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Candidemia from Genitourinary Tract Infection Complicated by Infection of Central Nervous System and Endophthalmitis in Patient with Newly Diagnosed Diabetes Mellitus Type 2

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Abstract

Infections due to *Candida* species have been major causes of morbidity and mortality in humans, responsible for a broad spectrum of clinical manifestations. The incidence of invasive candidiasis with deep organ infections increases steadily and is usually associated with immunosuppression and prolonged intensive care. We present a case of a patient with newly diagnosed diabetes type 2 complicated with multiple deep organ candidiasis with central nervous system involvement.

Keywords: Central nervous system candidiasis; CNS candidiasis; Diabetes mellitus type 2; Fungal endophthalmitis; Invasive candidiasis

Abbreviations

CNS	:	Central Nervous System
ESBL	:	Extended-Spectrum-Beta-Lactamase
MRI	:	Magnetic Resonance Imaging
BMI	:	Body Mass Index
eGFR	:	estimated Glomerular Filtration Rate
T2WI	:	T2-weighted imaging,
DWI	:	Diffusion Weighted Imaging
ABLC	:	Amphotericin B Lipid Complex

Introduction

Over the past few decades, infections due to *Candida* species have been major causes of morbidity and mortality in humans, responsible for a broad spectrum of clinical manifestations ranging from superficial and mucosal infections to invasive diseases associated with candidemia and secondary organ involvement [1]. The incidence of deep organ infections increases steadily and is associated with immunosuppressive treatment, broad spectrum antibiotics and prolonged intensive care. Candidemia is associated with up to 47% attributable mortality [2].

It is known that *Candida* may disseminate hematogenously and form microabscesses or small macroabscesses in major organs most commonly affecting the brain, choroid and retina, heart and kidneys [1]. Ocular complications occur in 14% of patients with candidemia and the majority of them develop chorioretinitis, while in 1.6% of patients the disease progresses to endophthalmitis.

Ocular involvement is associated with approximately 90% probability of abscess formation in multiple deep organs [1,3].

The pathogen, which is a part of commensal flora, enters the bloodstream through mucosal surfaces after growing to large numbers as a consequence of impaired immunologic response of the host. Apart from congenital and acquired immunodeficiency disorders, one of the most common risk factor predisposing to hematogenously disseminated candidiasis is diabetes mellitus.

More than 90% of invasive disease is caused by the most common pathogens: *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, however, *C. albicans* constitute approximately 50% of all relevant isolates and is the most common cause of central nervous infection and endophtalmitis [2].

Case

A 40-year-old, obese (BMI 39.78 kg/m²) male, with a 6-month history of recurrent fungal intertrigo and balanitis treated topically, was admitted to the Department of Gastroenterology, Hepatology and General Medicine in Rzeszow, Poland, on the 23rd of October 2016 due to fulminant necrotizing fasciitis of the perineum and genital area with coexisting hyperosmolar - hyperglycemic state being a complication of unrecognized diabetes type 2.

On admission the patient was confused, severely dehydrated, had fever up to 39°C, erythema and massive edema of the scrotum typical for Fournier's gangrene. There were no signs of respiratory failure, impaired hemodynamics and focal neurological deficits.

Laboratory examinations revealed significant hyperglycemia (1330 mg/dl), hypernatremia (150 mmol/l), features of acute kidney injury (serum concentrations of creatinine 2.25 mg/dl and urea 109 mg/dl, eGFR 35 ml/min/1.73m²) and elevated inflammatory markers (C-reactive protein 26.2 mg/dl [N<1mg/dl], leukocytes 15.8 G/l). Urine analysis showed leukocyturia. Blood cultures revealed candidemia. Microbiologic examination of urine and urethral smear were both positive to *Candida albicans*, too. Strain was susceptible to most antifungal drugs (fluconazole, itraconazole, voriconazole, flucytosine and amphothericin B).

Abdominal ultrasonography revealed enlarged kidneys (right - 151 mm, left - 171 mm) with bilateral thickened renal cortex suggesting pyelonephritis, enlarged liver (201mm) and spleen (142mm). Ultrasound examination of the pubic area and genitals showed massive edema of subcutaneous tissue and scrotal wall (22 mm) with inflammatory infiltration and increased vascular flow. Echocardiography did not show any features of endocarditis. Due to deterioration of vision, especially in the left eye, dilated ophthalmological examination was performed on the 8th of November 2016 and revealed multiple white, elevated fluffy lesions in choroid, retina and vitreous of both eyes, more advanced on the left side. Magnetic resonance imaging (MRI) of the CNS performed on the 09th of November 2016 showed multiple disseminated hyperintense parenchymal granulomas (up to 16 mm) in T2-weighted imaging (T2WI) with central low signal intensity in diffusion weighted imaging (DWI) located in white matter of both hemispheres, striate bodies, callosum and cerebellum. Due to impaired kidney function MRI was performed without contrast infusion (Figure 1).

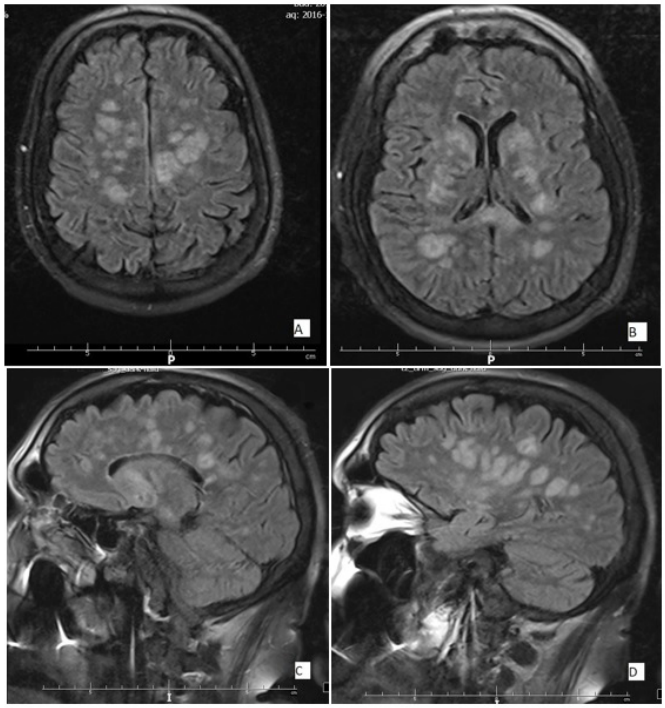

Figure 1: MRI of the CNS performed on the 8th of November 2016 - at the time of diagnosis of candidiasis with CNS involvement (T2-weighted images).

Patient required multidisciplinary diagnostic and therapeutic approach starting from correction of electrolyte imbalance, hyperglycemia, rehydration and broad spectrum antimicrobial treatment. Once the patient's general condition was stabilized several surgical procedures such as debridement and drainage of scrotal and pubeal area were performed.

On admission the patient received intravenous ceftazidime (1g twice daily), ciprofloxacin (200 mg twice daily), metronidazole (500 mg three times daily) and fluconazole (200 mg twice daily). Antibiotic therapy was changed to meropenem (1g twice daily) to manage urinary tract infection with *Klebsiella pneumoniae* ESBL(+).

In view of candidemia with CNS involvement, antifungal treatment was switched to Amphotericin B lipid complex (ABLC) on the 9th of November 2016.

On the 16th of November 2016 the patient was referred to the Department in Hospital of Infectious Diseases in Warsaw, Poland, to continue the treatment. On admission to our unit the patient was in a stable, improving condition, with hypertension (170/89 mmHg) and polyuria up to 10 liters a day, scrotal edema with signs of surgical incisions and drainage, and redness of the eyes mainly on the left side. Laboratory test showed moderate anemia, slightly elevated inflammatory markers, decreased creatinine level (1.73 mg/dl), leukocyturia. Blood and urine cultures were negative. Serum glucose level was controlled by three injections of short acting insulin and one injection of long acting insulin. Antibiotic therapy and antifungal treatment were continued. The patient was consulted in the Department of Ophthalmology Medical University of Warsaw and diagnosed with bilateral chorioretinitis with vitritis (Figure 2). Additional local treatment with fluconazole and two intravitreal injections of Amphotericin B (0.1 ml) into the left eye were performed.

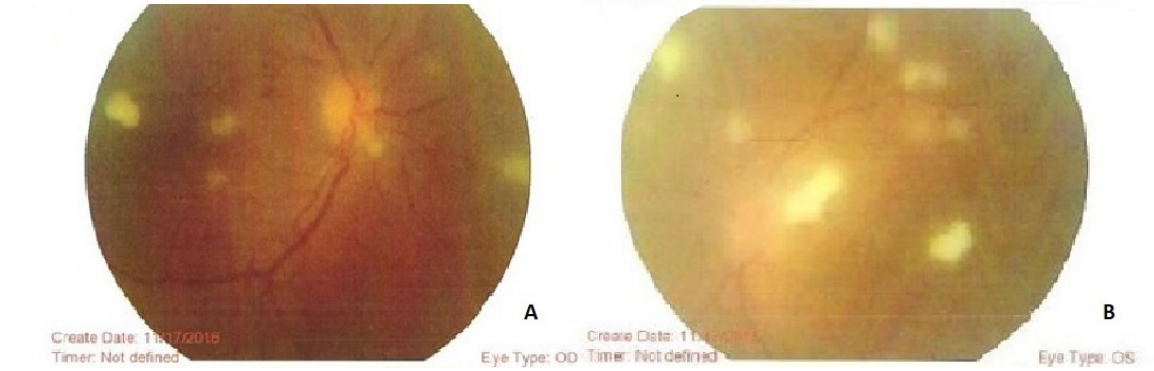

Figure 2: Colour photograph images showing right **(A)** and left **(B)** fundus with multiple creamy white lesions typical for fungal chorioretinis. Papilledema in the left eye.

Control MRI of the CNS performed on the 21st of November 2016 (after a two-week therapy with ABLC) revealed diffused hyperintense lesions in T2-weighted imaging (T2WI) in white matter of both hemispheres, striate bodies and callosum that indicated slight radiological improvement (Figure 3). In consequence, antimycotic therapy was changed to oral voriconazole (loading dose 400 mg twice daily, then 200 mg twice daily) and intravenous fluconazole (400 mg twice daily) administered simultaneously for 7 days and continued only with intravenous fluconazole. Since the third MRI of the CNS performed on the 15th of December 2016 revealed further significant regression of inflammatory changes, the patient received oral fluconazole (400 mg twice daily). Subsequent MRIs of the CNS performed after four and eight weeks of antifungal therapy showed further but still incomplete resolution of radiographic abnormalities. After fifteen weeks of adequate antifungal treatment, started on the 9th of November 2016, the dose of oral fluconazole was diminished to 200 mg twice daily and continued for 24 weeks. During that period each of three MRIs of the CNS showed further radiological improvement. The last examination, carried out on the 09th of August 2017, showed minimal residual post-inflammatory changes with no regression compared to previous examination, thus the antifungal therapy was finished (Figure 4).

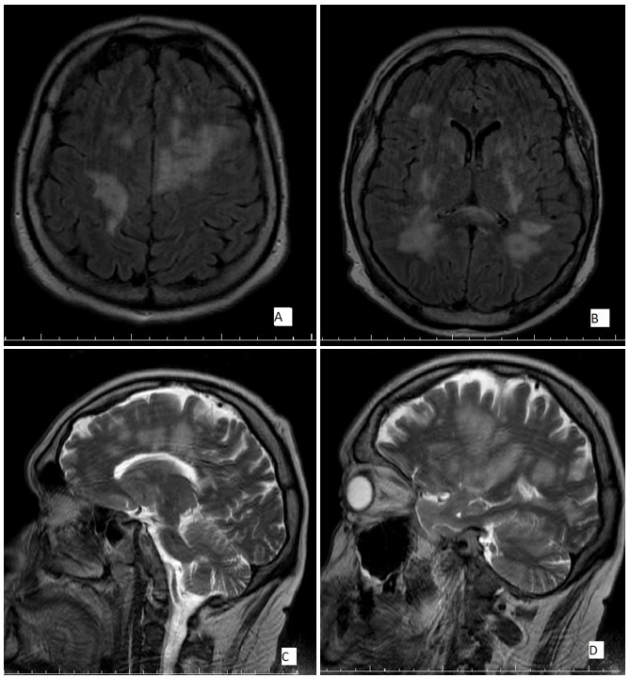

Figure 3: MRI of the CNS performed on the 21st of November 2016, after 2-week treatment with ABLC (T2-weighted images).

Because of endophtalmitis not responding to antifungal intravitreal injections given twice into the left eye, the patient underwent bilateral pars plana vitrectomies with silicone oil tamponade. The left eye was operated on the 9th of December 2016 and the lens was removed during the same procedure, while better, right eye was treated one month later (9th of January 2017) with lens phacoemulsification and artificial posterior chamber lens implantation. Finally, after silicone oil removal, the patient gained significant improvement of visual acuity. Postsurgical aphakia in the left eye was corrected with the use of contact lens, but taking into consideration increased risk of infectious keratitis in diabetic individuals, the patient underwent secondary artificial lens implantation, which was fixated to the iris in the left eye.

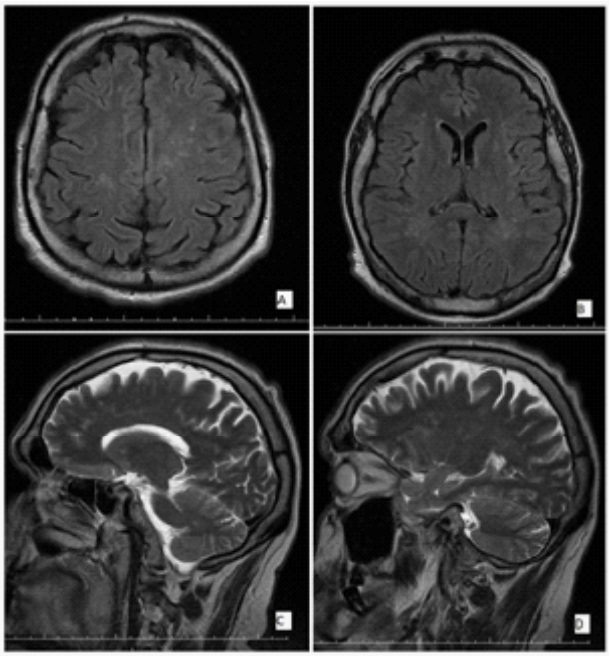

Figure 4: MRI of the CNS performed on the 9th of August 2017, after 40 weeks of antifungal treatment (T2-weighted images).

To sum up, antifungal treatment lasting nearly nine months included 2 weeks of ABLC, 1 week of simultaneous therapy with intravenous fluconazole (800 mg daily) and oral voriconazole (loading dose 800 mg a day, then 400 mg daily), 3 weeks of intravenous fluconazole (800 mg daily), 10 weeks of oral fluconazole (800 mg daily) and 24 weeks of oral fluconazole (400 mg daily). Such a long antifungal therapy supported by ophthalmic surgery and topical treatment led to almost complete regression of inflammatory changes in the CNS, significant improvement of vision and total resolution of genitourinary tract infection and kidney failure.

Furthermore, during the treatment, antidiabetic regimen was modified by adding metformin to insulin and finally, diabetes was controlled with one dose of linagliptin. Antihypertensive treatment consisting of ACE -inhibitor, calcium blocker and β - blocker was introduced. After a nine-month follow-up the patient lost around twenty kilograms of weight.

Discussion

Invasive candidiasis constitutes a disease of increasing importance, especially in seriously immunocompromised patients. The presented case shows that uncontrolled diabetes type 2 may lead to multiple deep organ candidiasis with CNS involvement which typically occurs in patients receiving immunosuppressive drugs or with acquired immune deficiency [4]. Such cases have not been reported in the literature so far. Thus, fungal etiology should be taken into consideration in all patients with uncontrolled diabetes and infection.

On admission, the patient was in an immediately life-threatening condition due to hyperglycemic - hyperosmolar state and progressing fasciitis which led to a slight delay in diagnosis of ocular candidiasis and the infection of the CNS. It is worth remembering that in every case of candidemia a direct ophtalmological examination should be performed, preferably during the first week of disease, even in patients without deterioration of vision [5]. Signs of endophtalmitis are highly suggestive for other deep organ candidiasis [1].

Decreased level of consciousness is the most frequent, but not characteristic manifestation of CNS candidiasis [4]. In our case the MRI of the CNS followed the result of ocular examination and we believe it should be considered in all similar cases.

After diagnosis of CNS candidiasis the patient received antifungal treatment according to the guidelines of Infectious Diseases Society of America (IDSA) from 2016 - ABLC (5 mg/kg daily) for initial treatment and fluconazole (400-800 mg daily) for step-down therapy. We decided to introduce fluconazole therapy early to avoid progression of kidney failure due to drug toxicity. Another argument was the fact that intravenous fluconazole achieves higher concentrations in the cerebrospinal fluid (50 - 90% of serum concentration) and brain parenchyma in comparison with ABLC, and is better tolerated [6].

The optimal treatment for endogenous ocular candidiasis has not been established, however, fluconazole and voriconazole seem to be most favorable. Voriconazole also penetrates brain tissue and abscesses, achieving peak concentrations exceeding those seen in serum (up to 230%) [6]. During fluconazole therapy our patient received voriconazole for 7 days to boost the effect of antifungal therapy. The treatment was associated with significant resolution of inflammatory changes seen in MRI and did not provoke any adverse effects. We believe that a short simultaneous therapy is worth considering in such cases [7].

Control MRIs of the CNS in course of subsequent pharmacotherapy with fluconazole showed further regression of inflammatory changes proving its effectiveness. The appropriate duration of pharmacotherapy in CNS candidiasis is not defined and the treatment should last until resolution of radiological abnormalities. More advanced imaging techniques are needed to decide on finishing antifungal therapy earlier.

Systemic antifungal therapy focused on CNS candidiasis was also appropriate for endophthalmitis. Due to macular involvement the patient required additional intravitreal injections of Amphotericin B. Since the effect of ophthalmological treatment was unsatisfying, bilateral vitrectomy was performed that, in case of vitritis, allowed to remove fungal exudates inaccessible to systemic agents. In our patient, complex antifungal therapy singificantly contributed to the preservation of vision.

Conclusions

All patients with candidemia should undergo a dilated ophthalmological examination within the first week after positive blood cultures to diagnose an early stage of chorioretinitis and avoid late recognition of CNS and other organ involvement.

In patients with CNS candidiasis antifungal therapy should be continued until the resolution of all signs, symptoms and radiological abnormalities.

Acknowledgment

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