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Fungaemia due to *Cryptococcus laurentii* as a complication of immunosuppressive therapy – a case report

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ABSTRACT

Recently, infections caused by *cryptococci non-neoformans* have been increasingly recognized. *Cryptococcus laurentii* was previously considered saprophyte and thought to be non-pathogenic to humans. However, in favorable circumstances like diminished immunity, it seems to be an important pathogen. We present a case of fungaemia caused by *Cryptococcus laurentii* in a young man with membranoproliferative glomerulonephritis on aggressive immunosuppressive therapy. We also considered a tick-borne infection because of the endemic area of ticks' occurrence. Most cases of fungaemia caused by *Cryptococcus laurentii* were successfully treated with fluconazole. We still observed septic fever and positive microbiological blood tests after 3 weeks of treatment with fluconazole in our patient. Therefore, among the others, a computer tomography of abdomen was done, which revealed an inflammatory (presumably mycotic) focus near right lobe of the liver. Accordingly, we started treatment with itraconazole. Controlled microbiological blood tests after 5 weeks of itraconazole therapy were negative. Until now, only one case of fungaemia caused by *Cryptococcus laurentii* with use of itraconazole was reported. Such an unusual fungal infection needs guidelines dealing with earlier diagnosis, treatment and prophylaxis to protect immunocompromised hosts.

Key words: *Cryptococcus laurentii*, immunosuppressive therapy, case report

INTRODUCTION

Patients with impaired immunity are at risk of fungal infections. Recently, there have been an increasing number of infections caused by *non-neoformans cryptococci*, e.g. *Cryptococcus laurentii,* which have been generally considered to be non-pathogenic [1]. It is widely distributed throughout the world, including the Caribbean, Antarctic and the Himalayas and can be acquired from air, water, wood, soil, pigeon excrements as well as various foods, such as cheese, fruit, pork products, bean and wine [1]. It has also been isolated from the milk of cows suffering from mastitis [2]. Pigeon excrements are most likely to be a major reservoir of *Cryptococcus laurentii* [3]. *Cryptococci*, commonly referred to as saprophytes, invade the human body via the respiratory routes, alimentary tract or injured skin. From the portal of entry, they are transported via bloodstream to other parts of the body [3,4]. *Cryptococcus laurentii* has been divided into two phylogenetic groups, according to assimilation patterns of the respective medium components [3,5]. The species is characterized by a substantial genetic diversity [3]. Resistance to antifungal therapy is caused by a change in the integrity of the cellular wall of the fungus, which is associated with melanin deposition [6].

Cryptococcus laurentii appears to be pathogenic rarely, and only in specific conditions, usually in patients with impaired immunity, e.g. due to leukaemia or HIV infection (especially with CD4+ cell count below 100/μl), immunosuppressive therapy (e.g. after organ transplantation) and neutropaenia. Until the year 2007, a total of twenty cases of *Cryptococcus laurentii* infection had been reported worldwide [1]. Most of them were clinically manifested by fungaemia with fever, hypothermia or septic shock. In others, the central nervous system, lungs, injured skin, eye and peritoneum were affected [1]. A study carried out in Poznań has confirmed that *Cryptococcus laurentii* is a rare cause of infections. Among 339 patients after kidney transplantation screened for yeast-

like fungal infections, this kind of infection was found in 33 cases out of which only one case was caused by *Cryptococcus laurentii* [7]. During the last 10-year-period, in our hospital, there was one documented case of *Cryptococcus neoformans* infection in a HIV-infected patient. The current report describes the first case of fungaemia due to *Cryptococcus laurentii* in our centre.

CASE PRESENTATION

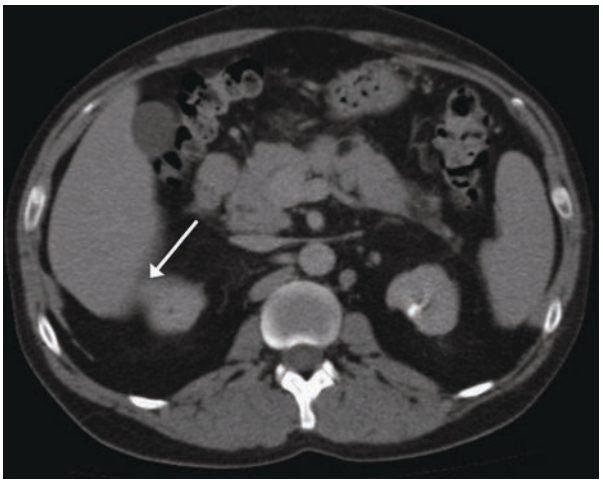
In September 2008, a 39-year-old patient was admitted to the Department of Nephrology due to persistent fever (38 - 39°C) of 7 days' duration. The temperature increased in the morning hours and decreased in the afternoon, both spontaneously and after taking antipyretics. After biopsy diagnosis of type I membranoproliferative glomerulonephritis in May 2008, the patient was treated for 3 months with prednisone at a dose of 1 mg/kg (60 mg) and cyclophosphamide (subsequent doses each month 408 - 612 - 510 mg/m^2 of the body's surface, respectively). The patient underwent removal and calibration of the posterior urethral valve due to nocturia at the age of 8 and 15 as well as endoscopic dilation of the urethra due to urethrostenosis in the year 2004 and had a history of chronic urinary tract infection and hypertension of a few months' duration. The immunosuppressive therapy was started taking into account the renal ultrasound scan (100 mm length and hyperechogenic cortex of each kidney), high azotaemia, proteinuria level > 1.5 g/24h and young patient's age.

On admission, the physical examination revealed the following: body temperature 37°C, dry mucosas, steroid-induced acne type changes on the chest skin, heart rate 100/min, RR 110/70 mmHg. No neurologic abnormalities were observed.

Accessory investigations showed elevated levels of urea (202 mg/dl) and creatinine (3.7 mg/dl), which were higher than a month before (149 mg/dl and 3.0 mg/dl, respectively). Other findings included proteinuria (30 mg/dl in a single urine sample), erythrocyturia, aseptic leukocyturia, elevated CRP level (30 mg/l) with leukopaenia (WBC 3,71x10^3/μl) and procalcitonin level below 0.5 ng/ml. The activity of complement fractions C3 and C4 was not reduced. Tests were negative for ANA, cANCA and pANCA, for IgM antibodies against cytomegalovirus, for IgM and IgG against *Borrelia burgdorferi* (endemic region), and IgM and IgG against toxoplasma. The result of the test for toxoplasma-specific IgG antibody was doubtful and that for IgM antibodies against tick-borne encephalitis virus (endemic region) was weakly positive. Neither viral hepatitis type C RNA nor type B antigen was detected in the blood.

The X-ray picture of the chest and echocardiographic examination were normal. The ultrasound scan of the abdomen was similar to those seen during previous hospitalizations: both kidneys were 98mm long, with hyperechogenic cortex and

Figure 1. **Inflammatory infiltration in the perirenal space.**



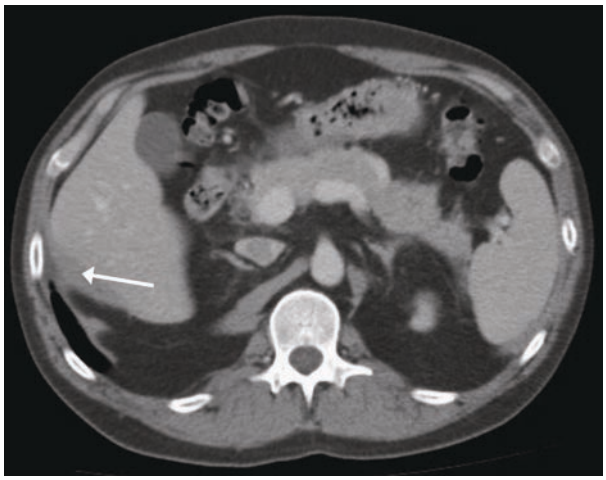
blurred parenchyma/sinus differentiation. No other abnormal findings were noted.

Microbiological investigations (urine and tonsillar swab cultures) showed no increase in pathogens. No bacteria were cultured from the blood cultures collected three times (every 15 min., different sites of needle puncture) at the fever peak. However, on day 6 of incubation, all the three samples demonstrated the growth of the fungus *Cryptococcus laurentii*, susceptible to amphotericin B, voriconazole, itraconazole and fluconazole. For an initial aerobic and microaerophilic bacterial as well as fungal identification an automatic system BactAlert 3D and BactAlert FA medium (bioMérieux Inc, Marcy l'Etoile, France) were used. The temperature of incubation was 37°C. Detailed fungal identification was performed in temperature 30 °C for 48 h with the Sabouraud medium (EMAPOL, Gdańsk, Poland). For distinction of the yeast-like fungi from Candida albicans species ChromoAGAR Candida medium (EMAPOL, Gdańsk, Poland) was used. In the case of non-Candida albicans fungal infection an automatic system VITEC 2 and YBC (bioMérieux Inc, Marcy l'Etoile, France) was used. Fungal drug-resistance was determined by ATBFUNGUS3 (bioMérieux Inc, Marcy l'Etoile, France) system.

Despite antifungal therapy (intravenous fluconazole 200 mg/24h for a week, then oral 200 mg for 2 weeks), *Cryptococcus laurentii* was still detected in blood cultures performed in the subsequent weeks, with identical drug-sensitivity as before. Computed tomography scans of the chest and abdomen were taken, revealing a hypodense fascicular area along the lower margin of the right hepatic lobe in the posterior part (width 12 mm, length 56 mm, mean density 40 HU, amplified to 60 HU, i.e. much less than in normal liver parenchyma), descending in segments towards the perirenal space (*Fig. 1; Fig. 2*).

Prior to obtaining the results of the first blood culture test, the patient received clinically ineffective therapy with amoxicillin + clavulanic acid. As fungaemia persisted despite fluconazole administration for 3 weeks, itraconazole treatment was started (once daily 200 mg oral for 5 weeks). No

Figure 2. **Inflammatory infiltration along the lower margin of the right hepatic lobe in the posterior part.**



subsequent cyclophosphamide pulses were administered and the prednisone dose was gradually decreased to 15 mg/24h. Nephroprotective treatment (ACEI, ARB, statin), hypotensive therapy (calcium channel blocker, loop diuretic), ASA, proton pump inhibitor, vitamin D_3 analogue and calcium carbonate application were continued.

After, three weeks of itraconazole therapy the fever subsided and the acute phase parameters and leucocytosis were normalized. The titres of IgM and IgG antibodies against tick-borne encephalitis, which were repeatedly determined as recommended by a specialist from the Neuroinfection Ward, were negative. During the fifth week of antifungal therapy, three subsequent blood cultures were performed, the results of which were also negative. A consulting surgeon prescribed observation of the perihepatic lesion. Follow-up CT scan of the abdominal cavity taken after 4 weeks revealed a decrease in the hypodense fascicular area to 9 mm (width) and 40 mm (length) in the vicinity of the right hepatic lobe. Itraconazole therapy (200mg/24h) has been continued for four weeks now, but its duration depends on the results of follow-up abdominal cavities CT.

DISCUSSION

The patient presented in this report was burdened with a risk of fungal infection. Leukopaenia occurred in the fourth month of treatment for membranoproliferative glomerulonephritis with cyclophosphamide and prednisone. Due to features of infection, despite partial remission of the primary disease, cyclophosphamide was withdrawn and only a small dose of prednisone was maintained. The patient was persistently febrile even though the pathogen was determined and antifungal therapy was instituted in accordance with drug sensitivity tests (fluconazole). Taking into account the patient's place of living, which is an endemic region for tick-borne diseases, as well as positive titres of IgM antibodies against tick-borne encephalitis, the coexistence of CNS viral infection and carrying the fungus by a tick was considered. Cross-reaction between IgM antibodies and viruses of the *Flaviviridae* family, including West Nile virus, Japanese encephalitis or yellow fever e.g. after vaccination before a planned trip to the countries with an endemic incidence of these diseases, was also taken into consideration [8]. However, the above viral infections were excluded as the titres of IgM and IgG antibodies in follow-up tests were negative and the patient had no history of vaccination or a possible exposure to *Flaviviridae.* In an abortive form of tick-borne encephalitis (lack of neurologic symptoms), the IgM and/or IgG antibodies should be maintained. In this case, a laboratory error is a likely explanation.

A three-week targeted therapy was not effective as the follow-up blood culture repeatedly showed the presence of *Cryptococcus laurentii*, with the same sensitivity to fluconazole and itraconazole as before. No therapeutic regimen has been proposed so far to treat persistent cryptococcosis. Major limitations are associated with a very small number of the reported cases, whereas the choice of antifungal drug depends on the location of the focus, course of infection and immunological condition of the patient. Most of the previously described fungaemias (6 cases) were successfully treated with fluconazole for 17 days on average [9,10]. Our patient failed to respond to fluconazole, as after 21 days of treatment, *Cryptococcus laurentii* was still isolated from his blood. CT examinations of the chest and abdominal cavity were performed, revealing an inflammatory focus in the vicinity of the right hepatic lobe that might correspond to a fungal lesion. The focus may have been inaccessible to fluconazole and hence no improvement occurred after the initial therapeutic stage. Itraconazole was instituted in accordance with fungus sensitivity test. Moreover, itraconazole, compared to fluconazole, is characterized by a better penetration to tissue organs, e.g. lungs, liver, kidney and a lower kidney elimination rate. The length of the therapy (5 weeks) depended on the clinical condition of the patient and follow-up blood cultures. So far, only one patient with fungaemia responded well to itraconazole therapy. He had a non-Hodgkin lymphoma and had been previously treated with ketoconazole as antifungal prophylaxis [1].

In our study, advanced renal failure and a likely accumulation of the antifungal drug and its metabolites caused additional problems. Physiologically, 35% of the itraconazole dose is excreted during the week in the urine in the form of metabolites, e.g. hydroxyitraconazole with *in vitro* activity, similar to that of the native compound. A substantial decrease in the immunosuppressive therapy could diminish renal function at any moment. Thus, creatinine clearance dosage adjustment did not correspond to the actual drug excretion capabilities.

CONCLUSIONS

Wide application of immunosuppressive drugs increases the possibility of infection due to new pathogens. Unfortunately, rare infections are difficult to detect and pose an increasing risk of complications. Until now, no standard procedure has been introduced for the prevention and treatment of this type of fungal infections. It seems that in the case of persistent fungaemia, antifungal therapy should last for at least a few months.

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