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Case Report and Literature Review

Primary cutaneous cryptococcosis in immunocompetent and immunocompromised hosts

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JOHN C. CHRISTIANSON*, WILLIAM ENGBER† & DAVID ANDES*

**Department of Medicine, Division of Infectious Diseases and †Department of Orthopedics, University of Wisconsin Hospital and Clinics, Madison, Wisconsin, USA*

A case of primary cutaneous cryptococcal infection is presented and cases of primary cutaneous cryptococcosis in normal and immunocompromised hosts are reviewed. Cutaneous cryptococcosis can occur from local inoculation or dissemination from a distant site of infection. Risk factors associated with development of primary cutaneous cryptococcosis are those which affect cell-mediated immunity, such as corticosteroid usage, solid organ transplantation, sarcoidosis and immunosuppression. The cutaneous manifestations of cryptococcosis are protean and may mimic other cutaneous diseases. Patients with a diagnosis of cryptococcosis from a skin biopsy or culture should undergo evaluation to exclude disseminated disease and an evaluation of cell-mediated immunity. Although some patients do well without antifungal therapy, these patients cannot be discerned prospectively and therefore antifungal therapy appears warranted in all patients with localized disease. Choice of therapy depends on the extent of disease and immunocompetence of the host.

Keywords cryptococcosis, cutaneous, inoculation, primary

Introduction

Death rates from cryptococcosis in HIV-infected hosts were reported with increasing frequency over the first decade of the HIV epidemic, in contrast to estimates done in the pre-AIDS era [1]. Incidence of cryptococcal infection estimates for four large metropolitan areas ranged from 0.2 to 0.9 per 100 000 between 1992 and 1994 [2], with approximately 12% not HIV infected and 3.8% not reporting any immunosuppressive condition or therapy. Cutaneous findings have been observed in 10–15% of all cases of disseminated cryptococcosis. Case reports have identified cutaneous cryptococcosis in patients without immunodeficiency and without evidence of disease dissemination (no apparent disease in other organ systems by examination or radiographic studies and no positive cultures or latex agglutination tests from other sites). We describe a case of primary cutaneous cryptococcosis from a puncture wound of the right hand and review primary cutaneous cryptococcosis cases reported in the literature.

Case report

The patient was a 41-year-old male referred from a local clinic with a painful nodule on the dorsum of the right hand. He developed an erythematous nodule

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Correspondence: David Andes MD, Department of Medicine and Section of Infectious Diseases, University of Wisconsin Hospital and Clinics, 600 North Highland Avenus, H4/574, Madison, Wisconsin 53792-5158. Tel.: (608) 263 1545; Fax: (608) 263 4464; E-mail: dra@medicine.wisc.edu

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within days of sustaining a puncture wound from a hay bail wire while renovating a barn. He sought medical attention and was treated with cephalexin for a presumed bacterial furuncle. Despite 14 days of antimicrobial therapy the nodule increased in size. The patient was subsequently referred to our Orthopedic Hand Clinic. Evaluation revealed a 2 cm erythematous, tender nodule. There was no fluctuance, ulceration or drainage. Palpation of the proximal epitrochlear and axillary lymph node groups was unrevealing. He had no fever or other abnormalities on physical exam. He underwent surgical extirpation 6 weeks after the initial injury. The nodule was removed *in toto*. There was no gross evidence of tendon sheath or bony involvement. Histopathology revealed numerous yeasts and a giant cell inflammatory process. Cultures grew *Cryptococcus neoformans*. Subsequent evaluation in the Infectious Diseases Clinic revealed no history of underlying immunodeficiency or evidence of cryptococcal disease elsewhere on examination. The patient had no HIV risk factors or other medical illnesses. He lived in southern Wisconsin and his work included renovation of older buildings including barns. Plain film radiographs of the hand revealed no bony abnormalities. Laboratory studies, including a complete blood count (CBC), absolute lymphocyte count, CD4/CD8 counts and percentages, erythrocyte sedimentation rate (ESR) and complete reactive protein (CRP) were normal. HIV-ELISA and serum cryptococcal antigen were negative. The patient received oral fluconazole, 400 mg/day, for 8 weeks following surgical excision. The wound healed well and his health has remained well since.

Material and methods

A literature search was performed using the PubMed and Medline databases. The keywords used included cutaneous and cryptococcosis. References of publications were checked to identify cases not apparent in the literature search. Our case definition of primary cutaneous cryptococcosis was evidence of cutaneous inflammation and identification of *C. neoformans*, either with culture confirmation and/or histology, without evidence of disseminated infection by culture and/or latex agglutination testing in serum, cerebrospinal fluid (CSF) or other sites tested, or radiologic evidence of healed or active cryptococcosis. Cases were excluded if microbiologic identification could not be easily correlated with *C. neoformans*.

Discussion and results

Cases identified

Seventy-three cases of primary cutaneous cryptococcosis meeting our definition were identified (including the case presented above). The cases were subdivided into two groups as follows. (i) Host immune state normal (Table 1) [3–24] and (ii) host immune state immunocompromised (Table 2) [22–49]. Statistical comparison of clinical presentation, acquisition risk factors, therapeutic interventions and treatment outcome was performed between the two groups.

Data analysis

Chi-squared analysis was used for comparison of groups, except when there was small group size, when Fischer's exact test was used instead. Comparison of two means was done using Student's t-test. Calculations were performed using the SigmaStat statistical software (SPSS Software, Chicago, IL).

Presentation

Clinical presentation of the patients in the two groups was very similar, usually as a new skin lesion that was refractory to conservative or antibacterial therapy. Unfortunately, several of the case reports did not have extensive clinical details beyond a description of the skin lesion(s). The lesions were often reported to be painful (21/31 where described). Patients were rarely febrile (5/22) and rarely appeared systemically ill (2/31). Systemic symptoms appeared much less frequently than in HIV-negative patients with other presentations of cryptococcosis [50], which led especially in non-immunocompromised patients to therapeutic antibacterial trials, delays in diagnosis and brief work-ups for disseminated disease. Several lesion types were reported, with the most predominant being nodular/granulomatous (26/71; 36.6%) and ulcerative (20/71; 28.1%). The type of skin lesions did not differ significantly between the groups (Table 3). However, immunocompromised patients were more likely to present with multiple lesions or cellulitis.

Site of infection

The most common sites of infection were the extremities, especially the upper-body extremities. Finger and facial sites were particularly common sites of infection in non-immunocompromised hosts (Table 3). Immunocompromised patients were more likely to have multiple sites of infection or infection localized to extremities of the lower-body or to the trunk. In the patient group

Table 1 Primary cryptococcocis cases in non-immunocompromised (normal) hosts

Reference	Age	Site	Trauma	Diagnosis	Surgery	Treatment, Duration	Outcome	Notes
Present	41	hand	yes	Cx/hist	Yes	Fluc 8 weeks	cured	
[3]	73	cheek	yes	Cx/hist	No		cured	Serotype D
[4]	67	cheek	no	Cx/hist	No	Fluc 5 months	cured	Serotype D
[5]	61	finger	yes	Cx	no	Itra 6 months	cured	Serotype D
[6]	n/l	finger	yes	Hist	Yes	5FC 4 weeks	cured	Lab inoculation
[7]	44	head	yes	Cx/hist	yes		cured	
[8]	81	arm	no	Cx/hist	no	Miconazole 2 months	cured	
[9]	52	finger	yes	Cx	yes	Debriedment	cured	Lymphadenitis
[10]	41	thigh	no	Hist	yes	amputation	cured	Pre-antifungal
[11]	14	chest	no	Hist	yes	Excision	cured	No systemic evaluation
[12]	60	head	no	Cx/hist	no		improved	No systemic evaluation, pre-antifungal
[13]	24	finger	yes	Cx	no	5FC 6 weeks	cured	Blood inoculation HIV/cryptococcus
[14]	27	face	no	Cx/hist	no	Ampho B+	cured	
[15]	76	leg	no	Cx/hist	no	Itra 3 months Fluc 5 months Ampho B/5FC, 1 month	Recurred 3 months recurred 5 months cured	Pigeon owner
[16]	85	face	yes	Cx	no	Fluc 10 weeks	cured	Topical steroid use
[17]	75	arm	yes	Cx/hist	no	Fluc 2 months	died	
[18]	71	finger	no	Cx/hist	no	Itra 3 months	cured	Serotype D
[19]	7	head	no	Cx	no	None	cured	Anergic
[20]	46	finger	yes	Cx	yes	Itra 10 months	cured	Cx. positive of metallic object causing trauma, intra-articular steroids in underlying joint
[21]	70	neck	yes	Cx/hist	yes	Excision	cured	Scorpion sting at infection site
[22]	79	finger	yes	Cx	no	Fluc 5 weeks	cured	Pigeon keeper
[22]	75	hand/fore-arm	no	Cx	no	Fluc 1 mo	cured	
[22]	68	hand	yes	Cx	yes	Fluc 1.5 months	cured	
[22]	44	finger	yes	Cx	no	Keto = 3 weeks	cured	
[22]	83	leg	no	Cx	no	Fluc 3 months, Itra 7.5 months	cured	
[22]	79	hand	no	Cx	no	Keto 2 weeks	cured	
[22]	50	hand	yes	Cx	yes	Fluc 4 months	cured	
[22]	34	finger	yes	Cx	yes	Fluc 1 months	regression	
[22]	58	finger	no	Cx	yes	Fluc 2 weeks	cured	Pigeon keeper
[22]	14	leg	yes	Cx	no	None	cured	
[22]	37	hand	yes	Cx	yes	Keto 1.5 months	cured	
[22]	44	hand	yes	Cx	yes	Fluc 3 weeks	cured	
[22]	39	eyelid	no	Cx	no	Itra 2 months	regression	
[22]	78	finger	yes	Cx	yes	Fluc 2 weeks	cured	
[23]	53	buttock	no	Cx	yes	Ampho B/5-FC 6 weeks	cured	Pigeon exposure
[24]	9	knee	no	Cx/hist	yes		cured	

Abbreviations: cx, culture; 5FC, 5-flucytosine; Fluc, fluconazole; hist., histology; Itra, itraconazole; Keto, ketoconazole; Pre-antifungal, treatment before widespread availability of systemic antifungal agents.

Table 2 Primary cryptococcosis cases with underlying diseases/immunocompromise

Reference	Age	Site	Trauma	Underlying Disease	Diagnosis	Therapy, Duration	Surgery	Outcome	Notes
[22]	72	buttock	yes	lymphoma	Cx	Fluc 4 months	yes	cured	
[22]	66	leg	no	RA	Cx	Fluc 10 weeks	none	cured	
[22]	61	face	no	Renal transplant	Cx	Ampho B 60days	yes	cured	
[22]	84	hand	yes	CLL	Cx	Fluc 2 weeks	no	regression	
[22]	47	hand	yes	Colon cancer	Cx	Fluc 3 weeks	yes	cured	
[22]	55	wrist	no	Renal transplant	Cx	Ampho B, 5-FC 4 weeks Fluc 3 months	yes	cured	
[22]	92	hand	no	Multiple myeloma	Cx	Fluc 2 months	yes	cured	Pigeon keeper
[22]	69	hand	yes	Myelodysplasia	Cx	Fluc 1 months	yes	regression	
[22]	66	hand	no	Breast cancer	Cx	None	yes	cured	
[25]	77	finger	no	corticosteroids	Cx/hist	AmphoB+12days, Fluc 6 weeks	no	cured	Pigeon breeder, serotype D
[26]	14	chest	no	varicella	Cx	Fluc 7days	yes I&D	cured	
[27]	62	arm	yes	sarcoidosis	Cx/hist	Itra++unknown	no	cured	
[28]	70	arm	no	COPD/steroids	Cx/hist	Fluc 6 weeks	no	cured	
[29]	38	arm	yes	Renal transplant	Cx/hist	Ampho B	no	cured	
[30]	27	Arm nose buttock	no	Corticosteroids azathioprine	Cx/hist (buttock)	Ketoconazole 6 months	no	cured	
[31]	58	arm	no	DM	Cx/hist	Fluc 6 months	no	cured	
[32]	50	face	no	CD4 lymphopenia	Hist	Fluc 6 weeks	no	cured	Positive LN bx.
[32]	84	thigh	no	CD4 lymphopenia	Hist	Fluc 4 weeks	no	died	
[33]	70	arm	yes	COPD/steroids	Cx/hist	Itra 6 months	no	cured	
[34]	75	hand	no	Renal failure	Cx/hist	Fluc10 weeks	no	cured	
[35]	76	Abdomen leg	Yes no	Connective tissue disease, steroids	Cx/hist	Fluconazole 6 weeks Ampho B Fluc 12 weeks	No no	Cured cured	
[36]	29	face	no	sarcoidosis	Cx/hist		no	cured	
[37]	41	shoulder	yes	Psoriasis, steroids	Cx/hist	Ampho B	no	died	
[38]	53	arm	no	Asthma, steroids	Cx/hist	Keto,, 3 months	no	cured	Pigeon keeper
[39]	40	thigh	no	DM	Cx	Ampho B	no	cured	
[40]	62	face	no	T-cell deficiency	Cx/hist	Ampho B	no	cured	roofer
[41]	67	chest	yes	DM	Hist/FA	Ampho B topical	no	cured	
[42]	85	hand	yes	Polymyalgia rheumatica, steroids	Cx/hist	Fluc 8 weeks	no	cured	
[43]	46	neck	no	NHL, chemotherapy	Cx/hist	Fluc 11days	no	cured	
[44]	52	calf	no	Renal transplant	Cx/hist	Ampho B	no	died	
[45]	74	calf, bilat	no	CML	Cx, L Cx/hist, R	Ampho B topical	no	died	Autopsy cxs. neg.
[45]	65	finger	no	M. myeloma, corticosteroids	Cx/hist	Ampho B	no	cured	
[46]	36	thigh	no	Liver transplant	Cx/hist	Fluc 3 months	no	cured	
[47]	57	leg	yes	Renal transplant	Cx/hist	Ampho B, 5FC	no	died	Autopsy cxs. neg.
[48]	49	hand	yes	Sarcoidosis, corticosteroids	Hist	Fluc 4 weeks	no	cured, died 3 months after tx.	Pigeon exposure, hist. positive at autopsy
[49]	75	arm	no	asthma	Cx/hist	AmphoB/5FC, 19days Fluc Ampho B/5FC/ Itra 3 months	no	Healing recurred resolved	Orchid grower, var. *gatti* isolated

Abbreviations: Ampho B, amphotericin B; cx., culture; 5FC, 5-flucytosine; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; DM, diabetes mellitus; FA, fluorescent antibody; Fluc, fluconazole; hist., histology; I&D, incision and drainage; Itra, itraconazole; Keto, ketoconazole; LN, lymph node; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis.

Table 3 Comparison of groups

	Group 1	Group 2 (healthy)	*P*-value (with associated illnesses)
Age (years)	53.1 ± 22.8	59.6 ± 18.0	0.18
Sex (M/F)	17M/18F	23M/14F	
Associated trauma	20/36 (55.0%)	13/37 (32.1%)	$P = 0.13$
Pigeon exposure	6/36(15.0%)	4/37 (11.1%)	$P = 0.52$
Serotype D	4/36(20.0%)	1/37 (3.7%)	$P = 0.19$
Race/ethnicity			
White/Caucasian	3	6	
Black	1	0	
Hispanic	0	2	
Other	4	3	
Unknown	28	26	
Lesion types			
Ulcers	6	14	
Cellulitis	5	4	
Plaque	4	2	
Nodule(s)/Granuloma	11	15	
Abscess/Pustule	2	1	
Papule	1	0	
Nodular with lymphangitis	1	0	
Whitlow	5	0	
Types of trauma			
Hollow bore needle puncture	2	0	
Puncture wound	3	0	
Laceration	0	1	
Abrasion/Scratch	2	4	
Contusion	1	2	
Sting/Bite/Peck	1	1	
Unspecified	11	5	
Geographical location			
North America	7	12	
South America	1	0	
Europe	21	19	
Africa	1	0	
Asia	4	3	
Australia	2	3	
Lesion location			
Extremity	25	26	$P = 0.85$
Face/head	8	4	$P = 0.31$
Trunk	3	4	$P = 1.0$
Multiple	0	3	$P = 0.24$
All exposed (face/head/finger/hand)	26	15	$P = 0.013$
Treatment modalities			
None/topical therapy	3	3	
Surgical debriedment/excision	6	1	
Surgery plus medical therapy	10	8	
5-flucytosine	2		
Amphotericin B IV	1	7	
Azole containing therapies	20	21	$P = 0.89$
Combination medical therapy	3	5	
Therapy failures	5/38 (13.2%)	9/37 (24.3%)	$P = 0.34$
Mortality while on therapy	1/36 (2.8%)	6/37 (16.2%)	$P = 0.11$
Attributable mortality	0/36	2/37 (5.4%)	$P = 0.49$
Treatment duration (months)	2.39 ± 2.94	2.16 ± 1.70	
Mean/median follow-up (months)	25.8/11.0	20.6/8.5	

having multiple sites of infection, two of the three patients had one site of infection in an exposed area, the other patient subsequently developed infection in a potentially unexposed area of skin, and all three had a negative work-up for dissemination as defined above. A local risk factor which may predispose infections to

certain areas appears to be underlying skin disease [22] or previous lesions which could provide a portal of entry.

Cutaneous manifestations

Cutaneous manifestations of primary cryptococcal infection is varied (Table 3) and descriptions in the literature range from acneiform lesions to vesicular lesions mimicking Herpes simplex or H. zoster, nodular, nodulo-ulcerative to frank ulceration, simulating pyoderma gangrenosum [51], molluscum contagiosum in non-HIV infected patients [52], and Kaposi's sarcoma [53], basal cell carcinoma [54] and molluscum contagiosum [55] in HIV patients. It should be noted that cellulitis often has a similar presentation to bacterial cellulitis. This mode of presentation is more common in highly immunocompromised individuals, such as solid organ transplantation patients, and carries a high 28–45% mortality [44,56]. A cellulitis presentation is more often a sign of dissemination than of primary cutaneous disease. In the patients in this series with cellulitis, serum cryptococcal antigen was positive in 8/9 patients checked [56]. A significant number of these cases develop vesiculation. Useful and quick diagnostic tools include the Tzanck smear or aspiration of the cellulitis edge.

Acquisition risk factors

Preceding trauma was the most frequently reported risk, both in the immunocompromised and in the immunocompetent groups. There was a trend toward an increased rate of trauma in normal patients (20/36 vs. 13/37 in immunocompromised patients; $P = 0.13$). The types of traumatic injury associated with acquisition are reviewed in Table 3. Many of the traumas in the normal group were of the puncture type (foreign body puncture and animal-related trauma). Needle stick inoculation as a subset of trauma was identified in two cases and included one laboratory inoculation and one inoculation with blood from a patient with cryptococcemia. Pigeon exposure was occasionally sought for but was not frequently identified (three in each group; Table 3). An environmental evaluation was undertaken in two cases to identify a source of *C. neoformans*. Culture of home fixtures were negative in one case [42] and a metallic foreign body from a puncture wound was positive for *C. neoformans* in a second case 5 months after trauma occurred [20]. In a large review of primary cutaneous cryptococcosis cases from France, the majority of patients (23/28) had an occupation or hobby that put them at risk of skin injury and 22/28 had exposure to soil, dust, wood sticks or debris or bird droppings [22].

Risk factors for immunocompromise

The most common risk factor identified was corticosteroid usage (17/37). Ten of seventeen patients were prescribed oral corticosteroids, with mean and median doses (in prednisone equivalents) of 15 and 13 mg/day, respectively. Six of seventeen patients were taking or had recently taken oral corticosteroids (doses not reported), and one patient used inhaled corticosteroids only. In 7/37 patients, corticosteroids were their only risk factor (Table 4), and in the remainder of cases other immunosuppressing conditions or immunosuppressive therapy was present. One case in the normal group had an intra-articular corticosteroid injection at the site of a later discovered cryptococcal cellulitis, which was felt not to be a locally immunocompromising factor by the reporting authors [20]. Solid organ transplantation (1/6 on tacrolimus), immunosuppression, diabetes mellitus and T-cell deficiency were less frequently reported risk factors.

Organism factors

Capsular antigen serotypes have been under evaluation since the early 1990s. *C. neoformans* var. *neoformans* comprises serotypes A, D and AD, and *C. neoformans* var. *gatti* comprises serotypes B and C. Serotype D is found in up to 21% of isolates in France [57]. However, serotype A has been shown to cause over 99% of all cryptococcal disease worldwide. Isolate serotype was identified in a minority of primary cutaneous cases (5/48) outside the French series. All were positive for serotype D. Four of five cases were in the normal group. In the French series, 71% of the cases were reported as serotype D, but details on a case-by-case basis were not

Table 4 Factors associated with primary cutaneous cryptococcosis

Factor	Number of cases
Corticosteroid use	7 (17/37 total)
Solid organ transplantation	6
Sarcoidosis (two on corticosteroids)	4
Corticosteroid/azathioprine use	3
Diabetes mellitus or impaired glucose tolerance	3
T-cell deficiency or CD4 lymphopenia	3
Lymphoma	2
Leukemia	2
Multiple myeloma	2
Cancer (non-leukemia/lymphoma)	2
Acute varicella	1
Rheumatoid arthritis	1
Myelodysplasia	1

specified [22]. In one small multivariate risk analysis from France, serotype D was reported to occur in higher percentages in skin lesions (54.2 vs. 18.7%), older individuals and those on corticosteroid therapy. However, this may be a geographical variant, as this case distribution was not seen in Australia and New Zealand, where 84% of skin lesions were caused by serotype A and only 5% by serotype D [58]. Serotype B and C (*C. n.* var. *gatti*) have been linked with a particular ecological niche associated with the eucalyptus tree, and infection occurs more commonly in immunocompetent patients from areas where eucalypts are found [58]. In a large epidemiological study in Australia and New Zealand, 6.0% of cryptococcal disease due to *C. neoformans* var. *neoformans* and 6.4% due to *C. neoformans* var. *gatti* identified the skin as a common manifestation of infection [58], although only a single case of primary cutaneous disease of the latter has been identified in the medical literature from outside Australasia [49]. Animal studies have identified strains of *C. neoformans* with dermatotrophic [59] and rhinotrophic [60] characteristics. In addition, serotype D strains have shown impaired growth *in vitro* compared to serotype A strains at higher temperatures, providing an alternate explanation to dermatotrophism of serotype D strains, given the lower temperature of the skin than of the core in humans [61].

Diagnostic evaluation

The majority of patients identified underwent testing to discern the host immune status and evaluate for disease dissemination. The group of patients without a previous diagnosis of immunocompromising illness (6/38) underwent an HIV-ELISA and T-cell flow cytometry, all of which were negative and normal, respectively. Many patients (27/38) had serum (23) and CSF (6) cryptococcal antigen studies and/or cultures (sputum, blood, urine or CSF) performed, with all culture and CSF antigen results negative. There were five patients in which no culture or latex agglutination data were obtained, three of these had no radiographic evaluation for pulmonary cryptococcosis (all before the use of cryptococcal antigen testing), one with a known acute inoculation of *C. neoformans* and one in a healthy individual with no suspicion of dissemination. No patient in the normal group developed dissemination during follow-up (mean 25.9 months). In the immunocompromised group, the majority of patients (32/37) were screened for disease dissemination by either serum (21) or CSF (15) cryptococcal antigen studies or cultures (33) of sputum, blood, urine, or CSF, with all culture and CSF antigen results negative. Similarly, this group of patients did not develop dissemination during follow-up (mean 20.6 months) or at autopsy. No evidence of active or healed pulmonary disease was found. It should be noted that 17 of these cases occurred before widespread availability of HIV antibody testing in 1987, and five of the cases occurred before widespread usage of serum or CSF antigen testing by latex agglutination, which was reported in these cases in 1965 [40]. As the clinical course of these patients prior to cryptococcal antigen testing appears identical to later cases reported where more extensive evaluation was available, the cases were included in this review. In the French Cryptococcosis Study Group review, the identifiable cases with positive serum cryptococcal antigen (4/28 cases) were excluded despite the absence of clinical evidence of dissemination [22].

Therapy

Therapy for these infections was varied, and because of the small numbers in these treatment groups it is difficult to differentiate success among the treatment strategies. Individuals without immunocompromise were more likely to have surgical extirpation as the primary treatment or to be managed with observation alone. In general, this treatment strategy was successful, perhaps related to the localized nature of the disease in this group. There was no apparent difference among the antifungal therapies utilized. Treatment duration did not differ significantly between the two groups and did not appear to impact outcome. Treatment failures in the non-immunocompromised group were due to relapses in the same patient, and may have been related to low azole dosages (50–200 mg/day). The single documented treatment failure in the immunocompromised group was discovered at autopsy after 3 months of antifungal therapy, and regressions in both groups were described without details [22]. The deaths in the immunocompromised group were not attributed to disseminated cryptococcal disease (Figs. 1 and 2). Overall mortality in primary cutaneous cryptococcosis (9.2%) and cause-specific mortality (0%) is lower than reported in HIV-negative patients with other forms or cryptococcal disease [50].

Conclusions

Cryptococcus neoformans is a pathogenic yeast which has been known to cause human infection since the first documented cases in the late 19th century, and considered by most to be always a hallmark of dissemination. Controversy has surrounded the existence of primary cutaneous cryptococcosis. The current

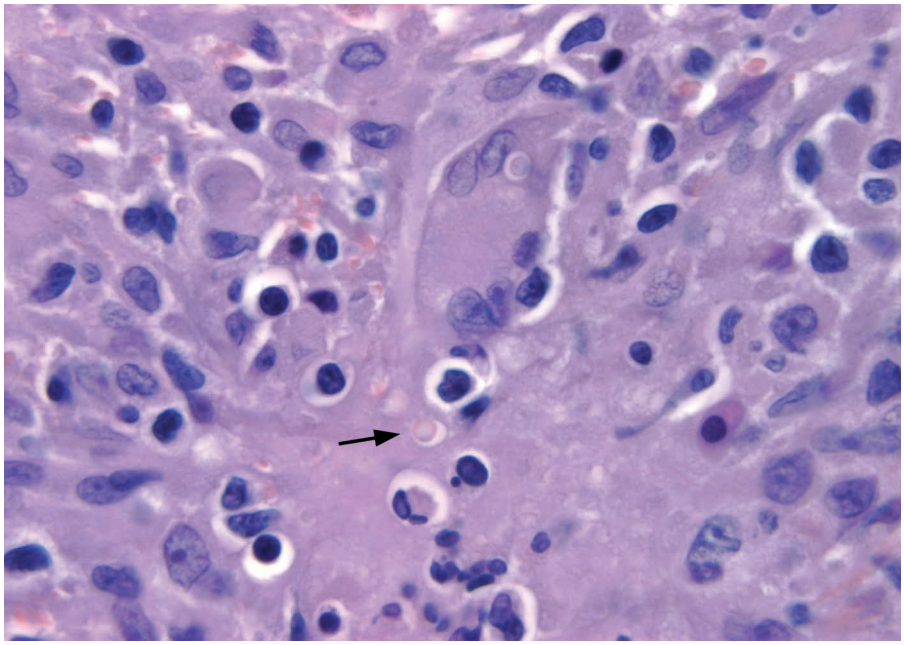

Fig. 1 Primary cutaneous cryptococcosis in immunocompetent and immunocompromised hosts. Histology section with hematoxylin and eosin stain showing cryptococcal organisms in case patient's skin biopsy.

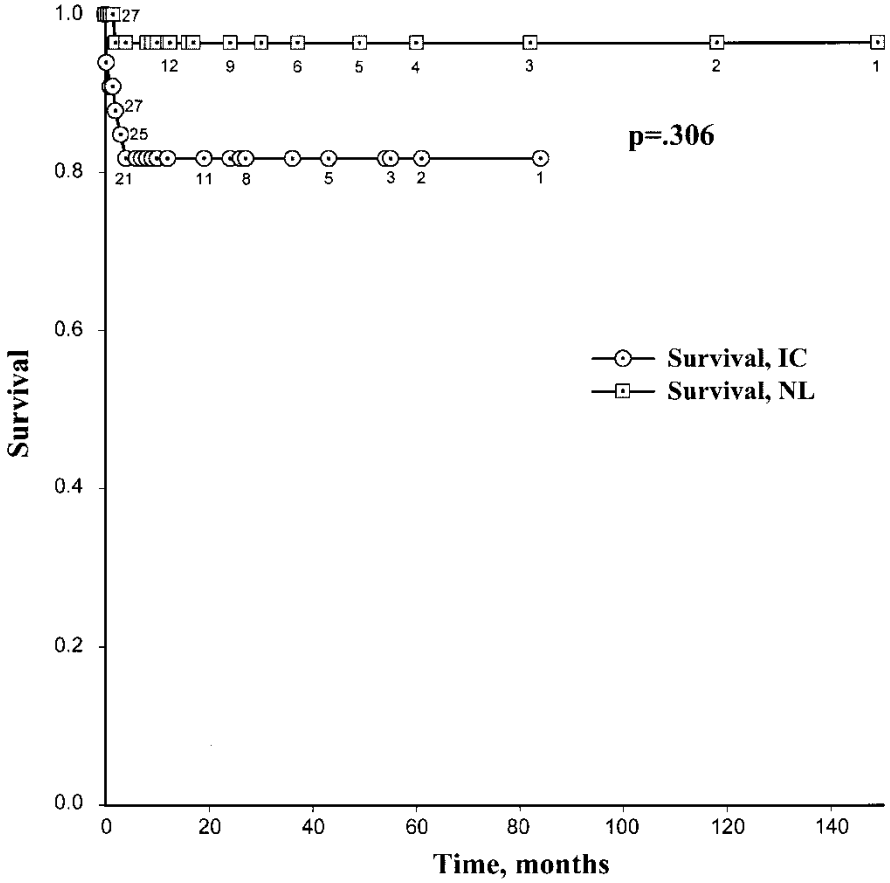

Fig. 2 Mortality in patients with primary cutaneous cryptococcosis in normal and immunocomprised patient groups.

case report and literature review identifies the clinical presentation, diagnosis, management and outcome of this uncommon cryptoccocal disease. The cases reviewed here illustrate several common features in cutaneous cryptococcal disease. Many primary cutaneous cases were related to trauma, which could have provided a portal of entry. Although earlier reports suggest cryptococcal infection is always via the inhalation route [28], the cases described here support the possibility of a cutaneous portal of entry. Although multiple cutaneous sites often suggest disease dissemination instead of multiple sites of cutaneous inoculation, the three cases included in this report had no evidence of disease dissemination based on our case definition. An alternate explanation for multiple sites of disease would be a primary cutaneous inoculation and secondary inoculation with a dermatotrophic strain, displaying satellite lesions but no evidence of dissemination. This pattern of disease has been described with a dermatotrophic strain in an animal model [59]. The infectivity of cutaneous inoculation of *C. neoformans* is not known. Four cases of cutaneous cryptococcosis due to inoculation including the present case, were in the non-immunocompromised group [6,13,17], and only a single case of *C. neoformans* inoculation without development of disease has been reported [62]. In light of the poorly defined infectivity and high mortality with disseminated disease, preemptive therapy for accidental laboratory inoculation is probably justified. The mean and median duration between inoculation and clinical presentation in these inoculation cases was almost 8 days, similar to that recently reported for blastomycosis [63]. Evidence of an inhalation portal of entry for *C. neoformans* in our patient group was sought, but no active or healed pulmonary disease was found. There was no significant difference in rates of trauma between groups, although there was a trend towards increased rates in the non-immunocompromised group. There was a limited association with pigeon exposure, which was higher than control populations for cryptococcal intradermal test positivity [64] or cryptococcal seropositivity [65]. In a large review of primary cutaneous cryptococcosis cases from France a majority of patients had a main occupation or hobby that put them at risk of skin injury and/or exposure to soil, dust, wood sticks or debris or bird droppings, which put them at risk of contact with *C. neoformans* [22] (Fig. 2).

The host risk factors predisposing to primary cutaneous cryptococcosis were similar to those recognized as important for systemic cryptococcal infection. These factors point to the role of cell-mediated immunity as the primary host defense against cryptococcosis. The most common immune-related risk factor for cutaneous cryptococcosis was systemic corticosteroid administration. In the solid organ transplant population, an increased risk of dermatologic presentation and decreased risk of CNS disease has been noted with use of tacrolimus as an immunosuppressive agent [66]. Only one of four of the solid organ transplantation cases described in detail in our review received tacrolimus. The effect of tacrolimus relative to cutaneous manifestations has been attributed to enhanced CNS penetration of tacrolimus (as opposed to cyclosporine) and intrinsic antifungal activity of calcineurin inhibitors which are enhanced at higher temperatures *in vitro* [67]. The single immunodeficiency state conspicuously absent in this review of primary cutaneous cryptococcosis was underlying HIV disease. This may be related to the high risk of disease dissemination in these patients.

Secondary work-up of patients found to have isolated cryptococcal skin lesions should be undertaken in all cases and should include evaluation for dissemination as well as underlying causes of immunodeficiency. This work-up should include serum cryptococcal antigen, blood, urine and sputum cultures if warranted, chest X-ray and a thorough dermatologic examination. As diabetes mellitus and defects of cell-mediated immunity are prominent reasons for immunocompromised conditions in patients with primary cutaneous cryptococcosis, screening with an HIV-ELISA, flow cytometry to evaluate T-cell subpopulations and fasting blood glucose should be performed. For non-immunocompromised patients, if any of the initial work-up indicates disseminated disease or symptomatology (headache or altered mental status) suggests CNS involvement, lumbar puncture for CSF cryptococcal antigen and fungal culture should be performed. In immunocompromised patients the index of suspicion of dissemination, and therefore the threshold for lumbar puncture, should be lower. The only exceptions to this appear to be known clinical or laboratory inoculation with *C. neoformans*, where prompt recognition in an otherwise normal host appears to preclude the risk of dissemination in a short time-frame, and preemptive therapy is given.

The case definition that was used in these cases, that of a localized cryptococcal skin infection without evidence of dissemination, either by latex agglutination or culture criteria, was chosen to try to exclude the possibility of occult or obvious cryptococcal disease in other organ systems and subsequent dissemination as a cause of cutaneous disease. This approach was used as a basis for the proposed criteria for diagnosis of primary cutaneous cryptococcosis by the French Cryp-

tococcosis Study Group [22], which provides a useful tool for evaluating the possibility of a patient having primary or secondary cutaneous cryptococcosis. Our data affirms most of these criteria, although some findings might be changed by immunosuppression, which may decrease the inoculum and severity of trauma needed to induce infection and obscure the epidemiologic relationships and clinical signs more obvious in the non-immunocompromised group. The strength of the relationship of cutaneous disease with rural setting and serotype D would benefit from study outside of France to determine whether these epidemiologic associations are present worldwide. Unanswered questions include whether the natural history and risk of dissemination of primary cutaneous cryptococcosis is the same in those patients with positive or negative serum latex agglutination studies. Although the French study included a small number of patients that were antigen positive, neither case series is able to answer this question.

Another issue in management of primary cutaneous cryptococcosis is the use of antifungal therapy. In light of the high mortality (approaching 70%) of disseminated disease, initial antifungal therapy appears to be warranted in all cases. Several data have relevance to duration and dose of therapy. The occurrence of disseminated disease can appear up to 8–10 months after initial evaluation [68,69], although most cases will become apparent within 8 weeks of presentation if not immediately via cryptococcal antigen testing. A few of the primary cases had follow-up cultures while on therapy [8,18,41], with cultures positive as long as 23 days [41] and yeast forms seen on histology as long as 48–150 days [8,20,47] after institution of therapy. Three recurrences occurred with low (less than 200 mg/day) doses of fluconazole [15]. The small number of cases and high success rate with all therapies preclude a more detailed assessment of therapeutic effectiveness of individual agents or combination therapy. The IDSA guidelines concerning cryptococcal disease do not speak directly to treatment of cryptococcal skin disease in the non-HIV population [70]. For pulmonary disease fluconazole is recommended as the primary therapy for mild to moderate cryptococcosis, and amphotericin B for severe or progressive disease. This strategy based upon host immune state and disease severity would seem reasonable for skin disease as well. In light of pathological and culture findings cited above, a reasonable duration of treatment would be 1–3 months. As existing evidence points to the infectiveness of Cryptococcus neoformans in laboratory inoculation and no cases of failure of pre-emptive therapy have been reported, the short course pre-emptive regimen of Casadevall *et al*. [6] (fluconazole 200 mg/day for 2 weeks) appears justified. The role of surgery appears to be both for diagnosis and to remove bulky areas of disease. Although no treatment failures were noted in the non-immunocompromised group treated with surgery alone, adjunctive antifungal therapy should considered.

There are limitations to this data, in that in many cases reporting on duration of therapy and follow-up was incomplete. In addition, variable work-ups were done to rule out dissemination, especially in the era before cryptococcal antigen testing was routine. Because of the uncommon occurrence of this disease, it is unlikely that a prospective evaluation will be forthcoming.

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