these three signs plus known risk factors should be evaluated for renal vein thrombosis.¹² While many patients have renal insufficiency at presentation, not every case of renal vein thrombosis includes data on renal function, and the degree of renal dysfunction varies.^{5,9,13,15} Hypertension has also been described at presentation but is considered a late sign.^{13,16} The majority of inferior vena cava thrombi are extensions from the iliofemoral veins, usually caused by central venous catheters.⁹ Malfunction of a central venous line, superior vena cava syndrome, discoloration of the limbs, or dilated collateral vessels can all be signs of line-associated thrombosis.¹⁰ Our patient was born prematurely and experienced severe respiratory distress and hypoxia following delivery. Umbilical venous and arterial catheters, two PICC lines, and a femoral vein Broviac line were all used to maintain vascular access prior to her decline in renal function. All of these are described as risk factors for development of renal vein thrombosis.^{9,12} She first became thrombocytopenic 10 days prior to transfer (the same day her Broviac line was placed) and had documented hematuria 6 days prior to transfer, both of which are cardinal signs of renal vein thrombosis.^{12,14}

While contrast angiography is considered the gold standard for diagnosis of renal vein thrombosis, it is not always possible in critically ill pediatric patients.¹⁰ Ultrasound is most widely used because it is noninvasive, readily available, repeatable, and can be performed at the bedside.^{10,13} Early ultrasound findings in renal vein thrombosis may show enlargement of the kidney, increased echogenicity, and perivascular echogenic streaking that likely represents thrombus within the arcuate and interlobular veins; later findings are more likely to show thrombosis in the renal vein and inferior vena cava, loss of corticomedullary differentiation, atrophy, or calcification.^{9,13} In fact, kidney size in the early stages may predict loss of glomerular filtration rate and

long-term prognosis.⁹ Organization, calcification, resistance to thrombolytic therapy, and extensive collateral circulation are indications that the clot originated prenatally.¹⁹ While occlusion of the renal veins and inferior vena cava were not seen in our patient until the third ultrasound study the day before transfer, the literature shows that these findings on ultrasound can develop later in the disease course.^{9,13} Our patient's first two ultrasounds seem to have shown increased resistive indices and dampened arterial waveforms that may have been earlier signs of developing thrombosis, especially considering her risk factors and clinical features.

Treatment options available for renal vein thrombosis include supportive care with serial imaging, anticoagulation therapy alone with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH), thrombolytic therapy followed by UFH/LMWH, and surgery. According to current guidelines, bilateral renal vein thrombosis with evidence of renal impairment should be managed with either UFH/LMWH or thrombolysis followed by UFH/LMWH.²¹ TPA is preferred to other thrombolytic agents when indicated,^{21,22} and surgical thrombectomy is indicated in life-threatening cases.²¹ Complications of renal vein thrombosis include renal atrophy,^{5,13-15} renal failure,^{5,14,15,19,20} hypertension,^{13,20} adrenal hemorrhage,^{13,14} ischemic stroke,¹³ and pulmonary embolism.¹³ Recommendations are for neonates with central venous access devices (CVADs) to receive prophylaxis with continuous UFH and children with CVADs to receive intermittent flushing of the catheter with normal saline or heparin or recombinant urokinase.²¹ If the CVAD becomes blocked, local thrombolysis is recommended.²¹ Data support the infusion of UFH with fluids to maintain patency of central catheters and to prevent line-associated venous thromboembolism.¹⁰ Some evidence indicates that prophylactic anticoagulation with LMWH prevents deep vein thrombosis associated with central venous lines in adults, but randomized controlled trials have not been completed in neonates or infants.¹⁰

The development of such extensive renal vein, renal artery, and inferior vena cava thromboses in this patient with multiple risk factors was possibly multifactorial; however, the decline in her platelet count and renal function shortly after placement of the Broviac line makes its placement a

likely explanation for the development of her thromboses. According to the outside hospital records, the patient's echocardiogram showed a patent foramen ovale that may have allowed for paradoxical embolization from the inferior vena cava thrombus to the renal arteries; however, direct extension of the thrombus from the renal veins to the renal arteries is also possible. Notably, the first two ultrasound studies did not reveal more definitive findings, but given the other clinical features (thrombocytopenia, hematuria, AKI), thromboses were likely developing even before occlusion of the inferior vena cava and renal vessels was seen on ultrasound. An autopsy was not performed in this case, so we are unable to report if any signs of development of thrombosis in utero (organization, calcification) were present.

CONCLUSION

The presentation of renal vein thrombosis is varied; however, currently available data show that most patients have at least one of the three cardinal features. Our case is notable not only because of the severity of our patient's presentation, but also because this case shows that quite extensive disease can develop before occlusion of the renal vessels is obvious on ultrasound. Given the still-limited data about diagnosis and management of abdominal venous thromboembolism in pediatric patients, our case also illustrates the need for comprehensive research into the diagnosis and management of pediatric abdominal venous thromboses and of renal vein thrombosis in particular. For now, a high index of suspicion should be maintained for any patient with risk factors and one or more of the cardinal features.

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