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Successful kidney transplantation in case of completely occluded inferior vena cava and iliac veins: a case of inherited antithrombin deficiency

Trasplante renal exitoso en paciente con oclusión completa de vena cava inferior y venas ilíacas: un caso de deficiencia hereditaria de antitrombina

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INTRODUCTION

Produced in the liver, Antithrombin III, now simply antithrombin (AT), is a vitamin K-independent serine protease inhibitor in the coagulation pathway. It is the most important primary physiologic inhibitor of thrombin in the human body. In addition to thrombin, AT also inhibits other coagulation serine proteases including VIIa, IXa, Xa, XIa, XIIa. (1-2) The deficiency of AT may be inherited or acquired. The incidence of inherited AT deficiency is about 1:2000-5000 in general population and is the least common of the three main anticoagulant deficiencies (the other two being protein C deficiency and protein S deficiency). (3) Its inheritance is generally in autosomal dominant fashion. The resultant procoagulant state leads to unprovoked recurrent venous thromboses and thromboembolic events such as deep vein thrombosis or pulmonary embolism which generally appear at the post-pubertal period, compared to the very low occurrence in the prepubertal period.(4) The diagnosis is based on both quantitative and qualitative measurement of AT level.(5) The measured AT activity in functional tests in healthy subjects is generally around 80% to 120%, and AT level of less than 70% is considered as being AT deficiency. This evaluation should be made while not on anticoagulation therapy, because heparin decreases AT levels for up to 10 days following its discontinuation and warfarin increases its level. (6) Patients with inherited AT deficiency rarely develops renal failure which may be caused by renal vein thrombosis or glomerular injury associated with fibrin accumulation. (7) In these young patients with end stage renal disease (ESRD), renal transplantation is currently the best therapeutic option to improve the quality of life and to avoid the risk of complications of other renal replacement treatment particularly thrombosis of the hemodialysis access. Kidney transplantation in patients with an occluded iliac veins and inferior vena cava (IVC) is a very challenging surgery to perform.(8-9) Despite the reported success in few cases for children, kidney transplant surgeries with thrombotic diseases in adults remain very limited in the

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literature. Herein, we present a successful kidney transplantation by using a polytetrafluoroethylene (PTFE) graft in a young male patient with AT deficiency associated with totally occluded IVC and iliac veins.

KEYWORDS: antithrombin deficiency; venous thrombosis; vascular graft; kidney transplantation; renal function; imaging evaluation

INTRODUCCIÓN

Producida en el hígado, la antitrombina III, ahora simplemente antitrombina (AT), es un inhibidor de la proteasa de serina, independiente de la vitamina K en la vía de la coagulación. Es el inhibidor fisiológico primario más importante de la trombina en el cuerpo humano. Además de la trombina, AT también inhibe otras proteasas de coagulación de serina que incluyen VIIA, IXA, XA, XIA, XIIA.(1-2) La deficiencia de AT puede ser heredada o adquirida. La incidencia de la deficiencia de AT heredada es de aproximadamente 1: 2000-5000 en la población general y es la menos común de las tres deficiencias anticoagulantes principales (las otras dos son la deficiencia de proteína C y la deficiencia de la proteína S).(3) Su herencia es generalmente autosómica, modo dominante. El estado procoagulante resultante conduce a trombosis venosa recurrente y eventos tromboembólicos, como trombosis venosa profunda o embolia pulmonar, que generalmente aparecen en el período pospuberal, en comparación con la ocurrencia muy baja en el período prepuberal.(4) El diagnóstico se basa tanto en la medición cuantitativa como cualitativa del nivel de AT.(5) La actividad de AT medida en la en las pruebas funcionales en sujetos sanos es generalmente de alrededor del 80% al 120%, un nivel inferior al 70% es considerado como deficiencia. Esta evaluación debe realizarse fuera de la terapia con anticoagulación porque la heparina disminuye los niveles de AT hasta 10 días después de su discontinuación y la warfarina aumenta su nivel.(6) Los pacientes con deficiencia hereditaria de AT rara vez desarrollan insuficiencia renal, que puede ser causada por la trombosis de la vena renal o por lesión glomerular asociada con la acumulación de fibrina.(7) En estos pacientes jóvenes con enfermedad renal en etapa final (ESRD), el trasplante renal es actualmente la mejor opción terapéutica para mejorar la calidad de vida y evitar el riesgo de complicaciones de otros tratamientos de reemplazo renal, particularmente la trombosis del acceso vascular para hemodiálisis. El trasplante de riñón en pacientes con vena cava inferior (VCI) y venas ilíacas ocluidas es un gran desafío quirúrgico.(8-9) A pesar del éxito informado en pocos casos en niños, las cirugías de trasplante de riñón con enfermedades trombóticas en adultos siguen siendo muy limitadas en la literatura. En este documento presentamos un trasplante de riñón exitoso utilizando un injerto de politetrafluoroetileno (PTFE) en un paciente masculino joven con deficiencia de AT asociada con VCI y venas ilíacas totalmente ocluidas.

PALABRAS CLAVE: deficiencia de antitrombina; trombosis venosa; injerto vascular; trasplante renal; función renal; evaluación por imágenes

CASE PRESENTATION

A 30-year-old male patient who was diagnosed with renal failure secondary to glomerulopathy associated with inherited AT deficiency at a level of function measured as 36% of normal at the age of 11, applied to our Kidney Transplantation Department. Over the next 6 years, renal functions gradually declined to end stage renal disease (ESRD). During this time, with the development of posthrombotic syndrome due to recurrent deep venous thrombosis (DVT) and pulmonary emboli, regular anticoagulant treatment with warfarin was started. As a renal replacement treatment, after 2 years of peritoneal dialysis which was finished due to bacterial peritonitis, hemodialysis was started with a permanent subclavian catheter used for 6 months without complications like thrombosis during this time. His applications to many hospitals for kidney transplantation have been rejected due to the complete thrombotic occlusion of the IVC and iliac veins, which we also confirmed with pretransplant radiological evaluation. Intravenous (IV) contrast enhanced abdominopelvic computed tomography (CT) showed markedly reduced caliber of the common iliac veins (CIVs) and IVC with irregular outline, except its suprahepatic segment. The azygous and hemiazygous veins were dilated. The renal veins were thrombosed and kidneys were atrophic, more prominently on the right side **(Figure 1)**. There were diffuse extensive dilated venous collaterals involving the abdominal

walls, peritoneal, retroperitoneal and pelvic cavities **(Figures 1 and 2)**. As an incidental finding, an accessory right infrahepatic vein was also observed **(Figure 3)**. Venography from the right femoral vein showed obstruction of iliac veins and the IVC in association with patent venous collaterals. **(Figure 2)**

Figure 1.IV contrast enhanced portal venous phase abdominopelvic CT images show markedly reduced caliber of the IVC with irregular outline; intrahepatic IVC **(1a, *thick arrow*)**, renal IVC **(1b, *thick arrow*)**, and infrarenal IVC **(1c, *thick arrow*)**. Dilated azygous and hemiazygous veins **(1a, *thin arrows*) and** obviously atrophic right kidney is shown **(1b; *thin arrow*)**. Dilated venous collaterals involving the abdominal walls are visible **(1b, 1c, *short arrows*).**

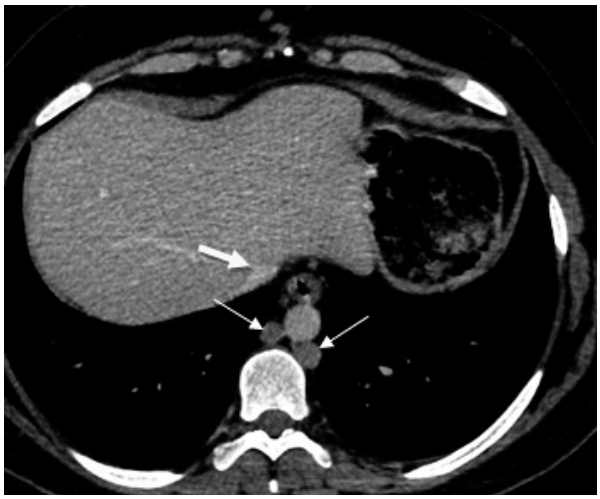

Fig. 1a.

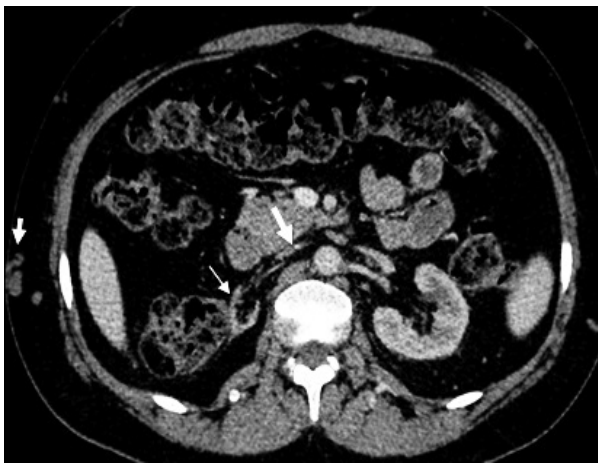

Fig. 1b.

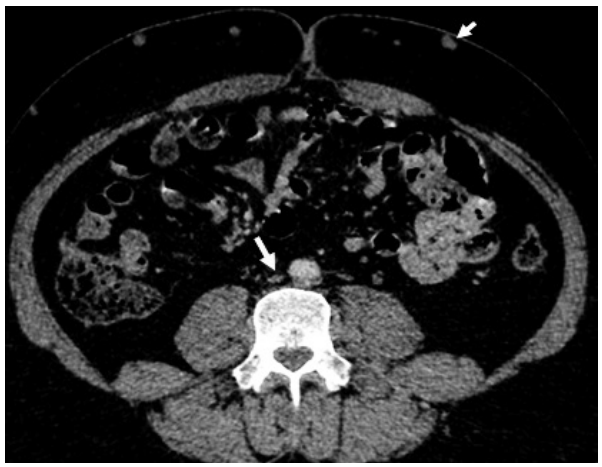

Fig. 1c.

Figure 2.
a, b) IV contrast enhanced portal venous phase abdominopelvic CT images show pelvic collateral veins **(2a, 2b, *thick arrows*).** Dilated venous collaterals involving the abdominal walls are visible **(2a, 2b, *short arrows*)**. **c)** Venography from the right femoral vein show obstruction of the IVC and iliac veins in association with dilated patent venous collaterals **(c, *thin arrow*)**

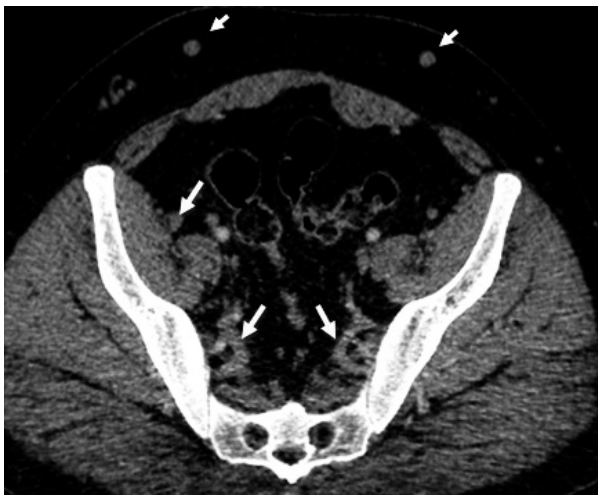

Fig. 2a.

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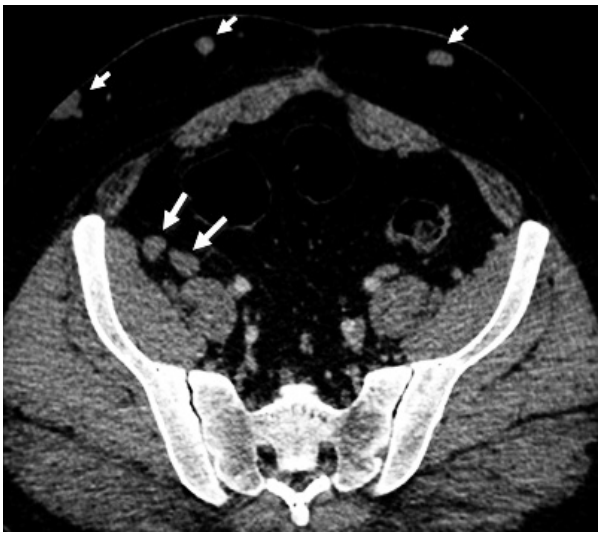


Fig. 2b.

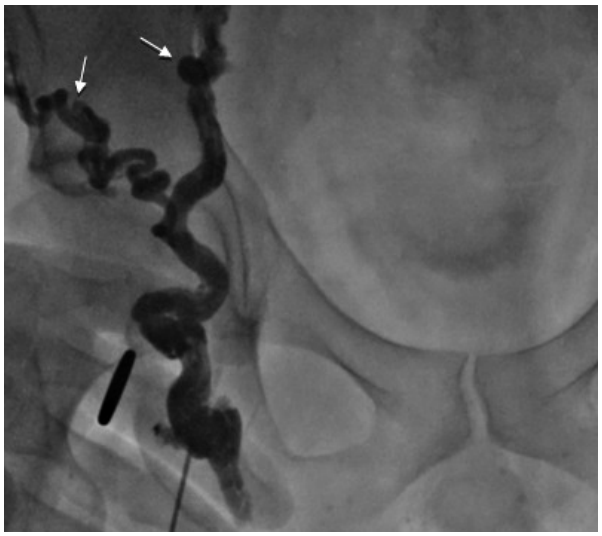
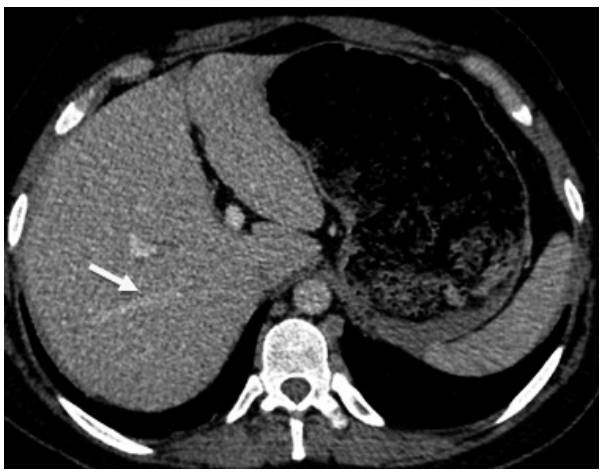


Fig. 2c.

Figure 3. IV contrast enhanced portal venous phase abdominopelvic CT image shows an incidental finding, an accessory right infrahepatic vein (***arrow***)



Considering the young age of the patient, we decided to try a new technique; the use of a prosthetic graft with anastomose to the IVC for a direct venous drainage. The difficulty of the procedure was explained to the patient and his family. After meeting with the transplantation team, the decision to perform living-related kidney transplantation from his father in whom AT deficiency was ruled out, was made. Their blood groups were the same, the panel reactive antibody (PRA) and the lymphocytes crossmatch tests were negative. He shared an haplotype with its donor regarding the human leucocyte antigen (HLA) compatibility for class I or class II. **(Table 1)**

Table 1. Donor and recipient HLA group

TEST	RECIPIENT	DONOR
HLA- A	A*01	A*01, A*11
HLA- B	B*40, B*57	B*15, B*40
HLA- C	C*06, C*15	C*08, C*15
HLA- DQA1	DQA1*01, DQB1*05	DQA1*01
HLA- DQB1	DQB1*02, DQB1*05	DQB1*05, DQB1*06
HLA- DRB1	DRB1*03, DRB1*14	DRB1*14, DRB1*15

Warfarin was discontinued and low-molecular-weight heparin (LMWH) was started 48 hours before the scheduled live-donor kidney transplantation. Since diffuse collateral vascularization was detected on both sides of the abdominal wall in the pre-operative imaging, a long median incision in order not to damage the collateral circulation was performed. A Cattell-

Braasch maneuver (complete mobilization of the distal small bowel, right colon, and duodenum) was performed to allow identification of the iliac vessels and IVC. The IVC, bilateral iliac and renal veins were found to be completely occluded and fibrotic. After mobilizing the right lobe of the liver, it was noted that the retrohepatic IVC was also thrombosed and fibrotic. Right nephrectomy was performed with the preservation of the distal part of the ureter for anastomosis with the transplanted kidney's ureter. The right hepatic vein was suspended and the accessory hepatic vein draining the segment 6 & 7 was ligated at its hepatic site. At its cava site, the accessory hepatic vein stump was extended downstream into the retrohepatic IVC, and a 14 mm PTFE graft was used to extend the transplant renal vein into the recipient's retrohepatic IVC **(Figure 4)**.

Figure 4: a) Intraoperative image shows the donor kidney **(*thin black arrow*),** venous graft with anastomosis to suprahepatic IVC **(*thick white arrow*)** and the arterial graft **(*short black arrow*)**. The site of renal vein anastomosis on the graft is shown **(*thin white arrow*)**. **b, c, d)** Postoperative CT images show the venous **(b, *arrow*)** and the arterial **(c, *arrow*)** grafts. The transplanted kidney with renal vein graft is shown **(d, *arrow*)**

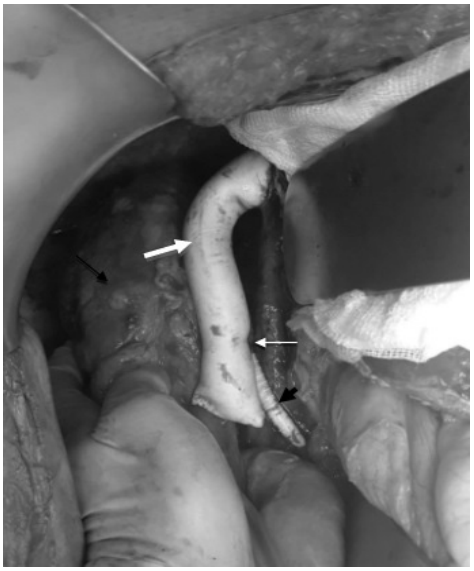


Fig. 4a.

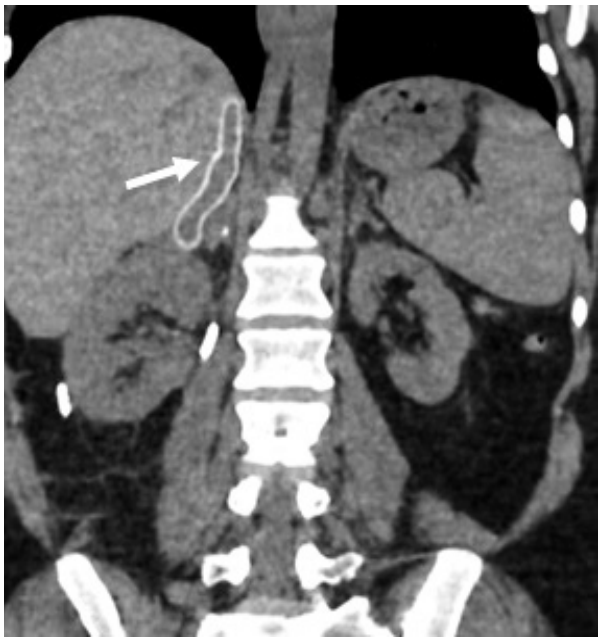


Fig. 4b.

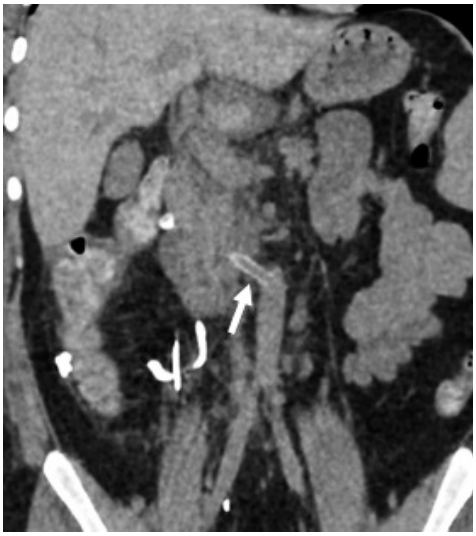


Fig. 4c.

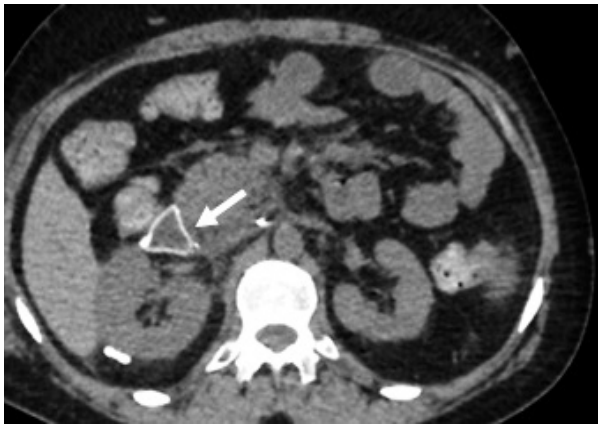


Fig. 4d.

Venous drainage was attained to the suprahepatic IVC. The renal artery of the graft was anastomosed to the aorta. After reperfusion of the graft, the kidney had good coloration. There was palpable pulse in

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the anastomosis of the kidney and an immediate function with the presence of urine was noted. Finally, uretero-ureterostomy was performed with a 12 F double J stent. 5000 units of intravenous heparin were given prior to the clamping of the IVC. Postoperatively, 5000 units of subcutaneous heparin was started every 8 hours and oral anticoagulation with low-dose warfarin was initiated. Heparin drip was discontinued 48 hours after the surgery. Low molecular weight heparin (LMWH) and warfarin were used together until reached INR of 2.5 on the postoperative day 6. It is also important to note that since plasma derived antithrombin is not available in Turkey, it could not be used in this patient. Induction therapy included antithymocyte globulin, methylprednisolone, mycophenolate mofetil (MMF), and tacrolimus (TAC). Maintenance immunosuppression consisted of 0,15 mg/kg TAC twice daily with blood level of 8 to 10 ng/ml in addition to 1000 mg MMF twice daily and steroid. The postoperative course was uneventful, with slightly delayed creatinine clearance without need for hemodialysis **(Table 2).** The patient was discharged on 7th postoperative day without any complications. One month after the transplantation, serum creatinine was 1.6 mg/dl with a glomerular filtration rate (GFR) of 62 ml/min. Doppler-ultrasound of transplanted kidney showed the patent vasculature with normal flow direction and resistive indices.

Table 2. Postoperative laboratory values

	Pre-op	1st day post-op	3rd day post-op	5th day post-op
creatinine	8.16 mg/dl	5.36 mg/dl	3.4 mg/dl	1.71 mg/dl
urea	90 mg/dl	73 mg/dl	88 mg/dl	73 mg/dl
e-GFR	7.95 mL/min/1.73 m2	12.45 mL/min/1.73 m^2	22.945 mL/min/1.73 m^2	59.0745 mL/min/1.73 m^2
BUN	42 mg/dl	34 mg/dl	41 mg/dl	34 mg/dl

e-GFR: estimated glomerular filtration rate; **BUN:** blood urea nitrogen

DISCUSSION

Acute or chronic renal injury associated with inherited AT deficiency is very rare and may be caused by renal vein thrombosis and/or glomerular fibrin deposition as a result of the defective anticoagulant and anti-inflammatory actions of AT in the vascular endothelium.(7) Since proteinuria further reduces the plasma AT level, the development of renal failure in patients with AT deficiency makes the hypercoagulation state more severe.(10-11) Therefore, in addition to adequate anti-coagulation therapy, renal replacement therapy for ESRD in these patients is very important. Although the risk of developing acute rejection or other vascular events is increased in patients with thrombophilia, with the appropriate anticoagulation therapy in the early period of transplantation to prevent recurrent thrombosis, renal transplantation may be the best therapeutic option for pediatric and young patients. Considering the difficulty of achieving adequate renal venous outflow and the risk of graft thrombosis, this operation can be very hazardous in cases with diffuse thrombosis of iliac veins and/or IVC. The iliac veins are used for venous anastomosis in usual renal transplantation. Although data in adults remain limited, different sites for venous anastomosis have been proposed in the pediatric kidney transplantation if the iliac veins and IVC cannot be used. In the study of Szymczak M. *et al*. among 951 pediatric kidney transplantations, diffuse thrombosis of iliac veins or IVC was found in 4 children and transplantation was performed with venous anastomoses made to infrahepatic IVC (end-to-end or end-to-side) in 3 patients and collateral circulation in 1 patient.(12) We used suprahepatic IVC for venous anastomose in our patient. In cases whose IVC cannot be used, the use of portal venous system may be an alternative way to consider, as previously described in the literature. In a case study, in two patients (24 and 68 years of age) with thrombosis of the infrahepatic IVC the superior mesenteric vein was used for venous drainage of transplanted kidney located in a retroperitoneal position.(13) While making this decision, detailed preoperative radiological evaluation of the vascular structures is critical. In the radiological evaluation of the IVC and its tributaries, the noninvasive choice of imaging modality is IV contrast enhanced CT scan of abdomen and pelvis in which the venous structures are easily identified at venous phase imaging. On routine portal venous phase abdominopelvic CT scans (60-70 seconds after IV administration of contrast agent) the admixture artifact in the infrarenal/renal IVC caused by flow of enhanced blood from renal veins and non-

opacified blood returning from lower limbs should be kept in mind to avoid misdiagnosis of this filling defect as a thrombus. In equivocal cases, increasing the delay after contrast material injection to 70-90 seconds allows more uniform enhancement of the entire IVC. Admixture artifact can also result from a contrast material injection rate faster than 3 mL/sec or retrograde flow of contrast material into the IVC due to right heart failure.(14-15)

CONCLUSION

The presence of IVC occlusion should not prevent a patient from having a kidney transplant and other alternatives should be searched. Careful assessment of appropriate options for venous drainage helps to define an approach that will allow long-term function of the renal graft. If any thrombotic complications are detected preoperatively, every effort should be made to plan the transplant either with a high IVC anastomosis or orthotopic placement of the renal graft. In our patient, we used a synthetic PTFE vascular graft interposition for venous drainage. It is very important for such a synthetic vein graft to remain patent for a long time. Therefore, an effective anticoagulation with INR monitoring and repeated radiological evaluation for graft patency will provide long term functioning kidney transplant.

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