Learning Objectives

Upon completion of this session, participants should be able to:

- Describe the role of fungi in inducing intense allergic inflammation in allergic bronchopulmonary aspergillosis and allergic fungal rhinosinusitis
- Describe the controversial role of fungi in inducing eosinophilic inflammation in chronic rhinosinusitis

Disclosure

- No relevant financial relationships to disclose

Invasive Fungal Rhinosinusitis

- Acute fulminate necrotizing fungal rhinosinusitis
- Chronic invasive fungal rhinosinusitis
- Granulomatous invasive fungal rhinosinusitis

Noninvasive Fungal Rhinosinusitis

- Fungal ball (sinus mycetoma)
- Allergic fungal rhinosinusitis (AFS)
  - 6-9% of all chronic rhinosinusitis (CRS)

Acute Fulminate Necrotizing Fungal Rhinosinusitis ("Mucormycosis")


58 y.o. renal transplant (culture result not reported).

Mycetoma

Allergic Fungal Sinusitis
Clinical/Surgical Presentation

- Chronic rhinosinusitis (CRS) with nasal polyps (also called hypertrophic/hyperplastic sinus disease (HSD), chronic eosinophilic rhinosinusitis, etc).
- Characteristic "allergic mucin" is seen grossly at surgery and further defined histopathologically.

Allergic Fungal Sinusitis
Clinical/Surgical Presentation (cont.)

- Allergic mucin is fungal stain positive for sparse scattered hyphae; non-tissue-invasive.
- Surgical sinus fungal culture usually positive (culture negative- 13%).
Allergic Fungal Sinusitis
Clinical/Surgical Presentation (cont.)

• Sinus CT hyperattenuation.
• Can be bi- or unilateral.
• Fungal-containing allergic mucin can erode through sinus bone margins into orbit or intracranium.
• Clinically chronic and often surgically recurrent.
Allergic Mucin

• A histopathological, not functional, term.
• A sinus luminal viscoelastic inspissate of massive numbers of pyknotic eosinophils.

H&E stain, x40

Allergic Fungal Sinusitis

Paranasal sinus, allergic mucin- GMS stain, x100

Allergic Mucin with Charcot-Leyden Crystals

Surgical sinus H&E stain
Allergic Fungal Sinusitis Mucosa

Minimum Required AFS Diagnostic Criteria
(developed over 8 years and 67 consecutive AFS patients)

1) Characteristic “allergic mucin” must be seen: on surgical sinus histopathology or grossly at surgery.

2) Evidence for fungi: GMS (or similar) fungal stain must be positive for hyphae within the allergic mucin or surgical sinus fungal culture positive.

3) Characteristic sinus mucosal inflammatory infiltrate: small lymphocytes, plasma cells, eosinophils; no necrosis, granulomas, or fungal invasion.

4) Other fungal diseases are excluded.


Allergic Fungal Sinusitis
Pathophysiologic Findings

• Allergic/hypersensitivity response to the presence of fungi within the sinus cavity(s).
• All pts. are atopic- will be allergy skin test positive to multiple aeroallergens.
• All pts. will have specific IgE to the AFS etiologic fungus when properly identified by intraoperative surgical culture of allergic mucin.


Allergic Fungal Sinusitis
Pathophysiologic Findings (cont.)

• Incidence- 6-9% of all surgical sinusitis.
• Southern and Southwestern U.S. are endemic, but has been reported throughout the country and world.
• Chronic and often recurrent.

Allergic Fungal Sinusitis Pathophysiologic Findings (cont.)

- Adults and children (mean age 33 y.o., range 8 y.o.- 67 y.o.).
- Nasal casts- 75%.
- Asthma- 64%.
- Immunocompetent.


Allergic Fungal Sinusitis Pathophysiologic Findings (cont.)

- Associates with HLA-DQB1*0301 and *0302 (other CRS HLA-DQB1*0301, *0302, *0303, *0304, *0305).
- Analogous (but not identical) to allergic bronchopulmonary aspergillosis (ABPA).
- Most common causes:
  - “dematiaceous” fungi, e.g., Bipolaris spicifera, Curvulana lunata, Exserohilum rostrum, Alternaria spp.
  - Aspergillus spp.


Is classic allergic mucin seen on histopathology?

- Yes

Is the allergic mucin fungal stain positive?

- Yes

Is the surgical sinus fungal culture positive?

- Yes

Fungi are noninvasive?

- Yes

Typical AFS mucosal inflammation?

- Yes

“Eosinophilic mucin rhinosinusitis” (EMRS)

- Yes

Eosinophilic mucin rhinosinusitis (EMRS)

36 y.o. female- CRS with nasal polyops, classic inspissated allergic mucin (EMRS), asthma, and inhalant allergy. Not ASA/NSAID sensitive. Negative for fungi on cultures and histopathology from all sinus surgeries.
Is classic allergic mucin seen on histopathology? No
Is classic allergic mucin seen grossly at surgery? No
CRS Yes

- Fungi are noninvasive?
  - Typical AFS mucosal inflammation? Yes
  - Is the surgical sinus fungal culture positive? No

AFS Invasive fungal sinusitis +/- AFS EMRS

**ABPA and AFS Compared**

<table>
<thead>
<tr>
<th></th>
<th>ABPA</th>
<th>AFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic mucin with noninvasive fungal hyphae</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Respiratory atopy</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Allergy skin test positive to fungal organism</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Total serum IgE elevated</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Fungal-specific IgG elevated</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Fungal-specific IgE elevated beyond common atopy</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Serum precipitins to fungal organism</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Peripheral eosinophilia</td>
<td>yes</td>
<td>no/yes</td>
</tr>
<tr>
<td>Change in total serum IgE prognostic</td>
<td>yes</td>
<td>yes</td>
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**ABPA and AFS Compared (cont.)**

<table>
<thead>
<tr>
<th></th>
<th>ABPA</th>
<th>AFS</th>
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<tbody>
<tr>
<td>MHC class II association</td>
<td>yes^a</td>
<td>yes^b</td>
</tr>
<tr>
<td>Favorable clinical response to systemic corticosteroids</td>
<td>yes</td>
<td>yes^c</td>
</tr>
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</table>

a^a HLA-DR2 and DR5, DQ2 was found to be protective. From: Chauhan B, Santiago L, Hutcheson PS, et al. J Allergy Clin Immunol 2000;106:723-9.


Figure 1. Representative IgE anti-fungal immunoblots from a CRS patient and an AFS patient.

Table 4. Comparison of mean number of positive IgE bands for each fungus between 10 AFRS and 11 CRS subjects.

<table>
<thead>
<tr>
<th>Fungus</th>
<th>AFRS mean (SD)</th>
<th>CRS mean (SD)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternaria</td>
<td>6.9 (1.8)</td>
<td>0.6 (0.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>5.2 (4.1)</td>
<td>0.7 (0.9)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Bipolaris</td>
<td>0.4 (1.9)</td>
<td>0.8 (1.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bipolaris/Curvularia</td>
<td>10.7 (1.5)</td>
<td>1.6 (1.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Epicoccum</td>
<td>6.7 (3.3)</td>
<td>0.8 (2.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fusarium</td>
<td>4.1 (2.1)</td>
<td>0.7 (0.6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Phoma</td>
<td>4.9 (2.3)</td>
<td>0.9 (2.2)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Significance p values calculated using Independent-samples t test.

Nasal endoscopy- fungal culture of paranasal sinus secretions in 50 CRS and 24 control pts.- positive in 2 CRS pts., negative in all controls. Neither Alternaria nor Aspergillus were able to stimulate IL-5 or γ-interferon transcription in vitro from PBMCs from 14 CRS pts. and 7 controls.

Other double-blind placebo controlled studies- topical and systemic antifungal treatments found ineffective in CRS treatment.

Allergic Fungal Sinusitis Treatment

- Aggressive sinus surgery.
- Topical corticosteroids.
- Antihistamines.
- Consider antileukotrienes.

Allergic Fungal Sinusitis Treatment (cont.)

- Allergen immunotherapy (etiologic mold may be included).
- Oral corticosteroids (OCS)- modified ABPA OCS or similar protocol (pre-op, intra-op, or ASAP post-op).
- Close medical-surgical cooperation and F/U.
- Monitor total serum IgE post-op.

Systemic antifungals (oral, parenteral) - not felt to be effective.
- Topical antifungals - not adequately studied yet; does make sense. Maybe as adjunct to OCS (eg., OCS + itraconazole in ABPA)?
- Omalizumab (anti-IgE)???
AFS oral corticosteroid (OCS) protocol

• Start post-operatively ASAP:
  • 0.5 mg prednisone/kg q AM for 2 weeks, then 0.5 mg/kg every other AM for 2 weeks with gradual taper to 7.5-5 mg prednisone every other AM by 3 months and continue on this dose.


AFS OCS protocol (cont.)

• Short “burst” of prednisone for any intercurrent acute rhinosinusitis episodes (with or without antibiotics as indicated).
  • Discontinue prednisone at 1 year, sooner, or later, as indicated.
  • If AFS surgically recurrent- restart OCS from time “zero” and repeat.


Allergic Fungal Sinusitis

Treatment Conclusions

• OCS significantly reduced rhinosinusitis symptoms and helped to forestall the need for recurrent sinus surgery.

• No significant side effects were seen with this AFS OCS protocol.

• Changes in both total serum IgE and fungal-specific IgG levels correlated with clinical status.


**Design:**
- 24 AFS pts.- randomized to receive OCS (n=12) or placebo (n=12) in the immediate postoperative period.
- OCS- 50 mg prednisolone daily for 6 weeks, then gradual taper off over 6 more weeks.
- All patients received nasal steroid spray and oral itraconazole (200 mg daily)

**Results:**
- OCS- 8 of 12 pts. disease-free at 6 weeks; 12 of 12 pts. disease-free at 12 weeks.
- Placebo- 1 of 12 pts. disease-free at 6 weeks; 1 of 12 pts. disease-free at 12 weeks.

**Conclusions:**
- OCS postoperatively are beneficial in AFS.
- Oral itraconazole ineffective in AFS.
- Need for addition of oral itraconazole to OCS was unaddressed.