CASE REPORT

Port J Nephrol Hypert 2010; 24(4): 309-312
Advance Access publication 16 September 2010

Quantitative determination of donor antibodies in monitoring acute humoral rejection

Susana Pereira[1], Sofia Pedroso[2], LaSalete Martins[2], Paulo Santos[3], Cristina Freitas[2], Manuela Almeida[2]. Leonídio Dias[2], António Castro Henriques[2], António Cabrita[2]

[1] Centro Hospitalar Vila Nova de Gaia. Gaia, Portugal.
[2] Renal Transplant Unit, Hospital Santo António. Oporto, Portugal.
[3] Instituto Português Oncologia. Oporto, Portugal.

Received for publication: 11/07/2010
Accepted in revised form: 09/08/2010

ABSTRACT

Numerous studies have recently demonstrated the importance of detecting and monitoring donor-specific antibodies in an attempt to diagnose and treat acute antibody-mediated rejection early. Identification of these antibodies with more sensitive and specific techniques is possible and can be a useful tool in the management of acute humoral rejection. We report the case of a 51-year-old female patient who received a second deceased kidney transplant in 2009. On day-8 posttransplant acute graft failure (plasma creatinine 3.5 mg/dl) was identified and antibody-mediated rejection was diagnosed; concomitantly, significant levels of donor-specific antibodies to human leukocyte antigen against B44 were detected by Quantiplex® (standard fluorescence intensity: 250853). Treatment with plasmapheresis and human immunoglobulin improved graft function with a decrease in plasma creatinine to 1.4 mg/dl and donor specific antibodies titres reduced to insignificant levels (SFI=73992). On day-20 posttransplant a second graft dysfunction occurred and the kidney graft biopsy again diagnosed antibody-mediated rejection. Donor-specific antibodies to human leukocyte antigen class II (DR1) were detected and quantified (DR1 003=226913; DR1 004=346868); rituximab was administered successfully, improving kidney function and significantly declining DR1 (DR1 003=113801; DR1 004=61670). This case illustrates the importance of detecting and quantifying donor-specific antibodies for early diagnosis and treatment, and monitoring antibody-mediated rejection.

Key-Words:
Acute rejection; donor-specific antibodies; kidney transplant.

INTRODUCTION

Diagnosis of antibody-mediated rejection (AHR) is essential for prolonging kidney graft survival[1,2]. Recent studies have demonstrated that quantification of donor-specific antibodies (DSA) may be a useful tool in early AHR detection and follow-up, particularly in high immunological risk patients[3]. Currently DSA can be quantified by more sensitive and specific new tests such as Quantiplex®. There is a strong correlation between DSA and acute or even chronic humoral rejection[4,5]. We present a case where the association of DSA and two episodes of acute AHR had clinical relevance.

CASE REPORT

A 51-year-old female patient underwent a second deceased kidney transplant in 2009. In 1999 she started regular haemodialysis due to end-stage renal disease secondary to chronic glomerulonephritis. No complications were registered during the dialytic period. Relevant past medical history revealed two uncomplicated pregnancies and two episodes of red blood cell transfusions with no date recorded. In 2000 the patient underwent her first deceased kidney transplant. Scant information about this episode was available because it was performed at another institution: human leukocyte antigen (HLA) typing of donor (A2; B44,51; DR7). The donor's kidney artery presented severe atheromatosis complicated by arterial thrombosis with consequent immediate graft removal and antibodies to donor B44 were detected in the serum. The patient returned to haemodialysis. In 2009 she had a second deceased kidney transplant. The donor was 47 years old and HLA typing was A2,33; B50,65; DR1.5. Crossmatch was negative by cytotoxicity and flow cytometry, and the patient's panel reactive antibody was ±0%. Induction immunosuppressive therapy included prednisone, tacrolimus, mycophenolate mophetil and antithymocyte globulin. The kidney transplantation procedure was unremarkable. The patient had immediate graft function, reaching normal serum creatinine (0.9 mg/dl) at day-5. On day-8 after transplant acute graft dysfunction with oliguria occurred, with serum creatinine rising to 3.5 mg/dl. Suspecting an acute graft rejection an empiric course of steroids was administered. The patient underwent graft biopsy and AHR was diagnosed (Banff grade II); immunofluorescence was positive for C4d (Fig. 1). Concomitantly, DSA to HLA B50 were detected and quantified by Quantiplex® technique (Figure 2). These DSA, related to the second donor, had a considerable SFI level

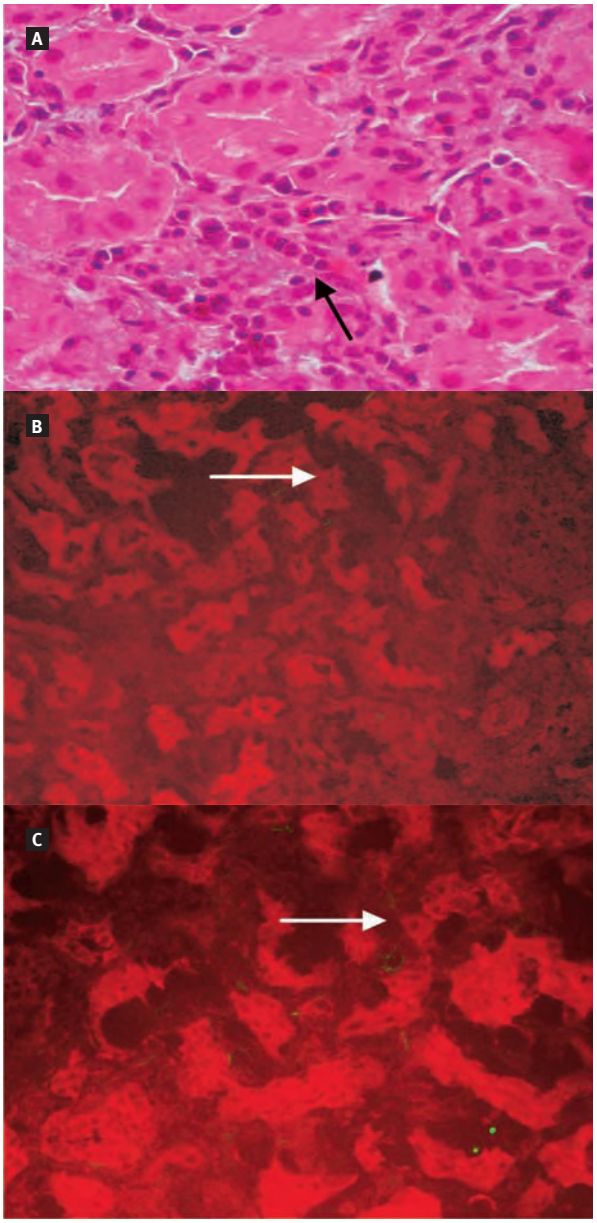

Figure 1

First graft kidney biopsy.

A – Optic microscopy with hematoxylin-eosin: capillaritis.
B and **C** – Immunoflurescence staining with peritubular C4d positive.

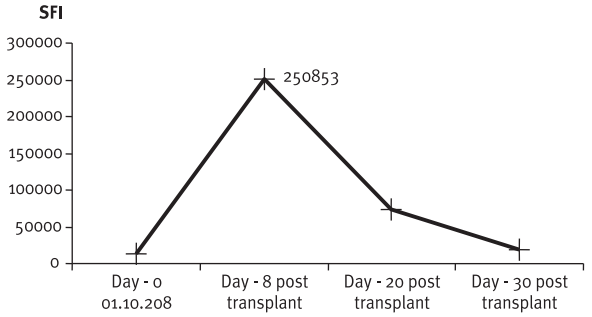

Figure 2

Detection of DSA to HLA B50 in first AHR at day-8 posttransplant

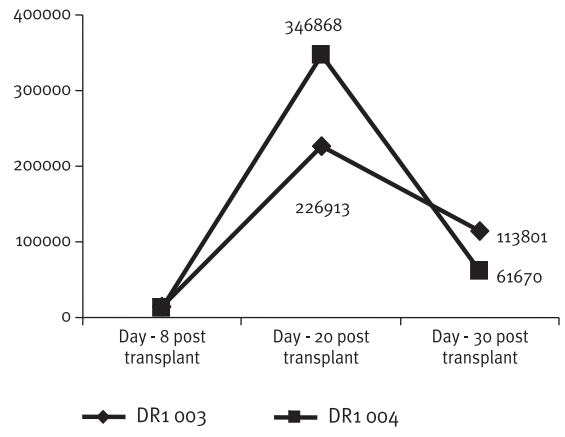

Figure 3

Detection of DSA to HLA DR1 in second graft biopsy at day-20 posttransplant

– 250853 (cut-off 200000). The treatment protocol consisted of methylprednisolone bolus during 3 days, plasmapheresis with one volume of albumin plasma exchange (daily for the first 5 days, followed by 5 sessions every other day) and intravenous human immunoglobulin (2g/Kg). Kidney graft function recovered (plasma creatinine 1.4 mg/dl) and simultaneously a decrease in B50 DSA levels to nonsignificant values (SFI=73992) was observed. On day-20 posttransplant a second decline in graft function occurred (creatinine 1.9 mg/dl) with different detectable DSA. A second graft biopsy confirmed an AHR and maintenance of positive C4d by immunofluorescence. The new DSA high titres were against HLA DR1 (SFI:DR1 003=226913; DR1 004=346868) (Figure 3). The antibodies to HLA class II were elevated seven times and to HLA class I remained stable. Rescue therapy with rituximab (375 mg/m^2) was initiated. Graft function improved (creatinine 1.3 mg/dl), correlating with downward of DR1 levels (SFI: DR1 003=113801; DR1 004=61670). Four months after kidney transplant graft function remained stable (creatinine 1.3 mg/dl) and no significant levels of DSA were detected.

DISCUSSION

The overall incidence of acute rejection has decreased due to progressively more powerful immunosuppression. Incidence of AHR with kidney graft dysfunction is estimated to be 3 to 10%[6,7]. An early diagnosis of AHR is essential as each event may have a major negative impact on graft survival and predicts chronic rejection[8,9]. DSA to HLA are one of the central mechanisms of acute kidney graft rejection. DSA preformed or *de novo* are associated with allograft dysfunction and diminished graft survival. Detecting and monitoring these antibodies in an attempt to prevent acute and chronic rejection and subsequently improve allograft survival may be a potential tool in kidney transplantation[10-12]. Recently numerous studies have demonstrated the association of DSA with AHR for diagnostic and prognostic purposes and the importance of monitoring these antibodies[1,3,8]. This case illustrates the clinical significance and temporal association between AHR and DSA. This supports the relevance in determining and quantifying DSA in AHR, particularly in high-risk patients. However, as new methods to detect antibodies become more sensitive and specific, the cut-off point must be determined, as the relevance of low-level antibodies remains unclear.

The management of antibody-mediated rejection is not completely defined[7]. Our approach, as described in a recent report, includes plasmapheresis, human immunoglobulin and, as a rescue therapy, rituximab. This protocol became an efficient strategy to successfully treat this case of AHR. Rituximab administration, defining the number of doses and interval between each dose, is also controversial. In our past experience, a single dose was sufficient to treat AHR[7].

CONCLUSION

This case is an example of the importance of quantifying DSA in AHR, to diagnose and/or monitor. This new technology may be a useful tool to allow prompt and efficient therapeutic approach in the management of kidney graft dysfunction. Currently there is no consensus on when to test for DSA, and its clinical significance is still under debate. More studies are needed to determine the frequency and magnitude of DSA levels and consequently enhance this diagnostic technique.

Conflict of interest statement. None declared.

References

1. Everly MJ, Terasaki PI. Monitoring and treating posttransplant human leucocyte antigen antibodies. Hum Immunol 2009;70:655-9

2. Mauiyyedi S, Colvin RB. Humoral rejection in kidney transplantation: new concepts in diagnosis and treatment. Curr Opin Nephrol Hypertens 2002;11:609-18

3. Pollinger HS, Stegall MD, Gloor JM, *et al.* Kidney Transplantation in patients with antibodies against donor HLA Class II. Am J Transplant 2007;7:857-63

4. Fernandez-Fresnedo G, Pastor JM, Lopez-Hoyos M, *et al.* Relationship of donor specific class I anti-HLA antibodies detected by ELISA after kidney transplantation on the development of acute rejection and graft survival. Nephrol Dial Transplant 2003;18:990-5

5. Viana H, Nolasco F, Santos MC, *et al.* Specificity and sensitivity of screening for anti-HLA antibodies in kidney allograft dysfunction. Transplant Proc 2009;41:859-61

6. Robert C. Antibody-mediated renal allograft rejection: diagnosis and pathogenesis. J Am Soc Nephrol 2007;18:1046-56

7. Gomes AM, Pedroso S, Martins LS, *et al.* Diagnosis and treatment of acute humoral kidney allograft rejection. Transplant Proc 2009;41:855-8

8. Worthington JE, McEwen A, McWilliam LJ, *et al.* Association between C4d staining in renal transplant biopsies, production of donor-specific HLA antibodies, and graft outcome. Transplantation 2007;83:373-4

9. Seveso M, Bosio E, Ancona E, *et al.* De novo anti-HLA antibody responses after renal transplantation: detection and clinical impact. Contrib Nephrol 2009;162:87-98

10. Zeevi A, Lunz JG, Shapiro R, *et al.* Emerging role of donor-specific anti-human leucocyte antigen antibody determination for clinical management after solid organ transplantation. Hum Immunol. 2009;70:645-50

11. Lee PC, Zhu L, Terasaki PI, *et al.* HLA-specific antibodies developed in the first year post-transplant are predictive of chronic rejection and renal graft loss. Transplantation. 2009;88:568-74

12. Lachmann N, Terasaki PI, Budde K, *et al.* Anti-human leucocyte antigen and donor-specific antibodies detected by luminex posttransplant serve as biomarkers for chronic rejection of renal allografts. Transplantation 2009;87:1505-13

Correspondence to:
Dr Susana Pereira
Rua Conceição Fernandes
Vila Nova de Gaia, Portugal
E-mail: sujpereira@gmail.com