Delayed immune tolerance through donor haematopoietic stem cell infusion 14 months after kidney transplantation

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See Online for appendix

A 28-year-old man, who received a two-haplotype matched renal transplant for end-stage renal disease secondary to IgA nephropathy, was evaluated for immunosuppression withdrawal using a novel method to develop delayed immunological tolerance. The kidney had been donated by his brother 14 months earlier. The patient had been maintained on standard triple therapy immunosuppression. A plasma donor-derived cell-free DNA test—obtained 8 months after the initial transplantation—was negative for allograft injury.

The donor's haematopoietic stem cells were mobilised using granulocyte colony-stimulating factor and plerixafor. Peripheral blood apheresis was followed by cell separation and processing; CD34+ and CD3+ cells were cryopreserved in preparation for infusion into the recipient; all interventions were done in an outpatient setting as part of a clinical trial (NCT05525507).

The recipient then had a conditioning regimen of rabbit anti-thymocyte globulin and total lymphoid irradiation. The donor's cryopreserved stem cells were thawed and then infused peripherally.

4 weeks after stem cell infusion, the recipient's serum creatinine rose from a baseline of 1·4 mg/dL (typical range 0·7–1·3) to a level of 1·9 mg/dL, prompting us to biopsy the transplanted kidney. Histopathological examination of a sample of the biopsy (figure) showed no evidence of rejection, but it did show focal isometric vacuolisation, and interstitial fibrosis and tubular atrophy with a striped pattern of injury—suggesting possible chronic calcineurin-inhibitor (CNI) toxicity and supporting the need for immunosuppression withdrawal. The patient demonstrated durable mixed chimerism (16–43% donor cells in peripheral blood; appendix) and, therefore, tacrolimus was reduced, with full immunosuppression withdrawal 228 days after stem cell infusion.

The renal allograft achieved a nadir serum creatinine of 1·2 mg/dL after immunosuppression withdrawal; chimerism levels ranged from 2–4% donor cells (appendix). No evidence of recurrence of IgA nephropathy has been found thus far.

Previously, immunological tolerance was only realised prospectively in transplant-naive patients. Here, we have described the first reported case of delayed immune tolerance. The benefits of the delayed approach include, most importantly, for patients with a pre-existing kidney transplant, the opportunity of immunosuppression withdrawal, mitigating the toxicities from these medications. Furthermore, a delayed approach facilitates carrying out tolerance trials in recipients of living-donor liver transplants, who may be unsuitable for radiation conditioning immediately after surgery.

The limitations of histomorphology to diagnose the possible chronic calcineurin-inhibitor toxicity are acknowledged. Furthermore, while immunosuppression may be lowered in HLA-matched recipients compared with mismatched counterparts, the presence of calcineurin-inhibitor toxicity in this case suggests that even well-matched transplant recipients may benefit from stopping immunosuppressive medications using tolerance protocols. Finally, a major consideration with delayed tolerance is the reintroduction of donor antigens prompted by stem cell infusion; patients previously sensitised to the donor by the kidney transplant may mount an immune response that could trigger rejection and the potential loss of the living-donor kidney transplant—a process not seen in this case.

Contributors

We were all involved in providing care for the patient, and for designing the study, analysing and interpreting the data. ELL and NM were involved in preparing the manuscript. Written consent for publication was obtained from the patient.

Declaration of interests

The study in which the patient was enrolled was supported by a clinical research grant from the OneLegacy Foundation (OL-RG:20173281).

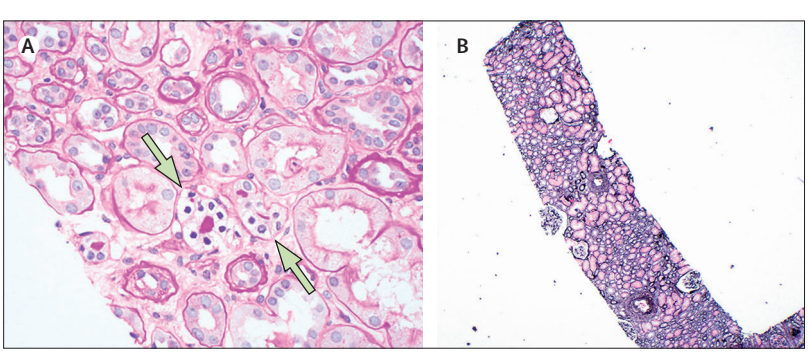

Figure: **Delayed immune tolerance through haematopoietic chimerism 14 months after kidney donation**
Histopathological analysis of a sample obtained at biopsy of the kidney shows (A) focal tubules with cytoplasmic isometric vacuolisation, and pyknosis of nuclei (arrows; periodic acid Schiff stain, ×200 magnification) and (B) mild scarring with a vaguely striped pattern of injury of the cortex at lower magnification (Jones silver stain, ×40 magnification).