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Case report

Disseminated *Lomentospora prolificans* infection that could have been predicted: A case report

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ABSTRACT

Lomentospora prolificans is a rare, filamentous fungus, that causes a disseminated infection in immunocompromised individuals. Disseminated infections caused by the fungus are difficult to diagnose early. It is resistant to multiple antifungal agents and has a high mortality rate. We encountered a case in which the involvement of this fungus was indicated by a history of antifungal prophylaxis and an elevated serum 1,3-beta-D-glucan (BDG) level. A 76-year-old female with myelodysplastic syndrome that developed into overt leukemia was administered oral posaconazole as antifungal prophylaxis. She was admitted to the hospital to determine the cause of her fever, where no new abnormalities other than an elevated serum BDG level were observed. Unfortunately, the patient died due to acute respiratory failure on the same day of admission. The day after her death, *L. prolificans* was detected in a blood culture taken upon her admission. *L. prolificans* should be suspected based on the history of antifungal prophylaxis and an elevated serum BDG level, as these are risk factors for infection by this pathogen. Blood cultures are useful to provide a diagnosis. If treated early, before it is detected in culture, the mortality rate can be decreased.

Introduction

Antifungal prophylaxis in patients with hematological malignancies is becoming more common, leading to changes in fungal epidemiology, including the detection of resistant fungal pathogens and novel species that cause breakthrough invasive fungal infections [1]. *Lomentospora prolificans* poses an emerging threat. As disseminated infection often occurs without local clinical findings, early diagnosis is difficult, and treatment is delayed. To date, no method has been established to predict the involvement of this fungus. In this case report, we describe that *L. prolificans* should be suspected based on the history of antifungal prophylaxis and elevated serum 1,3-beta-D-glucan (BDG) level, as these are risk factors for infection by this pathogen.

Case

A 76-year-old female was diagnosed with myelodysplastic syndrome developing into overt leukemia 6 months previously. As Eastern Cooperative Oncology Group Performance Status 1, the patient was treated with azacytidine and venetoclax chemotherapy for one month. However, owing to ineffective chemotherapy, it was discontinued and the patient was transitioned to comfort-only measures. She was administered oral levofloxacin (250 mg, once daily), trimethoprim-sulfamethoxazole (80 mg/400 mg, once daily), and posaconazole (300 mg, once daily) as antimicrobial prophylaxis. Forty-five days prior to admission, she was asymptomatic; however, laboratory blood tests showed a C-reactive protein (CRP) of 27.1 mg/L (reference range, 0–1.4 mg/L) and amoxicillin/clavulanic acid (500 mg/125 mg, three times daily) was added to her medication. Ten days prior to admission, she developed a fever of 37 ℃ and laboratory blood tests showed a CRP of 302.3 mg/L. She was admitted to our hospital because of severe fatigue that rendered her immobile. On physical examination, her vital signs were as follows: temperature 36.1 ℃, heart rate 76 beats/min, and blood pressure 87/58 mmHg. Her oxygen saturation level was 97 % on ambient air by pulse oximetry. There were no obvious local clinical findings. Laboratory blood tests, drawn at admission, showed: white blood cell count $1.6 \times 10^3/\mu L$, CRP 387.8 mg/L, and serum BDG 393.9 pg/mL. Blasts and neutrophils accounted for 27 % and 7 % (112/μL) of

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white blood cells, respectively. The patient died of acute respiratory failure on the same day. Autopsy imaging showed no obvious abnormal findings that could be the cause of death. Pathological autopsy revealed no abnormal findings on gross examination. On the day after her death, a filamentous fungus was detected in the blood culture taken upon admission (Fig. 1). The filamentous fungus was genetically identified as *L. prolificans* by analysis of the internal transcribed spacer of the 18 S ribosomal DNA sequence. Drug susceptibility testing showed that the minimum inhibitory concentrations were micafungin > 16 μg/mL, caspofungin 16 μg/mL, amphotericin-B > 16 μg/mL, itraconazole > 8 μg/mL, and voriconazole > 8 μg/mL. These values are clinically unattainable for any of the antifungal agents. Microscopic pathological examination using Grocott's stain revealed fungal infiltration from blood vessels to the heart, lungs, and kidneys (Fig. 2). Based on the above findings, we concluded that the main cause of death was multiorgan failure due to disseminated *L. prolificans* infection against a background of myelodysplastic syndrome that developed into overt leukemia.

Discussion

The presented case demonstrates the following two points. First, consideration should be given to disseminated *L. prolificans* infection in immunocompromised patients receiving oral posaconazole as antifungal prophylaxis who develop fever without local findings or an elevated serum BDG level. Second, blood cultures are useful for diagnosing disseminated *L. prolificans* infection. Oral posaconazole is recommended as antifungal prophylaxis for patients at risk of severe and prolonged neutropenia, such as those with acute myeloid leukemia, myelodysplastic syndrome, and following hematopoietic stem cell transplantation [2]. However, *L. prolificans* showed a minimum inhibitory concentration that is higher than what is achievable as a blood concentration for several antifungal drugs, including amphotericin B, micafungin, posaconazole, voriconazole, itraconazole, and isavuconazole [3,4]. Furthermore, *L. prolificans* is present in the environment, including the soil, making prevention of exposure difficult. Initially reported in arid climates such as Spain, Australia, and the southwestern United States, it has recently been reported in other varied climates such as Japan, Korea, Thailand, and Brazil [5]. When this fungus is detected in sterile specimens, the serum BDG level rises above 80 pg/mL even if not disseminated, typically increasing by a mean of 12 days before the culture collection date that tests positive [6]. The diagnostic accuracy of the serum BDG level for detecting this fungus has not been established [7]. However, when combined with a history of administration of oral posaconazole as an antifungal prophylaxis, the likelihood of fungal involvement can increase before the results of culture tests are available. If involvement of this fungus is suspected, combination therapy with voriconazole and terbinafine is recommended [8]. Blood cultures are useful for diagnosing disseminated *L. prolificans* infections and have been shown, in a previous study, to be positive in 75.3 % of the disseminated *L. prolificans* infections [5]. *Aspergillus* spp. and *Scedosporium* spp. are difficult to cultivate in blood; therefore, the growth of filamentous fungi in blood cultures increase the likelihood that the pathogen is *L. prolificans* [9,10]. However, blood culture may not always facilitate an early diagnosis. In a case review of 162 *L. prolificans* infections, 82 % of patients where the fungus was detected in a blood culture tested positive immediately before death [11]. In addition, Gram-stained *L. prolificans* detected in blood cultures was found in only three cases, as far as we could determine [12–14]. Laboratory staff and clinicians should consider the possibility of *L. prolificans* when filamentous fungi are present in cultures.

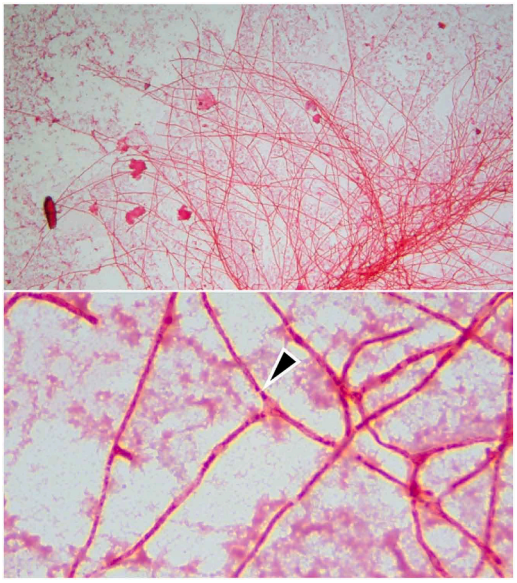

Fig. 1. Microscopic Gram staining in blood culture. (A) Original magnification, × 100. (B) Original magnification, × 1000. *L. prolificans* forms septate hyphae (arrowhead). Conidiogenesis cannot be observed.

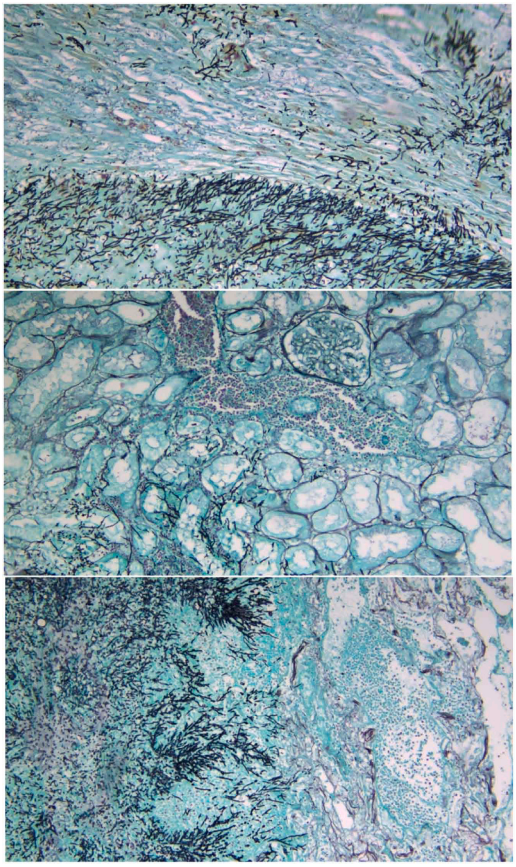

Fig. 2. Microscopic Grocott's staining in a tissue section (Original magnification, ×100). (A) Interventricular septum. (B) kidney. (C) Lung. *L. prolificans* is infiltrating into the tissue.

Conclusion

The high mortality rate of disseminated *L. prolificans* infections is due to both fungal resistance and the time to initiation of treatment. Based on the history of oral posaconazole use and an elevated serum BDG level, we suspected the involvement of *L. prolificans* before it was detected in culture. This suspicion, specifically when there is an elevated serum BDG level, allows for the earlier initiation of treatment, potentially the reducing mortality rate. Blood cultures remain useful for diagnosis;

however, early therapeutic intervention, based on clinical judgment and laboratory markers, could decrease the mortality associated with this infection.

Ethical approval

The local ethical committee approval does not apply in this case.

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CRediT authorship contribution statement

Koga Sato: Writing – original draft, Project administration. **Toshimasa Hayashi:** Writing – review & editing. **Takuma Ishizaki:** Writing – review & editing. **Masakazu Yoshida:** Writing – review & editing. **Akira Watanabe:** Writing – review & editing, Formal analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Patient consent

Written informed consent was obtained from the patient's family for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author's contributions

KS wrote a first draft of the manuscript. TH, TI, MY and AW critically revised and revised the manuscript. All authors read and approved the final paper.

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