Kidney-pancreas transplantation in a long-term non-progressor HIV-infected recipient

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Abstract

With the introduction of highly active antiretroviral therapy (HAART), HIV infection has become a chronic disease with more frequent end-stage organ failures. As a result, the question of transplantation in HIV patients is raised more often. Although still subject to controversies, HIV infection is no longer an absolute contraindication to solid organ transplantation. We report a case of combined kidney-pancreas transplantation in a HIV recipient. HIV has remained stable without any antiviral therapy for up to 2 years after transplantation and has reached criteria for inclusion in the long-term nonprogressor (LTNP) group. Grafted organs demonstrated good function without rejection. This case emphasizes the need to consider LTNP HIV patients as a specific subgroup, when discussing solid organ transplantation. HAART is not required, thus sparing drug interactions and their unique immunological features, such as CCR5 mutation, might prevent rejection. This subgroup of HIV patients should be offered less restricted access to transplantation.

Reference


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Kidney-Pancreas Transplantation in a Long-Term Non-Progressor HIV-Infected Recipient

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With the introduction of highly active antiretroviral therapy (HAART), HIV infection has become a chronic disease with more frequent end-stage organ failures. As a result, the question of transplantation in HIV patients is raised more often. Although still subject to controversies, HIV infection is no longer an absolute contraindication to solid organ transplantation. We report a case of combined kidney-pancreas transplantation in a HIV recipient. HIV has remained stable without any antiviral therapy for up to 2 years after transplantation and has reached criteria for inclusion in the long-term nonprogressor (LTNP) group. Grafted organs demonstrated good function without rejection. This case emphasizes the need to consider LTNP HIV patients as a specific subgroup, when discussing solid organ transplantation. HAART is not required, thus sparing drug interactions and their unique immunological features, such as CCR5 mutation, might prevent rejection. This subgroup of HIV patients should be offered less restricted access to transplantation.

Key words: HIV, kidney, long-term non-progressor, pancreas, transplantation

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Introduction

Until the mid-90s, HIV infection was considered a contraindication for transplantation. Major concerns were the risk of infection breakthrough as a result of immunosuppression, the pharmacological interactions between antiretroviral agents and immunosuppression, the risk of poor compliance and the ethical problem of offering organs to patients with shortened life expectancy while others are dying on the waiting list.

Since the implementation of HAART, the number of patients diagnosed with acquired immunodeficiency syndrome (AIDS) and the number of human immunodeficiency virus (HIV)-related deaths have sharply declined. During the same period, the number of individuals living with HIV has increased substantially. As a result, more HIV+ patients develop end-stage organ failure, and the question of transplantation is raised more often.

Although still marginal, increasing numbers of solid organ transplantations are now reported in HIV patients (1, 2) and HIV is no more considered an absolute contraindication (3). However, the criteria for transplantation in HIV patients remain inadequately delineated and some questions are unanswered regarding the opportunity to widen the access to transplantation for selected HIV patients, or the likelihood of a better outcome for these selected patients. We report a unique case of combined kidney-pancreas transplantation in a long-term nonprogressor (LTNP) HIV-infected patient. This case illustrates the feasibility of the procedure. We further discuss the advantages and constraints of transplantation in this subset of HIV patients.

Case description

The patient was a 39-year-old female with type I diabetes treated with insulin for 32 years. She had presented numerous diabetes-related complications such as arterial hypertension, arterial insufficiency of the lower limbs requiring several by-pass procedures and angioplasties, silent ischemic cardiopathy, polyneuropathy and retinopathy. She had been on hemodialysis for end-stage diabetic kidney disease for 2 years with major blood tension instability. Diabetes was poorly controlled.

She acquired HIV infection in 1995 via a blood transfusion during her vascular operations. The infected blood donor had been retrospectively identified and had donated during the window period between infection and detection of anti-HIV antibodies. Our patient had no history of drug abuse or behavior at risk and her husband was HIV negative. Until transplantation in 2000, her peripheral blood CD4+ cell count
remained greater than 600 cells/mm$^3$ and her HIV-1 RNA titers less than 50 copies/mL without antiviral treatment.

Simultaneous pancreas-kidney transplantation was performed with iliac venous drainage and enteric drainage of the exocrine secretions. Immunosuppression therapy included tacrolimus (Prograf, Fujisawa, Munich, Germany) with a trough level between 8 and 15 ng/mL during the first 3 months and between 5 and 10 ng/mL thereafter, mycophenolate mofetil (2 g/day; Cellcept, Roche, Basel, Switzerland) and steroids (1 g methylprednisolone on day 0 tapered to 20 mg prednisone at the end of the second week and to 5 mg at 5 months). Induction consisted of basiliximab (20 mg i.v. on days 0 and 4; Simulect, Novartis).

During the first 4 days after transplantation, infection prophylaxis included fluconazole (50 mg/day; Diflucan, Pfizer, Zurich, Switzerland), ceftriaxone (2 g/day; Rocephine, Roche) and metronidazole (250 mg b.i.d.; Flagyl, Aventis Pharma, Zurich, Switzerland). Fluconazole (2 × 100 mg/week) and trimethoprim/sulfamethoxazole (2 × 160/800 mg/week; Bactrim, Roche) were subsequently administered during the following 6 months. Both donor and recipient had negative CMV serologies. No anti-CMV prophylaxis was administered.

Peri-operative complications included a small-size acute myocardial infarction managed medically. During a 2-year follow up, both organs demonstrated good function with stable creatinine levels and without requiring exogenous insulin injection. A kidney biopsy performed 2 weeks after transplantation because of a transitory increase of creatinine, as well as a protocol biopsy performed at 2 years, did not demonstrate signs of acute rejection or drug-related toxicity. She presented two lower urinary tract infection episodes, but never showed HIV-related symptoms.

After transplantation, peripheral blood CD4+ cells remained within normal ranges. HIV viral load was stable after a transitory rise during the first 3 months. More than 2 years post-transplantation, the CD4+ cell count was 1350/mm$^3$ and HIV-1 RNA was 1400 copies/mL (Figure 1). No anti-HIV therapy was used at any time. With a follow up reaching 7 years, normal CD4+ cell count, low viral load and a lack of anti-HIV drugs, the patient was meeting the criteria for LTNP HIV infection.

Chemokine receptor 5 (CCR 5) was screened for a 32-bp deletion (CCRS$\Delta$32), which leads to an inactive receptor, resistance to HIV and a decreased graft rejection rate. DNA analysis of peripheral blood leukocytes, performed by PCR as previously described (4), did not demonstrate the deletion.

**Discussion**

The present case of a kidney-pancreas transplantation in a LTNP HIV-infected recipient is to our knowledge the first reported to date. It illustrates the feasibility and good outcome of such a transplant procedure in this subgroup of HIV-infected patients.

Until the mid-90s, most transplantation procedures in HIV patients had been performed without knowing the serological status. Recipients had a shorter AIDS-free time compared with nontransplanted HIV+ patients (5, 6) and survival was poor compared with the general kidney or liver recipient population (7). Mortality was mainly related to AIDS, with *Pneumocystis carinii* pneumonia, *Toxoplasma gondii*, tuberculosis or CMV infections as major causes (5, 8, 9). Accordingly dialysis was considered to be the best available treatment for end-stage kidney disease in HIV+ patients.

Since then, dramatic progress has been made in the understanding of HIV infection and of its treatment, and long-term graft survivals are now reported (10, 11). These cases, as well as the availability of HAART, led some groups, including ours, to stop considering HIV as an absolute contraindication to transplantation (3, 5, 12–14).

Although clear guidelines were lacking, general agreement was reached on the following criteria for the selection of HIV+ recipients (3, 12–14). The best recipient should not have AIDS, should have a high CD4+ cell count, a low viral load and should not have exhausted antiretroviral therapies (2).

Long-term nonprogressor HIV-infected patients meet all these criteria at their best, with a normal CD4+ cell count and low viral load in the absence of an anti-HIV agent during long-term follow up. Our case illustrates the outcome of a transplantation in this subgroup of HIV patients. With a more than 2-year follow up, HIV-1 infection remained stable without antiretroviral agent and no rejection episode was detected. This observation, in keeping with another report (11), suggests that all

![Figure 1: CD4+ cell count and HIV RNA load previous and after combined kidney-pancreas transplantation](image-url)
HIV+ patients are probably not equal with regard to transplantation.

The specific clinical behavior of LTNP HIV patients is linked to an attenuated virus and/or an effective immune response towards the virus. In both cases, antiretroviral drugs are not needed. This represents a substantial advantage in transplantation, considering the significant interactions between HAART and immunosuppressive drugs (15).

Although still controversial in vivo (16, 17), several immunosuppressive drugs like tacrolimus, cyclosporin, mycophenolate mofetil and sirolimus, have demonstrated clear protective effects against HIV (18–21). In our case, sirolimus was not available at the time of transplantation. The low viral replication could be in part linked to the use of mycophenolate mofetil and tacrolimus.

However, specific antiviral immune responses in LTNP HIV patients appear as the major point of interest. Among these specificities, a 32-bp deletion in the CCR5 gene (CCR5Δ32) prevents the entry of HIV in the macrophages and protects against HIV infection as well as progression to AIDS (21). Additionally, this mutant coreceptor protects kidney transplant recipients from acute rejection episodes (4). The CCR5Δ32 mutation was absent in our case. Other as yet unidentified immunologic specificities could however be present in LTNP HIV patients with similar protective features against allograft rejection.

Our case illustrates that transplantation in LTNP HIV recipients appears to be a reasonable option and may preserve a stable HIV status in the absence of antiretroviral therapy and without a rejection episode. Besides preventing HIV replication, the specific immune behavior of LTNP-HIV patients may protect the graft. This subtype of HIV+ patients should be considered separately to other HIV patients and they should be offered less restrictive access to transplantation.

References