Pediatr Transplantation 2008: 12: 251–255

Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2007.00857.x

Right atrial thrombosis complicating renal transplantation in a child

Bilginer Y, Ozaltin F, Duzova A, Erdogan I, Aki TF, Demircin M, Bakkaloglu M, Bakkaloglu A. Right atrial thrombosis complicating renal transplantation in a child.
Pediatr Transplantation 2008: 12: 251–255. © 2008 Blackwell Munksgaard

Abstract: Nephrotic syndrome represents a form of acquired thrombophilia thereby causing increased risk of thrombosis. In patients with nephrotic syndrome both venous and arterial thrombosis can occur; however, intracardiac thrombus is among the rarest reported in the literature. In this case report, we present a 10.5-yr-old boy with right atrial thrombosis and an acute rejection episode after renal transplantation due to end stage renal disease caused by focal segmental glomerulosclerosis manifested by nephrotic syndrome. The clinical course was successfully managed with surgical removal of thrombus, institution of anticoagulant as well as antirejection therapy. This report draws attention to the risks that could be associated with thrombosis in renal recipients with congenital or acquired thrombophilias and emphasizes the importance of identifying risk factors for thrombosis in these patients.

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Key words: acute rejection – atrial thrombosis – lipoprotein a – hyperhomocysteinemia – renal transplantation – thrombophilia

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Accepted for publication 11 October 2007

Vascular complications remain a common cause of graft loss in pediatric renal transplant recipients. According to the NAPRTCS data, vascular thrombosis accounts for 11.6% of graft losses in pediatric recipients (1). In addition to surgical complications and poor graft outcome, underlying thrombophilic disorders predispose patients to early thrombotic events, microvascular occlusion or acute rejection (2, 3). Disorders affecting the protein C system (i.e., protein C or S deficiency, FV Leiden mutation) or lupus anticoagulants and the prothrombin G20210A mutation increase the risk of early thrombotic allograft loss three- to fourfold (4). Nephrotic syndrome represents a form of acquired thrombophilia and has been reported to cause an increased risk of thrombosis (5). The pathophysiology is thought to be due to increased loss of anticoagulant proteins secondary to the protein wasting nephropathy (5). In patients with nephrotic syndrome both venous and arterial thrombosis can occur; however, intracardiac thrombus is among the rarest reported in the literature. Seven pediatric patients with intracardiac thrombi have been reported to date, all except one of which were diagnosed at postmortem examination (6, 7). Here we describe a child with focal segmental glomerulosclerosis who presented with nephrotic syndrome and developed an intracardiac thrombus concomitant with an acute rejection episode after renal transplantation.

Abbreviations: CyA, cyclosporin A; DTPA, 99mTc diethylenetriaminepenta-acetic acid; FSGS, focal segmental glomerulosclerosis; Lp(a), lipoprotein a; MMF, mycophenolate mofetil; MTHFR, methylene tetrahydrofolate reductase; NAPRTCS, North American Pediatric Renal Transplant Cooperative Study; SRNS, steroid resistant nephrotic syndrome.

Case report

This male patient was first admitted to the Hacettepe University Faculty of Medicine Pediatric Nephrology Unit because of SRNS when he was seven and a half-yr-old. SRNS had been managed in another center for two yr. His past and family history were uneventful. There was no consanguinity between parents. He progressed to chronic renal failure within four months. He did not come to the visits and suddenly showed up with cardiac failure one yr later since his last visit as he had reached to end-stage renal disease. Hemodialysis with fractioned heparin had to be started immediately through a jugular venous

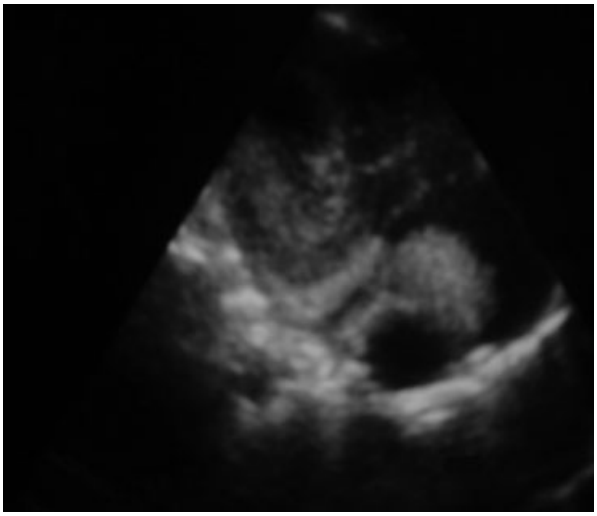

Fig. 1. Right atrial thrombus demonstrated by echocardiography.

catheter whose end was localized in the right atrium. Three wk later, a renal transplant from deceased donor with two HLA mismatch was performed and the catheter was removed. Immunosuppresive protocol was as follows: daclizumab (1 mg/kg days 0, 14, 28, 42, and 60), MMF (250 mg b.i.d), CyA (3 mg/kg/day) and oral prednisone (2 mg/kg/day). Two wk after transplantation, graft function was normal (GFR 173 mL/min/1.73 m^2). However, pretransplant proteinuria persisted at a level of 3.3 g/24 h. One wk later, the patient had clinical palpitations. Electrocardiogram revealed sinus tachycardia. An echocardiography revealed a thrombus (3×1.5 cm in diameter) in the right atrium (Fig. 1). At that time, the GFR was normal but 2.9 g/day of proteinuria persisted. He was hospitalized and the thrombus was removed surgically. The patient was screened for known risk factors for thrombosis. Of them (i.e., mutations for FV Leiden, prothrombin G20210A, MTHFR C677T as well as levels of homocysteine and lipoprotein a, levels of clotting factors, protein C, S, and antithrombin III), only heterozygous MTHFR C677T mutation and hyperhomocysteinemia were found consistently (Table 1). Plasma folate and vitamin B12 levels were 1.5 ng/mL (N 3–17) and 120 pg/mL (N 160–900), respectively. Plasma vitamin B6 level was within normal limits. Levels of plasma clotting factors (i.e., FII, FV, FVIII, and FX), which had been high at initial evaluation, returned to normal subsequently. At nine h post-surgical removal of the thrombose, he experienced a focal convulsion, which extended to a generalized tonic–clonic seizure. Since no response to diazepam and phenytoin was observed, anesthesia with propofol was administered. Cranial computed tomography was normal; however, hemiparesis was noted on the second day following cardiac surgery. Serum creatinine increased gradually from 1.34 to 1.94 mg/dL. DTPA radionuclide scintigraphy showed marked decrease in three functions of the graft, which were suggestive for acute rejection. A probability of an aneurysm of the abdominal aorta was also reported. Doppler ultrasonography of renal artery revealed nonspecific increases in resistive indexes. Magnetic resonance angiography of the transplanted kidney demonstrated no stenosis or occlusion of vessels of the graft. Pulse methyl prednisolone (15 mg/kg, three consecutive days) was given to treat the acute rejection episode. Plasma levels of CyA (both C0 and C2 concentrations) were depressed most likely due to increased metabolism caused by phenytoin. Therefore, CyA was increased to 6 mg/kg to obtain a therapeutic plasma level. Unfractioned heparin was started when thrombocytosis (900 000/mm^3) was manifested. The serum creatinine level declined gradually to 0.55 mg/dL on the 12th day. He was discharged with a minimal right hemiparesis. Three months after transplantation, he had no complaint except for hypertension most likely due to steroid side effect and minimal loss of strength in the right lower extremity that was detected on physical examination. Proteinuria gradually decreased and completely disappeared within three months following transplantation. His

Table 1. Thrombotic risk factors assessed in the patient

	Patient	Normal range
Thrombin time (%)	15.7	15–22
Fibrinogen (g/L)	428	144–430
Activated partial thrombin time (s)	26.4	25–40
ATIII activity (%)	127	80–120
Protein C activity (%)	131	70–130
Free Protein S (%)	150	60–130
Antiphospholipid antibody	Negative	Negative
Lupus anticoagulant	Negative	Negative
FII (%)	300	70–120
FV (%)	180	70–120
FVII (%)	85	70–130
FVIII (%)	223	53–170
FIX (%)	166	60–170
FX (%)	128	60–170
FXI (%)	118	70–150
FXII (%)	86	70–150
FXIII (%)	103	80–130
Homocysteine (μmol/L)	16.1	6–15
Lipoprotein a (mg/dL)	43.8	0–30
FV G1691A (Leiden) mutation	Negative	
Prothrombin G20210A mutation	Negative	
MTHFR mutation	Heterozygote	

laboratory values including GFR were completely normal. Echocardiographic examination was also normal. Steroids were tapered and enalapril was added to treat hypertension. He is now 11-yr old with normal physical examination and normal graft function (current GFR 116 mL/min/1.73 m^2).

Discussion

This is the first report of an intracardiac thrombus complicating renal transplantation in a pediatric patient. Intracardiac thrombus is a rare manifestation of nephrotic syndrome. It has been described in six patients with nephrotic syndrome at autopsy and in one patient who was asymptomatic (6–8).

Renal transplantation improves survival and quality of life for patients with end-stage renal disease. Improvements in immunosuppressive therapy have reduced early allograft loss due to acute rejection to low levels. Early allograft loss, because of acute thrombotic complications, remains a proportionally increasing complication of renal transplantation (1).

Here we present a case of a right atrial thrombosis and acute rejection episode following renal transplantation. In our patient, risk factors for atrial thrombosis were: (i) underlying primary kidney disease, i.e., FSGS, (ii) previous placement of jugular venous catheter, and (iii) heterozygous MTHFR mutation.

Patients with FSGS manifested by nephrotic syndrome are at increased risk for venous and arterial thrombosis (9). Thrombosis of the renal vein is particularly frequent, although both the venous and arterial vasculature, can be involved (9). Proteinuria results in a rise of plasma fibrinogen levels, platelet counts, and lipoproteins, while levels of protein S, C and antithrombin III, which are lost in the urine, are frequently diminished (9). In addition, there is an increase in clotting factors (i.e., FI, FII, FV, FVII, FVIII, FX and FXIII) (9). A significant increase in protein C activity in nephrotic syndrome patients represents a protective mechanism against thrombosis (9). In our patient, FII, FV, FVIII, homocysteine and serum lipoprotein a levels were found to be elevated, which could predispose the patient to thrombosis. These clotting factors returned to normal after proteinuria resolved, which suggested that the abnormalities were related to the nephrotic syndrome. It is well known that in FSGS patients who still have proteinuria, one should wait until anuria develops and thereby proteinuria disappears or should perform bilateral nephrectomy before transplant. However, renal transplant had to be performed without doing necessary preparation for this patient due to the following reasons: (i) before transplantation the patient did not come to visits for one yr and he showed up with end-stage renal disease, (ii) the patient was living in an area where hemodialysis facilities were not available, (iii) the family was reluctant for peritonel dialysis, and (iv) a kidney with a good HLA matching from a deceased donor in our country where organ donation is limited, was found.

Previous jugular catheter placement could have been a contributing factor for the atrial thrombosis in the presence of acquired thrombophilic state. There are no data in the literature about catheter-related atrial thrombus in patients with kidney disease. However, symptomatic thromboembolic complications of central venous catheters have been reported in 5% of oncology patients (10). Asymptomatic catheter related thrombi are more common, but their clinical significance is unclear (10). We believe that the jugular catheter facilitated the generation of the atrial thrombus in the protrombotic state of our patient.

Other risk factors contributing to thrombosis in our patient could be high plasma Lp(a) level and hyperhomocysteinemia. Lp(a) is structurally homologous to plasminogen and has a similar effect on coagulation, fibrinolysis, and endothelial function (11). An increased level of Lp(a) has been reported to be a risk factor for stroke in neonates and children (12–15). A recent meta-analysis has shown a significant association between high Lp(a) levels and the occurrence of venous thromboembolism in adults and has been concluded that the detection of Lp(a) could be of clinical relevance for venous thromboembolism (16). Patients with nephrotic syndrome exhibit high plasma Lp(a) concentrations, which can be reduced with antiproteinuric treatment (17). Patients with end-stage renal disease also have elevated Lp(a) levels, which decrease to values observed in healthy population following renal transplantation (17). Taken together, we believe that increased plasma Lp (a) level is most likely due to nephrotic syndrome and/or end stage renal failure as it returned to normal during the follow-up period and is a significant contributing factor for developing the atrial thrombus and maybe the hemiparesis in our patient. As for hyperhomocysteinemia, another risk factor for thrombosis, this phenomenon was most likely due to folate and vitamin B12 deficiency rather than the presence of the heterozygous MTHFR C677T variant. Of the number of conditions

potentially involved in the thromboembolic events, hyperhomocysteinemia illustrates the complex interactions between environment and genetic background. Diet, particularly folate intake on one hand and genetic conditions (i.e., MTHFR deficiency), on the other, are major determinants of plasma homocysteine levels. In some reports, homozygous but not heterozygous MTHFR mutations have been found to be related to an elevated plasma homocysteine level, which constitutes an important genetic risk factor for vascular disease (18). However, in a large case-control study, MTHFR C677T gene has not been found to be a risk factor for venous thromboembolism, either in isolation or in combination with FV Leiden or FII mutations (19). MTHFR mutations were initially thought as possible risk factor for coronary thrombosis but many reports have not confirmed this (20). As folate status significantly affects plasma homocysteine levels, it seems likely that folate balance is the dominant factor affecting the plasma homocysteine level. As there is strong evidence of an association between hyperhomocysteinemia and venous thrombosis and fatal coronary artery disease, the influence of the common MTHFR C677T variant is not significant compared to other factors that determine the homocysteine level (21). Taken together, it seems most likely in our patient that hyperhomocysteinemia is the result of folate and vitamin B12 deficiency, which is frequently encountered in nephrotic patients.

Another important finding in our patient was the acute loss of graft function. As the patient already had an atrial thrombosis, we first thought that this could be because of concomitant renal arterial thrombosis. However, we excluded this possibility by magnetic resonance angiography. It is unlikely that the renal impairment accompanied by hemiparesis had been secondary to cardiac surgery with renal hypoperfusion, as urine output during and after surgery did not diminish. Furthermore, renal impairment and hemiparesis were evident on the second day, not an immediate period of the surgery. The patient was suffering from an acute rejection episode. We could not perform a renal biopsy as the patient was receiving unfractioned heparin. However, a good clinical response to anti-rejection therapy confirmed our clinical impression. Possible explanations for the acute rejection episode could be (i) under-immunosuppression through increased metabolism of immunosuppressive drugs because of antiepileptic medication, (ii) renal arterial or arteriolar thrombosis with the prothrombotic state. In contrast to reversing declining graft function because of acute rejection with immunosuppressive strategies, early allograft loss because of acute thrombotic complications remains an increasing complication of renal transplantation. According to the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) data, vascular thrombosis accounts for 11.6% of graft losses in pediatric recipients (1). Children with protein C, S deficiencies or FV Leiden and prothrombin gene mutations are at increased risk for thrombosis. Two pediatric patients with the prothrombin mutation lost three renal allografts because of thrombosis (22). Although Heidenreich et al. (2) found an increased risk of acute rejection episodes within the first 90 days in adult recipients with the FV G1691A (Leiden), prothrombin G20210A and MTHFR T677T variants, this correlation was not found in children (23). In our patient acquired risk factors could be attributed to an increased risk for graft thrombosis and acute rejection episode with impaired graft function. Thrombosis at least of renal arteries was not present in our patient; however, we could not exclude the possibility of microthrombis in smaller branches of the renal arteries. Antirejection therapy with pulse methyl prednisolone and increasing the dosage of the calcineurin inhibitor to achieve therapeutic plasma levels resulted in a favorable outcome.

In conclusion, one should remember that a renal transplant (especially from living donor) should not be performed early in patients with FSGS because of serious thrombotic risks until a balance between coagulation and anticoagulation systems is established. Our patient demonstrates the risks associated with thrombosis in pediatric renal allograft recipients with congenital or acquired thrombophilias and emphasizes the importance of identifying risk factors for thrombosis in these patients.

Acknowledgment

Dr. Duzova is supported by The Turkish Academy of Sciences (Programme to Reward Successful Young Scientists, A.D/TUBA – GEBIP/2006-6).

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