Clinical Report

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 hemodialysis 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 interponate 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 fluorodeoxy-

Discussion

glucose (18F)-positron emission tomography (FDG-PET)

The choice of vascular access mode for haemodialysis

scan was performed 19 months after transplantation

depends on both past and planned RRT for each patient.
in order to detect inflammation in the renal artery

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

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 cryo-

preserved 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 aortociliac

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. There-

fore, we could not determine whether the HLA antibodies

were donor specific or not. However, we assumed the anti-

bodies to be donor specific as there were no other immu-
nizing 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 immuno-
suppression (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 transplan-
tation. In our experience <1% of dialysis patients in Scan-
dinavian 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 ob-
tained 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 pred-
nisolone, calcineurin inhibitor and mycophenolate might
have been considered rather than the HLA-identity proto-
col 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 increas-
ing demand for vascular allografts and human heart valve

allografts. The report does not mention the immunogeni-
city 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 al-

graft 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 immu-
nization [6], but a combination of cyclosporine A and pre-
nisolone 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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