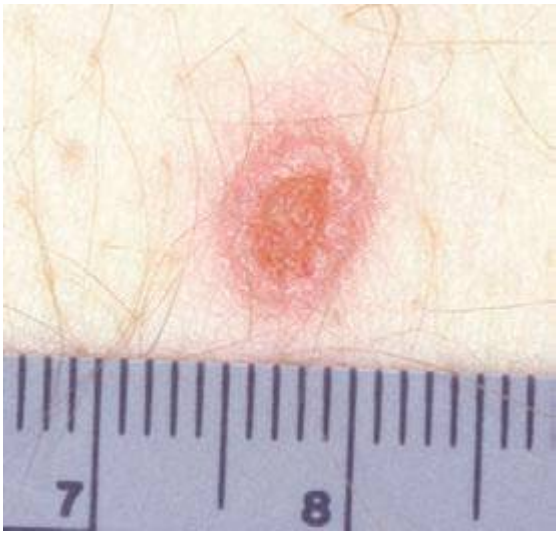

FIGURE 239-2 Disseminated fungal infection. A liver transplant recipient developed six cutaneous lesions similar to the one shown. Biopsy and serum antigen testing demonstrated *Cryptococcus*. Important features of the lesion include a benign-appearing fleshy papule with central umbilication resembling molluscum contagiosum. *(Photo courtesy of Dr. Lindsey Baden; with permission.)*

In areas of Africa where there is a high prevalence of HIV infection, routine screening of blood for CRAg in HIV-infected patients with low CD4+ T lymphocyte counts may identify individuals at high risk of cryptococcal disease who are candidates for antifungal therapy. Similarly, CRAg screening has shown that a significant proportion of HIV-infected patients hospitalized with pneumonia in Thailand harbor cryptococcal infection. Inexpensive point-of-care CRAg tests that are under development could be of great diagnostic benefit in resource-limited regions.

TREATMENT CRYPTOCOCCOSIS

Both the site of infection and the immune status of the host must be considered in the selection of therapy for cryptococcosis. The disease has two general patterns of manifestation: (1) pulmonary cryptococcosis, with no evidence of extrapulmonary dissemination; and (2) extrapulmonary (systemic) cryptococcosis, with or without meningoencephalitis. Pulmonary cryptococcosis in an immunocompetent host sometimes resolves without therapy. However, given the propensity of *Cryptococcus* species to disseminate from the lung, the inability to gauge the host's immune status precisely, and the availability of low-toxicity therapy in the form of fluconazole, the current recommendation is for pulmonary cryptococcosis in an immunocompetent individual to be treated with fluconazole (200–400 mg/d for 3–6 months). Extrapulmonary cryptococcosis without CNS involvement in an immunocompetent host can be treated with the same regimen, although amphotericin B (AmB; 0.5–1 mg/kg daily for 4–6 weeks) may be required for more severe cases. In general, extrapulmonary cryptococcosis without CNS involvement requires less intensive therapy, with the caveat that morbidity and death in cryptococcosis are associated with meningeal involvement. Thus the decision to categorize cryptococcosis as "extrapulmonary without CNS involvement" should be made only after careful evaluation of the CSF reveals no evidence of cryptococcal infection. For CNS involvement in a host without AIDS or obvious immune impairment, most authorities recommend initial therapy with AmB (0.5–1 mg/kg daily) during an induction phase, which is followed by prolonged therapy with fluconazole (400 mg/d) during a consolidation phase. For cryptococcal meningoencephalitis without a concomitant immunosuppressive condition, the recommended regimen is AmB (0.5–1 mg/kg) plus flucytosine (100 mg/kg) daily for 6–10 weeks. Alternatively, patients can be treated with AmB (0.5–1 mg/kg) plus flucytosine (100 mg/kg) daily for 2 weeks and then with fluconazole (400 mg/d) for at least 10 weeks. Patients with immunosuppression are treated with the same initial regimens except that consolidation therapy with fluconazole is given for a prolonged period to prevent relapse.

Cryptococcosis in patients with HIV infection always requires aggressive therapy and is considered incurable unless immune function improves. Consequently, therapy for cryptococcosis in the setting of AIDS has two phases: induction therapy (intended to reduce the fungal burden and alleviate symptoms) and lifelong maintenance therapy (to prevent a symptomatic clinical relapse). Pulmonary and extrapulmonary cryptococcosis without evidence of CNS involvement can be treated with fluconazole (200–400 mg/d). In patients who have more extensive disease, flucytosine (100 mg/kg per day) may be added to the fluconazole regimen for 10 weeks, with lifelong fluconazole maintenance therapy thereafter. For HIV-infected patients with evidence of CNS involvement, most authorities recommend induction therapy with AmB. An acceptable regimen is AmB (0.7–1 mg/kg) plus flucytosine (100 mg/kg) daily for 2 weeks followed by fluconazole (400 mg/d) for at least 10 weeks and then by lifelong maintenance therapy with fluconazole (200 mg/d). Fluconazole (400–800 mg/d) plus flucytosine (100 mg/kg per day) for 6–10 weeks followed by fluconazole (200 mg/d) as maintenance therapy is an alternative. Newer triazoles like voriconazole and posaconazole are highly active against cryptococcal strains and appear effective clinically, but clinical experience with these agents in the treatment of cryptococcosis is limited. Lipid formulations of AmB can be substituted for AmB deoxycholate in patients with renal impairment. Neither caspofungin nor micafungin is effective against *Cryptococcus* species; consequently, neither drug has a role in the treatment of cryptococcosis. Cryptococcal meningoencephalitis is often associated with increased intracranial pressure, which is believed to be responsible for damage to the brain and cranial nerves. Appropriate management of CNS cryptococcosis requires careful attention to the management of intracranial pressure, including the reduction of pressure by repeated therapeutic lumbar puncture and the placement of shunts. Recent studies suggest that the addition of a short course of interferon γ to antifungal therapy in patients with HIV infection increases clearance of cryptococci from the CSF.

In HIV-infected patients with previously treated cryptococcosis who are receiving fluconazole maintenance therapy, it may be possible to discontinue antifungal drug treatment if antiretroviral therapy results in immunologic improvement. However, certain recipients of maintenance therapy who have a history of successfully treated cryptococcosis can develop a troublesome immune reconstitution syndrome when antiretroviral therapy produces a rebound in immunologic function.

PROGNOSIS AND COMPLICATIONS

Even with antifungal therapy, cryptococcosis is associated with high rates of morbidity and death. For the majority of patients with cryptococcosis, the most important prognostic factors are the extent and the duration of the underlying immunologic deficits that predisposed them to develop the disease. Therefore, cryptococcosis is often curable with antifungal therapy in individuals with no apparent immunologic dysfunction, but, in patients with severe immunosuppression (e.g., those with AIDS), the best that can be hoped for is that antifungal therapy will induce remission, which can then be maintained with lifelong suppressive therapy. Before the advent of antiretroviral therapy, the median overall survival period for AIDS patients with cryptococcosis was <1 year. Cryptococcosis in patients with underlying neoplastic disease has a particularly poor prognosis. For CNS cryptococcosis, poor prognostic markers are a CSF assay positive for yeast cells on initial India ink examination (evidence of a heavy fungal burden), high CSF pressure, low CSF glucose levels, low CSF pleocytosis (<2/μL), recovery of yeast cells from extraneural sites, absence of antibody to capsular