# Primary Cutaneous Cryptococcosis: A Distinct Clinical Entity

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***Cryptococcus neoformans* is an encapsulated yeast responsible for disseminated meningitis in immunocompromised hosts. Controversies persist on the existence of primary cutaneous cryptococcosis (PCC) versus cutaneous cryptococcosis being only secondary to hematogenous dissemination. Thus, we reviewed cryptococcosis cases associated with skin lesions reported in the French National Registry. Patients with PCC ($n = 28$) differed significantly from those with secondary cutaneous cryptococcosis ($n = 80$) or other forms of the disease ($n = 1866$) by living area (mostly rural), age (older), ratio of men to women (~1:1), and the lack of underlying disease. Evidence of PCC included the absence of dissemination and, predominantly, a solitary skin lesion on unclothed areas presenting as a whitlow or phlegmon, a history of skin injury, participation in outdoor activities, or exposure to bird droppings, and isolation of *C. neoformans* serotype D. Therefore, PCC is a distinct epidemiological and clinical entity with a favorable prognosis even for immunocompromised hosts.**

*Cryptococcus neoformans* is a yeast present in the environment worldwide. The main portal of entry for infecting particles is assumed to be the respiratory tract [1], and clinical and experimental evidence indicates that cryptococcosis is usually a reactivation of a dormant infection [2, 3]. *C. neoformans* has been recovered from soil contaminated with avian excreta, especially pigeon droppings [4–10], and from decaying wood [11], fruits, vegetables, and dust [12, 13]. Four serotypes have been identified [14, 15]. Serotype A (also recently called *C. neoformans* var. *grubii* [16]) has a worldwide distribution, serotype D (corresponding to *C. neoformans* var. *neoformans*) is found mostly in Europe, and serotypes B and C (corresponding to *C. neoformans* var. *gattii*) are limited to tropical and subtropical areas.

Although *C. neoformans* has been found on the skin of healthy subjects without infection [17], this encapsulated yeast generally causes life-threatening infection in immunocompromised hosts [18]. The most common clinical manifestation is disseminated meningoencephalitis in patients with AIDS, but other diseases also predispose to cryptococcosis [19–22]. Skin lesions due to *C. neoformans* are found in ~5% of patients with cryptococcal meningitis [18], and the frequency is higher in liver transplant recipients receiving tracrolimus [23] or in patients infected with serotype D [24]. Most often, skin lesions are attributable to hematogenous dissemination (i.e., secondary cutaneous cryptococcosis). Despite some well-documented reports, the issue of lesions associated with a skin portal of entry

Received 6 September 2002; accepted 22 October 2002; electronically published 17 January 2003.

Presented in part: 41st Interscience Conference on Antimicrobial Chemotherapy, Chicago, 16–19 December 2001 (abstract 827); and 5th International Conference on *Cryptococcus* and Cryptococcosis, Adelaide, Australia, 3–7 March 2002 (abstract PO37).

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**Clinical Infectious Diseases 2003; 36:337–47**

1058-4838/2003/3603-0014$15.00

(i.e., primary cutaneous cryptococcosis [PCC]) is still controversial [18], except for anecdotal injuries caused by *C. neoformans*–contaminated needles [25].

Therefore, we decided to take advantage of the nationwide survey of cryptococcosis in France to identify the clinical and epidemiological features that characterize PCC and that could possibly distinguish PCC from secondary cutaneous cryptococcosis.

## MATERIALS AND METHODS

***Study design.*** A nationwide survey of cryptococcosis at the National Reference Center for Mycoses (NRCM) has been ongoing in France since 1985 [26]. Data on the patient and infection are recorded on a single-page questionnaire on a voluntary basis by the treating physician and/or the microbiologist. Most of the isolates are also sent to the NRCM for serotyping [27]. We retrospectively analyzed the cases reported to the NRCM from 1 January 1985 through 1 February 2000 and selected those with a positive result of skin culture for *C. neoformans.*

***Questionnaire.*** A specific 3-page questionnaire was mailed to the treating physician and/or the microbiologist to collect information on administrative, epidemiological, and biological clinical data as well as treatments and follow-up. Any missing information or ambiguous answers were checked by phone with the physician or microbiologist.

***Definitions.*** PCC was defined as skin lesion(s) confined to a circumscribed body region, a positive result of skin culture for *C. neoformans,* and no sign of simultaneous dissemination (a regional lymphadenopathy was not considered to be dissemination). All other cases were considered to be secondary cutaneous cryptococcosis.

At the end of the data collection, patients were classified as having unequivocal skin injury (identified as such by the patient and the clinician) or probable skin injury (presence of $\geqslant 2$ of the following criteria: outdoor occupation, activity predisposing to skin injury, exposure to potentially contaminated materials, or skin lesion located in an exposed area). Prescription of antifungal agent(s) or surgery done during the first 3 months after presentation was considered to be first-line treatment. Lesions were classified by the treating physician on the basis of the following criteria: cure, complete healing of the lesion with no sequelae at the end of the initial treatment; and progression or attenuation, incomplete healing or presence of sequelae at the last follow-up visit.

***Analysis.*** Anonymity was preserved as requested by the Commission Nationale de l'Informatique et des Libertés. All variables were coded and analyzed with EpiInfo software, version 6.0 (Centers for Diseases Control and Prevention and World Health Organization). Each variable had a code corresponding to the absence of information. Quantitative data were compared with use of the Kruskal-Wallis test, and qualitative data were compared with use of Fisher's exact test. A difference was considered to be statistically significant at $P < .05$.

***Review of reported cases.*** On the basis of the aforementioned criteria defining PCC, through a MEDLINE search, we reviewed and analyzed the literature published starting in 1966. All case reports published in French or English were selected, with use of "primary," "cutaneous," "skin," "dermal," "cryptococcosis," and "*Cryptococcus neoformans*" as key words or text words.

## RESULTS

***Epidemiological characteristics of the patients.*** Of the 1974 cases of cryptococcosis reported to the NRCM during the study period, 108 had a positive skin culture result, among which 28 were considered to be PCC and subsequently analyzed. The other 80 were considered to be secondary infections.

Sixteen male and 12 female patients had PCC (table 1). Risk factors predisposing to cryptococcosis were identified in 14 patients (including 3 HIV-infected patients and 1 HIV-seronegative patient for whom persistent idiopathic $CD4^+$ lymphocytopenia without a lymphoproliferative disorder was discovered). Of the 11 patients with an underlying disease or factor, 6 had malignancies, 2 were solid-organ transplant recipients, 5 were receiving long-term treatment with corticosteroids, and 4 were receiving immunosuppressive agents for treatment of malignancies. Overall, 6 patients (3 of whom had known malignancies) were not tested for the presence of anti-HIV antibodies, and none developed signs or symptoms suggestive of HIV infection during follow-up (median duration of follow-up, 13 months; range, 1–149 months).

Compared with patients who had secondary cutaneous cryptococcosis or other forms of cryptococcosis (table 2), patients who had PCC differed by age (they were older), sex (the ratio of men to women was close to 1), and underlying immunosuppression (a lower percentage had underlying immunosuppression); also, one-half of them lived in rural areas, and a higher percentage were infected with serotype D isolates. Of note, 23 patients with PCC had a main occupation or hobby predisposing to skin injury.

***Circumstances of inoculation.*** A previous injury at the site of the skin lesion was unequivocally identified for 16 patients, and a preexisting skin lesion was identified for 5 additional patients who did not recall having had any injury but who had chronic (leg ulcers in 2 cases) or acute (1 case each of shaving cut, scratch on the face, and insect bite on the hand) lesions positive for *C. neoformans.* For 80% of these patients, <1 month elapsed between the injury or former skin abrasion

**Table 1. Clinical and epidemiological characteristics of 28 patients with primary cutaneous cryptococcosis in France, 1985–2000.**

| | | | | | | | First-line treatment | | | Second-line treatment | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Sex, age in years | Main employment or hobby | Immune defect | Local factor | Type of lesion | Site of lesion | Agent (dosage, mg/day) | Duration, weeks | Surgical | Agent (dosage, mg/day) | Surgical | Outcome | Duration of follow-up, months |
| 1 | M, 72 | Retired | Lymphoma | Unequivocal injury | Ulceration | Buttock | Flu (400) | 12 | Ablation | — | — | Cured | 84 |
| 2 | M, 79 | Farmer, raised pigeons | — | Unequivocal injury | Whitlow | Finger | Flu (200) | 5 | Excision | — | — | Cured | 1.5 |
| 3 | F, 75 | Retired | — | Former lesion | Cellulitis | Hand, forearm | Flu (200) | 4 | None | — | Skin graft | Cured | 12.5 |
| 4 | F, 66 | Retired | Rheumatoid arthritis | Former lesion | Ulceration | Leg | Flu (400/200) | 2 + 8 | None | — | — | Cured | 26 |
| 5 | F, 68 | Farmer | — | Unequivocal injury | Phlegmon | Hand | Flu (400) | 6 | Excision | — | Skin graft | Regression | 1.5 |
| 6 | M, 44 | Hospital maintenance staff | — | Unequivocal injury | Whitlow | Finger | Ket (200) | 3 | None | — | — | Cured | 118 |
| 7 | F, 83 | Retired | — | Former lesion | Cellulitis | Leg | Flu (200), Itr (400) | 3 + 5 | None | Itr (400 for 14 weeks) | — | Cured | 9 |
| 8 | M, 61 | Retired | Kidney graft | Former lesion | Nodule | Chin | AmB (60) | 1.5 | Excision | — | — | Cured | 54 |
| 9 | M, 84 | Farmer | Chronic lymphoid leukemia | Unequivocal injury | Phlegmon | Hand | Flu (800) | 2 | None | — | — | Regression | 3 |
| 10 | M, 47 | Office work/handyman | Colon cancer | Unequivocal injury | Phlegmon | Hand | Flu (50) | 3 | Lancing | — | — | Cured | 55 |
| 11 | M, 55 | Carpenter | Kidney graft | Probable injury | Cellulitis | Wrist | AmB, 5-FC | 4 | Excision | Flu (200 for 12 weeks) | Skin graft | Cured | 61 |
| 12 | F, 79 | Farmer | — | Probable injury | Phlegmon | Hand | Ket (200) | 2 | None | — | — | Cured | 8 |
| 13 | M, 50 | Decorator | — | Unequivocal injury | Phlegmon | Hand | Flu (400) | 12 | Excision | — | — | Cured | 4 |
| 14 | M, 34 | Garbage man | — | Unequivocal injury | Whitlow | Finger | Flu (200) | 4 | Lancing | — | — | Regression | 0.5 |
| 15 | F, 58 | Farmer/raised pigeons | — | Probable injury | Whitlow | Finger | Flu (400) | 2 | Excision | — | — | Cured | 46 |
| 16 | F, 92 | Retired/raised pigeons | Multiple myeloma | Probable injury | Phlegmon | Hand | Flu (400) | 8 | Excision | — | — | Cured | 1 |
| 17 | M, 66 | Farmer | HIV infection | Probable injury | Whitlow | Finger | Flu (400) | 8 | None | Flu (200 lifelong) | — | Cured | 10 |
| 18 | M, 36 | Office worker/ soccer player | Sarcoidosis | Unequivocal injury | Nodule | Leg | Flu (200) | 8 | None | Flu (200 lifelong) | — | Cured | 27 |
| 19 | M, 14 | Middle school student | — | Unequivocal injury | Cellulitis | Leg | None | — | None | — | — | Cured | 82 |
| 20 | F, 37 | Physician/horse riding | — | Unequivocal injury | Phlegmon | Hand | Ket (200) | 6 | Excision | — | — | Cured | 149 |
| 21 | M, 44 | Wine industry worker | — | Unequivocal injury | Phlegmon | Hand | Flu (200) | 3 | Excision | — | — | Cured | 17 |
| 22 | M, 25 | Florist | HIV infection | Unequivocal injury | Whitlow | Finger | Flu (400) | 8 | Ablation of adenitis | Flu (400 lifelong) | — | Cured | 48 |
| 23 | F, 39 | Manual worker | — | Unknown | Nodule | Eyelid | Itr (200) | 8 | None | — | — | Regression | 1 |
| 24 | M, 69 | Sales representative/ handyman | Myelodysplasia | Unequivocal injury | Phlegmon | Hand | Flu (400) | 4 | Excision | Flu (200 for 16 weeks) | — | Regression; persistent edema | 8 |
| 25 | F, 78 | Retired/ gardening | — | Unequivocal injury | Whitlow | Finger | Flu (400) | 2 | Excision | — | — | Cured | 4 |
| 26 | M, 55 | Manager | Idiopathic $CD4^+$ lymphopenia | Former lesion | Ulceration | Forehead | Flu (400) | 3 | Ablation | — | — | Cured | 13 |
| 27 | F, 66 | Farmer | Breast cancer | Probable injury | Phlegmon | Hand | None | — | Excision | — | — | Cured | 43 |
| 28 | F, 32 | Cleaning woman | HIV infection | Unequivocal injury | Scratch-like | Hand | Flu (800/400) | 2/10 | None | Flu (400 lifelong) | — | Cured | 36 |

**NOTE.** AmB, amphotericin B; Flu, fluconazole; Itr, itraconazole; Ket, ketoconazole; 5-FC, 5-fluorocytosine.

**Table 2. Clinical and epidemiological characteristics recorded during a French nationwide survey of cryptococcosis (1985–2000) that distinguished patients with primary cutaneous cryptococcosis (PCC) from those with secondary cutaneous cryptococcosis (SCC) or other forms of cryptococcosis (other).**

| Characteristic | Patients with PCC ($n$ = 28) | Patients with SCC ($n$ = 80) | Other patients ($n$ = 1866) | $P$[a] |
|---|---|---|---|---|
| Ratio of male to female patients | 1.3 | 4.3 | 5.7 | <.0002 |
| Age, median years (range) | 59 (14–91) | 40 (4–75) | 36 (3–94) | $10^{-6}$ |
| HIV infection, % of patients | 11 | 58 | 87 | $10^{-6}$ |
| No underlying disease, % of patients | 50 | 10 | 3 | $10^{-6}$ |
| Area where patient lived or received diagnosis, % of patients | | | | |
| Paris area | 21 | 56 | 54 | <.003 |
| Countryside | 54 | NA | NA | — |
| Outdoor activities, no. of patients | 16 | NA | NA | — |
| Serotype D isolates, % (no. tested) | 71 (21) | 41 (44) | 20 (1057) | $10^{-6}$ |

**NOTE.** NA, not available.

[a] Determined with use of $\chi^2$ or Kruskal-Wallis test.

and the onset of the symptoms (median, 2.5 days; range, 0 days to 3 years). For 6 additional patients, the link between a previous injury and PCC was considered most probable because the clinical history included ⩾2 of the following circumstances: localization on the hand (6 cases), activities predisposing to skin injuries (5 cases), outdoor occupation (5 cases), and frequent contact with birds or bird droppings (4 cases). Finally, patient 23 had recalled no history of trauma, but she fed pigeons on her balcony and had a palpebral lesion containing cryptococci. Exposure to potential sources of *C. neoformans* was identified in 24 of 28 cases, as follows: exposure to bird droppings (14 cases), wood sticks or debris (8 cases), or soil or dust (4 cases) and exposure in a professional environment (2 cases).

***Clinical signs and symptoms during PCC.*** For 20 of the 28 patients, the lesion developed on the hand; for 7 others, it was located on an unclothed area. Initially, the lesion was unique for 25 patients and composed of several elements localized to a circumscribed area for the other 3. Only patient 17 developed a skin lesion on a remote body site (the nose); this occurred 3 months after development of the initial finger lesion. The most common lesion was a whitlow (17 cases, including 10 phlegmons; figure 1), followed by cellulitis (4 cases; figure 2) and nodule or ulceration (3 cases each). Of the 6 patients who had fever (temperature, >38°C) at the time of the diagnosis (including 5 patients who had immune defects), 4 had extensive cellulitis or a phlegmon and 3 had regional lymphadenopathy. Two patients with regional lymphadenopathy were afebrile, including 1 patient who presented with extensive cellulitis of the leg. The median time between the onset of symptoms and the diagnosis of cryptococcosis was 23 days (range, 3–275 days; $n$ = 25).

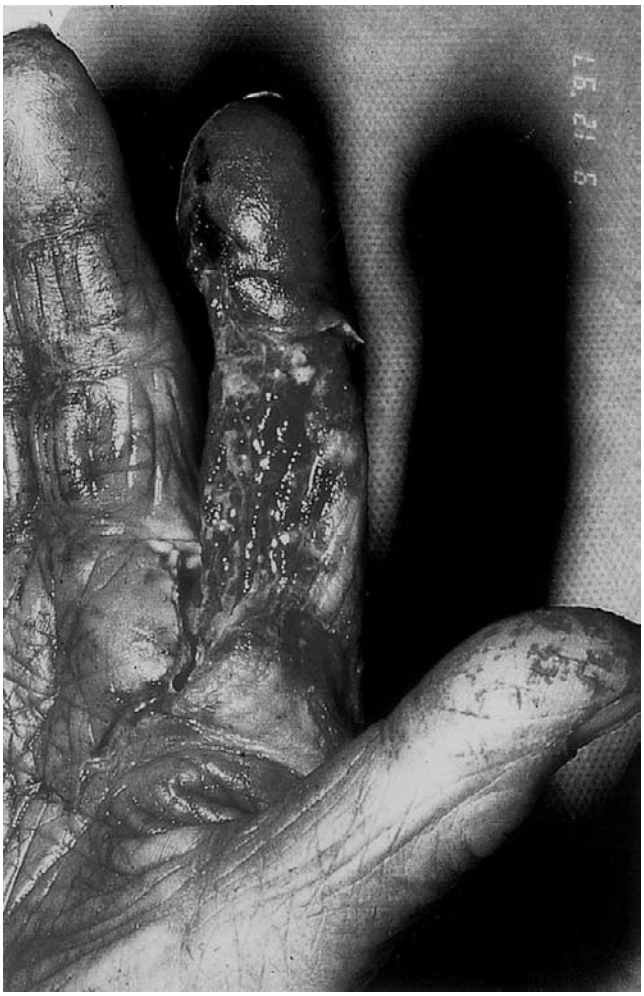

**Figure 1.** Whitlow due to *Cryptococcus neoformans* complicated by extension with phlegmon of flexor fascia (patient 5).

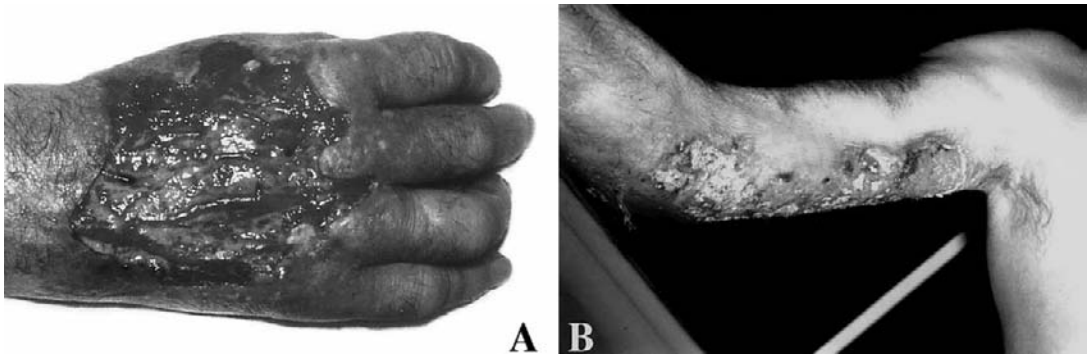


**Figure 2.** Extensive cellulitis of hand, with involvement of extensor fascias (*A;* patient 9), and widespread cellulitis of the arm *(B)* after an initial cryptococcal whitlow.

***Laboratory data.*** Routine laboratory test results were within normal values for most of the patients. Serum protein electrophoresis results, which were available for 10 patients, revealed hypogammaglobulinemia (patient 4) or hypergammaglobulinemia associated with HIV infection or myeloma (patients 16, 20, and 22). Blood cell counts revealed $CD4^+$ lymphocytopenia ($CD4^+$ cell count, <500 cells/$mm^3$), which was transient in 2 nonimmunocompromised patients (patients 7 and 25) and persistent without HIV infection or lymphoproliferation in 1 (patient 26; table 3). Analysis of CSF samples obtained from 12 patients did not detect any characteristics of meningitis (i.e., no cells were present and the findings of a biochemical evaluation were normal).

***Mycological data.*** Results of all skin lesion cultures were positive for *C. neoformans,* as were results of cultures of regional lymph node specimens in 2 cases (table 3). Granulomas were commonly observed (9 of 11 samples examined).

Of the 28 patients, 18 had ⩾1 body fluid (urine, blood, or CSF) sample obtained for culture (12 of 14 immunocompromised patients and 6 of 14 nonimmunocompromised patients). All specimens were sterile, except 1 urine sample (patient 26). Finally, of the 7 patients with positive results of serum antigen tests, 6 were immunocompromised and 3 had regional lymphadenopathies. Three patients (patients 22 and 28, who were HIV positive, patient 26, who had idiopathic lymphocytopenia) described a clinical history that evolved in 2 phases. For 2 patients (patients 22 and 26), it was suggestive of secondary dissemination: a skin lesion that did not heal, followed several weeks later by enlarged lymph nodes (for both patients), fever and a positive result of antigen testing of both serum and CSF specimens (patient 22), or a positive urine culture for another (patient 26).

***Radiographic data.*** Chest radiograph findings were normal for 15 of 18 patients examined. For 2 patients, abnormalities were explained by the underlying disease (sarcoidosis and multiple myeloma). For patient 26, chest radiography showed a micronodular lesion that disappeared after administration of antifungal treatment.

***Treatment and follow-up.*** In most cases, initial management consisted of medical (10 cases) or a combination of medical and surgical (debridement or ablation) treatments (16 cases). Surgery alone or antibiotics alone were used for 1 case each. Antifungal therapy was prescribed for a median duration of 32 days (range, 10–84 days), with no difference according to the immune status. Fluconazole was prescribed to 20 of 26 patients who received antifungal drugs (median total dose, 11.6 g; range, 1–44 g).

Five patients received maintenance therapy with fluconazole (lifelong therapy for 4 immunocompromised patients and 4 additional months of treatment after healing for patient 24, who was not immunocompromised). The skin lesions were considered to have been cured in 23 cases (median duration of follow-up, 26 months; range, 1–149 months) and attenuated in 5 cases (median duration of follow-up, 1.4 months; range, 0.6–7 months). One of the latter patients had persistent edema of the back of his hand.

No evidence of systemic involvement or relapse was found for any of the 21 patients who were observed for >3 months after the diagnosis of PCC, for the 2 patients who did not receive antifungals (duration of follow-up, >3 years), or for the 5 patients who did not have body fluid samples obtained (median duration of follow-up, 55 months; range, 8–149 months). None of the patients who were not tested for HIV infection and none of the patients who did not have underlying disease developed any complication that could be attributed to immunodepression during follow-up.

***Review of published cases of localized cutaneous cryptococcosis or PCC.*** Lesions that were considered to have been PCC by the authors and that were described in case reports were reviewed [25, 28–70]. One case referred to as PCC in an HIV-infected patient was obviously secondary and was subsequently excluded [71], as were a report that lacked enough

**Table 3. Results of main biological and mycological tests done at the time of diagnosis for 28 patients with primary cutaneous cryptococcosis, according to immune status.**

| Laboratory analysis | Underlying disease predisposing to cryptococcosis | | |
|---|---|---|---|
| | HIV infection ($n$ = 3) | Other causes ($n$ = 11) | None ($n$ = 14) |
| Cell count, median cells/mm$^3$ [range] (no. of patients) | | | |
| Total WBCs | 1880 [1730–4800] (3) | 5730 [900–12,000] (11) | 6650 [4100–9600] (12) |
| Total lymphocytes | 380 [378–1800] (3) | 974 [180–2640] (11) | 1700 [380–3200] (11)[a] |
| $CD4^+$ lymphocytes | 13 [2–72] (3) | 167 [56–700] (4) | 900 [487–1137] (5) |
| No. of antigen-positive patients/no. tested | | | |
| Serum (reciprocal titer range) | 3/3 (64–4000) | 3/10 (40) | 1/10 (ND) |
| CSF (reciprocal titer) | 1/2 (2) | 0/4 | 0/1 |
| No. of culture-positive patients/no. tested | | | |
| Lymphadenopathy | 2/2 | — | — |
| Blood | 0/2 | 0/4 | 0/4 |
| CSF | 0/2 | 0/7 | 0/3 |
| Urine | 0/3 | 1/6 | 0/6 |
| No. of patients with granulomas in skin/no. tested | 1/1 | 5/6 | 3/4 |

[a] Two patients with profound lymphocytopenia were not considered to be immunosuppressed because WBC counts subsequently normalized (patients 7 and 25).

details for proper classification [72] and the 5 reports that corresponded to cases included in our series (for patients 2, 3, 6, 9, and 17 [73–76]).

For the 46 patients analyzed, the ratio of male to female patients was 1.1:1, and the mean age was 54 years (range, 6–85 years). The majority of the cases reported were from Europe (19 cases), North America (14 cases), or Asia (9 cases). An underlying disease was noted for 22 patients (3 had HIV infection and 19 had other causes), and 24 patients had previously been healthy. A certain or possible prior injury was noted in 16 cases, including 6 in immunocompromised patients. The most common lesion was an ulceration (21 cases), followed by nodule (10 cases), cellulitis (8 cases), and whitlow (4 cases). Almost one-half of the lesions were observed on the hand (10 cases) or the arm (11 cases), and 86% of the lesions were located on unclothed areas. Regional lymphadenopathy was observed in 6 (13%) of 46 cases. The mean interval between the onset of symptoms and diagnosis was 15 weeks (range, 1–156 weeks; $n$ = 36). The findings of examinations for extracutaneous cryptococcosis varied. Cryptococcal antigen was detected in 5 of 26 serum samples and in 3 of 18 CSF samples tested, but the titer was usually not reported. All cultures of biological fluids, when done, yielded negative results (17 of 17 blood cultures, 21 of 21 CSF cultures, and 19 of 19 urine cultures). Only 11 patients underwent surgery, including 4 of the 7 patients who did not receive antifungal treatment. The majority of patients ($n$ = 27) were treated with an azole antifungal drug, 10 were treated with amphotericin B (including 5 who received it in combination with flucytosine), and 4 were treated with flucytosine alone. Favorable outcomes were recorded for all 46 patients, with residual scarring in 1 patient and 2 recurrences of a nodule in 1 patient, with a mean duration of follow-up of 19 months (range, 1–156 months; $n$ = 31).

***Proposed criteria for the diagnosis of PCC.*** On the basis of our data analysis and the literature review, we propose criteria for and against the diagnosis of PCC (table 4).

## DISCUSSION

Although sporotrichosis is the prototype of primary cutaneous fungal infection, theories regarding the abilities of other fungi that cause systemic infections to enter the body through the skin remain controversial. However, Wilson [77] reported cases in which *Coccidioides immitis, Blastomyces dermatitidis,* or other fungi, such as *Histoplasma capsulatum,* but not *C. neoformans,* had been inoculated via the skin and caused a chancriform syndrome similar to that seen with *Sporothrix schenckii* [77]. The existence of PCC is still controversial, even though the ubiquity of *C. neoformans* in the environment makes possible direct inoculation of infecting particles through skin injury, and inoculation injuries with *C. neoformans* provide unequivocal examples of its existence [25, 78].

Cases of PCC have been reported since the 1950s (reviewed in [31]), but the prevailing opinion is that cutaneous crypto-

**Table 4. Proposed criteria for and against diagnosis of primary cutaneous cryptococcosis (PCC) in patients with *Cryptococcus neoformans*–positive skin lesion cultures.**

| Criterion | Evidence for PCC | Evidence against PCC |
|---|---|---|
| Skin lesion | Solitary site or confined to limited body area | Scattered |
| | Whitlow | Molluscum contagiosum |
| | Unclothed area (limbs) | Site varied |
| Regional lymphadenopathy | Possible | — |
| Injury | History of prior injury or former skin lesion | — |
| | Identical body site for prior injury or former skin lesion and cryptococcal lesion | — |
| | Hobby or occupation predisposing to skin injury | — |
| Exposure to a possible contaminated source[a] | Yes | Possible |
| Living area | Rural | Varied |
| Underlying disease predisposing to cryptococcosis | None | Possible |
| Systemic signs | None | Concurrent |
| Extracutaneous sites positive for *C. neoformans* | None | Yes |
| Antigen detection | Negative | Positive |
| *C. neoformans* serotype | D | Varied |
| Outcome of infection | Favorable | Varied |

[a] Avian excreta, wood debris, soil, or needle contaminated with *C. neoformans*.

coccal infection cannot exist without previous, concurrent, or delayed systemic involvement [18, 61, 79, 80]. PCC is defined in the literature by the identification of *C. neoformans* in the skin lesion biopsy specimen or by culture and either clinical criteria (presence of a chancriform syndrome [59]) or histological criteria (lesion confined to the skin and subcutis [61]), together with the absence of dissemination. Our analysis of 28 French cases showed that additional evidence supports the existence of this clinical entity and that some distinctive parameters could help to distinguish PCC from secondary cutaneous cryptococcal infections (table 4).

By comparing demographic parameters among the patients with PCC, secondary cutaneous cryptococcosis, and other forms of the infection recorded in our database, we found that PCC occurred in a population different from the other 2 groups in terms of age, sex, living area, and underlying diseases, suggesting the existence of a real clinical entity. Furthermore, evidence that direct inoculation of *C. neoformans* could have caused the skin lesions was supported by a documented history of skin injury or a preexisting skin lesion at the same body site (75% of the patients) or indoor or outdoor hobbies or activities predisposing to wounds (61% of patients). Although skin injury is sometimes cited in the literature, the association between cutaneous cryptococcosis and the preexisting lesions has rarely been reported (varicella [39], lepromatous leprosy [30], and insect bite [70]). Of note, exposure to various environmental sources of *C. neoformans* (e.g., pigeon droppings, soil, and wood debris) was here recorded in an unusually high percentage of cases.

Skin lesions associated with PCC seem to differ from those commonly seen during disseminated cryptococcosis [81, 82]. During AIDS-associated secondary cutaneous cryptococcosis, skin lesions are usually multiple and scattered, located on both clothed and exposed areas (and, in the latter case, most commonly on the head and neck), whereas skin lesions characteristic of PCC were solitary or confined to a limited area and located on unclothed areas. Umbilicated papules resembling molluscum contagiosum are often described during disseminated cryptococcosis [83], whereas cellulitis, ulceration, and especially whitlow were the most common clinical features during PCC. Even though skin manifestations seem to differ between PCC and secondary cutaneous cryptococcosis, it should be remembered that almost every type of lesion can be seen during disseminated cryptococcosis, including extensive cel-

lulitis [84], pyoderma gangrenosum–like lesions [85], and a combination of polymorphic lesions [86]. Many different lesions can also be seen in HIV-uninfected patients, none of which are pathognomonic of cryptococcosis or typical of primary or secondary lesions [87].

Although some features seem to differentiate PCC from secondary cutaneous cryptococcosis, only careful investigation can ascertain the diagnosis. In our series, clinical and mycological evidence of simultaneous dissemination was absent in all patients. However, cutaneous lesions can be the only symptom and an early marker of disseminated disease [88–90]. Even if antigen positivity can indicate severe local infections, it can also be an early indicator of brewing cryptococcal meningitis [91–93] and should not be neglected. Thus, it is essential that biopsies and mycological cultures be done for prolonged and unexplained skin manifestations, especially in immunocompromised patients [83], even when the type of lesion (whitlow) and the clinical history (definite trauma, no known underlying disease) suggest PCC. In our series, a positive urine culture result and a positive result of antigen testing suggested subsequent dissemination in 2 immunocompromised patients.

Among parameters that seem to differentiate PCC from secondary cryptococcal infection is the immune status of the host. One-half of our cases and the published cases occurred in immunocompetent persons. However, the diagnosis of PCC should prompt analysis of the host's immune status. Indeed, a cellular immune defect, such as HIV infection [66], or severe lymphocytopenia independent of HIV infection (case 26 and [42]) can be discovered in this setting. In addition, qualitative or quantitative effector cell (especially lymphocyte) defects have been described in patients with disseminated cryptococcal meningitis [94] and were observed here transiently in otherwise healthy subjects (patients 7 and 25). Whether these defects may reflect the deleterious effects of the capsular polysaccharide [95] is not clear, but, in our series, the 2 patients with transient lymphopenia tested negative for antigenemia.

Although histopathological examination can contribute to the diagnosis, local inflammation does not distinguish between primary and secondary lesions. Indeed, most cutaneous *C. neoformans* lesions exhibit granulomatous patterns, regardless of the underlying disease, the presence of disseminated disease, and the outcome [61, 81]. However, although the cure rate for cryptococcal meningitis with prolonged and combined antifungal therapy is <80% [96], most patients with PCC responded favorably to short-term monotherapy. Additional evidence for the existence of PCC is that 5 of the 75 cases from our series (patients 19 and 27) and the literature [64, 67, 70] were cured without medical treatment and were free of symptoms with a prolonged follow-up (duration, 24–82 months). Whether surgery alone is an appropriate treatment remains questionable, even for immunocompetent patients. We believe that, in the era of active, orally administered antifungal agents, fluconazole should be prescribed.

Several hypotheses can explain the low frequency of PCC. The local immune response to *C. neoformans* is probably efficient enough to prevent the development of a local infection in most persons [77]. Indeed, even in immunocompromised patients, the inflammatory response is intense [61] compared with that observed in the brain [97–99] or lungs [100]. Misdiagnosis or underdiagnosis could be an alternative explanation. In fact, whitlow—one of the most common clinical features—may seem innocuous to persons used to repeated wounds, thereby preventing recording of the diagnosis. Even when medical advice is sought, the diagnosis of cryptococcosis may be unsuspected. For some patients, biopsy and culture had been necessary to establish the diagnosis for nondescript lesions that failed to heal after antibiotics.

A last difference between PCC and secondary cutaneous cryptococcosis seems to be geographic distribution. The majority of PCC cases were reported from Europe and Japan (published in Japanese and reviewed in [54] and [58]), whereas most of the large studies of cryptococcal meningoencephalitis came from the United States. In France, one-half of the PCC cases were reported from rural areas, whereas most secondary cutaneous cryptococcosis cases were reported from urban areas. An explanation could be the uneven distribution of serotype D around the world [4, 5, 15, 101, 102]. The association between serotype D and skin lesions has been noted independently of PCC [24, 54, 58, 103] and is thought to be related to differences in dermotropism or temperature tolerance between serotypes A and D [104].

Nevertheless, herein we have gathered evidence showing that the skin should be recognized as an additional portal of entry for *C. neoformans* and that PCC is a real, distinct clinical entity. Thus, clinicians should be aware that *C. neoformans* can be responsible for unexplained skin lesions that are unresponsive to antibiotics, even in apparently healthy persons. However, because skin lesions can be a first manifestation, thorough diagnostic evaluation, which actively looks for extracutaneous localizations and causes of immunosuppression, should be systematically completed to confirm the diagnosis of PCC. Finally, we recommend systematically prescribing an antifungal agent and considering maintenance therapy in the presence of chronic immunosuppression.

## FRENCH CRYPTOCOCCOSIS STUDY GROUP

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Jollivet (Blois); M. E. Bougnoux (Boulogne-Billancourt); C. Bazin, C. Duhamel, and A. Dompmartin (Caen); P. Boyer (Charly-sur-Marne); C. Allard, L. Launay, M. Mitteau, and O. Philippe (Cherbourg); V. Hervé and F. Vaylet (Clamart); A. Devidas, C. Malbrunot, and M. E. Matot (Corbeil Essonnes); S. Bretagne and I. Bournerias (Créteil); J. de Vregille (Devecey); A. Leblanc and O. Chapiro (Evry); J. M. Chevalier and P. Lafay (Flers); A. Bosseray and B. Lebeau (Grenoble); C. Murat (Libourne); B. Bouteille and P. Weinbreck (Limoges); M. A. Piens and A. Claudy (Lyon); A. Michel Nguyen (Marseille); M. Nezri (Martigues); C. Mourier (Melun); K. Brocart (Montivilliers); P. Alzieu, M. Hamidou, P. Poirier, and F. Raffi (Nantes); L. Lachaud and M. Pablo (Nîmes); H. Kreis (Paris); C. Kauffman-Lacroix (Poitiers); R. Jaussaud and D. Toubas (Reims); J. Belguise (Saint-Chaptes); A. Gregory and O. Prevot (St-Julien-en-Genevois); S. Liebeau (Saumur); M. Therizol-Ferly and P. Rosset (Tours); C. Bourgoin (Varrains); and J. P. Lheullier (Vouvray).

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