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Acute allograft dysfunction: a case hanging by a thread

Marta Sofia Costa[1], Sofia Coelho[2], Ivo Laranjinha[3], Mário Góis[4], Helena Viana[4], Fernando Nolasco[4]

[1] Nephrology Department, Centro Hospitalar Tondela-Viseu
[2] Nephrology Department, Centro Hospitalar de Setúbal
[3] Nephrology Department, Centro Hospitalar de Lisboa Ocidental / Hospital de Santa Cruz
[4] Nephrology Department, Centro Hospitalar de Lisboa Central

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CLINICAL PRESENTATION

A 49-year-old man with end-stage renal disease secondary to ANCA-MPO vasculitis received a deceased-donor allograft kidney with two mismatches. Zero-hour kidney biopsy revealed no alterations. Thymoglobulin, methylprednisolone, tacrolimus (FK), and mycophenolate mofetil (MMF) were used as induction therapy. ANCA titer at the time of transplantation was 506.7 UQ (normal < 20 UQ). He was discharged after thirteen days with a nadir serum creatinine of 0.9 mg/dL under prednisolone, FK, and MMF. The follow-up period was unremarkable except for ANCA-MPO titers that reached a maximum of 4099.8 UQ six months after transplantation.

At the 9th month post-discharge he was admitted with acute allograft dysfunction with a serum creatinine of 4.74 mg/dL. The remaining laboratory evaluation showed hemoglobin of 11.4 g/dL, a urinary protein to creatinine ratio of 795mg/g, urinary red blood cells of 86/ul, undetectable FK levels, and an ANCA-MPO titer of 3586.3 UQ. Four *de novo* donor specific antibodies were detected with titers between 1127 and 10800 UQ. Graft ultrasound with Doppler was normal. An allograft biopsy was performed.

FIRST BIOPSY

The first biopsy had eleven glomeruli and several vessels. A diffuse acute inflammatory infiltrate was present.

Figure 1

Silver Stain; 400X.

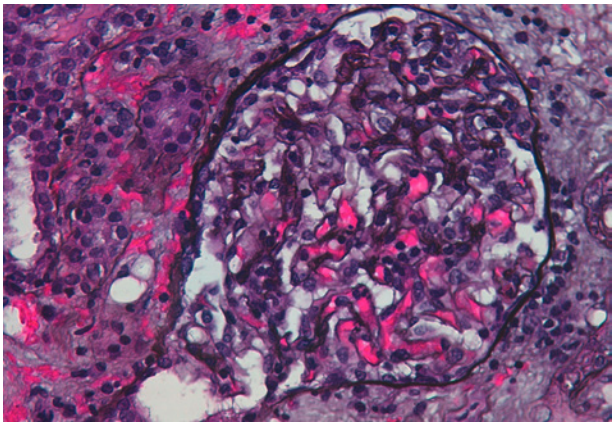
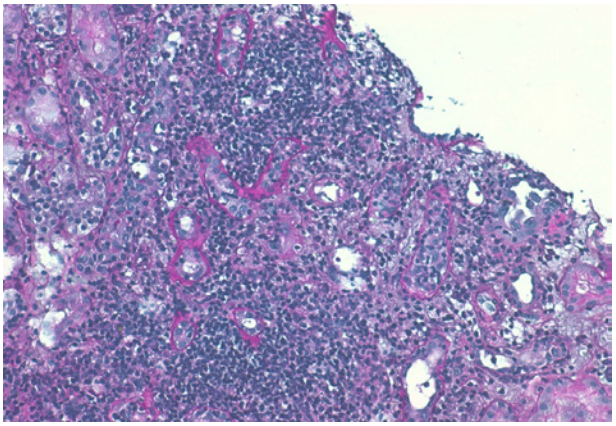


Figure 1 shows mononuclear cells in all the glomerular capillaries – glomerulitis (g3). The peritubular capillaries present more than 10 mononuclear cells (ptc3). Deposition of C4d in peritubular capillaries was negative.

In figure 2 we observe tubular invasion by mononuclear cells with destruction of the basement membranes – tubulitis (t3). Figure 3 confirms diffuse and severe tubulitis. Figure 3 shows a medium artery with endothelial cell swelling. The vascular lumen is frankly reduced. Capillaries and glomerular stasis are observed in Figure 4. These alterations are suggestive of thrombotic microangiopathy.

Figure 2

Periodic-acid Shift; 400X.



ANATOMO-CLINICAL DIAGNOSIS

Acute cellular rejection IB (i3+t3).

Acute humoral rejection (renal dysfunction+DSA+g3+ptc3).

Thrombotic microangiopathy probably in the context of acute humoral rejection.

TREATMENT AND EVOLUTION

The patient was treated with thymoglobulin, methylprednisolone, intravenous immunoglobulin, rituximab, and 5 sessions of plasma exchange. Twelve days after the last plasma exchange session a new allograft

Figure 3

Silver Stain; 400X.

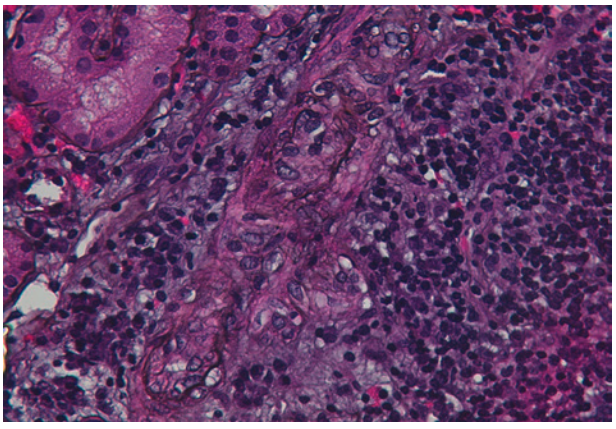


Figure 5

Silver Stain; 400X.

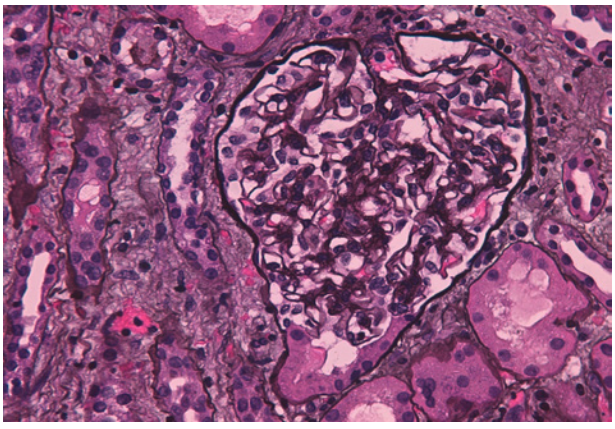


Figure 4

Masson's Trichrome; 400X.

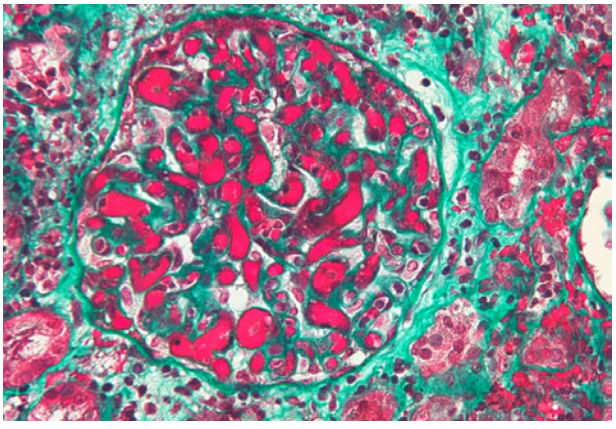
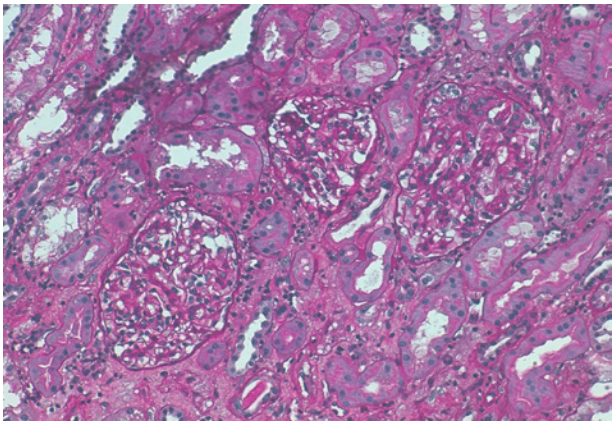


Figure 6

Periodic-acid Shift; 200X.



biopsy was performed – creatinine level was 4.46 mg/dL at this time.

SECOND BIOPSY

Figure 5 demonstrates segmental duplication of basal membrane in about 50% of capillaries tuft (cg2). In figure 6 glomerulitis is observed in 40% of glomeruli (g2) and peritubular capillaries present 5–10 mononuclear cells. In figure 7 we can see normal medium vessels. Figure 8 illustrates interstitial fibrosis and tubular atrophy and involves 50% of the cortical.

Figure 7

Periodic-acid Shift; 100X.

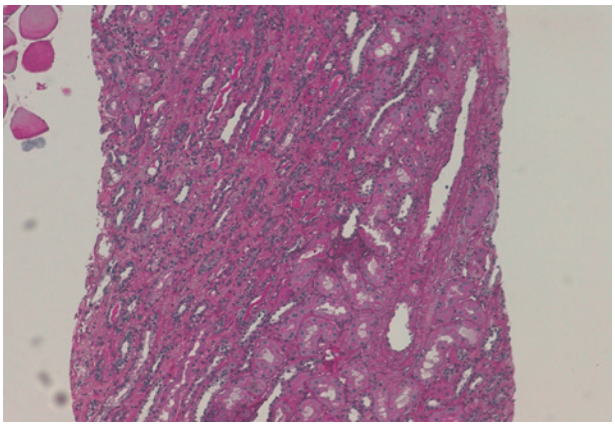
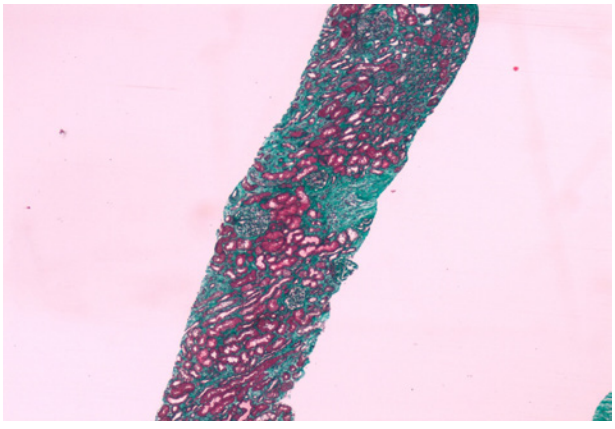


Figure 8

Masson´s Trichrome; 40X.



ANATOMO-CLINICAL DIAGNOSIS

Active chronic humoral rejection (cg2+g2+ptc2).

TREATMENT AND EVOLUTION

Based on the results of the second biopsy it was decided to treat with one more rituximab infusion and five more sessions of plasma exchange. The patient was discharged 38 days after the admission with a serum creatinine of 3.5 mg/dL, a urinary protein to creatinine ratio of 380.4 mg/g, and an ANCA-MPO title of 1254.7 UQ.

DISCUSSION

Acute rejection in renal transplantation is a major determinant of short-term and long-term allograft survival. Avoiding these episodes is crucial in the prevention of chronic transplant nephropathy and in the reduction of late transplant failure.

Acute rejection typically occurs between one week and several months after transplantation. It arises from two immunological mechanisms that may act alone together: a T cell dependent process (acute cellular rejection) and a B cell dependent process (acute humoral rejection).

Humoral rejection results from host recognition of non-self (donor) HLA antigens and the subsequent development of donor-specific anti-HLA antibodies (DSA). Antibody consequently binds to its respective target on the graft endothelial cells, shifting complement from an anti-inflammatory mediator to a potent proinflammatory effector mechanism via classical complement activation.

Cellular rejection occurs when pattern-recognition receptors (PRR) identify damage-associated molecular patterns (DAMP) and pathogen-associated molecular patterns (PAMP) that are released following renal damage, such as ischemia-reperfusion injury and infections. PRR-mediated signals activate dendritic cells, leading to antigen-presenting cell maturation and stimulation. They then migrate to secondary lymphoid organs and trigger differentiation of alloreactive naive T cells into effector T helper cells. These effector cells migrate into the graft where they activate macrophages and

granulocytes that have infiltrated the graft in response to inflammatory stimuli. Additionally, the three complement pathways can also be activated by DAMP as well as by the inflammatory environment.

The diagnosis of acute rejection is histological, according to an international classification system – the Banff classification for the kidney.

Acute rejection has decreased in the past decades – 15 to 20% – due to progresses in immunosuppressive therapy. However, it remains an important cause of death-censored graft loss. Both functional and histological responses to therapy appear to be important prognostic factors. Restoration of kidney function to pre-rejection levels is a strong determinant of graft survival[-] and a lower rate of histological response to therapy on control biopsies is associated with recurrent rejections.

Medical noncompliance is one of the most important causes of acute rejection with consequent graft dysfunction or loss. Several risk factors for noncompliance have been identified: female gender; younger age; non-Caucasians; unmarried; long-term recipients of living transplants; previous transplant history, and emotional problems. Identifying these patients, however difficult, is crucial in order to decrease financial costs (with additional therapy and dialysis), morbidity (graft loss and other complications) and mortality.

Another important cause of acute allograft dysfunction is the recurrence of the primary kidney disease in the graft. Transplanted AAV patients have lower vasculitis relapse rates compared with those on maintenance dialysis and patients with CKD who are not on dialysis. AAV relapses after renal transplantation may present as extra-renal disease flares and/or as disease recurrence in the graft. The extra-renal involvement is more common in PR3-ANCA than in MPO-ANCA-associated disease. Considering that our patient presented with high ANCA titles, the hypothesis of a vasculitis recurrence in the graft was also considered. This hypothesis was discarded after biopsy evaluation. However, the question of ANCA positivity at the time of transplantation remains controversial.

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Correspondence to:
Helena Viana, MD
Laboratory of Renal Morphology, Hospital Curry Cabral, Centro Hospitalar de Lisboa Central
E-mail: viana.helena@gmail.com