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MUCORMYCOSIS IN SOLID ORGAN TRANSPLANT RECIPIENTS (CLINICAL CASES AND LITERATURE REVIEW)

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Mucormycosis is a severe mycotic infection with high mortality among immunocompromised patients. Its incidence in solid organ transplant recipients is 2–8% of all invasive fungal infections. In most cases, it occurs in the late posttransplant period. Risk factors in this patient cohort are graft-versus-host disease (GvHD) and use of immunosuppressive drugs. The article describes clinical cases of mucormycosis and analysis of literature data on the problem of invasive mucormycosis in solid organ transplant recipients. It also reviews the main methods of diagnosis and treatment of the disease according to international guidelines.

Keywords: antimycotic therapy, liposomal amphotericin B, isavuconazole, mucormycosis, graft-versus-host disease, GvHD, transplantation, internal organ transplantation, liver transplantation, kidney transplantation.

INTRODUCTION

Mucormycosis is a severe infection that predominantly occurs in immunocompromised patients. Solid organ transplant recipients are one of the risk groups for this nosology. Internal organ transplantation (IOT) is a life-saving intervention. The number of solid organ transplants in Russia is increasing annually. In 2022, 2,555 organ transplants (1,562 kidney, 659 liver, 310 heart) were performed [1], and by December 2023, 2,906 (1728 kidney, 789 liver, 371 heart, 17 lung, 1 heart-lung) [2]. Increased IOTs has also been reported by numerous international publications [3]. This patient cohort has a high risk of infectious fungal complications such as invasive candidiasis, aspergillosis, cryptococcosis, pneumocystosis and mucormycosis [4].

Mucormycetes are widespread. The main causative agents of mucormycosis belong to the order Mucorales (*Rhizopus spp., Mucor spp., Lichtheimia spp.* (formerly *Absidia spp.*), *Rhizomucor spp.* and *Apophysomyces spp.*). Although the disease is considered a rare infection [5, 6], there was a rise in incidence worldwide during the COVID-19 pandemic [7]. The most common clinical forms of the disease are rhinocerebral mucormycosis (20–60%) and pulmonary mucormycosis (20–70%). The infection spreads rapidly, involving nearby organs – about 50% of all cases [6]. Mortality averages 28% and depends on the clinical form of the disease (from 10% for sinusitis and skin lesions to 90% for the central nervous system (CNS) lesions and dissemination) [6–10]. International and Russian recommendations have demonstrated the need for primary antimycotic prophylaxis in patients at high risk of developing the disease, as well as early antimycotic therapy and surgical treatment [11, 12].

Objective: to analyze published data in order to determine the main risk factors, etiology, clinical manifestations and treatment outcomes of invasive mucormycosis in IOT recipients.

MATERIALS AND METHODS

The article presents clinical cases of disseminated mycotic rhinosinusitis, involving the orbital and CNS tissues. The EORTC/MSG criteria, 2020 [13] were used to make a diagnosis of invasive fungal disease.

The authors analyzed publications on mucormycosis in patients after organ transplantation. PubMed (as of December 2023), ClinicalKey (as of December 2023), and e-library (as of December 2023) were used. The following keywords were used in the information search: antifungal therapy, mucormycosis, graft-versus-host disease, GvHD, transplantation, internal organ transplantation, liver transplantation, kidney transplantation.

CLINICAL CASE #1

A boy S., 10 years old, was admitted to the Children's Republican Clinical Hospital, Kazan on July 21, 2021 with complaints of lack of urine, abdominal pain, noisy breathing, impaired consciousness.

Past medical history: *The child fell ill acutely, his condition deteriorated progressively on July 16, 2021 –*

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his body temperature rose to 38.5 °C, stool increased to five times a day, with an episode of acholia. He received ibuprofen, which reduced his body temperature to 37.8 °C. A day later, he started vomiting and experiencing pain in the right hypochondrium. At stoma opening, 20 ml of bile was flowing out (cholangiostomy performed in 2021). Immunosuppressive therapy and accompanying therapy (orthotopic transplantation of a liver fragment from a related donor in 2020) were reduced. Within three more subsequent days, the patient's condition progressively worsened – the child was lethargic, motor activity and appetite decreased, he complained of nausea, experienced low urine output (up to 70–100 mL of urine), and developed dyspnea. The child was urgently hospitalized.

Life history: *A child after two pregnancies without pathology, 1 birth (1 miscarriage). Discharged from the maternity hospital with physiological jaundice. Jaundice syndrome increased from four months of life. Viral hepatitis B and C were ruled out, the clinical picture was considered as cytomegalovirus (CMV) infection; a course of antiviral therapy was administered. The course of jaundice syndrome in the boy was wavy. The jaundice syndrome intensified against the background of intercurrent diseases. Acholia, vomiting and regurgitation occurred periodically. At the age of 7 months, the boy started experiencing severe skin itching. Low weight and height gain, and delayed motor development attracted attention. A liver biopsy was performed in 2013 at the age of two years. Histological conclusion: Alagille syndrome. Congenital intrahepatic bile duct hypoplasia (Alagille syndrome) with cholestasis syndrome was diagnosed. Conservative therapy was administered: ursodeoxycholic acid, fat-soluble vitamins, nutrition therapy. The disease gradually progressed and in 2019 (8 years of life), a follow-up examination detected cirrhosis.*

On August 5, 2020, he underwent hepatectomy with preservation of inferior vena cava and orthotopic liver fragment transplantation from a living related donor (aunt); on September 24, 2020, his hepatic artery was stented and splenic artery embolized; the hepatic artery was re-stented on October 27, 2020. He received immunosuppressive therapy with calcineurin inhibitors (tacrolimus 2 mg) and glucocorticoids (methylprednisolone 6 mg). Liver graft dysfunction signs were detected repeatedly in 2021. He received complex antibacterial, immunosuppressive, antiplatelet, diuretic, choleretic and replacement therapy. On February 5, 2021, a cholangiostomy was installed.

Physical examination upon admission to the hospital: *his condition was extremely severe due to multiple organ dysfunction syndrome (respiratory, cardiovascular and acute renal failure) and systemic inflammatory response syndrome (up to 38.5 °C. fever), neurological symptoms (stunning) and metabolic disorders. On auscultation, heart tones were muffled, rhythmic, heart rate was 130 per minute, and he had fast breathing (40 per minute). Saturation was 86–88%.*

Laboratory tests. *Full blood count test: white blood cells 6.9 × 10^9/L, neutrophils 4.0 × 10^9/L, and lymphocytes 1.3 × 10^9/L. Chemistry panel: urea 34 mmol/L, creatinine 350 μmol/L, hyponatremia 129 mmol/L, C-reactive protein 10 mg/dL. Blood acid-base balance: pH 6.1–6.9, BE 24 mmol/L. Lung ultrasound: areas of reduced lung airiness – multiple B-lines (interstitial edema), no free fluid in the pleural cavities. Examination of throat and nasal swabs by PCR for SARS-CoV-2 RNA tested positive.*

Diagnosis: severe COVID-19 coronavirus infection, acute kidney injury grade 3 (KDIGO, 2012), oligoanuria; congenital hypoplasia of intrahepatic bile ducts (Alagille syndrome) with cholestasis syndrome; liver cirrhosis; orthotopic liver transplantation from related donor on August 5, 2020; hepatic artery stenting on April 29, 2020, hepatic artery re-stenting on October 27, 2020; cholangiostomy (February 5, 2021).

The following treatment was carried out: mechanical ventilation, antibacterial (cefepime + sulbactam, metronidazole, meropenem), anticoagulant and antifungal (caspofungin 70 → 50 mg/m^2) therapy, intravenous immunoglobulin 0.4 g/kg/day, pulse therapy with glucocorticoids (metipred until July 27), then dexamethasone 4 mg/day, tacrolimus was discontinued.

On July 22, 2021, the boy had a nosebleed, anterior and posterior nasal swab was performed. The child's condition worsened – two days after being hospitalized, viral (COVID-19) pneumonia was diagnosed. On July 27, 2021, signs of thrombotic microangiopathy (TMA) were revealed, respiratory failure, hemic hypoxia (severe anemia) increased. 20 mL/kg of fresh frozen plasma (FFP) and leukoreduced red blood cells were transfused. Signs of hepatic failure appeared, and therefore the dose of antibacterial drugs and caspofungin was reduced.

On day 12 of hospitalization (August 2, 2021), there were complaints of swelling and pain in the left eye. OS: eyelids were swollen, slightly hyperemic, edema mainly of the lower eyelid. In the area of the medial-inferior corner of the orbit, a voluminous dense mass, painful on palpation, was detected (Fig. 1). The conjunctiva was slightly hyperemic, swollen, mainly around the lower eyelid. Eye movements were full and painless. Deviation 0.

Antibacterial therapy was continued. Four days later, a lower eyelid abscess developed. The abscess was opened with subsequent drainage. A scanty pale-yellow discharge was isolated from the abscess cavity. Surrounding tissues were imbibed with pus. The operation went without complications. The drainage from the wound was removed on August 9, 2021. There was no discharge from the wound.

On August 10, 2021, there were complaints of impaired nasal breathing on the left side. A dense mass

was detected in the left nasal cavity, fused with nasal mucosa; a defect in the soft tissues of the hard palate was detected, the palatine bone was exposed.

Computed tomography (CT) scan of paranasal sinuses (dated August 11, 2021): foci of destruction in the medial walls of the orbits, in the bones of the nasal cavity, hard palate in the alveolar processes of the maxillary bones in the plates of the pterygoid process on the left upper wall of the ethmoidal labyrinth (Fig. 2, a). Brain CT scan (dated August 11, 2021): rounded foci in the frontal lobes on the right (14 × 24 mm, 7 × 16 mm), subperiosteal abscesses of both eye sockets (Fig. 2, a and 2, b).

Antibacterial therapy was adjusted: cefepime and amikacin, without positive dynamics. After 7 days, the patient was consulted by an otolaryngologist.

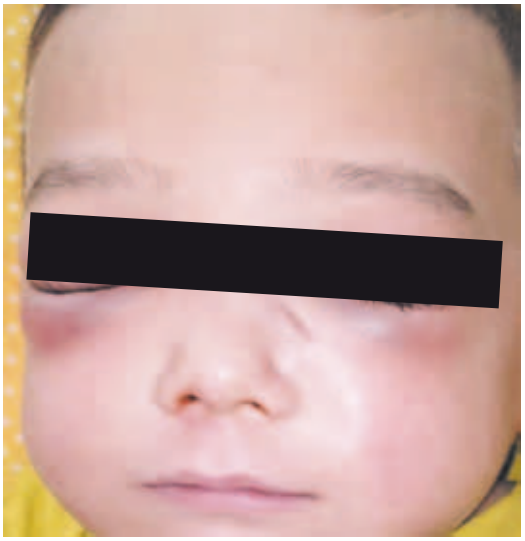

Fig. 1. Clinical manifestations: swelling, hyperemia of the skin of the lower eyelid of the left eye

Endoscopic examination of the nose: right nasal passage – the mucosa in the anterior parts was edematous, covered with black plaque in the form of dense crust, difficult to remove; left nasal passage – on the walls of the nasal cavity, there was a black formation, dense in structure, part of it was separated from the walls of the nasal cavity and removed, the bone tissue of the bottom of the nasal cavity on the left was exposed, necrosis of the inferior nasal concha on the left and middle nasal concha was revealed, the nasal septum was almost completely absent, the lumen of the nasal passages became passable up to the nasopharynx. On the oropharyngeal side, there was no mucosa on the hard palate 2.0 × 2.0 cm, the palate bone tissue was preserved.

Conclusion: necrosis of the nasal cavity with destruction of anatomical structures – the middle and inferior nasal concha on the left, the nasal septum, the lateral wall of the nasal cavity on the left, fungal infection? The formation was removed.

Antimycotic therapy was changed – voriconazole 400 mg/day was administered. Histological preparations of postoperative material revealed areas of necrotically altered tissue (mucosa) with fungal mycelium (mucormycosis?). The patient was consulted by the staff of the Department of Clinical Mycology, Allergology and Immunology at North-Western State Medical University. It was recommended to adjust the antimycotic therapy taking into account the histological examination results. Voriconazole was discontinued and liposomal amphotericin B 5 mg/kg/day was administered from August 23, 2021 (Fig. 3).

Based on clinical symptoms, CT scan of the brain and facial bones, and a histological report, a diagnosis was made: rhinocerebral mucormycosis with involvement of the paranasal sinuses, orbital tissues, facial bones, and brain. Acute pansinusitis. Abscess of the lower eyelid of the left eye (abscess drainage in August 6, 2021).

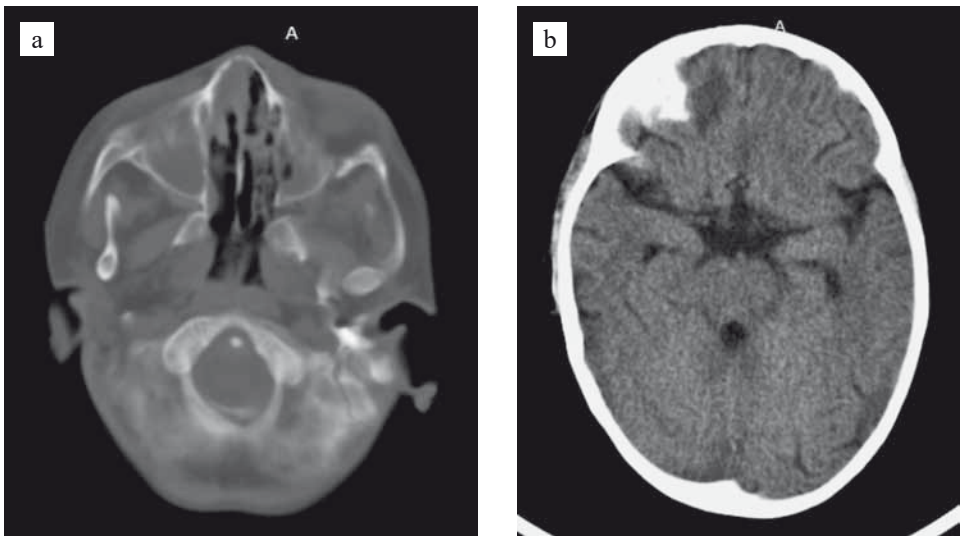

Fig. 2. CT scan: a, of paranasal sinuses; b, of brain

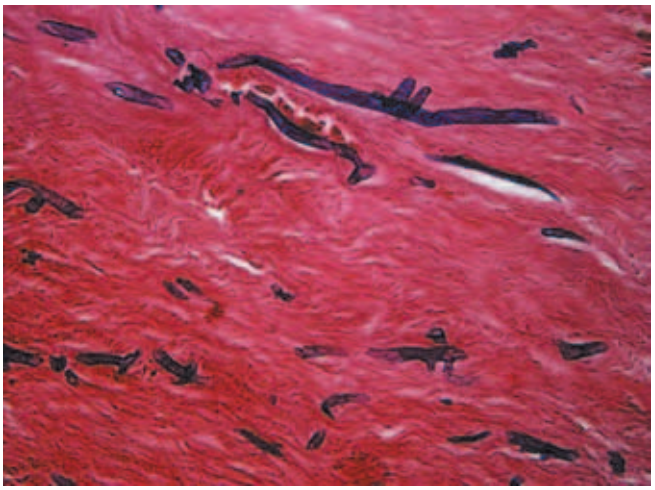

Fig. 3. Wide threads of non-septate mycelium in the postoperative material. Histological specimen: periodic acid-Schiff (PAS) staining; 400× magnification

Osteomyelitis of the bones of the nasal cavity, palate, alveolar processes of the maxillary bones, medial and lateral plates of the pterygoid process on the left side.

Antimycotic therapy was continued with liposomal amphotericin B at the same dose. The patient's general condition remained moderately severe with subfebrile body temperature. Two weeks later, brain CT and MRI showed negative dynamics in the form of increased volume of brain foci and progression of destruction of facial bones. Antifungal therapy was adjusted: the dose of liposomal amphotericin B 10 mg/kg/day was increased. Liver failure progressed during the therapy, and therefore the drug was replaced with isavuconazole 200 mg/day with a loading dose in the first 2 days. Over the next seven days, the patient's condition worsened: signs of systemic inflammatory response (sepsis) progressed, multiple organ failure increased and on October 7, 2021, the patient died on day 67 from the first clinical signs of invasive mucormycosis.

CLINICAL CASE #2

Patient O., 47 years old, in July 2022 came to the mycological clinic of Kashkin Research Institute of Medical Mycology, North-Western State Medical University with complaints of a significant decrease in visual acuity of the left eye, difficult nasal breathing, blood-stained purulent nasal discharge, periodic intense headaches.

From the patient's medical history, it is known that he was observed for a long time with chronic glomerulonephritis with an outcome of stage 5 chronic kidney disease (CKD) (d), corrected by chronic hemodialysis. The first kidney transplantation was performed in 2010. However, during the first year after transplantation, acute T-cell-mediated rejection occurred, which was controlled by pulse therapy with glucocorticoids (GCs). In 2017 (6 years after renal allotransplantation), humoral rejection occurred. By 2019, recurrent end-stage kidney disease in the graft was diagnosed. In April 2021, renal transplant nephrectomy was performed. In June 2021, repeat allotransplantation of a cadaveric kidney was performed. The patient received standard maintenance immunosuppressive therapy (tacrolimus, methylprednisolone, mycophenolic acid) to prevent graft rejection. In February 2022, he suffered a moderate COVID-19, complicated by viral pneumonia. He was on inpatient treatment. He received high GCs doses, antiviral drugs, broad-spectrum antibiotics, detoxification and oxygen therapy. Complete blood count revealed lymphocytopenia. The patient was discharged for outpatient treatment. After discharge from the hospital, he started complaining of intense headache, decreased visual acuity, and nasal breathing difficulties. He consulted an ophthalmologist and was recommended to go for a brain CT scan. CT scan revealed osteonecrosis of the upper jaw. The patient consulted an ENT doctor at his place of residence – necrotizing ethmoiditis and polysinusitis were diagnosed. In March 2022, endoscopic polysinusotomy was performed on the left side with decompression of the left orbit. According to results of cultures of the contents of the maxillary sinus on the left, bacteria were isolated and an antibacterial therapy course was administered. Histological examination detected osteonecrosis and signs of chronic inflammation. The patient's condition temporarily improved: the intensity and duration of headaches decreased, and nasal breathing was restored.

A month later, however, the patient's health began to deteriorate again: purulent nasal discharge with dark inclusions appeared, visual acuity in the left eye sharply decreased to complete blindness. MRI of April 2022: MRI picture of pathological infiltration with maximal changes in the retroorbital tissue, with involvement of the medial and superior rectus muscles of the eye, left optic nerve, probable destruction of the medial wall of the orbit and lesion of surrounding cells of the ethmoidal labyrinth extending to the superior orbital fissure area, left cavernous sinus and Meckel's space. Numerous focal changes in the white matter of the cerebral hemispheres, probably of vascular origin, foci in the paraventricular parts of the cerebellar vermis, persistent absence of contrast in the sigmoid sinus (consequences of thrombosis), signs of edema of the mucosa of the paranasal sinuses (ethmoidal labyrinth, lower frontal sinus and maxillary sinus on the left, condition after polysinusotomy on the left (Fig. 4).

He was hospitalized at Sechenov University in June 2022. Left maxillary resection with simultaneous bone grafting was performed. Revision of the left orbit and nasal cavity. According to microbiological examination of histological preparations, mycelium of fungi Mucorales spp. was detected. In connection with this, the patient visited the mycological clinic. The mycological clinic confirmed the diagnosis of mucormycosis with involve-

ment of the sinuses with bone destruction (B46.1) with involvement of retrobulbar tissue, destructive changes in the medial wall of the left eye socket and cells of the ethmoidal labyrinth on the left side. Considering the presence of kidney pathology, treatment with isavuconazole, repeated irrigation of paranasal sinuses, correction of immunosuppression (withdrawal of GCs), CT and MRI of the paranasal sinuses and brain once a month were recommended. Control cultures of nasal discharge and paranasal sinus aspirate were negative. After the treatment, control CT and MRI scans revealed remission of mucormycosis. The treatment for mucormycosis lasted for 12 weeks. The patient is under outpatient observation at the mycology clinic.

LITERATURE REVIEW

Infectious complications are the leading cause of death among patients within 1 year following organ transplantation (about 35%). In addition, they cause transplanted organ malfunction or rejection [4, 14, 15].

Micromycetes are opportunistic pathogens that can cause invasive diseases in critically ill patients as a result of a combination of several predisposing factors.

According to Livio Pagano et al., lung, heart and liver transplant recipients are considered to be at high risk of developing invasive fungal infections, while kidney transplant recipients are at lower risk of developing mycotic infection (Table) [16].

Published estimated incidences of mucormycosis in internal organ recipients have ranged from 0.4% to 16.0%, depending on the procedure and the geographical area [16]. Older studies found overall incidences of 0.2–2%, 0–2%, 0–3%, and 0–3% in kidney, liver, heart, and lung transplant recipients, respectively. A recent prospective multicenter TRANSNET study found that the 12-month cumulative incidence of mucormycosis was 0.07% in internal organ transplant recipients, with mucormycosis accounting for 2% of all invasive fungal infections [17]. Almyroudis et al. reported 10 cases of IOT-associated mucormycosis from their single institution and reviewed 106 other cases in the English-language literature from 1970 to 2002.

In this study, the transplanted organs were kidney (n = 73), heart (n = 16), lung (n = 4), heart and lung (n = 2), liver (n = 19), and kidney and pancreas (n = 2) [18]. At the same time, several researchers have shown that in

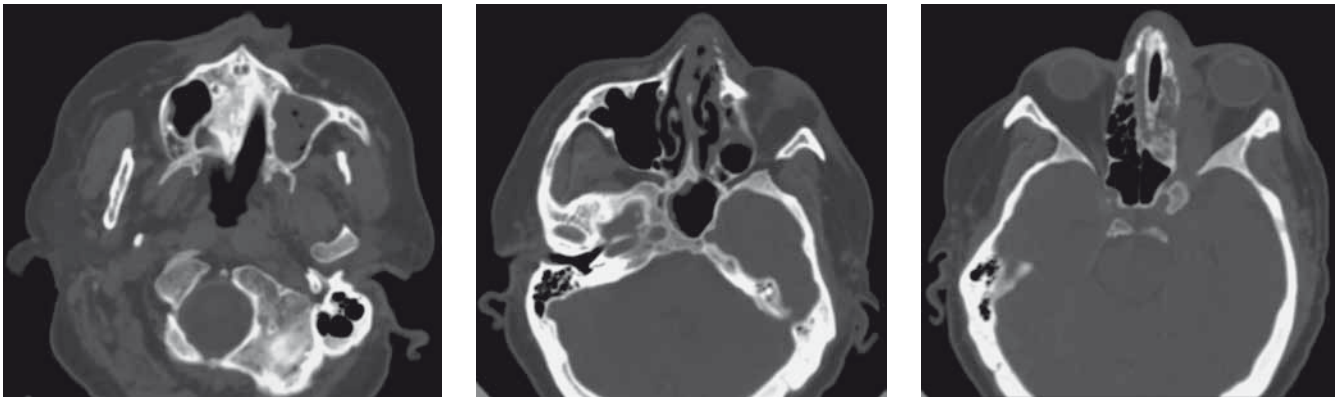

Fig. 4. MRI of the paranasal sinuses dated April 29, 2022. Inflammatory changes in the paranasal sinuses are most pronounced in the maxillary sinus on the left, with probable destruction of the medial wall of the orbit and lesion of the adjacent cells of the ethmoid labyrinth, spreading to the area of the superior orbital fissure, left cavernous sinus

Table

Categories of the degree of risk of developing invasive fungal diseases in accordance with morbidity and mortality rates

Low risk	Intermediate risk	High risk
Autologous HPSCT Hodgkin's lymphoma Chronic myeloproliferative diseases (CML and Ph conditions) Solid tumor Multiple myeloma Kidney transplantation Chronic immunologic diseases Systemic lupus erythematosus	Acute lymphoblastic leukemia Chronic lymphocytic leukemia Lymphoma COPD HIV/AIDS Myelodysplastic syndrome	Acute myeloid leukemia (primarily in the first induction) Allogeneic HPSCT (especially when cord blood is used) Heart, lung, liver transplantation

Note: HPSCT, hematopoietic stem cell transplant; CML, chronic myeloid leukemia; COPD, chronic obstructive pulmonary disease; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome.

some countries, there are higher rates of mucormycosis, ranging from 3% to 10%, which is associated with a larger number of immunocompromised patients [19]. Michael Osseis et al. analyzing the development of mucormycosis in liver transplant recipients, concluded that the frequency of infection in this patient cohort is 0.4%, with a mortality rate of 31–43% [20]. In a review by Rammaert et al., it was shown that 24% of patients with mucormycosis were organ transplant recipients [21]. This report demonstrates that mucormycosis can develop as a nosocomial infection associated with the transplant as a source of infection [21], as evidenced by the onset of clinical symptoms of the disease immediately after surgical intervention.

Mucormycosis is a late post-transplant complication [4]. The infection most often develops between 6 weeks and 12 months after transplantation (5–6 months on average) [15].

The main risk factors for mucormycosis in post-transplant patients are GvHD, use of GCs, renal failure, uncontrolled diabetes mellitus and previous use of voriconazole and/or echinocandins [15, 20, 21]. Interestingly, the use of tacrolimus has been associated with a reduced risk of mucormycosis in solid organ recipients, although they are usually potent immunosuppressants [22]. The role of calcineurin in the pathogenesis of invasive candidiasis and aspergillosis has been proven, but its exact role in the pathogenesis of mucormycosis has not been fully elucidated [22, 23, 24]. Calcineurin inhibitors and antifungals (amphotericin B) have been found to have synergistic or additive effects against *Mucorales spp.* [22]. Another important risk factor for mucormycosis is increased free iron in the bloodstream [25], which is most common in liver transplant recipients [20].

The most frequent clinical manifestations of mucormycosis are mycotic pneumonia [13–56%], rhino-orbital mucormycosis (26–87%), and skin lesions (22–13%) [14, 17, 18, 26, 27]. Focal CNS lesions develop in 2–5% of patients [14, 28]. Disseminated mucormycosis can develop in 26% of solid organ transplant recipients, most often in liver transplant recipients [20].

Clinical manifestations of mucormycosis are nonspecific and depend on the way mucormycetes penetrate the patient's body. For instance, inhalation of spores leads to mycotic sinusitis or mycotic pneumonia. When spores enter the gastrointestinal tract with food, necrotizing colitis and ileitis may develop [6]. The introduction of spores into soft tissues during trauma, maceration, and dressings leads to a localized skin process. The infection can spread to nearby tissues and organs if timely etiotropic treatment is not carried out. Dissemination through the bloodstream is possible [6, 7, 11].

The course of mucormycosis of the paranasal sinuses is similar to bacterial sinusitis or inflammation of the para-orbital tissue. Patients most often complain of headaches, paresthesias, pain over the area of the corresponding sinus, often irradiating along the course of the trigeminal or facial nerve; later, discharge from the nasal passages with streaks of blood appears. Swelling and hyperemia of mucous membranes, skin and soft tissues of the face increase [6, 14]. Patients are also bothered by pain in the eyeball and impaired skin sensitivity. There is a progressive decrease in visual acuity as a result of involvement of the ocular nerve in the infectious process or damage to the arterioles, which eventually leads to blindness and/or retinal infarction [10, 14, 19]. Examination reveals an ulcerative defect of the nasal or sinus mucosa with a focus of necrosis and an area of perifocal inflammation. The necrosis area increases daily, forming a "black scab" [6, 10]. At the same time, there may be no fever: only 50% of patients report an increased body temperature [14, 18]. The infection may then spread to the central nervous system. Nasal bleeding may be the first sign of infection penetration through the dura mater into the brain [6].

Clinical manifestations of pulmonary mucormycosis also require a differential diagnostic approach to clarify the genesis of the disease. Patients often present with fever (38–70%), persistent cough (50–61%), chest pain (22–37%), shortness of breath (19–34%) and hemoptysis (16–28%). There may be no increase in body temperature in neutropenic patients and organ transplant recipients receiving immunosuppressive therapy (10–15%) [6].

Mucormycosis of the skin and soft tissues is characterized by dense infiltrates that change the skin color from bright red to purple. Later, ulcerative defects with erythematous halo or subcutaneous nodules develop, merge and form necrotic areas ("black scab") [6, 8].

Mucormycosis of the gastrointestinal tract most often manifests itself as pain syndrome of varying intensity, abdominal bloating and other dyspeptic manifestations (nausea, vomiting), blood in stool may be detected. Laparotomy (for therapeutic or diagnostic purposes) reveals necrosis of intestinal tissues, intraperitoneal abscesses, and peritonitis [6, 9, 14].

Disseminated mucormycosis most often develops in liver transplant recipients and is manifested by prolonged elevations in body temperature above 38.50 °C, symptoms of secondary organ damage, where foci of dissemination and further development of signs of multiple organ failure are formed [6, 28].

Diagnosis of mucormycosis should be immediate, but this is hampered by the nonspecificity of clinical and radiographic signs.

First of all, it is necessary to rule out mucormycosis in recipients of internal organs with atypical sinusitis, pneumonia or fever of unknown origin. Diagnosis is based on the use of radiological and instrumental examination methods and detection of the pathogen in a material from the lesions.

The main radiological diagnostic method is high-resolution computed tomography. The most frequent

radiological signs of fungal damage to lung tissue are extensive lesions of lung tissue (involvement of several segments, lung lobes), subpleural foci, pleurisy, halo sign, crescent or reversed halo sign [6, 11, 14, 18]. Nonspecific signs include foci with indistinct contours, alveolar infiltration, and "frosted glass" changes. These symptoms are described in more than 50% of patients, they are not pathognomonic, as they are described in other mycotic lesions of lung tissue. When examining the paranasal sinuses by CT, the most commonly visualized area of the lesion is a zone of filling or tissue deficiency. As the process progresses, a bone destruction zone is determined. MRI is used if CNS lesions are suspected. In this case, single or multiple abscesses with a perifocal area of edema are more often detected [6, 11, 14, 18, 28, 29]. Serologic diagnostics for mucormycosis have not been developed.

The main methods of diagnostics of mucormycosis are mycological (microscopy, culture, histological) examination of material from the lesion [6, 14, 26, 30]. Microscopy of both native and stained preparations is performed. Most often, the smear is stained with calcofluor white. The stained preparation is microscoped using a microscope immersion system (900×, eyepiece 10×, lens 90×). This reveals a characteristic broad (10–50 μm) non-septate or sparsely septate mycelium branching at right angles. However, biopsy and culture of tissue samples from the lesion are frequently required because of the low diagnostic value of microscopy and culture of nasal aspirate, sputum, and bronchoalveolar lavage. Culture is performed in two repetitions, taking into account the different temperature regimes for growing filamentous fungi (37 °C and 28 °C), always at three points in the center of the dish. Incubation lasts for 10–14 days. Histological examination of the material reveals necrotizing abscesses and infarctions, inflammatory infiltration. Mucormycetes in tissues stain relatively well with hematoxylin and eosin, but additional staining, such as the PAS method or Gomori-Grocott silver impregnation, is often required [6, 11].

According to researchers, the pathogen is isolated in culture in 34–92% of patients. The most frequent causative agents of mucormycosis are: *Rhizopus spp.* (66–35%) and *Mucor spp.* (37%), *Lichtheimia spp.* (13%) [14, 31].

The mortality rate of patients with mucormycosis who did not receive systemic antimycotic therapy reaches 100%. Currently, the following groups of antimycotics are used to treat mucormycosis: polyenes (liposomal or lipid amphotericin B) and triazoles (posaconazole, isavuconazole). Administration of liposomal or lipid complex of amphotericin B at a dose of 5 mg/kg/day (AII) is recommended as a starter therapy, or 10 mg/kg/day for CNS lesions. The use of posaconazole and isavuconazole as starter therapy is less effective. Nevertheless, it is possible to use them in the form of infusion solutions if nephrotoxicity develops. Amphotericin B deoxycholate is not currently recommended for use [11]. The overall mortality in patients with mucormycosis treated with amphotericin B deoxycholate ranges from 39% to 57% [28]. An analysis of mucormycosis cases in organ transplant recipients confirmed the efficacy of therapy in 72% and 69% when lipid complex and liposomal amphotericin B were used as starting therapy [28]. The effect of antifungal therapy should be assessed on days 4–7. Additional CT or MRI scan is performed to visualize the focus of inflammation, and biochemical tests to assess the activity of the inflammatory syndrome. If initial treatment is ineffective, drugs from another group of antimycotics or combinations of drugs with different mechanisms of action are used, for example, liposomal amphotericin B and caspofungin, lipid amphotericin B and posaconazole [6, 11].

Antifungal therapy is continued until the clinical signs of the disease disappear, the pathogen is eliminated from the infection focus, radiologic signals start to return, and the immunosuppressive period is over. The average duration of treatment until the patient's condition stabilizes is 30–45 days, and it might take up to 180 days to reach complete remission. Antifungal medication is usually continued for at least 3 months. However, longer treatment or administration of secondary antimycotic prophylaxis is necessary in patients with persistent immunosuppression, such as with GvHD in organ recipients [6, 11].

Management strategies for patients with mucormycosis include correction of risk factors (recovery from ketoacidosis, withdrawal of immunosuppressive drugs, restoration of leukocyte levels in the peripheral blood, etc.) and use of surgical intervention – removal of affected tissues (necrectomy, lung lobe resection, pneumonectomy, maxillotomy, intestinal resection, etc.), in combination with antimycotic therapy with targeting drugs – level of evidence (AII) [6, 11].

CONCLUSION

Of all invasive fungal infections, mucormycosis accounts for 2–8% among solid organ recipients. Overall mortality rate reaches 38–48% in this patient cohort. Given the growing number of immunocompromised patients after solid organ transplantation and the existence of risk factors for the development of systemic fungal infections, transplant physicians should promptly conduct a diagnostic search algorithm to determine the best course of treatment for mucormycosis all in collaboration with a mycologist. Mycological vigilance by physicians, early biopsy and administration of targeted antimycotic therapy in conjunction with surgical procedures will optimize patients' prognosis and even save their lives.

The authors declare no conflict of interest.

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