

Venous Thromboembolism in Renal Transplant Recipients

The study by Kazory et al. (1) regarding the increased risk of venous thromboembolism (VTE) in renal transplant recipients with cytomegalovirus (CMV) infection was interesting. The authors have suggested that CMV has endothelial cell tropism and converts an anticoagulant phenotype into a procoagulant one leading to increased VTE in transplant recipients.

However, there are a few issues that need to be clarified. The observed incidence of VTE in CMV patients (9%) in the study was not significantly higher than that observed in the CMV-negative recipient population (chi-square value: 2.077, $P=0.15$). In a recent retrospective series by Abbott et al. (2) involving over 28,000 renal transplant recipients no significant association was found between CMV infection and VTE.

The breakup of the sites of VTE is interesting. This study had three patients with isolated calf vein thromboses of which two had pulmonary embolism

on ventilation-perfusion pulmonary scintigraphy. What was the clinical presentation in these three cases?

Symptomatic deep venous thromboses most often involve the proximal veins with isolated calf vein thromboses seen in less than 20% of the cases (3). Pulmonary embolism occurring secondary to tibial vein thrombosis is very uncommon in normal clinical practice (3). Is it possible that the authors were specifically looking for VTE or PE in patients admitted with CMV infection leading to increased detection of asymptomatic venous thrombosis?

Any infection or acute systemic inflammatory process can increase the risk of VTE. The slight increase seen in CMV infected patients may be similar to that seen during any other acute illness.

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REFERENCES

1. Kazory A, Ducloux D, Coaquette A, et al. Cytomegalovirus-associated venous thromboembolism in renal transplant recipients: a report of 7 cases. *Transplantation* 2004; 77: 597.
2. Abbott KC, Cruess DF, Agodoa LYC, et al. Early renal insufficiency and late venous thromboembolism after renal transplantation in the United States. *Am J Kidney Dis* 2004; 43: 120.
3. Anand SS, Wells PS, Hunt D, et al. Does this patient have deep vein thrombosis? *JAMA* 1998; 279: 1094.

Cytomegalovirus and Thromboembolism in Renal Transplantation

We welcome this interesting commentary on our article and appreciate the chance it gives us to further clarify some issues. The first point is the incidence of thromboembolic complications (TEC) in the two groups. Indeed, there are a great number of potential reasons for a kidney transplant recipient to develop TEC (1). In our opinion, it would not then be legitimate to perform any statistical analysis without taking into consideration all potential variables (e.g., immunosuppression regimen) that could greatly modify patients' risk for TEC. We did not perform any statistical analysis in our article because it is not meant to prove a causal relationship. Rather, it describes an observation-based hypothesis that needs further investigation.

In the retrospective cohort study by Abbott et al. (2), cytomegalovirus (CMV) infection was not defined. As the data in this study were extracted from a nationwide registry, definition of CMV infection was likely to have greatly varied from one center to another. More-

over, a great number of CMV infections are asymptomatic, and only a systematic CMV monitoring can estimate the true incidence of infection. As a consequence, the incidence of CMV infection is likely to be underestimated in that study, introducing a bias toward the null hypothesis. In our observation, CMV infection was monitored systematically and all the patients presenting with TEC were tested for CMV infection, many of them showing asymptomatic infection.

In our observation, all cases of TEC were symptomatic. These patients were hospitalized because of symptoms and signs compatible with a TEC, ranging from a simple calf pain to severe respiratory distress. In our opinion, the atypical presentation and localization of TEC in these patients might effectively show that these complications did not occur in a normal vascular bed but involved an endothelium carrying some degrees of preexisting CMV-induced lesions. Our article was a retrospective case study. Of note, we did not search for TEC in CMV patients but for CMV in

patients presenting with TEC. Based on this observation, it seems rather reasonable to search for CMV infection in renal transplant recipients presenting with TEC, especially if any clinical and/or biological sign compatible with this infection accompanies the event.

We agree with the author that CMV is not the sole agent associated with a transient increased hypercoagulability state, and that many other infectious/inflammatory conditions could cause the same effect. However, it should be noted that our article discusses clinical cases of venous thrombosis or emboli associated with CMV and not simply a transient mild alteration of biological markers commonly found in association with inflammatory processes.

Finally, based on biological evidence (3), we believe that CMV might be implicated in a number of coagulation disorders in a subset of renal transplant recipients. These represent a large spectrum of clinical pathologic situations ranging from bleeding dia-

thesis (4) to TEC. However, as we have emphasized in our article, this observation must only be considered as a preliminary report awaiting controlled prospective trials to prove or refute such a causative relationship.

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REFERENCES

1. Kazory A, Ducloux D. Acquired hypercoagulable state in renal transplant recipients. *Thromb Haemost* 2004; 91: 646.

2. Abbott KC, Cruess DF, Agodoa LYC, et al. Early renal insufficiency and late venous thromboembolism after renal transplantation in the United States. *Am J Kidney Dis* 2004; 43: 120.
3. Van-Dam Mieras MC, Muller AD, Van Hinsbergh VW, et al. The procoagulant response of cytomegalovirus infected endothelial cells. *Thromb Haemost* 1992; 68: 364.
4. Kazory A, Ducloux D, Chalopin JM. CMV-associated bleeding diathesis in renal transplant recipients. *Transplant Infect Dis* 2004; 6: 81.

Human Hepatocyte Isolation for Liver Cell Therapy: Whole Marginal Livers or Healthy Segments from Splitting?

We read with interest the article recently published in *Transplantation* by Mitry et al. (1). The authors reported their experience with human hepatocytes isolated from segment IV obtained from split-liver procedures and used the isolated liver cells for transplantation in a 1-day-old boy with antenatal diagnosis of ornithine transcarbamylase deficiency. The hepatocyte isolation procedure was carried out in three cases (in two cases the caudate lobe was also used) without affecting the outcome of the split-liver grafts transplanted into six patients. However, the authors do not state whether the right lobes (segment V to VIII) were transplanted into small-sized adult or large-sized pediatric recipients, nor the graft to recipient body weight ratio. The time (3 hr) required for ex-situ removal of segment IV might have jeopardized the quality of the graft, as several authors have reported better results for in situ than ex-situ split liver (2–3). Moreover, retaining segment IV with the right lobe graft could allow a greater hepatic volume for normal-sized adults without any problems related to the relative ischemia of the lateral part of segment IV (4). Regarding the isolation of human hepatocytes, according to our experience of routine use (almost 100 organs up to now) of marginal livers, deemed unusable for transplantation at harvesting (usually whole organs with macrosteatosis greater than 50%–60% but also several nonviral cirrhotic livers), for hepatocytes isolation we reported (5) an average cell yield of more than 7×10^6 hepatocytes per gram of liver tissue digested with a median

viability of $73\% \pm 14\%$. Recently we improved our results in terms of viability achieving an average value of $80\% \pm 13\%$ (unpublished data). The data from our experience using marginal livers are not different in terms of cell yield per gram of tissue digested (7×10^6 vs. 6.68×10^6) from those reported in the article by Mitry et al. (1), although we obtained a higher total number of hepatocytes (8×10^9 vs. 5.14×10^8). Median viability obtained by Mitry and collaborators was slightly higher ($89\% \pm 8\%$) presumably due to the better quality of the liver tissue used. Although the use of segment IV, obtained from split-liver, for human hepatocytes isolation might increase the hepatic tissue available for research and for clinical liver cell therapy, the routine use of livers not usable for organ transplantation produced similar results in terms of cell yield and viability. Moreover, it might permit the development of large-scale tissue banking without risk of harming the outcome of recipients of whole organ or split-liver transplants.

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REFERENCES

1. Mitry RR, Dhawan A, Hughes RB, et al. One liver, three recipients: segment IV from split-liver procedures as a source of hepatocytes for cell transplantation. *Transplantation* 2004; 77: 1614.
2. Gridelli B, Spada M, Petz W, et al. Split-liver transplantation eliminates the need for living-donor liver transplantation in children with end-stage cholestatic liver disease. *Transplantation* 2003; 75: 1197.
3. Reyes J, Mazareigos GM, Sindhi R, et al. A comparative evolution of ex-situ and in-situ split liver transplantation - the pittsburgh experience. *Transplantation* 1999; 67: s183.
4. Renz JF, Yersiz H, Reichert PR, et al. Split-liver transplantation: a review. *Am J Transplant* 2003; 3: 1323.
5. Baccarani U, Sanna A, Cariani A, et al. Isolation of human hepatocytes from livers rejected for liver transplantation on a national basis: results of a 2-year experience. *Liver Transpl* 2003; 9: 506.

Human Hepatocytes Isolation for Liver Cell Therapy: Whole Marginal Livers or Healthy Segments from Splitting?

We thank Baccarani et al. for their comments. All of the three right lobes were used in adult patients (age: 43, 57, and 62 years) without clinical syndrome of small for size graft. In our program we have performed ex situ split liver transplants in over 230 patients. Most of the adult patients received right lobe grafts without segment IV and the results with this technique (1) are comparable with other published reports. The authors also state that the results of ex situ split is inferior to in situ splitting. Our own published data does not support this even though we believe that in situ splitting has other advantages such as organ sharing between different centres. The

time taken to remove segment IV takes a maximum of 30 min and not 3 hr as the authors suggest. However, we agree that marginal grafts are a useful source of hepatocytes and remain a significant source of hepatocytes in our unit. However, we do believe that segment IV of a healthy liver not only increases the donor pool but also gives better quality hepatocytes.

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REFERENCE

1. Rela M, Vougas V, Muiesan P, et al. Split liver transplantation: King's College Hospital experience. *Ann Surg* 1998; 227: 282.

Is the Application of HLAMatchmaker Relevant in Kidney Transplantation?

HLAMatchmaker is a computer algorithm that determines HLA compatibility at the structural level. Last year, we published in *Transplantation* a study on triplet matching in two large kidney transplant databases (UNOS and Eurotransplant) of zero-HLA-DR mismatched kidney transplants (1). This study was designed to test the hypothesis that transplants with conventional HLA-A,B antigen mismatches but matched at the triplet level would be equally effective as the zero-HLA-A,B antigen mismatches. We found that up to two triplet mismatches in the UNOS database and up to four triplet mismatches in the Eurotransplant database had very similar graft survivals as the zero-HLA-A,B antigen mismatches. These findings suggest that the application of HLAMatchmaker will increase the number of well-matched donors and this strategy has been described elsewhere (2).

Laux et al. reported in the March 27, 2004 issue of *Transplantation* that they were unable to find a statistically significant association between triplet matching and kidney graft survival using the international Collaborative Transplant Study (CTS) database (3) and concluded from their data that the application of HLAMatchmaker has no significant effect on kidney transplant survival. This article was deemed impor-

tant enough to be accompanied by an invited commentary in the same journal issue (4).

This study had a different design in that graft survival was analyzed in relation to the number of mismatched triplets. Up to six mismatched triplets were considered "good" matches and the "poor" matches were subdivided according larger numbers of mismatched triplets, mostly 7–9, 10–12, and ≥ 13 triplet mismatches. Data shown for the 1 HLA-A antigen, the 1 HLA-B antigen, and the 1 HLA-A + 1 HLA-B antigen mismatched groups did not reveal statistically significant correlations between triplet matching and kidney graft survival.

Laux reported that their group of 4,455 zero-HLA-A, B antigen mismatches had a 5-year graft survival of $74.85\% \pm 0.78\%$. Another group of 6,172 0–6 triplet mismatches (which we presume, included the 4,455 zero-HLA-A, B antigen mismatches) showed $74.48\% \pm 0.70\%$, a practically identical value. Moreover, the 5-year graft survival of what the authors consider a "key" group of 1 HLA-A + 1 HLA-B antigen mismatches was highest for the 0–6 triplet mismatches. Especially, recent transplants performed between 1996 and 2001 showed a graft survival of $76.96\% \pm 4.95\%$ for the 0–6 triplet mismatches. Most cases were first trans-

plants done in Western Europe and their graft survival was $76.30\% \pm 3.11\%$. This result is quite comparable with the 76.8% rate we reported for the zero HLA-A, B antigen mismatches in Eurotransplant and similar percentages for the up to four triplet mismatches (1).

We must conclude that these findings by Laux et al. are quite consistent with the concept that HLAMatchmaker can identify a group of HLA-A, B antigen mismatches that give similarly high graft survivals as the HLA-A, B antigen matched combinations.

Another issue is the differential immunogenicity of the triplet mismatches, which was analyzed in the article by Laux et al. This assessment of triplet immunogenicity was based on preliminary data on antibody analyses (5) and must first be confirmed and extended before their role in graft survival can be analyzed.

We agree with Laux and co-workers that there are problematic issues about the current application of HLAMatchmaker. Serological HLA typing results are often insufficient for accurate determination of triplet matches. High-resolution DNA typing provides a more precise assessment of structural HLA compatibility and should also consider the effect of HLA-C triplets.

The most important clinical application of the HLAMatchmaker algorithm

relates to humoral sensitization as the program is based on amino acid polymorphisms in antibody accessible sites of the HLA molecules. Being an excellent tool for the definition of acceptable mismatches for highly sensitized patients, it is routinely used in Eurotransplant.

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REFERENCES

1. Duquesnoy RJ, Takemoto S, De Lange P, et al. HLA-Matchmaker: a molecularly based algorithm for histocompatibility determination III. Effect of matching at the HLA-A,B amino acid triplet level on kidney transplant survival. *Transplantation* 2003; 75: 884.
2. Duquesnoy R, Howe J, Takemoto S. HLA-

Matchmaker: a molecularly based algorithm for histocompatibility determination. IV. An alternative strategy to increase the number of compatible donors for highly sensitized patients. *Transplantation* 2003; 75: 889.

3. Laux G, Mytilineos J, Opelz G. Critical evaluation of the amino acid triplet-epitope matching concept in cadaver kidney transplantation. *Transplantation* 2004; 77: 902.
4. Middleton D. Analyses & Commentaries. Are Threesomes Worth Considering? *Transplantation* 2004; 77: 801.
5. Duquesnoy RJ, Marrari M. HLA-Matchmaker: a molecularly based algorithm for histocompatibility determination. II. Verification of the algorithm and determination of the relative immunogenicity of amino acid triplet-defined epitopes. *Human Immunology* 2002; 63: 353.

Sirolimus and ACE-Inhibitors: A Note of Caution

Sirolimus is a promising immunosuppressive drug, whose use in renal transplantation is particularly advantageous because of the lack of nephrotoxicity. Like most potent drugs, it has peculiar and occasionally severe side effects (common: thrombocytopenia, dyslipemia, retarded wound healing, hypertension; rare: bone pain, abacterial pneumonia, persistent acute tubular necrosis) (1–3).

ACE-inhibitors have three major indications in renal transplantation (antihypertensive, nephro-protective, and active in posttransplant erythrocytosis). An important side effect is the pro-allergic profile, but ACE-inhibitors are not considered to interfere with sirolimus (4). Of note, anaphylactoid reactions are very uncommonly reported and the cases so far published mainly deal with specific types of dialysis membrane, LDL apheresis, or rare situations such as Venom immunotherapy (5–6).

Here we report on two renal graft patients who developed an acute, severe allergic reaction when sirolimus and ACE-inhibitors were combined.

Case 1: 54-year-old woman, on RRT for 29 years (glomerulonephritis), recipient of a second kidney graft (initial immunosuppression with tacrolimus and steroid, followed by a reduction of tacrolimus levels to 4–7 ng/mL, and the addition of mycophenolate). Renal function was suboptimal (at hospital discharge, serum creatinine 1.8 mg/dL) and blood pressure control difficult. ACE-inhibitors were started at low doses (enalapril 2.5 mg/day) 2 years after the graft, with improvement in blood pres-

sure control and without a creatinine increase (2.5–2.8 mg/dL at the time). Two months later, a renal biopsy showed severe vascular damage, with signs of tacrolimus nephrotoxicity. Sirolimus was added to allow tacrolimus withdrawal. At that time, therapy consisted in sirolimus 2 mg, MMF 1,000 mg, prednisone 10 mg, furosemide 50 mg, atenolol 50 mg, felodipine 15 mg, aspirin 50 mg, and erythropoietin beta 12,000 units/week.

Nine days after the start of sirolimus, she developed an urticaria-like erythematous skin lesion, with localized non-pitting oedema, involving the face, neck, and upper thorax. Enalapril was stopped. Prednisone was up-titrated (25 mg/day, tapered to the previous levels within 1 week), with prompt resolution of the clinical picture.

Case 2: a 61-year-old man, on RRT since the age of 56 years (APKD). He received a kidney graft in August 2002 (immunosuppression with sirolimus, mycophenolate, and steroid; serum creatinine 2.2 mg/dL at 4 months). Ramipril was added at the fifth month after the graft, for antihypertensive and nephro-protective purposes. The patient did not take the drug regularly until May 2003; chronic therapy consisted in: sirolimus 9 mg, MMF 1,000 mg, methylprednisolone 4 mg, atenolol 100 mg, calcitriol 25 mcg, pantoprazole 20 mg, and erythropoietin beta 18,000 units/week. After few days of regular ramipril therapy, he suddenly developed non-pitting edema, involving the left cheek, eyelid, and lips, with paresthesia and respiratory distress. Sirolimus and ramipril

were both withdrawn, mycophenolate was increased to 2 g, and methylprednisolone to 8 mg. A daily intravenous infusion with methylprednisolone 100 mg was performed for the following 3 days. Respiratory symptoms rapidly improved and the facial oedema resolved over the next 10 days. Sirolimus was immediately restarted (1 mg, slowly up-titrated to 6 mg/day) without problems.

While only a potentially harmful pharmacologic challenge would definitely prove the presence of an allergic reaction triggered by either sirolimus or ACE-inhibitors, these two cases suggest caution when either drug is added to a chronic regimen.

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REFERENCES

1. Sacks SH. Rapamycin on trial. *Nephrol Dial Transplant* 1999; 14: 2087.

2. Johnson RWG. Sirolimus (Rapamune) in renal transplantation. *Curr Opin Nephrol Hypertens* 2002; 11: 603.
3. Van Hooff JP, Squifflet JP, Wlodarczyk Z, et al. A prospective randomized multicenter study of Tacrolimus in combination with sirolimus in renal transplant recipients. *Transplant* 2003; 75: 1934.
4. DRUG-REAX® Interactive Drug Interactions; MICROMEDEX Healthcare Series: Thomson MICROMEDEX, Greenwood Village, Colorado (Volume 119 expires [3–2004]). Available at: www.micromedex.com.
5. Verresen L, Waer M, Vanrenterghem Y, et al. Anaphylactoid reactions, haemodialysis, and ACE-inhibitors. *Lancet* 1991; 337: 1294.
6. Tunon-de-Lara JM, Villanueva P, Marcos M, et al. ACE-inhibitors and anaphylactoid reactions during venom immunotherapy. *Lancet* 1992; 340: 908.

Role of Ketoconazole in Renal Transplant Recipients

It was interesting to read the article (1) on the role of low-dose ketoconazole in reducing the maintenance dose of cyclosporine in renal transplant recipients. It was a prospective study with historical controls taken from 1992 to 1997. The authors concluded that the monthly expense of immunosuppression was reduced by 60%. However there are few issues that need to be discussed.

The ketoconazole group consisted of patients who were enrolled after January 1998 when newer immunosuppressive drugs were introduced. Here IL-2 blockers were used in three patients and mycophenolate mofetil (MMF) was used in seven (41%) patients compared with the control group where IL-2 blockers were not used and MMF was used only in one (7%) patient. MMF has been shown to have cyclosporine sparing effect and cyclosporine dose can be reduced safely without affecting the graft function (2, 3). Treatment with IL-2 blockers has been found to decrease acute rejection episodes in renal transplant recipients (4). This could have also

contributed to the similar graft function in both groups despite the low dose of cyclosporine in the study group.

An interesting finding in this study is that CMV disease is absent in the ketoconazole group compared with five cases in the control group. Though the authors think that it is an incidental finding it seems to be significant because this was despite the use of higher immunosuppressive drugs such as MMF (5) and IL-2 blockers in the study group. As the authors have pointed out this requires further validation in larger studies.

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REFERENCES

1. Carbajal H, Soltero L, Rodriguez-Montalvo C, et al. cyclosporine and low dose ketoconazole in renal transplant recipients: a single center experience. *Transplantation* 2004; 77: 1038.
2. Thervet E, Morelon E, Ducloux D, et al. Cyclosporine withdrawal in stable renal transplant recipients after azathioprine-mycophenolate mofetil conversion. *Clin Transplant* 2000; 14: 561.
3. Ducloux D, Motte G, Billerey C, et al. Cyclosporin withdrawal with concomitant conversion from azathioprine to mycophenolate mofetil in renal transplant recipients with chronic allograft nephropathy: a 2-year follow-up. *Transpl Int* 2002; 15: 387.
4. Nashan B, Moore R, Amlot P, et al. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. CHIB 201 International Study Group. *Lancet* 1997; 350: 1193.
5. Munoz MA, Andres A, Gallego R, et al. Mycophenolate mofetil immunosuppressive therapies increase the incidence of cytomegalovirus infection in renal transplantation. *Transplant Proc* 2002; 34: 97.

Cyclosporine and Low-Dose Ketoconazole in Renal Transplant Recipients: A Single Center Experience

After excluding three patients from our study that received monoclonal antibody therapy, acute rejection (AR) rates did not change much, 14% vs. 14% ($P=1.00$). As mentioned previously, this result is still surprising due to the disparity between cadaveric (71% in ketoconazole group) versus living donors (86% CyA group). A more valid concern raised by Navalkishor and Srinivas is that there was a 34% difference in mycophenolate mofetil (MMF) versus azathioprine (AZA) therapy between groups that could have influenced results. We agree that MMF is superior to AZA, however just how much better it is in such a small group of patients

such as ours is probably inconsequential.

From a pharmacokinetic standpoint, it must be made clear that MMF does not influence CyA whole-blood levels. On the other hand, it has been shown that CyA does lower mycophenolic acid (MFA) levels, through a mechanism that interferes with MFA glucuronidation (1–2). What impact ketoconazole may have on this relation, whether directly or indirectly, is not well known.

The absence of CMV was certainly interesting and needs greater attention. Hypotheses that remain to be proved or disproved in transplant patients are: (1) ketoconazole by itself exerts broad-spec-

trum activity against fungi, bacteria, and viruses, (2) ketoconazole raises the drug levels of other commonly used prophylactic antimicrobials, and (3) ketoconazole acts synergistically or potentiates other antimicrobials.

Ketoconazole has more than 20 years in the commercial market as an antimycotic agent. When it was first introduced in the early 1980s, it was considered risky for renal transplant patients to receive due to associated CyA toxicity, yet in the last decade the tables have turned and small doses of ketoconazole are precisely being used to therapeutically raise CyA whole-blood concentrations. However, more studies are still

needed in humans to determine the optimum dose (50–200 mg) and administration (QD, BID, TID, QOD) of ketoconazole in combination with other immunosuppressants.

Since pharmaceutical companies may lack the economic incentive to research drugs that safely lower the usage of a more lucrative line of agents, it is necessary for governmental health agencies to intervene and support further studies. Ketoconazole has become such an example. This is an approved drug whose full potential to benefit transplant patients has yet to be determined. Moreover, new research has spurred alternative therapeutic applications in oncology and endocrinology (3–5).

To reliably answer the remaining questions about the effects of ketoconazole in transplant medicine, a longitudinal and randomized clinical trial is needed that measures blood/serum levels of the entire immunosuppression

regimen (calcineurin/TOR inhibitors, antimetabolites, corticosteroids) as well as agents commonly used for antimicrobial prophylaxis. Adverse metabolic outcomes and infectious episodes must be followed-up with great detail. Although a large sample of patients may not be necessary to establish some simple pharmacokinetic conclusions, a large cohort will be needed to fully appreciate the clinical impact of these drug interactions over an extended period of time.

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REFERENCES

- Gregoor PJ, de Sevaux RG, Hene RJ, et al. Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. *Transplantation* 1999; 68: 1603.
- Filler G, Lepage N, Delisle B, et al. Effect of cyclosporine on mycophenolic acid area under the concentration-time curve in pediatric kidney transplant recipients. *Ther Drug Monit* 2001; 23: 514.
- Gylling H, Vanhanen H, Miettinen TA. Hypolipidemic effect and mechanism of ketoconazole without and with cholestyramine in familial hypercholesterolemia. *Metabolism* 1991; 40: 35.
- Engels FK, Ten Tije AJ, Baker SD, et al. Effect of cytochrome P450 3A4 inhibition on the pharmacokinetics of docetaxel. *Clin Pharmacol Ther* 2004; 75: 448.
- Wilkinson S, Chodak G. An evaluation of intermediate-dose ketoconazole in hormone refractory prostate cancer. *Eur Urol* 2004; 45: 581.

Aspirin Promotes Kidney Allograft Survival and Function

We read with interest the article by Grotz et al. describing the remarkable finding that aspirin is associated with improved allograft function and prolonged allograft survival after kidney transplantation (1). The results of the retrospective multivariate analysis indicate that low-dose aspirin was a highly significant and independent determinant of improved graft survival (relative risk 0.44; $P < 0.0001$) and function (1). In agreement with the prevailing view of aspirin acting primarily on platelets through cyclooxygenase inhibition, the authors speculate that aspirin's beneficial effects in kidney transplantation are due to platelet inhibition and subsequent deceleration of transplant vasculopathy. We wish to add that there is an increasing body of evidence indicating that aspirin targets dendritic cell maturation and function (2–4). Dendritic cells are uniquely well-equipped antigen presenting cells that initiate and regulate immune responses. We and others recently reported that aspirin profoundly inhibited CD40, CD80, CD86, and MHC class II expression on bone marrow-derived dendritic cells (2, 3, 5). Aspirin-exposed dendritic cells were poor stimula-

tors of T-cell proliferation and induced lower levels of interleukin-2 in responding T cells (2, 3). Furthermore, investigation of the in vivo function of aspirin-treated dendritic cells revealed an inability to induce normal cell-mediated contact hypersensitivity (2). Further experiments indicated that these effects were cyclooxygenase independent and were related to the suppression of the transcription factor NF- κ B (2, 3). Although these experiments were performed at concentrations exceeding those achievable after low-dose aspirin therapy (81–100 mg/day), they provided evidence that the most commonly used analgesic and anti-inflammatory agent aspirin targets key functions of dendritic cells. If we bear in mind that kidney transplant recipients are taking aspirin in combination with other immunosuppressive agents for several years, we suggest an alternative hypothesis that the "wonder drug" aspirin might promote allograft survival because of its effects on dendritic cells, nature's adjuvants in the initiation of antigen-specific immune responses. We entirely agree that further studies revealing aspirin's potential in organ transplantation are desirable.

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REFERENCES

- Grotz W, Siebig S, Olschewski M, et al. Low-dose aspirin therapy is associated with improved allograft function and prolonged allograft survival after kidney transplantation. *Transplantation* 2004; 77: 1848.
- Hackstein H, Morelli AE, Larregina AT, et al. Aspirin inhibits in vitro maturation and in vivo immunostimulatory function of murine myeloid dendritic cells. *J Immunol* 2001; 166: 7053.
- Matasic R, Dietz AB, Vuk-Pavlovic S. Cyclooxygenase-independent inhibition of den-

- dritle cell maturation by aspirin. *Immunology* 2000; 101: 53.
4. Hackstein H, Thomson AW. Dendritic cells - emerging pharmacological targets of immunosuppressive drugs. *Nature Rev Immunol* 2004; 4: 24.
5. Ho LJ, Chang DM, Shiau HY, et al. Aspirin differentially regulates endotoxin-induced IL-12 and TNF-alpha production in human dendritic cells. *Scand J Rheumatol* 2001; 30: 346.

The T-Tube Approach to Biliary Strictures in Liver Transplant Recipients

Nonanastomotic biliary strictures (BS) are challenging complications of liver transplantation (LT) with long-term patency rates of 25% after nonsurgical treatment (1, 2). We report on a novel approach in the management of early-onset, nonanastomotic BS by means of a radiology-assisted T-tube approach. This technique was employed in a LT recipient with a severe right hepatic duct stricture three months after LT.

A 52-year-old male patient was transplanted for HCV-related cirrhosis with an ABO-compatible, 50-year-old cadaver graft. Cold ischemia time was 9h10' and biliary reconstruction was over a T-tube (3). Three months after LT the patient was admitted to the hospital for the scheduled T-tube removal (3). His liver function tests (LFT) were elevated (total bilirubin 2.1 mg/dL; GGT 68 IU/L; alkaline phosphatases 337 UI/L), but no hepatic artery thrombosis was detected on Duplex US scan. On trans-tube cholangiography a severe stricture of the right hepatic bile duct was observed in close proximity to the biliary confluence and associated with a mild dilation of the left biliary duct (Fig. 1). Under fluoro-angiographic control, a hydrophilic, 150-cm long, 0.035" guide wire with a 3-cm flexible tip (Terumo Radiofrequency Guide Wire M, Radiofocus, Terumo Europe, Leuven, Belgium) was introduced in the T-tube and oriented through its ascending branch up to the distal aspect of the stricture. The T-tube was removed and a 6-Fr dilator (Fascial Dilator, Mediatech, Boston Scientific Corporation, Watertown, MA) was passed through the stricture. The flexible guide wire was removed and replaced with a PTFE-shafted, 145-cm long, 0.035" stiff one (Amplatz Super Stiff, Mediatech, Boston Scientific Corporation, Miami, FL). Cone-tipped dilators up to 10-Fr diameter were passed over the stiff wire to dilate the strictured duct.

A hydrophilic, 8-Fr catheter (Flexima Regular APD All Purpose Drainage Catheter Set, Mediatech, Boston Scientific Corporation, Watertown, MA)

was placed with drainage holes on either side of stenosis (Fig. 2). The cath-

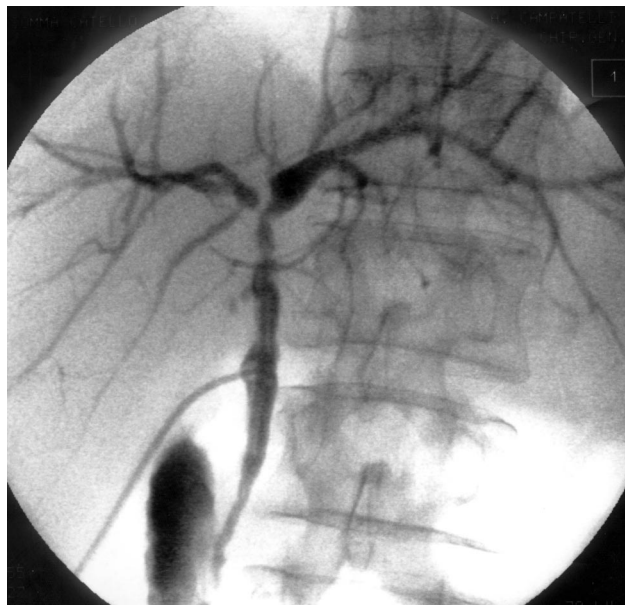


FIGURE 1. T-tube cholangiography showing a severe stricture of the right hepatic duct above the confluence and associated with a mild dilation of the left hepatic duct.



FIGURE 2. Percutaneous cholangiography showing proper positioning of the 8-Fr stent catheter.

eter was secured to the skin and left open for 12 hr. A control US scan 24 hr later confirmed proper placement of the catheter and the patient was dismissed 48 hr after the procedure. He was readmitted 1 month later for a scheduled cholangiography and the 8-Fr catheter was replaced by a 10-Fr one with no complications. This latter catheter was left in place for 1 month and removed under cholangiographic control. A magnetic-resonance cholangiography performed 1 month after stent removal did not disclose any stricture of the biliary tree and LFTs had returned to baseline. At a follow-up of 9 months post-LT the patient is alive without clinically evident relapse.

BS affect 9% to 15% of adult LT patients and their management varies according to type, location, and length of lesions and the availability of experienced radiologic or endoscopic teams (1, 2, 4). A recent survey reported that 67% of US centers favor the endoscopic or percutaneous approach with 2-year patency rates in excess of 70% (5). Nonsurgical management of nonanastomotic BS re-

quires multiple interventions and yields patency rates of approximately 25% in the long term (1, 2, 4, 5). Better results are reported for early, extrahepatic, single strictures, and those not associated with ductopenic rejection or hepatic artery thrombosis (1, 2, 4, 5). The T-tube approach may represent a valid alternative in the management of early-onset, proximally-sited BS, as it spares patients rendezvous techniques, and larger series are strongly favored to validate its results in the long term.

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REFERENCES

1. Moser MAJ, Wall WJ. Management of biliary problems after liver transplantation. *Liver Transpl* 2001; 7(suppl 1): S46.
2. Rizk RS, McVicar JP, Emond MJ, et al. Endoscopic management of biliary strictures in liver transplant recipients: effect on patient and graft survival. *Gastrointest Endosc* 1998; 47: 128.
3. Urbani L, Campatelli A, Romagnoli J, et al. T-tube removal after liver transplantation: a new technique that reduces biliary complication. *Transplantation* 2002; 74: 410.
4. Roumilhac D, Poyet G, Sergent G, et al. Long-term results of percutaneous management for anastomotic biliary strictures after orthotopic liver transplantation. *Liver Transpl* 2003; 9: 394.
5. Vallera RA, Cotton PB, Clavien PA. Biliary reconstruction for liver transplantation and management of biliary complications: overview and survey of current practices in the United States. *Liver Transpl Surg* 1995; 1: 143.

Hematopoietic Stem Cell Transplantation and Subsequent 80% Skin Exchange by Grafts from the Same Donor in a Patient with Herlitz Disease

Herlitz junctional epidermolysis bullosa (H-JEB), a rare heritable disease presenting from birth with widespread skin blistering, is characterized by an early demise of the patient, usually within the first year of life. H-JEB is caused by absence of laminin-5, an anchoring protein restricted to the basement membranes of stratifying squamous epithelia. At present, there is no specific therapy (1). We and others have investigated the use of allogeneic skin grafts or artificial skin equivalents to treat the cutaneous manifestations of this disease (2, 3), however, these approaches were limited by immune responses. Therefore, based on our previous experience with combined allogeneic bone marrow and skin transplantation (4), we attempted to overcome the immune barrier in a H-JEB patient by hematopoietic stem cell transplantation (HSCT) and subsequent skin exchange by grafts from the same donor.

HSCT from the HLA-haploidentical,

blood group-incompatible father was performed at the age of 4 months. The conditioning regimen consisted of cyclophosphamide (120 mg/kg), busulfan (18 mg/kg), melphalan (140 mg/m²), and anti-T lymphocyte globulin (60 mg/kg). Significant mucositis developed after conditioning. G-CSF-stimulated peripheral blood stem cells were harvested from the father and selected for CD34. A total of 33×10^6 CD34-positive cells/kg recipient body weight including less than 25×10^3 T cells/kg were transplanted. White blood cell counts began to rise on day 10 after HSCT, reaching $1,000/\mu\text{L}$ on day 15.

Approximately 4 weeks after HSCT a more rapid progression of junctional skin blistering occurred, resulting in a loss of two thirds of the total epidermis. This reflected most likely the natural course of the disease, but was possibly enhanced by the chemoconditioning. Histological examination of a skin biopsy provided no indication of graft-

versus-host disease (GvHD), and there were also no clinical and laboratory signs suggestive of GvHD. Skin transplantation was started at this time point by harvesting split thickness skin grafts (0.2 mm) from a thigh of the donor. These grafts were slit and transplanted on the whole dorsal trunk and the gluteal region of the child following complete necrectomy with a dermatome adjusted to 0.2 mm. The remaining wounds were covered with glycerolized allogeneic skin to reduce the massive fluid and protein loss. One week later this material was replaced by fresh donor skin. Since the amount available was only sufficient to cover ventral trunk and legs, glycerolized skin was used again for the arms. Three weeks after initial grafting both arms were transplanted with fresh donor skin. All skin grafts healed completely with excellent biomechanical and cosmetic results (Fig. 1). However, the clinical course was complicated by bacterial (multire-

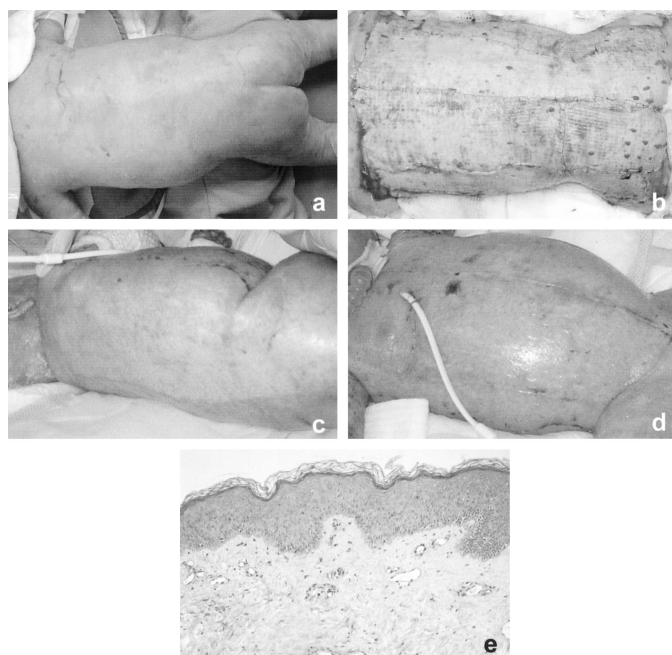


FIGURE 1. Back of the patient (a) before, (b) 5 days after and (c) 4 weeks after skin transplantation; (d) abdomen 3 weeks after the transplantation and (e) histological section of a biopsy from this site 3 weeks after the transplantation.

TABLE 1. Detection of the skin graft by quantitative PCR

Tissue investigated	Time of biopsy	Ratio of Y:X chromosomes \pm SD
Blood from patient	Before HSCT	0.00 \pm 0.00
Blood from HSC donor	Before HSCT	1.01 \pm 0.17
Epidermis from patient	After HSCT, before skin transplantation	0.03 \pm 0.00
Epidermis from HSC donor	After HSCT, before skin transplantation	1.05 \pm 0.09
Epidermis from patient	17 days after skin transplantation	1.07 \pm 0.07
Epidermis from patient	67 days after skin transplantation	1.03 \pm 0.14

sistant *Stenotrophomonas*) and viral (HHV-6) infections. Despite antimicrobial prophylaxis with colistin, trimethoprim-sulfamethoxazole, acyclovir, amphotericin B suspension, amphotericin B inhalation, and intravenous IgG application and aggressive therapy including acyclovir, ganciclovir, foscarnet, cefepime, ceftazidime, tobramycin, metronidazole, teicoplanin, trimethoprim-sulfamethoxazole, ciprofloxacin, meropenem, amikacin, clarithromycin, liposomal amphotericin B, voriconazole, and also an infusion of granulocytes harvested from the stem cell donor after dexamethasone stimulation, the infections could not be controlled necessitating continuous ventilation with temporarily high pressures, and finally the child suc-

cumbed due to pulmonary failure and hypoxia. In skin biopsies obtained 17 and 67 days after skin grafting, the presence of donor skin was confirmed by quantitative PCR detecting one Y chromosome per cell equivalent in the epidermis of the female patient (Table 1).

This first case demonstrates that an 80% exchange of a patient's skin is technically possible and supports our hypothesis that tolerance even to such extensive grafts can be achieved by a preceding HSCT from the same donor. However, it also highlights the great risks of haploidentical HSCT in H-JEB patients. Whereas serious or even fatal viral infections are typical complications of a haploidentical stem cell transplantation, chronic infections with multiresistant *Pseudomonas* species occur

regularly in patients with Herlitz disease. Still, the encouraging result of successful large scale skin exchange in our patient suggests that this novel therapeutic approach should be evaluated prospectively in a clinical trial involving a small series of H-JEB patients.

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REFERENCES

1. Eady RA. Epidermolysis bullosa: scientific advances and therapeutic challenges. *J Dermatol* 2001; 28: 638.
2. Roseeuw D, De Raev L, Dangoisse C, et al. Treatment of epidermolysis bullosa with human cultured epidermal allografts. *Dermatology* 1994; 189: 68.
3. Jiang Q-J, Izakovic J, Zenker M, et al. Treatment of two patients with Herlitz junctional epidermolysis bullosa with artificial skin bioequivalents. *J Pediatr* 2002; 141: 553.
4. Kopp J, Noah EM, Thiele J, et al. Solving a severe cutaneous graft-versus-host reaction after bone marrow transplantation by allogeneic skin transplantation. *Transplantation* 2003; 76: 1647.

Intravenous Immunoglobulin Treatment in a Kidney Transplant Patient with Chronic Allograft Nephropathy

Recent studies have implicated the role of antidonor specific HLA antibodies (DSA) in the pathogenesis of chronic allograft nephropathy (CAN) (1). DSAs were detected in 12%–60% of recipients after transplantation and associated with chronic rejection and lower allograft survival (1). C4d is accepted as a marker for humoral allo-immune responses and has been shown in 34%–61% of biopsy samples with CAN with 46%–88% of those patients had circulating DSAs (2–3). Intravenous immunoglobulin (IVIG) has been shown to decrease the titers of anti-HLA antibodies of highly sensitized patients awaiting transplant (4). In this report we present a patient with CAN associated with positive C4d staining and de novo donor specific anti-HLA antibodies, which responded to IVIG treatment.

The patient was a 47-year-old African-American female, who had kidney disease due to glomerulonephritis and received a kidney transplantation from her non-HLA identical sister. The tissue typing revealed A2,30, B27,42, and DR9,11, while the donor had A3,33, B49,50, and DR15,17. Her pretransplant PRA level was 0%, and there was no DSA by Luminex Flow beads. The immunosuppression included cyclosporin microemulsion, mycophenolate mofetil, and prednisone. The prednisone was de-

creased to 7.5 mg qd at 6 months and 5 mg qd at 1-year posttransplant. The cyclosporin levels were maintained between 150 and 250 ng/mL, and mycophenolate mofetil was dosed at 1,500 mg BID. The patient's baseline creatinine increased to 2.6 mg/dL from 1.5 mg/dL at 30 months after transplantation. The cyclosporin level at the time was 138 ng/mL. The patient's transplant kidney biopsy showed CAN grade II (Banff classification; g0, i0, ah0, v0, cg0, ci2, ct2, cv0) with diffuse C4d staining of peritubular capillaries (Fig. 1). Luminex flow beads demonstrated weak positivity of DSAs to A3, A33, B50, and DR15, and repeated PRA by Luminex Flow beads was 9% (4% to class I and 5% to class II). The patient received 200 mg/kg IVIG two consecutive weeks. The creatinine level decreased to 1.6 mg/dL 1 month after IVIG treatment and remained stable. Repeat tests for DSAs were negative, and the PRA was 0% at 2 months after the last IVIG treatment. Transplant kidney biopsy at 4 months after the IVIG treatment showed CAN grade I (g0, i0, t0, ah0, cg0, ci1, ct1, cv0), but the C4d staining remained positive. The clinical significance of remaining C4d positivity is not clear and requires further clinical follow-up of the patient.

Our case report demonstrates

the decrease in DSAs by IVIG treatment, and improvement in kidney function in a CAN patient with positive C4d staining and de novo DSAs. We have previously shown that using IVIG and thymoglobulin induction treatment in complement-dependent-cytotoxicity (CDC) B-cell and/or flow-cytometry (FC) T- and/or B-cell cross-match positive patients successfully down-regulates preformed DSAs (5). In the light of recent studies demonstrating the down-regulation of DSAs by IVIG, as well as our case report, IVIG has the potential to be used in the treatment of certain subgroups of CAN patients with positive C4d staining and DSAs.

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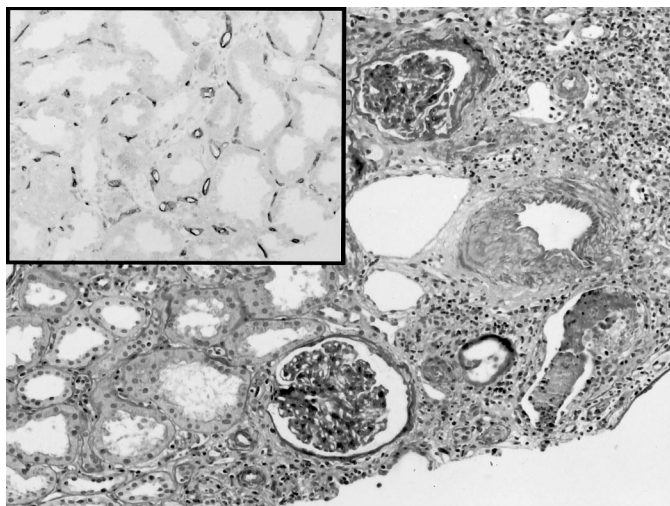


FIGURE 1. Transplant kidney biopsy. CAN grade II per Banff classification. (PAS stain, 100× original magnification). Positive C4d staining at peritubular capillaries. (C4d immunoperoxidase method, 200× original magnification).

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REFERENCES

1. McKenna R, Takemoto SK, Terasaki PI. Anti-HLA antibodies after solid organ transplantation. *Transplantation* 2000; 69: 319.
2. Mauiyyedi S, Pelle PD, Saidman S, et al. Chronic humoral rejection: identification of antibody-mediated chronic allograft rejection by C4d deposits in peritubular capillaries. *J Am Soc Nephrol* 2001; 12: 574.

3. Feucht HE. Complement C4d in graft capillaries- the missing link in the recognition of humoral alloreactivity. *Am J Transplant* 2003; 3: 646.
4. Jordan SC. Management of the highly HLA-

sensitized patient. A novel role for intravenous gammaglobulin. *Am J Transplant* 2002; 2: 691.

5. Akalin E, Ames S, Sehgal V, et al. Intravenous immunoglobulin (IVIG) and Thymoglobulin

facilitate kidney transplantation in complement dependent cytotoxicity (CDC) B cell and flow cytometry (FC) T and/or B cell cross-match positive patients. *Transplantation* 2003; 76: 1444.

Hypophosphatemia and the Live Liver Donor

We reaffirm, as clearly stated in the conclusion of our article (1), and agree with Pomposelli et al. (2) and others (3, 4) that "hypophosphatemia is a recognized morbidity with major hepatic surgery." We stand by our original conclusion and continue to highly recommend that "appropriate and aggressive replacement with either intravenous or oral phosphorous on a case by case basis has been more than adequate treatment for our population of patients undergoing right lobe living donor hepatectomies." "We feel there is no increased morbidity with this approach and is in the best interest of patient safety and recovery." We, at this time, cannot endorse the routine administration of total parenteral nutrition (TPN) whether it is or not to be used as a vehicle for phosphorus administration because of its potential

associated morbidity. So far none of our living donors have been placed on TPN as gastrointestinal function frequently returns in 2 to 4 postoperative days.

Donor safety continues to be of paramount importance, and we cannot overemphasize it. Even though our short-term donor morbidity is reported to be significantly lower than the pooled data from the entire world literature reports of 35% (5), we continue to strive to refine and improve this operation.

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REFERENCES

1. Tan HP, Madeb R, Kovach SJ, et al. Hypophosphatemia after 95 right-lobe living-donor hepatectomies for liver transplantation is not a significant source of morbidity. *Transplantation* 2003; 76: 1085.
2. Pomposelli JJ, Pomfret EA, Burns DL, et al. Life-threatening hypophosphatemia after right hepatic lobectomy for live donor adult liver transplantation. *Liver Transpl* 2001; 7: 637.
3. George R, Shiu MH. Hypophosphatemia after major hepatic resection. *Surgery* 1992; 111: 281.
4. Giovannini I, Chiarla C, Nuzzo G. Pathophysiologic and clinical correlates of hypophosphatemia and the relationship with sepsis and outcome in postoperative patients after hepatectomy. *Shock* 2002; 18: 111.
5. Pomfret EA. Early and late complications in the right-lobe adult living donor. *Liver Transpl* 2003; 9(suppl 2): s45.

Laparoscopic Nephrectomy Donor Death Due to Cerebral Gas Embolism in a Specialized Transplant Center: Risk Zero Does Not Exist

The shortage of cadaver donors and increasing renal transplant waiting lists have made live donor nephrectomy an option. The first laparoscopic (LSC) live donor nephrectomy was performed by Ratner et al. in 1995 (1).

LSC donor nephrectomy is widely accepted and is being performed in specialized centers. In the following, we report a fatal case of gas embolism in a LSC donor nephrectomy patient after an injury to the right phrenic vein.

A 34-year-old female patient underwent a LSC donor right nephrectomy in a tertiary care center with a large experience in laparoscopy and renal transplantation. During the mobilization of the liver, injury to the right phrenic vein occurred. The vein was ligated laparoscopically. Blood loss was estimated at 1,200 cc. The systolic blood pressure was between 60 and 70, O₂ saturation was

maintained at 100%, heart rate was normal, and end tidal PCO₂ decreased from 37 to 32. The blood pressure remained low for 15 min. Hemoglobin was 84. A unit of packed red cells was given. The rest of the surgery continued without further complications. The patient remained hemodynamically stable. After the patient was moved to the recovery room, writhing movements of the trunk and extremities were noticed. A chest radiograph was normal. Heart rate and blood pressure remained stable. An EEG showed diffuse abnormal epileptic activity suggesting cerebral anoxia. The CT scan of the head was negative. A cardiac ultrasound was normal. At this point, it was thought that the patient had suffered a cerebral gas embolism. Three hyperbaric oxygen treatments were undertaken. A repeat CT scan done 2 days later showed diffuse cerebral edema.

She died shortly afterwards and an autopsy was not done.

Complications specific to LSC right donor nephrectomy have been reported to include liver lacerations (5%), bleeding from vena cava (1%), and 9% graft loss because of vascular thrombosis (2–4). There are no reported cases of fatal gas embolism in donor nephrectomies. There is one report of this complication in a LSC left donor nephrectomy where the patient survived after aggressive resuscitation (5).

We believe that our patient suffered an unrecognized gas embolism through an injured phrenic vein. Gas embolism results in a sudden decrease of ETCO₂, hypotension, desaturation, and a mill-wheel murmur. Diagnosis can also be made by using transesophageal echocardiogram. Postoperative manifestations include pulmonary edema

and brain ischemia if the embolus goes into the arterial system by way of a patent foramen ovale or an AV malformation or fistula.

When gas embolus is suspected, it is imperative that pneumoperitoneum be released and the patient be placed in Trendelenburg. The procedure should be converted to open. One hundred percent oxygen ventilation should be used (5).

Although live donors help relieve organ shortage, major surgery in healthy patients is still ethically challenged. Gas embolism is a rare and fatal complication that surgeons and anesthesiologists should be aware of and be prepared to deal with.

LSC donor nephrectomy patients should be informed of the potential dan-

gers of the surgery. The risks should not be minimized.

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REFERENCES

1. Shaffer D, Sahyoun AI, Madras PN, et al. Two hundred one consecutive living-donor nephrectomy. *Surg* 1998; 133: 426.
2. Ratner LE, Montgomery RA, Kavoussi LR. Laparoscopic live donor nephrectomy: the four year Johns Hopkins University experience. *Nephrol dial trans* 1999; 14: 2090.
3. Matas AJ, Bartlett ST, Leichtman AB, et al. Morbidity and mortality after living kidney donation, 1999–2001: survey of United States transplant centers. *Am J Trans* 2003; 3: 830.
4. Buell JF, Edye M, Johnson M, et al. Are concerns over right laparoscopic donor nephrectomy unwarranted? *Ann Surg* 2001; 233: 645.
5. Martay K, Dembo G, Vater Y, et al. Unexpected surgical difficulties leading to hemorrhage and gas embolus during laparoscopic donor nephrectomy: a case report. *Can J Anesth* 2003; 50: 891.

Native Kidney BK Nephropathy Post Cardiac Transplantation

BK virus reactivation post renal transplantation has become increasingly diagnosed over the last decade, probably as a result of the widespread usage of more potent immunosuppressive agents. Manifestations of viral reactivation post renal transplantation include asymptomatic viruria, hemorrhagic cystitis, ureteric stricture, and interstitial nephritis, the latter often associated with progressive renal impairment and graft loss.

For reasons that remain poorly understood, BK virus induced interstitial nephritis (BKIN) and associated renal failure occurs very infrequently in the nonrenal transplant setting even in patients with similar or even greater levels of immune suppression. This is despite the fact that asymptomatic viral reactivation and shedding may be quite common in these patients (1). Only a handful of case reports appear in the literature describing BKIN in native kidneys; in association with HIV infection (2), congenital immunodeficiency (3), post bone marrow transplantation (4), and post pancreatic transplantation (5). We report a unique case of BKIN in native kidneys associated with severe renal failure occurring 2-years post cardiac transplantation.

The patient is a 59-year-old female who presented in October 2001 with increasing symptomatic cardiac failure. Past medical history included focal breast carcinoma resected in 1990 and

thyroidectomy in 1999. A severe dilated cardiomyopathy was confirmed on echocardiogram and cardiac biopsy revealed giant cell myocarditis. Despite treatment with pulse methylprednisolone and cyclosporine, the patient deteriorated requiring admission to intensive care for inotropic support and

insertion of a left ventricular assist device.

She remained in intensive care for 3 months until undergoing a heart transplant in January of 2002. This was complicated by three episodes of severe rejection treated with pulse methylprednisolone and antithymocyte

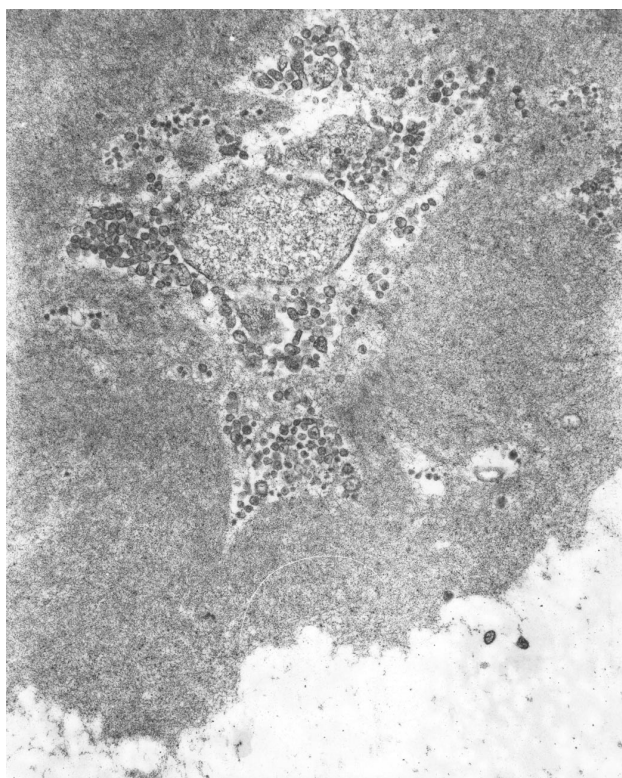


FIGURE 1. Electron microscopy of renal biopsy demonstrates viable and degenerate virions with morphology in keeping with polyoma virus infection.

globulin as well as by the development of steroid induced diabetes requiring insulin therapy. In view of the recurrent rejection a decision was made for increased maintenance immunosuppression including prednisolone, tacrolimus, mycophenolate mofetil, and sirolimus. Of note, serum creatinine was 0.04 mmol/L on admission and 0.16 mmol/L on discharge.

Over the subsequent 12 months, cardiac function remained stable but there was a gradual decline in renal function with serum creatinine climbing to 0.28 mmol/L despite early withdrawal of tacrolimus. In June of 2003 the patient underwent a renal biopsy, which confirmed BKIN (Fig. 1). Urine decoy cells were not detected but urine polyomavirus PCR was found to be strongly positive.

Immunosuppression was considerably reduced to prednisolone 5 mg and sirolimus 4 mg daily with serial cardiac biopsies reintroduced to monitor for cardiac rejection. Although cardiac function remained stable over the subsequent months, serum creatinine continued to rise to 0.40 mmol/L with ongoing strongly positive urine PCR for polyomavirus.

The patient was then treated with intermittent low doses of the antiviral agent cidofovir for a period of 3 months. Despite this, there was no improvement in renal function and urine PCR remained strongly positive for polyomavirus. Currently the patient has a serum creatinine of 0.44 mmol/L and preparations are being made for her to commence dialysis.

It is unclear why BKIN occurs relatively frequently post renal transplantation and so rarely in any other setting. Some authors have suggested that renal tubular injury specific to the process of renal transplantation or allograft rejection is a necessary cofactor in the pathogenesis of invasive BK virus infection (6).

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REFERENCES

1. Etienne I, Francois A, Redonnet M, et al. Does polyomavirus infection induce renal failure in cardiac transplant recipients? *Transplant Proc* 2000; 32: 2794.
2. Nebuloni M, Tosoni A, Boldorini R, et al. BK virus renal infection in a patient with the acquired immunodeficiency syndrome. *Arch Pathol Lab Med* 1999; 123: 807.
3. Rosen S, Harmon W, Krensky AM, et al. Tubulo-interstitial nephritis associated with polyomavirus (BK type) infection. *N Engl J Med* 1983; 308: 1192.
4. Bruno B, Zager RA, Boeckh MJ, et al. Adenovirus nephritis in hematopoietic stem-cell transplantation. *Transplantation* 2004; 77: 1049.
5. Haririan A, Ramos ER, Drachenberg CB, et al. Polyomavirus nephropathy in native kidneys of a solitary pancreas transplant recipient. *Transplantation* 2002; 73: 1350.
6. Fishman JA. BK virus nephropathy—polyomavirus adding insult to injury. *N Engl J Med* 2002; 347: 527.