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Case Study

Renal replacement therapy in the highly sensitised patient: a surgical science case report

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Renal replacement therapy, transplant, sensitisation.

Key Learning Points

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Kidney transplantation is the most successful treatment for end-stage renal failure and has rapidly expanded to become the optimal renal replacement therapy strategy. However, a mismatch between the demand for organs and supply of appropriate donors persists, making suitable donor organs a precious national resource. During the process of transplantation, the recipient immune system goes through a process of allorecognition whereby the recipient immune system identifies the allograft as foreign, initiating a process of allograft rejection, acutely mediated by cytotoxic T-cells and over the longer term, predominantly driven by alloantibody mediated graft injury. To minimise these processes, donor and recipient ABO blood group compatibility are ensured, HLA tissue typing and physical immunological cross-matching is performed prior to transplantation, reducing the immunological risk. At the time of transplantation, immunosuppression is required to avoid organ rejection and involves an induction therapy (given peri-operatively) and maintenance therapy taken for life. This immunosuppressive therapy is associated with numerous unwanted side effects such as the development of malignancies (particularly post-transplant lymphoproliferative disease (PTLD) and skin cancers), nephrotoxicity and metabolic complications such as new-onset diabetes after transplantation (NODAT), but is necessary for prolonged graft survival. In a minority of patients, such as Mr Carter, who receive multiple transplants, they develop preformed anti-HLA antibodies reactive to multiple potential donors and are therefore considered highly sensitised patients. Although these patients are notoriously challenging to transplant both technically and in terms of finding an appropriate immunological match, the advent of de-sensitization protocols, the paired exchange programme and the new allocation system have transformed the fortunes of this group of patients. In this case, we will explore some of the challenges faced by this cohort patient.

1 Introduction

Renal transplants are the most common transplant carried out in the United Kingdom (UK). As of March 2018, 5033 people were on the kidney transplant list in the UK. There were 1020 kidney transplants performed from living donors, and 2573 from deceased donors. 78 kidney transplantations were made possible by the paired living kidney donation programme1. The past ten years have seen an overall trend of increasing organ donor number, increase in the number of transplants and consequently a decreasing number of patients needing a kidney transplant in the UK1. Nonetheless, there remains a large disparity in the number of patients requiring transplants and the overall number of transplants performed.

This case report will discuss the case of Ivan Carter (pseudonym), a 37-year-old male primary school teacher who has undergone four failed kidney transplantations to date, and who presented to the Churchill hospital in February 2019 for a de-clotting of his dialysis fistula. It will begin by exploring Mr Carter's past medical history, focusing primarily on his previous renal transplantations for management of his renal failure, followed by details of his current hospital admission. Next, general aspects and challenges of kidney transplantation will be discussed within the framework of the Oxford University Hospitals (OUH) Trust and related back to Mr Carter's case, including

a discussion around the management of a highly sensitised patient. The final section will include a reflective narrative regarding Mr Carter's case and his own views regarding his condition.

2 The case of Mr Carter

Mr Carter is a 37-year-old primary school teacher who lives at home with his wife and 5-year-old daughter. Mr Carter has a complicated medical history beginning with foetal urethral stenosis which resulted in end stage renal disease at age 9 and led to his first kidney transplant in 1991 (age 10). To date, he has had a total of 4 kidney transplants, the last being in December 2015. Please see Box 1 for a summary of Mr Carter's major health problems timeline. There are multiple stages and options for renal replacement therapy, and throughout Mr Carter's life he has undergone many (Figure 1).

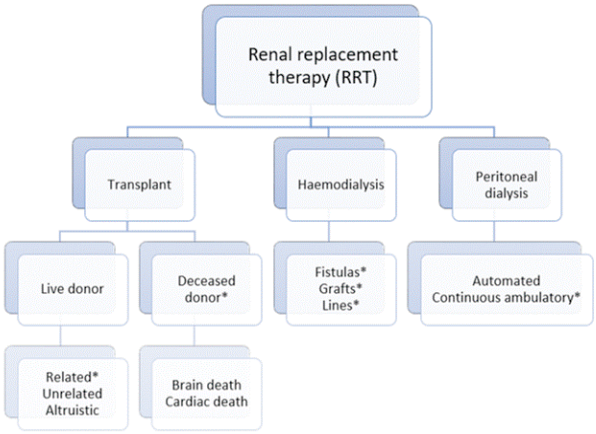

Figure 1. Methods of renal replacement therapy for the management of patients with renal failure. *denotes an RRT

2.1 Background leading up to current admission

At the time of Mr Carter's birth, due to his in utero urethral stenosis, his left kidney was non-functioning, and his right kidney was estimated to be functioning at 20%. He was on peritoneal dialysis (PD) for one year until he was 10 years old when he had his first renal transplant (cadaveric). In 1994 , aged 13, the kidney failed, and Mr Carter resumed peritoneal dialysis until he was 17 years old. In 1998 he received a kidney from his mother which lasted until 2005. He was put back on peritoneal dialysis, however it was sub-optimal due to scarring and adhesions from the multiple previous surgeries, therefore he was started on haemodialysis via a left arm radio-cephalic fistula. In 2011 Mr Carter received his third kidney transplant (cadaveric). Mr Carter suffered a severe pneumonia and acute respiratory failure which led to An acute hospital admission and ultimately resulted in the loss of his third kidney transplant, having lasted only 5 months. In 2015 he received a fourth transplant (cadaveric), which was in the context of a kidney that unexpectedly had 4 renal artery vessels and evidence of upper pole scarring at insertion (Table 1). The fourth kidney had delayed graft function and relatively poor function with a creatinine level of 420 at best. Mr Carter's fourth transplanted kidney was removed in October 2017; he was placed back on the kidney transplant

Table 1. Known transplant details

Transplant Dates	Known details of transplant procedure
2015 4th kidney transplant Failed in 2017 (lasted 2 yrs)	**Donor:** cadaveric heart beating **Transplant details:** Cold ischaemic time: CIT 49mins HLA mismatch: 0-0-0 CMV status: donor -ve; recipient +ve Immunosuppression induction: intra-operative alemtuzumab. Ongoing immunosuppression: mycophenolate mofetil and tacrolimus. Surgical details: general anaesthesia; median laparotomy; 4 renal arteries to aortic patch on external iliac artery; 1 renal vein to external iliac vein; single ureter to bladder. Showed delayed graft function 4 days post-op. Dense short urethral stricture reported.
2011 3rd kidney transplant Failed in 2011 (lasted 5 months)	**Donor:** cadaveric **Transplant details:** @ Oxford University Hospitals, but no electronic records of surgery Paper notes in archive Patient reports transplant failure due to "treatment needed for severe pneumonia"
1998 2nd kidney transplant Failed in 2005 (lasted 7yrs)	**Donor:** live related (mother) **Transplant details:** Patient notes held at Royal Berkshire Hospital, cannot access patient notes Patient reports transplant failure due to "normal wear and tear"
1991 1st Kidney transplant Failed in 1994 (lasted 2 yrs)	**Donor:** cadaveric **Transplant details:** Patient notes held at Royal Berkshire Hospital, cannot access patient notes Patient reports a "3/6 HLA match"

Box 1. Major health problems timeline with renal and transplant events highlighted in bold

05.02.2019 Clotted left arm PTFE graft to basilic, declotted in theatre
08.01.2019 Tesio® line removed
10.12.2018 left forearm PTFE graft surgically declotted and insertion of jump graft to basilic vein
27.11.2018 Insertion of temporary Tesio® line for dialysis
23.11.2018 Insertion of temporary femoral vascath® line access for dialysis
18.11.2018 Thrombosed left forearm PTFE AV graft
14.09.2018 PTFE AV graft (left forearm)
04.09.2018 Aneurysmal fistula with major haemorrhage and ligation
11.05.2018 Home haemodialysis
23.03.2018 Hospital haemodialysis
23.01.2018 Home haemodialysis
06.10.2017 Transplant graft nephrectomy
30.09.2017 Hospital haemodialysis
30.09.2017 4th transplant kidney graft loss
29.06.2017 Kidney transplant biopsy
12.02.2016 Transplant functioning kidney??Tx K function TX fu
08.01.2016 Tx Bx: Late Acute Tubular Injury ATI changes
22.12.2015 Transplant kidney acute haemodialysis
12.12.2015 4th kidney transplant – cadaveric DBD, HLA MM 0-0-0. Unexpected 4 arteries and upper pole scarring. @Oxford University Hospital
08.12.2015 Hospital haemodialysis
16.12.2013 Hospital haemodialysis
22.08.2013 Home haemodialysis on NxStage cycler
05.12.2011 Hospital haemodialysis
05.12.2011 3rd kidney transplant graft loss
10.11.2011 Severe pneumonia + acute resp. failure
08.08.2011 Tx Bx: normal kidney, donor vascular disease
01.07.2011 3rd kidney transplant – cadaveric @ Oxford University Hospital
10.07.2009 Hospital haemodialysis
18.02.2009 Prolonged hypocalcaemia after PTX
03.11.2008 Parathyroidectomy. For poorly controlled tertiary hyperparathyroidism
04.10.2007 Bowel perforation during PD op
07.09.2007 Hospital haemodialysis (via AVF)
28.08.2007 Continuous ambulatory peritoneal dialysis (CAPD)
14.07.2006 Bilateral native nephrectomies
14.07.2005 Peritoneal dialysis
14.07.2005 Hospital haemodialysis Previous poor compliance with medication
01.06.2005 Started haemodialysis via AVF (radiocephalic)
01.06.2005 Failed second transplant
06.03.1998 2nd kidney transplant – living related donor (mother)
01.01.1997 Rt knee arthritis
01.01.1994 Failed first kidney transplant
30.12.1991 1st kidney transplant – cadaveric
01.01.1990 End Stage Renal Disease, due to urethral stenosis
07.07.1981 Imperforate anus, treated surgically

list and on home haemodialysis. It was explained to him that he is highly sensitised due to his previous transplants and that his options for another kidney transplant may be limited.

In September 2018 Mr Carter was admitted to A&E due to bleeding from his left forearm radio-cephalic fistula. This was on a background of an aneurysmal AVF with infection over the needling site for the past week. The fistula was explored in theatre and the diseased needling segment was excised while salvaging the rest of the fistula. The fistula was successfully needled and reportedly working well post-operatively, with a palpable thrill and audible bruit.. However, since the fistula remained aneurysmal, a week later it was ligated and a polytetrafluoroethylene (PTFE) AV graft was inserted. Unfortunately, post-operatively his graft thrombosed twice, having to return to theatre for surgical de-clotting. In November 2018 his PTFE AV graft clotted again. During his hospital admission he underwent three unsuccessful surgical de-clotting procedures, ultimately requiring the insertion of a temporary femoral line and subsequently a Tesio® tunnelled central venous catheter for definitive dialysis access . His PTFE AV graft was revised and a jump graft to the basilic vein was inserted. After a few weeks of normal functioning of the jump graft, the Tesio line was removed and Mr Carter returned to home dialysis via his left forearm graft.

2.2 Current admission

In February 2019, Mr Carter was undergoing haemodialysis at home when his blood pressure dropped and he reported a feeling of lowering consciousness. He was admitted to the transplant ward at an OUH Trust hospital. His left forearm PTFE graft to basilic vein was shown to have clotted again. His graft was de-clotted in theatre and he underwent 3 hours of hospital haemodialysis.

On examination after the de-clotting procedure, on general inspection Mr Carter appeared well and comfortable at rest with a large body habitus. On inspection of the peripheries he was warm and well perfused, with signs of fluid overload in his ankles. On inspection of the abdomen there were four large scars – an upper and lower midline laparotomy scar, a transverse abdominal scar at the umbilical level, a left iliac fossa incision, and a right iliac fossa incision (Figure 2). The abdomen was soft and non-tender and there was no palpable organomegaly or masses. The abdominal aorta and native kidneys were not palpable. On auscultation, bowel sounds were present and sounded normal. An examination of external genitalia, inguinal hernial orifices, inguinal lymph nodes, urine dip and digital rectal exam were not performed.

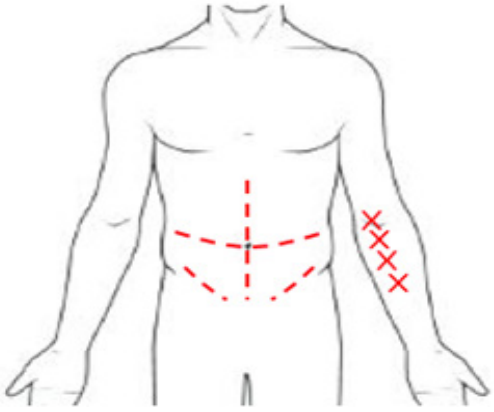

Figure 2. Diagrammatic representation of Mr Carter's scars. Red dashed lines indicate incision scars. Red X's indicate fistula formation and use scarring.

Mr Carter has known allergies to dipyridamole and midazolam. He undergoes home haemodialysis for 15hrs a

Table 2. Current medications

Medication	Indication
Alfacalcidol 0.25mg, oral, once a day	Maintenance vitamin D therapy (for severe renal impairment)
Aspirin 75mg, oral, once a day	Prevention of atherothrombotic and thromboembolic events
Atorvastatin 20mg, oral, once a day	Prevention of cardiovascular events
Calcium acetate (Phosex) 1 tablet, oral, three times a day	For hyperphosphataemia
Clopidogrel 75mg oral, once a day	Prevention of atherothrombotic and thromboembolic events
Epoeitin alfa (Eprex) 12000U, IV injection, three times a week	For symptomatic anaemia associated with chronic renal failure in patients on haemodialysis
Folic acid 5mg, oral, once a day	Prophylaxis of folate deficiency in dialysis
Iron isomaltoside 1000 (Diafer) 100mg, IV injection, once a week	For iron deficiency anaemia
Lansoprazole 30mg, oral, once a day	Acid-related dyspepsia
Midodrine hydrochloride 2.5mg, oral, three times a day	For severe orthostatic hypotension
Prednisolone 5mg, oral, once daily	Low dose maintenance immunosuppression

week, broken into 3hr sessions over five days. Please refer to Table 2 for details on Mr Carter's current medications. Regarding Mr Carter's social history, he works full time as a primary school teacher and lives with his wife and 5-year-old daughter. His wife suffers from Behcets disease and acts as his primary carer. He has never smoked nor does he drink alcohol.

3 Kidney Transplantation

3.1 Immunosuppression

Patients receiving organ transplants require immunosuppression to prevent rejection of the new organ. There are a variety of different immunosuppressive agents with different mechanisms of action, and a combination of different agents are usually used together to reach an effective level of immunosuppression. Which combinations to use are based on their efficacy, cost, and side effects. As new drugs have become available and new evidence regarding efficacy, protocols for immunosuppression are changing over time[2]. This report will discuss the immunosuppression regimes carried out by the Oxford University Hospitals (OUH) Trust for Mr Carter's 4th kidney transplant.

3.1.1 Induction immunosuppression

The first step of immunosuppression for a kidney transplant is induction therapy. Induction immunosuppression is given to ensure there is a high level of immunosuppression during the early postoperative phase following transplantation where there is the highest risk of acute rejection. Typically, UK transplant units use basiliximab, a chimeric mouse-human antibody against CD25 which is present on the interleukin-2 (IL-2) receptor, which therefore blocks T cell activation. It is given on day 0 and day 4 post-transplant and followed up with maintenance immunosuppression in the form of 'triple therapy'.

In the case of Mr Carter's fourth renal transplant, he received alemtuzumab (CAMPATH®) as induction therapy, as opposed to basiliximab. Alemtuzumab is a monoclonal antibody which targets CD52 present on all lymphocytes, resulting in a profound lymphocyte-depleting effect[3]. The 2017 National Institute for Clinical Excellence (NICE) guidelines for renal transplantation in adults noted than alemtuzumab does not have marketing authorisation in the UK for immunosuppression and is only available on a 'named patient' basis[4].

Randomised control trials have investigated alemtuzumab as an induction agent and have demonstrated lower levels of rejection in the early months following transplantation[5]. Additionally, alemtuzumab has been shown to preserve renal functional when used as an induction agent for heart transplantation and lung transplantation[6]. The University of Oxford Clinical Trials Service coordinated a study called the 3C Study, formed of a collaboration of transplant centres across the UK to conduct a series of national randomised clinical trials for kidney transplantation. The first analysis from the 3C study compared the immediate effects of basiliximab versus alemtuzumab as induction treatments and showed a highly significant reduction in rejection in patients treated with alemtuzumab[7]. A more recent trial from the 3C group illustrated that the use of alemtuzumab as an induction agent may allow for a reduction in the exposure to calcineurin inhibitors, a nephrotoxic agent which is used as maintenance therapy and associated with graft fibrosis and atrophy, worsening transplant function, and long-term transplant failure[8,9,10].

3.1.2 Maintenance immunosuppression

Immunosuppressive maintenance 'triple therapy' is administered to prevent allograft rejection after the transplantation of a non-identical immunogenetic kidney. Triple therapy refers to the combination of a calcineurin inhibitor (tacrolimus), anti-metabolite (mycophenolate mofetil), and steroid (prednisolone). The main classes of agents and their mechanisms of action are described below.

1. Calcineurin inhibitor – e.g. tacrolimus or cyclosporin

- Tacrolimus is a macrolide calcineurin receptor antagonist which acts by inhibiting calcineurin which normally acts to phosphorylate the transcription factor NFAT which increases the transcription of many genes involved in the immune response and synthesis of pro-inflammatory cytokines such as IL-210. Tacrolimus therefore leads to the reduction of activation and proliferation of T cells, leading to a reduced inflammatory response and risk of rejection[11].
- Cyclosporin is a drug which binds the cytosolic protein cyclophilin on lymphocytes, and this cyclosporin-cyclophillin complex then inhibits calcineurin[12,13]. There is a large body of evidence which suggests that tacrolimus leads to improved outcomes compared to cyclosporin, and as such tacrolimus is generally the calcineurin inhibitor used for triple therapy[12,14,15,16].
- It should be noted that calcineurin inhibitors are nephrotoxic, therefore the measurement of levels of these drugs in transplanted patients are an intrinsic part of their management, as there exists a relationship between the levels of the drug and kidney rejection and toxicity[17]. Current research into immunosuppression protocols aim to eventually reduce the use of nephrotoxic agents such as calcineurin inhibitors[8].

2. Antimetabolite – e.g. azathioprine or mycophenolate

- Azathioprine (AZA) is a drug which inhibits purine synthesis, thereby leading to less DNA and RNA produced for the synthesis of white blood cells, which ultimately causes immunosuppression. Azathioprine is converted in tissues to thioinosinic acid or thioguanylic acid which are nucleotides which can be incorporated into newly synthesized DNA in the place of inosinic acid and guanylic acid, respectively, causing a halt in DNA replication[18].
- Mycophenolate is administered as either the prodrug mycophenolate mofetil (MMF), or as mycophenolate sodium. Mycophenolic acid is a potent non-competitive inhibitor of inosine-5'-monophosphate dehydrogenase, an enzyme required for the de novo synthesis of purines. Inhibition of this enzyme has a particularly strong effect on lymphocytes because lymphocytes rely predominantly on de novo synthesis of purines rather than also salvaging free nucleotides. Therefore, mycophenolic acid results in a relatively selective inhibition of DNA replication in B and T cells thus leading to immunosuppression[17,19].
- Within the OUH Trust, both azathioprine and mycophenolate are used. Azathioprine is generally used for younger/adolescent patients who may benefit from once daily medications, and mycophenolate is given as part of the standard protocol. A 2015 Cochrane review concluded that MMF was superior to AZA for improvement in graft survival and prevention of acute rejection in kidney transplantation, but highlight that balancing the harms and benefits of both drugs remains a major task for the transplant physician to decide for each individual patient[20].

3. Corticosteroid – e.g. prednisolone

- Corticosteroids inhibit dendritic cells, the transcription of cytokines, and stages of T-cell activation. Non-specific immunosuppressive effects are due to the redistribution of lymphocytes from the vascular compartment back to lymphoid tissue and inhibition of monocyte migration at sites of inflammation[17].
- Corticosteroids are effective immunosuppressants, however, long-term use is associated with a wide range of side effects such as osteoporosis, osteonecrosis, diabetes, impaired wound healing, and depression[21].
- Corticosteroids do not form a part of the standard immunosuppression protocol at Oxford Transplant Centre, especially when CAMPATH® is used and the patient is not already on steroid therapy from a previous transplant or their underlying renal pathology.

Immunosuppressive therapy for transplantation has improved dramatically over the years. Nonetheless, late graft loss following kidney transplantation remains a challenge. Chronic rejection is caused by a gradual immunological response over years, where maintenance immunosuppression is not enough to prevent all immunological response to the donor kidney[22]. Table 3 refers to causes of allograft injury.

Table 3. Causes of allograft injury. Adapted from Jevnikar and Mannon, 2008[23]

Immunologic causes	Non-immunologic causes
Cellular immunity	*Organ viability*
Direct and indirect allorecognition	Donor senescence
Donor-host mismatch	Donor age
Subclinical inflammation	Prolonged cold ischaemic time
Inadequacy of immunosuppression	Delayed graft function/acute tubular necrosis
	Living versus deceased donor
Humoral immunity	*Treatment*
Anti-body mediated rejection	Drug toxicity e.g calcineurin inhibitor nephrotoxicity
Previous sensitization	
Infection	*Recipient factors*
Cytomegalovirus	Lipid disorders
BK polyomavirus	Diabetes
	Compliance
	Hypertension
	Recurrent disease

3.2 Donor considerations

The success of organ transplantation is highly associated with the status of the organ being donated. Kidneys can be received from a related living donor, a known unrelated living donor, a living altruistic donor, or from donors deceased after cardiovascular death (DCD) or deceased after brain stem death (DBD)[24]. Mr Carter has received both cadaveric and live donor kidneys. Three of his transplants were reported as cadaveric, however details regarding cardiac or brainstem death are not accessible. His transplant which lasted the longest duration (7 years) was from his mother, a live related donor.

Graft survival is negatively correlated with cold ischaemia time (CIT), which is the length of time elapsed between a kidney being cold flushed with preservation solution and removed from the donor, and being re-perfused at the time of transplant in the recipient. Generally, shorter the CIT is associated with less preservation injury better long-term graft outcome. DCD kidneys have equivalent medium and long term graft outcomes to DBDs but are more susceptible to preservation injury, therefore longer CIT in the context of DCD is associated with worse long term outcomes[25] . In addition to the cause of donor death, some examples of factors which influence the CIT include: transportation of the donor kidney from the retrieval hospital to the location of the recipient, tissue typing the donor and cross-matching the donor to potential recipients, preparing the transplant recipient, and access to the operating theatre[26].

3.2.1 HLA matching

A crucial step in renal transplantation is HLA typing either via serologic or molecular typing methods. The recognition of foreign HLA by recipient T lymphocytes would activate a cascade of mediators and trigger an immune response against the allograft. Matching donors and recipients based on HLA-A, HLA-B, and HLA-DR compatibility is shown to be related to long-term graft survival[27,28,29]. One allele for each HLA receptor is inherited from each parent, therefore up to six mismatches can be present between individuals. A study analysing the United Network for Organ Sharing registry from a period of 1987 to 2013 highlighted the importance of maximising HLA matches, illustrating a 13% higher risk with one HLA mismatch, and a 64% higher risk with six HLA mismatches[30]. Another study by Lim et al illustrated a Kaplan-Meier survival curve of graft failure according to the number of HLA mismatches for 10 years following transplant (Figure 3)[31]. It should be kept in mind, however, that despite the benefit seen in HLA matching cadaveric donor kidneys, worse matched unrelated living donors exhibit superior graft survival rates compared to better matched cadaveric donors[32]. This has been theorised to be due to the damage experienced by the donor kidneys during the shock of the patient before death. In accordance with this, the transplanted kidney which functioned for the longest period of time for Mr Carter was the one from a live donor, his mother.

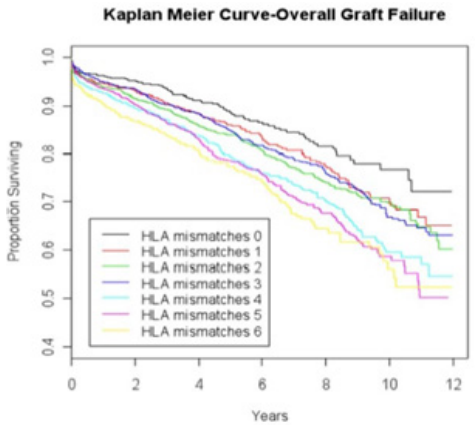

Figure 3. Kaplan Meier survival curve of overall graft failure according to the number of HLA mismatches with corresponding numerical table of the number at risk at 0, 4, and 8 years post-transplant. Reproduced from Lim et al., 2012.

A 0-0-0 mismatch it not a requirement for the transplantation of kidneys, however, due to the improved graft survival, the majority of renal transplant programmes preferentially allocate kidneys to candidates with favourable HLA compatibility. While the allocation process aims to achieve equity of access to transplantation, including HLA matching in the allocation process may be disadvantageous to transplant candidates with uncommon HLA phenotypes[33,34,35]. For example, ethnic minorities and indigenous populations endure longer transplant wait times[1].

3.3 The highly sensitised patient

Sensitisation to HLA remains a significant barrier to successful kidney transplantation for many patients. If a patient has HLA antibodies in their blood they are considered to be 'sensitised' to that specific HLA marker. Pregnancy, blood transfusion, and previous transplantations are all methods which can lead to HLA sensitisation. Sensitisation to HLA is seen in approximately 30% of patients, and a proportion of these patients are considered 'highly sensitised', meaning they have a panel of reactive antibody level of >80%[36]. Despite given priority in the organ allocation algorithm, highly sensitised patients have annual transplantation rates as low as 6.5% due to the inability to find a suitable organ[36]. Mr Carter has received 4 previous renal transplants, and as such is a highly sensitised patient who expresses multiple alloantibodies that will likely result in crossmatch positivity. The presence of donor-specific anti-HLA antibodies have been associated with hyperacute rejection, antibody mediated rejection, and high rates of organ loss[37].

3.3.1 Immunomodulatory desensitisation methods

A current area of research which has been developing over the last decade is immunomodulation therapies to allow for HLA sensitised patients increased access to kidneys for transplantation. Desensitisation therapies can reduce alloantibody titers to a low enough level to create an acceptable cross-match to allow for transplantation with a low risk for antibody mediated rejection[38]. Examples of such therapies include: anti-cytokine antibodies, IgG inactivating agents, costimulatory molecule blockers, plasma cell targeting agents, and complement inhibitors[39-43]. A brief table and mechanism of action of desensitisation therapies are listed in Table 4.

Montgomery and colleagues demonstrated that live-donor transplantation after desensitisation provided a significant survival benefit for sensitised patients compared to those waiting for a compatible organ, and showed that by 8 years the survival advantage was more than double[36].

A multi-centre study in 2016 demonstrated the benefits of desensitisation in improving life expectancy of patients with end stage renal disease. Patients who received kidney transplants from HLA incompatible live donors and underwent desensitisation has a substantial survival benefit compared to those who waited and received HLA

Table 4. Agents of desensitization. Adapted from Sethi et al. 2017

IVIg*	Exact mechanism unclear; however some mechanisms include regulation of B-cell antibody production, induction of B-cell apoptosis through FcyP mediated signals, inhibition of dendritic and macrophage cell maturation and function, inhibition of various proinflammatory cytokines, inhibition of complement mediated inflammation
Rituximab*	Anti-CD20
Obintuzumab*	Anti-CD20
Bortezomib*	Inhibiting proteasomes
Carfilzomib*	Inhibiting proteasomes
Tocilizumab	Anti-IL6 receptor blocker
IgG endopeptidase*	Cleaving IgG leaving behind Fc and F(ab')2
Belimumab	Inhibiting binding of B lymphocytes stimulator protein to the B-cell receptor
Eculizumab*	Blocking complement protein C5 and preventing generation of the terminal complement complex C5b-9
C1 esterase inhibitor*	Inactivating complement pathway players C1s and C1s
Belatacept	CTLA4-Ig may have potent effects on de novo donor specific antibody generation and plasma cell inhibition

*Immunotherapy agents require premedication with acetaminophen, antihistamine, and glucocorticoid thirty minutes before infusion

compatible transplants from deceased donors[32]. It should be kept in mind, however, that this increase in survival may also be in part due to the improved outcomes seen with live donors versus deceased donors. Increasing evidence is suggesting that sensitised patients can receive transplantations across the HLA barrier with the use of an intensified immunosuppressive therapy along with close immunologic, histologic, and clinical monitoring.

4 Reflection on quality of life

Quality of life has been conceptualised as a multidimensional construct that reflects an individual's subjective assessment of multiple domains of their life, including physical, social, and psychological functioning. While it is beyond the scope of this case report to explore in depth health-related quality of life in the context of paediatric onset of renal disease, Mr Carter appears generally content with his life. A study in 2016 by Tjaden and colleagues reported that adult survivors of paediatric ESRD report a reduced mental health related quality of life in childhood, but a normal quality of life in adulthood. Nonetheless, despite their subjective feeling of wellbeing as adults, these patients on average experience more difficulties in completing education, developing intimate relationships, and securing employment[44]. In addition to exhibiting a generally positive feeling of wellbeing on his current hospital admission, Mr Carter completed his educational degrees, is currently employed as a primary school teacher, and is happily married with a 5 year old daughter.

Mr Carter's general outlook regarding his renal failure stood out as quite positive, especially considering he has undergone four failed transplants, is back on the transplant waiting list, and his dialysis fistulas continue to clot. He attributes his demeanour to the fact that he has lived his whole life since childhood as a renal patient, and did not have to adjust to a disability later in life. He recalled undergoing peritoneal dialysis or haemodialysis from childhood and it has become a normal part of his life. He recounted stories of taking a portable PD machine on family vacations. He says he lives by the mindset of "you dialyse to live, not live to dialyse", and that he continues to try and enjoy his life, family, work, and hobbies as normally as possible without dialysis holding him back.

5 Conclusion

The above report explored the case of Mr Carter, a 37-year old man born with a urethral stricture which resulted in ESRD at the age of 10. He has undergone 4 kidney transplantations all of which have failed, which have resulted in him becoming a highly sensitised patient. He is currently back on the renal transplant list. A background on current OUH Trust protocols for kidney transplantation was discussed and options for treatment in a highly sensitised patient were explored. Finally, a reflection on health-related quality of life in relation to Mr Carter's case was reported. Mr Carter has been counselled on the fact that he is a highly sensitised patient and that the chances of finding a donor with a negative cross match will be difficult. He has mentioned that he may have other options for a life donor, and perhaps in light of the promising evidence regarding desensitisation therapies, a decision will be made in the future to use immunomodulation therapy with a non-matched living donor.

Conflicts of interest

None.

Funding

None.

Consent

The patient has consented for the publication of this case study.

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