MMTN
MEDICAL MYCOLOGY
TRAINING NETWORK

DIMORPHIC MYCOSES FROM ASIA

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Nov. 15, 2018 : 11:45-12:15

ASIA FUNGAL WORKING GROUP an ISHAM working group | ISHAM | MMTN – TAIWAN Nov.15-16, 2018

Outline

- Thermal dimorphic fungi in Asia
  - *Histoplasma capsulatum*
  - *Talaromyces marneffei*
  - *Emergomyces orientalis*
  - *Sporotrix schenckii*
- Epidemiology
- Diagnosis

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DIMORPHIC FUNGI

- Two morphologies in microbe itself
  - Thermal dimorphic fungi
    - **saprophytic form, mold form (25 – 30 C)**
    - **pathogenic form, tissue form, yeast form (35-37 C)**

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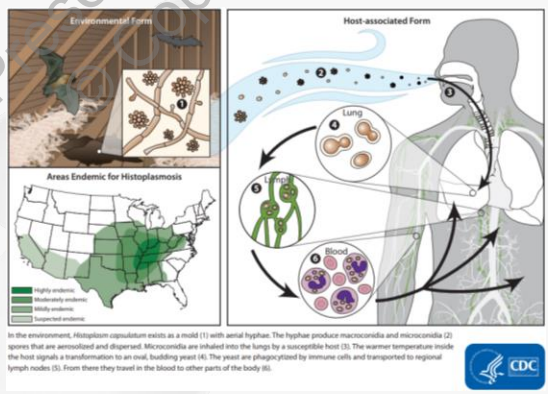
Histoplasmosis:

- *Histoplasma capsulatum* var. *capsulatum*
- *H. capsulatum* var. *duboisii,*
- *H. capsulatum* var. *farciminosum*
- *5* clades of var. *capsulatum*
- Early case: Australia (1948), India (1954)
- 37 reported cases : East India (1972)
- 19 cases in a single center in Southern India (2005)



In the environment, *Histoplasm capsulatum* exists as a mold (1) with aerial hyphae. The hyphae produce macroconidia and microconidia (2) spores that are aerosolized and dispersed. Microconidia are inhaled into the lungs by a susceptible host (3). The warmer temperature inside the host signals a transformation to an oval, budding yeast (4). The yeast are phagocytized by immune cells and transported to regional lymph nodes (5). From there they travel in the blood to other parts of the body (6).

Chakrabarti A. & Slavin MA. Med Myco.2011(49):337-44; Queiroz-Telles F. et al. The lancet ID 2016

Four Prt. Encoding genes:

Cl1: North American
Cl2: North American
Cl3: Central American
Cl4: South American gr.A (var. *farc.*)
Cl5: South American gr.B
Cl6: *H. cap.* var. *duboisii*
- Africa
- Imported case in Japan

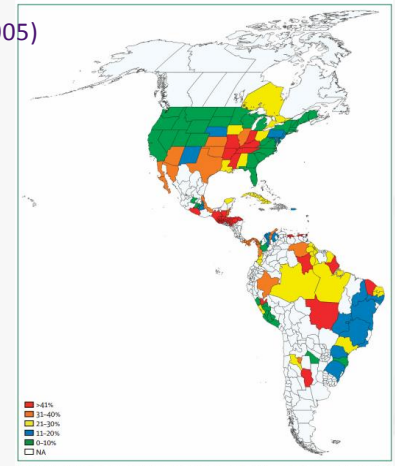


Figure 2: Frequency of positive intradermal reactions against histoplasmin in the Americas and the Caribbean
Data obtained from a review of 95 studies in 19 countries from 1949 to 2009.

Histoplasmosis: **More Widespread than Previously Thought**

- **SKIN TEST**
  - +ve higher in Hunan & Jiangsu (SE) than in Xinjiang Autonomous region (NE)
  - +ve in hospitalized > healthy residents (26%, 9%)
  - Among the above pt.: Pul. Tuberculosis & Lung Cancer (@33%)
  - Sichaun: 35% of students from Southern +ve; 6% from Northern.
- **REVIEWED CASES**
  - 82% of all reviewed cases : Yangtze River flows
  - 86% : disseminated cases
  - 52% : no underlying diseases were revealed
- **IMMUNOCOMPETENT Host in Jiangsu (2009)**
  - 45 yr-old female: intermittent fever for 6 mo. w low grade fever & abn liver fn.

Antinori S. Am J Trop Med Hyg 2014: 90(6) 982-3; Wang Y., et al. Am. J. Trop. Med. Hyg., 90(6), 2014, pp. 1180–1183

Histoplasmosis: THAILAND

FIGURE. 1. Map of Thailand with location of eight histoplasmin skin-test sites, and corresponding percentage of histoplasmin sensitivity.

- Year 1961: 329 student nurses in many area: 17-23 Female): 3.95%
- Year 1966: 609 residents in Rayong (Southeast): 24.8% reactor
- Year 1968: 4,211 residents of 8 geographic areas (Male / Female : 9.4 /1)
  - average 13.8% positive
  - Low histoplasmin sensitivity : N & NE regions (4.8 – 6.8%)
  - Highest activity in South & Central regions (14.3 – 34.4%)

Taylor RL. et al. The Am. J. Trop. Med & Hyg. 1968(17):4:579-83.

TABLE. DEMOGRAPHICS, CLINICAL,SYMPTOMS IN KCMH. JAN 2006-DEC 2016

	HIV (N=27)	Non-HIV (N=19)	P value
Age	34 (23-70)	60 (22-86)	0.00002
Male	19 (70.3)	18 (94.7)	0.060
Duration of presenting symptoms (mo)	2 (0.05-12)	3 (0.1-12)	0.155
CD_4	43.5 (3-454)	NA	
Presenting symptoms			
Fever	22 (81.4)	10 (52.6)	0.036
Fatigue	1 (3.7)	3 (15.7)	0.286
Weight loss	13 (48.1)	10 (52.6)	0.764
Hypotension	NA	1 (5.2)	
Adrenal insufficiency	1 (3.7)	5 (26.3)	0.068
Pneumonia	10 (37.0)	6 (31.5)	0.702
Skin manifestation	20(74)	7 (36.8)	0.012
- Hyperpigmentation	NA	3 (42.8)	
- *Ery. rash/umbilicated nodule*	13 (65.0)	2 (28.5)	0.023
- Oral ulcer	7 (35.0)	2 (28.5)	0.270
Lymph node enlarge	10 (37.0)	2 (10.5)	0.085
Hepatosplenomegaly	16 (59.2)	2 (10.5)	0.001
Diarrhea	4 (14.8)	1 (5.2)	0.386
Neurological symptom	2 (7.4)	1 (5.2)	1.000

Preudtipong Noopetch MD., et al.

TABLE. COINFECTIONS, UNDERLYING DISEASE, TREATMENT IN KCMH. JAN 2006-DEC 201

	HIV (N=27)[1]	Non HIV(N=19)[1]	P value[3 4]
Coinfection	14 (51.8)	2(10.5)	0.004
- Myco. Tuberculosis/MAC	11 (78.5) / 1 (7.1)	NA 1(50)	
- Salmonella	4 (28.5)	NA	
- Cryptococcus	2 (14.2)	NA	
- CMV	2 (14.2)	NA	
- Other	3 (21.4)	1(50)	
Underlying dis.			
- Type2DM	2 (7.4)	7 (36.8)	0.004
- Herbal used	1 (3.7)	4 (57.1)	
- Hematologic disorders	NA	2 (28.5)	
- IFN-γ autoAb & another immu.disorder	1 (3.7) NA	3 (42.8) 4 (57.1)	
Local/Disseminated			
Local	8 (29.6)	13 (68.4)	
Disseminated	19 (70.3)	6 (31.5)	0.009
Radiological features			
- Adrenal involvement	1 (3.7)	8 (42.1)	0.001
- Bilateral	1/1(100)	6/8 (75)	
- Tumor size (largest dia.)	9.8 (9.8) [9.8]	6.8 (3.8-8.4)	
Diagnosis by culture	5(18.5)	6(31.5)	0.306
Treatment			
- Amphotericin B	27(100)	17(89.4)	0.165
- Itraconazole		2(10.5)	
Mortality	6(22.2)	2(10.5)	0.439

Preudtipong N. MD., et al.

TALAROMYCOSIS

- 1956: 1st reported from Bamboo rats in South Vietnam *(Capponi)*
- 1959: Description of species :*Penicillium marneffei* *(Segretain)*
- 1973: Laboratory infected & 1st natural infection *(Disalvo)*
- 1984: five cases of penicillosis marneffei from Tertiary care in Bkk *(Jayanetra et al)*

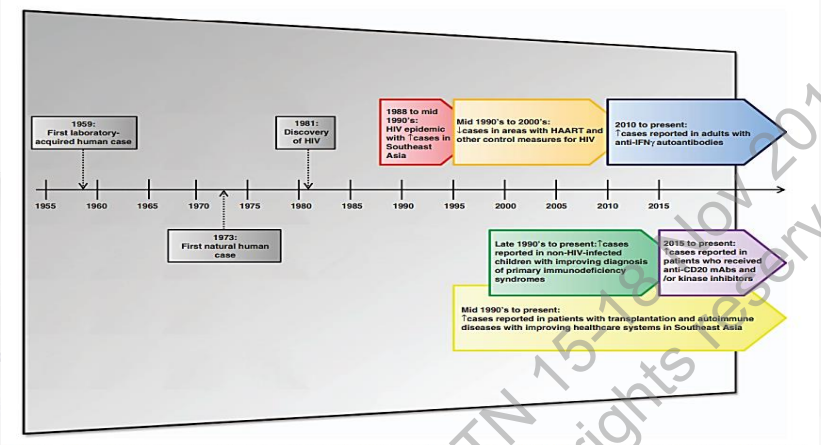


Figure 2 Major milestones in the changing epidemiology of *Talaromyces marneffei* infection. HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IFN-γ, interferon-gamma; mAb, monoclonal antibodies.

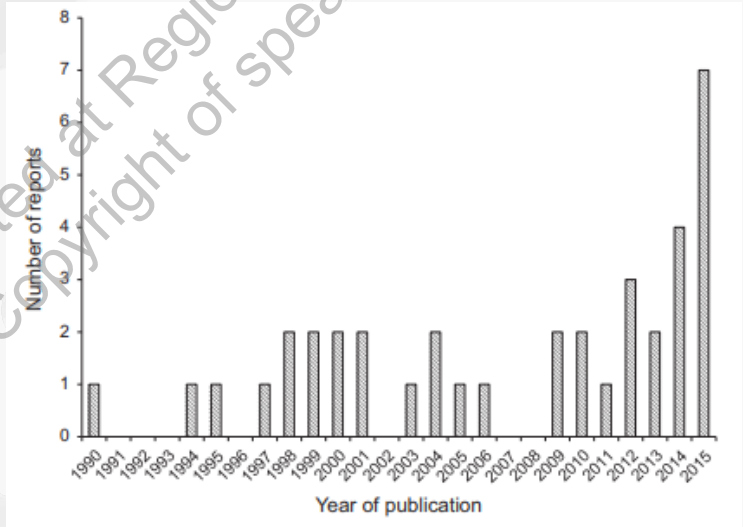


Figure 1 The number of reports of *Talaromyces marneffei* infection in non-HIV-infected adult patients described in the English-language literature between 1 January 1990 and 1 October 2015. Reports involving patients with uncertain human immunodeficiency virus infection status were excluded.

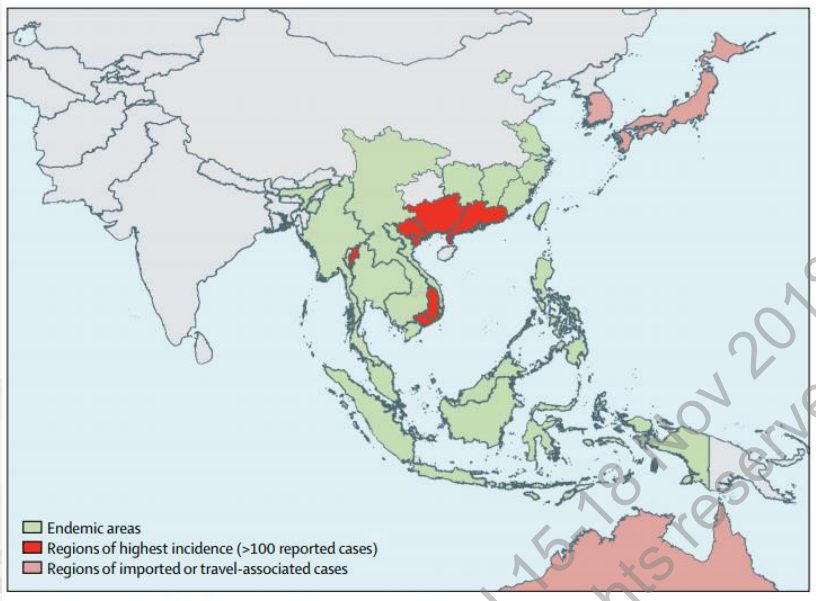


Figure 3: Geographical distribution of *Talaromyces marneffei* infection

Thanh NT, Thwaites G, Le T. Human talaromycosis (penicilliosis): Hunters Tropical Medicine, 10th Edition, Chapter 85. In press

Common Clinical Characteristics reported in the 155 reported cases of Penicillosis marneffei

Clinical Characteristic	No (%) of Patients
Fever	152 (98.0)
Anemia	116 (74.8)
Weight loss	111 (71.6)
Skin lesions	108 (69.7)
Fungemia	84 (54.2)
Lymphadenopathy	81 (52.3)
Cough	77 (49.7)

Clinical Infectious Diseases, 1996: 23:125-30

TALAROMYCES MARNEFFEI

Site of Culture positive infection in the 155 reports cases of Penicillosis marneffei

Site of Infection	No. (%) of Patients	Site of Infection	No. (%) of Patients
Skin	96 (61.9)	Spleen	8 (5.2)
Blood	85 (54.8)	Nasopharynx	5 (3.2)
Bone marrow	44 (28.4)	Bowel	3 (1.9)
Lymph nodes	33 (22.6)	Kidney	3 (1.9)
Liver	26 (16.8)	Pericardium	3 (1.9)
Lung	21 (13.5)	Finger*	1 (0.6)
Bone	12 (7.7)	Meninges	1 (0.6)

Clinical Infectious Diseases, Tuan Anh Duong 1996; 23:125-30

MMTN MEDICAL MYCOLOGY TRAINING NETWORK

HISTOPLASMOSIS & TALAROMYCOSIS

- Laboratory management
  - Collecting specimens
  - Processing specimens
  - Direct examination
    - Wright stain
    - Giemsa stain
    - Gomori's Methenamine Silver stain

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Immunology

- Immunodiffusion test (ID)
  - screening method
    - Histoplasmin as an antigen
    - H & M bands
      - H band indicates active infection
      - M band indicates early & persist after recovery
- Complement fixation test (CF)
  - very sensitive but less specific methods
    - Histoplasmin or yeast extract
    - 1:8 to 1:32 - presumptive evidence of disease
    - four fold change – either progress or regress of dis.
    - +ve – within 2 - 3 wk of exposure
    - -ve – not exclude the possibility of histoplasmosis

ID + CF - pt. progression

MMTN MEDICAL MYCOLOGY TRAINING NETWORK

Sporotrichosis – *Sporothrix schenkii*

- **Epidemiology:**
  - Decaying vegetation, esp used for mulching
  - Enters via splinters, thorn pricks
    - -Occupational hazard
- **Clinical Aspects:**
  - Primary nodular lesion →necrotic ulcer, suppurative
  - Proximal lymphatics may chronically infect (dissemination rare)
- ***Sporothrix schenckii*:**
  - Direct prep: RARE blastoconidia
  - *Sporothrix* is a thermal dimorph
  - At RT: DEMATIACEOUS colony, HYALINE septate hyphae, delicate lateral conidiophores w/ delicate rosettes of conidia
  - At 37°C *in vivo* & *in vitro*: oval, cigar-shaped blastoconidia.
- **Treatment:**
  - Itraconazole

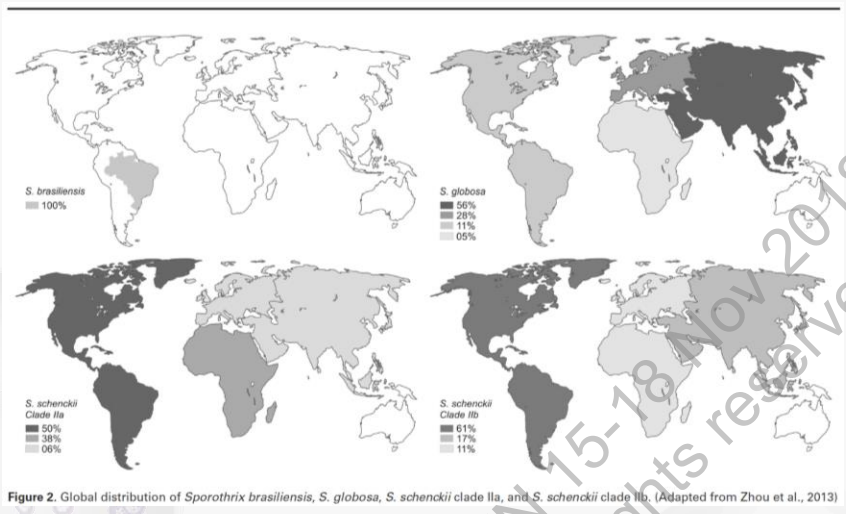
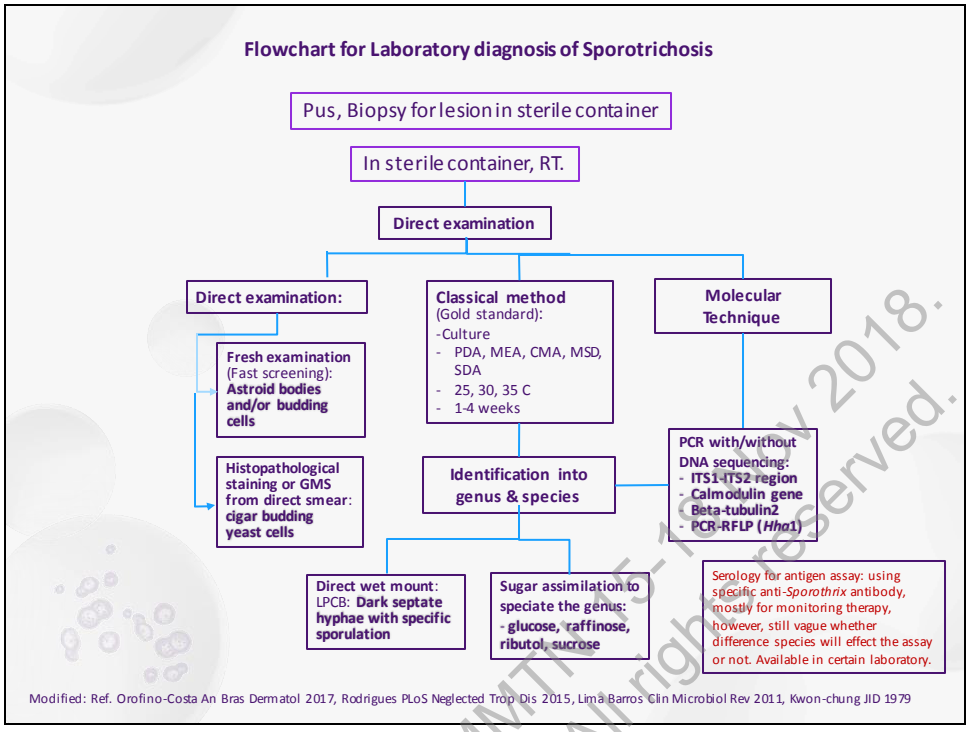


Figure 2. Global distribution of *Sporothrix brasiliensis*, *S. globosa*, *S. schenckii* clade IIa, and *S. schenckii* clade IIb. (Adapted from Zhou et al., 2013)

Chakrabarti A et al. Med Myco2015(53):3-14

Figure 1. Different clinical presentations of sporotrichosis. (a) Lymphocutaneous sporotrichosis, (b) fixed cutaneous sporotrichosis, (c) ulcerating lesions in a patient who slept with her cat, (d) oro-labial sporotrichosis in a patient who kissed her cat.

Chakrabarti A et al. Med Myco2015(53):3-14



ORIGINAL ARTICLE

WILEY mycoses

A novel dimorphic pathogen, *Emergomyces orientalis* (*Onygenales*), agent of disseminated infection

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[6]Division of Bioinformatics, Academy of Military Medical Science, Beijing Institute of Radiation Medicine, Beijing, China
[7]Division of Fungi, Academy of Military Medical Science, Beijing Institute of Radiation Medicine, Beijing, China

Summary

A novel dimorphic fungus, *Emergomyces orientalis* sp. nov. a close relative of systemic pathogens in the family *Ajellomycetaceae* (*Blastomyces*, *Histoplasma*). The fungus is reported in a 64-year-old male from Shanxi, China. The patient developed disseminated skin lesions, productive cough with fever and showed nodular opacities in his left lung on chest radiography. The patient had no identified cause of immunodeficiency apart from type-2 diabetes mellitus. Clinical, histopathological and mycological characteristics of the agent are given, and its phylogenetic position is determined with multilocus sequence data.

KEYWORDS

AIDS-related mycosis, diabetes, dimorphic fungi, *Emergomyces*, *Emmonsia*, endemic mycosis

Mycoses, 2016

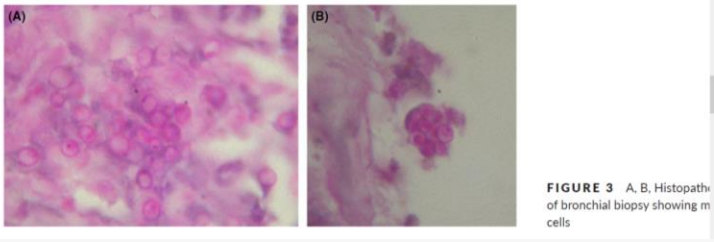
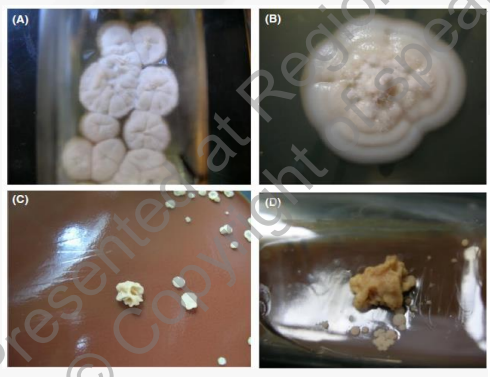


FIGURE 3 A, B, Histopath
of bronchial biopsy showing m
cells

FIGURE 1 A-C, Clinical aspect of disseminated cutaneous lesions on torso and legs

Mycoses, 2016



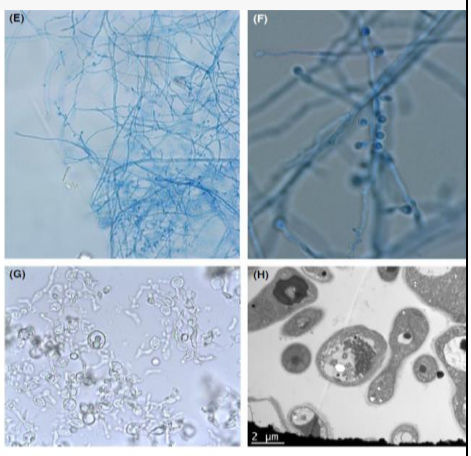


FIGURE 5 A, Initial culture from sputum on SDA after 20-30 days showing white to beige, felty satellite colonies; B, Detail of initial culture on CHL agar; C, D, Yeast-like colonies after 50 days of incubation at 37°C in BHI agar. E-F, Microscopy of slide culture on PDA at 28°C. G, Light microscopy of yeast-like cells after 50 days of incubation at 37°C in BHI broth; H, TEM microscopy of yeast-like cells

Mycoses, 2016

EMERGOMYCOSIS

Emergomyces africanus – southern Africa (South Africa, Lesotho), n>50
Emergomyces pasteurianus – Europe, Asia and South Africa, n=8
Emergomyces canadensis – Canada, n=4
Emergomyces europaeus – Germany, n=1
Emergomyces orientalis – China, n=1

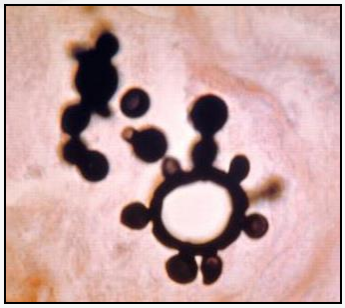
Refs:
- E. africanus – Kenyon NEJM 2013, Schwartz CID 2015, Schwartz OFID 2017, Crombie PLOS NTD 2018
- E. pasteurianus – Jiang Fung Divers 2018, E. canadensis – Schwartz EID 2018, E. europaeus – Jiang Fung Divers 2018
- E. orientalis – Wang Mycoses 2017

Emergomyces

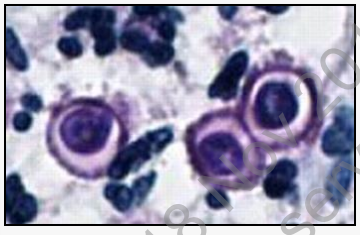
- The diagnosis: culture of blood and/or culture or molecular testing of affected tissue.
- Histopathology:
  - Skin lesions
  - Hard to distinguishing from *H capsulatum*.
- Molecular testing: Universal primers
- Emergomyces cross reacts with the *Histoplasma* galactomannan antigen test (IMMY), and patients with emergomycosis may test positive, although a negative test is not sufficient to exclude the diagnosis of emergomycosis.
- Can cross react with the *Blastomyces* DNA probe (Accuprobe)

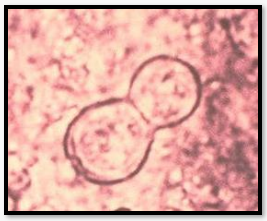
PATHOGENIC FORM

Thermal Dimorphic fungal infection



PARACOCCIDIOIDOMYCOSIS
- 5-15 um
- 10-20 um





BLASTOMYCOSIS

- Broad-based bud, 2-10 um

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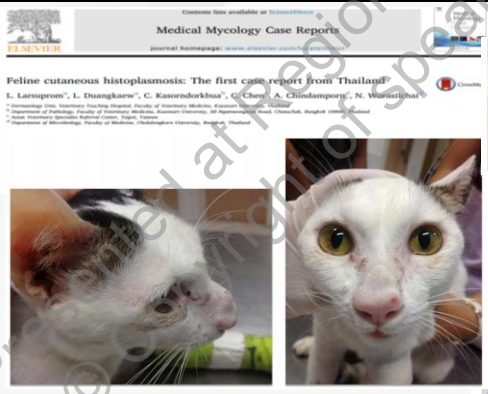

Medical Mycology Case Reports

Feline cutaneous histoplasmosis: The first case report from Thailand

L. Larsuprom, L. Duangkaew, C. Kasorndorkbua, G. Chen, A. Chindamporn, N. Wonsilchai

Fig1. Nodules on the nasal bridge at lateral and front views

Fig. 2. Multiple papules on both pinna and chronic wound on the left lateral radial area.

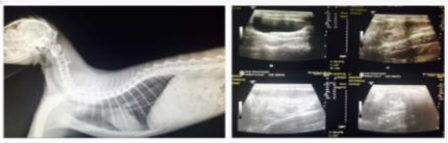

Fig. 3. Thoracic radiographs reveals no nodules in lung field. Abdominal ultrasonography shows homogeneity of liver parenchyma without mass effect

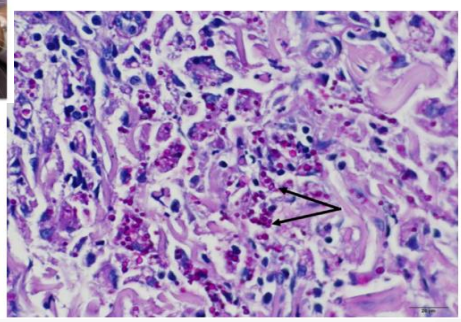

Fig. 4. The small 2–5 µm, oval-to-round, single-walled yeasts are found in the macrophages. PAS.

L. Lrsuprom et al. Med Mycology Case Reports 18 (2017) 28-30

BLASTOMYCOSIS

Medical Mycology Case Reports 15 (2017) 12–15

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Cutaneous blastomycosis and dermatophytic pseudomycetoma in a Persian cat from Bangkok, Thailand

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ARTICLE INFO

Keywords:
Blastomycosis
Pseudomycetoma
Persian cat
Bangkok
Thailand

ABSTRACT

This is a case report of concurrent of blastomycosis and pseudomycetoma in a 3 year-old Persian cat from Bangkok, Thailand. Histopathology from antemortem and postmortem samples revealed blastomycosis and dermatophyte pseudomycetoma. The PCR analysis of the formalin-embedded tissue of antemortem sample confirmed that blastomycosis was caused by *Blastomyces dermatitidis*. Dermatophyte infection was caused by *Microsporum canis*. According to the author's knowledge, this is the first case of *Blastomyces dermatitidis* and dermatophyte pseudomycetoma in South-East Asia.

BLASTOMYCOSIS

Fig. 1. A: Photograph of the cat showing alopecia, hyperpigmented and scaling skin. There were multifocal ulcerated nodules throughout the body. B: Photograph of the skin nodules at chin area with draining tract and bloody discharge.

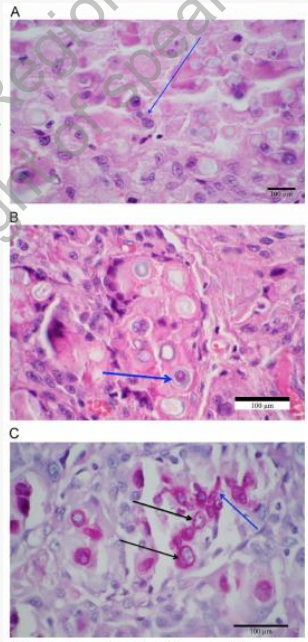

Fig. 2. A: Photomicrograph of broad-based budding yeasts of *Blastomyces* sp. (blue arrow). H & E). B: Photomicrograph of intralesional yeasts with thick, refractile, and double contoured cell wall (blue arrow). H & E). C: Photomicrograph of broad-based budding yeasts and thick, refractile, and double contoured cell wall (Black arrow) and branching septate hyphae (blue arrow), PAS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

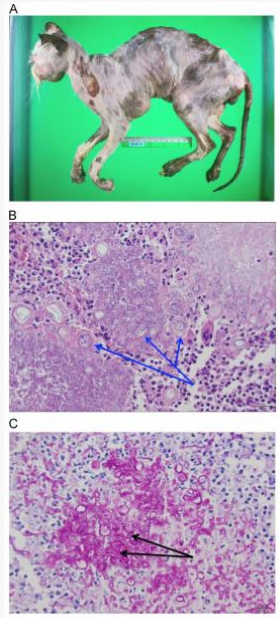

Fig. 3. A: Photograph of the cat (hair-clipped) with multiple ulcerated and proliferative skin nodules. B and C: Photomicrograph of the granulomatous lesion collected from the skin mass. B: Photomicrograph of the granuloma showing multifocal to coalescing granulomatous panniculitis containing numerous septate hyphae (blue arrow), epithelioid macrophages, plasma cells, neutrophils, and multinucleated giant cell. H & E. C: Photomicrograph of the septate hyphae in the granulomatous lesion (black arrow), PAS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

Message

- Awareness
- Alert
- Active

THANK YOU FOR YOUR ATTENTION.