

CUTANEOUS PRESENTATION OF CRYPTOCOCCOSIS IN AIDS. FLUCONAZOLE THERAPY

G. Gaddoni, L. Baldassari, B. Menni and I. Marinucci

ABSTRACT

In patients with AIDS *Cryptococcus neoformans* may cause widespread mycotic infections. Cutaneous involvement usually occurs in the context of diffuse infection. Amphotericin B has been the standard treatment.

We report five cases of HIV-positive patients who presented with early cutaneous manifestations of cryptococcosis. Systemic fluconazole is as successful in the clearance of infection and in maintenance suppressive therapy for cutaneous infection as it is in cryptococcal meningitis.

KEY WORDS

cutaneous cryptococcosis, AIDS, HIV, fluconazole

INTRODUCTION

Cryptococcus neoformans is a ubiquitous yeast present in soil, dust and pigeon excreta. In immunodepressed patients it may be the cause of widespread mycotic infections which are particularly virulent in patients with AIDS (1-5). The incidence of cryptococcal disease in these patients has been estimated to be 6-10% in the United States and Europe. It is the fourth commonest cause of death and mortality ranges from 50-100% (4).

The yeast enters the body through the respiratory system and diffuses into the circulation with particular tropism for the central nervous system. The skin is affected in 10-20% of cases and cutaneous involvement usually occurs in the context of diffuse cryptococcal

infection but may be the presenting feature in patients who are still asymptomatic offering the possibility to make an early diagnosis and initiate treatment (2).

CASE REPORTS

We report five cases of HIV-positive intravenous drug users, three males and two females, who presented with early cutaneous localization of *cryptococcus* which later evolved in systemic cryptococcosis. Cutaneous symptoms were accompanied by slight pyrexia, intense headache and cough. They are part of a group of seventeen patients with systemic cryptococcosis attending the hospital from 1992 to 1994. Haematological and serological values are

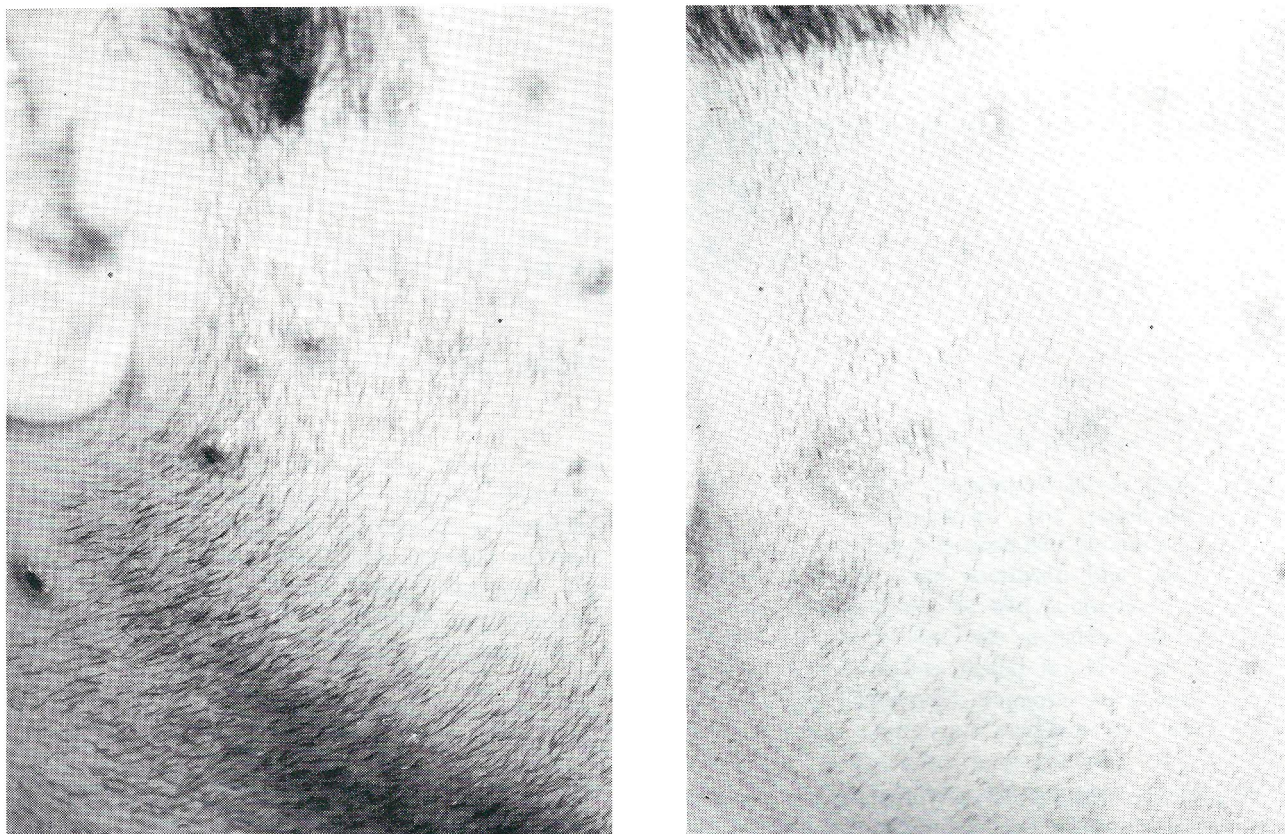


Fig. 1 a,b. Papulonodular lesions of the face with a central area of superficial necrosis (a). After one month of fluconazole treatment (b).

reported in Table 1.

These cases demonstrate the polymorphic character of the clinical presentation of cutaneous cryptococcosis. Lesions were mainly localized on the face, neck, auricles of the ears and upper trunk. They were usually papulo-nodular with a central area of superficial necrosis with crusting (Fig. 1a). On occasions, the

papules and the nodules are dome-shaped with a central depression, white-ivory in colour and resembling molluscum contagiosum. In one patient (No. 3) co-existing ulcerated lesions were localized in the extremities (Fig. 2a).

Histology showed the presence of cryptococci in the reticular dermis in all cases (Fig. 3).

Table 1. Haematological and serological parameters in five patients affected with AIDS.

Patients	Sex	Age (in years)	Sed. rate	Lymphocyte count/mm ³	CD4/mm ³	CD4/CD8	Platelets/mm ³	Cryptococcal antigen	
								in blood	in cerebrospinal fluid
1	M	37	58	1.300	156	0,2	60.000	+	+
2	M	33	7	600	0	0	140.000	+	+
3	M	29	131	1.000	33	0,04	112.000	+	+
4	F	29	60	200	0	0	153.000	+	-
5	F	26	118	500	5	0,02	132.000	+	-

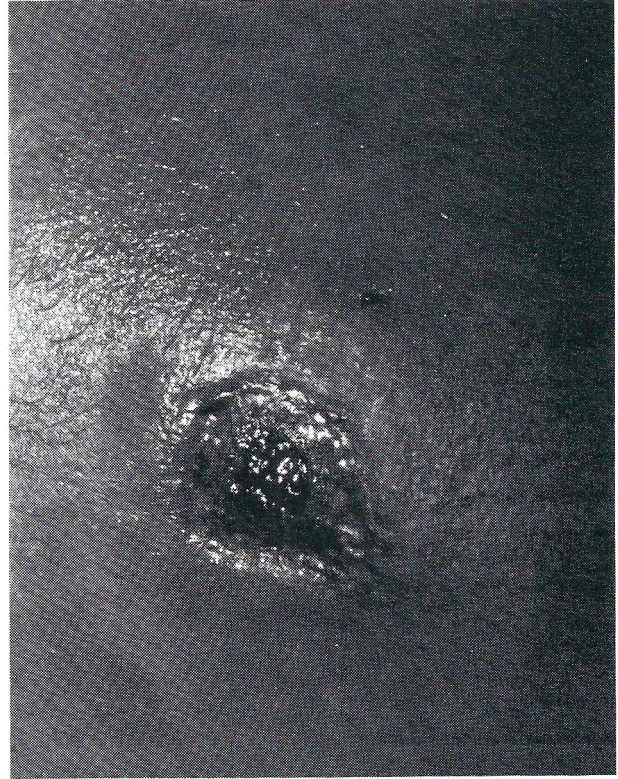


Fig. 2 a,b. In one case coexisted ulcerated lesions: a lesion of the left forearm (a). After one month of fluconazole treatment (b).

Four patients already expressed AIDS-defining symptoms. In patient No. 2 the cryptococcosis was the first AIDS-defining opportunistic infection; cutaneous cryptococcus infection was concomitant with pulmonary infection.

Cryptococcal antigen tests were positive in cerebrospinal fluid only in patients 1, 2 and 3 in whom the central nervous system was involved. Cryptococcal antigen was positive in serum in all cases and persisted after therapy, except in patient 1.

Patients 1 and 2 were treated with amphotericin B initially followed by maintenance therapy with fluconazole orally. Patients 3, 4 and 5 were treated

initially with intravenous fluconazole and then by oral maintenance therapy (Table 2). Resolution of the cutaneous and general symptoms was achieved in all cases (Fig. 1b, 2b).

The drug was well tolerated and no adverse reaction or biochemical or haematological changes occurred.

COMMENT

Standard treatment of cryptococcal infection is amphotericin B administered intravenously in daily doses ranging from 0,4 to 0,6 mg/Kg body weight

Table 2. Treatment of cryptococcosis in five patients affected with AIDS

Patients No.	Initial treatment	Maintenance therapy
1 - 2	Amphotericin B (i.v.) 25-40 mg/daily for 22-25 days	Fluconazole (oral) 200 mg/daily
3 - 4 - 5	Fluconazole (i.v.) 800 mg/daily for 20 days	Fluconazole (oral) 200 mg/daily

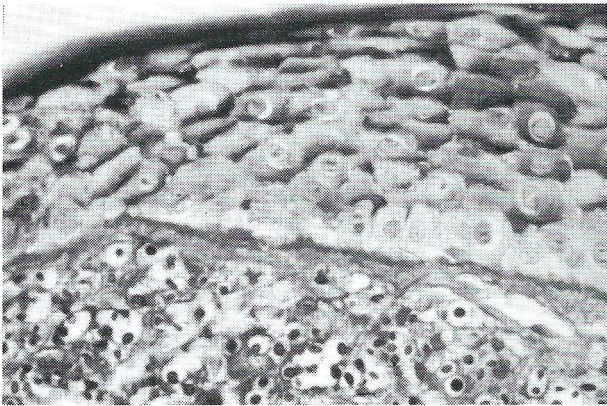


Fig. 3. In all cases histology revealed the presence of cryptococci in the reticular dermis (H.E. 120x).

alone or combined with oral flucytosine if renal function and peripheral leukocyte count allow this (6-8). Therapy may be discontinued after six weeks if there is a good clinical response; however, in many cases longer therapy may be required. The addition of flucytosine to amphotericin B neither enhances survival nor prevents relapse (7). As maintenance therapy amphotericin B was administered weekly (parenterally). And whilst not universally effective in prevention of relapse, it seems to offer improved survival. Ketoconazole is also useful for suppression but, as it does not enter the cerebrospinal

fluid easily, it is mainly effective in preventing recrudescence from extrameningeal sites (7). Fluconazole has been shown to be particularly efficacious in reducing the risk of a first episode of cryptococcal meningitis in HIV-infected patients (9), in the treatment of cryptococcal meningitis in patients with AIDS (10), and in prevention of secondary cryptococcosis (11, 12). The drug is well absorbed and relatively non-toxic. It penetrates the blood-brain barrier well and high levels of active drug are obtained in the cerebrospinal fluid following oral administration (13). A carefully controlled investigation of amphotericin B versus fluconazole showed that these two compounds had equal efficacy for cryptococcal meningitis in AIDS (14).

Fluconazole has been useful also in the therapy of primary cutaneous cryptococcosis in HIV-negative patients (15, 16). In the cases reported all patients recovered and remained free of cryptococcosis during the six months follow-up. Four subsequently died of other causes, one (patient 1) discontinued maintenance therapy as his cryptococcal antigen became negative.

In our experience, fluconazole was as successful in the treatment of infection and in maintenance suppressive therapy for cutaneous infection as it was for cryptococcal meningitis. This imidazole offers a useful approach for the treatment of cryptococcosis and for maintenance therapy thereafter.

REFERENCES

1. Borton LK, Wintroub BU. Disseminated cryptococcosis presenting as herpetiform lesions in a homosexual man with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1984; 10: 387-90.
2. Rico MJ, Penneys NS. Cutaneous Cryptococcosis resembling molluscum contagiosum in a patient with AIDS. *Arch Dermatol* 1985; 121: 901-2.
3. Azon-Masoliver A, Gonzales-Clemente J, Pedrol E. Herpetiform and mollusca contagiosa-like cutaneous cryptococcosis in a patient with AIDS. *Br J Dermatol* 1989; 121: 665-7.
4. Poizot-Martin I, Grob JJ, Fournier JR, Dhriver C, Andrac L, Gastaut JA, Bonerandi JJ. Cryptococcosse cutanée à forme de molluscum contagiosum au cours du SIDA: un cas. *Ann Dermatol Venereol* 1991; 118: 29-32.
5. Gaddoni G, Resta F, Baldassari L, Marinucci I, Menni B. Criptococcosi cutanea in corso di AIDS. *G Ital Dermatol Venereol* 1993; 128: 129-32.
6. Zuger A, Louie E, Holzman RS, Simberkoff MS, Rahal JJ. Cryptococcal disease in patients with the Acquired Immunodeficiency Syndrome. *Ann Intern Med* 1986; 104: 234-40.
7. Chuck SL, Sande MA. Infections with *Cryptococcus neoformans* in the acquired immunodeficiency syndrome. *N Engl J Med* 1989; 321: 794-9.
8. Coker RJ, Viviani M, Guzzard BG, Du Pont B, Pohle HD, Murphy SM, Atouguia J, Champalimaud JL, Harris JR. Treatment of cryptococcosis with liposomal amphotericin B (AmBisome) in 23 patients with AIDS. *AIDS* 1993; 7: 829-35.
9. Quagliarello VJ, Viscoli C, Horwitz RI. Primary prevention of cryptococcal meningitis by fluconazole in HIV-infected patients. *Lancet* 1995; 345: 548-52.

10. Stern JJ, Hartman BJ, Sharkey P, Rowland V, Squires KE, Murray HW, Graybill JR. Oral fluconazole therapy for patients with acquired immunodeficiency syndrome and cryptococcosis: experience with 22 patients. *Am J Med* 1988; 85: 477-80.
11. Sugar AM, Saunders C. Oral fluconazole as suppressive therapy of disseminated cryptococcosis in patients with acquired immunodeficiency syndrome. *Am J Med* 1988; 85: 481-9.
12. Bozzette SA, Larsen RA, Chiu J, Leal MA, Jacobsen J, Rothman P, Robinson P, Gilbert G, McCutchan JA, Tilles J et al. A placebo controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. *N Engl J Med* 1991; 324: 580-4.
13. Como JA, Dismukes WE. Oral azole drugs as systemic antifungal therapy. *N Engl J Med* 1994; 330: 263-72.
14. Saag MS, Powderly WG, Cloud GA, Robinson P, Grieco MH, Sharkey PK, Thompson SE, Sugar AM, Tuazon CU, Fisher JF et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. The NIAID Mycoses Study Group and the AIDS Clinical Trials Group. *N Engl J Med* 1992; 326: 83-9.
15. Schuttleworth D, Philpot CM, Knight AG. Cutaneous cryptococcosis: treatment with oral fluconazole. *Br J Dermatol* 1989; 120: 683-7.
16. Feldman SR, Fleischer AB. Fluconazole treatment of cutaneous cryptococcosis. *Arch Dermatol* 1992; 128: 1045-6

AUTHORS' ADDRESSES

Giuseppe Gaddoni MD, Department of Dermatology, Hospital of Faenza,
Viale Stradone 9, 48018 Faenza, Italy
Laura Baldassari MD, same address
Bruno Menni MD, Department of Infectious Diseases, Hospital of Faenza,
Viale Stradone 9, 48018 Faenza, Italy
Marinucci Ivana MD, same address