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Cutaneous protothecosis in immunosuppressed patients: a series of 14 cases

Prototecosis cutánea en pacientes inmunodeprimidos: una serie de 14 casos

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Key words:
Protothecosis, cutaneous protothecosis, itraconazole, immunosuppressed patients.

Palabras clave:
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Abstract

Introduction: Protothecosis is an infrequent infection in dogs, cats, cattle, and humans caused by a type of green algae known as Prototheca. Its incidence increases in immunosuppressed hosts and it's considered an emergent disease in such patients. **Material and methods:** This is a retrospective review of immunosuppressed patients with protothecosis seen at a single academic center in Mexico between 2010-2014. Their epidemiological, clinical, and therapeutic features are discussed. The diagnosis of protothecosis was established by mycologic culture and/or skin biopsy. **Results:** There were 14 patients. All of them were immunosuppressed. The majority (65%) were male. Average age was 48.8 years. The most frequent cause of immunosuppression was immunosuppressive drugs associated with renal transplantation (35.7%). The most frequent clinical presentation was subcutaneous nodules (64.2%). Diagnosis was established by mycologic culture (100% of patients) and skin biopsy (64%). All 14 patients were treated with itraconazole 200-400 mg PO QD for 8-12 weeks. Eight patients (57.1%) were completely cured. **Conclusions:** Herein, we report the largest series of patients with cutaneous protothecosis in immunosuppressed patients. Prognosis seems to be related to underlying pathology. Oral itraconazole is a relatively effective and available treatment option.

Resumen

Introducción: *La prototecosis es una infección rara causada por algas del género Prototheca. Debido a los factores inmunosupresores, los casos han aumentado, siendo considerada como una infección emergente en este grupo de pacientes.* ***Material y métodos:*** *Se describe una revisión retrospectiva de casos de prototecosis en pacientes inmunosuprimidos, vistos en un hospital de México entre 2010 y 2014. Se discuten datos epidemiológicos, clínicos y terapéuticos. El diagnóstico se realizó mediante cultivo micológico y/o estudio histopatológico.* ***Resultados:*** *Se encontraron 14 pacientes, todos inmunosuprimidos. La prototecosis predominó en varones (65%), con una edad promedio de 48.8 años. El principal factor de inmunosupresión asociado fue medicación asociada a trasplante renal (35.7%), siendo la lesión clínica más frecuente los nódulos subcutáneos (64.2%). El diagnóstico fue realizado por cultivo micológico (100%) y estudio histopatológico (64%). Todos los pacientes fueron tratados con itraconazol (200-400 mg/día) durante 8 y 12 semanas. Ocho pacientes presentaron curación completa (57.1%).* ***Conclusiones:*** *Ésta es la mayor serie de casos de prototecosis cutánea en pacientes inmunosuprimidos. El pronóstico se relaciona con la patología subyacente. El itraconazol por vía oral es una alternativa de tratamiento efectiva y asequible.*

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INTRODUCTION

The genus Prototheca described by Kruger in 1894, represents ubiquitous green algae that lack chlorophyll.[1,2] It includes 6 known species.[3,4] Prototheca can be found in soil and water. In humans, the infection by these algae is known as protothecosis. The first case was described in 1964 by Davies et al.[5] Cutaneous infection is very rare. Usually, it occurs through inadvertent trauma with an unknown incubation period. Clinically, there are 3 presentations: cutaneous, bursitis of olecranon, and disseminated.[6] Up until 2012, there were 160 cases reported worldwide. The most common presentation is cutaneous (58.1%). The most frequent species is *P. wickerhamii* (71.8%), followed by *P. zopfii* (6.8%).[7] Only five cases have been reported in Mexico, two with disseminated disease, and three with onychomycosis.[8-10] Protothecosis affects mainly immunosuppressed individuals; it can occur at any age, although, it's more frequent in the elderly.[11] The cutaneous form is clinically and histologically similar to many deep mycoses. Diagnosis depends on accurate morphologic identification of the etiologic agent through biopsy, culture, biochemical tests, and/or molecular biology.[6,11,12] Herein, we describe the clinical, epidemiological, and

therapeutic characteristics of a large series of patients with protothecosis from a single tertiary center.

MATERIAL AND METHODS

This is a retrospective review of patients with protothecosis seen at a single Department of Dermatology in Culiacan, Sinaloa. Mexico, between 2010 and 2014. Epidemiological data included age, gender, type of immunosuppression, clinical presentation, and time of evolution before diagnosis. Diagnosis was established via skin biopsy with periodic acid-Schiff stain and mycologic culture in Sabouraud media. Treatment was done with itraconazole 200-400 mg/ day for 8-12 weeks.

Results are presented with descriptive statistics using measures of central tendency.

RESULTS

There were 14 patients. Their characteristics are summarized in *table 1*. The majority were male (65%), with a male-to-female ratio of 1.8:1. The median age was 48.8 years (range 34-65) with 35.7% of cases in patients between 51-60 years old. Most patients (35.7%) had history of renal transplantation. All patients developed limited disease to skin.

The most common location of lesions was the lower extremities (78.5%). Only one patient (7.1%) had trunkal lesions. Four patients (28.4%) had lesions in 2 locations. Clinical lesions included subcutaneous nodules (64.2%), infiltrated plaques (35.7%), and ulcers (14.2%) *(Figure 1)*.

Thirteen patients (92.8%) had lesions for 3-6 months. Diagnosis was established via mycologic culture in all patients (100%), and skin biopsy in 9 patients (64%) *(Figure 2)*. Eight patients (57.1%) were treated with itraconazole 400 mg/day. Treatment resulted in cure in 8 patients (57.1%).

There were 6 deaths (42.9%): two patients (14.3%) died from sepsis and 4 (28.6%) from their underlying disease.

DISCUSSION

Protothecosis in humans is infrequent. There are approximately 160 cases described worldwide but only a few in the dermatological literature. Torres et al.[13] described the largest series of 13 patients with underlying cancer. In their report, only 5 patients (38%) had cutaneous disease exclusively: 2 with non-Hodgkin lymphoma, 2 with breast cancer, and 1 with cervical cancer.[13]

As regards the clinical presentation of protothecosis, Lass-Flörl described a spectrum of lesions including erythematous, verrucous, and atrophic hypopigmented plaques; papules, nodules, pustules, vesicles, and purulent and crusted ulcers.[14] In our series, we found 3 types of skin lesions: subcutaneous nodules, infiltrated plaques, and ulcers. This is in striking contrast with previous reports from Mexico showing predominantly onychomycosis.[8-10]

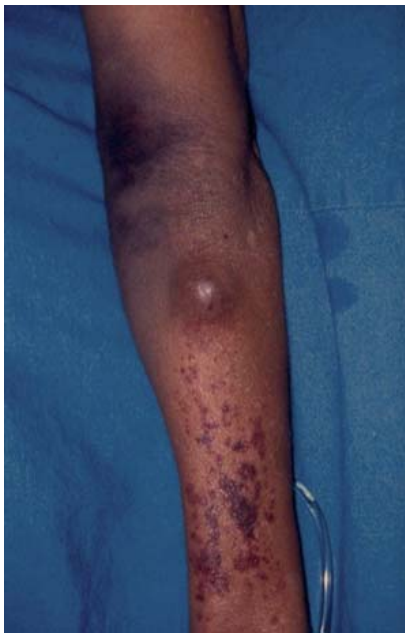

Figure 1. *Cutaneous protothecosis.*

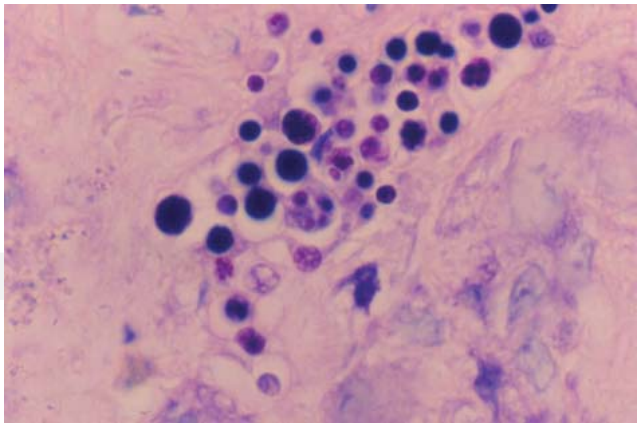

Figure 2. *Histopathologic analysis shows Prototheca spp. (PAS, 100x).*

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Table 1. Patients' characteristics (n=14).

	No. of cases	%
Gender		
Males	9	65
Females	5	35
Age group (years)		
31 - 40	4	28.6
41 - 50	3	21.4
51 - 60	5	35.7
61 - 70	2	14.3
Cause of immunosuppression		
Renal transplant	5	35.7
Chronic lymphocytic leukemia	4	28.6
Hodgkin's disease	4	28.6
Multiple myeloma	1	7.1
Duration of lesions		
< 3 months	5	35.7
3 - 6 months	8	57.1
> 6 months	1	7.1
Oral itraconazole dose		
200 mg/day	4	28.6
300 mg/day	2	14.3
400 mg/day	8	57.1
Therapeutic result		
Cure	8	57.1
Death due to prototecosis	2	14.3
Death due to underlying disease		
• Renal transplant medication	2	14.3
• Hodgkin's disease	2	14.3

In our patients, the diagnosis was established via mycologic culture in 100% of cases and with skin biopsy in 64%. Previously, Todd et al.[7] reported that culture was positive in 80.62% of cases and skin biopsy in 83.7%. In contrast to our study, this author identified the etiologic species.

There is not enough evidence to make a recommendation about standard treatment regimen and treatment may vary case by case.[11] In a review by Todd et al, from 167 evaluable treatments, there was an overall treatment success rate of 71%.[7] Cure rates for prototheocosis include intravenous amphotericin B (56-91%), itraconazole (49-82%), fluconazole (38-88%), caspofungin and voriconazole (19-99%).[6,7] Based on this, it is reasonable to use a combination of treatment. This leads to an success rate of 57-98%.[7] In our series, we treated our patients with itraconazole achieving a cure rate of 57.1%. We elected not to treat with amphotericin B because 35.7% of our patients were renal transplant recipients, and the rest had various other contraindications for its use. In addition to this, amphotericin B seems to be less effective in immunocompromised than itraconazole alone.[7] Another reason for choosing itraconazole, is its superiority in effectiveness than other antifungals in the treatment of localized infections.[11] The treatment with azoles can cause liver toxicity and hepatitis; amphotericin B carries the risk of renal failure, electrolyte imbalances, liver toxicity and blood dyscrasias. Less kidney toxicity has been reported with liposomal formulations of amphotericin B. The use of topical amphotericin B would avoid both the toxicity of systemic therapy and adverse effects of intravenous administration, but requires further research.[7]

Unlike the vast majority of cases of protothecosis, in the setting of immunosuppressed patients with exclusive cutaneous disease, it is recommended to start with the combination of itraconazole plus amphotericin B when possible. As a second line of treatment amphotericin B or azoles in topical preparation would be the choice. Finally, the systemic administration of either itraconazole, voriconazole or amphotericin B is indicated.

Unless toxicity appears in a short time, the trend is to treat for at least 1 month. The optimal dose and duration of therapy are uncertain.[14]

Immunocompromising underlying disease is associated with lower treatment success rates, nevertheless, its only significant when a therapy with corticosteroids is associated.[7] The prognosis depends on both the underlying disease and the efficacy of the treatment in avoiding the spread of the infection; when this happens, the forecast is ominous in the short term.

CONCLUSION

This is one of the largest series of cutaneous protothecosis in immunosuppressed patients. Protothecosis is clinically nonspecific. It may present with a varied morphology. The definitive diagnosis will depend on the morphological identification of the organism; therefore, both microbiological and histopathological tests are recommended. Therapy with itraconazole is an acceptable alternative for patients in whom amphotericin B is contraindicated, moreover, it seems to be more effective in immunosuppressed and in cutaneous disease. The limitations of this study were its retrospective nature and the scarcity of cases.

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BLIBLIOGRAPHY

1. Ricchi M, Cammi G, Garbarino CA, Buzzini P, Belletti GL, Arrigoni N. A rapid real-time PCR/DNA resolution melting method to identify Prototheca species. *J Appl Microbiol*. 2011; 110 (1): 27-34.
2. Krüger VW. Kurze Charakteristik einiger niedriger Organismen im Saftfluss der Laubbäume. *Hedwigia*. 1894; 33: 241-266.
3. Roesler U, Möller A, Hensel A, Baumann D, Truyen U. Diversity within the current algal species Prototheca zopfii: a proposal for two Prototheca zopfii genotypes and description of a novel species, Prototheca blaschkeae sp. nov. *Int J Syst Evol Microbiol*. 2006; 56 (Pt 6): 1419-1425.
4. Satoh K, Ooe K, Nagayama H, Makimura K. Prototheca cutis sp. nov., a newly discovered pathogen of protothecosis isolated from inflamed human skin. *Int J Syst Evol Microbiol*. 2010; 60 (Pt 5): 1236-1240.
5. Davies RR, Spencer H, Wakelin PO. A case of human protothecosis. *Trans R Soc Trop Med Hyg*. 1964; 58: 448-451.
6. Mayorga J, Barba-Gómez JF, Verduzco-Martínez AP, Muñoz-Estrada VF, Welsh O. Protothecosis. *Clin Dermatol*. 2012; 30 (4): 432-436.
7. Todd JR, King JW, Oberle A, Matsumoto T, Odaka Y, Fowler M et al. Protothecosis: report of a case with 20-year follow-up, and review of previously published cases. *Med Mycol*. 2012; 50 (7): 673-689.
8. Tello-Zavala MC, Mercado-Lara A, Gómez-Hernández N, Recio-Martinez V. Disseminated protothecosis in a Mexican child. *Pediatr Infect Dis J*. 2013; 32 (12): e476-477.
9. Buendía A, Patiño E, Rijlaarsdam M, Loredo ML, Rivera E, Ramírez S et al. Endocarditis due to an alga of the genus *Prototheca sp*. A saprophyte of water and of tree sap? *Arch Inst Cardiol Mex*. 1998; 68 (4): 333-336.
10. González-Avila M, Gómez-Gómez JV, Texis AP, Imbert-Palafox JL, Becerril-Flores MA, Blasco JL. Uncommon fungi isolated from diabetic patients toenails with or without visible onychomycoses. *Mycopathologia*. 2011; 172 (3): 207-213.
11. Hillesheim PB, Bahrami S. Cutaneous protothecosis. *Arch Pathol Lab Med*. 2011; 135 (7): 941-944.
12. Da Silva P, Silva S, Lima R, D'Acri A, Lupi O, Martins C. Cutaneous protothecosis. Case report. *An Bras Dermatol*. 2013; 88 (6): 183-185.
13. Torres HA, Bodey GP, Tarrand JJ, Kontoyiannis DP. Protothecosis in patients with cancer: case series and literature review. *Clin Microbiol Infect*. 2003; 9 (8): 786-792.
14. Lass-Flörl C, Mayr A. Human protothecosis. *Clin Microbiol Rev*. 2007; 20 (2): 230-242.

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