Cryptococcosis

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Overview

- Infection with encapsulated yeast *Cryptococcus neoformans* or *gattii*
  - *C. neoformans* is found in bird and bat droppings and contaminated soil/dust; *C. gattii* colonizes trees/wood debris
- Infection typically occurs following inhalation leading to variable pulmonary manifestations (ranging from asymptomatic mild pneumonitis to acute respiratory distress syndrome (ARDS))
  - The majority of cases will remain contained within the lungs
  - Reactivation can occur when immunosuppression prevents continued proper containment of a latent infection
- Cutaneous lesions almost always result from embolic hematogenous spread in disseminated disease
  - Approximately 10% of cryptococcal infections will become disseminated, typically occurring in immunocompromised patients (HIV/AIDS, chemotherapy, organ transplant, chronic steroid use); dissemination rates may reach up to 50% in AIDS patients, often occurring when CD4 counts are below 50–100/μL
  - In patients with disseminated disease, hematogenous spread leads to CNS (70–90%) and skin (10–15%) involvement most commonly
- Primary cutaneous cryptococcosis is very rare following direct innoculation; skin involvement should lead one to suspect and evaluate for systemic disease in all cases

Clinical Presentation

- Severe mengingo-encephalitis in immunocompromised patients is the most common clinical presentation of disseminated disease; most mycotic meningitis cases are secondary to cryptococcosis
  - Patients commonly experience fever, headache, and meningeal signs
  - Fatal if untreated; so a high index of suspicion is necessary
- Symptomatology is based on the distribution of disseminated disease and can include lymph nodes, skin, eye, kidney, bones, etc.

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- In disseminated disease cutaneous lesions are most commonly found on the head and neck and may present as umbilicated or crateriform nodules, indurated or soft plaques, ulcers, blisters, tumor-like masses, or draining sinuses
  - Molluscum-like papules with central umbilication, acneiform pustules, and Kaposi sarcoma-like lesions can be seen in AIDS patients.
- Cyrptococcal cellulitis is seen in severely immunocompromised hosts and has an abrupt onset of red-brown erythema with rapid progression
- In primary cryptococcosis lesions may be ulcers, nodules, abscesses, or plaques favoring exposed areas at the site of prior skin trauma with local adenopathy (Fig. 43.1)

Histopathology

- Pseudoepitheliomatous hyperplasia, acanthosis, or ulceration with gelatinous and/or granulomatous tissue reactions are typical (Fig. 43.2)
  - Gelatinous reactions are associated with an impaired immune response and consist of a high concentration of organisms free in the tissue with minimal associated inflammation/tissue reaction
  - Granulomatous reactions consist of fewer organisms which are mostly located within multinucleated giant cells with a surrounding dense dermal lymphohistiocytic infiltrate
- Organisms are round to ovoid yeasts (5–15 μm) with a thick-walled spherule with a polysaccharide capsule
- The capsule can be highlighted with mucicarmine (red), methylene blue (purple), alcian blue (purple), or Fontana-Masson/Melanin (dark brown to black) staining

Differential Diagnosis

- Molluscum contagiosum: can resemble the umbilicated papular type of crypto; bedside diagnostic testing can show characteristic Hendersson Patterson bodies of the pox-virus, and pathology can distinguish the two
- Acne: most patients with acne will have some comedonal lesions
- Histoplasmosis: varied morphologies and hard to distinguish clinically, biopsy is diagnostic
- Coccidioidomycosis: travel history and biopsy can be helpful
- Herpes simplex virus: clustered vesicles and uniform punched out erosions should prompt evaluation for HSV
- Cellulitis: bacterial cellulitis may be more rapidly developing than cryptococcal cellulitis, and should improve on antibiotics; persistent refractory cellulitis, or deeper indurated red-brown cellulitis may prompt evaluation for cryptococcal infection

Important Work-Up

- Thorough history should elicit potential exposures and immune status (e.g. HIV, chemotherapy use, transplant, etc); physical exam should assess for cutaneous lesions and other symptoms of systemic involvement
- In cases of disseminated disease without a known cause of immunosuppression an HIV test should be performed; in patients with known HIV/AIDS a current CD4 count should be obtained
- *If suspected pulmonary involvement*:
  - Chest X-ray or CT: infiltrates, nodules, pleural effusions
  - Sputum: culture often negative, may need bronchial lavage sent for cryptococcal antigen or open lung or bronchoscopic biopsy
- *If suspected CNS involvement*:
  - Head CT/MRI: perform prior to lumbar puncture; nodular lesions in basal ganglia, masses

  - Lumbar puncture: elevated intracranial pressure, normal cell count or mild pleocytosis (less than 20 cells/μL with 100% lymphocytes); cryptococcal antigen (CrAg) test on CSF—either latex agglutination (LA), ELISA, or lateral flow assay (LFA) tests
  - If no access to CrAg testing: India ink smear of CSF, and fungal culture of CSF
- *Evaluate for other systemic involvement, as appropriate*:
  - Serum, urine, pleural fluid, sputum: culture and/or CrAg
  - Tissue samples: skin, lung, lymph node, bone marrow
  - Other tests include ESR, CBC, BMP, LFTs, urinalysis

Treatment

- Consult infectious disease specialist
- Please refer to full protocol recommendations from the Infectious Diseases Society of America and WHO, as dosing and duration of treatment depend on burden of disease, sites of infection, and immune status of patient
- CNS Involvement:
  - Induction therapy: Amphotericin B + flucytosine for at least 2 weeks
  - Consolidation therapy: fluconazole for minimum 8 weeks
  - Maintenance therapy: fluconazole for at least 6–12 months; in HIV at least 12 months and with undetectable viral load and CD4 > 100 cells/μL (on two separate tests 6 months apart)
- No CNS Involvement:
  - If cryptococcemia or severe pulmonary disease: Same as CNS disease
  - Moderate pulmonary disease or single site infection in non-immunosuppressed patient: fluconazole for 6–12 months
- Antiretroviral Therapy (ART) in HIV-positive patients
  - Current recommendations from the WHO recommend deferring ART initiation in patients with cryptococcal meningitis due to the high risk of IRIS until there is evidence of sustained clinical response to anti-fungal therapy following 2–4 weeks of induction and consolidation treatment

Suggested Readings

1. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptoccal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(3):291–322.
2. Negroni R. Cryptococcosis. Clin Dermatol. 2012;30(6):599–609.
3. WHO HIV/AIDS Programme Rapid Advice. Diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents, and children. Geneva: WHO; 2011.

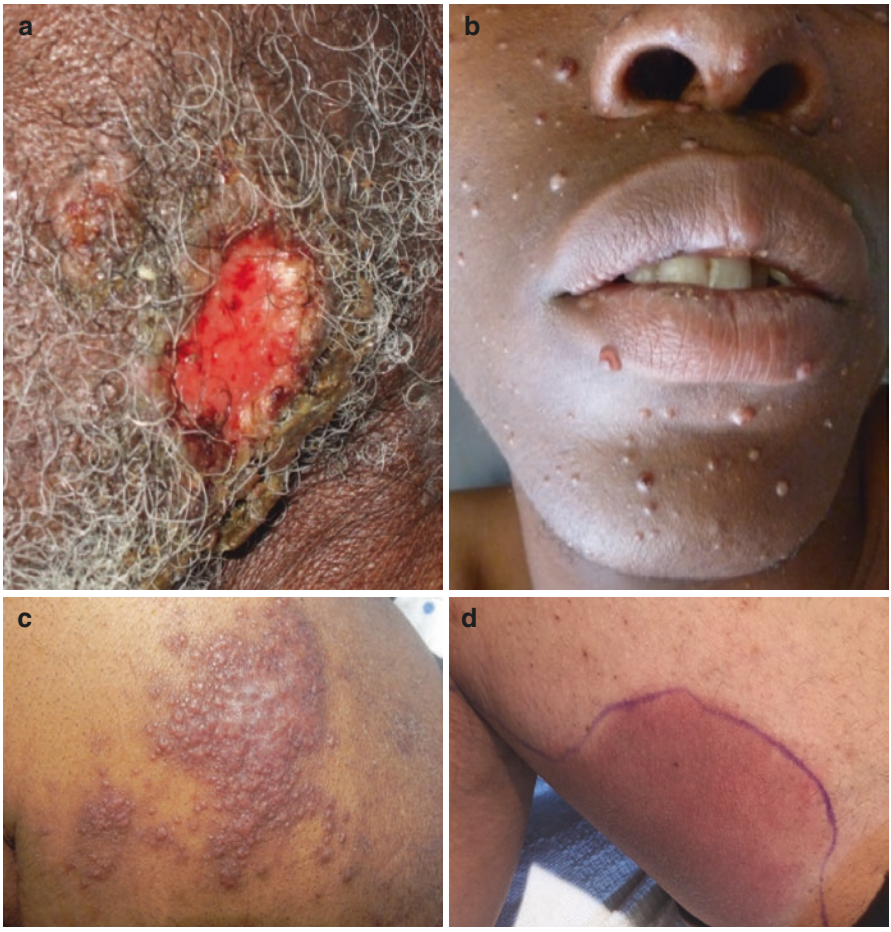

Fig. 43.1 Cryptococcal skin infection: (**a**) Ulcerated plaque of *Cryptococcus* with verrucous border in a patient with newly diagnosed HIV/AIDS. (**b**) Umbilicated papules on the face. (**c**) Cobblestoned plaque on the shoulder of a patient with disseminated Cryptococcus. (**d**) Cryptococcus is a rare cause of atypical recalcitrant cellulitis. This tends to be a deeper red-brown with indurated skin, as shown here in a heart transplant recipient who developed cryptococcal cellulitis with disseminated infection.

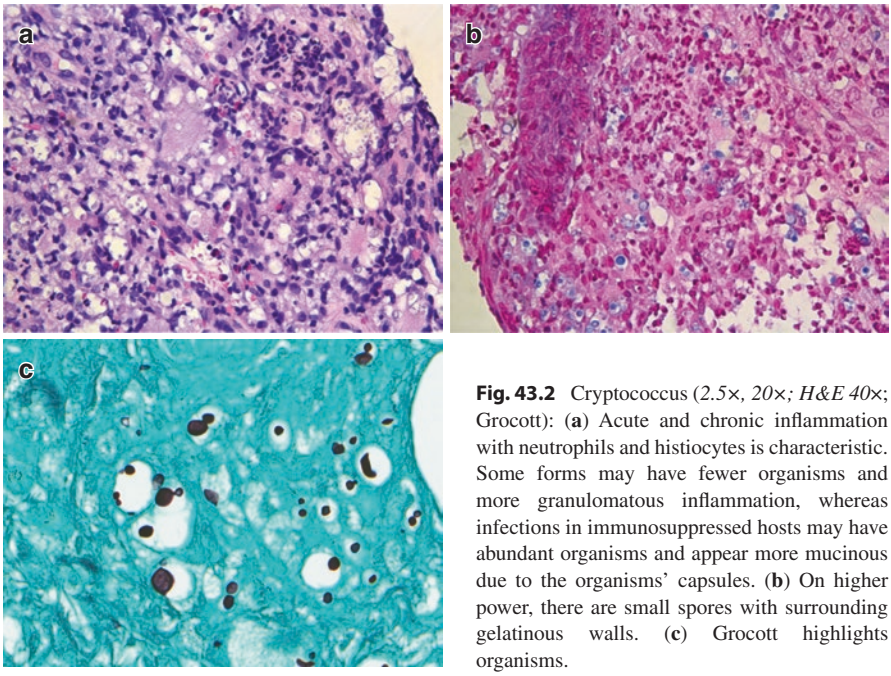

Fig. 43.2 Cryptococcus (*2.5×, 20×; H&E 40×*; Grocott): (**a**) Acute and chronic inflammation with neutrophils and histiocytes is characteristic. Some forms may have fewer organisms and more granulomatous inflammation, whereas infections in immunosuppressed hosts may have abundant organisms and appear more mucinous due to the organisms' capsules. (**b**) On higher power, there are small spores with surrounding gelatinous walls. (**c**) Grocott highlights organisms.