# Histoplasmosis

# 40

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## Overview

- Granulomatous infection caused by the dimorphic fungus, *Histoplasma capsulatum* var. *capsulatum*
- Worldwide distribution with prevalence in the Mississippi and Ohio River Valleys in the United States
- Found in soil and vegetal detritus contaminated by bird and bat droppings with acquisition via aerosol inhalation or less commonly via direct innoculation
- Risk factors include immunocompromised host and occupations with exposure to high risk environments
- Immunocompromised individuals are more likely to develop disseminated disease to various extrapulmonary locations (e.g. liver, spleen, lymph nodes, bone marrow, skin, CNS, adrenal glands)
  - Fever, malaise, loss of appetite and fatigue are common nonspecific presenting symptoms
  - Cutaneous involvement is uncommon (~5% of cases, may be higher in severely immunosuppressed hosts) but is a helpful diagnostic clue when present

## Clinical Presentation

- In the majority of cases the infection is asymptomatic or mild with a self-limited course
- Characterized by three different forms—namely pulmonary, primary cutaneous, and disseminated disease, the latter of which is severe
- Primary cutaneous histoplasmosis due to direct inoculation is uncommon and presents as an isolated ulcer with regional lymphadenopathy that self-resolves
- Secondary cutaneous histoplasmosis seen in disseminated disease is due to hematogenous spread and is characterized by diverse skin morphology including papules, plaques, nodules, umbilicated papules, acneiform, abscess, cellulitis, pyoderma gangrenosum-like lesions or painful mucocutaneous ulcers (Fig. 40.1)
  - Areas of involvement include the face, extremities, trunk, and mucosa (especially oral)

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- Depending on organ involvement in disseminated disease symptomatology will vary but may include: petechiae, easy bruising, fatigue, weakness (thrombocytopenia and anemia from bone marrow involvement), hepatomegaly, splenomegaly, lymphadenopathy, altered mental status, photophobia, headache (CNS involvement)

## Histopathology

- A varying degree of inflammation is seen characterized by a granulomatous, lymphocytic and/or a mononuclear infiltrate (Fig. 40.2)
- Yeast forms are 2–4 microns in size, often elongated, may demonstrate narrow budding, can have a peripheral rim of clearing
- Organisms are often parasitized by macrophages
- Yeast forms are highlighted by periodic acid-Schiff (PAS), Gomori-Grocott, or silver methenamine (GMS) stains

## Differential Diagnosis

In all cases, travel history and exposure history is essential in narrowing the diagnosis; pathologic findings are often diagnostic and biopsy should be considered if any of these entities are suspected.

- Blastomycosis: may see larger lesions with a raised, crusted border with or without ulceration
- Coccidioidomycosis: there may be clinical overlap, but pathology is different and diagnostic
- Cryptococcosis: may have varied clinical presentations and can overlap with histoplasmosis skin findings; biopsy, culture, and serologic testing are helpful
- Paracoccidioidomycosis: lesions may be larger crusted nodules, but biopsy is diagnostic
- Leishmaniasis: bite-site crusted ulcers, which may be grouped, and frequently involve the ear can be helpful; be cautious with pathology as both leish and histo can look similar
- Tuberculosis: can be varied depending on if primary cutaneous involvement or a tuberculid response; pathologic findings are diagnostic

## Work-Up

- A thorough history and physical exam should be obtained including evaluation of mucosal sites (oral and perianal)
- Histopathologic evaluation of a punch biopsy from a representative skin lesion should be performed
- Culture is considered the gold standard with an incubation time of 3–6 weeks
- Antigen testing of urine, serum, bronchial lavage or CSF is sensitive for acute disseminated and pulmonary histoplamsosis, but there is cross-reactivity with Paracoccidioides and Blastomyces
- Hypercalcemia has been described, which may be nonspecific (present in many granulomatous diseases)
- Evaluation for disseminated disease should be targeted based on potential organs of involvement
  - CBC: leukopenia, thrombocytopenia, anemia (bone marrow/spleen involvement)
  - Peripheral blood smear review to visualize the organism (Wright's stain)
  - CMP: abnormal AST, ALT, bilirubin
  - Chest x-ray: typically will show diffuse interstitial or reticulonodular pulmonary infiltrates
  - Abdominal CT (assess for enlarged liver, spleen, lymph node)
  - Brain CT/MRI, lumbar puncture (CNS involvement)
  - Endoscopy: Visualize GI lesions

## Treatment

- Treatment choice is based on disease severity and underlying comorbidities
- Amphotericin B is the agent of choice for induction therapy for severe disease
- Itraconazole is preferred for mild to moderate disease and is commonly used for maintenance therapy
- If conventional treatment fails additional options include voriconazole or posaconazole
- Patients with HIV/AIDS may require additional management and infectious disease experts should be consulted

## Suggested Readings

1. Chang P, Rodas C. Skin lesions in histoplasmosis. Clin Dermatol. 2012;30(6):592–8.
2. Fernandez-Flores A, Saeb-Lima M, Arenas-Guzman R. Morphological findings of deep cutaneous fungal infections. Am J Dermatopathol. 2014;36(7):531–53.
3. Gupta V, Singhal V, Singh MK, Xess I, Ramam M. Disseminated histoplasmosis with hypercalcemia. J Am Acad Dermatol. 2013;69(5):e250–1.

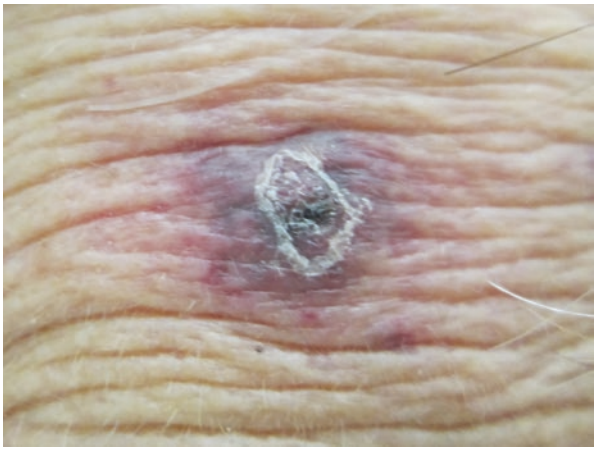

**Fig. 40.1** Cutaneous histoplasmosis: Necrotic verrucous violaceous plaque on the forehead.

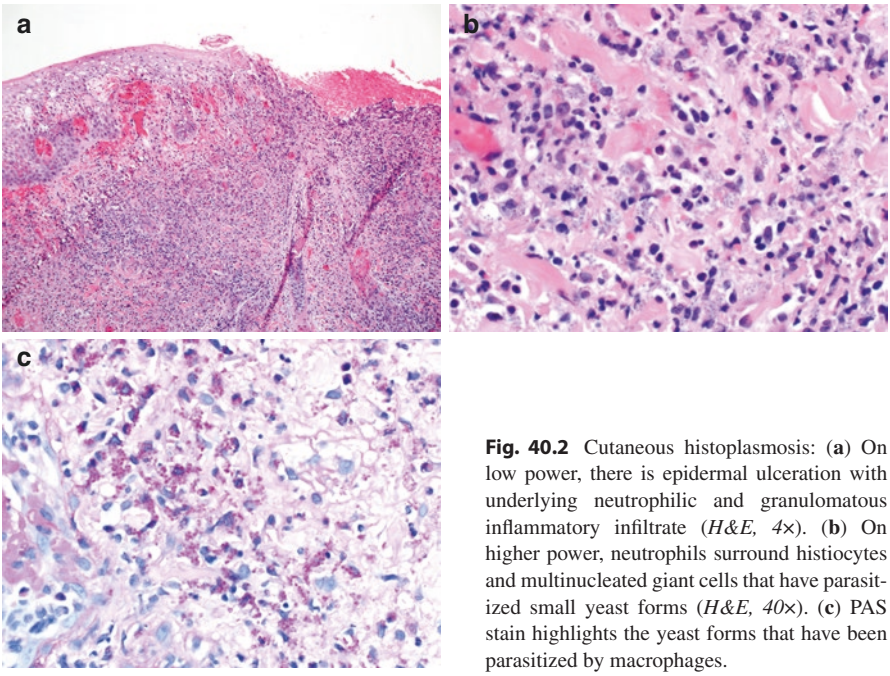


**Fig. 40.2** Cutaneous histoplasmosis: (**a**) On low power, there is epidermal ulceration with underlying neutrophilic and granulomatous inflammatory infiltrate (*H&E, 4*×). (**b**) On higher power, neutrophils surround histiocytes and multinucleated giant cells that have parasitized small yeast forms (*H&E, 40*×). (**c**) PAS stain highlights the yeast forms that have been parasitized by macrophages.