Presensitization revisited: pitfalls of vascular allografts in transplant candidates

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Abstract
Vascular allografts in end-stage renal disease (ESRD) patients represent a particular immunological challenge. A broad HLA immunization led us to study in depth the history of two patients with vascular allografts. In Case 1 the allograft was added to a Gore-Tex graft used for haemodialysis access and no immunosuppression was administered. In Case 2 the allograft was used to prolong a renal artery from living donor and immunosuppression was suboptimal. In vascular surgery, immunosuppression is mainly used to improve graft patency. ESRD patients are potential organ recipients and immunosuppression should therefore be tailored to reduce HLA immunization.

Keywords: allograft; allo-immunization; HLA immunization; renal transplantation; solid organ transplantation

Background
End-stage renal disease (ESRD) patients need lifelong renal replacement therapy (RRT), be it dialysis or renal transplantation. Frequently described risk factors for development of anti-HLA antibodies are previous transplantations, blood transfusions and pregnancies [1]. Vascular allografts are rarely mentioned as immunizing events, although both fresh and cryopreserved allografts elicit strong immune responses [2–6]. The following cases and brief review of the literature are intended to remind nephrologists and vascular surgeons that arterial and venous allografts trigger anti-HLA antibody production and should be used with caution in transplant candidates. Immunosuppression should always be considered when allografts are used.

Case reports

Case 1
A 44-year-old woman previously immunized by several pregnancies developed ESRD and started haemodialysis in 2009. The first arteriovenous fistula soon occluded. Neither surgical revisions nor prosthetic grafts resulted in long-term patency. Menometrorrhagia led to blood transfusions in 2009 and 2011. Antibodies to several HLA class I molecules were detected in a Luminex single antigen assay before the first blood transfusions, but by August 2010 only reactivity to HLA-A24 was observed (a mean fluorescence index >1000 defined as positive). Overweight delayed by 2 years acceptance to the renal transplant 'waiting list'. Meanwhile, graft thrombosis impaired dialysis access, necessitating insertion of a fresh arterial allograft from a deceased donor in September 2010. Antibodies to a broad range of HLA class I and II molecules were detected by Luminex single antigen assay in January 2012, but the panel reactive antibodies (PRAs), as determined by CDC cell screening, remained negative. Menometrorrhagia precluded anticoagulation. The arterial allograft was found obliterated at removal in February 2012 and replaced by another fresh arterial allograft. By April 2012, the PRA reactivity was 80% and Luminex analyses in June 2012 identified strong antibodies to almost all HLA class I and II molecules, including HLA-A1, -B60, -DR4 and –DQ8 present in the allograft.

Case 2
A man aged 55 received his first kidney transplant from an HLA-identical sibling in 2010 and was immunosuppressed with steroids and cyclosporine. Luminex screen test was negative in pretransplant sera, but positive (ratio >2.5) 1 year after transplantation. The Luminex single antigen assay then revealed multiple antibodies directed to HLA class I and II molecules. Since no blood transfusions had been performed, the only plausible immunizing event was an arterial interposition from a deceased donor inserted during the transplantation to prolong the donor renal artery. We suspected renal transplant artery stenosis as the patient developed hypertension requiring the addition of a selective alpha-1-receptor blocker to his preexisting regimen of beta-blocker, angiotensin-II-receptor antagonist and loop diuretics. Ultrasound investigations 13 and 19 months post-transplantation indicated moderate
proximal renal transplant artery stenosis. A fluorodeoxyglucose (18F)-positron emission tomography (FDG-PET) scan was performed 19 months after transplantation in order to detect inflammation in the renal artery interponate, but the result was negative. Twenty-three months post-transplantation, magnetic resonance imaging confirmed a proximal narrowing of the transplant artery, but no significant stenosis. Taken together with stable graft function at an eGFR of 42, indication for intervention was not found. Three years after transplantation graft function, blood pressure and medication remain unaltered.

Discussion

The choice of vascular access made for haemodialysis depends on both past and planned RRT for each patient. Native arteriovenous fistulas remain the gold standard. Prosthetic arteriovenous grafts are considered secondary access modalities because of greater morbidity, inferior patency and more demanding surgery [7]. Fresh and later cryopreserved allografts were established as tertiary access modalities, but when cryopreserved allografts were used for haemodialysis access, Benedetto et al. [3] found increased PRA values. A major reason to choose vascular allograft rather than prosthetic graft is to treat graft infections: Lopez-Cepero et al. studied 11 patients waiting for kidney transplants. Their prosthetic grafts were infected or other access alternatives were limited. After implantation of cryopreserved allografts, anti-HLA class I and II antibodies were detected in all patients. Antibody titres increased in previously immunized patients. Two out of 11 grafts were removed after thrombosis and histological examination revealed rejection [4]. Mirelli et al. studied HLA immunization the first 48 months after replacement of infected aortoiliac or aortobifemoral grafts by fresh or cryopreserved arterial allografts in 30 patients. Nine patients received cyclosporine (1–3 mg/kg/d). Postoperatively, an increase in PRA was observed in all patients and donor-specific antibodies (DSAs) were detected. No difference was found between fresh and cryopreserved allografts. The antibody responses among patients treated with cyclosporine were however delayed and less pronounced [6]. In our Case 2, cyclosporine and prednisolone (10 mg/day) did not prevent a broad HLA immunization, although prednisolone may have contributed to the negative result at FDG-PET scan.

Inflammation caused by DSA may lead to stenosis in arterial grafts due to chronic rejection [6]. In Case 2 we lack information about vascular allograft donor HLA, as this was not mandatory in our centre at that time. Therefore, we could not determine whether the HLA antibodies were donor specific or not. However, we assumed the antibodies to be donor specific as there were no other immunizing events. An association between renal graft rejection and development of transplant renal artery stenosis has been described previously [8, 9]. In the recipient of Case 2 a rejection of the arterial allograft due to low immunosuppression (HLA-identity protocol) could theoretically create a renal artery stenosis without simultaneous rejection of the renal graft. The major reason to perform a PET scan was to determine, without intervention, whether an inflammation in the arterial interponate could be detected and treated with increased immunosuppression.

Case 1 illustrates the high-risk scenario where a patient immunized by pregnancies and blood transfusions, still in dialysis, receives consecutive vascular allografts without any immunosuppression before the first kidney transplantation. In our experience <1% of dialysis patients in Scandinavian countries receive allografts for vascular access. First, because the waiting time for kidney transplantation is relatively short and secondly because vascular allografts are only available in transplantation centres. However, when vascular allografts are used in patients waiting for kidney transplantation, immunosuppression should be considered in an effort to reduce HLA immunization.

Case 2 directed our attention to a challenge in living donor transplantation where interponates must be obtained from a deceased donor. This exposes the recipient to two sets of allogeneic HLA molecules and the risk of allo-immunization increases accordingly. In the particular case described, standard immunosuppression with prednisolone, calcineurin inhibitor and mycophenolate might have been considered rather than the HLA-identity protocol omitting mycophenolate.

One might argue that such cases are rare and thus of little clinical interest. However, ESRD patients are at high risk for arterial calcifications and may need vascular surgery before renal transplantation. Vascular allografts are not only used for arteriovenous fistulas and arterial interponates, as described above, but also in thoracic surgery [5, 6, 10], in the treatment of peripheral arterial occlusive disease [11] and for replacement of infected Y-grafts [12]. Although synthetic grafts are used extensively and autologous tissue-engineered grafts are being developed [13, 14], vascular allografts are still used. Indeed, considering figures from the European Homograft Bank in Belgium [15], there is increasing demand for vascular allografts and human heart valve allografts. The report does not mention the immunogenicity of these grafts and it seems difficult to map the extent to which vascular allografts from tissue banks are used to future solid organ recipients. After insertion of a vascular allograft in candidates for solid organ transplantation, the need for immunosuppression should be evaluated and the level of immunosuppression tailored to the individual patient. Cyclosporine A alone may delay and reduce immunization [6], but a combination of cyclosporine A and prednisolone did not prevent extended HLA immunization in our Case 2. Therefore, a triple regimen of prednisolone, calcineurin inhibitor and anti-proliferative drugs might be considered.

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