Clinical Case Report

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Recurrent fever of unknown fungal infection in a low-risk patient

A case report

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Abstract

Rationale: Fungal infectious disease does not usually occur in low-risk patients. Clinicians tend to ignore the role of fungi in the fevers of low-risk patients. If there is not timely control of fungal infections and associated fever, the disease will continue to worsen, resulting in physical dysfunction or death.

Patient concerns: Recurrent fever continued for 1 month in a young adult.

Diagnoses and interventions: Non-albicans Candida (NAC) species probably was the main pathogen in this case based on the resolution of fever after capsofungin administration.

Outcomes: The fever and the associated indicators, including white blood cell count, C-reaction protein, erythrocyte sedimentation rate, and BDG levels, showed improvement quickly. The patient left the hospital successfully after 18 days of caspofungin treatment. There was no recurrent fever at a follow-up of 1 year.

Lessons: Clinicians should be aware that the incidence of fungal infection is increasing in low-risk patients. The BDG assay is still an effective tool used to diagnose invasive fungal diseases. Caspofungin is an effective drug for the treatment of some unknown fungal infections.

Abbreviations: BDG = (1,3)-β-D-glucan, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IFD = invasive fungal disease, MRI = magnetic resonance imaging, NAC = non-albicans Candida, NCAC = non-Candida albicans Candida, TOD = time of IFD diagnosis.

Keywords: (1,3)-β-D-glucan, caspofungin, fever, low-risk patient, non-albicans Candida, unknown fungal infection

1. Introduction

Fever is one common clinical presentation of internal medicine. The usual causes are viral infection, bacterial infection, tuberculosis, worms, autoimmune disease, hematological-lymphocytic malignancy, and other tumor diseases. Fungal infection does not usually occur in low-risk patients. In the last 30 years, there has been a significant increase in the incidence of fungal infections in humans,[1] especially when they have the following risks: longer-term use of broad-spectrum antibiotics, immunosuppressive therapies, intensive care unit patients, human immunodeficiency virus infection, and invasive surgical procedures (such as solid organ transplantation and hematopoietic stem cell transplant recipients).[2,3] Clinical diagnosis of invasive Candida infection is challenging. Late treatment or no treatment is independent predictor of death in invasive candidiasis.[3] If there is not timely control of fungal infections and associated fevers, the disease will continue to worsen, resulting in physical dysfunction, such as dysfunction of coagulation, liver and kidney function or cyclic respiratory failure.

2. Ethical statement and consent

Informed written consent was obtained from the patient's parents for publication of this case report and accompanying images. Ethical committee approval was not necessary. This study will not cause adverse effects on the patient.

3. Case presentation

A 35-year-old Chinese female in the Han population, a real estate salesperson, complained to her primary care physician of fever, small abscesses on the neck and vulva, and a slight cough with no expectoration. The highest body temperature reported was 41°C. With the fever, she complained of accompanying headaches,

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dizziness, fatigue, and muscle soreness, but not nausea, vomiting, abdominal pain, diarrhea or frequent urination. Diclofenac suppositories could reduce body temperature to normal, but fever reappeared 6 to 7 hours later. She received treatment with ceftazidime injection during the next 4 days, but the fever was not controlled. On the fourth day, a suspected allergy (fatigue and numbness on hands and mouth) to ceftazidime appeared. Then, she received a dexamethasone injection. The symptoms of fatigue and numbness were relieved. For further treatment, she came to our hospital. One week before, she had traveled overseas. She did not have a history of close contact with a sick person or unprotected sex with unspecified partners. She also lacked any relevant medical or family history. She was a nondrinker and had no smoking history. The patient had a history of suspected allergy to ceftazidime. Physical examination showed heart rate at 72 beats/min, blood pressure 106/72 mmHg, respiratory rate 19 breaths/min, temperature 35.8°C, and oxygen saturation 97% on room air. No abnormal rales on the lung field. Chest computed tomography showed a few funicular and patchy shadows on the bilateral lung (Fig. 1A). The white blood cell count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) levels were 7.74 g/L (4–10 g/L), 54.5 mg/L (the upper normal value of the CRP assay = 8 mg/L), and 92 mm/h (the upper normal value of the ESR assay = 20 mm/h), respectively. Assays for tuberculosis, pneumonia chlamydia, pneumonia mycoplasma, and HIV infection were negative. Widal assay was negative.

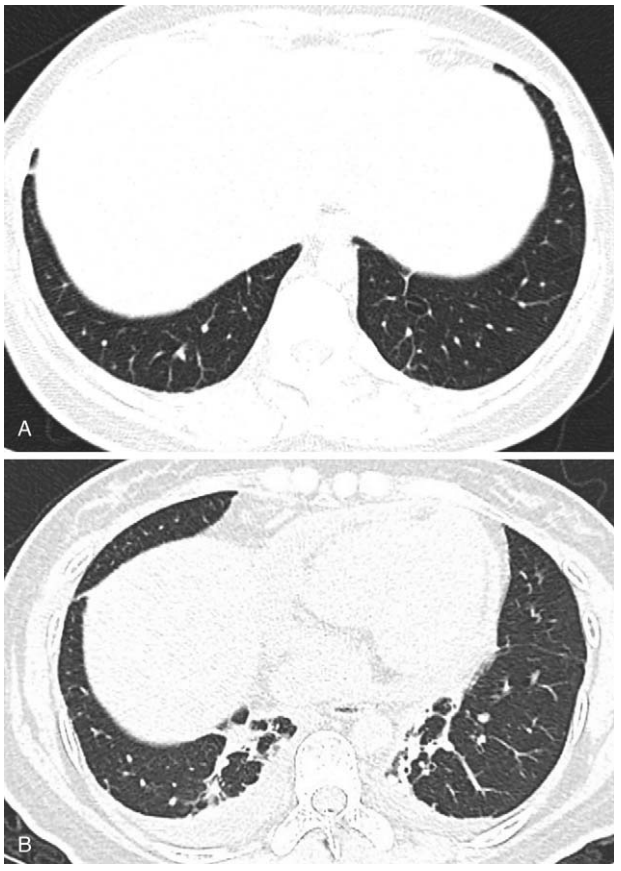

Figure 1. Chest computed tomography showed a few funicular shadows and patchy shadows on the bilateral lung on the third day (A). On the 18th day, there are obviously increased funicular shadows and patchy shadows on the bilateral lung compared to those in the initial chest computed tomography (B).

Ultrasonography of thyroid, heart, liver, spleen, pancreas, uterus, ovary, and urology were negative. Bone marrow punctures showed a proliferation of nuclear cells; the granulocytic series was 57.5%, and the erythrocytic series was 34.5%. An assay for antinuclear antibodies showed that SSA and Ro-52-Ab were positive; however, no symptoms of Sjogren syndrome or systemic lupus erythematosus were present. Expectorated sputum smears were negative for bacteria and acid-fast bacilli. Urinary routine assays were negative. Although it was difficult to determine the causative pathogen, a presumptive diagnosis of acute upper respiratory infection was considered. The treatment of moxifloxacin 0.4 g and lentinan (for enhancing immunity) intravenously every day was initiated. For the first 3days, the body temperature was normal. Three days later, the temperature rose to 37.1°C. Because the SSA and Ro-52-Ab were positive, we suspected rheumatism; we then added the treatment of hydroxychloroquine sulfate tablets (0.2 g, qd) and total glucosides of peony capsules (0.6 g, bid-traditional Chinese medicine with an immunoregulation effect, according the suggestion of the rheumatology and immunology department). On the 8th day, body temperature rose to 42°C; the white blood cell count and CRP were elevated. The result of the galactomannan assay was negative. The result of the (1,3)-β-D-glucan (BDG) assay was positive (253.6 pg/mL, the upper normal value of the BDG assay = 100.5 pg/mL). Itraconazole liquid (0.1 g Po twice a day) and Zhenqi Fuzheng capsule (traditional Chinese medicine with an immunoregulation effect, 2 grains, tid) were considered, along with stopping the use of peony capsules. The skin abscess could be associated with the *Staphylococcus aureus* infection. Teicoplanin injection (0.2 g intravenously every day) was used from the second day of itraconazole liquid treatment. Body temperatures showed improvement day by day until the 7th itraconazole liquid treatment. On the 18th day when she admitted to our hospital, there are obviously increased funicular shadows and patchy shadows on the bilateral lung compared to those in the initial chest computed tomography (Fig. 1B). Fever reappeared, and the patient's temperature reached 39.2°C. BDG assay levels, white blood cell count, CRP, and ESR levels were increased to 3732.6 pg/mL, 11.38 g/L, 188.17 mg/L, and 123 mm/h, respectively. Considering the aggravation of the immunological inflammatory response, loxoprofen tablets (60 mg, q8 h) and antelope horn capsules (0.45 g, q12 h) were used. Oral itraconazole liquid and intravenous teicoplanin were stopped. Then, the body temperature decreased but was still high, especially on the 9th day of loxoprofen treatment. The body temperature rose to 38.2°C. The next day, caspofungin injection (50 mg intravenously every day) was used. After a 1-week treatment of caspofungin, the fever was controlled gradually. The white blood cell count, CRP, ESR levels showed complete improvement (Fig. 2). BDG levels declined also, but slowly. The BDG level on the 47th day was 1013.1 pg/mL (Fig. 2). The changes in body temperature and adjustment of treatment in the hospital are summarized in Figure 3. The patient left the hospital successfully after 18 days of treatment.

4. Discussion

Fungi are conditioned pathogens. A few fungi can infect the normal human body directly. The incidence of invasive fungal infections has increased during the past 20 years, and the population of patients at risk has expanded to include those with a broad list of medical conditions.[4] China has a high rate of antibiotic usage for both inpatients and outpatients. Two-thirds

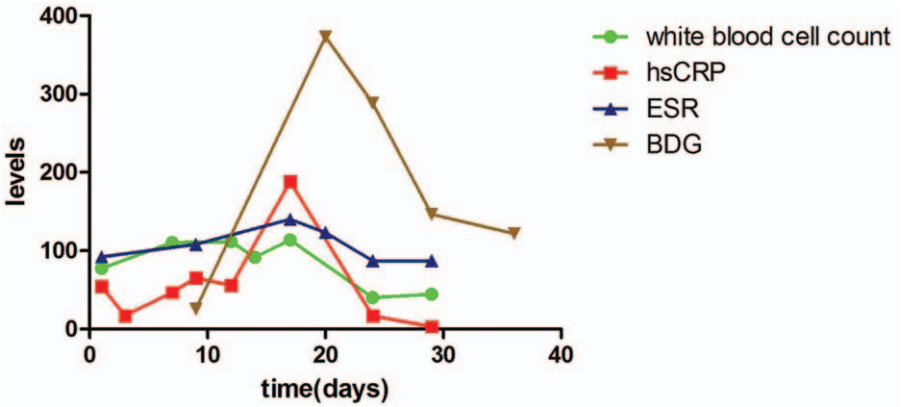

Figure 2. Changes in the levels of (1,3)-β-D-glucan (BDG), inflammatory markers, and white blood cell count. There were 4 treatment adjustments in the hospital. Only after the last adjustment using caspofungin treatment, the white blood cell count, CRP, and ESR levels showed complete improvement, and fever was controlled completely. Some data points in Figure 3 were adjusted as follows: "white blood cell count" data were presented as magnification of ×10. "BDG" data were presented as minification of ×0.1. ESR = erythrocyte sedimentation rate, hsCRP = high-sensitivity C-reactive protein.

of inpatients use antibiotics in China, compared to approximately one-third of inpatients in many other countries. The World Health Organization has recommended that Chinese hospitals decrease the rate of inpatient antibiotic usage to 30%; the Chinese Government has suggested a more modest reduction to a target rate of 50%.[5] Potential dangerous consequences of antibiotic abuse will encourage the rise of "superbugs" and conditioned pathogen infections (such as fungi). Low-risk patients infrequently suffered because of fungal infection. In modern Chinese society, the process of industrialization and informatization has accelerated, and the cost of living has risen. The rhythm of life and the pressure of work have increased for young people. Young people tend to be in suboptimal health.

In this case, we speculate that the conditional fungal infection emerged after 1 week treatment of antibiotics in the hospital. The patient's body temperature in the hospital showed increases 1 week later. During this time, the levels of BDG and inflammatory markers (white blood cell count, CRP, and ESR) mainly rose. After treatment with caspofungin injection, the patient's temperature was decreased and stable within the normal range. The inflammatory markers returned to nearly normal after 1 week. Following continuous treatment with caspofungin for 11 days, the patient remained in a stable condition. This outcome was supported by following 3 observations. First, the level of the BDG assay was slightly high initially. It rose along with the disease progression. Second, the lung lesions were close to normal when she was admitted to the hospital. Later, the lesions progressed even when broad-spectrum antibiotics were used (Fig. 1B). Third, the treatment was effective (the body temperature was controlled for >1 week, and inflammatory

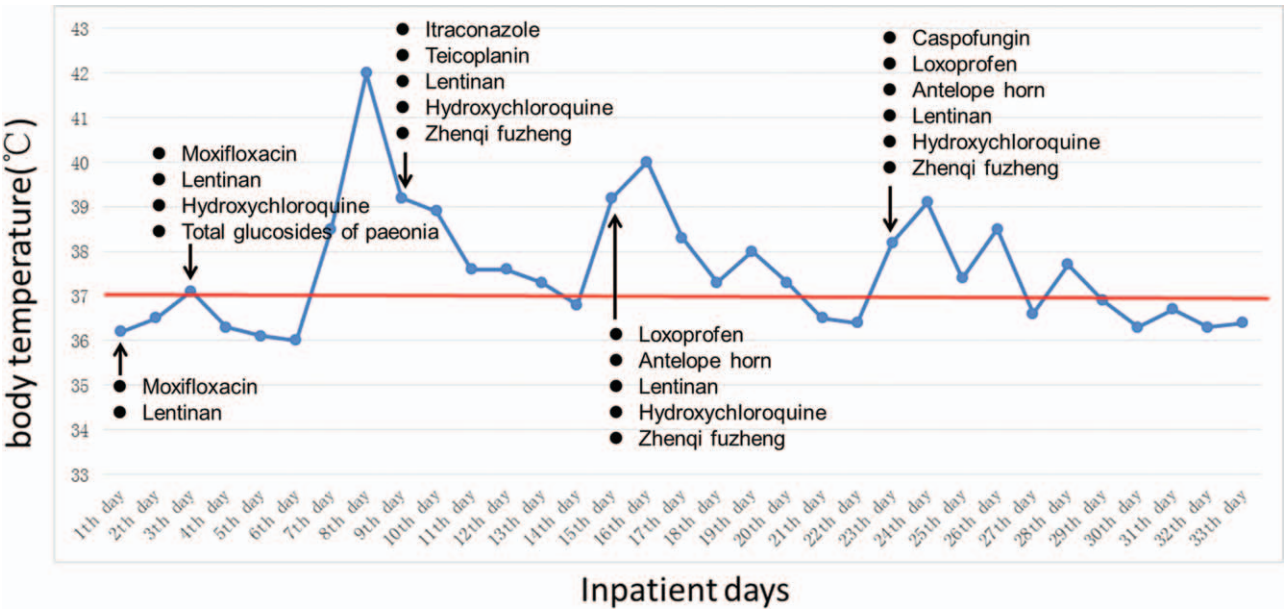

Figure 3. The changes in body temperature and adjustment of treatments in hospital. The body temperature gradually rose to peak. After nearly a week of adjusted treatment, the body temperature gradually dropped to normal, but it rose again until the use of caspofungin injection. After the treatment with caspofungin, the temperature was decreased and stable within the normal range.

marker and BDG levels decreased) when she received caspofungin injection. There were some risks for fungal infection, such as the use of broad-spectrum antibiotics (ceftazidime, moxifloxacin, and teicoplanin) in the past and the increased pressure of work for young people in modern China.

The diagnosis in this case is limited. Only by finding the pathogen or getting molecular techniques evidences can we draw an accurate conclusion. We just speculated that non-Candida albicans Candida (NCAC) species was the main pathogen in this case. Invasive candidiasis is the most common fungal disease among hospitalized patients in the developed world. The global shift in favor of NCAC species is troubling, as is the emerging resistance to antifungal drugs.[6] A report showed that NCAC species such as *Candida glabrata*, *Candida tropical*, *Candida kruseii*, and *Candida parapsilosis* are now frequently identified as human pathogens.[6] Among them, *C glabrata* was more common than other NCAC species in causing invasive fungal infections.[7] For many years, *Candida glabrata* was considered a relatively nonpathogenic saprophyte of the normal flora of individuals and certainly not readily associated with serious infection in humans. However, following the widespread and increased use of broad-spectrum antibiotic treatment, together with immunosuppressive therapies, the frequency of mucosal and systemic infections caused by *C glabrata* has increased significantly.[8] Compared with other NCAC species, *C glabrata* is more frequent in candidemia patients according the studies from Northern Europe and the United States, and *C glabrata* is also more common in the elderly.[9] Compared with that of other NCAC species infections, the mortality rate associated with *C glabrata* is the highest.[10] A report showed mortality among patients with invasive candidiasis is as high as 40%, even when patients received antifungal therapy.[5] Until recently, few studies had evaluated independent risk factors associated with nosocomial *C glabrata* acquisition and subsequent disease. Not much is known about the hospital reservoirs of *C glabrata*. Studies in this area will contribute toward the identification of prophylactic strategies against these recently emerged pathogens.

Early diagnosis and treatment are crucial in invasive fungal diseases (IFDs). BDG is a polysaccharide glucose polymer that is found in a broad range of fungal agents. The sensitivity of serum BDG as a diagnostic assay for fungal infection has been reported to be sufficiently high to reduce the number of cases treated empirically and the necessity for bronchoscopy, in addition to being sufficient for ruling out fungal infection.[11] However, there was not adequate sensitivity at the time of IFD diagnosis (TOD). Undetectable serum BDG does not rule out an early IFD, when the clinical suspicion is high.[12] This finding is consistent with the results of this case. After >10 days, the result of the BDG level reached 253.6 pg/mL in this case. More than 20 days later, BDG level reached the highest level of 3732.6 pg/mL. We observed a slower BDG decrease in this patient who received successful treatment of *C glabrata*, whereas patients with a follow-up showed persistently elevated BDG levels.[12] The BDG level on the 47th day was 1013.1 pg/mL. These findings are consistent with the results of other studies suggesting that in 70% of the patients with a follow-up, BDG negation occurred in >1 month for candidemia. The same study showed a trend toward more frequent deep-seated localizations associated with candidemia in patients with slow decrease profiles versus those with rapid decrease profiles.[12]

5. Conclusions

The frequency of systemic fungal infections has increased significantly in humans, even in humans who lack obvious risks. The BDG assay is still an effective tool used to diagnose IFDs. Clinicians should be aware that the incidence of fungal infections is increasing in low-risk patients. Early use of effective drugs against fungal infection, such as caspofungin, can effectively prevent disease progression.

Author contributions

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Writing – original draft: Tang-meng Guo.

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