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Mucormycosis of the maxillary sinus in an immunocompetent woman with oro-antral fistula – a case report

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ABSTRACT
Mucormycosis is a very rare fungal infection, characterized by vascular invasion, rapid progression and high mortality. Individuals suffering from systemic diseases influencing the immune system are predisposed to this infection which is caused by saprophytic fungi belonging to the class of Mucormycetes in the order of Mucorales. In this paper, we present an unusual case of mucormycosis of the maxillary sinus in an immunocompetent patient with oro-antral fistula. The infection may occur in either a fulminant or chronic form. In the patient described, the disease was chronic and characterized by a mild course with local symptoms. In the disseminated form of mucormycosis, the mortality rate is almost 100%. A definitively higher survival rate is observed in immunocompetent patients with a localized form of the infection. Diagnosis of the disease is very difficult because of its clinical and radiological similarity to the more common fungal infection, aspergillosis. Early diagnosis plays a key role in the course of treatment and allows to reduce the scope of surgical intervention. According to most authors, first line treatment should be the liposomal form of amphotericin B. Some also advise surgical treatment involving the removal of fungal masses. In the patient described, both surgical and pharmacological treatment was conducted resulting in the complete resolution of the fungal infection after 12 months.
Keywords: sinusitis; mucormycosis of the maxillary sinus; oro-antral fistula; Mucormycetes; fungal infection; amphotericin B.

INTRODUCTION

Mucormycosis, previously known as zygomycosis, is a very rare, life-threatening infection caused by saprophytic fungi belonging to the class of Mucormycetes (formerly known as Zygomycetes) in the order of Mucorales [1]. These fungi are common in the environment, and their abundant spores are found in the soil, air, on the surface of decaying organic matter, as well as in hospitals [2, 3, 4]. A characteristic morphological feature of Mucormycetes are thick right-angle branching 10–50 μm long non-septate hyphae [5, 6]. Mucormycosis is characterized by vascular invasion, rapid progression and high mortality. Infection occurs most often by droplet inhalation [2, 3] and, less frequently, through damaged skin [4, 7]. A post-extraction alveolus may also be a pathway for this fungal infection [8]. Systemic diseases such as immunological defects, hematological and hemato-oncological diseases, kidney diseases, malnutritional diseases, and, in particular, uncontrolled diabetes mellitus, predispose individuals to the disease [2, 9, 10, 11]. In healthy individuals, this mycosis occurs very rarely and represents only 4% of all fungal diseases. Cases of both the chronic and fulminant course of the disease have been encountered. A computed tomography (CT) image in the case of mucormycosis can often suggest aspergillosis, which may adversely affect the treatment of the disease, in particular by delaying it [4]. Differential diagnosis should consider conditions such as bacterial and allergic sinusitis, cancer, thrombotic sinusitis, and granulomatous disorders [3, 12, 13].

CASE REPORT

A 54-year-old woman came to a dentist's office in the county town for the removal of tooth 16. The tooth was removed but the oro-antral fistula formed after extraction was not recognized and treated. Due to persistent pain and the passage of fluids from the mouth to the nose, the patient was referred by her physician to the maxillofacial surgery clinic of NZOZ Ars Medica in Kielce. During the 1st visit, based on clinical symptoms, the patient was diagnosed with chronic exacerbated right maxillary sinusitis and oro-antral fistula following the removal of tooth 16. During subsequent visits to prepare for surgery, the sinus was flushed through the fistula with an 8.4% sodium bicarbonate solution and 0.9% sodium chloride solution. The diagnostics were extended to include a sinus CT, and the following description was provided: (i) segmental defect in the right inferior sinus wall; (ii) reduced volume of the right maxillary sinus with numerous mucosal thickenings; (iii) segmental thickening of the frontal sinus mucosa of up to approx. 8 mm and within the ethmoid bone; (iv) no obstruction of the ostiomeatal complexes; (v) slight nasal septum deviation to the left; (vi) normal rhinopharyngeal area (Figs. 1 and 2).

The patient was then referred to the hospital for surgical treatment. The patient was admitted to the Department of Maxillofacial Surgery at the hospital in Kielce (SP ZOZ MSWiA) as an urgent case. Basic laboratory blood tests were performed showing no deviations from reference values. During the interview, it became apparent that the patient had been treated

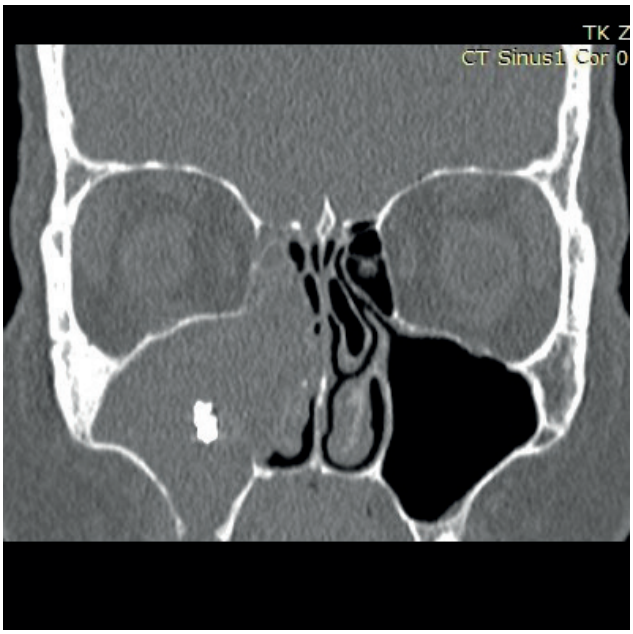

FIGURE 1. Preoperative frontal computed tomography scan of the maxillary sinus

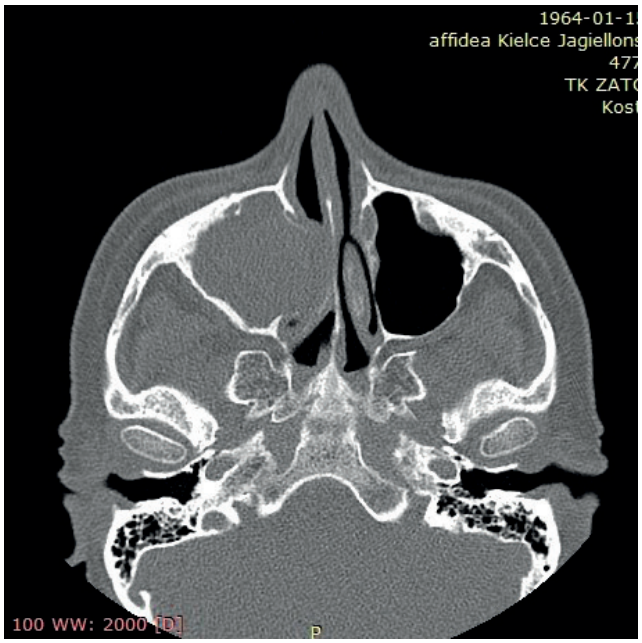

FIGURE 2. Preoperative horizontal computed tomography scan of the maxillary sinus

for arterial hypertension. Woman did not report any other systemic diseases, immunological defects, and did not take drugs that could affect the efficiency of the immune system. She reported no use of nicotine. Local clinical examination revealed considerable supragingival dental plaque. The patient received pharmacological treatment: Tarsime 3 x 1.5 g intravenously (i.v.), Metronidazole 3 x 0.5 g (i.v.), Perfalgan, IPP 1 x 0.04 g (i.v.), ACC 2 x 0.6 g per os (p.o.), Zyrtec 1 x 1, Sulfarinol 3 x 1 drop to the left and right nostril. Radical right maxillary sinus surgery using the Caldwell-Luc method was planned and performed as well as the excision and plastic surgery of the oro-antral fistula after the removal of tooth 16, through the Bichat fat pad using the Wassmund–Borusiewicz method. Calcified green-brown masses were found in the maxillary sinus during the surgery, suggesting a fungal infection. Due to a suspicion of sinus aspergillosis, itraconazole therapy was started (Orungal 1 x 0.2 g p.o.).

On the 4th day following surgery, the patient was discharged in good general condition, with a slight local swelling in the operated area. Postoperative wounds healed properly. The patient was referred to the maxillofacial surgery clinic for further checks. She was instructed to take the following drugs: Xorimax 2 x 0.5 g p.o., and Ketonal 1 x 0.05 g p.o. on an *ad hoc* basis, ACC 2 x 0.6 g p.o., Jovesto 1 x 0.005 g, Nasivin Soft 3 x 1, and Orungal 1 x 0.2 g p.o. On the 5th day after surgery, the results of the bacteriological examination were obtained, showing no pathogenic bacteria nor yeast-like fungi in the examined material. In the results of the mycological examination after 10 days of incubation, no yeast-like or mold-like fungi were found. On the 12th day following surgery, in the outpatient clinic, the patient's sutures were removed and the postoperative wound had healed properly. On the same day, the results of the histopathological examination of the surgical specimen were received, showing fungi with thick irregular hyphae that may correspond to fungi belonging to the Mucormycetes group. Additional staining (PAS, Grocott) also favored the presence of Mucormycetes (Mucor, Rhizopus). Due to the obtained results and some doubts concerning the purpose of the pharmacological treatment, a specialist in medical microbiology consulted the patient. From the results of the consultation, it was decided to implement treatment with liposomal amphotericin B (AmBisome). The patient was referred for pharmacological treatment of histopathologically confirmed mucormycosis of the right maxillary sinus to the Department of Maxillofacial Surgery at the hospital in Kielce (SP ZOZ MSWiA).

The patient was admitted to the hospital. Prior to implementation of antifungal treatment, morphological parameters, liver enzymes, kidney function, electrolyte and glucose levels were checked and the presence of human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) were excluded. A CT of the sinuses showed isointensitive tissue masses within the right maxillary sinus which could be inflammatory or polypoidal lesions. They were arranged in a circular manner partially filling the sinus lumen, with destruction of the inferior section of the anterior sinus wall and tissue masses protruding forward beyond the sinus lumen by up to about 6 mm. After administration of the contrast medium, the aforementioned tissue masses did not show any post-contrast enhancement. The ostiomeatal complexes were not obstructed on either side (Figs. 3 and 4).

AmBisome was given at a dose of 5 mg/kg body weight, administered once daily through a slow intravenous infusion. Treatment was continued for 4 weeks. Kidney and liver function, electrolyte and glucose levels, and peripheral blood morphology were monitored twice a week. No organ disorders, anaphylactic reactions or other adverse reactions associated with amphotericin B infusion were observed during the treatment. The patient developed hypokalemia during hospitalization, which was treated with intravenous and oral potassium supplementation. After completion of the treatment, the patient

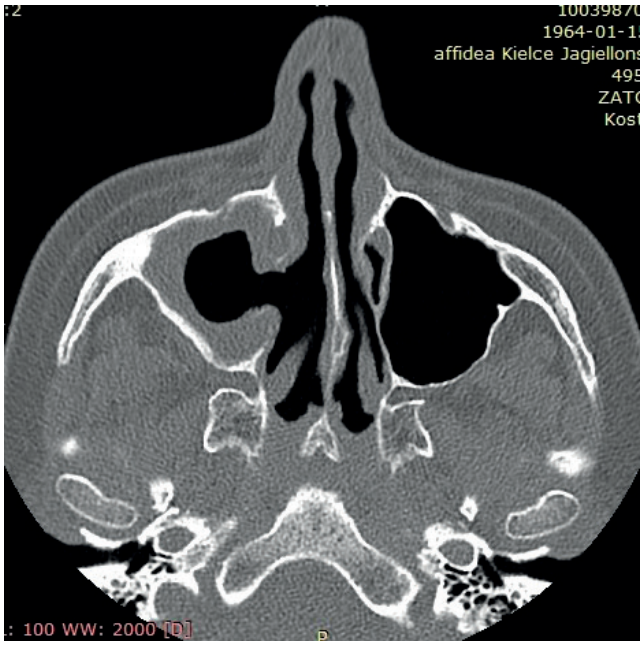

FIGURE 3. Postoperative frontal computed tomography scan of the maxillary sinus

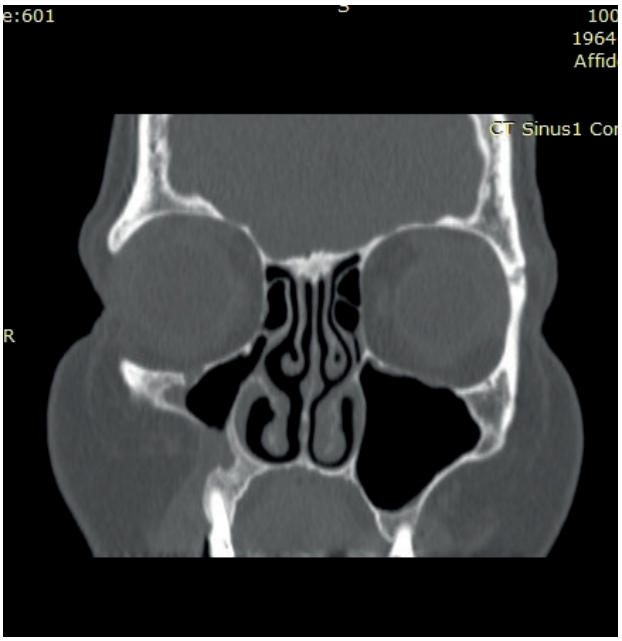

FIGURE 5. Frontal computed tomography scan of maxillary sinus after surgical and pharmacological treatment

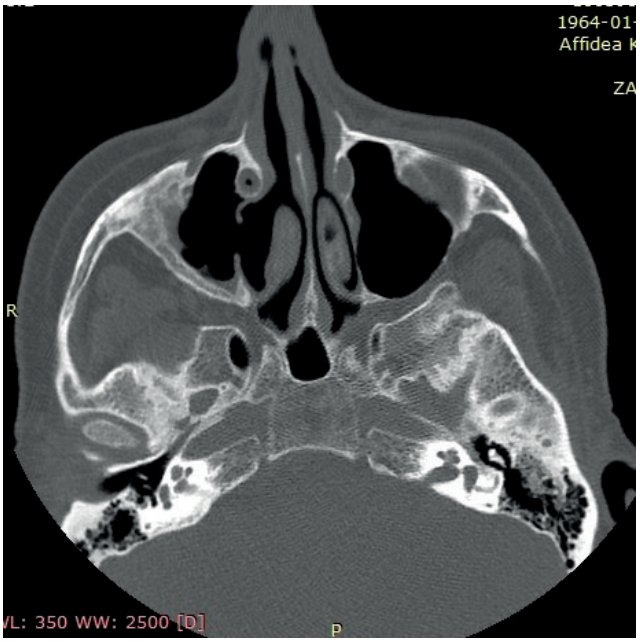

FIGURE 4. Postoperative horizontal computed tomography scan of the maxillary sinus

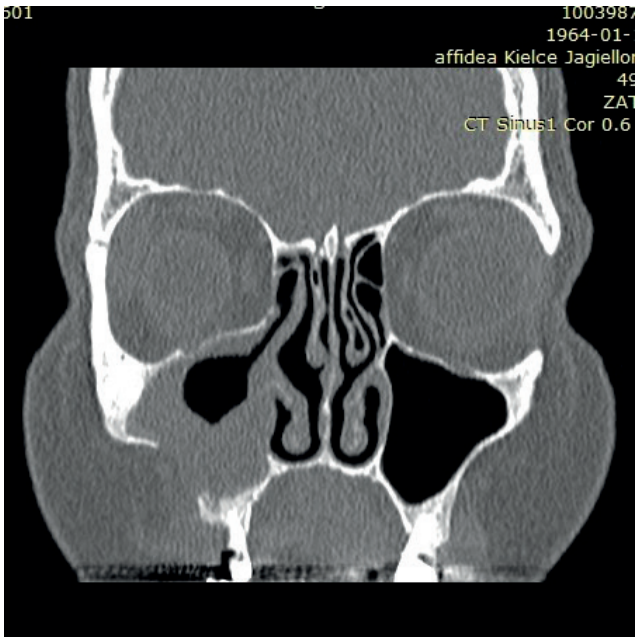

FIGURE 6. Frontal computed tomography scan of maxillary sinus after surgical and pharmacological treatment

was discharged from the ward in good general and local condition. About 12 months after surgical treatment, during the follow-up visit, the patient did not show any abnormalities in either her local or general condition. In order to verify the condition of the maxillary sinus, the patient underwent a sinus CT scan which showed that in the alveolar and zygomatic recesses of the right maxillary sinus, there were soft tissue masses/thickenings ranging 3–9 mm, which meant a partial regression when compared to the previous examination. There was no obstruction of the ostiomeatal complexes (Figs. 5 and 6).

DISCUSSION

Mucormycosis, formerly known as zygomycosis, is an extremely rare disease and as such is difficult to precisely diagnose. In the United States, incidence rates are estimated at approx. 1.7 patients per million inhabitants per year [14]. Incidence rates of mucormycosis are similar in both sexes. The mortality rate, according to the literature, ranges from 30% to as much as 100%. The disease is most often caused by fungi of the genera *Rhizopus* sp. (73%), *Mucor* sp. (13%), *Cunninghamella bertholletiae*

(6%), *Absidia* (4%), *Rhizomucor* (3%), and *Apophysomyses elegans* (1%) [15, 16, 17]. The vast majority of patients have one or more of the following risk factors:

— co-existing diseases (leukaemia, lymphoma, neutropenia, type 1 and 2 diabetes mellitus – especially uncontrolled chronic paranasal sinusitis and chronic kidney failure),

— high levels of iron, and high transferrin and ferritin saturation,

— undergoing chemotherapy, steroid therapy, immunosupressants, deferoxamine intake, transplantation (organ, bone marrow),

— local factors (burns, injuries),

— general conditions (malnutrition),

— living in a hot and humid climate zone [9, 10, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26].

Diseases in immunocompetent people (as in the case described here) are rare and account for only 4% of all cases.

Among the forms of mucormycosis, we distinguish the following:

1. naso-orbital-cerebral (33–49%),
2. skin (10–16%),
3. pulmonary (10–11%),
4. disseminated (6–11%),
5. gastrointestinal (2–11%),
6. other (about 3%) [15, 26].

Various authors show that the disease may occur in either fulminant or chronic form [5, 13]. The fulminant form is characterized by a sudden onset and development of many clinical symptoms within several hours after infection. The chronic form, on the other hand, is diagnosed when symptoms last more than a week [13] or more than a month [5]. In the past, cases of fulminant mucormycosis have been more commonly diagnosed. To date, more than 30 cases of chronic paranasal sinus mucormycosis [21, 27] have been described, the 1st of which was in 1964 [28]. This form affects both immunocompromised [5, 13, 16, 29] and immunocompetent [20, 21, 30, 31, 32, 33, 34] patients, although the latter show milder symptoms [29] and is more limited in terms of location [30, 35]. The chronic form of mucormycosis is often associated with a coexisting internal carotid artery stenosis [13]. The disease may begin in a fulminant manner and then develop into the chronic form. Celis-Aguilar et al. indicate that the implementation of pharmacotherapy alone without surgical treatment may result in the passage of invasive mucormycosis developing into its chronic form. A definitively higher survival rate is observed in immunocompetent patients and according to some authors, may be as high as 100% [18, 30, 31, 36, 37].

The mechanism of Mucorales infection consists of colonizing vessel walls and creating thromboses, resulting in ischemia and necrosis of the structures these vessels supply [38]. These fungi have a ketoreductase system, which, acting at a low pH existing in uncontrolled diabetes, facilitates vascular invasion. According to Abdollahi et al., a microorganism that particularly favors ketoacidosis is *Rhizopus oryzae* [2, 39].

The naso-orbital-cerebral form is the most common form of mucormycosis in diabetic patients [26]. It starts in the mucous membrane of the oral or nasal cavity, from where it spreads into the sinuses of the nasal cortex and then into the orbit and anterior fossa [40, 41]. Therefore, the observed symptoms include ophthalmoplegia (67% Yohai et al., 68% Nithyanandam et al., 89% Bhansali et al.), ptosis (41% Nithyanandam et al., 64% Yohai et al., 83% Bhansali et al.), blindness (65% Yohai et al., 68% Nithyanandam et al., 80% Bhansali et al.), chemosis (24% Yohai et al., 68% Nithyanandam et al., 74% Bhansali et al.), central retinal artery occlusion (16% Yohai et al., 20% Bhansali et al., 50% Nithyanandam et al.), eyelid necrosis (11% Yohai et al., 14% Bhansali et al.), periorbital oedema (43% Yohai et al., 66% Bhansali et al.) and eyeball inflammation (1% Yohai et al., 6% Bhansali et al.). Almost all diagnosed cases of naso-orbital-cerebral mucormycosis occur alongside nasal sinusitis (79–100%). Patients with this form also have nasal discharge (48–97%) and face pain and swelling (30–88%). The clinical picture is accompanied by the following symptoms: headache (17–97%), fever (26–70%), cavernous sinus thrombosis (11%), brain abscesses and ischemic strokes resulting in hemiparesis resulting from ischemic strokes [38, 41, 42, 43]. Due to the infection of the sinuses and adjacent structures, in some cases palatal and nasal mucosa necrosis occurs. Necrotic lesions may result in the perforation of the palatinal processes and nasal septum [38, 42].

The symptoms of skin mucormycosis can often suggest other conditions, such as tuberculosis [44]. The pulmonary form is usually associated with coughing, dyspnea and hemoptysis – in some cases, however, these symptoms do not occur [45, 46, 47]. The pulmonary form occurs most frequently in individuals affected by hematological tumors and appears more frequently in the upper lobes of the lungs due to better aeration [26]. The mortality rate of this form of disease reaches 65% [48, 49]. Gastrointestinal mucormycosis is associated with abdominal pain, nausea and vomiting blood [47]. One report describes gastric perforation as a result of gastric necrosis caused by invasive mucormycosis [48]. There is also a report of a patient with nasal-orbital-cerebral form of mucormycosis with symptoms suggesting Garcin syndrome [12].

Despite progress in the field of new antifungal drugs, mucormycosis is still associated with very high mortality rates. According to Jayalakshmi et al., more than 62% of patients with the naso-orbital-cerebral form of mucormosis die. Spellberg et al. report that, in the disseminated form, the mortality rate is almost 100% [6]. The most crucial factor for the success of therapy is timing, i.e., starting it as soon as possible. It has been shown that even a 12-hour delay in making a diagnosis can result in the patient's death [50]. The risk of therapy failure increases with eye infection, facial skin necrosis, hemiparesis, infection of bilateral paranasal sinuses, coexisting kidney failure and ketoacidosis [38, 42]. In their study, Trief et al. compared fungal infections of the paranasal sinuses caused by *Mucorales* (mucormycosis) and *Aspergillus* fungi, and indicated that mucormycosis is much more fatal than aspergillosis. In mucormycosis, the mortality rate was about 71% and in aspergillosis it was about 29%.

Many authors emphasize that early diagnosis of mucormycosis plays a key role in the course of treatment and allows to reduce the scope of surgical intervention. However, the diagnosis of mucormosis is very difficult due to the similarity of its clinical and radiological picture to aspergillosis. In order to distinguish between the two, one should determine the levels of

galactomannan and beta-D-glucan, the presence of which indicate aspergillosis [4]. In practice, diagnostics are usually based on direct microscopy and histopathological examination [40] following Gomori-Grocott and PAS staining, and microbiological culture [2, 3, 40]. However, according to Dzierżanowska et al., a microbiological culture is difficult to perform and often gives negative results due to damage to the delicate and fragile mycelium hyphae during the collection of the material for examination [1, 2, 4]. According to Lehrer, blood cultures can rarely be used for diagnosis and unambiguous diagnosis cannot be obtained from the examination of cerebrospinal fluid as this only shows ambiguous changes in the brain [38].

Imaging tests also play an important role in the diagnosis of the disease, with CT scans showing changes such as bone destruction, osteomyelitis or fluid levels in the sinuses [51]. Changes within the soft tissues of the orbit or nervous system are determined using magnetic resonance imaging [52].

However, there are new methods of diagnosing mucormycosis that are still under development that may form the basis for a more rapid diagnosis of the disease in the future. These include Mucorales-specific T lymphocytes, species identification by MALDI-TOF mass spectrography, and molecular techniques to detect gene fragments (*18SrRNA*, *ITS1*, *b cytochrome* gene) – among the latter, the most promising is the mucorales--specific CotH gene detection method [4, 53, 54].

There are still no uniform criteria for the treatment of mucormycosis. Most authors believe that amphotericin B should be the first-line treatment for this mycosis, with the liposomal form more advisable due to its significantly lower nephrotoxic effects. Mignogna et al., in their study on 5 patients with maxillary sinus mucormycosis, conclude that a course of liposomal amphotericin B was sufficient for their full recovery [21]. It was administered intravenously at a dose of 5 mg/kg body weight per day, as well as in the form of sinus irrigation and extraocular injections in case of orbital infection. Alternative pharmaceuticals include ketoconazole and postaconazole [3, 38, 42, 55, 56]. Mucormycetes have shown resistance to azoles (excluding posaconazole) and echinocandins [4].

Some authors postulate that in addition to pharmacological treatment it is advisable to use surgical methods to remove the main part of the fungal masses. Slonimsky et al., implemented pharmacological treatment as well as surgical treatment in 6 out of 13 patients with paranasal sinus mucormycosis [57]. Celis--Aguilar et al. consider that immunocompetent patients should only be treated surgically to guarantee a complete cure [18].

Surgical procedures for the removal of the infected tissues include open methods, e.g. maxillary sinus surgery using the Caldwell-Luc procedure, total maxillectomy, ethmoidectomy, sphenoidectomy, orbital extenteration and neurosurgical procedures – depending on the infected area [2, 38, 42]. In patients with a focal localized form of the disease, endoscopic surgery is successful and characterized by less radicality. There are also reports of the beneficial effects of hyperbaric oxygen therapy, which supports oxygen metabolism of phagocytic cells and increases oxygen pressure in ischemic tissues [58].

Spellberg et al. emphasize that 4 factors play a key role in the proper treatment of this mycosis:

1. early diagnosis,
2. the detection of factors conducive to the disease and their appropriate treatment,
3. proper surgical removal of infected tissues,
4. appropriate antifungal drug therapy [6, 24].

Immunocompetence is defined as the ability to produce a normal immune response after exposure to an antigen. This ability may be impaired by, among other things, systemic diseases or drugs. The patient described, treated in the Department of Maxillofacial Surgery of the hospital in Kielce, central Poland, can be classified as part of a narrow group of immunocompetent patients with diagnosed sinus mucormycosis. The occurrence of a post-extraction complication in the form of an oro-antral fistula may have led to chronic right-maxillary sinusitis, which is a significant risk factor for the development of mucormycosis. In the patient described, the disease was characterized by a mild course, only causing local symptoms in the form of periodic pain, obstructed drainage channels, and leakage of pathological secretion from the right nasal canal. In line with the position of most authors, both surgical and pharmacological treatment were implemented, resulting in a complete recovery confirmed after 12 months of observation.

CONCLUSIONS

Fast and correct diagnostics followed by early and adequate pharmacological and surgical treatment are the basis for success in patients with mucormycosis of the maxillary sinus.

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