dos, descendió el flujo arterial hasta 300 ml/min (habitual: 450 ml/min). La dosis de diálisis no se modificó significativamente, con un Kt/V Daugirdas siempre por encima de 1,5 y porcentaje de reducción de urea > 65 %.

Los parámetros de actividad lúpica (anti-DNA y $C_{3,4}$) fueron negativos en el primer episodio, y el C_3, ligeramente descendido en el segundo y el tercero. No se midieron anticuerpos antifosfólipido por la escasa relación de los niveles con la clínica y por estar bajo terapia anticoagulante (figura 2 B).

DISCUSIÓN

La ERC es considerada, *per se*, una importante entidad proateroesclerótica. Un mal control del metabolismo calcio-fósforo en el paciente en hemodiálisis aumenta exponencialmente el riesgo vascular, a similar escala que el hábito tabáquico o la diabetes[1]. De igual manera, el lupus eritematoso sistémico y síndrome antifosfolípido y las terapias utilizadas para su tratamiento (esteroides, anticalcineurínicos) contribuyen a la disfunción endotelial que presentan estos pacientes[2], además de la reciente asociación de estas enfermedades con la deficiencia o resistencia de la proteína C activada[3,4]. Pacientes con deficiencia de esta proteína parecen ser más susceptibles a la aparición de necrosis cutánea cuando se añade un dicumarínico[5].

Todos estos factores pueden, solos o en combinación, comprometer la perfusión distal. La coexistencia de todos ellos junto al hábito tabáquico, la exposición al frío, la hemoconcentración, la hiperhomocisteinemia y la aparición de robo sanguíneo funcional por parte del acceso vascular pueden constituir una «mezcla explosiva» para la evolución y reincidencia de la necrosis cutánea digital descrita.

Conflictos de interés

Los autores declaran que no tienen conflictos de interés potenciales relacionados con los contenidos de este artículo.

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351(13):1296-30.

2. Petri MA, Kiani AN, Post W, Christopher-Stine L, Magder LS. Lupus Atherosclerosis Prevention Study (LAPS). Ann Rheum Dis 2011;70(5):760-5.

3. Muñoz-Rodríguez FJ, Reverter JC, Font J, Tàssies D, Espinosa G, Cervera R, et al. Clinical significance of adquirid activated protein C resistance in patients with systemic lupus erythematosis. Lupus 2002;11:730-5.

4. Nojima J, Kuratsune H, Suehisa E, Kawasaki T, Machii T, Kitani T, et al. Acquired activated protein C resistance is associated with the co-existence of antiprothrombin antibodies and lupus anticoagulant activity in patients with systemic lupus erythemaosus. Br J Haematol 2002;118:577-83.

5. Vhan YC, Valenti D, Mansfield AO, Stansby G. Warfarin induced skin necrosis. Br J Surg 2000;87:266-72.

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De novo tacrolimus – associated hemolytic uremic syndrome after renal transplantation

Dear Editor,

De novo Hemolytic Uremic Syndrome (HUS) occurs in 1-5% of renal transplant recipients, most frequently within the first 3 months after transplantation.[1,2]

Thrombotic Microangiopathy (TMA) usually sets in the first weeks post-transplant when patients are treated with high dose of immunosuppressant.

De novo TMA has been documented in approximately 1% of patients receiving tacrolimus.[2] Calcineurin inhibitor – induced nephrotoxicity primarily results from dose dependent renal arteriolar vasoconstriction,[3] owing of the enhanced production of vasoconstrictive factors, particularly endothelin-1 and angiotensin II.[4,5] Moreover, calcineurin inhibitors might promote a procoagulant state enhancing platelet aggregation and activating plasminogen activator.[6] De novo post-transplant HUS has been reported both with the use of an mTOR inhibitor alone and in combination therapy.[7] The viral infections, to which patients on immunosuppression are susceptible, have been implicated in pathogenesis of de novo HUS in organ transplant recipients. A CMV infection[8] has been associated with both the novo and recurrent[9] forms of post-transplant HUS. Parvovirus B19 and polioma BK virus infection have also been associated with de novo HUS in renal transplant recipients.[10-12]

The authors describe the clinical case of a Caucasian male, 33 years old with a history of chronic kidney disease of unknown etiology, in hemodialysis for nearly 7 years, with past medical history of severe hypertension, severe hypertriglyceridemia and chronic pancreatitis. Family history was irrelevant.

In May 2010 he was underwent a renal transplantation with deceased kidney allograft (donor: man aged 23, suffered TCE) with CMV (D + / R +), HBV, HCV and HIV negative and with ABO compatibility. In the presence of low immunological risk situation with PRA 0% and with HLA 4:6 matches, he did not submitted to induction and began a immunosuppression regimen with mycophenolic acid (1440 mg/day), Tacrolimus LP (0.15mg/kg),

Table 1. Laboratorial evolution

	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Hemoglobin (g/dL)	12,9	10,1	7,4	7,6	7,1	6,9	7,9	6,6	6,7	7,8	7,5
Platelet count (/μL)	89000	86000	18000	19000	20000	20000	25000	31000	37000	40000	40000
Leucocytes (/μL)	4900	5900	4000	3800	5600	5400	6400	6100	5600	4700	4900
Total protein (g/dL)	5.3	5.3	5.3	5.4	5.7	5.8	5.9	5.3	5.4	6	5.6
Albumin (g/dL)	3.9	3.4	3.3	3.4	3.6	3.6	3.7	3.3	3.5	3.7	3.6
BUN (mg/dL)	46	46	61	52	73	91	77	108	95	95	105
Creatinine (mg/dL)	8.25	6.39	3.43	3.15	4.17	5.15	4.55	7.24	6.4	7.52	8.38
LDH (U/L)	221	184	1485	1050	1810	2038	1866	926	864	793	636
Total Bilirrubin (mg/dL)	0.6	0.7	1.2	2.5	2.7	2.8	3.1	1.9	2.3	2.1	1.6
Direct bilirrubin (mg/dL)				0.7	0.8	0.9	0.9	0.7	0.9	0.8	0.7
PCR (mg/dL)					3.23						
Haptoglobin (g/L)					<0.07						
PT (seg.)					14.3 (13.6)						
aPTT (seg.)					25 (28.0)						
INR					1.11						

aPTT: activated partial thromboplastin time; BUN: blood urea nitrogen; INR: international normalized ratio; LDH: lactate dehydrogenase; PT: prothrombin time.

methylprednisolone (8mg/kg) and adopting an initial maintenance scheme comprising mycophenolic acid (1440mg/day), LP tacrolimus (16mg) and prednisone (20mg/day).

Initial graft function was immediate, without surgical complications but with severe hypertension of difficult to control. Doppler renal graft was performed that excluded vascular complications and showed a normal resistance index.

The 2nd day postoperatively for 3rd day there was a deterioration of renal graft function (serum creatinine of 2.92 to 3.15mg/dL) associated with abrupt drop in platelet count (97,000 to 19.000/μL), drop in serum hemoglobin (10.4 to 7.6g/dL) and increase serum levels of lactate dehydrogenase (LDH 1485U/L) with tacrolimus plasma level of 10ng/mL. The Coombs test (direct and indirect) was negative, serum haptoglobin decreased and were found 3% of schistocytes in peripheral blood smear.

The survey of CMV, BK virus and parvovirus B19 in blood by P.C.R. were negative. It was found normal plasma activity of the ADAMTS13 in the absence of inhibitors. The autoimmunity study with anti-nuclear antibodies, anti-dsDNA and anti-cytoplasmic antibodies and antiphospholipid antibody were negative as well as was negative donor-specific antibody. In relation to severity of thrombocytopenia was not possible to perform biopsy of renal allograft.

The patient remained clinically well and without gastrointestinal or neurological changes. Given the evidence of worsening of renal function (acute dysfunction of renal allograft) associated with markers of intravascular hemolysis (nonimmune: Coombs direct and indirect negative) was established the diagnosis of *De novo* hemolytic uremic syndrome post-transplant, probably associated with tacrolimus.

We suspended tacrolimus and mycophenolic acid (by myelosuppressive effects) and was introduced everolimus on the 5th day. We obtained improved of blood pressure control. Despite the attitudes adopted on the 9th day maintained parameters hemolysis (6.6g Hb/dL, and 31,000/μL platelet LDH 926U/L) and worsening of graft function (7.24mg/dL) with diuresis maintained (Table 1). We decided to initiate daily plasmapheresis (D9 to D23) (1.5 x the plasma volume)

with fresh frozen plasma inactivated. The patient remained without neurological disorders. After 14 sessions of plasmapheresis and 3 daily hemodialysis sessions (D9 to D12) we observed recovery of renal graft function accompanied by the disappearance of markers of hemolysis. At discharge date he had a serum creatinine of 2.39 mg/dL and 6 months after the level of seric creatinine was of 1.0mg/dL, with no evidence of recurrent HUS (without analytical signal of intravascular hemolysis).

There are no treatment guidelines for this entity. Among 29 patients with De novo post-transplant TMA, 80% recovered graft function after cyclosporine stop and plasma therapy.[13] Our experience demonstrates that switching from tacrolimus to everolimus with plasmapheresis with fresh plasma proved be an adequate strategy for this situation without increased risk of acute rejection.

Conflict of interest
The authors declare that there is no conflict of interest associated with this manuscript.

1. Pham PT, Peng A, Wilkinson AH, Gritsch HA, Lassman C, Pham PC, et al. Cyclosporine and tacrolimus associated thrombotic microangiopathy. Am J Kidney Dis 2000;(36):844-50.

2. Reynolds JC, Agodoa LY, Yuan CM, Abbott KC. Thrombotic microangiopathy after renal transplantation in the United States. Am J Kidney Dis 2003;(42):1058-68.

3. English J, Evan A, Houghton DC, Bennett WM. Cyclosporine-induced acute renal dysfunction in the rat. Evidence of arteriolar vasoconstriction with preservation of tubular function. Transplantation 1987;(44):135-41.

4. Naesens M, Kuypers DR, Sarwal M. Calcineurin –inhibitor nephrotoxicity. Clin J Am Soc Nephrol 2009;(4):481-508.

5. Lanese DM, Conger JD. Effects on endothelin receptor antagonists on cyclosporine-induced vasoconstriction in isolated rat renal arterioles. J Clin Invest 1993;(91):2144-9.

6. Ponticelli C. De novo trombotic microangiopathy: an underrated complication of renal transplantations. Clin Nephrol 2007;(67):335-40.

7. Robson M, Côte I, Abbs I, Koffman G, Goldsmith D, et al. Trombotic microangiopathy with sirolimus –based immunossupression: potentiation of calcineurin inhibitor-induced endothelial damage? Am J Transplant 2003;(3):324-7.

8. Waiser J, Budde K, Rudolph B, Ortner MA, Neumayer HH, et al. De novo hemolytic uremic syndrome postrenal transplant after cytomegalovirus infection. Am J Kidney Dis 1999;(34):556-9.

9. Olie KH, Goodship TH, Verlaak R, Florquin S, Groothoff JW, Strain L, et al. Post transplantation cytomegalovirus-induced recurrence on atypical hemolytic uremic syndrome associate with a factor H mutation: successful treatment with intensive plasma exchanges and ganciclovir. Am J Kidney Dis 2005;45(1):e12-5.

10. Ardalan MR, Shoja MM, Tubbs RS, Esmaili H, Keyvani H. Postrenal transplant hematophagocytic lymphohistiocytosis and thrombotic microangiopathy associated with parvovirus B19 infection. Am J Transplant 2008;8:1340-4.

11. Murer L, Zacchello G, Bianchi D, Dall'Amico R, Montini G, Andreetta B, et al. Thrombotic microangiophaty associated with parvovirus b19 infection after renal transplantation. J Am Soc Nephrol 2000;11:1132-7.

12. Petrogiannis-Haliotis T, Sakoulas G, Kirby J, Koralnik IJ, Dvorak AM, Monahan-Earley R, et al. BK-related polyomavirus vasculopathy in a renal –transplant recipient. N Engl J Med 2001;345:1250-5.

13. Karthikeyan V, Parasuraman R, Shah V, Vera E, Venkat KK. Outcome of plasma exchange therapy in thrombotic microangiopathy after renal transplantation. Am J Transplant 2003;(3):1289-94.

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