



Candida glabrata as an aetiological factor of the fulminant course of panophthalmitis

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Abstract

Introduction. The role of fungi in infections in immunocompromised patients is a growing problem in both diagnosis and treatment. *Candida* species are the most common cause of fungal, endogenous endophthalmitis and infections of the cornea.

Case study. A patient was admitted to hospital due to acute inflammation of the tissue of the left orbit, 1.5 years after the corneal penetrating transplantation of the left eye with intracapsular extraction of lens and simultaneous anterior vitrectomy. The microbiological system identified: *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Candida glabrata* in the patient.

Conclusions. The factors conducive to fungal infections are: patient's old age, immune disorders and diabetes, as well as the presence of a necrotic tissue or a foreign body. All these parameters were met in this case. Only antibiotic therapy and long-term antifungal therapy, together with surgical debridement of the site of the ongoing infection produces clinical effects in such severe cases.

Key words

panophthalmitis, *Candida glabrata*, Corneal transplant

INTRODUCTION

The role of fungi in infections in immunocompromised patients is a growing problem in both diagnosis and treatment. The elderly often have diabetes, do not follow a proper diet, and a lack of control over an adequate glucose level increases the susceptibility to infections of fungal aetiology [1, 2, 3, 4, 5].

The *Candida* species are the most common cause of fungal, endogenous endophthalmitis and infections of the cornea, especially in patients with chronic immuno-deficiency dependent on the underlying disease [3].

Antimycotics belonging to four groups are used to treat fungal infections: polyene antibiotics, azoles, echinocandins and antimetabolites. Abuse of azole antifungals or the use of these drugs at subtherapeutic doses leads to an increase in the number of infections caused by fungi resistant to this drug. *Candida glabrata* demonstrates a natural reduced sensitivity to fluconazole [6]. Many strains of this species also demonstrate reduced sensitivity to amphotericin B. Infections of this aetiology are a huge therapeutic problem [7] because there is no possibility to treat patients on an outpatient basis – hospitalization is necessary. This significantly increases the cost of the treatment, which is already very high. In addition, fungal infections require long-term therapy [8]. Attention should be paid to the connection between fungal infections and the presence of a foreign body and therefore

the occurrence of therapeutic problems associated with biofilm [9, 10].

In order to make the correct diagnosis and determine the appropriate therapy for fungal infection, it is important to analyse risk factors and potential link between the infection and the presence of a foreign body [3] (catheters, drains, surgical sutures, necrotic tissue). Biofilm is a factor hindering therapy, and often without surgical debridement, preventing any treatment being undertaken. Drugs do not penetrate to biofilm [11]; moreover, it is believed that the formation of biofilm by the *Candida* species contributes to the invasiveness of these microorganisms, since a correlation between the formation of the polymeric matrix and the pathogenesis of fungal infections has been demonstrated. This has a significant impact on the fact that biofilms are responsible for 2 million infections annually [9].

Fungal infection can be the cause of fungaemia, and growing yeast-like fungi in the blood is a huge problem [12]. Studies have proven that in the United States in 2003, the annual incidence of blood infections of the *Candida* species aetiology ranged from 6 – 10 infections per 100,000 hospitalizations, and mortality due to sepsis was estimated to be 30–50%. Currently, invasive candidiasis is a common and serious therapeutic problem in patients with immuno-deficiencies around the world [7]. In the case of fungal infection, it is necessary to determine inflammation parameters and microbiological monitoring by performing control cultures during the implemented therapy. Fungal infection may also be accompanied by bacterial infection, and the inclusion of only antibiotics in empirical therapy is an excellent factor contributing to the multiplication

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of fungi at the site of infection [13]. Infections caused by streptococci and staphylococci are often associated with the carrier state of these microorganisms in the upper respiratory tract [14, 15]. Infection usually preceded by the state of being a carrier. By immune imbalance or uncontrolled diabetes, these microorganisms become the cause of serious infections. Toxins produced by *Streptococcus pyogenes* and *Staphylococcus aureus* are an additional factor affecting deterioration of the patient's condition [16]. Antibiotics that inhibit these toxins should be included [17]. Microbiological diagnostics and close cooperation between clinicians and microbiologists are very important, and only such cooperation gives a chance for therapeutic success and healing of the patient.

CASE STUDY

A 70-year-old female patient was admitted to hospital due to acute inflammation of the tissue of the left orbit. A few days before the onset of inflammation symptoms, the patient suffered from otitis media also on the left side complicated by perforation of the tympanic membrane and purulent discharge. Severe pain and inflammatory infiltration of the tissues of the orbit, which had been increasing for about 2 days, led the patient to come to the hospital.

In the patient's medical history, 1.5 years after the corneal penetrating transplantation of the left eye with intracapsular extraction of lens and simultaneous anterior vitrectomy. Postoperatively, the patient did not report for ophthalmologic monitoring, nor did she report for removal of the sutures. In the medical history it was established that the patient had undergone combined treatment of a malignant breast cancer, currently in remission. She did not report any symptoms from other organs or take any chronic medications.

On admission, the patient was cardiovascularly and respiratorily in a generally good condition, body temperature 36.7 °C. The examination revealed massive inflammatory infiltration of the upper and lower eyelids of the left eye, completely clenching the palpebral fissure and preventing the patient from seeing. Tissue oedema affected also the surrounding soft tissues of the temporal and buccal regions. In the area of palpebral fissure, a large amount of dry purulent discharge was found; on attempting to remove it, bleeding from the skin occurred. In addition, intradermal purulent reservoirs were visible [Fig. 1].

Laboratory tests produced the following results: CRP 323,7 mg/l, procalcitonin 7,14 ng/ml, leukocytosis $17,51 \times 10^3/\mu\text{l}$, glucose 234 mg/dL. However, no pathogen was grown in blood cultures collected from 2 different sites. Computed tomography revealed a significant degree of oedema and obliteration of the structure of the subcutaneous fat tissue within the left half of the face, but without evidently distinct fluid reservoirs or gas bubbles. In connection with the extent of the inflammatory infiltration and the need to collect the material for microbiological and histopathological examination, immediate incision and drainage of soft tissues in the area of the left orbit was performed [Fig. 2]

Intraoperatively collected material was transferred to the Central Microbiology Laboratory where it was cultured for standard microbiological media: Columbia agar with 5% sheep blood, Mannitol Salt Agar (Chapman Medium), MacConkey agar, enterococci culture medium, and broth medium (Oxoid). Cultures for anaerobic microflora on



Figure 1. Inflammation of tissues of the left orbit – local condition upon admission to hospital



Figure 2. Day one after drainage of tissues of the left orbit.

Schaeffer anaerobic agar and broth medium for the anaerobic culture were performed, where the culture was grown for 5 days under anaerobic conditions. In anticipation of the results of microbiological examination, empirical treatment was initiated: clindamycin with metronidazole which did not obtain the expected clinical or laboratory improvement.

After receiving the results of the microbiological tests, the following pathogens were found: *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Candida glabrata*. The antimicrobial treatment was modified by discontinuing Metronidazole and including amoxicillin with clavulanic

acid and caspofungin. In connection with the elevated glucose level in the blood serum, diagnostics for carbohydrate disorders was performed, diagnosing diabetes. Drugs normalizing glycaemic level were implemented.

In the following days of use of the above-mentioned drugs, improvement of the local condition and reduction of inflammation parameters in laboratory tests were observed. It is noteworthy that if the material had not been collected for microbiological test on the day of admission, it would have not been possible to obtain improvement in the patient's condition after administration of medicines routinely used in such cases.

During hospitalization, the patient was consulted ophthalmologically. The consulting ophthalmologist did not recommend topical treatment. Corneal transplant rejection was confirmed, recommending ophthalmologic monitoring on an outpatient basis after the current inflammation subsides. After 4 weeks of systemic antibacterial and antifungal treatment, and after several surgical debridement, the patient was discharged from hospital in a good general and local condition, with recommendations [Fig. 3].



Figure 3. Patient's local condition on day of discharge from hospital

DISCUSSION

A very important problem that needs to be addressed is the collection of material from the sites of ongoing infection; this should be performed immediately upon admission to hospital and before the start of treatment. Usually, doctors apply antibiotics at the beginning of therapy, without considering the possibility of fungal infection, although very often patients have mixed infections. In the presented case, clindamycin and metronidazole were applied at the beginning of the therapy. Infection with Gram-positive

bacteria and anaerobes was suspected. Including only clindamycin in the therapy is insufficient. In the case of infections caused by pyogenic *Streptococcus pyogenes* and *Staphylococcus aureus*, it is necessary to apply beta-lactams that inhibit cell wall biosynthesis and are active in the phase of rapid bacterial growth. Beta-lactam antibiotics should be associated with a high-dose of clindamycin, which plays the role of an inhibitor of toxins produced by both streptococci and staphylococci [17]. If, as in this case, only amoxicillin\ clavulanic acid was added to the therapy, no therapeutic effect would have been achieved, anyway.

After receiving the results of microbiological tests, the antifungal drug caspofungin, which is included in the group of echinocandins with fungicidal activity against many species of candida [7], was included in the therapy. Numerous studies have proven that it is equivalent to amphotericin B in the treatment of patients with serious fungal infections. In addition, this preparation is characterized by lower toxicity in relation to polyenes [8, 18].

Streptococcus pyogenes are pathogenic streptococci that often cause tissue inflammation. Due to the production of numerous virulence factors (M protein, pyrogenic exotoxins, haemolysins) they are responsible for recurrent strep throat, scarlet fever, myositis and fasciitis, endocarditis, arthritis, and ocular mucous membrane inflammation. This is a strictly human pathogen, associated with causing 500,000 deaths annually worldwide [19, 20]. In the presented case, the patient was probably a carrier of bacteria belonging to this species. Despite the widespread, antibiotic resistance among bacteria, *Streptococcus pyogenes* is still sensitive to penicillin, which is why drugs from this group are successfully used in the empirical treatment of throat infections, including strep throat. The reason for the infection in the current case was probably previous recurrent strep throat of this aetiology, although the patient did not provide such information in the medical history. *Staphylococcus aureus* grown in purulent material collected from the eye is also a pathogen that may be an aetiological factor of throat infections [21, 22]. Although the patient did not provide information about previous sore throat infections, a few days before admitting the patient to the hospital she had an infection in her left ear, with purulent exudate. Ear infection was probably associated with prior colonization of the throat by *Streptococcus pyogenes* and *Staphylococcus aureus*, and the infection of the orbit may have been an ear-like infection. Despite the *in vitro* sensitivity of streptococci and staphylococci to clindamycin, in this case, the empirical use of this antibiotic for the first few days did not produce a clinical effect. Only the inclusion of targeted antifungal therapy resulted in a slow improvement in the patient's condition. In the case of the described patient, the cause of the fungal infection was most likely exogenous orbital superinfection. It is very important that after the corneal transplant the patient did not report for a follow-up appointment.

Infections of the *Candida glabrata* aetiology due to the natural resistance of these fungi to fluconazole, are a huge problem. Treatment with echinocandins can only be carried out at hospital and is very expensive. Therapy of fungal infections is also a long-term process. If medications are stopped too soon, the infection will recur; if the doses of medications are too low (due to treatment costs), resistant strains may be generated. Mutations in FKS genes are responsible for the resistance to echinocandins. Among

the isolates resistant to echinocandins, the most important problem are the strains of *Candida glabrata*, especially in view of the fact that a third of these isolates may also be resistant to many other drugs. Antifungal therapy should be carried out for at least 3 weeks; in the current case, the patient was treated for a month. It is very important to monitor the patient microbiologically and perform control cultures to check if the microorganism has been eradicated [23].

The patient's problem was a mixed infection. The inclusion of broad-spectrum antibiotic therapy in the first days of hospitalization caused the destruction of the natural bacterial microflora, which is a very important barrier protecting against infection. Fungi could multiply successfully in bacterial niches, hence the lack of improvement or even worsening of changes at the site of infection in the first days after admission to hospital.

It is very important not only to perform microbiological culture regularly, but also to assess inflammation by controlling levels of procalcitonin, CRP, leukocytosis or temperature, and only the correlation between the results of the cultures and these parameters provides the full picture.

The factors conducive to fungal infections are: patient's old age, immune disorders and diabetes, as well as the presence of necrotic tissues or a foreign body. All these parameters were met in the presented case: the patient was a 70-year-old female after cancer, probably with an uncontrolled diet (obesity) and diabetes, as well as with the presence of a rejected corneal transplant, a foreign body, and surgical sutures which had not been removed. Sugar is an excellent medium for bacteria and yeast-like fungi, which is why not only diabetes but eating sweets in large quantities can cause mycosis.

Both yeast-like fungi and staphylococci are often the cause of infections related to biofilm. This is why pharmacological action is insufficient and surgical wound debridement is so important, because antibiotics and antifungal drugs are not able to penetrate into the biofilm [9]. Only antibiotic therapy and long-term antifungal therapy, together with surgical debridement of the site of the ongoing infection, can result in clinical effects in such severe cases. A very important aspect in the treatment process is the correct microbiological diagnostics for both bacteria and fungi, as well as the daily cooperation of the clinician and microbiologist. Laboratory methods are very important because they lead to identification of the aetiological factor of infection, which affects the optimization of therapeutic actions.

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