Disseminated lung tuberculosis and tuberculosis meningoencephalitis after kidney transplantation

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The epidemiological situation with tuberculosis in Russia continues to be strained. The issues of accurate diagnosis and treatment remain unsolved; these issues are particularly urgent for the patients after solid organ transplantation because of a higher risk of the disease development while on drug immunosuppression. This article has described the clinical case of a patient with a clinical presentation of disseminated pulmonary tuberculosis that emerged in a steroid-resistant rejection. The issues of drug therapy and drug interactions with anti-tuberculosis and immunosuppressive agents have been discussed.

Keywords: tuberculosis in transplantation, case report, drug interactions

CKD, chronic kidney disease

HIV, Human Immunodeficiency Virus

IST, immunosuppressive therapy

MBT, mycobacterium tuberculosis

MSCT, multislice spiral computed tomography

Despite the measures to combat the tuberculosis epidemics, the epidemiological situation in this one of the most socially significant diseases remains extremely tense. In Russia, in 2015, the number of newly reported cases of mycobacterium tuberculosis (MBT) infection, including HIV-infected patients, was 80 per 100 000 population; and the mortality still remains high (11 per 100 000 population). This creates an increased risk for patients after organ transplantation, and they constitute an obvious risk group. According to some data, the risk is 20-50 times higher than in general population, due to the effect of immunosuppressive therapy (IST) on the occurrence or reactivation of the tuberculosis process after surgery [1, 2]. In this regard, the issues of the timely, correct, and accurate diagnosis, prevention, and treatment remain open [3, 4].

Latent tuberculosis is also increasing; its detection in patients with chronic kidney disease (CKD) is difficult both before the kidney transplantation because of the anergy typical for patients on hemodialysis, and after transplantation.

Considering a blurred and atypical pattern of tuberculosis clinical manifestations and specific features of the immune response in persons receiving immunosuppressive drugs, the use of new diagnostic methods and treatment schemes for this disease is of great importance [5]. It is also

worthwhile to note that the current situation becomes specific because of an abruptly increased prevalence of MBT primary resistance to drugs [6, 7].

Emphasizing that the diagnosis and treatment of tuberculosis is difficult in persons who undergone transplantation, we want to present a clinical case report of the tuberculosis infection course in a patient after cadaveric kidney allotransplantation.

Clinical Case Report

Patient G., born in 1983, was hospitalized for kidney transplantation to the Samara Center for Transplantation of Organs and Tissues on July 20, 2014.

From medical history: the patient had suffered from renal pathology since 2 years of age, was treated for the diagnosis of chronic glomerulonephritis without morphological confirmation. It is known that he had a family history of the disease (the patient's brother suffered from the same pathology with the outcome in the end-stage CKD). By 2008, the patent had the outcome in the end-stage CKD. On 25.10.2008, the cadaveric kidney allotransplantation on the left was performed before starting the dialysis. The developed kidney allograft dysfunction resulted in transplantectomy performed on 14.07.2011. From June 2011, the chronic program hemodialysis was resumed. On 20.07.2014 the patient underwent a second surgery, the cadaveric kidney allotransplantation on the right from a deceased donor. After surgery the patient received a three-component IST: tacrolimus of extended release (concentration 10 ng/mL), mycophenolic acid 1440 mg/day, oral methylprednisolone according to the scheme. The postoperative course was complicated by acute steroid-resistant rejection of the renal allograft, which occurred on August 7, 2014. The rejection was

controlled by administering the therapy with antithymocyte immune globulin (Atgam): a total of 6750 mg. While on that therapy, the patient developed pharyngitis from August 18, 2014, that was qualified as of fungal origin.

Nevertheless, by 01.09.2014 the patient had experienced short-term episodes of increased body temperature to 39.2° C. Multislice spiral computed tomography (MSCT) of the lungs showed multiple polymorphic peribronchial foci of pulmonary tissue infiltration with a diameter of 6-8 mm, the pulmonary tissue infiltration of the "frosted glass" type in the core zone (Fig .1). The lymph nodes of the bifurcation and paratracheal groups were enlarged up to 13 mm. Fibrobronchoscopy showed the bronchy being evenly shaped on both sides, slightly deformed, the vascular pattern was more prominent, deformed; there are single enlarged capillaries, moderately pronounced contact bleeding. A microscopic study of sputum for M.tuberculosis gave negative result. Diaskintest was negative. Given the clinical presentation, physical examination, laboratory investigations and instrumental test results, the antibiotic therapy with doripenem 1,500 mg/day and levofloxacin 250 mg/day, intravenously, was administered, in addition to antifungal therapy. Thanks to conducted therapy, the foci resolved for 10 days, but the elevated body temperature persisted.

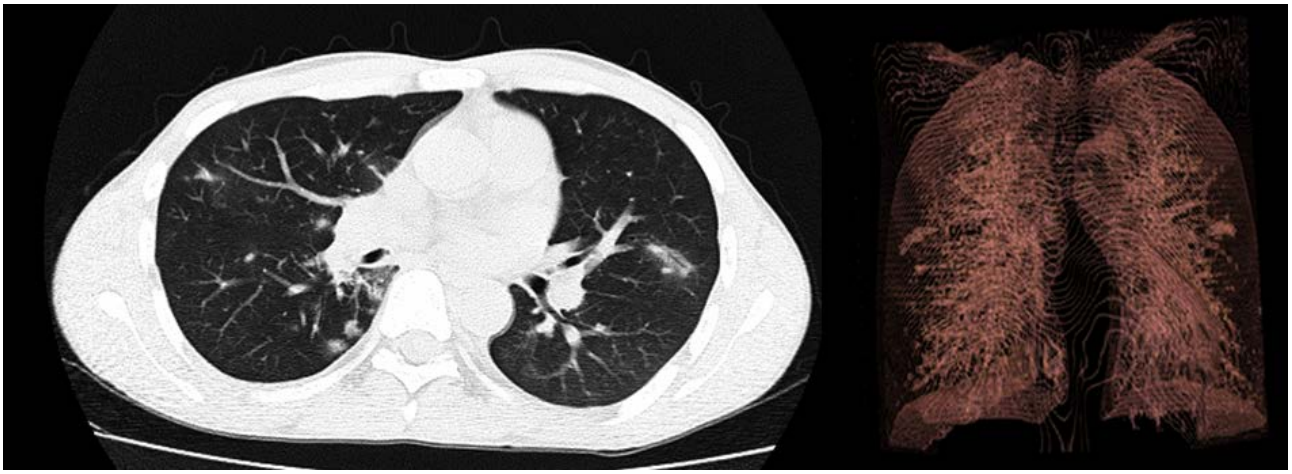

Fig. 1. Multislice spiral CT of the lungs of 01.09.2014 in Patient G.: multiple polymorphic foci of pulmonary tissue infiltration

On 01.09.2014 the patient had stiff neck muscles, a positive (++) test for Kernig's sign on both sides. By 08.09.2014, these phenomena had progressed, being aggravated with a diffuse decrease in the muscle tone of the upper and lower limbs, a peripheral paresis of the VII pair of cranial nerves on the right. The tendon and periosteal reflexes were reduced, S>D. The pathological Babinsky's reflex was identified on the left. The patient responded to painful stimuli on both sides with the limb removal. The cerebrospinal fluid demonstrated cytosis up to 1200 cells/μL, a slight increase in protein to 8.003 g/L, a slight decrease in chloride to 105 mmol/L. The Epstein-Barr virus was found in the CSF by the polymerase chain reaction. On the same day, the patient was examined by a psychiatrist for the persising meningitis signs, emerged delirium associated with a hallucinosis (shaking off non-existent objects), increased anxiety, and rapid exhaustion. Olanzapine was prescribed in a dose of 2.5 mg. As far as the given antibiotic therapy appeared inefficient (i.e. the patient's condition worsened, the

temperature rose to 39.2°C, confused consciousness), Ganciclovir 250 mg/day, and levofloxacin 250 mg/day were added to the treatment.

The patient was repeatedly examined by a consilium of specialists (transplantologists, pulmonologists, infectious disease specialists, phthisiatricians, neurologists, resuscitators). There was a debate about the etiology of the infectious disease. The consultant-phthisiatrist strongly denied the possibility of a tuberculous etiology of the condition as the diaskintest results were negative, and there were no positive cultures of for MBT. The neurologist insisted on the EBV etiology of meningitis, despite the literature data on an extremely rare (2 cases in the world) development of Epstein-Barr virus meningoencephalitis in adults. The therapy for the infectious process was performed ex juvantibus, without a clear idea of its etiology.

While on levofloxacin therapy in a dose of 250 mg/day, a decrease in cytosis to 13 cells/μL was noted. The repeated thoracic MSCT showed positive X-ray changes in the form of partial resolution of small-focal dissemination in the upper parts of the lungs seen in a series of MSCT images, and infiltration sites appeared in the lower-basal parts of the lungs, mainly on the right, with a triangular-shaped site with the base facing the pleura (Fig. 2). Thus, there was a positive dynamics in the patient receiving fluoroquinolone therapy. That again caused a debate on a probable tuberculosis etiology of the lung and brain damage.

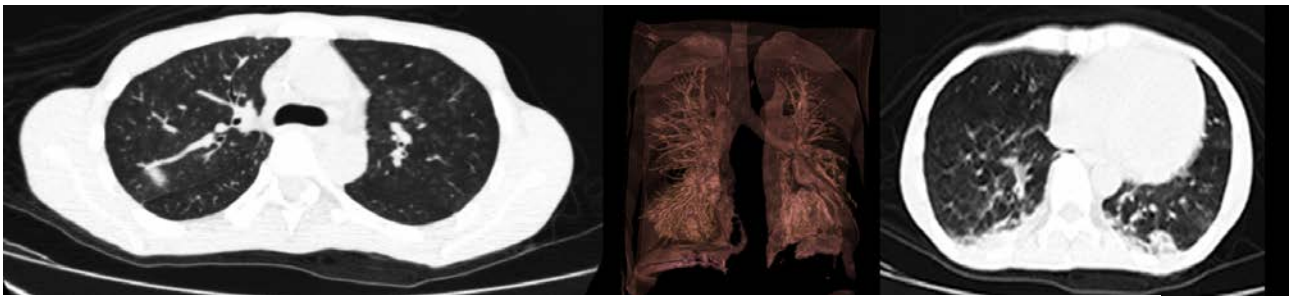

Fig. 2. Multislice spiral CT of the lungs of 09.10.2014 in patient G.: some of the foci became more dense, some others resorbed; the emerging pneumonia can be visualized in the lower-posterior segments of the lungs

The consilium of specialists was inclined to conclude that the course of disseminated MBT-negative pulmonary tuberculosis complicated by acute tuberculous meningoencephalitis could not be excluded in the patient. The reversion of focal changes in the lungs could have been explained by the administered levofloxacin therapy that produced an antimycobacterial effect. No abnormalities in the diaskintest were explained by the IST administered to the patient. No positive MBT cultures were explained by the absence of destructive changes. A presumptive anti-tuberculosis therapy was administered according to the following scheme: levofloxacin 500 mg/day, rifampicin 300 mg x 3 times/day, pyrazinamide 500 mg, 2 times a day, ethambutol 400 mg, 2 times a day, isoniazid 10%, 5 ml, and amphotericin b 50 mg/day, Ganciclovir 250 mg/day, 2 times. The patient received that treatment from 10.10.2014 to 30.10.2014. On the 2nd day of the prescribed therapy, a marked clinical effect was noted: the psychoneurological symptoms were stabilized the body temperature lowered to subfebrile values. No complications of anti-tuberculosis therapy were noted. The developed drug interaction of rifampicin and tacrolimus (as cytochrome

P450 inducers) required the correction of tacrolimus concentration. With the ongoing anti-tuberculosis therapy in combination with Ganciclovir, and sulperazone, a complete resolution of clinical and radiologic symptoms was achieved within a month, the body temperature and clinico-laboratory parameters returned to normal values. The neurologic status completely recovered, but the patient had residual abnormality of neurosensory hearing loss (Fig. 3). At 3 months from the onset of the disease clinical manifestations, the growth of MBT resistant to rifampicin and isoniazid was noted in the bronchoalveolar lavage culture on solid culture media. That finding verified the diagnosis of tuberculosis and confirmed that the chosen treatment tactics was correct.

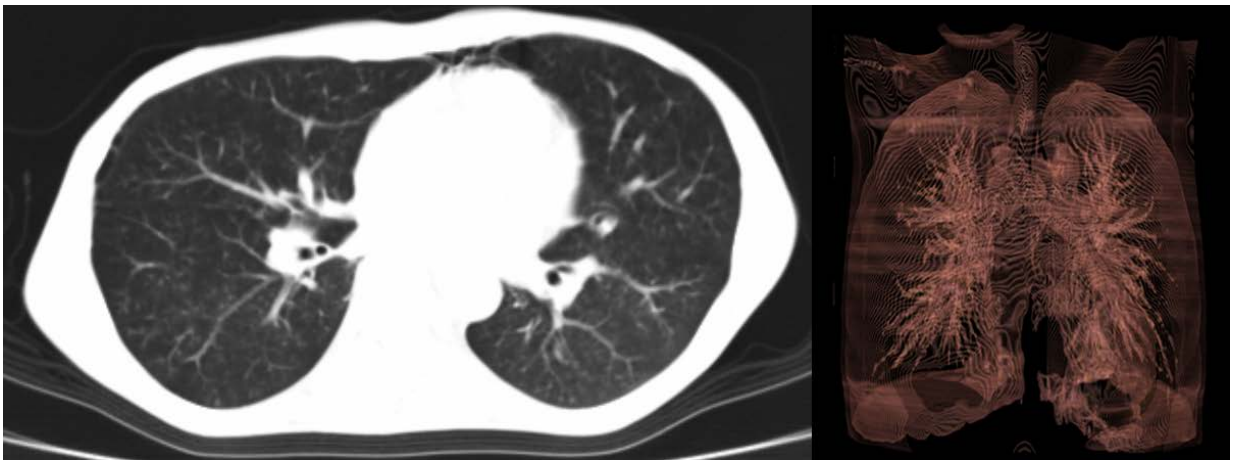

Fig. 3. Multislice spiral CT of the lungs of 29.10.2014 in patient G.: the foci have completely resolved; there is no pneumonic infiltration

Discussion

The case has demonstrated the difficulty in diagnosing tuberculosis infection in patients being on the IST after transplantation, as the clinical signs seem atypical. The diagnosis of tuberculosis in a patient after transplantation is complicated, unobvious, and controversial. The IST performed in these patients sometimes creates a morphological phenomenon

of "tuberculosis without tuberculosis" where the tissue mycobacterial infiltration appears present, but the classical small foci do not have enough time to be formed [8, 9]. This leads to absent classic radiographic and laboratory signs of the disease, which can be misleading even for an experienced phthisiatrician who, however, is not familiar with the problem of posttransplantation tuberculosis. This requires a special approach from the TB services, which would combine a high vigilance, a preventive approach, deep knowledge of the pharmacodynamics and pharmacokinetics of immunosuppressive drugs and their drug interactions with anti-tuberculosis medications. The complex anti-tuberculosis, antimycotic, antiviral therapy administered ex juvantibus, considering a high suspicion and taking into account the pharmacokinetics and pharmacodynamics of immunosuppressive drugs, provided positive dynamics in our case and allowed the patient's salvage earlier than came the opportunity to unambiguously diagnose the pathogen.

Conclusion

The presented clinical case report suggests the necessity of a special approach to the diagnosis of posttransplantation tuberculosis. There is no sense of waiting for the typical clinical signs of the disease in such patients. We should rather speak about the specific pathogenesis of posttransplantation tuberculosis, which causes atypical manifestations and demands other approaches to the diagnosis and treatment. Doctors involved in the identification of post-transplant tuberculosis should have additional knowledge in this matter. A more bold approach to the diagnosis and a broader administration of ex juvantibus therapy may be justified in treating this patient population.

Conflict of interests. Authors declare no conflict of interest.

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