Introduction

- Fungal and parasitic infections are a somewhat difficult topic to understand beyond the “overview textbook” level due to the
  - *rarity* of most of these infections
  - **selective geographic distribution**
  - tendency of some of the fungal infections to **affect restricted patients groups** with various types of immunocompromising conditions
Selective geographic distribution

Most of the parasites and several of the fungi have predilections to affect individuals only in certain regions of the world or the USA.

**Paragonimiasis**: south east Asia, Philippines, Indonesia, Papua New Guinea

**S. mansoni**: tropical Africa, Saudi Arabia, South America

**S. japonicum**: China, Philippines, Indonesia, Laos

**S. haematobium**: Nile Valley, Africa

**Angiostrongylus cantonensis**: south east Asia, Papua New Guinea, Pacific and Australia

**Histoplasma capsulatum**: Ohio and Mississippi River Valleys

**Coccidioidomyces immitis**: Argentina, Paraguay, Mexico, southwestern USA
Tendency to affect select patient groups

• This translates into understanding the terms “pathogenic” versus “opportunistic”

• Pathogenic= organism has the capability of producing disease in any individual, provided they have INTERACTION WITH, AND EXPOSURE TO, sufficient numbers of organisms

• Opportunistic= organism will only infect patients who have lowered resistance
Opportunistic risk factors go *beyond* AIDS and organ transplantation

Table I. Defects in host defences that predispose patients to infections with specific fungi.

<table>
<thead>
<tr>
<th>Fungal pathogen</th>
<th>Host factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Candida</em> (mucosal)</td>
<td>Impaired cell mediated immunity</td>
</tr>
<tr>
<td><em>Candida</em> (disseminated)</td>
<td>Impaired mucosa or integument, neutropenia</td>
</tr>
<tr>
<td><em>Aspergillus</em></td>
<td>Neutropenia, high-dose corticosteroids</td>
</tr>
<tr>
<td><em>Cryptococcus</em></td>
<td>Impaired cell mediated immunity, corticosteroids</td>
</tr>
<tr>
<td><em>Zygomycetes</em></td>
<td>Neutropenia, deferoxamine treatment, corticosteroids, diabetic ketoacidosis</td>
</tr>
<tr>
<td><em>Fusarium</em></td>
<td>Neutropenia, impaired integument, corticosteroids</td>
</tr>
<tr>
<td><em>Scedosporium</em></td>
<td>Neutropenia</td>
</tr>
<tr>
<td><em>Trichosporon</em></td>
<td>Neutropenia, impaired integument</td>
</tr>
</tbody>
</table>

2005 British Journal of Haematology, 129, 569–582
Taxonomy simplified for the rest of us

What *does* matter is whether fungi are *yeasts* (with or without pseudohyphae) versus *hyphal* forms (with or without septations)

Yeast are NOT vasoinvasive, hyphal forms ARE
## Taxonomy simplified

<table>
<thead>
<tr>
<th>Yeasts and yeast-like fungi</th>
<th>Hyphal and pseudohyphal fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NOT VASOINVASIVE</strong></td>
<td><strong>VASOINVASIVE</strong></td>
</tr>
<tr>
<td>Histoplasma</td>
<td>Candida</td>
</tr>
<tr>
<td>Blastomyces</td>
<td>Aspergillus and look-alikes</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>Zygomycetes</td>
</tr>
<tr>
<td></td>
<td>Fusarium</td>
</tr>
<tr>
<td></td>
<td>Coccidioides (sometimes)</td>
</tr>
</tbody>
</table>
Fungal CNS infections are classic examples of the \textbf{BALANCE} between host and organism.

**HOST**

\textbf{WINNING}

\textbf{Focal confined infection}

\textbf{Yeast}: granuloma

\textbf{Hyphae}: granuloma

**FUNGAL ORGANISM**

\textbf{WINNING}

\textbf{Diffuse infection +/- vasoinvasive lesions}

\textbf{Yeast}: meningitis

\textbf{Hyphae}: meningitis +/- superimposed/ predominant hemorrhagic infarction/cerebritis
Host immune status + Taxonomy simplified
    = pattern of disease
    + morphology*
    = workable classification schema

* H&E, methenamine silver, periodic acid Schiff
(PAS), mucicarmine, [IHC]
Fungal CNS Infections - from P to O*

1. Blastomyces dermatitidis
2. Histoplasma capsulatum
3. Coccidioides immitis
4. Cladosporium trichoides
5. Aspergillus sp. + wannabees
6. Rhizopus sp.
7. Candida sp. + look-alikes

*pathogenic to opportunistic
Blastomyces dermatiditis

- Usually a PATHOGENIC INFECTION
- Epidemiology: predominantly in North America, esp. southeastern USA, lower Mississippi valley, and near southern end of Lake Michigan. Called “Chicago disease” 100 years ago
- Even in endemic areas, incidence of infection is LOW (?under-reported due to lack of national statistics; disease only reportable in 3 states: Illinois, Wisconsin, Mississippi)
- Incidence of CNS infection extremely LOW
Blastomycosis: Contributions of Morphology to Diagnosis

A Surgical Pathology, Cytopathology, and Autopsy Pathology Study

Jerome B. Taxy, MD*†

Abstract: Blastomycosis is caused by the inhalation of spores of the dimorphic fungus, Blastomyces dermatitidis. The reporting of this disease is not required by all states. The diagnosis is established by culture or by identification of broad budding yeast forms in tissue or cytology samples. A retrospective review of blastomycosis was conducted using surgical pathology and cytopathology records of a large community based general hospital, for the years 1982 to 2002; the autopsy records of a university referral center were searched for the years 1992 to 2004. Thirteen surgical/cytology cases were retrieved: 8 localized to the lung (group 1) and 5 with extrapulmonary presentation (group 2). Three of the former were clinically thought to be tumors. Broad-based budding yeast forms with thick cell walls were seen in all but 1 case and identified on conventional routinely stained preparations. Microbiologic culture was positive in 2 lung cases only, in 1 of which it was the sole means of diagnosis. Culture was negative for Blastomyces in the only extrapulmonary case for which a specimen was submitted. One patient in group 2 died, but had a coexistent disseminated gastric adenocarcinoma. No autopsy was performed. Three Great Lakes, lower Mississippi valley, and the Southeast.8,17,21,29 Yet, an accurate national assessment of the occurrence of this disease is unclear because there are no nationally compiled statistics. It is, however, reportable in Illinois, Wisconsin, and Mississippi, where it is alleged to be most common.17,19 In Illinois, from 1990 to 2004, there have been 743 cases reported,7,28 although reporting has been mandatory only since 1994.13

Human disease is initiated by the inhalation of spores aerosolized from the soil or rotting wood.6,11,12,21 Rural and urban watershed areas also appear to be disease repositories.2,16 Some animals, especially dogs, may become ill from this organism; however, this is a feature of a common source of exposure because there is no interspecies transmission. In a host at normal body temperature, the spores transform into yeasts and give rise to lung infection, occasionally occult and subclinical, with the possibility of hematogenous dissemination. Most patients are immune competent and the evolution of blastomycosis from primary infection to spontaneous resolution, localized persistence in the lung, or dissemina-
Blastomyces dermatitidis
Lung-only involvement is most common

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Sex</th>
<th>Symptoms</th>
<th>Imaging</th>
<th>Clinical Diagnosis</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38/F</td>
<td>Fever, cough, left shoulder pain</td>
<td>LUL mass</td>
<td>Tumor</td>
<td>COPD, left basilar scarring (12 y)</td>
</tr>
<tr>
<td>2</td>
<td>6/M</td>
<td>Fever, cough 8 to 10lb weight loss</td>
<td>RUL infiltrate anterior mediastinal mass</td>
<td>Tumor</td>
<td>Ketoconazole, lived by river</td>
</tr>
<tr>
<td>3</td>
<td>49/M</td>
<td>Fever, short of breath</td>
<td>RUL infiltrate</td>
<td>Pneumonia</td>
<td>Itraconazole RUL scarring (29 mo)</td>
</tr>
<tr>
<td>4</td>
<td>82/F</td>
<td>Fever, cough, short of breath</td>
<td>LLL infiltrate</td>
<td>Pneumonia</td>
<td>Itraconazole, amphotericin</td>
</tr>
<tr>
<td>5</td>
<td>46/F</td>
<td>Not known</td>
<td>LLL mass</td>
<td>Tumor</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>60/M</td>
<td>Fever, cough</td>
<td>RLL infiltrate</td>
<td>Pneumonia</td>
<td>Bilateral basilar scars (10 mo); worked in attic Itraconazole</td>
</tr>
<tr>
<td>7</td>
<td>58/M</td>
<td>Abdominal pain</td>
<td>LLL infiltrate</td>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>80/F</td>
<td></td>
<td>RUL infiltrate</td>
<td>Pneumonia</td>
<td></td>
</tr>
</tbody>
</table>

COPD indicates chronic obstructive pulmonary disease; LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RUL, right upper lobe.
Blastomyces dermatididis
Lung-only involvement is most common
Blastomyces dermatiditis

CNS involvement uncommon:
Usually is a localized granuloma with histiocytes and giant cells
Even in disseminated disease, brain is involved in less than 1/3 of patients

<table>
<thead>
<tr>
<th>TABLE 5. Group 3 Autopsy Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>16</td>
</tr>
</tbody>
</table>

Time course for the disease: case 14, 15 d; case 15, 10 d; case 16, 10 d.
BAL indicates bronchoalveolar lavage; Dx, diagnosis; ESRD, end-stage renal disease.
Blastomyces dermatitidis

- Morphology of fungus
  - 8-15 microns
  - Yeast with broad-based bud on GMS, PAS
  - In well-fixed tissues, blastomyces has multiple nuclei
  - Mucicarmine stain yields very thin outline to yeast, unlike broad, thick, mucicarmine +, mucoid capsule of Cryptococcus. Fontana-Masson also is positive on Cryptococcus capsule, but not in blastomyces
Histoplasma capsulatum

- Usually a PATHOGENIC INFECTION, also with lung-only involvement
  - Benign illness confined and localized in lungs and mediastinal lymph notes; at autopsy small calcified nodules may be demonstrated in spleen, liver, and occasionally kidney but NOT CNS
  - Active cavitating pulmonary lesion without CNS involvement
- Epidemiology: US midwest river valleys
- Estimated that 25% of US population has contracted infection, but CNS involvement is uncommon.
- Most common endemic mycosis in North America (followed by coccidiodomycosis and blastomycosis)
Uncommon, localized granuloma in CNS histoplasmosis, as a surgical specimen, mimicking brain tumor in an immunocompetent host
Histoplasma capsulatum

• Occasionally an OPPORTUNISTIC INFECTION, with disseminated disease in immunocompromised patients
  – In infancy and childhood with lymphoreticular involvement and occasional basilar meningitis
  – In adults with caseous nodules in systemic organs and uncommon CNS infection (7%), which, when it does occur, is basilar meningitis
  – Disseminated disease may be AIDS defining illness
Histoplasma capsulatum

• Morphology of fungus
  – 2-4 microns
  – Yeast usually intracellular within macrophages; PAS+ with slight halo around yeast
  BUT yeast does not have a real capsule
  – On H&E appear MUCH SMALLER THAN ON PAS or GMS because only their central portion is visible
Coccidioides immitis

- Usually **PATHOGENIC** infection, occasionally **OPPORTUNISTIC**
- Epidemiology: Argentina, Paraguay, Mexico, southwestern USA
- Pathogenic infection: mild febrile illness followed relatively frequently by lung infection which may be clinically overlooked
- **Predilection for CNS**: Nervous system is involved in 1/3 of cases even in non-immunocompromised hosts
- Large granulomatous lesions rarely described but usually numerous small nodular granulomas occur at base of brain, necrotize and coalesce leading to basilar meningitis (granulomatous + purulent)
- CNS vasoinvasion sometimes occurs
Coccidioides immitis

Basilar meningitis
Coccidioides immitis

- Morphology of fungus:
  - 20-35 micron spherules (sporangia) containing endospores, seen easily on H&E, often in giant cells
  - PAS+ endospores
  - In nature, and exceedingly rarely in CNS, exist as hyphae with arthrospores
Coccidioidomycosis Meningitis With Massive Dural and Cerebral Venous Thrombosis and Tissue Arthroconidia

B. K. Kleinschmidt-DeMasters, MD; Michael Mazowiecki, MD; Lian A. Bonds, MD; David L. Cohn, MD; Michael L. Wilson, MD

To our knowledge we report the first case of meningitis from Coccidioides immitis associated with massive dural and cerebral venous thrombosis and with mycelial forms of the organism in brain tissue. The patient was a 43-year-old man with late-stage acquired immunodeficiency syndrome (AIDS) whose premortem and postmortem cultures confirmed C immitis as the only central nervous system pathogenic organism. Death was attributable to multiple hemorrhagic venous infarctions with cerebral edema and herniation. Although phlebitis has been noted parenthetically to occur in C immitis meningitis in the past, it has been overshadowed by the arteritic complications of the disease. This patient’s severe C immitis ventriculitis with adjacent venulitis appeared to be the cause of the widespread venous thrombosis. AIDS-related coagulation defects may have contributed to his thrombotic tendency. (Arch Pathol Lab Med. 2000;124:310–314)

Coccidioides immitis can be vasoinvasive under the right circumstances

thrombosis in AIDS patients. An additional unique microbiologic aspect to the case was the finding of the mycelial form of the organism within necrotic granulomas in the meninges.

REPORT OF A CASE

The patient was a 43-year-old man with history of injection drug use who was first noted to be HIV positive in 1987, and subsequently he was diagnosed as having oral candidiasis, seborrheic dermatitis, and hepatitis C. He had lived intermittently in Southern California between 1967 and 1974 and in Arizona in 1995. In December 1996 he presented with fever, cough, headache, and abnormal mental status. A chest x-ray film revealed bilateral nodular infiltrates; his CD4 cell count was 0.026 × 10⁶/L and plasma HIV RNA was 258 000 copies/mL. Initial computed tomographic (CT) scan of the head was normal, but a later scan subsequently showed frontal lesions consistent with meningeal inflammation with normal ventricles. Lumbar puncture demonstrated 390 white blood cells with 89% polymorphonuclear leu-
C. immitis in an AIDS patient
Cladosporium trichoides

- PATHOGENIC infection, occasionally OPPORTUNISTIC
- Rare organism that causes multiple brain abscesses
- PIGMENTED (dematiaceous), brown fungus on H&E
- GMS shows budding yeast that elongate into hyphae with rare branching
Aspergillus sp.

- Usually OPPORTUNISTIC infection, only occasionally PATHOGENIC
- When PATHOGENIC, Aspergillosis
  - usually involves **one** organ: lungs, paranasal sinuses, external ear
  - CNS involvement rare as pathogenic infection but has been described as isolated granulomas in immunocompetent patients either from environmental exposure (farmers) or after brain surgery
Aspergillus sp.

• When OPPORTUNISTIC,
  – Usually spreads from lung to brain via bloodstream but rarely may extend directly from paranasal sinuses or orbit
  – Extent of CNS involvement in OPPORTUNISTIC infection ranges considerably from one study to another (60%)
  – Patient risk: steroid use, neutropenia
Central Nervous System Aspergillosis: A 20-Year Retrospective Series

B.K. KLEINSCHMIDT-DEMASTERS, MD

Over the past 20 years at my institution, 71 patients with invasive necrotizing aspergillosis have been encountered; 42 have shown central nervous system (CNS) involvement by autopsy (40) or surgical biopsy (2). Most non-CNS aspergillosis patients had invasive disease confined to the lung, and only 2 with dissemination to 3 or more organs did not have spread to the CNS. In addition to the expected post-transplantation and hematologic malignancy cases, other risk groups identified included those with chronic asthma and steroid use, acquired immunodeficiency syndrome, thermal burn, hepatic failure, and postoperative infection. Unusual cases manifested with basilar meningitis, myelitis, proptosis caused by sino-orbital disease, or epidural and subdural Aspergillus abscesses. The extent of gross neuro-pathologic disease ranged from subtle abscesses to massive hemorrhagic necrosis causing herniation and death. In addition to the expected hemorrhagic necrosis, extensive hemorrhage, focal purulent meningitis, and subtle bland infarctions were also seen. Distinctive microscopic findings encountered included 1 case with numerous meningeal granulomas and multinucleated giant cells and 4 cases showing the Splendore-Hoeplli phenomenon. During the same period, single cases of cerebritis caused by morphologically similar fungi (Pseudoallescheria boydii [Scedosporium apiospermum], Scedosporium inflatum, Chaetomium sp) were identified and were indistinguishable from CNS aspergillosis clinically and pathologically. HUM PATHOL 33:116-124. Copyright © 2002 by W.B. Saunders Company

Key words: fungal, aspergillosis, Scedosporium, Pseudoallescheria, Chaetomium.

Abbreviations: CNS, central nervous system; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.
Spectrum exists from bland infarction due to vaso-occlusion to vaso-invasion with hemorrhagic cerebritis/abscesses;

Within immunocompromised patients, DEGREE OF IMMUNOCOMPROMISE plays a role in DEGREE OF INVASIVENESS OF THE ORGANISM.
Hemorrhagic cerebritis from Aspergillus sp. in renal transplant recipient
Aspergillus sp

**Morphology:**

- Hyphae seen on H&E as radiating in corona-like fashion away from central thrombosed & destroyed blood vessel. Organism capable of selectively destroying internal elastic lamina of cerebral vessels.
- Septate hyphae manifest uniform, acute angle (45 degree angle) dichotomous branching.
- In tissues, especially CNS, hyphae may be distorted and bulbous, simulating other fungi such as Rhizopus sp.
- Septations best seen on PAS.
- GMS stain may be overly dark.
Recognizing the role of the immune status of host makes *further sense* because it influences…

- the frequency of infection from various genus members within the same fungal species (ie., *A. fumigatus* vs. *A. terreus*)
Aspergillus sp.

- Most infections due to **A. fumigatus**, followed by **A. flavus**
- Recently **A. terreus** has emerged as a pathogen in patients with solid tumors, especially those that involve the brain
- Invasive aspergillosis is distinctly uncommon in patients with solid tumors, occurring in less than 1% of patients
- Characteristic risk factors of **profound and prolonged neutropenia** seen in hematologic cancer patients are not major risk factor in solid tumor patients
- In patients with solid tumors, **corticosteroid use and lymphopenia** are dominant risk factors
- In a small reported patient cohort, 7 of 13 patients (54%) with invasive aspergillosis had either a primary or metastatic brain tumor as the underlying solid malignancy (*Probably related to the large number of brain tumor patients requiring prolonged high dose corticosteroids for control of symptomatic peritumoral edema*)
- In series, 3 patients had aspergillosis brain infections and in 2 patients the isolated Aspergillus species was **A. terreus**.
A. Terreus
ILLUSTRATIVE CLINICAL HISTORY

- 60 year old female diagnosed 6 months previously with left temporal lobe GBM.
- Initial treatment for the primary brain tumor consisted of gross total surgical resection with Gliadel® wafer placement, external beam irradiation, and two cycles of temozolomide.
- Patient developed hallucinations and excess drowsiness; CT of chest showed multifocal lung opacities.
- 2 new brain lesions Interpreted as recurrent tumor; biopsy showed Aspergillus sp.; culture proven A. terreus.
- Patient succumbed 6 days later.
Aspergillus look-alikes

- Cannot distinguish different Aspergillus species members
- Pseudoallescheria boydii (Scedosporium apiospermum), Scedosporium inflatum, Chaetomium sp. are look-alikes
  - rarer than Aspergillus infections in the CNS
  - indistinguishable clinically and pathologically
  - Proven by culture methods only
  - almost exclusively OPPORTUNISTIC infections
Fusarium infections of CNS

- Another Aspergillus look-alike
- Epidemiology: soil saprophyte
- PATHOGENIC infection best documented in contact lens wearers
- Rare CNS/ disseminated infections exclusively OPPORTUNISTIC
- Morphology:
  - hyphal
Zygomyces sp.

- Almost exclusively OPPORTUNISTIC infection in CNS
- Epidemiology: classic emphasis on diabetic ketoacidosis, but also other acidotic or immunocompromised patients
- Rhizopus >>> Mucor >>> Absidia
- Infection usually due to direct extension from infected nasal or paranasal infections, via the orbit, NOT pulmonary infection
Zygomycetes sp.

- Classic presentation: thrombosis of large cerebral vessels at base of brain, with subfrontal bland infarctions
- Another vasoinvasive organism but in diabetics with ketoacidosis the organism is less invasive and vessel destructive (i.e., vessels are thrombosed but not destroyed, yielding infarcts)
- Need to sample Circle of Willis vessels
Zygomycetes sp.

from JJ Kepes
Zygomycetes infection: case history

72 year old male with poorly differentiated lymphoma, who 10 days after receiving his last chemotherapy developed transient right arm paralysis. On admission he was pancytopenic, hyperglycemia, acidotic, febrile, and had a pleural effusion. Despite aggressive measures, he succumbed 10 days after admission. Both brain and lung infections were identified at autopsy.
Zygomycetes sp.

- **Morphology:**
  - Broad hyphae 10-15 microns in diameter
  - Hyphae partially collapsed and distorted or twisted. Look almost artefactual on PAS, GMS
  - Folds may simulate septations
  - Branching irregular, in contrast to Aspergillus
  - Cross sections of large hyphae should not be mistaken for empty spherules of Coccidioides
Cryptococcus neoformans

- Almost exclusively OPPORTUNISTIC infection in CNS
- Epidemiology: most common mycosis in AIDS patients; constitutes initial symptom of AIDS in up to 26% of patients in older series
- Severely immunocompromised patients: diffuse meningitis, with absent host inflammatory response
- Localized infections (cryptococcomas) can be seen in some patients
Cryptococcus neoformans

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- Epidemiology: most common mycosis in AIDS patients; constitutes initial symptom of AIDS in up to 26% of patients in older series
- Severely immunocompromised patients: diffuse meningitis, with absent host inflammatory response
- Localized infections (cryptococcomas) can be seen in some patients
Cryptococcus neoformans

- **Morphology:**
  - 4-7 micron diameter yeast surrounded by 3-5 micron thick capsule (best seen on India ink preparation)
  - PAS and GMS show small budding yeasts; buds have short, narrow neck
  - Abundant capsule can form soap-bubble like lesions in tissue
  - Both cell wall and capsule stain with mucicarmine except in old, fibrotic, caseous, or poorly fixed tissues, when the carminophilic staining is lost
  - Small forms overlap with Histoplasma, large with Blastomyces. Distinction comes with recognizing the thick uniform capsule on mucicarmine stain
Candida sp.

- Always OPPORTUNISTIC INFECTION
- Epidemiology: normal gut flora that emerges as pathogen in patients with prolonged antibiotic therapy, abdominal operations, catheters, diabetes, drug abuse, pediatric necrotizing enterocolitis
- CNS lesions usually occur late in disseminated disease
- Corollary: Candidia infection is one of most common CNS fungal infections found at autopsy examination
Candida sp.

- **Morphology:**
  - Pseudophyphae and chains of oval budding yeast 2-3 microns
  - Vaso-invasive organism; hence CNS morphology is that of hemorrhagic infarcts, numerous hemorrhagic necrotic lesions, and often little host immune response
Candida look-alikes

- Torulopsis (Candida) glabrata
- Rhodotorula

*distinguishable only by culture*
Conditions simulating fungal infection

• Nocardia and actinomyces infections of CNS
  – Caused by bacteria with branching, filamentous, THIN, appearance
  – Both are uncommon infections, but nocardiosis >> actinomycosis in frequency
Actinomycosis

- Actinomycosis usually PATHOGENIC infection
- Organisms normally exist in oral cavity or large intestine
- Patient may have cervical-facial, thoraco-abdominal, or dental infection
- CNS infection results from hematogenous spread or direct extension from cervical-facial infected focus
- Gram +, “sulfur granules” (cohesive bacterial aggregates) in pus
Nocardiosis

- Nocardiosis SHARES with most CNS fungal infections:
  - Ubiquitous organism
  - Pulmonary lesions (which may be clinically inconspicuous or resolved at the time of CNS disease
  - Hematogenous spread to brain
  - Almost always an OPPORTUNISTIC INFECTION seen in severely immunosuppressed hosts: cancer patients, transplant recipients, AIDS
  - Ability to produce meningitis, abscesses or both
Nocardiosis: case history

57 year old male with mantle cell lymphoma, S/P autologous bone marrow transplant, followed by peripheral stem cell transplant which was complicated by graft versus host disease. The patient was found to have a right cerebellar mass, an abnormality in the right temporal lobe, and leptomeningeal enhancement by MRI; this was presumed to be involvement by his lymphoma and he was given whole brain radiation.
Several days later he had a seizure and CT of the chest revealed multiple pulmonary nodules. He had a downhill course, developed a pontine infarction & hydrocephalus, necessitating placement of an external ventricular drain. He succumbed 4 months after admission. Autopsy was performed.
Nocardia and Actinomyces

- **Morphology:**
  - Both nocardia and actinomyces are very thin; acid fast stain is supposed to differentiate the two but isn’t always that clear cut; culture is definitive
  - Gram stain +; GMS positive (improved with double length staining)
Summary of CNS fungal infections

- SOIL (except Candida)
- LUNG/BLOOD/BRAIN (except Rhizopus)
- P to O spectrum: Blastomycosis (Y); Histoplasmosis (Y); Coccidioidomycosis (Y+ rare H); Cladosporiosis (H); Cryptococcosis (Y); Zygomyces (H); Candidiasis (H)
- Yeast vs. hyphal = pattern of CNS disease: granulomas as localized infections, meningitis +/- infarction/hemorrhagic cerebritis in diffuse severe infections
CNS Parasitic infections

Classification problems *again*…

Classic taxonomy:
- Metazoal infections
  - Nematodes
  - Trematodes
  - Cestodes
- Protozoal infections
  - Amebiasis
  - Cerebral malaria
  - Toxoplasmosis
  - Trypanosomiasis
CNS Parasitic infections simplified

• All geographically relatively restricted

  **EXCEPTIONS:** cysticercosis, toxoplasmosis, and toxocariasis which are worldwide

• Comes down to
  – Roundworms with wandering larvae/worms (nematodes)
  – Flat flukes with wandering egg-layers (trematodes)
  – Tapeworms with wandering larvae (cestodes)
  – Protozoa with cellular size/intracellular location

• Pathogenic to opportunistic range, just like fungi
  – All worms and flukes, and most protozoa, are P
  – Trypanosomiasis and toxoplasmosis P and occ. O
Nematodes (roundworms and filiaria)

*Toxocara canis* (visceral larval migrans important for **ocular/retinal infection**)

*Trichinella spiralis* usually affects skeletal muscle

*Onchocerca volvulus* causes blindness in Africa

*Angiostrongylus cantonensis* (rat lung worm) Far East, classically causes eosinophilic meningoencephalitis

*Strongyloides* very rarely reported in immunosuppressed patients with suppressed cell-mediated immunity

*Loa loa* subcutaneous and subconjunctival migration of adult worm

**SKIP THE ROUNDWORMS, not because of geography but because of infrequent CNS disease**
CNS Metazoal infections: trematodes (flukes)

- Schistosomiasis and paragonimiasis seen in Africa or Asia
- Paragonimiasis is lung fluke, Schistosomiasis is blood fluke. Mature flukes rarely seen in CNS
- Disease occurs when EGGS are deposited in CNS tissues by wandering flukes, eliciting granulomatous reaction
Paragonimiasis
Schistosomiasis

Histology image from: Scope Monograph of Pathoparasitolgy Color Atlas, Michael Kenney, MD ©1973
Schistosomiasis
CNS Metazoal infections: cestodes

Cestodes (Tapeworms)

Echinococcus granulosus
(Hydatid disease)

Cysticercus cellulosae
(neurocysticercosis)

Key features: adult tapeworm is not the problem, the immature form is

Echinococcus:
- dog is definitive host; adult tapeworm is in dog intestine
- infection of man is from contamination of food by dog feces, frequent intimate contact with dogs + poor hygiene
- Brain cyst (3% patients) usually solitary, unilocular, cerebral hemispheres

CNS Metazoal infections: cestodes

- Cysticercosis is complicated by the fact that 2 diseases are possible in MAN:
- The pig tapeworm *Taenia solium* remains intestinal in MAN
- the larval stage *Cysticercus cellulosae* infects multiple systemic organs in MAN, the most important of which is the BRAIN
Lifecycle

Adult tapeworm

Cysticercus in muscle

Ingestion of infected pork, poorly cooked: Taeniasis

Human being (Definitive host)

Ingestion of T. solium eggs by faecal contamination: Human cysticercosis

Ingestion of T. solium eggs or proglottids: Porcine cysticercosis

Pig (Intermediate host)
Taeniasis

- An intestinal infection with the adult stage of large tapeworms
- May develop nervousness, insomnia, anorexia, weight loss, abdominal pain, digestive disturbances
- “except for the annoyance of having segments of worms emerging from the anus, many infections are asymptomatic”
- Cysticercosis
Systemic disease = cysticercosis

- Parasite can be found in brain, muscle, eyes or skin
- How the organism avoids the host immune system is largely unknown
  a) cyst with scolex in eye,
  b) calcifications on CT,
  c) MRI,
  d) pseudohypertrophy
Neurocysticercosis

Epidemiology

- The most common parasitic CNS infection: 50 million people infected
- In certain areas, up to 46% of population is seropositive and 18% have calcifications on CT
- NCC causes of 10% of new seizures in areas of Los Angeles and 6% in Albuquerque
Most cases seen in the US are import cases
Estimated that up to 1000 new cases in US per year
A striking example is an outbreak in a orthodox Jewish community in New York in 1990
CNS Parenchymal infection

- The cysticercus develops a cyst ~10 mm with a thin wall and a scolex formation. No significant immune response.
- After several (3-30) years, the cyst starts degenerating. Wall thickens due to inflammation. Cyst fluid becomes denser.
- The cyst shrinks with an increasing surrounding immune response. This can take months to years.
- Finally, the cyst resolves and is often replaced by a small calcification.
Diagnosis

Radiology

- Scolex is pathognomonic
- Viable cysts are non-enhancing, degenerating are enhancing
- Calcifications
Ventricular infection

- Normally unattached and can occasionally move between ventricles
- Most frequently located in the fourth ventricle, followed by the third
- Can block circulation of cerebrospinal fluid
CYSTICERCOSIS
CYSTICERCOSIS
CYSTICERCOSIS
CNS Protozoal infections: Ameba

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<th>• Entamoeba histolytica</th>
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<td>• Primary amebic encephalitis</td>
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<td>– Naeglia fowleri</td>
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<td>• Granulomatous amebic encephalitis</td>
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<td>– Acanthamoebia</td>
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Ameba

- **Entamoeba histolytica**
  - Spread to brain via hematogenous route from liver or lung
  - CNS involvement rare; meningoencephalitis in 1-2% of fatal cases
  - Trophozoites 15-25 microns, cysts are up to 25 microns and spherical with 4-8 nuclei

- **Naegleria fowleri**
  - Free living waterborne ameba affecting previously healthy children and young adults esp. in summer and autumn months; swimming in warm lakes or pools
  - Protozoa enter CNS through nasal mucosa and cribriform plate
  - Trophozoites 10-20 microns; cysts never seen in tissues due to rapidly fatal course in patient

- **Granulomatous amebic encephalitis (Acanthamoeba/Balamuthia)**
  - Trophozoites 15-45 microns; cysts 15-20 microns with wrinkled double wall
6 dead this year from brain-eating bug

By Chris Kahn
The Associated Press

PHOENIX» It sounds like science fiction, but it's true: A killer amoeba living in lakes enters the body through the nose and attacks the brain, where it feeds until you die.

Even though encounters with the microscopic bug are extraordinarily rare, it has killed six boys and young men this year.

The spike in cases has health officials concerned, and they are predicting more cases.

“This is definitely something we need to track,” said Michael Beach, a specialist in recreational waterborne illnesses for the Centers for Disease Control and Prevention.

“This is a heat-loving amoeba. As water temperatures go up, it does better,” he said. “In future decades, as temperatures rise, we'd expect to see more cases.”

According to the CDC, the amoeba Naegleria fowleri killed 23 people in the United States from 1995 to 2004. This year, health officials noticed a spike with six cases — three in Florida, two in Texas and one in Arizona. The CDC knows of only several hundred cases worldwide since its discovery in Australia in the 1960s.

In Arizona, David Evans said nobody knew his son, Aaron, was infected with the amoeba until after the 14-year-old died Sept. 17. At first, the teen seemed to be suffering from nothing more than a headache.

“We didn't know,” Evans said. “And here I am: I come home, and I'm burying him.”

After doing more tests, doctors said Aaron probably picked up the amoeba a week before while swimming in the balmy shallows of Lake Havasu, a popular man-made lake on the Colorado River.

Though infections tend to be found in Southern states, Naegleria lives almost everywhere in lakes, hot springs, even dirty swimming pools, grazing off algae and bacteria in the sediment.

Beach said people become infected when they wade through shallow water and stir up the bottom. If someone gets water up the nose, the amoeba can latch onto the olfactory nerve. It destroys tissue as it makes its way up into the brain, where it continues the damage, “basically feeding on the brain cells,” Beach said.

Once infected, most people have little chance of survival.

Beach cautioned that people shouldn't panic about the dangers of the brain-eating bug. Cases are extremely rare, considering the number of people swimming in lakes. The easiest way to prevent infection, Beach said, is to use nose clips when swimming or diving in fresh water.

“You'd have to have water going up in your nose to begin with” to be infected, he said.
Ameba
12 year old male who had lived in Mexico until approximately 1 year prior to onset of medical problems. He first presented 1 ½ weeks prior to admission with severe emesis which persisted for 3 days and necessitated a visit to the ED at a hospital on the Western Slope of Colorado. He was given antibiotics and discharged. Following this he developed diplopia, difficulty walking, and aphasia. An EEG was scheduled for possible petit mal seizures, but during the procedure he had a grand mal seizure, with persistent altered mental status. MRI scan was performed which showed 9-12 ring-enhancing lesions and severe edema. CXR normal. Transferred for biopsy; died soon thereafter.
GROSS BRAIN EXAMINATION
HISTOLOGICAL EXAMINATION
Balamuthia mandrillaris

- Children 4 months to 23 years affected by free living soil ameba, immunodeficiency has not clearly played a role in pediatric cases versus adults
- Can be definitively differentiated from Acanthamoeba only by antibodies
- Responsible for sporadic meningoencephalitis with mortality rates near 100%
- 2001: About 200 cases reported worldwide.
- Spreads hematogenously from cutaneous, ocular, or pulmonary lesion to the CNS
- In CNS, vasculitis dominates clinical picture
- Death within 6-8 weeks of diagnosis
CNS Protozoal infections: Malaria

- CNS involvement seen with only one species, *Plasmodium falciparum*
- Mortality in some parts of the world 20-50%, especially infants and children
- Well-nourished individuals more susceptible than malnourished ones in Africa, related to body iron status
- Infection common in pregnancy, possibly related to relative immunosuppression
- Steroid administration predisposes to severe infection: A TOUCH OF O
CNS Protozoal infections: Trypanosoma brucei & cruzi

- **African T. brucei**
- **South American trypanosomiasis** (Chagas disease) commonly involves autonomic nervous system, cause of the underlying megasyndromes. Protozoa has proclivity for infecting muscle
  - CNS involvement clinically not common
  - Acute form of disease occurs in children under age 1 yr.; protozoa infects astrocytes and endothelium of cerebral blood vessels
  - Chronic form occurs in 10% of cases
  - Disease well known to be severe in patients with AIDS and as a congenital disease, underscoring P+O biology of some protozoa
cysticercosis, toxoplasmosis, and toxocariasis are worldwide

- Roundworms with wandering larvae/worms *(Toxocariasis)*
- Flat flukes with wandering egg-layers *(Schistosomiasis)*
- Tapeworms with wandering larvae *(Cysticercosis)*
- Protozoa with cellular size/intracellular location *(Malaria, Toxoplasmosis)*

- Pathogenic to opportunistic range, just like fungi
- All worms and flukes, and most protozoa, are P
- Trypanosomiasis and toxoplasmosis P and occ. O