

**Development of a rejection crisis in a transplant
in the presence of leukopenia**

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The patient in the long term after cadaveric kidney allotransplantation developed leukopenia that required a dose reduction of immunosuppressive drugs. Against this condition, a rejection crisis occurred in the transplant. Thus, the presence of leukopenia in a patient after cadaveric kidney allotransplantation requires detecting early signs of not only infectious complications, but also a rejection crisis.

Keywords: allotransplantation, cadaveric kidney, immunosuppressive therapy, leukopenia.

The development of an acute rejection crisis (ARC) in a transplanted kidney is one of the most common complications developing after cadaveric kidney allotransplantation (CKAT). For ARC prevention and treatment, a wide range of drugs having immunosuppressive properties have been used [1, 2]. These drugs inhibit the functional capability of the recipient's immune system, reducing the level of immune inflammation in the graft (Gr), thereby contributing to a better function of the transplanted organ. However, in this situation there may be another problem: an excessive immunosuppression

may cause toxic effects of the drugs used [3, 4], a pronounced secondary immunodeficiency occurs that may lead to the development of severe infectious complications. Thus, the tactics of immunosuppression after CKAT procedure should consist of maintaining a constant balance in immunosuppression therapy between the doses that would ensure the normal functioning of the transplanted organ, on the one hand, and would prevent drug toxic effects, and infectious complications, on the other hand.

The reported case, in our opinion, may raise interest because the patient developed an ARC in the transplanted kidney secondary to the existing leukopenia (LP) in the long-term period after CKAT. In our experience of more than 200 patients who underwent kidney transplantation, it is a very rare combination.

Patient D., born in 1979, had suffered from chronic glomerulonephritis since 1995. In 2010, a terminal stage of chronic renal failure (CRF) was diagnosed. In January 2010, the treatment consisting of programmed hemodialysis was initiated. CKAT was performed on 27.09.11.

The patient was in a satisfactory condition during an outpatient follow-up period and received the following drugs: *Prograf*[®] 14 mg/day, *Mysept* 1000 mg/day, *Metypred*[®] 4 mg/day, *Sorbifer*[®] 2 tablets/day, *Eprex*[®] 2000 IU subcutaneously every other day, *Ursosan*[®] 500 mg/day, *Curantyl*[®] 150 mg/day, *Nolpaza*[®] 20 mg overnight, *Valcyte* 900 mg/day.

At a regular follow-up visit to the outpatient clinic (on 18.05.12), the patient demonstrated a decrease of white blood cell (WBC) count to $2.5 \times 10^9/L$ in the peripheral blood sample, the general patient's condition being satisfactory, the urine output making 2.5 L/day. The patient expressed no complaints. Nevertheless, LP was aggravating: on 21.05.12, the WBC count was $1.7 \times 10^9/L$. In this period, the urea level ranged between 18 and 21

mmol/L, creatinine ranged between 150 and 162 mg/dl, and alanine aminotransferase (ALT) was from 80 to 149 U/L.

Given the growing LP, it was decided to reduce the doses of immunosuppressants and to discontinue the drugs that could possibly produce the adverse effect of the WBC decrease. From 18.05.12 *Mysept* was discontinued, *Valcyte* dose was twice reduced. From 21.05.12 *Prograf*[®] and *Valcyte* were discontinued (polymerase chain reaction [PCR] for cytomegalovirus in blood was negative.)

Acute deterioration in the patient's condition occurred on 27.05.12 with fever up to 39-40°C (persisting for 3 days), the patient complained of general weakness, and pain in the lumbar region and was hospitalized for these complaints. Hematology study at admission demonstrated a pronounced LP with WBCs of 1.3×10^9 /L with the left shift in the complete blood count with differentials. Serum creatinine made 111 mmol/L, ALT was 71.5 U/L. Further, on 29.05.12, creatinine increased to 215 mmol/L, urea level made 19 mmol/L. The peak creatinine level (260 mmol/L) was documented on 02.06.12. In hospital, aspartate aminotransferase rose to 134 U/L and ALT reached 533 U/L. Serum alkaline phosphatase rose to 369.2 U/L, γ -glutamyl transferase made 205.2 U/L. At patient's admission, the platelet level was 32×10^9 /L with the following marked reduction to 20×10^9 /L seen on 30.05.12. Only by the patient's discharge from hospital the platelet level had risen to 55×10^9 /L. During treatment the WBC count rose to 4.0×10^9 /L.

Studying the immune status changes over time in the presence of LP, we revealed a considerably decreased absolute and relative counts of all lymphocyte subpopulations, as well as the decrease in serum IgA and IgM to 0.85 g/L, and 0.78 g/L, respectively. The relative lymphocyte counts were

always within the normal ranges, and the relative counts of NK-cells (CD3-, CD16+, CD56+) and T-NK-cells (CD3+, CD16+, CD56+) exceeded the normal ranges. Thus, the immunogram data were consistent with severe immunosuppression, meanwhile a marked activation of antiviral mechanisms was observed.

Ultrasonography at admission demonstrated an increase in the Gr size from 121-60-74 mm, Ri being 0.67, (on 30.05.12), to 121-70-79 mm (on 02.06.12), Ri being 0.69 (on 04.06.12). In the treatment course, Ri decreased to 0.63 (on 06.06.12), the Gr size lessened to 114-54-64 mm (on 08.06.12).

Throughout the treatment period, the blood sample tests for sterility, bacteriology urine culture, PCR assays for cytomegalovirus, herpes simplex virus in blood were negative.

At admission, *Metypred*[®] (4 mg/day) was administered and *Prograf*[®] (8 mg/day) was resumed, as well as were antibacterial and infusion therapies.

In view of persisting hyperthermia, a pronounced weakness, tenderness in the Gr area, a slightly decreased urine output, the US finding of the Gr size increase, excessive amounts of waste nitrogen at blood biochemistry, and the lack of clinical evidence of inflammatory process, the patient's condition was qualified as ARC in the kidney graft; and on 30.05.12, a pulse therapy with *Solu-Medrol*[®] was initiated at a dose of 500 mg/day (for a 3-day course), the *Prograf*[®] dose was increased to 14 mg/day.

The Gr nephrobiopsy taken on 31.05.12 demonstrated an acute Grade II B graft rejection (t3, i3, g1, v2) (Banff 97 histological classification).

Prograf[®] blood levels were 4.8 ng/ml at admission, 8.8 ng/ml on 01.06.12, afterwards the *Prograf*[®] dose was increased to 16 mg/day.

The patient's clinical condition became better on 03–04.06.12 when the pain in the graft area diminished, the weakness improved. On 15.06.12, after the patient's laboratory parameters had been normalized, he was discharged from hospital in a satisfactory condition.

Given the above, it can be assumed that, initially, LP was the manifestation of toxicity due to the use of calcineurin inhibitor (tacrolimus) and purine biosynthesis inhibitor (mycophenolate) [5]. LP and thrombocytopenia are well-known common adverse side effects of tacrolimus and mycophenolate mofetil on the blood system. Aimed at minimizing complications and preventing infectious processes, we decided to reduce doses of these drugs initially, and temporary discontinued them later due to the lack of expected effect. An international practice has shown it acceptable to use immunosuppressive monotherapy in small doses that blocks neo-formation of mature lymphocytes from native T cells, and in most cases it appears sufficient to develop and maintain a long-term quasi-tolerance, i.e. a long-term allograft function in the recipient being on immunosuppression therapy [6].

Based on improving clinical and laboratory parameters in the course of in-hospital treatment, and with the caution to avoid the ARC induction in conditions of leukopoiesis activation, no leukopoiesis-stimulating drugs were administered.

Unexpected was the development of ARC in the presence of severe LP. We considered that the ARC occurrence was confirmed by the following signs: a decreased urine output, emerging pain in the Gr area, increases in the Gr size and Ri of Gr main arteries, the Gr nephrobiopsy study result, and a positive effect of pathogenetic therapy for ARC. Noteworthy is the fact that the decreased urine output, the increased Gr size and Ri of Gr main

arteries, growing amounts of waste nitrogen, the decrease in platelet count became evident in hospital while the patient received a standard-scheme immunosuppressive therapy. This suggests that the developed ARC might be induced by the infectious complication of initial LP, probably due to unverified virus.

We must admit that the employed tactics of temporary discontinuation of calcineurin inhibitor, on its part, contributed to ARC development, even in the presence of existing LP.

Subsequent hepatotoxicity may be explained as being the result of *Prograf*[®] high dose therapy used to control ARC (estimated blood levels of the drug, however, suggested that the dose was within the normal range).

The main mechanism that could explain the ARC development in this case, was the activation of the innate immune system. By producing great amounts of proinflammatory cytokines in response to inflammation, this system activates the adaptive immune system inducing an acute rejection [7, 8]. In the post-transplant period, the inflammatory processes, particularly those of viral etiology, might also cause an acute or chronic Gr rejection through activation of the innate immune system [9].

Thus, the reported case has shown that the presence of LP in a patient after CKAT does not exclude the potential development of ARC and probably requires a more close and careful monitoring of clinical and laboratory parameters to detect early signs of both an infection, and also a rejection crisis. Meanwhile, a complete discontinuation of calcineurin inhibitors is unacceptable as this might act as an independent risk factor for ARC.

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