A case of conjunctival ulcer and uveitis caused by *Acrophialophora* sp. in an immunocompromised patient; a case report and literature review

Yusuke Watanabe, Takehito Kobayashi, Itaru Nakamura, Hiroaki Fujita, Midori Shimoinaba, Shinji Fukushima, Yoshitsugu Miyazaki, and Tetsuya Matsumoto

Received: October 27, 2017. Accepted: June 12, 2018
Published online: June 29, 2018
DOI:10.7883/yoken.JJID.2017.471

Advance Publication articles have been accepted by JJID but have not been copyedited or formatted for publication.
A case of conjunctival ulcer and uveitis caused by *Acrophialophora* sp. in an immunocompromised patient; a case report and literature review

Yusuke Watanabe¹², Takehito Kobayashi¹², Itaru Nakamura¹*, Hiroaki Fujita¹², Midori Shimoinaba⁴, Shinji Fukushima¹, Yoshitsugu Miyazaki³, and Tetsuya Matsumoto²

1) Department of Infection Prevention and Control, Tokyo Medical University Hospital, Tokyo, Japan

2) Department of Microbiology, Tokyo Medical University, Tokyo, Japan

3) Department of Chemotherapy and Mycoses, National Institute of Infectious Diseases, Tokyo, Japan

4) Department of Intensive Care, Kameda Medical Center, Chiba, Japan

*Corresponding author

Itaru Nakamura, M.D., Ph.D.
Department of Infection Prevention and Control

Tokyo Medical University Hospital

6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

Tel.: 03-3342-6111 (ext. 2525)

Fax: 03-5339-3817

Email: task300@tokyo-med.ac.jp

Running head: conjunctival ulcer and uveitis caused by Acrophialophora sp.

Keywords: Acrophialophora sp., conjunctival ulcer, uveitis, voriconazole, eye infection
渡邊裕介1)2), 小林勇仁1)2), 中村造1)*, 藤田裕晃1)2), 下緒葉みどり4), 福島慎二1),
宮崎義織3), 松本哲哉2)

1) 東京医科大病院 感染制御部
2) 東京医科大 微生物学分野
3) 国立感染症研究所 真菌部
4) 亀田総合病院 集中治療科

*責任著者連絡先

中村 造
東京医科大病院 感染制御部
郵便番号 162-0845 新宿区西新宿6-7-1

Tel.: 03-3342-6111 (内線 2525);
Fax: 03-5339-3817

E-mail: task300@tokyo-med.ac.jp
Summary

We report the first case of invasive ophthalmologic infection by *Acrophialophora* sp. that was successfully treated using voriconazole (VRCZ). *Acrophialophora* spp., which has been reported to be an opportunistic pathogen, is rare thermotolerant soil fungus, but its pathogenicity remains unclear. A 77-year-old man had neutropenia and prostate carcinoma, and was receiving hemodialysis. His right eye had been infected for 2 days. His conjunctiva was congested and partially formed an abscess. Liposomal amphotericin B (L-AMB) was administered following systemic itraconazole. However, treatment was changed from L-AMB to systemic VRCZ and VRCZ eye drops because his eye symptoms worsened. Subsequently, his symptoms stopped worsening and his vision was maintained. *Acrophialophora* sp. was identified by analyzing regions of internal transcribed spacer and domain 1 and 2 of rRNA gene. He finished the systemic VRCZ for 7 weeks. The mean minimum inhibitory concentration of VRCZ *Acrophialophora* spp. has been reported to be the lowest among various antifungal agents, and our results indicated the efficacy of VRCZ treatment against *Acrophialophora* sp. infection. Our results suggest that invasive *Acrophialophora* sp. infection may require long-term therapy. Further analysis of the clinical spectrum of *Acrophialophora* spp. infection and adequate treatment methods are required in the future.
Acrophialophora spp. is a thermotolerant soil fungus that is rarely detected in clinical samples, and exists in temperate and tropical regions. This fungus has often been misidentified as the genus Paecilomyces. Acrophialophora sp. forms grayish colonies that are black on the reverse side. With age they form pigmented, straight, septate, unbranched, and setae-like conidiphores with thick verrucose walls, which are fertile toward the apex, and flask-shaped, hyaline phialides grouped in verticils (1). Ten cases of infection or colonization with Acrophialophora spp. have been reported to date (Table 1). In most cases the patients were highly immunocompromised, but the pathogenicity and risk factors of Acrophialophora spp. remain unclear. Although voriconazole (VRCZ) demonstrates favorable effects in vitro (1), its efficacy and prognosis in clinical cases remain unclear. We here describe the first case of a human conjunctival ulcer and uveitis caused by Acrophialophora sp., which was successfully treated with VRCZ.

The patient was a 77-year-old man with neutropenia and prostate carcinoma, who was receiving hemodialysis. He was taking bicalutamide, esomeprazole, droxidopa, and febuxostat. He was also taking administration of cefazolin for prosthetic valve endocarditis that was caused by methicillin-sensitive Staphylococcus aureus. His hobby was gardening, and he had a history of travel to various overseas areas, such as the United
States of America, Columbia and other Latin American countries. He did not wear contact lenses and had no history of eye trauma. He was not using any immunosuppressive agents.

The patient came to Tokyo Medical University Hospital with a right eye that had been congested, painful, and blurry for two days (Fig. 1). Laboratory analyses showed a white blood cell count of 400/µL with 4.7% neutrophils, which was a result of drug-induced neutropenia, and a C-reactive protein level of 5.6 mg/dL. His renal function was lost. Liver, respiratory, and circulatory functions were normal, immunoglobulin and complement levels were average, and β-D glucan level was not increased. His right bulbar conjunctiva was congested and partially formed an abscess, which had the possibility of ocular perforation. His iris showed conglutinant uveitis. A corneal scraping was cultured and the administration of cefazolin, bicalutamide, esomeprazole, droxidopa, and febuxostat were stopped as they were causing pancytopenia. Then, the systemic administration of itraconazole (ITCZ), meropenem, and levofloxacin, as well as pimaricin eye drops were started. The corneal scraping was cultured and alternating arthroconidia and flask-shaped phialides were identified in the smear (Fig. 2). We therefore changed the treatment from ITCZ to liposomal amphotericin B (L-AMB, 5mg/kg/day), and VRCZ eye drops were added. However, after changing the treatment to L-AMB, his eye symptoms worsened. Because the fungus was suspected to be *Paecilomyces* spp. from
comparing the sequencing data between testing isolate and registered database such as mycobank and genebank, the treatment was changed from L-AMB to VRCZ (400 mg/day). Finally, the fungus was identified to be *Acrophialophora* sp. by analyzing regions of internal transcribed spacer (ITS) and domain 1 and 2 (D1/D2) of rRNA gene. A previous study of 33 *Acrophialophora* spp. strains demonstrated that they had high sensitivity to VRCZ (1). After systemic administration of VRCZ, the abscess stopped worsening and his vision was maintained. He was discharged after finishing the intravenous administration of VRCZ for 7 weeks without any major side effects, and continued the administration of VRCZ eye drops.

*Acrophialophora* spp. belongs to the sordariomycetes family Chaetomiaceae. The genus is classified into the strains *A. fusispora, A. levis,* and *A. seudatica.* *A. fusispora* was originally categorized in the genus *Paecilomyces. Acrophialophora* spp. is an opportunistic pathogen and a soil fungus found in temperate and tropical regions. We need measured judgement for infection or contamination. The fungus forms straight, septate, unbranched, setae-like conidiphores with thick verrucose walls (1). The colonies of *A. fusispora* appeared white to buff with darker concentric circles on Sabouraud dextrose agar, and a darker gray-brown on potato flake agar. This fungus was considered similar to *Paecilomyces* spp. in forming chains of ellipsoidal to fusiform conidia from basally
swollen phialides that were borne either on conidiophores or directly from the vegetative hyphae (2). Microscopically, previous studies report that this fungus is highly diverse. In some cases they have inflated phialides, as was found in our patient.

*Acrophialophora* spp. is isolated from immunocompromised patients. Only 10 cases have been reported to date, which were from India, France, Sudan, Portugal, and Spain (2, 3, 4, 5, 6) (Table 1). To our knowledge, there has never been a case in Japan. The patients were highly immunocompromised, such as having ALL or cystic fibrosis, or having undergone lung transplantation. Our case had multiple factors of immunocompromization, such as neutropenia, hemodialysis, and prostate carcinoma. These underlying factors were possible causes of the pathogenesis. As the patient had frequently travelled overseas, his infection may be a type of imported mycosis. Furthermore, as his hobby was gardening, there is also the possibility that he acquired this fungus from the soil.

Little data is available regarding the clinical spectrum and characteristics of *Acrophialophora* spp. To date, there have only been two reported cases of human keratitis caused by *Acrophialophora* sp. in which the infection was triggered by a minor trauma, but our case had no trauma. One of the keratitis patients required keratoplasty, and the other patient had only light perception. Because our case also had the possibility of eye
perforation, this fungus may have strong pathogenicity to the eye. In a case of brain abscess caused by this fungus, the patient also had pneumonia, which was presumably caused by the same pathogen. It may have originated from the lung. Therefore, the eyes and airway appear to be the major routes of infection of this fungus.

The in vitro antifungal susceptibility of 33 clinical isolates of Acrophialophora spp. has been reported (1). In this report, VRCZ had the lowest mean MIC of 0.17 µg/mL. However, AMB demonstrated the highest MIC of 5.66 µg/mL. L-AMB was also ineffective in our case. VRCZ also had low MIC values against Paecilomyces spp. in some reports (7, 8). When filamentous fungi are identified from corneal specimens of patients with fungal keratitis, treatment with polyenes is generally recommended. However, in cases in which Acrophialophora spp. and Paecilomyces spp. are suspected, VRCZ should be considered as a treatment. Our case also showed a favorable response to VRCZ.

Previous reports on cases of Acrophialophora sp. infection did not discuss the appropriate durations of therapy or their prognosis. The patient with a brain abscess required antifungal treatment for eight months. One of the patients with bronchitis demonstrated recurrence after 50 days of antifungal treatment. Therefore, Acrophialophora spp. infections may be resistant to treatment and require long-term
therapy.

We here reported the sixth case of *Acrophialophora* sp. infection in a patient with a conjunctival abscess and uveitis. In addition, this is the first report to our knowledge of successful treatment with VRCZ of a conjunctival ulcer and uveitis caused by *Acrophialophora* sp. in an immunocompromised patient. Because invasive *Acrophialophora* sp. infections may have obstinate characteristics and require long-term therapy, further analyses on their clinical spectrum and adequate treatment regimens are required.

**Conflicts of interest:** None to declare
References


7. Pastor FJ, Guarro J. Clinical manifestations, treatment and outcome of 


Fig. 1. Formation of an abscess on part of the right conjunctiva.

The bulbar conjunctiva was congested and an abscess with the possibility of perforation into the eye was formed.
Fig. 2. Filamentous characteristics of the *Acrophialophora* sp. colonies.

Colonies were stained with lactophenol cotton blue. The colonies had alternating arthroconidia and flask-shaped phialides.
Table 1. Summary of *Acrophialophora* sp. infections reported to date

<table>
<thead>
<tr>
<th>Cause of immunocompromization</th>
<th>Organ infected or colonized</th>
<th>Patient age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>Central nervous system</td>
<td>12</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Bronchus</td>
<td>4</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Bronchus</td>
<td>5</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Bronchus</td>
<td>13</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Bronchus</td>
<td>26</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Bronchus</td>
<td>Child*</td>
</tr>
<tr>
<td>Lung transplant</td>
<td>Lung</td>
<td>33</td>
</tr>
<tr>
<td>Lung transplant</td>
<td>Lung</td>
<td>67</td>
</tr>
<tr>
<td>Unclear</td>
<td>Cornea</td>
<td>55</td>
</tr>
<tr>
<td>Unclear</td>
<td>Cornea</td>
<td>40</td>
</tr>
</tbody>
</table>

* age unknown
Fig. 2.