Clinical and Experimental Dermatology and Therapies
Yan T, et al. Clin Exp Dermatol Ther 7: 191.
www.doi.org/10.29011/2575-8268.100191
www.gavinpublishers.com

Case Report

Primary Cutaneous Cryptococcosis Presenting Ulcers

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Citation: Yan T, Ma L, Hou S, Xing F, Zhang R, et al. (2022) Primary Cutaneous Cryptococcosis Presenting Ulcers. Clin Exp Dermatol Ther 7: 191. DOI:10.29011/2575-8268.100191

Received Date: 25 October 2022; **Accepted Date:** 01 November 2022; **Published Date:** 04 November 2022

Abstract

Cutaneous cryptococcosis is increasing in number in recent years. It may mimic various diseases, making the diagnosis difficult and delayed. Here we present a case of primary cutaneous cryptococcosis presenting rapid progressive ulcers. Voriconazole plus fluconazole was not efficient, which indicated the diagnosis of pyoderma gangrenosum and tumors. However, biopsy and blood cryptococcal antigen tests confirmed the diagnosis of cutaneous cryptococcal infection, and body tests excluded the systemic involvement. Intense antifungal regimen was added after diagnosis was confirmed, and ulcers were cured after four months treatment. What's more, we also reviewed articles and found that ulcerated type of cutaneous cryptococcosis may have a high death rate and require early recognition and adequate antifungal treatment. We hope that our founding may contribute to clinical practice.

Keywords: Cryptococcosis; Ulcer; Fungicidal; Immunosuppression

Introduction

Primary Cutaneous Cryptococcosis (PCC) is an opportunistic fungal infection that was first described and distinguished from systemic cryptococcal infection in 1928 [1]. It is defined as skin lesions localized to a circumscribed body region with a positive skin culture for *Cryptococcus neoformans* and no evidence of concurrent dissemination.

Pigeon contact, trauma, and inoculation have been recognized as risk factors for cryptococcosis [2]. Secondary cutaneous cryptococcosis is always seen in disseminated cryptococcosis or secondary to cerebral or pulmonary cryptococcosis. In recent years, there has been a marked increase in the number of reports of cryptococcosis. Cutaneous cryptococcosis maybe present as blister, nodular, or acne-like eruptions. However, ulcers are uncommon in cutaneous cryptococcosis. Here, we report a case of PCC presenting as ulcers that rapidly expanded. We also reviewed articles of cutaneous cryptococcosis and found that ulcerated type of cutaneous cryptococcosis may have a high death rate and require early recognition and adequate antifungal treatment.

Case Report

A 67-year-old female appeared with erythema and ulcers on the extensor portion of her right thigh for one month. She had been treated with ceftriaxone for four weeks and then voriconazole plus

fluconazole for one week while the lesions increased rapidly in size with significant pain. The patient had hepatitis B infection since 2010 and undifferentiated arthritis since 1990. She was treated with 5 mg of prednisone every other day for the underlying illness. Physical examination revealed two ulcers measuring nearly 13×8 cm and 10×4 cm on the extensor side of the right thigh, with marked edematous erythema at the edges of the ulcers and purulent discharge on the surface of the ulcers (Figure1a).

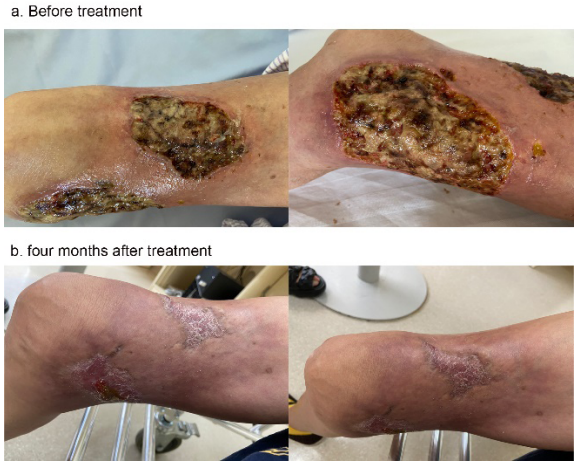

Figure 1a: Physical examination revealed two ulcers on the extensor side of the right thigh with marked edematous erythema at the edge of the ulcers and purulent discharge on the surface of the ulcers. There were also some satellite opacities around the ulcers. **Figure 1b:** After four months of antifungal treatment, the ulcers gradually decreased in size with only residual atrophic hypopigmentation.

The results of laboratory tests, including a complete blood cell count and absolute lymphocytes, were normal. The levels of complete reactive protein (23.03 mg/dL; normal range 0-5) and the sedimentation rate (51 mm/h; normal range 0-20) were both elevated. The human immunocompromised virus test was negative. Hepatitis B DNA quantities were $9.67x10^4$ IU/ml. Histological analysis revealed numerous yeast-like fungi, indicating cryptococcosis (Figure 2). The biochemical and genetic identification of purulent skin secretions proved that the isolated pathogen was *C. neoformans*. The serum cryptococcal antigen titer test was positive. Blood culture results were normal. Systemic involvement was ruled out by chest computed tomography (CT) and cerebrospinal fluid examination.

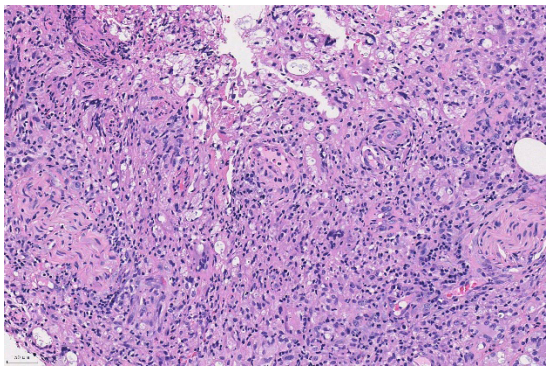

Figure 2: Histological analysis revealed an inflammatory granulomatous reaction formation in the dermis and subcutis with lymphocytes, histiocytes, neutrophils, plasma cells, and local necrosis, with capsuled spores and hyphae.

For the treatment, due to the severe ulcer, it was suspected to be pyoderma gangrenosum at first, and we prescribed methylprednisolone 40 mg daily for one week. However, the purulent discharge was more frequent. The diagnosis of PCC was confirmed after the biopsy result and laboratory findings. Methylprednisolone was discontinued. The patient received flucytosine 100 mg/kg/day for six weeks and fluconazole 800 mg/day for two weeks, after which fluconazole was reduced to 400 mg/day. The patient was also given entecavir and hydroxychloroquine for hepatitis B and rheumatoid arthritis. After four months of antifungal treatment, the ulcers gradually decreased in size with only residual atrophic hypopigmentation (Figure 1b).

Discussion

C. neoformans and *C. gattii* are the common culprits of cryptococcosis. Infections with *C. neoformans* are more common in immunosuppressive persons [3]. The most common sites of infection are extremities. Manifestations of cutaneous cryptococcosis are diverse, such as rash, pustules, purpura, vesicles, nodules, ulcers, sometimes mimicking herpes zoster, cellulitis, or pyoderma gangrenosum. Lesions may be single or multiple and often accompanied with pain.

Our patient was immune dysregulation and developed rapidly enlarged ulcers. The patient was treated with voriconazole for one week with a poor response, suggesting the possibility of pyoderma gangrenosum or tumors. Finally, biopsy and blood cryptococcal antigen tests confirmed cryptococcal infection. Fortunately, body tests excluded the systemic involvement. The patient received intensive antifungal medication promptly, and the ulcers healed after four months treatment.

Our patient is a clear case of cryptococcal infection. To date, a review of literature identified 20 patients presenting ulcerated cutaneous cryptococcosis (supplemental material). Summary of the cases, most cases (65%) were in the extremities and half cases were immunosuppressive. What's more, nearly a third of cases had systemic involvement and a fourth of cases died, which indicated that ulcerated cutaneous cryptococcosis might be more dangerous than other types [4,5] (Table 1).

Skin lesion sites			
Single site			Multiple sites
Extremities	Face	Trunk	
13/20 (65%)	2/20 (10%)	2/20 (10%)	3/20 (15%)
Medical history			
Immunologic disease	Other disease	No associated disease	NA
10/20 (50%)	5/20 (25%)	4/20 (20)	1/20 (5%)
Involved system organs			
Yes	No	NA	
6/20 (30%)	13/20 (65%)	1/20 (5%)	
Outcome			
Died	NA	Cured	Improved
5/20(25%)	2/20 (10%)	12/20 (60%)	1/20 (5%)
NA: Not applicable			

Table 1: Summary of previous cases presenting ulcerated cutaneous cryptococcosis.

A skin biopsy is necessary for diagnosis. Screening for systemic involvement, including pneumonia and cerebrospinal, is required after diagnosing cutaneous cryptococcosis. Chest CT and lumbar puncture are necessary, and bronchoalveolar lavage may be needed in some cases.

The high mortality rate of ulcerated cutaneous cryptococcosis needs to be validated by further clinical investigation. However, early recognition and treatment are essential to achieve a better prognosis. Current guidelines recommend fungicidal treatment with amphotericin B (0.7-1 mg/kg/day) and flucytosine (100 mg/kg/day) for at least four weeks, followed by consolidation therapy with fluconazole (400–800 mg/day) for eight weeks and maintenance therapy with fluconazole (200 mg/day) for 6-12 months for multiple organ involvement. For single-site infections, fluconazole (400 mg/day) is recommended for 6-12 months [6]. However, there is no standard treatment regimen for multiple sites skin lesions. For elderly patients, drug side effects such as myelosuppression and electrolyte disturbances must be noted. In conclusion, cutaneous cryptococcosis should be considered when rapid progressive ulcers are present in immunosuppressed population, and early intervention is critical.

Statement of Ethics

Ethics approval was not required for this study in accordance with local or national guidelines. Patient have given their written informed consent to publish their case (including publication of images).

Author Contributions

Tian meng Yan undertook the academic writing. Suchun Hou revised the article. Fanfan Xing and Ruiping Zhang made a contribution to the diagnosis of the patient. Li Ma and Xiaoming Liu helped make the antifungal regimen to the patient.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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Cutaneous Cryptococcosis Infection Present Ulceration												
Journal	Authors	Time	Age (year)/sex	History	Site of lesion	Associated disease	Regular medication drugs	Type of fungus	System involvement	Treatment	Treatment time	Outcome
Australas J Dermatol	Haady Fallah, et al	2011	73/M	4 weeks	Upper limb	Chronic obstructive pulmonary disease	Prednisolone	C. neoformans	No	Flucytosine and amphotericin	2 weeks	NA
			81M	4 weeks	Upper limb	Rheumatoid arthritis and hypertension	Methotrexate 10mg/w and prednisone 6mg/d	C. neoformans	No	Fluconazole	12 months	Cured
			70/M	NA	Forearm	Rheumatoid arthritis and chronic renal failure and gout	Azathioprine 100mg/d and prednisolone 10mg/d	C. neoformans	Cerebral	Flucytosine and amphotericin for 10 days and fluconazole for 6 months	NA	Cured
Acta Derm Venereol	Nobuyuki Kikuchi, et al	2016	85/F	NA	Upper limb	Erythroderma	Prednisolone 20mg/d	C. neoformans	Pneumonia cerebral	Fluconazole 20mmg/d	NA	Die
			74/F	6 months	Lower leg	Diabetes mellitus and chronic kidney disease and bronchial asthma	NA	C. neoformans	Pneumonia	NA	NA	Die
			93/F	months	Lower leg	NA	NA	C. neoformans	NA	Fluconazole 100mg/d	NA	Die
			79/F	2 months	Lower leg	Rheumatoid arthritis and diabetes	Methotrexate and prednisone	C. neoformans	Pneumonia	Fluconazole 400mg/d	NA	NA
Rev Soc Bras Med Trop	Agatha Ramos Oppenheimer, et al	2020	53/M	4 months	Lower leg	Gouty arthritis	Corticosteroids	NA	No	Fluconazole 400mg/d	>80 days	Improved
J Am Acad Dermatol	Mary C. Massa, et al	1981	33/M	4 months	Upper and lower limbs and shoulder and chest	Chronic ulcerative colitis, pulmonary embolus, segmental glomerular sclerosis	Furosemide and prednisone and warfarin	C. neoformans	Gastric and pneumonia	Amphotericin B and 5-fluorocytosine	27 days	Die
An Bras Dermatol	Qiang Zhou, et al	2019	43/F	4 months	Axillary fold and shoulder	No	No	C. neoformans	No	Fluconazole 400mg/d	9 months	Cured

Ir J Med Sci	Y.Liu, et al	2015	23/M	NA	Trunk	Nephrotic syndrome	Prednisone 30-60mg/d, leflunomide, cyclophosphamide	C. neoformans	No	Fluconazole 600mg/d for 4 days and itraconazole 500mg/d for 5 days	NA	Die
Med Mycol J	Hiromitsu Noguchi, et al	2016	68/M	32months	Chest	No	No	C. neoformans	No	Fluconazole 400mg/d	12 weeks	Cured
JAAD Case Rep	Alana Deutsch, BA, et al	2020	67/M	2 months	Eyelid	Renal transplant and pneumocystis jiroveci pneumonia multidrug resistant urinary tract infections, enteroaggressive Escbericbia coli colitis, carbapenem resistant enterobacteriaceae klebsiella Pneumonia, and an enterococcus faecalis urinary tract infection	Tacrolimus, mycophenolate mofetil and prednisone	NA	Cerebral	Amphotericin B and fluorocytosine	NA	Cured
JAAD Case Rep	Meghan Beatson, BS, et al	2019	80/M	4 weeks	Check and ear	Hypertension, gout, hypercholesterolemia	No	C. neoformans	No	Fluconazole 200mg/d	2 months	Cured
Case Rep Dermatol	Guy Shalom, et al	2020	30s/F	2 months	Lower leg	Cirrhosis and myelodysplasia	Azathioprine and prednisone 15mg/d	C. neoformans	No	Amphotericin-B four days then switch to fluconazole 400mg/d	6 weeks	Cured
Eur J Dermatol	Nana Inoue, et, al	2021	81/M	80 days	Lower leg	Seronegative symmetrical synovitis with pitting oedema syndrome	Prednisolone 15mg/d	C. neoformans	No	Amphotericin-B and flucytosine for 4 weeks then switch to fluconazole 400mg/d for 6 weeks	10 weeks	Cured
Rev Inst Med Trop Sao Paulo	Da Silva Lacaz C, et al	2002	65/M	50 days	Forearm	No	No	C. neoformans	No	Fluconazole 150mg/d	45 days	Cured
Case Rep Dermatol	Gaviria Morales E, et al	2021	60/F	4 days	Finger	No	No	C. neoformans	No	Itraconazole 100 mg/12 h	6 months	Cured

Dermatology	Hunger RE	2000	36/F	5 weeks	Forearm	Liver transplantation, polycythemia vera	Prednisone 5mg/d, azathioprine 50mg/d, tacrolimus 8mg/d	C. neoformans	No	Fluconazole 200mg/d	12 weeks	Cured
J Am Acad Dermatol	Patel P, et al	2000	85/F	12 weeks	Nose	Hypertension and coronary artery disease	NA	C. neoformans	No	Fluconazole 200mg/d	16 weeks	Cured
NA: Not applicable												