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The dynamics of immunological parameters in early stages after bilateral lung transplantation in patients with various pulmonary pathology

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Background. *The diseases leading to the need for lung transplantation include chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, cystic fibrosis, alpha-1-antitrypsin deficiency, idiopathic pulmonary hypertension, histiocytosis X, and sarcoidosis. Primary lung transplant dysfunction is a frequent complication after transplantation and represents a multifactorial injury of the transplanted lung, its pathogenesis being associated with a severe hypoxemia of the lung transplant and diffused damage to the alveoli. The clinical presentation is in many ways similar to an acute respiratory distress syndrome, which pathogenesis is primarily*

effected by the activation of immune system cells. The cytokine production by immunocompetent cells, the synthesis of reactive oxygen and nitrous oxide, being the mediators of inflammation, trigger inflammatory processes in the lungs; the immunoglobulin synthesis derangements also lead to the development of inflammatory abnormalities in the lungs and a poor transplantation outcome.

The objective *was to study the immunological response in the lung transplant recipients suffering from the underlying disease of various etiology and to determine the immunological predictors of adverse outcome in the early period after bilateral lung transplantation.*

Material and methods. *Twenty nine patients were examined within 2 weeks after lung transplantation: Group 1 comprised 10 patients with cystic fibrosis (6 women, 4 men) aged 27.8 ± 2.7 years; Group 2 included 19 patients (7 women, 12 men) at the age of 38.5 ± 10.4 years having other lung diseases. Mortality was 10% (1 patient) in Group 1, and 52.5% (10 patients) in Group 2. The patients were followed-up according to the standard protocol of postoperative treatment and immunosuppression therapy schemes. Immunological monitoring included the lymphocyte phenotyping, and the assessment* of *phagocytic activity* of *neutrophils, the HCT-test, the blood levels of immunoglobulins (Ig) A, M, G, circulating immune complexes, and C-reactive protein. Statistical significance was assessed at p <0.05.*

Results. *On day 5, the T-lymphocyte count in patients of Group 1 was 674 cells/μL (Me), which was 26.7% lower than the lower limit of the reference range, but 2.5 times higher than that in patients of Group 2 (266*

cells/μL). The number of T-lymphocytes in patients of the 2nd group was recorded at 71.1% below the lower limit of the reference interval (p <0.05). The blood level of IgA (Me) in patients of Group 1 was within the normal range (Me 1.9g/L), the blood level of IgA (Me) in patients of Group 2 was 1.4 g/L, which was 26.3% lower than below the lower limit of the reference values and lower than in Group 1 (p<0.05).

By day 13, the count of T-lymphocytes in Group 1 had increased 2.2 times compared to day 5, reaching the reference values (Me), and made 1479 cells/μL. In the 2nd group, there was a 1.5-fold increase in T lymphocyte count (Me 408 cells/μL), which was 3.7 times lower than the lower limit of the reference range and lower than in the 1st group (p <0,05). The level of IgA in patients of the 1st group increased by 20.8% and amounted to 2.4 g/L (Me), and in patients of the 2nd group, the level of IgA for 2 weeks remained almost unchanged (Me 1.5 g/L) and was 1.7 times lower than in the 1st group (p<0.05).

Conclusions. *On day 5 after transplantation, the patients with cystic fibrosis demonstrated the increase in the T-lymphocyte count and IgA level by 2.5 and 1.4 times, respectively, compared to the patients with other lung diseases. By the end of week 2, T-lymphocyte and IgA values in patients with cystic fibrosis, unlike patients with other lung diseases, had reached the reference range. The T-lymphocyte count and the concentration of IgA below the reference range in the first 2 weeks after lung transplantation were the immunological predictors of adverse outcome.*

Keywords: lung transplantation, graft dysfunction, immune response, lymphocytes, immunoglobulins

A1AD, alpha-1-antitrypsin deficiency
ALIS, acute lung injury syndrome
ARDS, Acute Respiratory Distress Syndrome
CIC, circulating immune complexes
COPD, Chronic Obstructive Pulmonary Disease
CRP, C-reactive protein
Ig, immunoglobulin
IPAH, idiopathic pulmonary hypertension
IPF, idiopathic pulmonary fibrosis
ISHLT, International Society for Heart & Lung Transplantation
LT, lung transplantation
Me, median
PLGD, primary lung graft dysfunction

Lung transplantation (LT) is a method to treat patients with persistently progressing lung diseases that are refractory to conservative therapy [1]. The most common indications for LT include chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis, alpha-1-antitrypsin deficiency (A1AD) and idiopathic pulmonary hypertension (IPAH), as well as end-stages of diseases such as lymphangioleiomyomatosis, histiocytosis X, sarcoidosis, etc. The above-described nosological forms account for 85% of surgical interventions performed worldwide.

Despite significant achievements in the field of LT, donor organ preservation, surgical equipment, and anesthesia, the lung transplant loss and recipient's death in the early posttransplant period, as reported in literature, reach 30-50% [2]. The most common complication after transplantation is a

primary lung graft dysfunction (PLGD). According to the International Society of Heart and Lung Transplantation (ISHLT) and a number of authors, the occurrence of PLGD accounts for more than 30% of perioperative patient mortality [2-7]. Early lung graft dysfunction (PLGD, ischemia-reperfusion) represents a multifactorial damage to the transplanted lung that occurs within the 72 hours after transplantation and is characterized by severe hypoxemia, pulmonary edema, and radiographic signs of diffuse lung opacification. A typical histological pattern in PLGD is a diffuse damage to the alveoli. The clinical presentation of PLGD is in many ways similar to an acute respiratory distress syndrome (ARDS), which is a special case of the acute lung injury syndrome (ALIS). In the ARDS pathogenesis, the main role is played by the activation of the immune system cells, namely, neutrophils, monocytes, macrophages, and lymphocytes. The production of cytokines by immunocompetent cells, the synthesis of reactive oxygen and nitric oxide, being the mediators of inflammation, trigger inflammatory processes in the lungs [8, 9]. Increased IL-8 levels and changed ratio of IL-6 (pro-inflammatory) to IL-10 (anti-inflammatory) levels correlate with the PLGD development and a 30-day mortality rate [10–12]. Deranged synthesis of immunoglobulins (Ig) and, especially, a decreased level of IgA producing a protective effect in pathological processes in the lungs, impair the barrier functions of mucous membranes, lead to the lung colonization by infectious pathogens and to increased inflammation [13, 14]. Thus, the imbalance between pro-inflammatory and anti-inflammatory immune responses after transplantation may affect the graft function in the

post-transplant period and contribute to the development of inflammatory abnormalities in the lungs.

The immunological studies we conducted earlier in patients after solid organ (liver) transplantation showed that immunological monitoring in the first 2 weeks after transplantation yields information for assessing the severity of a recipient condition and for predicting possible complications. The optimal timing for immunological testing included the 2nd, 5th, and 12–14th days after transplantation. At early stages (at 2–5 days) after organ transplantation, the most pronounced changes in immunological parameters occurred against the background of the ongoing multicomponent immunosuppressive therapy and the formation of allogenic lymphocytic clones. By the end of posttransplant week 2 (12–14th day), the immune response to antigens of bacterial and viral nature, and to alloantigens (the graft) had completely been formed resulting in quantitative and qualitative changes of immunocompetent cells, the changes that could be recorded by immunological testing [15, 16].

The purpose of the study was to investigate the specific features of immunological response in recipients and to identify the immunological predictors of the adverse outcome developing in early period after bilateral LT, with regard of the etiology of the underlying lung disease

Material and methods

Immunological monitoring was made in 29 patients during 2 weeks following LT. The patients were divided into two groups: 10 patients with cystic fibrosis were included in the 1st group, 19 patients with COPD and

other lung diseases were included in the 2nd group. Characteristics of patient groups are given in Table 1. As seen from the Table, there was no statistically significant difference in mean age between the patients in the 1st and 2nd groups: 27.8 ± 2.7 and 38.5 ± 10.4 years, respectively ($p > 0.05$). The study included the patients who were treated as based on a single methodological approach under the conditions of a uniform treatment and diagnostic tactics with using a standard protocol for postoperative therapy. From the first day after LT, all recipients received an antibacterial, antiviral, antifungal therapy, a standard four-component immunosuppressive therapy that included: immunosuppression inductors (antithymocyte globulin, anti-CD25 antibodies), calcineurin inhibitors (tacrolimus), Methylprednisolone, a mycophenolic acid product (Cellcept).

Table 1. Characteristics of patient groups

Groups	**Number**	**Gender, M/F**	**Age, years**	**Diagnosis**	Bed- days	Mortality
1st group	10	F 6 M 4	27.8 ± 2.7	Cystic Fibrosis: - pulmonary form 3 - pulmonary intestinal form 7	50 ± 21.5	1 (10%)
2nd group	19	F 7 M 12	38.5 ± 10.4	COPD 4 IPF 6 IPAH 2 Primary emphysema 2 Histiocytosis X 1 Allergic alveolitis 1 Bronchiectasis 1 Lymphangioleiomyomatosis with cystic lung transformation 1 Sarcoidosis 1	74 ± 25.3	10 (52.6%)

Immunological tests

Blood sampling for immunological tests was performed in patients in the morning on day 5 ± 2 and 13 ± 2 days after LT. We assessed the cellular and humoral immunity. The following parameters were determined: the levels of C-reactive protein (CRP), three classes of Ig: A, M and G, circulating immune complexes (CIC) of three fractions; the phagocytic activity and oxygen metabolism of neutrophils were evaluated by the HCT-test. Phenotyping of the main lymphocyte populations (CD3, CD19) was performed using a FACS Canto II cytofluorometer with monoclonal antibodies from Becton Dickinson (USA); CRP was assessed using the BN Pro Spec nephelometer manufactured by Behring.

The statistical analysis was made using non-parametric methods: (Mann–Whitney test), the median (Me) and quartiles were determined. The statistical significance of the results was evaluated at $p < 0.05$. Graph Pad Prism 5 Software was used.

Results

The immunological parameters analyzed in the groups on day 5 after LT revealed leukocytosis 15.1 (11.8; 21.4) $x10^3$ cells/μL in the 1st group and 12.6 (9.9; 17.8) $x10^3$ cells/μL in the 2nd group, high CRP values (52.6 mg/L and 54.8 mg/L, respectively), and CIC total number (377 and 324, respectively), confirming the presence of an inflammatory response in patients of both groups, however, without statistically significant differences in the above listed parameters ($p>0.05$). The measured activity of metabolic

processes in neutrophils (HCT-test) in patients of both groups was within the reference range (Table 2). The B-lymphocyte absolute count in the peripheral blood was below the reference range by 39.4% and 26.9%, respectively; no statistically significant differences were found between the groups (see Table 2).

Table 2. Comparison of immunological parameters between patient groups at 5 ± 2 days after lung transplantation

Parameter	Reference range	1st group	2nd group	R
		Me (LQ; UQ)	Me (LQ; UQ)	
Leukocytes, $x10^3$ cells/μL	4.0–9.0	15.1 (11.8; 21.4)	12.6 (9.9; 17.8)	0.9268
T-lymphocytes, cells/μL	920–2310	674 (487; 819)	266 (157; 608)	**0.0316**
B-lymphocytes, cells/μL	160–590	97 (80; 206)	117 (55.3; 152)	0.8213
Phagocytosis with latex,%	40–50	32.0 (26.0; 60.0)	48.5 (30.3; 67.3)	0.6217
Spontaneous HCT-test,%	5–15	7.0 (3.0; 23.0)	7.5 (4.0; 13.5)	0.3238
IgA, g/L	1.8–2.5	1.9 (1.6; 2.22)	1.4 (1.2; 2.0)	**0.0339**
IgM, g/L	1.1–2.1	0.84 (0.62; 0.97)	0.84 (0.65; 1.28)	0.6650
IgG, g/L	10.0–14.0	6.2 (6.2; 8.4)	6.3 (6.35; 8.3)	0.9228
CIC total	112–230	377 (263; 534.3)	324 (185; 398)	0.4089

CRP mg/L	0–3	52.6 (31.5; 176.8)	54.8 (27.4; 78.2)	0.7920

Meanwhile, by day 5, the T-lymphocyte absolute count in patients of the 1st group was 674 cells/μL (Me), being 26.7% lower than the reference range, but statistically significantly higher (2.5 times) than in patients of the 2nd group ($p<0.05$) in whom the T-lymphocyte absolute count was by 71.1% lower than the reference range and made 266 cells/μL (see Table 2). The measured serum IgA level (Me) in the patients of the 1st group was within the normal range (1.9 g/L), and in patients of the 2nd group it was 1.4 g/L that was 26.3% lower the reference values and statistically significantly lower than the value of this parameter in the 1st group ($p <0.05$). IgM levels were within the lower limit of the reference range and did not differ significantly between the groups. A decrease in IgG values by 1.7–2 times was noted in both groups that was probably associated with the ongoing multicomponent immunosuppression and occurred due to the suppression of T-dependent Ig synthesis; the differences between the groups were statistically insignificant (see Table 2).

By day 13, the leukocyte count in patients of the 1st group had increased to 16.3 $x10^3$ cells/μL (Me), which was 1.8 times higher than the upper limit of the reference range, whereas in patients of the 2nd group, a decrease to 11.8 $x10^3$ cells/μL (Me) was seen, which was 1.3 times higher than the reference range and 1.4 times lower than that in the 1st group; the differences between the groups were not statistically significant ($p> 0.05$). At the same time, despite the absence of statistically significant difference in

the dynamics of CRP (Me) between the groups, it is noteworthy that the CRP (Me) in patients of the 1st group decreased 2-fold compared to the value recorded on day 5 (52.6 vs. 27.7 mg/L, respectively), whereas in patients of the 2nd group it remained almost unchanged (54.8 mg/L vs. 58.4 mg/L, respectively) (Table 3). Similar dynamics was also observed with respect to the activation of neutrophil oxygen metabolism (HCT-test): by day 13, the HCT-test result in the 1st group of recipients had been 2.4 times higher compared to that recorded on day 5, no trend to such changes was registered in the patients of the 2nd group (see Table 3). By day 13, the B-lymphocyte count of in peripheral blood in patients of both groups was within the lower limit of the reference range. At the same time, the T-lymphocyte absolute count in patients of the 1st group increased 2.2 times compared to day 5, reaching reference values (Me) and making 1,479 cells/μL; and in patients of the 2nd group, although the T-lymphocyte absolute count (Me) increased by 1.5 times, up to 408 cells/μL (Me), however, this parameter was significantly lower than the reference values and statistically significantly (3.7 times) lower than in patients of the 1st group ($p < 0.05$) (see Table 3). The IgA level (Me) increased by 20.8% and made 2.4 g/L in patients of the 1st group; and in the 2nd group, the level of IgA (Me) was almost unchanged (1.5 g/L) for the period of 2 weeks, remaining below the reference range and statistically significantly (1.7 times) lower than in the patients of the 1st group ($p < 0.05$) (see tab. 3).

Table 3. Comparison of immunological parameters between patient groups at 13 ± 2 days after lung transplantation

Parameter	Reference range	1st group	2nd group	R
		Me (LQ; UQ)	Me (LQ; UQ)	
Leukocytes, $x10^3$ cells/μL	4.0–9.0	16.3 (13.0; 18.9)	11.8 (9.3; 20.0)	0.3584
T-lymphocytes, cells/μL	920–2310	1479 (968; 2464)	408 (255; 695)	**0.0016**
B-lymphocytes, cells/μL	160–590	170 (100; 246)	154 (82.5; 233)	0.7383
Phagocytosis with latex,%	40–50	38.0 (25.0; 64.0)	54 (34.0; 75.5)	0.3408
Spontaneous HCT-test,%	5–15	17.0 (4.0; 36.0)	7.5 (4.7; 18.5)	0.2041
IgA, g/L	1.8–2.5	2.4 (2.0; 2.8)	1.5 (1.0; 1.7)	**0.0049**
IgM, g/L	1.1–2.1	1.2 (0.9; 1.3)	0.9 (0.71; 1.0)	0.2430
IgG, g/L	10.0–14.0	7.2 (6.7; 7.6)	6.8 (5.4; 8.2)	0.8435
CIC total	112–230	442 (379; 505)	405 (243; 495)	0.8051
CRP mg/L	0–3	27.7 (14.4; 128.4)	58.4 (24.8; 109.2)	0.6010

Discussion

Comparing the immunological parameters between two groups of patients on day 5 and day 13, we found statistically significant differences in

the dynamics of T-lymphocyte count and the IgA level, and the differences in the trends of other studied immunological parameters.

As soon as from day 5 after LT, the T-lymphocyte count (Me) recorded in patients of the 1st group was statistically significantly higher than that in patients of the 2nd group. By the end of week 2, the number of T-lymphocytes had increased statistically significantly up to reference values ($p < 0.05$) (Fig. 1). From day 5, the measured IgA level (Me) was within the reference range; and by the end of week 2, its measured value was at the upper limit of the reference range ($p < 0.0454$) (Fig. 2). However, it is necessary to note the changes in immunological parameters over time in patients of the 1st group indicating the activation of the immune response. By the end of week 2 after LT, a slight increase (by 1.2 $x10^3$ cells/μL) was revealed in the leukocyte count (up to 16.3 cells/μl) and a 2.4-time increase in the activity of the neutrophil oxygen metabolism was found in the HCT test results. Against the background of the increased phagocytic activity, a 2-fold decrease in the blood level of the inflammatory marker CRP was registered, which was accompanied by positive clinical dynamics in patients of this group: the mean length of hospital stay was 50 days, mortality was 10% (1 patient) (see Table 1).

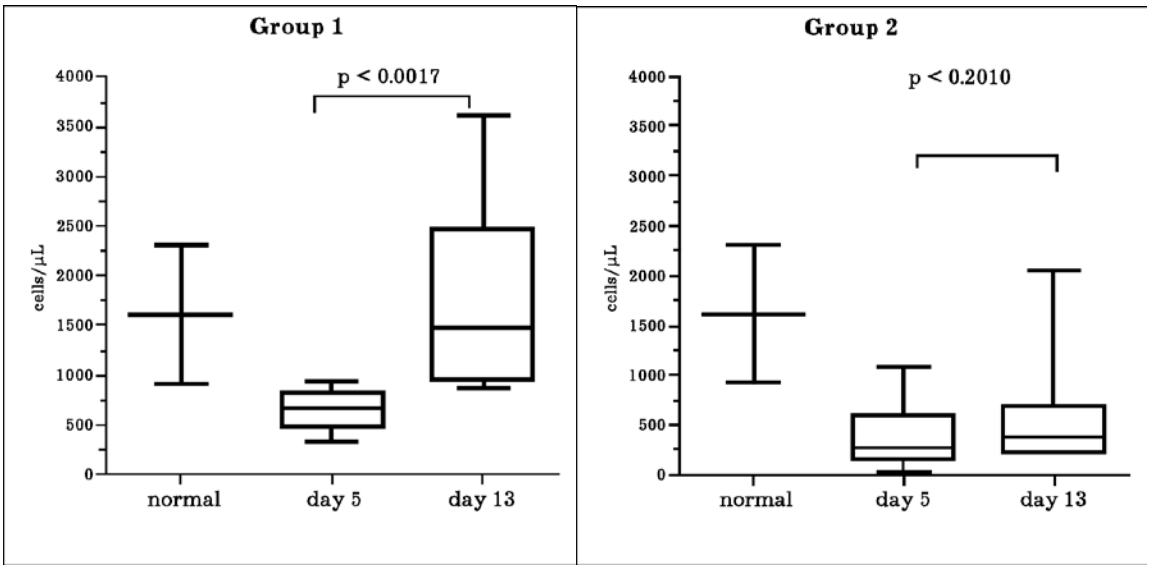

Fig. 1. Changes in T- lymphocyte count in groups in initial 2 weeks after lung transplantation

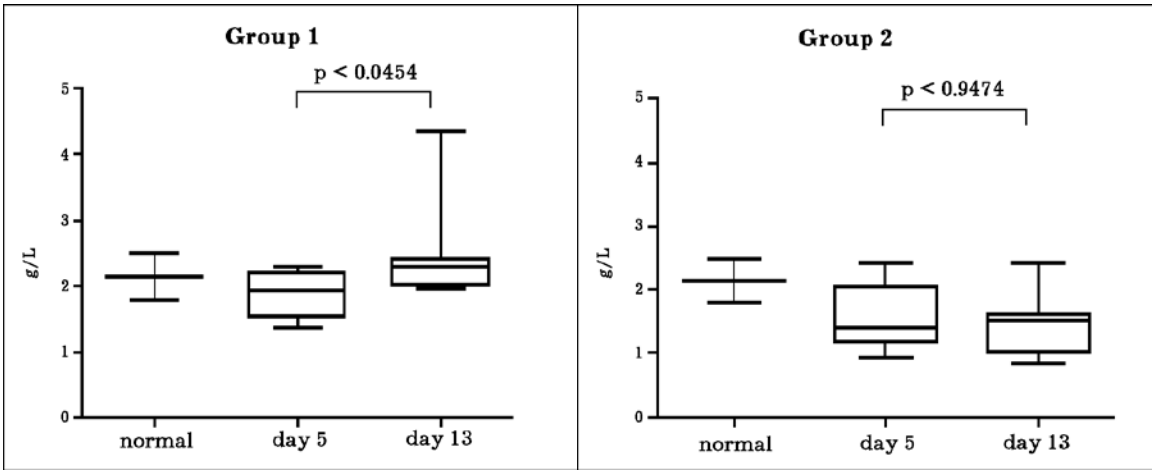

Fig. 2. Changes in IgA level in groups in initial 2 weeks after lung transplantation

In patients of the 2nd group, the T-lymphocyte count (Me) (see Fig. 1) and the IgA level (Me) (see Fig. 2) were almost unchanged in the period between day 5 and day 13 after LT, and remained below the reference range. The leukocyte count in peripheral blood was decreasing from day 5 to day

13 and made 11.3 $x10^3$ cells/μL, the activity of redox processes in neutrophils did not change and remained within the reference range, which makes a marker of an inadequate phagocytic response to inflammation in the presence of inflammation signs in the early period after LT. The CRP level that serves one of the indicators of the body overall inflammatory response had increased compared to posttransplant day 5, despite the ongoing intensive therapy (see Table 3). Such dynamics of laboratory parameters indicated the clinical condition of patients in the 2nd group that affected the length of their hospital stay (74 bed-days) and the mortality making 52.6% (10 patients) in the group.

The decrease in T-lymphocyte count impedes the processes of signal transmission from T- (Tx) to B-lymphocytes and the processes of switching the synthesis of nonspecific IgM class antibodies to the synthesis of antigen-specific antibodies of the IgA and IgG classes. The reduced serum IgA level in a patient results in a reduced production of the secretory IgA (sIgA-sIgA) on mucous membranes that has protective properties for mucosa. All that leads to an impaired elimination of various antigens from the lungs, their colonization with infectious agents resulting in the migration activated phagocytes (neutrophils, monocytes, macrophages) into the lungs [17]. The increased production of cytokines and reactive oxygen species by phagocytes leads to the destruction of lung epithelial barrier, enhanced inflammation, disruption of the lung graft function, and a poor prognosis [8, 9, 13, 14].

Thus, the laboratory monitoring of patients after lung transplantation helped to specify the immune response features associated with various

etiology of pulmonary insufficiency. The immunological predictors of complications early after lung transplantation were identified as being the T-lymphocyte absolute count and the IgA level. We demonstrated the differences in the dynamics of immunological parameters early after lung transplantation were demonstrated between patients with cystic fibrosis (group 1) and chronic obstructive pulmonary disease and other lung diseases (group 2). The dynamics of the T-lymphocyte count and IgA in the first 2 weeks after lung transplantation allowed us to estimate the immune system reserves of the lung transplant recipient and predict complications, specifically the primary lung graft dysfunction.

Conclusions

1. In patients with cystic fibrosis (group 1), an increase in the number of T-lymphocytes and IgA levels was recorded on the 5th day after lung transplantation compared to those in patients with chronic obstructive pulmonary disease and other lung diseases (group 2) by 2.5 and 1.4 times respectively. By the end of week 2, the values of T-lymphocytes and IgA in patients of the 1st group, in contrast to patients of the 2nd group, reached the reference range.
2. The T-lymphocyte count and the IgA concentration below the reference range in the first 2 weeks after lung transplantation were immunological predictors of adverse outcome.

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