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D.H.C. and T.H. carried out the initial clinical trial. T.H. liaised with the clinicians and collated the data. D.H.C. and T.H. analyzed the data and drafted the manuscript. K.A.M. performed statistical analyses. D.K. enrolled more than three posttransplant lymphoproliferative disease patients to the clinical trial. All the authors read and commented on the final version of the manuscript.
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Achievement of a Continuous Complete Remission in a Kidney Transplant Patient With Advanced Donor-Derived Small Cell Carcinoma

Herein, we report a case of a donor-derived small cell lung cancer (SCLC) of the graft in a 48-year-old male kidney transplant recipient who achieved a long-term complete remission (CR) after cessation of immunosuppression.

He had renal failure as a consequence of chronic glomerulonephritis and received a cadaveric kidney transplant in December 2005 for the second time. Immunosuppression consisted of prednisone, mycophenolate, and tacrolimus. In September 2006, a mass lesion was detected in the donor kidney, and the biopsy confirmed SCLC metastasis that proved to be donor derived by molecular profiling using capillary sequencing (published previously) (*1*). Staging revealed the involvement of iliac and retroperitoneal lymph nodes. The kidney was explanted, immunosuppression was discontinued, and the patient returned to hemodialysis. Chemotherapy with an adapted dose of carboplatinum (300 mg/m^2 day 1) and etoposide (50 mg/m^2 day 1–3) was initiated 4 weeks after explantation and combined with regular dialysis after carboplatinum infusions. After completion of four cycles in January 2007, the staging procedures confirmed a partial response (PR) of the involved lymph nodes. During follow-up, the patient remained in PR after chemotherapy. In February 2008, no evidence of nodal disease could be detected by magnetic resonance imaging, and thus CR was achieved, which continues to be durable to date.

Small cell cancer most often arises from the lung (SCLC) but can also be of extrapulmonary origin with a similar aggressive biology (*2*). It can be assumed that the donor-derived tumor of the kidney represents a metastasis of SCLC because immunohistochemistry revealed thyroid transcription factor-1 (TTF-1)A positivity. The prognosis of SCLC is poor with a reported median survival of 8 to 12 months when treated with chemotherapy. The key predictors of long-term survival are the extent of the disease along with the achievement of a CR. In our patient with extensive nodal involvement, best response to chemotherapy was a PR. Subsequently, with discontinued immunosuppression, the tumor regressed, providing evidence for an alloreactive response of the host's immune system against the transplanted tumor cells. It remains to speculate that CR might have been achieved by the omission of immunosuppression alone. However, in our patient's consecutive magnetic resonance imaging and computed tomography scans between organ explantation and initiation of chemotherapy showed progressing lymph node metastases, which make this assumption unlikely. This is in line with a case report by Bodvarsson et al. of a donor-derived small cell cancer in a kidney transplant patient, which showed rapid tumor growth after cessation of immunosuppression but responded well to chemotherapy. However, this patient had a paraneoplastic elevation of adreno corticotropic hormone (ACTH), which might by itself have caused immunosuppression (*3*). Alloreactivity against hematologic malignancies has been observed frequently after allogeneic hematopoietic stem-cell transplantation. However, the studies using allogeneic hematopoietic stem transplantation for the treatment of solid tumors (e.g., renal cell cancer) have been performed with limited success partially because of the requirement for immunosuppression to prevent graft versus host disease (*4*). Other solid tumors transmitted by organ transplantation, for example, malignant melanoma have been shown to respond well to the omission of immunosuppression (*5*). Experimental data published by Koebel et al. (*6*) in 2007 demonstrated that the adaptive immune system is able to keep cancer in a so-called equilibrium or dormant stage or may even lead to its complete elimination. This is clearly supported by the well-known increase in incidence for certain types of cancer of host origin in immunosuppressed transplant patients (*7*).

In summary, our report underlines the presence of an allogeneic antitumor effect against SCLC cells. This observation warrants further investigations both experimental and clinical for allogeneic adoptive immunotherapy concepts.

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CD4+CD25+ T Cells Play a Complex Role in the Pediatric Combined Liver-Intestinal Graft Acceptance

The ability of regulatory T cells (Tregs) to prevent allograft rejection and to induce tolerance has been demonstrated in rodents (*1*) but less clearly in humans (*2*). In transplantation, this apparent discrepancy may be related to the organs—liver, heart, lung, and intestine—and to the immunosuppressive therapies (*3–7*). In humans, Tregs are enriched in CD4+CD25+^{high}FoxP3+ T cells (*8*).We address the question whether their density in the intestinal mucosa correlated with small bowel transplantation outcome, and thus, give new clues for the role of Tregs in human transplantation. We had previously reported the beneficial effect of liver transplantation associated with the small bowel on patients and grafts survivals, independently from the clinical and therapeutical characteristics. Particularly, thymoglobulin was not used except for one liver small bowel transplantation (LSbTx) and small bowel transplantation (SbTx), who both died (*9*). In this study, we have evaluated the density of CD4+CD25+ T cells by double immunostaining (CD4: AF-379-NA R&D Systems; CD25: NLC-CD25–305 Novo Castra) and FoxP3 cells by single immunostaining (FOXP3 ab2481 Abcam) on paraffin sections from intestinal biopsies collected from day 0 to 24 months after transplantation. Our analyses were performed in the cohort of pediatric small bowel transplantation, isolated (SbTx; n=7) or combined with the liver (LSbTx; n=8) and controls—normal mucosa (NC; n=8) and inflammatory mucosa (IC; n=7)—that we had previously described (*9*).

In contrast with other studies, we did not find that the density of Tregs correlates with immunosuppressive drugs, but rather with transplantation type (*9*, *10*). Interestingly, at day 0 (=6 hr) after transplantation, we found a statistically significant lower density of CD4+CD25+ T cells in SbTx intestinal mucosa (P=0.01) compared with LSbTx. The level was closed to IC and NC controls (Fig. 1A). The higher amount of Tregs in LSbTx is consistent with the observation that higher Tregs density was associated with a better graft outcome (*7*). We found that FoxP3+ cell density did not necessarily follow the CD4+CD25+ T cells changes in the grafted intestinal mucosa, although it did in NC. FoxP3+ cells density in SbTx remained similar to NC, close to LSbTx, and different from IC, whereas CD4+CD25+ T cells decreased in SbTx, suggesting different modulation of each cellular subtype. These results suggest that CD4+CD25+ T effectors cells, rather than Tregs, were implicated in the better clinical outcome of the LSbTx. In fact, in situ CD4+CD25+ T cells analysis did not differentiate CD25+^{high}—regulatory—from CD25+^{low} effector cell. Our results may therefore mean that effector CD4+CD25+ T cells could be the pivotal cells for the beneficial role of the liver graft on intestinal graft, whereas maintenance of FoxP3+ regulatory cells within SbTx intestinal mucosa was insufficient to protect from rejection and graft loss. We found significant differences only at day 0; the Park's Score was slightly higher in LSbTx (2.3±1.6) than in SbTx (2.0±1.4), although patients and graft LSbTx survivals were increased and mean ischemia time was longer in LSbTx (7.4±1.6 hr) than in SbTx (4.2±1.6 hr) (*11*). Interestingly, the higher Park's Score could explain the higher number of apoptotic intestinal epithelial cells (apoptotic body counts [ABC]) found in LSbTx (Fig. 1B) (*9*). Therefore, protective immunity may need induction of CD4+CD25+ effector T cells possibly through ABC presentation. ABC increase may also correlate to the emergence of effectors CD4+CD25+ T cells. Long-lasting patients follow-up revealed a state or a trend toward equilibrium for the different parameters: ABC, patients and grafts survival rates, CD4+CD25+ T cells, and FoxP3 cell density. Especially, we did not find significant differences in CD4+CD25+ T-cell densities from day 5 to 24 months after transplantation. This may explain why the role of CD4+CD25+ effector T cells was probably underestimated in most studies investigating Tregs in human transplantation. These studies were performed on late samples, several weeks or months after transplantation (*7*, *10*, *12*, *13*).

Our results are consistent with an early setup of the liver beneficial effect in pediatric intestinal transplantation, probably through the differential control of effector Tregs balance. It emphasizes the need to have multiparametric follow-up strategy for the intestinal transplantation and the importance of the intestinal mucosa analysis at day 0. Because ABC and CD25+ T cells are the acute rejection hallmark in intestinal transplantation, they need to be analyzed according to the other cell markers, particularly