DOI:10.23873/2074-0506-2019-11-2-141-149

Pulmonary and intestinal tuberculosis in a kidney transplant recipient

R.O. Kantariya*, A.V. Vatazin, A.B. Zul'karnayev, V.A. Stepanov

Moscow Regional Research and Clinical Institute n.a. M.F. Vladimirskiy, 61/2 Schepkin St., Moscow 129110 Russia

*Correspondence to: Rusudana O. Kantariya, Cand. Med. Sci., Associate Professor of Transplantology, Nephrology and Artificial Organs Department, Faculty of Medical Postgraduate Education in Moscow Regional Research and Clinical Institute n.a. M.F. Vladimirskiy, e-mail: rusiko_k@mail.ru

Received: February 18, 2019

Accepted for publication: March 4, 2019

Introduction. *Tuberculosis is one of the most common infections in the general population, as well as among the recipients of solid organs. In kidney transplant recipients, the diagnosis of tuberculosis is often extremely difficult to make because of unclear clinical and radiological symptoms, and a highly frequent atypical (extrapulmonary) localization. The tuberculosis treatment in patients on drug immunosuppression is a significant problem.*

Clinical case. *At five years after renal transplantation, the patient noted the onset of fever up to 38 degrees C. It was suspicious of respiratory infection. Chest X-ray, computed tomography, and ultrasound examination of the graft revealed no pathology. Antibacterial and antiviral therapy brought stable improvement. A repeated computer tomography demonstrated an enhanced pulmonary pattern in S6 of the left lung with visualization of small grouped lesions located peribronchially, the terminal ileitis in the abdominal cavity: (an intensive contrast accumulation in the mucosa of the affected part of the small intestine, the mesentery hypervascularity at this level). A colonoscopy with a small intestine biopsy was performed; the findings were highly consistent with a tuberculous*

process. A targeted treatment of tuberculosis was carried out, which had a marked positive trend.

***Conclusion**. Thus, the diagnosis of tuberculosis in kidney transplant recipients is extremely complex; the clinical signs and instrumental test results are often ambiguous, which greatly complicates the timely diagnosis. An integrated approach with the use of modern diagnostic methods is required.*

Keywords: tuberculosis, renal transplant recipients, transplantation

Conflict of interests. Authors declare no conflict of interests

Financing. The study was performed without external funding

Kantariya R.O., Vatazin A.V., Zul'karnayev A.B., Stepanov V.A. Pulmonary and intestinal tuberculosis in a kidney transplant recipient. *Transplantologiya. The Russian Journal of Transplantation.* 2019;11(2):141–149. (In Russian). DOI:10.23873/2074-0506-2019-11-2- 141-149

CT, computed tomography
ESR, erythrocyte sedimentation rate
US, ultrasonography
CKD, chronic kidney disease

Introduction. Tuberculosis is one of ten leading causes of death in the world. In 2016, 10,400,000 people suffered from tuberculosis, and 1,700,000 people (including 400,000 people with HIV) died from the disease. Among the total number of cases, 64% accounted for 7 countries, among which India ranks first, followed by Indonesia, China, Nigeria, Pakistan, the Philippines and South Africa. Multidrug-resistant tuberculosis remains a challenge for public healthcare system. From 490,000 to 600,000 new cases of resistant to treatment tuberculosis forms are registered annually [1].

About one-fourth of the world's population has latent tuberculosis. However, people with immune deficiencies are at a much higher risk of developing a clinically significant disease. Symptoms of active tuberculosis (cough, fever, night sweats, weight loss, etc.) can be moderate for many months. This can lead to patient's delayed referrals to medical facilities for care. Without proper treatment, about 45% of people with tuberculosis and almost all immunocompromised patients with tuberculosis will die. [2, 3].

Tuberculosis is one of the most common infections after kidney transplantation, especially in developing countries with large population. The incidence of tuberculosis in immunocompromised patients 20–74 times exceeds its incidence in the general population. Meantime, the incidence of tuberculosis among kidney transplant recipients, according to different authors, varies widely (from 0.5 to 15%); it is slightly lower among the recipients in highly developed countries than in developing ones [4–7].

The topicality of tuberculosis in transplantation is determined by a number of factors, the main of which is its prevalence. In a prospective analysis of 4388 port-transplant patients in Spain, the incidence of tuberculosis was 512 per 100,000 per year, whereas in the general population it was 19 per 100,000 population per year. These epidemiological data suggest that the incidence of tuberculosis in solid organ recipients is 27 times higher [1].

It is known that the latent infection is often activated after the chronic kidney disease (CKD) progression to the 5th stage and the initiation of renal replacement therapy. The incidence of tuberculosis in individuals receiving treatment with hemodialysis or peritoneal dialysis is significantly higher (ranging from 1 to 6%) than in the general population,

The immunodeficiency state, which is aggravated in immunosuppressive therapy administered after transplantation, contributes to *de novo* infection, including the nosocomial one. Despite the fact that the airborne route of infection from patients with active tuberculosis is quite rare, such infection has a severe course in patients receiving immunosuppression.

Post-transplant patients have another unique source of infection as a result of organ transplantation from an infected donor. The incidence of such infection makes less than 5%. A retrospective cohort study in Spain, which enrolled over 19,000 donors in the period from 1998 to 2011, demonstrated that in case the donor had tuberculosis, the risk of infecting the recipient made 27% [6].

The immune disorders typical for CKD patients and incompletely corrected by a renal replacement therapy, as well as the drug immunosuppression after transplantation, contribute to primary infection with mycobacteria; but more often they cause activation of old foci with the dissemination of the tuberculosis process. Therefore, it is of vital importance to identify the patients with latent tuberculosis and conduct anti-tuberculosis chemotherapy before the development of an active tuberculosis process; and this requires a targeted diagnostic measures as early as at the stage of their inclusion in the “waiting list”. The risk of developing active tuberculosis due to mycobacterial infection increases in post-transplant patients having underlying diseases such as diabetes mellitus, chronic liver disease, and related infectious complications, including CMV infection, pneumocystosis, invasive mycoses.

Mortality in recipients with active tuberculosis is very high and amounts to 20–30%, while the anti-crisis therapy, the use of antithymocyte

antibodies are significant adverse factors activating tuberculosis and increasing the risk of death [5, 8]. The treatment difficulties in this category of patients also lie in their decreased response to therapy, an increased risk of the combination therapy toxic effects, and a high incidence of the drug resistance developing in mycobacteria [9, 10]. This is partly caused by the fact that immunosuppressive drugs of calcineurin inhibitor group (cyclosporine and tacrolimus), being the basic components of many current immunosuppression protocols, and rifampicin, one of the main anti-tuberculosis drugs, have a common pathway of metabolism: through the cytochrome P450 (CYP450) enzyme system. In this regard, rifampicin administered to post-transplant patients leads to an abrupt decrease and instability of calcineurin inhibitor blood levels. This interaction can lead to a dramatic decrease in the serum calcineurin inhibitor concentrations resulting in an increased risk of a graft rejection. Careful monitoring of the calcineurin inhibitor concentrations and timely correction of their dose is required. In anti-tuberculosis therapy, the drug dose corrections are also often necessary in case of a decreased glomerular filtration rate in graft dysfunction. Thus, the treatment of tuberculosis in kidney transplant recipients is a serious problem, and the development of an active process results in a particularly severe course. Here is an interesting clinical case of an atypical course of tuberculosis in a patient after kidney transplantation.

Clinical Case Report

A patient of 50 years old had a previous history of abnormal urinalysis results first noted at the age of 15, and was diagnosed with chronic glomerulonephritis (from patient's words). He made irregular visits to the nephrologist's for follow-up. He noted a deterioration of his condition

in 2011. The increased serum creatinine and arterial hypertension were identified. He was placed on a conservative therapy, but despite this, his renal function progressively deteriorated.

In June 2013, predialysis cadaveric kidney allotransplantation was performed. He had a primary graft function. On post-transplant day 2, his serum creatinine was 0.26 mmol/L. As induction therapy, the patient received basiliximab, 20 mg, on days 0 and 4; methylprednisolone, a total of 1.25 g; cellcept, 2 g per day; cyclosporine, 400 mg per day (0.4 mg per kg of body weight); prednisolone, 30 mg per day. The early postoperative period was uneventful. The cyclosporine concentration at zero time-point ranged from 120–140 ng/mL. From day 7 the patient received a prophylactic antiviral therapy with ganciclovir. The patient was discharged home on day 27 having serum creatinine of 140 μmol/L, hemoglobin 105 mg/L, glomerular filtration rate 56 ml/min, daily proteinuria 0.5 g. During the outpatient follow-up, the graft function remained stable. However, his visits to the clinic for follow-up became irregular from 2015.

The patient noted a deterioration of his condition in September 2017. He had fever up to 39° C, weakness, unproductive cough. He was admitted to a local hospital in his place of residence with the diagnosis of graft acute pyelonephritis, acute respiratory viral infection. A complete blood count (CBC) test results showed the following: hemoglobin 121 g/L, leukocytes 5.3 x 10^9/L, erythrocyte sedimentation rate (ESR) 28 ml/min. At urinalysis: specific gravity 1015, no protein was found, WBCs 4–6 at high power field. Blood biochemistry: urea 16.2 mmol/L, creatinine 188 μmol/L, total protein 53.4 g/L. Ultrasonography of the abdomen and retroperitoneal space revealed the signs of chronic pancreatitis, a cyst in the upper segment of the donor kidney, no dilation of the renal collecting system. The treatment

included antibacterial therapy with Sumamed®, Metrogyl®, and Canephron®, Valtrex®. The patient received the immunosuppressive therapy with cyclosporine 400 mg, mycophenolic acid 1440 mg, prednisone 20 mg. The patient's condition improved, and he was discharged home. Meanwhile, the body temperature decreased, but it did not stabilize at normal range, there were episodes of body temperature elevations to 37.5° C, and a rare unproductive cough persisted.

In October 2017, the patient referred to the nephrologist's at MONICI [Transliterated Russian Abbreviation for Moscow Regional Research and Clinical Institute n.a. M.F.Vladimirskiy] with complaints of weight loss, cough, hyperthermia up to 38° C in evenings, chills. The condition was qualified as bronchopulmonary infection. The immunosuppressive therapy was changed: mycophenolic acid was canceled. The patient was recommended an additional examination in the hospital at the place of residence. Chest x-ray, computed tomography (CT), graft ultrasonography detected no pathology. The prescriptions included: sulperazone, 4 g/day; Valcyte®, 900 mg/day; Biseptol®, 1440 mg/day. The CBC tests showed hemoglobin 117 g/L, leukocytes 4.8 x 10^9/L, ESR 28 mm/h. In urinalysis no protein was detected, the number of WBCs was *2–3 at high power field. Blood biochemistry: urea 17.9 mmol/L, creatinine 185 mmol/L. No radiological signs of pathology were seen in the lungs. The patient was clinically diagnosed with chronic bronchitis with secondary immunodeficiency. A course of antibiotic therapy was prescribed that included Zyvox®, Sulperazon, Biseptol®, Valganciclovir. The patient was discharged home on day 17 having slight improvements. The creatinine at discharge was 187 µmol/L.*

Due to the persistent fever up to 39.5° C, chills, sweating, severe weakness, he was hospitalized in the Transplantation Department. At examination, the patient's condition was qualified as severe, characterized by marked weakness, poor appetite, nausea, shortness of breath on exertion. The skin was of moderate pallor, moist. No peripheral edema was seen. Round-shaped dark eruptions of up to 1 cm in diameter with clear boundaries present on the skin of the chest and abdomen were diagnosed as pityriasis versicolor. Peripheral lymph nodes were intact. A pulmonary percussion sound was noted above the pulmonary fields; hard breathing, scattered wheezing, single dry rales in the basal sections, fine moist bubbling rales in the upper sections were noted at auscultation. There was no dyspnea at rest. Heart tones were muffled, heart rate was 80 beats per minute, blood pressure was 100/60 mm Hg. The abdomen was soft without tenderness, the liver protruded at 2 cm from under the costal arch. The graft in the right iliac region was elastic. Peristalsis was normal. Given the difficulties of a rapid verification of the diagnosis, the patient was administered ex juvantibus complex therapy aimed at suppressing the mixed infection: linezolid, meropenem, ganciclovir, Biseptol®. During therapy, fever persisted max to 39.5° C with chills, severe weakness.

CBC test showed hemoglobin 116 g/L, WBCs 3,3x10^9/L, platelets 407 x10^9/L, lymphocytes 14.1%. At urinalysis, protein was not detected, pH was 5.5, WBCs 1-2 at high power field. Biochemistry showed urea 15 mmol/L, creatinine 150 μmol/L, total protein 61 g/L, albumin 34 g/L. Polymer chain reaction to CMV, EBV, VZV, HSV-1, -2, HHV-6 and -7 DNAs in blood gave negative results. At chest X-ray, lung fields were without focal and diffuse infiltrations.

A contrast-enhanced computed tomography of the chest (Fig 1.), abdominal organs, retroperitoneal space, and pelvis (Fig. 2) demonstrated the enhanced lung pattern in left lung S6 with the visualization of small grouped foci located peribronchially. There were individual consolidation foci of 3 cm in diameter. Other thoracic organs were without abnormalities, the lymph nodes were not enlarged. The graft was located in the right ileal area of the abdominal cavity, there was a focal lesion of 13 mm in diameter in its upper pole, not responding to a contrast enhancement (suggested as a cyst). The liver was enlarged, the spleen was without abnormalities. Uneven thickening of the terminal ileum wall was of note. An intense accumulation of contrast in the mucosa of the abnormal colon segment was seen; a mesentery hypervascularization was also noted at that level. The surrounding fatty tissue was edematous, with a small amount of fluid being visualized. Moreover, the rest of the small intestine had similar sites of wall local abnormalities. Enlarged lymph nodes were visualized along the mesenteric vessels. The organs of the urinary system were without abnormalities. The conclusion read as follows inflammatory bronchiolitis (?), a specific process in the left lung (?), a donor kidney cyst, infection was not excluded, hepatomegaly, distal ileitis.

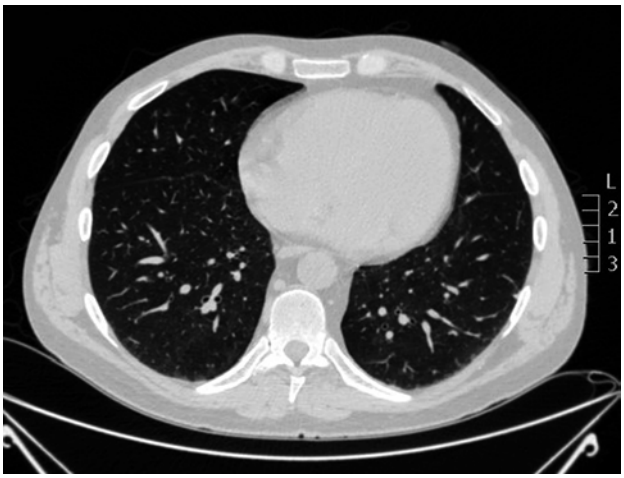

Fig. 1. Computed tomography imaging of thoracic organs

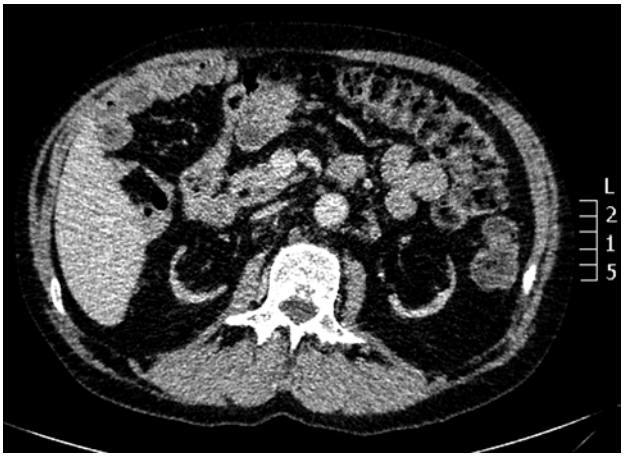

Fig. 2. Computed tomography imaging of abdominal organs

A colonoscopy with a small intestine biopsy was performed. Histological examination of the biopsy specimen demonstrated the fragments of the small intestine mucosa with edema, focal fibrosis, a severe inflammatory infiltration of lamina propria with lymphocytes, plasma cells, with admixture of eosinophils and neutrophils, the presence of numerous epithelioid cell granulomas with multinucleated giant cells of Pirogov-Langhans type, isolated granulomas necrotic by nature with accumulated neutrophils in the center. PAS stain procedure and Ziehl–Neelsen staining detected no fungi or acid-resistant rod forms. The conclusion made was

granulomatous ileitis. The findings were highly suspicious of a tuberculosis process.

The patient was consulted by the phthisiologist who made the conclusion that pulmonary tuberculosis, intestinal tuberculosis could not be excluded. Phthisiologist's recommendations included: isoniazid 0.3 g BID; vitamin B6 30 mg TID; pyrazinamide 1.5 g once a day, ofloxacin 0.4 mg BID, for 2 months.

The therapy was tolerated by the patients satisfactorily. The patient's condition improved, the body temperature returned to normal, the appetite restored. The graft function remained stable. The patient had serum creatinine of 150 μmol/L, hemoglobin 119 g/L, leukocyte count 6.2 × 10^9/L. Further, the patient was followed-up in the local TB dispensary at the place of residence.

Currently, the patient continues receiving the anti-tuberculosis therapy on an outpatient basis. He is regularly seen by the doctor in the Center of K*idney Transplantation at MONICI [Transliterated Russian Abbreviation for Moscow Regional Research and Clinical Institute n.a. M.F.Vladimirskiy]. No exacerbation of the tuberculous process has been noted.*

Discussion

Thus, in the patient, tuberculosis was diagnosed at 5 years after kidney transplantation; the process was generalized and preceded with the damage to the lungs and intestine. Probably, the process resulted from the activation of a latent infection due to secondary immunodeficiency. The treatment success was achieved thanks to an individual comprehensive approach, the undertaken examinations and tests, and a timely initiated therapy.

This case has demonstrated the difficulty in diagnosing tuberculosis infection in post-transplant patients due to atypical clinical signs. The lack of classic x-ray and laboratory signs of the disease may mislead even an experienced phthisiologist unfamiliar with the problem of post-transplant tuberculosis. This requires a multidisciplinary approach combining high alertness and a preventive approach.

Tuberculosis course in renal transplant recipients has peculiar features. In a significant percentage of patients, active tuberculosis occurs in the first year after transplantation or in the long-term postoperative period (even despite a decrease in immunosuppressive load) [11].

Exceptional polymorphism of clinical, laboratory, and instrumental test signs creates great diagnostic difficulties for a clinician. An overwhelming majority of solid organ recipients are hospitalized with suspected pulmonary tuberculosis, but extrapulmonary location of the process has also been noted. Meanwhile, the incidence of generalized tuberculosis in this patient population is extremely high (up to 40% of all those with the disease).

The clinical manifestations of tuberculosis in solid organ transplant recipients can be quite non-specific. One third of the patients are hospitalized for disseminated or extrapulmonary tuberculosis. In addition, pyomyositis, skin ulcers or abscess formation, tenosynovitis or tuberculous lymphadenitis are common. Often, the patients with the later confirmed TB were initially admitted to hospital with a fever of unknown origin. As for the patients after transplantation, clinicians should also be aware of the possibility of isolated tuberculosis lesion in the native non-functioning kidneys. However, a long-term fever resistant to antibiotic therapy, general

weakness, fatigue, weight loss, and night sweats are observed in almost all recipients with most forms of tuberculosis.

Imaging techniques play a major role in the diagnosis of respiratory tuberculosis, but the X-ray diagnosis of active tuberculosis in kidney transplant recipients has its peculiar features. Standard radiography often fails to visualize abnormalities in the lung tissue. In these cases, CT of the chest helps making a correct diagnosis, establishing the location, extent and complications of the tuberculosis process without increasing a radiation exposure. High resolution CT imaging has a high diagnostic value in immunosuppressive patients with pulmonary infections.

Diagnostic difficulties after kidney transplantation are predisposed by several factors: a high percentage of negative microbiology results of sputum and other biological fluids, a low informative value of tuberculin skin tests and anti-tuberculosis antibody assays (even in active tuberculosis), a high rate of false-negative results due to altered immune status, absent typical tuberculous granuloma (due to macrophage dysfunction), a frequent atypical location in the lungs; a frequent combination of tuberculous process with other pathogens causing severe disseminated processes in the lungs (invasive mycoses, severe bacterial pneumonia, viral infections), an ambiguous clinical presentation of the disease. In addition, the chest X-ray data of recipients may be non-typical. For example, focal infiltration, miliary patterns are often found in the recipients whereas the areas of lung tissue destruction, the caverns, being characteristic mainly of the tuberculous process, are quite rare.

The difficulties in diagnosing the tuberculosis in renal transplant recipients require using the modern highly informative diagnostic techniques, the Diaskintest and the quantiferone test being the examples.

These tests possessing a greater informative value than a traditional tuberculin test (due to the development of anergy to tuberculin), could accelerate the identification of tuberculosis.

It is difficult to overestimate the importance of screening for tuberculosis in the kidney transplant candidates placed on the waiting list. Early detection of such candidates and a timely preventive treatment are obviously the best way to prevent active tuberculosis after transplantation. The difficulty in this case lies in the fact that the traditional tuberculin test (Mantoux test) does not allow differentiating between the patients infected with mycobacteria and those vaccinated with BCG. Nevertheless, taking into account the possible consequences of tuberculosis after transplantation, the Russian Guidelines [12, Revision of 2019] recommend giving the preventive treatment against tuberculosis to all recipients with positive Mantoux tests.

Conclusion

Thus, making diagnosis of tuberculosis in renal transplant recipients is associated with certain difficulties; and clinical signs and instrumental results are often ambiguous, which significantly complicates a timely diagnosis. This requires an integrated approach using up-to-date techniques.

References

1. Sulis G., Roggi A., Matteelli A., Raviglione M.C. Tuberculosis: epidemiology and control. *Mediterr J Hematol Infect Dis*. 2014;6(1):e2014070. PMID:25408856 DOI:10.4084/MJHID.2014.070

2. Haley C.A. Treatment of Latent Tuberculosis Infection. *Microbiol Spectr*. 2017;5(2). PMID:28409555 DOI:10.1128/microbiolspec.TNMI7-0039-2016

3. Nagavci B.L., de Gelder R., Martikainen P., et al. Inequalities in tuberculosis mortality: long-term trends in 11 European countries. *Int J Tuberc Lung Dis*. 2016;20(5):574-581. PMID:27084808 DOI:10.5588/ijtld.15.0658

4. Boubaker K., Gargah T., Abderrahim E., et al. Mycobacterium tuberculosis infection following kidney transplantation. *Biomed Re*s *Int.* 2013;2013:347103. PMID:24222903 DOI:10.1155/2013/347103.

5. Muñoz P., Rodríguez C., Bouza E. Mycobacterium tuberculosis infection in recipients of solid organ transplants. *Clin Infect Dis*. 2005;40(4):581-587. PMID:15712081 DOI:10.1086/427692

6. Coll E., Torre-Cisneros J., Calvo R., et al. Incidence of tuberculosis in deceased-organ donors and transmission risk to recipients in Spain. *Transplantation.* 2013;96(2):205-210. PMID:23774810 DOI:10.1097/TP.0b013e3182977adf.

7. Prokopenko E.I., Shcherbakova E.O., Vatazin A.V., et al. Lung infections in renal transplant recipients Data of single-center study. *Nephrology and dialysis*. 2011;13(2):101-111.(In Russian).

8. Krstich M., Vetchinnikova O.N., Astakhov P.V., Zul'karnayev A.B. Urosepsis in patients with chronic kidney disease: risk factors, clinical features and treatment strategy. *Almanac of Clinical Medicine*. 2012;26:28-34. (In Russian).

9.Dorman S.E., Chaisson R.E. From magic bullets back to the magic mountain: the rise of extensively drug-resistant tuberculosis. *Nat Med*. 2007;13(3):295-298. PMID:17342143 DOI:10.1038/nm0307-295

10.Falzon D., Jaramillo E., Schünemann H.J., et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011

update. *Eur Respir J*. 2011;38(3):516-528. PMID:21828024 DOI:10.1183/09031936.00073611

11.Ulubay G., Kupeli E., DuvenciBirben O., et al. A 10-year experience of tuberculosis in solid organ transplant recipients. *Exp Clin Transplant*. 2015;13(Suppl 1):214-218. PMID:25894157

12. Vatazin A.V., Gautier S.V., Moysyuk Ya.G., et al. *Diagnosis, treatment and prevention of infectious complications in patients with a transplanted kidney: clinical guidelines*. Moscow, 2014. Available at: http://nonr.ru/?page_id=3178. (In Russian).

Information about authors

Rusudana O. Kantariya, Cand. Med. Sci., Associate Professor of Transplantology, Nephrology and Artificial Organs Department, Faculty of Medical Postgraduate Education in Moscow Regional Research and Clinical Institute n.a. M.F. Vladimirskiy, ORCID:0000-0003-4388-7759;

Andrey V. Vatazin, Prof., Dr. Med. Sci, Head of the Surgical Department of Kidney Transplantation, Head of Transplantology, Nephrology and Artificial Organs Department, Faculty of Medical Postgraduate Education in Moscow Regional Research and Clinical Institute n.a. M.F. Vladimirskiy, ORCID:0000-0001-8497-0693;

Alexey B. Zul'karnayev, Dr. Med. Sci., Chief Researcher of the Surgical Department of Kidney Transplantation, Moscow Regional Research and Clinical Institute n.a. M.F. Vladimirskiy, ORCID:0000-0001-5405-7887;

Vadim A. Stepanov, Cand. Med. Sci., Senior Researcher of the Surgical Department of Kidney Transplantation, Moscow Regional Research

and Clinical Institute n.a. M.F. Vladimirskiy, ORCID:0000-0002-0881-0599.