Histoplasmosis

Definition - a granulomatous infection* initiated as a primary pulmonary disease, that may range in severity from inapparent and subclinical to acute, chronic or systemic and is caused by intracellular pathogen *Histoplasma capsulatum*, the anamorph of *Ajellomyces capsulatus*, a cleistothecial ascomycete.

Synonyms (most common) U.S. forms
- **Darling's disease**
- **Cave fever (Spelunker's disease)**
- **Ohio Valley Disease**

Histoplasmosis duboisii, African forms
Large cell histoplasmosis

***resolution → protective immunity**

a 1^{o} "endemic" mycosis; 1^{o} "pulmonary" mycosis

Maybe best example of # vs virulence vs resistance paradigm.

Histoplasmosis vs Cryptococcsis

Differences:

1. **Caused by ascomycete vs basidiomycete**
2. **Resolution of primary pulmonary form → life-long protective immunity**
3. **Anamorph a tissue dimorphic* hyphomycete**
4. **Mainly associated with particular endemic region(s)**
5. **in vivo considered to be an intracellular yeast*pathogen of reticuloendothelial system****

Similarities:

1. **Opportunistic form - originally considered a fatal disease; only type known before resolving pulmonary forms discovered in 1944**
2. **Often associated with birds**
   European starling in U.S. vs pigeons
   (also bats)
3. **AIDS-related mycosis**

* **tissue dimorphic - vs life cycle dimorphic**

** **system that produces & consists of cells that have the power to phagocytize - mΦ, histiocytes[+], Kupffer cells[++] of liver, etc., etc.**

[+] **resident MΦ of different types**

[++] **Kupffer cells are fixed phagocytic cells of liver**

Main Historical Event in Understanding Histoplasmosis

1944 - Amos Christie, an American, discovered that the rare, usually fatal disease known as Darling's disease was not a rare medical curiosity, but a very common U.S. <u>pulmonary</u> disease.

Today = skin testing has suggested that over 40 million U.S. residents have encountered *H. capsulatum* → conversion from skin test -- to +. (Histoplasmin) estimated 200K → 500K/year

hospitalizations - conservative estimates ~ 4000/year with ~ 100 deaths/year (before AIDS)

In highly endemic areas ~ 1 case of chronic pulmonary histoplasmosis/100,000 population.

Patients with AIDS at high risk (2 - ~ 30% of AIDS patients in endemic area & different cities).

Abbreviated Clinical Picture

I. Benign forms (95%)* in normal hosts (mostly 1^o pulmonary)
- **A. low dose - mild symptomatic or asymptomatic**
- **B. heavy dose - acute resolving or → acute disseminated (resolving)**

II. Opportunistic forms (5%) (2^o)
- **A. chronic progressive lung disease**
- **B. chronic cutaneous systemic disease**
- **C. acute, rapidly fulminating disease,often fatal systemic disease of children.**
- **D. AIDS disseminated or extrapulmonary**

*** defined by skin test, ID, CF tests, X-ray and autopsy (calcified lesions)**

History

1904 - Darling* - Panama Canal Zone Hospital (American pathologist)
- described 1st case at autopsy (worker from Martinique)
- named organism
***Histoplasma* because protozoan-like organisms in lung lesions were in histiocytes. *capsulatum* because appeared to be encapsulated.**

Wrong on 2 out of 3 counts:
1. did reside in histiocytes (+)
2. was not a protozoan (-)
3. was not capsulated (–)

***also described 2nd and 3rd cases; 1 & 2 were in blacks, #3 was in oriental**

1913 - da Rocha - Lima (Brazilian pathologist)
- concluded that the horse disease he was studying and which was caused by a fungus that was the same as that of Darling's disease.

1926 - 1st U.S. case - woman, Minn., @ autopsy (4th case)

1929 - Catherine Dodd (MD) at Vanderbuilt U. -studied 1st human case before autopsy - (fulminate)

-W. de Monbreun did mycology
1. grew out fungus
2. discovered its dimorphic nature
3. established cultural characteristics of yeast and mold phases
4. established disease in animals
5. described results in 1933, but had to share credit with Hensmann & Schenkan

1944 - Amos Christie
-discovered pulmonary benign form of disease
- 1904 --> 1945, 71 cases, all fatal.
1948 - Chester Emmons - NIH
-isolated fungus from nature for 1st time (rat burrows)
1972 - Kwon-Chung
-discovered teleomorph - a heterothallic cleistothecial ascomycete.
***Emmonsiella capsulata* (Kwon-Chung)**
1979 - McGinnis & Katz
-*Ajellomyces capsulatus* (Kwon-Chung) McGinnis et Katz 1979
Ascomycota
Euascomycotina
Plectomycetes
Order - Onygenales
Family - Gymnoascaceae

Taxonomy

Ajellomyces capsulatus

Ascomycota - endogenous meiospores
Euascomycotina - ascocarps
Plectomycetes - cleistothecia
Onygenales* - blastoconidium**
Gymnoascaceae* - sessile ascocarps
Ajellomyces capsulatus* var. *capsulatus
A. capsulatus* var *duboisii
heterothallic - strains self-sterile***
dimictic - mating controlled by single sets of idiomorphic sequences at same locus, A & a

currently same order as *Arthroderma*; same genus as teleomorph of *Blastomyces dermatitidis
****holoblastic - aleurioconidia (?)**
H. capsulatum* var *farciminosum* found in horses is most likely also a variety of *A. capsulatus
*****albino and brown hyphal varients**

Symptoms of "Benign" Forms

I. Benign forms (Endemic forms?)
A. Usual dose (low dose)
1. Subclinical (asymptomatic)
skin test conversion
X-ray findings
2. Symptomatic*
summer flu - children
fungus flu - adults
mild -
non-productive cough
chest pain
shortness of breath
hoarseness
more severe - above^{+}**
fever, sweats, weight loss
B. Heavy dose, acute, pulmonary

***cough & associated sputum may become productive; yeasts may be seen in bone marrow cells **most patients show one or more lesions on one or both lungs**
+more acute; many cases originating from some place at same time - "epidemic"
Resoltuion → immunity

Symptoms etc. of Disseminating Opportunistic Histoplasmosis

1. **Fulminant of children (<1 year)**
   - a. **rapid progression**
   - b. **usually fatal**
   - c. **Mϕ increase and engulf yeasts in large numbers**
   - d. **Mϕ clog capillaries and cause circulatory collapse**
2. **Chronic diseases of adults**
   - a. **several months to many years**
   - b. **usually involves only one or two organs (other than lungs)**
   - c. **requires antimycotic therapy or surgery for resolution**
3. **Fulminant of adults**
   - a. **associated with immunosuppression (e.g. (HIV) New - Ampho B (DC), itraconazole, fluconazole**
   - b. **also drugs (drug induced immunocollapse)**
   - c.. **lupis, hepatitis, malignancies, etc.**

Diagnosis

General:

1) **symptoms, serology**
2) **culture or staining of yeasts**
   culture on Blood agar plates or SABs for 4 → 8 wks
3) **ID by morphology or gene-probe (AccuProbe™) gene technology**

Serodiagnosis

1. **CF test (traditional)**
   - a.. **as tube or microtitration test**
   - b. **detects 90% of culturally proven cases**
   - c.. **sera must be monitored by testing every 2-3 weeks for a number of months**
   - d. **some cross-reactions - particularly with blastomycin (also coccidioidin etc.)**
   - e. **involves histoplasmin (a mycelial-form soluable antigen) harvested from 6-month-old cultures**
   - f. **titers**
     1:8 > presumptive
     >1:32 or rising strong evidence

2. **ID detects preciptins against H&M protein antigens of histoplasmin**
3. **LA test**
   - a. **histoplasmin coated latex particles**
   - b. **1:16 > 1:32 > diagnostic of acute histoplasmosis**

4. **FA stains**

Therapy:

Benign - bed rest and supportive therapy usually
Opportunistic - usually Ampho B; after disease arrest often surgical excision of large cavities or granulomatous masses