Clinical Cases

Monday, 5 September 2011

Clinical Cases 1 – Kidney and other – surgical

CC-001 **USE OF ENDOVASCULAR TECHNIQUES TO CONTROL BLEEDING FROM RENAL TRANSPLANT ASSOCIATED SECONDARY HAEMORRHAGE**

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Introduction: Secondary haemorrhage following renal transplantation is a recognized but rare complication often requiring difficult emergency surgery in a shocked patient. We report two cases with delayed presentations following transplant nephrectomy in which bleeding was successfully controlled using endovascular techniques.
Case 1: A 50 year old male who received a deceased donor transplant developed aggressive refractory acute rejection resulting in nephrectomy. This was complicated by retroperitoneal haemorrhage and subsequent abscess formation in the renal bed. Re-exploration and drainage were undertaken. He represented to hospital 6 months later with pain associated with the wound and fever. Intermittent bleeding from the stumps of the 2 residual donor renal arteries was noted. Selective embolisation of these using multiple coils was undertaken. Following this no further bleeding occurred but he subsequently succumbed to uncontrolled sepsis and multi-organ failure.
Case 2: A 40 year old female developed delayed graft function after deceased donor transplantation. Her post-operative course was subsequently complicated by pseudomonal and fungal sepsis. Involvement of the graft required emergency nephrectomy. She recovered but represented 3 months later with secondary haemorrhage from the remnant stump of the donor renal artery. Bleeding was controlled by endovascular placement of a non drug eluting covered stent into the external iliac artery excluding the donor aortic patch and residual renal artery stump.
Discussion: Conventional management of secondary haemorrhage following deceased donor renal transplantation has been excision of external iliac artery and extra-anatomic bypass if required. Selective use of endovascular techniques may warrant consideration as an alternative initial option for definitive management or as a temporizing measure for stabilization of the unstable patient.

CC-002 **SUCCESSFUL AUTOTRANSPLANTATION OF A FUNCTIONING CADAVERIC RENAL TRANSPLANT WITH A MYCOTIC ANEURYSM: A CASE REPORT**

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A 72kg 40 year old male developed symptoms of prolonged sepsis 3 months after successful cadaveric renal transplantation These included generalised maculopapular and peticheal rash, mouth ulcers and symtoms of cold. The white and platelet count dropped significantly so imunosupression was reduced to Tacrolimus monotherapy with SCr84mmol/l. Virology was negative as well as all the other cultures. Sonography showed aneurysmal change at the arterial patch. CT angiography confirmed 31 by 18mm mycotic pseudoaneurysm involving both the external iliac artery (EIA) and the graft arterial patch. Following 2 weeks of treatment with intravenous antibiotics there were no changes to patient's status, rash remained the same. A decision was then made to proceed with nephrectomy together with EIA excision and subsequent reconstruction to prevent aneurysmal rupture and remove the infectious focus. Intraoperatively, no infective hilar scarring was seen and the graft was excised with successful back table perfusion using Soltran solution. The pseudoaneurysm was dissected together with 8cm of external iliac artery; defect was reconstructed with an ipsilateral long saphenous vein graft. The excised renal graft was re-implanted using the contraleral iliac vessels. Two short arteries were anastomosed to the internal iliac artery and one vein to the external iliac vein following a cold ischaemia time of 150minutes (Warm Ischemia exposure 97seconds), 500mg of Methylprednisolon was given. Immediately post operatively, the septic rush disappeared, renal function restored with serum creatinine 130mmol/l.

Conclusions: Mycotic aneurysm after kidney transplant is associated with a risk of major bleeding because of the rupture. Literature shows that most of these kidneys are lost. Our case demonstrates early diagnosis prevented such a rupture. Successful autotransplantation to the contraletaral side was permitted as the graft hilum was not infected. The patient is recovering without complication.

CC-003 **ARM TRANSPLANTATION-TO TRANSPLANT? NOW, LATER OR NEVER**

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A 22 year old caucasian female lost her left forearm at the age of 5 due to trauma. She was left with a small stump below the elbow. She learned of the possibility for hand and arm transplantation and came for an evaluation.
Stated reason for seeking a transplant is the need to off-load her remaining arm and hand and wishing to be able to manage some motor skills better than she can coupe currenlty. She attempted myoelectric prostheses without success. Felt that they were cumbersome and did not aid her in improving her quality of life.
Medical exam revealed a healthy 22 year-old female. Excellent renal funciton, Good functional status. Excellent support structure. Concerns during the medical evaluation were obesity BMI 31.7 and hypertriglycerdemia. She is CMV and EBV postive. All other testing unremarkable.
How would you counsel this patient?

Clinical Cases 2 – Infection / malignancy

CC-004 **SUCCESSFUL TREATMENT OF CENTRAL NERVOUS SYSTEM (CNS) POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD) USING RITUXIMAB AND CRANIAL RADIOTHERAPY (CR)**

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Various modalities of treatment have been put forward for the treatment of Ebstein-Barr virus (EBV)-driven CNS PTLD including reduction of immunosuppression, CR, intravenous and intrathecal rituximab when CD20 is expressed on B-lymphocytes and PTLD cells.
We report the successful treatment of EBV-driven CNS PTLD by reduction in immunosuppression, CR and intravenous rituximab. An 11-year old boy with a living-related renal transplant for end-stage renal failure secondary to posterior urethral valves and bilateral renal dysplasia and on triple immune suppression with prednisolone, tacrolimus and azathioprine had a rising EBV load which was managed with reduction in tacrolimus dose to achieve low levels, withdrawal of azathioprine and introduction of MMF. He presented 6 years post-transplant with a seizure and abnormal neurology secondary to polymorphous hyperplastic lesions in the brain.
He required ventilation for his depressed neurological state and intravenous antibiotics until culture-negative. A brain MRI and brain biopsy were suggestive of PTLD. MMF was stopped, prednisolone treatment intensified and he received a rituximab infusion followed by 15 sessions of CR. His allograft function remained stable throughout with creatinine at his baseline of 120μmol/l. Prior to this presentation his EBV count had fluctuated between 1000 copies up to 6 million copies/ml whole blood and they were high in both his cerebrospinal fluid and blood at this time. He made an excellent neurological recovery with some residual speech impairment but with negative EBV viral load in his blood and almost complete resolution of his brain lesions on MRI within two months from treatment.
We illustrate a case of EBV-driven CNS CD-20+ PTLD which responded to reduction in immunosupression, rituximab and CR. He remains well on immune suppression with prednisolone only and supportive treatment for chronic kidney disease.

CC-005 CHRONIC LYMPHOCYTIC LEUKEMIA: CONTRA-INDICATION FOR TRANSPLANTATION?

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Background: Chronic Lymphocytic Leukemia (CLL) is a malignant hematological disorder characterized by accumulation of small B-lymphocytes. Until now kidney transplantation (Tx) has only been reported in five CLL patients with end stage renal disease (ESRD), four of which experienced severe complications postTx.
Case: A 59-year-old woman, with ESRD due to familial hepatorenal polycystic disease, was diagnosed with CLL 13 years ago. During this period she was treated twice with a short course of chlorambucil and the disease had remained stable since then. Both clinical staging and new prognostic markers (normal karyotype/deletion of 13q14/mutated variable region immunoglobulin heavy chain/no CD38 expression) predicted a slowly progressive disease. During the last months her general condition deteriorated quickly due to severely handicapping polycystic hepatomegaly with ascites, a very low performance status, and a dramatic loss of quality of life (QOL). Pro's (curative treatment, no QOL, good prognosis of CLL) and contra's (infectious/malignant complications, possible progression of CLL) of combined liver and kidney Tx were discussed multidisciplinarily and the decision for combined Tx was taken. The first weeks postTx were uncomplicated with spectacular amelioration of her general condition. However, one month postTx, she was admitted because of fever and pancytopenia. Bacterial and viral infections, drug fever, postTx lymphoproliferative disorder and graft-versus-host-disease were excluded. Bone marrow examination showed infiltration with CLL cells with no residual hematopoiesis. She finally expired due to persistent pancytopenia and fatal invasive pulmonary aspergillosis.
Conclusion: This case illustrates the ethically difficult question as to whether hematological disorders -apparently stable and of good prognosis- should be considered as a contra indication to Tx. This case indicates that, even though classical and new prognostic markers are predictive of a slow progressive disease, complications and recurrence can develop and are very difficult to manage.

CC-006 PROPHYLAXIS WITH LIPOSOMAL AMPHOTERICINE B AFTER LIVER TRANSPLANT AND ITS IMPACT ON IMMUNE SYSTEM AND INFECTIONS AND MORTALITY WITHIN FIRST YEAR

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Aim of the present study was to evaluate the Liposoma Amphotericine B (LAmB) prophylaxis compared to Fluconazole and the related impact on immune response, survival and episodes of infections within first year from OLTx. We have evaluated from Jannuary 2006 to July 2009 all patients undergoing to OLTx in our transplant center. Patients having risk factor according to IDSA Guidelines 2009 received as antifungal prophylaxis LAmB 2mg/day or Fluconazole 400mg/day for 7-14 days. Enrolled patients were followed-up for 12 months at T0, T14d and every three months for: IL-10, TNF-α, IL-6, infective episodes, Candida and Aspergillus antigen assays, Liver and renal function test.
Results: 44 patients were prophylaxed (25 with LAmB Group A and 19 with Fluconazole Group B). All patients had negative Aspergillus and Candida antigens in serum at each time point while just one died for Candida sepsis after CMV infection having received Fluconazole treatment. Patients receiving LAmB had a reduced serum levels of pro-inflammatory cytokines with increased IL-10 compared to those underwent Fluconazole ($p < .01$). Further 5 out 25 patients in Group A had infective episodes (2 cholangitis, 1 Pneumonia, 2 gastrointestinal infection) while 12 out 19 pts in Group B had infective episodes during follow-up (3 cholangitis, 3 pneumonia, 4 gastrointestinal infection, 2 sistemic fungal infection). No renal impairment have been found in both group. Three episodes of reject were present in Group B, while 1 in Group A.
Conclusion: Patients undergoing LAmB prophylaxis had a reduced number of infections during first year after OLTx showing a balanced T helper network with an increased production of IL-10 compared to those undergoing azoles treatment.

Tuesday, 6 September 2011

Clinical Cases 3 – Liver – surgical

CC-007 UNFLUSHED DONOR BILE DUCTS... TO TRANSPLANT OR TO DISCARD?

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Intra-Hepatic Biliary Strictures (IHBS, non-anastomotic) following liver transplantation (LTx) represent an important cause of morbidity, graft loss, extra-costs and even mortality. It can result from an ischemic insult to the peribiliary vascular plexus (hepatic artery thrombosis, high dose of vasopressors during LTx, prolonged cold and warm ischemia times and the use of highly viscous preservation solutions), from an immunological mediated injury (ABO incompatibility, CMV infection, chronic rejection, auto-immune hepatitis, primary sclerosing cholangitis), and from cytotoxic injury induced by cold bile and bile salts. For this reason it is crucial to adequately flush the bile duct at the time of procurement.
We report a case of an imported liver with an accidentally ligated and subsequently completely unflushed common bile duct. Suboptimally flushed livers are –unfortunately- often encountered. But this case represented an extreme form of a liver where the biliary tree was not flushed at all. The dilemma of this unforeseen situation raised the question of: Transplant or discard this liver for transplantation?
Given the organ shortage, the pressure to use less-than-ideal organs, the otherwise normal aspect of the liver and our incapacity to predict with certainty the development (or not) of IHBS, we accepted this liver. The recipient, a 60 year-old man underwent the LTx (ABO identical). The indication was a micronodular post-alcoholic cirrhosis and concomitant hepatocellular carcinoma. The immediate post-operative course was uneventful and the patient was discharged after 18 days. Two months after LTx, post-operative evaluation showed the development of cholestasis. Subsequent magnetic resonance imaging and endoscopic-retrograde-cholangiopancreaticography revealed diffuse IHBS without an anastomotic stenosis. Percutaneous liver biopsy excluded a rejection component and displayed ischemic cholangitis. Echo duplex showed a patent hepatic artery. Due to a rapid clinical and biochemical deterioration without therapeutic option, patient was relisted and re-transplanted successfully.

CC-008 LATE GRAFT DYSFUNCTION FOLLOWING LIVER TRANSPLANTATION: DIAGNOSTIC DILEMMA

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Late graft dysfunction following liver transplantation (LT) often results from late onset acute rejection, chronic rejection, disease recurrence or late vascular problems. Occasionally clinicians are faced with challenging scenarios as described herein.
Presented case is a 19 year old AB+ve previously healthy male diagnosed with pulmonary and spinal tuberculosis (TB). Acute liver failure (ALF) ensued following commencement of standard anti-TB regimen. He underwent a super-urgent LT with a right lobe split graft (22 year old, blood group compatible donor; cold ischemic time 10:53h, graft weight 780g). Standard calcineurin based triple immunosuppression (IS) was started along with a least hepatotoxic anti-TB regimen. Isoniazid/rifampicin were gradually re-introduced. He was dependant on long term renal dialysis and his post-operative period was further complicated by abdominal collections and a bleeding gastric ulcer. 3 months post LT there was a rapid deterioration of his liver function (LF), with mild transaminitis and significant hyperbilirubinaemia (peak 680μmol/L) and thrombocytopaenia. Vascular causes were excluded. Serum EBV titres were high (49224 copies/ml). Liver biopsy excluded rejection, however the specimen showed a plasma cell-rich hepatitis and panacinar necrosis that was similar to the explant liver histology. Bone marrow biopsy excluded lymphoproliferative disorders, peripheral blood film demonstrated haemolysis. The diagnostic problems that arose form this clinical scenario were: 1) Graft failure from anti-TB drugs 2) Post transplant haematological disorders 3) Calcineurin inhibitor (CNI) induced TTP 4) De novo hepatitis. Patient was managed with CNI free minimal IS, and anti-TB drugs were temporarily withheld resulting in improvement of LF.
Questions to the expert panel: Role of plasmacytosis in the presumed diagnosis of isoniazid induced ALF and recurrence of this pattern in the graft? Late graft dysfunction from any other causes mentioned above and further diagnostic markers?

CC-009 PERSISTANTLY ABNORMAL LIVER FUNCTION IN A YOUNG PATIENT AFTER LIVER TRANSPLANTATION: A COMPLEX CASE

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An 18 year old patient presented with non A, non B seronegative hepatitis requiring a super-urgent orthotopic liver transplant. The procedure was uneventful and the patient was transferred to the ward after 48 hours on intensive care.
3 days post transplantation, the patient developed a sudden deterioration in liver function tests as well as a general deterioration in her physiological parameters (AST 10, 930, Bilirubin 218, Alkaline Phosphatase 343). CT scan revealed a patent hepatic artery and portal vein prompting the diagnosis of non thrombotic infarction.This was confirmed as haemorrhagic necrosis on histologocal examination.
The patient was put on the super-urgent list for a regraft and duly received this 48 hours later. The patient made a slow recovery with gradual normalisation of liver function and was discharged 12 days after her second transplant.Her immunosuppresion consisted of steriods, mycophenolate and cyclosporin.
In clinic her LFTS started to deteriorate 6 weeks post transplantation prompting an ultrasound scan of the graft (normal) and a liver biopsy (moderate cellular rejection). The patient was given high dose steriods with resultant improvement in liver function. However, she needed further treatment for rejection and subsequent liver biopsies raised the possibility of antibody mediated rejection with deposits of C4d in the stroma of the portal tracts.Serum analysis also revealed high levels of donor specific antibody. Plasmaphoresis was considered a therapeutic modality against antibody mediated rejection.The diagnosis was complicated as the patient was non-compliant with her medication.
Finally, the patient was admitted to the ward to ensure compliance. Her immunosuppression was changed to tacrolimus with minimal side-effects and her liver function tests have to improve.
Our case illustrates the importance of considering multiple factors including antibody mediated rejection as well as non compliance in instances of liver dysfunction post liver transplantation.

Clinical Cases 4 – Kidney – medical

CC-010 SICKLE CELL TRAIT IN LIVING KIDNEY DONORS

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A 37 year old Afro-Caribbean woman with 3 uncomplicated pregnancies, came forward as a potential kidney donor to her sister, a patient with stage V CKD secondary to lupus nephritis.
Initial screening showed them to be blood group compatible (B to B) with a 0,0,0 mismatch. The recipient, did not have any HLA antibodies on luminex screening. The crossmatch was negative using both CDC and flow techniques. The donor was fit and well with no past medical history. She was not on regular medication, smoked 2 cigarettes a week and did not drink alcohol. She had a BMI of 26.4 and she was normotensive with a blood pressure of 96/60. There were no abnormal physical findings. Urinalysis was negative for blood and protein. She had normal blood chemistry (including an oral glucose tolerance test) with an eGFR of 83ml/min. Serology for hepatitis B, C and HIV were negative. There was evidence of past infection with CMV and EBV. Her albumin:creatinine ratio was $<$2.5. Ultrasound revealed 2 normal kidneys and she had a normal chest radiograph and ECG. Her isotope EDTA clearance was measured as 96ml/min corrected for surface area.
She was not anaemic (Hb 12.9 g/dl) but Hb electrophoresis revealed her to have sickle cell trait with 37% HbS. More detailed testing was then carried out - a crude test for urine concentrating ability reveals a specific gravity of 1.010 on 2 separate early morning urine samples (NR$>$1.010). She also mentioned that she was considering further pregnancies.
This lady has normal kidney function with no proteinura but she has sickle cell trait with 37% HbS and evidence of impaired urine concentrating ability. What should our advise be about the long term safety of kidney donation.

CC-011 CRESCENTS IN TRANSPLANT BIOPSY: WHAT COULD BE THE CAUSE? CLINICAL CASE

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Male patient age 48 with chronic kidney disease due to hypertonic nephropathy.
Concomitant dyslipidemia. Negative test for ANA, ANCA, hepatitis and HIV. After 6 months of hemodialysis the patient has received kidney transplant from deceased donor, F/58, kidney category C.
CIT was 10 h, 3 HLA missmatches PRA 3%. After Tx there was DGF and 1 hemodialysis was required. Implantation (0) biopsy result: Glomeruli: Normal (12/12);Interstitium 5% of parenchyma inflamed (i0),no fibrosis (ci0);Tubules: tubulitis (2 cells/tubular cross section) (t1) mild tubular atrophy (ct1); Arteries and arteriolesarteries: no arteritis (v0); no chronic vascular changes (cv0), arterioles: no hyaline thickening (ah0)
Standard immunosuppression with TAC+MMF+Steroids. Nadir creatinine was 1,5 mg/dl.
After 3rd month posttransplant protocol kidney biopsy was performed. Biopsy findings: Glomeruli: Glomerulosclerosis (3/14), Glomerular tuft shrunken, periglomerular fibrosis (8/14) including 4 with crescents in Bowman space; Interstitium: $<$10% of of parenchyma inflamed including subcapsular cortex (i0) fibrosis (5%) (ci0); Tubules:tubulitis (10 cells/tubular cross section) (t2) mild tubular atrophy (ct1)
Arteries and arterioles: no arteritis (v0); no chronic vascular changes (cv0), arterioles: mild to moderate hyaline thickening (ah1); AR (–). Immunostaining: C4d minimal: positive in 10% biopsy area (C4d1)
Glomeruli: IgM (–), IgA(–), IgG(–), C9(–)C1(+/–) and C3 (+/–) in mesangium. CMV and BK DNA negative.
What could be the cause of the crescents?

CC-012 CALCIFIC UREMIC ARTERIOLOPATHY

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This is a case of a 64-year-old caucasian woman who has presented bilateral necrotic and painful ulcers in lower extremities.
This woman is a kidney transplanted patient who has a second functioning allograft from a cadaveric donor implanted 6 years ago. Her primary renal disease was a mesangiocapillary glomerulonephritis and her total time in haemodyalisis was 7 years.
She had received a mechanic aortic valve replacement and a pacemaker 8 years ago and now is under treatment with sintrom (dicumarinic).
She was partially parathyroidectimized 5 months before transplant because of a secondary hyperparathyroidism with parathyroid hormone (PTH) levels of 993 pg/mL. The biopsy showed nodular hyperplasia. PTH was 158 pg/mL after one year.
At this time, the patient came because she had developed really painful necrotic ulcers in both calves, with erythematous edges and without previous trauma. Serratia marcescens and Staphylococcus Aureus grew in the smear of the ulcer. The radiography by mammogram technique showed important calcification of arteries of the calf. The skin biopsy showed edema of dermis and epidermis, calcification of the wall of arteries of subcutaneous cellular tissue and ischemic changes in adipose tissue.
The blood test showed Creatinine of 2.76 mg/dL (0.3-1.30 mg/dL), BUN 58 mg/dL (6-25 mg/dL), MDRD 18.51 ml/min, Calcium 8.4 mg/dL (8.5-10.5 mg/dL), Albumin 37 g/L (34-48 g/L), phosphorus 3.6 mg/dL (2.3-4.3 mg/dL), alcalin phosphatase 159 U/L (80-240 UI/L), PTH 98 pg/mL (10-65 pg/mL) and 25-OH-D 23 ng/mL ($>$30 ng/mL).
The patient was in that moment under treatment with sintrom, oral calcium, calcitriol, oral iron, subcutaneous eritropoyetin, sodic mycophenolate, tacrolymus, prednisone (7.5 mg/day), amlodipine, atorvastatine, furosemide and proton pump inhibitors.
Here we have a renal transplant patient with low clearance, previously parathyroidectomized, who has developed a calcific uremic arteriolopathy (calciphylaxis). What should we do?

Wednesday, 7 September 2011

Clinical Cases 5 – Early post-transplant problems

CC-013 RENAL TRANSPLANTATION IN A PATIENT WITH CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME AND HEPARIN INDUCED THROMBOCYTOPENIA

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Case Report: We present a rare case of a 29 years old female with end stage renal disease who suffered from catastrophic anti-phospholipid antibody syndrome (APLS) manifesting with renal artery thrombosis of her single kidney, splenic artery thrombosis and hepatic vein thrombosis. Anticoagulation with low-molecular weight heparin (LMWH) was further complicated with heparin induced thrombocytopenia (HIT), deep vein thrombosis in the right arm and grand mal seizures. Nine years later, while on warfarin treatment, the patient underwent live-donor renal transplantation using bridging between warfarin to bivalirudin (Angiomax) 0.15 mg/kg/hr which was discontinued two hours before the surgery and reinstituted six hours thereafter. The aPTT was measured every 4 hours, and the bivalirudin dosage was tittered to an aPTT 1.5-2 times the baseline value. Immediately after transplant, severe thrombocytopenia developed reaching a nadir of 10,000 platelets at postoperative day 3 associated with occlusion of the A-V fistula and abrupt cessation of urine output. In a biopsy performed on post-op day 10 acute tubular necrosis with areas of renal infarction was noted. After five weeks of non-function renal function gradually improved and at nine months after transplant creatinine levels are 2.53 mg/dl.
Conclusion: Patients with catastrophic APLS and HIT should be considered for renal transplantation using bivalirudin anticoagulation. Strict monitoring of coagulation function with careful titration of the drug is required to prevent development of catastrophic APLS during the peri-operative period.

CC-014 SEVERE UNEXPLAINED TMA AFTER ABOi, A CONTRAINDICATION TO RETRANSPLANTATION?

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ABOi kidney transplantation is increasingly common, and outcomes are normally excellent. We present a case for discussion in which early graft failure occurred.
Mrs T, a 36 year-old woman, received a kidney from her partner after 2 years on the deceased donor list. The transplant was B into O. No DSAs were identified. Initial anti-B titre was 1:256. She received Rituximab, then 5 sessions of immunoadsorption. Titres were 1:8 on the day of transplant. Surgery was uneventful. She received basiliximab/methylprednisolone induction followed by tacrolimus/MMF/prednisolone maintenance. Post-operative ultrasound confirmed normal perfusion. The kidney functioned immediately. Despite this she became fluid overloaded and required 24hr CVVH. She commenced Tazocin for possible chest infection. At 48hrs post-operatively her urine output suddenly declined, then stopped. Ultrasound showed global perfusion with high resistance waveforms. Flow was maintained in the vein. Simultaneously, thrombotic microangiopathy developed, characterised by haemolysis with thrombocytopaenia. She received empirical methylprednisolone, plasma exchange and IVIg. Daily ultrasounds remained unchanged. By day six there was no response. She proceeded to exploration and open biopsy. At surgery the kidney was patchily perfused. The arterial anastomosis was revised, without improvement. The biopsy showed both humoral and cell mediated rejection with areas of infarction. Shortly afterwards the anastomosis dehisced, resulting in cardiac arrest and emergent transplant nephrectomy. After a stormy recovery with a pulmonary embolus, she went home. Repeat crossmatch was negative, post-operative anti-B titres never rose above 1:4, no DSA or anti-MICA was identified. Thrombophilia screen showed factor V Leiden heterozygosity and possible lupus anticoagulant. Factor H/I results are pending.
Five months later she came to clinic interested in another ABOi transplant.
Questions:
1) Why did she develop TMA?
2) Would you transplant her again and, if so, would complement blockade help?
3) Would you do an ABOi?

CC-015 WHAT IMMUNOSUPPRESSIVE TREATMENT SHOULD ONE ENVISAGE WHEN TRANSPLANTECTOMY HAS TO BE CARRIED OUT IMMEDIATELY AFTER TRANSPLANTATION?

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We report the case of a 65 year-old woman who underwent nephrectomy within 24h of renal transplantation, due to thrombosis of the renal vein. Despite the fact that the graft had been in place for only few hours and immunosuppressive treatment had been initiated the day of grafting and maintained until day 4, less than two months later this non-immunized patient had developed an immunization against mismatched HLA antigens of the donor. Use of Luminex assay with single HLA allele beads, analyzed with the HLAmatchmaker program, which considers the mismatched epitopes presented by the immunizing antigens, enabled us to identify the epitopes inducing the specific antibodies. Thus, the patient HLA-A*03:01; B*35:01, B*51:01; C*04:01, C*14:02; DRB1*01:01, DRB1*13:01; DRB3*01:01, DQB1*05:01, DQB1*06:03, transplanted with a kidney HLA-A*02:01, A*11:01; B*15:01, B*51:01; C*01:02, C*15:02; DRB1*07:01; DRB4*01:03, DQB1*02:02, had become immunized against the epitopes 62GE and 127K expressed by A*02:01, against the epitope 4Q expressed by DRB1*07:01 and against the epitope 84QL expressed by DQB1*02:02. As these mismatched epitopes were shared by other HLA antigens, the immunization had "spread" to the molecules (i) HLA-B57 and B58 (epitope 62GE), (ii) HLA-A68, A69, A23 and A24 (epitope 127K), (iii) HLA-DR9 and DR53 (epitope 4Q) and (iv) HLA-DQ4, 7, 8 and 9 expressing, like DQB1*02:02, epitope 84QL.
This case highlights the extreme difficulty of foreseeing an immunization appearing as a consequence of the very early necrosis of a transplanted kidney Should one maintain the immunosuppressive treatment – which is not without side effects – or interrupt it prematurely, since the transplanted kidney is no longer there, but with the risk of discovering an immunization which will accordingly restrict the choice of a new transplant.

Clinical Cases 6 – Rejection

CC-016 NEPHROTIC PROTEINURIA AS THE MAIN CLINICAL PRESENTATION OF ACUTE REJECTION IN A RENAL TRASPLANTED PATIENT

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Patient: female, 53 years old. Transplant (Tx) date: May 15th, 2006. Donor: live related, daughter. ESRD ethiology: unknown, glomerulopathy suspected. Immediate renal function. Immunosuppression: Basiliximab,steroids, cyclosporine, everolimus.Uneventful evolution except for overweight and dyslipidemia. One year post Tx: creatinine 1.1mg%,proteinuria: negative. Two years and 8 months post-Tx she developed nephrotic proteinuria with a creatinine of 1.13 mg%.A graft biopsy was performed and acute rejection grade IA of Banff diagnosis was made. She received metilprednisolone pulses. Four months later, her creatinine was 1.17mg%,proteinuria 1.24gr/24hs. Everolimus was switched to MFS due to proteinuria. Three years and six months later, her creatinine was 1.12mg%with no proteinuria till November 2010when she again developed nephrotic proteinuria (9gr/24hs) and creatinine was 1.4mg%. A second biopsy was carried out showing acute rejection grade IB plus extracapilar proliferation. Tests for DNA, FAN, C3,C4,CH50, RR,Latex,ANCAp,ANCAc,were negative.She received other corticosteroids pulses, cyclosporine was switched to tacrolimus. Even though a partial remission of the proteinuria was achived,the creatinine increased up to 1.6mg%,so a new biopsy was performed in January 2011 and it showed: borderline rejection plus tubular atrophy, interstitial fibrosis and glomerulosclerosis. As creatinine did not decrease and proteinuria did not disappear, a new biopsy was performed in February, before treatment decision: focal segmental glomerulosclerosis plus tubulitis as a sign of acute rejection was seen. Immunofluorescence negative.
Your diagnosis and treatment approach? Biopsy pictures available.

CC-017 LATE RENAL ALLOGRAFT DYSFUNCTION-BK-ACUTE REJECTION: A CONUNDRUM

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A 52 male patient with renal allograft dysfunction. 10 years previously he had developed ESRD due to Alport's syndrome. Received a living related re-

nal transplant (LURD). That kidney lasted one year and was lost due to BK nephropathy. Remained on dialysis for 4 years. Received his second and current kidney 3 years later which was LURD also. This was a positive cross match kidney transplant. Was doing well with diminished but stable renal allograft function.
Was seen 6 month earlier for routine anual. visit. Graft function stable. No BK virus was detected in the blood and urine (routine screening). He presented with an elevation of creatinine from his baseline of 1.9 -2.1 to 2.5 and peaked to 3.1. This was accompanied by an elevation of his blood pressure and increased dose of lisinopril.
A biopsy was reluctantly performed. This showed positive in-situ hybridizatio for BK virus, interstitial inflammation and postive C4d. He received IV immunoglobulin (IVIg) at 2g/kg in two divided doses, Cidofovir was started at 0.25 mg/kg every two weeks and immunosuppression was reduced. Achieved tacrolimus levels were 5-7 ng/ml and mmf 1.5-2.2 ng/ml. Creatinine remained stable. BK virus counts decreased in the blood by 8 weeks down to 11 k copies/ml. His follow up biopsy 8 weeks after initial diagnoses showed an intense plasma cell rich infiltrate. C4d was negative.
Creatinine remained elevated but stable, pulse corticosteroids and repeat courses of IVIg and Cidofovir were re-initialted.
Creatinine at last follow up 3.5mg/dL.

CC-018 SALVAGE THERAPY FOR REFRACTORY REJECTION AND PERSISTENCE OF DONOR-SPECIFIC ANTIBODIES AFTER INTESTINAL TRANSPLANTATION USING THE PROTEASOME INHIBITOR BORTEZOMIB

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Antibody-mediated rejection (AMR) is a challenge in intestinal transplantation (ITx) and poorly characterized. Persisting levels of donor-specific anti-HLA-antibodies (DSA) constitute a major risk, especially when appearing in the first year after transplantation. AMR is less responsive to anti-rejection-treatment, entailing chronic graft-manifestations and allograft losses.
Plasmapheresis and rituximab reduce the concentration of HLA-antibodies, but are ineffective against antibody-producing plasma cells. Bortezomib, a proteasome-inhibitor, was shown to deplete antibody-producing plasma cells and reduce DSA with long-term suppression after kidney transplantation. We report the successful treatment with bortezomib in a patient with refractory rejection associated with persisting DSA-levels after ITX.
On POD14, DSA-testing revealed high DSA-levels, entailing immediate plasmapheresis. On POD19, the patient experienced a mild ACR and received steroid pulse therapy and rituximab (375mg/m2), which decreased histological rejection signs. Inspite of anti-rejection therapy with steroids and thymoglobuline, allograft biopsies continued to display rejection signs. C4d-staining was inconclusive. Since 3 intervals of plasmapheresis, high-dose ivIG and 2 applications of rituximab failed to reduce DSA, bortezomib was applied (4x1.3mg/m2) and well tolerated. Within 4 weeks after bortezomib-application, DSA decreased significantly and histological rejection signs disappeared.
Bortezomib was reported to successfully reduce/eliminate DSA. Recent priming of B-cells or recall stimulation of memory B-cells shortly after transplantation may generate short-lived plasma cells with a high DSA-production, which may be susceptible to proteasome inhibitors. Because bortezomib targets antibody-producing plasma cells, but not circulating antibodies, which have already caused graft injury, circulating antibodies still need to be eliminated by plasmapheresis and rituximab.
We applied bortezomib as a rescue-therapy in a highly endangered patient with persistent DSA-levels and ongoing graft injury in the early phase after ITX. Bortezomib as an adjunct-agent to plasmapheresis, ivIG, and rituximab might be a new treatment option for AMR after ITX.

Clinical Cases 7 – Late breaking

CC-019 ALTRUISTIC DONATION: DO THE MEDICAL PROFESSIONALS EVER HAVE THE RIGHT TO SAY NO?

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Introduction: Altruistic donation has contributed to the increase in living donor transplantation worldwide. However, the donor's wishes are sometimes antagonistic to the medical team's views. In the current age of patient involvement in treatment decisions, where do we draw the line between patient's autonomy and medical team's unbiased ability to make treatment decisions? How do we reconcile the two aspects if they are contradictory?
Methods: We illustrate this ethical dilemma with the case of an 82 year-old blood group AB, potential altruistic kidney donor, who's late husband suffered from renal failure.
Results: Despite an initial reluctance from the team, following an exhaustive list of investigations and a thorough psychiatric assessment, no obvious contraindication to donation were found. The patient was extremely well informed and keen to see this process through.
Given the age of the prospective donor, and the potential fallout for the entire living donation programme, discussion at the national level were held to ensure acceptance of this donation process. The prospective recipient was also informed and agreed to proceed. The transplant was carried out successfully.
Discussion: As clinicians we are not seldom confronted with patients who have very clear views on how their medical care should be conducted. However, without infringing on patients rights and disrespecting their wishes, the medical teams should not be coerced into actions that they are not comfortable with.
Are we right to seek political backing for our decisions? Does any individual decision have to be justified by the "bigger picture"? Difficult decisions should be taken with complete transparency and in consultation with patients and independent of any fallout.
Conclusion: Altruistic donation epitomises the ethical challenges of living donation. However, these dilemmas should not deter clinicians and one should explore each case on individual merit, unbiased by personal believes.

CC-020 INTERDISCIPLINARY EFFORT TO DIAGNOSE AND TREAT A POSTTRANSPLANT PATIENT WITH SEVERE CEREBRAL LESIONS IN SYNOPSIS WITH THE INTRAINDIVIDUALLY COMPLEX PHARMACOLOGICAL SITUATION

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In all fields of transplantation proliferative disorders account for life-threatening disease in the immunosuppressed posttransplant patients.
To get convincing advices we present a current status of a 56yrs old female patient (P) being left side unilateral lung transplanted because of sarcoidosis in 2005 and immunosuppressed with triple maintenance incl. cortisone, tacrolimus (TAC) and mycophenolate mofetil (MMF). Cerebral lesions documented by magnetic resonance imaging had been treated for Toxoplasmosis based on coincident antibodies before we first saw her with neurological absentees up to hemiparesis and somnolence in our neurological department. Performance of brain biopsy and EBV-analysis confirmed our suspected diagnosis of cerebral manifestation of an EBV-associated posttranplant lymphoma. In keeping with current state of knowlegde we withdrew immunosuppression as far as possible i.e. MMF and TAC to switch to Sirolimus (SIR) with its well-documented antiproliferative effects. The P developed severe infection disease partly associated with E.coli exclusively sensitive to meropenem and imipenem resp. The concomitant application of SIR and meropenem resulted in continuously sharp rise of hepatobiliary enzymes. This might as well be intensified by the intolerable co-administration of voriconazol despite achieving therapeutic trough levels of SIR. To avoid hepatic failure SIR was cancelled and exchanged to lowest dose of TAC as long as meropenem was obligatory. The narrow therapeutic path resulting from pharmacological side effects and interactions forced us to leave a therapeutic strategy that already seemed convincing by the P's neurological improvement and e.g. uplifting CD4/CD8 inversion.
For further intervention we would like to discuss 3 aspects:
1. To reinstate SIR and substitute caspofungin for voriconazol if necessary, yet being aware of interactions
2. To treat with CD-20 antibodies plus radiotherapy of cerebrum
3. Any other options to avoid chemotherapy.

CC-021 **STRONGLY DONOR-SPECIFIC ANTIBODIES AND ABSENCE OF ACUTE REJECTION AFTER COMBINED HEART AND LIVER TRANSPLANTATION, CASE REPORT**

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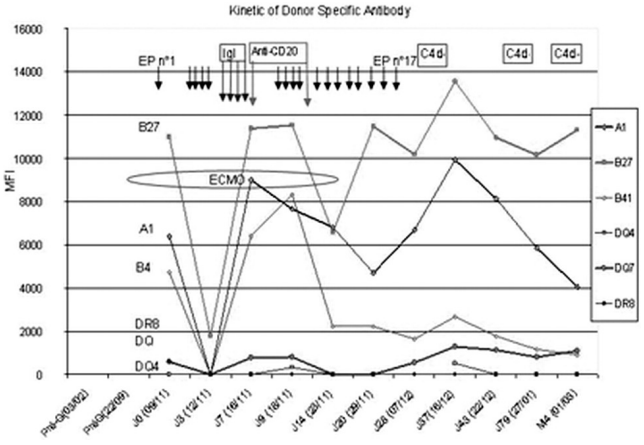
Since the introduction of new technologies based on luminex assays, the frequency of human leucocyte antigen (HLA) antibody screening in transplant recipient has increased.The presence of pre transplantation donor-specific anti HLA antibodies (DSA) has generally been considered as a risk factor for acute humoral rejection. Here, we present a patient who received a combined orthotopic heart and liver allograft for congenital heart disease and secondry cirrhosis. He had a pre transplant high level of DSA against a large number of HLA antigens. Immediately after liver transplantation patient dropped all of the anti-HLA antibodies, as well as the DSA. Three days later, preformed DSA levels subsequently rebounded. Then, he received an aggressive protocol therapy using plasma exchange, IVIg and anti CD20. Surprisingly DSA MFI remained high 3 months after transplantation and no acute rejection episode occurred during the 12 months of follow-up. Negative retrospective cross match and negative repetitive immunostaining for C4d may be related to DSA inability to trigger complement pathway activation. Antibody avidity, antibody isotype (e.g., IgG4) and antigenic epitope also are probably major determinants. Undoubtedly certain minimum conditions must be met in order to initiate alloantibody-mediated rejection. Other hypothesis is that liver probably absorb antibodies from the circulation and permit to speculate for immunoprotective effect of liver in combined organ transplantation. However DSA levels rebound may indicate that liver could be exceeded and the risk of acute rejection persist. It will be important to observe the long terme consequences of these DSA on clinical events.



Keywords: Donor-specific antibodies; Solid-phase assays; Clinical relevance; Sensitization; Combined heart and liver transplant.