**Brief History of Disease**

- The clinical nomenclature 'hyalohyphomycosis' first used by Ajello (1982) is a broad term used to classify opportunistic infections caused by soil-dwelling and plant saprophytic hyaline moulds.
- This terminology allows for the inclusion of all future hyaline fungi and disease states, rather than creating a multitude of unnecessary names for new and evolved species.
- *Hyalohyphomycosis itself does not have any characteristic clinical syndrome or entity.*

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**Brief History of Disease (cont’d)**

- "It is estimated that the number of fungal species is now in excess of 100,000, with approximately 1500 new species described each year," (Clinical Mycology).

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**‘Hyalohyphomycosis’**

- "The term hyalohyphomycosis is clinically useful when hyaline septate fungi are observed on histopathology without recovery of a pathogen. When the causative agent is recovered (e.g., *Fusarium solani*) a more specific term (fusariosis or infection by *Fusarium spp.*) should be used," (Clinical Mycology).

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**Brief History of Disease (cont’d)**

- The hyalohyphomycetes are a heterogeneous group, sharing a common characteristic in host tissue: hyaline septate hyphae
  - These hyphae are either branched or unbranched, and occasionally they are toruloid (knotted or beaded)
  - "Hyphae are parallel-walled, typically showing irregular branching at both 45 and 90 degrees. Hyphal diameter can vary substantially (2-8 um)," (Medical Mycology, pg. 749).

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**Etiology/Causative Agent(s)**

**Agents of hyalohyphomycosis**

- ubiquitous in nature
- plant parasites or saprobes
- world-wide distribution

"Currently known agents of hyalohyphomycosis are many and varied, presently totaling more than 20 genera and 70 species. Some of these species are well documented in causing disease; others have been encountered less often," (Medical Mycology, pg 749).
Etiology/Causative agent(s)

Etiological agents of Hyalohyphomycosis:

- Acremonium spp.
- Aphanoascus spp.
- Arthrobotrys spp.
- Beauveria spp.
- Chrysosporium spp.
- Colletotrichum spp.
- Coprinus spp.
- Cylindrocarpon spp.
- Fusarium spp.
- Geotrichum spp.
- Gibberella spp.
- Gymnoascus spp.
- Lecythophora spp.
- Microascus spp.
- Myriodon spp.
- Paecilomyces spp.
- Penicillium spp.
- Pseudallescheria spp.
- Scedosporium spp.
- Schizophyllum spp.
- Scopulariopsis spp.
- Scytalidium spp.
- TriCrachium spp.
- Trichoderma spp.
- Volutella spp.

(This list varies in all of the books that we have looked at)

Causative Agent #1: Fusarium

Hyalohyphomycoses

Genus: Fusarium

- currently contains over 20 species
- the most common human pathogens are F. solani (50%), F. oxysporum (14%), F. verticilloides (11%), F. moniliforme (10%), F. proliferatum (5%)
- Most virulent: Fusarium solani

Causative Agent #1

Fusarium (cont’d)

- Fusarium derives its name from its fusiform conidia
- ‘Fusiform’ is formed like a spindle, wider in the middle and tapering toward the ends; comes from the Latin “fusus” meaning “spindle”

Causative Agent

Fusarium (cont’d)

- Generally anamorphic filamentous organisms that propagate by producing conidia
- Conidiophores are simple (non-branched) or branched monophialides (phialides with a single opening).

‘Sporodochia’ clusters of conidiogenous cells/conidia viewed as raised areas with the naked eye

Causative Agent

Fusarium (cont’d)

- Found as saprophytes on organic debris and in soil
- Commonly implicated as plant pathogens
- Some only found in tropical or temperate climates
- Others are more geographically widespread (e.g., desert and arctic areas)

“Despite worldwide distribution, most cases of invasive fusariosis have been reported from the U.S. and Southern Europe, particularly France. Fusarium spp. are more abundant in the air during the rainy summer-autumn months, coinciding with increased infection rates,” (Medical Mycology, 2005).
The number of organisms causing Hyalohyphomycosis increases each year
- Localized infections may occur among otherwise healthy individuals (usually following penetrating trauma)
- Disseminated infections tend to occur among severely immunocompromised patients such as those undergoing transplants (stem cell or organ)

Most people are frequently exposed to these agents, however infections caused by them are rare in people with a normal immune system. Invasive disease usually occurs in those with impaired host defenses.
- Even though the number of infections that are encountered is small, associated mortality is disproportionately high.
- "Persistent neutropenia is probably the key risk factor for infection with hyaline molds. Highly susceptible patients include those with underlying hematological malignancies, bone marrow transplant recipients, and solid organ transplantation," (Medical Mycology, '05).

"Interestingly, Hyalohyphomycosis in individuals infected with HIV appears to be relatively uncommon. HIV specifically targets the T-lymphocyte population whereas hyaline mold pathogens are primarily granulocyte-controlled infections," (Medical Mycology, 2005).

Hyaline hyphomycetes are capable of causing a wide spectrum of disease that can be further divided into superficial, deep tissue, and disseminated infections

Deep infections
- involve lungs, sinuses, heart, liver, spleen, kidney, bones or central nervous system
- commonly acquired through the respiratory tract, gastrointestinal tract (e.g., after major surgery), or blood vessels (e.g., catheter-related)

Incidence of infection with hyalohyphomycosis increasing with medical advances:
- aggressive anticancer chemotherapy
- organ transplantation
- immunosuppressive treatments
When present in infected tissue (e.g., the lung) these molds appear as **hyaline**, septate, branching filamentous fungi that may be indistinguishable from Aspergillus.

The tissue morphology of the causative organism is **mycelial**.

Identification of the fungi can also be based on microscopic morphology of their reproductive structures: **phialides** (fertile cells) and **conidia** (spores).

**Port of acquisition**

- Lung, skin, foreign bodies
- Normally community-acquired but is sporadically acquired nosocomially
- Rarely causes infection
- Most organisms exhibit broad-spectrum resistance to existing antifungal drugs

**Uncommon but emerging** cause of severe and frequently fatal focal respiratory or disseminated opportunistic infections in severely compromised hosts.

Such agents of disease are commonly encountered as laboratory contaminants.

- Uncommon causes of allergic sinusitis or asthma
- Some organisms (e.g., Fusarium species, Acremonium species) can grow in blood cultures

**Fusariosis Infection in Humans**

- Fusariosis is the second most common invasive mycosis, after aspergillosis, among acute immunocompromised patients undergoing induction chemotherapy
- The potential adhesive properties of **Fusarium** spp. may also contribute to the pathogenesis of fusariosis. These molds can adhere to silastic catheters, and infections of CVCS, continuous ambulatory peritoneal dialysis catheters, and contact lenses have been reported
- Also, the formation of hyphae-to-hyphae structures with thickened cell walls has been postulated to protect **Fusarium** spp. from the neutrophil insult
Early diagnosis is important; it can however be problematic...
- Isolation of the fungus, particularly from respiratory tract sites, may simply represent colonization, which may or may not progress to infection depending primarily on the **immunological status of the host** and the **virulence** of the organism.

**Pathogenesis (cont’d)**

**Host response to infection (cont’d)**
- Decreasing proliferation and function of lymphocytes, protein synthesis, and phagocytosis by macrophages and chemotaxis of neutrophils (most common type of white blood cell to arrive at a site of infection, through a process known as **chemotaxis**).

**Diagnosis (cont’d)**
- “A positive culture from a nonsterile site must be interpreted with caution. Nevertheless, since these infections can be rapidly devastating, isolation of the fungus must not be automatically dismissed without investigation, particularly in the immunosuppressed host,”
- “Definitive diagnosis requires the histological detection of hyphae in normally sterile body fluids and/or tissue sections, together with a positive culture whose morphology matches that seen by microscopy,” (Medical Mycology ‘05).

**Diagnosis (cont’d)**
- Sputum, bronchial washings, and aspirates should be examined using 10% potassium hydroxide and Parker ink (1:1), Gram stain, or, preferably, a fluorescent chitin dye such as Calcofluor (to increase sensitivity).
- Body fluids and exudates should be concentrated by centrifugation and the sediment similarly examined microscopically.

**Pathogenesis (cont’d)**

**Virulence factors:**
- Fusarium spp. possess several virulence factors including the production of fumonisins, fusarins, moniliformin, and other mycotoxins.
- These factors can cause mycotoxicoses in humans due to suppression of humoral and cellular immunity.

**Diagnosis (cont’d)**
- Direct microscopy may be helpful in preliminary diagnosis
- The test is rapid and the diagnostic yield may be higher than culture alone.
- It will rarely indicate which fungus is responsible, but should distinguish the zygomycetes and hyalohyphomycetes.
- If both microscopy and culture are positive, the likelihood of invasive disease is much higher
• Tissue biopsies should be stained with a fungal stain in parallel with standard stains. Periodic acid-Shiff (where cell walls will be red) or a silver stain such as Gomori methenamine silver or Grocott stain (which will stain cell walls black) is recommended.

• Absence of melanin in the cell wall can usually be confirmed with a melanin stain (Fontana-Masson stain).

• In histological preparations, it can be almost impossible to distinguish between the various genera of hyaline moulds, and agents of hyalohyphomycosis may be misidentified as Aspergillus. Also, the histological appearance may be altered after antifungal therapy.

• Immunohistological staining and in situ hybridization have both been used on tissue sections to differentiate Fusarium and Scedoporiom spp. from other hyalohyphomycetes.

• Since direct microscopy or histopathology may not be reliable means of distinguishing between the various genera of hyaline moulds, all specimens should be cultured using a primary isolation medium, such as Sabouraud glucose agar.

• Incubate cultures for 4-6 weeks, generally at 30 degrees Celsius.

• Definitive identification of the etiologic agent can then be accomplished using macroscopic and microscopic morphology.

• Identification is crucial for guiding antifungal therapy since intrinsic resistance to one or more drugs has been noted in many genera.

“Every attempt should be made to ensure immunocompromised patients avoid exposure to potential environmental sources in hospitals.

Potential reservoirs
• hospital water supplies, soil of potted plant, nearby landscaping or construction work, contaminated drinking water or foodstuffs such as nuts and spices

“Paecilomyces spp. are resistant to standard sterilization methods and outbreaks have been associated with contaminated skin lotion,” (Medical Mycology, 2005).
**Disease Prevention (cont’d)**

- Empirical treatment in febrile neutropenic patients
- Amphotericin B (many agents are clinically resistant to this drug and invasive infection may develop regardless of therapy)
- Use of fluconazole prophylaxis is successful in reducing the frequency of Candida infections.

**Case Report #1 (cont’d)**

- A 6-month-old male green iguana was presented to the Veterinary Teaching Hospital of Autonomous University of Barcelona on September 2006 due to skin thickening over the distal aspect of the left hind leg
- The animal was kept in a glass tank with a broad spectrum of UV lighting and coconut bark and at a temperature of 28-30 degrees Celsius. The animal was bright and alert and ate and drank well and in overall good body condition.
- A sample of hyperplastic skin was removed from the lesion and submitted for microbiological culture

**Case report #1 (cont’d)**

- Examination of the scales revealed hyaline septate hypha
- Numerous white fungal colonies were obtained in pure culture consistent with *Chrysosporium* on Sabouraud dextrose agar and incubated at 25 degrees Celsius
- Treatment was initiated with ketoconazole in combination with 2% chlorhexidine solution and terbinafine administered topically
- The lizard was re-evaluated after one month and new healthy skin was developing at the site of the previous lesion, which was improving with each ecdysis (molting or shedding of outer layer of skin)

**Case report #2**

- A 48-year-old man, when neutropenic on day 12 of remission induction chemotherapeutic regimen for B-acute lymphoblastic leukemia, developed pulmonary probable invasive fungal infection, according to EORTC classification.
- On day 34, after the introduction of posaconazole as salvage treatment, he became afebrile and showed improvement of pulmonary imaging on chest computed tomography and could resume his chemotherapeutic course
- On day 64, after full hematological recovery, the patient presented low-grade fever and left upper quadrant abdominal pain

**Case Report #2 (cont’d)**

- An abdominal CT disclosed a 6cm solid splenic lesion suggestive for abscess
- The patient underwent laparotomic splenectomy while receiving antibiotic therapy in addition to posaconazole
- Histological examination on hematoxylin-eosin staining revealed extensive necrotizing inflammation of splenic tissue
- Immunological findings were strongly suggestive for invasive aspergillosis
- Splenic hyalohyphomycosis was indeed disclosed in the patient only when abdominal pain was manifested
- Results of molecular and immunological analysis were consistent with invasive aspergillosis

**Case report #2**

- *Splenic hyalohyphomycosis, molecularly and immunologically consistent with invasive aspergillosis in a patient with B-acute lymphoblastic leukemia*
• Fabio Forghieri, Guilo Rossi, Leonardo Potenza, Monica Morselli, Patrizia Barozzi, Daniela Vallerini, Massimino Messino, Fabio Rumpianesi, Monica Pecorari, Giuseppe Torelli and Mario Luppi.


Citation Page

