Clinical Findings in Rare and Emerging Fungal İnfections

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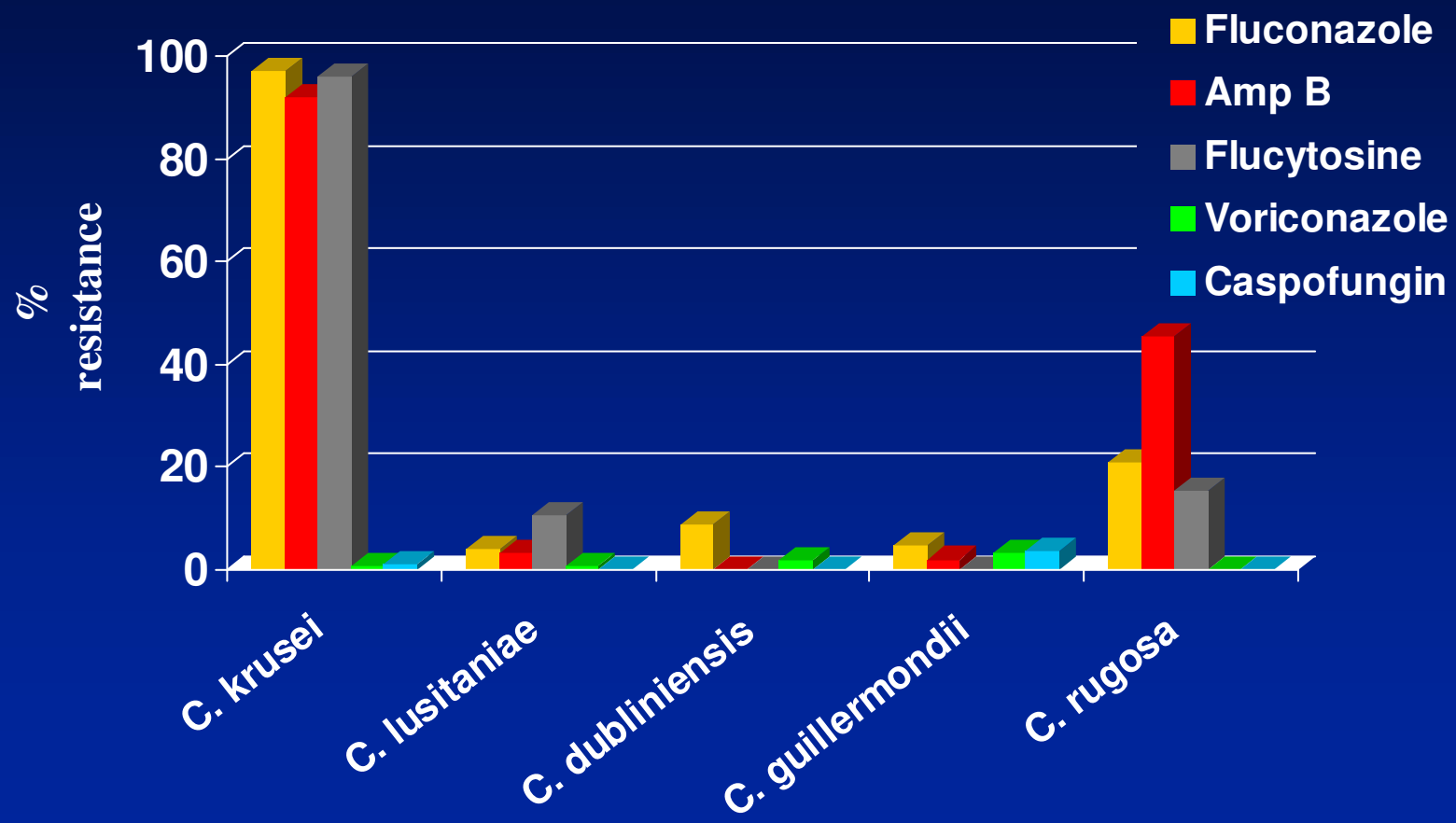
Rare and Emerging Opportunistic Fungal Pathogens

- **Candida species**
  - C. krusei
  - C. lusitaniae
  - C. dubliensis
  - C. guillermondii
  - C. rugosa
- **Opportunistic yeast-like fungi**
  - Trichosporon spp.
  - Rhodotorula spp.
  - Blastoschizomyces capitatum (Geotrichum capitatum)
- **Hyaline molds**
  - Aspergillus terreus
  - Zygomycetes
  - Other molds
    - Fusarium spp.
    - Acremonium spp.
    - Scedosporium spp.
    - Paecilomyces spp.
    - Trichoderma spp.
- **Dematiaceous molds**
  - Bipolaris spp.
  - Exophiala spp.
  - Phialophora spp.
  - Wangiella spp.

Phaller & Diekema. J Clin Microbiol 2004;42:4419

Resistance to Antifungals Amongst Rarely Isolated *Candida spp.*



Phaller & Diekema. J Clin Microbiol 2004;42:4419

Opportunistic Yeast-like Fungi

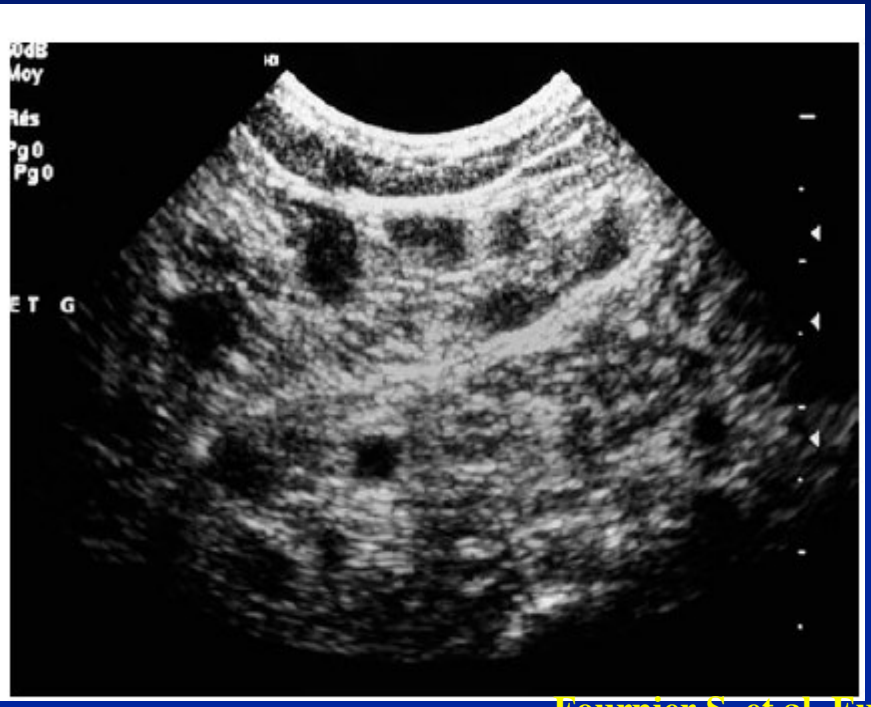
- Similar clinical picture as seen in candidiasis
- Frequent CNS involvement
- Mucositis/catheter-related
- Peristant fever and progressive skin lesion while receiving Amp-B
- High mortality

Febrile Neutropenic Patient

- 45 years old, male with AML
  - 4 cycle Ara-C, the last one 2 weeks ago
- On admission
  - Body temperature, 39.5 ℃, PMNL 100/mm^3
  - Had a central venous catheter
  - Many cutaneous papulopustular lesions with central necrosis, a few purpuric
  - Subcutaneous painful nodules in both legs

Fournier S, et al. Eur J Clin Microb Infect Dis 2002;21:892

Fundoscopic examination



Muscular ultrasonography of the left leg

Fournier S, et al. Eur J Clin Microb Infect Dis 2002;21:892

Febrile Neutropenic Patient

- Blood cultures and skin biopsy revealed a yeast
- Amp B initiated with GCSF
- Catheter was removed
- Fever persisted, fluconazole was added 3 days later
- On 8th day PMNL was 1500/mm^3
- No defervescence

Fournier S, et al. Eur J Clin Microb Infect Dis 2002;21:892

Febrile Neutropenic Patient

- Chest X-ray: Bilateral pulmonary nodules
- Pulmonary CT: Bilateral multiple nodules
- Abdominal CT: Hepatosplenomegaly with multiple hepatic abscesses

Fournier S, et al. Eur J Clin Microb Infect Dis 2002;21:892

Trichosporon spp.

- ***T. asahii*** **and** ***T. mucoides*** **cause invasive infection**
  - **Most common noncandidal yeast infection in hematologic cancer patients**
    - **Mortality >80%**
  - **Catheter-associated fungemia in neutropenics**
  - **Multiple cutaneous lesions**
  - **Mimics hepatosplenic candidiasis**
  - **Decreased susceptibility to Amb B and "old" azoles**

Flemming RV, et al. Infect Dis Clin N Am 2002;16:915

Rhodotorula spp.

- Commensals in skin, nails and mucous membranes, cheese and milk products
- Widely disseminated in environement
- Cause of infections
  - Fungemia
  - Ocular infections
  - Peritonitis
  - Meningitis
- Highly sensitive to Amp B

Blastoschizomyces capitatus

- Widely distributed in nature
  - May be a normal skin colonizer
- Very similar picture to that of *Trichosporon spp.* in patients with hematologic malignancies
  - Disseminated organ involvement including brain
  - 60-80% mortality

Martino R, et al. Clin Infect Dis 2004;38:335

Malassezia spp.

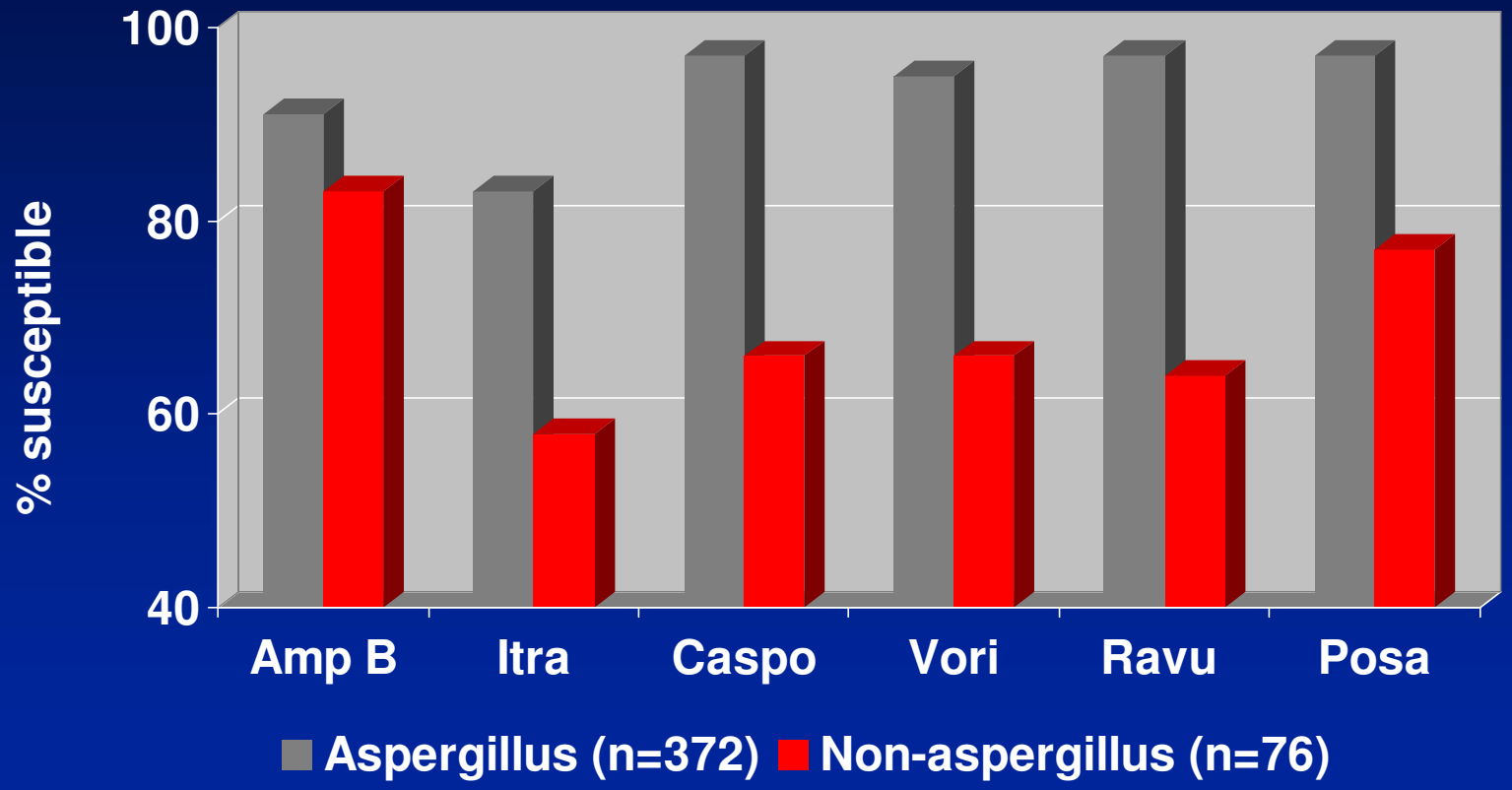
- Lipophilic yeasts
- In immunocompromised patients with iv lipids
  - Persistent fever, pulmonary infiltrates, thrombocytopenia
  - Folliculitis
  - Catheter-related fungemia

Walsh TJ, et al. Clin Microb Infect 2004;10(suppl.1):48

Non-*Aspergillus* Molds

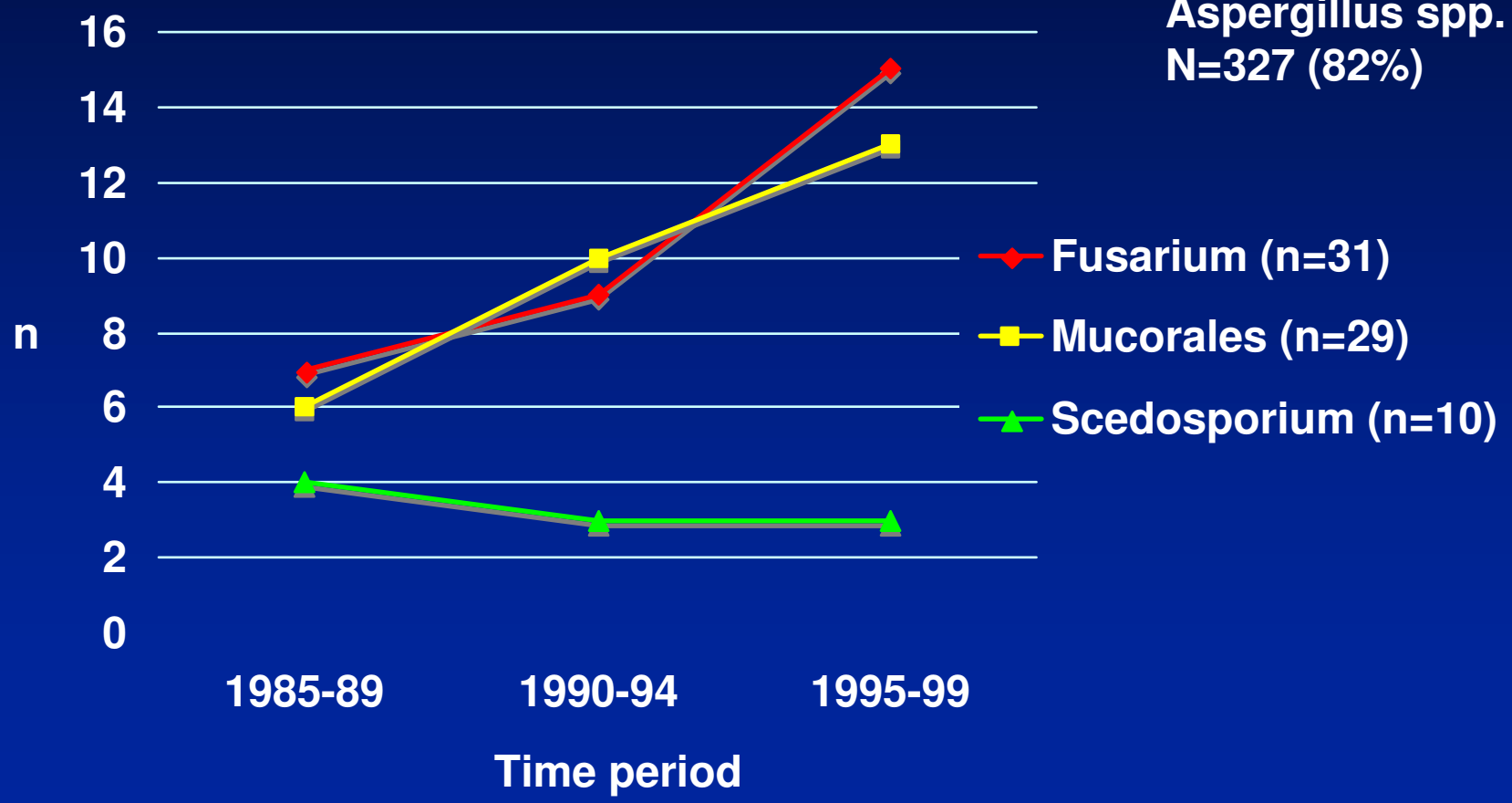
- Similar clinical picture as seen in aspergillosis
- More frequent skin lesions
- More frequent CNS involvement
- Fungemia
- Persistant fever in severly immunosuppressed patients receiving conventinal antifungal therapy
- Difficult-to-diagnose and -to-treat
- High mortality

Susceptibilities of *Aspergillus spp.* and *Non-Aspergillus* moulds



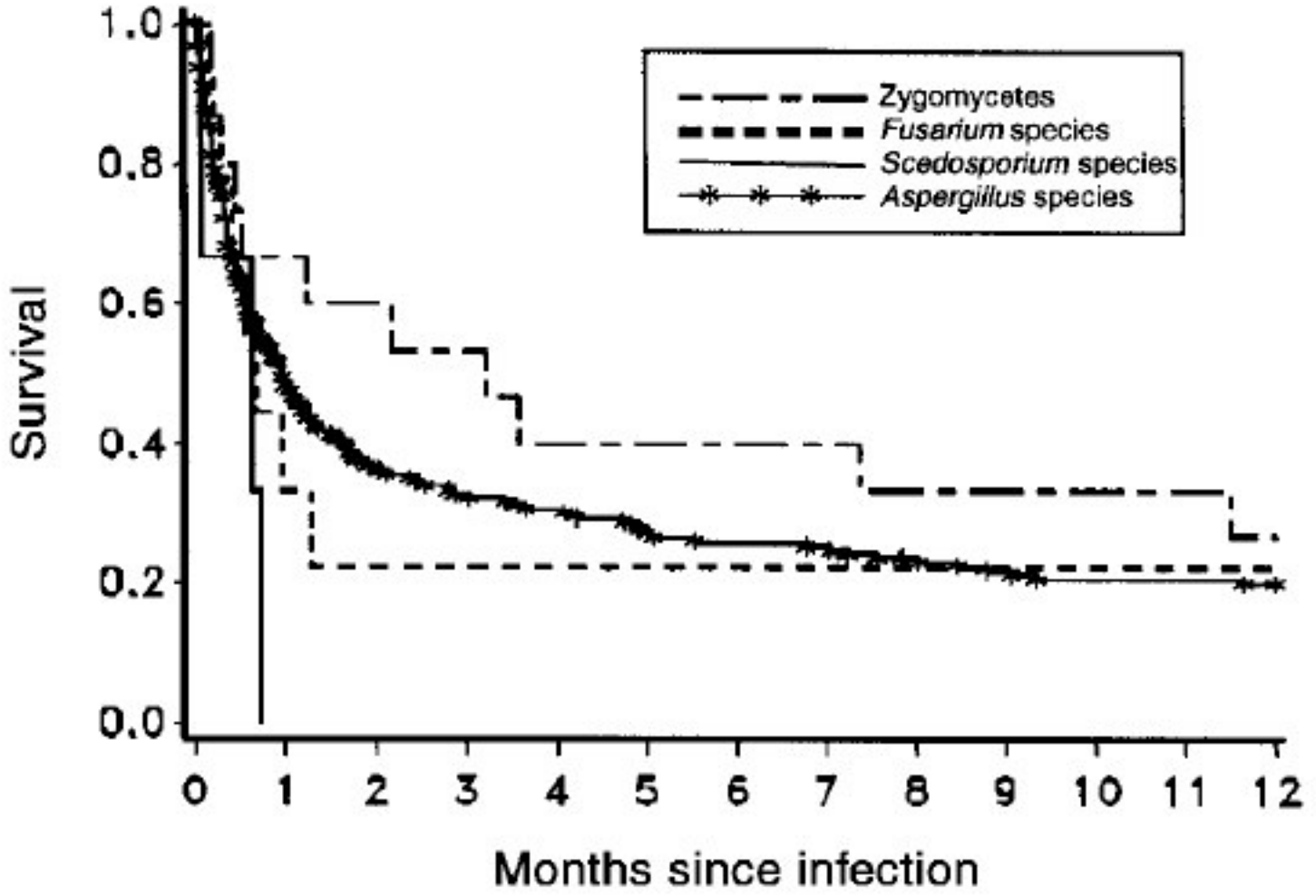
Diekema DJ, et al. J Clin Microbiol 2003;41:3623

Mold Infections in HSCT Recipients



Marr K, et al. Clin Infect Dis 2002;34:909

1-year Survival Rate



Marr K, et al. Clin Infect Dis 2002;34:909

Aspergillus terreus

- 3-12.5% of invasive aspergillosis
- Found in
  - Showerheads, water storage tanks, potted plants
- Adventitous sporulation
  - Yeast-like spores (aleurioconidia) in tissues
  - Can be detected in blood collected for culture
  - Causes true aspergillemia
- Resistant to Amp B

Iwen PC, et al.Clin Infect Dis 1998;26:1092

Patient with Acute Leukemia-1

- 72 years old, male, AML M2
- Previously treated for 6 months
  - No remission
  - Several tansfusions
  - Empirical antibacterila therapy, 6 times
  - Recieved L-Amp B for probable pulmonary aspergillosis
  - Recieves voriconazole for seceondary prophylaxis

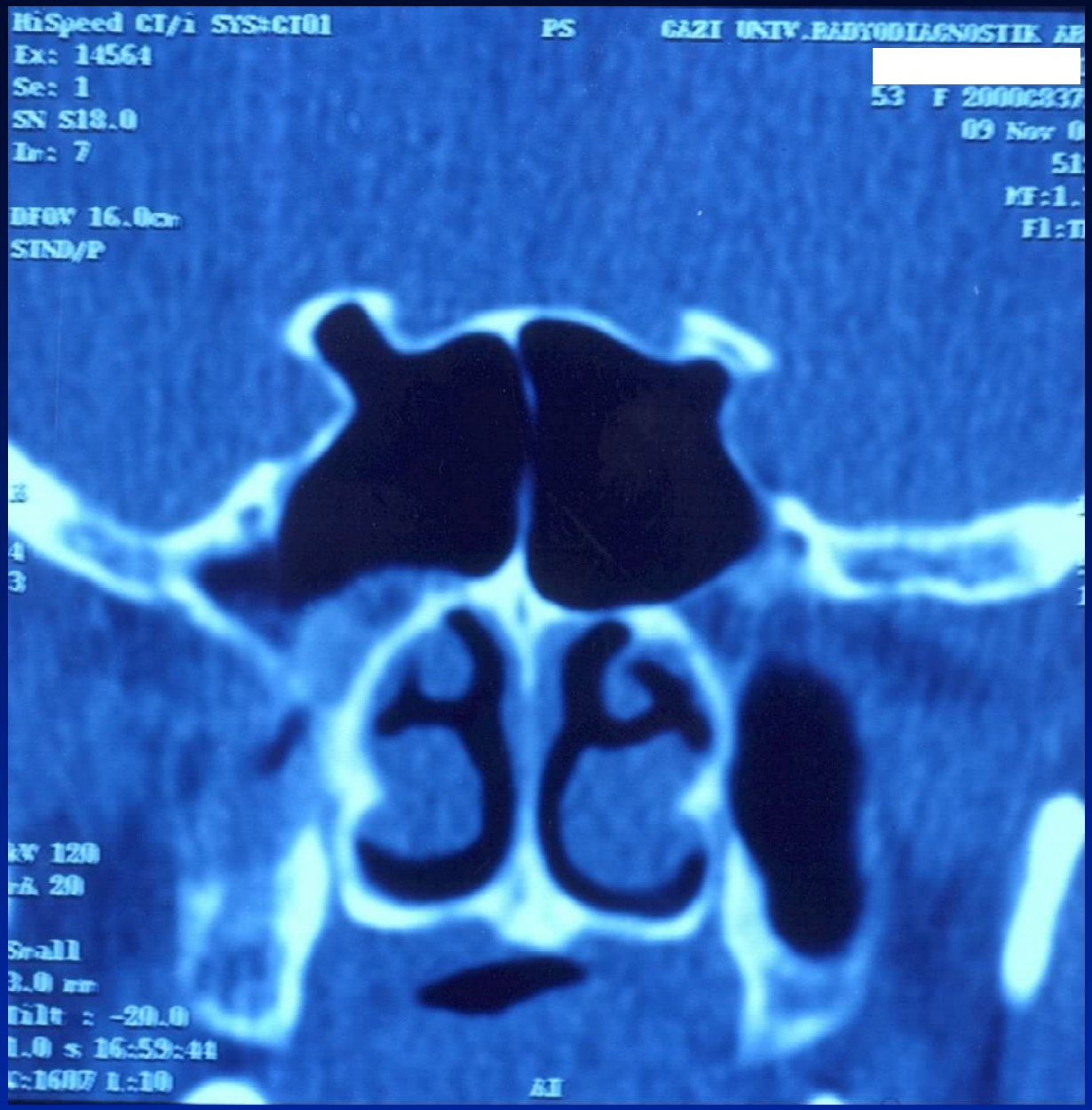
Patient with Acute Leukemia-2

- After low dose ara-C, neutropenia and fever develops
  - 38.7 ℃, PMNL: 75/mm^3
  - Pulmonary CT: left basiler nodular infiltration
  - Defervesces after empircal antibacterial and L-Amp B therapy

Patient with Acute Leukemia-3

- During follow up, neutropenia persists (PMNL<250/mm^3)
  - 50% blasts in peripheral smear
  - Regular desferoxamin infusions for secondary hemachromathosis
  - Oral voriconazole for maintenance therapy
- 6 months after admission, he develops pain, erythema and edema in right periorbital, maxillary and perinasal region

Courtesy of Esin Senol, MD



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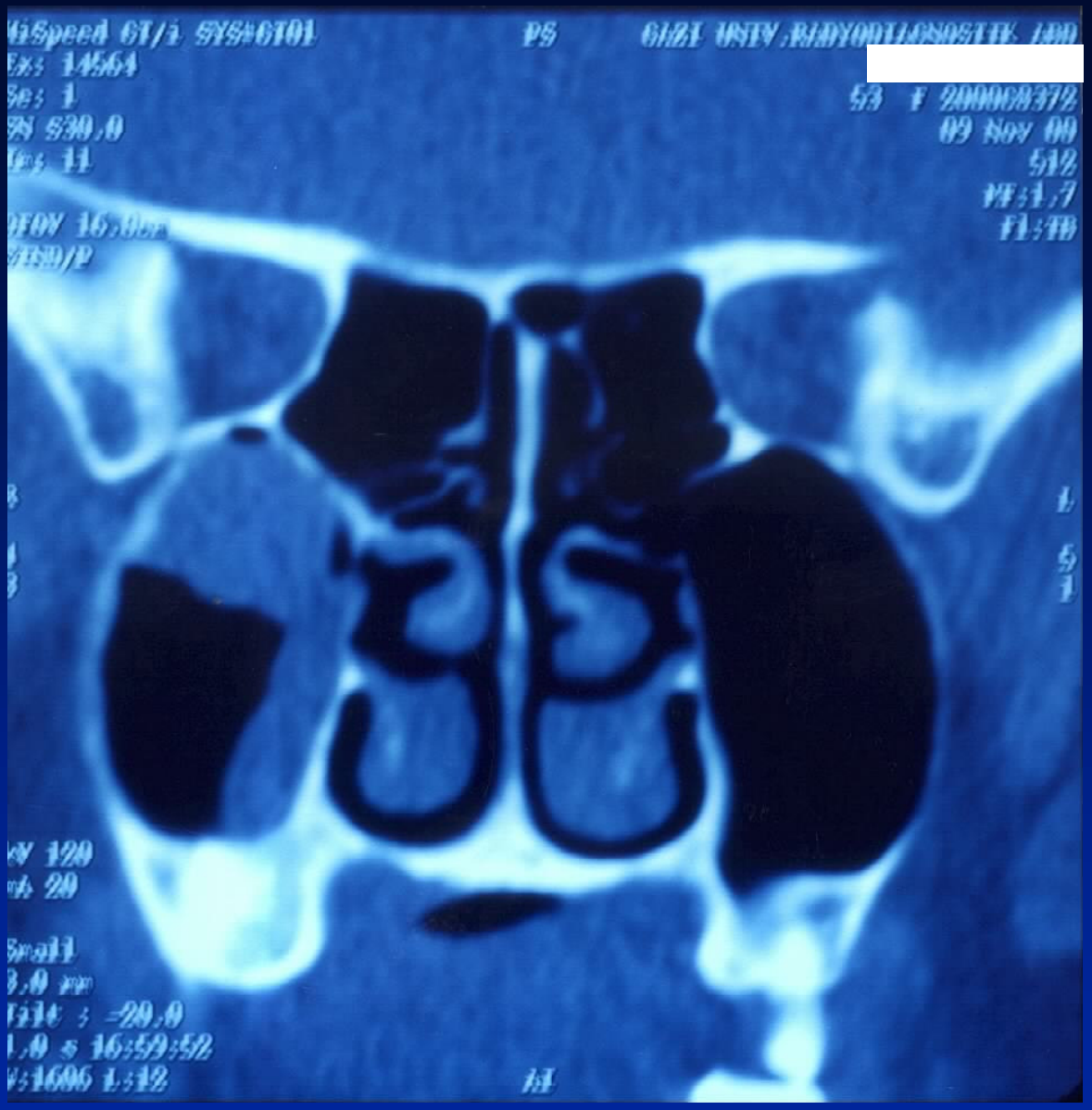

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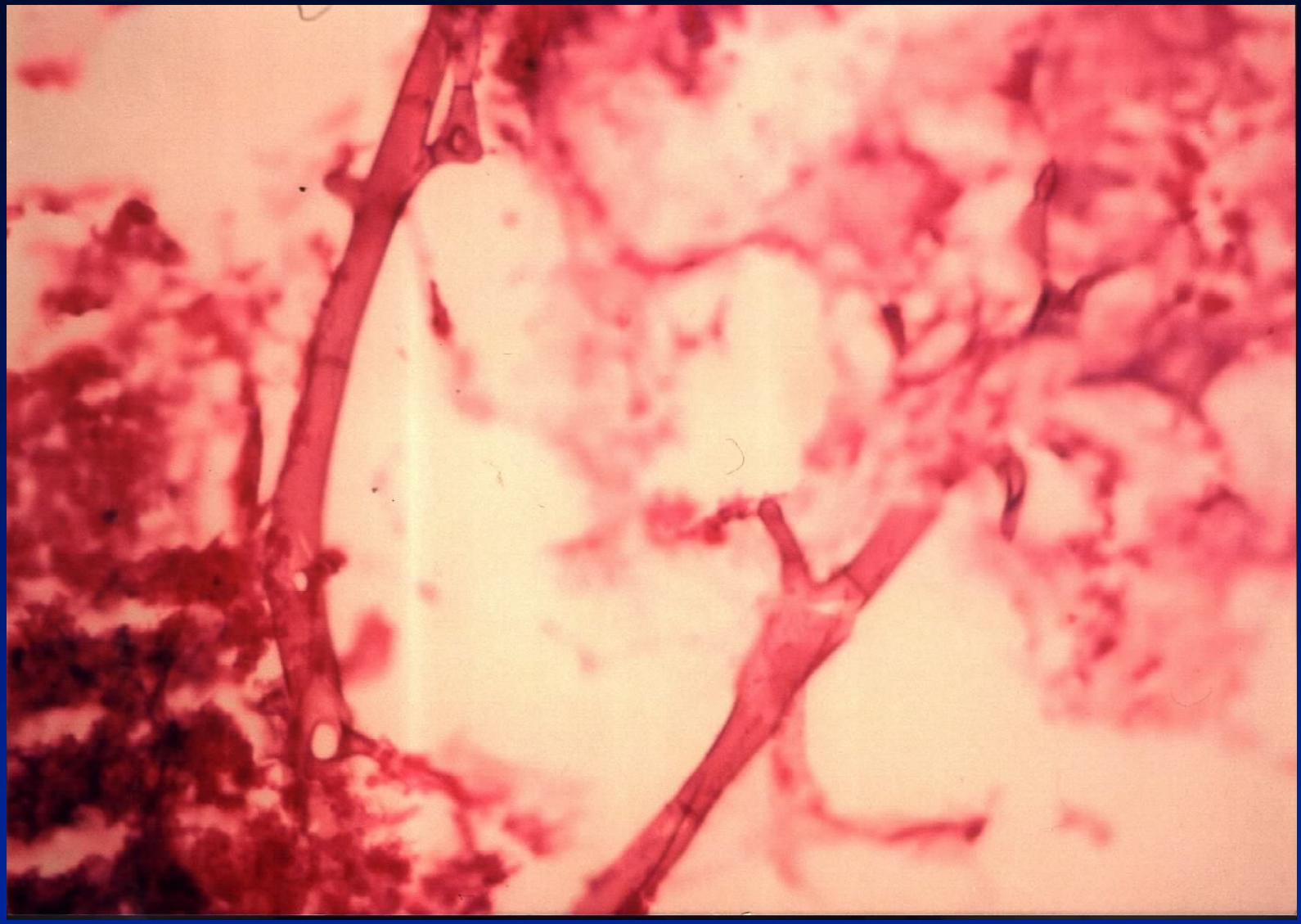

Courtesy of Esin Senol, MD

Zygomycetes

- Members of genera *Rhizopus*, *Mucor*, *Absidia*
- Annual rate in US: 1.7 per million population
  - 0.9-1.9% of all allogeneic BMT recipients
  - Incidence increased through ’90s
- 70-100% mortality
- Rhinocerebral and pulmonary forms are most frequent
  - Cutaneous, gastrointestinal, disseminated

Modified from PrabhuRM, PatelR. Clin Microb Infect 2004;10(suppl. 1):31

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Skin lesions for Mucormycosis

Pre-treatment



After AmB treatment


Aspergillus lesion

Major Risk Factors for Mucormycosis

- Hematological malignancy
- Neutropenia
- Pharmacological immunosuppression
  - Antineoplastic chemotherapy
  - Corticosteroid therapy
  - Antirejection therapy
- PBSC or solid organ transplantation
- Diabetes mellitus
- Deferoxamine therapy
- Burns, trauma, iv drug abuse
- Previous therapy/prophylaxis with antifungals

Modified from PrabhuRM, PatelR. Clin Microb Infect 2004;10(suppl. 1):31

Mucormycosis in Patients with Stem Cell Transplantation

- Voriconazole prophylaxis since May 2003
- 45 patients with PBSCT
  - 4 disseminated/pulmonary mucormycosis (8.9%)
  - 3 invazive aspergillosis (6.6%)
    - None received voriconazole prophylaxis
- Before May 2003
  - No cases with mucormycosis
  - 12% invasive aspergillosis

Siwek GT, et al. Clin Infect Dis 2004;39:584

Mucormycosis in Patients with Stem Cell Transplantation

- September 2002-June 2003
  - 124 PBSCT
  - 4 patients with mucormycosis
  - All patients had Grade II-IV GVHD prior to infection
  - All recieves prophylactic/empirical voriconazole
  - Diagnosis after 21-99 days of voriconazole use
- During 32 months previously
  - 370 PBSCT
  - Only 2 patients with mucormycosis

Marty FM, Cosimi LA. N Engl J Med 2004;350:950

Indicators for Poor Prognosis in Mucormycosis

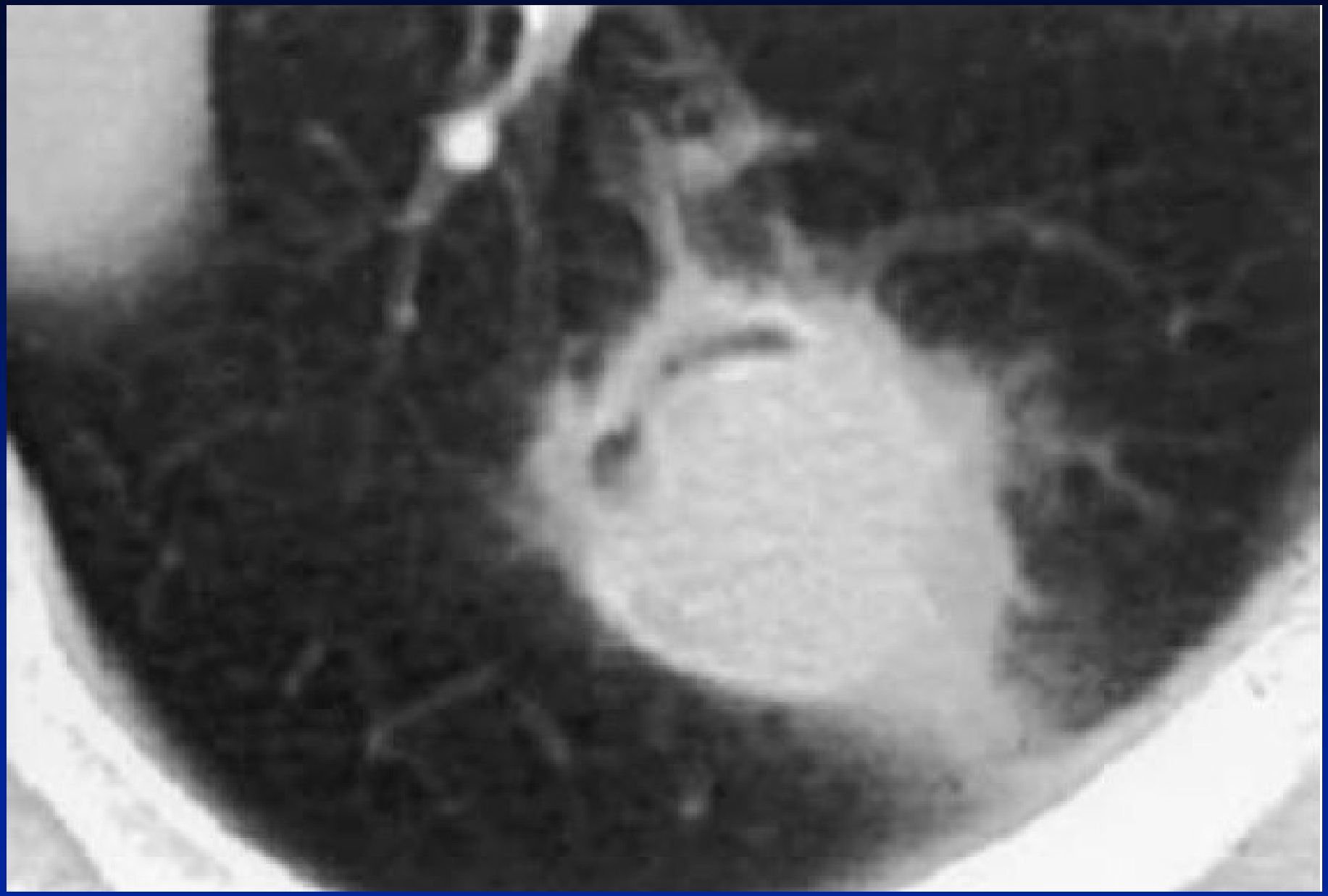
- Delay in therapy (>6 days)
- Symptomatic intracranial involvement with hemiparesis
- Bilateral sinus involvement
- Palatal or orbital involvement
- Underlying leukemia
- Deferoxamine treatment
- Facial necrosis

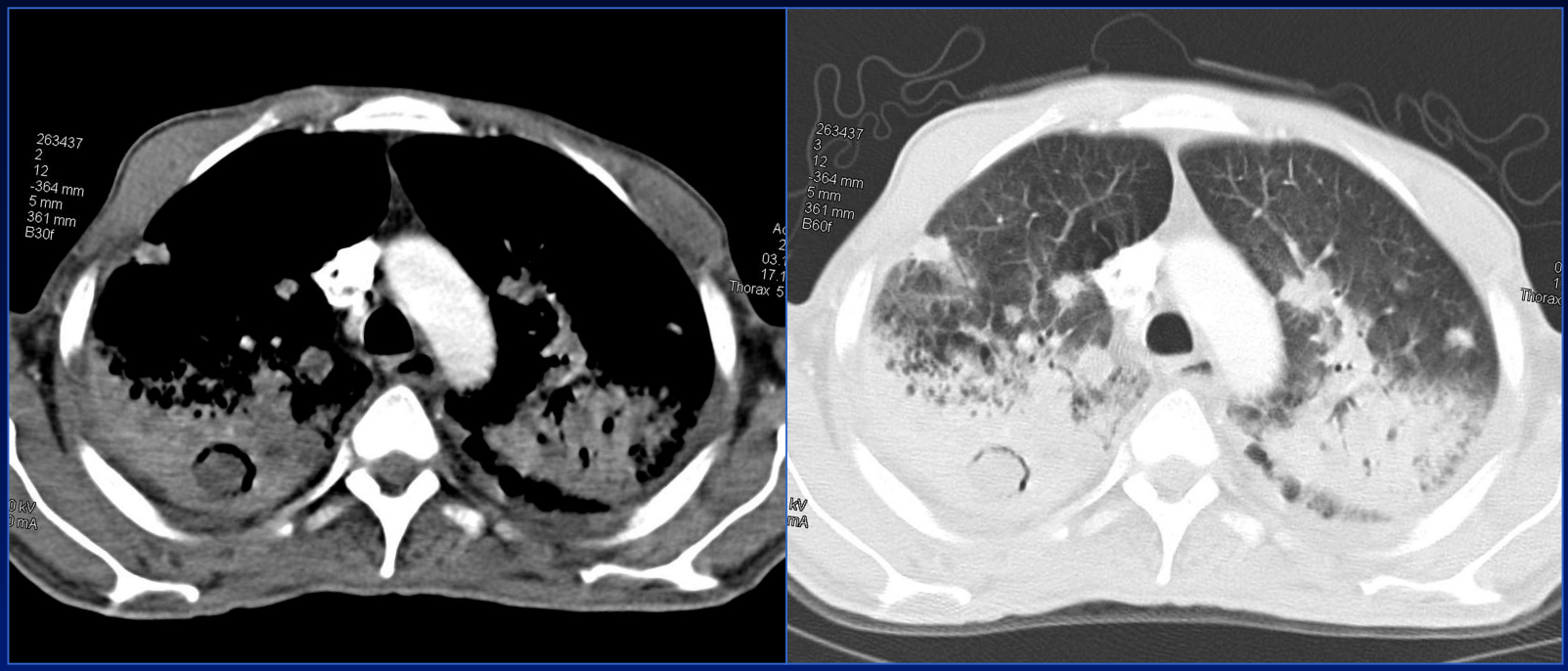
Prabhu RM, PatelR. Clin Microb Infect 2004;10(suppl. 1):31

Pulmonary Mucormycosis

- Similar findings as in pulmonary aspergillosis
  - Clinical presentation
  - Radiological findings
    - Air crescent sign in 12-32% of cases
- Majority of cases have acute leukemia and/or diabetes mellitus
  - Diabetics may have endobronchial lesions

Lehrer RI, et al. Ann Intern Med 1980;9:93
Parfrey NA. Medicine 1986;65:113

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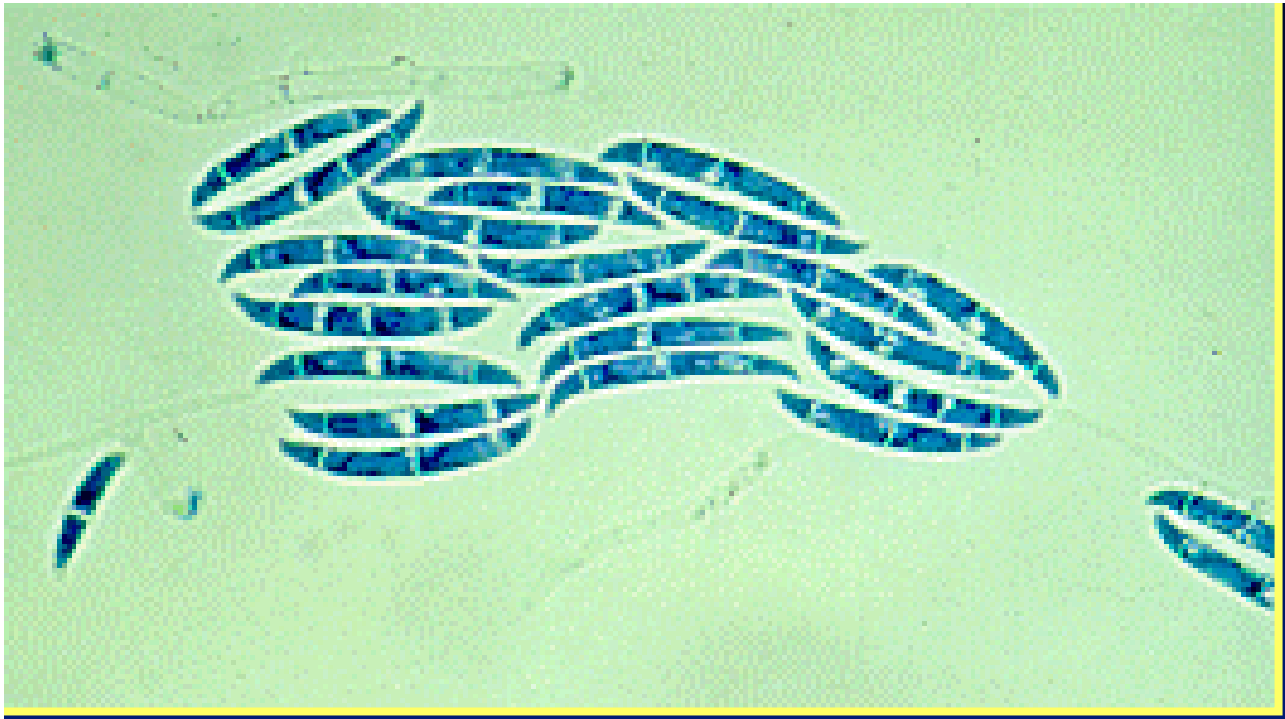
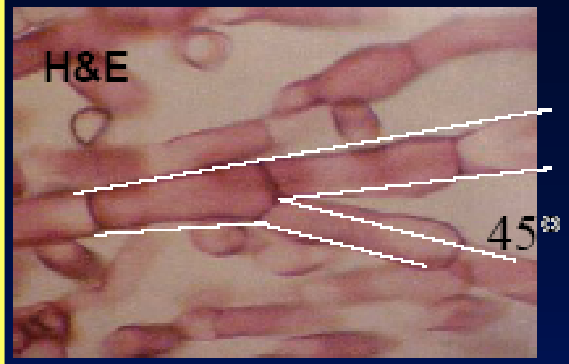
Other Hyaline Molds

- "Hyalohyphomycosis"
  - Non-pigmented, septate, branching filamentous fungi
- May be indistinguisable from *Aspergillus spp.* in tissues
- Causes infections in neutropenics
- Produces spores in tissues with concomitant fungemia and multiple cutaneous lesions
- Less susceptible to systemic antifungals than *Aspergillus spp.*

Walsh TJ, et al. Clin Microb Infect 2004;10(suppl.1):48

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Fusarium and Acremonium spp.

- Exclusively in neutropenics and other types of immunosuppresive patients
- Similar clinical pictures
  - Hematogenous dissemination
  - Nodular skin lesions
- Resistant to Amp B
  - Breakthrough infections during therapy

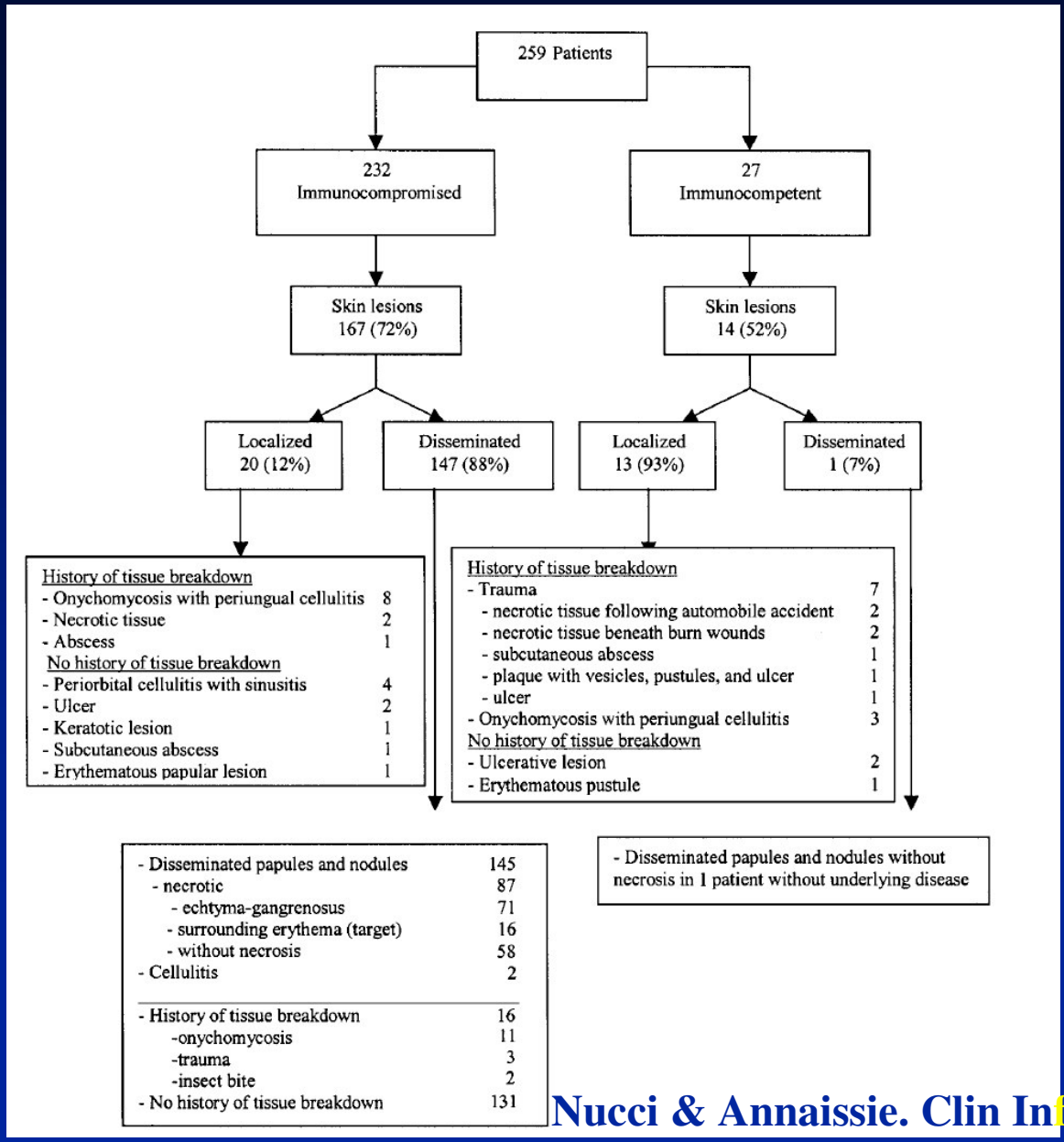
Walsh TJ, et al. Clin Microb Infect 2004;10(suppl.1):48

Fusariosis

- 2nd most frequent filamentous fungal infection in transplant patients
- Fever, pulmonary infiltrates and / or sinusitis
- 40-60% recovered from blood cultures

Walsh TJ, et al. Clin Microb Infect 2004;10(suppl.1):48

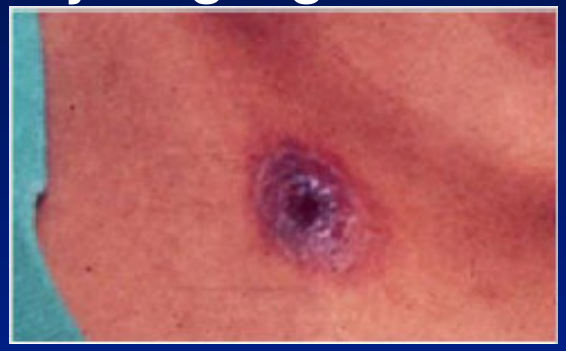
Skin Lesions Caused by *Fusarium spp*.



Nucci & Annaissie. Clin Infect Dis 2002;35:909

Fusarial Skin Lesions in Immunosuppressed Patients

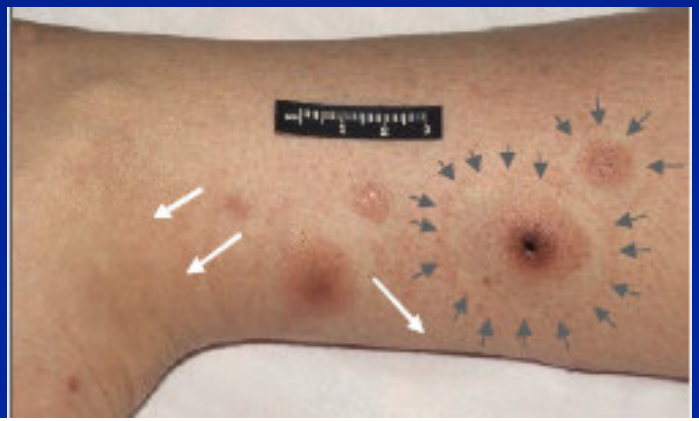
Echtyma gangrenosum



- disseminated
- painful

Multiple lesions

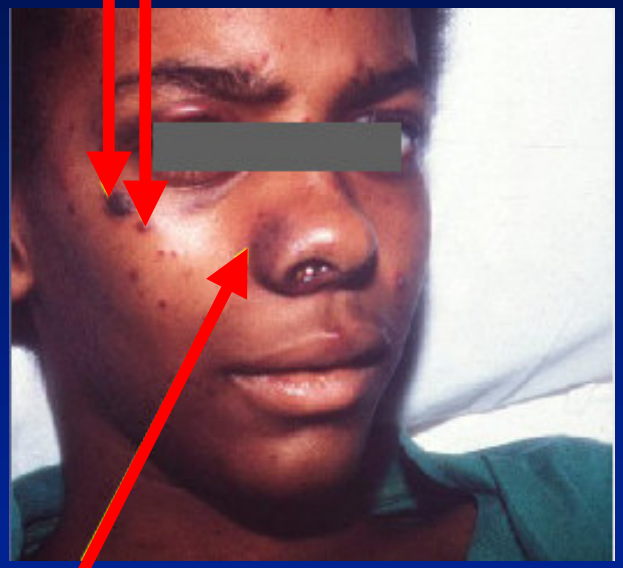
Target lesion



Nucci & Anaissie. Clin Infect Dis 2002; 35: 909

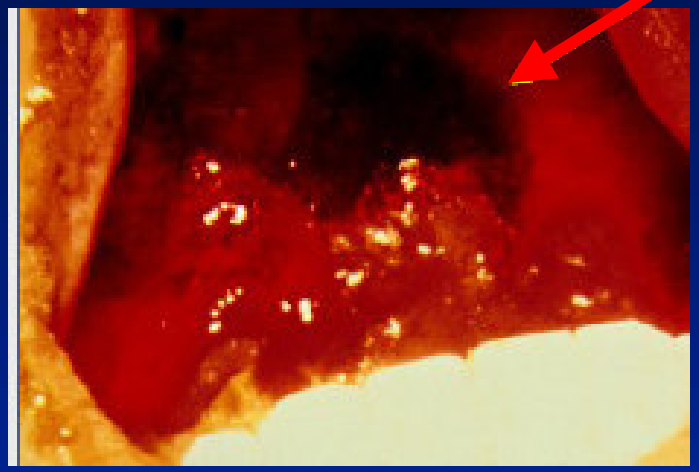
Fusarium: Paranasal Sellulitis and Sinusitis

Papular lesions



Paranasal sellulitis

Necrosis on hard palate



- Similar to aspergillosis
- Usually with disseminated disease

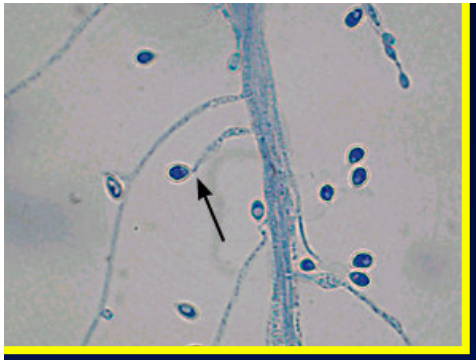
Nucci & Anaissie. Clin Infect Dis 2002; 35: 909

Fusarium Infections: Who, When?

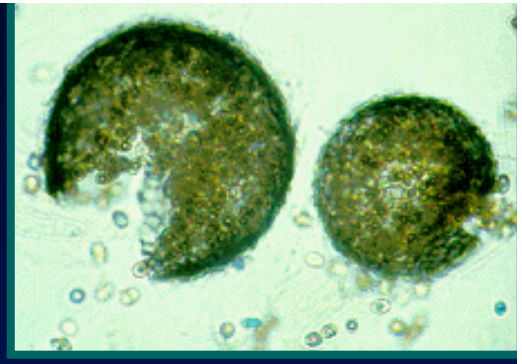
- **Patients with acute leukemia:**
  - **Peristent fever and neutropenia**
- **Patients with HSCT**
  - **GVHD and steroid therapy (non-neutropenics)**

- **Fungemia**
- **Sellullitis**
- **Metastatic skin lesions**

Nucci & Anaissie. Clin Infect Dis 2002; 35: 909



Scedosporium spp.



- ***S. apiospermum (Pseudoallescheria boydii)***
  - **Mycetoma**
  - **Deep tissue abscesses (e.g. brain) in BMT recipients and other neutropenics**
- ***S. prolificans (S. inflatum)***
  - **Bone and soft tissue infections in immunocompetant**
  - **Disseminated infection in immunocompromised**

Walsh TJ, et al. Clin Microb Infect 2004;10(suppl.1):48

Scedosporium Infections in Transplant Recipients

- 80 cases of transplant reicipients
  - 57 solid organ
    - 59% disseminated infecton
  - 23 HSCT
    - 69% disseminated infection
- HSCT recipients were more likely
  - have infections caused by Scedosporium prolificans
  - to have an earlier onset of infection
  - to be neutropenic
  - to have fungemia

Husain S, et al. Clin Infect Dis 2005;40:89

Mycetoma

- After penetrating trauma in immun-competant host
- The drainage from sinus tracts contains ‘grains’ that are microcolonies within a matrix

Dematiaceous Molds

- Phaeohyphomycosis
- Pigmented molds
- Cutaneous infections in immunocompetant host
  - Black pigmented mycetoma
- Disseminated infections in immunocompromised
- Several neurotrophic agents
  - Brain abscesses

Phaeohyphomycosis Presenting as a Cyst

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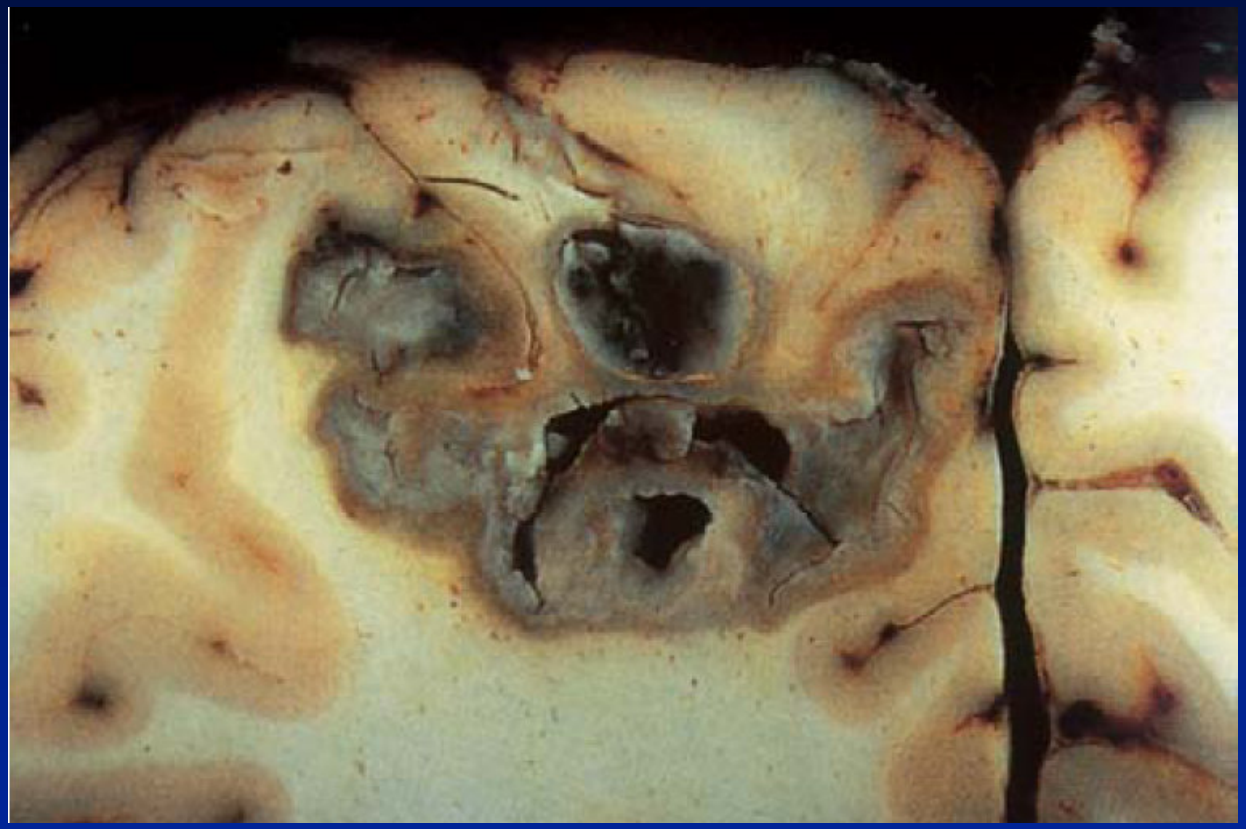
From Chandler FW, Watts JC. Phaeohyphomycosis.
In: Connor DH, Chandler FW, Schwartz DA, et al, eds.
Pathology of Infectious Diseases. Norwalk, CT: Appleton & Lange; 1997

Phaeohyphomycosis of the Brain Caused by Cladophialophora sp.



From Chandler FW, Watts JC. Phaeohyphomycosis.
In: Connor DH, Chandler FW, Schwartz DA, et al, eds.
Pathology of Infectious Diseases. Norwalk, CT: Appleton & Lange; 1997

Conclusions

- Any fungal species found in nature

can cause infection in a compromised host

- Clinical picture may overlap with those

of caused by more common fungi