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Case Report

Long-term unexpected consequence of two kidney transplants with full-match grafts: a report of two cases

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Abstract: HLA typing is the cornerstone of kidney transplantation. Here, we present two full-match kidney transplants with early uneventful course but late c4d-mediated rejection and recurrent pauce-immune necrotizing crescentic glomerulonephritis, as each in one. Case 1: A 49 years old Caucasian female patient, received a six-matched cadaveric kidney and had nonspecific changes in 6th and 12th month protocol biopsies. The first and third year serum creatinin value was 1.8 and 2.0 mg/dl. Immunosuppressive drugs were gradually reduced due to recurrent infections at the 3rd year. She admitted with allograft dysfunction and serum creatinin 5.8 mg/dl. Kidney biopsy of graft dysfunction at the 4th year was diagnosed C4d-mediated rejection. Case 2: A 61 years old Caucasian female patient received a HLA-identical kidney 8.5 years ago from her sibling had a primary vasculitis mediated necrotizing crescentic glomerulonephritis. Her serum creatinin values in the 1st and 8th years were 1.3 and 1.7 mg/dl. In recent years, immunosuppressive dosage has been gradually reduced due to recurrent lower respiratory tract infections. She admitted with hematuria, purpuric rash, dyspnea. and serum creatinin 5.7 mg/dl. Renal biopsy revealed necrotizing crescentic glomerulonephritis. The patient was treated with pulse steroid, double filtration plasmapheresis and rituximab. She is being followed with a functioning graft and with serum creatinin 2.0 mg/dl. In case of recurrent infection, immunosuppressive drugs should be modified cautiously even in patients with full-match grafts to prevent late acute rejection or recurrence of the primary disease.

Keywords: Full match, kidney transplantation, late rejection, necrotizing crescentic glomerulonephritis, rituximab

Introduction

Kidney transplantation is the treatment of choice for end-stage renal failure. Near-normal renal function, survival prolongation and significant improvement in quality of life has been observed after a successful kidney transplantation. Despite the significant improvement in early graft survival due to development in medical treatment, surgical technique and experience, similar improvements in the long-term survival has not been achieved [1-3]. Late-onset chronic rejection and recurrence of primary renal disease significantly restricts organ survival [1-4].

The assessement of HLA typing in organ transplantation is the cornerstone of immunological evaluation [5, 6]. HLA-identical and full-match grafts have excellent early and late survival rates [7-9]. Today, the immune-mediated damage (C4d-mediated rejection) is claimed to be the cause of the majority of graft loss which had been attributed to chronic allograft nephropathy previously [1, 2]. There is no sufficient data about the impact of C4d-mediated rejection on graft survival of full-match kidney transplants. Recurrent glomerulonephritis significantly reduce early and late graft survival [4]. Although this recurrence depends on the nature and type of glomerulonephritis with the genetic differences among patients, it can lead to graft failure approximately in 20% of kidney transplant [4]. However, there is still not enough information in the literature about recurrent pauci-immune necrotizing crescentic glomerulonephritis. Here, we present two cases (1 cadaveric, 1 living donor) of kidney transplants who had had uneventful early course but experienced c4d-mediated acute rejection four years after and recurrent pauci-immune necrotizing crescentic glomerulonephritis 8.5 years after transplantation.

Case presentation

Case 1

A 49 years old female patient with unknown primary, received a six-matched cadaveric kidney from a 47 years old female donor with spontaneous subarachnoid bleeding induced brain-death 4 years ago. She had a history of pre-transplant two years hemodialysis. She had 2 children and no history of blood transfusion. Results of the HLA of patient and donor were A26, A30, B8, B51, DRB1-03, DRB1-15. Her PRA class I & II titers were positive before transplantation, however donor-specific antibody evaluation was not made. Cross match tests were negative. The early post-transplant period was uneventful with SCr: 1.4 mg/dl and a maintenance therapy of 15 mg/d prednisolone (P), 1080 mg/d mycophenolate sodium (MPS) and 250 mg/d cyclosporine (CsA). The protocol biopsy findings at 6 months and 1 year follow-up were nonspecific. At 1 year, she was receiving P 10 mg/d , MPA 1080 mg/d, CsA 200 mg/d and S.Cr was 1.8 mg/dl. She had the history of recurrent urinary tract infections. after the first year and gradual dose modifications in CsA and MPS treatment within the three years. S.Cr at 3 years was 2.0 mg/dL. The patient's clinical course was shown in **Table 1**. In the fourth year of transplant, the patient admitted with complaints of fatigue and low-grade fever while taking P 5 mg/d + MPS 360 mg/d + CSA 50 mg/d. The laboratory analysis were: S. Urea: 124 mg/dL, S.Cr: 5.8 mg/dL. CRP: 1.23 mg/dL and Liver Function tests were normal. Complete blood count and spot urine analysis were unremarkable and spot urine protein to creatinine ratio was 0.3 g/d. Urine cultures were negative. Doppler ultrasound demonstrated increased echogenicity and high RI: 0.85, without urinary tract obstruction. Renal biopsy was indicative of C4d mediated rejection with features of dilated PTCs with C4d deposition (30-40%), mononuclear cell infiltration (i3) with lymphocytic predominance (CD3 + cells 60%, CD20 + cells 40%), tubulitis (t1), interstitial hemorrhage and mild chronic changes as IFTA (15-20%) and glomerulosclerosis (20%). PRA Class I and II were positive (50%) and subgroup analysis revealed antibodies against (HLA A2, A3, B17) and (HLA DR7, DQ9). The treatment protocol consisted pulse steroid (500 mg/d. X 3), ATG (750 mg total dose), 2 g/kg IVIG, 3 sessions dB plasmapheresis. Maintenance immunosuppression was P (10 mg/d) + MPS (1080 mg/d) + FK 506 (2 mg/d). During the follow-up, serum creatinine did not fall affectively and remained 4.8 mg/dL. On the 15th day of the treatment, the patient developed high fever with pyuria and leukocytosis. Piperacillin-Tazobactam sensitive Klebsiella pneumoniae sp. was detected in urine culture. The patient recovered following treatment however her renal function worsened progressively with ultimate graft loss at the 8th month following the diagnosis of C4d-mediated rejection. She is already alive in hemodialysis.

Case 2

61 year old female patient received an HLA-identical kidney 8.5 years ago from 49 years old brother. Pretransplant PRA was negative. She was diabetic for 6 years and had the history of kidney failure following severe lower respiratory tract infection. At that time, the kidney biopsy revealed a possible small-vessel vasculitis secondary to necrotizing crescentic glomerulonephritis with negative immunofluorescence staining. She was on hemodialysis for one year before transplantation. Pre-transplant antibody analysis were as follows: ANA: 1/400 positive, antidsDNA: negative, p-Anca and c-ANCA: negative. She was transplanted in November 2005. She did not receive induction immunosuppression. Maintenance treatment comprised of P (20 mg/d), MPS (1080 mg/d) and CsA (400 mg/d). Early follow-up period was not problematic and CMV and Polioma BK virus DNA analysis were negative. Scr at one year was 1.3 mg/dL. She had an orthopedic intervention (hip prothesis) eighteen months after the transplantation due to steroid induced avascular necrosis and steroids were discontinued afterwards. SCr and immunosuppressive dosage at the 8th year was 1.7 mg/dL and MPN (720 mg/d) + CsA (125 mg/d) respectively. CsA was withdrawn because of severe gingival hyperplasia and the patient switched to tacrolimus therapy (2 mg/d). Then, MPA and FK506 dosages were reduced to 360 mg/d and 1 mg/d. respectively, due to recurrent lower respiratory tract infections. At 8.5 years after transplantation, she was admitted with shortness of breath, macroscopic hematuria , purpuric rash on legs and SCrand SUrea value of 5.7 mg/dL and 183 mg/dl. CRP was 66.6 mg/dl, LFT tests were normal and serum albumin was 4.0 g/dl. Haemoglobin was 9.6 mg/dl, Leukocyte: 6520/mm^3 and platelet count was

Table 1. The clinical course of Case 1

Date	Serum Creatinine Dip-stick Urine-analysis	Graft Biopsy	Immunsupresive Treament	Infection Complication in Post Transplant Course
Basal	1,4 mg/dL Normal	Unremarkable (Protocol)	Prednisolon (P) 15 mg/day Mikofenolat sodium (MPS) 1080 mg/day Cyklosporine (CSA) 250 mg/day	unremarkable
6 months	1,6 mg/dL Normal	(Protocol) 12 glomerulus: glomerulosclerosis: 0/12 Focal acute tubular necrosis, Tubulitis (t): 0, interstitial infiltration (i): 0-1, cv: 0, ah: 0 İnterstisyel fibrosis and tubular atrophy (IFTA): 5-10%	P 10 mg/day MPS 1080 mg/day ↓ CSA 200 mg/day	unremarkable
12 months	1,8 mg/dL Normal	(Protocol) 10 glomerulus: glomerulosclerosis: 1/10 Glomerular mesangial matrix expansion, i: 0-1, t: 0, cv: 1, ah: 1 IFTA: 5-10%	P 5 mg/day MPS 720 mg/day ↓ CSA 200 mg/day	asymptomatic bacteriuria (twice)
36 months	2,0 mg/dL Many Leukocytes		P 5 mg/day MPS 360 mg/day ↓ CSA 100 mg/day ↓	acute pyelonephritis (twice)
48 months	5.8 mg/dL Normal	16 glomerulus: Glomerulosclerosis: 3/16 PTCs with C4d deposition (30-40%), i:3 (CD3 + cells 60%, CD20 + cells 40%), t: 1, interstitial hemorrhage IFTA: 15-20%.	P 5 mg/day MPS 360 mg/day CSA 50 mg/day ↓	Candidal vulvovaginitis

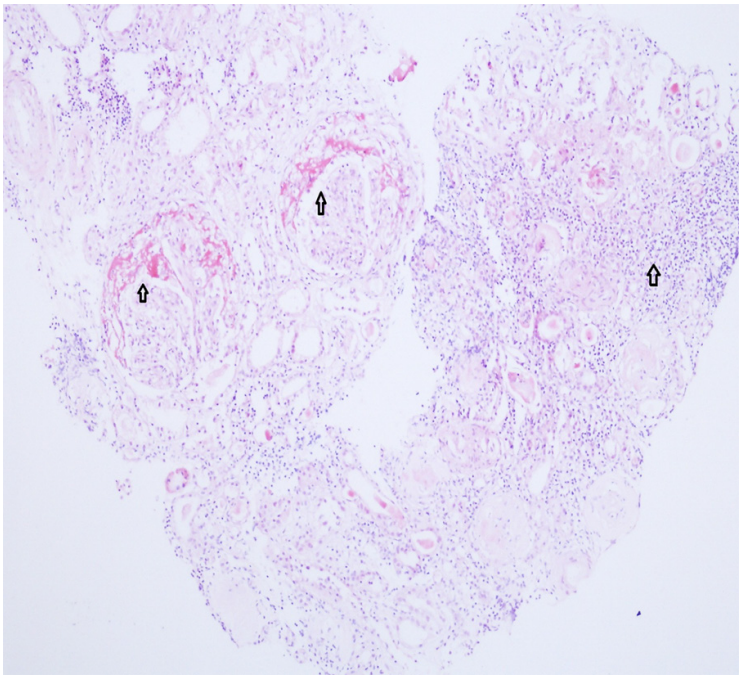

Figure 1. Kidney biopsy findings in Case 2.

204000/mm^3. Spot urine protein to creatinine ratio was 4.8 g/d. Urinary tract ultrasonography was normal. PA chest X-ray showed heterogeneous reticulonodular opacities in the mid and lower zones of both lungs. High-resolution computed tomography of chest revealed bilateral diffuse ground glass appearance at mid and lower zones. The initial clinical diagnosis was pulmonarenal syndrome with severe graft dysfunction and macroscopic hematuria accompanied by bilateral pneumonic infiltrations. Renal biopsy demonstrated moderate global sclerotic glomeruli (25-50%) and necrotic changes with cellular cresents in all non-sclerotic glomeruli. There were foci of tubular atrophy and interstitial fibrosis (25%) ,arteriolar hyalinosis (ah1) and arterial intimal fibrosis (cv1) with diffuse interstitial inflammation (i2) and tubulitis (t1). C4d staining in PTC and immunoflourescence examination was negative. Renal biopsy findings were shown in **Figure 1** Antibody titers were: ANA 1/320 positive, anti-dsDNA, antiglomerular basement membrane (anti-GBM) antibody, P and c ANCA were negative. The final diagnosis was pauciimmune recurrent necrotizing crescentic glomerulonephritis. Treatment protocol consisted pulse steroid (1 gm/d. X 3), 7 sessions of alternate day double filtration plasmapheresis and single dose rituximab administration (375 mg/m^2) after the first plasmapheresis. Tacrolimus was withdrawn temporarily and MPN dosage was increased to 1440 mg/d. Haemodialysis was required for three times during treatment. The symptoms recovered quickly, macroscopic hematuria vanished and on the 14th day of treatment serum creatinine levels began to improve with SCr: 4.2 mg/dl. At the second week, the patient's treatment protocol was shown in **Figure 2**. She was discharged with P (20 mg/d) and mycophenolate sodium (1440 mg/d). He is very well six months after treatment with SCr: 2.0 mg/dl and still being followed in our clinic.

Discussion

Today, the significant improvement in early graft survival rate has not been obtained in the long term of kidney transplantations. Recent studies argue thatimmunological causes (chronic rejections) are essentially responsible from this process [1, 2]. As shown in various studies , there is a positive correlation between graft survival and tissue compatibility which is reflected by improved early and late graft survival [7-9]. According to United Network for Organ Sharing (UNOS) data, the half-life of full-matched grafts were 1.5 times better when compared to other degrees of HLA-matches (12.5 vs. 8.6 years) [10]. However, long-term graft survivals is also significantly affected by alloantigen independent factors as hypertension, atherosclerotic changes, marginal donor kidney implantation, recurrent infections and relapse of the primary disease [1, 2]. Admission with severe graft dysfunction in a patient with six-matched cadaveric graft after four years and the evidence of calcineurin toxicity findings in previous protocol biopsies with history of recurrent urinary tract infections, suggested alloantigen independent graft dysfunction in the differential diagnosis. Therefore, biopsy proven C4d-mediated acute rejection was surprisingly an unexpected diagnosis. Conversly, the history of two pregnancies, pre and post-transplant class 1 and class 2 antiHLA-antibody positivity (post-transplant Class I & II 50% positive) and dose reductions

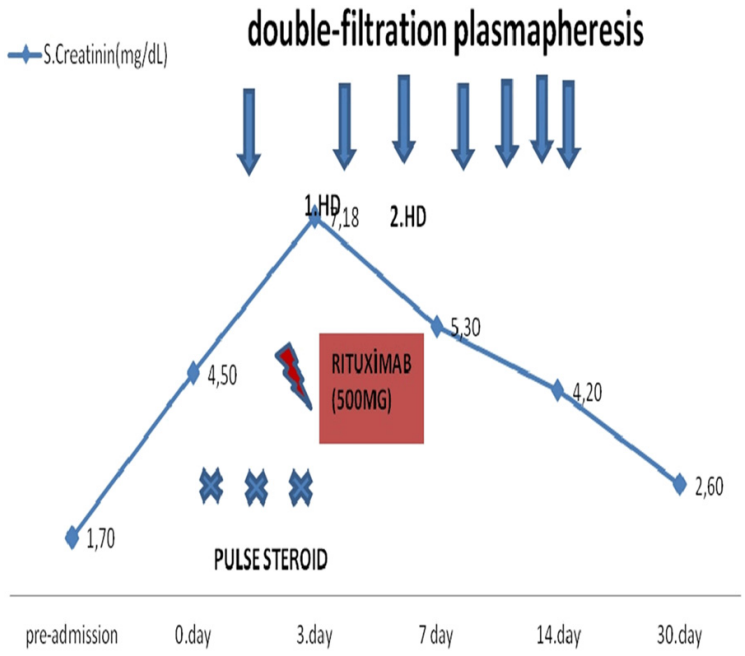

Figure 2. The treatment protocol of Case 2.

in immunosuppressive drugs due to recurrent bacterial infections in recent years (especially in the last 6 months) seemed to support the diagnosis of antibody mediated rejection. There is not adequate data about the clinical importance of anti-HLA antibody positivity in patients with six-matched cadaveric renal grafts. The histocompatibility of six-matched cadaveric kidney is somehow different from an haploidentical living donor kidney, thus; HLA A, B and DR loci subgroups, the possible C locus differences and even non-HLA antibodies may contribute to this process or may be immunologically responsible from antibody-mediated acute rejection [6, 11, 12]. The clinical outcome of our patient clearly demonstrates that; fully compatible cadaveric transplants, albeit low, may develop late C4d-mediated rejection and modifications in maintenance immunosuppressive therapy significantly contributes to this process.

Late recurrence of glomerulonephritis is the third most common cause of allograft losses [4]. Pauci-immune necrotizing crescentic glomerulonephritis (PNCGN) might develop as recurrent or denovo after kidney transplantation [13]. The majority (75-80%) of PNCGN is associated with ANCA positivity (microscopic polyangitis or granulomatosis with polyangitis-Wegener's granulomatosis). Though rare, ANCA-negativ cases can be seen [14]. The recurrence of ANCA-associated PNCGN ranged from 9-40% and average time to recurrence is three years after transplantation [15, 16]. There is no sufficient data about the recurrence of ANCA-negative PNCGN.ANCA testiing might be false-negative due to blurred ANCA titers because of the prolonged use of immunosuppressive drugs after renal transplantation. This phenomenon may be responsible from negative test results in our patient. However, our patient had evidence of small vessel vasculitis in renal pathology with concomittant petechial rushes and pulmonary findings closely resembling PNCGN and therefore considered and treated as the mentioned disease. Relatively late recurrence of PNCGN (8.5 years after transplantation) in our patient, particularly soon after the reduction of immunosuppression is interesting and reminds the importance of maintenance immunosuppressive therapy.

In the literature, except few studies with pulse steroids, cyclophosphamide, and plasmapheresis, sufficient data is not available regarding the effective treatment for the recurrent PNCGN [13-17]. But, rituximab treatment as an alternative therapy is available in the current studies for the treatment of cyclophosphamide-resistant primary renal disease as well as post-transplant recurrent disease [18-20]. Geetha [18] et.al. reported rituximab induced remission in two cases; one ANCA associated-PNCGN with moderate creatinine elevation and one with histologically negative but already considered to have active disease. Murakami et al [20] treated five ANCA-associated PNCGN patients with rituximab and successfully obtained remission in four patients. Similarly, despite severe graft dysfunction on admission, we obtained remission with rituximab in our patient.

As a result, despite excellent early graft survival, primary disease recurrence (especially necrotizing crescentic glomerulonephritis) and/or

antibody-mediated rejection may occur late after transplantation in patients with haploidentical or six-matched cadaveric kidney grafts. The maintenance of immunosuppressive drug dosage in these patients is of great importance. In addition, rituximab treatment may be an important option in the treatment of recurrent pauci-immune necrotizing crescentic glomerulonephritis.

Acknowledgements

Two crescentic glomeruli including necrosis on the left side, and interstitial inflammation and the global sclerotic glomeruli on the right side.

Disclosure of conflict of interest

None.

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