Fungal Rhinosinusitis

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Disclosures

None
Microbes causing Infectious Rhinosinusitis

**Bacteria**
- Prokaryotic
- Single cell
- Reproduce per fission

**Fungi**
- Eukaryotic
- Multi-cellular (except yeast)
- Reproduce sexual/asexual
Fungal Rhinosinusitis

- 20,000 fungal species identified
- About 300 are pathogenic in humans
- At least 24 have been implicated in fungal rhinosinusitis
### Table 1. SOME FUNGAL GENERA AND SPECIES IMPLICATED IN FUNGAL RHINOSINUSITIS

<table>
<thead>
<tr>
<th>Category</th>
<th>Genera</th>
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<tbody>
<tr>
<td>Zygomycetes</td>
<td>Absidia</td>
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<tr>
<td></td>
<td>Cunninghamella</td>
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<td>Mucor</td>
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<td></td>
<td>Rhizomucor</td>
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<td>Rhizopus</td>
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<td>Hyaline moulds</td>
<td>Aspergillus</td>
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<td>Blastomyces dermatitidis</td>
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<td>Chrysosporium</td>
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<td>Fusarium</td>
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<td>Paecilomyces</td>
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<td>Penicillium</td>
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<td>Pseudallescheria boydii</td>
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<td>Scedosporium</td>
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<td>Scopulariopsis</td>
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<td>Dematiaceous moulds</td>
<td>Alternaria</td>
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<td>Bipolaris</td>
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<td></td>
<td>Cladosporium</td>
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<td>Curvularia</td>
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<td></td>
<td>Exserohilum</td>
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<td>Ascomycetous yeasts</td>
<td>Candida</td>
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<tr>
<td>Basidiomycetes</td>
<td>Coprinus</td>
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<tr>
<td></td>
<td>Cryptococcus neoformans</td>
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<td></td>
<td>Schizophyllum</td>
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<td>Ustilago</td>
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Pathophysiology of Fungal RS

• Exact mechanism unknown
• Fungal spores are ubiquitous
• Normal nasal physiology typically clears fungi
• Situations that alter this physiology or the immune system may lead to infection
Approach to Diagnosis

• Clinical observation

• Laboratory and histopathology

• Radiologic testing
Histopathologic Exam

- Must obtain adequate tissue
- Collect aseptically
- Fresh specimen rapid transport
- Notify pathologist of possible fungus
Light Microscopy

• Sine qua non of fungal detection is identification of a cell wall
• KOH±calcofluor
  • Increases recognition with UV illumination
• Gram stain
  • Does not stain cell wall well
Histologic Testing

- Takes longer to perform
- H&E Stain
- Gomori Methenamine Stain (GMS)
- Periodic Acid-Schiff Stain
- Fontana Masson Stain
Fungal Morphology in RS

- Fungi can grow as molds or yeasts
- Nasal pathogens can be broken down into three categories of molds
  - Zygomycosis
  - Hyalohyphomycosis
  - Phaeohyphomycosis
- Important to view width, branching, and septations
Fungal Culture

- Unreliable
  - May be positive up to 50% of time
  - Sabourand’s agar
- Ponikau et al (1999)
  - Able to culture fungi in 91% of patients with chronic rhinosinusitis
- Must use clinical judgment
Classification of Fungal RS

- Non-invasive
  - Allergic Fungal Rhinosinusitis (AFRS)
  - Mycetomas
- Invasive
  - Acute fulminant invasive
  - Chronic invasive
  - Granulomatous invasive
Allergic Fungal Rhinosinusitis (AFRS)

History
- 1971 McCarthy and Pepys
  - 10% ABPA pts expectorated nasal plugs
- 1981 Milar
  - 5 cases in which sinus contents were similar to the bronchial mucus plugs of ABPA
  - “allergic aspergillosis of the paranasal sinuses”
Allergic Fungal Rhinosinusitis

- Clinical features
  - Probably underdiagnosed (7% CRS surgery)
  - Consider in young, atopic individuals that have intractable sinus disease that has failed both medical and surgical therapy
  - Patients are hyperimmunocompetent
  - Nasal polyps
Allergic Fungal Rhinosinusitis

• Clinical features
  • Young patients usually 20’s-40’s
    • Kupferberg et al, 10 children with AFRS
    • Youngest age reported is 6
  • No male/female predilection
  • “hot spots” for disease are warm humid areas
  • May have had previous sinus surgery, asthma treatment, immunotherapy
AFRS Pathophysiology

- Non-invasive disease associated with allergic mucin
- Allergic Hypertrophic Rhinosinusitis Model (Schubert et al 2000)
- Pts are atopic
Allergic Hypertrophic RS Model

- Starts with allergen initiating the cascade
- Mucosal hypertrophy and hyperplasia perpetuate anatomic obstruction which leads to a chronic cycle
Allergic Hypertrophic RS Model

- AFRS organism may enter the obstructed sinuses and then stimulate an intense fungal Type I rxn, worsening the cycle.
- The organism may stimulate the initial Type I rxn in an atopic pt.
AFRS Pathophysiology

- Much of what is known is due to similarity to ABPA (ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS)
  - Type I and III Gel and Coombs hypersensitivity
  - ABPA can be diagnosed with specific elevated IgE and IgG to Aspergillus
- Most of AFRS fungi are not available
- Total serum IgE and IgG are usually elevated
AFRS History and Physical

- Similar to findings of chronic RS
- 75% patients will describe expelling casts
- On endoscopic exam will see mucosal hypertrophy, polyps, and may see allergic mucin
- May see proptosis
- Children may have hypertelorism
AFRS Clinical Features
Histopathology

- “Allergic Mucin”
  - Brown or greenish-black material with the consistency of peanut butter
  - Accumulation of intact and desquamated eosinophils (Charcot-Leyden crystals), cellular debris and sparse hyphae
Allergic Mucin
Charcot-Leyden Crystals
Allergic Mucin
Histopathology

- Adjacent mucosa with inflammatory rxn
- Mucus glands hypertrophied and distended
- No evidence of invasion into mucosa, submucosa, vessels, or bone
- No intradural or intraorbital extension
- Special stains and cultures
- Most commonly isolated is *Bipolaris*
Diagnostic Criteria

- Bent et al
- 1. Type I hypersensitivity
- 2. Nasal polyps
- 3. Characteristic CT findings
- 4. Positive fungal stain or culture
- 5. Allergic mucin with fungal elements and no invasion
Suggested Work-Up For AFRS

- Total Eosinophil count
- Total Serum IgE
- Antigen specific IgE (skin test or RAST)
- Fungal antigen specific IgG (if available)
- Precipitating antigens (if available)
- Micro exam of mucin
- Fungal culture of mucin

• Houser et al 2000
AFRS Radiology

- CT usually shows area of increased attenuation
- Areas likely due to heavy metals, calcium, and/or dried secretions

Fig. 1. Coronal computed tomography (CT) scan of patient 2 showing opacification of the left maxillary and ethmoid sinuses. Note the erosion of the medial orbital wall and hyperattenuation.
Fig. 1. Patient 1 with expansile sphenoid disease. CT demonstrates speckled pattern of high attenuation on both soft-tissue (A) and bone windows (B). Noncontrast.
AFRS Treatment

- Treatment options
  - Surgery
  - Antifungals
  - Oral steroids
  - Immunotherapy
  - Adjunctive therapies
AFRS Treatment

- Bent et al
  - Successful therapy depends upon
    - Surgically debriding patient of fungal antigens, allergic mucin, and irreversibly damaged mucosa
    - Preventing recurrent fungal growth and colonization
    - Modifying the pathological immune response
AFRS Treatment

• Surgical Goals
  • Complete removal of allergic mucin and fungal debris
  • Impart drainage and ventilation to the affected sinuses while preserving the mucosa
  • Allow for post-op access to previously diseased area
AFRS Treatment

• Surgery
  • Endoscopic vs. open
  • Maybe difficult anatomy (localization useful)
  • Incomplete removal of disease leads to faster recurrence
AFRS Treatment

- Antifungal therapy
  - Do not reach concentrations in allergic mucin
  - Bent et al
    - 22 fungal cultures in vitro against antifungals
    - Ketoconazole and Amphotericin B were only effective agents
    - Postulated they maybe useful as intranasal irrigations
AFRS Treatment

- Oral Steroids
  - How much for how long?
  - Prednisone may be started after surgery
  - Different dosing strategies
  - Do well on steroids, but may recur when tapered or taken off
  - Can’t use on everyone
  - Side effects
AFRS Treatment

- Adjunctive Therapies
  - Intranasal steroids
  - Anti-histamines
  - Nasal saline lavage
  - Decongestants
  - Anti-leukotriene meds
AFRS Treatment

• Immunotherapy (IT)
  • How long and what will happen when done?
  • Thought to be contraindicated in AFRS
    • Theoretically IT produces levels of IgG4 blocking antibody. IT increases levels of IgG in a disease with elevated IgG and IgE
    • Surgeon can remove allergic fungal load at surgery. IT will then down regulate specific IgE and decrease inflammation
AFRS Follow-Up

- Bent and Kuhn endoscopic classification
  - Stage 0  no evidence of disease
  - Stage 1  mucosal edema/allergic mucin
  - Stage 2  polypoid edema/allergic mucin
  - Stage 3  polyps and fungal debris
- Endoscopic staging does not often correlate with patient symptoms
Endoscopic Classification
Sinus Mycetoma (Fungus Ball)

- Not a good term
- Immunocompetent
- May be asymptomatic or may have those of chronic rhinosinusitis
- Incidence of atopy similar to general population
- Average age 50-60’s
Fungus Ball

• Physical Exam
  • May have
    • Polyps
    • Purulent drainage
    • Mucosal changes
  • Normal exam
Fungus Ball

- **Pathophysiology**
  - Most likely represents persistence of fungal spores in the nasal cavity or the sinuses, and subsequent germination and growth
  - Some have implicated dental pastes used in endodontics
Fungus Ball

- **Histopathology**
  - Non-invasive extramucosal mass of densely packed hyphae with alternating zones of dense and less dense growth
  - Layered look
  - Can be seen on H&E and special stains
  - Difficult to identify the species without culture
Fungus Ball

• Culture
  • Low viability (23-50% grow in culture)
  • Klossek et al (French)
    • 55/109 previous endodontic procedure
    • GMS positive 102/109 (94%)
    • KOH positive 78/109 (72%)
    • Culture positive 33/109 (30%)
  • Most frequently *Aspergillus*
Fungus Ball

- Radiology
  - May show focal round area of increased attenuation that is usually centered in a diseased maxillary sinus
  - Bony thickening and erosion possible
  - Rest of sinuses may be normal or show signs of chronic rhinosinusitis
Fungal Ball Radiology
Fungus Ball Radiology
Fungus Ball Radiology
Fungus Ball

• Diagnostic Criteria
  • Radiologic studies show typical presentation
  • Mucopurulent, cheesy or clay-like material is present at the time of surgery
  • Histology reveals no mucin, but a matted conglomerate of fungal hyphae
  • Mucosa with chronic inflammatory response
  • No invasion
Fungus Ball

- Treatment
  - Removal of the fungus ball
  - Aeration and ventilation of the sinuses
  - If asymptomatic may follow
- FESS
  - Large middle meatal antrostomy and irrigation
  - May be invasive with immunosuppression
Acute Fulminant Invasive Sinusitis (AFIS)

- History
  - Mackenzie 1893 described necrotic fungal infection of the nose
  - 1956, Amphotericin B discovered
  - Key to turning around mortality rate
Acute Fulminant Invasive Sinusitis

- A rapidly progressive fungal infection of less than 4 weeks duration that may directly invade mucosa, submucosa, or bone. The fungi may also invade blood vessels and spread by angioinvasion and enter nerve and travel perineurally. Mortality 50-80% if untreated.
AFIS Risk Factors

- Diabetics
- 1° or 2° immunodef.
- Hemochromatosis
- Aplastic anemia
- Organ/Bone marrow transplants
- Protein-caloric malnutrition
- Immunosuppression

- Incidence of AFIS rising
- Pts with diabetes do better because their underlying condition can be controlled
AFIS Risk Factors

- 2° risk factors
  - Prolonged course of steroids
  - >2 weeks broad spectrum antibiotics
- Patients at greatest risk when absolute neutrophil counts are <500 cells/ml
- Bone marrow transplant patients
  - Risk post transplant    GVHD    Solid organ
AFIS Pathophysiology

- Fungi grow on retained secretions and crusts in the nasal cavity. When the immunity is lowered they spread into the sinuses and into the mucosa and adjacent structures.
- The fungi enter the blood vessels and cause thrombosis and ischemic infarction and hemorrhagic necrosis.
AFIS Pathophysiology

• Fungal elements can also spread via nerves
• Fungal elements invade the necrotic tissue where they further thrive and reproduce, leading to more tissue destruction
AFIS Clinical Features

- **History (early signs)**
  - 90% FUO that has not responded to 48° of broad spectrum antibiotic
  - Facial/periorbital pain
  - Nasal congestion, rhinorrhea, headache
  - Facial numbness
AFIS Clinical Features

• History (late signs)
  • Eye complaints
  • Mental status changes
  • Focal neurological complaints
  • Lethargy
  • Seizures
  • Palatal necrosis
AFIS Clinical Features

- Physical Exam
  - Neuro: mental status, focal deficits, lethargy, cranial nerve deficits
  - Eye: ophthalmoplegia, proptosis, orbital apex syndrome, loss of visual acuity
  - Nasal endoscopic exam: decongest and look for nasal mucosal changes
AFIS Clinical Features
AFIS Clinical Features
AFIS Clinical Features

- Endoscopic exam
  - Black or brown appearance
    - Tissue necrosis
  - Blanched or white appearance
    - Tissue ischemia
  - Asensate tissue or lack of bleeding
    - Ominous sign
    - 25 or 27 gauge spinal needle
AFIS Clinical Features

- Endoscopic Exam (Gillespie et al)
  - Involvement in AFIS
    - Middle turbinate  67%
    - Septum           29%
    - Palate           19%
    - Inferior Turbinate  6%
AFIS Histopathology

- Fungal hyphae invasive
- Fungal hyphae invade blood vessels causing vasculitis with thrombosis, hemorrhage, and ischemic tissue infarction
- Surrounding tissue neutrophilic rxn
- Mucor
  - Non septated hyphae branching at 90°
AFIS Endoscopy
AFIS Pathology
AFIS Culture

• If fungi grows may take several days
• Invasive fungi usually from zygomycetes but can be from hyaline moulds
• Treat based on histology and clinical suspicion
AFIS Radiology

- CT may initially show nonspecific inflammation or mucosal thickening
- May have normal CT if only involving nasal cavity
- Less likely to have bony expansion, erosion later in course
  - Into canine fossa, pterygopalatine fossa, eye, or brain
AFIS Radiology

- May see brain/orbit involvement
  - With direct extension
  - Without direct extension
    - Will enhance with contrast on CT and MRI
    - Ring enhancement with intracerebral abscess
- MRI
  - Superior for intracranial extension
AFIS Treatment

• Surgery
  • Emergent aggressive surgery
    • Open vs. endoscopic
    • Endoscopic
      • No increased mortality
      • Decreased morbidity
  • Must debride all devitalized tissue
    • Bleeding margins
AFIS Treatment

• Surgery
  • Controversy regarding orbital exenteration
    • Cases must be individualized
  • If persistence is suspected 2\textsuperscript{nd} look at 48-72\degree
• biopsy surrounding healthy tissue
AFIS Treatment

• Goals of Surgery
  • Slow the progression of disease allowing time for the recovery of neutrophil function
  • Reduce the fungal load, which reduces the burden for recovering neutrophils
  • Provides specimen for identification
AFIS Treatment

- Control underlying cause
  - Diabetics
    - Control sugar and correct acidosis
  - Neutropenics
    - Correct neutropenia/GCSF
- Surgery does not prolong survival in neutropenic patients that do not recover WBC function
AFIS Treatment

- Antifungals
  - Amphotericin B
    - 1.0-1.5 mg/kg/day (minimum 14 days)
    - Dosage of 2.5-3.0 grams total in immunosuppressed
    - Cost $6 a day
  - Liposomal Amphotericin B (AmBisome)
    - Better efficacy/lower toxicity
    - Cost $220 a day
  - Other: B lipid complex, B colloidal dispersion, Posaconazole, Isavuconazole, Capsofungin
  - Hyperbaric Oxygen?
AFIS Prophylaxis

- Prophylaxis
  - Regular cleaning of duct work
  - No birds on sills or roof of building
  - Minimize patient time outside room
  - Visitor precautions
  - Biggest risk is construction areas
  - Antifungals do not play role
    - Unless 48° FUO unresponsive to IV Abx
Chronic Invasive Sinusitis

- At one time included granulomatous invasive disease
- **Clinical Presentation**
  - Immunocompetent diabetics
  - Any age but usually 40-50’s
  - May have history of chronic RS, atopy, or polyps
Chronic Invasive Sinusitis

- Pathophysiology
  - Unknown
  - Similar to AFIS except the course is >4 weeks and more slowly progressive
  - Patients may be asymptomatic for long period of time
Chronic Invasive Sinusitis

• Signs/Symptoms
  • May take months to years to appear and may not be present until skull base erosion has occurred
  • When symptoms occur similar to AFIS
  • Indolent course, will be very aggressive
Chronic Invasive Sinusitis

• Pathology
  • Most common isolated fungi is *Aspergillus fumigatis*
  • Zygomycetes can be cultured
• Radiology
  • Similar to AFRS and AFIS
Chronic Invasive Sinusitis

Treatment

- No studies to evaluate
- Small numbers
- Controversy exists
  - Wide aeration vs. thorough exenteration
- Amphotericin B
  - At least 2 grams after surgery
Chronic Invasive Sinusitis

- Follow-Up
  - Persistence/recurrence common
  - CT scan 1 month post-op
    - Then every 3-4 months
  - Endoscopic exams at regular intervals
Granulomatous Invasive Sinusitis (GIS)

- Not much in literature
- Primary paranasal granuloma
- Most cases reported from Sudan
  - Also from US, Pakistan, and India
- Immunocompetent
- Protracted clinical course
Granulomatous Invasive Sinusitis

- **Pathophysiology**
  - Unknown
  - Thought to be instigated by the hot, dirty environment

- **Pathology**
  - Profuse fungal growth with regional tissue invasion (superficial mucosa) with non-caseating granulomas
Granulomatous Invasive Sinusitis

- **Pathology**
  - Central microgranulomata of eosinophils, fibrinoid necrosis, fibrosis, and vasculitis
  - Periarterial inflammation without direct involvement of fungal elements
  - Gross appearance firm, hard, rubbery, fibrous, grey-white masses with irregular surfaces
  - *Aspergillus flavus* most commonly isolated
Granulomatous Invasive Sinusitis

• Signs/symptoms
  • Proptosis most commonly reported in Sudan
  • Chronic rhinosinusitis

• Radiology
  • Similar to AFRS with expansion of sinus cavities causing proptosis
  • May just show mucosal thickening
Granulomatous Invasive Sinusitis

- **Treatment**
  - Surgical removal
  - Aeration and ventilation of the sinuses
  - Post-op Amphotericin B
    - 1-2 grams
    - ±itraconazole (8-10 mg/kg/day)
Conclusions

• High index of suspicion for these disorders
  • AFRS in pts recalcitrant to meds and surgery
  • AFIS in patients that are immunocompromised
Thanks for listening!