Primary Cutaneous Cryptococcosis: A Distinct Clinical Entity

Ségoëne Neuville,1 Françoise Dromer,1 Odile Morin,2 Bertrand Dupont,1,2 Olivier Ronin,1 Olivier Lortholary,1,4 and the French Cryptococcosis Study Group*

1Centre National de Référence des Mycoses et des Antifongiques, Unité de Mycologie Moléculaire, Institut Pasteur, and 2Service de Maladies Infectieuses et Tropicales, Hôpital Necker, Paris, 3Laboratoire de Parasitologie-Mycologie, Hôtel-Dieu, Nantes, and 4Service de Maladies Infectieuses et Tropicales, Hôpital Avicenne, Bobigny, France

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 tacrolimus [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...
(i.e., primary cutaneous cryptococcosis [PCC]) is still controversial [18], except for anecdotal injuries caused by *C. neoforms*—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 ≥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 EpilInfo 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.

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

* 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 $\geq 2$ 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, $>38^\circ C$) 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).](https://example.com/supplementary-figure-1.png)
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, &lt;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 &gt;3 months after the diagnosis of PCC, for the 2 patients who did not receive antifungals (duration of follow-up, &gt;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  | Other causes | None |
|                     | (n = 3)       | (n = 11)     | (n = 14) |
| Cell count, median cells/mm³ [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) |
| 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 |

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

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 source⁸     | 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                                |

⁸ 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 dermotelism 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**

Members of the French Cryptococcosis Study Group who enrolled patients in the present study (in alphabetical order by city) are as follows: J. P. Bouchara and D. Chabasse (Angers); A. Lecuit (Bagneux); F. Aubin, C. Bresson-Vautrin, P. Imbert, and G. Reboutx (Besançon); A. Bertrand, A. Dayan, and J. P.
References

1. Powell KE, Dahl BA, Weeks RJ, Tosh FE. Airborne Cryptococcus neoformans: particles from pigeon excreta compatible with alveolar deposition. J Infect Dis 1972;125:412–5.

2. García-Hermoso D, Janbon G, Dromer F. Epidemiological evidence for dormant Cryptococcus neoformans infection. J Clin Microbiol 1999;37:3204–9.

3. Goldman DL, Khine H, Abadi J, et al. Serologic evidence for Cryptococcus neoformans infection in early childhood. Pediatrics 2001;107:E66.

4. Ansheng L, Nishimura K, Taguchi H, Tanaka R, Shaoxi W, Miyaji M. The isolation of Cryptococcus neoformans from pigeon droppings and serotyping of naturally and clinically sourced isolates in China. Mycopathologia 1993;124:1–5.

5. Baro T, Torres-Rodriguez JM, Morera Y, Alia C, Lopez O, Mendez R. DNA typing suggests pigeon droppings as a source of pathogenic Cryptococcus neoformans serotype D. J Clin Microbiol 1997;35:2683–5.

6. Halliday CL, Bui T, Kroackdenber M, Malik R, Ellis DH, Carter DA. Presence of α and a mating types in environmental and clinical collections of Cryptococcus neoformans var. gattii strains from Australia. J Clin Microbiol 1999;37:2920–6.

7. Lachaud M, Pablos (Nimes); H. Kreis (Paris); C. Kauffmann-Lacroix (Poitiers); R. Jaussaud and D. Toubas (Reims); J. Belguique (Saint-Chaptes); A. Gregory and O. Prevot (St-Julien-Lacroix (Poitiers); R. Jaussaud and D. Toubas (Reims); J. Belguique (Saint-Chaptes); A. Gregory and O. Prevot (St-Julien-

10. Ruiz A, Fromtling RA, Bulmer DS. Distribution of Cryptococcus neoformans in a natural site. Infect Immun 1981;31:560–3.

11. Lachaud M, Pablos (Nimes); H. Kreis (Paris); C. Kauffmann-Lacroix (Poitiers); R. Jaussaud and D. Toubas (Reims); J. Belguique (Saint-Chaptes); A. Gregory and O. Prevot (St-Julien-

12. Lopez-Martinez R, Castanon-Oliveraz LR. Isolation of Cryptococcus neoformans var. neoformans from bird droppings, fruits, and vegetables in Mexico City. Mycopathologia 1995;129:25–8.

13. Swinne D, Keyembe K, Niyimi M. Isolation of saprophytic Cryptococcus neoformans var. neoformans in Kinshasa, Zaire. Ann Soc Belg Med Trop 1986;66:57–61.

14. Bennett JE, Kwon-Chung KJ, Howard DH. Epidemiologic differences among serotypes of Cryptococcus neoformans. Am J Epidemiol 1977;105:582–6.

15. Kwon-Chung KJ, Bennett JE. Epidemiologic differences between the two varieties of Cryptococcus neoformans. Am J Epidemiol 1984;120:123–30.

16. Franzot SP, Salkin IJ, Casadevall A. Cryptococcus neoformans var. grubii: separate varietal status for Cryptococcus neoformans serotype A isolates. J Clin Microbiol 1999;37:838–40.

17. Randhawa HS, Palival DK. Occurrence and significance of Cryptococcus neoformans in the oropharynx and on the skin of a healthy population. J Clin Microbiol 1977;6:325–7.

18. Kwon-Chung KJ, Bennett JE. Cryptococcosis. In: Kwon-Chung KJ, Bennett JE, eds. Medical mycology. Philadelphia: Lea & Febiger, 1992:397–446.

19. Diamond RD, Bennett JE. Prognostic factors in cryptococcal meningitis: a study in 111 cases. Ann Intern Med 1974;80:176–81.

20. Dromer F, Mathoulin S, Dupont B, Brugiere O, Letenneur L. Comparison of amphotericin B and fluconazole efficacy in the treatment of cryptococcosis in HIV-negative patients: retrospective analysis of 83 cases. French Cryptococcosis Study Group. Clin Infect Dis 1996;22(Suppl 2):S154–60.

21. Lewis JL, Rabinovich S. The wide spectrum of cryptococcal infections. Am J Med 1972;53:315–22.

22. Pappas PG, Perfect JR, Cloud GA, et al. Cryptococcosis in human immunodeficiency virus–negative patients in the era of effective azole therapy. Clin Infect Dis 2001;33:690–9.

23. Singh N, Gayowski T, Wagener MM, Marino IR. Clinical spectrum of invasive cryptococcosis in liver transplant recipients receiving tacrolimus. Clin Transplant 1997;11:66–70.

24. Dromer F, Mathoulin S, Dupont B, Letenneur L, Ronin O. Individual and environmental factors associated with Cryptococcus neoformans serotype D infections in France. French Cryptococcosis Study Group. Clin Infect Dis 1996;23:91–6.

25. Casadevall A, Mukherjee J, Yuan R, Perfect J. Management of injuries caused by Cryptococcus neoformans–contaminated needles. Clin Infect Dis 1994;19:951–3.

26. Dromer F, Mathoulin S, Dupont B, Laporte A. Epidemiology of cryptococcosis in France: 9-year survey (1985–1993). French Cryptococcosis Study Group. Clin Infect Dis 1996;23:82–90.

27. Dromer F, Guélot E, Ronin O, Dupont B. Serotyping of Cryptococcus neoformans by using a monoclonal antibody specific for capsular polysaccharide. J Clin Microbiol 1993;31:359–63.

28. Abdel-Fatah A, Abuzid MS, Ghaly AF. Primary cutaneous cryptococcosis in Egypt. Int J Dermatol 1975;14:606–9.

29. Anthony SA, Antony SJ. Primary cutaneous Cryptococcus in non-immunocompromised patients. Cutis 1995;56:96–8.

30. Azulay RD, Muri Mendonca IR, Marca Santos C, et al. Cutaneous cryptococcosis associated with lepromatous leprosy. Int J Dermatol 2001;40:412–4.

31. Baes H, Van Cutsem J. Primary cutaneous cryptococcosis. Dermatologica 1985;171:357–61.

32. Bee OB, Tan T, Pang R. A case of primary cutaneous cryptococcosis successfully treated with miconazole. Arch Dermatol 1981;117:290–1.

33. Bellosta M, Gaviglio MR, Mosconi M, Cavanna C, Viglio A, Rabbiosi G. Primary cutaneous cryptococcosis in an HIV-negative patient. Eur J Dermatol 1999;9:224–6.

34. Blanc C, Bazex J. Un cas de cryptococcose cutanée primitive chez un sujet sain. Ann Dermatol Venereol 1979;106:807–11.

35. Bohne T, Sander A, Pfister-Warthia A, Schop E. Primary cutaneous cryptococcosis following trauma of the right forearm. Mycoses 1996;39:457–9.

36. Butler WP, Kaufer GL. Primary cutaneous cryptococcosis successfully treated with outpatient amphotericin B and 5-fluorocytosine. NITA 1985;8:295–7.
37. Difonzo EM, Palleschi GM, Vannini P, Panconesi E. Therapeutic experience with ketoconazole. Drugs Exp Clin Res 1986; 12:397–403.
38. Dounis E, Giamarelou H, Peppas T, Sifakis P, Skull, patella, and thigh cryptococcosis after a crushing injury of the temporal bone. J Chemother 1991; 1(3):130–3.
39. Erdem G, Connelly BL. Isolated cutaneous cryptococcosis in an otherwise healthy girl. Pediatr Infect Dis J 2000; 19:85–6.
40. Feldman SR, Fleischer AB, Resnick SD. Fluconazole treatment of cutaneous cryptococcosis. Arch Dermatol 1992; 128:1045–6.
41. Gatti M, Di Silverio A, Cespa M, Mosca M. Primary unusual cutaneous cryptococcosis in an HIV former drug-abuser patient. Mycoses 1997; 40:101–2.
42. Geyer SJ, Wober JC. Localized cutaneous cryptococcosis in an immunosuppressed man. Int J Dermatol 1984; 23:673–5.
43. Goh CL. Cutaneous cryptococcosis successfully treated with itraconazole. Cutis 1993; 51:377–80.
44. Goonetilleke AKE, Krause K, Slater DN, Dev D, Wood ML, Baran GS. Primary cutaneous cryptococcosis in an immunocompromised pigeon keeper. Br J Dermatol 1993; 130:60–2.
45. Gordon PM, Ormerod AD, Harvey G, Atkinson P, Best PV. Cutaneous cryptococcal infection without immunodeficiency. Clin Exp Dermatol 1994; 19:181–4.
46. Granier F, Kanitakis J, Hermier C, Zhu YY, Thivolet J. Localized cutaneous cryptococcosis successfully treated with ketoconazole. J Am Acad Dermatol 1987; 16:243–9.
47. Hamann ID, Gillepsie RJ, Ferguson JK. Primary cryptococcal cellulitis showing necrotizing vasculitis. Mycoses 2001; 44:115–8.
48. Handa S, Nagaraja, Chakraborty A, Kumar B. Primary cutaneous cryptococcosis in an immune competent patient. J Eur Acad Dermatol Venereol 1998; 10:167–9.
49. Hurwich BJ, Domonkos AN. Primary cutaneous cryptococcosis: sero-immunologic and fluorescent antibody studies. N Y State J Med 1970; 70:1075–9.
50. Hunger RE, Paredes BE, Quattropanni C, Krahnenbuhl S, Braithen LR. Primary cutaneous cryptococcosis in a patient with systemic immunosuppression after liver transplantation. Dermatology 2000; 200: 352–5.
51. Iacobellis W, Jacobs MI, Cohen RP. Primary cutaneous cryptococcosis. Arch Dermatol 1979; 115:984–5.
52. Kimura M, Kadota E, Satou T, Yoneda E, Furuta T. Case report: cryptococcal cellulitis showing necrotizing vasculitis. Mycoses 2001; 44:115–8.
53. Micilizzi C, Persi A, Parodi A. Primary cutaneous cryptococcosis in an immunocompetent pigeon keeper. Clin Exp Dermatol 1997; 22:7.
54. Miura T, Akiba H, Saito N, Seiji M. Primary cutaneous cryptococcosis. Dermatologica 1971; 142:374–9.
55. Moreno C, Taddeucci P, Donati D, Miracco C, Massai L. Primary cutaneous cryptococcosis due to Cryptococcus neoformans var. gattii in an immunocompetent host. Mycoses 2001; 44:252–9.
56. Moreno Castillo JL, Del Negro G, Heins-Vaccari E, Takahashi de Melo N. Primary cutaneous cryptococcosis. Mycopathologia 1986; 96:25–8.
57. Moriom-Rousel N, de Dobondeer G, Mindlin A, Song M. Un cas de cryptococcosse cutanée primitive. Arch Belg Dermatol 1974; 30: 275–7.
58. Naka W, Masuda M, Konohana A, Shinoita T, Nishikawa T. Primary cutaneous cryptococcosis and Cryptococcus neoformans serotype D. Clin Exp Dermatol 1995; 20:221–5.
59. Ng W, Loo KT. Cutaneous cryptococcosis—primary versus secondary disease: report of two cases and review of the literature. Am J Dermatopathol 1993; 15:372–7.
60. Nicolas C, Truchetet F, Christian B, Dorvaux V, Cuny JF. Ulcération étendue du cuir chevelu révélant une cryptococcosse chez un malade VIH positif. Ann Dermatol Venereol 2000; 127:188–90.
61. Noble RC, Fajardo LF. Primary cutaneous cryptococcosis. Am J Clin Pathol 1972; 57:13–22.
62. Patel P, Ramanathan J, Kayser M, Baran J. Primary cutaneous cryptococcosis of the nose in an immunocompetent woman. J Am Acad Dermatol 2000; 43:344–5.
63. Rao TV, Rao KS, Satyanarayana CV. Primary cutaneous cryptococcal granuloma in a child. J Pediatr Surg 1976; 11:267–8.
64. Salm R, Groth D, Kappe R, Muller J. Primary cutaneous cryptococcosis after microtrauma of the right index finger. Mycoses 1988; 31(Suppl 1):588–92.
65. Saito T, Koski S, Takahashi S, Maie O. Localized cutaneous cryptococcosis successfully treated with itraconazole: review of medication in 18 cases in Japan. Mycoses 1990; 33:453–63.
66. Song IC, Hunter JG. Primary cutaneous cryptococcosis as the presenting manifestation of AIDS. Plast Reconstr Surg 1992; 90:1065–7.
67. Sussman EJ, McMahon F, Wright D, Friedman HM. Cutaneous cryptococcosis without evidence of systemic involvement. J Am Acad Dermatol 1984; 11:371–4.
68. Vandersmissen G, Meuleman L, Tits G, Verhaeghe A, Peertmans WE. Cutaneous cryptococcosis in corticosteroid-treated patients without AIDS. Acta Clin Belg 1996; 51:111–7.
69. Vogelaers D, Petrovic M, Deroo M, et al. A case of primary cutaneous cryptococcosis. Eur J Clin Microbiol Infect Dis 1997; 16:150–2.
70. Weibling DD, Majahani A. Localized dermal cryptococcosis following scorpion sting. Australas J Dermatol 1981; 22:127–8.
71. Wu CI. Primary cutaneous cryptococcosis in a patient with the acquired immunodeficiency syndrome. Arch Dermatol 1991; 127:1849–50.
72. Yu RW. Cutaneous cryptococcosis. Mycoses 1996; 39:207–10.
73. Grégoire A, Meillet D, Salem M, Prévost O. Cryptococcus cutanea primitive. Feuillets de Biologie 1999; 40:69–72.
74. Lacroix C, Gandon P, Lacroix P, Cazeneve-Roblot F, Jacquemin JL. Cryptococcose cutanée primitive traitée par fluconazole. J Mycol Med 1993; 3:118–20.
75. Quéréux G, Milpied B, Morin O, et al. Cryptococcoses cutanées primitives chez des sujets sérénégatifs pour le VIH. Ann Dermatol Venereol 2001; 128:1009–13.
76. Verneuil L, Dompmalinkt A, Duhamel G, et al. Panaris cryptococcique chez un malade VIH positif. Ann Dermatol Venereol 1995; 122: 688–91.
77. Wilson JW. Cutaneous (chancriform) syndrome in deep mycoses. Arch Dermatol 1963; 87:121–5.
78. Glaser JB, Garden A. Inoculation of cryptococcosis without transmission of the acquired immunodeficiency syndrome. N Engl J Med 1985; 313:266.
79. Ray HJ. Cryptococcus neoformans and cutaneous cryptococcosis. Semin Dermatol 1985; 4:252–9.
80. Perfect JR, Seaworth BA. Penile cryptococcosis with review of mycotic infections of penis. Urology 1985; 25:528–31.
81. Murakawa GJ, Kerschmann R, Berger T. Cutaneous Cryptococcus infection and AIDS: report of 12 cases and review of the literature. Arch Dermatol 1996; 132:545–8.
82. Pema K, Diaz J, Guerra LG, Nahban D, Verghese A. Disseminated cryptococcosis: comparison of clinical manifestations in the pre-AIDS and AIDS era. Arch Intern Med 1994; 154:1032–4.
83. Cockrell CJ. Human immunodefiency virus infection and the skin: a crucial interface. Arch Intern Med 1991; 151:1295–303.
84. Anderson DJ, Schmidt C, Goodman J, Pomeroy C. Cryptococcal disease presenting as cellulitis. Clin Infect Dis 1992; 14:666–72.
85. Massa MC, Doyle JA. Cutaneous cryptococcosis simulating pyoderma gangrenosum. J Am Acad Dermatol 1981; 5:32–6.
86. Crounse RG, Lerner AB. Cryptococcosis. AMA Arch Dermatol 1958; 77:210–3.
87. Rook A, Woods B. Cutaneous cryptococcosis. Br J Dermatol 1962; 74:43–9.
88. Wolfson JS, Sober AI, Rubin RH. Dermatologic manifestations of infections in immunocompromised patients. Medicine (Baltimore) 1985; 64:115–33.
89. Chu AC, Hay RJ, McDonald DM. Cutaneous cryptococcosis. Br J Dermatol 1980; 103:95–100.
90. Sarosi GA, Silberfarb PM, Tosh FE. Cutaneous cryptococcosis: a sentinel of disseminated disease. Arch Dermatol 1971; 104:1–3.
91. Feldmesser M, Harris C, Reichberg S, Khan S, Casadevall A. Serum cryptococcal antigen in patients with AIDS. Clin Infect Dis 1996; 23:827–30.
92. Manfredi M, Maroni A, Marzoni A, et al. Isolated detection of cryptococcal polysaccharide antigen in cerebrospinal fluid samples from patients with AIDS. Clin Infect Dis 1996; 23:849–50.
93. Temstet A, Roux P, Poirot JL, Ronin O, Dromer F. Evaluation of a monoclonal antibody-based latex agglutination test for diagnosis of cryptococcosis: comparison with two tests using polyclonal antibodies. J Clin Microbiol 1992; 30:2544–50.
94. Diamond RD, Bennett JE. Disseminated cryptococcosis in man: decreased lymphocyte transformation in response to Cryptococcus neoformans. J Infect Dis 1973; 127:694–7.
95. Vecchiarelli A. Immunoregulation by capsular components of Cryptococcus neoformans. Med Mycol 2000; 38:407–17.
96. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the managemnet of cryptococcal disease. Clin Infect Dis 2000; 30:710–8.
97. Lee SC, Dickson DW, Casadevall A. Pathology of cryptococcal meningitis: analysis of 27 patients with pathogenetic implications. Hum Pathol 1996; 27:839–47.
98. Lortholary O, Improvisi L, Rayhane N, et al. Cytokine profiles of AIDS patients are similar to those of mice with disseminated Cryptococcus neoformans infection. Infect Immun 1999; 67:6314–20.
99. Chretien F, Lortholary O, Kansau I, Neuvile S, Gray F, Dromer F. Pathogenesis of cerebral Cryptococcus neoformans infection after fungemia. J Infect Dis 2002; 186:522–30.
100. Lortholary O, Dromer F, Launay O, et al. Cytokine profiles in bronchoalveolar lavage fluid and blood in HIV-infected patients with Cryptococcus neoformans pneumonia [abstract 128]. In: Program and abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago). Washington, DC: American Society for Microbiology, 2001.
101. Hironaga M, Ikeda R, Fukazawa Y, Watanabe S. Mating types and serotypes of Cryptococcus neoformans isolated in Japan. Sabouraudia 1983; 21:73–8.
102. Rozenbaum R, Goncalves AJR, Wanke B, et al. Cryptococcus neoformans varieties as agents of cryptococcosis in Brazil. Mycopathologia 1992; 119:133–6.
103. Tortorano AM, Viviani MA, Rigoni AL, Cogliati M, Roverselli A, Pagano A. Prevalence of serotype D in Cryptococcus neoformans isolates from HIV positive and HIV negative patients in Italy. Mycoses 1997; 40:297–302.
104. Martinez LR, Garcia-Rivera J, Casadevall A. Cryptococcus neoformans var. neoformans (serotype D) strains are more susceptible to heat than C. neoformans var. grubii (serotype A) strains. J Clin Microbiol 2001; 39:3365–7.