Fungal Sinusitis

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INTRODUCTION

- Fungi are ubiquitous
- Immune system keeps organisms suppressed
- Most infections are benign, non-invasive
- Immunocompromised – higher risk of invasive disease
- Non-invasive vs. invasive
Basic Mycology

- 20,000 – 1.5 million fungal species
  - Few dozen species cause human infection
- Forms: yeast or mold
  - Yeast
    - Unicellular
    - Reproduce asexually by budding
      - Pseudohyphae – when bud doesn’t detach from yeast
  - Mold
    - Multicellular
    - Grow by branching – hyphae
PSEUDOHYphae VS. HYPhaE

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<td>Blastoconidium formation</td>
<td>Fission formation</td>
<td>Pseudo-hyphae</td>
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<td>Coenocytic hyphae</td>
<td>Septate hyphae</td>
<td>Sepitate hyphae with clamp connections</td>
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BASIC MYCOLOGY

 Spore

• Reproductive structure produced in unfavorable conditions

• Withstand many adverse conditions
• Favorable environment → growth

• Inhalation of spores – most common way fungi infiltrate sinuses to cause disease
Basic Mycology

- Microscopic Appearance of Specific Fungi
  - Aspergillus
    - Septated hyphae with branching at 45°
  - Mucromycosis
    - Nonseptated hyphae with branching at 90°
Aspergillus

Note septations (yellow arrows) and 45 degree branching (red arrows)
Mucormycosis of paranasal sinus

Note the 90 degree branching and lack of septations
Classiﬁcation of Infection

- Non-invasive
  - Saprophytic fungal infestation
  - Sinus fungal ball (mycetoma)
  - Allergic fungal sinusitis

- Invasive
  - Acute fulminant invasive fungal sinusitis
  - Chronic invasive fungal sinusitis
  - Granulomatous invasive fungal sinusitis
Saprophytic Fungal Infestation

- Visible growth of fungus on mucus crusts without invasion
- Minimal to no sinonasal symptoms

**Diagnosis**
- Endoscopic visualization of crusts with fungi

**Treatment**
- Removal of crusts
- Nasal saline irrigations
- Weekly nasal endoscopy with removal of crusts until disease process resolves
Sinus Fungal Ball (Mycetoma)

- Sequestration of fungal elements within a sinus without invasion or granulomatous changes
- Inhaled spores → grow while evading host immune system (no invasion)
- Aspergillus most common species
- Maxillary sinus most often involved (70-80% of cases)
Sinus Fungal Ball (Mycetoma)

- Clinically
  - Symptoms due to mass effect and sinus obstruction
  - Presents similar to rhinosinusitis
    ○ Congestion, facial pain, headache, rhinorrhea

- Physical examination
  - Mild to minimal mucosal inflammation
  - Polyps in 10% of cases
Sinus Fungal Ball (Mycetoma)

Diagnosis

- CT Scan
  - Single sinus in 59-94% of cases (maxillary)
  - Complete or subtotal opacification of sinus
  - Radiodensities within the opacifications
    - Due to increased heavy metal content
  - Bony sclerosis; destruction is rare (3.6-17% of cases)
- Biopsy = fungal elements
Images show thickening of bony walls (short arrows) and heterodense material within the sinus with calcifications (long arrows)
Sinus Fungal Ball (Mycetoma)

Treatment

- Complete surgical removal of fungal ball
- Irrigation of involved sinuses
- Antifungal therapy
  - Only if patient is high risk for invasive disease (very rare)
    - Severely immunocompromised
    - Continued recurrence of disease despite proper medical/surgical management
  - Consider topical antifungal irrigation first and then systemic therapy if no improvement
ALLERGIC FUNGAL SINUSITIS

- Fungal colonization resulting in allergic inflammation without invasion
- IgE mediated response to fungal protein

Symptoms:
- Nasal obstruction (gradual)
- Rhinorrhea
- Facial pressure/pain
- Sneezing, watery/itchy eyes
- Periorbital edema
ALLERGIC FUNGAL SINUSITIS

Diagnostic Criteria

1. Eosinophlic mucin
2. Nasal polyposis
3. Radiographic findings
4. Immunocompetance
5. Allergy to fungi
ALLERGIC FUNGAL SINUSITIS

Eosinophilic Mucin

- Pathognomonic
- Thick, tenacious and highly viscous
  - Tan to brown or dark green in appearance
- Microscopic examination
  - Branching fungal hyphae
  - Sheets of eosinophils
  - Charcot-Leyden crystals
    - Breakdown of cells by enzymes produced by eosinophils
    - Slender and pointed at each end
    - Pair of hexagonal pyramids joined at bases
EOSINOPHILIC MUCIN
ALLERGIC FUNGAL SINUSITIS

- Radiographic findings
  - CT
    - Unilateral (78% of cases)
    - Sinus expansion
    - Bone destruction in 20% of cases
      - More often in advanced or bilateral disease
    - "Double Densities"
      - Heterogeneity of signal → increased heavy metal content (iron and manganese) and calcium salts
ALLERGIC FUNGAL SINUSITIS

Arrows show double densities. Note sinus expansion
Double densities (arrows). Expansion of sinus with extension of disease into the nasal cavity (star)
Allergic Fungal Sinusitis

Radiographic findings

MRI

- Variable signal intensity on T1 (usually hyperintense)
- T2 – hypointense central portion (low water content of mucin) with peripheral enhancement due to edema
Allergic Fungal Sinusitis

T1 MRI – high signal intensity of debris

T2 MRI – central area of low intensity surrounded by high intense signal
ALLERGIC FUNGAL SINUSITIS

T1 MRI – high signal intensity of debris

T2 MRI – central area of low intensity surrounded by high intense signal
Allergic Fungal Sinusitis

- Allergy to Fungi
  - Most patient with AFS will have allergy to fungus causing disease

- Manning et al
  - Prospective study
  - Compared
    - 8 patients with AFS and (+)culture with Bipolaris
    - 10 controls with chronic rhinosinusitis
  - All 8 patients showed (+) skin testing, RAST, and ELISA to Bipolaris
  - 8 of 10 controls (-) for all tests

- IgE levels > 1000 IU/mL
ALLERGIC FUNGAL SINUSITIS

Treatment

- **Surgical**
  - Remove all mucin
  - Provide permanent drainage and ventilation of affected sinuses
- **Systemic +/- topical steroids**
  - Systemic steroids decrease rate of recurrence
    - Course can range from 2-12 months
      - Schubert showed that longer courses had better results, but more side effects
    - 0.5mg/kg Prednisone starting dose and taper over 2-3 months
Allergic Fungal Sinusitis

- Immunotherapy
  - Decrease recurrence
  - Alleviate need for steroids

- Prospective review
  - All patients had surgery and systemic steroids
  - One group got immunotherapy, the other did not
    - Consisted of fungal and non-fungal antigens to which patients were sensitive
  - After 1 year:
    - No requirement for systemic or topical steroids by patients in immunotherapy group
    - Recurrence of disease significantly less in immunotherapy group
Allergic Fungal Sinusitis

Immunotherapy

- Folker et al
  - Retrospective study
  - Compared 11 patients who received immunotherapy post-operatively vs. 11 who did not
  - Recurrence rates did NOT decrease
  - However:
    - Quality of life scores and mucosal edema were much better in those who received immunotherapy
ACUTE FULMINANT INVASIVE FUNGAL SINUSITIS

- **Patient population**
  - Most often compromised immune system
    - DM, AIDS, hematologic malignancies, organ transplant, iatrogenic (chemotherapy and steroids)

- **Most common fungi**
  - Aspergillus
  - Mucormycosis
    - Mucor, Rhizopus, Absidia

- **Less common fungi**
  - Candida
  - Bipolaris
  - Fusarium
ACUTE FULMINANT INVASIVE Fungal Sinusitis

Pathogenesis

- Spores inhaled → fungus grows in warm, humid sinonasal cavity
- Fungi invade neural and vascular structures with thrombosis of feeding vessels
- Necrosis and loss of sensation → acidic environment → further fungal growth
- Extrasinus extension occurs via bony destruction, perineural and perivascular invasion
  - Nasal and palate mucosa destroyed
  - Facial anesthesia
  - Proptosis
  - Cranial nerve deficits
  - Mental status changes
Acute Fulminant Invasive Fungal Sinusitis

Other signs/symptoms

- Fever (most common – 90% of cases)
- Loss of sensation over face or oral cavity
- Ulceration of face and sinonasal/palatal mucosa
- Rhinorrhea, facial pain/anesthesia, headaches
- Seizures, CN deficits
- Fast progressing symptoms
  - In some cases, hours to days till death!
**Acute Fulminant Invasive Fungal Sinusitis**

- **Endoscopic findings**
  - Loss of sensation and change in appearance of mucosa (pale or black)
    - Most consistent finding
  - Ulcerations and black mucosa are late findings
  - Serial examinations are required
Acute Fulminant Invasive Fungal Sinusitis

- **Biopsy + Culture**
  - Should always be performed when:
    - Suspect fungal disease
    - Change in sensation or color of mucosa
    - Any immunocompromised patient with signs of sinusitis who fails to improve after 72 hours of IV antibiotics
  - Where?
    - Diseased mucosa (pale, insensate, ulcerative, black)
    - Normal appearance/sensation
      - Middle turbinate – most common spot for AFIFS (67%)
      - Septum – 24% of cases
  - Must request silver staining
  - Culture
    - Very difficult to get (+) result, especially with Mucormycosis
Acute Fulminant Invasive Fungal Sinusitis

- Radiographic studies
  - CT sinus
  - MRI to assess tissue invasion, and orbital, intracranial, or neural involvement
- Findings
  - CT
    - Bone erosion and extrasinus extension – classic finding
    - Severe, unilateral mucosal thickening
    - Thickening of periantral fat planes
CT scans; **Left image:** Destruction of medial wall of orbit with extension of disease into the orbit. **Right image:** Destruction of medial and inferior walls of the orbit with extension of disease into the orbit.
Axial CT scans. **Left image:** invasion through lateral wall of the sphenoid sinus and into the cavernous sinus. **Right image:** lack of enhancement of the cavernous sinus due to fungal thrombosis.
ACUTE FULMINANT INVASIVE FUNGAL SINUSITIS

MRI

- Obliteration of the periantral fat
- Leptomeningeal enhancement (intracranial extension)
- Granuloma formation
  - Hypointense on T1 and T2
- Extrasinus extension
- Cavernous sinus involvement
  - Absent flow void of carotid
  - Soft tissue thickening of the involved sinus
Axial MRI, T2 – left sphenoid sinus with central hypointense region with surrounding hyperintensity. Flow void in left cavernous sinus absent (arrow)

Axial MRI, T2 – Acute infarction of the left temporal lobe in same patient
**Acute Fulminant Invasive Fungal Sinusitis**

- Combination of medical and surgical treatment
  - **Medical**
    - Correct the underlying compromised state
      - Reverse DKA and improve hydration
        - 80% survival if done promptly
      - Absolute neutrophil count
        - < 1000 = poor prognosis
        - WBC transfusion and granulocyte colony stimulating factor to increase ANC
Acute Fulminant Invasive Fungal Sinusitis

- **Medical treatment**
  - **Systemic antifungals**
    - Amphotericin B infusion
      - 1mg/kg/day
      - Serious side effects
        - ototoxicity, nephrotoxicity (occurs in 80% of cases)
    - Lipid-based form of Amphotericin B
      - More expensive
      - Less toxic
      - Can achieve higher concentrations of drug
    - Voriconazole or itraconazole
      - Used most often when Aspergillus involved
      - Much less toxic than Amphotericin B
      - Mucormycosis are resistant to these
ACUTE FULMINANT INVASIVE FUNGAL SINUSITIS

- **Topical Amphotericin B rinses**
  - Have shown some success, but mixed results

- **Surgical treatment**
  - **Goals**
    - Decrease pathogen load
    - Remove devitalized tissue
    - Establish pathways for sinus drainage
  - Debride until clear, bleeding margins
ACUTE FULMINANT INVASIVE FUNGAL SINUSITIS

- **Endoscopic vs. Open procedures**
  - Recommend endoscopic in early course of disease
    - Decreased morbidity
    - Similar survival rates as open procedures
  - Advanced disease (orbit, palatal, skin)
    - Open approach required
    - Once disease has gone intracranial, prognosis is very poor
      - Must be considered prior to partaking in extensive surgical resection
**Acute Fulminant Invasive Fungal Sinusitis**

- Retrospective review out of Turkey
  - Examined treatment of AFIFS
  - 26 patients
    - 19 – endoscopic resection
    - 7 – open resection
      - 5 orbital exenteration (2 survived)
  - All patients with skull base/intracranial extension died
  - Overall mortality rate – 50%
  - Survival rates
    - Endoscopic – 90% (less severe disease)
    - Open – 57%
  - In those who died, Mucormycosis were involved in 62% of cases
    - More aggressive with early orbital and intracranial invasion
**Acute Fulminant Invasive Fungal Sinusitis**

- **Prognosis**
  - Mortality rate: 18-80%
    - Early detection and treatment = much better chance of survival
    - **Intracranial involvement**
      - Most predictive indicator for mortality
      - 70%+ mortality rate
    - Absolute Neutrophil Count (ANC) < 1000
      - Worse prognosis
      - Recovery from neutropenia = most predictive indicator for survival
    - Mucormycosis = more fatal
    - Diabetics tend to do worse
      - Greater incidence of Mucormycosis in these patients
CHRONIC INVASIVE FUNGAL SINUSITIS

- Slower disease process than acute
- Rare
- Biggest difference:
  - Most patients are immunocompetent
- Common fungi
  - Aspergillus (most common - >80% of cases)
  - Bipolaris
  - Candida
  - Mucormycosis
CHRONIC INVASIVE FUNGAL SINUSITIS

- Signs/Symptoms
  - Similar to symptoms of chronic rhinosinusitis
    - Nasal congestion, rhinorrhea, facial pressure, headaches, polyposis
  - Proptosis, visual changes, anesthesia of skin, epistaxis
    - More concerning
  - Does not respond to antibiotics
  - Worsens with steroids
CHRONIC INVASIVE FUNGAL SINUSITIS

- **Diagnosis**
  - Full H&N examination with nasal endoscopy
    - Nasal polyps, thick mucus
    - Rarely find ulcerations
    - Biopsy if suspect fungal disease or note any changes

- **CT & MRI**
  - Similar findings to AFIFS – bony destruction, extrasinus extension, unilateral
CT showing destruction of right lateral maxillary sinus and zygomatic arch

CT showing opacification of left maxillary sinus with extrasinus extension of disease into the periantral tissues (arrows)
CHRONIC INVASIVE FUNGAL SINUSITIS

Diagnosis

- Pathology
  - Invasion of blood vessels, neural structures, and surrounding mucosa
  - Few if any inflammatory cells
    - Major difference between acute and chronic invasive disease
  - No Granuloma formation
    - Main difference between chronic invasive fungal disease and granulomatous invasive fungal disease
CHRONIC INVASIVE FUNGAL SINUSITIS

Treatment
- Similar to AFIFS – surgical + medical

Surgery
- resect all involved tissue to expose bleeding margins

Systemic antifungals
- Start with Amphotericin B until can rule out Mucormycosis
- Best length of treatment not well studied
  - Most recommend 3-6 months of therapy

Topical Amphotericin B sinus rinses

Close F/U and debridement required
- Biopsy anything that is suspicious as asymptomatic recurrence is not uncommon
Granulomatous Invasive Fungal Sinusitis

- Appears exactly like CIFS
- Very rare
- Presence of multinucleated giant cell granulomas
  - Most important difference between Chronic and Granulomatous disease
- Aspergillus flavus
- Most often seen in North Africa and Southeast Asia
Granulomatous Invasive Fungal Sinusitis

- Presentation and work-up are exactly the same as CIFS

- Treatment
  - Surgical resection to bleeding margins
  - Topical antifungal rinses
  - Systemic antifungals
    - Oral voriconazole or itraconazole
    - Minority of authors believe systemic antifungals not required
  - Close F/U and debridement required
    - Biopsy anything that is suspicious as asymptomatic recurrence is not uncommon
CONCLUSION

- Fungi are ubiquitous

- Disease in immunocompetent is nearly always benign, but must consider invasive disease

- Invasive fungal disease must be considered in all immunocompromised patients
  - Low threshold for biopsy
CONCLUSION

• Surgical debridement
  • Mainstay of treatment of fungal sinus disease
  • Invasive disease – debride until clear, bleeding margins
  • Weigh extent of surgery with prognosis
    ○ Skull base/intracranial involvement very poor prognosis even with aggressive therapy

• Systemic antifungals required for invasive disease
  • Monitor for severe side effects

• Close follow-up with debridement and biopsy of any suspicious lesions


