A 48-year-old Woman With Acute Allograft Dysfunction

Pedram Ahmadpoor,[1] Mitra Mahdavi-Mazdeh,[2] Mohsen Nafar,[1]
Fatemeh Pour-Reza-Gholi,[1] Fariba Samadian,[1] Mahmoud Parvin[3]

[1]Division of Nephrology, Department of Internal Medicine, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Division of Nephrology, Department of Internal Medicine, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Pathology, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

CASE PRESENTATION
Patient

Dr Nafar: A 48-year-old lady was admitted 45 days after unrelated living kidney transplantation because of acute allograft dysfunction. She was on hemodialysis for 2 months before transplantation due to kidney failure caused by autosomal dominant polycystic kidney disease. The donor was a healthy 28-year-old man. Panel reactive antibodies test and cytotoxicity leukocyte cross-match were negative. The patient had been discharged 11 days after transplantation with a serum creatinine level of 0.9 mg/dL. The immunosuppressive regimen consisted of cyclosporine, mycophenolate mofetil, and prednisolone. Seventeen days earlier, she was admitted to hospital because of increased serum creatinine to 1.78 mg/dL. She was treated with 3 doses of 500-mg methylprednisolone and cyclosporine dose reduction because of the high serum cyclosporine trough level (429 ng/mL). She was discharged after 7 days with a serum creatinine of 1.2 mg/dL.

On this second posttransplant admission, she was febrile (body temperature, 38.5°C) and hypertensive (160/85 mm Hg). History and physical examinations were unremarkable, and no localized source of infection, organomegaly, lymphadenopathy, or skin rashes were found. There was no recent contact with febrile persons. The kidney allograft was not enlarged or tender. No abnormality was reported on chest radiography. Laboratory data are shown in the Table.

Wide spectrum antibiotics and ganciclovir were

started. The patient became afebrile within the next 24 hours. The results of blood and urine cultures for microorganisms, anti-human leukocyte antigen (HLA) antibodies, and cytomegalovirus antigenemia tests were negative. The trough level and 2-hour postdose level of cyclosporine were 270 ng/mL and 614 ng/mL, respectively. Ultrasonography revealed mild pyelocaliceal dilatation, and allograft diethylene triamine pentaacetic acid scan revealed some decrement in perfusion and function with no evidence of stasis or urinary leakage. On peripheral blood smear, there were about 4% schistocytes.

Steroid pulse was administered, and cyclosporine was reduced to 50 mg, twice per day. A kidney

Results of Laboratory Tests on Admission

Test	Result
Leukocyte count, × 10⁹/L	9.0
Platelet count, × 10⁹/L	153.0
Reticulocyte, %	1.1
Hemoglobin, g/dL	11.0
Blood urea nitrogen, mg/dL	80.0
Serum creatinine, mg/dL	4.8
Serum sodium, mEq/L	138.0
Serum potassium, mEq/L	4.8
Serum calcium, mEq/L	8.3
Serum Phosphate, mEq/L	5.6
Creatine phosphokinase, U/L	180.0
Lactate dehydrogenase, U/L	780.0
Alanine aminotransferase, U/L	36.0
Aspartate aminotransferase, U/L	54.0
Total bilirubin, mg/dL	0.8
Urine protein (dipstick)	2+
Urine leukocyte count, /HPF	20 to 25
Urine erythrocyte count, /HPF	Many

biopsy was taken (its results will be discussed later on). On day 4, platelet count reduced to 80×10^9/L. Plasma exchange was started and cyclosporine was changed to sirolimus.

Would you please comment on the possible causes of allograft dysfunction in this patient?

Dr Mahdavi-Mazdeh: We face a febrile female patient with allograft dysfunction after 1.5 months of her unrelated kidney transplantation, with thrombocytopenia and anemia but not leukocytosis. The most common complication of kidney transplantation a transplant nephrologist should deal with is allograft dysfunction. The differential diagnosis of acute kidney allograft dysfunction varies with the time after transplantation. Traditionally, posttransplantation period is divided into 3 phases: immediate (1st week of transplantation), early (1 to 12 weeks), and late (after 3 months). Our patient is in the early phase. There is no supporting data in favor of low-volume state in her history, and ultrasonography was not on the side of obstruction. Therefore, the cause of her acute kidney failure is intrinsic to the kidney and prerenal and postrenal are ruled out.

The following conditions are the most common differential diagnoses in this time period: rejection. After that is calcineurin-inhibitor toxicity or recurrence of primary glomerular disease and thrombotic microangiopathy. Another important diagnosis after the 1st month to the 6th month of transplantation is opportunistic infections, especially cytomegalovirus or polyoma virus.

The primary cause of end-stage renal disease was polycystic kidney, and recurrence is not considered for her present illness. Plasma cyclosporine level was not elevated and she became afebrile in 24 hours. Cytomegalovirus antigenemia test was negative. Although the specificity of the pp65 antigenemia test is from 20% to 64%, depending on the level of antigenemia chosen for cutoff, its sensitivity is high enough to make the diagnosis unlikely in the patient.[1]

Kidney impairment in conjunction with typical laboratory findings of intravascular coagulation (6% schistocytes in blood smear, thrombocytopenia, and high lactate dehydrogenase) support the uncommon but well-recognized de novo thrombopathic microangiopathic hemolytic anemia, which can be mainly due to calcineurin inhibitors. It may be localized within the transplanted kidney or be

associated with a full-blown systemic hemolytic uremic syndrome. It is possible that the reduction of cyclosporine and/or switching to tacrolimus or sirolimus accompanied by plasmapheresis saves the allograft. It is not necessary to have high blood levels of cyclosporine for diagnosis. It can also be a manifestation of antibody-mediated rejection (AMR). Therefore, a C4d staining should always be performed.[2]

The other diagnosis which cannot be ruled out by clinical setting is rejection in this case. I think with these two main diagnoses in mind, kidney biopsy should be considered.

Pathologic Examination

Dr Nafar: I would like to ask Dr Ahmadpoor to describe the biopsy findings. What is your impression? What other tests would you request?

Dr Ahmadpoor: An allograft core needle biopsy was taken on the 3rd day of admission (Figure 1). Biopsy specimen revealed endocapillary proliferation and focal obliteration of capillary lumens along with neutrophil margination in glomerular capillaries, consistent with acute glomerulitis. No evidence of intraluminal thrombi was present in the glomeruli. In the tubulointerstitial area, there is peritubular capillary congestion with neutrophil margination in the cortical and medullary areas, consistent with peritubular capillaritis. There were no evidence of tubulitis or arteritis in the reviewed pathology slides. Interstitial fibrosis and/or tubular atrophy were minimal. Neutrophils in peritubular capillaries can be seen in ischemia reperfusion and ischemic acute tubular necrosis, but
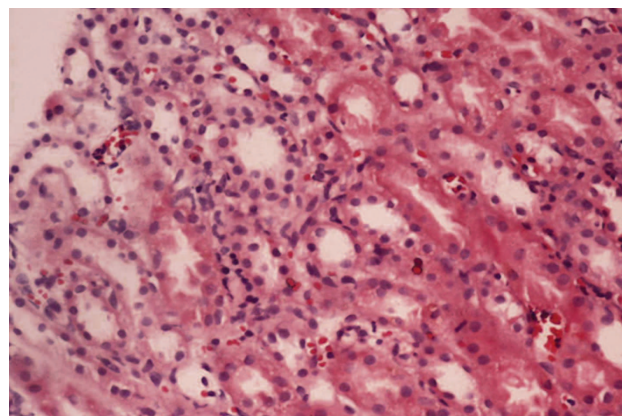
Figure 1. Endocapillary proliferation and focal obliteration of capillary lumens along with neutrophil margination in glomerular capillaries.

they are usually confined to medullary peritubullar capillaries. In this case, there are no supporting history regarding ischemic acute tubular necrosis, and presence of neutrophils in the cortical area and acute glomerulitis are against this diagnosis.

Glomerular margination and infiltration of neutrophils in glomerular capillaries can be associated with acute exudative glomerulonephritis and sometimes in cytomegalovirus glomerulitis, but the glomeruli of the patient are not heavily hypercellular as expected in a diffuse proliferative exudative glomerulonephritis, and also there are no cytopathic changes in favor of cytomegalovirus glomerulitis.[3] Moreover, the cytomegalovirus antigenemia test results are negative that makes this diagnosis unlikely.

Sensitivity and specificity of neutrophils in peritubular capillaries for diagnosis of AMR are 76% and 86%, respectively, and for neutrophils in glomeruli are 47% and 91%. Overall, the light microscopic changes in this allograft biopsy seems most likely to be due to an AMR, and results of C4d staining and anti donor specific antibodies may increase the predictive value of these pathological findings.[4]

Dr Nafar: The allograft was assessed for the presence of C4d by immunohistochemistry (Figure 2). Dr Mahdavi-Mazdeh, would you comment on the clinical significance of C4d and rejection?

Dr Mahdavi-Mazdeh: Historically, the diagnosis of AMR was based on the lack of response to usual cell-mediated acute rejection regimens and possible existence of severe histological findings. In recent years, the poor prognosis of recipient de novo alloantibody production against HLAs
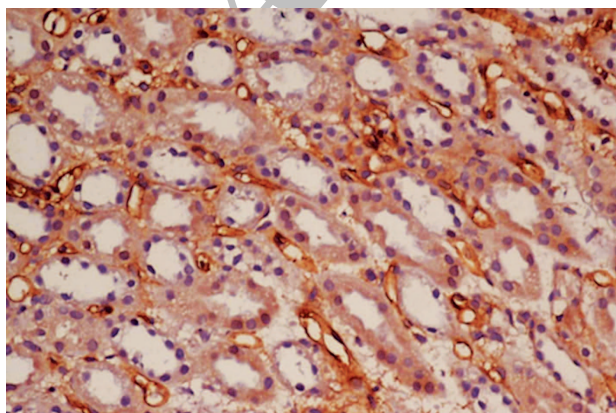
Figure 2. Presence of C4d on immunohistochemistry.

of the donor has been largely studied.[5-7] These antibodies preferentially attack a different "location," peritubular and glomerular capillaries, in contrast to T cells, which characteristically infiltrate tubules and arterial endothelium.[7] A new diagnostic technique led to a major change: C4d, product of complement activation in the classical pathway. Staining of C4d along the peritubular capillaries, but not in glomerular mesangium or the glomerular basement membrane, has been shown to be a sensitive and established marker for antibody-mediated (humoral) rejection in kidney transplant biopsies.[6,8-10] There was also some concern that reperfusion injury (especially in heart transplantation), leading to endothelial damage, could be a probable trigger of C4d deposition. However, Haas and colleagues' study proved that in peri-operative biopsies of living donor and cadaveric kidney allografts, deposition of C4d in peritubular capillaries was rare.[7] Among 82 biopsies, deposition was only seen in 1-hour postreperfusion biopsies of a small fraction of allografts (2 of 13) who developed C4d-positive AMR within the first 5 weeks posttransplantation, which points to AMR and not ischemia.[7] The unique feature of C4d is that it remains covalently bound to the endothelial and collagen basement membrane, for several days (4 to 8 days) after complement 1 and immunoglobulin release and acts as an in situ footprint of antibody activity.[7,11]

There are 2 methods for detecting C4d on tissue: using a monoclonal antibody and immunofluorescence for detection in frozen tissue sections and using a polyclonal antibody and immunohistochemistry on formalin-fixed and paraffin-embedded tissue sections.[12] Staining for C4d is classified as positive when at least 10 capillaries surrounding the nearby tubules reveal C4d and diffuse when it involves greater than 50% of peritubular capillaries.[11,13]

The criteria for acute AMR according to the Banff classification are evidence for antibody activity in 3 different areas: (1) serology, circulating antibody to donor HLA or other antidonor endothelial antigens; (2) immunopathology, C4d and/or (rarely) immunoglobulin in peritubular capillaries or immunoglobulin and complement in arterial fibrinoid necrosis; (3) morphologic signals of tissue injury, vasculitis, glomerulitis with neutrophils in the glomerular and peritubular capillaries,

fibrin thrombi, fibrinoid necrosis, and interstitial hemorrhage in kidney biopsy.[13,14] It should be kept in mind that all are necessary for diagnosis and none is diagnostic enough alone.

There are correlations between a positive C4d staining, donor-specific antibodies, and histopathologic findings in patients with humoral rejection.[5,7,11] The specificity of C4d staining for the presence of donor-specific antibodies was more than 95%, but the sensitivity was reported from 31% to 96%, which could reflect some differences in the two techniques of staining and the identified threshold level for positivity.[13]

Mechanistically preformed antidonor antibodies present as hyperacute rejection in the operating room or in the first 24 hours after transplantation, usually in a setting of inadvertent ABO incompatible or positive crossmatch transplantation. Antidonor antibodies can be detected in a recall process that originates from previous antigenic exposures like pregnancies or transfusions or previous transplanted organs. This kind of rejection can take place within early weeks after transplantation. The third way of antidonor antibody production is de novo that presents as a smoldering AMR (chronic active AMR) or as an acute AMR after months of organ transplantation.

The simultaneous occurrence of antibody- and cell-mediated rejection or "mixed rejection" is also possible, and major histological findings of cell-mediated rejection may mask those of AMR.

Treatment

Dr Nafar: As the last part, I would like to ask about treatment options in AMR and in this particular patient.

Dr Ahmadpoor: After administrations of wide-spectrum antibiotics and after being afebrile, the patient has been treated with steroid pulses and then plasma exchange and substitution of cyclosporine with sirolimus, because of clinical suspicion of AMR or cyclosporine thrombotic microangiopathy. Finally, because of persistent allograft dysfunction, the patient received a dose of rituximab on day 11 of admission and was discharged with improved allograft function.

Antibody-mediated rejection is estimated to occur in 3% to 10% of kidney transplant patients, but as it has been mentioned, it may be accompanied by cellular rejection in 20% to 30% of cases. In high risk groups like those transplanted after desensitization for a positive crossmatch donor or in ABO incompatible transplantation, up to 60% of allograft rejections may be due to AMR.

Compared to acute cellular rejection, AMR portends poor prognosis that warrants early diagnosis and accomplishment of effective treatment strategies. Treatment strategies in AMR consists of suppression of T-cell-dependent antibody response, removal of donor reactive antibodies, blockade of residual allo-antibodies, depletion of naive and memory B cells, and more recently, antiplasma cell therapy.[15] In order to achieve better results in treatment of AMR, applying more than one option is usually required. Antithymocyte globulin, calcineurin inhibitors, mycophenolate mofetil, and sirolimus not only are effective against T cells, but also have direct anti-B-cell effects and can reduce antidonor antibodies and protect endothelial cells from unwanted adverse events of these antibodies. Antithymocyte globulin (especially rabbit's) has antibodies against CD19, CD20, CD38, and CD138 and is especially useful when AMR and cell-mediated rejection are present concomitantly. Among calcineurin inhibitors, the bulk of evidence is more in favor of tacrolimus. There are reports of reversal of AMR with high doses of tacrolimus. Moreover, non-HLA antibodies like antivimentin antibodies seem to be lower in tacrolimus-treated group.

Combination of therapeutic plasma exchange (1 PV to 1.5 PV daily or every other day) and intavenous immunoglobulin, 100 mg/kg, after each plasma exchange session, and 500 mg/kg, at the last session, up to maximum 1 g/kg was associated with encouraging results.[15,16]
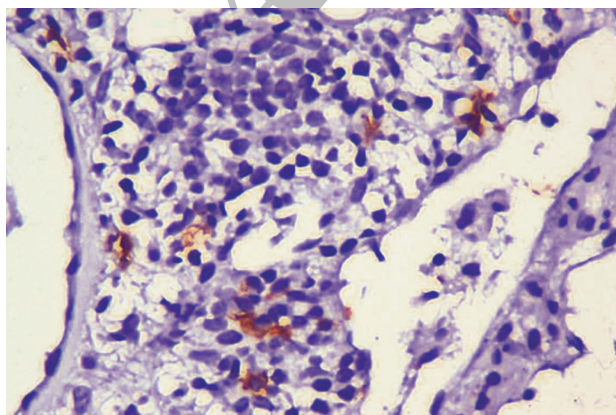
In 2003, Sarwal and colleagues found a high percentage of allograft biopsy specimens taken for evaluation of rejection were infiltrated by CD20-positive B cells, and the rejections were more likely steroid-resistant compared to those of CD20-negative specimens.[17] Later on, a worse allograft outcome was found in those allograft specimens infiltrated with CD20-positive cells.[18,19] Rituximab (anti-CD20) was then considered for treatment of AMR and in those with a positive C4d staining.[20] Interestingly, CD20 infiltration was not associated with C4d staining or donor-specific antibody, and indeed, CD20-positive B cells can be a part of pure acute cellular rejection, playing their role as

antigen-presenting cell and/or involved in cytokine secretion and/or dendritic-cell/T-cell regulation. On the other hand, long-lived plasma cells (CD38+ and CD138+) infiltrated in allograft are not only associated with poor prognosis but also are highly correlated with donor-specific antibody and also C4d staining.[18,19] It seems rituximab, by depleting plasma cell precursor, is effective in treating AMR. Recently, an antiplasma cell agent, bortezomib, that is used in the treatment of multiple myeloma was associated with encouraging results in AMR and mixed AMR and cellular-mediated rejection by the virtue of its anti-T-cell effects.[21,22]

In our patient we have used a combination of steroid pulse therapy with plasma exchange and rituximab, with excellent results. Serum creatinine level was 0.8 mg/dL 2 months later.

The question here is who may benefit from rituximab? Retrospectively, we have studied the specimen for presence of CD20+ infiltration. As it is shown in Figure 3, infiltration of CD20+ B cells was seen in the specimen, but no clusters of B cells were found, and still there was a dramatic response. Staining the allograft biopsies that were taken for allograft dysfunction for presence of CD20+ B cells and CD38+ plasma cells infiltration may not only provide useful information regarding steroid responsiveness and graft outcome, but also be very valuable regarding selection of more targeted therapy.

There are many questions regarding how to continue the patient's immunosuppressive regimen. We did not change sirolimus to tacrolimus based on favorable clinical response and beneficial effects of mTOR inhibition on adverse impact of anti-HLA antibodies on endothelial cells.[23] The other question is whether we should repeat rituximab administration, and if so, at which intervals? Are lower doses as effective as this dose?

Follow-up antibody titre and/or repeat biopsy for evaluation of antibody-mediated injury and especially persistence of C4d staining along with monitoring allograft function may help in making decision about administration of rituximab or tacrolimus or more intensive therapies.

QUESTIONS

Dr Tamadondar (Nephrologist, Bandarabbas University of Medical Sciences): Could it be possible that anti-HLA antibody be negative in a C4d-positive biopsy specimen classified as AMR?

Dr Ahmadpoor: This is a very good question. I refer you to a study that was published in January 2010 issue of *Transplantation*.[24] In that study, only 9 of 19 C4d+ biopsies classified as AMR were positive for either class I or class II anti-HLA antibody. The major histocompatibility complex -class-I-related chain gene A antibody was found in 2 of them as the only antidonor antibody detected. Recently, it was found that about 20% of the general population is null for gluthatione S transferase T1. If a kidney from a donor positive for gluthatione S transferase T1 be donated to a recipient who is gluthatione S transferase T1 positive, the recipient can produce antibody against it that may lead to AMR. In this study, anti-gluthatione S transferase T1 was found in 6 patients and in 3 of them, it was the only antibody detected.[24,25] Antidonor antibody can also be formed against angiotensin receptor I that presents as a vascular rejection associated with severe hypertension. Moreover, monocyte endothelial antigenic system can be a source of antibody production, and finally, absorption of anti-HLA antibody to the graft in the setting of acute rejection may be the cause of a negative anti-HLA antibody in AMR.[26] Because of this, it seems the presence of donor-specific antibody is not essential for the diagnosis of AMR in high-risk groups if there is a positive C4d staining and light microscopic features characteristic of AMR.[27]

Dr Abbasi-Loraki (Nephrology Fellow, Tehran University of Medical Sciences): I have two questions. Is it possible to have C4d-negative AMR? Is there any adverse effect of C4d on long-term allograft function?

Dr Mahdavi-Mazdeh: Many factors contribute to

Figure 3. Infiltration of CD20+ B cells with no clusters of B cells.

the varied prevalence of C4d in humoral rejection. First of all, immunohistochemistry should be evaluated only in nonfibrotic and non-necrotic area of parenchyma. Secondly, as mentioned before, C4d is a dynamic marker. So, timing of biopsy is another important issue. The production of donor-specific antibody would be expected to precede C4d deposition, and a biopsy performed early in the course of AMR may only detect minimal or focal C4d deposition. In cases of serial biopsies, C4d-negative biopsies could turn into positive within as short as 4 days; positive biopsies could switch to negative within as short as 8 days.[13] Cases in which C4d staining is positive but donor-specific antibody cannot be detected may also result from donor-specific antibody being below the level of detection due to immunoadsorption by the allograft. C4d can be negative because the antibody is not complement fixing. With the newer highly sensitive donor-specific antibody detection methods, the clinical relevance of low-level antibodies identified remains unclear. In addition to in vivo and in vitro testing of complement fixation (C4d), other characteristics including antigen specificity and binding strength may assist in determining the clinical relevance of such donor-specific antibody.

Regarding the second question, unfortunately long-term prognosis is often poor. Graft survival was considerably shorter in C4d-positive versus C4d-negative biopsies.[11-13] Ranjan and colleagues found C4d positivity in 37% of 41 cases of chronic allograft nephropathy, and they showed that transplant glomerulopathy had a significant association with C4d positivity and concluded that C4d staining is a useful marker not only for acute humoral rejection, but also for late posttransplant nephropathy.[28]

Dr Naderi (Urologist, Tehran University of Medical Sciences): Did you check panel reactive antibodies or cross-match after transplantation, which are so important in differential diagnosis?

Dr Ahmadpoor: Unfortunately, at the time of allograft dysfunction, we did not do it. We all know that after starting polyclonal antibodies, the test will not be valuable, but I agree with you that having the results would be interesting.

Dr Nafar: The patient received rituximab, 500 mg, on the 11th day of admission. She was discharged 12 days later with a declining serum creatinine. After 2 months of discharge, her serum

creatinine was 0.8 mg/dL.

I would like to appreciate the team involved in treating, preparing, and presenting the case: Drs Pour-Reza-Gholi, Ahmadpoor, Mahdavi-Mazdeh, Parvin, Samadian, and Sotoodeh and Ms Farhangi.

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Correspondence to:
Pedram Ahmadpoor, MD
Department of Internal Medicine, Shahid Labbafinejad Medical Center, 9th Boustan St, Pasdaran Ave, Tehran, Iran
Tel: +98 21 2258 0333
Fax: +98 21 2258 0333
E-mail: pedram.ahmadpoor@gmail.com