Endemic mycoses

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SA HIV Clinician's Society Conference
Gallagher Convention Centre • Midrand, Johannesburg
26 October 2018

Definition

- Heterogeneous group of fungi that occupy specific ecological niches
- Circumscribed geographic ranges
- Thermally dimorphic, existing as moulds in the environment and as yeasts (or spherules) within the human body
- Primary pathogens because they cause disease in healthy as well as immunocompromised hosts

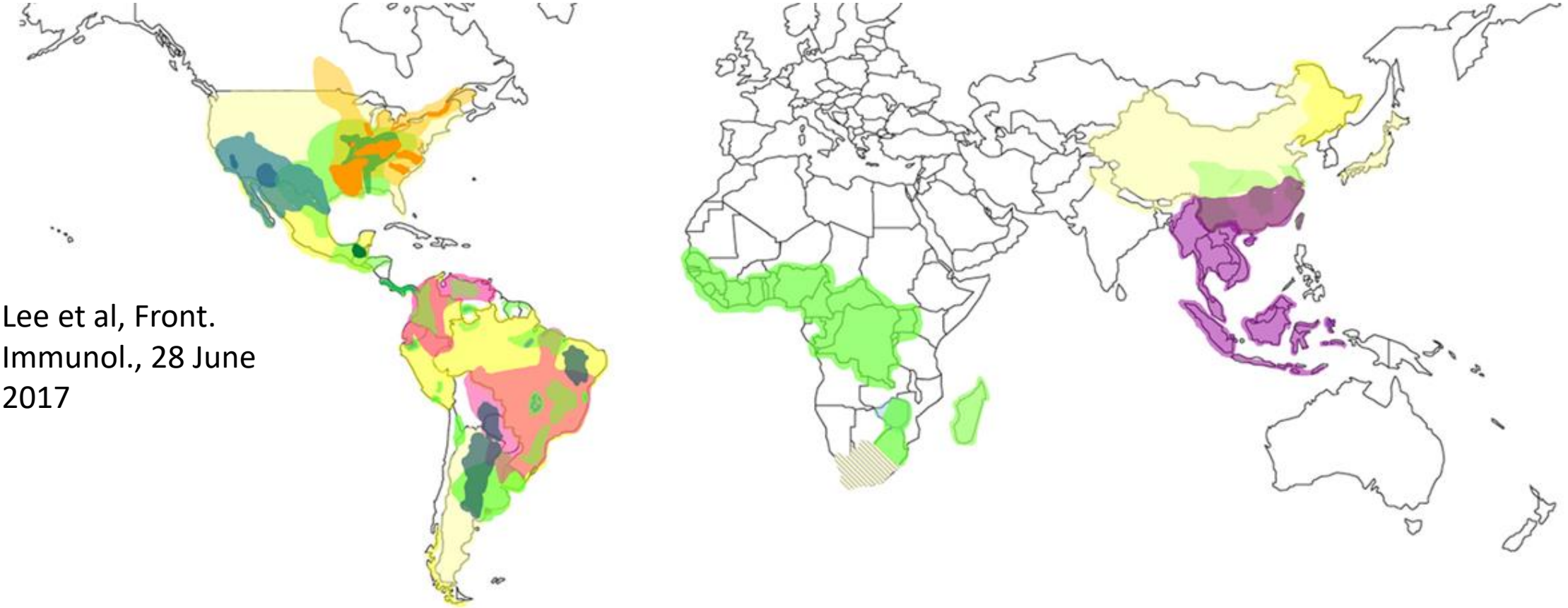
Malcolm and Chin-Hong, Curr Infect Dis Rep. 2013 December

Endemic mycoses

- Blastomycosis
- Coccidiodomycosis
- Paracoccidiodomycosis
- **Histoplasmosis**
- **Emmonsiosis**
- Sporotrichosis
- Penicilliosis

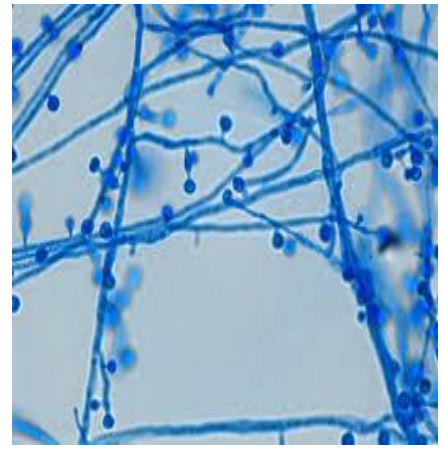
Geographical distribution of endemic mycoses

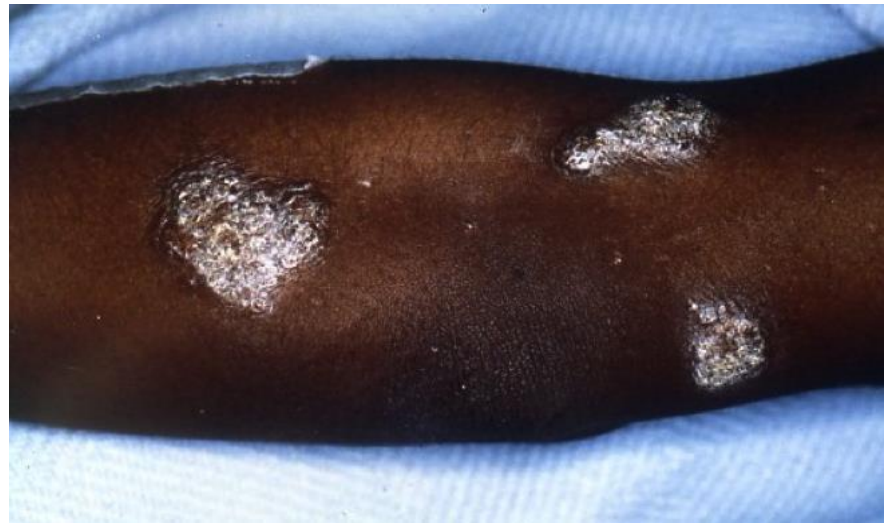
Lee et al, Front. Immunol., 28 June 2017



Blastomycoses

- Causative organism: *Blastomyces dermatitidis*
- Immunocompetent: subclinical disease
- Immunocompromised: relatively uncommon, severe pneumonia and/or extra-pulmonary dissemination frequently involving skin, bones, joints, genitourinary system and CNS
- Treatment: Amphotericin B and itraconazole

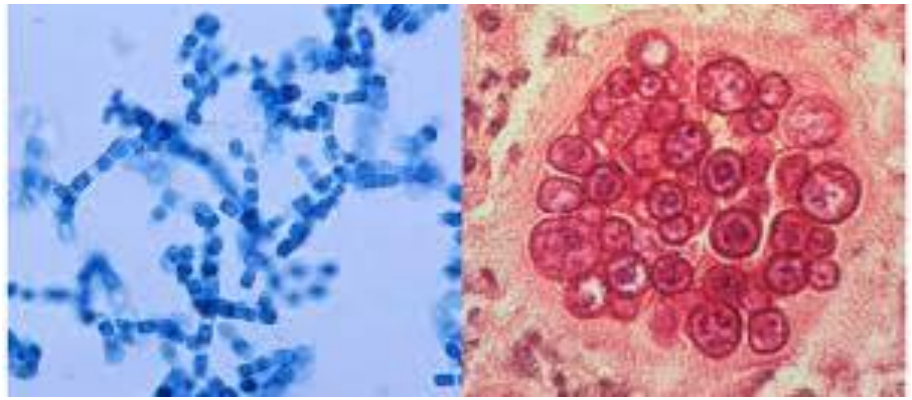


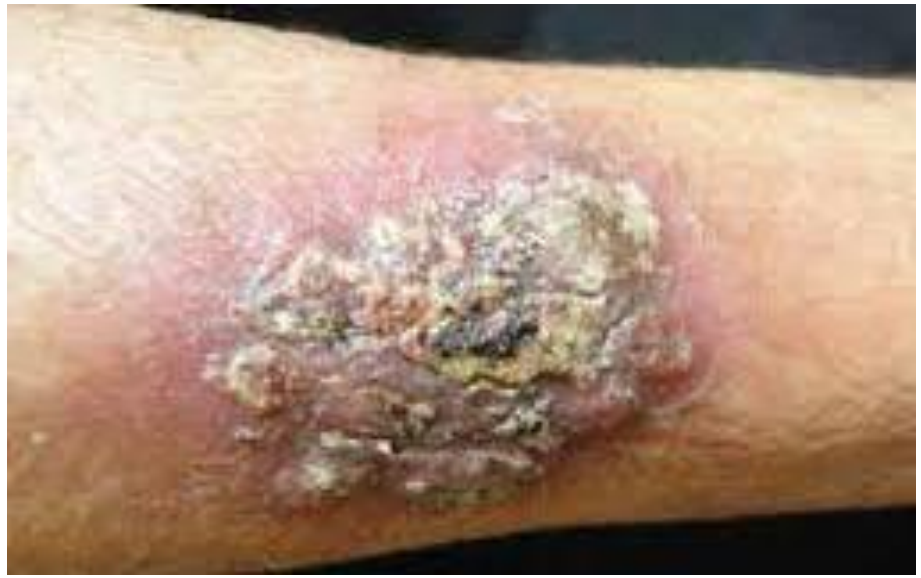


Malcolm and Chin-Hong, Curr Infect Dis Rep. 2013 December

Coccidioidomycosis (Valley fever)

- Causative organism: *Coccidioides immitis, coccidioides posadasii*
- Immunocompetent: subclinical or asymptomatic
- Immunocompromised: 30–50% with extrapulmonary dissemination, frequently involving skin, bones, and meninges
- Treatment: Fluconazole

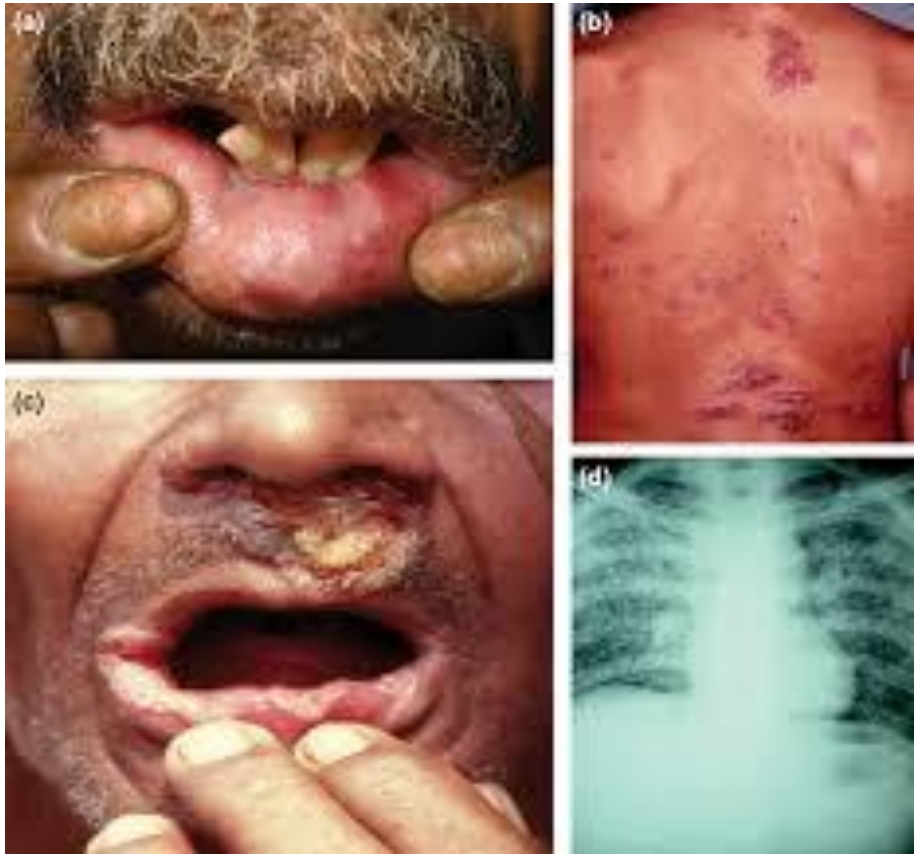




Malcolm and Chin-Hong, Curr Infect Dis Rep. 2013 December

Paracoccidiodomycoses

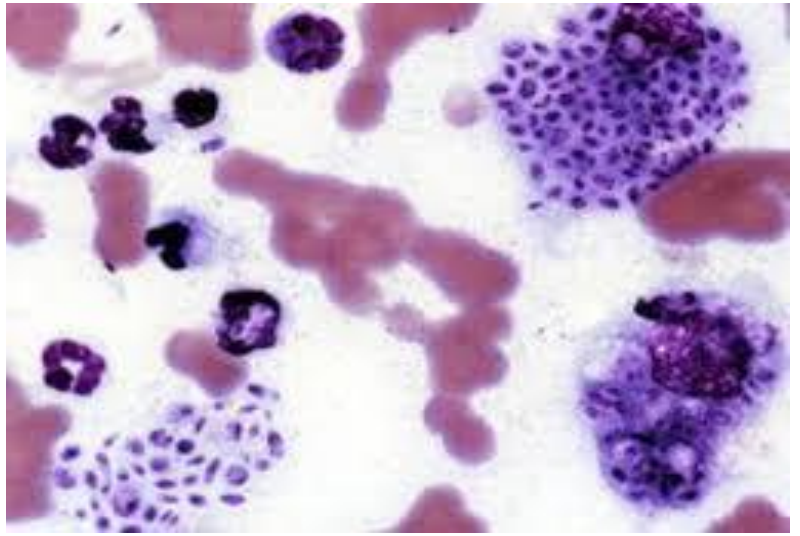
- Causative organism: *Paracoccidioides brasiliensis*
- Immunocompetent: subclinical, 90% may progress to chronic disease.
  Disseminated to mucosa, skin, adrenal glands and CNS common
- Immunocompromised: infrequent
- Treatment: Itraconazole, severe cases Amphotericin B

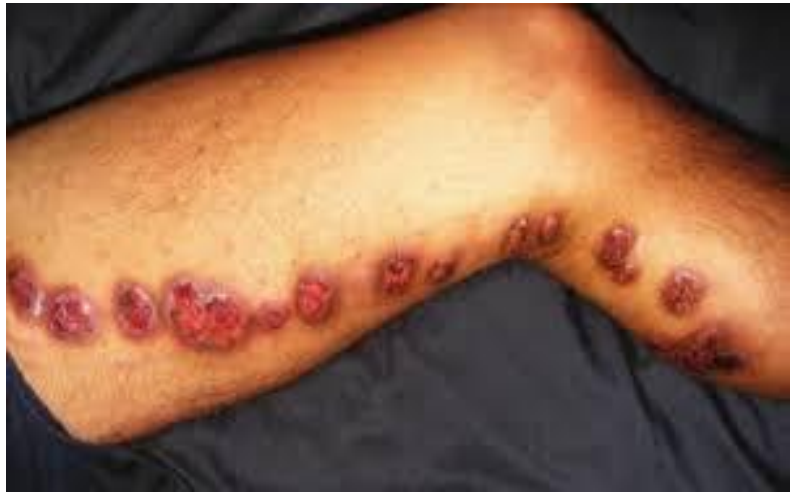


Malcolm and Chin-Hong, Curr Infect Dis Rep. 2013 December

Sporotrichosis (Rose gardener's disease)

- Causative organism: *Sporothrix schenkii* species complex
- Immunocompetent: Cutaneous nodules and ulcerations
- Immunocompromised: Osteoarticular, pulmonary, mucosal, disseminated, and systemic infections. Widespread cutaneous ulceration.
- Treatment: Itraconazole, severe disease Amphotericin B

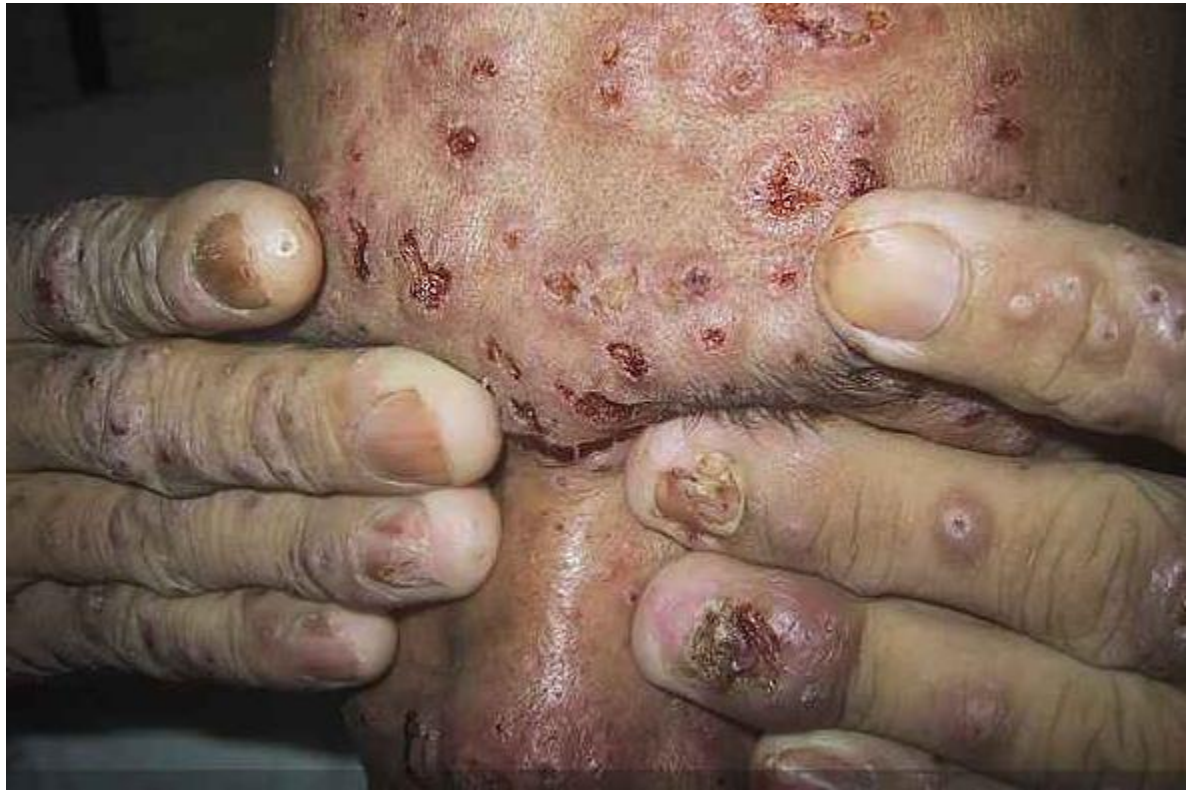




Malcolm and Chin-Hong, Curr Infect Dis Rep. 2013 December

Penicillinosis

- Causative organism: *Penicillium marneffe*
- Immunocompetent: Asymptomatic pulmonary infection
- Immunocompromised: Chronic disseminated disease with cutaneous lesions and lymphadenopathy
- Treatment: Amphotericin B with or without flucytosine and itraconazole



Malcolm and Chin-Hong, Curr Infect Dis Rep. 2013 December

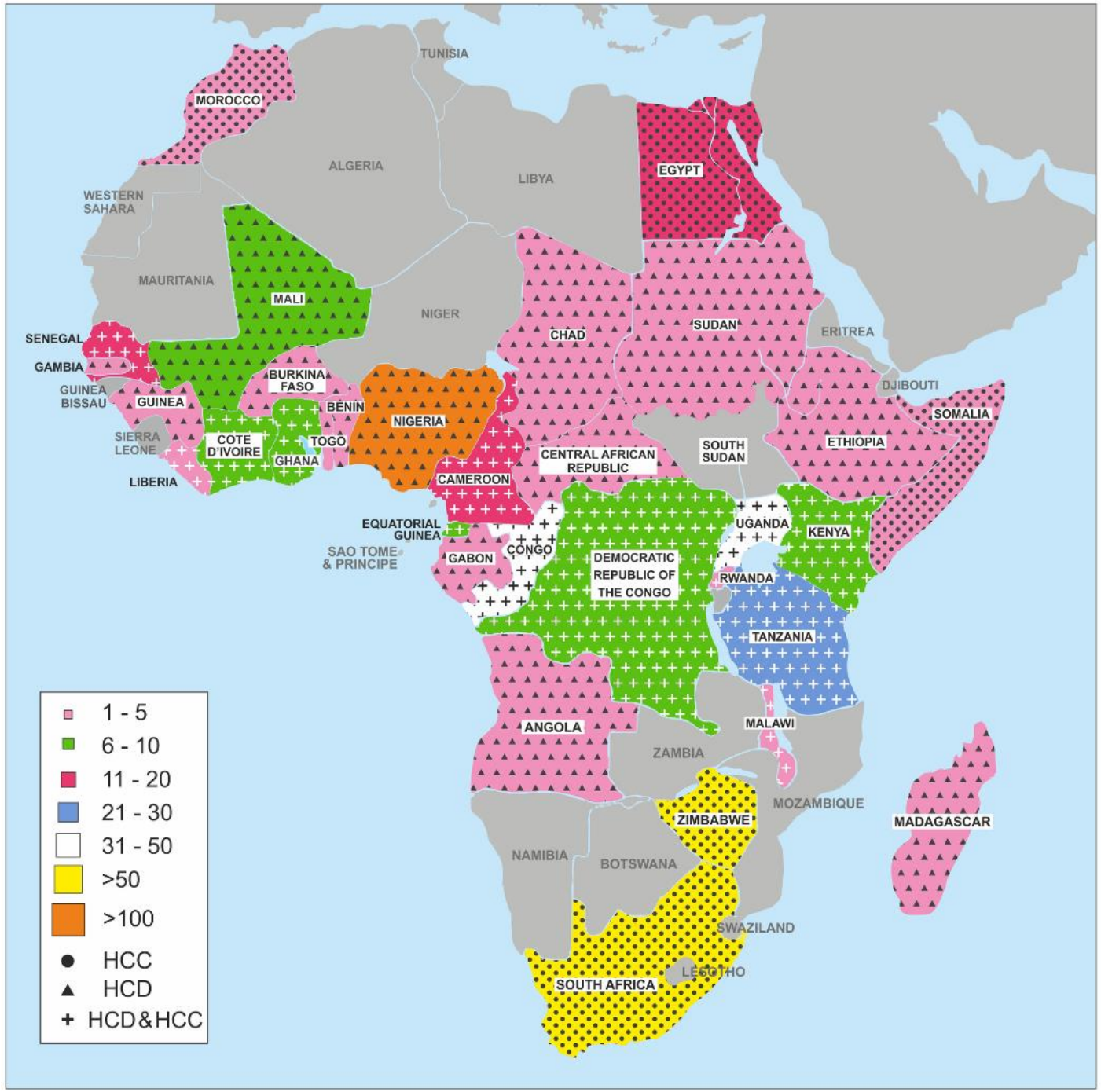
Histoplasmosis

- Causative organism: Histoplasma capsulatum var capsulatum (global), Histoplasmosis capsulatum var duboisii (Africa)
- Transmitted in droppings of birds and bats

Reported cases in Southern Africa (1952-2017)

Country	Total number of cases	*H. capsulatum* var. *dubosii*	*H. capsulatum* var. *capsulatum*	HIV positive	HIV negative
South Africa***	61	-	61	27	33
Namibia	-	-	-	-	-
Zimbabwe	57	1	56	56	-
Lesotho	-	-	-	-	-
Tanzania****	24	1	1	10	7
Botswana	-	-	-	-	-
Malawi	3	2	1	2	1
Madagascar	5	5	-	-	5
Zambia	-	-	-	-	-
Swaziland	-	-	-	-	-
Mozambique	-	-	-	-	-
Summary S/A	150	9	119	95	46

Oladele et al, PLoS Negl Trop Dis 12(1): e0006046.



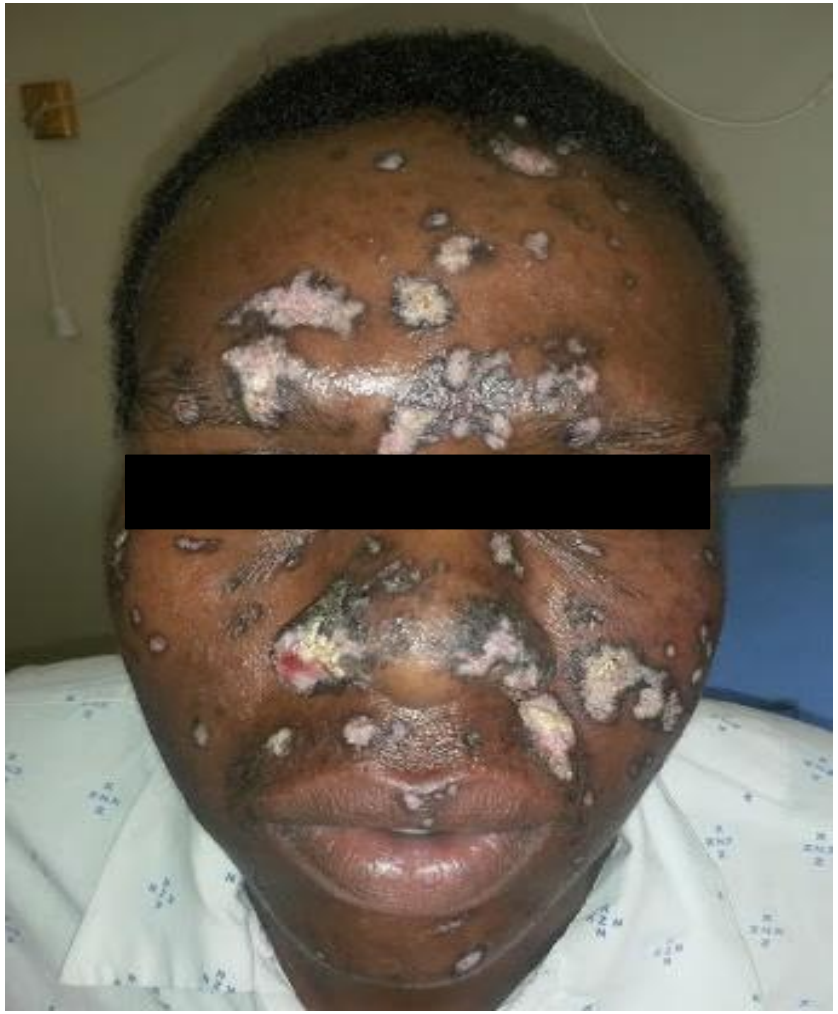
Oladele et al, PLoS Negl Trop Dis 12(1): e0006046.

Clinical presentation

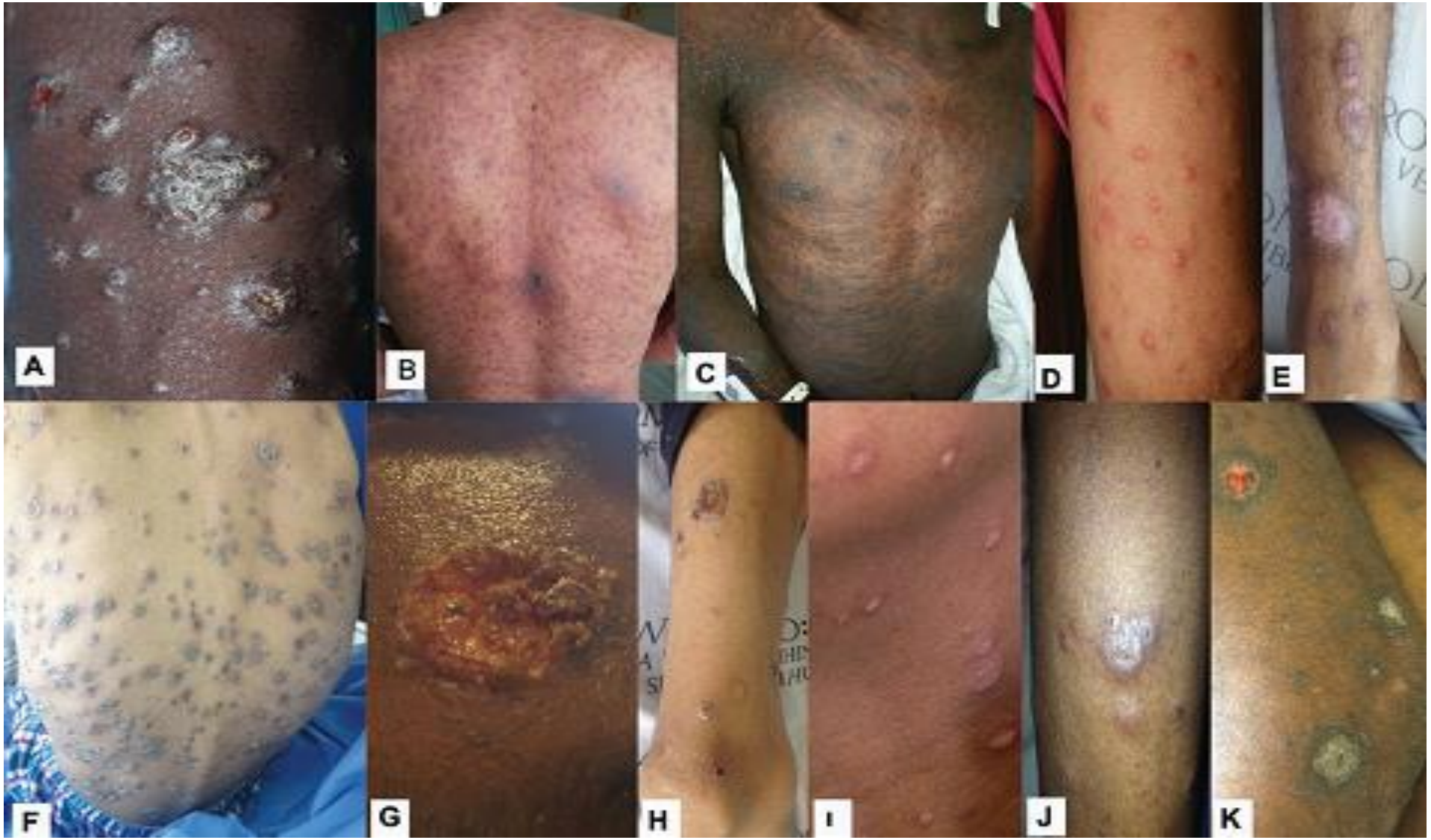
- Asymptomatic
- Localized: skin, lymphadenopathy, lungs
- Disseminated disease: Fever, constitutional symptoms, acute and subacute pulmonary histoplasmosis
- Chronic: chronic pulmonary histoplasmosis, lymph nodes, CNS, bone, joints, bone marrow, pericardium, ocular, adrenal, gastrointestinal
- Progressive disseminated: constitutional symptom, gastrointestinal, cardiac, CNS, mucosa

Oladele et al, PLoS Negl Trop Dis 12(1): e0006046.

Histoplasmosis of the skin

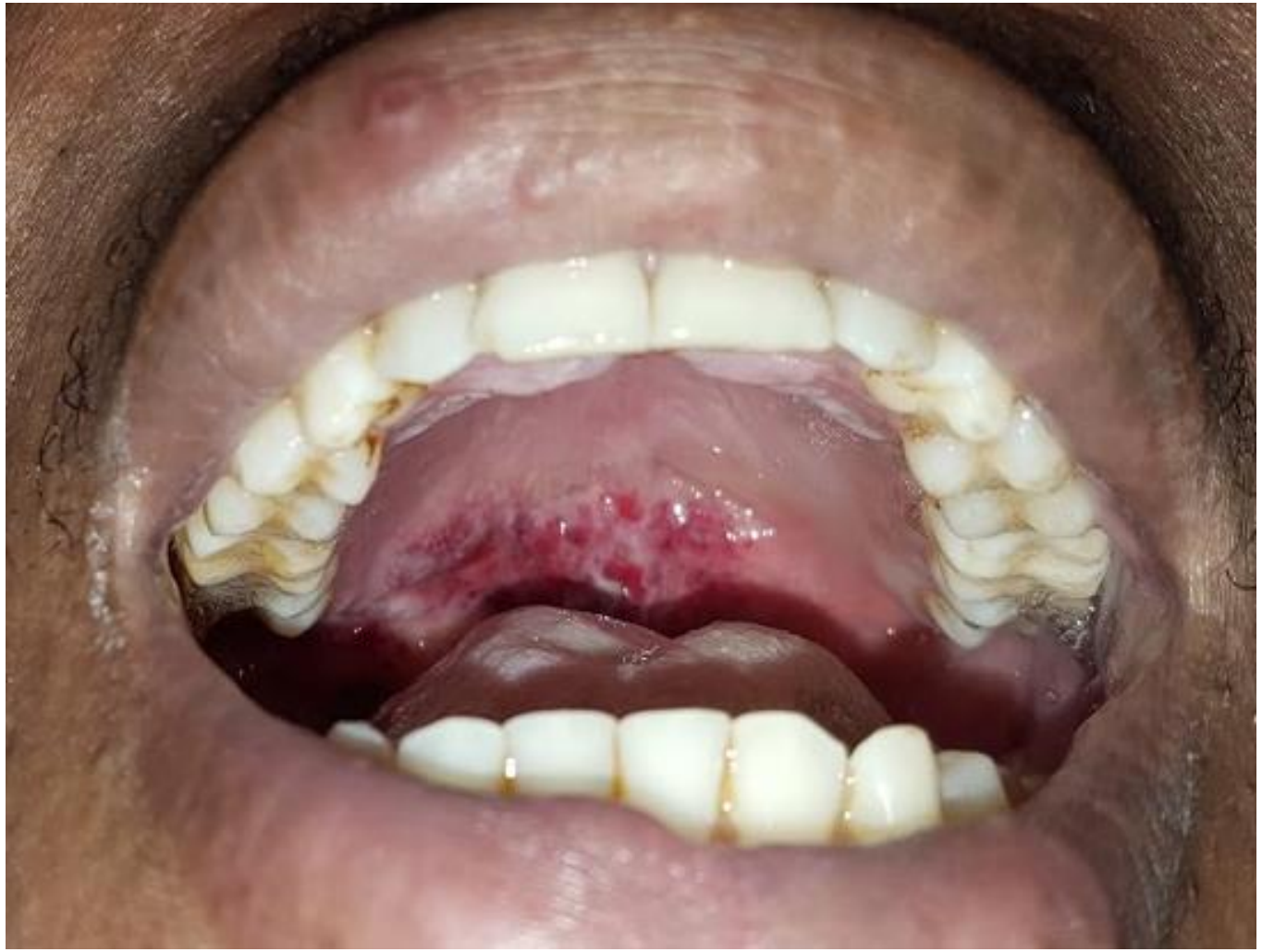


Histoplasmosis of the skin

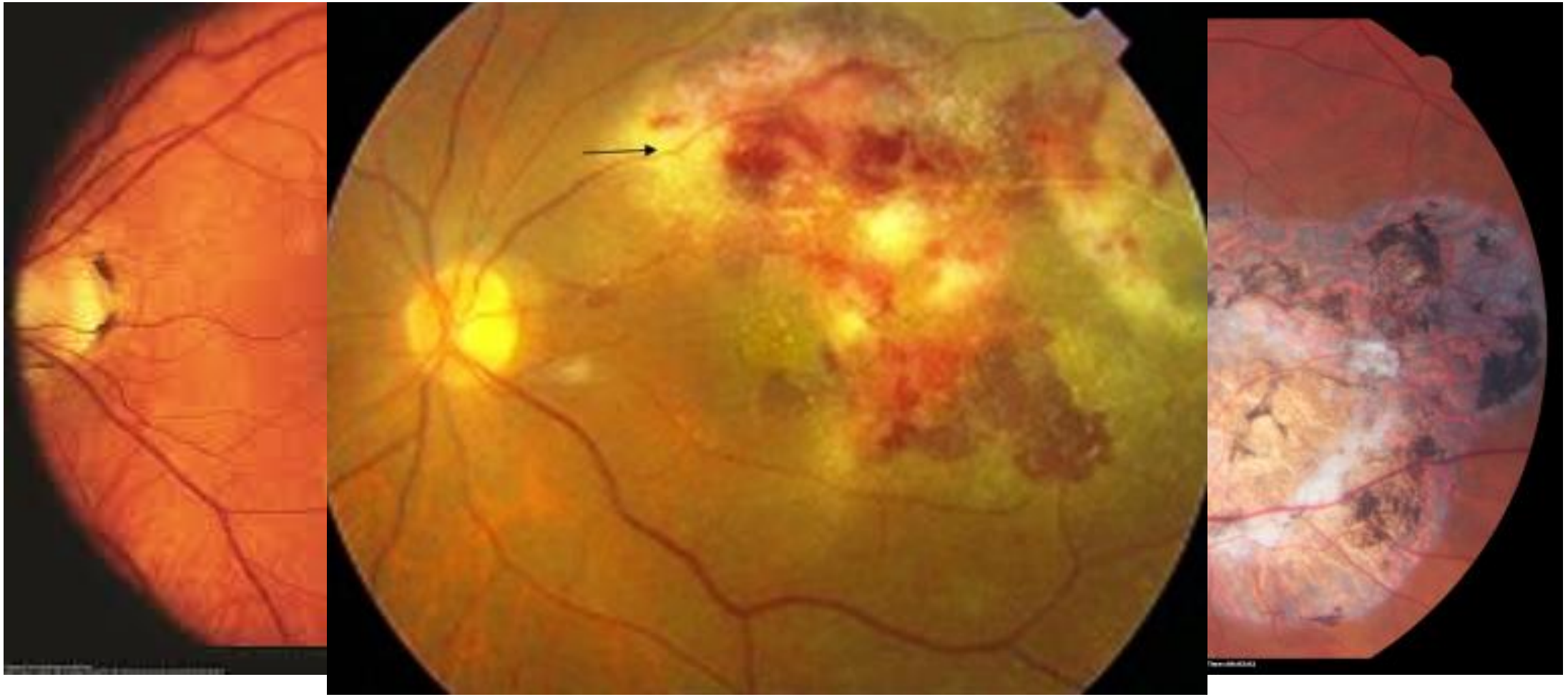


Schwartz et al, OFID, 2017

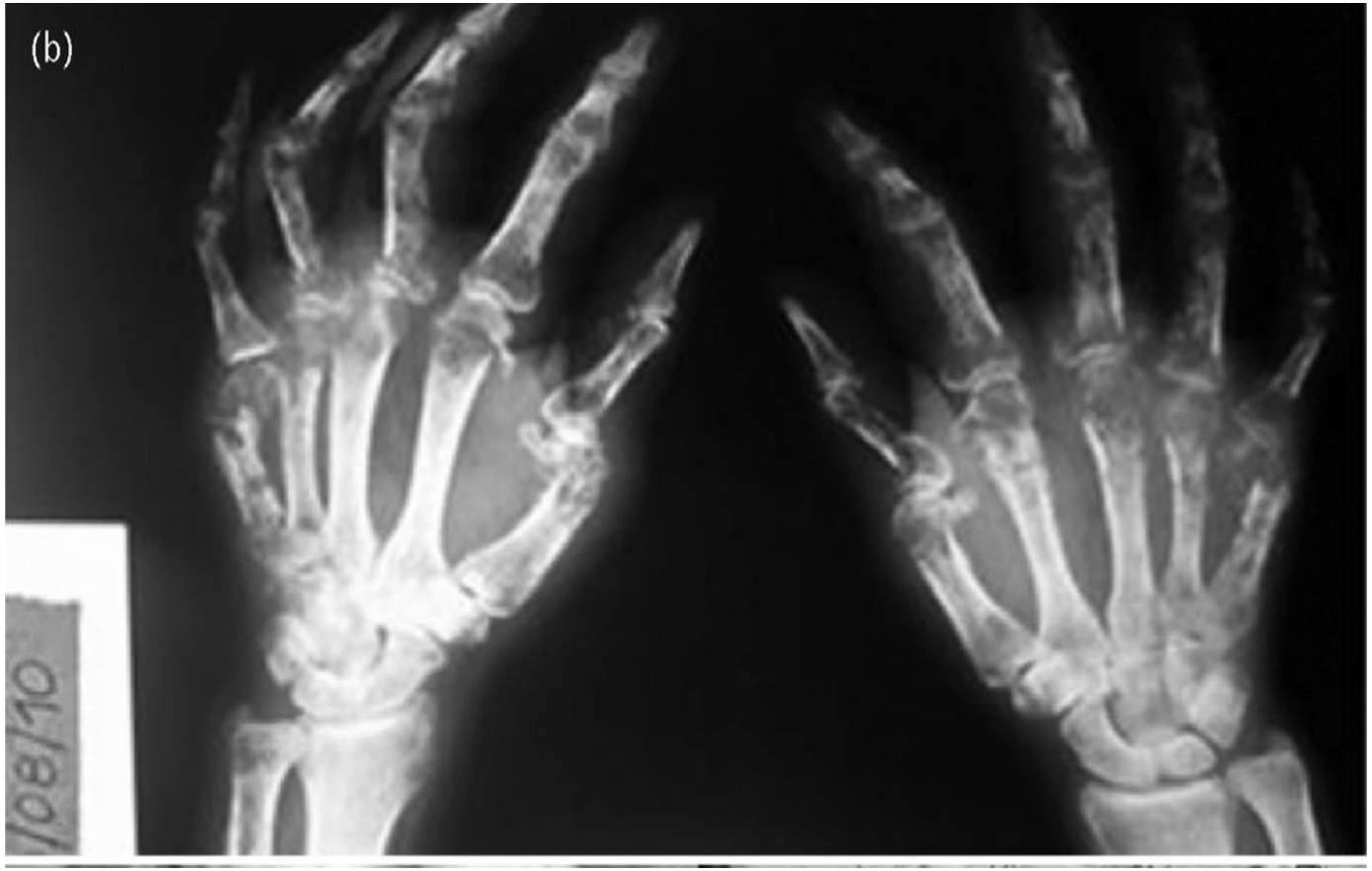
Oral histoplasmosis

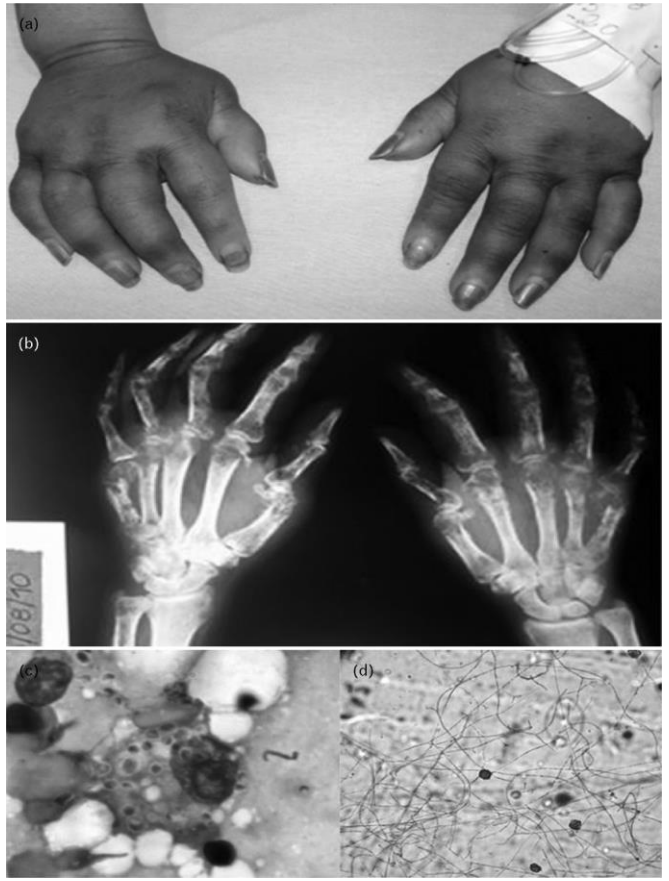


Ocular histoplasmosis



Histoplasmosis of the bone





Marianelli et al, AIDS, 2014

Criteria for the diagnosis of endemic mycoses

Proven endemic mycosis

In a host with an illness consistent with an endemic mycosis, 1 of the following:

Recovery in culture from a specimen obtained from the affected site or from blood

Histopathologic or direct microscopic demonstration of appropriate morphologic forms with a truly distinctive appearance characteristic of dimorphic fungi, such as *Coccidioides* species spherules, *Blastomyces dermatitidis* thick-walled broad-based budding yeasts, *Paracoccidioides brasiliensis* multiple budding yeast cells, and, in the case of histoplasmosis, the presence of characteristic intracellular yeast forms in a phagocyte in a peripheral blood smear or in tissue macrophages

For coccidioidomycosis, demonstration of coccidioidal antibody in CSF, or a 2-dilution rise measured in 2 consecutive blood samples tested concurrently in the setting of an ongoing infectious disease process

For paracoccidioidomycosis, demonstration in 2 consecutive serum samples of a precipitin band to paracoccidioidin concurrently in the setting of an ongoing infectious disease process

Probable endemic mycosis

Presence of a host factor, including but not limited to those specified in table 2, plus a clinical picture consistent with endemic mycosis and mycological evidence, such as a positive *Histoplasma* antigen test result from urine, blood, or CSF

NOTE. Endemic mycoses includes histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, sporotrichosis, and infection due to *Penicillium marneffei*. Onset within 3 months after presentation defines a primary pulmonary infection. There is no category of possible endemic mycosis, as such, because neither host factors nor clinical features are sufficiently specific; such cases are considered to be of value too limited to include in clinical trials, epidemiological studies, or evaluations of diagnostic tests.

De Pauw et al, Clin Infect Dis. 2008 June 15

Host factors

- Solid-organ transplant
- Hereditary immunodeficiencies
- Connective tissue disorders
- Immunosuppressive agents— corticosteroids or T cell immunosuppressants, such as calcineurin inhibitors, anti–TNF-α drugs, anti-lymphocyte antibodies, or purine analogues
- HIV/AIDS

De Pauw et al, Clin Infect Dis. 2008 June 15

Diagnosis

- Culture and microscopy
    - Gold standard
    - Usually growth seen after 2-3 weeks but can be delayed up to 8 weeks
- Histology
    - Need clinical context to determine active disease
    - May be confused with other organisms
- Cytology
    - Provides a presumptive diagnosis
    - Antigen testing increases the sensitivity

2017, Azar et al, Journal of clinical microbiology

Diagnosis

- Antigen test
    - Widely available, can provide a “probable” diagnosis
    - May be applied to BAL fluid, CSF, urine, serum
    - Cross reactivity with other fungi but usually a low positive
- Serology
    - Antibodies develop between 4-8 weeks
    - Not useful in acute infection
    - Not useful in determining response to treatment

2017, Azar et al, Journal of clinical microbiology

Diagnosis

- Molecular testing
  - Advantages: specific, rapid turn-around-time, may be more sensitive than culture
  - DNA probe applied to the specimen after the organism has been cultured

2017, Azar et al, Journal of clinical microbiology

Summary of diagnostic tests for histoplasmosis

	Acute Pulmonary Histoplasmosis	Subacute Pulmonary Histoplasmosis	Chronic Pulmonary Histoplasmosis	Progressive Disseminated Histoplasmosis
Culture	0 - 20%	53.8%	66.7%	74.2%
Pathology	0 - 42%	42.1%	75.0%	76.3%
Antigen	82.8 - 83.3%	30.4%	87.5%	91.8%
Serology	64.3 - 66.7%	95.1%	83.3%	75%

2017, Azar et al, Journal of clinical microbiology

Treatment

- Amphotericin B
  - Dose 0.7-1 mg/kg/day
  - Side effects: renal impairment, hypokalaemia, hypomagnesaemia, anaemia, thrombocytopaenia
- Liposomal Amphotericin B
  - Dose: 3-5 mg/kg/day
  - Better tolerated and used in patients with renal failure
  - However, evidence that better mortality rates in disseminated histoplasmosis
- Itraconazole
  - 300 mg twice daily for 3 days, 200 mg twice daily for 12 weeks
  - Maintenance: 200-400 mg daily for up to a year
  - Ideally itraconazole levels should be done to ensure levels ≥2 μg/mL
- Antiretroviral therapy

Wheat et al, Clinical Infectious Diseases 2007; 45:807–25

Other treatment options

- Fluconazole: Used in patients intolerate of Amphotericin B and itraconazole. High relapse rates.
- Ketoconazole: high relapse rate
- Echinocandins (caspofungin): inadequate activity in murine models
- Voriconazole: significant in vitro activity especially in CSF, but poorly tolerated
- Posaconazole: Effective in cases where standard treatment has failed (small study of 7 patients)

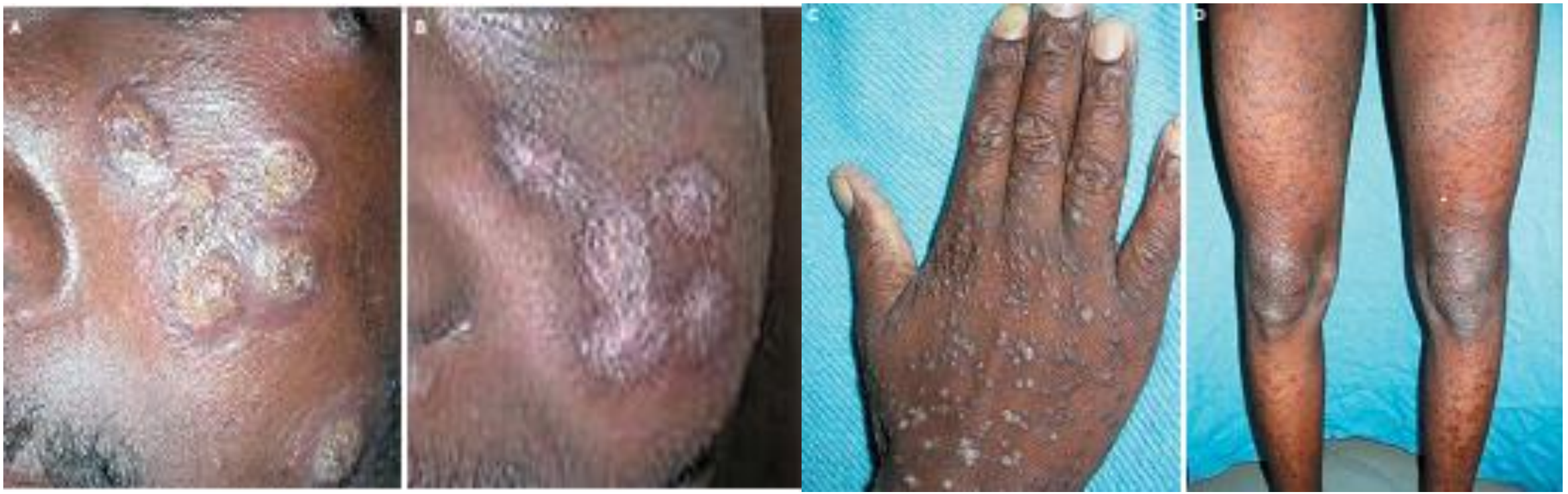
Wheat et al, Clinical Infectious Diseases 2007; 45:807–25

Emmonsiosis

- Causative organism: *Emmonsia pasteuriana, Emmonsia crescens, Emmonsia parva*
- Emmonsiosis previously described in horse population
- Fungal culture and clinical presentation: histoplasmosis
- Easier to identify with molecular testing
- Largest case series: South Africa (10 Cape Town, 3 Bloemfontein)
- Patients have a similar profile to histoplasmosis
  - Low CD4 count
  - Stage 4 disease

Kenyon et al, N Engl J Med 2013;369:1416-24

Emmonsiosis



Kenyon et al, N Engl J Med 2013;369:1416-24

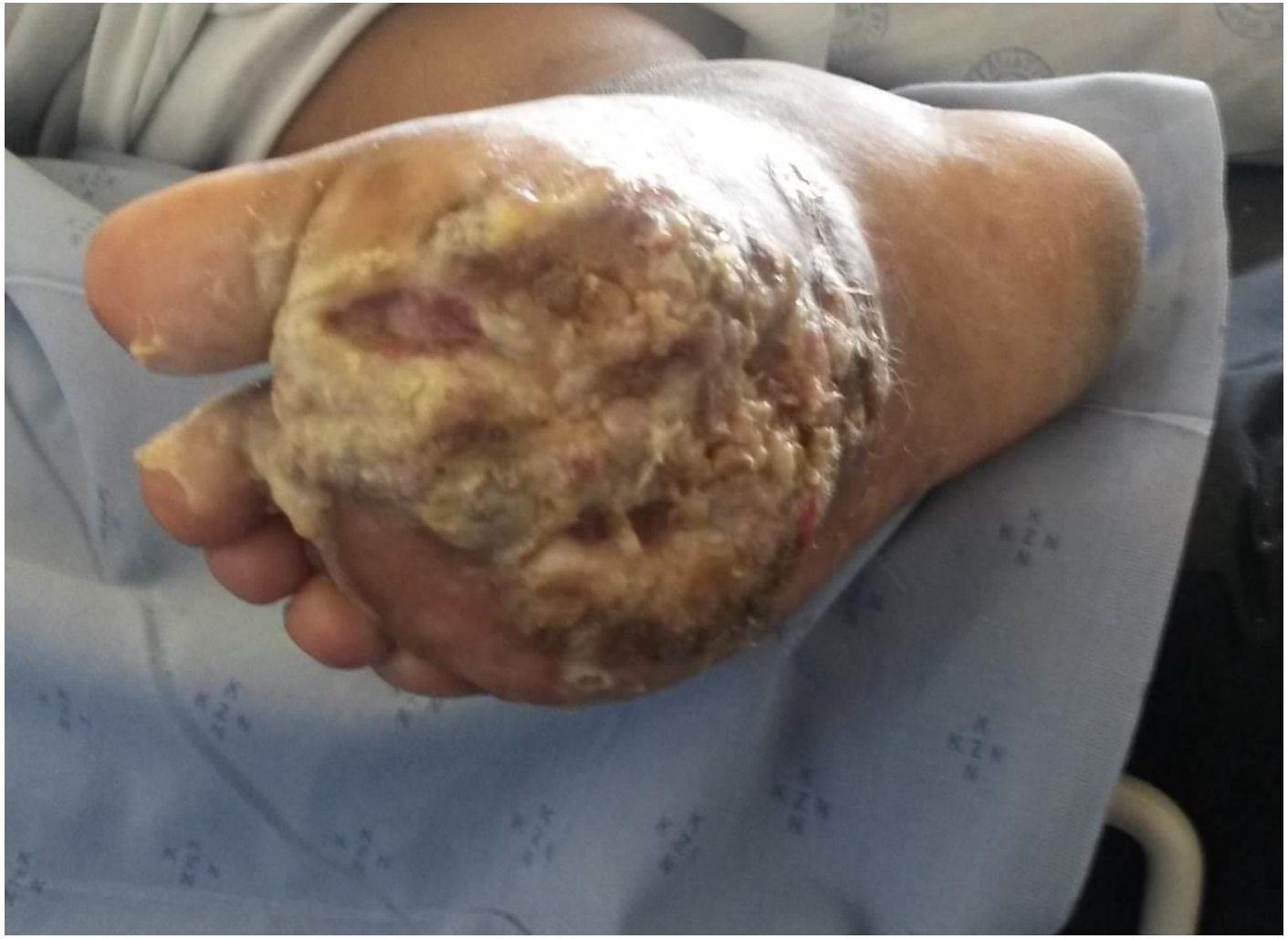
Histoplasmosis Immune Reconstitution Syndrome

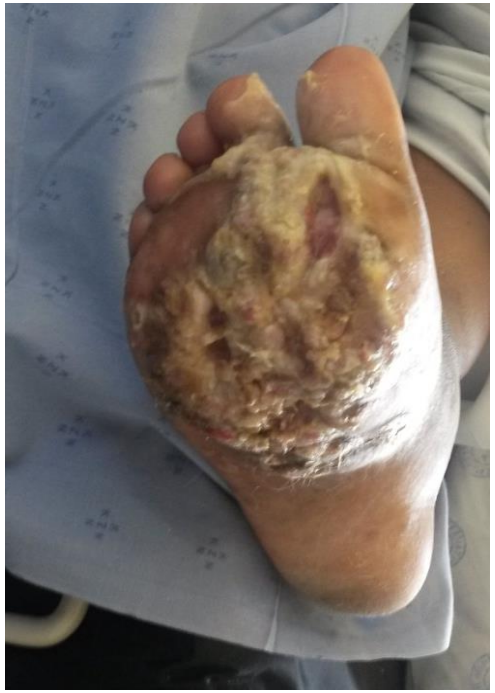
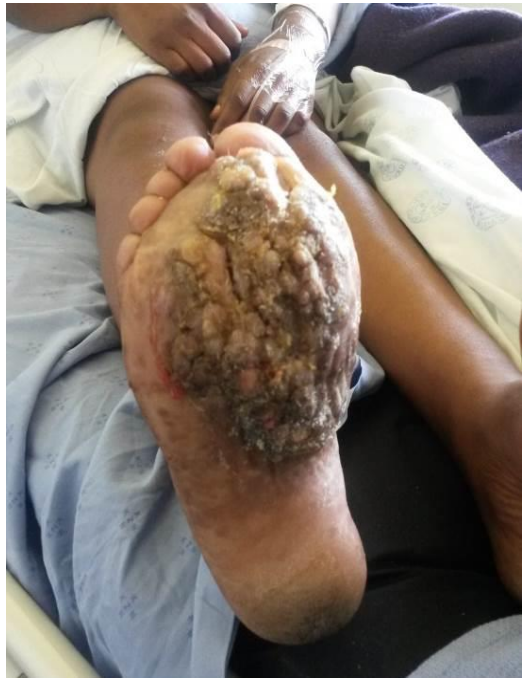
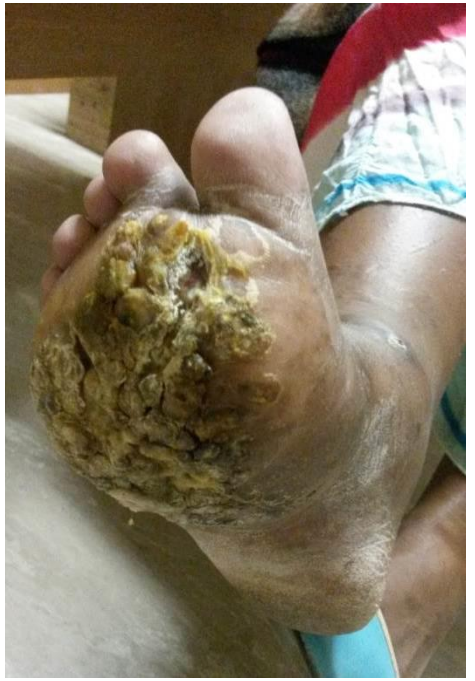
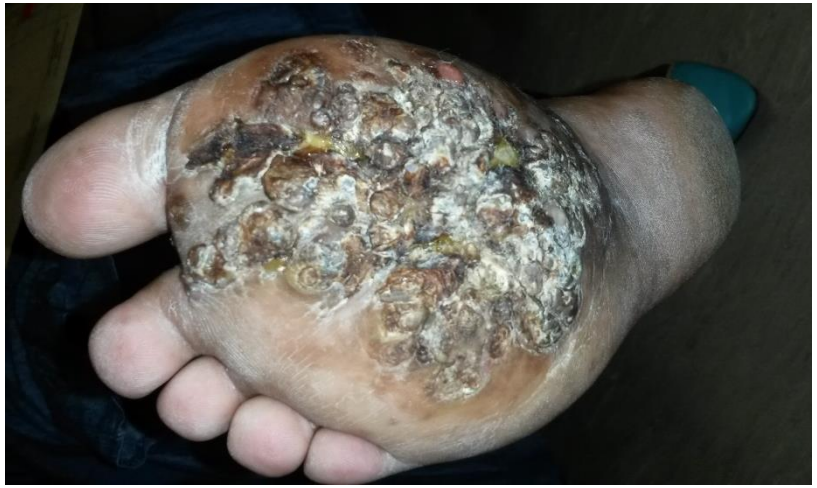
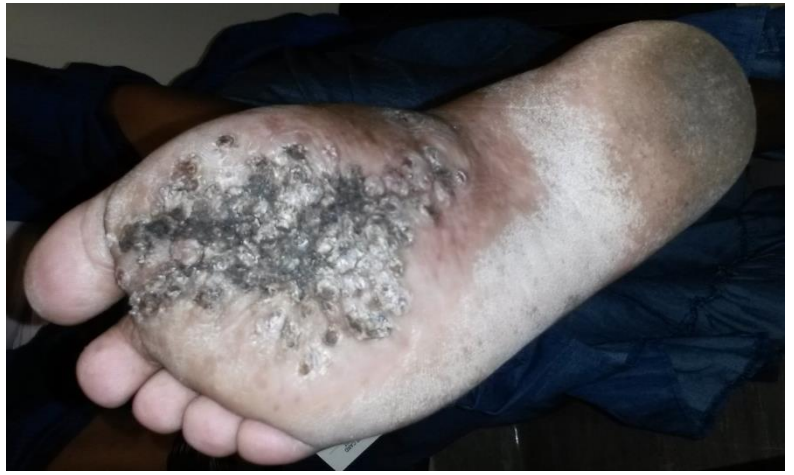
- 8 reported case
- 2 in South Africa (Dawood 2011, Sacoor 2017)
- Usually associated with low baseline CD4 count and rapid decline in viral load.
  - Skin (4)
  - Laryngeal (1)
  - Hepatosplenomegaly (1)
  - Osteomyelitis (2)
  - Lymphadenitis (1)
  - Mucocutaneous (1)
- All the cases reported responded well to standard therapy.

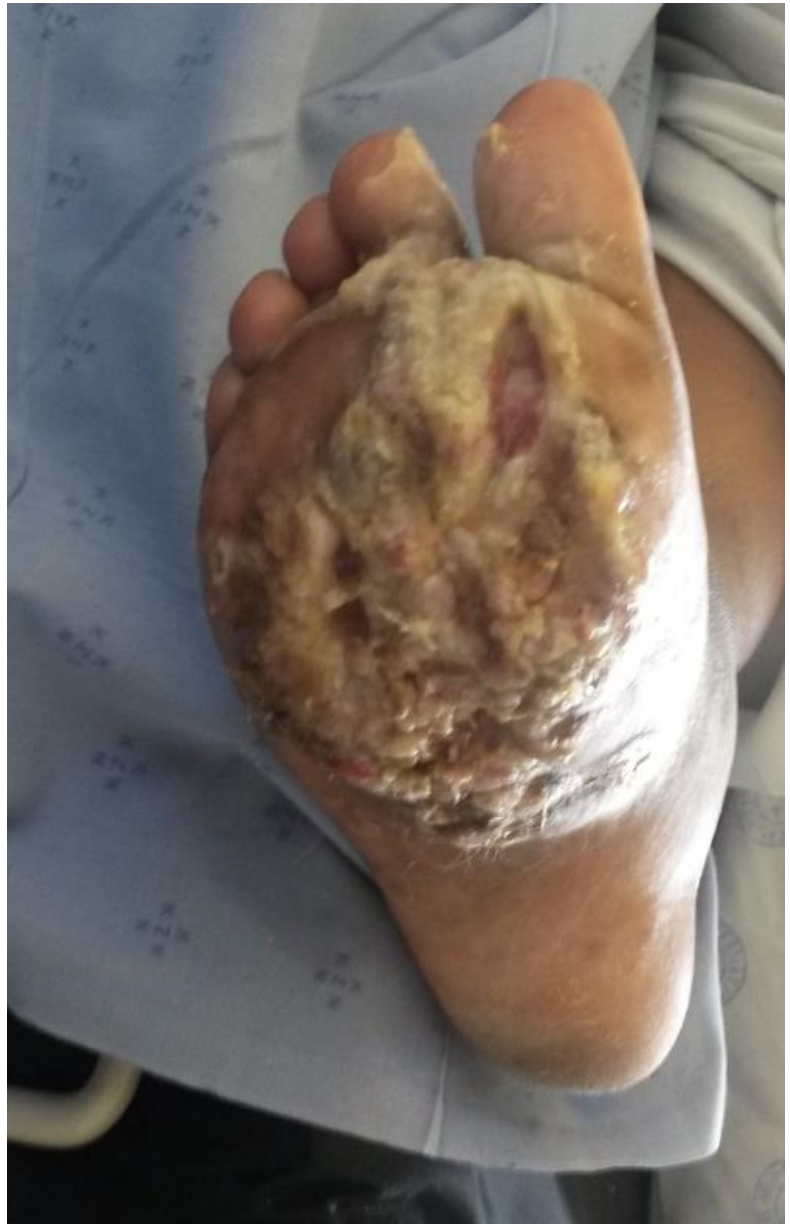
Conclusion

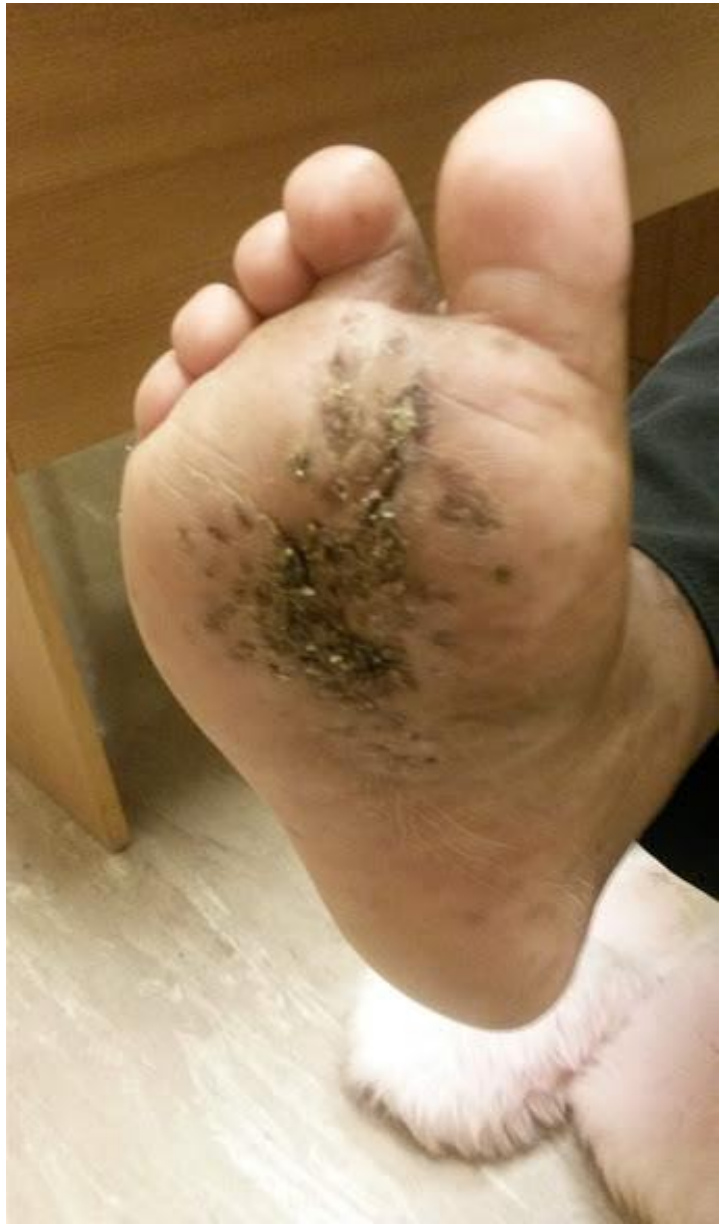
- Histoplasmosis and emmonsiosis are endemic to SA
- Consider them as a differential
- Use the antigen test if it is available
- Always chase after a microbiological or histopathological diagnosis even if you suspect TB

What is the diagnosis?







Acknowledgments

- Patients of Grey’s Hospital and Ngwelezana Hospital