https://doi.org/10.23873/2074-0506-2024-16-2-197-208

Clinical case of disseminated histoplasmosis in a kidney graft recipient

G.P. Titova[1], N.V. Shmarina✉[1,2], K.E. Lazareva[1,3], G.A. Nefedova[1], I.V. Dmitriev[1,2], A.G. Balkarov[1,2,4]

[1]N.V. Sklifosovsky Research Institute for Emergency Medicine, 3 Bolshaya Sukharevskaya Sq., Moscow 129090 Russia;

[2]Department of Transplantology and Artificial Organs, N.I. Pirogov Russian National Research Medical University, 1 Ostrovityanov St., Moscow 117997 Russia;

[3]Department of Transplantology and Artificial Organs of the Scientific and Educational Institute "N.A. Semashko Higher School of Clinical Medicine", Russian University of Medicine, 4 Dolgorukovskaya St., Moscow 127006 Russia;

[4]Research Institute for Healthcare Organization and Medical Management, 30 Bolshaya Tatarskaya St., Moscow 115184 Russia

✉Corresponding author: Nonna V. Shmarina, Cand. Sci. (Med.), Senior Researcher, Surgeon, the Department of Kidney and Pancreas Transplantation, N.V. Sklifosovsky Research Institute for Emergency Medicine, Associate Professor of the Department of Transplantology and Artificial Organs, N.I. Pirogov Russian National Research Medical University, shmarinanv@sklif.mos.ru

Abstract

Introduction. *Histoplasmosis is not an endemic form of fungal infection in Russia; its sporadic cases are mainly associated with the import of the fungus from endemic countries. We consider it necessary to demonstrate a rare case of the disseminated histoplasmosis development in a kidney transplant recipient.*

Objective. *Demonstration of a case of the disseminated histoplasmosis development in a kidney transplant recipient.*

Results. *The clinical manifestations of the disease were described; the affected organs were macroscopically and histologically studied, which made it possible to diagnose disseminated histoplasmosis.*

Conclusions. *This case prompts being on alert to potential occurrence of fungal infections, including non-endemic ones, in patients receiving immunosuppressive therapy.*

Keywords: histoplasmosis, kidney transplantation, fungal infections in kidney graft recipients

Conflict of interest The authors declare no conflict of interest

Funding The study was conducted without sponsorship

For citation: Titova GP, Shmarina NV, Lazareva KE, Nefedova GA, Dmitriev IV, Balkarov A.G. Clinical case of disseminated histoplasmosis in a kidney graft recipient. *Transplantologiya. The Russian Journal of Transplantation.* 2024;16(2):197–208. (In Russ.). https://doi.org/10.23873/2074-0506-2024-16-2-197-208

BMI, body mass index
CKD, chronic kidney disease
ECM, electrocardiomonitor
GFR, glomerular filtration rate
HIV, human immunodeficiency virus
ICU, Intensive Care Unit
IST, immunosuppressive therapy
PCR, polymerase chain reaction
RAG, renal allograft
RRT, renal replacement therapy

Introduction

Histoplasmosis is one of the most endemic mycoses in the regions of North, Central and South America, and has also been reported in parts of Asia and Africa [1]. For Europe, this type of fungal infection is not endemic, but this disease can be observed all over the world, and a number of authors do not recommend overlooking it in patients with

unexplained pulmonary or systemic diseases [2]. As a result of climate change and changes in anthropogenic land use, the conditions suitable for the dimorphic fungus Histoplasma capsulatum change, leading to corresponding changes in epidemiology [3]. With the increasing number of travelers and immunocompromised patients, histoplasmosis caused by this species has become a nationwide disease in America [4]. More than 500 thousand cases of infected with histoplasmosis people are registered annually [2, 5]. In vivo Histoplasma capsulatum lives in moist soil enriched with plant or animal remains. The disease occurs with inhalation of soil dust containing fragments of mycelium or conidia, which, upon entering the lungs, turn into the tissue form of the fungus after 5–7 days [6]. The clinical manifestations of histoplasmosis are varied and may resemble other common diseases such as community-acquired pneumonia, tuberculosis, sarcoidosis, Crohn's disease, or malignancies [3, 7]. Most often, histoplasmosis occurs in the form of acute respiratory infection with symptoms of fever, headache, cough, and chest pain, which occur 1 to 3 weeks after infection and spontaneously regress in people with normal immunity. The disseminated form of histoplasmosis is rare and occurs in immunocompromised individuals [8]. Progressive disseminated histoplasmosis is characterized by the generalized involvement of the reticuloendothelial system, with hepatosplenomegaly, lymphadenopathy, bone marrow involvement, and sometimes ulceration in the oral cavity or gastrointestinal tract. Its course is usually subacute or chronic with vague, often subtle signs [9]. The risk of histoplasmosis is highest in patients with HIV infection, especially in patients with a CD 4+ count <200 cells/μL [10]. Thus, in Africa, HIV-infected patients accounted for 38% of histoplasmosis cases [11]. Progressive disseminated histoplasmosis is a life-threatening disease and is an opportunistic infection. This disease is often underdiagnosed and

misdiagnosed as cancer or tuberculosis, with fatal consequences. In 2017, the World Health Organization noted that disseminated histoplasmosis is a significant cause of mortality among patients with acquired immunodeficiency syndrome. In recent years, an increase in the incidence of this disease has been noted in North and South America, the Caribbean, Southeast Asia and Latin America [12], as well as Africa [13]. For Russia, histoplasmosis is not endemic, but an extremely rare disease and its diagnosis is mainly made using microscopy, rather than testing for antigens and PCR that are not common. However, one should remember that in immunocompromised patients, infection due to Histoplasma may occur.

The objective was to demonstrate a case of the disseminated histoplasmosis development in a kidney recipient.

Case Report

Patient V., 36 years old, with a known clinical diagnosis of “type 1 diabetes mellitus, the target level of HbA1c was < 7.0%, unsatisfactory glycemic control. Diabetic microangiopathy: diabetic nephropathy, chronic kidney disease C5D, renal replacement therapy with program hemodialysis since 2017; proliferative retinopathy (laser coagulation). Diabetic neuropathy: distal form – sensorimotor, autonomic form – gastrointestinal, cardiovascular. Neuroischemic form of diabetic foot syndrome. Nephrogenic anemia. Secondary arterial hypertension. Bone tissue mineral disorders in a chronic kidney disease: Secondary hyperparathyroidism”. In June 2021, she was admitted at N.V. Sklifosovsky Research Institute for Emergency Medicine for kidney transplantation.

From *the medical history* it was known that type 1 diabetes mellitus had been diagnosed at the age of three, at which time insulin replacement therapy was immediately started in the basal-bolus mode. The patient was

followed-up by an endocrinologist at the local outpatient medical facility; glycemic parameters were unstable, ranging from 6 to 24 mmol/L, the glycated hemoglobin level was high, Hb1Ac 12%. In the year of 2000, proteinuria, an increase in blood creatinine levels above reference values, a decrease in glomerular filtration rate (GFR) were detected and diabetic nephropathy was diagnosed. Since 2011, progressive diabetic retinopathy was diagnosed, and therefore, laser coagulation of the retina was repeatedly performed. Since 2014, the appearance and progression of arterial hypertension had been noted (maximum blood pressure readings were 210/110 mm Hg). In dynamics, by 2017, the progression of chronic renal failure to the terminal stage had been noted, and renal replacement therapy with program hemodialysis was started. In February 2021, the patient referred to the N.V. Sklifosovsky Research Institute for Emergency Medicine; indications for kidney transplantation were determined, and the patient was placed on the waiting list for kidney transplantation at the N.V. Sklifosovsky Research Institute for Emergency Medicine.

Kidney transplantation

With a renal allograft (RAG) compatible for blood group and HLA antigens being available, on June 24, 2021, a kidney allotransplantation from a posthumous donor was performed into the right iliac region using a standard surgical technique. The total surgery duration was 2 hours 45 minutes. Cold ischemia time for the graft did not exceed 14 hours. It was known that the posthumous donor was a 41-year-old man diagnosed with "Acute cerebrovascular accident of the hemorrhagic type. Brain death." According to the organ passport data, the quality of the kidney graft was regarded as standard. There were 5 HLA system mismatches for the donor-recipient pair.

To prevent a graft rejection, the patient received induction immunosuppressive therapy in the following amount: methylprednisolone 500 mg intravenously intraoperatively, later on, 250 mg intravenously on the first and second postoperative days; basiliximab 20 mg as intravenous drop infusion intraoperatively and on the 4th postoperative day and also a maintenance triple immunosuppressive therapy (IST): tacrolimus of extending release, mycophenolic acid, and methylprednisolone. To prevent infectious complications, ceftriaxone was administered at a dose of 2000 mg intravenously once daily for 7 days from the date of surgery. Insulin therapy was adjusted. In order to prevent thrombotic complications, anticoagulant therapy given in the amount of heparin 10,000 units for 24 hours through an infusion pump; on the 11th postoperative day, a switch from heparin to subcutaneous administration of low molecular weight heparin was performed.

Peculiarities of the hospital treatment stage

No immediate function of the kidney graft was seen, and that required a renal replacement therapy with program hemodialysis (No. 9). Diuresis had been restored on the 25th postoperative day, the graft nitrogen excretory function was observed on the 42nd day - serum creatinine decreased to 135 μmol/L. The early postoperative period was complicated by the development of a surgical complication: on the 26th post-transplant day (5 days after suture removal), failure of the postoperative suture was noted. Daily dressings with levomekol ointment and chymotrypsin did not show any effect, for which reason, starting from the 34th day from the moment of surgery and on the 8th day from the start of wound treatment, they began to use a system of prolonged vacuum aspiration. Based on the results of a bacteriological examination of the wound discharge, the growth *of Staphylococcus aureus* and

Klebsiella pneumonia was detected, and an etiotropic antibacterial therapy was started: amoxicillin 875 mg + clavulanic acid 125 mg intravenously twice a day. After 20 days of prolonged vacuum aspiration (54th day after transplantation), positive changes were noted: the wound was cleaned, no swelling or hyperemia was observed, and fresh granulations were noted in the wound. During a control bacteriological examination of the postoperative wound, no microbial growth was detected. On the 58th day after kidney transplantation, the patient refused further in-hospital treatment and was discharged to be followed-up by a nephrologist at the Moscow City Nephrology Center, and by a surgeon and endocrinologist at her local medical facility. Upon discharge from the hospital, no findings of the infectious process were seen in the laboratory and instrumental diagnostic test results; the graft function was relatively satisfactory (blood creatinine was 169 μmol/L, urea was 19 mmol/L). In order to prevent *Pneumocystis pneumonia* and cytomegalovirus infection, the patient continued to receive prophylactic doses of cotrimoxazole and valganciclovir.

Readmission

On the 74th day after transplantation (16 days after discharge from hospital), the patient noted a deterioration in her condition in the form of decreased daily diuresis to 600–800 ml, and an increased body temperature to 38°C. For 2 days the patient did not contact the doctors, but on the 3rd day she noted the appearance of back pain, increased general weakness and self-referred to the N.V. Sklifosovsky Research Institute for Emergency Medicine. With the above mentioned complaints and for the suspicion of acute RAG dysfunction, she was hospitalized at the Kidney and Pancreas Transplantation Department.

Upon admission she displayed severe peripheral edema of the lower extremities, decrease in daily diuresis to 100 mL/day. There was a wound of 20x5 cm in size persisting in the right iliac region, with the signs of slow granulation and a slight fibrin deposit and scanty serous discharge; the bottom of the wound was the aponeurosis of the external oblique abdominal muscle. There was a wound of 0.5 cm in diameter in the hypogastrium on the left with fibrin deposits and a moderate amount of purulent discharge with an infiltrate around the wound up to 5 cm in diameter, the skin over it being moderately swollen, slightly hyperemic. The wounds were treated with aqueous solutions of antiseptics and levomekol ointment.

The results of the blood tests showed that anemia persisted (hemoglobin 83 g/L, hematocrit 24%, red blood cells 2.79×10^{12}/L), leukopenia (1.5×10^{9}/L), hyponatremia (117 mmol/L), hypoproteinemia (55.7 g/L), increased levels of lactate (3.4 mmol/L), glucose (15.8 mmol/L), nitrogenous wastes (blood creatinine 268.5 μmol/L, blood urea 32.96 mmol/L), metabolic acidosis (ABE 13.4 mmol/L). According to chest X-ray, multiple foci and infiltrates of moderate intensity were identified, merging to each other (Fig. 1).

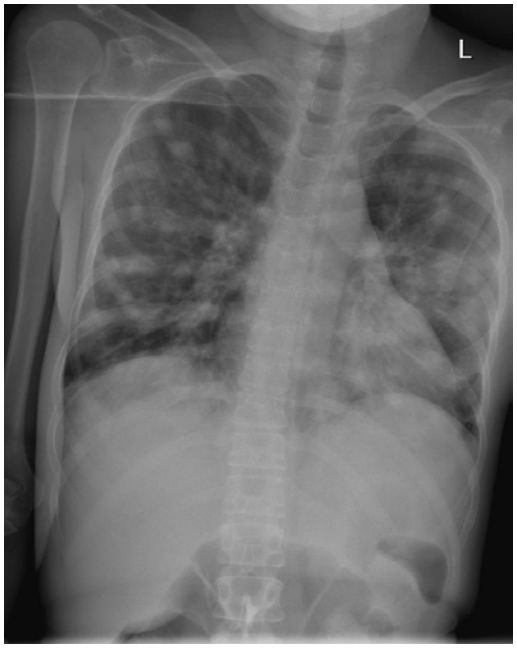

Fig. 1. Chest X-ray. Multiple foci and infiltrates of moderate intensity merging together

During the first 3 hours from the moment of hospitalization (from 19:40), the patient's condition progressively worsened and at 22:45, in a stuporous state, she was transferred to the Intensive Care Unit (ICU), where, due to her condition severity manifested by an acute depression of consciousness (stupor) and breathing, she was placed of mechanical ventilation. Upon admission to the ICU, unstable hemodynamics with the rapid development of arterial hypotension were noted requiring the administration of vasopressors and inotropes; the increases in lactate (7 mmol/L), hyperglycemia (20.8 mmol/L), and acidosis (ABE 19 mmol/L) were recorded.

An ultrasound examination of the abdominal organs and RAG revealed diffuse changes in the liver, prompted the inability to exclude the presence of free gas in the abdominal cavity, diffuse changes in the RAG parenchyma, and high resistivity indices in the arcuate and segmental arteries.

One and a half hours after admission to the ICU, an acute deterioration of patient's condition was noted: asystole and areflexia were noted on the electrocardiomonitor (ECM). Life Support measures undertaken for 17 minutes produced a positive effect: the heart rhythm was restored. After 2 hours, the condition worsened again: there was bradycardia, turning into asystole on the ECM; the Life Support measures were carried out in full for 30 minutes without effect, the patient was declared biologically dead.

Post-mortem (preliminary) diagnosis

Principal diagnosis: "Type 1 diabetes mellitus, target HbA1c < 7.0%, unsatisfactory glycemic control. Kidney allotransplantation (left) to the right from a posthumous donor." Pharmacological immunosuppression.

Complications of the underlying disease: Diabetic microangiopathy: diabetic nephropathy, chronic kidney disease C5D, renal replacement therapy with program hemodialysis since 2017. Acute kidney graft dysfunction. Slow-granulating postoperative wound of the right iliac region. Proliferative diabetic retinopathy. Diabetic neuropathy: distal form - sensorimotor, autonomic form - gastrointestinal, cardiovascular. Neuroischemic form of diabetic foot syndrome. Nephrogenic anemia. Leukopenia. Secondary arterial hypertension. Mineral-and-bone disorders in chronic kidney disease: Secondary hyperparathyroidism. Bilateral polysegmental pneumonia. Sepsis. Multiple organ failure syndrome. Life support resuscitation measures.

Concomitant conditions: Abscessing furuncle of the anterior abdominal wall.

From the autopsy pathologist's report

In the right iliac region, a defect of the skin and subcutaneous fat (surgical incision) measuring 14x6 cm and a depth of 1.2 cm with diastasis of the wound edges was noted; the wound edges were smooth, pink in color with isolated whitish overlays, the bottom of the defect was aponeurosis. In the left inguinal area, an infiltrate with abscess formation and purulent contents in the lumen was noted (Fig. 2).

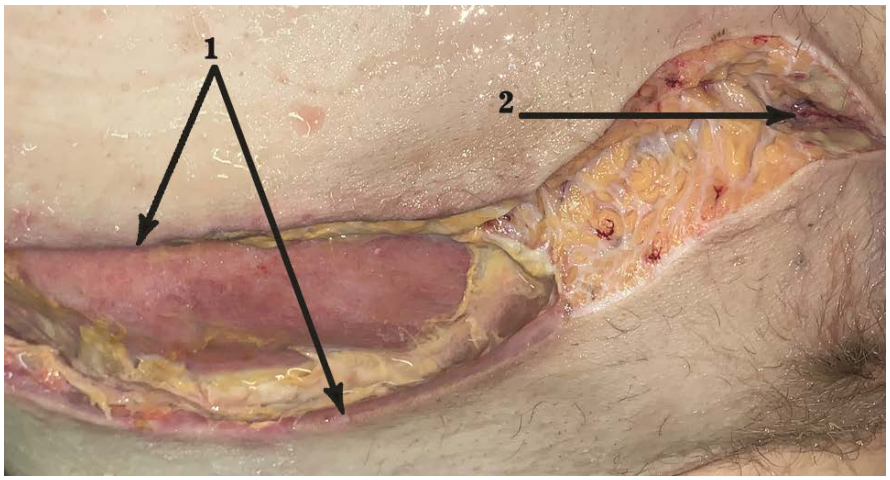

Fig. 2. Postoperative wound. Diastasis of the wound edges (1), abscess of the subcutaneous fatty tissue in the left inguinal area (2)

When opening the chest cavity, no fluid or adhesions were noted in the pleural cavities, the lungs were completely filled the pleural cavities, the right lung measured 25x12x7 cm, the left lung was 25x16x10 cm, weighing 600 g and 500 g, respectively; on section, it had a pasty consistency, dark red color, with multiple dense, whitish infiltrates, located both subpleurally and in the thickness of the parenchyma, without clear boundaries, ranging in size from 0.7 cm in diameter to dimension of 3x2x1.5 cm (Fig. 3). Foaming dark-red liquid was noted on the surface of the cuts.

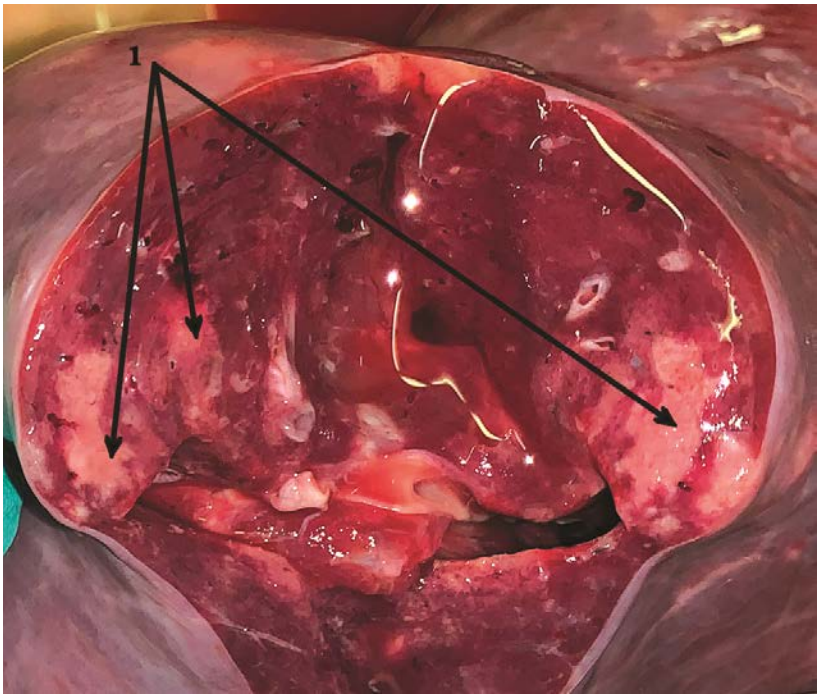

Fig. 3. Lung tissue inflammatory infiltrates of various dimensions (1)

In the retroperitoneal tissue in the projection of the right iliac region there was a RAG measuring 12x6x5 cm, weighing 135 g, with a thin capsule, smooth shiny surface of gray-red color, in section with bluish-burgundy pyramids and pale bark. The calyces and pelvis were not dilated, their mucosa was smooth, shiny; a 10 cm long ureter was freely passable, the formed neoureterocystoanastomosis was competent and quite patent. The paravesical and paraurethral fatty tissue was dull in appearance, with the foci of greenish staining; the perinephric fatty tissue was moderately developed, with a yellow lobular appearance in the section (Fig. 4).

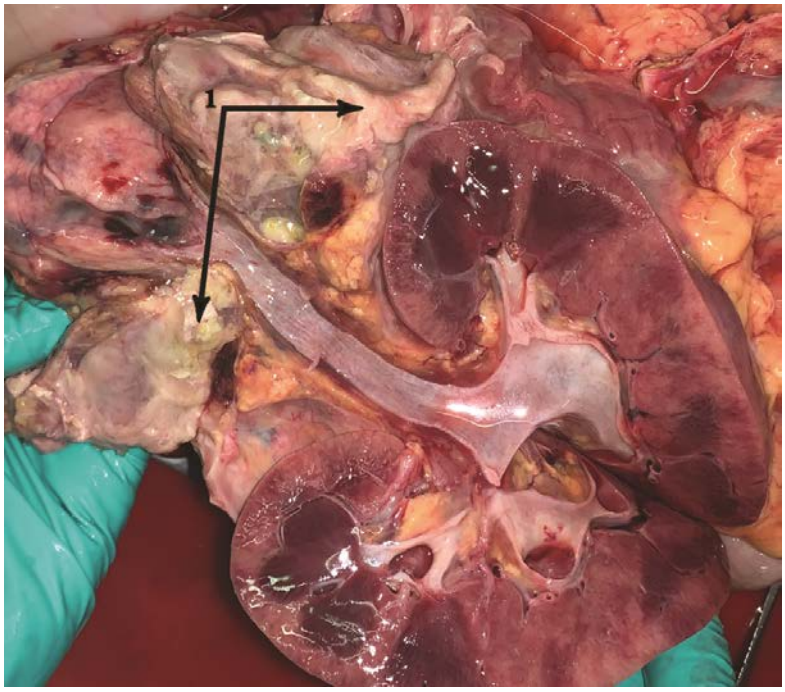

Fig. 4. Kidney allograft in section. Suppuration and necrosis of paravesical tissue in the area of neoureterocystoanastomosis (1)

There were end-to-side competent anastomoses between the right external iliac artery and the aortic platform of RAG and between the right external iliac vein and the RAG vein.

Histological examination

For histological and histochemical examination of organ tissues, the material was fixed in 4% neutral formalin, embedded in paraffin; histological sections were stained with hematoxylin and eosin, and the PAS reaction was done. Microphotography was performed a Leica EC 3 digital camera.

Histologically, in the lung tissue in the area of the above-described infiltrates, there were areas of inflammatory-necrotic changes of different scale with preserved alveoli contours with necrotic alveolar septa, with an inflammatory infiltrate of mononuclear cells, histiocytes, alveolocytes in the alveoli lumen, with diffuse and large-foci fungal infiltration with

clearly distinguishable fungal conidia at PAS reaction, with fungal invasion of alveolar septa, walls of blood vessels, with the presence of free-lying fungal bodies in the lumen of vessels with secondary wall and occlusive thrombi (Fig. 5 A–D).

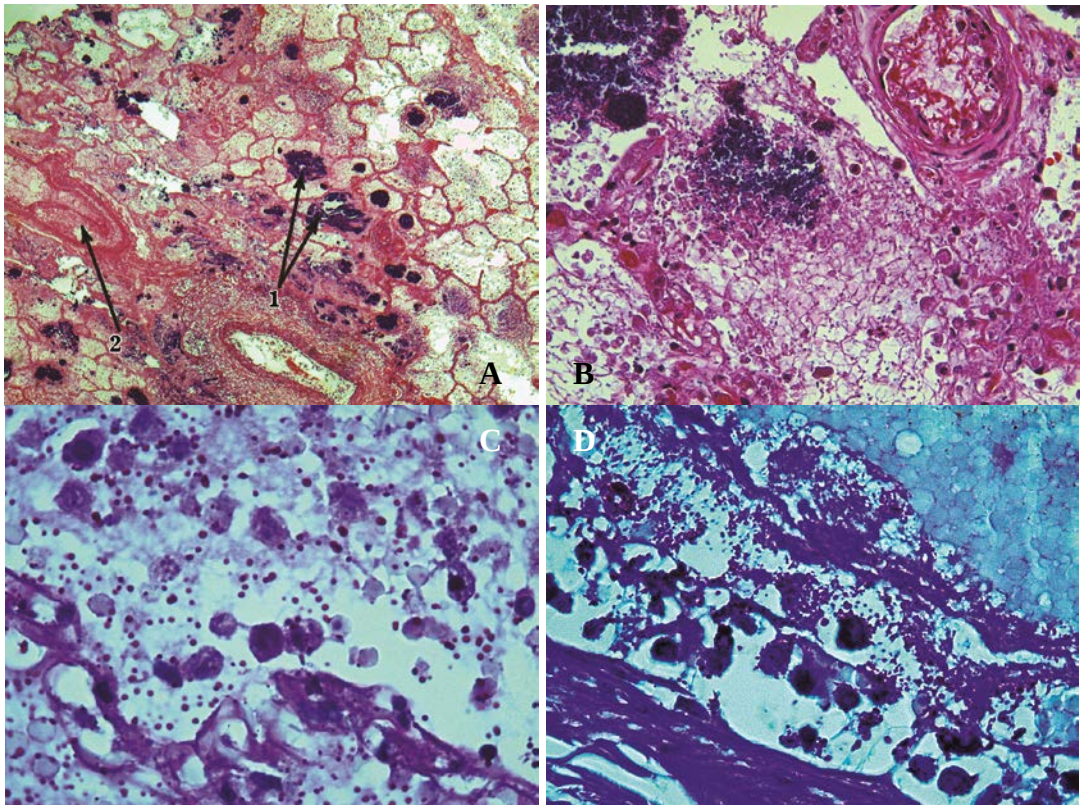

Fig. 5. Abnormal lung findings. A. Large-foci fungal clusters (1), thrombus in the pulmonary artery lumen (2); hematoxylin and eosin staining (x200). B. Large-foci fungal clusters; hematoxylin and eosin staining (x400). C. Large fungal colonies and single fungi (Histoplasma capsulatum) in the alveoli lumen; PAS staining, x1000). D. Fungal spore collections in the pulmonary artery wall and lumen; PAS staining, (x1000)

There was no reactive inflammatory infiltration in the transition zones of necrobiotic and viable areas of the lungs, but the fungal invasion of the tissues of these zones persisted.

Histologically, in the subcutaneous fatty tissue of the surgical wound edges, subcutaneous infiltrate of the iliac region, retroperitoneal paravesical tissue, there were large-scale necrotic changes of adipose tissue with lymphocytic-histiocytic inflammatory infiltration with diffuse clearly distinguishable fungal invasion with large colonies of fungi, full-blooded capillaries with the presence of fungal emboli in the lumen of arteries and veins (Fig. 6).

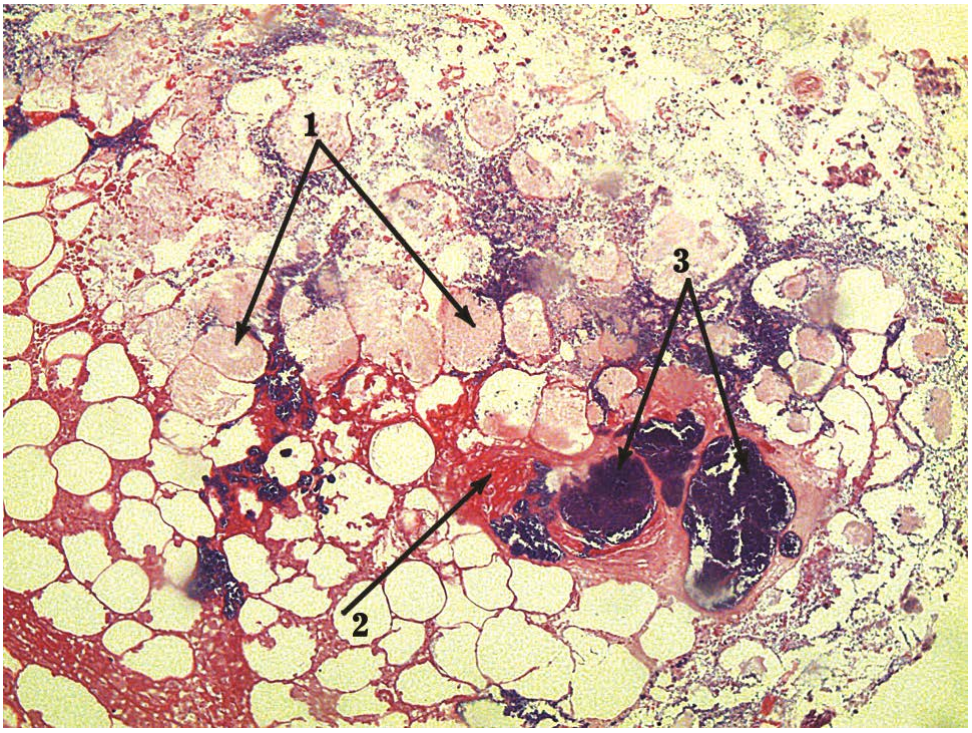

Fig. 6. Fatty tissue necrosis (1), focal hemorrhages (2), clusters of Histoplasma capsulatum colonies (3). Hematoxylin and eosin staining (x200)

Histologically, in RAG there were revealed signs of acute congestion in the glomerular capillaries and intertubular vessels, lumen dilation of the proximal tubules with hydropic changes of the nephrocytic cytoplasm, disruption of the brush border integrity, the presence of fungal conidia in the cytoplasm of the epithelium cells and in the lumen of the tubules (Fig. 7).

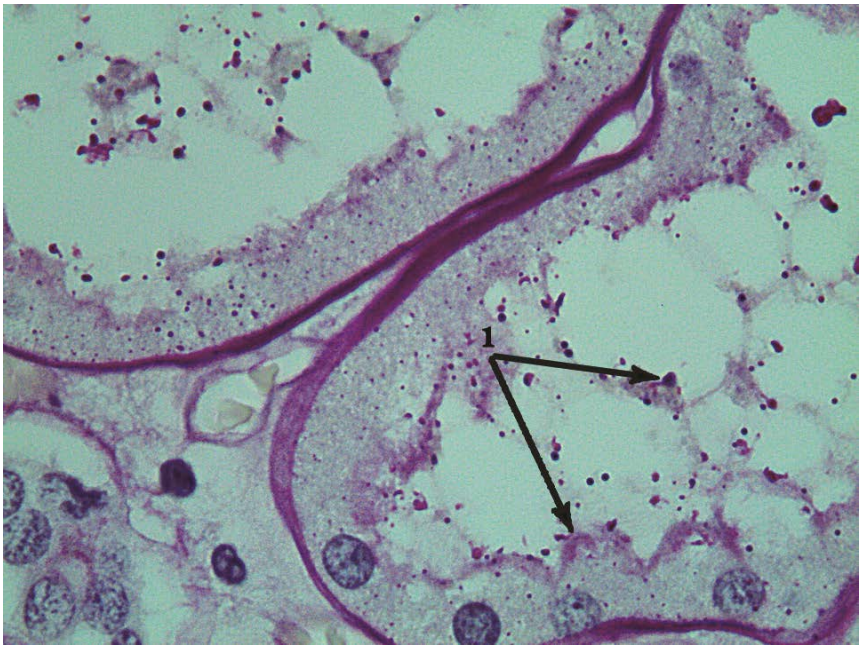

Fig. 7. Histoplasma capsulatum microspores in the cytoplasm of nephrocytes and in the lumen of the renal allograft proximal tubules (1); PAS staining (x1000)

In the medulla, there were large-foci lymphohistiocytic infiltrates with the presence of fungal conidia between the cells of the inflammatory infiltrate and intracellularly.

Diagnosis by pathologist

The final pathologist-made diagnosis formulated after histological and histochemical examination was as follows: Diabetes mellitus type 1, insulin-dependent, severe, unsatisfactory glycemic control: hyperglycemia (blood glucose level 23 mmol/L), stage III diabetic retinopathy with the previous history of laser coagulation therapy, polyneuropathy, angiopathy, the previous history of diabetic foot, neuroischemic form. Severe fibrosis, hyalinosis and atrophy of the insular system and pancreatic tissue; severe microangiopathy with diabetic nephrosclerosis (kidney weight 55 g), end-stage renal disease (GFR <15 ml/min/1.73 m^2, CKD: stage 5), replacement therapy with program hemodialysis since 2017.

Surgical interventions: “Kidney allotransplantation (left) to the right from a posthumous donor” dated June 24, 2021.

Complications of the underlying disease: Progressive disseminated histoplasmosis (*Histoplasma capsulatum*) against the background of immunosuppressive therapy with ext. release tacrolimus, mycophenolic acid, methylprednisolone, basiliximab; diffuse focal fungal necrotizing pneumonia; inflammatory-necrotic infiltrates in the kidneys with fungal dissemination into the epithelium of the graft proximal tubules, in the adipose tissue of the perivesical and paraureteral tissue, subcutaneous fatty tissue of the surgical wound edges, and the left inguinal area with abscess formation. Sepsis. Acute nephrograft dysfunction. Acute renal failure: oligoanuria, hyperazotemia (creatinine 268.5 μmol/L, urea 32.9 mmol/L). Swelling and dislocation of the brain. Suppuration of a postoperative wound. Cachexia: BMI 16.8 kg/m^2.

Surgical intervention: “Placement of the system of prolonged vacuum aspiration of the wound.”

Conclusion. The death of patient V., 36 years old, after kidney transplantation for stage 5 CKD in the outcome of diabetic nephropathy as a complication of type 1 diabetes mellitus with predominant kidney damage occurred from disseminated histoplasmosis with predominant lung damage and progressive cardiopulmonary failure.

Discussion

Kidney transplantation in patients with diabetic nephropathy presents significant difficulties due to severe comorbid pathology due to abnormal changes in many organs and systems. Even at the end of the 20th century, diabetes mellitus was a contraindication to kidney transplantation due to a high risk of infectious complications and increased mortality from cardiovascular complications. Currently, kidney

allotransplantation is an effective treatment for patients with end-stage diabetic nephropathy, since the survival rate of these patients after transplantation is significantly higher compared to the survival rate of patients receiving dialysis RRT treatments.

The initially aggravated somatic condition of patients with stage 5 CKD in the outcome of diabetic nephropathy, which is caused by metabolic disorders and associated micro- and macrovascular complications, a high risk of surgical intervention, and the use of IST contribute to the development of infectious complications and an aggravation of carbohydrate metabolism decompensation after transplantation, which is rather difficult to be corrected in this time period due to the multifactorial nature of adverse effects; all this complicates recovery in the postoperative period. This Case Report has demonstrated a rare unpredictable infectious complication of the postoperative period.

Considering the location of Histoplasma capsulatum fungi colonies detected in the graft, in the anastomotic area, postoperative wound and in the lungs, we should be suspicious of possible donor-derived initial fungi contamination transmitted from the donor suffering from histoplasmosis, which was undetected before transplantation. For this purpose, the history of another kidney recipient from the same donor was monitored. The recipient of the paired kidney was a 38-year-old woman who underwent transplantation in our hospital on the same day as patient B. Over the previous two years of follow-up, the recipient of the paired kidney had no infectious complications, and the graft function was satisfactory.

Therefore, most likely, the initially severe somatic condition of the patient, the latent chronic infection with unidentified primary focus location, aggravated by IST, led to a slowdown in the healing process, wound infection, dissemination, the sepsis development and death. Macroscopic and histological examination of organ tissues using the PAS

reaction to polymucosaccharides during an autopsy by pathologic revealed a *Histoplasma capsulatum* fungal infection with fungal cells in the form of single yeasts, large colonies, and the invasion into the lumen of blood vessels, which led to generalized infection.

In opportunistic mycoses, the disease development should be considered in relation with on internal immunodeficiency states and acquired secondary immunodeficiency associated with IST after organ transplantation. Secondary immunodeficiency syndrome determines the severity of the fungal infection, the peculiarity of the body's morphological response and the prevalent damage to one or another system causing their functional insufficiency. The presence of severe systemic endotoxicosis with a generalized fungal infection determine multiple organ functional failure with a predominant damage to one of the systems. Thus, the pulmonary heart failure in this case was the immediate cause of death.

Conclusion

The results of the presented Case Report of a generalized fungal infection with the opportunistic *Histoplasma capsulatum* fungi developed in a patient after kidney transplantation having decompensated diabetes mellitus and receiving immunosuppressive therapy, indicate the need for increased vigilance regarding the diagnosing infections caused by fungi, including non-endemic ones, in patients with concomitant comorbid pathology and compromised immune status.

References

1. Araúz AB, Papineni P. Histoplasmosis. *Infect Dis Clin North Am.* 2021;35(2):471–491. PMID: 34016287 https://doi.org/10.1016/j.idc.2021.03.011

2. Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C. Histoplasmosis. *Infect Dis Clin North Am.* 2016;30(1):207–227. PMID: 26897068 https://doi.org/10.1016/j.idc.2015.10.009

3. Azar MM, Loyd JL, Relich RF, Wheat LJ, Hage CA. Current concepts in the epidemiology, diagnosis, and management of histoplasmosis syndromes. *Semin Respir Crit Care Med.* 2020;41(1):13–30. PMID: 32000281 https://doi.org/10.1055/s-0039-1698429

4. Azar MM, Hage CA. clinical perspectives in the diagnosis and management of histoplasmosis. *Clin Chest Med.* 2017;38(3):403–415. PMID: 28797485 https://doi.org/10.1016/j.ccm.2017.04.004

5. Lipnitsky AV, Markin AM, Surkova RS, Victorov DV, Toporkov AV. Molecular diagnostics of histoplasmosis. *Problems of Particularly Dangerous Infections.* 2019;(3):14–18. (In Russ.). https://doi.org/10.21055/0370-1069-2019-3-14-18

6. Prokhvatilova EV, Tkachenko GA, Ledeneva ML, Polovetz NV, Belitskaya LI, Plekhanova NG, et al. The perspective of application of sets of reagents for diagnostic of histoplasmosis using polymerase chain reaction in laboratory practice. *Clinical Laboratory Diagnostics.* 2017;62(7):426–431. (In Russ.). https://doi.org/10.18821/0869-2084-2017-62-7-426-431

7. Jawale PM, Gulwani HV. Histoplasmosis presenting as laryngeal ulcer in a post-renal transplant male: an unusual case from India. *Mycol Med.* 2017;27(4):573–576. https://doi.org/10.1016/j.mycmed.2017.06.003

8. Popova AY, Toporkov AV, Lipnitsky AV, Polovets NV, Viktorov DV. Spread of especially dangerous mycoses in the world. *Journal of microbiology, epidemiology and immunobiology.* 2016;(3):120–126. (In Russ.). https://doi.org/10.36233/0372-9311-2016-3-120-126

9. Taylor M, Ghodasara A, Ismail A, Gauhar U, El-Kersh K. Disseminated histoplasmosis in an immunocompetent patient after

COVID-19 pneumonia. *Cureus.* 2021;13(8):e17269. PMID: 3454049 https://doi.org/10.7759/cureus.17269

10. Tobón AM, Gómez BL. Pulmonary histoplasmosis. *Mycopathologia*. 2021;186(5):697–705. PMID: 34498137 https://doi.org/10.1007/s11046-021-00588-4

11. Oladele RO, Ayanlowo OO, Richardson MD, Denning DW. Histoplasmosis in Africa: an emerging or a neglected disease? *PLoS Negl Trop Dis.* 2018;12(1):e0006046. PMID: 29346384 https://doi.org/10.1371/journal.pntd.0006046

12. Bongomin F, Kwizera R, Denning DW. Getting histoplasmosis on the map of international recommendations for patients with advanced HIV disease. *J Fungi (Basel).* 2019;5(3):80. PMID: 31480775 https://doi.org/10.3390/jof5030080

13. Ocansey BK, Kosmidis C, Agyei M, Dorkenoo AM, Ayanlowo OO, Oladele RO, et al. Histoplasmosis in Africa: Current perspectives, knowledge gaps, and research priorities. *PLoS Negl Trop Dis.* 2022;16(2):e0010111. PMID: 35202403 https://doi.org/10.1371/journal.pntd.0010111

Information about the authors

Galina P. Titova, Prof., Dr. Sci. (Med.), Head of the Scientific Department of Pathological Anatomy, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0001-7843-5782, titovagp@sklif.mos.ru

30%, research concept, analysis and interpretation of the data obtained, writing the manuscript, approval of the version for publication

Nonna V. Shmarina, Cand. Sci. (Med.), Senior Researcher, Surgeon, the Department of Kidney and Pancreas Transplantation, N.V. Sklifosovsky Research Institute for Emergency Medicine; Associate

Professor of the Department of Transplantology and Artificial Organs, N.I. Pirogov Russian National Research Medical University, https://orcid.org/0000-0002-8199-905X, shmarinanv@sklif.mos.ru

20%, study design, collection of material for research, analysis and interpretation of the data obtained, writing the manuscript

Kseniya E. Lazareva, Cand. Sci. (Med.), Endocrinologist at the Department of Kidney and Pancreas Transplantation, N.V. Sklifosovsky Research Institute for Emergency Medicine; Associate Professor of the Department of Transplantology and Artificial Organs of the Scientific and Educational Institute "N.A. Semashko Higher School of Clinical Medicine", Russian University of Medicine, https://orcid.org/0000-0002-0473-9932, lazarevake2@sklif.mos.ru

20%, study design, analysis and interpretation of data, writing the manuscript

Galina A. Nefedova, Cand. Sci. (Med.), Senior Researcher of the Pathological Anatomy Department, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-8452-8499, nefedovaga@sklif.mos.ru

10%, data analysis, writing the manuscript

Ilya V. Dmitriev, Dr. Sci. (Med.), Head of the Department of Kidney and Pancreas Transplantation, N.V. Sklifosovsky Research Institute for Emergency Medicine; Associate Professor of the Department of Transplantology and Artificial Organs, N.I. Pirogov Russian National Research Medical University, https://orcid.org/0000-0002-5731-3310, dmitrieviv@sklif.mos.ru

10%, data analysis, writing the manuscript

Aslan G. Balkarov, Cand. Sci. (Med.), Head of the Scientific Department of Kidney and Pancreas Transplantation, N.V. Sklifosovsky Research Institute for Emergency Medicine; Associate Professor of the

Department of Transplantology and Artificial Organs, N.I. Pirogov Russian National Research Medical University; Head of the Organizational and Methodological Department for Transplantology, Research Institute for Healthcare Organization and Medical Management, https://orcid.org/0000-0002-1396-7048, balkarovag@sklif.mos.ru

10%, data analysis, writing the manuscript

The article was received on February 5, 2024;
Approved after reviewing March 5, 2024;
Accepted for publication March 27, 2024