Human Disseminated Protothecosis: The Skin is the “Window”?

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Human disseminated protothecosis is a rare infection caused by members of the genus Prototheca, an achlorophyllic algae always associated with debilitated hosts. The presence of non-budding cells and large, spherical cells (sporangia) with endosporulation (morula) in histology is proof of Prototheca infection. Regrettably, due to the lack of specificity of clinical features and low awareness among clinicians, protothecosis is always underestimated and misdiagnosed. The available data on a species-specific analysis of this infection are limited. In this review, we summarize the etiological, epidemiological, and clinical aspects of disseminated protothecosis. The potential pathogenicity and clinical differences between P. zopfii and P. wickerhamii were observed. Additionally, the skin not only became the main invasion site but also the most involved organ by the pathogen. With the increasing numbers of immunocompromised individuals throughout the world, the incidence of disseminated infection caused by Prototheca is bound to increase, and disseminated protothecosis that accompanies skin symptoms should be taken into account by clinicians.

Keywords: humans, immunosuppression, skin diseases, diagnostic errors, Prototheca

INTRODUCTION

In humans, disorders caused by Prototheca species can be cutaneous, olecranon bursitis, systemic, or disseminated (1). In contrast to the former two types of infection, disseminated protothecosis is mainly associated with immunocompromised hosts, such as patients under immunosuppressive therapy or with longstanding intravascular catheters, cancer, AIDS, diabetes mellitus or solid organ transplantation (2). This infection type had the worst prognosis, with only 33% cure or improvement, and 56% death (1). Thus, characterized by high mortality rates and with the increasing numbers of immunocompromised individuals throughout the world, disseminated protothecosis has aroused a gradual interest in the study of the various aspects of this infection and its causative microorganism.

Abbreviations: CARD9, caspase recruitment domain-containing protein 9; AIDS, Acquired Immune Deficiency Syndrome; PMN, polymorphonuclear; PAS, periodic acid Schiff reaction; GMS, Gomori methenamine silver stain; MALDI-TOF MS, Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry.
Regrettably, due to the lack of specificity of clinical features and the lack of awareness among clinicians, up to date, only around 200 cases of *Prototheca* infection have been reported worldwide and systemic infection cases account for about 9% of the cases (1). Moreover, even after the start of the phycology working group in ISHAM (The International Society for Human & Animal Mycology) in 2017, little is known about *Prototheca* spp. or the disease caused by these algae, especially the disseminated type (1). Also, whether there are possible differences in pathogenicity within or between *Prototheca* species compared to other types of infection? This review provides a summary of the literature addressing this issue.

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DISSEMINATED PROTOTHECOsis

Prototheca infection could spread through exogenous or endogenous routes. The former is related to defects in the skin and mucosa (such as postoperative wounds). Compared to traumatic inoculation with the algae from the environment, dermal barrier destruction caused by hospital-acquired cases, including surgical operations and catheter-related procedures, are main exogenous route of invasion. *Prototheca* spp. may survive chlorination by forming biofilms (43) and be returned to the environment via sewage effluent and household waste. Cows with mastitis caused by *P. zopfii* (genotypes 1) may be a source for infection in humans, with immunocompromised farmers at the highest risk (44). Although the possibility of human-to-human transmission was raised with the outbreak of *P. wickerhamii* algaemia and sepsis in a tertiary care chemotherapy oncology unit recently (45), although contrary to our traditional understanding, the report cannot be ignored because of the public safety concerns. Endogenous colonization during prolonged immunosuppression in the gut followed by translocation resulting in algaemia and sepsis is suspected to be the cause of the outbreak.

Disseminated protothecosis is common in patients with underlying immunosuppression or several underlying diseases (2). Our review indicated that there were still four patients (10.8%) with normal immune status, but all of them were successfully treated and had a good prognosis, and most of the cases were associated with *P. wickerhamii* (3/4, 75.0%) (Table 3). Among the other 33 immunocompromised cases, organ...
TABLE 1 | Clinical description of patients with disseminated protothecosis collected during the study period.

| Patient | Year | Age | Sex | Country | Underlying condition | Immunity state | Neutropenia | Infectious site | Initial symptom | Species | Coinfection | Sample | Treatment | Outcome | Ref |
|---------|------|-----|-----|---------|----------------------|---------------|-------------|---------------|----------------|----------|-------------|--------|-----------|---------|-----|
| 1       | 1974 | 29  | Male | New Zealand | Healthy | Immunocompetent | No | Skin, blood, liver | Skin papules, jaundice, diarrhea | P. wickerhamii | N/A | Skin | AMB | Cure | (3) |
| 2       | 1978 | 30  | Male | USA | Liver transplant | Immunocompromised | N/A | Skin | Skin papules | P. wickerhamii | Candida albicans, Proteus mirabilis, Klebsiella | Skin | None | Death | (4) |
| 3       | 1986 | 41  | Female | Australia | CAPD | Immunocompromised | N/A | Peritoneum | Abdominal pain | P. wickerhami | N/A | Dialysate | AMB | Cure | (5) |
| 4       | 1990 | 39  | Male | USA | Healthy | Immunocompetent | No | Liver, gut | Abdominal pain, nausea | P. wickerhami | N/A | Stool | AMB | Cure | (6) |
| 5       | 1990 | 72  | Male | USA | CAPD | Immunocompromised | N/A | Peritoneum | Abdominal pain, Fever | P. wickerhami | N/A | Dialysate | AMB | Cure | (7) |
| 6       | 1991 | 7   | Male | USA | Leukemia | Immunocompromised | N/A | Blood | Peritoneum | P. wickerhami | Pseudomonas aeruginosa | Blood | AMB | Cure | (8) |
| 7       | 1991 | 45  | Male | England | CAPD | Immunocompromised | N/A | Blood | Abdominal pain, Fever | P. wickerhami | N/A | Dialysate | FLC | Cure | (9) |
| 8       | 1992 | 24  | Female | USA | Diabetes mellitus | Immunocompetent | No | Nasopharynx, esophagus | Nausea, vomiting | P. wickerhami | Staphylococcus aureus | Esophageal and Nasopharyngeal lesion | AMB | Cure | (10) |
| 9       | 1992 | 13  | Male | Japan | Anemia | Immunocompetent | N/A | Gut, liver | Fever | P. wickerhami | N/A | Stool | AMB | Cure | (11) |
| 10      | 1992 | 80  | Male | Japan | Diabetes mellitus | Immunocompetent | N/A | Skin | Skin papules | P. wickerhami | N/A | Skin | KET | Cure | (11) |
| 11      | 1992 | 25  | Female | USA | AIDS, Skin trauma | Immunocompromised | No | Brain | Fever, headache | P. wickerhami | Cryptococcus neoformans | CSF | AMB | Death | (12) |
| 12      | 1996 | 59  | Female | USA | Lung transplant | Immunocompromised | N/A | Blood | Fever, headache | P. zopfi | N/A | Blood | FLC | Death | (13) |
| 13      | 1996 | 20  | Male | Japan | Anemia | Immunocompetent | N/A | Brain | P. wickerhami | N/A | CSF | AMB | Cure | (14) |
| 14      | 1997 | 75  | Male | USA | Myasthenia gravis | Immunocompromised | N/A | Blood, skin | Skin papules, fever | P. wickerhami | N/A | Blood | FLC | Cure | (15) |
| 15      | 1998 | 36  | Male | Israel | Candidiasis | Immunocompromised | N/A | Gut | Abdominal pain | Prototheca spp | Candida albicans | Colon tissue | ITC | Cure | (16) |
| 16      | 2002 | 39  | Male | USA | Adenocarcinoma | Immunocompromised | N/A | Lung | Fever | Prototheca spp | N/A | Bronchoalveolar lavage | FLC | Death | (17) |
| 17      | 2002 | 19  | Male | USA | Stem cell transplant | Immunocompromised | N/A | Blood | Fever | Prototheca spp | N/A | Blood | AMB | Cure | (17) |
| 18      | 2004 | 56  | Male | USA | Stem cell transplant | Immunocompromised | N/A | Blood, skin | Skin papules, fever | P. wickerhami | Klebsiella pneumoniae | Blood | AMB | Death | (18) |
| 19      | 2004 | 49  | Male | USA | AIDS | Immunocompromised | N/A | Blood, skin | Fever, swelling of skin | P. wickerhami | N/A | Skin | AMB | Death | (19) |
| 20      | 2004 | 58  | Male | Australia | Stem cell transplant | Immunocompromised | N/A | Blood, skin | Skin papules, fever | P. zopfi | N/A | Blood | VRC, AMB | Death | (20) |

(Continued)
| Patient | Year | Age | Sex | Country | Underlying condition | Immunity state | Neutropenia | Infectious site | Initial symptom | Species | Coinfection | Sample | Treatment | Outcome | Ref |
|---------|------|-----|-----|---------|----------------------|----------------|-------------|----------------|----------------|---------|-------------|--------|-----------|---------|-----|
| 21      | 2005 | 58  | Male | USA     | Stem cell transplant | Immunocompromised | No           | Blood, skin, lung, liver | Skin papules | *P. wickerhamii* | N/A     | Blood     | AMB     | Death (21) |
| 22      | 2007 | 24  | Male | China   | Healthy             | Immunocompetent  | No           | Brain          | Headache       | *P. wickerhamii* | N/A     | CSF       | AMB, ITC | Cure (22)  |
| 23      | 2008 | 61  | Male | USA     | Liver transplant    | Immunocompromised | No           | Blood, skin   | Skin papules   | *P. wickerhamii* | *Escherichia coli* | Blood   | AMB     | Death (23) |
| 24      | 2008 | 10  | Male | India   | Skin trauma         | Immunocompromised | Yes          | Skin, spleen   | Skin papules   | *P. wickerhamii* | N/A     | Skin      | AMB     | Cure (24)  |
| 25      | 2010 | 49  | Female | England | Leukemia          | Immunocompromised | Yes          | Blood, skin   | Fever, skin necrosis | *P. wickerhamii* | *Enterococcus faecium* | Skin, blood | VRC | Cure (25) |
| 26      | 2011 | 78  | Female | Australia | Cardiac transplant | Immunocompromised | N/A          | Blood, skin   | Skin papules, fever | *P. wickerhamii* | *Escherichia coli* | Blood   | AMB, ITC | Death (26) |
| 27      | 2012 | 61  | Male | Malaysia | Renal transplant   | Immunocompromised | N/A          | Blood         | Fever           | *P. wickerhamii* | *Prototheca dermatidis* | Blood   | None | Death (27) |
| 28      | 2013 | 2   | Female | Mexico | Healthy           | Immunocompetent   | N/A          | Skin          | Skin abscess, fever | *P. wickerhamii* | *Blastomyces dermatitidis* | Skin | ITC | Cure (28) |
| 29      | 2014 | 4   | Female | Singapore | Liver transplant | Immunocompromised | No           | Blood, skin   | Skin papules, fever | *P. wickerhamii* | N/A     | Blood     | AMB     | Cure (29)  |
| 30      | 2014 | 74  | Male | USA     | Leukemia           | Immunocompromised | N/A          | Skin          | Skin papules   | *P. wickerhamii* | N/A     | Skin      | ITC     | Cure (30)  |
| 31      | 2014 | 56  | Female | Australia | Stem cell transplant | Immunocompromised | N/A          | Blood, skin   | Fever, skin cellulitis | *P. zopfii* | N/A     | Blood     | AMB     | Death (31) |
| 32      | 2015 | 46  | Female | Japan   | Leukemia           | Immunocompromised | Yes          | Skin          | Skin papules   | *P. zopfii* | N/A     | Skin      | None    | Death (32) |
| 33      | 2018 | 36  | Male | India   | Liver transplant   | Immunocompromised | N/A          | Blood, skin, lung | Skin papules, chest pain | *P. zopfii* | *Klebsiella* | Blood   | AMB     | Death (33) |
| 34      | 2018 | 8   | Female | Turkey | Inherited CARD9 deficiency | Immunocompromised | No           | Gut           | Abdominal pain, diarrhea | *P. zopfii* | N/A     | Blood     | AMB     | Cure (34)  |
| 35      | 2018 | 19  | Male | Spain   | Leukemia           | Immunocompromised | Yes          | Blood         | Fever           | *P. zopfii* | *Candida albicans* | Blood   | AMB     | Death (35) |
| 36      | 2019 | 31  | Male | Morocco | Candidiasis        | Immunocompromised | N/A          | Gut           | Abdominal pain diarrhea | *P. zopfii* | N/A     | Colon tissue | FLF     | Death (36) |
| 37      | 2019 | 13  | Male | China   | Leukemia           | Immunocompromised | Yes          | Blood         | Skin papules, fever | *P. zopfii* | N/A     | Blood     | FLF     | Death (37) |

CAPD, chronic ambulatory peritoneal dialysis; AIDS, Acquired Immune Deficiency Syndrome; CSF, cerebrospinal fluid; AMB, amphotericin; FLC, fluconazole; VRC, voriconazole; ITC, itraconazole; KET, ketoconazole. N/A, Data is not available.
transplantation was the most common, with twelve (32.4%) cases of solid organs and stem cell transplantation, followed by six (16.2%) cases of leukemia, and three (8.1%) cases of chronic ambulatory peritoneal dialysis (Table 2). Intestinal neutropenia does not appear to be an important risk factor for protothecosis. In our review, only 5 of the 14 patients for whom neutrophil counts were available showed neutropenia. Additionally, only two cases of AIDS were found, which is consistent with previous studies and suggests that a type of immunodeficiency other than AIDS contributes to susceptibility to protothecosis (12, 19). Interestingly, the case of CARD9 deficiency caused by P. zopfi provides a new insight into the mechanism of anti-Prototheca immunity (34). All cases of AIDS and diabetes are related to P. wickerhamii, whereas transplantation and leukemia do not seem to be associated with the species type. However, more data are needed to prove the relevance of this association (Table 3).

### Table 2 | Presenting characteristics of patients with disseminated protothecosis. Values are numbers.

| Characteristics                  | Total (37) | Death (17) | P-Value |
|----------------------------------|------------|------------|---------|
| Median Age, years                |            |            |         |
| <30 years                        | 14 (37.8%) | 3 (21.4%)  |         |
| ≥30 years                        | 23 (62.2%) | 14 (60.9%) | <0.05   |
| Sex                              |            |            |         |
| Female                           | 11 (29.7%) | 5 (45.5%)  |         |
| Male                             | 26 (71.1%) | 12 (46.1%) | .969    |
| Underlying condition             |            |            |         |
| Transplantation                  | 12 (32.4%) | 10 (83.3%) | <0.05   |
| Renal transplant                 | 1 (2.7%)   | 1 (100.0%) |         |
| Lung transplant                  | 1 (2.7%)   | 1 (100.0%) |         |
| Liver transplant                 | 4 (10.8%)  | 3 (75.0%)  |         |
| Cardiac transplant               | 1 (2.7%)   | 1 (100.0%) |         |
| Stem cell transplant             | 5 (13.5%)  | 4 (80.0%)  |         |
| Candidiasis                      | 2 (5.4%)   | 1 (50.0%)  |         |
| Myasthenia gravis                | 1 (2.7%)   | 0 (0%)     |         |
| Leukemia                         | 6 (16.2%)  | 3 (50.0%)  |         |
| Anemia                           | 2 (5.4%)   | 0 (0%)     |         |
| AIDS                             | 2 (5.4%)   | 2 (100.0%) |         |
| Diabetes mellitus                | 2 (5.4%)   | 0 (0%)     |         |
| Chronic ambulatory peritoneal dialysis | 3 (8.1%) | 0 (0%) |         |
| Adenocarcinoma                   | 1 (2.7%)   | 1 (100.0%) |         |
| Skin trauma                      | 1 (2.7%)   | 0 (0%)     |         |
| Inherited CARD9 deficiency       | 1 (2.7%)   | 0 (0%)     |         |
| Skin trauma/surgery/catheter-relateda | 22 (59.5%) | 13 (59.1%) |         |
| Sign and symptoms at disease onset|            |            |         |
| Fever                            | 20         | 11         |         |
| Skin papules                     | 19         | 11         |         |
| Abdominal pain                   | 7          | 1          |         |
| Headache                         | 3          | 1          |         |
| Diarrhea                         | 3          | 1          |         |
| Species                          |            |            |         |
| P. wickerhamii                   | 25 (67.6%) | 9 (36.0%)  | <0.05   |
| P. zopfi                         | 8 (21.6%)  | 7 (87.5%)  |         |
| Prototheca spp. (unidentified)    | 4 (10.8%)  | 1 (25.0%)  |         |

Data are number/total number (%) unless indicated otherwise.
*Defined as the above causes of skin barrier destruction.

### Table 3 | Underlying conditions according to the species in 37 cases with disseminated protothecosis.

| Underlying conditions  | P. wickerhamii n mortality (%) | P. zopfi n mortality (%) | Prototheca spp. n mortality (%) | Total n mortality (%) |
|------------------------|---------------------------------|--------------------------|---------------------------------|-----------------------|
| Transplantation†       | 7 (68.5)                        | 4 (41.0)                 | 1 (0.0)                         | 12 (103.3)            |
| AIDS††                 | 2 (21.0)                        | 0 (0.0)                  | 0 (0.0)                         | 2 (21.0)              |
| Leukemia               | 3 (0.0)                         | 3 (31.0)                 | 0 (0.0)                         | 6 (50.0)              |
| Diabetes mellitus      | 2 (0.0)                         | 0 (0.0)                  | 0 (0.0)                         | 2 (0.0)               |
| Skin trauma            | 1 (0.0)                         | 0 (0.0)                  | 0 (0.0)                         | 1 (0.0)               |
| Inherited CARD9 deficiency | 0 (0.0)                      | 1 (0.0)                  | 0 (0.0)                         | 1 (0.0)               |
| Others†††              | 7 (114.3)                       | 0 (0.0)                  | 2 (15.0)                        | 9 (22.2)              |
| Healthy                | 3 (0.0)                         | 0 (0.0)                  | 1 (0.0)                         | 4 (0.0)               |
| Total                  | 25 (96.0)                       | 8 (87.5)                 | 4 (125.0)                       | 37 (106.9)            |

†Renal transplant, Lung transplant, Liver transplant, Cardiac transplant, and Stem cell transplant.
††One patient suffered AIDS and skin trauma.
†††Myasthenia gravis, Candidiasis, Anemia, Adenocarcinoma, CAPD.
In addition to one traumatic implant, 22 (59.5%) patients had a history of surgical and instrument injury related to defects in the skin and mucosa. Although glucocorticoid therapy might be considered the highest risk factor for *Prototheca* infection, it was not found among the patients reviewed (2). We believe this situation still exists because of the high proportion of organ transplantation cases and the one case of myasthenia gravis (15), in which large doses of glucocorticoids must be used for long periods. A likely explanation for the glucocorticoids as predisposing factors to infection may include exogenous or endogenous aspects. It may be on one hand to shrink and thin the epidermis to weaken the barrier function of the skin and, on the other hand, may suppress lymphocyte activation and impair PMNs and macrophages to increase endogenous colonization (46).

Protothecosis occurs globally and has been reported on every continent except Antarctica (2). In this review, the world distribution of 37 disseminated cases is shown in Figure 1. It predominated in the USA (fifteen, 40.5%), where it is prevalent in the southeast, followed by Australia and Japan (four each, 10.8%). Two of the cases were from England (5.4%), two from India (5.4%), two from China (5.4%), and one each from Israel, Malaysia, Singapore, Spain, Mexico, Turkey, Morocco, and New Zealand (2.7%). In general, *Prototheca* species seem to have a preference for warm and humid climates, which matches the epidemiology of the disease in both humans and animals. Similar to what has been reported in previous studies (2), the organs most commonly affected in dissemination are the skin (19 cases, 51.4%) and blood (17 cases, 45.9%), followed by the gut (5 cases, 13.5%) and liver (4 cases, 10.8%), then the lungs (3 cases, 8.1%), peritoneum (3 cases, 8.1%), and brain (3 cases, 8.1%) (Figure 2). There are various forms of skin lesions without specificity that can be manifested as erythematous papules, plaques, nodules, ulcers, papules, necrotic crusts, pustules, and bullae with purulent discharge, even presenting as an eczematoid eruption (4, 15, 19, 25, 31). At least three patients had lesions at the site of catheter implantation (23, 25, 37). Unfortunately, even though skin lesions are the most common initial signs of this disseminated type, the mortality of patients with visual lesions was not lower than that of other factors, suggesting that atypical lesions were indeed overlooked or misdiagnosed by clinicians. In addition, algaemia, which represents blood involvement, is more easily covered up and ignored by bacteremia and fungaemia (45), especially under the condition of administration of

CLINICAL FEATURES

No specific clinical features were noted. Clinical initial signs of disseminated protothecosis in humans can include fever, skin lesions, abdominal pain, diarrhea, and headache, which are associated with the infectious sites. Similar to what has been reported in previous studies (2), the organs most commonly affected in dissemination are the skin (19 cases, 51.4%) and blood (17 cases, 45.9%), followed by the gut (5 cases, 13.5%) and liver (4 cases, 10.8%), then the lungs (3 cases, 8.1%), peritoneum (3 cases, 8.1%), and brain (3 cases, 8.1%) (Figure 2). There are various forms of skin lesions without specificity that can be manifested as erythematous papules, plaques, nodules, ulcers, papules, necrotic crusts, pustules, and bullae with purulent discharge, even presenting as an eczematoid eruption (4, 15, 19, 25, 31). At least three patients had lesions at the site of catheter implantation in this review (23, 25, 37). Unfortunately, even though skin lesions are the most common initial signs of this disseminated type, the mortality of patients with visual lesions was not lower than that of other factors, suggesting that atypical lesions were indeed overlooked or misdiagnosed by clinicians. In addition, algaemia, which represents blood involvement, is more easily covered up and ignored by bacteremia and fungaemia (45), especially under the condition of administration of
Among all, 8, 87.5% of patients infected with *P. wickerhamii* showed a higher rate of mortality (7/25, 28%) compared to those infected with *P. zopfi* (11/26, 42.3%) who were not co-infected.

### CHALLENGE

Prototheca remains a diagnostic and therapeutic enigma. For the diagnosis, combining histopathological and microbiological tests is recommended for cases where protothecosis is suspected. Histopathologic examination of infected tissue may be accomplished using the PAS, GMS, or Gridley fungus stain to visualize the endosporulating sporangia (morula form) of *Prototheca* spp. (Figure 3). In addition to the size differences noted previously, the two species of *Prototheca* differ in that *P. wickerhamii* tends to form symmetrical morula forms, whereas these forms are rare in *P. zopfi*, which exhibits more random internal segmentation (2). However, in the absence of these morphological features, the organism may resemble other fungi such as *Blastomyces*, *Coccidioides*, *Cryptococcus*, *Emergomyces*, *Paracoccidioides*, *Pneumocystis*, *Rhinosporidium*, and chromoblastomycosis agents (2). Of note, diseases caused by these fungi differ clinically from protothecosis in the presence of respiratory symptoms since the infection is mainly acquired by inhalation. However, chromoblastomycosis is an implantation mycosis but has a chronic nature and is characterized by the presence of darkly pigmented muriform cells in the infected tissue.

The inflammatory response in protothecosis is predominantly granulomatous but can consist of lymphocytes, plasma cells, eosinophils, neutrophils, macrophages, epithelioid cells, and giant cells. *Prototheca* species grow rapidly on routine laboratory media such as Sabouraud’s glucose agar, blood culture bottles, and blood agar (47). For confirmation, the presence of unicellular organisms, 3–30 µm in diameter, and sporangium containing autospores is indicative of *Prototheca* infection (Figure 4). Nevertheless, situations such as contamination of growth by co-infecting yeasts or bacteria, or growth of a single colony on solid media, often lead to missed diagnosis (45).

There are possible differences in pathogenicity and treatment between *P. wickerhamii* and *P. zopfi*, so the identification of these algae to species level has become an inevitable trend. In addition to the traditional morphological methods, commercial physiological systems such as API 20C or API 20C-AUX and the database of VITEK 2 have been developed (48). Currently, rapid automated identification of *Prototheca* is possible using matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI-TOF MS) (49). In addition, the sequencing of 18S and 28S rDNA has been applied for the identification and genotyping of species (50, 51). Recently, the mitochondrial *cytb* gene has been proved effective for discrimination and suggested as the gold standard for the identification of the *Prototheca* microalgae (40) (Figure 5).
Therapeutically, in addition to the fact that algae in general have low susceptibility to antimicrobial agents, there has been no consistency in the clinical responses. Treatment of protothecal infections remains a challenge (32). Antifungals such as amphotericin B and itraconazole form the mainstay of treatment, although *Prototheca* is susceptible to voriconazole, miconazole, clotrimazole, tetracycline, gentamicin, amikacin, and polymyxin B (29). Disseminated patients treated with an antifungal regimen that included amphotericin B were more likely to survive than those treated with a triazole alone. Amphotericin B and its lipid-based formulations provide broad spectrum cover, however, treatment failures even with combination antifungal therapy with amphotericin B have been reported (46). Our data also suggest that amphotericin B is effective in only 56.5% (13/23) of the disseminated patients. Antifungal treatment needs to be reassessed in cases of no clinical improvement. Furthermore, catheter removal should be the first consideration in treating a catheter-related *Prototheca* infection.

**CONCLUSIONS AND PROSPECT**

Human Disseminated Protothecosis is an emerging environmental algal disease with high mortality that typically occurs in immunocompromised individuals. Under the condition of immune deficiency, the destruction of the skin barrier caused by surgery and catheter is highly considered to be associated with this type. Organ transplantation is the most common risk factor,
followed by leukemia. *P. wickerhamii* and *P. zopfi* are the dominant species that cause disseminated infection. The former has a significantly lower mortality than the latter, but is associated with brain infections. Low susceptibility to antimicrobial agents and *Prototheca* biofilms contributes to the hard-to-treat character of this algal infection.

Significantly, our study confirmed that disseminated protothecosis most frequently involves the skin, which is indeed different from other opportunistic biofilm-forming fungi prevalent in intensive care units (ICUs) and transplant patients. *Candida auris*, for example, is usually associated with bloodstream infections rather than skin infections (52). The difference in clinical manifestations could be related to the biological behavior of the species. The dominant species *P. wickerhamii*, which causes disseminated protothecosis, has an optimum growth temperature between 25 and 37°C and cannot grow above 40°C (53), however, *C. auris* could grow well at 42°C (52). Based on the difference in this thermal tolerance property, it is hypothesized that the skin is a window through which *Prototheca* spp. diffuses back into the environment to escape the powerful thermoregulatory immunity of the body. Since this study has limitations due to the small sample, more research work, especially the association of each species type with distinct profiles of clinical manifestation and response to treatment and epidemiological patterns, should be launched.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

**AUTHOR CONTRIBUTIONS**

XW and YR carried out the literature search and participated in the data analysis and drafted the manuscript. YaJ designed this project, phylogenetic tree construction, participated in the data analysis, and revised the manuscript. SJ and XL carried out the statistical analysis. SA and YiJ contributed to the discussion and revision of the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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![Phylogenetic tree constructed through maximum likelihood analysis based on cyt b sequences. The bootstrap values obtained by the analysis are marked at the nodes.](image-url)
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